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Iowa Gambling Task Performance in Overweight Children and Adolescents

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**Iowa Gambling Task Performance in Overweight Children and Adolescents At-Risk
for Obstructive Sleep Apnea**

A dissertation submitted to the

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Abstract

Obstructive sleep apnea (OSA) is a frequent disorder, associated with cognitive and behavioral sequelae, including impairments in executive functions (EF). Previous literature has focused on the “cool” aspects of EF, and has largely ignored the impact OSA may have on “hot” EF that involves the regulation of affect and emotion. The present study examined performance on the Iowa Gambling Task (IGT), a task believed to assess “hot” EF, in a population of overweight adolescents at risk for OSA. We found that IGT performance was related to tasks that required working memory and behavioral inhibition, but not associated with other measures of “cool” EF. Further, whereas individuals with minimal evidence of OSA learned to make more beneficial decisions on the IGT over time, participants with OSA did not benefit from feedback and continued to make choices associated with higher initial rewards, but greater long-term losses. This provides evidence that OSA is associated with impairments in decision-making, particularly aspects of “hot” EF that have been purported to be mediated by ventromedial prefrontal cortical functioning. Finally, although we hypothesized that developmental level would be related to IGT performance, we found that this relationship was moderated by OSA status. Individuals with OSA did not demonstrate the expected developmental gains in performance on the decision-making task. This finding suggests that OSA may impact the development of critical aspects of EF.

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Chapter 1: Background and Significance

Obstructive sleep apnea (OSA) is a relatively frequent disorder, with prevalence rates of 1-3% in children and up to 2-4% in adulthood (Ali & Stadling, 2000; Arens, 2000). OSA is characterized by repeated partial (hypopneas) and complete (apneas) upper airway obstructions during sleep that result in immediate physiologic disturbances such as sleep fragmentation, increased respiratory effort, and intermittent blood gas disturbances (hypoxemia and hypercarbia; Gozal, 2000). In severe cases, long-term consequences of this disorder in childhood can include pulmonary hypertension and failure to thrive (Marcus & Carroll, 1994). Even in mild cases of OSA, however, a number of studies have documented emotional and behavioral consequences in children and adolescents including depression, low self-esteem and quality of life, hyperactivity and behavioral problems (Beebe, 2006). Certain subgroups appear to be at particularly high risk for this disorder. For example, Beebe and colleagues (2007) reported that half of overweight adolescents met criteria for broadly-defined sleep-disordered breathing (SDB; i.e. including sub-clinical OSA and other markers of increased upper airway resistance including snoring), and 1 in 8 met strict criteria for OSA; no demographically matched healthy-weight controls met OSA cutoffs, and only 14% of these controls met the broader criteria for SDB.

OSA is also associated with neuropsychological dysfunction, which is relatively specific to sustained attention, executive functioning (EF) and, less consistently, memory deficits. In a review of the literature, Aloia et al. (2004) found that the majority of studies examining adults with OSA reported deficits in attention/vigilance, EF, and memory, in the context of relatively preserved global cognitive functioning and language skills.

Beebe and colleagues (2003) reported similar results in a meta-analysis, providing further evidence that, in adults, OSA has a substantial impact on EF and vigilance. In studies of children with sleep-disordered breathing (SDB), impairment in EF, attention, and behavioral regulation is also commonly reported (e.g. Dahl, 1996; Hansen & Vandenberg, 1997; Gozal, 1998; Archbold, Giordani, Ruzicka & Chervin, 2004; Beebe, 2006). Although findings have not been consistent across studies, there is some evidence that more severe OSA, as determined by oxygen desaturation levels (Lewin, et al, 2002) and sleep architecture patterns (Archbold, 2004), is associated with greater EF impairment.

The unique role of the prefrontal cortex (PFC) in sleep and sleep deficits implicates this brain region as being disproportionately affected by OSA (Beebe & Gozal, 2002). It has been said that the PFC is the ‘hardest working’ region of the brain and, thus, requires the greatest recovery during sleep, rendering it most vulnerable to sleep disturbances (Harrison & Horne, 2000). Behavioral evidence from sleep deprivation studies as well as neuroimaging data have provided support for this notion that the PFC is particularly vulnerable to sleep disturbance (see Beebe & Gozal, 2002 for a discussion). Furthermore, the neuropsychological evidence of EF impairment also provides evidence that OSA may result in PFC dysfunction. There is a long line of literature implicating PFC integrity and EF across many populations. For example, fMRI and PET activation of the PFC has been associated with tasks of cognitive flexibility, such as Trails B (e.g. Moll, de Oliveira-Souza, Moll, Bramati & Andreiuolo, 2005) and the Wisconsin Card Sorting Test (e.g. Berman et al., 1995); spatial planning, such as the Tower of London (e.g. Baker et al., 1996); response inhibition, such as go/no tasks (e.g. Menon, Adleman,

White, Glover, & Reiss, 2001); and verbal fluency (e.g. Elfgren & Risberg, 1998). Thus, impairments on tasks of EF associated with OSA suggest involvement of the PFC in this population.

While the PFC (and EF) have been identified as particularly vulnerable in OSA, the vast majority of neuropsychological studies to date have focused on EFs that are generally associated with the dorsolateral PFC. These include behavioral inhibition (typically measured using the Stroop Color-Word Interference test), set-shifting (often measured by perseverative errors on the Wisconsin Card Sorting Test [WCST] or Trail Making Test, Part B), attention regulation (often measured clinically by continuous performance tests), working memory and generative fluency. According to one classification, these types of tasks are thought of as “cool,” relatively emotion-neutral cognitive aspects of EF. This is in contrast to the “hot” aspects of EF, which are thought to be mediated by the ventral and medial portions of the PFC (Zelazo & Mueller, 2002). According to this framework, cool EF is elicited by abstract, decontextualized problems, whereas hot EF is related to problems that involve the regulation of affect and motivation. Individuals with lesions to the ventromedial PFC often perform normally on traditional measures of EF; however they tend to exhibit functional impairments in their social and emotional decision-making, both experimentally and in real-life situations (e.g. Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). This contrasts to those with lesions to the dorsolateral PFC, who tend to display impairments on traditional neuropsychological tasks of “cool” EF (see Roth, Randolph, Koven & Isquith, 2006 for a review).

While no previous studies have explicitly studied the effects of OSA on ventromedial PFC functioning, a substantial body of research on sleep deprivation has indicated that sleep loss is associated with impairments in emotional regulation (Horne, 1993), decision making (Killgore et al., 2006), and moral judgment (Killgore et al., 2007). Thus, it is possible that SDB and its associated disturbances of the restorative aspects of sleep are associated with ventromedial PFC dysfunction in addition to the known impairment of PFC-mediated skills. Furthermore, children with OSA tend to have increased social and behavioral problems (Beebe, 2006), possibly suggestive of impaired decision-making.

One of the most widely used measures of ventromedial PFC functioning is the Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994). This task was specifically developed to measure the deficits in decision-making in patients with lesions to the ventromedial PFC. This task consists of four decks of cards (either real or computerized), from which selections must be made; cards are associated with varying “monetary” rewards and punishments. Without the test-taker’s knowledge, two of the four decks have been set to provide high rewards each time a card is pulled, but result in higher punishments over time (and consequently are disadvantageous in the long run). The other two decks have lower rewards but also lower punishments over time, and thus are advantageous in the long run. Participants are instructed to make selections from the decks in order to win the most “money.” Over time, neurologically and psychiatrically healthy individuals learn to choose more frequently from the advantageous decks; however, individuals with ventromedial PFC damage tend to continue to select from the disadvantageous decks (Bechara et al., 1994). Although the IGT was originally

developed to measure the cognitive effects of frank ventromedial PFC lesions, poor performance has also been documented in other patient populations whose behaviors are characterized by excessive risk-taking and poor decision-making, such as substance abusers (Bechara, Dolan, Denburg, Hindes, Anderson & Nathan, 2001), pathological gamblers (Cavedini, Riboldi, Kelly, D'Annuncci & Bellodi, 2002) and adolescents with externalizing behavior disorders (Blair, Colledge, & Mitchell, 2001).

