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Rhythmic Masticatory Muscle Activity during Sleep: Etiology and Clinical Perspectives

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Rhythmic Masticatory Muscle Activity during Sleep: Etiology and Clinical Perspectives

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Résumé

L'activité rythmique des muscles masticateurs (ARMM) pendant le sommeil se retrouve chez environ 60% de la population générale adulte. L'étiologie de ce mouvement n'est pas encore complètement élucidée. Il est cependant démontré que l'augmentation de la fréquence des ARMM peut avoir des conséquences négatives sur le système masticatoire. Dans ce cas, l'ARMM est considérée en tant que manifestation d'un trouble moteur du sommeil connue sous le nom de bruxisme. Selon la *Classification Internationale des Troubles du Sommeil*, le bruxisme est décrit comme le serrement et grincement des dents pendant le sommeil. La survenue des épisodes d'ARMM est associée à une augmentation du tonus du système nerveux sympathique, du rythme cardiaque, de la pression artérielle et elle est souvent en association avec une amplitude respiratoire accrue. Tous ces événements peuvent être décrits dans le contexte d'un micro-éveil du sommeil.

Cette thèse comprend quatre articles de recherche visant à étudier *i)* l'étiologie de l'ARMM pendant le sommeil en relation aux micro-éveils, et à évaluer *ii)* les aspects cliniques du bruxisme du sommeil, du point de vue diagnostique et thérapeutique.

Pour approfondir l'étiologie de l'ARMM et son association avec la fluctuation des micro-éveils, nous avons analysé le patron cyclique alternant (ou cyclic alternating pattern (CAP) en anglais), qui est une méthode d'analyse qui permet d'évaluer l'instabilité du sommeil et de décrire la puissance des micro-éveils. Le CAP a été étudié chez des sujets bruxeurs et des sujets contrôles qui ont participé à deux protocoles expérimentaux, dans lesquels la structure et la stabilité du sommeil ont été modifiées par l'administration d'un médicament (la clonidine), ou avec l'application de stimulations sensorielles (de type vibratoire/auditif) pendant le sommeil. Dans ces deux conditions expérimentales caractérisées par une instabilité accrue du sommeil, nous étions en mesure de démontrer que les micro-éveils ne sont pas la cause ou le déclencheur de l'ARMM, mais ils représentent plutôt la «fenêtre permissive» qui facilite l'apparition de ces mouvements rythmiques au cours du sommeil.

Pour évaluer la pertinence clinique du bruxisme, la prévalence et les facteurs de risque, nous avons effectué une étude épidémiologique dans une population pédiatrique (7-17 ans) qui était vue en consultation en orthodontie. Nous avons constaté que le bruxisme est un trouble du sommeil très fréquent chez les enfants (avec une prévalence de 15%), et il est un facteur de risque pour l'usure des dents (risque relatif rapproché, RRR 8,8), la fatigue des muscles masticateurs (RRR 10,5), les maux de tête fréquents (RRR 4,3), la respiration bruyante pendant le sommeil (RRR 3,1), et divers symptômes liés au sommeil, tels que la somnolence diurne (RRR 7,4). Ces résultats nous ont amenés à développer une étude expérimentale pour évaluer l'efficacité d'un appareil d'avancement mandibulaire (AAM) chez un groupe d'adolescents qui présentaient à la fois du bruxisme, du ronflement et des maux de tête fréquents. L'hypothèse est que dans la pathogenèse de ces comorbidités, il y a un mécanisme commun, probablement lié à la respiration pendant le sommeil, et que l'utilisation d'un AAM peut donc agir sur plusieurs aspects liés.

À court terme, le traitement avec un AAM semble diminuer l'ARMM (jusqu'à 60% de diminution), et améliorer le ronflement et les maux de tête chez les adolescents. Cependant, le mécanisme d'action exact des AAM demeure incertain; leur efficacité peut être liée à l'amélioration de la respiration pendant le sommeil, mais aussi à l'influence que ces appareils pourraient avoir sur le système masticatoire. Les interactions entre le bruxisme du sommeil, la respiration et les maux de tête, ainsi que l'efficacité et la sécurité à long terme des AAM chez les adolescents, nécessitent des études plus approfondies.

Mots-clés: Bruxisme du sommeil, micro-éveil, adolescents, appareil d’avancement mandibulaire.

Abstract

Approximately 60% of the general adult population experiences rhythmic masticatory muscle activity (RMMA) during sleep. The etiology of this movement is not yet understood. However, it has been demonstrated that an increased frequency of RMMA may have detrimental consequences on the stomatognathic system. In this case, RMMA is considered the manifestation of a sleep-related motor disorder known as sleep bruxism (SB). According to the definition of the *International Classification of Sleep Disorders,* SB is the activity of tooth grinding and clenching during sleep. The occurrence of SB-related activity, i.e., RMMA, is associated with rises of sympathetic tone, heart rate, blood pressure, and it is frequently concomitant with larger respiratory breaths. All these events can be described within a sleep arousal.

The present thesis includes four research articles aimed to study *i*) the etiology of RMMA during sleep in relation to sleep arousal; and *ii*) the clinical perspectives of SB assessment and management.

To further investigate the etiology of RMMA and its association with sleep arousal fluctuations we analyzed the cyclic alternating pattern (CAP), a scoring method to assess sleep instability and describe sleep arousal pressure. CAP was scored in SB subjects and controls that participated in two experimental protocols in which sleep architecture and stability were altered by either a medication (i.e., clonidine), or sensory stimulations (i.e., vibratory/auditory). Under these experimental conditions known to increase sleep instability, we were able to show that sleep arousal is not the trigger or cause of RMMA, rather the "permissive window" that facilitates the occurrence of RMMA during sleep.

To evaluate the clinical relevance of SB, we conducted a survey on a 7-17 year old orthodontic population to investigate the prevalence and risk factors associated with SB. It appeared that SB is a highly prevalent sleep disorders in children (15% of prevalence), and is a risk factor for tooth wear (odds ratio, OR 8.8), jaw muscle fatigue (OR 10.5), frequent headache (OR 4.3), loud breathing during sleep (OR 3.1), and several sleep complaints, such as daytime sleepiness (OR 7.4). These findings led us to design an experimental trial

using a mandibular advancement appliance (MAA) in adolescents in order to investigate the possible relationship between SB, snoring, and headache. We hypothesized that a common underlying mechanism related to breathing during sleep may be responsible for all concomitant conditions.

The short-term use of an MAA appeared to reduce SB (up to 60%), and improve snoring and headache complaints in adolescents. However, the precise mechanism of action of MAA remains under debate; its effectiveness can be either related to the improvement of breathing during sleep, or its influence on the masticatory system. The interactions between SB, breathing, and headache as well as the long-term effectiveness and safety of the MAA in adolescents need further investigations.

Keywords: Sleep bruxism, sleep arousal, adolescents, mandibular advancement appliance.

Riassunto

L’attività ritmica dei muscoli masticatori (ARMM) durante il sonno si osserva in circa il 60% della popolazione generale adulta. L'eziologia di questo movimento non è stata ancora del tutto compresa. Tuttavia, è dimostrato che un’aumentata frequenza di ARMM può avere conseguenze negative sul sistema stomatognatico. In questo caso, l’ARMM è considerato la manifestazione di un disturbo motorio del sonno noto come bruxismo. Secondo la *Classificazione Internazionale dei Disturbi del Sonno*, il bruxismo è l'attività di digrignamento e serramento dei denti durante il sonno. La comparsa di episodi di ARMM durante il sonno è associata a un aumento del tono del sistema nervoso simpatico, della frequenza cardiaca, della pressione arteriosa, ed è spesso in concomitanza con un aumentato volume inspiratorio. Le variazioni di questi parametri fisiologici sono compresi nel contesto di un arousal (micro risveglio) del sonno.

Questa tesi comprende quattro articoli di ricerca volti a studiare *i)* l'eziologia dell’ARMM durante il sonno in relazione all’arousal, ed a valutare *ii)* l’inquadramento clinico del bruxismo nel sonno.

Per approfondire l'eziologia dell’ARMM e l’associazione con l’arousal nel sonno, abbiamo analizzato il cyclic alternating pattern (CAP), che permette di valutare l'instabilità del sonno e descrivere la potenza degli arousals. Il CAP è stato esaminato in soggetti con bruxismo e soggetti controllo che hanno partecipato in due protocolli sperimentali, in cui la struttura e la stabilità del sonno sono stati modificati con la somministrazione di un farmaco (la clonidina), o con l’applicazione di stimolazioni sensoriali (di tipo vibratorio/uditivo) durante il sonno. In queste condizioni sperimentali caratterizzate da un’aumentata instabilità del sonno, siamo stati in grado di dimostrare che l’arousal non è la causa o il generatore dell’ARMM, ma piuttosto la "finestra permissiva" che facilita il verificarsi di questi movimenti ritmici durante il sonno.

Per valutare la rilevanza clinica del bruxismo, abbiamo condotto uno studio epidemiologico in una popolazione pediatrica afferente alla clinica di ortodonzia per studiare la prevalenza e i fattori di rischio associati al bruxismo. Questa ricerca ha

evidenziato che il bruxismo è un comune disturbo del sonno nei bambini (con una prevalenza del 15%), ed è un fattore di rischio per usura dentale (odds ratio, OR 8.8), fatica dei muscoli masticatori (OR 10.5), mal di testa frequenti (OR 4.3), respirazione rumorosa durante il sonno (OR 3.1), e diversi sintomi legati al sonno, quali la sonnolenza diurna (OR 7.4). Questi risultati ci hanno portato a progettare uno studio sperimentale per valutare l'efficacia di un apparecchio di avanzamento mandibolare (AAM) in un gruppo di adolescenti che presentavano al contempo bruxismo, russamento e frequenti cefalee. L'ipotesi è che nella patogenesi di tali comorbidità, vi sia un meccanismo comune, probabilmente legato alla respirazione durante il sonno, e che l'utilizzo di un AAM possa quindi avere un beneficio multiplo.

Il trattamento a breve termine con un AAM sembra diminuire l'ARMM (fino al 60%) e migliorare il russamento e i mal di testa negli adolescenti. Tuttavia, l'esatto meccanismo di azione degli AAM rimane incerto; la loro efficacia può essere correlata sia al miglioramento della respirazione durante il sonno, ma anche all'influenza che questi apparecchi svolgono sul sistema masticatorio. Le interazioni tra il bruxismo nel sonno, la respirazione, e le cefalee, così come l'efficacia e la sicurezza a lungo termine degli AAM negli adolescenti, necessitano di ulteriori studi clinici.

Keywords: Bruxismo nel sonno, arousal, età pediatrica, apparecchi di avanzamento mandibolare.

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
CAP	Cyclic Alternating Pattern
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
HA	Headache
MAA	Mandibular Advancement Appliance
NREM	Non-Rapid Eye Movement
PSG	Polysomnigraphy
REM	Rapid Eye Movement
RLS	Restless Leg Syndrome
RMMA	Rhythmic Masticatory Muscle Activity
SB	Sleep Bruxism
SDB	Sleep-Disordered Breathing
SEM	Standard Error of the Mean
SWA	Slow Wave Activity
SWS	Slow Wave Sleep
TC	Tooth Clenching
TMD	TemporoMandibular Disorders
TMJ	TemporoMandibular Joint
VT/AD	Vibro-Tactile and Auditory

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Ai miei cari genitori,

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Introduction

Few episodes of rhythmic masticatory muscle activity during sleep occur in approximately 60% of the general adult population as a physiologic jaw movement probably related to swallowing and breathing. However, this motor behavior may fall into a pathological range if occurring with increased frequency during sleep and if associated with clinical signs and symptoms. In this case, we talk about sleep bruxism, a sleep-related movement disorder included in the *International Classification of Sleep Disorders* as the oral parafunction of grinding and clenching of the teeth during sleep.

Although the precise etiology of sleep bruxism remains unclear, its pathophysiology is researched in the complex mechanisms that regulate sleep. Sleep is a highly organized brain state of quiescence that entails several important functions, such as physical and psychological recovery, biochemical refreshment, memory consolidation and emotional regulation. Within sleep, physiological, endocrine and neurological functions follow a cyclic fluctuation controlled by the homeostatic and ultradian drives. It seems probable that also phasic events during sleep, such as sleep arousals and sleep bruxism, obey to this fluctuating pattern of occurrence.

From a clinical perspective, sleep bruxism has been frequently described in association with other sleep disorders (e.g., obstructive sleep apnea), pain complaints (e.g., headache), and, especially in children, with behavioral problems (e.g., inattention and hyperactivity). Thus, tooth-grinding should be considered more than an oral parafunction causing tooth wear, rather it should be accounted in a wider clinical assessment of the patient's health.

The present thesis aims to better understand the pathogenesis and regulation of rhythmic masticatory muscle activity during sleep to untimely provide support for an evidence-based management of sleep bruxism.

Chapter 1: Literature Review

1.1 Historical Aspects of Bruxism

The word “bruxism” originates from the Greek word βρυγμός (brygmós), meaning gnashing of the teeth. The first description of the phenomenon in the scientific literature is dated 1907, when the French term *bruxomanie* was used to describe an involuntary and ”nervous” grinding of the teeth, as observed in patients who were afflicted with lesions in the central nervous system like meningitis, dementia, and epilepsy (1). Later in 1931, Frohman, a physician, was one of the earliest to use the word bruxism, defined as a problem of a dental nature resulting from non-physiological movements of the mandible related to psychological factors (2). From then on, multiple definitions and several terms have been referred to bruxism: “occlusal habit neurosis”, “neuralgia traumatic”, “teeth gnashing-grinding”, and “parafunction” (3, 4). Few authors also attempted to distinguish between different forms of bruxism. Miller alluded to bruxism to indicate the teeth grinding during sleep, whereas bruxomania was used to denote the habit of grinding during daytime (5). Ramfjord and Ash described clenching as a “centric bruxism”, while grinding as “eccentric bruxism” (6). From the perspective of different medical disciplines, bruxism ranged from being considered a neurological tic or automatism, to a parasomnia or a sleep-related movement disorder (7). The many descriptions and classifications applied to this disorder merely reflect the variety of etiologic factors that over the years have been deemed to cause bruxism.

1.2 Definition and Classification of Sleep Bruxism

According to the *Glossary of Prosthodontic Terms*, bruxism is considered an oral parafunction consisting of involuntary rhythmic or spasmodic nonfunctional gnashing, grinding, or clenching of the teeth (8). Although this definition describes the main movement-related characteristics of the disorder, it lacks a substantial and important

distinction between the wake and sleep states in which this oral parafunction may occur. There is clinical and research evidence to consider the wake-time habit of clenching, grinding, or gnashing the teeth a distinct nosologic entity, probably with different etiology and pathophysiology, that should be distinguished from bruxism during sleep (7).

The *American Academy of Orofacial Pain*, indeed, defines bruxism as the diurnal or nocturnal parafunctional activity of clenching, bracing, gnashing, and grinding of the teeth (9). However, the use of the words "diurnal" and "nocturnal" is obsolete; the more precise "wake-time" and "sleep-related" terms should be preferred since they respect the fact that being awake or asleep does not always coincide with daytime and nighttime, respectively.

According to the *International Classification of Sleep Disorders*, second edition (ICSD-II), published by the American Academy of Sleep Medicine in 2005 (10), sleep bruxism (SB) is classified as a sleep-related movement disorder. The characteristic electromyography (EMG) pattern of SB is found in repetitive and recurrent episodes of rhythmic masticatory muscle activity (RMMA) of the masseter and temporalis muscles that are usually associated with sleep arousals (7, 10). The RMMA shows a frequency of 1 Hz and typically occurs cyclically during sleep (Figure 1.1). RMMA episodes are observed in 60% of the general adult population as physiological activity of the jaw muscles during sleep (11, 12). Many other forms of masticatory and facial muscle activity are also observed during sleep, such as swallowing, coughing, sleep talking, smiling, lip sucking, jaw movements, and myoclonus (7, 13). These orofacial activities account for approximately 85% of EMG events scored on the masseter and temporalis muscles in control subjects and 30% in SB subjects (14-16). In fact, RMMA frequency is three times higher in SB subjects than in controls, and is typically associated with tooth grinding sounds (in 45% of cases), as reported by the patient, bed partner, parents, or siblings (7).

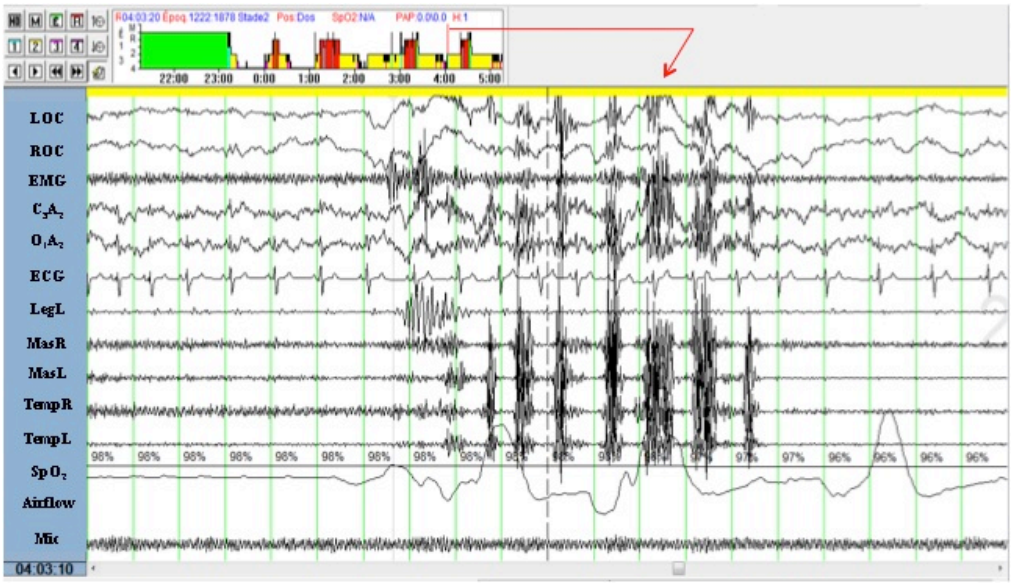
SB may be an extreme manifestation of a physiological orofacial motor behavior during sleep (RMMA and chewing-like activity) whereby certain factors increase its occurrence until it falls into the pathological range of jaw-muscle activity. Therefore, SB

refers to the sleep motor disorder, whereas RMMA is the characteristic EMG pattern that is scored during sleep to make a polysomnographic diagnosis of SB.

1.3 Assessment and Diagnosis of Sleep Bruxism

The assessment and diagnosis of SB are often challenging. Generally, the assessment is based on reports of tooth-grinding sounds during sleep and the presence of clinical signs and symptoms (10). However, only an electromyographic (EMG) recording of the masticatory muscles can confirm the SB diagnosis. A number of portable diagnostic tools have been developed to record masseter and/or temporalis EMG activity during sleep in order to avoid using the more sophisticated but highly cost- and time-consuming polysomnography (PSG). However, the reliability of most portable devices has not yet been validated, and their use may be considered only as a support in the clinical assessment of SB. In fact, the SB diagnosis is usually clinical, although the gold standard remains a full-night PSG with audio-video recording (Table 1.1). The future direction for SB assessment would be to develop a handy tool that can directly, reliably, and rapidly measure ongoing bruxism activity, and that can be used in both clinical (for diagnosis, treatment outcome evaluation, and follow-up) and research settings.

Figure 1.1 Hypnogram and polysomnographic tracing showing an episode of rhythmic masticatory muscle activity (RMMA) during sleep.



The full night hypnogram (graph in the upper left represents sleep stage distribution in non-REM sleep 1, 2, 3, 4 and REM sleep) and a 20-sec polysomnographic page with a clear example of RMMA during sleep are shown. The subject is in non-REM sleep stage 2. RMMA is defined when at least 3 consecutive EMG bursts (frequency 1 Hz) lasting ≥ 0.25 sec are scored on the masseter and temporalis channels. Corresponding with the RMMA episode, note the increased frequency in cortical activity (EEG central (C_3A_2) and occipital (O_1A_2) derivations), increased heart rate (on the ECG channel), and increased amplitude of respiratory airflow (naso-cannula). Immediately before the RMMA onset, an increase in the EMG activity of the suprahyoid muscle (EMG channel) and a leg movement (LegL channel) are observed (From ambulatory PSG recording Siesta, Compumedics).

LOC: left electrooculogram; ROC: right electrooculogram; EMG: electromyographic activity of the suprahyoid muscle; C_3A_2: the central derivation of the electroencephalogram (EEG); O_1A_2: the occipital derivation of the EEG; ECG: electrocardiogram; LegL: EMG of the left tibialis muscle; MasR and MasL: EMG of the right and left masseter muscles; TempR and TempL: EMG of the right and left temporalis muscles; SpO_2: oxygen saturation level (expressed as %); Airflow: naso-cannula airflow; Mic: microphone.

Table 1.1 Methods for assessing sleep bruxism.

Methods for assessing sleep bruxism (order of increasing reliability)	
Method	*Notes*
• **Patient's history**	Many subjects may not be aware of their tooth-grinding habit during sleep. More reliable if the bed partner, parents, or siblings report current tooth grinding sounds during sleep.
• **Clinical assessment**	To assess the clinical signs and symptoms that suggest SB (e.g., tooth wear; refer to Box 1) and the presence of potential risk factors for other comorbidities (e.g., enlarged tonsils, skeletal Class II, and Mallampati score III or IV for the risk of concomitant SDB).
• **Questionnaires**	To investigate the patient's general and oral health, sleep quality, sleep habits, oral parafunctions, presence and characteristics of pain, headache, fatigue, depression, anxiety and stress, and comorbidities.
• **Ambulatory EMG monitoring**	Allows recording EMG activity during sleep from the temporalis or masseter muscles, depending on the device used. However, very low specificity and sensitivity in distinguishing actual RMMA episodes from the many other orofacial and motor activities that occur dung sleep. Furthermore, no monitoring on awakening from sleep, arousal, sleep staging, or other sleep variables. This could be a valuable tool in the clinical assessment of SB and in large-sample studies (e.g., general population epidemiological studies).
• **Ambulatory PSG recording (Type II, III, and IV)**	Usually performed at the patient's home. Normally, no audio-video monitoring. Specificity and sensitivity in detecting RMMA depends on the device used, and more particularly, on the number of variables monitored (EEG, EOG, ECG, EMG, and respiratory channels). This method may be used for scoring sleep stages, sleep arousals, leg movements, and EMG activity, and for monitoring breathing.
• **Full audio-video PSG recording (Type I)**	Remains the gold standard for the diagnosis of SB and the assessment of comorbidity with other sleep disorders (e.g., SDB, PLMS, RLS, RBD, parasomnias). Normally, it allows full-night monitoring of EEG, EOG, EMG, ECG, leg movements, respiratory effort, airflow, and oxygen saturation. Concomitant audio-video recording increases the specificity and sensitivity in RMMA detection and scoring by distinguishing between RMMA episodes and orofacial (e.g., swallowing, coughing, sleep talking) and other muscular activities (e.g., head movements, eye blinking) that occur during sleep.

