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Sleep-disordered breathing: effects on brain structure and function

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Abstract

Sleep-disordered breathing is accompanied by neural injury that affects a wide range of physiological systems which include processes for sensing chemoreception and airflow, driving respiratory musculature, timing circuitry for coordination of breathing patterning, and integration of blood pressure mechanisms with respiration. The damage also occurs in regions mediating emotion and mood, as well as areas regulating memory and cognitive functioning, and appears in structures that serve significant glycemic control processes. The injured structures include brain areas involved in hormone release and action of major neurotransmitters, including those playing a role in depression. The injury is reflected in a range of structural magnetic resonance procedures, and also appears as functional distortions of evoked activity in brain areas mediating vital autonomic and breathing functions. The damage is preferentially unilateral, and includes axonal projections; the asymmetry of the injury poses unique concerns for sympathetic discharge and potential consequences for arrhythmia. Sleep-disordered breathing should be viewed as a condition that includes central nervous system injury and impaired function; the processes underlying injury remain unclear.

Keywords

Obstructive sleep apnea; magnetic resonance imaging; autonomic; neural injury; hypoxia; dyspnea; congenital central hypoventilation

1. Introduction

Sleep-disordered breathing (SDB), which includes obstructive sleep apnea (OSA) and periodic, or Cheyne-Stokes breathing patterns, results in injury to multiple brain areas, with damage so extensive in some neural sites in patients with severe SDB that structural recovery is unlikely. Injury appears in brain sites that exert significant control over hormonal and autonomic functions, and especially the sympathetic arm of the autonomic

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nervous system, as well as areas that regulate aspects of breathing. Damage also appears in brain areas mediating affect, memory and cognition. By “affect” is meant motivational drives; some affective drives develop from negative perceptions, and include air hunger or dyspnea. On first glance, such drives may appear irrelevant to respiration, but indeed provide significant influences on breathing.

Another condition associated with a loss of drive to breathe during sleep is congenital central hypoventilation syndrome (CCHS), a condition associated with mutation of the PHOX2B gene, resulting in severe autonomic dysfunction and loss of effective chemoreception sensitivity, and loss of dyspnea and affective influences on breathing (Patwari et al., 2010). The injured sites that mediate dyspnea and other affective roles contribute to management of sympathetic actions, resulting in interference with a wide range of metabolic and cardiovascular regulatory systems, some of which can indirectly affect breathing. Sleep-disordered breathing should be seen as a syndrome that elicits brain injury in structures that affect multiple regulatory systems, with many of these systems interacting such that breathing and cardiovascular regulation can be further compromised. This manuscript reviews findings of neural injury from sleep-disordered breathing conditions, and focuses on the integrated outcomes that emerge from such damage.

2. “Classic” respiratory and cardiovascular area injury

2.1 Medullary and pontine injury

Before considering damage from more-rostral brain areas mediating affect and other influences on breathing, injury to classic respiratory and cardiovascular regions of the medulla and pons should be outlined. This injury appeared in all three sleep-disordered breathing conditions considered here: OSA, heart failure, and CCHS.

The injury in OSA includes damage to both the dorsal, ventral, and ventrolateral medulla, as shown in Figure 1 (Kumar et al., 2012). Ventrolateral and dorsal medullary injury also occurs in CCHS (Kumar et al., 2008b). It should be noted that the structure corresponding to the ventrolateral medulla in animals is dorsally-displaced in humans (Allen et al., 1998; Macefield and Henderson, 2010). In OSA, the damage is preferentially right-sided in ventrolateral medullary, cerebellar, and insular sites. The medullary injury indicates that primary respiratory sites for chemosensing and pacing aspects of breathing control are affected in OSA, not just forebrain areas acting on classic medullary structures.

Injury to the ventrolateral medulla represents damage to a structure serving as the final common path for sympathetic outflow to the intermediolateral column of the spinal cord. The consequences of that outcome could be substantial, and may contribute significantly to the high sympathetic tone and minimal responsiveness to dynamic challenges in blood pressure found in the conditions. The preferential right-sided injury to the ventrolateral medulla poses particular concern for exerting asymmetrical output of sympathetic tone, with the potential to lower thresholds for cardiac arrhythmia (Lane et al., 1992; Oppenheimer, 2006; Schwartz et al., 1975).

