REVIEW
Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits

DEAN W. BEEBE 1 and DAVID GOZAL 2
1Children’s Hospital Medical Center, Cincinnati, OH, USA and 2Division of Pediatric Sleep Medicine, Department of Pediatrics, University of Louisville, Louisville, KY, USA

Accepted in revised form 14 January 2002; received 17 July 2001

SUMMARY Obstructive sleep apnea (OSA) is accompanied by significant daytime cognitive and behavioral deficits that extend beyond the effects of sleepiness. This article outlines a causal model by which to understand these psychological effects among OSA patients. The model proposes that sleep disruption and blood gas abnormalities prevent sleep-related restorative processes, and further induce chemical and structural central nervous system cellular injury. This, in turn, leads to dysfunction of prefrontal regions of the brain cortex (PFC), manifested behaviorally in what neuropsychologists have termed ‘executive dysfunction’. Executive dysfunction is proposed to markedly affect the functional application of cognitive abilities, resulting in maladaptive daytime behaviors. The proposed model (1) accounts for the specific psychological phenotype associated with OSA, (2) accommodates developmental components in this phenotype, (3) bridges between physical and psychological phenomena, (4) suggests mechanisms by which the nocturnal disorder might have effects on daytime functioning, (5) is empirically testable, (6) generates unique research hypotheses, and (7) has practical implications. The model is intended to act as a catalyst for future research and as a preliminary guide for clinicians.

KEYWORDS sleep, apnea, adults, children, neuropsychology, prefrontal cortex, cognition

INTRODUCTION Obstructive sleep apnea (OSA) is a frequent and insufficiently recognized condition that is associated with upper airway obstruction during sleep. In adults, obesity, genetic predisposition and abnormal hormonal regulation of upper airway musculature represent the most frequent risk factors (Arens et al. 2000; Guilleminault 1985; McNamara et al. 1994; Skatrud et al. 1999), whereas by far the most common cause of childhood OSA is enlargement of tonsils and adenoids in association with increased upper airway collapsibility (Greene and Carroll 1997; Owens 1998). OSA is frequent, with estimated prevalence of 1–3% in children, 2–4% of adults, and up to 15% in aging people (Ali et al. 2000; Arens et al. 2000; McNamara et al. 1994; Skatrud et al. 1999).

Sleep fragmentation, increased respiratory effort, and intermittent blood gas abnormalities (hypoxemia and hypercarbia) are the most immediate physiologic disturbances associated with the exaggerated increase in upper airway resistance that occurs with sleep onset in OSA patients (Gozal 2000). Such episodic events may in turn lead to systemic and pulmonary hypertension, increased incidence of cardiovascular and cerebrovascular disease, arrhythmias and, in children, failure to thrive (Bradley and Floras 2000; Guilleminault et al. 1994; Marcus et al. 1994; McNamara et al. 1994; Owens 1998; Perkin 1999). The first line of treatment for adult OSA is the application of continuous positive airway pressure (CPAP) via a nasal mask, and surgery is used only in selected cases (Arens et al. 2000;
The relationship between OSA and daytime sleepiness, especially in adults, has long been recognized. However, behavioral research conducted over the past two decades has also documented significant daytime cognitive and behavioral dysfunction that seems to extend beyond that associated with simple sleepiness (see, e.g. Arens et al. 2000; Marrone et al. 1998). The causal mechanism of these psychological effects remains open to debate, and much of the existing literature has been primarily descriptive, rather than based on well-defined theory. In some cases, stroke precipitated by OSA (resulting from transient and cumulative alterations in cerebral vaso-motor reactivity, metabolism, and platelet and endothelial function (Diomedi et al. 1998; Dyken et al. 1996; Mohsenin 2001; Parra et al. 2000) is the immediate and evident cause of neuropsychological disturbance. However, it is unlikely that stroke plays a major role in the vast majority of adult or pediatric OSA patients.

This article presents a model that begins to build a conceptual framework to allow us to better understand the cognitive and behavioral effects of OSA in the majority of individuals suffering from the disorder. There are several reasons to develop such a model. First, the model will clearly link the nighttime medical disorder to its daytime psychological consequences. Clinical experience suggests that many practitioners and medical insurance companies summarily dismiss the psychological effects of OSA simply because they do not understand this link. Second, closing the gap between the medical and psychological aspects of the disorder will encourage clinicians to look beyond the medical status of the patient, thereby promoting earlier consideration and detection of psychological morbidity when making management decisions. Thirdly, and perhaps more importantly, research to date has been hampered by the absence of a formal and testable theoretical model. One sign of advancement in a given scientific realm is that its research becomes theory driven (Barkley 1997a). The formulation of a theoretical model provides structure to seemingly disparate findings, stimulates research by generating novel hypotheses, and guides research methodology. Such a model has been absent in the case of OSA – much has been learned in the last 20–25 years, but the vast majority of published research to date has been exploratory or descriptive in nature.

The theoretical model presented here is intended to act as a catalyst for further research on the daytime effects of OSA and as a comprehensive, albeit preliminary guide for clinicians. Its development was molded by several a priori goals. First, the model should account for the specific psychological symptom picture associated with OSA. Secondly, the model should accommodate developmentally related differences in the symptom picture. Thirdly, the model should bridge between medical and psychological aspects of OSA, and suggest a mechanism by which the nocturnal disorder might have effects on daytime functioning. Finally, as with all theoretical models, the model should be empirically testable, generate research hypotheses, and if possible, have practical implications. A theoretical model that emphasizes prefrontal cortical involvement in OSA appears to meet these criteria. In this article, an overview of this model will be provided, followed by a review of each of its components that summarizes the relevant literature and outlines directions for future research. We will then address developmental aspects of the neurobehavioral manifestations associated with OSA. Finally, preliminary suggestions for the clinical application of the proposed model will be delineated.

MODEL OVERVIEW

The model is schematically summarized in Fig. 1. In brief, patients with OSA experience to some extent sleep disruption and exhibit intermittent hypoxemia and hypercarbia. These disturbances putatively alter the efficacy of restorative processes occurring during sleep and induce a variety of cellular and biochemical stresses that lead to disruption of functional homeostasis and altered neuronal and glial viability within particular brain regions. We suggest that dysfunction of prefrontal regions of the brain cortex (PFC), manifested behaviorally by what neuropsychologists have called ‘executive dysfunction’, is a primary manifestation of the adverse cellular and biochemical events triggered by OSA. In the model, the ‘executive system’ is composed of behavioral inhibition, set-shifting, self-regulation of affect and arousal, working memory, analysis/synthesis, and contextual memory. Executive dysfunction can markedly alter the functional recruitment of cognitive abilities, thereby resulting in mal-adaptive daytime behaviors such as those listed at the bottom of Fig. 1.

