Functional role of neural injury in obstructive sleep apnea

Julian P. Saboisky1,2, Jane E. Butler1,2, Simon C. Gandevia1,2 and Danny J. Eckert1,2*

1 Neuroscience Research Australia, Sydney, NSW, Australia
2 Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

The causes of obstructive sleep apnea (OSA) are multifactorial. Neural injury affecting the upper airway muscles due to repetitive exposure to intermittent hypoxia and/or mechanical strain resulting from snoring and recurrent upper airway closure have been proposed to contribute to OSA disease progression. Multiple studies have demonstrated altered sensory and motor function in patients with OSA using a variety of neurophysiological and histological approaches. However, the extent to which the alterations contribute to impairments in upper airway muscle function, and thus OSA disease progression, remains uncertain. This brief review, primarily focused on data in humans, summarizes: (1) the evidence for upper airway sensorimotor injury in OSA and (2) current understanding of how these changes affect upper airway function and their potential to change OSA progression. Some unresolved questions including possible treatment targets are noted.

Keywords: sleep apnea, upper airway muscles, neuropathy, myopathy, upper airway physiology, upper airway reflexes

INTRODUCTION

In the upper airway there are changes in sensation, muscle properties, and neural drive in patients with obstructive sleep apnea (OSA). These changes are loosely termed upper airway remodeling and may adversely affect upper airway function during sleep. Changes in nerve and muscle properties may result from vibration through snoring, hypoxia, or both.

The extent to which snoring and hypoxia exacerbate the disease and lead to important damage is unresolved. In this review, some of the more convincing evidence for and against upper airway remodeling in which data have been acquired in both OSA patients and non-OSA controls is highlighted. We review the pathophysiological evidence under three separate headings: (1) anatomical remodeling of the upper airway muscles, (2) efferent changes, and (3) afferent changes (see Figure 1). This encompasses evidence from a variety of neurophysiological approaches including histological, electrophysiological, and physiological studies. The function of upper airway reflexes and tongue force/fatigue characteristics in OSA vs. non-OSA subjects is also briefly reviewed. Finally, we discuss how upper airway remodeling and neural injury might contribute to upper airway closure during sleep.

ANATOMICAL STRUCTURE OF UPPER AIRWAY MUSCLES

Several histological studies support the presence of upper airway remodeling in patients with OSA (Tables 1 and 2). Broadly, this includes changes in: muscle fiber type, direction of muscle fibers, and anatomical arrangement of nerve fiber terminals. Sixteen studies are summarized in Table 2. Most of these studies did not rule out OSA in the healthy non-OSA/control groups (full polysomnography evaluations are reported in only four studies). Thus, the reported magnitude of these changes may be an underestimation. The upper airway muscles are composed of a variety of fast and slow muscle fiber types (Table 1) with conventional myosin heavy chain (MHC) isoforms and three primary MHC phenotypes and two subtypes (in order of prevalence for the adult genioglossus muscle in non-OSA subjects MHCI > MHCIIX > MHCI > MHCI-IX > MHC-IIX; Daugherty et al., 2012). A limitation of biopsies is that they are obtained from a limited area and may not represent the characteristics of the whole muscle. Nonetheless, a number of studies have shown an increase in the percentage of Type IIA muscle fibers in the order of ~15% in several upper airway muscles in OSA patients including the uvula, genioglossus, medium pharyngeal constrictor, and palatopharyngeus (see Table 1; Smirne et al., 1991; Ferini-Strambi et al., 1998; Carrera et al., 1999; Series et al., 2000; Lindman and Stal, 2002; c.f. Friberg et al., 1998a). Type IIA muscle fibers are fast twitch fibers that can use both aerobic and anaerobic metabolism. While the cause for this increase in fiber type remains unknown, the change is likely to reflect training. Repetitive loading with regular nightly eccentric contractions (neural drive advancing the tongue anteriorly with negative airway pressure pulling the tongue posteriorly) combined with hypoxia may lead to fiber type alterations in the upper airway muscles indicative of an endurance trained muscle (Hildebrand et al., 1991; Pette and Staron, 2001). However, studies to definitively isolate the effects of training on upper airway muscle fiber type have not been done.

Anatomical changes consistent with upper airway muscle remodeling in OSA in adults include: increased prevalence of angulated muscle fibers, increased diameter of muscle fibers (Smirne et al., 1991; Ferini-Strambi et al., 1998; Series et al., 2000; Sauleda et al., 2003; Svanborg, 2003; De Vuono et al., 2007; Stål et al., 2009), atrophied muscles fibers (Edstrom et al., 1992; Friberg et al., 1998a), changes in capillary density and mitochondria content (Stål et al., 2009; Stål and Johansson, 2012), fiber type grouping (Edstrom et al., 1992; Ferini-Strambi et al., 1998; see Table 2), and increased neural cell adhesion molecule (N-CAM) expression (Boyd et al., 2004). However, one study found similarly widespread neurogenic changes in children both with and without...
FIGURE 1 | Types of evidence for neuromuscular pathology in OSA. MUSCLE: Remodelling may be reflected via anatomical changes within the upper airway muscles (red); EFFERENT: changes in the electromyogram (EMG) of the upper airway muscles innervated via the cranial nerves (blue); AFFERENT: changes in sensory pathways (green). NCAM=neural cell adhesion molecule.

