The human body relies on an adequate supply of oxygen for healthy functioning. The brain is just one organ sensitive to oxygen deprivation, especially when it occurs over extended periods of time. There are several medical conditions commonly associated with limited oxygen supply to the brain, including chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and acute respiratory distress syndrome (ARDS). The literature demonstrating the detrimental effects of oxygen deprivation on neuropsychological functioning has developed rapidly over the past few decades. This chapter focuses on the neuropsychological effects of disorders with limited supply of oxygen, addressing questions designed to both summarize the existing literature and theorizing about the potential mechanisms behind the findings and their implications for future research.

**Definitions**

Hypoxia literally means “deficient in oxygen.” It can refer to ably low oxygen availability to body as a whole (generalized) or to a specific region of the body (tissue hypoxia). An example of generalized hypoxia is that which is seen at high altitudes, where reduced atmospheric pressure lessens the availability of oxygen in the environment. Generalized hypoxia can occur in otherwise healthy individuals and can result in altitude sickness, high-altitude pulmonary edema or high-altitude cerebral edema. Tissue hypoxia, on the other hand, is described in more local terms. It is generally due to a more specific restriction in blood supply (and therefore oxygen supply) to a specific organ. Hypoxemia, a term commonly confused with hypoxia, refers to an ab deficiency in the concentration of oxygen in arterial blood. Anoxia refers to the complete deprivation of oxygen supply. Finally, hypercapnia is an associated state marked by an ably high level of carbon dioxide (CO2) in the blood. Hypercapnia can be the result of a variety of causes such as hypoventilation, lung disease, or diminished consciousness. Hypercapnia is less often the focus of cognitive studies, but it is associated with hypoxia and may be a more sensitive variable in some clinical populations. This chapter focuses on hypoxia and hypoxemia, using the definition that best fits the study in question, but each term is employed to refer to a limitation in oxygen supply to the brain.

**Medical Syndromes Associated with Hypoxia**

There are many medical conditions that can be associated with limited oxygen supply, but three in particular are associated with hypoxia (or hypoxemia): COPD, OSA, and ARDS.

**Chronic Obstructive Pulmonary Disease**

COPD primarily encompasses emphysema and chronic bronchitis. The World Health Organization rated COPD tied with HIV/AIDS.
Neuropsychiatric Disorders

Neuropsychological Functioning in COPD.

Chronic hypoxemia in COPD has a known and well-studied negative effect on cognition. Systematic investigations of neuropsychological functioning in COPD began in the 1970s, and initially demonstrated deficits on measures of perceptual-motor functioning and simple motor functioning in hypoxic participants with COPD (Krop et al., 1973). These findings were extended by two large multicenter trials conducted in the 1980s, the Nocturnal Oxygen Therapy Trial (NOTT) (Grant et al., 1982) and the Intermittent Positive Pressure Breathing Trial (IPPB) (Prigatano et al., 1983), which demonstrated impairments in perceptual-motor, simple motor, abstracting, executive functioning, and verbal and nonverbal learning and memory abilities in COPD patients. The data from these studies were combined in order to more thoroughly examine the relationship between hypoxemia severity and neuropsychological functioning in a total of 302 COPD patients with varying hypoxemia severity (Grant et al., 1987). Cognitive functioning was impaired in the COPD patients as a whole, with 42% of the combined sample demonstrating neuropsychological impairments. The proportion of cognitively impaired patients increased with worsening hypoxemia, with 27% of the mildly hypoxic and 61% of the severely hypoxic patients demonstrating impairments. A factor analysis was performed on the 27 test measures used in these studies, resulting in a four-factor solution. Multivariate analysis of variance on the factors revealed that performance on three of the four factors declined with worsening hypoxemia. The affected factors were perceptual learning and problem solving, alertness and psychomotor speed, and simple motor skills. No group differences emerged on a factor measuring verbal intelligence. Multiple regression analyses demonstrated that hypoxemia had a modest relationship to neuropsychological functioning, and that medical and pulmonary function variables did not significantly contribute to the prediction of neuropsychological impairment. Within the last decade, multiple studies have examined the profile of neuropsychological impairments associated with COPD and potential relationships between cognitive functioning in COPD and other medical or pulmonary variables.

