SLEEP DISTURBANCE, COGNITION, AND BEHAVIOR IN DOWN SYNDROME

by

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DEDICATION

To Sean and Fiona

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ABSTRACT

Children and adolescents with Down Syndrome (DS) have a high incidence of sleep problems, including Obstructive Sleep Apnea Syndrome (OSAS). They are also likely to have deficits in neuropsychological tasks tapping prefrontal function and hippocampal function. There has recent revival of literature suggesting an active role for sleep in memory consolidation and problem-solving in both children and adults. Furthermore, given the cognitive and behavioral sequellae of OSAS in typically developing children it is logical to test if the hypoxemia and increased sleep fragmentation, the two major pathophysiological mechanisms of OSAS, seen in children with DS and OSAS may exacerbate learning or behavior disorders.

Forty children with DS aged 7-18 were administered the Arizona Cognitive Test Battery (ACTB) for DS (Edgin et al., 2010, 2010), and in-home ambulatory polysomnography. Their parents were asked to complete several questionnaires assessing their child's sleep and behavior. Seventy-seven percent (n = 40) of our sample met criteria for pediatric sleep apnea (AHI > 1.5), and the mean apnea hypoppnea index (AHI) was 8.4 events per hour. Our sample had a mean arousal index of 10.3, a respiratory arousal index of 3.2, and a SaO_2 nadir of 86.9%. Over 70% of our sample had a SaO_2 nadir below 90%. We examined the relationship between OSAS severity and cognitive and behavioral outcomes. We found that children with DS with a lower apnea hypopnea index (AHI) attained a greater number of stages on the CANTAB PAL task compared to chronologically age-matched children with higher AHI, and the variance in performance was partially explained by sleep fragmentation (i.e., the arousal index) and

experimenter-rated “attention” but not hypoxemia. In addition, we also found that the low apnea group showed a trend toward outperforming the high apnea group on the KBIT-II Verbal IQ scale and DAS-2 Pattern Construction subtest.

These findings have important clinical implications. First, these results suggest that early screening for OSAS in DS is important, as OSAS severity seems to explain some of the variance in cognitive functioning. Second, these findings suggest that an early intervention for OSAS might be warranted.

INTRODUCTION

Neuropsychology of Down Syndrome

Down syndrome (DS) is a genetic disorder that results in varying degrees of intellectual disability. It is one of the most prevalent neurodevelopmental disorders, accounting for close to 40% of cases of moderate to worse intellectual disability, with an incidence of 1 per 600 live births. Ninety-five percent of cases are due to a meiotic non-disjunction event that occurs prior to conception, resulting in an extra copy of chromosome 21. This condition is known as trisomy 21. Down syndrome may also result from Robertsonian translocation, in which the long arm of chromosome 21 attaches to another chromosome (2-3% of DS cases); or more rarely, mosaicism, in which some of the embryonic cells undergo a nondisjunction event during early cell division (1-2%) (Epstein,1995). Given that the majority of cases of DS are due to trisomy 21, the variability in cognitive outcome is remarkable. At this point, it is unclear which genes contribute to the neuroanatomical and neurocognitive features of DS, although post mortem and neuroimaging studies have identified widespread differences in the brains of individuals with DS.

A number of studies have reported virtually no differences at birth between brains of individuals with and without DS (e.g., Schmidt-Sidor, Wisnieski, Shepard, & Sersen 1990). Differences begin to appear during the first few months of life and include delayed myelination (Wisniewski & Schmidt-Sidor, 1989), reduced growth in the frontal lobes, a narrowing of the superior temporal gyrus, diminished size of the brainstem and cerebellum, and a major reduction (20%-50%) in the number of cortical granular neurons

(Nadel, 1999). Structural magnetic resonance imaging (MRI) studies of children and adolescents with DS have reported microcephaly and relatively smaller volumes of frontal cortex, hippocampus and cerebellum (Jernigan, Bellugi, Sowell, Doherty, & Hesselink., 1993; Pinter et al., 2001). By adulthood, the brains of individuals with DS are markedly abnormal and characterized by reductions in total volume (microcephaly) and specific volume reductions in the prefrontal cortex, hippocampus, and cerebellum (Aylward et al., 1999; Kesslak, Nagata, Lott, & Nalcioglu, 1994; Raz et al., 1995; Weis, Weber, Neuhold, & Rett, 1991; White, Alkire, & Haire, 2003).

From a neuropsychological perspective, it may be the case that reductions in volume of the prefrontal cortex, hippocampal, and cerebellar regions of the brain correspond to impairments of the learning and memory or executive cognitive functions commonly associated with these structures. Pennington, Moon, Edgin, Stedron, and Nadel (2003) found evidence of specific hippocampal dysfunction in a sample of 28 adolescents with DS but little evidence of prefrontal dysfunction using a battery of nonverbal tasks. In a follow-up study, Edgin et al. (2008) used verbal tasks to investigate prefrontal functioning and found that both younger and older adults with DS showed deficits relative to mental age-matched controls in both hippocampal and prefrontal tasks. Rowe, Lavender, and Turk (2006) reported deficits in cognitive executive functioning in adults with DS relative to learning disabled adults without DS who were matched for age and vocabulary. More recently, Edgin et al. (2010) found evidence of hippocampal and prefrontal impairment using a battery of nonverbal tasks in children and adults with DS.

While these results suggest an overall pattern of learning and memory impairment, it is important to note that not all individuals with DS are similarly impaired in these areas.

Sleep Problems in Down Syndrome

In addition to cognitive impairments, sleep problems are frequently reported by individuals with DS or their parents. These include sleep maintenance problems in children (Cotton & Richdale, 2006), snoring, and other symptoms of sleep disordered breathing in both children and adults. Laboratory polysomnographic (PSG) studies have reported the presence of obstructive sleep apnea syndrome (OSAS) in this population, estimated to be somewhere between 30-79% (Dyken, Lin-Dyken, Poulton, Zimmerman, & Sedars, 2003; Ng et al., 2006; Schott et al., 2006). In children with DS whose parents reported snoring, the prevalence of OSAS was found to be 97% (Fitzgerald, Paul, & Richmond, 2007). OSAS is best described as a pattern of sleep abnormalities that includes complete and partial airway obstruction, as well as chronic obstructive hypoventilation with hypercapnia and hypoxemia (Marcus, Keens, Bautista, von Peckmann, & Davidson Ward, 1991). The primary symptom of OSAS is excessive daytime sleepiness. Individuals with DS are susceptible to the development of OSAS. In children with DS, it is quite common for the airway to be anatomically narrowed due to midfacial and mandibular hypoplasia, glossoptosis, and adenoidal and tonsillar hypertrophy (Uong et al., 2001; Donnelly, Shott, LaRose, Chini, & Amin, 2004; Schott, 2006). Individuals with DS have increased secretions and may be especially vulnerable to respiratory tract infections, which can further compromise the patency of the airway (Marcus et al., 1991). Other predisposing factors to OSAS in DS include obesity and

increasing chronological age (Shires et al., 2010), hypothyroidism, and generalized hypotonia. The presence of any combination of these factors greatly increases the probability that the airway will collapse during inspiration.

Obstructive Sleep Apnea Syndrome and Cognition

Many different factors contribute to the high prevalence of OSAS in children with DS. In typically developing children and healthy adults, there is ample evidence to suggest that the quality and quantity of sleep contribute to performance on tasks that measure learning and memory, cognitive executive function, and attention and vigilance. First, sleep is clearly important for the consolidation of memory. A number of hippocampal-dependent tasks require post-training sleep for successful consolidation (Rauchs et al., 2004; Peigneux et al., 2004; Plihal & Born, 1997; Plihal & Born, 1999). Importantly, slow-wave sleep (SWS), which is often shortened dramatically when sleep is fragmented due to frequent awakenings, is critical for this variant of memory consolidation. Children with DS demonstrate increased arousals and have a higher number of stage shifts from "deeper" to "lighter" sleep stages (i.e., from SWS to stage 2 sleep or REM sleep to stage 2 sleep) (Levanon, Tarasiuk, & Tal, 1999; Shott et al., 2006).

OSAS has been linked to cognitive sequellae in typically developing children in a manner that is consistent with the cognitive profile of many children with DS. Children with symptoms of OSAS scored significantly lower than those children without OSAS symptoms on tests of attention and executive function, memory, and general intellectual ability. Both Blunden et al. (2000, 2005) and Archbold, Giordani, Ruzicka, and Chervin (2004) reported that mild OSAS was associated with impairments in sustained attention

and vigilance on a computerized continuous performance test (CPT), a measure of attention and executive function. Associations between OSAS symptoms and deficits on a number of NEPSY subtests of executive function, including the auditory CPT, Tower of London task, and the visual attention, and verbal fluency subtests, have also been reported (Beebe et al., 2004; O'Brien et al., 2004b). Children with OSAS symptoms have also scored lower than controls on several different memory tests, including the WRAML memory screening index (Blunden, Lushington, Kennedy, Martin, & Dawson, 2000), Luria verbal learning task, and the Rey figure delay test (Kurnatowski, Putynski, Lapienis, & Kowalska, 2006).

Several recent studies using community samples have reported full scale IQ deficits among children with OSAS symptoms relative to controls (O'Brien et al., 2004a,b; Gottlieb et al., 2004; Montgomery-Downs et al., 2005; but see Kaemingk et al., 2003, Emanicipator et al., 2006). Lower school performance has also been reported in children with OSAS compared to controls (Gozal, 1998; Richards & Ferdman, 2000; Stradling, Thomas, Warley, Williams, & Freeland, 1990). On the other hand, OSAS has little association with a child's typical mood, expressive language skills, or visual perception (Beebe, 2006). Visual perception and construction are relative strengths for children with DS (Silverstein, Legutski, Friedman, & Tayakama, 1982).

Obstructive Sleep Apnea Syndrome and Behavior

A number of studies have reported associations between sleep-disordered breathing and behavioral problems, including hyperactivity,impulsivity, inattention, and externalizing behaviors such as rebelliousness and aggression as measured by the

Conners Parent or Teacher Rating Scales (CPRS, CTRS) or the Child Behavior Checklist (CBCL) in typically developing children (Ali, Pitson, Stradling, 1993; Arman et al., 2005; Blunden, Lushington, Kennedy, Martin, & Dawson, 2000; Chervin et al., 2002; Gottlieb et al., 2003; Rosen et al., 2004). Current prevalence estimates of neurobehavioral and psychiatric co-morbidity in children with DS range from 18% to 38% (Capone, Goyal, Ares, & Lannigan, 2006). Behavior problems, including symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) are among the most commonly reported mental health issues in community and clinical samples of DS (Pueschel et al., 1991; Coe et al., 1999; Clark & Wilson, 2003). It remains unclear how sleep disturbance or OSAS may contribute to the etiology of ADHD in DS. Carskadon, Pueschel, and Millman (1993) administered a 20-item screening questionnaire to parents that assessed nocturnal sleep symptoms and daytime behavior problems. Direct comparisons of the children with DS and their siblings revealed children with DS were more likely to be mouth breathers, snore, stop breathing at night, have excessive daytime sleepiness, and were more likely to disrupt "school activities with irritable, sleepy, or aggressive behavior."

Snoring and other symptoms of OSAS are associated with measures of attention and executive function, memory, and behavioral problems. The pathophysiological mechanisms underlying these daytime deficits are thought to include hypoxia secondary to obstructive apneas/hypopneas, and sleep fragmentation as a result of frequent arousals. Hypoxemia refers to an abnormal drop in blood oxygen levels. When it occurs intermittently as a consequence of OSAS, brain tissue is briefly deprived of oxygen

before normal levels are resumed. In rodent models of OSAS, intermittent hypoxia increases oxidative stress (Row, Liu, Xu, Kheirandish, & Gozal, 2003), up-regulates pro-inflammatory cytokines (Li et al., 2004), and induces excessive nitric oxide levels, all of which contribute to cortical and hippocampal neuronal cell death (Xu et al., 2004). This is hypothesized to result in decreased hippocampal long-term potentiation (LTP) and deficits in spatial learning (Decker et al., 2003). Several authors have suggested that intermittent hypoxia over the course of development may have adverse neurocognitive consequences (Row et al., 2003; Decker et al., 2003; Decker, Jones, Solomon, Keating, & Rye, 2005; Gozal and Kheirandish-Gozal, 2007). In children, intermittent hypoxia has been reported to have adverse effects on measures of daytime cognitive, behavioral, and academic performance (Bass et al., 2004).

Pathophysiology of Obstructive Sleep Apnea Syndrome

An arousal during sleep functions as a protective mechanism. When a child experiences an obstructive event during sleep, the arousal helps to curtail the obstruction and reestablish a patent airway. Arousals occur in response to hypoxemia and hypercarbia, but not every instance of hypoxemia is accompanied by an arousal. Frequent arousals may lead to sleep fragmentation, which has been associated with daytime sleepiness. Sleep fragmentation is not limited to OSAS, but may also occur as a consequence of other sleep disorders (e.g., periodic limb movement disorder, restless legs syndrome). When the source of the sleep fragmentation is non-respiratory in nature, it is easier to assess the independent contribution of sleep fragmentation to daytime deficits. Several studies of pediatric non-respiratory sleep disordered populations report an

association between sleep fragmentation and parental reports of daytime behavior problems (Picchietti et al., 1999; Chervin et al., 2002). Sadeh, Gruber, and Raviv (2002) reported that typically developing children with fragmented sleep performed more than controls on a continuous performance task and a digit symbol substitution task and had higher rates of behavior problems as reported by their parents on the CBCL. Marcus et al. (1991) has posited that the increased arousal rate and resulting sleep fragmentation seen in children with DS may affect their daytime functioning and could exacerbate learning or behavior disorders.

Specific Aims

In the present study, we examined the relationships between sleep, cognition, and behavior in DS. Specifically, we: (1) Examined the relationship between OSAS severity and cognitive outcomes. We anticipated that children with DS with a higher apnea hypopnea index (AHI) would score lower than children with DS of the same chronological age with a lower AHI on measures of hippocampal and prefrontal functioning. We did not expect to find differences on DAS-II Pattern Construction, since performance on visuoconstructive tasks is not related to OSAS (or to hypoxemia) in typically developing children, and visuoconstructive tasks are a relative strength for children with DS. We also (2) Examined whether or not these relationships could be explained by sleep fragmentation or hypoxemia. We predicted that the score differences on hippocampal measures would be explained in part by hypoxemia, and that score differences on prefrontal measures would be explained by sleep fragmentation.