Table 1 | Percentage of Type I, Type IIA, and Type IIB muscle fibers in non-OSA and patients with OSA.

| Muscle                  | Non-OSA % of fibers | OSA % of fibers | Author                  |
|-------------------------|---------------------|-----------------|-------------------------|
|                         | Type I | Type IIA | Type IIB | Type I | Type IIA | Type IIB |                     |
| Genioglossus            | 61     | 39      | 41       | 33.3   | 53.3     | 11.6     | Carrera et al. (1999) |
|                         | 33.3   | 48.8    | 18.3     | 33     | 53.3     | 11.6     | Series et al. (1996)  |
| Palatopharyngeus        | 13.7   | 31.5    | 1.6      | 22.1   | 58.4     | 0.5      | Lindman and Stal (2002) |
|                         | 26     | 77      | 77       | 16     | 87       |          | De Vuono et al. (2007) |
| Medium pharyngeal constrictor | 49     | 41.3    | 9.7      | 22.4   | 75.2     | 2.4      | Smirne et al. (1991)  |
|                         | 51.9   | 36.1    | 11.8     | 30.7   | 61.8     | 75       | Ferini-Strambi et al. (1998) |
| Uvula                   | 15.2   | 69.2    | 10.1     | 10.7   | 82.6     | 4.3      | Series et al. (1995)  |
|                         | 10.6   | 73.5    | 15.9     | 8.1    | 82.3     | 9.6      | Series et al. (1996)  |
|                         | ~15    | 76.1    | ~1.8     | ~1.8   | 89.4     | ~        | Series et al. (2000)  |
|                         | 12.8   | 65.3    | 4.8      | 19.5   | 55.8     | 16.1     | Lindman and Stal (2002) |

Histological biopsy studies have confirmed differences in the muscle properties between non-OSA subjects and patients with OSA. There is an increase in the fraction of Type IIA fiber types in human upper airway musculature. Note: Type IIB fibers in humans are now referred to as Type IIX. Note: some rows do not total 100%. In some cases the number of Type IIB fibers were too low to be considered for calculation (e.g., Series et al., 2000), specialized MHC isoforms were calculated in some cases and are not displayed in the Table (see Lindman and Stal, 2002), and others reflect estimations based on available data.

OSA (De Vuono et al., 2007). Thus, questions remain as to what degree of chronic partial denervation is “normal” for upper airway muscles.

Snoring is a key feature of OSA. The vibration induced by snoring and the mechanical strain caused by repetitive upper airway closure is associated with inflammatory changes to soft tissue structures of the upper airway (Berger et al., 2002; Boyd et al., 2004). The local inflammation increases the thickness of the surrounding tissues and may narrow the upper airway to exacerbate obstructive apneas (Rubinstein, 1995; Sekosan et al., 1996; Berger et al., 2002). Patients with severe snoring have soft palate swelling in the morning that recedes while awake (Sekosan et al., 1996).

There is also increased fat in and around the muscles of the upper airway in patients with OSA (Horner et al., 1989; Stauffer et al., 1989; Schwartz et al., 1991; Zohar et al., 1998b; Berger et al., 1999).
Table 2 | Anatomical structural changes.

