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Sleep-Disordered Breathing, Physiological Sequelae, and the Neurobiological Relationship with Psychopathology

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Abstract

Sleep-Disordered Breathing is empirically related to at least three forms of mental illness: Autistic Disorder (AD), Attention Deficit/Hyperactivity Disorder (ADHD), and Major Depressive Disorder (MDD). A review of the literature revealed that SDB and/or its correlates are both cause and effect of critical neurobiological mechanisms contributing to these forms of psychopathology during gestation, childhood/adolescence, and adulthood, respectively. Time-specific SDB sequelae correlate with cortical alterations that mirror the known neuroanatomical signatures of the aforementioned mental illnesses. Thus, SDB may be not only a general risk factor for psychopathology but a specific risk factor for at least three types of mental illness when viewed in its age-specific developmental context. Since in many cases SDB is readily treatable, implications of this theory include a number of treatment strategies for diverse types of psychopathology.

Keywords: Attention deficit hyperactivity disorder (ADHD), Autistic disorder (AD), Major depressive disorder (MDD), Psychopathology, Sleep-disordered breathing (SDB)

Sleep-Disordered Breathing, Physiological Sequelae, and the Neurobiological Relationship with Psychopathology

Sleep Disordered Breathing (SDB) characterizes a broad range of disorders described by abnormalities in respiratory pattern and intake during sleep (Okawa & Inoue, 2007). These range from snoring to upper-airway resistance syndrome (UARS) to severe obstructive sleep apnea syndrome (OSAS) as defined by the International Classification of Sleep Disorders, Second Edition (American Academy of Sleep Medicine, 2001; Yudofsky & Hales, 2007). SDB is common, affecting approximately ten percent of adult females and twenty-five percent of adult males (Young et al., 1993), with its most severe form—obstructive sleep apnea (OSA)—plaguing two percent of women and four percent of adult men (Strollo & Rogers, 1996).

Sleep-disordered breathing appears to have many biochemical and clinical correlates. It is known to be associated with innumerable adverse changes in the cardiovascular, metabolic, and neurological systems. For example, SDB has been shown to have independent associations with obesity, increased age, smoking, excessive alcohol intake, and other medical conditions including gastroesophageal reflux disease and various diseases of the heart (Franklin, Rehnqvist, & Axelsson, 2007). SDB seems to have a strong genetic component (Kaparianos, Sampsonas, Karkoulias, & Spiropoulos, 2006; Pillar & Lavie, 1995; Redline, Tosteson, Tishler, Carskadon, & Millman, 1992) and pregnancy increases the risk of SDB by 2-3 times (Izci et al., 2006).

Extensive research has identified these conventional clinical correlates, but relatively little attention has been paid to the relationship that has been emerging between SDB and three specific forms of psychopathology. To date, SDB has been shown to have significant empirical relationships with autistic disorder (AD), attention deficit/hyperactivity disorder (ADHD), and major depressive disorder (MDD). The present paper serves to review these relationships while

developing a neurobiological framework that proposes potential mechanisms as a function of the age of exposure to SDB. While it is possible that other forms of psychopathology may be related to SDB, empirical relationships outside of those in this review have not been elucidated.

Autistic Disorder and the Correlates of Maternal SDB in Utero

A recent study funded by the Center for Disease Control and Prevention estimated that 3-7 out of 1000 children have some form of Autism spectrum disorder, the most common of which is autistic disorder (Yeargin-Allsopp et al., 2003). Troublingly, the prevalence of autistic disorder is most likely rising (Fombonne, 2003). Autism not only has great costs in terms of the afflicted—sensory, cognitive, and interpersonal impairments—but vast repercussions with regard to healthcare spending. Recent projections for the cost of taking care of an individual with autism across his or her lifetime amounted to over $3.2 million (Moldin & Rubenstein, 2006). In fact, the cost for caring for all people with autism across their lifetimes may be as high as $35 billion per year.

Thus, it is of great concern that many studies have empirically linked SDB in early childhood with autistic disorder. A recent study found that sleep-disordered breathing was related to “autistic-relating behavior” in a cohort of young subjects (O'Donoghue et al., 2005; see also Malow, McGrew, Harvey, Henderson, & Stone, 2006, Liu, Hubbard, Fabes, & Adam, and Halbower et al., 2006). Most of the research linking SDB to autism to date suggests that “sleep-disordered breathing predicted children's stereotyped behavior, social interaction problems, and overall level of autism” (Hoffman et al., 2005).