SB: sleep bruxism; SDB: sleep-disordered breathing; EMG: electromyogram; RMMA: rhythmic masticatory muscle activity; EEG: electroencephalogram; EOG: elecrooculogram; ECG: electrocardiogram; PLMS: periodic limb movement during sleep; RLS: restless leg syndrome; RBD: REM sleep behavior disorder

(Carra MC. based on (7, 17))

1.3.1 Clinical Diagnosis of Sleep Bruxism

The clinical diagnosis of SB should be based on the international diagnostic criteria proposed by the American Academy of Sleep Medicine (Table 1.2) (10, 18). Grinding sounds due to tooth contacts are the pathognomonic sign of SB, and they are usually reported by the patient, bed partner, siblings, or parents. However, not all RMMA episodes are accompanied by tooth grinding, and many patients or family members may not be aware of this.

A clinical examination of the oral cavity allows identifying signs and symptoms that are markers of tooth-grinding activity and a clenching habit. These signs and symptoms include hypertrophy of the masseter and temporalis muscles, tongue indentation, tooth wear, jaw muscle tenderness or pain on digital palpation, and reports of morning headache (7, 19). However, none of these signs and symptoms constitutes direct proof of current SB activity. For example, although tooth wear is widely reported in the literature as the classic dental sign of bruxism (both awake and during sleep), it may be related to many other factors that can induce attrition and erosion on dental surfaces (e.g., age, occlusal conditions, enamel characteristics, diet, carbonated drinks, medications, gastroesophageal reflux, and alimentary disorders)(7, 19-23). Moreover, it was recently demonstrated that tooth wear cannot be used as an absolute criterion to assess SB severity: no difference in tooth wear grade was found between low and high frequency of muscle contractions in young adults with SB (21).

During the clinical examination, dental clinicians can also identify early risk factors for SB and other sleep or medical disorders (e.g., sleep-disordered breathing), and promote further investigations when necessary. In particular, the risk of having or developing sleep-disordered breathing (SDB) increases with retrognathia, micrognathia, macroglossia, adenotonsillar hypertrophy, and a Mallampati score of III and IV (24). The Mallampati score qualifies oropharyngeal obstruction, with I standing for no obstruction (tonsils, pillars, and soft palate are clearly visible) and IV for high obstruction (where only the hard

palate is visible)(25). In addition, clinicians can directly observe breathing habits (mouth breathing vs. nasal breathing), behavioral attitudes (agitation, anxiety), and a tendency to fall asleep. Although it remains under investigation, some of these factors have been associated with an increased risk for both SB and SDB.

Appropriate questionnaires can also be used to investigate general health, quality of life, pain, headache, sleep quality, and sleepiness. Some questionnaires have been validated for both clinical and research purposes (e.g., the Pittsburg Sleep Quality Index and the Epworth Sleepiness Scale). Questionnaire assessments may give the clinician an indication of the risk of comorbidity between SB and other, more severe sleep disorders, such as SDB or restless leg syndrome (RLS) (Table 1.1).

Table 1.2 American Academy of Sleep Medicine (AASM) clinical diagnostic criteria for sleep bruxism.

AASM clinical diagnostic criteria for sleep bruxism	
1)	Patient history: Recent patient's and/or parent's and/or sibling's report of tooth grinding sounds occurring during sleep for at least 3 to 5 nights per week in the last 6 months
2)	Clinical evaluation:* - Abnormal tooth wear - Hypertrophy of the masseter muscles on voluntary forceful clenching - Discomfort, fatigue, or pain in the jaw muscles (and transient morning jaw muscle pain and headache)
3)	Jaw muscle activity cannot be better explained by another current sleep disorder, medical or neurologic disorder, medication use, or substance use disorder.

**None of these signs and symptoms constitutes direct proof of current SB activity. Full-night PSG with audio-video recording remains the gold standard for SB diagnosis.*

(Carra M.C. based on (7, 10))

1.3.2 Ambulatory Assessment of Sleep Bruxism

A number of portable EMG monitoring systems have been developed to assess SB activity. They differ in degree of complexity, ranging from miniature self-contained EMG detectors to ambulatory PSG systems (levels II, III, and IV)(17), which allow monitoring only a limited number of channels (Table 1.1). These devices enable multiple-night recordings in the patient's home at minimal expense, and could be useful research tools in large sample studies. However, the lack of standardized scoring criteria and evidence-based validity limit their application to both clinical and research settings.

Because automatic EMG detectors and analyzers usually use a unique algorithm for RMMA activity scoring, their validity remains to be demonstrated. Conversely, ambulatory PSG recordings provide very good quality EMG signals, and depending on their complexity, they can usually assess other sleep parameters, such as sleep EEG (essential for sleep staging) or respiratory variables. In addition, on the masseter and/or temporalis EMG channels, RMMA episodes can be distinguished as phasic, tonic, or mixed. Furthermore, episode and burst frequency and muscular strength can be calculated (Table 1.3)(7). However, ambulatory PSG is usually performed in the patient's home without audio-video monitoring. This may lead to overestimation of RMMA episodes due to confounding and non-SB-specific motor activities during sleep. We are currently validating RMMA scoring criteria on ambulatory PSG recordings, and have observed a modest concordance rate between RMMA scored with and without video on the same night (*Carra et al., unpublished data*). Although preliminary, this finding suggests that, in the absence of audio-video recording, more rigorous criteria should be applied to the clinical assessment and EMG scoring of SB-related activity.

Table 1.3 Polysomnographic research diagnostic criteria for sleep bruxism

Polysomnographic research diagnostic criteria for sleep bruxism **for scoring rhythmic masticatory muscle activity (RMMA) episodes**
Mean EMG amplitude: at least 10% of maximum voluntary clenching activity
Types of RMMA episodes: • **PHASIC**: at least 3 EMG bursts lasting ≥ 0.25 sec and < 2 sec • **TONIC**: 1 EMG burst lasting > 2 sec • **MIXED**: phasic and tonic bursts EMG bursts must be separated by < 2 sec to be considered part of the same episode.
SB diagnosis can be made based on:***** • **The RMMA INDEX**: number of RMMA episodes per hour of sleep • **The BURST INDEX**: number of EMG bursts per hour of sleep • **The BRUXISM TIME INDEX** (%): total time spent bruxing / total sleep time x 100 • **TOOTH-GRINDING SOUNDS**: at least 1 RMMA episode with tooth grinding sounds
Positive SB diagnosis (based on the frequency of EMG episodes with positive tooth grinding history or confirmation in a sleep laboratory):***** • **LOW FREQUENCY**: when the RMMA Index ≥ 2 and < 4 • **HIGH FREQUENCY**: when the RMMA Index is ≥ 4 and/or the Burst Index ≥ 25

***Best level of reliability when performing audio-video PSG recordings and the presence of at least 2 RMMA episodes associated with tooth-grinding sounds.*

(Carra MC. based on (7, 10, 15, 26-29)).

1.3.3 Polysomnographic Diagnosis of Sleep Bruxism

PSG for SB is mainly used for research purposes (Table 1.1). The research diagnostic criteria have been developed on the basis of PSG with audio-video recordings performed in a hospital setting with a sleep technician attending full-night monitoring (15, 18). This PSG (referred to as level I)(17) allows assessing several sleep physiological parameters (e.g., electroencephalogram, electrooculogram, electromyogram, electrocardiogram, airflow, respiratory effort, oxygen saturation), while audio-video recording enables documenting tooth grinding sounds and distinguishing between RMMA

and orofacial (e.g., swallowing) and other muscular activity (e.g., head movements) during sleep. The validated criteria for a sleep laboratory diagnosis of SB showed 72% sensitivity and 94% specificity (15). Based on RMMA index (number of episodes/h of sleep), the diagnosis of SB is made when RMMA index ≥ 2 (low-frequency SB – mild bruxism). A RMMA index greater than 4 is considered moderate to severe bruxism (high-frequency SB) (Table 1.3)(7, 15, 30).

PSG recordings are not usually indicated for subjects who report SB only. However, the clinician should refer the patient to a sleep physician for further investigation and diagnosis if other sleep disorders are suspected (e.g., sleep apnea, sleep-related epilepsy, REM sleep behavior disorder, periodic limb movement, or other neurological disorder).

1.4 Epidemiology of Sleep Bruxism

In large population-based studies, it is difficult to assess SB by objective measures such as PSG recordings. The epidemiology of SB is therefore largely determined by questionnaires, self-reports, and/or clinical findings (e.g., tooth wear).

SB is reported by 8% of the general adult population (31, 32). It typically peaks during childhood (with prevalence approaching 40% below the age of 11 years)(33-38), and tends to decrease after adulthood. During elderly (>60 years of age) SB is reported with a low prevalence (3%)(31, 32). However, this may be explained by the presence of edentulism, denture wearing, and changes in sleeping behaviors (i.e., in isolation) that are often observed in elderly populations. Overall, no gender difference has been observed (31, 38, 39).

Many confounding factors should be considered when interpreting the epidemiology of SB. The wide prevalence range (from 8% to 40%) reported in the

literature is most probably because many studies failed to distinguish between wake-time and sleep-related bruxism or to assess the presence of medical comorbidities that may influence its occurrence. Indeed, SB is frequently concomitant (approximately one third of the subjects) with wake-time bruxism, which is characterized mainly by a tooth clenching habit (40). Wake-time bruxism tends to increase with age, with an estimated prevalence of 13% in children (38) and over 30% in adults (41-43).

Notwithstanding the limitations related to its objective assessment, SB is a common sleep disorder and its actual prevalence is probably much higher since individuals are often un-aware of sleep-related motor behaviors, especially if subjects sleep alone.

1.5 The Masticatory System during Wake and Sleep

Rhythmic masticatory movements, like chewing, are controlled by the central nervous system. Specifically, it is the trigeminal system that is responsible for the activation and regulation of the masticatory muscles (44). Indeed, the muscles of the jaw are innervated by trigeminal motoneurons located in the trigeminal motor nucleus, in the rostral part of the pons. Trigeminal motoneurons receive both excitatory (i.e., glutamatergic) and inhibitory (i.e., GABA-ergic and glycinergic) synapses. The excitatory and inhibitory inputs onto trigeminal motoneurons are coming from premotoneurons surrounding the trigeminal motor nuscleus. During mastication, trigeminal motoneurons fire to produce very regular and repetitive jaw movements on the three planes of the space. These jaw movements are determined by the activation (i.e., contraction) of the jaw-opening muscles (e.g., digastric muscles) during mouth opening, and of the jaw-closing muscles (e.g., masseter and temporalis muscles) during mouth closing. The rhythmical and alternated activation of the jaw muscles is produced by the brainstem nuclei that compose the central pattern generator (CPG) (45). The CPG is responsible of initiating and

maintaining the motor activity through pattern generation and rhythm generation. These activities in the CPG can be triggered both from the cortex and from the sensory signals from the periphery. In facts, although chewing can continue without feedback, the movement is fine-tuned by sensory signals acting through the action of reflexes (e.g., the stretch reflexes; the periodontal reflexes) (46). This mechanism guarantees that muscle activity, muscle force, and jaw position are adjusted to deal with the changing conditions that occur when different foods are being chewed. Therefore, mastication is neither a purely voluntary movement nor a purely reflex (44, 46). A complex combination of both drives the rhythmicity and coordination of the masticatory muscles, whose movement is centrally programmed (47).

Chewing-like rhythmic jaw movements during wakefulness can also be cortically evoked by electrical stimulation, resulting in a pattern of jaw-opening and jaw-closing muscle activity that resembles natural food chewing (48). Conversely, rhythmic masticatory movements during sleep (e.g., RMMA) occur spontaneously without any food triturating purpose, and with a co-contraction of both the jaw-closing and jaw-opening muscles. Moreover, RMMA occurs without apparent cortical involvement—unlike chewing, which is initiated at the cortical level— and it is strongly influenced by autonomic nervous system activity and arousals during sleep (20, 49, 50). Nevertheless, many studies suggest that SB is centrally regulated—probably in the brainstem—and its genesis is more likely multifactorial (7, 51-53).

The brainstem neuronal networks which control the genesis of rhythmic masticatory movements during wakefulness has been studied in animal models, which allowed describing the cortico-bulbar pathway that drives mastication (45, 47). In particular, it seems that cortico-bulbar inputs to controlateral brainstem structures first activate a relay in the medial pontomedullary reticular formation that eventually reaches the trigeminal motor nuclei and activates jaw-opening or jaw-closing muscles to produce jaw movements (47, 54). During sleep, these cortico-bulbar influences are not dominant, rather they seem to be partially de-activated to preserve sleep continuity (55, 56). Interestingly, several of the

brainstem reticular nuclei that are involved in the masticatory regulation are also involved in sleep genesis and maintenance, as well as in respiratory control (51).

The ascending arousal system originating in the brainstem is crucial in maintaining wakefulness with well-defined cell groups involved in two major pathways (57). The major inputs come from the cholinergic pedunculopontine and laterodorsal tegmental nuclei. These nuclei activate thalamic relay neurons and the thalamic reticular nucleus that are crucial for transmission of information to the cerebral cortex. The other pathway originates in centers in the upper brainstem and caudal hypothalamus, including the locus coeruleus, dorsal and median raphe nuclei, ventral periaqueductal gray matter, and the tuberomammillary nucleus. This ascending arousal pathway bypasses the thalamus, activating the lateral hypothalamus and basal forebrain and then the cerebral cortex. The activity of both the wake-promoting pathways is inhibited by a system of gamma-aminobutyric acid (GABA)-containing neurons, in which the lateral hypothalamic ventrolateral preoptic nucleus (VLPO) appears to play a key role (58). Wake- and sleep-promoting systems have mutually inhibitory influences on each other. Indeed, during wakefulness the activity of the VLPO is strongly inhibited by the noradrenergic locus coeruleus and other wake-promoting centers. As the activity of these centers decreases at sleep onset, the VLPO becomes active, in turn reciprocally inhibiting wake-promoting neuron activity. This mutually inhibitory self-reinforcing loop has the characteristic of a "flip-flop switch" that acts to produce stable states of wakefulness or sleep with sharp transitions between them (57). Glycinergic and GABAergic inhibitory neurons active during sleep are known to directly project to the respiratory centers, such as the hypoglossal motor nucleus (59), and to influence the activity of the masticatory CPG nuclei. In fact, during sleep there is a general reduction in muscle tone in comparison with wakefulness. This could result from a reduction in the cortico-bulbar drive, and/or tonic hyperpolarization of masticatory muscle motoneurons, making them less excitable, and/or a reduction in the arousal driven monoaminergic tone (51). Similar to the decrease in postural muscle tone, sleep causes the suppression of masticatory muscles activity, which typically

occur immediately at sleep onset indicating a primary suppressant effect of sleep neural mechanisms. This inhibition (i.e., decrease in trigeminal motoneurons excitability) is higher during REM sleep, a sleep stage characterized by powerful generalized muscle “atonia” (or better hypotonia) of the limb and jaw muscles. However, even during REM sleep transient and sudden periods of increased trigeminal motoneurons excitability are observed, and RMMA activity can be manifest (50, 51).

1.6 Etiology and Pathogenesis of Sleep Bruxism

The exact etiology and pathophysiology of SB are still unknown (60). The putative etiologic mechanisms for the genesis of RMMA during sleep include sleep arousal, autonomic sympathetic cardiac activation, genetic predisposition, neurochemicals, psychosocial components, exogenous factors, and comorbidities (Table 1. 4).

1.6.2 Sleep Arousal

As stated in the ICSD-II definition, the majority of RMMA episodes occur in association with sleep arousals (10, 18, 61). This association was first observed by Reding et al. (62) in 1968 and by Satoh and Harada (63) in 1971, who described tooth-grinding activity as an “arousal reaction”. Since then, many studies have used polysomnography and electrophysiology to investigate the complex relationship between SB and sleep arousal (60, 61, 64-67).

Table 1.4 Etiology and pathophysiology of sleep bruxism.

Etiology and pathophysiology of sleep bruxism	
Putative etiologic factors and mechanisms	*Evidence**
Sleep arousal Over 80% of RMMA episodes occur in association with sleep arousal. However, sleep arousal is considered the 'permissive window' that facilitates RMMA occurrence during sleep rather than a trigger or cause of SB.	+++
Autonomic sympathetic cardiac activity A rise in sympathetic cardiac activity precedes the majority onset of the majority of RMMA episodes. This rise is also followed by rise in heart rate and blood pressure immediately before the muscular activity of the jaw opening and closing muscles.	+++
Neurochemicals The potential role of catecholamines (adrenaline, noradrenalin, and dopamine). SB subjects appear to have higher urinary levels of catecholamines. The putative role of other neurochemicals: GABA, orexin, serotonin, and acetylcholine (all involved in the genesis and maintenance of wake and sleep. As yet unknown roles).	+
Genetic and familial predisposition In more than 80% of cases, SB persists from childhood to adulthood. Higher concordance in monozygotic than dizygotic twins. Approximately one-third of SB subjects have a direct family member with a positive tooth grinding history.	+
Psychosocial factors Anxiety and stress are risk factors for SB. Subjects with SB appear to have maladaptive coping strategies and a more task-oriented personality than subjects without SB.	++
Exogenous factors Alcohol, caffeine, cigarette smoking, illicit drug use (e.g., cocaine, ecstasy), and medication intake (e.g., SSRI) can trigger or increase wake-time bruxism and SB activity.	++
Comorbidity A common underlying pathogenetic mechanism is suspected, e.g., SB and SDB: does SB play a role in reinstating airway patency following an apnea event, or is SB an apnea-related arousal reaction?	++

**Strength of available scientific evidence.*
+ weak evidence; ++ moderate evidence; +++ strong evidence
(Carra MC. based on (7, 20, 51, 60, 61, 64, 68-74)).

1.6.2.1 The sleep arousal system

Sleep arousal is defined as a brief awakening from sleep (for at least 3 seconds) characterized by an abrupt shift toward higher EEG frequencies (including alpha, theta and/or frequencies greater than 16 Hz, but not spindles), generally associated with cortical, autonomic and behavioral activations in the absence of the return of consciousness (18). Arousals normally reoccur from 6 to 14 times per hour of sleep as the response of the

sleeping brain to external (environmental) and internal (physiological or pathological) stimuli. In the presence of certain sleep disorders, breathing anomalies or chronic pain, arousals are more frequent.

Although sleep is defined as a reversible behavioral state of reduced responsiveness to environmental stimuli, the sleeping brain is still active and able to control the autonomic, metabolic and hormonal changes that take place within the body. Some cerebral areas remain gradually and partially activated and they are able to scan and weight information filtered through the thalamocortical pathways, and simultaneously trigger behavioral responses to given external stimuli. Such activation is stimulated by the arousal system (57, 75). The arousal system comprises cholinergic, monaminergic, histaminergic, and orexinergic neurons located in the brainstem, which fire at different rate during wakefulness, NREM and REM sleep (57, 76). Their activity finely regulates the sleep-wake transition and the sleep cycle (57). Sleep arousals can be seen as the body's attempt to prepare the sleeping individual (who is in a low vigilance state) to react to a potential risk, i.e., a « fight or flight » state. However a high arousal index (number of arousals per hour of sleep) is also a sign of sleep fragmentation, a detrimental alteration of sleep architecture, and thus a poor quality of sleep (75).

The arousal threshold (the probability to elicit an arousal from sleep) changes throughout the night. In the wake-to-sleep transition, usually sleep stage N1, the arousal threshold is very low and thus sleep can be easily discontinued by environmental stimuli. In stage N2 and N3 an incrementally more intense stimulus is required to produce arousal. Conversely, the arousal threshold during REM sleep is quite variable throughout the night (77, 78). Beside the behavioral state, the arousal response depends also on the nature of sensory stimulations (e.g., intensity, modality) (79).

RMMA episodes are observed predominantly during sleep stages N1 and N2 (*light sleep*), whereas only the 10% of episodes occur during REM sleep (7, 61). Between 70% and 88% of RMMA episodes are temporally correlated with an arousal (61, 64), and related

autonomic-cardiac activations (See Section 1.5.2). Although the number and index of arousal do not generally differ between young otherwise healthy SB subjects and controls, experimental evidence suggested that SB subjects may have a higher responsiveness to sleep arousal (65). Whether this condition may influence the onset and recurrence of RMMA is unclear.

1.6.2.2 The cyclic alternating pattern

The cyclic alternating pattern (CAP) is a marker of cerebral activity occurring under conditions of reduced vigilance (e.g., sleep). CAP is considered the expression of a basic arousal modulator, which represents states of sleep instability but also belongs to physiological sleep (80-82). Terzano and colleagues have extensively studied the features of CAP for 30 years, and they have demonstrated that most of the arousal-related phasic events, which can appear either spontaneously or after external perturbation, follow this cyclic and rhythmic time organization during NREM sleep (83, 84). CAP is described as the structural framework that ties together both sleep-preserving features (low EEG frequency, high amplitude bursts) and sleep-disrupting events within 20-40 seconds periodicity.