| Reference                      | Main findings                                                                 | Comments                                                                 |
|--------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Woodson et al. (1991)          | Soft palate and uvula biopsy; histological differences in soft palate and uvula in OSA vs. snorers and non-snorers measured via electron microscopy  | Notes A and B                                                                |
|                                | • Focal degeneration of myelinated nerve fibers and axons in OSA               |                                                                         |
|                                | • Focal muscle fiber atrophy in snorers and OSA                                |                                                                         |
|                                | • Muscle bundle disruption and fiber degeneration in all snorers and OSA       |                                                                         |
| Edstrom et al. (1992)          | Palatopharyngeal muscle biopsy; neurogenic changes in OSA vs. non-OSA          | Note A                                                                   |
|                                | • ↑ Number of angulated atrophic fibers                                       |                                                                         |
|                                | • Fiber type grouping                                                         |                                                                         |
|                                | • Muscle fiber atrophy                                                        |                                                                         |
| Series et al. (1995)           | Uvula biopsy; altered anatomy and function in OSA patients vs. snorers        | All subjects had sleep studies                                          |
|                                | • ↑ Cross-sectional area and Type IIA muscle fiber area in OSA                 | No healthy control group                                                 |
|                                | • Creative kinase, GADPH, phosphofructokinase, and phosphorylase ↑ in OSA      | Findings consistent with a muscle training effect                         |
|                                | (all elements in the anaerobic pathway)                                       |                                                                         |
|                                | • ↑ Twitch and tetanic tension in OSA                                         |                                                                         |
|                                | • Fatigability index similar between the two groups                           |                                                                         |
| Series et al. (1996)           | Uvula and genioglossus biopsies; altered anatomy in OSA patients vs. snorers  | All subjects had sleep studies                                          |
|                                | • Uvula ↑ glycolytic, glycogenolytic, and anaerobic enzyme activities          | No healthy control group                                                 |
|                                | • No difference in genioglossus glycolytic and anaerobic enzyme activities    | Snorers had a low AHI                                                    |
|                                | • Uvula and genioglossus: ↑ Type IIA, ↓ Type IIB muscle fiber %, and no change in muscle fiber area | Findings consistent with a muscle training effect                         |
| Friberg et al. (1997)          | Soft palate mucosa biopsy; neurogenic changes in OSA vs. snorers and non-snorers| Note A                                                                   |
|                                | • ↑ Density of afferent nerve endings in epithelium                           | Non-OSA = chronic tonsillitis and one pharyngeal tumor                   |
|                                | • ↑ Number of varicose nerve endings in epithelium                            | Epithelium thicker in OSA                                                |
|                                | • ↑ Nerves containing neuropeptides ↑ PGP9.5 density indicating increased neurons and nerve fibers|                                                                         |
| Ferini-Strambi et al. (1998)   | Medium pharyngeal constrictor and quadriceps biopsies; altered anatomy of pharyngeal constrictor, but, not quadriceps muscle in OSA vs. non-OSA | OSA based on clinical symptoms and portable monitor                      |
|                                | • ↑ % Type I, ↑ % Type IIA, and ↓ % Type IIB                                  |                                                                         |
|                                | • ↑ Type IIA fiber diameter                                                   |                                                                         |
| Friberg et al. (1998a)         | Palatopharyngeal and anterior tibial biopsies; altered anatomy of palatopharyngeal, but, not in anterior tibial muscle in OSA vs. non-OSA | Note A, interviewed history, and spouses                                 |
|                                | • Similar palatopharyngeal muscle fiber type distribution                    | Non-OSA = tonsillectomy                                                  |
|                                | • ↑ Palatopharyngeal muscle fiber size variations                            | Chronic tonsillitis, 2 for tumor                                          |
|                                | • Rounded atrophic palatopharyngeal muscle fibers                            |                                                                         |
|                                | • ↑ Incidence of centrally located nuclei and split palatopharyngeal muscle fibers |                                                                         |
|                                | • Palatopharyngeal muscle fiber type grouping                                 |                                                                         |
| Carrera et al. (1999)          | Genioglossus biopsy; altered anatomy and function in OSA vs. non-OSA         | Note A                                                                   |
|                                | • Untreated OSA patients ↑ % Type II muscle fibers, and ↑ fatigability        | No break down of muscle fibers into Type IIA and B                       |
|                                | • No differences in muscle fiber distribution and fatigability in a separate analysis of CPAP treated patients vs. non-OSA | Not the same subjects pre- and post-treatment                            |
| Series et al. (2000)           | Uvula muscle biopsy; altered anatomy in OSA patients vs. snorers             | All subjects had sleep studies                                          |
|                                | • ↑ % Type IIA muscle fibers                                                 | No control group                                                         |
|                                | • No difference in muscle fiber area in Type I or II, thus, no evidence for atrophy or hypertrophy |                                                                         |
| Paulsen et al. (2002)          | Uvula mucosa biopsy; altered anatomy in OSA patients vs. snorers and non-OSA | Note B                                                                   |
|                                | Measured via electron microscopy                                             |                                                                         |
|                                | • Absence of connective tissue papillae                                       |                                                                         |
|                                | • ↓ Cytokeratins                                                             |                                                                         |
### Table 2 | Continued

