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10 Respiratory disorders and neuropsychological dysfunction

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During the early portion of the last century, health professionals began addressing the relationship between respiratory and psychological function (Farran-Ridge, 1926; Jellife, 1926). This focus continued for another several decades but ended about as abruptly as it started. It was not until recently that a renewed focus on this interface re-emerged, but it continued to advocate the relationship between respiratory function and psychological problems, particularly anxiety and affective ones (e.g., Caldirola, Bellodi, Cammino, & Perna, 2004). During the last several years, new areas of research began to develop from traditional health psychology, to include a more neuropsychological perspective with an emphasis on sleep apnea (Ridgway & McFarland, 2006). This paradigm shift notes the specific yet subtle changes in thought processing, decision making, and executive functioning.

The general public has understood the importance of sleeping uninterrupted in terms of psychological, behavioral, and emotional well-being. While there are an exhaustive number of variables that qualify as inhibitors of this process, disruptions in rates of respiration – sleep-disordered breathing (SDB) – may have long and detrimental consequences. SDB is a common affliction roughly effecting anywhere from 1% to 3% of children and 2–4% of adults (Ali, Pitson, & Stradling, 1993; Gislason & Benediktsdottir, 1995; Young, Dempsey, Skatrud, Weber, & Badr, 1993). Rates of SDB increase as we age, sometimes reaching as high as 42% among those aged 65 and over (Ancoli-Israel et al., 1991b). For example, Young et al. (2002) found the rate of those with SDB among 35- to 45-year-olds to be 5–10%, but it increased dramatically to 25–35% in the 75–85 age group. Snoring, the chief symptom of SDB, affects an even larger group of children and adults, with several population estimates around 25–30% (Ferreira et al., 2000; Gislason & Benediktsdottir, 1995).

SDB, defined as either a partial or full airway interruption leading to hypoxia (e.g., diminished oxygen supply to tissue), hypercarbia (e.g., abnormal cellular pH and increased carbon dioxide levels in the blood), and sleep fragmentation, refers to a general category of sleep respiratory disorders. Common disorders under this general heading include obstructive sleep apnea (OSA) and upper airway resistance syndrome. Other physical complaints associated with SDB are hyperpnea (e.g., breathing that is deeper and more rapid than normal), daytime drowsiness, failure to thrive, and poor cardiovascular function (Guilleminault & Robinson, 1997; Owens, 1990; Partinen & Guilleminault, 1990; Perkin, Downey, & MacQuarrie, 1999; Sanner et al., 2000) SDB has also been linked to increases in depression and anxiety (Aikens, Caruana-Montaldo, Vanable, Tadimeti, & Mendelson, 1999; Aikens & Mendelson, 1999).

Typical procedures used to measure the degree of SDB include the respiratory disturbance index (RDI) and oxygen saturation levels. The RDI is simply the average number of apneas or breaks in respiration lasting at least 10 seconds and hypopneas (e.g., slow breathing) that occur during 1 hour of sleep. The American Academy of Sleep Medicine Task Force (1999) suggests an RDI of at least five disturbances of air through the nose and mouth for the diagnosis of sleep apnea, with a moderate OSA level of 15–30 events per hour and severe OSA levels of > 30. Oxygen saturation levels (SPO_2), while one is sleeping, are used to measure the level of hypoxemia (e.g., insufficient oxygenation of arterial blood) during SDB. Traditionally, normal levels of SPO_2 are greater than 97%, but SPO_2 during SDB can decrease to as low as 60–80% (van der Post et al., 2002). van der Post et al. (2002) noted decreases in cognitive tasks, seen particularly among binary choice tasks and serial word recognition, when the SPO_2 levels among their volunteers were maintained at around 80% for 2 hours.

Although daytime sleepiness is indeed a frequent symptom of SDB and may contribute to the various cognitive maladies associated with it (e.g., inattention, impulsiveness, emotional outbursts, and poor verbal memory), research beginning during the 1980s seems to indicate that these behavioral and cognitive deficits may be the result of more than just a lack of sleep (Beebe & Gozal, 2002; Marrone, Bonsignore, Insalaco, & Bosignore, 1998). Instead, these respiratory interruptions may facilitate permanent changes and deficits in the brain, specifically the prefrontal cortex (Dahl, 1996; Harrison & Horne, 1997, 1998, 1999, 2000; Naegele et al., 1995; Thomas et al., 2000). It is unclear in the literature, however, if the cognitive and neuropsychological deficits such as inattention and poor verbal memory are fully reversible with treatment or if symptom reversibility is contingent upon how long one has experienced respiratory dysfunction and SDB. In other words, are the cognitive and neuropsychological deficits of an individual who has experienced SDB for several years less likely to improve versus the condition of an individual who has experienced SDB for a shorter length of time?