Like all cognitive tests, the IGT requires skills that are subserved by a number of brain regions and systems, but it is one of only a few tasks that have been demonstrated to be sensitive to lesions in the ventromedial prefrontal cortex (e.g. Bechara et al., 1994; Bechara, Tranel, & Damasio, 2000). Functional neuroimaging evidence has linked IGT performance to activation of the ventromedial prefrontal cortex, as well as other regions including orbitofrontal cortex (London et al., 2000). The ventromedial prefrontal cortex has been described as a brain region where environmental stimuli are linked to emotional body states (Bechara, Damasio, Tranel & Damasio, 1997; Damasio, Bechara & Damasio, 2002). According to the somatic marker hypothesis, “somatic markers” are anticipatory emotions that may not be readily verbalized by individuals but are measurable by skin conductance responses (SCRs), and that are thought to act as an early warning system that is activated prior to risky decisions. Through learning, these somatic markers become linked to predicted outcomes, and eventually may guide decision-making behavior. Deficits in this system have been described as “myopia for future consequences,” not unlike that observed in risk-taking populations, such as substance abusers or pathological gamblers (Bechara, Dolan, & Hindes, 2002). Impairments on the IGT are thought to be linked to a deficit in the somatic marker system (Tomb, Hauser, Deldin, & Caramazza,

2002). Somatic markers, measured by SCRs, are significantly increased from baseline in healthy adults just prior to selecting from disadvantageous decks on the IGT (Damasio, Bechara & Damasio, 2002).

The IGT has also been used as a probe to better understand the developmental changes in performance, as this may lend information as to the development of the ventromedial PFC. Using a cross-sectional design, Hooper and colleagues (2004) investigated age-related changes in performance on the IGT in adolescents aged 9-17. They found that, in general, participants tended to shift their preference towards advantageous decks over the course of the task; however, this shift occurred earlier during the task among older as compared to younger adolescents. There was a significant effect of age on overall performance, indicating a developmental trend in performance on the IGT. Another study (Crone, Vendel, & van der Molen, 2003) reported a similar developmental trend on the Hungry Donkey Task, which was developed as an analogue of the IGT and targeted for use with younger children. They demonstrated better performance with increasing age across the range of 12-25 years.

Other recent research has examined the neuropsychological predictors of IGT performance. Several studies have investigated the relationship between traditional measures of cool EF and the IGT but have yielded variable results. Many studies have failed to find a significant relationship between performance on the IGT and other EF measures, such as the WCST (Overman, Frassand, Ansel, Trawalter, Bies & Redmond, 2004; Sweitzer, Allen & Kaut, 2008) in healthy adolescents age 11-18, Controlled Oral Word Association Test (Barry & Petry, 2008) in substance using adults, Digit Span and a go/no-go task (Hooper et al., 2004) in healthy adolescents ages 9-17. In contrast, other

studies have reported significant associations between IGT performance and the Trail Making Test (Barry & Petry, 2008) and auditory working memory (PASAT; Fein, McGillivray & Finn, 2007) in healthy adults. Verdejo-Garcia and Perez-Garcia (2007) used factor analysis to elucidate the relationship between several traditional measures of EF and the IGT in a population of adult substance abusers. They found that the IGT stood alone, as no other EF measures included in their study loaded on the IGT/“decision-making” factor. However, the authors did note that a substantial proportion of the variance was shared between the IGT and the other EF measures. Taken together, prior research findings suggest that “cool” EF abilities may contribute to IGT performance to some degree, but cannot fully account for it.

Aims and Hypotheses

The goal of the present study was to characterize the IGT performance pattern in a group of children and adolescents who, because they were overweight, were at high risk for sleep-disordered breathing (e.g., OSA). In line with previous literature (e.g. Hooper et al., 2004), it was predicted that participants would learn to chose more frequently from advantageous decks over the course of the task and that older adolescents would learn to do so more quickly than younger participants, even in this sample with potential PFC deficiencies. A further aim of the study was to determine the neuropsychological predictors of IGT performance in this sample. Although the literature is largely discrepant regarding the contribution of “cool” aspects of EF to IGT performance, it was hypothesized that a measure of behavioral inhibition (Gordon Diagnostic System, commission errors) would be related to performance on the IGT. This prediction was based on previous research in clinical populations that perform poorly on the IGT (i.e.

risk-takers) and also because features of the IGT may elicit impulsivity (i.e. high initial rewards in decks that are disadvantageous in the long-run). The final aim was to investigate the effects of sleep-disordered breathing on IGT performance. It was hypothesized that participants with higher apnea + hypopnea indices (a polysomnographically-derived index of severity of sleep-disordered breathing) as well as more fragmented sleep (as measured from actigraphy) and a shorter nightly sleep duration would have more impaired performance on the IGT.

Chapter 2: Research Design and Methodology

Participants

Participants were drawn from a larger study investigating the broad neurobehavioral effects of OSA and other sleep disturbances in children and adolescents. Only baseline data were considered for the present study. Participants ($n = 111$) were overweight (BMI > 95th percentile for age and sex) children and adolescents, ages 10-16. Participants were recruited from a weight management clinic ($n = 82$) or the sleep clinic ($n = 29$) at Cincinnati Children's Hospital Medical Center. Exclusion criteria were: diagnosis of a neurodevelopmental disorder (e.g., autism spectrum disorder); current or prior neurological condition (e.g., epilepsy, head injury that resulted in loss of consciousness), treatment for OSA (by positive airway pressure or adenotonsillectomy) within the past two years; and use of psychoactive medications (with the exception of stimulant medication, which was discontinued at least 24 hours prior to assessment). The rationale for not excluding participants who are taking stimulant medications ($n = 4$) is that children with sleep apnea often display behavioral features characteristic of Attention-Deficit/Hyperactivity Disorder (ADHD), and hence may be prescribed stimulants. Excluding these individuals may artificially suppress effects or lead to a non-representative sample of children with SDB (Beebe, 2006; Owens et al., 2000). Substance abuse was not assessed for during participant screening.

Procedure

Parents were contacted by phone or approached at clinic visits, and the study rationale and procedures were explained. Written informed parent consent and child assent were obtained at the baseline study visit. Families were compensated \$50 for their

time and travel to the assessment, and each received individualized summary feedback on findings from neuropsychological testing and sleep assessment procedures. All procedures were approved and overseen by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

Participants were administered a neuropsychological assessment battery, which included the IGT, beginning between 3:30 and 5:00 pm to minimize variability due to circadian rhythm effects on test performance. In most cases, participants were then fed dinner and underwent an overnight polysomnogram (PSG) study to assess for SDB. In a few cases, scheduling limitations precluded conducting both assessments on the same evening; in these cases the neuropsychological testing was conducted on an afternoon other than the one immediately following the PSG to avoid the potential adverse effects of having slept in an unfamiliar setting. Participants also completed a nightly sleep diary and wore an actigraph to document nocturnal activity and sleep patterns, generally during the week prior to the neuropsychological evaluation and PSG.

Measures

Polysomnogram (PSG) Study

Participants underwent an overnight inpatient PSG study, as this method is the “gold-standard” for assessing OSA and several other types of sleep pathology. During the PSG study, sleep stage, respiration, cardiovascular functioning, and muscle movements were simultaneously and continuously monitored. Specifically, the following parameters were monitored using a computerized system (Astro-Med Grass System; Heritage, West Warwick, RI): Electroencephalogram (EEG; C₃-A₂, C₄-A₁, O₁-A₂, O₂-A₁), right and left electroculgram (EOG), submental electromyogram (EMG), tibial EMG,

electrocardiography (ECG), nasal/oral airflow through a three pronged thermistor and/or nasal pressure transducer, end tidal CO₂ (at the nose via infrared capnometry), snoring microphone, O₂ saturation by pulse oximeter, oximeter pulse waveform, actigraphy to measure limb movements, infrared video monitoring, and rib cage and abdominal volume changes (computer-assisted respiratory inductance plethysmograph).