Several studies have sought to characterize the profile of neuropsychological impairments in COPD and compare the pattern to patterns seen in other disorders, Alzheimer’s disease (AD) being the most common (Antonelli Incalzi et al., 1993). Antonelli Incalzi and colleagues performed a discriminant function analysis of the cognitive profiles of participants with COPD, AD, MID, and no known cognitive disorders (elderly). Of the COPD participants, 48.5% had a specific cognitive profile, with impairments in verbal functions and verbal memory, a diffuse decline in other cognitive functions, and visual attention. Relatively equal proportions of the remaining COPD participants were classified as belonging to each of the other groups. Cognitive impairments in the COPD patients were not as severe as documented in previous samples, (e.g., Grant et al., 1982), but all participants with COPD included in this study were on oxygen therapy, which may have ameliorated or slowed the progression of some cognitive deficits. Increasing age and duration of chronic respiratory failure were correlated with cognitive impairment. In a subsequent study, Antonelli Incalzi et al. (1997) again utilized discriminant function analysis to examine memory performance of hypoxic COPD patients, AD patients, older healthy subjects, and controls (Antonelli Incalzi et al., 1997). Only 19% of the participants with COPD were classified as having memory impairment, while 38% exhibited a unique memory pattern, 17% were classified as AD, and 26% were classified as older controls. The participants with COPD exhibited memory deficits suggesting impairments in both the encoding and retrieval of verbal information.

Findings from studies examining the neuropsychological profiles of nonhypoxic or mildly...
hypoxic COPD patients have been less conclusive. Kozora et al. (1999) compared the performance of mildly hypoxic patients with COPD on oxygen therapy with AD patients and elderly (Kozora et al., 1999). The AD group performed significantly more poorly than both the COPD and control groups on most neuropsychological measures, and both the participants with AD and those with COPD performed more poorly than controls on verbal fluency to letter cues. However, the performance of the COPD group on this measure was not in the clinically impaired range. Results indicated that mildly hypoxic participants with COPD who were treated with oxygen therapy and who had no neurologic histories may not exhibit cognitive deficits. This finding contrasted somewhat with findings of neuropsychological impairments documented in samples of untreated mildly hypoxic participants with COPD (e.g., Prigatano et al., 1983) or more severely hypoxic participants with COPD (Antonelli Incalzi et al., 1993). Antonelli Incalzi et al. (2003) examined cerebral perfusion in nonhypoxic participants with COPD, hypoxic participants with COPD, AD participants, and healthy controls. Nonhypoxic COPD participants had cerebral perfusion, while hypoxic COPD participants demonstrated an intermediate level of perfusion, between that of the nonhypoxic COPD and AD participants (Antonelli Incalzi et al., 2003). Hypoxic COPD and AD participants had reduced perfusion in anterior areas, while AD participants also had reduced perfusion in association areas. Both the nonhypoxic and hypoxic COPD participants performed better than those with AD on neuropsychological testing, and both groups performed below normative standards on measures of verbal memory, attention, and deductive thinking. The authors hypothesized that differences between the nonhypoxic and hypoxic COPD participants did not emerge because the hypoxic participants did not exhibit severe hypercapnia, which may have a greater link to cognitive dysfunction.

In addition to characterizing the neuropsychological profile associated with COPD, many studies have examined potential relationships between neuropsychological functioning and pulmonary or other medical variables. In general, findings have been more robust in patients with more advanced disease or greater hypoxemia, and potential associations have been observed between cognitive functioning and measures of blood oxygenation, carbon dioxide, and fitness. An uncontrolled study of 18 COPD participants found that complex attention, information-processing speed, and memory were correlated with measures of carbon dioxide and oxygen partial pressure (Stuss et al., 1997). When participants from this study were divided into mildly hypoxic and severely hypoxic groups, the severely hypoxic group demonstrated poorer memory and attention functioning, and had more evidence of abilities on brain CT and EEG. Poorer baseline lung functioning (% predicted forced vital capacity (FVC) and forced expiratory volume in one second (FEV1)) and more depressive symptoms were predictive of decline over a 2-year period on the Mini-Mental Status Exam (MMSE) in a sample of 40 COPD participants, while depressive symptoms and performance of activities of daily living remained stable (Antonelli Incalzi et al., 1998). Findings suggested that more severe lung disease and onset of depression are risk factors for cognitive decline in COPD. Significant relationships between aerobic fitness and pulmonary functioning and measures of fluid intelligence, speed of processing, and working memory were found in a sample of 98 COPD participants, although findings related to pulmonary function were variable (Etnier et al., 1999). Aerobic fitness was felt to be a protective factor, serving to minimize or slow the decline of cognitive functioning. Again, findings from studies investigating the relationship between pulmonary and medical variables and neuropsychological functioning in samples of nonhypoxic COPD participants have been mixed. Liesker et al. (2004) found poorer performance on measures of information-processing speed and no differences in performance on measures of memory or executive functioning in a group of 30 nonhypoxic COPD participants compared to age- and education-matched controls (Liesker et al., 2004).