The majority of the cognitive and neuropsychological deficits associated with SDB center around executive function (Bedard, Montplaisir, Malo, Richer, & Rouleau, 1993; Berry, Webb, Block, Bauer, & Switzer, 1986; Greenberg, Watson, & Deptula, 1987; Incalzi et al., 2004; Naegele et al., 1995). Executive function is considered to be located in the frontal lobes, specifically in the prefrontal cortex (PFC). It controls our ability to engage in higher order cognitive functioning and future decision making while using basic proficiency methods (e.g., auditory and visual memory; see Baddeley, 1998, for further information). Common examples of executive function include planning, judgment, and decision making. For several reasons, the degree of executive function difficulty noted in SDB individuals is different than what may be expected to be the effect of simply missing sleep. First, changes in blood gas levels associated with SDB correlate better with executive function deficiencies than with self-reported measures of sleepiness (Bedard, Montplaisir, Richer, & Rouleau, 1991). Second, despite uninterrupted sleep or treatment such as continuous positive airway pressure (CPAP), deficits in executive function still persist in some individuals (Aloia, Arnedt, Davis, Riggs, & Byrd, 2004; Gozal & Pope, 2001). Third, children with SDB tend to show the effects of sleep loss when their RDI reaches levels of 15 but they demonstrate executive function problems with much lower RDI levels (Gozal, Wang, & Pope, 2001b). Executive function problems are so common with SDB that this trend has been nicknamed executive "dysfunction" in the research literature (Archbold, Giordani, Ruzicka, & Chervin, 2004).

The cognitive and neuropsychological deficits associated with SDB are now beginning to gain attention from the research community. OSA appears to be the most researched, partly due to the differences in symptoms and treatment approaches between children and adults. Additional studies of the cognitive and neuropsychological effects of respiratory dysfunctions, including chronic obstructive pulmonary disease (COPD), lung transplantations, and traumatic brain injury (TBI), will be discussed. Finally, the authors will comment on the common methodological limitations of the SDB research literature. Future research avenues, including the use of the level of SDB to diagnose and predict the likelihood and type of neuropsychological deficits expected in Alzheimer's disease and stroke, will be addressed.

Obstructive sleep apnea (OSA)

Obstructive sleep apnea is a form of SDB considered to be more severe in nature. Although snoring is a major clinical symptom of OSA, sleep apnea must also be present. If not, the diagnosis of primary snoring is given and is often seen as a more favorable situation, especially among children, since its occurrence rate can regress with age (American Academy of Pediatrics Policy Statement, 2002; Topol & Brooks, 2001). Still, research by Blunden, Lushington, Kennedy, Martin, and Dawson (2000) and O'Brien et al. (2004a) found evidence of neuropsychological deficits in children diagnosed with only primary snoring.

Children and adults not only differ from each other in terms of the causes of OSA but also in various cognitive and neuropsychological symptoms (Greene & Carroll, 1997; Guilleminault, 1985). For children, the primary cause is tonsil and adenoid enlargement, while obesity, genetics, age, or an imbalance in the hormonal levels responsible for controlling the upper airway muscles are the primary causes among adults (Greene & Carroll, 1997; Guilleminault, 1985). Children with OSA tend to exhibit attention deficit hyperactivity disorder (ADHD)-like symptoms, which sometimes lead to misdiagnoses, while adults tend to display daytime sleepiness and more pronounced deficits in their executive function (Chervin et al., 2006; Day, Gerhardstein, Lumley, Roth, & Rosenthal, 1999; Doghramji, 1993; Perkin et al., 1999).

Obstructive sleep apnea in children

Children with OSA have a number of common symptoms, including hyperactivity, inattention, learning problems, and decreased intelligence scores (Beebe et al., 2004; Blunden, Lushington, & Kennedy, 2001; Chervin et al., 2002; Gozal & Pope, 2001; Guilleminault, Eldridge, Simmons, & Dement, 1976; Guilleminault, Korobkin, & Winkle, 1981). These findings, however, are not supported by all studies (Blunden et al., 2000; O'Brien et al., 2004a). In fact, the amount of sleep disturbance that children experience has a strong relationship with their levels of behavioral hyperactivity and inattention (Aronen, Paavonen, Fjallberg, Soininen, & Torronen, 2000;

Guilleminault et al., 1981; Lewin, Rosen, England, & Dahl, 2002). These children do differ from those diagnosed as ADHD because SDB is not significantly associated with ADHD symptoms or significantly higher in those with ADHD (O'Brien et al., 2003). The related cognitive and neuropsychological deficits persist in children with OSA after being matched to control children along the lines of gender, racial origin, age, measures of socio-economic status (e.g. level of maternal education), and maternal rate of cigarette smoking (O'Brien et al., 2004b).