Sleep staging was scored according to standardized criteria (Rechtschaffen & Kales, 1968). Consistent with conventional practices at the time of the study (American Thoracic Society, 1996; Marcus et al., 1992; Uliel et al., 2004) obstructive apneas were defined as >80% decline in airflow over two respiratory cycles, despite chest/abdominal wall movement (indicating continued respiratory effort). Obstructive hypopneas were defined as a 50-80% decline in airflow over two respiratory cycles, (a) accompanied by chest/abdominal wall movement and (b) associated with oxygen desaturation or followed by arousal. The apnea + hypopnea index (AHI) was defined as the total number of obstructive apneas and hypopneas, divided by the number of hours in sleep (which was used as the sleep duration variable).

Actigraphy and Sleep Diary

In order to document sleep behaviors for several nights at home, participants were asked to wear an actigraph during sleep for 7 consecutive nights. The actigraph used in this study (MicroMini-Motionlogger, Ambulatory Monitoring, Inc., NY) was a wrist-watch-sized device that records and stores movement information that, when entered into a validated mathematical algorithm, yields proxy measures of sleep, wake, and arousals based upon activity patterns (Acebo, Sadeh, Seifer, et al., 1999; Sadeh, Hauri, Kripke, et al., 1995). Participants also completed a prospective sleep diary, in which they recorded

bedtime, wake time, and number of nightly awakenings during the period in which they wore the actigraph device. This information was used when screening the actigraph data for artifacts, particularly lack of movement due to removal of the unit. For the present study, we generated an actigraphy-based arousal index (AAI), defined as the number of arousals that lasted >5min during the sleep period, divided by the total sleep duration. To obtain the most stable estimate, each subject's AAI was defined as the average index score across the nights that he or she wore the actigraph.

Iowa Gambling Task

A computerized version of the IGT was administered (Bechara, 1994), using a pre-publication version of software that was recently made commercially available through Pearson. Participants were presented with 4 decks of cards on a computer screen, from which participants could “draw” cards by clicking on each deck. Participants began the task with a \$2,000 loan of hypothetical money (shown on the computer screen). With each card drawn, participants won some amount of “money”; however, with some cards they also lost money. Participants were instructed that the object of the game was to win as much money as possible by trying to figure out which deck(s) of cards were better than the others. They were free to pick from any deck and could change decks as often as they wanted. As participants “drew” each card, they received visual and auditory feedback on the money they won, and any they might have lost in that draw. Green and red bars at the top of the screen displayed a running total of money won and money lost during the task. The task continued until participants drew 100 cards.

As noted earlier, the task was set up such that drawing from two of the decks (C and D) would eventually net more money than drawing from the other decks (A and B).

Each time a participant chose any card from deck A or B they won an average of \$100 and when they chose a card from decks C or D they won an average of \$50. With each draw, there was also a chance of losing money as well, with the amount and probability systematically varied across decks. The higher paying decks (A and B) yielded larger penalty amounts, such that in the long-run they were disadvantageous. Decks A and B were identical in net yield, though deck A was associated with more frequent punishment of smaller amounts, whereas deck B was associated with less frequent punishment of larger amounts. Similarly, decks C and D had the same net yield; however, C had more frequent, but smaller punishment amounts (see Figure 1).

	Disadvantageous		Advantageous	
	A	B	C	D
\$ Gain/10 Cards:	\$1000	\$1000	\$500	\$500
Frequency of Loss:	50%	10%	50%	10%
\$ Loss/10Cards:	\$1250	\$1250	\$250	\$250
Net \$/10 Cards:	-\$250	-\$250	\$250	\$250

Figure 1. Iowa Gambling Task Schedule of Reinforcement

The task is conventionally scored in 5 blocks of 20 card-pulling trials. Within each block, the number of draws from *disadvantageous* decks (A and B) is subtracted from the number of draws from *advantageous* decks (C and D). Thus, there are 5 data points for each participant, with positive scores representing a pattern of more

advantageous draws, and negative scores representing more disadvantageous draws. Scores for each block range from -20 (when all cards are drawn from disadvantageous decks) to 20 (when all choices are from advantageous decks).

Other Executive Functioning Measures

As part of a larger neuropsychological battery, participants were administered a number of standardized measures that are thought to tap into different domains of EF. For all measures, standard scores were calculated based on published norms. *Working memory*, or the ability to hold and manipulate information in very short-term storage, was assessed using the Letter-Number Sequencing (LNS) subtest from the Wechsler Intelligence Scale for Children, Third Edition (WISC-IV; Wechsler, 2003). In this task, participants are asked to immediately recall and place into sequence a series of numbers and letters. The Gordon Diagnostic System (Gordon, 1983) was used to measure both *vigilance* (the ability to sustain attention for an extended period) and *inhibition* (the ability to prevent a prepotent response from occurring). In this task, participants are presented with a series of numbers that flash quickly on a screen; they are asked to push a button each time a particular number sequence appears (and inhibit the response when distracter stimuli are presented). The number of omission errors (GDS-O), or number of times they miss the target stimulus, was used as a measure of *vigilance*. Commission (GDS-C) errors, or the number of false-alarms, was used as a measure of *inhibition*, or impulsivity. Another domain of EF, *selective attention*, involves that ability to attend to relevant stimuli and ignore non-relevant stimuli. This was measured using the Map Mission subtest from the Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, et al., 1999). On this measure, children are asked to search a

visually complex map and identify as many instances of a particular symbol as they can as quickly as possible. The age-based scaled score for total number of targets identified was utilized. Another subtest from the TEA-Ch, Creature Counting, as well as the letter fluency portion of the Verbal Fluency subtest from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) were both used as measures of *Mental Flexibility*. This domain of EF involves the ability to shift fluidly from one idea or concept to another. The letter fluency portion of the Verbal Fluency task requires participants to rapidly generate as many words as they can think of that begin with a particular set of letters. Scaled scores for total number of words generated were used. In the Creature Counting task, participants must flexibly alternate between counting “creatures” forwards and backwards, based upon symbols embedded within the array of creatures. The scaled score for total number correct was used. A final domain of EF that was measured is *planning*, or the ability to generate and execute multi-step plans to reach a goal. This was measured using the Drexel edition of the Tower of London (Culbertson & Zillmer, 2000), a task that requires participants to execute a plan to solve a problem (manipulating beads into a particular pattern, while following a set of rules) in as few steps as possible. The standard score for total moves was used in the analyses.

Demographics and Descriptive Characteristics

Demographic information was collected by parent report and included information regarding parent education level, household income, and zip code of residence. This information was used to compile a single Socioeconomic Status (SES) variable that could be entered as a potential covariate. To create this variable, mother and father education level (in years), family income, and median income from the family’s

zip code of residence were each expressed as a Z-score, relative to the other scores in the sample. The average of the available Z-scores for each subject defined the SES composite, which prorated missing values (e.g., missing paternal education).

Participants' height and weight were measured immediately prior to the PSG. This information was used to calculate body mass index ($BMI = \text{mass in centimeters} / \text{squared height in meters}$) and a BMI Z-score based upon normative data for the child's age and sex provided by the Centers for Disease Control and Prevention.

Because we were interested in the impact of developmental level on IGT performance, participants were also administered a self-report questionnaire to assess pubertal status (Carskadon & Acebo, 1993). All participants rated their development on a 5-point likert scale in the following domains: changes in height, skin changes and presence of body hair. In addition, boys were asked to rate changes in their voice and facial hair; girls were asked to rate breast development and were asked if and when they began menstruating (score of 4 if menarche had occurred and 1 if not). The pubertal development scale score was computed by taking an average of the gender-relevant items and was used as a continuous variable ranging from 1 to 4.