We also sought to (3) Examine the relationship between OSAS and behavioral

outcomes. We anticipated that children with DS with a higher AHI would score lower than children with DS of the same chronological age with a lower AHI on measures of inattention, impulsivity, and hyperactivity. Given the relationship between snoring and ADHD symptoms in typically developing children, we (4) Examined whether or not this relationship could be explained by sleep fragmentation in DS.

METHODS

Participants

Sixty children and adolescents (age range 7-18) with DS were recruited through local and parent organizations and advertisement in Tucson, AZ and Phoenix, AZ. Exclusion criteria included the presence of Robertsonian translocation (1 case), mosaicism (0 cases), Autistic disorder diagnosis (4 cases), past head injury (0 cases), or incident of loss of consciousness (i.e., greater than 5 minutes in length; 0 cases). Of the remaining 55 cases, 1 parent was unsure of the karyotype of their child with respect to the extra chromosome 21, and the remaining 54 endorsed that their child carried chromosome 21.

Of this sample, 50 families attended their cognitive assessment appointment, and 48 of these families kept their sleep study appointment. All of the cognitive assessments generated usable although not always complete data due to participant fatigue or inattention. Due to the concurrent data collection for the Arizona Cognitive Test Battery (ACTB) validation study (Edgin et al., 2010), the number of participants varied based on the introduction and, in some cases, removal of specific tasks. Of the 48 sleep studies, 40 yielded scorable data on the first or second attempt (six children had two PSG attempts). One study was lost due to technical problems, and the remaining seven studies were not completed due to participant intolerance of the PSG hookup.

After exclusions and attrition, the final sample included 40 individuals (17 male, 23 female) with DS, ages 7-18 years old. The mean KBIT-II IQ of the full sample was 45.20±7.82 (range 40 – 74) and the mean SIB-R scaled score of adaptive behavior was 50.08±28.37 (range 0 – 105). The mean total family income of the sample was $60-80,000 (corresponding to a score of "5" on a 10 point scale), with a substantial range starting from $0-15,000 to over $200,000. The ethnic distribution of the sample (i.e., maternal ethnicity) included 50.0% Caucasian, 40.0% Hispanic, 5.0% African American, 2.5% Asian American, and 2.5% Hawaiian or Pacific Islander.

TABLE 1

Frequency and Cumulative Frequency for Categorical Demographic Variables

Variable	**Frequency**	**Cumulative Frequency**
Sex		
Males	17	17
Females	23	40
Ethnicity		
Hawaiian or Other Pacific Islander	1	1
Asian American	1	2
African American	2	4
Hispanic or Latin American	16	20
Non-Hispanic Caucasian	20	40
Surgical History		
None	15	15
Tonsillectomy	3	18
Adenoidectomy	3	21
Adenotonsillectomy	17	38
Unknown	2	40

TABLE 2

Descriptive Statistics for Continuous Demographic Variables

Variable	*N*	*Minimum*	*Maximum*	*Mean*	*Median*	*Mode(s)*	*Standard Deviation*
Age	40	7.0	18.16	11.15	10.29	7.66, 8.33, 11.00, 11.42, 12.83	3.35
BMI	24	10.90	44.30	22.03	21.45	None	6.49
Income	37	0	10	4.78	5	5	2.95
KBIT-II total score	40	40	74	45.15	42.00	40	7.73
SIB-R adaptive behavior standard score	34	0	105	50.08	48.50	0	28.37

Procedures

All procedures were approved by the University of Arizona Biomedical Institutional Review Board. Participants completed a 2.5 hour testing session during which they completed the Arizona Cognitive Test Battery for Down syndrome, a customized battery of hippocampal, general cognitive ability, and visuoconstructive test measures described in the next section (Edgin et al., 2010). Each participant was seen by a trained psychometrician. The testing session was completed in a laboratory setting, hotel conference room, or the home in a location with minimal distractions. The tests from the ACTB have been to shown to be robust for home-based testing (Edgin et al., 2010). The test battery followed a two-version, counterbalanced order to avoid position effects. When half of the tasks were completed, participants were allowed a break in

which they were able to rest and choose a prize; in cases in which participants seemed to lose focus or become tired, more breaks were allowed. Behavior and attention during the testing session were recorded.

At the time of the testing visit, parents completed the Children's Sleep Habits Questionnaire, Medical History Questionnaire and the Conners 3 Parent Rating Scale. They were also given a Conners 3 Teacher Rating Scale to give to the child's teacher. Parents were also asked to consent to a thorough medical review for their child, including a geneticist's report of Trisomy 21 and background medical factors.

After the neuropsychological testing session in the laboratory or child's home, an unattended home polysomnogram was scheduled. Every effort was made to test participants as soon as possible after the neuropsychological assessment, and we stopped pursuing polysomnography (PSG) scheduling after the three month mark. The PSGs were scored immediately, and if the child had OSAS, desaturations, or arrthymias, the parents were immediately notified and referred to their physician for follow-up. We sent all parents feedback about their child's performance on neuropsychological testing as well as a brief summary of their sleep characteristics.

Measures

IQ and Benchmark measures

Kauffman Brief Intelligence Test, Second Edition (KBIT-II)

The Kauffman Brief Intelligence Test, Second Edition (KBIT-II) is a brief, individually administered measure of both verbal and nonverbal intelligence appropriate

for individuals from 4 to 90 years old (Kaufman and Kaufman, 2004). Standard scores for the KBIT-II have a mean equal to 100, standard deviation of 15.

Scales of Independent Behavior-Revised (SIB-R)

The Scales of Independent Behavior-Revised (SIB-R) is a caregiver completed checklist-style rating scale designed to assess adaptive functioning and everyday skills (Bruininks, Woodcock, Weatherman, & Hill, 1997). The SIB-R measures Motor, Social and Communication, Personal Living, and Community Living Skills. The measure spans a wide range of ages, from infancy to adulthood.

Differential Ability Scales, Second Edition Pattern Construction subtest

The Differential Abilities Scale has been used extensively for the profiling of cognitive skills in children , and provides T-scores for each subtest (Elliott, 2003). The DAS-II has been well-validated in populations with intellectual disabilities and provides a substantial range of scores, with the lowest IQ measured at 30. The range of lower-end scores is important in studies of cognitive function in DS, as many individuals may reach floor, especially when IQ decreases across age. The DAS-II is also normed outside of the traditional age-range cut-offs. For example, the early years battery is normed through 8 years. The DAS Pattern Construction subtest was used as an assessment of visuoconstructive ability. It is a nonverbal subtest that measures visual-perceptual matching, especially of spatial orientation, and spatial visualization. Children copy block patterns and reproduce designs with colored blocks and flat foam squares. Both accuracy and completion time ere used to calculate the subtest raw score. The pattern construction subtest has an internal reliability coefficient that ranges from r = .95 to r =

.97, and the test-retest reliability was reported to be r = .87.

Behavior Ratings During the Assessment

Task Completion Checklist/Task-specific Behavioral Ratings

In line with other studies that have tested individuals with ID, we included a detailed rating system of the completion of each neuropsychological measure. For each individual task, experimenters rated the participant's attention to task, cooperation, affect, and anxiety level on a 5 point scale. If children were unable to complete a measure, the reasons for non-completion was noted.

Descriptive measures

Children's Sleep Habits Questionnaire (CSHQ)

The CSHQ yields both a total sleep disturbance score and eight subscale scores, reflecting key sleep domains that encompass the major medical and behavioral sleep disorders in school-aged children. The CSHQ has been used previously with the DS population (Shott et al., 2006; Carter, McCaughey, Annaz, & Hill, 2009; MacCrosain & Byrne, 2009) and has been validated in school-aged children (Owens, Spirito, & McGuinn, 2000b). In school-aged children, the internal consistency of the entire CSHQ was 0.68 for the community sample and 0.78 for the clinical sample alpha coefficients for the various subscales of the CSHQ ranged from .36 (Parasomnias) to .70 (Bedtime Resistance) for the community sample, and from .56 (Parasomnias) to .93 (Sleep-Disordered Breathing) for the sleep clinic group. Test-retest reliability was acceptable (range .62 to .79). CSHQ individual items, as well as the subscale and total scores were able to consistently differentiate the community group from the sleep-disordered group,

demonstrating validity. A cut-off total sleep disturbance score of 41 generated by analysis of the Receiver Operator Characteristic Curve (ROC) correctly yielded a sensitivity of .80 and specificity of .72.

Conners 3 Parent and Teacher Rating Scales Short Forms(Conners 3-P and Conners 3-T)

We administered the inattention and hyperactivity subscales of the Conners 3 Parent Rating Scale and Conners 3 Teacher Rating Scales. In a large representative normative sample based on the latest U.S. census data, these measures were found to demonstrate high levels of internal consistency across samples (i.e., General Population, Clinical) and across types of administration (i.e., extracted from the full-length form, administered independently). Internal consistency ranges from $\alpha = .80$ to $\alpha = .97$, and the item-total correlations ranged from $r = .59$ to $r = .91$. Two to four week test-retest reliability ranges from $r = .64$ to $r = .99$ (all correlations significant at $p < 0.001$) in the validation sample (Rzepa et al., 2007). Group membership (e.g., General Population, ADHD, Behavior Disorder, Learning Disorder) has been found to significantly affect all of the scale scores, suggesting good discriminative validity (Rzepa et al., 2007).

Medical History and Family Background Questionnaire (MHQ)

The medical history and family background questionnaire asked about the participant's health history from birth. It inquired about medical complications frequently associated with DS. It ascertained if a diagnosis of obstructive sleep apnea syndrome had been made, and if so, whether or not any form of treatment (i.e., adenotonsillectomy) was received. It also asked about conditions that might influence pulse oximetry, such as allergic rhinitis, nocturnal asthma or anemia. Basic family background data was

collected, including total family income (adjusted for the number of family members) and maternal and paternal education.

Measures of Hippocampal Function

CANTAB Paired-Associates Learning (PAL)

The PAL task requires the participant to learn associations between abstract visual patterns and their hidden locations on a computer screen. The task increases in difficulty from 1 to 8 patterns to be remembered. The outcome measure focused on here is the number of trials to be completed on first view. This task has been shown to be impaired in two previous studies of DS (Pennington et al., 2003; Visu-Petra, Benga, Tincas, & Miclea, 2007). Humans with damage to the hippocampus showed significantly impaired performance on a similar measure (Miller, Munoz, & Finmore, 1993). This measure has been found to have good levels of test-retest reliability ($r = .86$ for trials to success, $r = .87$ for stages completed) in pediatric populations (Luciana, 2003).

Computer-generated Arena (c-g arena)

The c-g arena is as assessment of hippocampal functioning based on a paradigm from the animal literature (Thomas, Hsu, Laurance, Nadel, & Jacobs 2001; Morris, 1984). Across several trials, participants learn to find a target hidden on the floor of a computer-generated arena, presented from a first-person perspective. The fixed target position can be learned by relating its position to the landmarks (distal cues) surrounding the arena. The main outcome variable is the percentage of time participants spend searching the quandrant of the arena in which the target is located (max. = 100%). This task has been used successfully with individuals with DS and other developmental

disabilities (Pennington et al., 2003; Edgin & Pennington, 2005 used this task in autism). Midway through data collection for this study, distal visual cues in the arena were changed slightly.

Measures of Prefrontal Function

CANTAB Intra-Extra Dimensional Set Shift (IED)

The IED task requires the maintenance, shifting, and flexibility of attention. Participants are initially presented with two color-filled shapes, and must learn which shape is "correct" through trial and error. After several trials of recognizing the correct rule, the "correct" shape is reversed. Now, the participant must recognize this rule shift and choose the new correct shape. In later trials, a second shape is transposed onto each shape, so that the participant must take another dimension into consideration when determining which shape is "correct." The number of stages completed was the main outcome variable in this investigation. The IED has been found to be impaired in DS in our previous studies and has been used effectively in other ID populations (i.e., autism, Ozonoff et al., 2004). The test is primarily sensitive to changes in the fronto-striatal areas of the brain. For instance, it has been found to be impaired in autism, a population which has shown deficits in prefrontal function on a variety of tasks. Previous studies have found adequate levels of reliability for the IED, particularly the total errors prior to the ED shift and stages completed ($r = .70$ & $r = .75$, respectively) (Lowe & Rabbitt, 1998; Cambridge Cognition, 2008).

Modified DOTS Task

The Modified DOTS task is a measure of inhibitory control and working memory

suitable for participants aged 4 years to adulthood. There are 3 task phases. During the first phase, children learn the rule associated with the cat stimuli (i.e., the congruent location rule). They are asked to press the button located directly below the cat on a computer touch screen. In the second phase, children see frogs presented on the left or right hand side and must touch the button located on the other side of the computer screen from the frog (incongruent trials). In the final phase, participants are asked to respond to trials in which these rules are alternated randomly. Scores for the current investigation are calculated based on the percentage of correct responses for each phase of the test (max. = 100%). Behavioral inhibition is required on incongruent trials to over-ride the prepotent tendency to respond on the same side as the visual stimulus.

Sleep measures

Ambulatory Polysomnography

Polysomnography was accomplished by unattended home PSG. The Compumedics P Series and Compumedics Somté PSG systems (Abbotsford, Victoria, Australia) were used for data acquisition, based on their portability, sampling (rate up to 500 Hz), storage capabilities (20-40 megabytes), and the flexibility of its software. Each system included a Patient Interface Box (PIB "headbox") containing amplifiers and filters to which electrodes and sensors are connected. The PIB was attached by a cable to a data acquisition recorder containing a computer with a PCMCIA flash memory card, a rechargeable battery, and a pulse oximeter. The PIB and loose electrode wires and sensor cables were supported by a cloth "vest" that is placed over the participants' nightclothes. In the case of the P Series, the recorder was placed on the participant’s nightstand or

mattress. For the Somté PSG system, the recorder was placed inside the vest with the PIB.

The home polysomnograms were performed by 2 person teams comprised of a lead polysomnography technician and an assistant. Home visits, including BMI measurement and equipment setup, were typically completed within a 1 to 1.5 hour time period. Details about efforts to ensure adherence to the PSG are provided in the Appendix. After set-up, the participants and their parents were instructed on what to do during the night and how to remove the equipment in the morning. One of the technicians picked up the equipment at a prearranged time from the participant's home and downloaded the data.