The neurobehavioral disruptions, as consequences of OSA and primary snoring, are more pronounced among children than adults. In O'Brien et al. (2004a), children diagnosed with primary snoring had more anxiety, depression, aggression, and inattention than those in the control group. Furthermore, Lewin et al., (2002) found higher Child Behavior Checklist (CBCL) scores among children with OSA. Although O'Brien et al. (2004b) found no behavioral differences between their SDB children and control groups, they attributed this to the small sample size.

Surgical treatment for children with OSA does seem to alleviate the neurobehavioral deficits (Chervin et al. 2006; Goldstein, Fatima, Campbell, & Rosenfeld, 2002; Goldstein, Post, Rosenfeld, & Campbell, 1998; Montgomery-Downs, Crabtree, & Gozal, 2005). In what is commonly known as tonsillectomy and adenoidectomy (T&A), surgeons remove adenotonsillar tissue. Again, it is recommended that hypoxia be present first, because snoring in children is common and usually resolves on its own during later years.

While it is easy to notice the presence of neurobehavioral effects of OSA in children, research attention has begun to focus on measuring the possibility of any additional cognitive and neuropsychological deficits (Blunden et al., 2000; Lewin et al., 2002; O'Brien et al., 2004a, 2004b). Children with OSA have been found to score significantly lower than control children on a host of neuropsychological and intelligence tests: Wechsler, NEPSY processing subtest, NEPSY verbal attention subtest, and general conceptual ability scores from the Differential Ability Scales (DAS) (Lewin et al., 2002; O'Brien et al., 2004b). Some other studies, however, have been unable to replicate these test results. It is suggested that children have at least an RDI score of 15 (e.g., moderate OSA) to begin demonstrating deficits on standardized psychological testing (Aloia et al., 2004; Lewin et al., 2002; O'Brien et al., 2004b). Research by O'Brien et al. (2004b) and O'Brien, Tauman, and Gozal (2004c), however, has found a decrease in the verbal and language abilities of children, with RDI scores between 5 and 10.

The effects of OSA on the cognitive and memory performance of children are mixed. Blunden et al. (2000) and Rhodes et al. (1995) found significantly reduced memory performance in children with OSA, where the greater the level of OSA, the more severe the memory deficits. O'Brien et al. (2004b) noted problems in visuospatial ability and overall cognitive function in their sample of OSA children. Other studies, however, by O'Brien et al. (2003) and Owens, Spirito, McGuinn, and Nobile (2000) found no difference between OSA and control children even when considering various levels of OSA severity. Some have suggested that the memory and cognitive deficits associated with OSA are really due to sleep fragmentation because shorter periods of sleep disruption appear to have less of an effect on memory performance than longer periods (Epstein, Chillag, & Lavie, 1998; Randazzo, Muehlbach, Schweitzer, & Walsh, 1998; Wolfson & Carskadon, 1998).

It is indeed common to see executive dysfunction in adults with OSA, but many in the research community suspect similar deficits in children as well, which are harder to measure and diagnose because they may not be permanent or as noticeable (Blunden et al., 2000; Dahl, 1996; Lewin et al., 2002; O'Brien et al., 2004b). O'Brien et al. (2004b) found impairments in executive function and phonological awareness in OSA children that appear to resolve somewhat with a return to normal sleeping behavior. Much like the effects of OSA on executive function in adults, to be discussed in the next section, the executive dysfunction in children is attributed to hypoxia levels rather than sleep fragmentation (Beebe et al., 2004). This is especially troubling given the fact that the brains of children, particularly the PFC, do not develop fully until much later in their lives. If executive dysfunction is occurring now it could hinder further development, which would affect them permanently as adults.

Another area evaluating the effects of OSA on children involves monitoring school performance (Gozal, 1998; Gozal & Pope, 2001; Perkin et al., 1999). Gozal and Pope (2001) found that even with T&A treatment, children between 13 and 14 years of age who snored as young children were in the bottom quartile of their perspective classes with regard to academic performance. Furthermore, Gozal (1998) noted high rates of OSA in first grade children who ranked in the bottom 10% of their classes academically. It appears that if OSA is not treated at an early enough stage, it may cause enough dysfunction to still influence the academic performance of children when they become teenagers and possibly even as adults.