Dorsal medullary areas are also affected in heart failure (Kumar et al., 2011b). The dorsal injury, sited in classic sensory areas for respiratory integration for breathing control as well as sympathetic regulation, may especially contribute to the impaired moment-to-moment control of sympathetic tone. Disruption of afferent activity also provides an opportunity to interfere with normal chemosensory and other sensory stimuli that provide triggering for timely upper airway discharge.

Especially affected in CCHS are ventrolateral medullary areas, and sites near the parabrachial pons (Kumar et al., 2008b), critical for respiratory phase switching (Gautier and Bertrand, 1975), with damage overlapping the locus coeruleus; regions near the locus coeruleus and the nearby adrenergic pools show injury in MRI studies, and loss of neurons in the locus coeruleus has also been identified in an isolated CCHS case in autopsy (Tomycz et al., 2010). Adrenergic neurons in the subcoeruleus and neighboring areas play roles in upper airway muscle responses to intermittent hypoxia (Herr et al., 2013).

3. Cerebellar injury

3.1 Cerebellar injury affects breathing and cardiovascular action

Of all the structures injured in OSA, cerebellar structures are usually overlooked in considering affected breathing or cardiovascular regulation, since cerebellar roles classically are solely assigned to coordination of the musculature, and, (only in recent years) cognitive roles via cerebellar projections to the frontal cortex (E et al., in press; Lu et al., 2012). Cerebellar roles in SDB during early development have long been recognized with genetic conditions such as Joubert's syndrome (Wolfe et al., 2010) or injuries resulting from cerebellar tumors, such as medulloblastoma or surgical resections for similar tumors (Chen et al., 2005). Cerebellar alterations due to genetic conditions and surgical resection are frequently accompanied by reduced muscle tone; a major cerebellar role in muscle control is maintenance of tone, and further reduction of that muscle drive in the upper airway during sleep could enhance the propensity for OSA. The relationships between cerebellar injury and sleep-disordered breathing are not confined to pediatric cases; similar breathing issues are encountered in adults (Chokroverty et al., 1984), and cerebellar injury through stroke or surgery is now recognized to contribute significantly to a risk for OSA.

3.2 Cerebellar damage in OSA, and parallel animal models

Among the brain structures heavily affected in OSA is the cerebellum. The injury in the cerebellum appears with multiple neuroimaging methodologies, including voxel-based morphometry using high-resolution T1-weighted images (Macey et al., 2002), T2-relaxometry (Kumar et al., 2005), and diffusion tensor imaging (DTI)-based measures (Kumar et al., 2012; Kumar et al., 2006, 2008b; Macey et al., 2008). These different procedures show similar patterns of brain tissue damage in areas which include both the cerebellar cortex and deep nuclei (Figure 1, 2).

The pathological processes underlying the preferential injury to the cerebellum remain unclear, but likely parallel development of excitotoxic damage found in cerebellar Purkinje neurons to a range of ischemic or other challenges (Welsh et al., 2002). Dendritic processes of the Purkinje neurons show a relationship with the long climbing fibers from the inferior olive, resulting in an environment optimal for injury from hyperexcitation of those fibers. That relationship is wellknown to toxicologists, since activation of the inferior olive by other toxic agents leads to such excitotoxic injury (O'Hearn and Molliver, 1997). One such hyper-exciting influence is hypoxia, a defining characteristic of OSA, which has the potential to injure Purkinje neurons. Since Purkinje neurons project to the cerebellar deep nuclei, damage to the Purkinje cells will certainly affect the recipients of those projections, resulting in damage to the deep nuclei, the sole output from the cerebellum. Among these are the fastigial nuclei, the so-called "autonomic nuclei" of the cerebellum, which serve, among other roles, to dampen the extremes of blood pressure elevation or depression, respond to H⁺ ion stimulation, and are involved in responding to mechanical afferent stimulation for respiratory timing (Lutherer et al., 1983; Xu et al., 2006; Xu and Frazier, 2000; Xu et al., 1994). Animal models which mimic intermittent hypoxic aspects of OSA also show cerebellar deep nuclei and Purkinje cell injury, with Purkinje cell damage appearing after as