Analytic Strategy

The dependent variables of interest, IGT performance, consisted of 5 blocks of 20 "card-pulling" trials each; thus, for each subject there are 5 data points. Because we are interested in how performance changes over the course of the task, a General Linear Mixed Modeling (GLMM) approach was used with a random coefficients model. With this method, both *within subject* and *between subject* factors are considered. The *within subject* variability captures person-specific changes over time, whereas the *between*

subject variability captures the between-person variability in task performance over time (which allows for modeling of predictors of this variability). GLMM is associated with two levels of analysis. The first level describes how variables change over time at both the individual and population level. At the second level of analysis, predictors can be added to the model to predict change over time. It is considered a “random coefficients” model because both intercept and slope estimates are allowed to vary by individuals (i.e., they are specified as random effects). The mixed model approach is preferred over traditional repeated-measures analysis of variance because mixed models can handle missing data points, both continuous and categorical predictors can be incorporated into the model, and appropriate covariance structures can be specified (DeLucia & Pitts, 2005). Analyses were conducted using the SAS Mixed Procedure (SAS Institute, 1990) using restricted maximum likelihood estimation. In all analyses, each predictor variable was centered on its mean value and the “block” or task period variable was transformed, such that time 0 represents performance on the first block of the IGT.

The first level of analysis described how IGT performance changed over time within each subject and across the population. In the second level, relevant inter-subject predictors were added in order to investigate the relationship between IGT performance and sleep variables, other measures of executive functioning, as well as potential covariates.

Hypothesis 1: Modeling Iowa Gambling Task Performance Over Time

In order to describe the trajectory of IGT performance over the course of the task, a model was fit with time period (“block”) as the only predictor. To determine the covariance matrix that best fit the data, several models were constructed with different

covariance structures specified, and model fit statistics (Akaike's Information Criterion (AIC; Brown & Prescott, 1999) were compared. The covariance matrices tested were: compound symmetry, autoregressive, topelitz, and unstructured (where all elements of the residual covariance matrix were freely estimated). Next, to determine potential polynomial effects in the model, linear, quadratic, and cubic effects were tested. When the final level 1 model was specified, the variance components were investigated in order to determine if there was significant variability in either the intercept or slope that could be predicted in the second level analysis.

Hypothesis 2: Developmental Effects on IGT Performance

To test for potential covariate effects, developmental level, SES, and sex were entered into the second level analysis. Developmental level was estimated in two ways - age and puberty rating, run in separate analyses - since it is not clear which is the most relevant variable with respect to IGT performance. Each variable was entered in a step-wise manner. Variables that improved model fit statistics (i.e. reduced AIC values) were retained as covariates in all subsequent analyses. Variables that reduced model fit (i.e., increased AIC values) were dropped.

Additional exploratory analyses were also conducted in order to determine if sleep apnea status moderated the relationship between developmental level and IGT performance. For this analysis, the three-way interaction between time period, development (age or puberty rating), and AHI was tested.

Hypothesis 3: Relationship between IGT and Executive Functioning Measures

To investigate the relationship between IGT performance and other measures of EF, models were constructed in which IGT performance was predicted from time period

(“block”), performance on EF measures, and the associated interaction terms. The following EF measures were investigated: LNS, GDS commissions, GDS omissions, Verbal Fluency (total words scaled score), Creature Counting (total correct scaled score), Map Mission (total correct scaled score), and Tower of London (total move scaled score). As in the other analyses, these variables were entered in a step-wise manner and models were compared based on AIC values.

Hypothesis 4: Predicting Iowa Gambling Task Performance from Sleep Variables

To determine the relationship between sleep variables and IGT performance, models were constructed where IGT performance was predicted from time period (“block”), sleep variables, and associated interaction terms. Analyses were conducted in a step-wise manner in which polysomnography-based apnea + hypopnea index (AHI), actigraphy-based arousal index (AAI), and sleep duration were entered into the model. As each sleep variable was entered, model fit statistics (AIC) were compared, and if fit improved (i.e. AIC value decreased) the variable was retained.

Chapter 4: Results

Preliminary Analyses

Like traditional regression and general linear model (GLM) analyses, GLMM assumes that the entered variables are normally distributed. Upon inspection, the AHI variable was markedly positively skewed – which is common in studies of pediatric OSA -- and could not be normalized using traditional transformations (e.g. logarithmic, inverse, etc.). Consequently, the AHI variable was trichotomized based on clinically relevant criteria and following previous research in the field (Beebe, et al., 2004; Amin et al., 2002, Owens et al., 2000). The sample was divided into three groups: individuals with $AHI < 1$ ($n = 37$); those with AHI between 1 and 5 ($n = 43$; characterized as *mild OSA*) and those with AHI greater than 5 ($n = 31$; *moderate to severe OSA*). A comparison of groups on demographic and sleep variables is presented in Table 1. Analysis of Variance (ANOVA) revealed that these three groups were not significantly different with respect to age, pubertal status, SES composite, total sleep time, or AAI; chi square analysis further indicated that, across groups, proportions were not significantly different for race or stimulant medication use. By design, AHI was significantly different across groups ($F(2)=116.35, p < .001$). Furthermore, the *moderate to severe OSA* group consisted of a significantly larger proportion of boys ($\chi^2(2) = 13.14; p < .001$) and BMI Z-scores were significantly different across groups ($F(2) = 5.95; p < .01$); Scheffe post hoc tests indicated that the *moderate to severe OSA* group had significantly higher BMI Z-scores than the group with $AHI < 1$, although the mean BMI Z-score was quite high in all three groups, reflecting average adiposity beyond the 99th percentile for age and sex. As expected, BMI was significantly correlated with AHI ($r^2 = .28; p < .01$). BMI was not

related to IGT performance in this sample ($r^2 = .08$; $p = .62$), although of note, by design, the present sample only included individuals with BMI beyond the 95th percentile for age and sex.

Table 1. Demographic and sleep characteristics

	AHI <1	1<AHI<5	AHI >5	<i>p</i>
	(N = 37)	(N = 43)	(N = 31)	
Age	13.29 (1.94)	13.59 (2.08)	14.04 (1.85)	.30
Pubertal Development Score	3.02	3.07	3.10	.90
% Boys	21.62%	37.20%	64.51%	<.001
% White	29.73%	34.88%	41.93%	.46
SES Composite (Z-score)	-0.15 (.72)	0.23 (.85)	-0.05 (.79)	.14
% on Stimulant Medication	0%	6.97%	3.23%	.26
BMI (Z-score)	2.37 (0.26)	2.49 (0.27)	2.59 (0.26)	.004
Obstructive AHI	0.46 (.31)	2.61 (1.06)	10.61 (5.26)	<.001
Total Sleep Time (min)	402.32 (45.37)	378.92 (64.24)	378.76 (68.46)	.15
Actigraphy-based Arousal Index	1.94 (.73)	2.01 (.72)	1.92 (.66)	.85

Data are percentages and mean (standard deviation). AHI = apnea + hypopnea index; SES = socioeconomic status; BMI = body mass index.

Hypothesis 1: Modeling IGT Performance

The first level of analysis describes the trajectory of IGT performance over the course of the task. It was hypothesized that participants would learn to draw more frequently from advantageous decks over the course of the task (i.e. the trajectory would have a positive slope).

First, to determine the model specifications that best fit the data, preliminary analyses were conducted to test different covariance structures as well as potential polynomial effects. Comparisons of model fit statistics revealed that an unstructured covariance matrix (AIC = 3506.31) better fit the data than compound symmetry (AIC = 3514.99), autoregressive (AIC = 3514.99), and topleitz (AIC = 3514.99). To test for polynomial effects, models were fit with linear, quadratic, and cubic terms. Results of

the GLMM analysis revealed a significant linear effect ($p = .01$) and non-significant quadratic ($p = .06$) and cubic ($p = .15$) effects. Because the quadratic effect was nearing significance, preliminary analyses included this term in subsequent models; however, in no cases was there a significant quadratic effect. Thus, only linear effects were considered in subsequent analyses.