Sensors were placed and equipment was calibrated by technicians during the evening home visit. The following channels were included in the recording montage: electroencephalogram (C3/A2 and C4/A1), electrooculogram, chin electromyogram, thoracic and abdominal displacement (inductive phlethysmography bands), airflow (nasal-oral thermocouples), finger pulse oximeter, a single bipolar electrocardiogram, body position and ambient light (only when the P Series was used). Flow limitation, which is characteristic of the Upper Airway Resistance Syndrome (UARS), was evaluated with the use of a nasal cannula which was be integrated with the thermistor.

Data, stored in real time on PCMCIA cards, was transferred to a study computer upon return to the study office. Following each sleep study, the recording will be reviewed, and problems with hook-up or data acquisition were noted. Data were then transferred to DVDs for scoring and analysis, and permanent archival. Final scoring was

done manually on an epoch-by-epoch basis with the assistance of Compumedics computer scoring software using standard pediatric criteria (American Sleep Disorders Association Atlas Task Force, 1992; Iber et al., 2007).

To determine if a child met criteria for OSAS, we calculated the Apnea Hypopnea Index (AHI), defined as the number of respiratory events (apneas and hypopneas) per hour of the total sleep time. According to Witmans, Keens, Ward, and Marcus (2003), the statistically significant AHI in healthy children is 1.5 events per hour (i.e., the mean ±2 SD). Compumedics software calculated this index separately for REM and NREM sleep, and for different body positions. Summary measures of desaturation, sleep stages, arousal frequencies, and heart rate variation were also computed. To measure hypoxemia, we calculated the the SaO_2 nadir, and the desaturation index, or the number of desaturation events (≥4%) per hour. For our primary analysis, we used the SaO_2 nadir. To measure sleep fragmentation, we calculated the arousal index, or the number of arousals per hour, as well as the respiratory arousal index, which only includes respiratory-event related arousals. Scoring of sleep and identification of arousals were performed using standard criteria (American Sleep Disorders Association Atlas Task Force, 1992; Iber et al., 2007). All studies were scored by one registered polysomnographic technologist.

Analyses

All analyses were conducted with SPSS 19.0. First, we detailed the descriptive statistics and distribution for each cognitive variable. To measure the normality of test distributions, we calculated levels of skewness and kurtosis for each measure. Floor

effects were calculated by determining the percentage of individuals receiving the lowest possible score in the total sample in which the test was administered, or in some instances, the percentage of individuals failing to meet acceptable criteria for task performance (i.e., a threshold for the total number of trials).

After calculating descriptive statistics and distribution information for each cognitive variable, we calculated descriptive statistics for each polysomnographic parameter. We compared sleep macroarchitecture variables to those reported for children with DS as well as TD children by Miano et al. (2008). We calculated similar statistics for the Children's Sleep Habits Questionnaire, and compared their scores to those of typically developing children (Owens et al., 2000b). For the Conners 3 Parent and Teacher Rating Scales, we reported descriptive statistic for each of the ADHD indices.

We then examined the relationship between chronological age and key outcome variables. We examined the relationships between chronological age and cognitive and behavior measures, as well as apnea severity. We found that chronological age was associated with greater performance on the cognitive test battery, improvement in ADHD symptoms, as well as increased apnea severity (see Table 6). For these reasons, we divided our sample into 20 chronological age-matched pairs, in which one member of each pair had a higher AHI and the other member had a clinically less insignificant AHI. Groups were equivalent for sex, IQ, adaptive behavior, and surgical status. Using one-way ANOVAs, we then compared the high and low apnea severity groups on cognitive battery performance and ADHD symptomology as assessed by the Conners 3 parent and

teacher rating scales. When differences were found, we followed up with ANCOVAs to assess if these differences could be explained by hypoxemia or sleep fragmentation.

RESULTS

Distribution Data For Each Battery Measure

We first examined the distribution and floor effects of each test for the entire sample (n = 40), as well as the skewness and kurtosis values for each measure (Table 3). Seven individuals had incomplete cognitive test battery data, due to participant fatigue, behavioral difficulties, or computer error. Percent of individuals with floor levels of performance was calculated based on the number achieving the lowest possible scores in the total sample. Specifically for the each measure, the floor was equivalent to: 1) attaining the lowest standard score on the SIB-R, 2) attaining a raw score of zero on the KBIT-II subtests, 3) attaining a raw score of zero on the DAS-II pattern construction subtest, 4) by not correctly completing any of the first trials on the PAL, 5) spending 0% time in the target quandrant on the virtual water maze task, 6) completing no stages on the IED, 7) detecting less than chance (50%) on any phase of the Modified Dots task. Even when floor effects were present, most test outcomes had a normal distribution, generating values of skewness and kurtosis between -1 and 1, with the remaining measures showing only mild deviations from normality.

In their development of the Arizona Cognitive Test Battery (ACTB), Edgin et al. (2010) examined the mean number of floor effects occurring across ages in their DS sample (n = 74). They reported a significant negative correlation between age and the mean number of floor effects ($r = -0.38$, $p = 0.001$). Floor effects peaked around 9 -10 years, and were significantly lower after this age. Over half of the current sample (21/40;

52.5%) was under the age of 11, which may explain our higher rate of floor effects (compared to Edgin et al., 2010).

TABLE 3

Distribution data for each battery measure in the final DS sample

Measure	**n**	**% floor**	**Mean**	**SD**	**Range**	**Skewness**	**Kurtosis**
Background and benchmark							
SIB-R adaptive behavior standard score	34	14.7	50.08	28.37	0 - 105	-0.06	-0.26
KBIT-II verbal standard score	40	0	48.20	10.01	40 - 76	1.07	0.15
KBIT-II non-verbal standard score	40	0	49.37	11.05	40 - 87	1.43	2.27
DAS-II pattern construction T-score	37	18.9	20.16	7.78	10 - 35	0.28	-0.97
Hippocampal							
CANTAB PAL stages completed	39	5.1	4.07	2.70	0 - 8	0.28	-1.36
Computer generated arena % time in target quandrant	33	17.5	26.56	23.71	0 – 88	0.85	0.15
Prefrontal							
CANTAB IED stages completed	37	16.2	6.16	3.26	0 - 9	-1.14	-0.25
Modified dots task inhib. control phase percent correct	40	25.0	50.83	31.11	0 -100	-0.01	-0.98
Modified dots task combined phase percent correct	40	25.0	47.24	18.00	9 - 100	0.89	2.30
Inattention and Hyperactivity/Impulsivity							
Conners 3 Parent Rating Scale ADHD Index	31	-	6.97	5.18	0 - 20	0.78	0.09

Conners 3 Teacher Rating Scale ADHD Index	20	-	5.95	5.45	0 - 15	0.63	-1.23

Polysomnography Results

Polysomnographic results are shown in Table 4. In an effort to provide a frame of reference for the PSG macroarchitecture data, we listed results obtained by Miano et al. (2008) in their laboratory PSG study. The children in their DS sample had a mean age of 13.8 years (SD = 3.96), and the children in their TD sample had a mean age of 15.0 years (SD = 5.72). Our sample had greater time in bed ($t(39) = 1.99$, $p = 0.05$), total sleep time ($t(39) = 4.55$, $p < 0.001$), sleep efficiency ($t(39) = 6.10$, $p < 0.001$), and a shorter sleep onset latency ($t(39) = -2.78$, $p = 0.008$) and wake after sleep onset ($t(39) = -2.50$, $p = 0.01$) than the Miano et al. (2008) DS sample. However, our sample did have a longer REM latency ($t(39) = 2.63$, $p = 0.01$), as well as more N1($t(39) = 3.05$, $p = 0.004$) and N2 sleep ($t(39) = 7.61$, $p < 0.001$) than their DS sample. Both DS samples showed lower sleep efficiency ($t(39) = -5.52$, $p < 0.001$), greater wake after sleep onset ($t(39) = 5.70$, $p < 0.001$), a greater percentage of stage N1 sleep ($t(39) = 5.61$, $p < 0.001$), and a lower percentage of REM sleep ($t(39) = -2.84$, $p = 0.007$) compared to the Miano et al. (2008) TD sample.

Seventy-seven percent of our sample met criteria for pediatric sleep apnea ($n = 40$; AHI > 1.5), and the mean apnea hypoppnea index (AHI) was 8.4 events per hour. Our sample had a mean arousal index of 10.3, a respiratory arousal index of 3.2, and a SaO_2 nadir of 86.9%. Over 70% of our sample ($n = 40$) had a SaO_2 nadir below 90%.

TABLE 4

Polysomnographic parameters in present DS sample, Miano et al. (2008) DS and TD samples

	1 – DS sample (n = 40)		**2 – Miano et al. (2008) DS sample (n = 9)**		**3 – Miano et al. (2008) TD sample (n = 26)**	
Parameter	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Time in bed (TIB), min	560.4	87.82	532.8	115.99	518.9	51.98
Total sleep time (TST), min	489.2	82.19	430.0	106.62	484.1	43.71
Sleep efficiency (SE), %	87.4	6.90	80.8	10.84	93.5	4.43
Sleep onset latency (SOL), min	24.8	22.46	34.7	50.12	18.5	13.76
Wake after sleep onset (WASO), min	46.3	39.86	62.1	38.67	10.4	10.38
REM latency (RL), min	183.6	69.84	154.6	59.58	114.7	50.47
Stage N1 sleep, %	9.2	6.42	6.1	2.73	3.5	3.87
Stage N2 sleep, %	47.8	6.62	39.9	5.76	46.5	5.81
Stage N3 sleep, %	23.7	9.30	22.7	6.40	25.1	7.2
Stage REM sleep, %	19.2	7.44	17.9	5.61	22.6	5.01
Arousal index, N/hr	10.3	6.83	-	-	-	-
Respiratory arousal index, N/hr	3.2	6.09	-	-	-	-
Apnea hypopnea index (AHI), N/hr	8.4	13.02	-	-	-	-
SaO_2 nadir, %	86.9	4.53	-	-	-	-

Sleep Questionnaire Results

On the Children's Sleep Habits Questionnaire, we found that 90 percent of our sample (n = 30) had total sleep disturbance scores in the clinical range, i.e., greater than 41 (M = 51.93, SD = 10.01, range = 38-79). Thirty-three percent of our sample (n = 30) regularly needed a parent in the room in order to fall asleep, and 43% fell asleep (n = 30) in a parent or sibling's bed at least two nights per week. Thirteen percent of our sample (n = 30) had difficulty falling asleep within 20 minutes of going to bed at least two nights per week. Once asleep, 40% (n = 30) were described as occasionally restless while 47% (n = 30) were described as usually restless during sleep. Commonly described parasomnias included bruxism, or grinding of the teeth, which occurred at least two nights per week in 53% of children (n = 30) and sleep talking, which occurred in 30% (n = 30). Sixty-six percent of our sample (n = 30) endorsed at least one symptom of sleep disordered breathing, including loud snoring, cessation of breathing, and snorting and gasping during the night. Importantly, each daytime sleepiness item was endorsed by at least 25 percent of our sample (n = 30). Over half of our sample (n = 30) routinely fell asleep while watching television (47%) or while riding in the car (57%).

Compared to published data for typically developing children in a community sample aged 4-10 years, our sample also had significantly elevated scores on the Bedtime Resistance ($t(29) = 3.36$, $p = 0.002$), Sleep Anxiety ($t(29) = 3.12$, $p = 0.004$), Night Wakings ($t(29) = 4.50$, $p < 0.001$), Parasomnias ($t(29) = 6.45$, $p < 0.001$), Sleep Disordered Breathing ($t(29) = 4.46$, $p < 0.001$), and Daytime Sleepiness ($t(29) = 3.26$, p

=0.003) subscales. We found a trend toward reduced scores on the Sleep Onset Delay subscale ($t(29) = -1.84$, $p = 0.07$), and a trend toward elevated scores on the Sleep Duration subscale ($t(29) = 1.87$, $p = 0.07$) .

We also examined the relationship between chronological age and subscale or sleep disturbance scores in this sample using linear regression. Age was significantly related to the Parasomnias subscale, with lower scores in older versus younger children ($F(1, 28) = 5.64$, $p = 0.02$, $\beta = -.41$). There were trends toward a decreases in Night Wakings ($F(1, 28) = 3.31$, $p = 0.08$, $\beta = -.32$), Sleep Disordered Breathing ($F(1, 28) = 2.86$, $p = 0.10$, $\beta = -.30$), and the Total Sleep Disturbance score with increasing age ($F(1, 28) = 2.93$, $p = 0.09$, $\beta = -.30$).

TABLE 5

Children's Sleep Habits Questionnaire (CSHQ) subscale scores in present DS sample and Owens et al. (2000b) TD sample

	1 – DS sample			**2 – Owens et al. (2000b) TD sample**		
Subscale	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
Bedtime Resistance	9.13	3.37	30	7.06	1.89	382
Sleep Onset Delay	1.13	0.34	30	1.25	0.53	403
Sleep Duration	3.86	1.33	30	3.41	0.93	398
Sleep Anxiety	6.46	2.76	30	4.89	1.45	374
Night Wakings	4.96	1.77	30	3.51	0.89	384
Parasomnias	10.06	1.65	30	8.11	1.25	371
Sleep Disordered Breathing	4.66	1.74	30	3.24	0.63	382

Daytime Sleepiness	11.63	3.34	30	9.64	2.80	381

Behavior Rating Scale Results

We administered the Conners 3 Parent Rating Scale to the parents and teachers of our study participants, and had a 77.5% response rate (31/40) from parents and a 50.0% response rate (20/40) from teachers. Of those whose parents completed the questionnaire, 29% (n = 31) had at least 6 of the symptoms of inattention or hyperactivity/impulsivity required to meet Criterion A of the DSM-IV criteria for a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). According to teacher reports, 30% of our sample (n = 20) met Criterion A for a diagnosis of ADHD. The mean AHHD index was 6.97 on the CPRS-3 and 5.95 on the CTRS-3.

TABLE 6

Conners 3 Rating Scales ADHD subscale scores

	1 – Parent Rating Scale (n = 31)			**2 – Teacher Rating Scale (n = 20)**		
	Mean	**SD**	**% Meeting symptom criteria**	**Mean**	**SD**	**% Meeting symptom criteria**
ADHD inattentive symptom count	3.45	2.59	25.8	3.70	2.94	30.0
ADHD hyperactive-impulsive symptom count	3.13	2.64	16.1	2.30	2.27	10.0
ADHD index	6.97	5.18	-	5.95	5.45	-

We examined the relationships between chronological age and cognitive and behavior measures, as well as apnea severity. We found that chronological age was associated with greater performance on the cognitive test battery, improvement in ADHD symptoms, as well as increased apnea severity (see Table 7). For these reasons, we divided our sample into 20 chronological age-matched pairs, in which one member of each pair had a higher AHI (M = 14.9, SD = 15.98) and the other member had a clinically less insignificant AHI (M = 1.8, SD = 1.63) (see Figure 1). Groups were equivalent for sex, IQ, adaptive behavior, and surgical status.