The present model is not the first to propose that PFC dysfunction is associated with disordered sleep. Harrison and Horne (1997, 1998, 1999, 2000a, b), Harrison et al. (1997, 2000), and Horne (1988) have cogently argued that sleep-deprived adults display PFC-related cognitive dysfunction. Furthermore, Dahl and colleagues (1996a, b) have also applied a PFC model to account for the relationship between sleep disruption and emotional disturbances in children, while other investigators have made reference to the PFC to account for their research findings (Decary et al. 2000; Feuerstein et al. 1997; Naegle et al. 1995, 1998). However, our proposed model is unique because it accounts for a broader range of cognitive and behavioral pathology than has been previously described, covers a broader developmental span, provides a more detailed account of PFC functions, proposes specific mechanisms underlying PFC dysfunction, and yields specific research hypotheses.

© 2002 European Sleep Research Society, J. Sleep Res., 11, 1–16
The development of this model was prompted by observations suggesting that OSA presents a relatively specific behavioral and cognitive ‘footprint.’ Thus, we will initially describe cognitive and behavioral sequelae, and then move upstream through the proposed etiologic cascade.

**Adverse daytime effects of OSA**

The most heavily investigated and perhaps the most prominent daytime feature of adult OSA is excessive daytime sleepiness, conventionally defined as subjective fatigue or objectively measured sleep propensity. However, adult OSA is also associated with occupational and social failures related to poor planning, disorganization, diminished judgement, rigid thinking, poor motivation, and affective lability (e.g. Day et al. 1999; Doghramji 1993; Redline and Strohl 1999). Childhood OSA is associated with school failure and behaviors reminiscent of attention-deficit/hyperactivity disorder (ADHD) (e.g. Bower and Gungor 2000; Gozal 2000; Guilleminault et al. 2000; Perkin 1999). Though it is tempting to attribute all of these difficulties to excessive daytime sleepiness, doing so requires expansion of the already multidimensional construct of sleepiness to include conceptually distinct cognitive functions. As will be summarized below, such a conceptual agglomeration is inconsistent with current data on OSA. Moreover, such a stance discourages...
investigation of the relationships between disordered sleep, subjective sleepiness, sleep propensity, and various aspects of cognitive functioning. In particular, it discourages examination of a clear area of cognitive pathology in OSA – executive dysfunction.

**Executive dysfunction and OSA**

As defined by neuropsychologists, ‘executive functioning’ refers to the ability to develop and sustain an organized, future-oriented, and flexible approach to problem situations (Denckla et al. 1996; Eslinger et al. 1996; Goldberg 2001; Lezak 1995). The executive functions allow individuals to adaptively use their basic skills (e.g., core language skills, visual-perceptual ability, rote memory capacity) in a complex and changing external environment (Eslinger et al. 1996; Goldberg 2001). For example, persons of high intellect but poor executive functioning may experience occupational and social failure because their verbal discourse is disorganized and disjointed, marked by ‘losing track’ of what was being said, redundant, at times irrelevant or tangential, rigid, or lacking appropriate emotional overtones.

In this section, we divide the executive function ‘family’ into six members – behavioral inhibition, set-shifting, self-regulation of affect and arousal, working memory, analysis/synthesis, and contextual memory. This subdivision is based upon recent theoretical models by Barkley (1997b, 1998, 2000), Barkley et al. (1994), Pennington et al. (1997) and Fuster (1999, 1997). Though we present each executive function individually for heuristic purposes, in fact they are interrelated, and any given ‘executive functioning test’ is likely to tap multiple executive functions (Pennington et al. 1996). Moreover, a given author’s definition and subdivision of the executive functions is generally influenced by his or her realm of investigation. Whereas cognitive neuropsychologists have developed sophisticated tasks that can be conducted in controlled laboratory settings with relatively plentiful healthy subjects, clinical neuropsychologists focus on constructs and measures that differentiate neurologically impaired clinical groups in less controlled settings. These approaches are complementary. Current research on the neuropsychological effect of OSA relies on clinical measures, so we use terms derived from clinical neuropsychology. However, we also cite terms that derive from a cognitive neuropsychology tradition, particularly that adopted by Harrison and Horne (2000a) in their recent review of the effects of sleep deprivation on decision making.

Following is a summary of each executive function and relevant empirical studies of OSA, particularly the case-controlled studies recently reviewed by Engleman et al. (2000). To allow comparisons across domains, and to effectively combine studies that used identical or near identical measures, we report individual or pooled effect size (ES) estimates (Lipsey and Wilson 2001). Effect size refers to the difference between clinical and control group means, expressed in standard deviation units.

The first executive function in the model is behavioral inhibition. As defined by Barkley (1997b):

Behavioral inhibition refers to three interrelated processes: (a) inhibition of the initial prepotent response to an event; (b) stopping of an ongoing response, which thereby permits a delay in the decision to respond; and (c) the protection of this period of delay and the self-directed responses that occur within it from disruption by competing events and responses (interference control) (p. 67).

Prepotent responses generally have immediate survival benefit or have been previously met with a favorable risk-to-benefit ratio, making them the ‘default’ responses that would occur without behavioral inhibition. Behavioral inhibition, defined in this way, is required for Harrison and Horne’s (2000a) construct of ‘appreciation of a complex situation while avoiding distractions’ (emphasis added). One laboratory measure of behavioral inhibition is the Stroop Color–Word Interference Task, which requires test-takers to inhibit the prepotent response of word-reading to name the nonmatching colors in which a series of words are printed (e.g., the word ‘red’ printed in blue ink) (Golden 1978). Adult patients with untreated OSA perform poorly on this task (ES = 0.79, P < 0.05) (Naegele et al. 1995). They also make more impulsive errors than controls on tests of maze completion (ES = 1.6 for moderate OSA, 4.38 for severe OSA, both P < 0.01) (Bedard et al. 1991); they often impulsively move into ‘blind alleys’, even after exhortations not to do so.

The second executive function in the model is set shifting. Closely tied to behavioral inhibition, this involves the ability to flexibly move from one cognitive or behavioral strategy to another. This does not necessarily require self-generation of a new strategy, as patients with frontal lobe lesions may perseverate on a given strategy or behavior while verbalizing a more appropriate response (Diamond and Taylor 1996; Goldberg 2001; Lezak 1995). Set shifting is a necessary but not sufficient function underlying the Harrison and Horne (2000a) concept of ‘thinking laterally and being innovative.’ Clinical measures of set shifting include the perseveration index of the Wisconsin Card Sorting Test (WCST, Heaton et al. 1993); and the second subtest of the Trailmaking Test (Trails B, Heaton 1991). On the WCST, the test taker is required to develop problem-solving strategies based upon examiner feedback, then to switch strategies without warning when the task contingencies change. The WCST perseveration index relates to the latter task: switching cognitive set. Adults with untreated OSA score poorly on this measure (mean ES = 0.55, P < 0.01; Naegele et al. 1995; Redline et al. 1997). Trails B requires the test taker to rapidly alternate between well-established number and letter cognitive sets on a connect-the-dot task (i.e. A-1-B-2,…); untreated OSA patients find this difficult (mean ES = 0.37, P < 0.001, Bedard et al. 1991; Greenberg et al. 1987; Kim et al. 1997; Naegele et al. 1995; Redline et al. 1997).