During NREM sleep, CAP is composed by the alternation of two EEG patterns (phase A and phase B) each lasting 2 to 60 seconds. Phase A is considered the active phase associated with heightened arousal levels, while phase B corresponds to the periodic replacement of the background EEG activities peculiar to the specific NREM sleep stage. On the basis of the reciprocal correlations between EEG and polygraphic parameters, it is possible to distinguish three types of CAP phase A (of increasing arousal pressure)(85):

- Phase A1: comprising exclusively synchronized EEG patterns that generally show only slight simultaneous variations in muscle tone and autonomic functions. It represents the weakest arousal power;

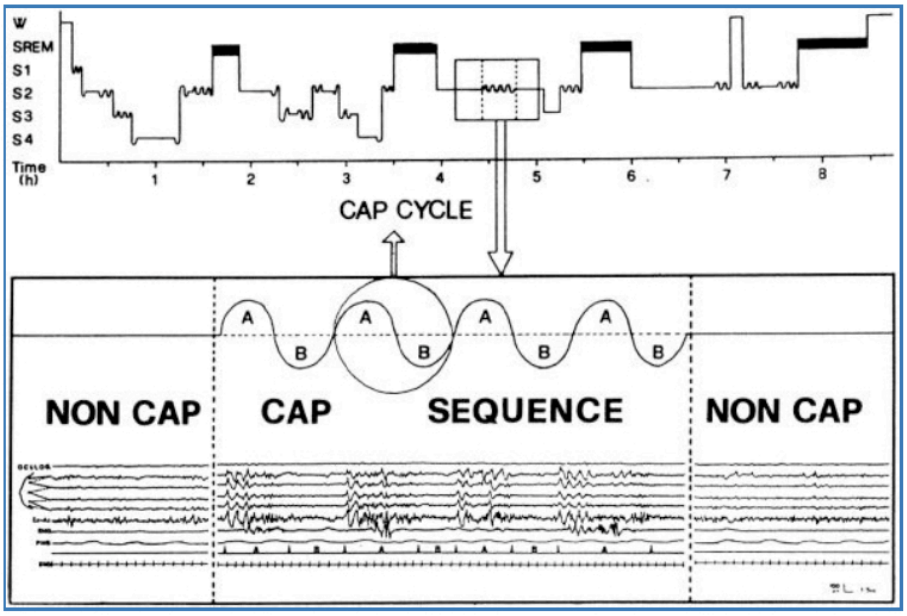
- Phase A2: composed of a mixture of slow and fast rhythms. It represents a transition phase and fits an intermediate arousal power level;
- Phase A3: characterized predominantly by EEG desynchronized patterns. It corresponds to the most powerful arousal pressure, as it is usually accompanied by relevant changes in muscle tone, heart rate and respiratory activity.

When the interval between 2 consecutive phase A and phase B exceeds 60 seconds, the CAP sequence ends and sleep enters the non-CAP (NCAP) mode characterized by stable EEG rhythms with very few and randomly distributed arousal-related phasic events (Figure 1.2). On the basis of the reciprocal occurrence and respective meaning of both CAP (marker of unstable sleep) and NCAP (stable and consolidated sleep), it is possible to define the sleep variable *CAP rate* (the ratio of total CAP time over the total NREM sleep time) as the measure of arousal instability during sleep (83). CAP rate is enhanced when sleep is disturbed by internal or external factors and its variations correlate with the subjective appreciation of sleep quality, with higher CAP rate associated with poorer sleep quality (82). CAP rate in normal sleepers shows a low intra-individual variability from night-to-night, while remarkable age-related differences have been reported. In particular, CAP rate was found to be progressively increasing from pre-school age to adolescence, and then U-shaped with a minimum in young adults and increasing again in late adulthood and elderly (86-88).

The distribution of CAP has been proven to be different across the sleep cycle. CAP sequences normally predominate in close temporal connection with major dynamic events, such as falling asleep, sleep stage shift, NREM/REM sleep transitions, nocturnal awakenings and body movements. It has been hypothesized that the abundance of A1 subtypes in the descending phase of the sleep cycle is the EEG expression of the cerebral mechanisms involved in the build-up and maintenance of deep NREM sleep, whereas subtypes A2 and A3 are predominant in the period preceding the onset of REM sleep (ascending phase) and may express the subject's arousability (89). This hypothesis is also supported by the topographic distribution of CAP A phases. Indeed, the A1 activity is

thought to be generated primarily by the frontal lobes where also slow waves are predominantly detected, whereas CAP A2 and A3 activity is thought to be generated by the posterior brain regions (90).

Figure 1.2 Schematic representation of cyclic alternating pattern (CAP).



1a. Histogram of physiological sleep in which CAP sequence (comb-like oscillation) and NCAP sequence (horizontal stretches) are outlined. **1b.** A specimen of sleep stage 2 is expanded to highlight the sequence of 4 CAP cycles (phase A + phase B) framed between portion of NCAP. (From Parrino et al. 1996, J Clin Neurophysiol)(91).

W, wakefulness; SREM, REM sleep; S1, S2, S3, S4, NREM sleep stages.

CAP and arousals are considered active adaptive responses of the sleep regulatory mechanisms, which tend to remove the stimulus-disturbance effect and re-establish an internal equilibrium. The total amount of CAP can be seen as the effort to maintain sleep at the microstructural level. While a limited amount of CAP is considered physiological, larger quantities reflect the brain difficulties to consolidate and preserve sleep and they may be associated with detrimental effects. The arousal system plays a cardinal neurophysiologic role in protecting and tailoring sleep duration and depth. CAP oscillation participates in the dynamic organization of sleep. Physiologic, paraphysiologic and pathologic motor activities during NREM sleep are associated with a stereotyped arousal pattern characterized by an initial increase in EEG delta power and heart rate, followed by a progressive activation of faster EEG frequencies (91-93).

In this perspective, there is evidence that supports the hypothesis that the frequency of RMMA episodes is modulated by the cyclic occurrence of sleep arousals, *i.e.* CAP (60, 61, 64). As previously mentioned, RMMA episodes are more frequently observed in NREM sleep stages 1 and 2 (light sleep), in sleep stage shifts, and especially in the transition period from non-REM to REM sleep (64). Over 80% of RMMA episodes are time-correlated with CAP phase A, and they recur in rhythmic clusters, with a periodicity of 20 to 30 seconds, which is similar to the physiological arousal rhythm of CAP.

Notwithstanding this association between sleep arousal and the occurrence of SB, the role of CAP and sleep instability in the pathogenesis of RMMA remains to be elucidated.

1.6.3 Autonomic Sympathetic-Cardiac Activity

Recent evidence on SB pathophysiology highlights the role of the autonomic nervous system (60, 64, 94). It has been well demonstrated that RMMA onset is associated

with a sequence of physiological events that occur within a sleep arousal. Briefly, the genesis of most RMMA episodes is preceded by the following cascade of events (7):

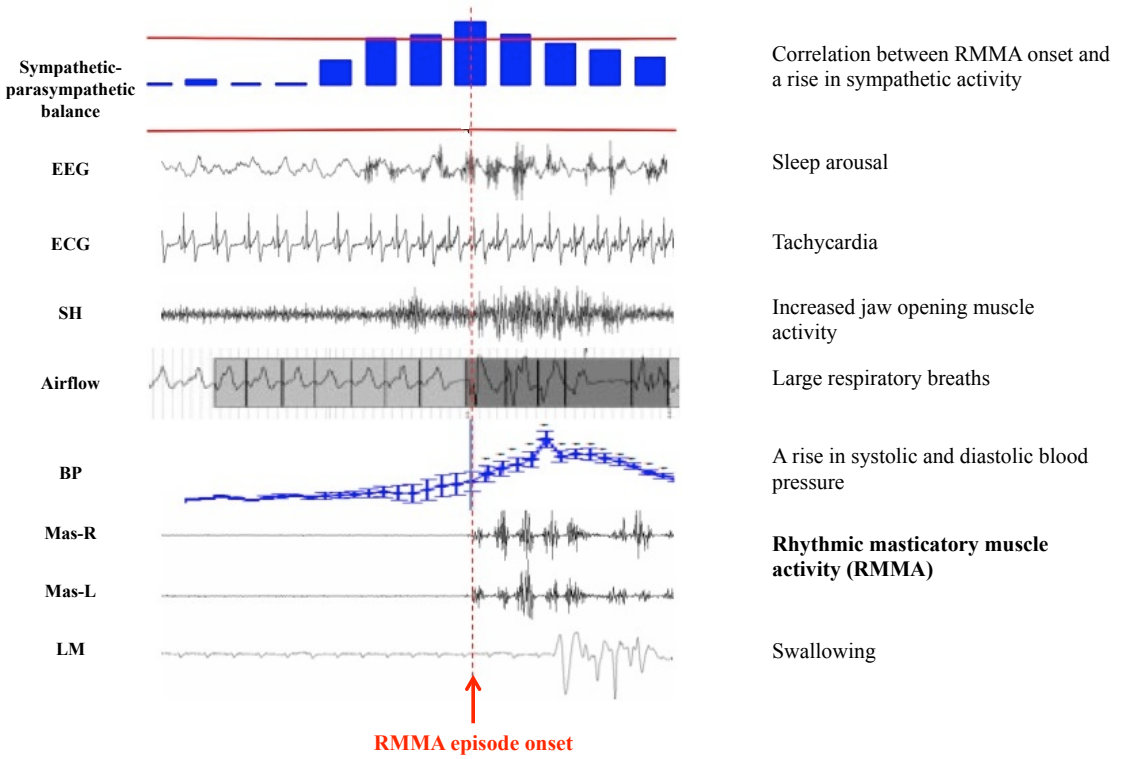
- A rise in the autonomic sympathetic-cardiac activity with a concomitant withdrawal of parasympathetic influences (from 8 to 4 minutes before RMMA onset)(64)
- The appearance of rapid-frequency EEG cortical activity (sleep arousal; approximately 4 seconds before RMMA onset)(60)
- A rise in heart rate of about 25% (beginning 1 second before RMMA onset), concomitant with
- An increase in jaw opener muscle tone (the suprahyoid muscle, probably responsible for mandible protrusion and airway opening), concomitant with
- An increase in the amplitude of the respiratory effort (nasal airflow)(69), preceding or concomitant with
- A rise in diastolic and systolic blood pressure (95)
- And finally, an observable EMG incident in the jaw-closing muscles (masseter and temporalis), scored as RMMA with or without tooth-grinding sounds (7). Almost 60% of RMMA episodes are followed in the 5 to 15 seconds after onset by swallowing (96) (Figure 1.3).

The activity of autonomic nervous system is physiologically modulated during sleep (97, 98). NREM sleep is characterized by a period of relative autonomic stability, with a vagal nerve dominance and sinusoidal modulation of heart rate variation due to a coupling with respiratory activity. Hypotension, bradycardia, and reduction of cardiac input are also progressively observed with deepening stages of NREM sleep. Conversely, during REM sleep the brain's increased excitability can result in major surges in cardiac sympathetic nerve activity, striking fluctuations of blood pressure and heart rate, and marked episodes of tachycardia and bradycardia (97). Finally, as describe above, significant autonomic changes (approximately 90% increase in sympathetic activity and 35% decrease in

parasympathetic activity)(99) accompany electrocortical arousals from sleep as well as periodic movements during sleep (64, 95, 98).

The autonomic nervous system activity can be non-invasively assessed by analyzing the heart rate variability during both wakefulness and sleep (100). Power spectral analysis of heart rate can then be evaluated as low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.5 Hz) ranges of modulation, reflecting the sympathetic+parasympathetic, and parasympathetic activities respectively. By calculating the LF/HF ratio, an index of sympathovagal balance can be obtained (100, 101). It has been reported that SB subjects have higher LF power and higher LF/HF ratio during wake compared to healthy controls, supporting that heart rate variability in SB subjects might be altered toward an increase in sympathetic activity also during wakefulness (94). This hypothesis was already suggested by the observation of phenomena like peripheral vasoconstriction, tachycardia and skin potential changes during tooth-grinding events, which might be a consequence of increased sympathetic activity (67). However, the power spectral analysis of heart rate variability during sleep showed no difference between SB subjects and controls for LF and HF powers, neither for the sympathovagal balance, even though a rise in sympathetic cardiac activity is registered in the minutes preceding RMMA episodes (64).

Figure 1.3 Genesis of an RMMA episode (schematic representation of the cascade of physiologic events that precedes RMMA onset)



EEG: electroencephalogram; ECG: electrocardiogram; SH: EMG of the suprahyoid muscle; BP: blood pressure; Mas-R and Mas-L: EMG of the right and left masseter muscles; LM: laryngeal movements.

(Lavigne G., Huynh N. based on (60, 64-66, 69)).

1.6.4 Neurochemicals

Many neurochemicals and neurotransmitters may be involved in the genesis and modulation of jaw movements during sleep, especially those that participate in controlling motoneuron activity and regulating sleep and wake states (acetylcholine, noradrenalin, dopamine, orexin) (51, 57). The dopaminergic system was first investigated after the early observation of tooth-grinding activity in a patient with Parkinson's disease treated with L-dopa (102). However, further studies using dopamine precursor L-dopa and domaninergic agonist bromocriptine demonstrated only a modest effect on SB (103-105). Dopamine is not usually very active during sleep, but it may be linked to sleep arousal re-activation (106). Conversely, clonidine, an adrenergic agonist, reduced RMMA episodes by 60%, supporting the role of sympathetic cardiac activation, adrenaline, and noradrenalin in the genesis of RMMA (64). Because noradrenergic action is critical during non-REM sleep in the minutes preceding REM sleep onset, it may participate in the transition from NREM to REM sleep, a state associated with muscle hypotonia (107).

Other neurotransmitters, such as serotonin, gamma-aminobutyric acid (GABA), cholecystokinin, and orexin, may have a role in modulating RMMA during sleep. Ionic channels, receptors, and their cellular expression may be also involved in SB genesis. However, either data are not yet available or the findings are supported by indirect evidence only, derived from case reports on drug and medication use. Prospective and randomized control experimental trials are needed before firm conclusions can be drawn on neurochemical participation in SB genesis.

1.6.5 Genetic Factors

There is evidence for a genetic predisposition for SB. Children of SB subjects are more likely to be affected than children of individuals who never had SB or who suffer from wake-time bruxism only (108). From 20% to 50% of SB subjects have a direct family

member who ground his or her teeth in childhood, and childhood SB persists in adulthood in 87% of subjects (70, 109). In a Finnish twin cohort study, higher concordance was found among monozygotic than dizygotic twins (68, 109).

Despite this early evidence of a genetic basis for SB, the inheritance pattern remains unknown, and no genetic marker has been identified to date. Further research on population-based samples is needed to explore and delineate the probable genetic component in SB genesis. It would be more likely related to genetic polymorphism than a single gene mechanism. Moreover, links to other wake and sleep behaviors would probably emerge (110, 111). It is worth noting that SB assessment tools in large populations—frequently based on a positive history of tooth grinding alone—have yet to be validated for acceptable sensitivity and specificity, especially in the general population. A clinical diagnosis of SB supported with portable systems or single-channel EMG recording is feasible and promising, but still lacking in specificity.

1.6.6 Psychosocial Factors: Stress, Anxiety, and Behavior

Aside from a probable genetic predisposition, many other causal or risk factors may play a role in the genesis of SB activity. Psychosocial components in particular, such as anxiety and stress, have frequently been associated with SB (32, 72, 73, 112-114). Both child and adult subjects reporting SB were found to have higher levels of urinary catecholamines (adrenaline, noradrenaline, dopamine) than controls (115-117). These results were attributed to stress factors that activate the hypothalamic-adrenal axis, which controls the catecholamine release. Other studies, mainly questionnaire-based, suggest that SB subjects may have maladaptive coping strategies: they appear to be more anxious, stressed, and task-oriented as a result of their personality and coping style (e.g., type A personality)(32, 73, 112, 113, 118, 119). Especially in children, SB has been associated with behavioral habits and complaints. These include neuroticism, perfectionism,

aggressiveness, lack of concentration and attention (e.g., at school), thought disorders, antisocial behaviors, and conduct disorders (120-122). Moreover, all these psychosocial factors may be also related to wake-time bruxism. In fact, tooth clenching may be an adaptive or reactive learning behavior—to cope with stress, anxiety, and social life—that may also occur during sleep. However, the overlapping and interactions between wake-time and sleep-time bruxism are still matters of debate.

Alternatively, SB has been considered a tic, an automatism, a movement fragment, or tardive dyskinesia, which may manifest during wake-time and persist during sleep (123). In any case, the many and contrasting findings in the literature indicate that further research is needed to better understand the role of psychosocial factors in SB pathophysiology (72).

1.6.7 Exogenous Factors and Comorbidities

Several exogenous factors and medical conditions have been associated with SB or bruxism-like activities during either sleep or wake-time. The exogenous risk factors for SB include alcohol consumption, cigarette smoking, caffeine intake, medication use (e.g., SSRI), and drug use (e.g., ecstasy)(32, 71, 124-133). Sensory stimulations, experimentally applied or naturally occurring during sleep, may also influence SB occurrence. However, this effect seems to be indirect: it has been shown that sensory perturbing stimuli (e.g., vibratory and auditory) can induce arousals from sleep, and therefore increase the chance of RMMA occurrence (65, 79). Nociceptive stimuli as well interfere with sleep continuity and trigger fluctuation in the autonomic nervous system (134, 135). However, the effects of pain stimulations delivered during sleep in SB subjects are unknown.

SB may also be observed in comorbidity with medical disorders such as attention deficit hyperactivity disorder (ADHD)(136, 137), movement disorders (e.g., Parkinson's disease and Huntington's disease)(138, 139), dementia (140-142), epilepsy (143-145), gastroesophageal reflux (96), and other sleep disorders such as parasomnias (e.g., sleep

walking, sleep talking, enuresis, REM sleep behavior disorder), periodic limb movements, restless leg syndrome (RLS), and sleep-disordered breathing (SDB) (Table 1.5)(74, 146-149). It remains to be assessed, however, whether these are cases of intersecting prevalence between two parallel disorders or if one condition causes or exacerbates the other (150).

In the past, SB was considered a consequences of occlusal interferences, malocclusion and tooth pre-contacts, which were advocated as the major causes and risk factors for the development of this oral parafunction during sleep. There is little scientific evidence, however, to support a predominant role for peripheral factors, such as occlusal interferences, in the etiology of SB (53, 151, 152).

When SB is associated with medication or drug intake or with medical diseases, it is defined as secondary or iatrogenic SB. Conversely, in the absence of medical causes, SB is considered to be primary, or idiopathic, and it can in turn lead to several clinical consequences on the stomatognatic system, such as tooth wear, tooth damage, tooth fractures, muscle fatigue, orofacial pain, temporomandibular disorders (TMD), and headache (7).

1.6.7.1 Sleep bruxism, orofacial pain, and temporomandibular disorders

Orofacial pain is reported by 66% to 84% of SB subjects (153, 154). However, the presence or intensity of pain does not appear to be directly correlated with the frequency of RMMA episodes (26, 155, 156). In fact, SB subjects with low frequency of RMMA (2–4 episodes/h of sleep) appear to have higher risks for orofacial pain and headache than SB subjects with high frequency of RMMA (>4 episodes/h of sleep)(26, 157). Furthermore, note that SB may coexist with wake-time tooth clenching and other oral parafunctions (e.g., lip, cheek, or nail biting), which can also cause or contribute to the development and persistence of orofacial pain (158-163).

SB has been largely considered a sign and/or cause of TMD in both adult and pediatric populations (164-169). Several studies suggest that SB may play a role in TMD genesis—especially the myogenous component—due to muscle hyperactivity during sleep. Nevertheless, TMD pain and morning jaw muscle pain may be different entities. Most patients with TMD report a pain intensity peak in the late afternoon, whereas SB subjects report transient masseter and temporalis muscle pain or soreness mainly in the morning (26, 170, 171). The association between SB and TMD needs to be further elucidated (172).

Table 1.5 Sleep bruxism and comorbidities.

Sleep bruxism and comorbidities	
Parasomnias	Enuresis
	Sleep talking
	Sleep walking
	REM sleep behavior disorder (RBD)
Other sleep-related disorders	Sleep-disordered breathing (snoring, obstructive sleep apnea)
	Sleep-related epilepsy
	Periodic limb movements (PLM) and restless legs syndrome (RLS)
	Sleep-related gastroesophageal reflux
Medical and psychological conditions	Hypertrophic tonsils and/or adenoids
	Allergies
	Attention deficit hyperactivity disorder (ADHD)
	Headaches
	Orofacial pain and temporomandibular disorders (TMD)
	Stress and anxiety
	Neurological and psychiatric disorders (e.g., dementia; depression)
	Movement disorders (e.g., Parkinson's disease; oralmandibular dystonia; tics)
Oral habits and parafunctions	Tics
	Nail biting, pen biting, etc
	Wake-time tooth clenching

(Carra MC. based on (26, 96, 136-138, 143, 144, 149, 153, 156, 173, 174)).

1.6.7.2 Sleep bruxism and headaches

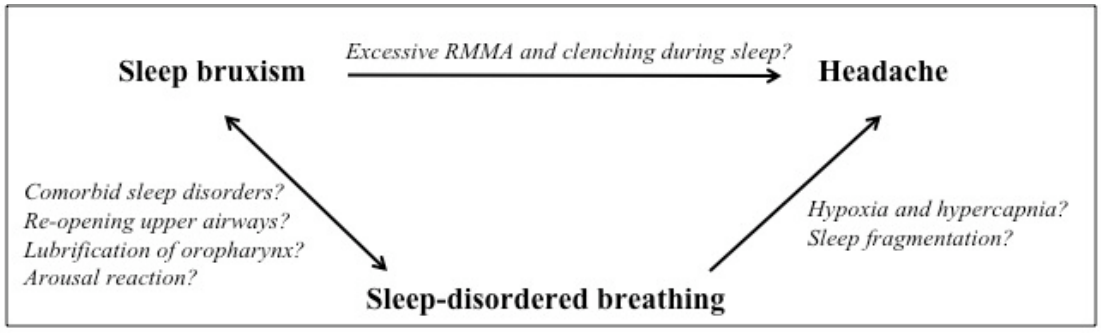
SB has been frequently associated with headaches (148, 174-179). From 30% to 50% of adult SB subjects complain of headache either in the morning (most frequently) or during the day (176). However, the exact mechanism underlying the possible interactions between SB and headaches remains unknown. It can be hypothesized that SB, which is characterized by repetitive rhythmic and sustained contractions of the masticatory muscles during sleep, may cause tension-type headaches during daytime. In fact, this comorbidity is controversial due to the overlap with forms of TMD pain and TMD-related headaches (180, 181). Furthermore, the presence of an underlying sleep disorder, such as sleep-disordered breathing (SDB), has often been associated with both SB and headache. In this latter case, the role of intermittent hypoxia and hypercapnia and sleep fragmentation (subsequent to obstructive respiratory events) may be the actual cause of the headaches (Figure 1.4). Alternatively, SB, headache, and SDB may share common risk factors or pathophysiological substrates without a specific cause-and-effect relationship. For example, it has been shown that children with headaches frequently have concomitant sleep problems, such as SB and SDB, and a higher incidence of TMD (182, 183).