Linear Regression of Chronological Age with Each Battery Measure and AHI

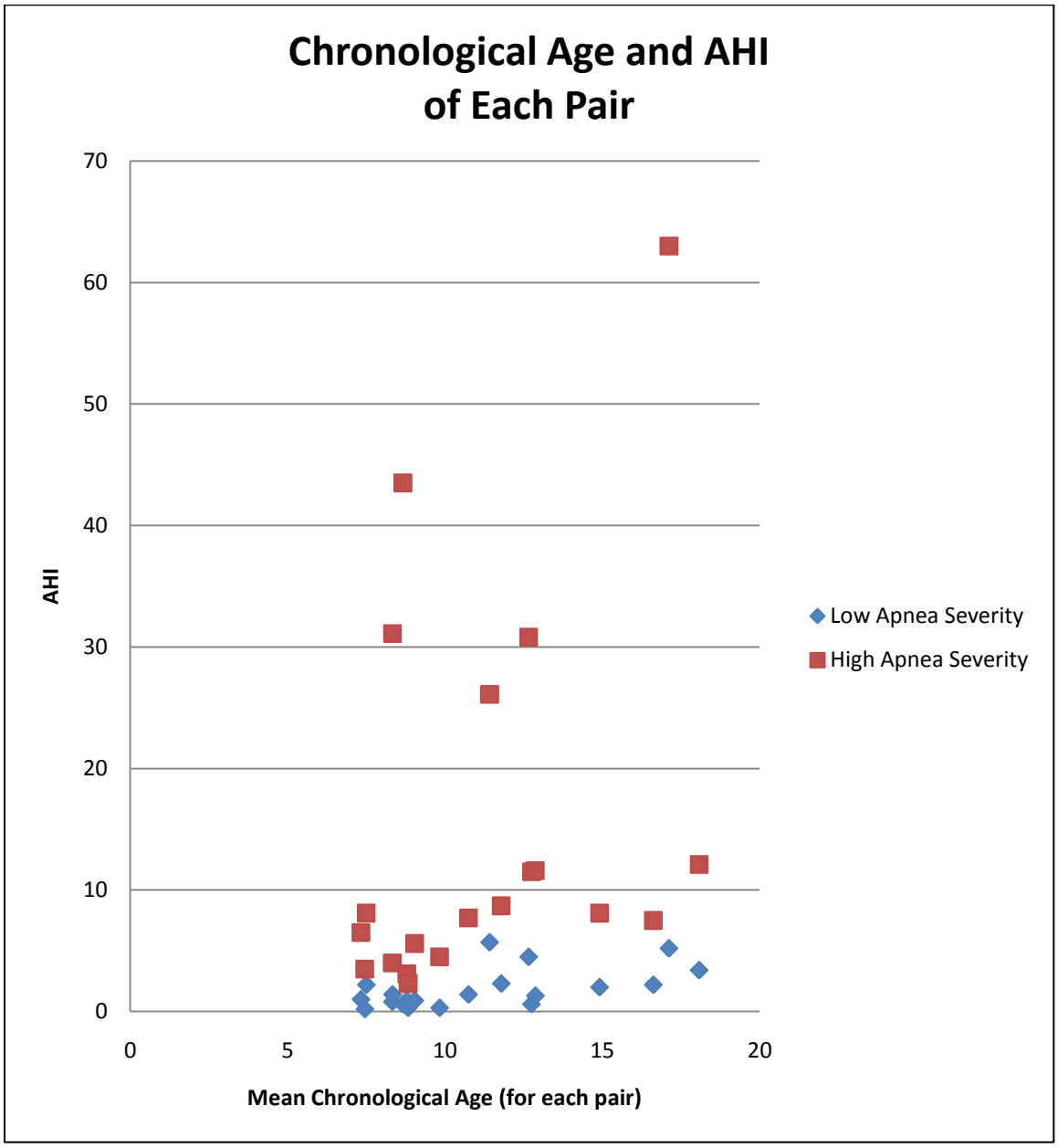
TABLE 7

Linear regression of chronological age with each battery measure and AHI

Variable	**df**	**F**	**p**	**β**
SIB-R adaptive behavior standard score	1, 32	0.19	0.66	-0.07
KBIT-II verbal raw score	1, 38	19.32	< 0.001	0.58
KBIT-II nonverbal raw score	1, 38	13.21	0.001	0.50
DAS-II pattern construction raw score	1, 35	8.57	0.006	0.44
CANTAB PAL stages completed	1, 37	1.71	0.19	0.21
Computer generated arena % time in target quandrant	1, 31	3.38	0.07	0.31
CANTAB IED stages completed	1, 35	0.16	0.68	0.06
Modified dots task inhib. Control phase percent correct	1, 38	1.48	0.23	0.19

Modified dots task combined phase percent correct	1, 38	5.05	0.03	0.34
CPRS-3 ADHD index	1, 30	4.61	0.04	-0.37
CTRS-3 ADHD index	1, 19	2.60	0.12	-0.35
Apnea hypopnea index (AHI)	1, 38	2.76	0.10	0.26

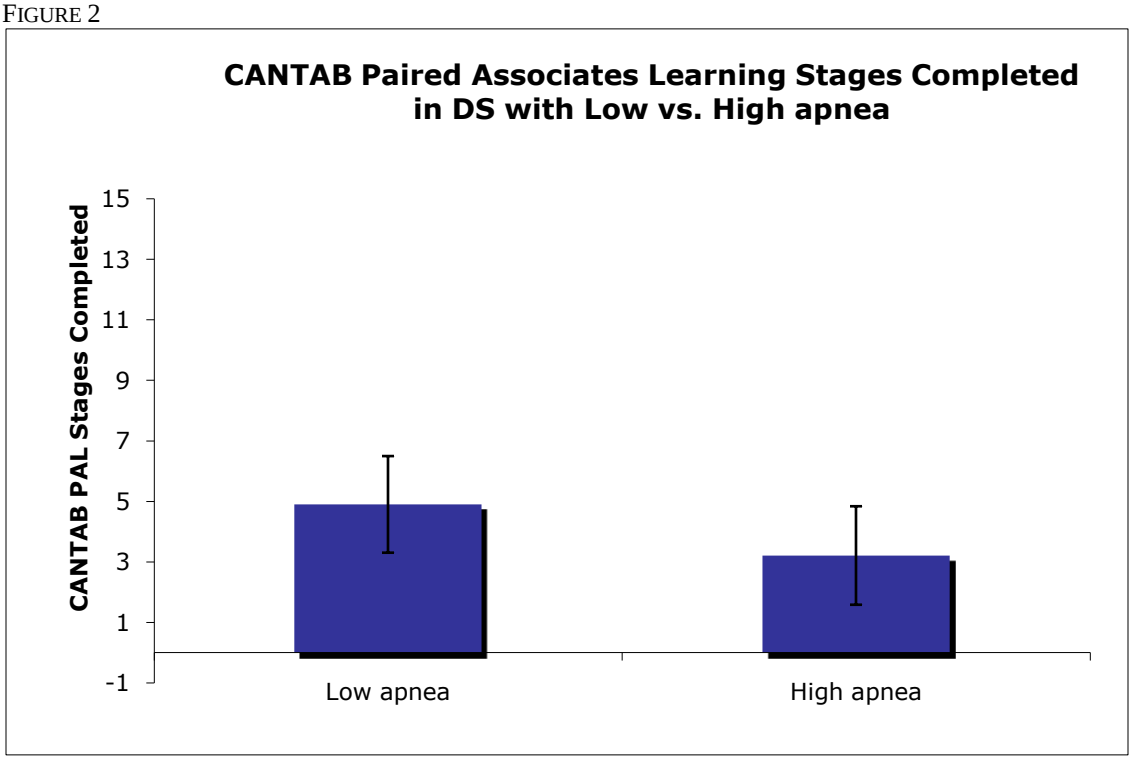
FIGURE 1


Chronological Age and AHI of Each Pair
AHI
70
60
50
40
30
20
10
0
0
5
10
15
20
Mean Chronological Age (for each pair)
Low Apnea Severity
High Apnea Severity

One-Way ANOVAs for Each Battery Measure

When we compared our high and low apnea severity groups, we found that the low apnea severity group attained a greater number of stages on the CANTAB PAL task (Figure 1). In order to assess the relative contributions of hypoxemia and sleep fragmentation, we added them each individually to the model as covariates. Hypoxemia did not explain any of the variance in CANTAB PAL performance ($F(1,36) = 0.08$, $p = 0.77$), but sleep fragmentation (i.e., the arousal index) was significantly related to performance ($F(1,36) = 8.13$, $p = 0.008$). The addition of experimenter-rated participant "attention" ($F(1,36) = 12.44$, $p = 0.002$) as a covariate increased the overall variance accounted for to 53.7%.

FIGURE 2



In addition, we noted that the low apnea severity group trended toward better performance on the KBIT-II verbal subtest as well as on the DAS-II pattern construction measure. Sleep fragmentation was significantly related to KBIT-II verbal score ($F(1,37) = 3.94$, $p = 0.05$), but hypoxemia was not ($F(1,37) = 0.45$, $p = 0.50$). Neither hypoxemia ($F(1,34) = 0.22$, $p = 0.63$) nor sleep fragmentation ($F(1,34) = 0.57$, $p = 0.45$) explained any of the variance in DAS-II pattern construction performance. However, there was a trend for a relationship between experimenter-rated participant "affect" and DAS-II pattern construction performance ($F(1,34) = 3.73$, $p = 0.06$), but there were no relationships between any of the other behavior ratings(i.e., attention, cooperation, or anxiety) and DAS-II pattern construction performance.

We found that the low apnea severity group had higher ADHD index score on the CTRS- 3, but not on the CPRS-3. For the CTRS-3, we had a low response rate overall (50%), and there was a disproportionate response rate between the apnea severity groups, such that 70% of the questionnaires in the low apnea severity group (14/20) were returned, and 30% of the questionnaires in high apnea severity group were returned (6/20). In addition, when we entered chronological age as a covariate, we found a trend for a relationship between age and ADHD index score on the CTRS-3 ($F(1,17) = 3.61$, $p = 0.07$). We found no differences between the high and low apnea severity groups on the SIB-R, KBIT-II nonverbal score, cgArena score, CANTAB IED stages completed, Modified dots task scores, or Conners Parent Rating Scale 3 ADHD index.

TABLE 8

One-way ANOVAs for each outcome measure

	Low Apnea Severity Group, n = 20		High Apnea Severity Group, n = 20					
	Mean	**SD**	**Mean**	**SD**	**df**	**F**	**p**	**d**
Background and benchmark								
SIB-R adaptive behavior standard score	55.50	24.72	44.00	31.69	1, 32	1.40	0.24	0.40
KBIT-II verbal standard score	50.70	10.75	45.70	8.77	1, 38	2.59	0.11	0.50
KBIT-II non-verbal standard score	48.85	11.64	49.90	10.71	1, 38	0.08	0.76	-0.09
DAS-II pattern construction T-score	22.39	7.94	18.05	7.19	1, 35	3.03	0.09	0.57
Hippocampal								
CANTAB PAL stages completed	4.90	2.55	3.21	2.65	1, 37	4.10	0.05	0.64
Computer generated arena % time in target quandrant	26.78	19.90	26.27	28.90	1, 31	0.01	0.95	0.02
Prefrontal								
CANTAB IED stages completed	6.63	2.58	5.66	3.86	1, 35	0.80	0.37	0.29
Modified dots task inhib. control phase percent correct	45.83	29.40	55.83	32.72	1, 38	1.03	0.31	-0.32
Modified dots task combined phase percent correct	45.30	13.23	49.18	21.95	1, 38	0.45	0.50	-0.21
Inattention and Hyperactivity/Impulsivity								
Conners Parent Rating Scales 3ADHD index	7.19	5.51	6.73	4.97	1, 29	0.05	0.81	0.08

Conners Teacher Rating Scales 3 ADHD index	7.86	5.43	1.50	1.51	1, 18	7.73	0.01	1.59

DISCUSSION

Summary of Sleep, Cognition, and Behavior Findings

Consistent with previous studies and our expectations, there was substantial variability in cognitive performance, behavior ratings, and apnea severity in our final sample of 40 children with DS. Our hypothesis that children with DS with a higher AHI would score lower than children with DS of the same chronological age with a lower AHI on measures of hippocampal functioning was partially supported. We found that children with DS with a higher AHI completed fewer stages on the CANTAB PAL task. In addition, inclusion of the arousal index and experimenter-rated participant "attention" as covariates resulted in significant additional variance accounted for on the CANTAB PAL stages completed measure. Contrary to our original hypothesis, inclusion of the SaO_2 nadir as a covariate did not add to the variance explained by our model. On the cgArena, the high and low apnea severity groups performed nearly identically. We did not find support for our hypothesis that children with DS with a higher AHI would score lower than children with DS of the same chronological age with a lower AHI on measures of prefrontal functioning. Our data contradicted our hypothesis that there would be no differences between the high and low apnea severity group on performance on the DAS-II Pattern Construction subtest, as we found a trend for a difference in performance. This trend was not accounted for by the arousal index or hypoxemia, but the addition of experimenter-rated participant "affect" resulted in an increase in the variance accounted for on this task.

On measures of hyperactivity, impulsivity, and inattention, we did not find

support for our hypothesis that children with DS with a higher AHI would score lower than children with DS of the same chronological age with a lower AHI on measures of hyperactivity, impulsivity, and inattention. On the CPRS-3, there were no differences in the behavioral ratings for the high and low apnea severity groups. On the CTRS-3, the low apnea severity group had higher scores on the ADHD index than the high apnea severity group. Inclusion of chronological age as a covariate resulted in significant additional variance accounted for on the CTRS-3 ADHD index.

We also found that children with DS with a higher AHI had worse performance on the KBIT-II verbal subtest. Inclusion of the arousal index as a covariate resulted in significant additional variance accounted for, but inclusion of the SaO_2 nadir as a covariate did not add to the variance explained by our model.