The third executive function in the model is self-regulation of affect and arousal. This component, which refers to the internal modulation of affective and arousal states to meet a goal
(Barkley 2000), is implied in Harrison and Horne’s (2000a) ‘maintaining interest in outcome’ and, in combination with behavioral inhibition, underlies their construct ‘controlling mood and uninhibited behavior.’ Self-regulation of affect, motivation, and arousal is difficult to assess in a laboratory situation, though anecdotal reports of irritability and affective lability are consistent with a weakness in this executive function. Clinically, the continuous performance tests (CPTs) are relevant, as they require sustained vigilance to a monotonous task over time. Poor CPT performance has been well-documented among individuals with OSA (e.g. Kotterba et al. 1998), and is more prominent towards the end of such tasks than at their beginning (ES $= 0.76$, $P = 0.01$ vs. ES $= 0.22$, $P > 0.20$; Redline et al. 1997). This suggests problems sustaining effort and attention, rather than poor initiation or short-term maintenance of attention.

Working memory (Barkley 1997b, 2000; Pennington et al. 1996, 1997) is an active, extremely short-term memory system, sometimes referred to as a ‘sketch pad’ for visual information and a ‘phonological loop’ for auditory/verbal information (Baddeley 1986). It has both a retrospective function, in which recent information is held ‘on line’ for a brief period, and a prospective function, which actively maintains anticipated events – a necessary feature for effective planning (Fuster 1997). This underlies Harrison and Horne’s (2000a) concept of ‘keeping track of events and developing and updating strategies’ (emphasis added) and, to a lesser degree, ‘assessing risk – anticipating range of consequences.’ The ability to repeat back digit strings or visual sequences, and the ability to mentally reverse the sequences, reflects working memory capacity. Untreated adult patients with OSA perform poorly on such tasks (mean ES $= 0.75$, $P < 0.001$; Greenberg et al. 1987; Naegele et al. 1995; Redline et al. 1997).

The fifth executive function in the model is analysis/synthesis. This involves mentally dismantling old experience/information and synthesizing these pieces in novel ways (Barkley 1997b, 2000). This is the foundation for creative, goal-directed thought and problem solving. Together with set-shifting, analytic/synthetic skills parallel Harrison and Horne’s (2000a) ‘thinking laterally and being innovative.’ This divergent thought process is difficult to measure on formal tests, but neuropsychologists sometimes use fluency tasks. For example, the ability to quickly provide words that start with a given letter, when compared with verbal lexicon and general mental processing speed, indirectly measures mental flexibility and analytic/synthetic skills. Adults with untreated OSA have poor verbal fluency (mean ES $= 0.55$, $P < 0.001$; Bedard et al. 1991; Greenberg et al. 1987; Kim et al. 1997; Naegele et al. 1995), even when their language skills are otherwise normal (Bedard et al. 1991; Naegele et al. 1995).

Finally, ‘contextual memory’ places information into a meaningful time (temporal memory) and space (source memory) context (Pennington et al. 1997). Contextual memory allows the individual to remember when and in what situation information has been learned, which can be dissociated from the content of what has been learned. Temporal source memory corresponds to Harrison and Horne’s (2000a) ‘remembering when rather than what’ concept. We are unaware of any published studies that examine contextual memory in individuals with OSA. However, we include it in the present model because of its known relationship to prefrontal cortical functioning, and because temporal memory is adversely affected by sleep deprivation (Harrison and Horne 2000a, b).

Sleepiness and executive function

Conventionally defined sleepiness cannot account for the executive functioning deficits displayed by patients with OSA. Executive functioning deficits correlate better with the degree of blood gas abnormalities and sleep fragmentation than with either self-reported or objectively measured sleepiness (Bedard et al. 1991; Cheshire et al. 1992). Though it is often held that the effect of sleepiness is most evident on long monotonous tasks (Dinges et al. 1991), many of the executive functioning deficits cited above were found on brief tasks. Moreover, as summarized in the next section, patients whose sleep has been normalized with CPAP may nonetheless continue to display executive functioning deficits. It is also worth noting that prepubertal children with OSA are less likely to manifest daytime sleepiness unless their disease is moderately severe to severe (Gozal et al. 2001a), yet they frequently display executive function deficits (Gozal et al. 2001b). Thus, although excessive daytime sleepiness is an important consideration in the neurobehavioral manifestations of OSA, it is likely that its effects are rapidly reversible with sleep recovery during treatment, and as such cannot account for the more persistent executive dysfunction of OSA. If this assumption is further supported by studies designed to examine this issue, then we need to consider the possibility that neurological damage has occurred as a result of sleep-disordered breathing, and that this damage may be only partially reversible. This has major implications for the approach to diagnosis and treatment of patients with OSA.

Summary of past findings

Individuals with untreated OSA display executive dysfunction that is not attributable to simple sleepiness. In fact, aside from sleepiness, executive dysfunction appears to be the most prominent area of cognitive impairment in untreated sleep-disordered breathing. Studies that have included multiple cognitive tests have generally found poorer performances of untreated adults on measures of executive functioning than on measures of visual ability (Bedard et al. 1991; Greenberg et al. 1987), verbal ability (Bedard et al. 1991; Greenberg et al. 1987; Hayward et al. 1992; Naegele et al. 1995), and long-term memory (Bedard et al. 1991; DeAlberto et al. 1996; Feuerstein et al. 1997; Hayward et al. 1992; Naegele et al. 1995; Redline et al. 1998). Recent data from our laboratories further extend such observations to the pediatric age. Children with OSA perform more poorly on a composite executive functioning measure than on measures of verbal or visual ability (Gozal
et al. 2001b). Though we are only beginning to use formal neuropsychological tests to assess the effects of pediatric OSA, children with sleep-disordered breathing are reported by their parents to be unusually inattentive, hyperactive, impulsive, aggressive, and rebellious (Ali et al. 1996; Stradling et al. 1990). Findings from such psychiatrically focused behavior rating scales are indicators of adverse daytime effects rather than the mediating factor of executive functioning. Even so, these findings are consistent with poor behavioral inhibition and diminished self-regulation of affective and arousal state. A similar pattern of behavior ratings is found in ADHD, a neurodevelopmental disorder that centrally involves executive dysfunction (Barkley 1997a, b, 1998, 2000).

Though application of effective CPAP treatment during sleep has been reported to improve daytime functioning, residual deficits on tests of executive functioning remain particularly evident (Bearpark et al. 1987; Bedard et al. 1993; Feuerstein et al. 1997; Naegele et al. 1995). Similarly, though preliminary studies of childhood OSA have also suggested that improvements occur in post-treatment daytime behavior regulation (Ali et al. 1996; Gozal 1998; Guilleminault et al. 1981; Rains 1995; Stradling et al. 1990), most of these studies entailed uncontrolled clinical trials or were subject to rater biases. There is some evidence that residual learning deficits may occur long after sleep-disordered breathing has resolved in children (Gozal and Pope 2001).