1.6.7.3 Sleep bruxism and sleep-disordered breathing

Although SB and SDB (e.g., upper airway resistance, obstructive sleep apnea, and central sleep apnea) have frequently been associated, the possible cause-and-effect relationship has not yet been elucidated (32, 184-186). Two clinical open studies and one case report have provided indirect evidence for this relationship by showing a decrease in SB after different SDB treatments (e.g., adenotonsillectomy and continuous positive airway pressure)(187-189). These findings support the hypothesis that RMMA may be an oromotor activity that helps reinstate airway patency following an obstructive respiratory event during sleep (69). An alternative hypothesis considers RMMA a physiological motor

event that is required to lubricate the oropharyngeal structures during sleep, a period when salivary flow and swallowing rate are normally reduced (96, 190). The factors that induce RMMA to reach abnormal frequency in SB subjects remain to be elucidated.

Figure 1.4 Comorbid sleep bruxism, headache, and sleep-disordered breathing: putative mechanisms.



RMMA: rhythmic masticatory muscle activity.

(Carra MC.)

1.7 Sleep Bruxism and Sleep Quality

Sleep quality can be objectively and subjectively assessed by using respectively PSG recordings or self-report questionnaire. In general, healthy individuals with SB show and report a good sleep quality.

SB may be noticed in children, usually by the child parents, once the teeth erupt. The frequency of RMMA may largely vary during childhood and adolescence, and frequently persisting toward adulthood (7). Generally, children and adolescents do not

report disrupted sleep because of SB, rather they may present modifications of the normal sleep architecture related to growth or associated medical or sleep disorders.

It is known that in children and adolescents slow wave sleep (i.e., deep NREM sleep) is largely represented, while drastically decreases (-40-60%) by the age of 20 years old (191-194). This decline appears to be related more to chronological age than to the pubertal maturation (195), although it cannot be excluded that common neuronal and hormonal triggers might underlie these two phenomena. In both pre-pubertal children and adolescents, as in adults, slow wave activity (SWA) follows the homeostatic decline across successive NREM sleep episodes (196). The occurrence of SB does not seem to influence this parameter (64). During adolescence, sleep is also characterized by an increased proportion of stage 2, a reduction of total sleep time and a phase delay of the sleep-wake cycle (194, 197, 198). These modifications are not only a consequence of psychosocial, life-style and environmental factors that typically accompany adolescence, but they are also attributed to maturational processes in the biologic, circadian and homeostatic regulation of sleep that occur during adolescence (199, 200). Whether these natural changes in sleep physiology may influence the occurrence of RMMA remains unknown and definitely deserves further investigation. Moreover, the microstructure of sleep in children with SB has rarely been evaluated. This analysis may give clues on the objective quality of sleep and the actual influence of this motor disorder on childhood and adolescence sleep.

SB, however, may be concomitant with other medical conditions, which in turn can influence sleep quality and structure. During childhood, SB has been frequently observed in association with chronic respiratory problems, allergy, gastroesophageal reflux, ADHD, night terrors, somnambulism, parasomnias, and sleep disordered breathing (201, 202). In these cases, sleep quality may be drastically worsened, and diagnostic and treatment consultations are necessary.

Young adult SB subjects generally display normal sleep architecture in terms of total sleep time, sleep latency, sleep efficiency and percentage of sleep stage distribution (15, 61, 64). Most RMMA episodes occur during light NREM sleep and occasionally

during REM sleep, without disturbing the regular succession of sleep cycles. The main sleep parameters used to quantify the level of sleep disruption, such as SWA, sleep stage shift, and sleep arousal index (number of sleep arousal/h of sleep), are generally in the normal ranges and do not differ from control subjects (12, 15, 61, 64, 65). Conversely, differences have been observed at the micro-structural level of sleep, i.e., CAP. SB subjects have higher number of CAP phase A3, associated with the most powerful activation of muscle tone and autonomic cardiac activity (61). However, it must be mentioned that the majority of PSG studies on the pathophysiology of SB have been conducted on young and otherwise healthy SB subjects, which did not have any additional medical or sleep disorders. Sleep parameters may be different in older SB subjects with concomitant sleep disorders, such as insomnia, restless leg syndrome, sleep disordered breathing, or medical problems, such as pain syndromes.

In absence of pain, SB subjects generally report a good quality of sleep, and they are not disturbed by the tooth-grinding activity (7). On the contrary, the bed-partner frequently complains for the annoying noises that are produced by tooth contacts during RMMA. Indeed, this usually represents the chief complaint that drives SB subjects to have a medical consultation for treatment.

1.8 Management of Sleep Bruxism

No therapy to date has been proven effective to cure SB. The available treatment approaches aim at managing and preventing the harmful consequences of SB to the orofacial structures (Table 1.6) (203, 204).

1.8.1 Behavioral Strategies

SB can be managed by behavioral strategies, including the avoidance of SB risk factors and triggers (e.g., consumption of tobacco, alcohol, caffeine, and drugs), patient education (e.g., control of wake-time oral parafunctions), relaxation techniques, sleep hygiene, hypnotherapy, biofeedback, and cognitive behavioral therapy (205-209). However, the majority of these strategies have not been adequately tested in controlled trials. Nevertheless, a recent study showed that a new biofeedback device that applies electrical pulses to inhibit EMG activity in the temporalis muscle was effective in the short term in reducing EMG activity during sleep, without disrupting sleep quality (205, 210). In addition, a 12-week cognitive behavioral therapy (CBT) session with SB subjects was found to reduce SB, but showed no significant benefits over occlusal splint therapy (207). Although these behavioral techniques have not yet shown clear or persistent effects, they appear to improve the patient's well-being, and should be considered the first-line management approach in SB subjects.

1.8.2 Oral Appliances

In order to protect dental surfaces and relax the masticatory muscles, occlusal splints, either on the maxillary or the mandibular arch, have been extensively used in clinical practice. However, the exact mechanism of action is still under debate, and there is no evidence to support their role in halting SB. Moreover, the lack of well-designed randomized controlled clinical trials and long-term studies in the literature makes it difficult to assess their effectiveness (211). The majority of studies show a decrease (40%–50%) in the RMMA index in the first period of treatment (2–6 weeks), regardless of the type of occlusal splint (i.e., covering the occlusal teeth surfaces or just the palate)(29, 212-214). However, the effect appears to be transitory, with values returning to baseline after a short time, and the outcomes are highly variable between subjects. Moreover, it has been

reported that approximately 20% of SB subjects show increased EMG activity during sleep when wearing an occlusal splint, especially the soft mouth guard type (215, 216). A placebo effect, related to the behavioral intervention of the doctor toward the patient, can be also advocated to explain the transitory benefit that occlusal and palatal splints appear to have in SB subjects.

Table 1.6 Management of sleep bruxism.

Management of sleep bruxism		
Clinical approach	*Functions*	*Potential side effects*
Behavioural strategies Patient education, sleep hygiene, relaxation techniques, hypnotherapy, biofeedback, and cognitive behavioral therapy	• Avoid SB risk factors (e.g., smoking, alcohol, caffeine, drugs) • Control wake-time oral parafunctions • Improve sleep habits and sleep environment • Control and reduce stress and anxiety (coping) • Relax muscles and reduce EMG activity during sleep	None identified to date
Intraoral appliances • Occlusal or stabilization splint • NTI	• Protect tooth surfaces • Reduce EMG activity (?)	• Impaired occlusion* • Increased SB activity • Posterior dental overeruption or anterior dental intrusion (for NTI)*
• Mandibular advancement appliances (commonly used for snoring and mild to moderate OSA)	• Reposition and stabilize the lower jaw, tongue, and soft tissues • Open the upper airway space	• Excessive salivation or dry mouth • Tenderness in the teeth, TMJ, muscles • Perception of abnormal occlusion in the morning • Occlusal changes (e.g., reduced overjet and overbite)*
Pharmacotherapy (recommended in the short-term only)	• Reduce SB activity + extra effects related to the kind of medication used (e.g., hypnotic, analgesic)	• Depends on the medication used: - Clonazepam: tolerance, physiologic dependence, fatigue, somnolence - Clonidine: hypotension - Botulinum toxin: risk of retrograde transportation from the site of injection to CNS with systemic side effects

*****Only in long-term treatment
NTI: Nociceptive trigeminal inhibition system; OSA: obstructive sleep apnea; TMJ: temporomandibular joint; CNS: central nervous system.

(Carra MC. based on (7)).

Occlusal and anterior tooth appliances (e.g., the nociceptice trigeminal inhibition system, NTI) are also used in cases of SB comorbid with orofacial pain and TMD in order to relief muscle and joint pain (217-221). Their effectiveness is still controversial, as they rarely halt RMMA occurrence (222). However, it has been hypothesized that these devices may make patients more conscious of their oral parafunctional habits by altering proprioceptive inputs, thus helping them reduce clenching activity, albeit mainly during wake-time (223, 224). TMD patients appear to find relief with occlusal splints compared to other or no treatment, especially the most severe cases with TMD pain (225). Physiotherapy sessions targeting the masticatory muscles may also be useful in cases of SB associated with orofacial pain and/or TMD (226, 227).

It is worth mentioning that occlusal appliances and anterior tooth splints are not free of unwanted side effects, including changes in dental occlusion, single tooth positioning, dental hypersensitiveness, and worsening of orofacial pain and SDB (228). For example, in a pilot study in 10 patients with obstructive sleep apnea (OSA), a maxillary occlusal splint was found to increase the hypopnea/apnea index (AHI) in half the subjects, probably by reducing the intraoral space for the tongue, which changes the tongue position during sleep (228). When SB is concomitant with OSA, or when SDB are suspected, a mandibular occlusal splint—custom-made for the lower jaw—or a mandibular advancement appliance would be preferable.

Mandibular advancement appliances (MAA), which are currently used to treat snoring and mild to moderate forms of OSA, have also been tested in the short term to challenge the role of the airways in the genesis of RMMA episodes and to assess therapeutic benefits in SB patients. These oral devices are generally custom-made double arch appliances designed to retain or protrude the mandible in order to enlarge the upper airway space. An MAA was demonstrated effective in decreasing SB (up to 70%), especially when worn in advanced positions (50%–75% of the maximum protrusion) (229, 230). They also appear to relieve daily morning headaches in patients with low frequency of RMMA during sleep (231). The possible mechanisms of action, which may explain the

reduction of RMMA with the MAA, include: dimension and configuration of the appliance, restriction of jaw movements, presence of pain, or change in airway space and breathing during sleep. Although the use of an MAA for SB showed good effectiveness (203), all these studies assessed the effect after short-term treatment only (2 weeks average). It remains to assess their effectiveness and side effects in long-term studies (232, 233).

1.8.3 Pharmacotherapy

Several medications and drugs have been associated with decreased or increased SB activity, supporting the probability of central mechanisms for SB genesis (Table 1.7) (124). In particular, the dopaminergic, serotoninergic, and adrenergic systems are thought to be involved in this orofacial motor activity. However, evidence is lacking on both the effectiveness and safety of using medications in SB subjects. Therefore, in symptomatic and most severe patients, pharmacological treatments should be considered as a short-term therapy only (7).

A recent placebo-controlled study demonstrated a 40% reduction in SB activity with an acute dose of clonazepam (1 mg)(234, 235). Clonazepam is a benzodiazepine with hypnotic, anxiolytic, anticonvulsive, and myorelaxing effects. It acts at various levels of the central nervous system. The beneficial effect on SB genesis may result from actions on different systems linked to muscle activity, emotions, and behaviors. However, there is no available data on long-term treatment or potential side effects such as sleepiness (risk of transportation or work-related accidents), pharmaco-behavioral tolerance, and dependence.

Antidepressant drugs have also been recommended for SB, as well as for chronic orofacial pain. However, there is little evidence to support their use. Low doses of amitriptyline (a tricyclic antidepressant) were found to be ineffective against SB (236, 237), and SSRI medications (e.g., fluexetine, sertraline, paroxetine) actually increased tooth-grinding and clenching (130, 238, 239).

Adrenergic beta-blockers such as propranolol were shown to be ineffective on SB (240). Conversely, an acute dose (0.3 mg) of the alpha$_2$-adrenergic agonist clonidine reduced SB by 60%, supporting the role of autonomic cardiac activation in the genesis of this sleep-related motor disorder. However, clonidine is associated with sleep structure changes (e.g., less REM sleep) and severe morning hypotension (240). Its use for SB therapy is highly controversial.

Anecdotal reports suggest a positive effect on SB of gabapentin (241), tiagabine (242), buspirone (243), topiramate (244), and botulinum toxin (245, 246). However, their effectiveness and safety need to be assessed in randomized controlled clinical trials. Potential candidates for more specific or more potent medications are substances that regulate the wake–sleep balance (e.g., acetylcholine, noradrenaline, dopamine, orexin, histamine, serotonin), ionic channels, and cellular receptors (on neurons and glia).

Table 1.7 Effect of medications and chemical substances on sleep bruxism and SB-like activities.

Effect of medications and chemical substances on sleep bruxism (SB) or SB-like activity*	
Increased SB activity	• SSRI (e.g., paroxetine, fluoxetine, sertraline) • NSRI (e.g., venlafaxine) • Antipsychotic (e.g., haloperidol) • Flunarizine • Amphetamines (e.g., methylphenidate) • MDMA (ecstasy) • Cocaine • Caffeine • Nicotine • Alcohol
Decreased SB activity	• Clonazepam • Diazepam • Methacarbamol • Buspirone • Levodopa • Pergolide • Clonidine • Gabapentin • Topiramate • Botulinum toxin
No effect on SB activity	Propranolol, Bromocriptine, L-Tryptophan

**The scientific evidence is based primarily on case reports (except for two randomized controlled clinical trials with PSG (235, 240)). No long-term studies have assessed safety or benefits.*

(Carra MC. based on (104, 124-126, 132, 234, 235, 238, 240, 241, 244, 246-248)).

Chapter 2: Thesis Objectives and Hypotheses

2.1 Objectives

Sleep bruxism is a sleep disorder in which both clinicians and researchers show great interest. Only in the last 10 years, more than 250 scientific articles have been published in the English literature. This great interest is probably driven by the several clinical consequences that are associated with SB, such as orofacial pain, TMD, headache, tooth wear, and failing dental restorative treatments. However, a considerable attention is also reserved to research the etiology of this spontaneous rhythmic masticatory muscle activity (RMMA) that occurs apparently unpurposely during sleep. Recent hypotheses suggested a possible role in lubricating the oropharynx and reinstating the upper airway patency during sleep.

Despite the large amount of available literature, it remains difficult to establish a valid and accurate diagnosis of SB (except for the use of in lab audio-video PSG) and to manage this condition in an effective and reliable way. Indeed, it is still a matter of debate the distinction between wake-time and sleep bruxism, the etiologic role of central vs. peripheral factors, and the nature of the association between SB and other comorbid conditions (e.g., sleep disordered-breathing). All these open questions on the genesis of RMMA make arduous to support evidence-based treatments.

The objectives of the present thesis were *i*) to elucidate the pathogenesis of RMMA in relation to sleep arousal fluctuation, and *ii*) to investigate the clinical perspectives of SB in association with other orofacial, sleep and behavioral complaints. All these conditions should be considered and addressed in SB assessment and management.

2.2 Hypotheses

The present thesis is built on two distinct although related hypotheses, covering the etiology and physiology of RMMA (Section 2.2.1), and the SB-related clinical aspects (Section 2.2.2).

2.2.1 First Hypothesis

The first hypothesis concerns the relationship between RMMA and sleep arousal. Since the early work of Satoh and Harada in 1971 (63), "tooth-grinding" during sleep has been suggested as an arousal reaction, the consequence of an arousal-related reactivation of the sympathetic nervous system, and the final outcome of a cascade of physiological events that naturally occur within an arousal (60, 61, 63, 64, 66, 67). However, many questions are still unanswered:

- Is there a cause-effect relationship between sleep arousal and RMMA? Is sleep arousal fluctuation the trigger or the cause of rhythmic masticatory movements during sleep in SB subjects?
- What is the role of sleep instability on RMMA occurrence?
- Is the cyclic arousal fluctuation, described as cyclic alternating patter (CAP), the pacemaker of the RMMA episodes during sleep?
- Do the responsiveness to sleep arousal in SB subjects differ from control subjects?

The hypothesis is that RMMA occurrence is influenced and paced by arousal fluctuations that occur in period of sleep instability.

The first two research articles included in Chapter 3 aimed to investigate this hypothesis and attempted to answer the aforementioned questions (Sections 3.1 and 3.2).

2.2.2 Second Hypothesis

The second hypothesis is related to SB and its frequent association with other sleep disorders and medical conditions (26, 32, 74, 175, 179, 184, 249-251). However, these associations are mainly supported by indirect evidence, which need further investigations. In particular:

- Are SB subjects more at risk of having, headache, orofacial pain, sleep disorders (e.g., SDB), and behavioral problems?
- What is the role of breathing and breathing abnormalities in the genesis of RMMA? Is there a cause-effect relationship?
- From the clinical perspective, if SB is concomitant with other sleep disorders (e.g., snoring or sleep apnea) and/or it is manifest with clinical symptoms, such as headache, is there a treatment that, by addressing the underlying conditions, will be of benefits for all comorbid disorders?

The hypothesis is that SB and certain comorbidities may share common underlying pathogenetic mechanisms, which may occur during sleep. In particular, we hypothesized that breathing anomalies may lead to arousal and increased sleep instability; concomitant RMMA episodes may occur as part of the reaction mechanisms that help to reinstate the upper airway patency. In this perspective, HA complaints, frequently associated with both SB and SDB, may be the consequence of the repetitive rhythmic and sustained contractions of the masticatory muscles during sleep, or the result of the intermittent hypoxia and sleep fragmentation, which follow the obstructive respiratory events (See Figure 1.4, page 28).

The last two research articles included in Chapter 3 were designed to investigate the association and risk factors of sleep bruxism with comorbid conditions (Section 3.3), and to test the effectiveness of a mandibular advancement appliance in adolescents reporting SB, snoring, and headache (Section 3.4).

2.3 Materials and Methods

As described above, the present thesis is divided into two sections related to two different hypotheses: *i*) focused on the pathophysiologic mechanisms that may explain the genesis of RMMA episodes during sleep; *ii*) focused on the clinical aspects related to the disorder, sleep bruxism. Four research articles have been included to support this work.

i. The first hypothesis was tested by quantitatively assessing EEG spectral activity, CAP variables and time correlation between RMMA and sleep arousal in two different studies in which sleep was experimentally disturbed by:
   - The administration of a single dose of clonidine, a cardio-active medication known to reduce sympathetic nervous system activity (Section 3.1);
   - The application of repeated sensory stimulations while the subjects was asleep (Section 3.2).

ii. The second hypothesis was investigated in:
   - A population-based survey on the prevalence and risk factors of wake-time and sleep-related bruxism conducted in a pediatric population seeking orthodontic treatments (Section 3.3);
   - An experimental trial using a mandibular advancement appliance in sixteen adolescents reporting concomitant SB, snoring, and headache (Section 3.4).

Detailed information on the methods applied can be found in the specific "*Materials and Methods*" section of each research article (Chapter 3).

Chapter 3: Research Articles

3.1 First article: "Clonidine Has a Paradoxical Effect on Cyclic Arousal and Sleep Bruxism during NREM Sleep"

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Abstract

Study Objective: Clonidine disrupts the NREM/REM sleep cycle and reduces the incidence of rhythmic masticatory muscle activity (RMMA) characteristic of sleep bruxism (SB). RMMA/SB is associated with brief and transient sleep arousals. This study investigates the effect of clonidine on the cyclic alternating pattern (CAP) in order to explore the role of cyclic arousal fluctuation in RMMA/SB.

Design: Polysomnographic recordings from a pharmacological study.

Setting: University sleep research laboratory.

Participants and Interventions: Sixteen SB subjects received a single dose of clonidine or placebo at bedtime in a crossover design.

Measurements and Results: Sleep variables and RMMA/SB index were evaluated. CAP was scored to assess arousal instability between sleep-maintaining processes (phase A1) and stronger arousal processes (phases A2 and A3). Paired *t*-tests, ANOVAs, and cross-correlations were performed. Under clonidine, CAP time, and particularly the number of A3 phases, increased ($P \leq 0.01$). RMMA/SB onset was time correlated with phases A2 and A3 for both placebo and clonidine nights ($P \leq 0.004$). However, under clonidine, this positive correlation began up to 40 min before the RMMA/SB episode.

Conclusions: CAP phase A3 frequency increased under clonidine, but paradoxically, RMMA/SB decreased. RMMA/SB was associated with and facilitated in CAP phase A2 and A3 rhythms. However**,** SB generation could be influenced by other factors besides sleep arousal pressure. NREM/REM ultradian cyclic arousal fluctuations may be required for RMMA/SB onset.

Keywords: Clonidine, sleep bruxism, rhythmic masticatory muscle activity, cyclic alternating pattern.

Introduction

Clonidine, a selective α_2-agonist, is known to alter the ultradian NREM/REM sleep cycle by reducing REM sleep in a dose-dependent manner (1-3). Clonidine also has been shown to decrease sleep bruxism frequency by 61% (4). Sleep bruxism (SB) is a sleep-related movement disorder characterized by frequent rhythmic masticatory muscle activity (RMMA) associated with tooth grinding and clenching (5-7). The pathophysiology of RMMA/SB has been studied in relation to sleep arousal, both spontaneous and experimentally induced (8-11). More recently it was suggested that RMMA/SB is the final event in a sequence of naturally occurring neurovegetative changes during sleep (12). Most RMMA/SB episodes are preceded by increased sympathetic cardiac activity (8 to 4 min before RMMA/SB onset), electroencephalographic (EEG) arousal (4 sec before), accelerated heart rate, and increased breathing amplitude (1 sec before)(12-15). Furthermore, RMMA/SB events appear to follow the ultradian NREM/REM sleep cycle, with peak activity during the NREM to REM transition, which is stronger for the second and third sleep cycles (12-15). Thus, the effect of clonidine on RMMA/SB may be linked to its influence on sympathetic/ parasympathetic balance, sleep structure, and motor activities during sleep. However, the effect of clonidine on cyclic sleep arousal fluctuation has not yet been investigated.