little as 5 hrs of intermittent hypoxia exposure (Pae et al., 2005). Intermittent hypoxic effects are especially a concern in early development, a circumstance that can easily appear with apnea of prematurity; γ -aminobutyric acid-A receptor levels are altered in perinatal rat cerebellum with such exposure (Pae et al., 2011), an outcome that has the potential to establish long-term consequences for motor coordination.

Although reduced upper airway tone from cerebellar injury may contribute to OSA in pediatric cases, tone to the genioglossal muscles in adult OSA is enhanced during waking (Mezzanotte et al., 1992). Although the status of muscle tone may be a state-related issue with cerebellar injury, i.e., cerebellar injury may induce reduced tone specifically in sleep states over waking, it is more likely that disruption of the complex timing of disfacilitation or inhibition of upper airway musculature with respect to activation of the diaphragmatic musculature is a more-feasible mechanism for the cerebellar injury/OSA relationship. Such regulation failure would presumably involve classic cerebellar structures that serve motor coordination roles, but may be an outcome involving inappropriate or delayed transient blood pressure rises accompanying suppression of the respiratory musculature that normally follows such rapid elevation, i.e., the timing interaction between the normal suppression of diaphragmatic and upper air way muscles by blood pressure rise is compromised (Marks and Harper, 1987; Trelease et al., 1985).

3.3 Cerebellar injury affecting neural response amplitude and timing

Timing of neural responses between coordinating areas of the cerebellum to pressor or ventilatory challenges indeed is distorted in OSA, as shown in Figure 3 and Figure 4. The distortion in functional MRI signals evoked by successive Valsalva maneuvers is substantial, and is reflected in delayed signal rises from cerebellar cortex and deep nuclei, and significantly muted or non-existent responses (Henderson et al., 2003), Figure 3. Close examination of specific cortical regions of the cerebellum (Figure 4) shows that such responses can be lateralized, presumably a consequence of asymmetric injury, with early, and undampened responses to the Valsalva maneuver in the left Crus II, but only exaggerated responses on the right side. Comparable lateralized distortions are found in the ventral cerebellum in CCHS (Ogren et al., 2010).

The implications for the timing alterations are especially significant for conditions where dynamic responses to a blood pressure change are needed, such as sudden rising from a supine position, standing from a sitting position, straining, or rapid lung inflation efforts for speech, coughs, or breathing. There is substantial evidence that such regulation is deficient in OSA (Henderson et al., 2003; Macey et al., 2006; Macey et al., 2003), with severe consequences for limiting transient increases in hypertension or hypotension in a population prone to stroke. In particular, heart rate and respiratory responses are especially delayed in the immediate recovery period after certain pressor challenges, such as the Valsalva maneuver, an outcome that would be important if a transient blood pressure elevation were to trigger a respiratory pause (the normal response to such elevation is to induce an apnea (Trelease et al., 1985); such an activation might produce an out-of-phase suppression of upper airway muscles when a normal response would be in recovery).

Axonal projections to and within the cerebellum are also affected in OSA, with a preferentially unilateral distribution of fiber injury. The fiber injury can be revealed with fiber tracking techniques (Wang et al., 2007), and is illustrated with pontocerebellar fibers in Figure 5. Other procedures illustrate the significant injury to multiple systems using radial and axial diffusivity measures, indicating lost integrity of the myelin sheath or fibers respectively (Kumar et al., 2008b; Kumar et al., 2010; Song et al., 2002), with significant injury within climbing fibers and caudal raphe projections to the cerebellum. The unilateral damage in these fiber systems has particular importance for function, since influences from

one side of the brain would be less effective, leading to exaggerated influences of the opposite side. Lateralized dampening of cerebellar modulation on sympathetic outflow could lead to the potential for enhanced, asymmetric sympathetic discharge, an optimal condition for production of cardiac dysrhythmia.