Implications for future research

The following list of potential research hypotheses is based heavily upon reviews by Barkley (1997b), Grafman et al. (1999), Harrison and Horne (2000a) and Pennington et al. (1997). The interested reader is encouraged to examine these reviews, as well as citations listed with each hypothesis, for conceptual and methodological details. Replication of previous findings has merit, but we focus on tasks and hypotheses not yet addressed in the OSA research literature. Though the tests listed below often tap multiple executive functions, they are listed with the most prominent function for ease of presentation. Strong research in this area involves dissociating effects on executive function tests (which are expected to be significant) from those obtained on tests of more basic skills (which are expected to be negligible). Examples of dissociations are summarized below.

Deficits of ‘behavioral inhibition’ should be evident in adults and school-age children on go-no-go tasks (Diamond and Taylor 1996; Trommer et al. 1988), A–X paradigm continuous performance tests (Gordon et al. 1983), and antisaccade tasks (Guitton et al. 1985). In younger children, modified Stroop-like tasks (Diamond and Taylor 1996; Gerstadt et al. 1994) and structured observations such as the ‘snack delay’ and ‘wrapped gift’ paradigms (Kochanska et al. 2000) should similarly reveal inhibitory deficits. A dissociation is expected between significant effects on behavioral inhibition tasks and negligible effects on measures of task comprehension and compliance (e.g. verbalizing the rules of a go-no-go task, inhibiting responses to unattractive stimuli during an observation task).

Poor set-shifting should be evident on intradimensional/extradimensional shift tasks (Hughes et al. 1994) and applied problem-solving ‘games’ that involve changing reinforcement contingencies, such Harrison and Horne’s (1999) Masterplanner, especially if responses to these games are scored for perseverative errors (similar to the WCST). One key dissociation that was demonstrated in a sleep deprivation experiment (and should be assessed in OSA) is between performance on Masterplanner vs. performance on a convergent reasoning task that did not require set-shifting (Harrison and Horne 1999). In childhood, the ‘Creature Counting’ subtest from the ‘Test of Everyday Attention for Children is sensitive to set-shifting difficulties in other populations (Manly et al. 1999) and is expected to be sensitive to untreated OSA as well. The relevant dissociation is between poor performance on Creature Counting vs. intact performance in simple counting ability and task comprehension.

As noted above, ‘self-regulation of affect and arousal’ is difficult to assess in the clinical or laboratory setting. Instead, validated rating scales such as the Behavior Rating Inventory of Executive Functioning (Gioia et al. 2000) may be used to test the hypothesis that individuals with OSA have: (1) heightened reactions to emotionally charged immediate events and (2) decreased ability to modulate overt emotional reactions based upon their social appropriateness. Such deficits should be dissociated from ratings of behaviors less closely associated with executive functioning, such as social isolation and anxiety (e.g. Reynolds and Kamphaus 1992).

Working memory deficits are expected on the n-back test paradigm, in which test-takers attend to a series of verbal or visual stimuli, then respond to a target by indicating the stimulus that was presented a prespecified number of places earlier (Kwon et al. 2001; Nelson et al. 2000; Thomas et al. 1999). Poorer performance, relative to controls, is expected on such tasks than on simple vigilance tasks in which the individual is asked to respond to the target stimulus only (essentially a zero-back condition). In young children with OSA, delayed response and delayed alternation tasks (Espy et al. 1999) are expected to reveal working memory deficits. Here, task performance is expected to be much worse than on analogous tasks in which the stimuli are fully in view at all times (thereby minimizing working memory demands).

Complex games such as Masterplanner may also be used to assess for analysis/synthesis deficits if responses are coded for efficiency of problem-solving after successful set-shifting. Qualitative scoring of complex visual-construction tasks (e.g. the Rey Complex Figure; see Bernstein and Waber 1996) should reveal a haphazard or piecemeal approach, despite normal performance on construction tasks in which visual-perception or visual-motor skills (but not visual planning skills) are stressed (e.g. Beery 1982).

Finally, contextual memory deficits are expected on tasks reviewed by Grafman et al. (1999). The critical comparison is between contextual memory indexes (e.g. sorting accuracy, free

sequence production) and recognition memory (typically true-false or multiple-choice items). Such an approach is sensitive to experimentally induced sleep deprivation (Harrison and Horne 1999).

When testing these hypotheses, it is critical that the methods used truly place stress on executive functioning. Such methodological issues have been discussed in detail elsewhere (Boone et al. 1999; Denckla et al. 1994, 1996; Pennington et al. 1996; Robbins et al. 1998). Generally, the tasks should be novel, and it may be necessary to introduce unexpected changes in the demands of a task during its course to assess cognitive flexibility. The goal of the task should be clear, but how to reach it should be intentionally vague. Because executive dysfunction causes inefficient task completion even when the task is ultimately completed accurately, it is important to examine the process of work performance, and to make tasks time-sensitive to highlight this inefficiency. If measuring self-regulation of affect and arousal, it is important to limit intrinsically motivating aspects of the tasks, and to avoid external motivators for success (e.g. rewards) altogether. All tasks must be developmentally appropriate in content and difficulty. Finally, the tasks must also be psychometrically sound, with evidence of strong reliability, validity in the measurement of executive functioning, and broad enough ‘ceilings’ and ‘floors’ to ensure meaningful variability. All of the tests listed above have both theoretical and empirical support for their validity in measuring executive functioning and/or the effects of known prefrontal cortical pathology (e.g. Pennington et al. 1997).

Prefrontal cortical dysfunction and OSA

There are two lines of evidence that implicate the prefrontal cortex (PFC) in OSA. The first relates to the specific cognitive deficits seen in OSA. The second relates to the unique role of the PFC in sleep and sleep deficit.

Cognitive evidence

Studies of patients with PFC lesions and, more recently, studies using functional neuroimaging have confirmed that successful performance on executive functioning tests requires intact prefrontal processing (e.g. Barkley 2000; Fuster 1999; Goldberg 2001; Kolb and Whishaw 1996; Malloy and Richardson 1994; Rolls et al. 1998). Specific PFC regions heavily subserve particular executive functions (e.g. behavioral inhibition is subserved by orbital PFC, working memory has a dorsolateral PFC focus; Barkley 2000). However, the conceptual interrelationship between the executive functions is paralleled by abundant neuronal connections within and between prefrontal regions. Indeed, it the multitude of connections within the PFC and between it and other brain regions that allows it to coordinate cognitive and behavioral output in an ‘executive’ manner (Goldberg 2001). Under these circumstances, it is not surprising that poor performance on a given executive function test may relate to dysfunction of a more primary cognitive skill. For example, an individual with a primary language deficit may score poorly on an executive functioning test that incidentally requires language processing (e.g. verbal fluency). However, as noted earlier, the cognitive deficits seen in OSA tend to be much greater on executive functioning tests than on tests of more basic cognitive abilities, and these executive functioning deficits occur regardless of whether the task places incidental demands on verbal or spatial functioning. This relative specificity of cognitive effects argues for localization of the dysfunction within the PFC, or within its rich interconnections.