Fluctuations in sleep arousal over time (i.e., sleep microstructure) can be evaluated by examining the cyclic alternating pattern (CAP). CAP is composed of electrocortical events that can be visually scored as patterns of sleep periods under arousal pressure during NREM (16-18). CAP displays a 20–40 s cyclic pattern characterized by arousal-related phasic events (phase A) followed by deactivation (phase B). Phase A is further classified into three subphases of increasing arousal strength: A1, A2, and A3. Phase A1 is thought to be an EEG correlate of events that promote sleep onset and maintenance. Phase A2 is a transient phase toward increased arousal pressure. Phase A3, the higher arousal phase, is characterized by desynchronized EEG patterns. Phases A2 and A3 are associated with increased muscle tone and cardiorespiratory rate (19-21). The A-B alternating pattern

(cycle) is clustered in sequences. CAP variables, e.g., CAP time, CAP rate (% ratio of total CAP time to total NREM sleep time), and CAP sequence, are markers of sleep fragmentation and arousal instability (17). During NREM sleep, 88% of RMMA/SB episodes occur in clusters, following the same rhythm as the CAP oscillation. RMMA/SB activity has been observed mainly within CAP phase A3 (9).

Although advances have been made in understanding SB pathophysiology, the exact generator of RMMA/SB events during sleep remains unknown. The aim of this study was to examine CAP variables to explain the effect of clonidine on arousal fluctuation and to explore the role of sleep arousal instability on RMMA/SB occurrence. As clonidine reduces SB activity and modifies sleep macrostructure, we hypothesized that the probable alterations in sleep microstructure would influence RMMA/SB occurrence.

Methods

Subjects

We analyzed polysomnographic data of 16 SB subjects (6 males and 10 females; mean age 24.5; range 21 to 31) in our laboratory from 2000 to 2004 (4). Subjects were selected based on a history of tooth-grinding (>3 nights/week) and clinical signs and symptoms of SB (tooth wear, masseter muscle hypertrophy, morning jaw muscle fatigue or tenderness). SB diagnosis was confirmed if subjects met the standard polysomnographic research criteria (>4 episodes of RMMA/hour of sleep) in the second night of sleep recording (22). The experimental protocol was approved by the research ethics board of the Hôpital du Sacré-Coeur, Montreal.

Study Design

All subjects underwent 4 nights of audio-video polysomnographic recordings. The first night was for habituation and the second for SB diagnosis. The experimental protocol

was conducted during the third and fourth nights. Subjects received a single dose of either placebo or clonidine (0.3 mg by mouth) 1 hour before bedtime in a randomized double-blind crossover design. A 1-week washout interval between the 2 experimental nights was provided (4). According to its pharmacokinetic profile, clonidine reaches a plasmatic peak within approximately 2 h following oral administration (3,23).

Sleep Data Collection and Scoring

The following polysomnographic variables were recorded and analyzed blind to medication or placebo allocation: EEG (C_3A_2, O_2A_1), electrooculogram (EOG), electrocardiogram (EKG), chest respiratory movements, and electromyographic (EMG) activity in the suprahyoid, masseter, temporalis and anterior tibialis muscles. All signals were digitalized at 128 Hz using commercial software (Harmonie, Stellate, Montreal, Canada), as described elsewhere (4). Sleep stages, sleep arousals, and RMMA/SB episodes were scored according to standard criteria (7,22,24,25). CAP was scored according to the published rules (26). Each CAP phase A was visually detected during NREM sleep on the C_3A_2 derivation by the use of Somnologica (Embla, Germany), then classified into subtypes A1, A2, or A3. The following CAP parameters were evaluated: total CAP time, CAP rate, number and duration of CAP sequences, number and duration of A phases, number and duration of B phases, and number and percent of subtypes A1, A2, and A3.

Data Analyses and Statistics

Duration of the first 4 NREM/REM sleep cycles was normalized within each subject by dividing NREM periods into 20 intervals and REM periods into 5 intervals, for 100 intervals over the entire night (27,28) Each sleep cycle was then averaged into 4 NREM sections and 1 REM section (each comprising 5 intervals). Both placebo and clonidine nights were normalized. However, for clonidine nights, REM sections were time estimated due to the strong reduction in REM sleep duration. Frequency distributions of RMMA/SB

episodes and CAP phases A1, A2, and A3 per hour of sleep were calculated over sleep cycles.

Statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA). The paired *t*-test was applied for within-group comparison (placebo vs. clonidine) and repeated measures ANOVAs (treatment × cycle × section) were applied to CAP variables and RMMA/SB episode distribution over sleep cycles. Placebo and clonidine nights were compared for NREM sleep only, as CAP cannot be scored during REM. Repeated measures ANOVAs were also performed for each NREM cycle (treatment x section) due to the clonidine pharmacokinetics profile. The Huynh-Feldt correction for sphericity was applied to all ANOVA calculations. P-values were considered significant at ≤0.05.

RMMA/SB episodes were cross-correlated with CAP phases A1, A2, and A3. Cross-correlation plots are used to identify temporal associations between 2 series of events at individual time lags. Each time lag corresponds to 4 minutes. A significant correlation at lag 0 indicates that the 2 events occur at the same time. Correlations at positive lags relate values in the first series to subsequent values in the second series. Similarly, correlations at negative lags relate values in the first series to preceding values in the second series.

Results

CAP Variables and Sleep Bruxism

CAP time and CAP sequence increased significantly (≤0.001) with clonidine compared with the placebo night. Because clonidine increased the duration of both total CAP time and NREM sleep, the CAP rate did not change. The number of CAP A3 phases increased significantly with clonidine compared with the placebo night (P = 0.01) (Table 3.1.1). As previously reported (4), both RMMA/SB and sleep variables change significantly under the influence of clonidine. RMMA/SB index decreased by 61% (P = 0.02), sleep

stage 2 increases, and REM sleep was markedly reduced (both $P < 0.001$). The number of sleep arousals per hour of sleep did not change under clonidine.

RMMA/SB and CAP Phase A Distribution over Sleep Cycles

Clonidine blunted the linear crescendo pattern of RMMA/SB occurrence across the NREM/REM transition period compared to placebo (overall treatment effect $P = 0.002$). This effect was stronger in the third and fourth sleep cycles (ANOVA for cycles 3 and 4, $P = 0.001$). Under clonidine, phase A1 frequency (number/hour of sleep) was slightly reduced (overall treatment effect, $P = 0.02$), but no difference was observed between placebo and clonidine nights for the phase A1 ultradian NREM/REM fluctuation pattern. In contrast, phase A2 and A3 distributions across the sleep cycle changed markedly under clonidine (overall treatment x section interaction, $P = 0.0005$ and 0.0009, respectively). Within each cycle, the linear crescendo mode of phase A2 and A3 frequencies disappeared from cycles 2 to 4 (ANOVA for each cycle, placebo linear contrast $P < 0.002$; clonidine linear contrast $P > 0.2$) (Fig. 3.1.1).

Cross-Correlation Analysis between RMMA/SB Episodes and CAP A Phases

For both placebo and clonidine nights, an equipotent positive correlation was found between RMMA/SB episodes and CAP phases A2 and A3 (Fig. 3.1.2). During the placebo night the time correlation for phase A2 was significant at lag 0 (RMMA/SB onset), and lasted for the next 8 min (lag 0 coefficient = 0.287, $P = 0.004$). For phase A3, a significant time correlation began in the 4 min preceding RMMA/SB episodes and lasts for the next 8 min (lag 0 coefficient = 0.637, $P < 0.0001$). Under clonidine, a significant positive time correlation at RMMA/SB onset is still present for A2 (lag 0 coefficient = 0.304, $P = 0.002$) and A3 (lag 0 coefficient = 0.569, $P < 0.0001$). However, the time correlations in clonidine nights were significantly higher in the 40 min preceding RMMA/SB episodes for both A2 and A3 phases.

Discussion

This experimental pharmacological study evaluated the relationship between RMMA/SB and CAP phase A. Polysomnographic recordings showed that both CAP phase A patterns and RMMA/SB occurrence change under clonidine. Specifically, the cyclic rise in phase A2 and A3 frequency and RMMA/SB activity in the pre-REM periods were blunted under clonidine. Paradoxically, the number of RMMA/SB decreased and the number of phase A3 rose. In addition, in both placebo and clonidine nights, RMMA/SB episodes were temporally correlated with CAP phases A2 and A3 and their endogenous fluctuation across ultradian NREM/REM sleep cycles. Previous studies showed the association between CAP phases A2 and A3 with RMMA/SB, but no time correlation (9).

The present study found that clonidine increases CAP time, CAP sequence, and phase A3, indicating increased arousal instability and sleep perturbation (16,17), probably related to clonidine action on the brainstem neuronal systems that regulate the switch from NREM to REM sleep (29). However, whether the effect of clonidine on sleep arousal instability is linked to the observed reduction in RMMA/SB episodes remains to be demonstrated (30).

CAP as the Permissive Window for RMMA/SB Occurrence

Previous studies have described RMMA/SB as a motor activity secondary to sleep arousal (8-10,13), and have associated it with CAP phase A (9). Our study provides new insights into the role of phase A and the differences between phases A1, A2, and A3. Phase A1 corresponds to the slow EEG oscillations, and is associated with the build-up and maintenance of NREM sleep (21,31,32). In contrast, arousal subtypes A2 and A3 are lower in NREM deep sleep and they increase linearly before REM sleep onset. The RMMA/SB occurrence pattern reflects the ultradian fluctuation in CAP phases A2 and A3. Phase A1 is also negatively correlated with RMMA/SB episodes, while phases A2 and A3 are strongly time-correlated with RMMA/SB onset. In fact, the time correlation between RMMA/SB

activity and phases A2 and A3 is preserved even in clonidine nights. Although the quantitative time-correlation analysis did not reveal a causal relationship between CAP phase A and SB, it suggests that phases A2 and A3 constitute the permissive physiological window for RMMA/SB generation during sleep.

A recent study evaluating the time relationship between RMMA/SB episodes and autonomic nervous system activity showed a change in sympathetic/parasympathetic modulation starting approximately 8 to 4 minutes before RMMA/SB onset (12,13). Our analysis goes further to show that the balance between subtypes A1 to A3 shifts within the same time range as the previously described shift in sympathetic cardiac activity. This suggests that phase A changes are the EEG counterpart of the sympathetic/parasympathetic balance in sleep arousal (16).

Other studies (33-36) support the facilitatory role of CAP phase A in the occurrence of motor events during sleep. For example, periodic limb movements in sleep (PLMS) have been reported to occur frequently within CAP, with 96% of PLMS episodes observed in phases A2 and A3 (37). However, the CAP itself does not generate these movements during sleep; instead, it is the temporal window in which arousal and motor events are grouped and in which their rhythmic occurrence is facilitated.

Putative Effects of Clonidine on SB and CAP

Clonidine is an α_2-adrenergic agonist that acts on multiple sites in the central and peripheral nervous systems (38). It has both a direct and indirect influence on the autonomic nervous system (39,40), sleep cycles (41), motor control (42,43), and most probably arousal instability.

Clonidine exerts a strong sympathetic inhibitory effect by altering the balance from sympathetic to parasympathetic tone (4,39) due to activation of the α_2-adrenergic autoreceptors and post-synaptic receptors in the brainstem and the imidazoline-I_1 receptors in the rostral ventrolateral medulla (44). By preventing sympathetic rise, clonidine may

blunt the cascade of arousal-related neurovegetative responses that precede RMMA/SB episodes, thereby inhibiting SB.

Clonidine also has marked effects on sleep macrostructure (4). Significant increases in stage 2 as well as reduced deep and REM sleep duration have been reported (1-3). REM sleep onset appears to be strongly influenced by the adrenergic and noradrenergic systems (45,46). The neurotransmitters in these systems are implicated in inhibitory mechanisms that mainly involve postsynaptic α_2-adrenoceptors in the locus coeruleus area of the brainstem (47). However, clonidine may also activate non-adrenergic neurons in the pontine reticular formation and thereby exert an indirect influence on the GABA-ergic and cholinergic neurons that modulate REM sleep onset (48-50). In the present study, clonidine strongly reduced REM sleep duration, blunting the cyclic rise of CAP phases A2 and A3 in the NREM/REM transition period. Thus, clonidine perturbation of the NREM/REM ultradian cycle may by itself have prevented RMMA/SB onset. This fluctuation in ultradian arousal may be required for RMMA/SB occurrence. Experimental protocols using pharmacological or physical REM alteration (REM sleep deprivation or enhancing methods) may help determine the nature of this influence (51-53).

Clonidine may also affect motor control pathways. RMMA/SB are spontaneous motor events that occur during sleep. So far, the exact mechanism responsible for the generation of RMMA/SB remains unknown. Possible contributing factors include autonomic sympathetic cardiac activity (13,54), the hypothalamic-adrenal axis (55-57), genetics (58,59), and complex neurochemical influences involving catecholamines, serotonin, histamine, acetylcholine, or orexin (60). Moreover, because clonidine affects the noradrenergic pathways, it may indirectly influence dopamine release from the nucleus striatum (40,61,62). However, there is only weak evidence for the role of catecholamines in generating RMMA/SB, with conflicting results and a lack of randomized controlled trials (60,63,64).

Conclusion

RMMA/SB is associated with and facilitated by CAP phase A2 and A3 rhythms within a sleep arousal. However, under clonidine, increased CAP phase A3 frequency (arousal pressure) is observed, with a paradoxical reduction in RMMA/SB activity. Although CAP phases A2 and A3 could reflect permissive physiological windows, RMMA/SB generation could be influenced by other factors besides arousal pressure. Notably, fluctuations in the NREM/REM ultradian cyclic arousal may be required for RMMA/SB to occur.

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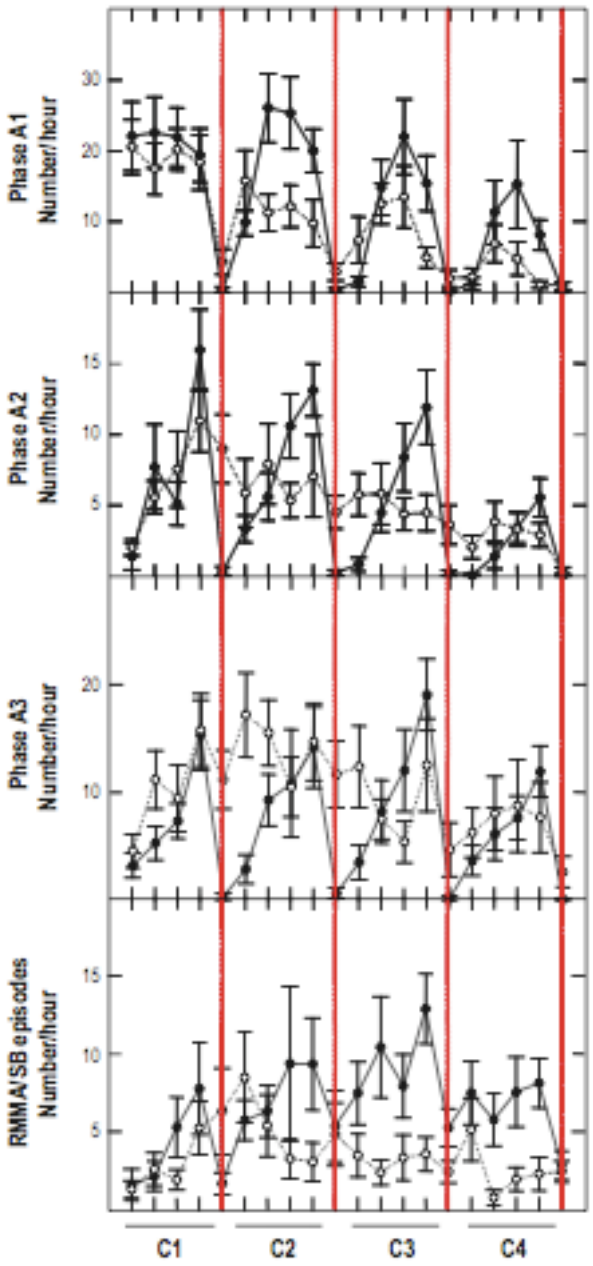
Figure 3.1.1 CAP and RMMA distribution over NREM/REM sleep cycles.

The NREM/REM sleep cycle distribution of CAP phases A1, A2, and A3 (number/h), and RMMA/SB activity (episodes/h) are displayed for placebo (black circles) and clonidine (white circles) nights. Vertical dotted lines represent each NREM/REM sleep cycle. Mean values (SEM) are shown.



c1 = first sleep cycle; c2 = second sleep cycle; c3 = third sleep cycle; c4 = fourth sleep cycle; RMMA/SB = rhythmic masticatory muscle activity/sleep bruxism.

Figure 3.1.2 Cross-correlation between RMMA/SB episodes and CAP phases.

The cross-correlation plots between RMMA/SB episodes and CAP phases A1, A2, and A3 are displayed for placebo (A) and clonidine (B) nights. Horizontal upper and lower lines denote significant P value at 0.05. The vertical line denotes lag 0, or RMMA/SB onset. Each lag lasts 4 minutes (minus 40 min before SB onset and plus 40 min after SB onset).

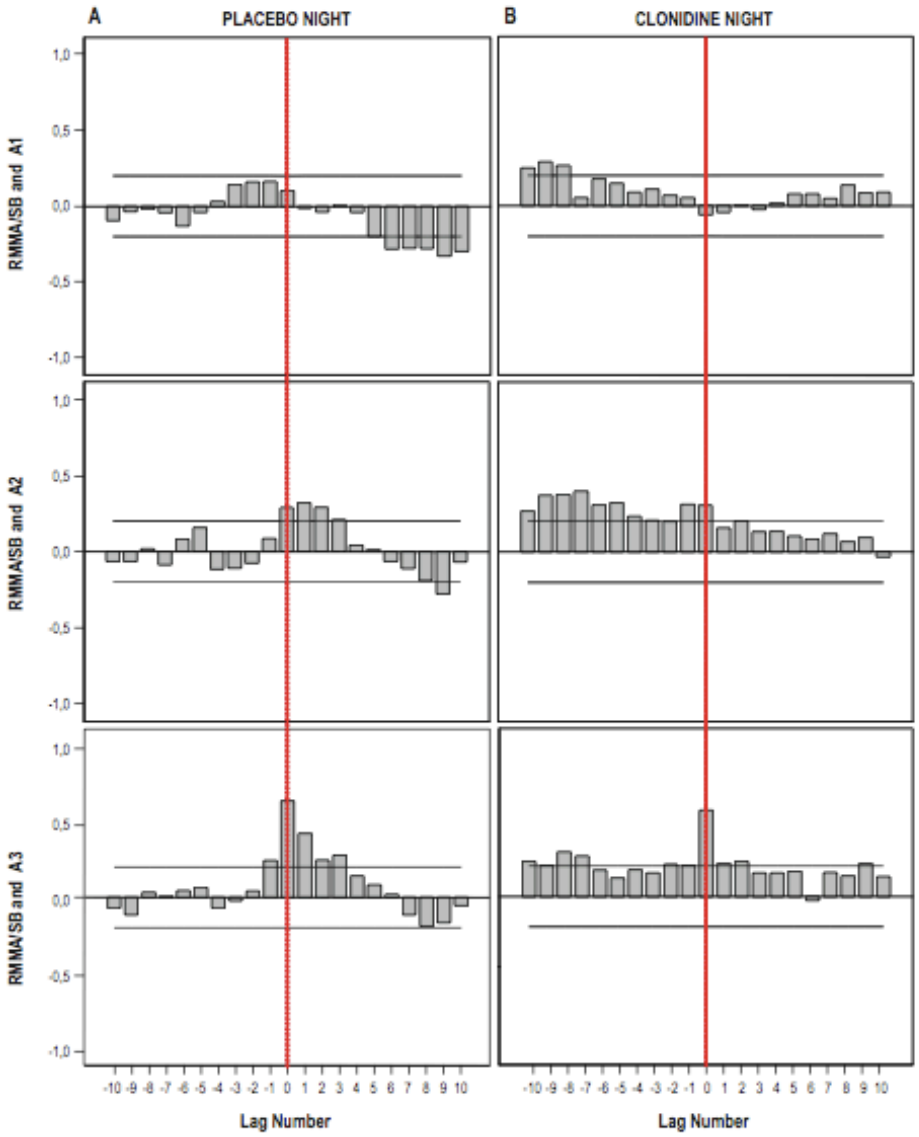


Table 3.1.1 CAP variables during placebo and clonidine nights

	PLACEBO NIGHT	CLONIDINE NIGHT	P value
CAP rate (%)	27.8 ± 1.2	27.3 ± 1.4	0.65
CAP time (min)	99.8 ± 4.6	127.7 ± 6.1	<0.001
CAP sequence (n)	36.5 ± 1.3	44.4 ± 1.8	0.001
A1 (n)	99.4 ± 9.1	84.5 ± 8.2	0.19
A2 (n)	40.1 ± 5.2	48.8 ± 6.6	0.12
A3 (n)	59.2 ± 6.2	96 ± 13.9	0.01
A1 (%)	49.2 ± 2.7	37.9 ± 3.6	0.01
A2 (%)	19.8 ± 1.7	21.2 ± 2.5	0.47
A3 (%)	31 ± 3.5	40.9 ± 4.5	0.03
Phase A duration (s)	8.9 ± 0.4	9.1 ± 0.4	0.58
Phase B duration (s)	21.6 ± 0.5	24.6 ± 0.6	<0.001
CAP cycle duration (s)	30.5 ± 0.7	33.7 ± 0.6	<0.001
A1 duration (s)	5.6 ± 0.2	5.5 ± 0.2	0.5
A2 duration (s)	7.9 ± 0.3	7.7 ± 0.4	0.58
A3 duration (s)	15.2 ± 0.6	13.5 ± 0.6	0.03

Data are presented as mean ± SEM. CAP refers to cyclic alternating pattern.