The T&A treatments in children do appear successful in reversing the effects of neurobehavioral, cognitive, and executive dysfunction (Ali, Pitson, & Stradling, 1996; Chervin et al., 2006; Montgomery-Downs et al., 2005). Although there is yet to be an established time period where one would expect to see improvements following T&A treatment, Chervin et al. (2006) waited 1 year before conducting postoperative testing. The T&A treatments seem to have three general effects. First, the children in the Montgomery-Downs et al. (2005) study following T&A treatment fell asleep at much quicker rates and spent more time in delta wave sleep when apnea indexes were the same as the control group. Second, the "ADHD-like" hyperactivity seemed to literally disappear in most of the children after T&A treatment (Chervin et al., 2006). Parental ratings of hyperactivity and inattention declined, and in the original sample (n = 105) about half of the children no longer met the diagnostic criteria for ADHD (Chervin et al., 2006). Third, improvements in cognitive and executive function, demonstrated by increased scores on the DAS, were found by Montgomery-Downs et al. (2005) after T&A treatments. Montgomery-Downs et al. (2005) were hopeful that the OSA-related cognitive and executive deficits could return to normal levels if caught during an early enough stage of brain development. Despite the fact that the majority of the children in this study were from impoverished environments, they continued to improve cognitively following the T&A treatment (Montgomery-Downs et al., 2005).

Obstructive sleep apnea in adults

The research literature outlining the effects of OSA in adults in terms of emotional, cognitive, and neuropsychological consequences is extensive (Aloia et al., 2004;

Bardwell, Ancoli-Israel, Berry, & Dimsdale, 2001; Beebe & Gozal, 2002; Lojander, Kajaste, Maasilta, & Partinen, 1999; Thomas, Rosen, Stern, Weiss, & Kwong, 2005; Walsleben, Squires, & Rothenberger, 1989). Questions typically answered include how OSA manifests itself differently in adults, whether the cognitive and neuropsychological deficits are permanent, and if the primary mode of treatment in adults – CPAP – is effective. Also, while rates of snoring begin to decrease in children as they approach adolescence, the opposite occurs in adults, with rates of SDB increasing in frequency as they near late adulthood. This may lead to more adverse effects in older adults who already suffer from poor general health.

The emotional symptoms associated with OSA in adults (i.e., fatigue, aggression, irritability, anxiety, and depression) are attributed to excessive daytime sleepiness (Chugh, Weaver, & Dinges, 1996; Stepansky, Lamphere, & Badia, 1984). These symptoms put adults at a higher risk for motor vehicle accidents and workplace injuries (Aldrich, 1989; Ayalon, Ancoli-Israel, Aka, Drummond, & McKenna, 2009; George, Nickerson, Hanly, Millar, & Kryger, 1987; George & Smiley, 1999). It is generally agreed in the literature (see Kheirandish & Gozal, 2006) that these symptoms seem to disappear after normal sleep is achieved.

The cognitive and neuropsychological deficits in adults with OSA seem to persist despite a return to normal patterns of sleep (Bardwell et al., 2001; Beebe & Gozal, 2002; Greenberg et al., 1987; Incalzi et al., 2004; Redline et al., 1997). These deficits seem to center around executive dysfunctions such as poor planning and judgment, inflexible thinking, impulsive decision making, and problems with working memory, as well as verbal memory and fluency dysfunction (Bedard et al., 1993; Day et al., 1999; Doghramji, 1993; Naegele et al., 1995; Redline et al., 1997; Thomas et al., 2005). In fact, adults with OSA and other forms of SDB tend to perform poorly when compared to adult controls on such neuropsychological tests as the Stroop Color–Word Interference Test, the Wisconsin Card Sorting Test, the Trail Making Test, and Continuous Performance tests (Kotterba et al., 1998; Naegele et al., 1995; Redline et al., 1997; Torun-Yazihan, Aydin, & Karakas, 2007). Similar test results are seen in those with damage to the PFC (Beebe & Gozal, 2002).

Although some studies point to clear deficits caused by OSA in adults, other researchers conclude that verbal memory and global cognitive function remain relatively intact (Yaouhi et al., 2009). In their analysis of the literature, Aloia et al. (2004) attributed these discrepancies to the wide variety of neuropsychological tests used, which may still ultimately evaluate the frontal cortex, possibly in areas other than executive function. The authors also speculated that the level of sleep apnea (i.e., mild versus severe) or the length of time exposed to OSA might also serve as other variables influencing the disruption of cognitive function (Aloia et al., 2004). In other words, the relationships among the levels of OSA, patient's age, length of exposure, and degree of impaired global cognitive function are not linear. Instead, a plateau that takes shape once the values of a number of variables, yet to be determined, are either reached or surpassed could represent this relationship.