Evidence from sleep and sleep deficit

Functional neuroimaging data suggest that there are marked regional fluctuations in brain metabolism across the stages of sleep (Braun et al. 1997, 1998; Buchsbaum et al. 1989; Madsen 1993; Maquet et al. 1996, 1997, 2000; Finelli et al. 2000). Although the pattern of fluctuation is complex, two findings are particularly relevant to the present discussion. First, whereas the majority of other structures of the brain are active at some point during sleep, the PFC displays reduced activity across all sleep stages. Second, the PFC appears functionally disconnected during sleep from other regions with which it normally interacts during daytime hours (Braun et al. 1997, 1998; Hobson and Stickgold 1998; Maquet 2000). These findings may reflect a unique requirement for ‘recalibration’ of PFC circuits without input interference from other brain regions (Dahl 1996b). Horne (Harrison and Horne 2000a; Horne 1988) has maintained for some time that the PFC is the ‘hardest working’ region of the brain during wakefulness, necessitating the greatest recovery during sleep. Indeed, recent quantitative EEG work suggests that frontal regions are differentially sensitive to sleep deprivation and recovery sleep (Finelli et al. 2001), and that this effect is related to time awake rather than circadian influences (Cajochen et al. 2001).

If the PFC has a unique requirement for sleep-related recovery, then disturbances in sleep should result in both diminished performance on measures sensitive to PFC functioning and alterations in cerebral response to such tests. Indeed, experimentally induced sleep deprivation and disruption differentially affect executive functioning (Fallone et al. 2000; Harrison and Horne 1997, 1998, 1999, 2000a, b; Harrison et al. 1997, 2000; Herscovitch et al. 1980; Horne 1988; Lewin and Glaubman 1975; Pilcher and Huffcutt 1996; Randazzo et al. 1998; Reichardt et al. 2000; Wimmer et al. 1992). Furthermore, functional neuroimaging and magnetic resonance spectroscopy have documented changes in prefrontal metabolism and neurochemistry following sleep deprivation in healthy adults (Dorsey et al. 2000; Koves et al. 2001; Thomas et al. 1993, 1998). Using different methodologies, Drummond et al. (1999) and Thomas et al. (2000) independently found that sleep deprivation results both in poor performance on tasks involving working memory and in diminished activation of the PFC in response to these tasks.
Summary of previous findings

The specific behavioral ‘footprint’ of OSA, as well as research related to sleep and sleep disruption in general, suggest PFC dysfunction in OSA. However, considerable research is needed to better confirm and detail selected aspects of PFC dysfunction.

Research implications

The recent refinement of functional neuroimaging techniques has allowed for unprecedented views of the brain at work. This family of techniques seeks to localize the specific brain regions involved in particular mental and behavioral activities. The studies by Drummond et al. (1999, 2000, 2001) illustrate the potential and pitfalls of this line of research. They used functional magnetic resonance imaging (fMRI) to examine the effects of sleep deprivation on cognitive functioning. Whereas a working memory task activated PFC in well-rested young adults, PFC activation was diminished in the same subjects following 35 h of sleep deprivation. However, in these subjects, a verbal learning task and a ‘divided attention’ task (verbal learning + working memory) each elicited increased activation of the PFC following sleep deprivation. These data were based upon a small sample (n = 13) of highly educated (mean ed. 16.5 years) young adults, and should be interpreted cautiously. Even so, the findings highlight the complexity of functional imaging interpretation. Because sleep disorders result in inefficient performance, rather than an inability to perform, the individual may activate unusual neural processing pathways that may not themselves be functioning well. Although subjective sleepiness correlated with PFC activation in response to Drummond and colleagues’ verbal learning and divided attention tasks, the degree of neuronal activation was unrelated to performance on either task. Thus, we could argue that the PFC was recruited to assist in memory or divided attention processing after sleep deprivation, but failed to contribute in a substantive manner because it was itself impaired. We would therefore anticipate that in future functional imaging studies patients with OSA will display poor scores on executive functioning tests and diminished PFC activation during these tests relative to control subjects. Moreover, tests of skills other than executive function may elicit PFC activation for patients with OSA that does not occur in healthy controls. However, recruitment of PFC under such conditions is not expected to improve task performance (i.e. level of PFC activation will not correlate with task performance within the OSA group).

Refined EEG-based techniques may also be applied in future research. These techniques allow for increasingly specific measurement of cortical electrical activity in subjects who cannot meet the demands of functional neuroimaging (e.g. too young to lie still during imaging: Bell and Fox 1992; Dawson 1994). In adults with OSA, evoked potential techniques have documented abnormal event-related electrical activity that is consistent with PFC dysfunction (Kotterba et al. 1998; Neau et al. 1996; Sangal and Sangal 1997). This technology should also be applied to pediatric OSA. EEG-based techniques might also document localized alterations in the PFC during targeted psychological tasks. Such studies are currently underway in our laboratories, but no published report has yet attempted to correlate sleep-related EEG response to tasks known to rely heavily upon PFC integrity, even though similar approaches have been applied to the study of other patient populations. For example, children with ADHD have been found to have altered frontal EEG activity in response to sustained attention and behavioral inhibition tasks compared with healthy controls (Pliszka et al. 2000; Silberstein et al. 1998). It will be a worthwhile research endeavor to apply topographically sensitive EEG and evoked potential techniques to the study of OSA neuropsychological deficits. In such research, the driving hypothesis would be that OSA elicits abnormalities in PFC activity, especially during activities that demand high levels of executive functioning, and that such deficits are differentially correlated to the sleep and gas-exchange alterations that characterize OSA.

OSA, restoration during sleep, and structural aberrations

In the model, the effect of OSA on PFC dysfunction is mediated by a disruption in the restorative features of sleep and/or by a structural or chemical aberration. Included to simulate future research, this is its most speculative stage, largely because of the relative paucity of consensus on the neurobiological effects of sleep in general, and specifically of sleep-disordered breathing.

Although the exact function of sleep remains elusive, it is likely to play a restorative role, particularly within the CNS (Horne 1988; Madsen 1993; Maquet 1995). Based on functional neuroimaging and EEG findings, as well as studies of the cognitive effects of sleep deprivation, several investigators have suggested that sleep is particularly important for restoring PFC functions (Cajochen et al. 2001; Dahl 1996b; Finelli et al. 2001; Horne 1993; Maquet 1995). Indeed, sleep may be the only time when such restoration is possible, as the PFC is one of the most active brain regions while humans are awake, even during conscious rest (Binder et al. 1999). At present, such restorative processes remain poorly understood at the cellular level; Benington (2000) recently reviewed several hypotheses and found shortfalls in each. However, if we assume a more macroscopic view, it is reasonable to assume that, insofar as these processes require extended periods of sleep, disruption of sleep continuity can prevent homeostatic process(es) from taking place. In addition, limitation in tissue oxygen delivery (i.e. hypoxia) and decreases in intra- and extra-cellular pH (both hypoxia and hypercarbia) could also adversely affect sleep-related functions by creating a suboptimal environment for any number of cellular processes that have been implicated in restoration (e.g. mitochondrial integrity, protein synthesis, gene regulation).