References:

1. Miyazaki S, Uchida S, Mukai J, Nishihara K. Clonidine effects on all-night human sleep: opposite action of low- and medium-dose clonidine on human NREM-REM sleep proportion. Psychiatry Clin Neurosci 2004;58:138-44.

2. Gentili A, Godschalk MF, Gheorghiu D, Nelson K, Julius DA, Mulligan T. Effect of clonidine and yohimbine on sleep in healthy men: a double-blind, randomized, controlled trial. Eur J Clin Pharmacol 1996;50:463-5.

3. Spiegel R, DeVos JE. Central effects of guanfacine and clonidine during wakefulness and sleep in healthy subjects. Br J Clin Pharmacol 1980;10 Suppl 1:165S-8S.

4. Huynh N, Lavigne GJ, Lanfranchi PA, Montplaisir JY, de Champlain J. The effect of 2 sympatholytic medications--propranolol and clonidine--on sleep bruxism: experimental randomized controlled studies. Sleep 2006;29:307-16.

5. American Academy of Sleep Medicine. Sleep related bruxism. International classification of sleep disorders, 2nd ed.:Diagnosis and coding manual. Westchester, IL: American Academy of Sleep Medicine; 2005:189-92.

6. De Laat A, Macaluso GM. Sleep bruxism as a motor disorder. Mov Disord 2002;17 Suppl 2:S67-9.

7. Lavigne GJ, Rompre PH, Poirier G, Huard H, Kato T, Montplaisir JY. Rhythmic masticatory muscle activity during sleep in humans. J Dent Res 2001;80:443-8.

8. Sato T, Harada Y. Tooth-grinding during sleep as an arousal reaction. Experientia 1971;27:785-6.

9. Macaluso GM, Guerra P, Di Giovanni G, Boselli M, Parrino L, Terzano MG. Sleep bruxism is a disorder related to periodic arousals during sleep. J Dent Res 1998;77:565-73.

10. Kato T, Rompre P, Montplaisir JY, Sessle BJ, Lavigne GJ. Sleep bruxism: an oromotor activity secondary to micro-arousal. J Dent Res 2001;80:1940-4.

11. Kato T, Montplaisir JY, Guitard F, Sessle BJ, Lund JP, Lavigne GJ. Evidence that experimentally induced sleep bruxism is a consequence of transient arousal. J Dent Res 2003;82:284-8.

12. Lavigne GJ, Huynh N, Kato T, et al. Genesis of sleep bruxism: motor and autonomic-cardiac interactions. Arch Oral Biol 2007;52:381-4.

13. Huynh N, Kato T, Rompre PH, et al. Sleep bruxism is associated to micro-arousals and an increase in cardiac sympathetic activity. J Sleep Res 2006;15:339-46.

14. Khoury S, Rouleau GA, Rompre PH, Mayer P, Montplaisir JY, Lavigne GJ. A significant increase in breathing amplitude precedes sleep bruxism. Chest 2008;134:332-7.

15. Lavigne GJ, Manzini C, Kato T. Sleep bruxism. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine. 4th ed. Philadelphia: Saunders, 2005:946-59.

16. Halasz P, Terzano M, Parrino L, Bodizs R. The nature of arousal in sleep. J Sleep Res 2004;13:1-23.

17. Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). Sleep Med Rev 2000;4:101-23.

18. Parrino L, Smerieri A, Rossi M, Terzano MG. Relationship of slow and rapid EEG components of CAP to ASDA arousals in normal sleep. Sleep 2001;24:881-5.

19. Terzano MG, Parrino L. Clinical applications of cyclic alternating pattern. Physiol Behav 1993;54:807-13.

20. Smerieri A, Parrino L, Agosti M, Ferri R, Terzano MG. Cyclic alternating pattern sequences and non-cyclic alternating pattern periods in human sleep. Clin Neurophysiol 2007;118:2305-13.

21. Terzano MG, Parrino L, Rosa A, Palomba V, Smerieri A. CAP and arousals in the structural development of sleep: an integrative perspective. Sleep Med 2002;3:221-9.

22. Lavigne GJ, Rompre PH, Montplaisir JY. Sleep bruxism: validity of clinical research diagnostic criteria in a controlled polysomnographic study. J Dent Res 1996;75:546-52.

23. Keranen A, Nykanen S, Taskinen J. Pharmacokinetics and side-effects of clonidine. Eur J Clin Pharmacol 1978;13:97-101.

24. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007:37.

25. Rechtschaffen A, Kales A, eds. A manual of standardized terminology, technique and scoring system for sleep stages of human subjects. Los Angeles: Brain Information Service / Brain Research Institute, 1968.

26. Terzano MG, Parrino L, Sherieri A, et al. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med 2001;2:537-53.

27. Gaudreau H, Joncas S, Zadra A, Montplaisir J. Dynamics of slow-wave activity during the NREM sleep of sleepwalkers and control subjects. Sleep 2000;23:755-60.

28. Achermann P, Dijk DJ, Brunner DP, Borbely AA. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. Brain Res Bull 1993;31:97-113.

29. Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 2001;24:726-31.

30. Carra MC, Macaluso GM, Huynh N, et al. NREM/REM Cyclic fluctuation of sleep arousal is blunted by clonidine. Sleep 2009;32:abstract # 0941.

31. Terzano MG, Parrino L, Smerieri A, et al. CAP and arousals are involved in the homeostatic and ultradian sleep processes. J Sleep Res 2005;14:359-68.

32. Boberly AA, Achermann P. Sleep homeostasis and models of sleep regulation. In: Kryger MH, Roth T, Dement WC, eds. Principles and practices of sleep medicine. 4th ed. Philadelphia: Elsevier Saunders; 2005;4:405-17.

33. Zucconi M, Oldani A, Ferini-Strambi L, Smirne S. Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. J Clin Neurophysiol 1995;12:147-54.

34. Terzano MG, Monge-Strauss MF, Mikol F, Spaggiari MC, Parrino L. Cyclic alternating pattern as a provocative factor in nocturnal paroxysmal dystonia. Epilepsia 1997;38:1015-25.

35. Terzano MG, Parrino L, Garofalo PG, Durisotti C, Filati-Roso C. Activation of partial seizures with motor signs during cyclic alternating pattern in human sleep. Epilepsy Res 1991;10:166-73.

36. Sforza E, Montagna P, Rinaldi R, et al. Paroxysmal periodic motor attacks during sleep: clinical and polygraphic features. Electroencephalogr Clin Neurophysiol 1993;86:161-6.

37. Parrino L, Boselli M, Buccino GP, Spaggiari MC, Di Giovanni G, Terzano MG. The cyclic alternating pattern plays a gate-control on periodic limb movements during non-rapid eye movement sleep. J Clin Neurophysiol 1996;13:314-23.

38. Fornai F, Blandizzi C, del Tacca M. Central alpha-2 adrenoceptors regulate central and peripheral functions. Pharmacol Res 1990;22:541-54.

39. Szabo B. Imidazoline antihypertensive drugs: a critical review on their mechanism of action. Pharmacol Ther 2002;93:1-35.

40. Grenhoff J, Svensson TH. Clonidine regularizes substantia nigra dopamine cell firing. Life Sci 1988;42:2003-9.

41. Autret A, Minz M, Beillevaire T, Cathala HP, Schmitt H. Effect of clonidine on sleep patterns in man. Eur J Clin Pharmacol 1977;12:319-22.

42. Morilak DA, Jacobs BL. Noradrenergic modulation of sensorimotor processes in intact rats: the masseteric reflex as a model system. J Neurosci 1985;5:1300-6.

43. Katakura N, Chandler SH. Iontophoretic analysis of the pharmacologic mechanisms responsible for initiation and modulation of trigeminal motoneuronal discharge evoked by intra-oral afferent stimulation. Brain Res 1991;549:66-77.

44. De Sarro GB, Ascioti C, Froio F, Libri V, Nistico G. Evidence that locus coeruleus is the site where clonidine and drugs acting at alpha 1- and alpha 2-adrenoceptors affect sleep and arousal mechanisms. Br J Pharmacol 1987;90:675-85.

45. Gaillard JM. Biochemical pharmacology of paradoxical sleep. Br J Clin Pharmacol 1983;16 Suppl 2:205S-30S.

46. Pal D, Mallick BN. Neural mechanism of rapid eye movement sleep generation with reference to REM-OFF neurons in locus coeruleus. Indian J Med Res 2007;125:721-39.

47. Crochet S, Sakai K. Alpha-2 adrenoceptor mediated paradoxical (REM) sleep inhibition in the cat. Neuroreport 1999;10:2199-204.

48. Tononi G, Pompeiano M, Cirelli C. Suppression of desynchronized sleep through microinjection of the alpha 2-adrenergic agonist clonidine in the dorsal pontine tegmentum of the cat. Pflugers Arch 1991;418:512-8.

49. Moroni F, Tanganelli S, Antonelli T, Carla V, Bianchi C, Beani L. Modulation of cortical acetylcholine and gamma-aminobutyric acid release in freely moving guinea pigs: effects of clonidine and other adrenergic drugs. J Pharmacol Exp Ther 1983;227:435-40.

50. Tsurusaki M, Yoshida M, Akasu T, Nagatsu I. Alpha 2-adrenoceptors mediate the inhibition of cholinergic transmission in parasympathetic ganglia of the rabbit urinary bladder. Synapse 1990;5:233-40.

51. Rasch B, Pommer J, Diekelmann S, Born J. Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. Nat Neurosci 2009;12:396-7.

52. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. Sleep 2006;29:145-51.

53. Nielsen T, Paquette T, Solomonova E, Lara-Carrasco J, Colombo R, Lanfranchi P. Changes in cardiac variability after REM sleep deprivation in recurrent nightmares. Sleep;33:113-22.

54. Marthol H, Reich S, Jacke J, Lechner KH, Wichmann M, Hilz MJ. Enhanced sympathetic cardiac modulation in bruxism patients. Clin Auton Res 2006;16:276-80.

55. Seraidarian P, Seraidarian PI, das Neves Cavalcanti B, Marchini L, Claro Neves AC. Urinary levels of catecholamines among individuals with and without sleep bruxism. Sleep Breath 2009;13:85-8.

56. Ohayon MM, Li KK, Guilleminault C. Risk factors for sleep bruxism in the general population. Chest 2001;119:53-61.

57. Vanderas AP, Menenakou M, Kouimtzis T, Papagiannoulis L. Urinary catecholamine levels and bruxism in children. J Oral Rehabil 1999;26:103-10.

58. Dauvilliers Y, Maret S, Tafti M. Genetics of normal and pathological sleep in humans. Sleep Med Rev 2005;9:91-100.

59. Hublin C, Kaprio J, Partinen M, Koskenvu M. Parasomnias: co-occurrence and genetics. Psychiatr Genet 2001;11:65-70.

60. Lavigne GJ, Kato T, Kolta A, Sessle BJ. Neurobiological mechanisms involved in sleep bruxism. Crit Rev Oral Biol Med 2003;14:30-46.

61. Grenhoff J, Svensson TH. Clonidine modulates dopamine cell firing in rat ventral tegmental area. Eur J Pharmacol 1989;165:11-8.

62. Morrow BA, George TP, Roth RH. Noradrenergic alpha-2 agonists have anxiolytic-like actions on stress-related behavior and mesoprefrontal dopamine biochemistry. Brain Res 2004;1027:173-8.

63. Magee KR. Bruxisma related to levodopa therapy. JAMA 1970;214:147.

64. Winocur E, Gavish A, Voikovitch M, Emodi-Perlman A, Eli I. Drugs and bruxism: a critical review. J Orofac Pain 2003;17:99-111.

3.2 Second Article: "Sleep Bruxism and Sleep Arousal: an Experimental Challenge to Assess the Role of Cyclic Alternating Pattern".

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Abstract

Rhythmic masticatory muscle activity (RMMA) is the characteristic electromyographic pattern of sleep bruxism (SB), a sleep-related motor disorder associated with sleep arousal. Sleep arousals are generally organized in a clustered mode known as the cyclic alternating pattern (CAP). CAP is the expression of sleep instability between sleep maintaining processes (phase A1) and stronger arousal processes (phases A2 and A3). This study aimed to investigate the role of sleep instability on RMMA/SB occurrence by analyzing CAP and electroencephalographic (EEG) activities. The analysis was performed on the sleep recordings of 8 SB subjects and 8 controls who received sensory stimulations during sleep. Baseline and experimental nights were compared for sleep variables, CAP, and EEG spectral analyses using repeated measure ANOVAs. Overall, no differences in sleep variables and EEG spectra were found between SB subjects and controls. However, SB subjects had higher sleep instability (more phase A3) than controls ($p=0.05$). The frequency of phase A3 was higher in the pre-REM sleep periods ($p<0.001$), where peaks in RMMA/SB activity were also observed ($p=0.05$). When sleep instability was experimentally increased by sensory stimuli both groups showed an enhancement in EEG theta and alpha power ($p=0.04$ and 0.02 respectively), and significant increases in sleep arousal and all CAP variables. No change in RMMA/SB index was found within either groups (RMMA/SB occurred in all SB subjects and only one control during the experimental night). These findings suggest that CAP phase A3 may act as a permissive window rather than a generator of RMMA/SB activity in predisposed individuals.

Keywords

Sleep bruxism, rhythmic masticatory muscle activity, sleep instability, cyclic alternating pattern, EEG spectral analysis

Introduction

Sleep bruxism (SB) is a common sleep-related movement disorder characterized by tooth grinding or clenching (1, 2). The typical movement pattern of SB is the rhythmic masticatory muscle activity (RMMA). Almost 60% of normal sleepers engage in RMMA during sleep, but with a frequency three times lower than in SB subjects (3). RMMA/SB episodes occur more frequently during NREM sleep stage 1 and 2. Only 10% are observed during REM sleep (3-5). Evidence on the pathophysiology of RMMA/SB supports the hypothesis that RMMA/SB is associated with autonomic sympathetic-cardiac activity and sleep arousals (5-8). Sleep arousal is defined as a brief awakening (at least 3 seconds) characterized by increased electroencephalographic (EEG), muscle, and heart activity without return to consciousness (9). Arousals are the response of the sleeping brain to external (environmental) and internal (physiological or pathological) stimuli. Sleep arousals normally occur between 6 to 14 times per hour of sleep.

Within NREM sleep, the majority of these arousal responses have been found to occur in an orderly, repetitive manner known as the cyclic alternating pattern (CAP). CAP is characterized by sequences of transient electrocortical events (phase A of CAP) that are distinct from the background EEG activity (phase B of CAP). A CAP sequence is composed of a succession of CAP cycle (A-B phases), which recurs with a periodicity of 20-40 seconds. CAP variables serve as polysomnographic markers of unstable sleep; in contrast the absence of CAP (scored as non-CAP when the interval between two successive A phases is more than 60 seconds) reflects stable and consolidated sleep (10-12). The arousal phase of CAP, phase A, is further classified into three subtypes of increasing arousal strength: A1, A2, and A3 (13). Sleep patterns associated with phase A1 are thought to be unstable but preserved by the cortical mechanisms that reinforce and protect sleep maintenance. By contrast, phase A2 represents a transition phase toward increased arousal pressure (phase A3). The occurrence of phases A2 and A3 correspond to a higher arousal activity and sleep instability, usually coupled with an increase in muscle tone and cardio-respiratory rate (12, 14-16). It has been observed that most RMMA/SB episodes occur in

clusters with a periodicity of 20-30 seconds (7), similar to the physiological arousal rhythm of CAP. Moreover, 88% of RMMA/SB events scored during NREM sleep have been found to occur within CAP phase A, particularly subtype A3 (5).

A previous study has shown that following experimentally induced arousals, RMMA/SB activity occurs more frequently in SB subjects compared to controls. Thus, suggesting that SB subjects may have a higher responsiveness to sleep arousal (17). However, whether the shift in balance from sleep-maintaining processes toward arousal processes effects RMMA/SB activity remains unknown. The aim of the present study was to examine the role of sleep instability on RMMA/SB occurrence. This was achieved by analyzing CAP variables and quantitative EEG activity in subjects whose sleep was disturbed by experimental sensory stimuli.

Materials and Methods

Subjects

This study analyzed polysomnographic data on 16 young subjects who participated in a previously published experimental study (17). The sample comprised of 8 SB subjects and 8 age- and gender-matched controls (Table 1). SB subjects were selected based on tooth-grinding history (more than 3 nights/week) and the presence of clinical signs and symptoms suggestive of SB (tooth wear, masseter muscle hypertrophy, morning jaw muscle fatigue or tenderness). Control subjects had none of these clinical findings. SB diagnosis was then assessed in the second night of audio-video sleep recording based on the standard polysomnographic research diagnostic criteria (18). Only SB subjects with an RMMA/SB index ≥ 4 episodes per hour of sleep were included. None of the participants had a history or showed signs of sleep or medical disorders. None of the participants were taking medications. The experimental protocol was approved by the research ethics board of the Hôpital du Sacré-Coeur in Montreal.

Study design

As described in a previous publication (17), all subjects underwent three or four nights of audio-video polysomnographic recordings. The first night was used for habituation to the sleep laboratory environment. The second night was used to establish SB diagnosis in SB subjects and to confirm the absence of SB in control subjects. The experimental protocol was conducted during the third and/or fourth nights. The baseline night (night 2) was compared to the experimental night (night 3 or 4) that consisted of SB and control subjects being stimulated by a vibro-tactile and/or auditory stimulation (VT/AD) as generated by AC motors in contact with the subject's arm. The VT/AD stimuli were used to induce experimental arousals without eliciting a complete awakening from sleep. Stimuli were delivered for a duration of 1 second at 60-second intervals during all sleep stages (17).

Sleep data collection and scoring

The following polysomnographic variables were recorded, as described in the previous publication (17): EEG, electro-oculogram, electrocardiogram, chest respiratory movements, and electromyogram from the suprahyoid, masseter, temporalis and tibialis muscles. Sleep stages and sleep arousal were scored according to the standard criteria (19, 20). RMMA/SB activity was analyzed according to published research diagnostic criteria (18). CAP was scored according to the published rules (21). Each CAP phase A was visually detected during NREM sleep using Somnologica (Embla, USA) then classified into subtypes A1, A2, or A3. The following CAP parameters were then evaluated: total CAP time, CAP rate, number and duration of CAP sequence, number and duration of A phases, number and duration of B phases, and number and percent of subtypes A1, A2, and A3.

Data analyses and statistics

The duration of the first 4 NREM/REM sleep cycles was normalized within each subject by dividing NREM periods into 20 intervals and REM periods into 5 intervals to obtain 100 intervals for the entire night (22, 23). Furthermore, each sleep cycle was averaged into four NREM sections and one REM section (each made by 5 intervals). Power spectra of EEG delta (0.50–4.00 Hz), theta (4.00–8.00 Hz), and alpha activities (8.00–13.00 Hz) were analyzed over 4-second mini-epochs on the EEG central derivation computed by fast Fourier transform (FFT) after excluding mini-epochs of EEG artifacts. Mini-epoch values were averaged for each interval. Further, the number of RMMA/SB episodes and CAP phases A1, A2, and A3 per hour of sleep were calculated for each NREM and REM sleep section separately.

Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, USA). Repeated-measures ANOVAs were performed for group comparisons and influence of VT/AD stimulus, with group as the between subject variable and VT/AD as the within subject variable. Repeated measures ANOVA were also performed for EEG spectral analyses, CAP variables, and RMMA/SB episodes distribution over sleep cycles. In the EEG spectral analyses data are expressed as log10 because they did not follow a normal distribution. NREM and REM sleep were evaluated separately. Huynh-Feldt correction for sphericity was applied to all ANOVA calculations. P value was considered significant when ≤ 0.05.

Results

Sleep bruxism, sleep arousal and CAP variables

All SB subjects had a RMMA/SB index greater than 4 episodes/h of sleep (mean 7.1 ± 0.9). SB subjects showed a higher number and percentage of CAP phase A3 (1.5 times more than controls, p=0.05 and 0.002 respectively; Table 3.2.1, Group column), and a

longer duration of overall phase A compared to controls (p=0.025; Table 3.2.1, Group column). The other sleep and CAP variables did not differ between groups.

The VT/AD stimulus during sleep did not affect RMMA/SB frequency over night for both groups (Table 1, VT/AD column; and Figure 3.2.1). Sleep arousal index was increased (p=0.001), but a significant interaction was observed between group and VT/AD variables (p=0.02). Hence, we performed paired sample t-tests for this index for each group separately. This post hoc analysis showed that the number of sleep arousals during the experimental night was significantly higher than during baseline night in control subjects only (p=0.001) (Figure 3.2.1). The application of VT/AD stimuli also increased CAP time by 34% (p<0.001), as well as CAP rate, CAP sequence, and number of phases A1, A2, and A3 for both groups (Table 3.2.1). The number of A3 phases found in the experimental nights of the control subjects was increased to a value similar to that seen in the baseline nights of the SB subjects (Figure 3.2.1).

RMMA/SB and CAP phase A distribution in relation to sleep cycles

In SB subjects, RMMA/SB episodes occurred with higher frequency (number of episodes/hour of sleep) in the pre-REM intervals and followed a linear crescendo pattern from NREM toward REM sleep in the baseline night (p=0.05). In the experimental night, the frequency of RMMA/SB episodes over sleep cycles remained unchanged (Figure 3.2.2). Overall, there was no group difference in the distribution across sleep cycles of CAP phases A1, A2, and A3 occurrence. However, SB subjects showed higher frequency (number/h) of phase A3 in both baseline and experimental nights (p=0.01). Phase A1 frequency followed a quadratic distribution (p=0.003). Indeed, phases A2 and A3 frequencies increased linearly during NREM sleep, peaking in the transition period between NREM and REM sleep (both p<0.001). The frequency of CAP phases A2 and A3 was significantly increased for both SB subjects and controls when VT/AD stimuli were applied (p=0.03 for A2 and 0.0006 for A3) (Figure 3.2.2).