| Reference                     | Main findings                                                                 | Comments                                                                 |
|-------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Acanthosis of epithelium     |                                |                                                                          |
| Leukocytes inside the lamina  |                                |                                                                          |
| propria                       |                                |                                                                          |
| Lindman and Stal (2002)       | Uvula and palatopharyngeus biopsies; altered anatomy in OSA patients vs. non-OSA | Note B                                                                   |
|                               | • ↓ Ratio of area of palatopharyngeus muscle fibers to connective tissue in OSA patients |                                                                          |
|                               | • ↑ Palatopharyngeus muscle Type I, ↑ Type IIA, and ↓ Type IIAB and IIB muscle fibers in OSA patients |                                                                          |
|                               | • ↓ Uvula muscle fiber diameters for all fiber types except Type IIC/IM        |                                                                          |
| Boyd et al. (2004)            | Soft palate and/or tonsillar pillar biopsies; denervation in OSA patients vs. non-OSA | Note A, screened via questionnaire                                         |
|                               | • ↑ PGP9.5 specifically expressed in the neurons and nerve fibers            |                                                                          |
| De Vuono et al. (2007)        | Palatopharyngeal biopsy; similar findings in children with OSA, vs. snorers vs. controls with the presence of each of the following in similar proportions | All subjects had sleep studies                                             |
|                               | • Muscle fiber size variability                                               | Findings suggest that these histological features may reflect a “normal” muscle rather than neurogenic or myopathic pathology |
|                               | • Rounded atrophic muscle fibers                                              |                                                                          |
|                               | • ↑ Type II muscle fibers                                                    |                                                                          |
|                               | • Irregular muscle fiber architecture “moth-eaten”                           |                                                                          |
| Stål et al. (2009)            | Uvula and palatopharyngeus biopsies; altered anatomy in OSA patients vs. non-OSA | Note A, no history of any significant disease                             |
|                               | • ↓ Capillary density per muscle fiber area                                   | Note B                                                                   |
|                               | • Histopathological in all OSA muscle biopsies: fibrosis, variability in fiber size, developmental MyHC isoforms |                                                                          |
| Bassiouny et al. (2009)       | Uvula biopsies; degenerative anatomical changes to both myelinated and unmyelinated nerve endings in OSA patients vs. snorers vs. non-OSA | Note A, confirmed via partners and medical history                        |
|                               | • Myelin sheath had obvious signs of: degenerated and irregular Schwann cells, lamellated bodies, neurofilament loss, and fatty degeneration | Non-OSA died from causes unrelated to head and neck                       |
| Stål and Johansson (2012)     | Uvula and palatopharyngeus biopsies; altered anatomy in OSA patients vs. non-OSA | Note A, previously physically healthy                                      |
|                               | • ↓ Capillaries around abnormal muscle fibers                                | Note B                                                                   |
|                               | • Abnormal mitochondrial distribution                                        |                                                                          |
|                               | • Uvula ↑ fiber hypertrophy                                                  |                                                                          |
|                               | • Palatopharyngeus muscle fibers display signs of both atrophy and hypertrophy in OSA vs. controls |                                                                          |

**Note A:** indicates that overnight sleep studies were not performed in the non-OSA group.  
**Note B:** indicates that samples from the non-OSA group were obtained via autopsy.

et al., 2002). The importance of increased fat is highlighted by the observation that weight loss in obese OSA patients can eliminate airway obstruction. While infiltration of fat is not a result of neural changes, it will alter the dynamics of the upper airway. With increased intramuscular fat, contractile performance may change via altered loading of individual muscle fibers and altered “passive” properties (Busha et al., 2002). Given that some of the tension developed in one part of the muscle can be transmitted via shear links to other parts of the muscle (Kjaer, 2004), increased fat may alter the force distribution across muscle fibers in OSA patients. Nevertheless, maximal voluntary tongue protrusion force is the same, or increased in OSA patients (e.g., Mezzanotte et al., 1992; Mortimore et al., 2000; Eckert et al., 2011).

**EVIDENCE FOR UPPER AIRWAY EFFERENT CHANGES**

In addition to changes in the soft tissues and muscle fibers, there are also electrophysiological changes in the muscles of patients with OSA (Table 3). During wakefulness patients with OSA have higher levels of multunit electromyographic activity (EMG) recorded in the upper airway muscles compared to healthy control subjects (Mezzanotte et al., 1992, 1996; Fogel et al., 2001; c.f. Series et al., 2009). The apparent increase in drive was ascribed to a neural compensation for a narrow upper airway. This concept became widely accepted. The neural compensation was thought to be analogous to that in diaphragm and other obligatory inspiratory muscles of patients with chronic obstructive pulmonary disease where more motor units are recruited and their average discharge frequencies are higher (De Troyer et al., 1997; Gorman et al., 2005) because of the increased resistive load. Recent studies indicate that motor unit discharge frequencies also increase with higher neural drive to the genioglossus (Bailey et al., 2007; Saboisky et al., 2010). However, there is currently no strong evidence to support an overall increase in the discharge frequencies, or recruitment of additional motor units...
### Table 3: Efferent changes.