Medical treatment does appear successful in alleviating to some degree the cognitive and neuropsychological dysfunction associated with OSA, but these procedures are different to those used in children (Bardwell et al., 2001; Lojander et al., 1999; Redline et al., 1998). During CPAP, adults wear a breathing mask while sleeping and air is forced into the throat so that it will not close during inhaling. This treatment has been shown to improve cognitive function and mental flexibility significantly (Engleman, Kingshott, Martin, & Douglas, 2000; Lamphere et al., 1989; Montplaisir, Bedard, Richer, & Rouleau, 1992; Roehrs et al., 1995). CPAP has been found to increase overall neuropsychological performance significantly when compared to placebo CPAP where a lower level of air pressure is used (Bardwell et al., 2001). Although these authors could not find any significant increases on specific neuropsychological tests, they attributed this inability to the fact that their treatment only lasted 1 week (Bardwell et al., 2001). Redline et al. (1998) also noticed an improvement in mood, vigilance, cognitive, and executive function following CPAP, but no significant differences were found among the various patient levels of OSA (e.g. mild, moderate, and severe). The overall consensus of this literature is that CPAP is beneficial in cognitive and neuropsychological recovery, but a few studies indicated no real CPAP benefit, with symptoms appearing to continue despite treatment. This may be related to the types of measurement instruments used or differences in patient hypoxia/hypoxemia levels (Aloia et al., 2004; Engleman, Cheshire, Deary, & Douglas, 1993; Gozal & Pope, 2001).

Although an exact mechanism explaining how OSA and SDB lead to neurobehavioral, cognitive, and executive dysfunction in children and adults remains elusive, several theories have been proposed (Aloia et al., 2004; Beebe & Gozal, 2002; Kato et al., 2000; Lanfranchi & Somers, 2001). One unifying theme among these available theories seems to be related to the amount of hypoxia/hypoxemia present, which may lead to metabolic or neurochemical changes in the PFC (Aloia et al., 2004; Beebe & Gozal, 2002; Berry et al., 1986; Harrison & Horne, 1998; Naegele et al., 1995). One general theory suggests that the reason for the differences between OSA symptoms in children and adults is a likely result of the hypoxia/hypoxemia influencing a child's still developing PFC versus that of an adult's PFC where development is complete (Aloia et al., 2004; Beebe & Gozal, 2002). Another category of theories still attributes executive dysfunction to hypoxia/hypoxemia disrupting the PFC but links the neurobehavioral disruptions, especially those commonly seen in children, to sleep fragmentation and reductions in the percentage of rapid eye movement (REM) sleep (O'Brien et al., 2004a). According to this theory, the neurobehavioral deficits should disappear after normal sleep, but the neuropsychological dysfunction may continue if the changes in the PFC, probably metabolic in nature, are not resolved. The third category of theories, demonstrated primarily by the Lanfranchi and Somers (2001) model, postulates that hypoxia/hypoxemia causes changes in hormonal and endocrine levels, thereby modifying blood vessel structure. This change in blood vessel structure may explain why many older patients with OSA and SDB often have heart and hypertension problems, but it does explain why OSA seems to cause only executive dysfunction (Aloia et al., 2004). One would expect to see a host of other brain dysfunctions, such as visual, auditory, or coordination problems to name just a few.

Chronic obstructive pulmonary disease and lung transplant

Hypoxia/hypoxemia, if present during COPD or in those awaiting lung transplants, has also been linked to similar mood, cognitive, and neuropsychological deficits seen in

patients with SDB and OSA (Emery, Honn, Diaz, Lebowitz, & Frid, 2001; Emery, Leatherman, Burker, & MacIntyre, 1991; Parekh et al., 2003; Prigatano, Parsons, Wright, Levin, & Hawryluk, 1983; Williams et al., 1997). In one unusual exception, Ridgway and McFarland (2006) found no real differences in their sample of underwater divers who held their breath for sustained periods of time, exposing them to reoccurring hypoxemia, despite extensive neuropsychological testing. COPD is generally used to describe end stage disease where patients experience a decrease in overall health plus an increase in shortness of breath. Lung transplant surgery is used only during cases of COPD or other serious respiratory disorders. Stuss, Peterkin, Guzman, Guzman, and Troyer (1997) have attributed these cognitive and neuropsychological impairments to increased levels of carbon dioxide found in patient blood samples.