IGT performance was then predicted from task period or “block” using an unstructured covariance matrix and linear estimation. As predicted, the slope of the resulting model indicated that, on average, participants’ performance on the IGT task significantly improved over the course of the task (slope estimate = 0.52, $p = .01$). During the first block of the task, participants drew an average of 2.79 (SD = 5.41) more disadvantageous cards (decks A or B) than advantageous cards (decks C or D). By the conclusion of the task, on average, participants drew an equal number of advantageous and disadvantageous cards (block 5 mean = 0.00; SD = 7.76). Importantly, inspection of the level 1 analysis variance estimates indicated that this general pattern differed considerably across subjects, as indexed in significant variability in both slope and intercept that could be predicted at the second level of analysis.

Hypothesis 2: Developmental Effects on IGT Performance

It was hypothesized that developmental level would be related to IGT performance, such that older children (or those who were further along in pubertal development) would learn to draw from advantageous decks more quickly than their younger counterparts. As an initial test of this hypothesis, age, task period (“block”), and the age by task period (“block”) interaction were entered into the second level model predicting IGT performance. Contrary to predictions, model fit was *reduced* with the

addition of the age variable (AIC of level 1 model = 3506.13; AIC of conditional model with age = 3509.67) and there was no significant effect of age on model intercept ($p=.73$) or slope ($p=.65$). As an alternative test of the hypothesis, the age variable was replaced by pubertal rating. Fit statistics improved somewhat (AIC = 3333.43), but there was not a significant effect of pubertal rating on model intercept ($p = .14$), nor on slope ($p = .67$). Thus, contrary to prediction, developmental level did *not* significantly relate to overall IGT performance (model intercept) or the rate of change in IGT in performance across the task (slope) when the sample was taken as a whole.

SES level and sex of participant were also entered as potential covariates. SES improved model fit (AIC = 3320.75). There was not a significant effect of SES on the model intercept (i.e., modeled performance during the first block of the task; $p = .66$); however, SES was significantly related to the rate of change in IGT performance ($p = .001$); children with higher SES tended to learn more quickly than those with lower SES. When sex was entered, model fit was reduced (AIC = 3490.78), and there was not a significant effect of sex on model intercept ($p = .17$) nor slope ($p=.89$).

Because addition of both pubertal rating and SES improved model fit statistics, both of these variables were retained and entered as potential covariates in all subsequent analyses. Age and sex, each of which did not improve model fit, consequently were dropped from subsequent analyses.

Hypothesis 3: Relationship between IGT Performance and EF Measures

To test the third hypothesis, the relationship between IGT and other measures of EF was investigated. Measures of EF were added into the model in a step-wise manner, and those variables that improved model fit were retained. Table 2 presents the effects of

EF measures on overall IGT performance as well as on rate of change in IGT performance. Those variables that increased AIC values (i.e., reduced model fit) and had no significant effect on IGT performance were dropped from the model; these included measures of *vigilance* (GDS Omissions), *mental flexibility* (TEA-Ch CC and D-KEFS Verbal Fluency), *planning* (Tower of London), and *selective attention* (TEA-Ch Map Mission).

The final model predicting IGT performance from EF measures included commission errors from the GDS (a measure of *inhibition*) and LNS from the WISC-IV (a measure of *working memory*). As presented in Table 3, LNS had a significant effect on the model intercept ($p = .02$), whereas GDS-C had a significant effect on the rate of change in IGT performance ($p = .03$). Figure 2 depicts the relationship between LNS (Figure 1a), GDS-C (Figure 1b) and IGT. Probing the interactions by looking at simple effects revealed that individuals with higher LNS scores (upper quartile) had significantly higher overall IGT performance ($M = 2.81$; $SD = 23.51$) as compared to those with lower LNS scores ($M = -12.27$; $SD = 17.92$; $t(243) = -5.54$, $p < .01$). Individuals with fewer commission errors on the GDS tended to improve in IGT performance over the course of the task (slope = 1.39; $p < .01$); whereas performance did not improve in individuals who demonstrated poorer inhibition (slope = -0.13; $p = .72$).

Table 2. Relationship between EF measures and IGT

Domain	EF Measure	p (effect on intercept)	p (effect on slope)	AIC
<i>Inhibition</i>	GDS Commissions	.42	.01	3368.64
<i>Working Memory</i>	LNS	.04	.66	3377.21
<i>Vigilance</i>	GDS Omissions	.77	.09	3380.59
<i>Mental Flexibility</i>	TEA-Ch CC	.67	.58	3470.69
<i>Planning</i>	Tower of London	.86	.60	3485.96
<i>Mental Flexibility</i>	D-KEFS Verbal Fluency	.51	.85	3492.59
<i>Selective Attention</i>	TEA-Ch Map Mission	.62	.14	3510.19

Table 3. GLMM: Predicting IGT performance from EF

<u>Fixed Effects</u>	Coefficient (SE)	95 % CI
Average intercept	-4.82* (2.21)	-9.20 – -0.44
Effect of LNS on intercept	0.50* (0.20)	0.09 – 0.90
Effect of GDS-C on intercept	-0.22 (0.54)	-1.30 – 0.86
Effect of pubertal rating on intercept	6.04 (3.40)	-.710 – 12.79
Effect of SES on intercept	-0.54 (0.62)	-1.78 – 0.70
Average Slope	1.01 (0.90)	-0.77 – 2.81
Effect of LNS on slope	0.05 (0.08)	-0.21 – 0.12
Effect of GDS-C on slope	0.50* (0.22)	0.06 – 0.93
Effect of pubertal rating on slope	-0.76 (1.38)	-3.51 – 1.99
Effect of SES on slope	0.78* (0.25)	0.28 – 1.28
<u>Variance Components</u>		
Within-person	22.83* (1.86)	19.46 – 26.79
In intercept	11.21* (3.75)	5.82 – 21.58
In rate of change	1.73* (0.61)	0.86 – 3.46
Covariance	-1.34 (1.24)	-3.77 – 1.09

* significant $p < .05$

Figure 2. Effect of EF measures on IGT performance, plotting best-fit prediction lines in black over the obtained mean scores for groups derived by dichotomizing the LNS score and GDS commissions. 1a. Letter-Number Sequencing had a significant effect on overall IGT performance such that individuals with higher scores on LNS performed better on the IGT. 2b. Commission errors on the GDS were related to the rate of change in IGT performance. Individuals with fewer commission errors improved on IGT performance over the course of the task.

Hypothesis 4: Predicting IGT Performance from Sleep Variables

To test the final hypothesis, sleep variables (apnea/hypopnea index(AHI), actigraphy-based arousal index (AAI), and sleep duration) were entered into the model to predict IGT performance. Sleep variables were entered in a step-wise manner, and those variables that improved model fit statistics were retained. AHI was entered into the model first, and model fit (AIC = 3312.63) was improved as compared to the model with task period and the covariates (SES and pubertal rating) as the only predictors (AIC = 3320.75). Next AAI was entered, and again the AIC estimate improved (AIC = 2955.01); thus, both AHI and AAI were retained in the model. When sleep duration was entered into the model, the AIC worsened (i.e. fit decreased; AIC = 2969.77), and thus sleep duration was dropped from the model.

Model estimates are presented in Table 2. As illustrated in Figure 3, AHI had a significant effect ($p = .02$) on the rate of change in IGT performance (slope), represented by the significant task period by AHI interaction. Probing of the interaction using simple effects revealed that individuals in the $AHI < 1$ group tended to improve on the IGT over the task (slope = 1.04, $p < .01$), whereas individuals in the *mild* and *moderate to severe OSA* groups slopes were not significantly different from 0, thereby indicating no reliable evidence of learning across the course of the task in these groups (*mild OSA* group slope = 0.31, $p = .33$; *moderate to severe OSA* group slope = 0.16, $p = .70$). There was no significant effect of AHI on the model intercept ($p = .99$). Similarly, SES did not have a significant effect on the intercept ($p = .41$); however, there was a significant interaction between SES and task period ($p = .002$), indicating an effect of SES on slope. Individuals with higher SES (upper quartile on SES variable) tended to improve on IGT performance

over the task (slope = 1.48, $p < .01$) as compared to those with lower SES (lower quartile; slope = -0.61, $p = .09$). Importantly, AHI impacted slope beyond the effect of SES.