| Reference                        | Main findings                                                                 | Comments                                                                 |
|----------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Mezzanotte et al. (1992)         | Fine-wire intramuscular multiunit genioglossus electromyography; increased neural drive in OSA vs. non-OSA | Note A                                                                  |
|                                  | • ↑ Peak EMG during quiet breathing                                          |                                                                          |
| Fogel et al. (2001)              | Fine-wire intramuscular genioglossus electromyography; increased neural drive in OSA vs. non-OSA | Note A                                                                  |
|                                  | • ↑ EMG during wakefulness (↑ tonic activation and ↑ negative-epiglottic pressure during entrained iron-lung ventilation in inspiration) | Primary analysis included older OSA patients                           |
|                                  | • No difference in mean EMG/Pepi relationship in OSA and controls under all conditions (basal breathing, iron-lung ventilation and heliox breathing) | Not matched for BMI                                                     |
|                                  | • Age matched sub-analysis EMG not increased (but trended ↑ in OSA tonic, peak, and phasic) |                                                                          |
| Svanborg (2005)                  | Concentric needle single motor unit palatopharyngeus electromyography; neurogenic changes in OSA patients vs. snorers and controls | Note A                                                                  |
|                                  | • 10/12 OSA evidence of lesions: polyphasic potentials, 3/15 snorers exhibited “moderate” lesions |                                                                          |
| Saboisky et al. (2007)           | Monopolar needle single motor unit genioglossus electromyography; neurogenic changes in OSA patients vs. controls | Note B                                                                  |
|                                  | • ↑ Area and longer duration action potentials                               | Not matched for BMI                                                     |
|                                  | • Distribution of six unit types identical between groups                    |                                                                          |
|                                  | • Inspiratory units recruited earlier in OSA patients                       |                                                                          |
|                                  | • ↑ Peak discharge frequencies of Inspiratory Phasic units but, inspiratory tonic ↓ in OSA |                                                                          |
| Series et al. (2009)             | Transcranial magnetic stimulation and surface genioglossus and diaphragm electromyography; different responses in OSA patients vs. controls | Note B                                                                  |
|                                  | • ↓ Latency of genioglossus MEPs during tongue protraction                   |                                                                          |
|                                  | • Negative correlation between genioglossus MEP latency and AHI             |                                                                          |
|                                  | • Similar baseline genioglossus EMG activity in OSA patients and controls during quiet breathing |                                                                          |
| Ramchandren et al. (2010)        | Hypoglossal nerve conduction; abnormalities in patients with OSA vs. controls | Note A                                                                  |
|                                  | • ↓ Compound muscle action potential amplitudes                             | Treated OSA subjects                                                   |
| Saboisky et al. (2012)           | Concentric needle MACRO and single motor unit genioglossus electromyography; neurogenic changes in OSA patients vs. controls | Note B                                                                  |
|                                  | • ↑ Duration, size index, relative irregularity coefficient, phases, turns, area to amplitude ratio area/phase, and MACRO duration amplitude and area | Large sample: no timing data minimal frequency data No snoring data BMI matched subjects |
|                                  | • No difference in peak to peak amplitudes                                  |                                                                          |
|                                  | • Irregularity coefficient correlated with minimal overnight oxygen saturation |                                                                          |

Note A: indicates that overnight sleep studies were not performed in the non-OSA group.

Note B: indicates that both the OSA and non-OSA group had overnight sleep studies.

In the genioglossus in OSA during wakefulness (Saboisky et al., 2007, 2012). During the pre-inspiratory phase of the respiratory cycle the overall excitability of the genioglossus motoneuron pool appears to be increased in OSA patients vs. controls. The timing of the initial activation of phasic inspiratory motor units is earlier (Saboisky et al., 2007). Similarly, during late expiration, the conduction times of motor evoked potentials elicited via transcranial magnetic stimulation of the motor cortex are shorter in the genioglossus in OSA patients than in controls (Wang et al., 2010). Thus, while there is currently no evidence for increased discharge frequencies or additional recruitment of motor units there are quantifiable changes in the timing of neural drive to genioglossus in OSA. Therefore, how do the new findings fit with these earlier studies?

An alternative explanation is that the elevated EMG in the upper airway muscles in patients with OSA is secondary to neurogenic remodeling. This is characterized as chronic partial denervation of muscle fibers, with reinnervation of the orphaned muscle fibers by collateral sprouting of surviving motor axons (Boyd et al., 2004; Gonzalez-Forero et al., 2004). The overall duration of motor unit potentials increase, often with increased amplitude (Bertorini et al., 1994; Preston and Shapiro, 2002). Recent investigations
using single motor unit techniques have shown that the motor unit potentials of upper airway muscles in OSA patients are larger in area, longer in duration, and more complex (Svanborg, 2005; Saboisky et al., 2007, 2012; see also Podnar and Dolenc Groselj, 2010). These changes could contribute to the increased multiunit EMG in OSA. Thus, active remodeling may help to preserve the functional capacity of the muscles. However, the presence of denervation and subsequent axonal sprouting may lead to changes in fine motor control such as speech (Goldstein et al., 2011). An additional potential problem with the initial reports of increased multiunit EMG in OSA (awake) is that values were normalized to the EMG produced during a maximal volitional task and may not be comparable between OSA patients and controls.

## EVIDENCE FOR UPPER AIRWAY AFFERENT CHANGES

If the anatomically deeper upper airway motor axons are affected by vibration, sensory afferents, closer to the airway surface, should also be impaired. However, the evidence supporting sensory nerve impairment in OSA is less convincing than that for motor nerves. If sensory nerves are affected, this may impair normal reflex mechanisms which contribute to upper airway function.

A variety of techniques have revealed potential sensory impairments in OSA. Two-point discrimination and detection of vibromechanisms which contribute to upper airway function.

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### UPPER AIRWAY REFLEXES

The integrity of the swallowing reflex is impaired in OSA patients (Mayer et al., 1999; Fanfulla et al., 2000; Lüdemann et al., 2001; Dziewas et al., 2007). Two studies report slower sensory conduction and smaller amplitude responses (Mayer et al., 1999; Fanfulla et al., 2000). In addition, it is notable that comparable changes have been observed for the compound muscle action potential in the median, sural, and ulnar nerves (Mayer et al., 1999; Dematteis et al., 2000; Lüdemann et al., 2001; Dziewas et al., 2007). This finding occurs when controlling for the increased body mass index in OSA (Dziewas et al., 2007). Thus, intermittent hypoxia may mediate systemic neural changes in OSA that are not isolated to the upper airway.