**Posttreatment Neuropsychological Functioning in COPD.** Several investigators have examined the association between treatments designed to improve brain oxygenation and
changes in neuropsychological functioning in COPD. Studies have focused primarily on three types of intervention: the provision of supplemental oxygen, exercise training and rehabilitation, and lung-volume reduction surgery.

It was initially hypothesized that supplemental oxygen would improve neuropsychological functioning in participants with COPD by alleviating their chronic hypoxia. Early findings suggested improvements following short-term supplemental oxygen therapy (Krop et al., 1973). The NOTT sought to examine the effects of long-term supplemental oxygen therapy on cognition, as a follow-up of these early findings (Heaton et al., 1983). A total of 150 patients were enrolled, 78 of whom received continuous oxygen therapy and 72 of whom received nocturnal oxygen therapy. Following six months of treatment, both groups demonstrated slight improvements compared to controls on three individual neuropsychological measures (sequencing ability, simple motor speed, and motor strength). When a subsample of 37 participants was examined following 12 months of treatment, the continuous oxygen therapy group exhibited improved performance relative to the nocturnal therapy group on three of five neuropsychological summary measures (i.e., WAIS Performance IQ, HRB Average Impairment Rating, and Brain Age Quotient). No significant improvement, however, was noted on measures of emotional functioning or quality of life. In a smaller sample of 10 hypoxemic COPD participants followed through three months of treatment, COPD was associated with poorer baseline attention, information-processing speed, and memory relative to age-matched controls (Hjalmarsen et al., 1999). Although neuropsychological performance among the COPD participants subjectively improved following treatment, changes were not statistically significant. Findings may have been due to practice effects or insufficient power. There were also no significant changes noted on measures of cerebral blood flow.

With the increasing acceptance of exercise and rehabilitation therapy in the treatment of COPD, investigators began to examine the effect of these treatments on psychological and neuropsychological functioning. Improved cognitive functioning following exercise had been previously observed in older individuals, and potentially related to reduced postexercise sympathetic hyperarousal and improved neurotransmitter regulation associated with greater oxygen carrying capacity of the blood (Dustman et al., 1984). A number of studies have subsequently examined the effects of exercise and rehabilitation on cognitive functioning in COPD patients. Emery et al. (1998) examined psychological and cognitive outcomes in participants with COPD randomized to a 10-week exercise plus education and stress management condition as compared to those randomized to education and stress management only and a wait-list control. While no improvement in pulmonary functioning was observed, the exercise group demonstrated improved physical endurance and reduced symptoms of anxiety and depression. Interestingly, depressive symptoms also declined in the wait-list control group (Emery et al., 1998). Participants in the exercise group demonstrated improved verbal fluency/verbal processing, suggesting some possible improvement in frontal lobe executive functions. No group differences emerged on measures of attention, motor speed, and mental efficiency. The authors hypothesized that changes in the release and re-uptake of neurotransmitters and in sympathetic nervous system activity associated with the exercise intervention may have led to the observed improvements in mood and cognition, but no direct evidence of this was given. Emery et al. (2001) also demonstrated a similar improvement in cognitive functioning in participants with COPD immediately following exercise. Both COPD patients and healthy controls completed a brief neuropsychological test battery immediately before and immediately after both an exercise condition (bicycle stress test) and a video-viewing control condition. Neither group improved following the control condition, and the COPD group demonstrated improved verbal fluency/verbal processing postexercise, superior to that seen in the controls (Emery et al., 2001). Improved neurotransmitter functioning postexercise was hypothesized to contribute to the changes observed in the COPD participants, but this study remains to be replicated.