However, it is unlikely that sleep-disordered breathing during early childhood *causes* autistic disorder. Rather, many authors have formulated a different theory based on the facts that AD is usually diagnosed very early in life, AD is not alleviated by continuous positive airway

pressure (CPAP), and SDB is highly heritable. It has been proposed that deviant behavioral patterns of autistic infants may arise from cortical insult due to maternal SDB in *utero* (see Table 1) (Msall, Bier, LaGasse, Tremont, & Lester, 1998; Naeye & Peters, 1987; Robertson & Finer, 1993). Numerous prior studies have noted fetal neurobiological changes associated with maternal sleep-disordered breathing sequelae (Ayalon & Peterson, 2007; Gale & Hopkins, 2004). Maternal SDB, therefore, appears to be an important target in autism research.

Maternal SDB correlates (hypoxia, metabolic fluctuations, hemodynamic changes, sympathetic activations, vasculature abnormalities, etc,) have been shown to be especially dangerous for developing fetuses. The most direct route to fetal cortical abnormalities may involve the induction of fetal hypoxia resulting from blood oxygen desaturation of the pregnant mother, although this is currently under debate. If such a phenomenon occurs, one route to this desaturation could be SDB. This is manifested in the short-term by physiological changes including fetal heart rate deceleration (Roush & Bell, 2004). In a general sense, at least one study has found that maternal SDB is related to poor fetal outcome as indexed by lower APGAR scores and higher rates of neonatal healthcare unit admission (Sahin et al., 2008). Specifically, SDB-related correlates can lead to placental ischemia, resulting in serious abnormalities ranging from fetal growth restriction to fetal bradychardia (Ritchie, 1980) and, of particular importance to this review, abnormalities in fetal brain development.

Based on an extensive review of the literature, maternal SDB correlates in animals are most likely associated with cortical abnormalities ranging from alterations in neuronal migration, to increased apoptosis to macrocephaly. Previous models to date have looked at more extreme forms of hypoxia and thus should be viewed as more analogous to full-blown sleep apnea. However, they

should not be completely discounted for milder forms of SDB as it is likely that they have an attenuated but nevertheless important effect.

Previous studies have shown correlations between maternal SDB correlates and fetal neuropathology including documented damage to the frontal cortex (Kheirandish, Gozal, Pequignot, Pequignot, & Row, 2005), hippocampus (Falkowski, Hammond, Han, & Richardson, 2002; Gerstein et al., 2005; Mallard, Williams, Johnston, & Gluckman, 1994), pons (Kheirandish et al., 2005), cerebellum (Lee et al., 2001), amygdala (Ke et al., 2005) and the subcortical pathways of the basal ganglia and thalamus (Derrick et al., 2004). Mallard and his colleagues (1999) found that periodic fetal hypoxia was associated with overall gray-matter deficiencies and that placental insufficiency such as that associated with chronic intermittent hypoxic episodes was associated with the enlargement of the cerebral ventricles and reduced area of the cerebral cortex relative to controls (Mallard, Rehn, Rees, Tolcos, & Copolov, 1999). Brunel and colleagues (2004) proposed that two out of every three fetuses exposed to hypoxic conditions develop a chronic response consisting of ventricular dilation and ventricular wall abnormalities accompanied with an overall decrease in white matter. These white matter injuries resulting from fetal hypoxia can be associated with a compensatory increase in cerebrospinal fluid (CSF) (Inder et al., 1999).

Viewing Maternal SDB correlates in the Context of Neurobiology: Autistic Disorder Mechanisms and Implications

The relationship between maternal SDB and brain changes becomes especially important when viewed in a broader context. While it is difficult to determine the exact prevalence of fetuses exposed to SDB correlates in *utero*, data suggest that it may as high as 30%, since pregnant women are 2-3 times more likely to experience SDB than non-pregnant women (Izci et al., 2006). In a survey of over 500 new mothers, results showed that rates of SDB (specifically snoring) jumped

from 4% before pregnancy to 23% on the day of delivery, with the largest increase during the third trimester (Franklin et al., 2000). In most studies, women returned to their pre-pregnancy levels of SDB as little as three months after delivery (Hedman, Pohjasvaara, Tolonen, Suhonen-Malm, & Myllyla, 2002). The increase in SDB during pregnancy may be due to a variety of factors including gestational weight gain, nasopharyngeal edema, decreased functional reserve capacity, and increased arousals from sleep (Pien & Schwab, 2004).

Because maternal SDB is associated with abnormalities in many of the same areas known to be damaged in the autistic brain, it is possible that SDB serves as a contributing factor in some cases of AD. Specific areas of overlap include (see Table 1): the amygdala (Howard et al., 2000; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001), amygdala-hippocampal region (Kemper & Bauman, 1992; Otsuka, Harada, Mori, Hisaoka, & Nishitani, 1999), frontal cortex (Otsuka et al., 1999), cerebellum (Salmond, Vargha-Khadem, Gadian, de Haan, Baldeweg, 2007), thalamus (Hardan et al., 2006), lateral ventricles (Piven et al.,1995), pons (Hashimoto et al., 1991), and basal ganglia (specifically caudate enlargements) (Sears et al., 1999). In an area of heated debate during recent years, Rojas et al. (2006) found both volumetric gray matter decreases (in the cerebellum) and volumetric gray matter increases (in the medial frontal gyri, caudate nuclei, hippocampus, etc.) in the brains of autistic individuals relative to controls.