In summary, these findings reveal varying levels of sensory impairment to certain sensory stimuli in OSA. While the precise pathophysiological role of sensory impairment remains uncertain, sensory testing using calibrated airflow has been proposed as a screening test for OSA (Dematteis et al., 2005). There may also be different populations of OSA patients; those with sensory impairments and those patients without (Nguyen et al., 2005). Thus, while sensory impairments may play a key role to obstructions in some patients with OSA, neuromuscular, and anatomical influences may be more important in others.

## FUNCTION

The integrity of the swallowing reflex is impaired in OSA patients and snorers compared to controls (Table 5). A greater bolus volume is required to elicit the swallowing reflex, swallowing onset latency is delayed, and bolus leakage throughout the pharynx occurs more frequently in OSA patients and snorers compared to controls (Zohar et al., 1998a; Teramoto et al., 1999; Jäghagen et al., 2000).

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### Table 4 | Afferent changes.

| Reference                  | Main findings                                                                                                                                                                                                 | Comments |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| McNicholas et al. (1984)    | Inspiratory resistive load detection thresholds; decreased ability to detect inspiratory resistive loads in OSA patients vs. non-OSA                                                                     | Note C   |
| Clerk et al. (1994)         | Inspiratory resistive loads detection thresholds; not different in normal weight OSA patients vs. non-OSA                                                                                            | Note C   |
| Friberg et al. (1998b)      | Soft palate mucosa Laser Doppler perfusion/electrical stimulation; altered afferent nerve regulation in OSA Patients vs. snorers and non-OSA.  
\* ↓ Vasodilatation of the peripheral mucosa of severe OSA patients vs. non-OSA | Note A   |
| Tun et al. (2000)           | Inspiratory resistive load magnitude perception; reduced in untreated OSA vs. non-OSA.  
\* Reversed after 2 weeks CPAP therapy | Notes A and C |
| Kimoff et al. (2001)        | Two-point discrimination and vibration sensation in the oropharynx, lip, and hand; reduced oropharynx, but, not lip and hand sensation in OSA and non-apneic snorers vs. controls  
\* Partial reversibility of changes post-CPAP in OSA, but, still impaired  
\* Anesthesia abolished two point discrimination in all patients and ↓ vibratory sensation  
\* Similar impairment in both snorers and OSA | Note B and C Not matched for BMI |
| Guilleminault et al. (2002) | Two-point palatal discrimination; reduced in OSA vs. UIARS and controls                                                                                                                                   | Notes B and C |
| Gora et al. (2002)          | Respiratory-related evoked potentials (RREP); no difference in P1 amplitude or latency in OSA vs. non-OSA                                                                                            | Note A   |
| Akay et al. (2003)          | Respiratory-related evoked potentials; reductions in early RREP activity in OSA vs. non-OSA                                                                                                                  | Note A   Predominantly CPAP treated OSA patients |
| Afifi et al. (2003)         | Respiratory and auditory evoked potentials; no difference in early waveform components in OSA vs. non-OSA                                                                                            | Note B   RDI defined using portable monitor |
| Nguyen et al. (2005)        | Sensory detection thresholds for air-pressure pulses delivered to the oropharynx, velopharynx, hypopharynx, and larynx determined via endoscope; specific alternations in certain OSA patients vs. controls  
\* Two subgroups of patients with and without abnormal sensory measures at multiple upper airway sites  
\* Correlations between laryngeal sensory measures and apnea severity and nadir SaO2 | Notes B and C Reproducible measures after 3 months |
| Dematteis et al. (2005)     | Sensory perception thresholds at the soft palate to varying airflow rates; reduced sensitivity in OSA patients vs. controls  
\* Pharyngeal sensitivity correlated with OSA severity | Notes B and C OSA patients untreated |
| Hlavac et al. (2007)        | Inspiratory resistive load magnitude perception; reduced in untreated OSA vs. controls                                                                                                                     | Notes B and C |
| Donzel-Raynaud et al. (2009)| Respiratory-related evoked potentials; no difference in P1 amplitude or latency in OSA vs. controls                                                                                                  | Note B   |
| Eckert et al., 2011         | Respiratory-related evoked potentials and genioglossus and tensor palatini electromyography; no difference in early P1 component and reflex onset latency to brief negative upper airway pressure pulses in untreated OSA patients vs. controls | Note B   |
| Sunnergren et al. (2011)    | Soft palate and lip temperature detection thresholds; impaired in OSA patients vs. controls  
\* Soft palate thresholds: 6.6°C OSA, 5.1°C Snorers, 2.8°C non-snorers | Notes B and C |
| Grippio et al. (2011)       | Respiratory-related evoked potentials; reductions in early RREP activity in OSA vs. controls                                                                                                   | Note B   OSA patients untreated |

**Note A:** indicates that overnight sleep studies were not performed in the non-OSA group.

**Note B:** indicates that both the OSA and non-OSA group had overnight sleep studies.

**Note C:** indicates that finding may not represent primary sensory impairment; potentially influenced by confounders such as impairments in cognitive processing or edema related to OSA.
### Table 5 | Functional changes.