Although AAI improved the overall fit of the model, there was not a significant relationship between AAI and model intercept or slope. Pubertal rating was not significantly related to model intercept ($p = .29$) or slope ($p = .26$).

In order to obtain some measure of effect size for the model, an estimate of r^2 was calculated by correlating the predicted values with the observed values. The resulting estimate of effect size was .31, which can be interpreted as a moderate effect (Brown & Prescott, 2006).

Participants with little to no evidence of SDB improved in IGT performance over the course of the task and did so at a faster rate than individuals with evidence of OSA. However, it was unclear if, even participants without SDB, demonstrated adequate learning of the IGT task demands. According to the binomial probability distribution, participants must draw ≥ 4 more advantageous than disadvantageous cards in a block of 20 draws to conclude that performance was greater than chance level (at $p < .05$). Thus, on average, even in the AHI < 1 group, performance remained lower than chance level at the final block of the task (mean net advantageous draws at block 5 = 2.1). The sample was dichotomized into groups based on those participants who adequately learned the task (i.e. drew more advantageous cards than chance level at the final task block) vs. those who did not; 31% of the sample drew ≥ 4 net advantageous cards at block 5. There was a trend indicating that participants who adequately learned the task were associated with lower AHI (mean AHI = 2.83, SD = 4.81) than those who did not (mean AHI = 4.51, SD = 5.31), although this was not a significant difference ($p = .065$). However, the

proportion of participants in the $AHI < 1$ group was higher amongst those who adequately learned the task (44%) as compared to those who did (28%; $\chi^2 = 7.10, p = .03$).

Table 4. GLMM: Predicting IGT performance from sleep variables

<u>Fixed Effects</u>	Coefficient (SE)	95 % CI
Average intercept	-3.32 (2.21)	-7.71 – 1.07
Effect of AHI on intercept	-0.01 (0.68)	-1.36 – 1.34
Effect of AAI on intercept	-0.60 (0.76)	-2.11 – 0.91
Effect of pubertal rating on intercept	3.60 (3.38)	-3.11 – 10.32
Effect of SES on intercept	-0.58 (0.69)	-1.96 – 0.80
Average slope	0.24 (0.89)	-1.54 – 2.01
Effect of AHI on slope	-0.66* (0.27)	-1.20 – -0.12
Effect of AAI on slope	-0.17 (0.31)	-0.78 – 0.44
Effect of pubertal rating on slope	0.35 (1.36)	-2.36 – 3.07
Effect of SES on slope	0.92* (0.28)	0.36 – 1.48
<u>Variance Components</u>		
Within-person	23.26* (1.97)	19.69 – 27.48
In intercept	11.99* (4.07)	6.17 – 23.31
In rate of change	1.88* (0.67)	0.93 – 3.76
Covariance	-1.63 (1.35)	-4.28 – 1.02

* significant $p < .05$

Figure 3. Iowa Gambling Task (IGT) performance by apnea + hypopnea index (AHI) group. GLMM analysis revealed that AHI had a significant effect on rate of change in IGT performance.

Exploratory Analysis: Does sleep apnea status moderate the relationship between developmental level and IGT performance?

It was hypothesized that older children would perform better on the IGT as compared to younger children. As noted above, surprisingly, this relationship was not present in the sample when taken as a whole. Because there was, however, evidence that OSA suppressed learning on the task, it remained possible that developmental effects might be evident in children without OSA that are nullified in the presence of OSA. To further investigate this possibility, we sought to determine if OSA status moderated the relationship between developmental level and IGT performance. Thus, the three-way interaction between task period, age and AHI was entered into one model, then the model was repeated, substituting pubertal rating for age as an estimate of developmental level.

No significant effects were found with the three-way interaction term of age, AHI, and task period ($p = .50$). As depicted in Figure 4, there was a significant three-way interaction between pubertal rating, AHI and task period ($p = .047$). This exploratory finding suggests that AHI moderates the relationship between IGT performance and pubertal status. Figure 3a illustrates the relationship between puberty status and IGT performance in participants with *moderate to severe OSA*; whereas Figure 4b depicts the relationship in participants without OSA. When only considering individuals without OSA (AHI <1), the expected relationship between development and IGT emerges; participants with higher pubertal status are associated with a positive slope, or increasing performance on the IGT (slope = 1.42; $p = .02$) and IGT performance does not significantly change over the task in participants with lower pubertal ratings (slope = 0.65; $p = .14$). However, when individuals with *moderate to severe OSA* are considered there is no effect of developmental level (see Figure 4a).

Figure 4. Relationship between pubertal status and Iowa Gambling Task performance is moderated by obstructive sleep apnea (OSA) status. 3a. In individuals with *moderate to severe OSA* there is no relationship between developmental level (pubertal status) and IGT performance. 3b. In individuals without OSA (AHI <1), higher pubertal ratings are associated with increasing performance on IGT; performance did not significantly change in individuals with lower pubertal ratings.

DISCUSSION

In this study, we examined several potential predictors of IGT performance in a group of children and adolescents aged 10-16 years old who, by virtue to being considerably overweight, were at high risk for OSA and other sleep pathology. Based upon prior research, we hypothesized that (a) in the sample as a whole, participants would begin the IGT by drawing from disadvantageous decks but learn from feedback on rewards and losses to draw more often from advantageous decks over time; (b) among several demographic factors, development would be associated with faster learning across the course of the IGT; (c) at least some aspects of “cool” executive functioning, particularly behavioral inhibition, will be related to learning across the course of the IGT; and (d) children and adolescents with evidence of sleep-disordered breathing (e.g., OSA), restlessness during sleep, and/or short sleep duration would have more trouble benefiting from experience during the IGT than those with healthier sleep. As will be detailed below, while several of these hypotheses were at least partially supported, the findings were more nuanced than initially expected.

Characterization of IGT Performance in the Sample as a Whole

The first aim of the study was to characterize IGT performance in this adolescent sample, thereby building upon the growing literature on adolescent problem-solving in the context of risky decision-making. As expected, early in the IGT, participants chose from the disadvantageous decks more frequently, and performance generally improved over the course of the task. Despite this improvement, even in the final block of the task (draws 80-100), on average, participants drew an equal number of disadvantageous and advantageous cards, such that most participants never recouped the losses they incurred

early in the task. This level of performance towards the end of the task is somewhat lower than was reported in sample of healthy individuals of a similar age range by Hooper and colleagues (2004). In their study, by the final block, participants drew an average of around 3 ½ more advantageous than disadvantageous cards. That is more comparable to the performance towards the end of the task among our participants with minimal or no evidence of SDB (AHI < 1; net advantageous draws at block 5 = 2.1). The risk level for SDB may be a critical difference between these studies; although Hooper and colleagues did not assess sleep, it is likely that few if any of their participants had OSA, because it is uncommon in otherwise healthy, normal-weight teens.

Demographic Predictors of IGT Performance

We considered three potential demographic predictors of IGT performance: developmental level, sex, and socioeconomic status. In line with previous literature (Hooper et al., 2004; Crone, Vendel, & van der Molen, 2003), we predicted that developmental level (as measured by age or pubertal status) would be related to IGT performance: participants further along in development were generally expected to learn fastest over the course of the task. This relationship was not present in our sample when taken as a whole but, as will be discussed later, exploratory follow-up analyses again suggested that it is critical to take into account the potential effect of SDB when interpreting these results. Importantly, prior research studied groups that were at low risk for OSA, whereas the current sample was at very high risk due to their overweight status.