Long-term changes in neuropsychological functioning following exercise interventions
have also been studied (Emery et al., 2003; Etnier & Berry, 2001). Etnier and Berry (2001) found an apparent association between improved performance on a measure of fluid intelligence and aerobic fitness following a 3-month exercise intervention in participants with COPD. Participants were subsequently randomized into either a 15-month structured exercise program or a control condition in which they were simply encouraged to continue exercising. At follow-up, there were no group differences in cognitive performance, although findings suggested that individual subjects demonstrating the greatest improvement in aerobic fitness also showed the greatest improvement on a measure of fluid intelligence. Their findings suggest that relatively short exercise interventions can lead to improved cognitive functioning. Emery et al. (2003) examined the relationship between adherence and the long-term effects of exercise treatment in a sample of 28 COPD participants who had completed a 10-week exercise intervention. Participants were re-assessed 1 year after treatment and determined to be exercise adherent or nonadherent. While no subsequent improvements were noted, adherent participants maintained gains in physical endurance and cognitive functioning made following the 10-week intervention. In contrast, nonadherent participants exhibited decline at follow-up on measures of physical endurance, cognitive functioning (psychomotor speed and sequencing), and psychological symptoms (increased depression and anxiety). While continued adherence with exercise interventions did not result in continuing improvement in neuropsychological functioning, it may have been a protective factor, maintaining previous gains and preventing further decline.

The National Emphysema Treatment Trial (NETT) demonstrated that non-high-risk COPD patients undergoing lung-volume reduction surgery exhibited significant improvement on measures of both physical functioning and quality of life (“The National Emphysema Treatment Trial [NETT]: How strong is the evidence?,” 2003). Kozora et al. (2005) examined neuropsychological functioning in a sample of 39 participants with emphysema and 39 matched controls at baseline, following 6–10 weeks of rehabilitation, and 6 months post-randomization to either lung-volume reduction surgery \( (n = 19) \) or continuing medical therapy \( (n = 20) \). At follow-up, participants undergoing lung-volume reduction surgery improved on measures of delayed verbal recall and sequential psychomotor skills, and had a trend toward improved verbal naming (Kozora et al., 2005). Additionally, lung-volume reduction surgery was associated with reduced depressive symptoms and improved quality of life. Participants in the medical therapy condition improved only on one measure of accuracy of visual attention at follow-up, and also exhibited an increase in depressive symptoms. The potential mechanisms contributing to this change were difficult to identify, as improvements in the surgery group relative to the medical therapy group could not be accounted for by changes in physical endurance, pulmonary function, psychological symptoms, or medication changes, although improved quality of life may have influenced improved neuropsychological functioning.

**Obstructive Sleep Apnea**

OSA is a sleep disorder that affects at least 4% of middle-aged men and 2% of middle-aged women (Young et al., 1993) and 70% of older men and 56% of older women (Ancoli-Israel et al., 1991). It is a well-recognized clinical disorder characterized by repeated obstructions of the upper airway during sleep. OSA results in sleep fragmentation that disrupts the sleep architecture and periodic oxygen desaturations that can drop to dangerously low levels. Sleep fragmentation and hypoxemia are generally inextricably tied in OSA, making it difficult to make explicit statements regarding the independent effects on any single cognitive factor. Primarily correlative techniques have been used to try to tease the effects apart.

**Neuropsychological Functioning and OSA.**

OSA can cause significant daytime behavioral and adaptive deficits. Functional impairments like sleepiness, impaired driving, increased risk of accidents, and decreased quality of life are frequent consequences of sleep apnea (Engleman & Douglas, 2004; George & Smiley, 1999). Behavioral effects of OSA are often referred to...
as “neurobehavioral” consequences because they are presumed to be directly related to brain function (Beebe, 2005). Neurobehavioral functioning is a broad term that includes several specific cognitive functions. Numerous studies have examined these specific cognitive functions and some have attempted to identify a “pattern” of cognitive dysfunction in OSA. Such patterns, when they exist, will be summarized below. Following that summary, theoretical models describing potential mechanisms involved in this relationship are discussed.

Neurocognitive testing is common in studies involving OSA. The cognitive sequelae of the disorder have been repeatedly discussed, but are not always consistent across studies (e.g., Aloia et al., 2004; Engleman et al., 2000; Sateia, 2003). Some inconsistencies may be associated with the heterogeneity of the samples, while others may be the result of the different tests utilized in the studies. Too few studies utilize the same cognitive tests to draw any definitive conclusions as to the degree or pattern of cognitive deficits in OSA.