Power spectral analysis of EEG delta, theta, and alpha activities

SB and control subjects showed no difference in the NREM/REM ultradian homeostatic fluctuation of delta activity. Delta power gradually declined from the first sleep cycle to the third sleep cycle ($p<0.001$), with very low activity during REM sleep. The VT/AD stimuli did not affect delta power in either group ($p=0.5$). Theta and alpha power did not differ between SB subjects and controls ($p=0.7$ and $p=0.3$ respectively), but they were higher in the experimental night compared to baseline for both groups ($p=0.04$ for theta and $p=0.02$ for alpha activities)(Figure 3.2.3).

Discussion

The present study describes the occurrence of RMMA/SB episodes in relation to CAP phase A with and without experimental sleep perturbation for SB and control subjects. Overall, SB subjects did not differ from controls for sleep variables and EEG spectral analysis. However, the analysis of sleep microstructure (CAP variables) revealed that SB subjects had more CAP phase A3 than controls. In the experimental night, both groups showed greater sleep instability without major changes in sleep homeostasis (e.g., sleep cycles, delta activity). SB subjects showed a higher RMMA/SB index than controls at baseline, as reported in the previous publication (17). In addition, this difference between groups in RMMA/SB index was maintained in the experimental night when sleep arousals were induced. However, no changes in RMMA/SB activity were observed within groups from baseline to VT/AD night (RMMA/SB activity was observed in all SB subjects and only one control). These data provide new insight into how sleep instability affects the genesis of RMMA/SB episodes within normal sleep processes.

RMMA/SB is described as a sleep-related motor activity secondary to sleep arousal (5, 7, 8, 24). Its association with phase A of CAP has also been previously reported (5, 25). However, recent evidence supports the hypothesis that sleep arousal and particularly phase

A of CAP are not the generator of RMMA/SB activity, but rather the permissive window for its occurrence during sleep (26). The present study supports this hypothesis.

The SB subjects of this study displayed higher sleep arousal strength (phase A3) compared to controls. However, overall sleep instability was within a normal range since the other CAP variables did not differ between groups. EEG spectral analysis did not reveal significant differences between SB and control subjects for delta, theta and alpha activities, suggesting that sleep homeostatic processes are normal in young and otherwise healthy SB subjects. Delta and theta activities are the EEG hallmarks of NREM slow wave sleep, also known as deep or restorative sleep (27). In particular, the power density in the delta band, usually referred as slow wave activity (SWA), has proven to be a very useful and popular parameter to quantify the homeostatic sleep pressure and to indirectly estimate sleep quality (28-30). Delta activity follows the ultradian NREM/REM sleep cycle and shows a physiological decline in the course of sleep that reflects the inner decline of sleep propensity. This pattern was observed in SB subjects as well as in controls. The analysis of CAP variables and EEG activity revealed that SB subjects had normal sleep maintenance processes but higher sleep instability compared to control subjects. Since arousals are a physiological structural component of sleep that ensures the reversibility of sleep in response to sensorial inputs, noisy environments, and movements (11), it could be that the higher sleep instability found in the baseline nights of the SB subjects was attributed to the RMMA/SB motor events themselves.

For the experimental nights, since they involved applying sub-threshold stimulations, an increase in CAP (or sleep instability) would be expected (31). In fact, CAP is the more sensitive response to internal or external factors of perturbation at the micro-structural level of sleep. Sensory stimulations, such as acoustic or vibratory inputs administered during sleep have been shown to induce a CAP sequence and increase CAP rate (32, 33). The analysis of sleep data performed in this study on the experimental nights did reveal an increase in the sleep arousal index and all CAP variables for both SB and control subjects: i.e., an increase of arousal influence and sleep instability. However, the

ultradian fluctuation of delta activity was preserved in both groups. In contrast, theta activity was increased in the experimental night, indicating a more sensitive response of this frequency band to sensory inputs during sleep. Furthermore, alpha activity was also enhanced when the VT/AD stimuli were applied. Since the alpha frequency band is the major component contributing to the spectral power density of REM sleep and sleep arousal (34), the experimental perturbations successfully induced sleep arousal within normal sleep process in both groups. Interestingly, only control subjects showed a significant increase in sleep arousal in the experimental night compared to baseline. This finding may suggest that different arousal responsiveness to external perturbing stimuli exists between the two groups. It can be hypothesized that the arousal response to the VT/AD stimuli in the SB group, which consisted of young and healthy subjects, reached a plateau. New experimental studies are needed to better understand this finding. However, the CAP analysis performed revealed that the VT/AD stimuli disrupted sleep microstructure in both groups. Although the phases A of CAP were experimentally increased, control subjects did not develop RMMA/SB activity (except for one control subject). Therefore, arousal and sleep instability seem to be facilitating but not sufficient factors for RMMA/SB occurrence during sleep. Other predisposing or initiating factors are probably required.

Previous studies on the genesis of RMMA/SB episodes have suggested that autonomic and central nervous system activations may have a primary role (7, 35-37). The occurrence of RMMA/SB episodes reached its peak in the pre-REM sleep section of the sleep cycle when also higher frequency of CAP phases A2 and A3 were observed. The pre-REM period is characterized by more rapid EEG rhythms and greater autonomic and muscle activities (21, 38), supporting the hypothesis that RMMA/SB might be facilitated in the pre-REM sleep period.

Study Limitations and Future Research

The present study is characterized by a complex experimental protocol that was designed to examine the role of sleep arousal on RMMA/SB occurrence. However it suffers from some limitations. First of all, the small sample of subjects recruited in this sleep laboratory experimental study reduces its external validity. Moreover, since in the paradigm of this study only instantaneous VT/AD sensory stimulations were used, we cannot speculate on how SB subjects may respond to other types of perturbing stimuli applied during sleep. For example, it is unknown to our knowledge how biofeedback devices that deliver electrical pulses to inhibit EMG muscle activity during sleep affect sleep arousal and sleep instability.

The relationship between SB and sleep arousal is a challenging field. Further studies are required to better understand what are the triggers of RMMA/SB activity during sleep, as this is still unknown. Experimental protocols using pharmacological or physical manipulation of the NREM/REM sleep cycle may assist in determining the nature of SB genesis.

Conclusions

The present study supports the hypothesis that sleep arousal (CAP phase A) is not the generator of RMMA/SB movements, but rather provides the permissive window for these sleep motor events to occur during an unstable sleep condition (11, 39). That is, other predisposing and initiating factors are required to generate RMMA/SB episodes (40, 41). In particular, this motor activity seems to be facilitated by transient increases in arousal pressure (phases A2 and A3) and autonomic-sympathetic activation, which are observed in the pre-REM sleep periods.

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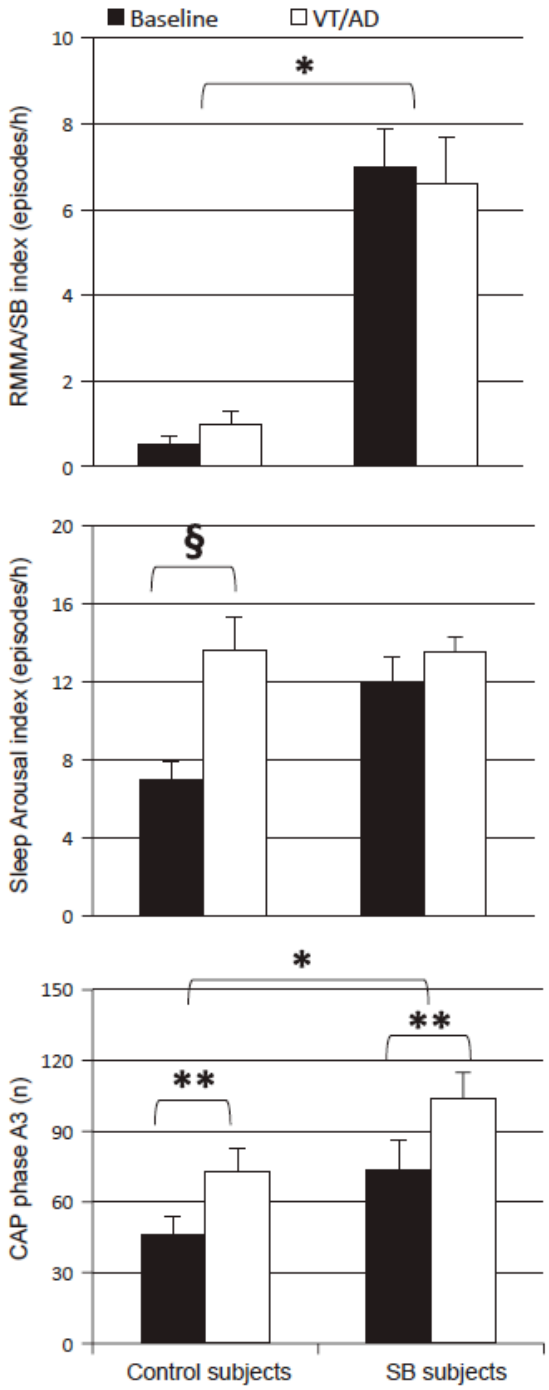
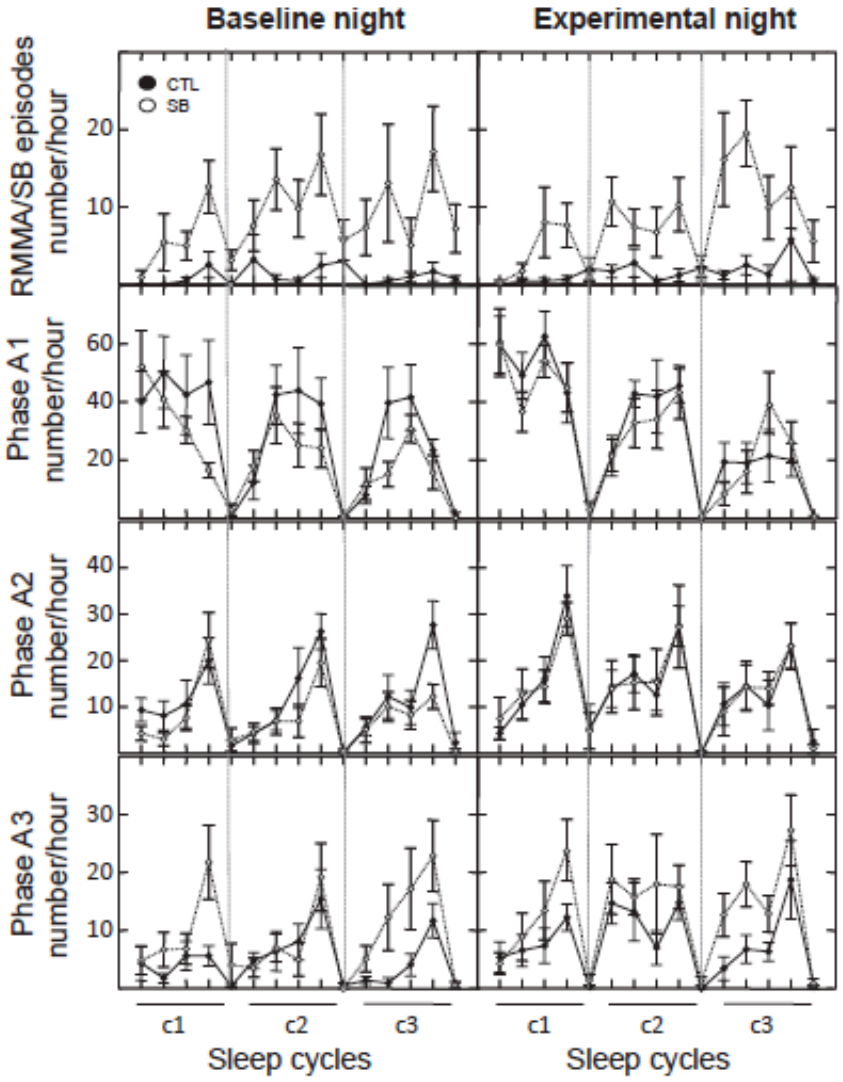
Figure 3.2.1 Comparison between control and SB subjects for RMMA/SB index, sleep arousal index and number of CAP phase A3 in baseline and experimental (VT/AD) nights.



* significant value in ANOVAs for group comparison.
** significant value in ANOVAs for VT/AD comparison.
§ significant value in paired t-tests (post hoc analysis).
Standard error bars are included.

Figure 3.2.2 RMMA/SB activity (episodes/h) and CAP phases A1, A2, A3 (number/h).

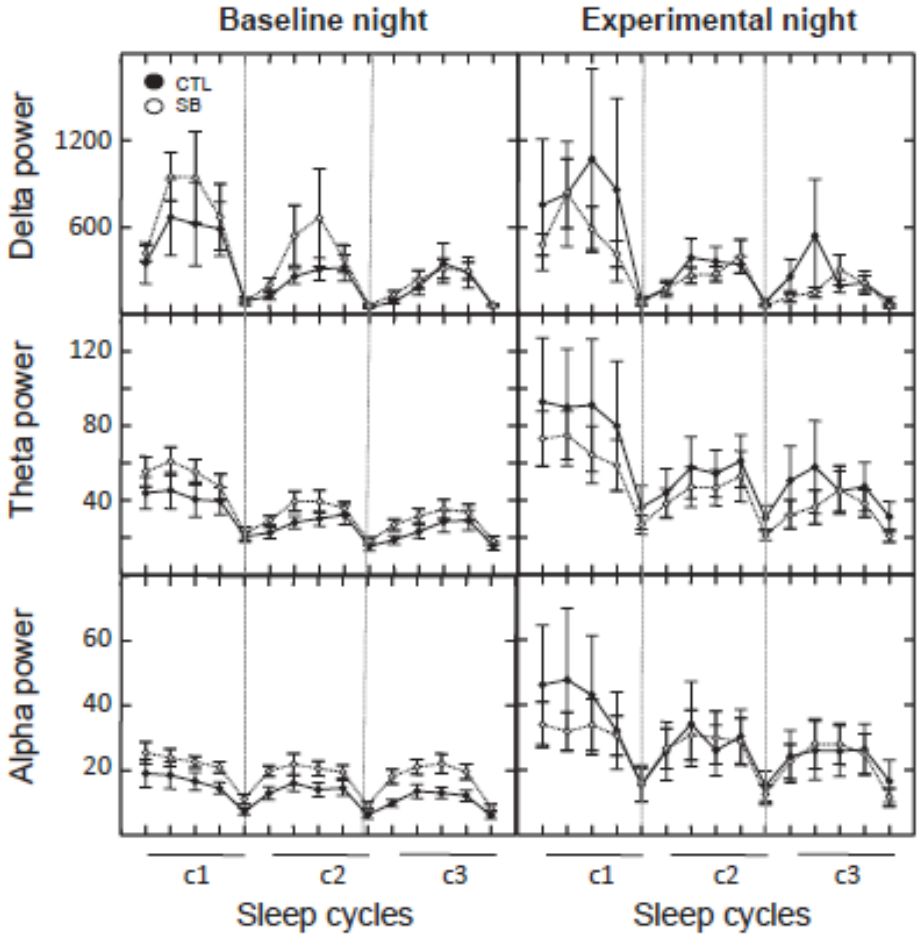
Graphs show the distribution over NREM/REM sleep cycles for controls (CTL; black circles) and SB subjects (SB; white circles) in baseline and experimental (VT/AD) nights. Vertical dotted lines delimit each sleep cycle. Only the first three sleep cycles are displayed due to missing data for the last one.



c1 refers to the first sleep cycle; c2 to the second sleep cycle; c3 to the third sleep cycle; RMMA/SB to rhythmic masticatory muscle activity/sleep bruxism.

Figure 3.2.3 Power spectral analysis of EEG delta (0.5–4.0 Hz), theta (4.0–8.0 Hz) and alpha (8.0–13.0 Hz) activities.

Graphs show the distribution over NREM/REM sleep cycles for controls (CTL; black circles) and SB subjects (SB; white circles) in baseline and experimental (VT/AD) nights. Vertical dotted lines delimit each sleep cycle. Only the first three sleep cycles are displayed due to missing data for the last one.



c1 refers to the first sleep cycle; c2 to the second sleep cycle; c3 to the third sleep cycle.

Table 3.2.1 Demographic, RMMA/SB, sleep, and CAP variables during baseline and experimental nights in 8 controls and 8 SB subjects.

	Control subjects		SB subjects		*P* value	
Age	23 (20–26)		22·8 (21–27)			
Gender	4M, 4F		5M, 3F			
	Baseline night	Experimental night	Baseline night	Experimental night	Group	VT/AD
RMMA/SB (episodes/h)	0·5 ± 0·2	1 ± 0·3	7·1 ± 0·9	6·6 ± 1·1	<0·001	0·95
Sleep time (min)	461 ± 21	470 ± 12	437 ± 13	471 ± 7	0·35	0·21
Sleep arousals (*n*/h)*	7·0 ± 0·9	13·6 ± 1·7	12 ± 1·3	13·5 ± 0·8	0·12	0·001
Stage 1 (%)	3·2 ± 0·7	5·2 ± 1·2	2·6 ± 0·8	3·3 ± 0·6	0·27	0·05
Stage 2 (%)	48·7 ± 1·9	57·0 ± 2·3	47·1 ± 0·9	56·5 ± 1·6	0·54	<0·001
Stage 3 (%)	8·4 ± 0·8	7·9 ± 0·7	8·9 ± 1·3	7·8 ± 1·0	0·84	0·40
Stage 4 (%)	14·9 ± 1·5	8·8 ± 1·8	13·9 ± 2·0	8·3 ± 2·2	0·68	0·007
REM stage (%)	24·9 ± 1·5	21·1 ± 1·6	27·6 ± 1·6	24·1 ± 2·0	0·09	0·06
CAP rate (%)	41·0 ± 3·5	52·4 ± 5·1	43·8 ± 3·9	52·7 ± 3·6	0·79	<0·001
CAP time (min)	144 ± 16	193 ± 18	141 ± 18	189 ± 16	0·89	<0·001
CAP sequence (*n*)	40·1 ± 2·2	46·6 ± 1·4	37·4 ± 2·3	44·4 ± 2·2	0·19	0·01
Phase A (*n*)	305 ± 32	407 ± 41	289 ± 40	413 ± 48	0·93	<0·001
A1 (*n*)	176 ± 22	226 ± 26	153 ± 19	208 ± 24	0·48	0·004
A2 (*n*)	82·3 ± 10·1	108 ± 12	62·3 ± 13·0	102 ± 26	0·53	0·009
A3 (*n*)	46·4 ± 7·2	73·1 ± 9·8	73·6 ± 12·6	104 ± 11	0·05	<0·001
A1 (%)	57·8 ± 2·4	55·4 ± 2·2	53·2 ± 2·4	50·4 ± 4·1	0·18	0·26
A2 (%)	27·1 ± 2·2	26·7 ± 1·6	21·1 ± 2·6	23·2 ± 3·4	0·11	0·69
A3 (%)	15·1 ± 1·7	17·9 ± 1·9	25·7 ± 2·6	26·4 ± 2·9	0·002	0·43
Phase A duration (s)	6·8 ± 0·4	6·6 ± 0·2	7·9 ± 0·2	6·9 ± 0·3	0·025	0·052
Phase B duration (s)	21·3 ± 0·4	21·9 ± 0·5	21·5 ± 0·6	20·9 ± 0·8	0·63	0·94
CAP cycle duration (s)	28·1 ± 0·7	28·4 ± 0·5	29·3 ± 0·6	27·9 ± 0·9	0·62	0·38
A1 duration (s)	5·0 ± 0·3	4·9 ± 0·2	5·3 ± 0·2	4·8 ± 0·1	0·51	0·13
A2 duration (s)	6·7 ± 0·5	6·6 ± 0·3	7·6 ± 0·6	6·6 ± 0·3	0·43	0·11
A3 duration (s)	14·2 ± 0·6	12·2 ± 0·6	13·7 ± 0·5	12·0 ± 1·0	0·70	0·004

(*) Significant interaction (group x VT/AD) was found for sleep arousal index (p =0.02). No significant interaction was found for all the other variables (see Results).

Data are presented as mean ± SEM or median (min-max). Repeated measures ANOVA was performed and p value was considered significant when ≤ 0.05. P values in the group column represent the comparison between control subjects and SB subjects (baseline and experimental nights combined). P values in the VT/AD column represent the comparison between baseline and experimental nights (control and SB subjects combined).
VT/AD refers to vibratory-auditory stimulation applied in the experimental night; RMMA to rhythmic masticatory muscle activity; SB, sleep bruxism; REM, rapid eye movement; CAP, cyclic alternating pattern.

References:

1 AASM. Sleep Related Bruxism. *American Academy of Sleep Medicine (AASM) eds ICSD-2 International classification of sleep disorders, 2nd ed:Diagnosis and coding manual Westchester, Illinois*. 2005: 189-92.

2 De Laat A., Macaluso G. M. Sleep bruxism as a motor disorder. *Mov Disord*. 2002;**17 Suppl 2**: S67-9.

3 Lavigne G. J., Rompre P. H., Poirier G., Huard H., Kato T., Montplaisir J. Y. Rhythmic masticatory muscle activity during sleep in humans. *J Dent Res*. 2001;**80**: 443-8.

4 Lavigne G.J., Manzini C., Kato T. Sleep Bruxism. In: MH Kryger, T Roth, D W.C. ed *Principles and Practice of Sleep Medicine*. 4 ed. Philadelphia: Saunders 2005: p. 946-059.

5 Macaluso G. M., Guerra P., Di Giovanni G., Boselli M., Parrino L., Terzano M. G. Sleep bruxism is a disorder related to periodic arousals during sleep. *J Dent Res*. 1998;**77**: 565-73.

6 Lavigne G. J., Huynh N., Kato T., Okura K., Adachi K., Yao D., Sessle B. Genesis of sleep bruxism: motor and autonomic-cardiac interactions. *Arch Oral Biol*. 2007;**52**: 381-4.

7 Huynh N., Kato T., Rompre P. H., Okura K., Saber M., Lanfranchi P. A., Montplaisir J. Y., Lavigne G. J. Sleep bruxism is associated to micro-arousals and an increase in cardiac sympathetic activity. *Journal of sleep research*. 2006;**15**: 339-46.

8 Kato T., Rompre P., Montplaisir J. Y., Sessle B. J., Lavigne G. J. Sleep bruxism: an oromotor activity secondary to micro-arousal. *J Dent Res*. 2001;**80**: 1940-4.