4. Neurotransmitter systems

4.1 Injury to serotonergic, adrenergic, and peptidergic systems

The range of affective and autonomic deficits that accompany OSA suggests that major neurotransmitter systems are affected in the syndrome. The possibility for such injury in the serotonergic system appears to be especially likely, considering the role that 5-HT plays in modulating the upper airway musculature (Kubin et al., 1994), the numerous changes in the vasculature, partially regulated by serotonin (5-HT), and the marked incidence of depressive signs, a condition in which serotonin plays a significant role, in approximately half of OSA patients. Indeed, the caudal raphe is affected, as shown by diffusion imaging measures (Figure 2), areas of the midbrain with dopaminergic fibers, and the hypothalamus, with acetylcholine, orexin and an array of hormonal circuitry are injured. Damage to neurotransmitter systems is more enhanced in CCHS, with severe injury to the raphe system, locus coeruleus (noradrenergic neurons), ventral midbrain, hypothalamus, and to the basal ganglia, recipient of dopaminergic fibers (Kumar et al., 2006, 2008b; Kumar et al., 2005; Kumar et al., 2010). The injury to those neurotransmitter systems must impact function, and therefore likely contributes to the high incidence of depression and other affective comorbidities in OSA (DeZee et al., 2005; Douglas et al., 2013; Macey et al., 2010; Sharafkhaneh et al., 2005), and to alterations in cardiovascular control (Gottlieb et al., 2010).

The current resolution of current MR procedures does not allow differentiation of the multiple fiber systems near the hypothalamus, with its many peptide systems including orexin and leptin, as well as histamine and intermixed cholinergic neurotransmitters. Leptin appears to have significant impact on breathing (Inyushkin et al., 2009); however, it is unclear whether its influence is exercised through temperature or direct influences on structures modifying respiratory patterns, among other possibilities. An examination of the hypothalamic region in OSA patients shows diffuse injury ranging from the rostral through caudal hypothalamus (Figure 2). Differentiation of specific fiber injury awaits improved MR technology, but the potential for major alterations to hormonal systems and systems such as orexin, which exerts influences on a range of other neurotransmitters, is high. The injury to the hypothalamus may underlie a large range of sequelae of OSA.

5. Cortical injury

5.1 Cortical influences on breathing and cardiovascular regulation

Multiple cortical areas are damaged in OSA, and some of these sites have long been known to modify respiratory patterning or specifically alter upper airway or diaphragmatic muscle tone (Marks et al., 1987). These areas include the primary sensory motor regions (Macey et al., 2002), as well as ventromedial prefrontal cortex. Of all the cortical areas damaged, those associated with autonomic regulation are disproportionately injured in OSA, and include the insular, (Figures 1, 6) cingulate, and ventromedial prefrontal cortices (Figure 6). The damage is largely unilateral, with the right side more commonly affected. The insular cortex exerts a major role in sympathetic tone, with direct projections to the hypothalamus and other limbic structures. The anterior insula modulates the baroreflex, as shown by stimulation evidence, and insular stroke is frequently followed by myocardial infarctions a few weeks after the incident. Damage to the insula is significant in OSA, and is even more

exaggerated in heart failure patients who have a high incidence of OSA and Cheyne-Stokes breathing (Woo et al., 2003).

5.2 Sensory and Motor injury

Primary sensory and motor areas of the cortex also show injury in OSA (Macey et al., 2002), an outcome that may underlie enhanced low negative pressure reflexes found during waking in OSA patients (Berry et al., 2003). Primary projection areas of the ventrolateral thalamus are also injured (Kumar et al., 2012; Macey et al., 2002; Macey et al., 2008). Since cortical areas, and especially orbital frontal cortex areas, often inhibit reflexes, removing such cortical influences through injury should be expected to enhance certain airway reflexes.