Cognition in OSA has been examined as both a unitary function and one divided into several specific domains (e.g., memory, attention, executive functioning, etc.). The utility of each type of examination depends upon the question being asked and the degree to which each approach would adequately address a given hypothesis. Studies of global impairment may be better suited for addressing the overall effects of a particular variable on cognition. Impaired cognition among OSA patients is not, however, global. In fact, apnea patients may exhibit relatively few deficits in the global cognitive domain when compared to controls (for review see Aloia et al., 2004). Studies that limit themselves to global functioning may not have a true appreciation for the various components of cognition that contribute to this global score, and specific cognitive deficits can be masked. Domain-specific hypotheses can remedy this problem. Domains can be divided in several ways, but common domain names include executive functioning, memory, attention, vigilance, visuospatial ability, constructional ability, psychomotor functioning, and language. One should remember, however, that each of these domains may also have subdomains that further break apart their complex nature (e.g., executive functioning) and that domains are not mutually exclusive in their functions. For OSA patients, the domains of cognitive functioning may be differentially affected. Vigilance, including sustained attention, controlled attention, efficiency of information processing, and response time, is the most commonly assessed cognitive construct in OSA and has been found to be the most consistently affected cognitive domain in apnea patients.

Executive functioning, which includes processes involved in planning, initiation, and the execution of goal-oriented behavior and mental flexibility, is another affected domain. Some argue that it is the most prominent area of cognitive impairment in untreated sleep-disordered breathing and that the dysfunction extends to children with sleep apnea as well as adults (Beebe & Gozal, 2002). The broad construct of executive functioning makes it difficult to accurately describe the deficits and to construct a model explaining causes of the impairment. Examples of executive functioning include working memory, set shifting, perseveration, planning, abstract reasoning, and verbal fluency. Even more, executive functions are in part supported by adequate attention. Therefore, complex attentional problems could represent the root cause of executive dysfunction. Despite its being a broad construct, OSA patients clearly perform consistently more poorly on tests of executive functioning than matched controls (Bedard et al., 1991, 1993; Feuerstein et al., 1997; Naegele et al., 1995; Salorio et al., 2002; Verstraeten et al., 1997). Several investigators have documented executive dysfunction in OSA. Initially, these findings allude to frontal lobe deficits associated with the disorder (Beebe & Gozal, 2002). Such a theory is supported by animal studies and neuroimaging, but foundation functions like attention might also contribute to what is seen to be prominent executive dysfunction. Moreover, the cause of executive dysfunction is often complex.

Learning and memory are also impaired in patients with OSA. Learning and memory constitute a broad, complex domain that includes verbal memory, visual memory, short-term memory, and long-term memory. Memory performance deficits can be attributed to several areas: initial learning, free recall, or forgetfulness, each of which has different implications (Aloia et al., 2004). OSA patients perform...
more poorly on tests of memory and learning than matched controls (e.g., Aloia et al., 2004; Feuerstien et al., 1997; Naegele et al., 1995). A recent study, which examined the specific type of memory impairment in OSA by comparing performance on tests of list learning, procedural memory, and working memory (a combination function including executive functions as well as memory), found the most compelling evidence for cognitive dysfunction in OSA exists in working memory. At first glance this finding suggests that executive dysfunction could tip the scales in favor of working memory being the most commonly affected memory impairment in OSA. However, another recent study attempted to parse out the various cognitive functions underlying working memory to determine in fact whether or not working memory deficits were primarily the result of learning impairments, free recall impairments, motor dyscoordination, or executive dysfunction. This study concluded that the impairments were most commonly seen on complete tests of working memory than on any specific cognitive subfunction. This suggests that this construct may be quite sensitive to the consequences of OSA.

Psychomotor performance is a domain that has been assessed less frequently. Most studies, however, show OSA patients to be impaired in psychomotor performance relative to controls (see Aloia et al., 2004 for review). Specifically, OSA patients perform relatively poorer on tests of fine motor coordination (Bédard et al., 1991, 1993; Greenberg et al., 1987; Verstraeten et al., 1997). Not all studies have reported impairment on tests of motor speed (Knight et al., 1987; Verstraeten et al., 1997). Overall, there has been relatively little discussion of this domain as a primary source of impairment. The mechanism for psychomotor dysfunction is not clear. One explanation for psychomotor difficulties is excessive sleepiness, but this does not account for the discrepancy between tests of fine motor skills and motor speed.

Few studies have been conducted examining cognitive dysfunction associated with OSA in older adults. A large-scale study in France reported that participant reports of snoring and/or breathing cessation during sleep were associated with greater impairment on tests of attention and information processing, even after controlling for several extraneous variables (Ohayon & Vecchierini, 2002). These findings were significantly associated with cognition only when daytime sleepiness was also reported. A longitudinal study employed more stringent criteria for diagnosing OSA. Ancoli-Israel and colleagues examined the sleep and global cognitive functioning of 46 community-dwelling older adults over the course of 4 years (Cohen-Zion et al., 2001), finding that increases in apnea severity and daytime sleepiness were associated with respective decreases in global cognitive functioning over time. Moreover, the findings seemed to be driven by daytime sleepiness when regression models were employed. An intriguing study by Antonelli Incalzi and colleagues compared older individuals with sleep apnea to patients with either AD or multi-infarct dementia (MID) on a battery of neuropsychological tests (Antonelli Incalzi et al., 2004). This study suggested that the cognitive profile of apnea is most like that seen in MID. They relate this finding to the probable involvement of subcortical brain regions in apnea, a relationship that has also been posited by other investigators (Aloia et al., 2003, 2004).