Conflicting data with regard to the cortical destruction associated with SDB correlates suggest that the relationship between autism and sleep-disordered breathing is undoubtedly complex. For example, a vast majority of the data citing the effects of SDB in utero indicate that related correlates contribute to neuronal breakdown (apoptosis). However, it is well-documented that the brains of most individuals with autism younger than twelve years old actually have a larger cortical volume, which seemingly contradicts the above data (Aylward, Minshew, Field, Sparks, &

Singh, 2002; Hardan et al., 2001). Recent research has not only shed light upon this apparently paradoxical relationship, but also substantiated the relationship between maternal SDB and autism by proposing specific neurobiological mechanisms.

In their paper, Kern and Jones (2006) argue that there may be a complex interplay between neuronal apoptosis and proliferation (gliosis) in autism. Specifically, purkinje cell loss (prevalent in the cerebellum of the autistic brain) leads to the release of glial fribrillary acidic protein (GFAP) indicative of nervous cell damage (Ahlsen et al., 1993). This causes a compensatory response that results in an increased rate of glial cell production (glial cell hyperplasia). In other words, well-documented damage to purkinje fibers resulting in a short-term cortical volume *decrease* is accompanied by overall cortical volume *increases* via glial cell hyperplasia. The offsetting effects of these processes may explain why children with autism are born with normal head circumferences and therefore presumably normal brain volumes (Courchesne et al., 2001). It has been suggested that the compensatory response continues during the postnatal years, which may explain why children with autism tend to show increases in cortical brain volume generally manifested in the toddler years (Courchesne et al., 2001). SDB correlates have been suggested as a possible vehicle whereby purkinje cell loss can occur, leading to a neural compensatory response that is consistent with the development of autistic disorder (Ahlsen et al., 2003).

A minority of articles suggests that SDB-correlates can lead to the increase in brain volume seen in autism in other ways. For example, a few authors (Bauman & Kemper, 1994; Vajda, 2002) have posited that the damage done to the purkinje cells results in a compensatory mechanism in which the purkinje cells *themselves* become enlarged. Evidence for this inflammatory reactive edema is seen in the swelling response of purkinje cells when they are exposed to a variety of neural toxins (Kiefer, Knoth, Anagnostopoulos, & Volk, 1989). Some research has elaborated on

the relationship between cortical toxicity, SDB correlates, and brain enlargement by suggesting complex mechanisms whereby SDB correlates lead to forms of immunosuppression, thereby making the brain vulnerable to a buildup of toxic materials in the post-natal period (Sarafian et al., 1999). SDB correlates may lead to the compromise of antioxidant proteins, which may result in the sequestering of toxic metals such as lead in the autistic brain (Bradstreet, Geier, Kartzinel, Adams, & Geier, 2003). Buildup of these metals has been shown to lead to purkinje cell death which, as noted above, may result in a compensatory purkinje edema or gliosis.

Attention Deficit/Hyperactivity Disorder and the Correlates of Childhood SDB

Attention deficit/hyperactivity disorder (ADHD) also has a strong empirical relationship with SDB. Recent research estimates that almost 1 out of 12 school-aged children has been reported by their parents as having ADHD; this may explain why 4.4 million youth between the ages of 4-17 have been diagnosed with ADHD (Faraone, Sergeant, Gillberg, & Biederman, 2003). Using less restrictive methods, some have found the prevalence of ADHD in children to be as high as 16 percent (Birnbaum et al., 2005). Individuals with ADHD have more co-morbid mental problems than other populations ranging from anxiety, depression, conduct disorders, antisocial personality disorder, and delinquent behavior (Birnbaum et al., 2005). Estimates have shown that ADHD costs Americans almost $80 billion per year (Birnbaum et al., 2005).

Like autism, childhood ADHD has been shown to have a strong empirical relationship with SDB. Chervin et al. (2002) found that children who snored habitually were twice as likely as non-snoring controls to have a high score on a hyperactivity index. Similar results were observed for an inattention/hyperactivity scale developed based on the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition. Another investigation of the effects of childhood SDB on ADHD revealed odds ratios over 2.0 for inattention, hyperactivity, and aggressiveness in a group

of 5-year-old patients with diagnosable SDB compared to controls (Gottlieb et al., 2003). It therefore makes sense that 50% of a childhood ADHD sample had some form of SDB (Golan, Shahar, Ravid, & Pillar, 2004).