Sleep, Cognition, and Behavior Findings In Context

We found a relationship between apnea severity and performance on the CANTAB PAL, but not between apnea severity and performance on the cgArena. Both tasks assess hippocampal functioning, but our test-retest data suggest that the CANTAB PAL may be a more reliable measure in this population (Edgin et al., 2011). Luciana (2003) reported good test-retest reliability ($r = 0.87$) for the CANTAB PAL stages completed measure in a pediatric population. Due to the concurrent development of the ACTB, the distal visual cues in the arena were changed slightly midway through the data collection phase for the present study. It is unclear if this alteration of the task limited our ability to detect group-level differences.

ANCOVA revealed that when the number of arousals/ hour (arousal index) and experimenter-rated "attention" were taken into account, there continued to be a significant difference between the high and low apnea severity groups on the CANTAB PAL stages completed measure, but that inclusion of these variables as covariates resulted in significant additional variance accounted for. Adding the SaO_2 nadir as a covariate did not eliminate differences between the high and low apnea severity groups or add to the variance explained by our model. These findings are largely consistent with those of Spruyt, Capdevila, Kheirandish-Gozal, and Gozal (2009) and Kaemingk et al. (2003).

Using a visual-verbal paired-associate learning task (NEPSY Memory for Names), Spruyt et al. (2009) found that the apnea index was inversely related to performance in their group of TD children with OSAS who had deficits in one or more of the following domains: attention, executive, language (the modal deficit area) or visuospatial functioning ($r = -0.91$, $p < 0.001$). Within this group, they also found a strong positive correlation ($r = 0.96$, $p < 0.001$) between Memory for Names trial 2 and the arousal index. These relationships were not observed in their group of TD children with OSAS who had no co-morbid deficits.

Kaemingk et al. (2003) found a trend for a relationship between the apnea hypopnea index and immediate recall on the CAVLT ($r = -0.12$, $p = 0.08$) in TD children. They found that differences between groups in memory performance decreased once the number of arousals was taken into account, there was a greater percentage of stage 1 sleep in the group with AHI ≥ 5, and that the percentage of stage 1 sleep was negatively

related to performance on later learning trials, overall learning across trials, and immediate and delayed recall. They did not find relationships between hypoxemia and any of their memory measures.

Several authors (Rhodes et al., 1995; Blunden et al., 2000; Gottlieb et al., 2004; and Beebe, 2006) have suggested the possibility of an attentional capacity deficit that might interfere with memory encoding in OSAS, which could potentially explain the relationship between experimenter-rated "attention" and CANTAB PAL performance in our sample. OSAS has been consistently related to attention, and when group differences in memory scores are reported, they often co-occur with group differences in attention scores. Unfortunately, this relationship has not been clearly delineated due to most studies having small sample sizes that limited the sophistication of their statistical analyses. Blunden et al. (2000) found that children with mild OSAS had deficits on the auditory continuous performance test (ACPT) as well as the WRAML memory screening test. Although we did not find a relationship between the CPRS-3 or CTRS-3 index scores and PAL performance, it is possible that our experimenter ratings were more sensitive as they assessed state levels of attention rather than trait levels of attention.

We did not find support for our hypothesis that children with DS with a higher AHI would score lower than children with DS of the same chronological age with a lower AHI on measures of prefrontal functioning. On the CANTAB IED, we found that our higher apnea severity group had impaired performance compared to the low apnea severity group, though this difference did not reach statistical significance. Our effect size was small (d = .29), which suggests that a larger sample would be required to detect

a group-level difference. Our high apnea severity group actually had better performance on both Modified DOTS task measures, although this difference did not reach statistical significance.

If these performance differences turn out to be robust, this dissociation could reflect a difference in the effect of OSAS on different dimensions of prefrontal functioning. The CANTAB IED assesses maintenance, shifting, and flexibility of attention, whereas the Modified DOTS task is a measure of inhibitory control and working memory. Among TD children with OSAS, Beebe (2006) has noted there is little evidence of deficits in short-term working-memory functioning, as evidenced by a consistent lack of findings on measures that require immediate recall of strings of rote verbal or visual material. Most investigators have reported deficits in the ability to sustain attention or vigilance over time (Beebe et al., 2004; Blunden et al., 2000; Blunden, Lushington, Lorenzen,,Martin, & Kennedy, 2005; O'Brien et al., 2004b; Archbold et al., 2004).

Contrary to our hypothesis, we found a trend for a difference between the high and low apnea severity group on performance on the DAS-II Pattern Construction subtest. This trend was not accounted for by the arousal index or hypoxemia, but the addition of experimenter-rated participant "affect" resulted in an increase in the variance accounted for on this task. Visual perception and construction have been shown to be relative strengths for children with DS (Silverstein, Legutski, Friedman, & Tayakama, 1982), and most investigators have reported no deficits on block design in TD children with OSAS (Owens et al, 2000a; Lewin, Rosen, England, & Dahl, 2002; Beebe et al.,

2004; Blunden et al., 2005). Of the three studies reporting positive findings, two of them were on the DAS-II Pattern Construction (O'Brien et al., 2004a; O'Brien et al., 2004b), with effect sizes ranging from d = 0.30 to d = 0.50. While we can only speculate about the relationship between experimenter-rated "affect" and DAS-II Pattern Construction performance, it suggests that children who performed better on this task also presented with a euthymic mood.

Surprisingly, we did not find support for our hypothesis that children with DS with a higher AHI would score lower than children with DS of the same chronological age with a lower AHI on measures of hyperactivity, impulsivity, and inattention. On the CPRS-3, there were no group-level differences in the behavioral ratings, and our low apnea severity group had slightly higher index scores. One of the most robust findings in the literature has been the positive association between sleep-disordered breathing and parent-reported symptoms of hyperactivity and impulsivity in TD children, with effect sizes ranging from d = 0.50 to d = 0.60 (Beebe, 2006; Owens, 2009). Several studies have also reported relationships between sleep-disordered breathing and parent-reported inattention in TD children (Owens et al., 2000a; Mitchell & Kelly, 2005; Mulvaney, Kaemingk, Goodwin, & Quan, 2006). One reason that we may have failed to detect group-level differences in ADHD symptoms in this study is that our sample was older than those in previous studies, and the prevalence of ADHD is higher in early childhood. Another possible reason is that parents of children with DS may be less sensitive to variation in their child's symptoms, as they may attribute them to the DS phenotype and may have less of a basis for comparison.

Only a few studies have examined the relationship between sleep-disordered breathing and teacher-reported hyperactivity, impulsivity, and inattention, and only one study found elevations on these indices in children with sleep-disordered breathing (Ali et al., 1993). Still, our finding that the low apnea severity group had higher scores on the ADHD index than the high apnea severity group on the CTRS-3 was quite surprising. Inclusion of chronological age as a covariate resulted in significant additional variance accounted for on the CTRS-3 ADHD index. We believe that our CTRS-3 findings may have resulted from the disproportionate response rate between apnea severity groups, differences in chronological age between groups (the high apnea severity group was older), as well as variability in how well each teacher knew each participant. Anecdotal reports from parents also suggested that parents whose children had greater behavioral problems in the classroom were less likely to ask their child's teacher to complete the form.

We also found that children with DS with a higher AHI had worse performance on the KBIT-II verbal subtest. Inclusion of the arousal index as a covariate resulted in significant additional variance accounted for, but inclusion of the SaO_2 nadir as a covariate did not add to the variance explained by our model. Several studies have found deficits in general intelligence in TD children with sleep-disordered breathing compared to controls (O'Brien et al., 2004a,b; Gottlieb et al., 2004; Montgomery-Downs et al., 2005), although a subset of these have been criticized for having control participants who were significantly different in maternal education or socio-economic status. IQ deficits have been demonstrated in TD children along the entire spectrum of sleep-disordered

breathing, with and without gas exchange abnormalities (i.e., Primary snoring), which suggests that sleep fragmentation may play a more important role than hypoxemia.

Polysomnography Findings in Context

Consistent with previous prevalence reports of OSAS in DS, we found that seventy-seven percent of our sample (31/40) met criteria for pediatric sleep apnea, and the mean AHI was the mild severity range for pediatric OSAS. Our sample had a mean arousal index of 10.3, a respiratory arousal index of 3.2, and a SaO_2 nadir of 86.9%. Over 70% of our sample (29/40) had a SaO_2 nadir below 90%. In terms of PSG macroarchitecture, our sample had greater TIB, TST, SE, and a shorter SOL and less WASO than the Miano et al. (2008) DS sample. However, our sample did have a longer RL, as well as a higher percentage of stages N1and N2 sleep than their DS sample. Some of these differences may reflect a difference between ambulatory in-home PSG and laboratory PSG, as there is less of a "first night effect" with ambulatory in-home PSG. Both DS samples showed reduced SE, more WASO, a higher percentage of time spent in N1 sleep, and a lower percentage of time in REM sleep compared to the Miano et al. (2008) TD sample. These differences reflect typical changes in sleep macroarchitecture as a result of OSAS.

On our subjective sleep measure, the CSHQ, we found that 90 percent of our sample had total sleep disturbance scores in the clinical range. Parents of children with DS endorsed symptoms of sleep-disordered breathing as well as symptoms of other sleep disorders. Compared to published data for typically developing children in a community

sample aged 4-10 years (Owens et al., 2000b), our sample had significantly elevated scores on the Bedtime Resistance, Sleep Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing , and Daytime Sleepiness subscales. We found a trend toward reduced scores on the Sleep Onset Delay subscale, and a trend toward elevated scores on the Sleep Duration subscale. These findings are consistent with those of Carter et al.(2009) and MacCrosain & Byrne (2009).

Clinical Implications of Our Findings and Future Directions

Our study is consistent with previous studies that have reported a high prevalence of OSAS in children with DS. We also report relationships between apnea severity and cognitive functioning in this population. Specifically, we found that children with DS with a lower apnea hypopnea index (AHI) attained a greater number of stages on the CANTAB PAL task compared to chronologically age-matched children with higher AHI, and the variance in performance was partially explained by sleep fragmentation (i.e., the arousal index) and experimenter-rated "attention" but not hypoxemia.

These findings have important clinical implications. First, they suggest that early screening for OSAS in DS is important. Children with DS who experience symptoms of sleep disordered breathing should have a sleep assessment performed as early as possible (American Academy of Pediatrics, 2001). The present study suggests that OSAS contributes to cognitive problems, particularly memory and IQ deficits, in Down syndrome. Second, they suggest that an early intervention for OSAS may be warranted. If they meet criteria for an obstructive sleep apnea diagnosis, most children with DS have an adenotonsillectomy. Children with DS often experience a reduction in their OSAS

symptoms but frequently still meet criteria for OSAS after surgery (Merrell & Shott, 2007). In children with DS whose OSAS falls into the mild range, positional treatments and mandibular advancement devices may be useful, although these devices have not been systematically evaluated in this population. In addition, the mandibular advancement device might also assist in reducing bruxism. Although we did not replicate this finding, Shires et al. (2010) has shown that body mass index (BMI) has a statistically significant association with the presence of OSAS in children with DS, which suggests that weight loss may also help to reduce the incidence and severity of OSAS in this population. In children with DS with moderate to severe OSAS, nasal continuous positive airway pressure (nCPAP) has been shown to be an effective treatment. O'Donnell, Bjornson, Bohn, and Kirk (2006) found that 72% of children with DS (n = 22) accepted and adhered to nCPAP treatment. Future studies should investigate the impact of interventions on cognitive functioning in children with DS.