**Posttreatment Neuropsychological Functioning in OSA.** The most common and effective treatment for OSA is positive airway pressure (PAP). When properly used, PAP has been shown to dramatically reduce morbidity and mortality (Campos-Rodriguez et al., 2005; He et al., 1988; Keenan et al., 1994). Due in part to these encouraging findings, the effect that PAP treatment has on cognition has been an area of interest for many investigators. Long-term adherence to PAP treatment, however, is less than optimal, with approximately 25% of patients discontinuing use within a year (McArdle et al., 1999). Commonly cited reasons for poor adherence include physical discomfort as well as psychosocial factors (Aloia et al., 2001, 2005a; Hoffstein et al., 1992; Kribbs et al., 1993; Waldhorn et al., 1990).

Aloia and colleagues published a critical review of the literature on the neuropsychological sequelae of OSA. They concluded that the majority of studies examining the connection between PAP and OSA have indeed cited a positive relationship between treatment adherence
and improved performance on various cognitive tests. Response to treatment, however, may be a factor of the particular test being measured. Just as some tests are more sensitive to dysfunction, some are likely to be more sensitive to the effects of treatment.

Ancoli-Israel and colleagues examined the effect of continuous PAP (CPAP) treatment on cognitive function in patients with mild-to-moderate AD and OSA. Results suggested that 3 weeks of CPAP treatment, with an average of 5 hours of use a night, resulted in improvements in episodic verbal learning and memory and some aspects of executive functioning such as cognitive flexibility, and mental processing speed (Ancoli-Israel et al., 2006).

Two recent studies concluded that the number of hours of CPAP adherence needs to be evaluated when examining other outcome measures. Zimmerman et al. (2006) split a group of memory-impaired OSA patients into three adherence groups based on average PAP use at three months. The reference group for the study comprised poor users—those using 1 or fewer hours per night on average. Moderate users (2–5 hours’ use a night) were 3 times as likely to develop memory over 3 months with PAP compared to poor users. This was not a significant effect. Optimal users (6 or more hours a night), however, were 8 times as likely to improve memory compared to poor users at 3 months. This finding was not due to baseline differences in memory or any other intervening variables, suggesting that it takes as many as 6 hours of use per night to improve memory in OSA patients who demonstrated memory impairments at baseline.

In a second study of adherence, Weaver et al. demonstrated that subjective sleepiness can change with as little as 4 hours of CPAP use a night, while objective sleepiness (as measured by the Multiple Sleep Latency Test) might take 6 hours of use, and changes to functional outcomes associated with sleepiness might require over 7 hours of use per night. These two studies demonstrate that adherence as well as test sensitivity and specificity must be incorporated into efficacy trials.

Potential Mechanisms for Neurobehavioral Dysfunction in OSA. The theoretical models discussed below propose certain mechanisms that may be involved in the relationship between OSA and cognition. Beebe and Gozal hypothesized that OSA has a predilection for affecting the frontal lobes of the brain compared to other brain regions. Two primary mechanisms (i.e., sleep fragmentation and hypoxemia) were outlined as the causes of frontal lobe dysfunction (Beebe & Gozal, 2002). The model suggested that OSA has a predilection for affecting the frontal lobes of the brain compared to other brain regions. Hypoxemia is thought to result in cellular changes to the prefrontal cortex that directly affects function, while sleep fragmentation is posited to preferentially affect the frontal lobes of the brain by disrupting the restorative process of sleep. Together, hypoxemia and sleep fragmentation adversely affect the executive functioning of the frontal lobes. Sleep deprivation studies provide evidence for this model by showing a strong relationship to executive functions. The executive model has several strengths. First, it was one of the first models to thoughtfully take a neurofunctional approach to explain the cognitive dysfunction seen in OSA. The model also employed both basic and clinical studies as evidence. There were, however, some weaknesses to the model. Data from carbon monoxide poisoning studies and sleep deprivation studies were extrapolated to the conditions of hypoxemia and sleep fragmentation in general. These analogies may or may not be appropriate. In addition, the effects of sleep fragmentation and hypoxemia on brain regions other than frontal lobes were not incorporated into this early model. Finally, as mentioned above, executive dysfunction is complex and multifactorial, something acknowledged by the authors. Regardless of this criticism, the authors undertook a very complex task: to develop a comprehensive, neurofunctional model of OSA.