Sleep disruption and sleep-related blood gas abnormalities can also lead to biochemical changes within the CNS.
Although rarely addressed in the OSA literature, there is evidence that sleep disturbances affect neurochemical systems. For example, individuals with major depressive disorder display a temporary improvement in their symptoms after one night of total sleep deprivation, suggesting a short-term antidepressant effect (e.g. Dahl 1996b; Dahl et al. 1999). Bedard et al. (1993) also reviewed research suggesting that synthesis of monoamines and acetylcholine may be disrupted by brief or intermittent hypoxemia, and in fact such neurochemical shifts may be particularly prominent in the frontal lobes (Dorsey et al. 2000).

Disruption of neuroanatomical integrity is also a possible consequence of OSA. Though we are unaware of carefully conducted studies of neural structure in OSA, the persistence of post-treatment cognitive difficulties has led some investigators to suggest that irreversible anoxic brain injury can occur in OSA patients (Bedard et al. 1993; Kotterba et al. 1998). This injury may be subtle. Despite having apparently normal MRI brain scans, alterations in markers of neuronal integrity can be identified in OSA patients when using more sensitive techniques such as magnetic resonance spectroscopy (MRS, Kamba et al. 1997).

One of many potential mechanisms of neuronal damage involves the neurotransmitter glutamate. During transient ischemia or hypoxia, increased glutamate release occurs into the synaptic cleft, and can lead to overstimulation of glutamate receptors. These receptors, and more specifically N-methyl-D-aspartate (NMDA) receptors, have been extensively implicated in neuronal excitotoxicity (Engelsen 1986; Fung 2000; Schousboe et al. 1997). Of interest to our proposed model, rats exposed to chemical hypoxia with carbon monoxide displayed an immediate and significant increase in glutamate release, followed days later by neuronal damage that was particularly striking in the frontal cortex (Piantadosi et al. 1997). More recently, work from our laboratories (Gozal 2000; Gozal et al. 2001c) was able to correlate structural abnormalities to behavioral outcomes in an animal model of simulated sleep apnea. Rats exposed to 2 weeks of intermittent hypoxia during sleep displayed poor maze learning and increased neuronal apoptosis in particular regions of the hippocampus and the overlying cortical region. Furthermore, neuronal cell loss was particularly prominent among NMDA glutamate receptor neurons. Ongoing research would further suggest that the PFC is particularly vulnerable to the cyclical hypoxia of OSA, (D. Gozal, E. Gozal and B.D. Row 2001, unpublished observations), and that the developing brain exhibits a unique window of vulnerability to OSA (Gozal et al. 2001d).

Summary of past findings

There is indirect evidence that OSA-related disruptions in the restorative process of sleep may differentially affect PFC-related cognitive functions. The scant evidence published thus far also suggest the presence of neurochemical and/or anatomical alterations that may preferentially involve the PFC. Ongoing animal studies have expanded our understanding of these structural–functional relationships, and hold significant promise in clarifying the link between the sleep and gas exchange abnormalities of OSA and their cognitive and behavioral consequences, particularly as they relate to the mechanisms underlying cellular injury, plasticity, and repair.

Research implications

The model proposes sleep-associated restorative processes that might be experimentally manipulated. A similar research paradigm has been applied to declarative memory consolidation, which seems to be facilitated during sleep (Deming et al. 1991; Plihal and Born 1999; Robins 1999; Smith 1995; Tilley et al. 1989). Based upon an understanding of the chemical processes associated with sleep and those associated with memory consolidation, Plihal and Born (1999) were able to chemically block sleep-associated memory consolidation in healthy young adults. It is predicted that, once restorative sleep processes are better understood, artificially blocking these processes in healthy subjects will result in daytime evidence of PFC dysfunction. Conversely, adverse neurochemical and cellular injury effects might be pharmacologically blocked once we better understand the mechanisms involved in such OSA-induced damage. For example, therapeutic interventions through such antioxidants or agents that enhance the expression of antiapoptotic signaling molecules may selectively block a neuronal injury-related pathway elicited by the cyclical oxygen deprivation and re-oxygenation, and provide a useful adjunct to OSA treatment as well.

As mentioned above, the neuroanatomical changes associated with OSA are expected to be subtle. It is predicted that in animal (especially nonhuman primate) models of OSA: (1) microscopic structural aberrations will be most evident in frontal cortical tissues, (2) the severity of the OSA-like model will be closely related to the degree of PFC injury and to its neurobehavioral measures (e.g. applying Goldman–Rakic’s landmark methods to study PFC functions in primates; see Goldman–Rakic et al. 1998), and (3) the degree of behavioral dysfunction will correlate with the delicate balance between neuroanatomical injury and repair. In the clinical setting, research using MRS and functional imaging is expected to document particular neurochemical, metabolic, and microcirculatory alterations in the PFC of patients with OSA (see Dorsey et al. 2000) that will closely covary with the severity of sleep and/or blood gas disturbances. The extent and severity of these alterations is further expected to correlate with the severity of cognitive dysfunction, and may be most prominent among patients with persistent cognitive impairments despite OSA treatment.

Primary features of OSA

At the top of the model are two primary medical features of OSA: sleep disruption and intermittent blood gas abnormalities, hypoxemia and hypercarbia. As discussed earlier,
disrupted sleep is sufficient to cause significant executive dysfunction but is fully reversible once sleep integrity is restored. However, it is unclear whether sleep disruption is the necessary priming mechanism for the cognitive disturbance experienced by adults with OSA (Bedard et al. 1991; Cheshire et al. 1992; Kingshott et al. 1998; Kotterba et al. 1998), which in turn will increase vulnerability to the injurious effects of hypoxemia and hypercarbia. The role of sleep deprivation in pediatric OSA is even less clear. Children with OSA have far fewer frank obstructive events than adults, instead displaying sustained periods of increased upper airway resistance associated with gas exchange abnormalities, a situation that has been termed obstructive hypoventilation (Arens et al. 2000; Carroll and Loughlin 1995a; Marcus et al. 2000). Some children with OSA experience few if any frank sleep arousals (Carroll and Loughlin 1995a). While arousals are not the only potential causes of sleep disturbance (e.g. restlessness or increased ventilatory effort might disturb sleep; Carroll and Loughlin 1995a), preliminary reports suggest that sleep architecture, when evaluated with the currently available clinical tools, is grossly intact in pediatric OSA (Arens et al. 2000; Marcus et al. 2000). Thus, though sleep disturbance may be a primary cause of daytime cognitive and behavioral disturbance, the partial reversibility of such disturbances strongly suggests that other mechanisms are involved, likely to include the episodic asphyxia of OSA (Arens et al. 2000; Loughlin et al. 2000). Indeed, blood gas measures significantly correlate with cognitive test performance in adults with OSA or even with ‘heavy snoring’ (Bedard et al. 1991; Berry et al. 1986; Block et al. 1986; Cheshire et al. 1992; Findley et al. 1986; Kotterba et al. 1998; Montplaisir et al. 1992; Naegle et al. 1995). However, this correlation is moderate at most – around the 0.3–0.4 range – raising questions about the sensitivity of our current methods in assessing physiologically relevant hypoxia and hypercarbia at the end-organ tissue level. Alternatively, we can surmise the hypothesis that gas-exchange abnormalities may play a peripheral, albeit synergistic role with sleep disruption, in eliciting the neurocognitive abnormalities of OSA. This controversial point is even more obscure in childhood OSA, and clinical cutoffs for blood gas abnormalities have been arbitrarily defined, without any consideration given to which blood gas thresholds are associated with end-organ injury (Arens et al. 2000; Carroll and Loughlin 1995b; Loughlin et al. 2000).