| Reference | Main findings | Comments |
|-----------|--------------|----------|
| **UPPER AIRWAY REFLEXES** | | |
| Mortimore and Douglas (1997) | Fine-wire intramuscular multifunction levator palatini and palatoglossus electromyography; reduced EMG responses to negative upper airway pressure pulses in OSA patients vs. non-OSA | Note A  
Large MTA (100 ms) not appropriate for examining reflexes  
EMG latencies unknown |
| Zohar et al. (1998a) | Swallowing provocation test and scintigraphy testing; altered swallowing reflex in OSA  
• Impaired bolus clearance in the oral cavity  
• Surgery (UPPP) improved bolus clearance but was not related to reductions in RDI | Minimal sleep monitoring  
(sound and 
\( \text{O}_2 \)) in non-OSA |
| Teramoto et al. (1999) | Swallowing provocation test; altered swallowing reflex in OSA vs. age, gender, and BMI matched controls  
• ↓ Onset latency  
• ↓ Inspiratory suppression time from the termination of swallowing to the next onset of inspiration  
• ↑ Provocant required to elicit swallow reflex | Note B |
| Jäghagen et al. (2000) | Swallowing provocation and videoradiographic testing; altered swallowing function in OSA patients and snorers vs. non-OSA  
• No correlation between swallowing function and severity of snoring | Note A |
| Leving Jäghagen et al. (2003) | Swallowing provocation and videoradiographic testing; altered swallowing function in OSA patients and snorers vs. controls  
• Dysfunction in 50% with AHI of >30, 61% AHI of 5–29, and 43% with AHI of <5 events/h | Note A |
| Berry et al. (2003) | Multunit surface and intramuscular genioglossus electromyography; slightly increased amplitude of EMG response to brief negative pressure pulses of moderate but not large magnitude | Note A  
OSA treated  
MTA not appropriate for examining reflexes per se |
| Eckert et al. (2011) | Fine-wire intramuscular multifunction genioglossus and tensor palatini electromyography; similar EMG responses in OSA patients vs. controls  
• No difference in short latency reflex timing or amplitude to negative pressure pulses  
• Peak genioglossus EMG and epiglottic pressure not different during passive iron-lung ventilation | Note B  
Not matched for BMI |
| Valbuza et al. (2011b) | Swallowing provocation and nasal fibroscopy; Swallowing dysfunction in OSA vs. controls  
• 64% had premature oral leakage to a food/liquid bolus | Note B |
| Valbuza et al. (2011a) | Palatal and gag reflexes; absence of reflexes in moderate and severe OSA patients vs. controls | Note B  
Pressure not standardized |
| **VOLUNTARY TONGUE PROTRUSION FORCE/FATIGABILITY** | | |
| Mezzanotte et al. (1992) | Maximal tongue protrusion force; not different in four very severe OSA patients vs. four non-OSA (30 vs. 38 N) | Note A  
Likely underpowered |
| Mortimore et al. (2000) | Tongue protrusion tasks; similar in OSA vs. non-OSA  
• No difference in maximal protrusion strength  
• No difference in tongue fatigability measured as time to hold a 50% of maximal contraction | Note A  
Max tongue force only explained ~4% of the variance in AHI |

(Continued)
Table 5 | Continued

| Reference                     | Main findings                                                                                                                                                                                                 | Comments               |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Busha et al. (2002)            | Tongue protrusion tasks; similar in OSA vs. non-OSA                                                                                                                                                    | Note A                  |
|                               | • Optimum length of the genioglossus longer in OSA patients vs. non-OSA                                                                                                                                   |                        |
|                               | • At longer muscle lengths ⊿ maximal protrusion force in OSA patients                                                                                                                                    |                        |
|                               | • Endurance times similar between the two groups                                                                                                                                                    |                        |
| Blumen et al. (2004)          | Tongue protrusion tasks; recovery longer in OSA vs. controls                                                                                                                                               | Note B                  |
|                               | • No change in endurance time or fatigability in OSA patients                                                                                                                                                 |                        |
|                               | • ⊿ Time to recovery of initial maximal force in the OSA patients                                                                                                                                          |                        |
|                               | • Final EMG median frequency was significantly higher and the final low-frequency EMG component smaller in the OSA patients                         |                        |
|                               | • Mean endurance time in the OSA patients 75% shorter                                                                                                                                                   |                        |
| Shepherd et al. (2006)        | Maximal tongue protrusion force; increased in severe OSA (AHI 49 h) vs. mild/non-OSA (AHI 8 h) supine but not seated                                                                                   | Note B                  |
|                               | • Tongue strength not related to AHI                                                                                                                                                                     |                        |
| Eckert et al. (2011)          | Tongue protrusion tasks; altered voluntary tongue protrusion force and fatigability in OSA patients vs. controls                                                                                         | Note B                  |
|                               | • ⊿ Maximal protrusion force                                                                                                                                                                                |                        |
|                               | • ⊿ Time to task failure (70% maximal force 5 s on 5 s off)                                                                                                                                              |                        |

Note A: indicates that overnight sleep studies were not performed in the non-OSA group.  
Note B: indicates that both the OSA and non-OSA group had overnight sleep studies.