The cognitive and neuropsychological deficits, especially those seen in individuals who qualify for lung transplant, are of concern because these patients must follow very strict medical guidelines after the surgery. Patients with COPD appear to have deficits in neuropsychological functions of memory, reasoning, verbal processing, and performance speed, as well as anxiety and depression (Emery et al., 2001; Prigatano et al., 1983). With so many different types of neuropsychological and emotional dysfunction found among these patients, the possibility of an unsuccessful postoperative period and eventual rejection of the transplanted organ is likely due to a failure to follow proper guidelines.

Administering oxygen to patients with COPD has been shown to increase cognitive and neuropsychological function, and introducing exercise regimens is also beneficial (Emery, Shermer, Hauck, Hsiao, & MacIntyre, 2003; Etnier et al., 1999; Heaton, Grant, McSweeny, Adams, & Petty, 1983; Parekh et al., 2005). For example, Parekh et al. (2005) found that high exercise capacity (e.g., furthest distance walked within 6 minutes) was significantly related to cognitive improvement on the Halstead-Reitan battery. Emery et al. (2003) noted that their COPD patients had to continue to exercise just to maintain their past gains of emotional, cognitive, and neuropsychological improvements, while those who stopped exercising experienced decreases in the functioning of these three areas. Essentially, the COPD patients reached a plateau and had to continue to exercise for maintenance, but exercise was not seen by these authors as a means to improve cognitive and neuropsychological function (Emery et al., 2003). Levels of hypoxia/hypoxemia do seem to play a major role in the amount of cognitive and neuropsychological dysfunction in both COPD and SDB, but different approaches with varying degrees of success are used to treat these conditions separately.

Traumatic brain injury (TBI)

The role of SDB as a precursor, symptom, or consequence of TBI is now beginning to be addressed in the research literature (Makley, Drubach, Tarwater, & Kreuz, 2008). Levels of SDB among TBI subjects are as high as 36% (Webster, Bell, Hussey, Natale, & Lakshminarayan, 2001) and 46% (Castriotta et al., 2007). Interestingly, both of these previously mentioned studies found no evidence that the degree of SDB was indicative of TBI levels, meaning that those with high levels of SDB did not have more serious brain injury than those with only mild or moderate head injury.

Currently, three general questions regarding the link between SDB and TBI remain unanswered. First it is unclear, although theorized, that TBI acts as a precursor or catalyst for future SDB. An individual who sustains a TBI has increased chances of developing SDB. Another possibility is that excessive daytime sleepiness and executive dysfunction experienced by those with SDB may lead to lapses in judgment (e.g., driving a car), ultimately leading to TBI. Current research has not yet successfully answered this question. Secondly, does the likelihood of SDB increase as the amount of time elapsed since the TBI also increases? For example, Castriotta et al. (2007) found about a 10% higher rate of SDB in individuals evaluated at least 90 days after the TBI, while Webster et al. (2001) evaluated their subjects less than 90 days from the time of the brain injury. Is there a posttrauma period of 6 months or 1 year where the likelihood of SDB following a TBI peaks, or is there a time interval after which the majority of those with TBI develop some form of SDB? Third, it is unknown why TBI severity is not a useful predictor of SDB levels. There is mention in the literature that SDB is associated with abnormal brain function such as seizures, particularly in children, and stroke (Chihorek, Abou-Khalil, & Malow, 2007; Miano et al., 2009; Nasr, Pavy-Le Traon, Czosnyka, Schmidt, & Larrue, 2009). One would expect that the more severe the head injury, the more severe the SDB, but research by Webster et al. (2001) and Castriotta et al. (2007) found no significant relationship. Even though additional questions are likely to develop as research in this specific area is furthered, knowledge of SDB may provide additional insight into the mechanisms of TBI.

Conclusion

The present review of the literature indicates that respiratory dysfunction such as noted in OSA and COPD will contribute to a host of neurobehavioral, cognitive, and neuropsychological deficits. Although the symptoms of these deficits may manifest somewhat differently in children and adults, it does appear that the level of hypoxia/hypoxemia involved is a critical contributor. The neurobehavioral, cognitive, and neuropsychological deficits responded overall to treatment fairly well, although the long-term consequences of respiratory dysfunction remain unclear, especially in children where brain development is not yet completed.