Summary of past findings

Sleep disruption, especially in adults, and blood gas abnormalities in both adults and children, are primary features of OSA. Both have been linked to cognitive dysfunction, but their relative contributions to this dysfunction remain unclear.

Research implications

Current theoretical models suggest that sleep-disordered breathing falls on a spectrum from normal breathing to frank OSA (Greene and Carroll 1997; Loughlin et al. 2000; Owens 1998; Perkin 1999). However, studies that have correlated disease factors with cognitive outcome have generally focused on limited portions of this spectrum. It is predicted that studies that cover a wider range of sleep-disordered breathing will produce more robust correlations between daytime cognitive functioning and disease factors than have been previously reported. Findings should be bolstered by methodologies that include relevant subject matching (e.g. matching by age, education, blood pressure or other marker for cerebrovascular integrity, or by prospective identification of individual vulnerability markers). Further, it is expected that duration of illness will predict the presence and persistence of cognitive impairment.

Blood gas abnormalities and sleep disruption are expected to correlate with direct measures of PFC functioning, PFC chemical and structural integrity, and sleep restorative processes, once such measures are developed. Correction of nocturnal breathing should lead to at least partial reversal of these indexes of PFC dysfunction in all but the most severe and prolonged cases. However, to achieve such goals, we may have to refine our measurements of tissue oxygenation and pH changes, and apply novel or existing technologies such as near infrared spectroscopy to the continuous assessment of brain tissue oxygenation, rather than rely on peripheral extremity oxyhemoglobin saturation.

The relative contribution of hypoxia and sleep disruption (or their interaction) in producing the detrimental effects of OSA remains unclear. Neuropsychological studies of patients with OSA have been complicated by covariance between these factors, and attempts to compare OSA patients with other conditions that have superficially similar medical features are fraught with confounds. For example, Roehrs et al. (1995) compared the neuropsychological functioning of patients with OSA to those with chronic obstructive pulmonary disease. Significant differences were found on two of 14 tests, and both groups displayed significant deficits compared with norms on a number of tests. Such ambiguous results can be cited as evidence for or against a specific effect of sleep disruption on functioning in OSA, but close examination of the groups raises questions about either interpretation. In addition to differing in level of sleep disturbance, the groups were known to differ systematically in the nature of the hypoxic events (intermittent vs. chronic), whether or not the events were ongoing (i.e. untreated vs. treated), race and age. Unstated, but also potentially influential, were disease duration and severity. Our goal here is not to dismiss that study, which has significant merit, but to highlight the complications that have arisen in clinical research in this area.

Improved neuroimaging techniques may allow for better documentation of localized oxygen availability and consumption during and between apneic events in clinical samples. Positron emission tomography (PET) scans have documented oxygen extraction aberrations other conditions (e.g. Bednarczyk et al. 1998), but the temporal resolution of PET (≥ 2 min) is insufficient to visualize acute changes associated with apneic events. The MRI-based technologies have better temporal and spatial resolution than PET and are sensitive to
changes in oxygenation. However, they have had limited use in sleep research caused by difficulties maintaining sleep in an immobile, noisy state. Development of ‘silent’ MRI scanners is in process (Frank 2000) and has exciting implications, but has not yet been applied to OSA. In addition to human studies, animal models and studies of in vitro tissue samples allow for precise experimental manipulation of sleep continuity and oxygen supply. Ongoing work by the second author (DG) is beginning to explicate the potential role of intermittent hypoxia on rats at the cellular, tissue, and behavioral level (Gozal 2000; Gozal et al. 2001c, d).

**OTHER RESEARCH QUESTIONS**

Several other OSA-related factors are worthy of investigation, though specific hypotheses are not proposed here. The effect of comorbid conditions such as hypertension, cardiac complications, central apneas, daytime hypoventilation, or behavioral sleep disorders on daytime cognitive functioning remains unclear. Similarly, the potential contribution of hormonal changes in OSA in affecting daytime cognition and behaviors has not yet been explored. Individual susceptibility and tolerance factors clearly emerge as important areas of future investigation. Finally, cognitive and behavioral outcomes of any medical condition such as OSA may be modified by personal and environmental factors (e.g. Yeates et al. 2000), such as gender, age at onset (and treatment), premorbid cognitive and emotional function, and the presence of a supportive family, social, and/or environmental network.

**DEVELOPMENTAL ISSUES**

One puzzling aspect of OSA is the difference in behavioral manifestations of prepubertal children vs. adults. Children with OSA display an overlay of hyperactive behaviors and poor impulse control that is less evident in adults with this disorder. Indeed, children with OSA are often misdiagnosed as having ADHD (Chervin et al. 1997; Harnish et al. 2001a, b), the symptoms of which follow a developmental course similar to that seen in OSA. Most children with ADHD have prominent problems with impulse control and behavioral regulation (Barkley 1998). As in OSA, these childhood ADHD symptoms diminish over time, bringing symptoms of inattention and poor judgement to the fore during adult age. Of note, the dominant theory of neuropathology in ADHD clearly focuses around PFC dysfunction (Barkley 1997b, 1998, 2000; Barkley et al. 1994).

It is therefore reasonable to use the available ADHD literature as guidance for the developmental differences in daytime symptoms associated with OSA. At least three nonmutually exclusive possibilities emerge from this vast body of literature. One possibility is that behavioral abnormalities emanating from OSA during childhood persist into adulthood, but are less often noted by others. Carefully controlled studies of ADHD in adults have documented ongoing impulsivity, disorganization, inattention, and social problems that are more subtle and do not pose as great a challenge to others (e.g. parents, teachers) (Barkley 1998). Similarly, carefully controlled studies have documented inattention and impulse control problems in adults with OSA (Bedard et al. 1991; Feuerstein et al. 1997; Kotterba et al. 1998; Naegle et al. 1995).