Childhood SDB correlates are much more likely to be etiological factors in ADHD than in autism primarily because ADHD diagnosis is usually made much later in childhood, around seven years (Ray et al., 2006). Furthermore, the treatment of problematic sleep during childhood appears to have a more therapeutic effect for ADHD patients than those with autism (Ballas, 2008).

However, pinpointing the specific aspect of problematic sleep in childhood ADHD has led to some debate. It has been proposed that the symptoms of ADHD develop in childhood as a result of repeated, persistent sleep interruption, but recent literature suggests that neurological changes associated with SDB correlates may be crucial in the development of ADHD. Notably, childhood SDB and its downstream correlates may be related to changes in brain structure and function that include damage to the hippocampus and right frontal cortex (Gadian et al., 2000), basal ganglia (Barkovich, 2005), cerebellum (Lai et al., 2003), pons (Ramanathan, Gozal, & Siegel, 2005), thalamus (Douglas et al., 2007), and corpus callosum associated with overall white matter and cortical volume decreases (Ment, Schwartz, Makuch, & Stewart, 1998).

Viewing Childhood SDB correlates in the Context of Neurobiology: ADHD Mechanisms and Implications

Evidence in support of an association between neurobiological alterations, SDB correlates, and ADHD necessarily spurs an investigation into the mechanisms that underlie the ADHD clinical presentation. First, while repeated, persistent sleep interruption likely plays a part in ADHD symptoms (Ballas, 2008), neurobiological research reveals that sleep interruption may be one of the many *symptoms* of SDB. For example, if sleep interruption was an important etiological

factor, it would be expected that a vast majority of young patients would respond to stimulant medication designed to compensate for low arousal levels (Chervin, Dillon, Bassetti, Ganoczy, & Pituch, 1997). However, some groups are responsive to stimulants and some are not, indicating that the true etiology may be more complex than a simple lack of arousal secondary to sleep interruption in these children. It is possible that SDB correlates may account superficially for low arousals but more importantly the cortical abnormalities known to be present in ADHD. Thus, stimulants most likely treat the symptoms of ADHD rather than an etiological factor.

There is a significant subgroup of young ADHD patients that respond to CPAP (Engleman, Martin, Deary, & Douglas, 1997; Kotterba et al., 1998; Tirosh, Tal, & Jaffe, 1995). Since CPAP is known to maintain airway opening and increase oxygenation in the brain, many consider this to be a more efficacious target in pinpointing the major ADHD etiological factor (Chervin et al., 1997). This perspective gains credence by considering that the brain areas known to be altered as a result of childhood SDB correlates are almost all present in the neuroanatomical signature of ADHD. One study showed that individuals with ADHD show abnormalities in overall white matter (decreases specifically in the left hemisphere), superior frontal gyrus, corpus collosum, right posterior cingulate gyrus, and basal ganglia (Overmeyer et al., 2001). Furthermore, ADHD patients have problems in the right frontal cortex (Castellanos et al., 2001), cerebellum (Berquin et al., 1998), hippocampus (Plessen et al., 2006), brain stem (bilateral pons) (Zang et al., 2007), thalamus (Kim, Lee, Shin, Cho, & Lee, 2002), and overall gray matter deficiencies with net cortical volume decreases (Halbower et al., 2006).

Evidence suggests that damage to all but two of the regions known to be abnormal in ADHD may be associated with childhood SDB correlates (See Table 2). Key cortical abnormalities found in the neuroanatomical signature of ADHD that may be related to chronic SDB during

childhood include decreases in overall cortical volume and white matter and damage to the right frontal cortex, basal ganglia, cerebellum, pons, thalamus, corpus calossum, and hippocampus.

Major Depressive Disorder and the Correlates of Adult SDB

A recent study found that as many as 18 percent of Americans may have Major Depressive Disorder (Williams et al., 2007). This estimate has been rising steadily in recent years (Lambert, 2006). MDD can be crippling to its victims, resulting in inordinate guilt, poor concentration and indecisiveness, suicidal thoughts, and a myriad of psychopathological co-morbidities (Grote & Frank, 2003). These maladies severely impact function in everyday activities. One study found that treating MDD actually *lowers* overall health care costs for its patients due to decreasing its many other problematic correlates (Katon et al., 2006).