Another proposed model is the attentional model. Certainly attentional problems have been implicated in OSA. Verstraeten and Cluydts (2004) have recently published two papers making the case that higher-order cognitive dysfunction in OSA can be explained by the impairment of basic attentional processes and slowed mental processing. The first paper proposed a theoretical model of neurocognitive functioning marked by the hierarchical ordering of cognitive processes that can lead to the
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appearance of higher-order cognitive dysfunction. This theoretical paper is quite interesting as it is the first to recognize that higher-order cognitive processes are complex enough to often rely on more basic attentional and lower-level cognitive processes. The authors made the case that executive dysfunction per se should be interpreted cautiously in the case of sleep apnea, given the potentially profound effects of sleep disruption on arousal, basic processing speed, and attentional ability. The conclusion of this paper is that investigators should consider developing studies that allow them to systematically control for lower-level functions in the assessment of high-order cognitive ability. The second study attempted to demonstrate this theory by fractionating these functions to determine the degree to which the reliance of higher-order functions on attention can lead to the misinterpretation when considering the functional deficits in OSA. Deficits in OSA patients were seen in processing speed, attentional capacity, and short-term memory span, with no differences seen in executive functions per se. The investigators provided these data as evidence for this hierarchical model of dysfunction in OSA, making the case that executive dysfunction may be misinterpreted without knowledge of lower-order skills. This series of studies is quite compelling and encourages investigators to consider cognitive functions in a hierarchical manner (Verstraeten et al., 2004). Indeed, identifying the basic functional deficits that underlie these more complex deficits can lead to a better understanding of the neurofunctional mechanisms impaired in OSA. The one lacking component of this work is the provision of data to support any specific mechanisms related to sleep fragmentation or hypoxemia. Future research will undoubtedly address this gap in the model and may augment the executive model described above.

The microvascular theory as a model for cognitive dysfunction in OSA was first put forth by Aloia and colleagues in 2004, owing in large part to the work of Somers and colleagues (Lanfranchi & Somers, 2001). Aloia and colleagues culled mechanisms of dysfunction from the cardiovascular literature and determined that cardiovascular dysfunction was indeed present in OSA and may represent microvascular disease. Several supporting studies for this model were presented, highlighting the involvement of the white matter in OSA, an area fed primarily by small vessels and susceptible to ischemic disease. Functional and structural studies were presented, though few had been completed at the time of the original publication. In closing the paper, it was demonstrated in a small sample that evidence of microvascular disease could be seen on brain MRI in OSA. Since the publication of this review, several studies have been published to support and refute this model. One supportive study identified a subgroup of OSA patients with cognitive dysfunction that likened a pattern seen in MID. However, other studies have failed to find an association between white matter ischemic disease and OSA severity using large-scale epidemiological data in older adults. One primary limitation of the model was that it did not attend strongly to the differential effects of sleep fragmentation and hypoxemia. The model is promising in that it is parsimonious and incorporates a known mechanism of dysfunction in OSA, vascular compromise, into the cognitive realm. Further research, however, is needed to defend, refute, or expand the model and to relate its effects to complaints of fatigue and sleepiness.