A second possibility is that developmental differences in OSA characteristics and in vulnerability result in different behavioral effects. Several reviews have summarized key differences in the medical features of OSA in children compared with adults (Arens et al. 2000; Brouillette et al. 1984; Carroll and Loughlin 1995a, b; Marcus et al. 2000; Owens 1998; Redline and Strohl 1999; Rosen 1996). While five obstructive events per hour of sleep would be viewed as minimal if any disease in adult subjects, such a respiratory disturbance index would be considered to reflect significant disease requiring treatment in prepubertal children. In addition, whereas adults with OSA typically experience intermittent hypoxic episodes and sleep arousals, prepubertal children more often experience obstructive hypventilation without frank arousals. As noted earlier, the pathophysiological mechanisms leading to OSA differ, and it is likely that the duration of OSA differs as well between adults and children. Given that sleep disruption is cited as a cause of sleepiness in adults with OSA, the relatively preserved sleep architecture in prepubertal children may protect against daytime sleepiness (Brouillette et al. 1984; Carroll et al. 1995; Marcus et al. 2000).

A third possibility relates to brain maturation processes enhancing the vulnerability of PFC to OSA disruption. The PFC is one of the last areas of the brain to mature, with some functional components not completing maturation until adolescence or even later (Fuster 1997). Though PFC-mediated behaviors are evident as early as infancy and preschool years (Diamond 1990, 1996; Diamond and Taylor 1996), children do not reach adult levels on many executive functional tasks until age of 10–12 years (Luciana and Nelson 1998; Welsh et al. 1991). As such, the peak period of OSA incidence in childhood may constitute a period of particular susceptibility to both intrinsic and extrinsic disruption in PFC (Gozal et al. 2001d).

The potential for long-term effects is of particular concern in children (Gozal et al. 2001d). First, OSA-mediated injury to the developing PFC may be only partially reversible, despite increased maturational plasticity. Second, the cognitive and behavioral effects of OSA may directly impact on the child’s learning and social development, altering his or her developmental potential (Hansen and Vandenberg 1997). Childhood is a critical time for acquiring core academic and social skills, and repeated failures at critical stages of development may fundamentally influence the child’s motivation, self-image, and approach to the world. The longer OSA remains untreated, the more likely the child’s environment will expect, and inadvertently reinforce, poor academic and social functioning. This sort of internal–external interplay (biological and psychosocial interactions), has been described in the developmental etiology of ADHD (Taylor 1999), and could be applied to pediatric OSA. Given the evidence of long-term cognitive deficits in
adult patients, our preliminary findings of long-term scholastic difficulties in children with sleep-disordered breathing (Gozal and Pope 2001) are particularly concerning and should warrant serious consideration.

CLINICAL APPLICATIONS OF THE MODEL

Despite the ongoing research efforts, both the lay public and many professionals still fail to recognize OSA (BaHammam 2000; Richards and Ferdman 2000). The daytime effects of OSA are often misattributed to personality issues in adults, and to a learning disability or to psychiatric disorder in children. Such misdiagnoses delay disease detection, prevent the implementation of necessary treatments, and expose patients to the secondary medical complications of OSA. Thus, a major clinical implication of the present model strongly contends that the public and medical and psychological care professionals should be educated. Stated simply, sleep-disordered breathing causes daytime cognitive and behavioral symptoms, a model of causality has been outlined, and medical treatment is available and has the potential to improve the individual’s quality of life, particularly if implemented early in the course of the disease.

A second implication relates to treatment. Like the medical sequelae of OSA (e.g. cardiovascular complications), daytime psychological sequelae should also be considered and evaluated when making treatment decisions. In addition to diminishing the overall quality of life, the daytime effects of OSA can have a long-term impact by leading to scholastic, occupational, and relationship failures. Moreover, such cognitive and behavioral effects suggest underlying neurological changes that may become irreversible without adequate treatment. Thus, practicing sleep professionals should routinely inquire about the psychological functioning of individuals presenting with signs of sleep disordered breathing. Beyond sleepiness, particular attention should be paid to executive dysfunction and its impact on daily functioning, and this should ultimately lead to timely referrals and consultative involvement of mental health professionals. If cognitive evaluation is undertaken, it will be critical to directly assess executive functioning, rather than rely on tests of basic cognitive skills (e.g. vocabulary) or measures that only partially reflect executive issues (e.g. intelligence tests). Behavioral assessments and interventions derived from the executive functioning model (e.g. Barkley 1998; Denckla et al. 1993) may be important if the medical treatment is delayed, if the treatment(s) do not correct OSA, or if the patient continues to display cognitive or behavioral deficits despite successful medical treatment.

Conversely, individuals who display evidence of executive dysfunction, including children with symptoms of inattention, hyperactivity, impulsivity, and emotional lability, should be screened for signs of sleep disordered breathing. Clinicians treating adults whose occupational, interpersonal, or cognitive functioning has declined concurrent with an increase in snoring and/or daytime sleepiness should be alert to the possibility of OSA. Because clinical history and symptoms are insufficient to make a definitive diagnosis, positive screening results should yield a referral to a sleep center that can conduct more thorough evaluation. When psychiatric and/or cognitive disorders are found to be comorbid with OSA, the sleep disorder deserves treatment in its own right.

CONCLUSION

This article outlined a model by which OSA causes impairments in daytime cognitive and behavioral functioning via disruption of prefrontal cortical processes. By design, it accounts for the specific symptom picture associated with OSA, accommodates developmental changes in this symptom picture, bridges the boundary between the physical and behavioral, suggests a mechanism by which the nocturnal disorder might have effects on daytime functioning, is empirically testable, generates unique research hypotheses, and has practical implications. Even so, the model is considered preliminary and in need of external validation. We expect and welcome tests of the model and modifications or disconfirmation of its tenets over time.

ACKNOWLEDGEMENT

D.B. is supported by a faculty research award from the University of Cincinnati and a Trustee Award from Children’s Hospital Medical Center. D.G. is supported by grants from the National Institutes of Health (HL-65270 and HL-63912), The Commonwealth of Kentucky Research Challenge Trust Fund, and the American Heart Association (AHA-0050442N).

REFERENCES


© 2002 European Sleep Research Society, J. Sleep Res., 11, 1–16
Beery, K.
Bednarczyk, E. M. et al.
"et al"


Grimm, D. W. Beebe and D. Gozal


© 2002 European Sleep Research Society, J. Sleep Res., 11, 1–16


Marrone, O. et al. What is the evidence that obstructive sleep apnoea is an important illness? Monaldi Archives of Chest Disease, 1998, 53: 630–639.


1Effect size was computed from studies with identical or very similar measures as the difference between the OSA and control group means, divided by their pooled standard deviation (Lipsey and Wilson 2001). We elected to report unweighted mean effect sizes, which treat each study’s findings equally, rather than a weighted mean effect size, which places more importance on studies of larger samples. This is because in one study, Kim et al. (1997), studied an unusually large sample (total n = 841 compared with 20–49 in each of the other studies), yet used an unusually low pathology ‘cutoff’ (apnea/hypopnea index > 5) compared with the other studies. Statistical significance for single-study findings correspond to those in the individual reports, while significance for mean effect sizes is based upon the pooled samples. When a given study reported on subcomponents of a measure (i.e. digits forward and backwards, Naegele et al. 1995; Redline et al. 1997, each letter on a phonemic fluency task, Naegele et al. 1995) we computed the mean effect across task subcomponents within that study prior to combining it with other studies.