Inhibition of inspiration associated with swallowing is also less pronounced in OSA (Teramoto et al., 1999). While these changes would favor aspiration laryngeal penetration was uncommon. This indicates that alterations in swallowing are predominantly subclinical in OSA. CPAP may improve subclinical swallowing dysfunction in OSA (Okada et al., 2000). Palatal reflexes to tactile stimuli such as the gag reflex are diminished, particularly in severe OSA (Valbuza et al., 2011a). The extent to which these changes are caused by sensory impairments or efferent changes and whether or not they influence OSA severity remains unknown.

Conversely, the upper airway negative pressure reflex, crucial for maintaining airway patency, does not appear to be impaired in OSA patients during wakefulness. Studies that were not optimally designed to measure reflex responses have shown reduced EMG activation in the palatal muscles (Mortimore and Douglas, 1997), comparable genioglossus EMG activation to high levels of negative pressure (−20 cm H₂O), and elevated genioglossus EMG activity to moderate suction pressures (−10 to −13 cm H₂O; Berry et al., 2003). However, a recent study using sensitive neurophysiological techniques found no differences in the timing or the amplitude of the genioglossus and tensor palatini negative pressure reflex during wakefulness between OSA patients and controls (Eckert et al., 2011).

TONGUE PROTRUSION FORCE AND FATIGABILITY

Maximum voluntary force of the tongue protuders is comparable (Mezzanotte et al., 1992; Mortimore et al., 2000; Busha et al., 2002; Blumen et al., 2004) or increased (Shepherd et al., 2006; Eckert et al., 2011) in OSA patients. While the maximal force generating capacity in the tongue protuders does not appear to be impaired in OSA, whether or not they are more vulnerable to fatigue remains uncertain. Fatigability, quantified as time to task failure during sustained isometric tongue protrusion tasks at 30, 50, and 80% of maximum, were not different between OSA patients and controls (Mortimore et al., 2000; Blumen et al., 2004). Conversely, time to task failure during an intermittent isometric tongue protrusion task (5 s on 5 s off at 70% maximal force) occurred approximately twice as quickly in OSA patients vs. controls (Eckert et al., 2011). Similarly, recovery of maximal force capacity following submaximal isometric tongue protrusion tasks was prolonged in OSA patients (Blumen et al., 2004). How various voluntary tongue protrusion measures during wakefulness relate to upper airway patency during sleep and OSA severity remains unclear. In an earlier study, maximal tongue protrusion force positively correlated with OSA severity, albeit it only weakly ($r^2 = 0.04$), whereas fatigability to a submaximal isometric sustained task did not (Mortimore et al., 2000). In a subsequent study, there was no correlation between maximal tongue protrusion force and OSA severity (Shepherd et al., 2006).

SUMMARY AND POTENTIAL ROLE OF NEURAL INJURY IN OSA

Remodeling of the upper airway muscles occurs in OSA. The most commonly reported finding is an increase in the proportion of Type IIA muscle fibers, a change which is consistent with muscle training. Changes in multiunit EMG are difficult to interpret. Recent single motor unit studies reveal chronic partial...
denervation in OSA. Upper airway sensory impairments to a range of stimuli also occur in OSA. However, it remains challenging to differentiate the relative contribution of afferent neural injury vs. the confounding influences of OSA (e.g., edema) to primary impairments in sensation.

Given that long-term vibration causes neurogenic changes in limb muscles (Takeuchi et al., 1986; Dahlin and Lundborg, 2001), snoring and its mechanical effects are likely to contribute to the observed upper airway anatomical, efferent, and afferent changes. However, intermittent hypoxia may also impair peripheral nerves in OSA. Thus, there is the potential for synergistic effects to mediate upper airway remodeling in OSA. Some of the changes in muscle properties and sensory impairments resolve, at least in part, with CPAP treatment (e.g., Carrera et al., 1999; Mayer et al., 1999; Tuin et al., 2000; Kimoff et al., 2001; Nguyen et al., 2005; Dziwas et al., 2007).

The evidence for a link between upper airway remodeling and the integrity of upper airway reflexes is limited. The swallowing and gag reflexes are impaired in patients with OSA. However, the existing data does not support a link between the presence of swallowing impairment and OSA severity (Jäghagen et al., 2000) and the potential for an impaired gag reflex to influence OSA severity is uncertain. Other subtle alterations, such as changes in speech, may also occur in OSA. Importantly, there is no strong evidence to suggest that key protective reflexes involved in maintaining upper airway patency are impaired in OSA. In addition, the ability of the tongue to generate volitional protraction force is similar or enhanced in OSA. Importantly, there is no strong evidence to suggest that key protective reflexes involved in maintaining upper airway remodeling in OSA. Some of the changes in muscle properties and sensory impairments resolve, at least in part, with CPAP treatment (e.g., Carrera et al., 1999; Mayer et al., 1999; Tuin et al., 2000; Kimoff et al., 2001; Nguyen et al., 2005; Dziwas et al., 2007).

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