The link between SDB and MDD is empirically well documented. Some older studies found that almost half of their entire adult sample with SDB had depressive symptoms (Millman, Fogel, McNamara, & Carlisle, 1989), often times meriting a diagnosis of Major Depressive Disorder (Mosko et al., 1989). Depressives were significantly more likely to have SDB in other studies (Bliwise,1993; Kupfer et al., 1981; Schroder & O'Hara, 2005). Recently, Deldin et al. (2006) found that SDB predicted accurate grouping in 81.3% of subjects with MDD and 80.6% of controls. In fact, one investigation found that, after controlling for obesity and hypertension, the adjusted odds ratio was 5.6 for having SDB for individuals with MDD (Ohayon, 2003).

These findings reinforce the virtually axiomatic relationship between emotional well-being and adequate sleep. This can be explored further by first noting the similarities in the psychological correlates. Documented cognitive symptoms of *both* MDD and SDB include deficiencies in overall memory (Peng, Li, Kang, & Huang, 2004; Richards & Ruff, 1989), selective attention (Kales et al., 1985; Landro, Stiles, & Sletvold, 2001), and communication (Berry, Webb, Block, Bauer, &

Switzer, 1986). Furthermore, individuals with SDB and MDD tend to both have high levels of guilt, pessimism, and low self-esteem (Aikens, Caruana-Montaldo, Vanable, Tadimeti, & Mendelson, 1999).

Recent reports suggest that the cyclical nature in which SDB and MDD might be related (i.e., SDB leads to MDD which leads to more SDB) may be rooted in the neurobiological effects of SDB-related correlates in adulthood. A thorough review of the literature for the present paper revealed that SDB correlates experienced as an adult are associated with numerous cortical abnormalities. These abnormalities are generally similar but distinguishable from brain changes known to take place with regard to fetal or childhood hypoxia. The SDB correlates endured in adulthood result in sleep fragmentation and neuronal damage characterized by a reduction of neuronal excitability or neuronal apoptosis (Morrell et al., 2003). The most extensive study on the cortical implications of OSAS was done by Macey et al. (2003). They found overall gray-matter deficiencies and specifically noted a decrease of gray matter in the right postcentral gyrus, posterior lateral parietal cortex, anterior superior frontal gyrus, left ventral lateral frontal cortex, and numerous sites in the lateral prefrontal cortex. Abnormalities in the temporal lobe included the inferior temporal gyrus and parahippocampal gyrus. An overall cortical volume decrease was noted in the left side of the brain extending dorsally, including the caudal extent of the lateral sulcus. Gray matter decreases were also found in the right hippocampus and the quadrangular lobule of the medial, deep cerebellar cortex.

Additional studies have found abnormalities in the amygdala (Gozal et al., 2001), hippocampus (Bartlett et al., 2004; Cervos-Navarro & Diemer, 1991), anterior cingulate cortex (Henderson et al., 2006), basal ganglia (Macey et al., 2006), prefrontal cortex (Beebe & Gozal, 2002), specifically, the dorsolateral prefrontal cortex (Thomas, Rosen, Stern, Weiss, & Kwong,

2005), and cerebellum (Morrell et al., 2003). Sugita et al. (1985) found that OSAS is associated with episodic elevation of cerebrospinal fluid (CSF). While most researchers found little relation between apnea-hypopnoea index and white matter function, Kamba et al. (2001) noted a significant degree of metabolic impairment in the white matter of patients with OSAS.

Viewing Adult SDB correlates in the Context of Neurobiology: MDD Mechanisms and Implications

These findings are especially important when one notes that, while the most conservative estimates have suggested that ten percent of women and twenty five percent of men suffer from some form of SDB, projections for older adults (aged fifty to seventy years) have been as high as 30 percent for males and 28 percent for females (Zamarron et al., 1999).

While some have argued that these symptoms may be due to the sleep fragmentations that occur in response to intermittent hypoxia (Sforza, de Saint Hilaire, Pelissolo, Rochat, & Ibanez, 2002; Yue et al., 2003), numerous authors have pointed to similarities in the neuroanatomical signatures of adulthood SDB and MDD (Kamba et al., 1997; Silverstone, McPherson, Li, & Doyle, 2003; Thomas, O'Brien, Barber, McMeekin, & Perry, 2003). As CPAP has been shown to alleviate many of the symptoms common to both adult SDB and MDD (Engleman et al., 1997), it is unlikely that the MDD is heavily influenced by organizational changes related to SDB correlates early in life. Rather, changes to brain morphology secondary to SDB later in life appear to be supported by the fact that most individuals are not diagnosed with depression until their mid-twenties (Solis, Khan, & Brown, 2006).