The most recent model, posited by Beebe (Beebe, 2005), is the most comprehensive to date and pulls upon the strengths of previous models to develop a heuristic model of the mechanisms underlying cognitive dysfunction in OSA. He hypothesized that the effects of sleep
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fragmentation and hypoxemia are not likely to be effectively isolated from one another. He stated that their interaction may in fact be synergistic. Moreover, he presented the likelihood that these mechanisms interact with certain vulnerable brain regions, highlighting specifically the hippocampus, the prefrontal cortex, subcortical gray matter, and white matter. The inclusion of the subcortical gray and white matter reflects an appreciation for the potential involvement of the small vessels of the brain. Beebe also attended to the possibility that findings in studies of the potential mechanisms of cognitive dysfunction are dependent in part on task demands and the environment under which testing is conducted. This addition shows an appreciation for the complexity of executive dysfunction as multifactorial and broadens the executive and attentional models by including several other cognitive tasks that may be impaired in OSA simply due to the demands that they present for the implicated brain regions. Finally, Beebe went beyond the other models by incorporating two additional areas to consider: (1) risk and resilience factors, and (2) direct effects on cognition outside of those involved in OSA. When discussing risk and resilience, Beebe acknowledged recent work by Alchanatis and colleagues showing that there may be moderators of dysfunction in OSA; for example, intelligence has been proposed as one moderator for vigilance problems in OSA (Alchanatis et al., 2005). This study identified cognitive reserve (high premorbid cognitive ability that results in resistance to cognitive decline with insult) as a resilience factor, but the heuristic model also includes age, sex, sociodemographic factors, and duration of illness. Others have also proposed the inclusion of moderators of dysfunction noting that several patients with severe OSA do not suffer dysfunction at all, while others with mild OSA show significant impairment. Finally, the model incorporates genetic endowment, prior experience with testing, and sociodemographic factors as possible extraneous variables when considering the mechanisms of cognitive dysfunction in OSA. The model needs to be tested, but there are more strengths to this model than there are weaknesses. The model is testable with large datasets and is more inclusive than previous models. It is not, however, overly inclusive and specifies brain regions likely to be involved without implying that all regions are equally vulnerable. Perhaps most importantly, the model highlights the likely effect of moderating factors for cognitive impairment in OSA, something that has only recently been addressed in the literature.

Acute Respiratory Distress Syndrome

ARDS results from injury to the microvasculature of the lungs, which can lead to leakage of fluid into the alveoli resulting in hypoxemia, dyspnea, and in some cases death. ARDS is generally seen in hospitalized patients with severe illnesses, including sepsis, pneumonia, severe blood loss, chest and head injuries, aspiration of stomach contents, and breathing injurious fumes. The syndrome affects roughly 13–18 people per 100,000, with prevalence rates between 15% and 18% among ventilated patients. ARDS can result in death, with mortality rates between 35% and 70%. Few studies have examined the cognitive effects of ARDS. Hopkins and her colleagues have conducted the majority of these studies in an attempt to provide evidence for cognitive dysfunction, identify the pattern of dysfunction, and address the consequences of such dysfunction in longitudinal designs (Hopkins et al., 2004, 2005, 2006; Hopkins & Herridge, 2006). In general, there are consistent findings of cognitive dysfunction in ARDS. Global cognitive function is impaired in the majority of patients immediately following discharge. There is some recovery of function over the first year after discharge, but Hopkins et al. (2005) have demonstrated that cognitive dysfunction can persist as long as 2 years after discharge. One additional study documented cognitive dysfunction as long as 6 years postdischarge, raising concerns over long-lasting and permanent damage to the brain (Rothenhausler et al., 2001). Indeed, neuroimaging studies have demonstrated early evidence of cortical atrophy (Hopkins et al., 2006). Objective and subjective data suggest that the majority of the cognitive deficits in ARDS fall into the realm of memory, with some impairment occurring in executive functioning, with psychomotor speed and impulsivity contributing to these deficits. This is surprisingly consistent with the OSA
data presented above. Even more compelling is that the ARDS cognitive data do not correlate with illness severity, age, or smoking history. These data mirror much of what has been demonstrated in OSA and call into question the presence of moderators that may make certain individuals more susceptible to the effects of hypoxemia compared to others.

Conclusions and Comments

This chapter covered the effects that hypoxia has on neuropsychological functioning in several different medical conditions. In closing, it appears clear that hypoxemia and hypoxia have unmistakable detrimental effects on cognitive functioning. It is also obvious, however, that these findings are not necessarily pervasive across all patients. The focus of positive studies to date has been on the mediators of cognitive dysfunction in disease states, including hypoxia. Future studies should also attempt to tackle the question of moderators of cognitive dysfunction in persons with hypoxic conditions. For example, studies have demonstrated that high cognitive reserve spares some individuals with OSA from developing cognitive problems (Alchanatis et al., 2005). Investigators have also considered the possibility of substances that are thought to be protective from inflammation (e.g., antioxidants) as potential moderators of dysfunction (Baldwin et al., 2005). Genetic factors are also only now being considered. Probably, our understanding of the role of hypoxia in cognitive dysfunction will only be made clear with these mediator and moderator studies. The future of this line of research is appealing, and the need for additional studies remains strong.

References


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**AQ1:** Please provide the remaining author names for reference Emery et al., 2003’.

**AQ2:** Please provide the remaining author names for reference Emery et al., 1998’.

**AQ3:** Please provide the remaining author names, and also please provide cross-reference for reference ‘Weaver et al., 2007’ in the text.