5.3 Limbic cortex

Among the limbic cortical regions affected, the anterior cingulate is especially damaged, with injury appearing with voxel-based morphometry, mean diffusivity, T2 relaxometry and, in the cingulum bundle fibers within the cortex, by fractional anisotropy and fiber tractography procedures (Figure 6; (Kumar et al., 2012; Kumar et al., 2006; Kumar et al., 2011a; Macey et al., 2008). Injury to the anterior cingulate likely contributes to the very high incidence of depression in OSA, and electrical stimulation of the anterior cingulate greatly improves depressive signs (Mayberg et al., 2005). Over half of OSA patients show enhanced depressive symptoms, and over a third show high levels of anxiety (Douglas et al., 2013). The anterior cingulate shows significantly more injury in OSA patients with high depressive symptoms over those without such signs (Cross et al., 2008).

6. Laterality of injury, and lateralized, distorted timing in functional responses

6.1 Asymmetry of structural injury and distorted responses

A remarkable aspect of the injury in different sleep disordered breathing conditions is the preferential laterality of the damage. This asymmetry should be viewed in the context that substantial lateralization of the autonomic nervous system normally exists in the brain, just as with language, or representation of primary sensory and motor functions for one side of the body vs the other. The right insular cortex, for example, primarily mediates sympathetic regulation, while the left normally mediates parasympathetic action (Hilz et al., 2001; Oppenheimer, 2006; Oppenheimer et al., 1992). The right rather than the left medial prefrontal cortex, mediates pressor challenges, and the left or right hippocampus responds to similar challenges, with laterality dependent on the individual (Harper et al., 2000). Injury primarily appears in the right insula, medial frontal cortex and right ventrolateral medulla in OSA and heart failure (Kumar et al., 2011b; Woo et al., 2009), with the resulting injury likely underlying the preferential sympathetic injury in the syndromes.

6.2 Amplitude and timing distortions

The structural injury is accompanied by distorted patterning of functional MRI signals in OSA, with both amplitude and time distortions in response to pressor or ventilatory challenges (Figures 3, 4). As in the case of cerebellar injury, the distorted timing of evoked signals in the insular cortex suggests the potential for time altered and enhanced sympathetic output (enhanced due to disinhibition) since insular signals are muted in OSA, and it appears the insular influences on sympathetic discharge are largely inhibitory. The insular damage also likely contributes to the enhanced perception of dyspnea in OSA and heart failure, since the perception of breathlessness recruits areas within that cortical region (Banzett et al., 2000; Peiffer et al., 2001). Such perceptions are exaggerated in some conditions with sleep-disturbed breathing, including chronic obstructive pulmonary disease (COPD), heart failure,

and OSA, but fail completely in CCHS. The former conditions of exaggerated perceptions of dyspnea result in patients being hesitant to increase ventilation for even mild increases in everyday movements, while the latter conditions of reduced dyspnea and sensitivity to CO₂ in CCHS result in failure to breathe during quiescent periods, leading to severe waking hypoxia until such time as the patient consciously increases his ventilation. It is likely that the lowered threshold for pain found in heart failure stems from insular cortex injury as well, since the insula serves as a primary projection area for pain (Henderson et al., 2007).

7. Metabolic and hormonal regulation

7.1 Injury to metabolic and hormonal regulatory sites

The damage to hypothalamic regions, insular areas modifying sympathetic discharge, and the raphe system with its serotonergic and thyrotropin-releasing hormone (TRH) neurons, establishes circumstances that lead to the potential for disruption of normal hormone release responsible for a range of physiological functions, including glycemic regulation, a major issue in OSA. TRH is classically known for its role in pituitary functions and thyroid disorders, with neurons originating from the hypothalamus, but the raphe pallidus also appears to have cell bodies, with considerable potential to modify vagal outflow (Lechan and Segerson, 1989; Yuan and Yang, 2000). The high sympathetic tone of OSA will alter glucagon levels, and distorted vagal outflow will modify pancreatic insulin release; the raphe damage will alter serotonergic output, and also TRH release, a principal hormone for metabolic control through its influences on the vagal parasympathetic system. Neural injury in OSA is markedly enhanced if the OSA patient concurrently has Type 2 diabetes, with much greater damage in the cingulate, hippocampus, and insula, among other structures (Harper et al., 2009).