A second demographic covariate that we investigated was gender. Previous research on gender disparities in IGT performance has been somewhat mixed. Reavis & Overmann (2001) reported that adult men consistently outperformed women on a version

of the IGT. Crone and van der Mollen (2007) also reported some evidence of a gender disparity in performance on the Hungry Donkey Task, a child version of the IGT. They found that younger boys (ages 8-12) and older adolescent boys (ages 16-18) outperformed girls, but no gender differences were present in children ages 12-14. In contrast, Hooper and colleagues (2004) did not report a gender difference in IGT performance in youth ages 9-17, across age groups. Similarly, we did not find any effect of gender in the present study. One explanation for the differences in findings may be variations in task parameters. Reavis and Overmann (2001) used a version of the IGT with 150 card selections, rather than the traditional 100, and they reported the largest gender disparity occurring in the final 50 draws. Crone and van der Mollen (2007) also utilized a variation on the IGT, where as Hooper and colleagues (2004) utilized the traditional 100 selection version of the IGT (Bechara et al., 1994), as was used in the present study. An alternate explanation for the variation in findings may be related to developmental effects. Gender differences have been reported in a sample of adults, as well as in a subgroup of older adolescents (ages 16-18). It is possible that sex effects do not emerge until later in development, or may be dependent on stage of pubertal development. Further research is necessary to fully understand gender differences in the development of ventromedial prefrontal cortical functioning.

A final demographic covariate, family socioeconomic status, was found to be significantly related to IGT performance in the current sample. This relationship is not unique to the IGT, as there is a large body of literature indicating strong associations between neuropsychological test performance and socioeconomic background. For example, SES has been shown to account for up to 20% of the variance in children's IQ

(Gottfried, Gottfried, Bathurst, Guerin & Parramore, 2003). Although the exact mechanism for this relationship is unclear (e.g., differences in scores may be related to many factors including differences in experiences that impact brain development, genetic differences, or cultural biases in test instruments), it is common to include SES as a covariate in research to minimize the chances that demographic confounds could account for findings. Consistent with this, we controlled for SES in all subsequent models of IGT performance.

Executive Functioning Predictors of IGT Performance

A third aim of this study was to investigate the relationship between IGT performance and other measures of executive functioning. Although the IGT is sensitive to ventromedial prefrontal cortical functioning, it is not necessarily specific, as other brain regions have also been shown to be active during this task. Using PET imaging, Ernst and colleagues (2002) demonstrated activation in orbital and dorsolateral PFC, anterior cingulate, inferior parietal cortex, thalamus and cerebellum during the IGT. Many of these regions are also activated during more traditional tests of EF, including tests of working memory and inhibitory control (Braver, Barch, Gray, Molfese & Snyder, 2001; Owen, 2000). Thus, it is not surprising that we found relationships between performance on the IGT and measures of verbal working memory (LNS) and inhibitory control (commission errors on the Gordon). Working memory ability was related to overall IGT performance, whereas inhibitory control was related to the rate of change in performance over the course of the task.

Although previous research has been somewhat discrepant regarding the contribution of working memory to IGT performance, from a practical standpoint, it

seems to make sense that working memory is necessary for intact IGT performance. It is likely that working memory skills are necessary to keep in mind previous choices made, remember outcomes that have been associated with a given deck, and to manipulate this information to make some determination of each deck's net worth (Hooper, Luciana, Conklin & Yarger, 2004). Working memory was related to overall IGT performance (intercept) rather than the rate of change in IGT performance (slope). This may suggest that, even early in the task, participants who are better able to keep previous choices and outcomes in mind, are more successful at determining a deck's worth, and thus make more advantageous choices. Whether verbal versus visual working memory is more essential to effective IGT performance is not clear; the current study did not include a strong measure of visual working memory skills.

Elements of the IGT also seem to require intact inhibitory control; the task is set up such that the disadvantageous decks are associated with the highest initial rewards. Thus, to choose from more advantageous decks, it is necessary to inhibit the prepotent response to continue to draw from decks that provide an immediate large reward. Furthermore, spatially, the task is set up such that the disadvantageous decks are on the left hand side (decks A and B). A long line of literature suggests that from an early age, individuals from Western cultures tend to direct their attention and action rightward on many different visual tasks (Speedie et al., 2002). Thus, initially, participants tend to choose cards from left to right; this prepotent response must also be inhibited in order to draw from the advantageous decks located on the right side of space. Our finding that the IGT is related inhibitory control was in line with some (Crone et al., 2003), but not all (Hooper et al., 2004) previous reports. One reason why our results may conflict with

Hooper and colleagues (2004) may be our use of a GLMM approach to analyzing the IGT data. Because normal participants tend to begin the task by drawing more frequently from disadvantageous decks and then shift their preference over the course of the task, it is important to look at the rate of change, or slope in IGT performance modeled over time, rather than just analyzing the overall number of advantageous draws. GLMM is preferred for this type of repeated measures analysis (DeLucia & Pitts, 2002) and allows for variables to depend on model coefficients (i.e. both intercept and slope). We found that inhibitory control was related to the slope, but not the intercept of IGT performance. Participants with poor inhibitory control did not change their strategy over the course of the task (i.e slope was not different from 0), and did not benefit from feedback to shift their preference based on feedback, rather they continued to select from the prepotent, disadvantageous decks. It is, therefore, difficult to compare our results directly to those of Hooper and colleagues (2004) that were the result of a different statistical procedure.

Performance on the IGT was related to some measures of “cool” EF (working memory and inhibitory control) but not others. No significant relationship was seen between IGT performance and measures of sustained attention (GDS omission errors), selective attention (TEA-ch Map Mission), spatial planning (Tower of London), and mental flexibility (TEA-ch Creature Counting and DKEFS verbal fluency). This finding lends support to the notion that, although IGT performance involves some aspects of “cool” EF, it taps into functions (i.e. “hot” EF) that are distinct from most traditional EF tasks. In agreement with this, Verdejo-Garcia and Perez-Garcia (2007) found that the IGT comprised its own factor, unique from other traditional measures of “cool” EF. This also aligns with neuroimaging findings during tasks such as the Tower of London (Wagner,

Koch, Reichenbach, Sauer & Schlusser, 2006), verbal fluency (Abrahams et al., 2003), and continuous performance tests (Simmonds, Pekar, & Mostofsky, 2008) that reveal activation mainly focused in the dorsolateral, rather than ventromedial, portions of the PFC.

Sleep-Disordered Breathing (SDB) and IGT Performance

A final aim was to investigate the effects of SDB on IGT performance. In line with our predictions, we found that AHI was related to IGT performance; individuals with OSA failed to benefit from experience across the task, whereas those with little to no evidence of SDB showed the expected improvement in performance over its course. To our knowledge, this is the first study to assess performance on a task sensitive to ventromedial prefrontal cortical functioning in individuals with SDB of any age, child, adolescent or adult. However, Killgore and colleagues reported IGT impairments (2006) and impaired moral decision making (2007) in adults exposed to experimental sleep deprivation. Thus, impairments in ventromedial PFC functioning may not be specific to OSA, rather, may be related to other types of sleep pathology as well. Indeed, emotional regulation has long been cited as a deleterious effect of sleep deprivation, with studies documenting irritability, impatience, immature humor, lack of regard for normal social conventions, and inappropriate interpersonal behavior associated with sleep loss (Horne, 1993). Furthermore, Dahl and Lewin (2002) have reported pilot findings suggesting that tasks requiring simultaneous challenges of cognitive and emotional processing may be particularly sensitive to sleep deprivation in adolescents. The IGT may be similarly sensitive to sleep pathology, given that it is a decision-making task that taps into both emotional and cognitive functioning.

A potential relationship between OSA and ventromedial prefrontal cortical dysfunction is in line with many other models implicating the prefrontal cortex in disordered sleep (e.g. Beebe & Gozal, 2002; Harrison & Horne, 1997). According to Beebe and Gozal's (2002) model, sleep disruption and blood gas abnormalities prevent the restorative process of sleep, which lead to further chemical and structural injury, which in turn, leads to dysfunction of the PFC. OSA is characterized by a repeated collapsing of the upper airway; during these events, breathing either partially or completely stops. These episodes are associated with brief periods of oxygen desaturation, which in severe cases may produce hypoxemia in brain tissue (Aljadeff et al., 1996). In animal models, intermittent hypoxia has been linked to increased oxidative stress, inflammatory processes and neurochemical changes in the prefrontal cortex as well as the hippocampus, a limbic structure with important reciprocal connections to medial and orbitofrontal cortex, (Kheirandish, et al., 2005; Row et al., 2002, 2003). However, it is unlikely that hypoxia alone can explain the cognitive and behavioral manifestations SDB, especially in children. Sleep fragmentation and deprivation may also play an important role and may, in fact, operate via similar pathophysiological mechanisms (Beebe, 2006). Animals models have also provided evidence of oxidative stress and inflammation in the prefrontal cortex of sleep deprived animals (Everson, Laatsch & Hogg, 2005; Hu et al., 2003). Further research is needed to elucidate the exact mechanisms by which SDB contributes to cognitive and behavioral impairments in humans at different developmental levels.