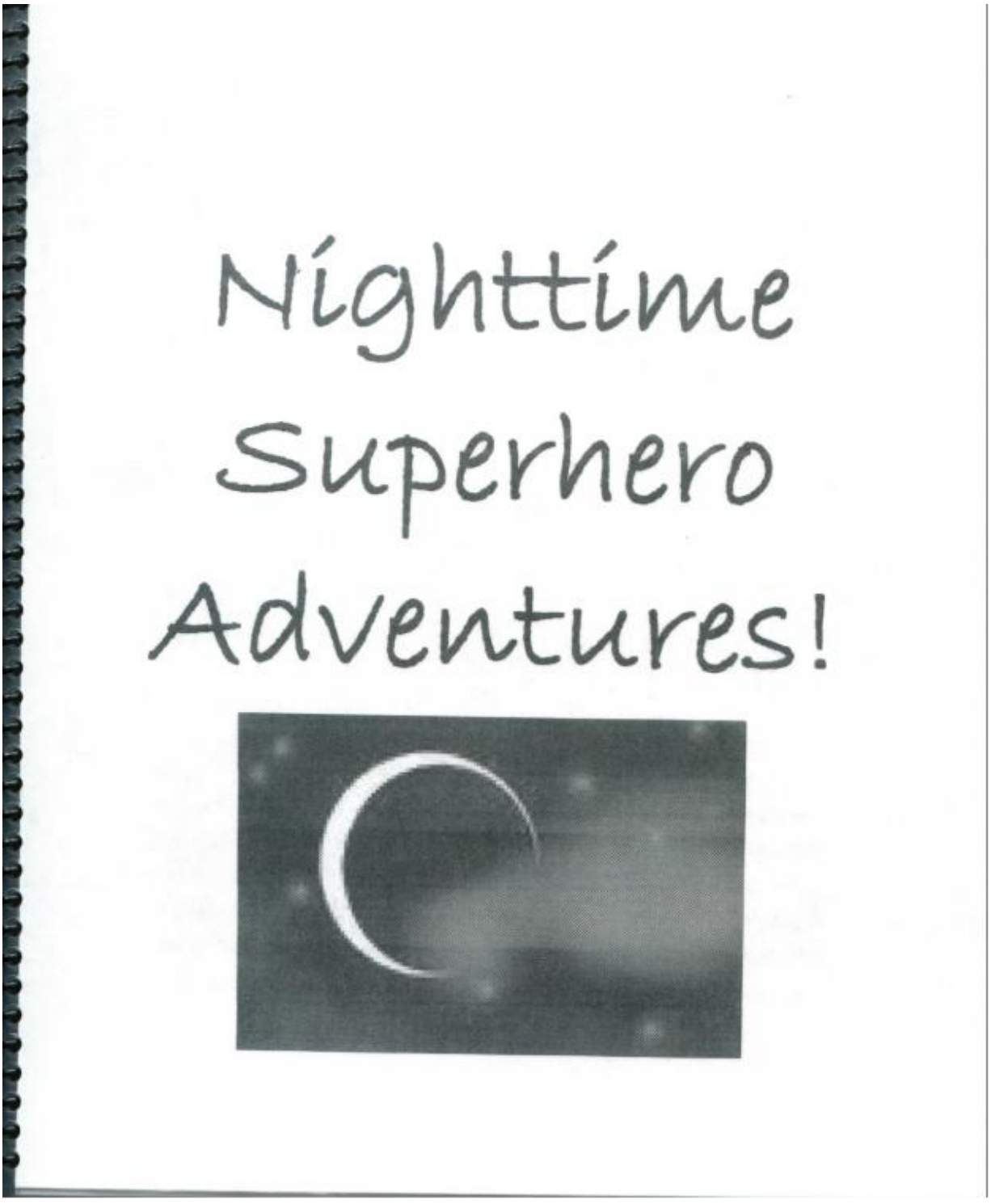
APPENDIX A

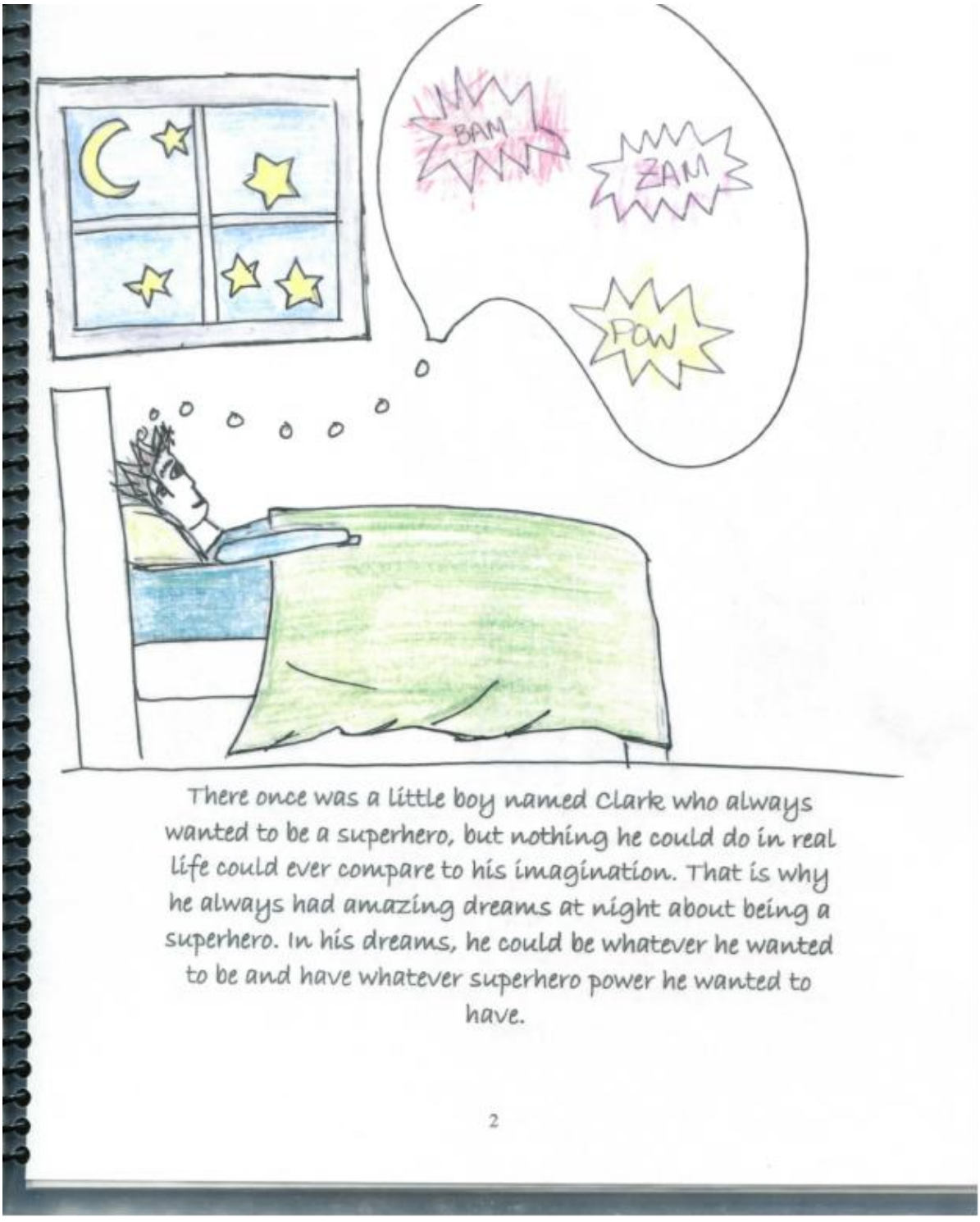
MEASURES TAKEN TO INCREASE ADHERENCE TO AMBULATORY IN-HOME PSG IN CHILDREN WITH DS

Time	**Action(s)**
Pre-Sleep Visit Phone Contact	Experimenter described the procedure to the parent, and defined the parent's role. Experimenter inquired about any sensory issues (i.e., Does the child have difficulty wearing band-aids? Does the child need to be sedated for routine medical procedures?). Experimenter discussed how parent could talk to child beforehand about the sleep study.
Sleep Study Visit	Experimenter clarified procedures for parent and child during the consent/assent process. Experimenter read a storybook entitled "Nighttime Superhero Adventures" to child prior to beginning PSG hookup (see Appendix B). Experimenter encouraged parent to take an active role. When necessary, experimenter allowed parent to apply electrodes/sensors with coaching from the experimenter. Children were given small prizes during and after electrode application. Experimenter suggested that parent(s) check on child during the night, and reapply any electrodes/sensors that fell off or were removed by child. Experimenter emphasized the importance of the cannula and oximeter in the diagnosis of OSAS, and explained that five hours of data were required for a scoreable study. Experimenter also encouraged parents to follow their normal bedtime routine and sleeping arrangements as closely as possible, including co-sleeping. Approximately half of our participants routinely co-slept with a parent, grandparent, or sibling.

APPENDIX B

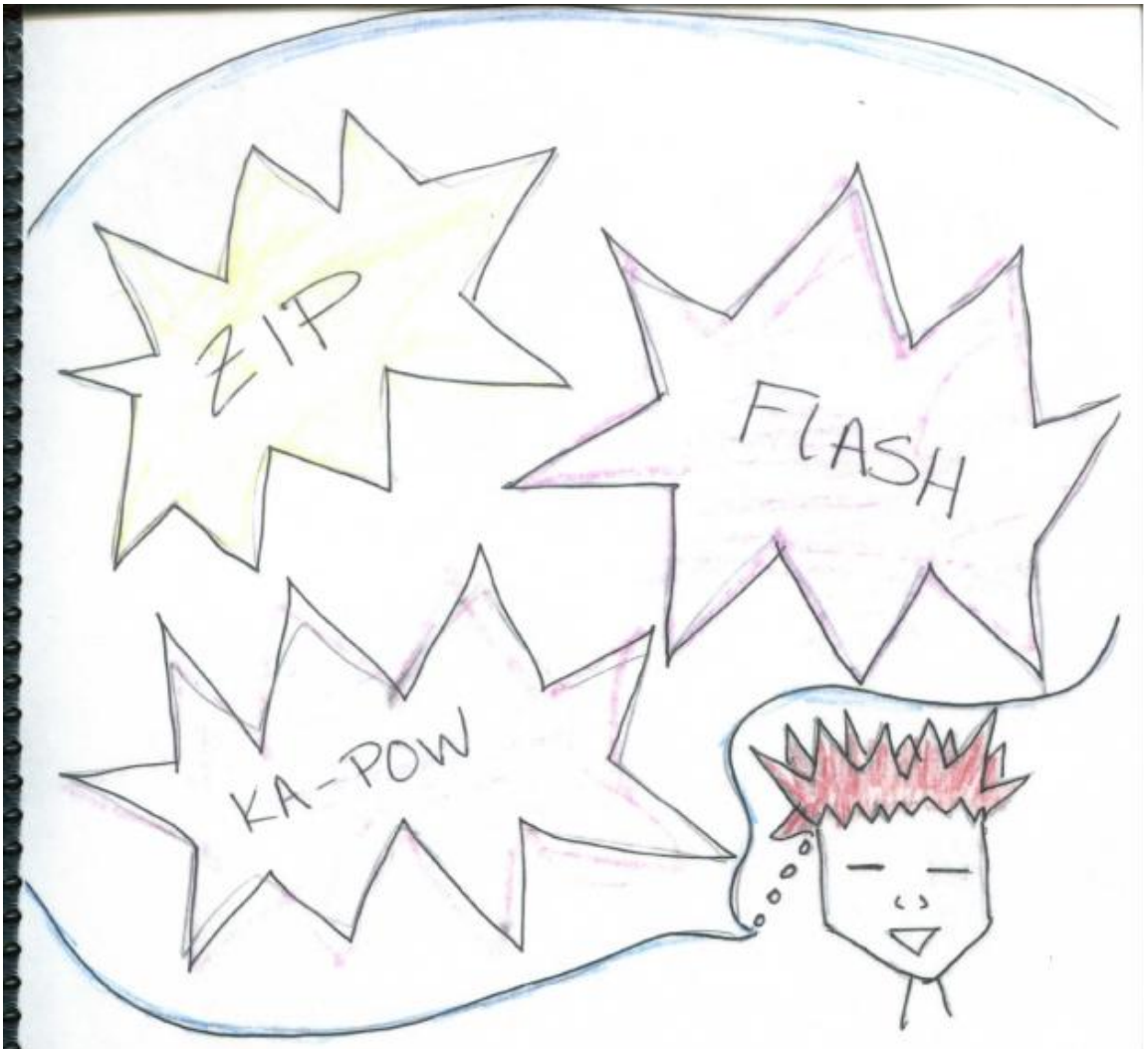
NIGHTTIME SUPERHERO ADVENTURES BOOK




BAM
ZAM
POW
There once was a little boy named Clark who always wanted to be a superhero, but nothing he could do in real life could ever compare to his imagination. That is why he always had amazing dreams at night about being a superhero. In his dreams, he could be whatever he wanted to be and have whatever superhero power he wanted to have.
2

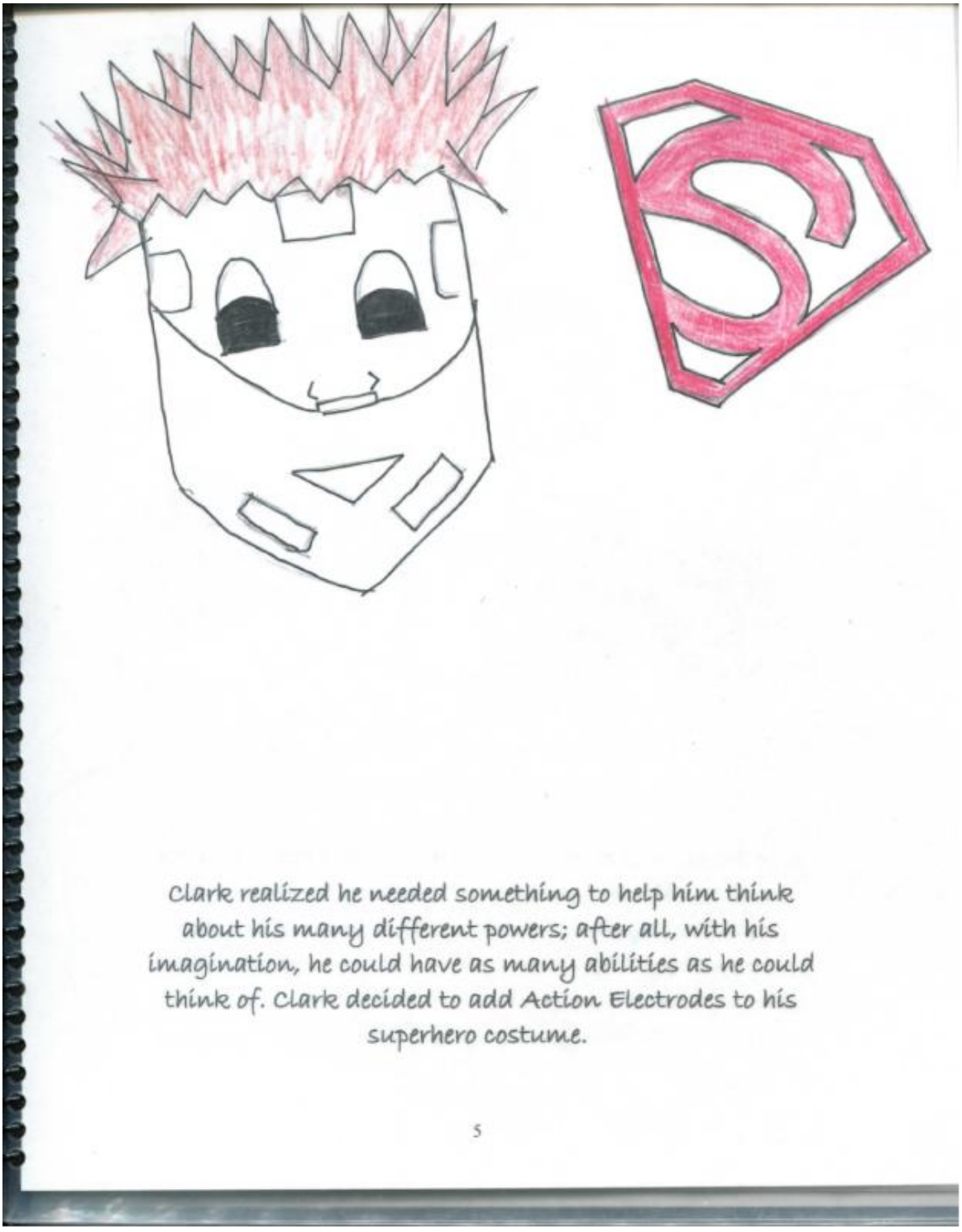
One day, Clark decided that every superhero needs a signature superhero outfit, so he set out to make his Supervest. Every night, before he went to bed, Clark put on his Supervest to prepare for his nighttime adventures. He also realized that every superhero needs to have his abilities come from somewhere, so he attached his Power Pack.