7.2 Raphe injury, TRH, OSA, and depression

The potential interference with TRH loss from caudal raphe injury has even more insidious implications for OSA, although these implications are speculative. Analogs of TRH show significant neuroprotective properties to ischemia in the forebrain of mice (Urayama et al., 2002), suggesting that some protective options may exist for more-rostral brain injury in OSA. Administration of TRH also appears to improve depressive signs (Marangell et al., 1997; Prange et al., 1972), a significant comorbidity in OSA. Addressing the hormonal alterations in OSA may be able to reduce the structural injury resulting from the syndrome, and lessen the functional impact of some of the behavioral sequelae.

8. Memory and cognitive systems

8.1 Hippocampus

A most remarkable aspect of the deficits appearing in OSA is the presence of short-term memory impairments, which appear in the majority of patients, and persist after resolution of the breathing condition by CPAP (Ferini-Strambi et al., 2003). The structures serving those memory roles are well-known, and include the hippocampus, a principal fiber output to the mammillary bodies, the fornix, the mammillary bodies themselves, and their projections to the anterior thalamus and downstream sites (Buckley et al., 2004; Lavenex et al., 2006; Ridley et al., 2004; Santin et al., 1999). These areas are affected in OSA and CCHS.

The hippocampus also participates in several aspects of physiological function; electrical stimulation evokes dramatic changes in blood pressure (Ruit and Neafsey, 1988), and MRI studies of the brain in depressed patients uniformly show hippocampal injury (Frodl et al., 2002; Neumeister et al., 2005). Damage to the hippocampus has been repeatedly shown in

OSA in adults (Kumar et al., 2012; Macey et al., 2002; Morrell et al., 2003) and children (Halbower et al., 2006). The processes underlying the injury are unclear, but may parallel the damage found by excitotoxic processes in temporal lobe epilepsy, which induces loss of tissue in CA1 and CA3 regions, likely from excessive activation of Schaffer collaterals; hypoxic processes may result in similar exaggerated discharge and injury paralleling the mechanisms found in the climbing fibers for cerebellar injury.

8.2 Mammillary bodies

A remarkable aspect of injury to the memory system is damage to the mammillary bodies, widespread in OSA patients, preferentially one-sided, and often reaching a volume loss of one-half or more (Figure 7; (Kumar et al., 2008a). Similar injury also occurs in another SDB condition, CCHS (Kumar et al., 2009). Such injury is classically associated with diseases such as beriberi, chronic alcoholism, Wernicke-Korsakoff's syndrome, Alzheimer's disease, hepatic disease, or severe malnutrition (Copenhaver et al., 2006; Gupta et al., 2012; Harper, 2006; Kornreich et al., 2005; van Asselen et al., 2005), all conditions associated with severe thiamine deficiency. Conditions accompanied by high fluid loss, such as diuresis in heart failure, are typically associated with low thiamine levels (da Cunha et al., 2002; Hanninen et al., 2006; Harper, 2006), since thiamine is water-soluble. Magnesium is also water-soluble, and is usually deficient in similar conditions; thiamine requires magnesium for its role in ATP synthesis. OSA patients are seldom malnourished, and usually do not consume alcohol in excess, since alcohol accentuates the severity of OSA. However, they do show substantial fluid loss, with the high sympathetic tone in the syndrome eliciting profuse sweating at night. Moreover, OSA patients frequently show acid reflux (Morse et al., 2004), which is often treated with over-the-counter proton pump inhibitor antacids. Such agents interfere with gut bacteria that produce thiamine and other neuroprotective B vitamins (e.g. B₁₂), leading to deficiencies even in a diet adequate for normal production of B vitamins. Low thiamine levels would assist excitotoxic injury, since hypoxic processes hyper-activate cellular activity, requiring more energy; low thiamine leads to inadequate ATP availability, and cellular starvation. Compromised glial support is part of this injury process, since reduced cellular energy to glia would lead to neuronal damage. Although the prevalence of thiamine deficiency in OSA has not been established, the collective findings suggest evaluation of thiamine and magnesium levels, with aggressive intervention to correct such deficiencies for neuroprotection against the substantial injury in the syndrome.