Furthermore, that brain changes secondary to SDB correlates may be related to MDD supports rather than detracts from other known etiological factors of MDD such as stress (Southwick, Vythilingam, & Charney, 2005). Higher levels of stress in individuals with SDB may

cause the muscles in the upper throat to contract and essentially narrow the upper airway, thereby increasing the chances of SDB (Southwick, Vythilingam, & Charney, 2005). Stress is also associated with obesity, especially in individuals with MDD, which may have a similar constricting effect (Franklin et al., 2007). Furthermore, stress may cause an increase in the immunomodulating agents known as cytokines, leading to an immune response characterized by inflammation (Mills & Dimsdale, 2004). Prolonged inflammation may be associated with compromises in upper throat airflow, asthma, and infections that are known to increase the prevalence of SDB (Mills & Dimsdale, 2004). Interestingly, since serotonin is known to excite the dilatory muscles of the upper throat (Veasey, 2001), it has been suggested that patients with a baseline compromise of the upper airway (perhaps due to stress) and a decrease in serotonin (possibly resulting from or causing depression) are particularly susceptible to SDB (Veasey, 2001). In fact, some studies have attempted to treat SDB by administering selective serotonin reuptake inhibitors (SSRIs), with mixed results (Berry, Yamaura, Gill, & Reist, 1999; Kraiczi, Hedner, Dahlof, Ejnell, & Carlson, 1999).

Explanations of a neurobiological relationship between adult SDB and MDD are strengthened by findings that show that the brains of individuals with MDD show abnormalities in the left subgenual prefrontal cortex (SGPFC) (Botteron, Raichle, Drevets, Heath, & Todd, 2002), dorsolateral prefrontal cortex (DLPFC), specifically hypoactivity of the left DLPFC and hyperactivity in the right DLPFC (Brody et al., 1999; Frodl et al., 2007; Grimm et al., 2008; Maletic et al., 2007; Matsuo et al., 2007), caudate, amygdala, and putamen (Beyer & Krishnan, 2002), ventromedial prefrontal cortex (VMPFC), lateral orbital prefrontal cortex (LOPFC), anterior cingulate cortex (ACC), the ventral striatum including the nucleus accumbens, the amygdala, and the hippocampus (Davidson, 2003; Drevets, 1998). Further abnormalities in MDD were found in

the cerebrospinal fluid (CSF), specifically increases (Kumar et al., 1997), the cerebellum (Fatemi et al., 2004), post central gyrus, superior frontal gyrus, ventral lateral prefrontal cortex (Keedwell et al., 2005), and parahippocampal gyrus (Aihara et al., 2007).

The literature has documented that MDD patients show abnormalities in twelve of the seventeen brain regions known to be affected by adult SDB (See Table 3). Overlap between the cortical consequences of SDB correlates and MDD include the SGPFC, DLPFC, VMPFC, LOPFC, ACC, hippocampus, cerebellum, CSF, parahippomcampal gyrus, amygdala, basal ganglia, and postcentral gyrus.

Limitations

The main contention of this paper is that SDB and/or its correlates are both the cause and effect of critical neurobiological mechanisms contributing to three major forms of psychopathology (see Figure 1). SDB-related correlates appear to have similar yet distinguishable effects on cortical morphology and function depending upon the developmental period in which they are experienced. When a pregnant mother experiences SDB, data has shown that the effects on fetal neurobiology may be so profound that it may correlate with the development of autism in her child. Childhood SDB appears to be associated with a cortical transformation to the neuroanatomical signature of children with ADHD. Lastly, SDB correlates experienced as an adult seem to be closely tied to the development of a cortical pattern indicative of major depression.

There are some limitations to the present proposal. First, psychopathology and SDB undoubtedly arise in complex biological and psychological contexts. This makes the association between psychopathology and *specific* correlates of SDB complex and surely not simply causal. For example, while many of the findings presented in this paper were obtained using animals exposed to hypoxia at different developmental time periods, generalizations based on the findings

become difficult, because hypoxia is not the only vehicle whereby neurobiological changes can be induced. In fact, there is a subset of SDB patients that do not experience significant hypoxia at all. Other known correlates of SDB, including metabolic changes (Aerts, 2001; Edwards et al., 2002; Kamba et al., 2003; Kheirandish et al., 2005; Seicean et al., 2008; Thomas & Kwong, 2003) hemodynamic fluctuations, sympathetic activations, immunological abnormalities, hypercarbia, sleep fragmentation, and sleep deprivation may actually be the major factors (Lin et al., 2004; Luthar, 1997; Mayes, 1999; Terzidou & Bennett, 2001). Some researchers have proposed that these correlates may be *caused* by hypoxia, and not independent consequences of SDB (Aw, Shan, Sillau, & Jones,1991; Fletcher, Lesske, Qian, Miller, & Unger,1992). It is likely that many of the correlates work in concert and to varying degrees based on a myriad of individual variables. Furthermore, cortical changes are likely a function of the severity of SDB insult, so studies made to simulate snoring versus obstructive sleep apnea should be viewed with caution in the formulation of blanket statements about the effects of SDB.