3



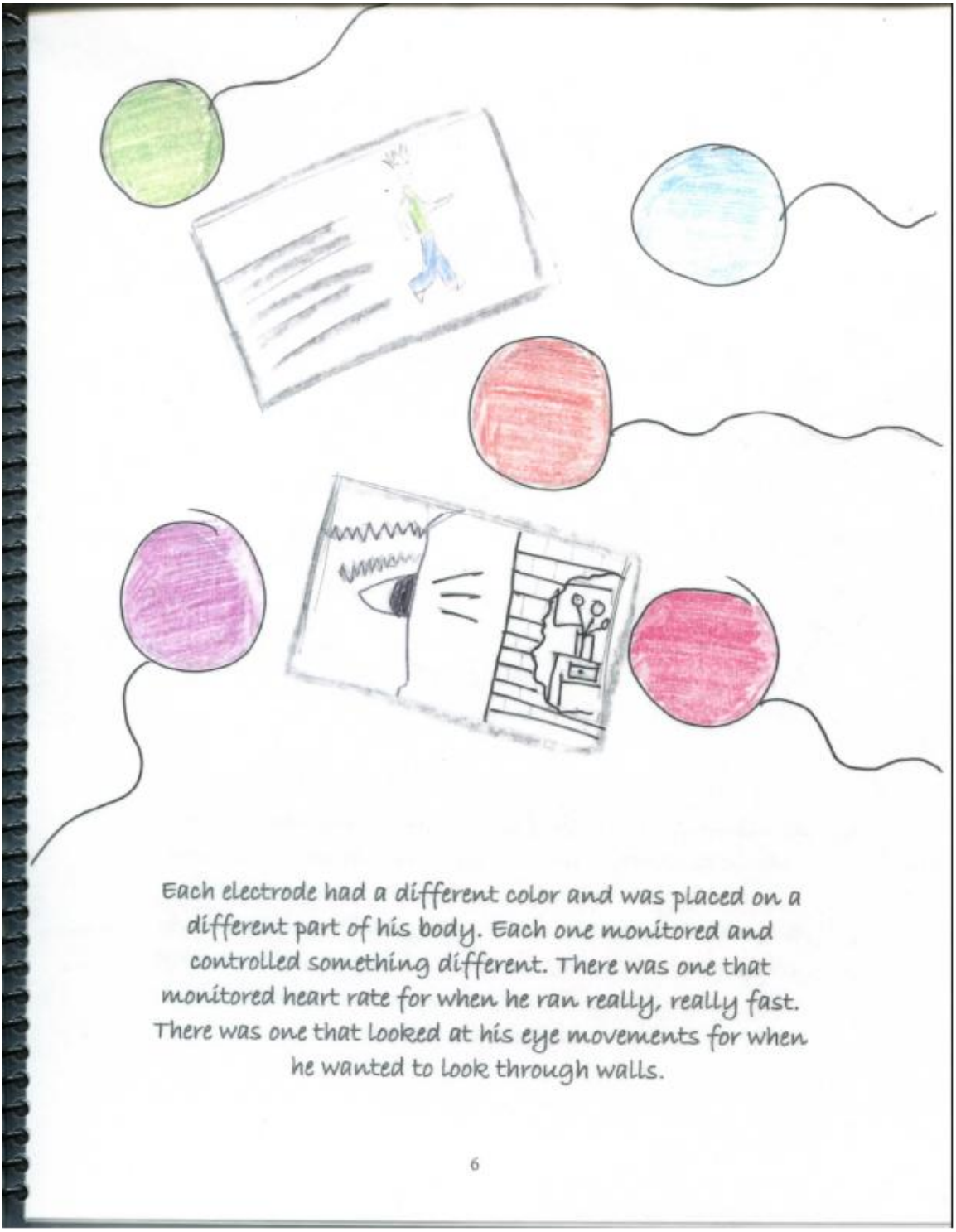
That night, with his Supervest and Power Pack he definitely had some super-dreams, but something was missing. He thought, and thought, and thought about what he was missing. Then, eureka! ...

4



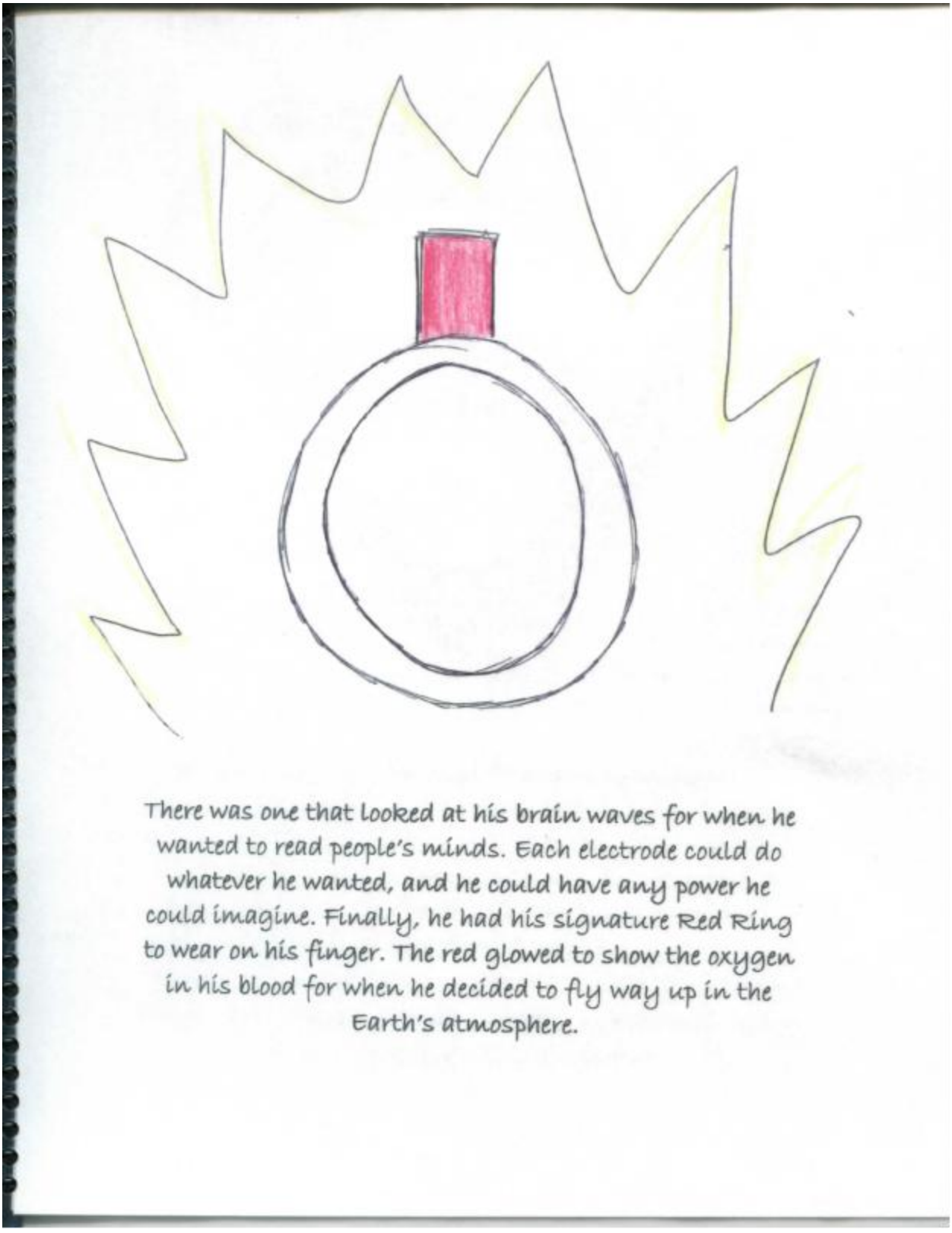
Clark realized he needed something to help him think about his many different powers; after all, with his imagination, he could have as many abilities as he could think of. Clark decided to add Action Electrodes to his superhero costume.

5



Each electrode had a different color and was placed on a different part of his body. Each one monitored and controlled something different. There was one that monitored heart rate for when he ran really, really fast. There was one that looked at his eye movements for when he wanted to look through walls.

6



There was one that looked at his brain waves for when he wanted to read people's minds. Each electrode could do whatever he wanted, and he could have any power he could imagine. Finally, he had his signature Red Ring to wear on his finger. The red glowed to show the oxygen in his blood for when he decided to fly way up in the Earth's atmosphere.

Sweet Dreams!

Tonight, Clark lent his superhero gear to use with you while you sleep if you don't mind. Here is your Supervest that we are going to put on you, just like Clark wore his. We also have a Power Pack to put on your nightstand. We also are going to place some Action Electrodes on your head. He couldn't give us his Red Ring, but he did give us this Junior Superhero Red Racer for your index finger. It will light up to tell us that you are ready to fly, up, up, and away into the night sky.

REFERENCES

Ali, N.J., Pitson, D.J., & Stradling, J.R. (1993). Snoring, sleep disturbance, and behaviour in 4-5 year olds. *Archives of Disease in Childhood*, *68*(3), 360-366.

American Sleep Disorders Association Atlas Task Force. (1992). EEG arousals: Scoring rules and examples:A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep, 15*(2), 173-184.

Archbold, K.H., Giordani, B., Ruzicka, D.L., & Chervin, R.D. (2004). Cognitive executive dysfunction in children with mild sleep-disordered breathing. *Biological Research for Nursing*, *5*(3), 168-176.

Arman, A.R., Ersu, R., Save, D., Karadag, B., Karaman, G., Karabekiroglu, K., Karakoc, F., Dagli, E., & Berkem, M. (2005). Symptoms of inattention and hyperactivity in children with habitual snoring: Evidence from a community-based study in Istanbul. *Child: Care, Health, and Development*, *31*(6), 707-717.

Aylward, E.H., Li, Q., Honeycutt, N.A., Warren, A.C., Pulsifer, M.B., Barta, P.E. (1999). MRI volumes of the hippocampus and amygdala in adults with Down syndrome with and without dementia. *American Journal of Psychiatry*, *156*(4), 564-568.

Bass, J.L., Corwin, M., Gozal, D., Moore, C., Nishida, H., Parker, S. et al. (2004). The effect of chronic or intermittent hypoxia on cognition in childhood: A review of the evidence. *Pediatrics, 114*(3), 805-816.

Beebe, D.W. (2006). Neurobehavioral morbidity associated with disordered breathing during sleep in children: A comprehensive review. *Sleep*, *29*(9), 1115-1134.

Beebe, D.W., Wells, C.T., Jeffries, J., Chini, B., Kalra, M., & Amin, R. (2004). Neuropsychological effects of pediatric obstructive sleep apnea. *Journal of the International Neuropsychological Society*, *10*(7), 962-975.

Blunden, S., Lushington, K., Kennedy, D., Martin, J., & Dawson, D. (2000). Behavior and neurocognitive performance in children aged 5-10 years who snore compared to controls. *Journal of Clinical and Experimental Neuropsychology*, *22*(5), 554-568.

Blunden, S., Lushington, K., Lorenzen, B., Martin, J., & Kennedy, D. (2005). Neuropsychological and psychosocial function in children with a history of snoring or behavioral sleep problems. *Journal of Pediatrics*, *146*(6), 780-786.

Bruininks, R.K., Woodcock, R.W., Weatherman, R.F., & Hill, B.K. (1997). *Scales of*

independent behavior – Revised. Chicago: Riverside Publishing.

Cambridge Cognition. (2008). CANTAB reliability study. Retrieved from http://www.camcog.com/cdownloads/CANTAB_reliability_study.pdf

Capone, G., Goyal, P., Ares, W., & Lannigan, E. (2006). Neurobehavioral disorders in children, adolescents, and young adults with Down syndrome. *American Journal of Medical Genetics*. Part C, Seminars in medical genetics, *142*(3), 158-172.

Carskadon, M.A., Pueschel, S.M., & Millman, R.P. (1993). Sleep-disordered breathing and behavior in three risk groups: Preliminary findings from parental reports. *Child's Nervous System*, *9*(8), 452-457.

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.

Clark, D., & Wilson, G.N. (2003). Behavioral assessment of children with Down syndrome using the Reiss psychopathology scale. *American Journal of Medical Genetics, Part A, 118A*(3), 210-216.

Coe, D., Matson, J., Russell, D., Slifer, K., Capone, G., Baglio, C., & Stallings, S. (1999). Behavior problems of children with Down syndrome and life events. *Journal of Autism and Developmental Disorders*, *29*(2), 149-156.

Cotton, S., & Richdale, A. (2006). Brief report: Parental descriptions of sleep problems in children with autism, Down syndrome, and Prader-Willi syndrome. *Research in Developmental Disabilities*, *27*(2), 151-161.

Chervin, R.D., Archbold, K.H., Dillon, J.E., Panahi, P., Pituch, K.J., Dahl, R.E., & Guilleminault, C. (2002). Inattention, hyperactivity, and symptoms of sleep-disordered breathing. *Pediatrics*, *109*(3), 449-456.

Decker, M.J., Hue, G.E., Caudle, W.M., Miller, G.W., Keating, G.L., & Rye, D.B. (2003). Episodic neonatal hypoxia evokes executive dysfunction and regionally specific alterations in markers of dopamine signaling. *Neuroscience*, *117*(2),417-425.

Decker, M.J., Jones, K.A., Solomon, I.G., Keating, G.L., & Rye, D.B. (2005). Reduced extracellular dopamine and increased responsiveness to novelty: Neurochemical and behavioral sequelae of intermittent hypoxia. *Sleep, 28*(2), 169-176.

Donnelly, L.F., Shott, S.R., LaRose, C.R., Chini, B.A., & Amin, R.S. (2004). Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with Down syndrome as depicted on static and

dynamic Cine MRI. *American Journal of Roentgenology, 183*(1), 175-181.

Dyken, M.E., Lin-Dyken, D.C., Poulton, S., Zimmerman, MB., & Sedars, E. (2003). Prospective polysomnographic analysis of obstructive sleep apnea in Down syndrome. *Archives of Pediatric and Adolescent Medicine, 157*(7), 655-660.

Edgin, J.O., Mason, G.M., Allman, M.J., Capone, G.T., DeLeon, I., Maslen, C., …Nadel, L. (2010). Development and validation of the Arizona Cognitive Test Battery for Down syndrome. *Journal of Neurodevelopmental Disorders*, *2*(3), 149-164.

Edgin, J.O., Moon, J.H., Nadel, L., Hutaff, C., & Pennington, B.F. (2008). *Neuropsychological development across the lifespan in DS: What's the shape of change?* Unpublished manuscript.

Edgin, J.O., & Pennington, B.F. (2005). Spatial cognition in autism spectrum disorders: Superior, impaired, or just intact? *Journal of Autism and Developmental Disorders, 35*(6), 729-745.