8.3 Animal models; cognitive deficits and limbic injury

Animal models of intermittent hypoxia exposure to simulate aspects of OSA have illustrated injury in limbic, and especially hippocampal structures. These studies include areas of the septum and basal forebrain (Veasey et al., 2004), and the hippocampus, as well as glial tissue (Gozal et al., 2001; Gozal et al., 2003). The animal studies have also been useful in demonstrating cognitive impairments to intermittent hypoxia exposure, with hippocampal injury showing significant memory and other cognitive issues (Row et al., 2003).

9. Conclusions

The neural injuries accompanying sleep-disordered breathing are extensive, extend from rostral brain areas to the brainstem, and include the cerebellum and axonal structures between brain regions. The structural damage is accompanied by impaired neural functional responses to blood pressure and ventilatory challenges in essential regulatory areas, with the distortions including both amplitude and timing alterations. Brain areas mediating hormonal regulation are also affected, and may influence the metabolic issues associated with the condition. Processes underlying the injury remain unclear, but likely include hypoxic processes and extreme changes in vascular aspects that accompany apneic periods, and may

include excitotoxic mechanisms similar to those causing injury in epileptic discharge. Providing some degree of neuroprotection against such injury may be possible.

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Highlights

Injury to neural structures and axons accompanies sleep-disordered breathing.

Autonomic and major neurotransmitters systems are especially affected.

Injury occurs as water diffusion, myelin and axonal changes, and tissue loss.

Time- or amplitude-distorted fMRI signals emerge to ventilatory/autonomic challenges.

Sympathetic, breathing, memory, mood, and cognitive deficits result from the injuries.

Figure 1. Decreased mean diffusivity, an index of injury in A, the dorsal medulla, B, right ventral medulla, C, ventrolateral medulla, D, posterior insula, and E, coronal view, cerebellar cortex in 23 OSA subjects vs 23 controls (from Kumar et al., 2012).

Figure 2. Fractional anisotropy (FA) measures in 3 OSA vs 3 control subjects showing injury in the cerebellum (A-1), midbrain (A-2), and hypothalamus (A-3), midline raphe projecting to the cerebellum (B-4), and insula cortex (B-5)

Fastigial Nucleus

Insula

Figure 3.

Functional MRI signals to three Valsalva challenges (shaded areas) in the insular cortices and fastigial deep nuclei of the cerebellum; time 0 represents onset of first challenge (from Henderson et al., 2003). Asterisks indicate significant differences on curves. SI = Signal Intensity.

Figure 4.

Exaggerated and asymmetric responses in left and right cerebellar Crus II areas to the Valsalva maneuver. Controls, $n=62$, OSA, $n=43$. The patterns (mean $\pm$ SEM) differ in both the challenge and recovery periods. Asterisks = significant differences, repeated-measures ANOVA.

Figure 5. Tracking of pontocerebellar fibers through comparable regions of interest in one Control (A) and one OSA (B) subject; fiber numbers are unilaterally diminished on the left side in the OSA subject.

Figure 6. Decreased fractional anisotropy values, showing loss of axonal integrity in the anterior cingulate cortex (ACC), internal capsule (IC), portions of the anterior corpus callosum (CC), and the prefrontal cortex (PFC; the anterior insula (AI) is also affected). (From Macey et al., 2008).

Figure 7.

Damage to the hippocampus (A) using surface morphometry techniques; blue areas show no change, colored areas, loss of tissue; mammillary bodies (MB) in one control (B) and one OSA subject (C); scatterplot of left and right combined mammillary body volumes in 43 OSA and 66 control subjects (D). (From Kumar et al., 2008a)