In addition to the complexity of the variables *within* the SDB-psychopathology pathway, there are most definitely factors outside the body that mediate the context in which the relationships cited in this paper function. Evidence for this can be found in the fact that despite significant overlaps in SDB and neuroanatomical signatures, there was never a complete overlap in effected brain regions. Different environmental influences may impact the extent to which the genetic and other biological aspects of psychopathology are manifested, with SDB in the context of mental illness a key example of a diathesis-stress phenomenon.

Furthermore, the *directionality* of the claims implied in this paper must be taken with some caution. It is unclear whether SDB causes psychopathological cortical changes or whether cortical

changes (i.e., in the respiratory control center) lead to SDB. It is also unclear under what circumstances either becomes the causative agent and it is likely situation specific.

The mental disorders outlined in this review are a small sample of the psychopathologies that may be related to SDB but were not chosen randomly. Autism, ADHD, and MDD are disorders whose relationship to SDB has been suggested in prior work, and thus they served as a good starting point for the present paper in trying to determine a neurobiological framework. Some other disorders considered did not seem to be linked to SDB as closely, such as generalized anxiety disorder (GAD). Thus, while the scope of the illnesses affected by SDB can surely be broadened, the extent to which specific psychopathologies relate to SDB should be acknowledged as variable. Further research can elucidate links between SDB correlates and other mental disorders.

Conclusions

The present paper reinforces the case for empirical relationships between SDB and psychopathology by proposing that life stage-specific SDB correlates may be neurobiologically related to the cortical signatures of AD, ADHD, and MDD. A review of the literature revealed that, depending upon the time in which SDB correlates were experienced, the neurological correlates are generally similar but distinguishable. The differences in cortical effects of SDB reflect well the differences between psychopathologies associated with SDB in utero, childhood, and adulthood, which may be AD, ADHD, and MDD, respectively.

While the mechanisms behind the relationship between SDB and mental illness are largely hypothetical at the present time, health professionals would benefit by beginning to view SDB as one of the many important factors in elucidating etiological and diagnostic factors in mental disorders both generally and perhaps even more so specifically. Much like smoking, we should regard individuals with sleep-disordered breathing as susceptible to diverse deleterious

psychological correlates. Certain high-risk populations (pregnant women, obese, diabetic, etc.) should be routinely screened for SDB.

In light of the present proposal, health-care providers might be able to assess both the likelihood of the patient developing mental illness and a possible means for therapeutic intervention at a deeper level of etiology. Current interventions to treat symptoms in psychopathology (like stimulants used in ADHD) should be combined with treatments for SDB to obtain maximal efficacy.

Furthermore, as many patients report cessation of the debilitating effects of SDB and improved quality of life upon treatment (Banno & Kryger, 2007; Ito et al., 2005; Noda et al., 2007), a greater effort should be made by both clinicians and researchers to utilize and improve upon current CPAP, oral appliances, and surgical corrections for SDB. It is unclear when and to what extent the effects of prolonged SDB become irreversible, so placing a high priority on diagnostic screening and utilization of current treatments has a great deal of potential clinical significance.

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Table 1.

Damages to Specific Cortical Regions Implicated in Maternal SDB in utero and Autistic Disorder with Similarities Noted

Maternal SDB	**Autistic Disorder (AD)**
Amygdala	Amygdala
Basal ganglia	Basal Ganglia
Cerebrospinal fluid (increases)	No Overlap
Cerebellum	Cerebellum
Cerebral ventricles (enlargement)	Cerebral ventricles (enlargement)
Cortical volume decrease (overall)	No Overlap
Frontal Cortex	Frontal cortex
Gray Matter (overall deficiencies)	Gray Matter (overall deficiencies)
Hippocampus	Hippocampus
Pons	Pons
Thalamus	Thalamus
White Matter (overall deficiencies)	No Overlap

Table 2.

Damages to Specific Cortical Regions Implicated in Childhood/Adolescent SDB and ADHD with Similarities Noted

Childhood/adolescent SDB	**ADHD (ADHD)**
Basal ganglia	Basal Ganglia

Cerebellum	Cerebellum
Frontal Cortex	Frontal Cortex
Hippocampus	Hippocampus
Pons	Pons
Thalamus	Thalamus
Corpus Collosum	Corpus Collosum
Cortical Volume Decreases	Cortical Volume Decreases
White Matter (Overall Deficiencies)	White Matter (Overall Deficiencies)
No Overlap	Gray Matter (overall deficiencies)
No Overlap	Right posterior cingulate gyrus

Table 3.