It may be noteworthy that, in the present study, only the AHI variable (and not the actigraphy-based arousal index or sleep duration variables) was related to IGT

performance. AHI is relatively specific to respiration, while the other two variables relate to a much wider range of factors that can impact sleep. It may be that SDB, and not other aspects of sleep, is particularly relevant to ventromedial prefrontal functioning. However, this is in contrast to previous reports demonstrating that sleep deprivation and disruption, in the absence of SDB, can be sufficient to result in neurobehavioral deficits (see review by Blunden & Beebe, 2006). Furthermore, a number of recent studies have documented impairments in executive functions (Killgore, Grugle, Reichardt, Killgore, & Balkin, 2009), emotional intelligence (Killgore, Kahn-Greene, Lipizzi, Newman, Kamimori, & Balkin, 2008), and increased symptoms of psychopathology (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007) with short-term experimental sleep deprivation alone, without the respiratory effects of SDB. Further research is warranted to determine a potential threshold of SDB or specific physiological markers that are most strongly related to impairment on executive tasks, such as the IGT.

As alluded to above, understanding the impact of SDB on IGT performance may provide the key to interpreting findings related to overall group performance and differences in performance across development. By design, overweight participants were studied because they are at high risk for SDB and other sleep pathology (Beebe et al., 2007) without the confounds that accompany other high-risk groups (e.g., those with craniofacial anomalies). Given that increased SDB, particularly diagnosable OSA, seems to suppress learning effects on the IGT, it makes sense that our current sample tended to learn more slowly as a group than other samples of healthy participants, who are at much lower risk for SDB.

Because the current sample included only adolescents with a BMI $\geq 95^{\text{th}}$ percentile for sex and age, this restricted range made us unable to render any inferences about the effect of BMI (without SDB) on IGT performance in general. In our sample, BMI was not related to IGT performance; however, it is unclear if this relationship would become apparent if a larger range, including healthy weight individuals, were studied. In fact, a relationship may be expected given the building evidence that the physiological consequences of obesity are associated with neurocognitive impairment, possibly even in adolescents and young adults (Gunstad et al., 2006 and 2007). Alternatively, it is possible that reduced cognitive or executive functioning may increase subsequent risk of becoming overweight (Chandola, Deary, Blane, & Batty, 2006). Of note, in the current sample, IGT performance in the AHI < 1 group (i.e. a group with high BMI but no evidence of SDB) was largely comparable to prior studies who did not select for overweight participants.

A final, exploratory finding in the present study was that AHI moderated the relationship between developmental level, as measured by pubertal ratings, and IGT performance. Individuals with OSA did not seem to benefit from experience with the task, regardless of their developmental level. Whether this is due to an immediate (potentially reversible) effect of OSA on some aspect of performance versus a more insidious impact on the development of ventromedial and/or orbitofrontal cortex is not known. However, even if reversible, the impact of OSA during adolescence is potentially substantial for two reasons. First, OSA is unlikely to be transient in this population because (a) the primary contributors to OSA in adolescents, such as overweight, tend to persist over time (Wang, Chyen, Lee & Lowry, 2008), (b) surgical

interventions for OSA in overweight adolescents are much less likely to be curative than in lean, younger children (Mitchell & Kelly, 2004), and (c) non-surgical interventions, such as positive airway pressure (PAP) are often unsuccessful because adolescents have notoriously poor adherence to these interventions (Budhiraja, Parthasarathy, Drake, Roth, Sharief, Budhiraja, 2007). Second, even if OSA were to remit, short-term poor emotional decision-making might have lasting effects on social and behavioral functioning. For example, even short-lived periods of poor decision-making during adolescence can lead to snares, such as a criminal record, incarceration, addiction, poor school record or drop-out, early parenthood, sexually transmitted disease, or injury (Moffitt, Caspi, Harrington & Milne, 2002).

In contrast to participants with OSA, participants with minimal evidence of SDB showed the expected relationship between IGT performance and developmental level: participants who were more advanced developmentally performed better over time on the IGT. This is in line with previous reports suggesting that adolescence is an important period for the development of skills mediated by the PFC, including the ventromedial PFC (Hooper et al., 2004, Crone, Vendel, & van der Molen, 2003). However, one difference between our results and those reported by Hooper et al. and Crone et al. is that, with our data, pubertal status was related to IGT performance, and child age was not. It is unclear as to why other studies found a relationship with age and we did not. It is possible that the relationship between age and IGT performance may have been attenuated by a restricted range in our sample; the number of participants in the middle age range (i.e. 12-13.9 year olds, 49% of the sample) was overrepresented as compared to younger (10-11.9 year olds; 23%) or older adolescents (14-16 year olds; 28%). It is possible that if more

participants were represented at either end of the age spectrum, a significant relationship may have emerged.

Of note, no other studies have investigated the role of pubertal development on IGT performance. There is neuroimaging evidence suggesting that the development of the PFC may be linked more closely with pubertal level than age (Lenroot & Giedd, 2006; Blakemore & Choudhury, 2006). Adolescence is a dynamic period for brain development. Structural imaging studies have shown linear increases in white matter during this time; however more complex changes occur in cortical gray matter, that differ based on brain region. In the frontal cortex, gray matter development follows an inverted U-shaped distribution, that peaks around puberty (around age 11 for girls and 12 for boys). It has been hypothesized that the peak in frontal gray matter at puberty may be related to a wave of synapse proliferation, followed by a period of synaptic reorganization and pruning that is reflected in the volume decreases (Blakemore & Choudhury, 2006). Thus, in normally developing adolescents, the development of executive functioning skills, including the IGT, may be more closely linked to pubertal stage than age.

Limitations and Future Directions

Although this study provides interesting findings regarding the impact of OSA on IGT performance, findings are tempered by several design limitations. The first limitation lies in the sample characteristics and the lack of a lean control group. In the present study, we compared groups of overweight children and adolescents with no evidence of OSA, mild OSA and moderate to severe OSA; however, we did not include a group of lean participants as controls. It is possible that even those participants without OSA

demonstrated cognitive impairments related to other health complications associated with excess weight. In order to fully understand the relationship between IGT performance, development and other tasks of EF, further research should be conducted on healthy adolescents. Additionally, it may have been informative to include a group of lean adolescents with OSA in order to separate the effects of obesity and SDB on IGT performance. However, given that excess weight is the single greatest risk factor for OSA by adolescence (at least among individuals without other syndromes that affect the airway), obtaining such an otherwise healthy lean group of adolescents with OSA will be difficult. A second limitation is with the cross-sectional design of the study. To fully understand the effects of OSA on cognitive development, a longitudinal design is necessary. Further research is also required to determine if the effects of OSA on decision-making ability in adolescence persist into adulthood.

Despite these limitations, the present study provides further evidence to support the growing body of literature suggesting that OSA in children and adolescents is associated with cognitive impairments. This report expands upon previous findings by suggesting that the impairments associated with SDB are not specific to the “cool” aspects of executive functioning. “Hot” executive functioning, or tasks that involve emotional decision-making, are also affected in children and adolescents with OSA. This impairment in decision-making ability may be related to some of the behavioral manifestations of OSA in adolescents. This study also provides preliminary evidence that OSA may impact the development of critical aspects of executive functioning. The underlying neurological changes may be irreversible without appropriate treatment. Thus,

these results provide further evidence to support early detection and treatment in children and adolescents with OSA.

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