Edgin, J.O., Pierpont, E.I., Mason, G.M., Rosser, T., Reeves, R.H., Sherman, S.,... Nadel, L. (2011). *Further Validation of the Arizona Cognitive Test Battery for Down Syndrome: Test-retest Reliability and Practice Effects*. Manuscript in preparation.

Elliott, C.D. (2003). *Differential Abilities Scale – Second Edition*. San Antonio, Texas: Harcourt Assessment Company.

Epstein, C.J. (1995). Down syndrome (Trisomy 21). In C.R. Scriver, A.L. Beaudet., W.S. Sly, D. Valle (Eds.), *The metabolic and molecular bases of inherited disease* (pp.749-794). New York: McGraw-Hill.

Fitzgerald, D.A., Paul, A., & Richmond, C. (2007). Severity of obstructive apnoea in children with Down syndrome who snore. *Archives of Disease in Childhood, 92*(3), 423-425.

Gottlieb, D.J., Vezina, R.M., Chase, C., Lesko, S.M., Heeren, T.C., Weese-Mayer, D.E., Auerbach, S.H., & Corwin, M.J. (2003). Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. *Pediatrics 112*(4), 870-877.

Gottlieb, D.J., Chase, C., Vezina, R.M., Heeren, T.C., Corwin, M.J., Auerbach, S.H., Weese-Mayer, D.E., & Lesko, S.M. (2004). Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. *Journal of Pediatrics*, *145*(4), 458-464.

Gozal, D. (1998). Sleep-disordered breathing and school performance in children. *Pediatrics, 102*(3), 616-620.

Iber, C., Ancoli-Israel, S., Chesson, A., Quan, S.F., for the American Academy of Sleep Medicine. (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications*. Westchester, IL: American Academy of Sleep Medicine.

Jernigan, T.L., Bellugi, U., Sowell, E., Doherty, S., & Hesselink, J.R. (1993). Cerebral morphological distinctions between Williams and Down syndrome. *Archives of Neurology, 50*(2), 186-191.

Kaemingk, K.L., Pasvogel, A.E., Goodwin, J.L., Mulvaney, S.A., Martinez, F., Enwright, P.L.,…Quan, S.F. (2003). Learning in children and sleep disordered breathing: Findings of the Tucson children's assessment of sleep apnea (TuCASA) prospective cohort study. *Journal of the International Neuropsychological Society, 9*(7), 1016-1026.

Kaufman, A.S., & Kaufman, N.L. (2004). *Kaufman Brief Intelligence Test*. Second Edition. Circle Pines, MN: Pearson Assessments.

Kesslak, J.P., Nagata, S.F., Lott, I., & Nalcioglu, O. (1994). Magnetic resonance imaging analysis of age-related changes in the brains of individuals with Down's syndrome. *Neurology, 44*(6), 1039-1045.

Kurnatowski, P., Putynski, L., Lapienis, M., & Kowalska, B. (2006). Neurocognitive abilities in children with adenotonsillar hypertrophy. *International Journal of Otorhinolaryngology, 70*(3), 419-424.

Levanon, A., Tarasiuk, A., & Tal, A. (1999). Sleep characteristics in children with Down syndrome. *Journal of Pediatrics, 134*(6), 755-760.

Lewin, D.S., Rosen, R.C., England, S.J., & Dahl, R.E. (2002). Preliminary evidence of behavioral and cognitive sequelae of obstructive sleep apnea in children. *Sleep Medicine, 3*(1), 5-13.

Li, R.C., Row, B.W., Kheirandish, L., Brittian, K.R., Gozal, E., Guo, S.Z. et al. (2004). Nitric oxide synthase and intermittent hypoxia-induced spatial learning deficits in the rat. *Neurobiology of Disease, 17*(1), 44-53.

Lowe, C., Rabbitt, P. (1998). Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: Theoretical and practical issues. Cambridge neuropsychological test automated battery. International study of post-operative cognitive dysfunction. *Neuropsychologia, 36*(9), 915-923.

MacCrosain, A.M., & Byrne, M.C. (2009). Are we ignoring the problem of sleep disorder in children with intellectual disabilities? *Irish Journal of Medical Science 178*(4), 427-431.

Marcus, C.L., Keens, T.G., Bautista, D.B., von Pechmann, W.S., & Davidson Ward, S.L. (1991). Obstructive sleep apnea in children with Down syndrome. *Pediatrics, 88*(1), 132-139.

Merrell, J.A., & Shott, S.R. (2007). OSAS in Down syndrome: T&A versus T&A plus lateral pharyngoplasty. *International Journal of Otorhinolaryngology, 71*(8), 1197-1203.

Miller, L.A., Munoz, D.G., & Finmore, M. (1993). Hippocampal sclerosis and human memory. *Archives of Neurology, 50*(4), 391-394.

Mitchell, R.B. & Kelly, J. (2005). Child behavior after adenotonsillectomy for obstructive sleep apnea syndrome. *The Laryngoscope, 115*(11): 2051–2055.

Morris, R. (1984). Developments of a water-maze procedure for studying spatial learning in the rat. *Journal of Neuroscience Methods, 11*(1), 47-60.

Mulvaney, S.A., Kaemingk, K.L., Goodwin, J.L., & Quan, S.F. (2006). Parent-rated behavior problems associated with overweight before and after controlling for sleep disordered breathing. *BMC Pediatrics, 14*(6), 34.

Nadel, L. (1999). Down syndrome in cognitive neuroscience perspective. In H. Tager-Flusberg (Ed.), *Neurodevelopmental disorders* (pp. 197-221). Cambridge, MA: MIT Press.

Ng, D.K., Hui, H.N., Chan, C.H., Kwok, K.L., Chow, P.Y, Cheung, J.M., & Leung, S.Y. (2006). Obstructive sleep apnoea in children with Down syndrome. *Singapore Medical Journal, 47*(9), 774-779.

O'Brien, L.M., Mervis, C.B., Holbrook, C.R., Bruner, J.L., Klaus, C.J., Rutherford, J., …Gozal, D. (2004a). Neurobehavioral implications of habitual snoring in children. *Pediatrics, 114*(1), 44-49.

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

O'Donnell, A.R., Bjornson, C.L., Bohn, S.G., & Kirk, V.G. (2006). Compliance rates in children using noninvasive continuous positive airway pressure. *Sleep, 29*(5), 651-658.

Owens, J.A. (2009). Neurocognitive and behavioral impact of sleep disordered breathing in children. *Pediatric pulmonology, 44*(5), 417-422.

Owens, J., Spirito, A., Marcotte, A., McGuinn, M., & Berkelhammer, L. (2000a). Neuropsychological and behavioral correlates of obstructive sleep apnea syndrome in children: A preliminary study. *Sleep and Breathing, 4*(2), 67-78.

Owens, J.A., Spirito, A., & McGuinn, M. (2000b). The children's sleep habits questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. *Sleep, 23*(8), 1043-1051.

Ozonoff, S., Cook, I., Coon, H., Dawson, F., Joseph, R.M., & Klin, A. …Wrathall, D. (2004). Performance on Cambridge Neuropsychological Test Automated Battery subtests sensitive to frontal lobe function in people with autistic disorder: Evidence from the Collaborative Programs of Excellence in Autism network. *Journal of Autism and Developmental Disorders, 34*(2), 139-150.

Peigneux, P., Laureys, S., Fuchs, S., Collette, F., Perrin, F., Reggers, J., …Maquet, P. (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron, 44*(3), 535-545.

Pennington, B.F., Moon, J., Edgin, J., Stedron, J., & Nadel, L. (2003). The neuropsychology of Down syndrome: Evidence for hippocampal dysfunction. *Child Development, 74*(1), 75-93.

Picchietti, D.L., Underwood, D.J., Farris, W.A., Walters, A.S., Shah, M.M., Dahl, R.E., …Hening, W.A. (1999). Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *Movement Disorders, 14*(6), 1000-1007.

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience, 9*(4), 534-547.

Plihal, W., & Born, J. (1999). Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology, 36*(5), 571-582.

Pinter, J.D., Brown, W.E., Eliez, S., Schmitt, J.E., Capone, G.T., & Reiss, A.L. (2001). Amygdala and hippocampal volumes in children with Down Syndrome: A high resolution MRI study. *Neurology, 56*(7), 972-974.

Pueschel, S.M., Bernier, J.C., & Pezzullo, J.C. (1991). Behavioural observations in children with Down's syndrome. *Journal of Mental Deficiency Research, 35* (Part 6), 502-511.

Rauchs, G., Bertran, F., Guillery-Girard, B., Desgranges, B., Kerrouche, N., Denise, P., …Eustache, F. (2004). Consolidation of strictly episodic memories mainly requires rapid eye movement sleep. *Sleep, 27*(3), 395-401.

Raz, N., Torres, I.J., Briggs, S.J., Spencer, W.D., Thornton, A.E., Loken, W.J., …Acker, J.D. (1995). Selective neuroanatomic abnormalities in Down syndrome and their cognitive correlates: Evidence from MRI morphometry. *Neurology, 45*(2), 356-366.

Rhodes, S.K., Shimoda, K.C., Waid, L.R., O'Neil, P.M., Oexmann, M.J., Collop, M.A., & Willi, S.M. (1995). Neurocognitive deficits in morbidly obese children with obstructive sleep apnea. *Journal of Pediatrics, 127*(5), 741-744.

Richards, W., & Ferdman, R.M. (2000). Prolonged morbidity due to delays in diagnosis and treatment in obstructive sleep apnea in children. *Clinical Pediatrics, 39*(2), 103-108.

Rosen, C.L., Storfer-Isser, A., Taylor, H.G., Kirchner, H.L., Emancipator, J.L., & Redline, S. (2004). Increased behavioral morbidity in school-aged children with sleep-disordered breathing. *Pediatrics, 114*(6), 1640-1648.

Row, B.W., Liu, R., Xu, W., Kheirandish, L., & Gozal, D. (2003). Intermittent hypoxia is associated with oxidative stress and spatial learning deficits in the rat. *American Journal of Respiratory Critical Care Medicine, 167*(11), 1548-1553.

Rowe, J., Lavender, A., & Turk, V. (2006). Cognitive executive function in Down's syndrome. *British Journal of Clinical Psychology, 45*(Prt 1), 5-17.

Rzepa, S., Conners, C.K., Gallant, S., Pitkanen, J., Sitarenios, G., & Marocco, M-L. (2007). *Development and psychometric properties of the Conners 3 Short Forms*. Poster session presented at the meeting of the American Psychological Association, San Francisco, CA.

Sadeh, A., Gruber, R., & Raviv, A. (2002). Sleep, neurobehavioral functioning, and behavior problems in school-age children. *Child Development, 73*(2), 405-417.

Schmidt-Sidor, B., Wisnieski, K.E., Shepard, T.H., & Sersen, E.A. (1990). Brain growth in Down syndrome subjects 15 to 22 weeks of gestational age and birth to 60 months. *Clinical Neuropathology, 9*(4), 181-190.

Shires, C.B., Anold, S.L., Schomacher, R.A., Dehoff, G.W., Donepudi, S.K., & Stocks, R.M. (2010). Body mass index as an indicator of obstructive sleep apnea in pediatric Down syndrome. *International Journal of Pediatric Otorhinolaryngology*, *74*(7), 768-772.

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 & Neck Surgery*, *132*(4), 432-436.

Silverstein, A.B., Legutski, G., Friedman, S.L., & Tayakma, D.L. (1982). Performance of Down syndrome individuals on the Stanford-Binet intelligence scale. *American Journal of Mental Deficiency*, *86*(5), 548-551.

Spruyt, K., Capdevila, O.S., Kheirandish-Gozal, L., & Gozal, D. (2009). Inefficient or insufficient encoding as potential primary deficit in neurodevelopmental performance among children with OSA. *Developmental Neuropsychology*, *34*(5), 601-614.

Stradling, J.R., Thomas, G., Warley, A.R., Williams, P., & Freeland, A. (1990). Effect of adenotonsillectomy on nocturnal hypoxaemia, sleep disturbance, and symptoms in snoring children. *Lancet*, *335*(8684), 249-253.

Thomas, K.G.F., Hsu, M., Laurance, H.E., Nadel, L., & Jacobs, W.W. (2001). Place learning in virtual space III: Investigation of spatial navigation training procedures and their application to fMRI and clinical neuropsychology. *Behavior Research Methods, Instruments, and Computers*, *33*(1), 21.

Uong, E.C., McDonough, J.M., Tayag-Kier, C.E., Zhao, H., Haselgrove, J. Mahboubi, S., …Arens, R. (2001). Magnetic resonance imaging of the upper airway in children with Down syndrome. *American Journal of Respiratory Critical Care Medicine, 163*(3 Pt 1), 731-736.

Visu-Petra, L., Benga, O., Tincas, I., & Miclea, M. (2007). Visual-spatial processing in children and adolescents with Down's syndrome: A computerized assessment of memory skills. *Journal of Intellectual Disability Research*, *51*(Part 12), 942-952.

Waber, D.P., De Moor, C., Forbes, P.W., Almli, C.R., Botteron, K.N., Leonard, G., …Brain Development Cooperative Group. (2007). The NIH MRI study of normal brain development: performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. *Journal of the International Neuropsychological Society*, *13*(5) 729-746.

Weis, S., Weber, G., Neuhold, A., & Rett, A. (1991). Down syndrome: MR quantification of brain structures and comparison with normal control subjects. *American Journal of Neuroradiology*, *12*(6), 1207-1211.

White, N.S., Alkire, M.T., & Haier, R.J. (2003). A voxel-based morphometric study of nondemented adults with Down syndrome. *Neuroimage*, *20*(1), 393-403.

Wisniewski, K.E., & Schmidt-Sidor, B. (1989). Postnatal delay of myelin formation in brains from Down syndrome infants and children. *Clinical Neuropathology*, *8*(2), 55-62.

Witmans, M.B., Keens, T.G., Davidson Ward, S.L., & Marcus, C.L. (2003). Obstructive hypopneas in children and adolescents: Normal values. *American Journal of Respiratory and Critical Care Medicine*, *168*(12), 1540.

Xu, W., Chi, L., Row, B.W., Xu, R., Ke, Y., Xu, B., …Liu, R. (2004). Increased oxidative stress is associated with chronic intermittent hypoxia-mediated brain cortical apoptosis in a mouse model of sleep apnea. *Neuroscience*, *126*(2), 313-323.