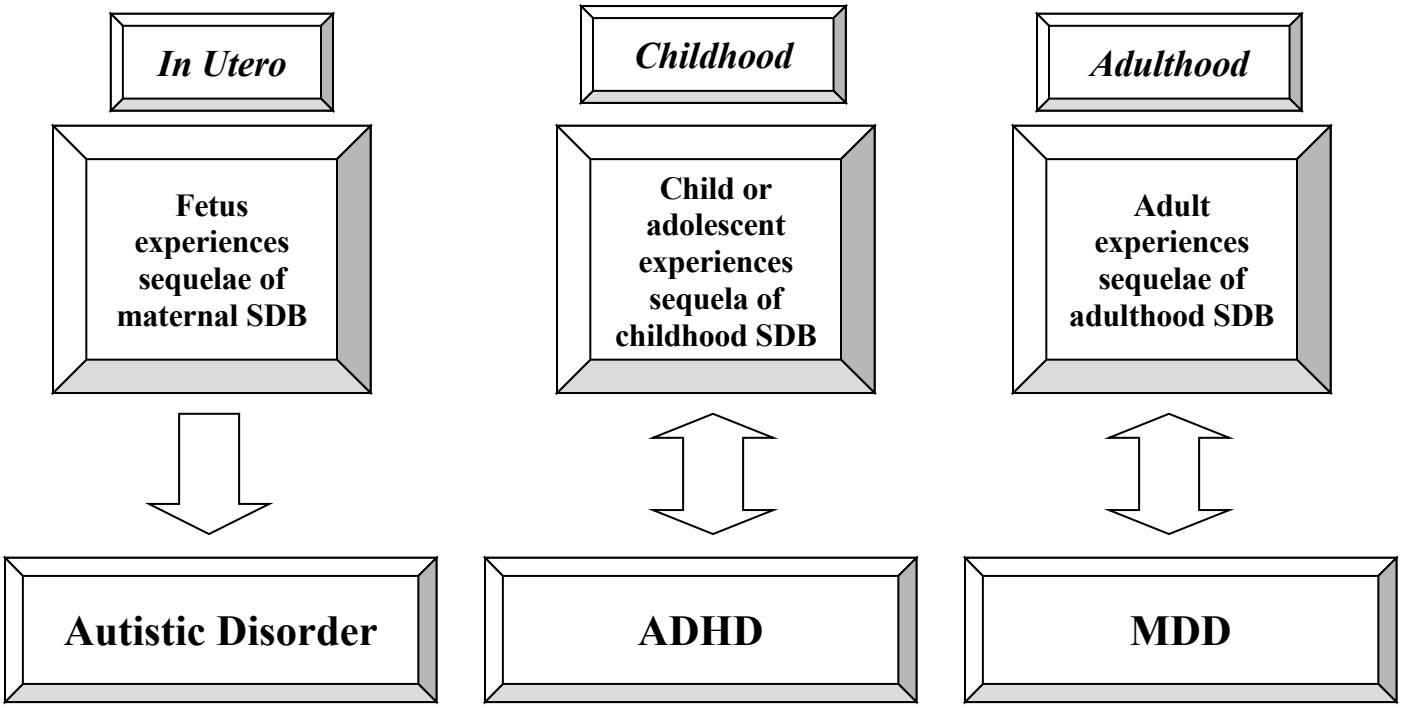
Damages to Specific Cortical Regions Implicated in Adult SDB and Major Depressive Disorder (MDD) with Similarities Noted

Adult SDB	**Major Depressive Disorder (MDD)**
Amygdala	Amygdala
Anterior cingulate cortex	Anterior cingulate cortex
Anterior superior frontal gyrus	Anterior superior frontal gyrus
Assorted sites on lateral prefrontal cortex	Associated sites of lateral prefrontal cortex (subgenual PFC, lateral orbital PFC)
Basal Ganglia	Basal Ganglia
Cerebrospinal fluid (increases)	Cerebrospinal fluid (increases)
Cerebellum	Cerebellum
Cortical volume decrease (overall)	No overlap
Dorsolateral prefrontal cortex	Dorsolateral prefrontal cortex
Gray matter (overall deficiencies)	No overlap
Hippocampus	Hippocampus
Inferior temporal gyrus	No overlap
Lateral sulcus	No overlap

Left ventral lateral frontal cortex	Left ventral lateral frontal cortex
Parahippocampal gyrus	Parahippocampal gyrus
Posterior lateral parietal cortex	No overlap
Right postcentral gyrus	Right postcentral gyrus
White matter (overall deficiencies)	No overlap

Figure Caption

Figure 1. Proposed Theoretical Relationship between Developmental Timing of SDB correlates and Psychopathology


In Utero
Childhood
Adulthood
Fetus experiences sequelae of maternal SDB
Child or adolescent experiences sequela of childhood SDB
Adult experiences sequelae of adulthood SDB
Autistic Disorder
ADHD
MDD