Several methodological limitations do seem to appear regularly in the literature. First, a number of studies examining the effectiveness of treatment in SDB in patients have low numbers of subjects in their studies, as noted in the following: $n = 12$ (van der Post et al., 2002), $n = 14$ (Walsleben et al., 1989), $n = 16$ (Thomas et al., 2005), $n = 28$ (Emery et al., 2003), and $n = 36$ (Bardwell et al., 2001). Other studies, however, have been successful in recruiting larger subject populations, especially among children: $n = 105$ (Chervin et al., 2006), $n = 299$ (O'Brien et al., 2004a), and $n = 718$ (Foley et al., 2003). Those studies with smaller numbers of volunteers raise questions of statistical power and generalization but may also be reflective of the nature of this research topic. Participants with both respiratory dysfunction and hypoxia/hypoxemia are difficult to recruit and may be unwilling to submit fully to the experimental procedures (i.e., complete all cognitive and neuropsychological evaluations, participate in exercise programs lasting several months, or return for an 18-month follow-up procedure).

Second, although some studies have been criticized for instituting quick follow-ups after treatment (e.g., 2–7 days) in OSA, patients have been found to improve cognitively and neuropsychologically during a relatively short time period (Bardwell et al., 2001; Chervin et al., 2006; Emery et al., 2003; Montgomery-Downs et al., 2005; Scheltens, Visscher, Van Keimpema, & Lindeboom, 1991). Longer term follow-up, as well as tracking the possibility of increasing morbidity, would greatly add to the effect of treatments such as CPAP on neuropsychological function.

Third, there is some debate regarding the methods used to assess cognitive and neuropsychological deficits. Several studies have found global cognitive and neuropsychological dysfunction, but patients' scores on individual tests were either inconclusive or only some but not all of the various tests in the battery indicated deficiencies (Greenberg et al., 1987; Parekh et al., 2005; Rodrigue, Kanasky, Marhefka, Perri, & Baz, 2001). More subtle measures, including reaction time and computer-based cognitively focused neuropsychological measures, may aid in determining critical yet difficult to measure deficits. Also, there is concern that the respiratory dysfunction in children marked by executive deficits and the adult neurobehavioral problems are on a greater scale than what has been hypothesized in the literature (Kheirandish & Gozal, 2006). In such instances, the cognitive and neuropsychological tests available may not be sensitive enough for detection, not utilized properly, or other factors developing prior to testing (i.e., an undefined operational definition of hypoxia/hypoxemia, either by nadir oxygen level or number of desaturations) are not fully considered (Cheshire, Engleman, Deary, Shapiro, & Douglas, 1992; Kingshott et al., 2000). Neuropsychological test insensitivity may be overcome by using different methods, including functional imagery or auditory event-related potentials (Thomas et al., 2005; Walsleben et al., 1989).

Fourth, recruitment for these studies comes from mostly clinic-referred individuals or healthy volunteers (O'Brien et al., 2004b). Although those participants referred from clinics tend to have the more severe forms of SDB and OSA (e.g., who finally sought medical treatment), individuals with mild forms of SDB and OSA may be unaware they have a medical condition and are less likely to show up in these types of studies. In such cases, researchers may be at a disadvantage, missing how respiratory dysfunction manifests itself during early stages of development (Knight et al., 1987).

The future of respiratory dysfunction research and neuropsychology

Although the precise neural mechanism of SDB and OSA in humans remains relatively unclear, animal models have had some success in pointing towards cell loss in the hippocampus and PFC as an explanation for the related cognitive and neuropsychological deficits (Gozal, Daniel, & Dohanich, 2001a; Kheirandish, Row, Li, Brittian, & Gozal, 2005; Payne, Goldbart, Gozal, & Schurr, 2004). This research has also been successful by demonstrating in rats, especially males, that the level of hypoxia/hypoxemia during sleep is linked to the degree of neurobehavioral disruption (Kheirandish & Gozal, 2006). As well as further investigating the susceptibility of the PFC to respiratory dysfunction, it may be of benefit to examine other factors

that may have interacting relationships. Possibilities include genetic, nutritional, or environmental variables among those susceptible to the more severe forms of OSA, mechanisms responsible for the increase of SDB with age, or a time period, when passed, where the various neurobehavioral, cognitive, and neuropsychological deficits become either irreversible or resistant to treatment. Such questions will be easier to answer through the use of animal models.

A second area of research involving the effects of respiratory disruption centers on its usefulness as a predictor of the degree of neurobehavioral, cognitive, and neuropsychological dysfunction that one may expect in Alzheimer's disease and stroke (Ancoli-Israel, Klauber, Butters, & Parker, 1991a; Askenasy & Goldhammer, 1988; Decary, Rouleau, & Montplaisir, 2000). For example, during Alzheimer's disease, these cognitive and neuropsychological deficits could represent an early sign of eventual dementia or an association with respiratory dysfunction where the effects of dementia escalate within a shorter time period. Ancoli-Israel et al. (1991a) and Ancoli-Israel, Klauber, Kripke, Parker, and Cobarrubias (1989) noted higher rates of SDB among patients with Alzheimer's disease. Other studies, however, have found either a slight relationship between SDB and Alzheimer's disease (Hoch, Reynolds, Kupfer, & Houck, 1986) or no relationship at all (Bliwise, Yesavage, Tinklenberg, & Dement, 1989). Sleep apnea is common in stroke patients, with rates of occurrence ranging anywhere from 54% to 95% in those studied (Bassetti, Aldrich, Chervin, & Quint, 1996: Dyken, Somers, Yamada, Ren, & Zimmermann, 1996). In these studies, OSA represents a possible predisposition for stroke since its occurrence increases in hypertension and cardiac disease (Bassetti et al., 1996). Physical examination of the patient's level of hypoxia/hypoxemia and degree of airway closure during sleep may serve as an indication that a stroke is imminent (Mohsenin, 2001). Respiratory dysfunction may also compound the effect of the stroke on cognitive and neuropsychological function as well. This, however, may be more difficult to detect because strokes disrupt a number of numerous brain areas.

The relationship between respiratory dysfunction and neuropsychological deficits is not surprising. Disruptions in the flow of oxygen to the brain during periods of alertness and sleep have been known to cause brain dysfunction for quite some time. What is unusual, however, is that SDB appears to influence only certain cognitive and neuropsychological processes, specifically those related to executive function and the PFC. SDB also appears to influence children and adults differently. Research on respiratory dysfunction is gaining momentum by studying animal models of symptom manifestation as well as the effects of interventions such as CPAP on the possible amelioration or control of neuropsychological deficits. Research should address SDB levels as predictors of the degree of neuropsychological disruption that one would expect to see in individuals at risk for suffering from Alzheimer's and cerebrovascular disease, including stroke.

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11 Fibromyalgia, chronic fatigue, and related "neurasthenic" disorders

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This chapter presents the modern conceptualization of an illness well recognized at the turn of the 19th century – neurasthenia (Wessely, Hotopf, & Sharpe, 1998). Because the primary feature of neurasthenia was fatigue, the major focus in modern-day syndromes discussed in this chapter is fatigue. The "new" syndromes to be described are chronic fatigue syndrome (CFS) and fibromyalgia (FM). While fatigue is not the primary defining feature of FM, fatigue indeed plays a prominent role and thus may also be considered related to the older concept of neurasthenia. Several other syndromes with "unexplained symptoms" have been recognized, such as multiple chemical sensitivity, irritable bowel syndrome, sick building syndrome, temporomandibular disorder (TMD), atypical connective tissue disease after silicone breast implants, mitral valve prolapse, dental amalgam disease, and most recently Gulf War illness (Aaron, Burke, & Buchwald, 2000; Kipen & Fiedler, 1999; Wessely et al., 1998), some of which will be mentioned briefly toward the end of this chapter.

The chapter will begin with an initial description of each syndrome, followed by the historical development of fatigue, and then its conceptualizations and reformulations into the modern-day syndromes. This will be followed by a description of each of the modern syndromes, including controversial issues and potential future developments.

Description and diagnostic criteria

Fibromyalgia (FM) and chronic fatigue syndrome (CFS) share clinically important characteristics, including similar medical and psychological symptomatologies, wide arrays of symptom fluctuations and levels of disability, poorly understood etiologies, and lack of effective "cures" (Wessely et al., 1998). Some of the overlapping symptoms include persistent chronic fatigue, generalized and chronic pain, sleep disorders, neurocognitive difficulties, and bowel complaints (Aaron et al., 2000), while disability can range from bed-ridden to specific debilitating problems in social, occupational, financial, and recreational activities (Assefi, Coy, Uslan, Smith, & Buchwald, 2002). For example, up to 95% of FM patients complain of general fatigue (Buchwald & Garrity, 1994; Wessely et al., 1998). Up to 70% of persons with FM met the criteria for CFS (Aaron et al., 2000; Buchwald & Garrity, 1994) and up to 70% of persons with CFS have concurrent FM (Afari & Buchwald, 2003). Tender points, which are the hallmark of FM, are also present in significant amounts among persons with CFS (Aaron et al., 2000). Neither FM nor CFS has a clearly defined cause. Due to the lack of biological markers and specific diagnostic tests, diagnoses