9 AASM, Iber C., Ancoli-Israel S., Chesson A., Quan S.F. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. *American Academy of Sleep Medicine*. 2007;**Westchester, IL**: 37.

10 Terzano M. G., Parrino L., Spaggiari M. C. The cyclic alternating pattern sequences in the dynamic organization of sleep. *Electroencephalogr Clin Neurophysiol*. 1988;**69**: 437-47.

11 Halasz P., Terzano M., Parrino L., Bodizs R. The nature of arousal in sleep. *Journal of sleep research*. 2004;**13**: 1-23.

12 Terzano M. G., Parrino L. Origin and Significance of the Cyclic Alternating Pattern (CAP). REVIEW ARTICLE. *Sleep medicine reviews*. 2000;**4**: 101-23.

13 Terzano M. G., Parrino L. Clinical applications of cyclic alternating pattern. *Physiol Behav*. 1993;**54**: 807-13.

14 Smerieri A., Parrino L., Agosti M., Ferri R., Terzano M. G. Cyclic alternating pattern sequences and non-cyclic alternating pattern periods in human sleep. *Clin Neurophysiol*. 2007;**118**: 2305-13.

15 Parrino L., Smerieri A., Rossi M., Terzano M. G. Relationship of slow and rapid EEG components of CAP to ASDA arousals in normal sleep. *Sleep*. 2001;**24**: 881-5.

16 Terzano M. G., Parrino L., Rosa A., Palomba V., Smerieri A. CAP and arousals in the structural development of sleep: an integrative perspective. *Sleep medicine*. 2002;**3**: 221-9.

17 Kato T., Montplaisir J. Y., Guitard F., Sessle B. J., Lund J. P., Lavigne G. J. Evidence that experimentally induced sleep bruxism is a consequence of transient arousal. *J Dent Res*. 2003;**82**: 284-8.

18 Lavigne G. J., Rompre P. H., Montplaisir J. Y. Sleep bruxism: validity of clinical research diagnostic criteria in a controlled polysomnographic study. *J Dent Res*. 1996;**75**: 546-52.

19 Rechtschaffen A., Kales A. A Manual of Standardized Terminology, Technique and Scoring System for Sleep Stages of Human Subjects. Loa Angeles: Brain Information Service / Brain Research Institute 1968.

20 ASDA American Sleep Disorder Association. EEG arousal: sccoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of th ASDA. *Sleep*. 1992;**15**: 174-84.

21 Terzano M. G., Parrino L., Sherieri A., Chervin R., Chokroverty S., Guilleminault C., Hirshkowitz M., Mahowald M., Moldofsky H., Rosa A., Thomas R., Walters A. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. *Sleep medicine*. 2001;**2**: 537-53.

22 Gaudreau H., Joncas S., Zadra A., Montplaisir J. Dynamics of slow-wave activity during the NREM sleep of sleepwalkers and control subjects. *Sleep*. 2000;**23**: 755-60.

23 Achermann P., Dijk D. J., Brunner D. P., Borbely A. A. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. *Brain research bulletin*. 1993;**31**: 97-113.

24 Sato T., Harada Y. Tooth-grinding during sleep as an arousal reaction. *Experientia*. 1971;**27**: 785-6.

25 Zucconi M., Oldani A., Ferini-Strambi L., Smirne S. Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. *J Clin Neurophysiol*. 1995;**12**: 147-54.

26 Carra M.C., Macaluso G. M., Rompre P., Huynh N., Parrino L., Terzano M.G., Lavigne G.J. Clonidine has a paradoxical effect on cyclic arousal and sleep bruxism during NREM sleep. *Sleep*. 2010;**33**.

27 Roth T. Characteristics and determinants of normal sleep. *J Clin Psychiatry*. 2004;**65 Suppl 16**: 8-11.

28 Burgess H. J., Holmes A. L., Dawson D. The relationship between slow-wave activity, body temperature, and cardiac activity during nighttime sleep. *Sleep*. 2001;**24**: 343-9.

29 Borbely A. A. From slow waves to sleep homeostasis: new perspectives. *Arch Ital Biol*. 2001;**139**: 53-61.

30 Borbély A.A., Achermann P. Sleep homeostasis and models of sleep regulation. In: RT Kryger MH, Dement WC (eds). ed *Principles and Practices of Sleep Medicine* Philadelphia: Elsevier Saunders 2005: p. 405-17.

31 Kato T., Montplaisir J. Y., Lavigne G. J. Experimentally induced arousals during sleep: a cross-modality matching paradigm. *Journal of sleep research*. 2004;**13**: 229-38.

32 Terzano M. G., Parrino L., Fioriti G., Farolfi A., Spaggiari M. C., Anelli S., Arcelloni T. Variations of cyclic alternating pattern rate and homeostasis of sleep organization: a controlled study on the effects of white noise and zolpidem. *Pharmacol Biochem Behav*. 1988;**29**: 827-9.

33 Terzano M. G., Parrino L., Fioriti G., Orofiamma B., Depoortere H. Modifications of sleep structure induced by increasing levels of acoustic perturbation in normal subjects. *Electroencephalogr Clin Neurophysiol*. 1990;**76**: 29-38.

34 Cantero J. L., Atienza M. Alpha burst activity during human REM sleep: descriptive study and functional hypotheses. *Clin Neurophysiol*. 2000;**111**: 909-15.

35 Marthol H., Reich S., Jacke J., Lechner K. H., Wichmann M., Hilz M. J. Enhanced sympathetic cardiac modulation in bruxism patients. *Clin Auton Res*. 2006;**16**: 276-80.

36 Lobbezoo F., Naeije M. Bruxism is mainly regulated centrally, not peripherally. *Journal of oral rehabilitation*. 2001;**28**: 1085-91.

37 Lavigne G.J., Tuomilehto H., Macaluso G. M. Pathophysiology of Sleep Bruxism. In: CP Lavigne GJ, Smith MT (eds) ed *Sleep Medicine For Dentists A Practical Overview*. 1 ed: Quintessence Publishing Co, nc 2009: p. 117-24.

38 Terzano M. G., Parrino L., Boselli M., Smerieri A., Spaggiari M. C. CAP components and EEG synchronization in the first 3 sleep cycles. *Clin Neurophysiol*. 2000;**111**: 283-90.

39 Parrino L., Boselli M., Buccino G. P., Spaggiari M. C., Di Giovanni G., Terzano M. G. The cyclic alternating pattern plays a gate-control on periodic limb movements during non-rapid eye movement sleep. *J Clin Neurophysiol*. 1996;**13**: 314-23.

40 Lavigne G. J., Kato T., Kolta A., Sessle B. J. Neurobiological mechanisms involved in sleep bruxism. *Crit Rev Oral Biol Med*. 2003;**14**: 30-46.

41 Lavigne G. J., Khoury S., Abe S., Yamaguchi T., Raphael K. Bruxism physiology and pathology: an overview for clinicians. *Journal of oral rehabilitation*. 2008;**35**: 476-94.

3.3 Third Article: "Prevalence and Risk Factors of Sleep Bruxism and Wake-Time Tooth Clenching in a 7-17 Year Old Population"

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Abstract

Sleep-related bruxism (SB) and wake-time tooth clenching (TC) have been associated with temporomandibular disorders (TMD), headache, sleep and behavioral complaints. The study aimed to assess the prevalence and risk factors of these signs and symptoms in a 7-17 year old population (n=604) seeking orthodontic treatment. Data were collected by questionnaire and a clinical examination assessing craniofacial morphology and dental status. SB was reported by 15% of the population, TC by 12.4%. The SB group (n=58) was mainly composed of children (67.3% ≤12 years old); the TC group (n=42) of adolescents (78.6% ≥13 years old). Over 60% of SB subjects were found to be a dental class II and 28.1% a brachyfacial type. Compared to controls (n=220), SB subjects were more at risk of experiencing jaw muscle fatigue (adjusted odds ratio; AOR=10.5), headache (AOR=4.3), and loud breathing during sleep (AOR=3.1). Compared to controls, TC subjects reported more TMJ clicking (AOR=5), jaw muscle fatigue (AOR=13.5), and several sleep and behavioral complaints. Sleep- and wake-time parafunctions are frequently associated with signs and symptoms suggestive of TMD, sleep and behavioral problems. Their clinical assessment in the orthodontic treatment planning is recommended.

Keywords – Headache, sleep bruxism, sleep disorders, temporomandibular disorders, tooth clenching

Introduction

Bruxism, reported during sleep or during wake-time, is a stereotypical movement characterized by tooth grinding or clenching. Bruxism is commonly observed in children and adolescents with an overall prevalence of 8-38 % (1-3). This wide range in prevalence is due to the fact that the majority of epidemiological studies on bruxism has been based on self-reports and often fails to distinguish wake-time from sleep bruxism. Despite some similarities, wake-time and sleep bruxism are suspected to have different etiologies and physiopathologies (4).

Wake-time bruxism is considered an oral parafunctional activity mainly characterized by sustained masticatory muscle contractions. It is defined in the clinic as tooth clenching (TC)(5). The subject is often not aware of the habit. TC activity seems to be exacerbated by anxiety and is associated with lower stress coping responses (6, 7). Wake-time bruxism is also considered to be the cause of temporomandibular joint (TMJ) and masticatory muscle pain (5). Long-lasting tooth clenching, particularly at low contraction levels, has been associated with pain in the jaw and cranial muscles (8, 9). This form of post-exercise pain is considered to be a consequence of tonic muscular hyperactivity of the masticatory muscles (especially the lateral pterygoid, temporal and masseter muscles), which may or may not adapt to overload (8, 10).

Sleep bruxism (SB), is a sleep-related movement disorder also classified as a parafunction in dentistry (11, 12). SB is characterized by episodes of rhythmic masticatory muscle activity (RMMA) of the masseter and temporalis muscles that can be observed on electromyographic recordings performed during sleep (4). Grinding sounds due to tooth contacts may or may not occur during RMMA/SB episodes. However, this is the pathognomonic sign of SB that is usually reported by the subject, bed partners, and parents. Although the etiology of SB remains unknown, its physiopathology is partly explained by a re-activation of cerebral and autonomic nervous systems during periods of sleep instability (a process called sleep arousal) (13). Genetic predisposing factors and psychosocial components (such as anxiety and stress sensitivity) also seem to play a role in the

mechanisms that regulate the occurrence of SB (14, 15). However, further studies are needed to increase our understanding of the central physiopathology of SB.

Especially in children, SB has been described in relation to behavioral problems (e.g., hyperactivity, attention deficit, sleepiness, poor school performance), with a frequent comorbidity with the Attention Deficit and Hyperactivity Disorder (ADHD)(16-18).

In addition, SB has been associated with sleep disordered breathing (SDB), in particular with snoring and obstructive sleep apnea (19-21). Up to half of children with sleep apnea also present SB (22). Two clinical open studies have also demonstrated that the prevalence of SB decreases in pediatric patients after a tonsillectomy or adenotonsillectomy performed to treat SDB (22, 23). SDB can occur in the presence of adenotonsillar tissue hypertrophy, craniofacial abnormalities, and neuromuscular deficits. While the cause and effect links have yet to be demonstrated, it has been suggested that such conditions create airway obstruction (24); the resulting intermittent airflow cessation, oxygen desaturation and sleep fragmentation are serious causes of metabolic, cardiovascular and neuro-cognitive morbidity in children (25). Certain evidence supports the hypothesis that SB activity may help to reinstate airway patency following an obstructive respiratory event during sleep (26). However, the relation between SB and SDB, as well as its health consequences, needs to be further investigated.

Both SB and TC habits may have detrimental consequences for orofacial structures, e.g. temporomandibular disorders (TMD), orofacial pain, headache, muscle discomfort or fatigue upon awakening, masticatory muscle hypertrophy, tooth wear and fractures (27). However, little data is available regarding the type of impact these disorders have on the pediatric population.

The present study aims to evaluate the prevalence of reported sleep- and wake-time bruxism and related conditions in a pediatric population, and assess the role of SB and TC as risk factors for: TMD signs and symptoms, sleep problems, and behavioral complaints. To achieve these objectives, we performed a subgroup analysis on a population of 7-17 year-olds seeking orthodontic treatment in a university based center (28).

Materials and methods

Population

The study population was composed of a multi-ethnic sample of 604 subjects (82.4% Caucasians) recruited at the Orthodontic Clinic of the University of Montreal during clinical screening examinations. Subjects were between 7 and 17 years of age (mean age ± SD, 13 ± 2.28 years old). All subjects were seeking orthodontic treatment for different forms of craniofacial anomalies and/or aesthetic reasons. The study was conducted in accordance with the institutional ethical standards. All subjects and their parents or guardians gave their written consent to participate in the study.

Instruments: questionnaire and clinical evaluation

This cross-sectional investigation was conducted using a four section-questionnaire, which consisted of questions regarding medical and dental history, bruxism, tooth clenching, TMD, sleep disorders (e.g., cessation of breathing suggestive of sleep apnea, a delay of more than 30 min in falling asleep suggestive of insomnia), and daytime behaviors. The majority of the questions were of the dichotomous “yes” or “no” type. In selected cases with multiple variables, the data was reduced: “never” and “rarely” into “no”; “often” and “always” into “yes”. The entire questionnaire was in French. The sleep section was composed from a modified and translated version of the Pediatric Sleep Questionnaire (29) and the validated French version of the Pittsburg Sleep Quality Index (30). The parents or guardians present at the clinical examination were asked to complete the questionnaire with their children on their behalf.

An experienced orthodontist (AP), blind to the questionnaire answers, examined all subjects by performing a standard orthodontic clinical evaluation (31). The clinical examination consisted of an orthodontic evaluation of various standard dental, skeletal, functional and aesthetic factors. The facial evaluation included profile analysis (convex, straight or concave), frontal view for facial thirds analysis (brachyfacial, mesofacial or

dolicofacial) and mandibular plane angle visualisation (flat, normal, or steep). Asymmetries of the facial to dental midlines were noted. Tonsil size (normal or hypertrophy with greater than 50% obstruction), tongue size (small, normal, large, or scalloped), lateral mandibular movements (normal or limited), amount of overjet, amount of overbite and maximal mouth opening were also assessed. Palatal vault shape was noted as either deep, round, or flat. Finally, a visual clinical evaluation of the dental components of the malocclusion, molar and canine Angle classifications, and number and location of crossbites were charted (28).

Variables

The presence of SB was assessed with the question: "Does your child grind his/her teeth during sleep?" The presence of TC was assessed using the question: "Does your child clench his/her teeth during daytime?" Other oral parafunctions were also assessed using questions concerning lip and nail biting and gum chewing.

SB and wake-time TC were then analyzed in relation to demographic variables (age, gender and body mass index), craniofacial morphology, other orofacial habits, TMD signs and symptoms (e.g. temporomandibular joint clicking and locking, tooth wear, dental occlusion, jaw muscle fatigue, pain, headache), sleep complaints (e.g. poor sleep quality, frequent awakenings, daytime sleepiness, sleep disordered breathing, parasomnias), and daytime behaviors (e.g. lack of attention and organization, agitation) (Annex 1).

Data analyses

Based on the above-mentioned selected questions, the entire sample was divided into the following three groups: 1) control subjects (CTL), who did not report SB or TC or other oral parafunctions (such as lip and nail biting); 2) SB subjects (SB), who reported SB only; 3) TC subjects, who reported wake-time tooth clenching only. A fourth group was initially identified: the group of subjects reporting both SB and TC. However, due to the

small sample size and the absence of any statistical difference between this latter group (SB+TC) and SB or TC groups, it was omitted from the present study.

Statistical comparisons between groups were performed using Pearson Chi-square Test and Fisher's Exact Test. Binary Logistic Regression was performed in order to control for the age, gender and body mass index (BMI) factors; adjusted odds ratios (AOR), with the 95% confidence intervals (CI), were also calculated to assess the strength of the association. Independent variables with results $p<0.2$ from univariate analyses were incorporated into the logistic regression analysis. Statistical significance was assessed at $p\leq0.05$. Data analysis was performed using SPSS (SPSS Statistics, Version 17.0.0 for Macintosh, Chicago, Illinois).

Results

In the entire sample, 15% reported SB and 12.4% TC. The prevalence of other variables over the 604 subjects is shown in Table 3.3.1.

Bruxism (SB, TC), age, gender and body mass index

Following the distribution of data according to reports of SB or TC, three groups were identified: 1) the CTL group (220 subjects); 2) the SB group, (58 subjects) and 3) the TC group (42 subjects). Twenty-four subjects reported both SB and TC. However, significant differences for any of the variables evaluated were not evident when compared with SB or TC groups separately. It seems that the risks for TMD, sleep, or behavioral complaints are not increased when SB and TC coexist. For this reason and for the small sample size, data concerning the statistical comparison for this latter group of subjects has been omitted. The remainder of subjects did not meet the inclusion criteria of any of the groups.

Variables concerning medical and dental history did not statistically differ between groups (data not shown). Group comparisons for TMD, sleep and behavioral signs and symptoms are reported in the following paragraphs and tables.

A significant age difference was observed between groups. The mean age ± SD for the SB group was 12.0 ± 2.3; for the TC group 13.6 ± 2.4; and for the CTL group 12.2 ± 2.2 (overall ANOVA, p=0.001; SBvsCTL, p=0.5; SBvsTC, p=0.001; TCvsCTL, p<0.0001). Considering the age distribution between children (aged ≤ 12 years old) and adolescents (≥ 13 years old), the SB group was mainly composed of children (67.3%), while the TC group was predominantly adolescents (78.6%) (Pearson chi-square, p<0.0001). Control subjects were equally distributed between children and adolescents. No gender difference was observed between the three groups (p=0.5).

BMI was evaluated based on age- and sex-specific charts used to calculate BMI in pediatrics (32). Using percentiles, subjects were classified into four BMI categories (underweight, healthy weight, overweight, and obese) (33). The majority of the sample was in the healthy weight range (70.3% of CTL, 85.5% of SB and 83.3% of TC subjects). Nine CTL subjects and 1 SB subject were underweight, while 18 CTL, 1 SB and 3 TC subjects were obese. Due to the small numbers in certain categories, we regrouped the BMI variable into 2 categories: normal weight (healthy weight) and overweight (overweight + obese). No difference was observed between the three groups (p=0.09; Pearson chi-square).

Craniofacial characteristics

At the clinical examination, no difference between the three groups was observed for the following variables: palatal morphology, tongue size and tonsil size.

SB subjects were assessed to be brachyfacial type in 28.1% of the group and dental class II in 60.3%. These prevalence values were significantly higher than in control subjects (p=0.001 and 0.01 respectively; Table 3.3.2). Interestingly, SB subjects showed a lower prevalence of posterior crossbite compared to controls (15.5% vs 33.8% respectively;

p=0.006). No difference was observed between TC group and controls for facial morphology, dental class and crossbite prevalence (Table 3.3.2). Overall, there were no differences between groups for maximal mouth opening (mean 50.3 mm; sd 6.2). However, limited lateral movements were observed in TC subjects compared to control and SB subjects (p=0.005 and 0.02 respectively).

TMD signs and symptoms

SB and TC subjects showed no statistical difference for other reported oral parafunctions such as: biting lips (26.3% for the SB group; 36.6% for the TC group), biting nails (47.4% for the SB group; 51.2 % for the TC group) and biting pencils or pens (20.7% for the SB group; 28.6% for the TC group). Control subjects were selected based on the absence of these oral parafunctions.

The prevalence of tooth wear complaints was significantly higher in SB and TC subjects compared to control subjects (14% for SB, 9.8% for TC and 1.8% for CTL subjects). However, after controlling for the age factor, only SB subjects seem to be more at risk of reporting tooth wear (AOR 8.8). Complaints such as TMJ clicking, uncomfortable dental occlusion, jaw muscle fatigue and difficulties in yawning were significantly more frequent in SB and TC subjects than control subjects. Moreover, 12% of SB subjects reported experiencing frequent headaches in comparison to 4.1 % of controls (p=0.05) (Table 3.3.3).

Sleep complaints

Both SB and TC subjects reported more sleep problems than controls (Table 3.3.4). More specifically, the SB group reported significantly higher frequencies of daytime sleepiness, feeling unrefreshed in the morning, difficulties waking up in the morning, and failing to fall asleep within 30 min at least 3 times/week (suggestive of insomnia). The SB group also showed a higher prevalence of loud breathing during sleep compared to controls

(p=0.009). The TC group reported experiencing daytime sleepiness, feeling unrefreshed in the morning, and frequent awakenings more frequently than controls. Over 57% of the TC group reported having a dry mouth on awakening, suggestive of oral breathing during sleep (p=0.001). Other parasomnias, such as nightmares and nocturnal enuresis, and sleep disordered breathing, such as snoring and sleep apnea (cessation of breathing reported during sleep), did not differ between groups (Table 3.3.4).

Behavioral complaints

Several behavioral complaints were significantly higher in SB and TC groups compared to controls. SB and TC subjects were described as not listening when spoken to, as being easily distracted and as interrupting or intruding other people's conversations. No difference was observed between SB and TC subjects (Table 3.3.5).

Odds Ratio

Adjusted Odds Ratio (AOR) was calculated for each group comparison. When compared to controls, either the bruxism groups (SB and TC) revealed that AOR were significantly higher for the following reported complaints: 1) orofacial: tooth wear, uncomfortable occlusion, jaw muscle fatigue, difficulties in yawning; 2) sleep-related: daytime sleepiness, feeling unrefreshed in the morning, difficulties awakening in the morning; 3) behavioral: easily distracted by external stimuli and prone to interrupting others (Table 3.3.6). The comparison between the SB group and the TC group revealed only a few variables with high and significant AOR: mouth breathing (AOR=4.2; CI=1.5-11.2; p=0.004), feeling unrefreshed in the morning (trend; p=0.06), difficulty awakening in the morning (AOR=2.6; CI=1-6.9; p=0.04) and feeling hot during sleep (AOR=5.4; CI=1.7-17); p=0.004). All these findings were higher in the TC subjects compared with the SB subjects.

Discussion

The present study investigated the association between wake-time and sleep-related bruxism with TMD signs and symptoms, sleep problems and behavioral complaints in a pediatric population (7-17 years old) seeking orthodontic treatment.

The prevalence of SB and TC in our sample reflects previous reports in literature concerning both general and orthodontic populations (21, 34). Both SB and wake-time tooth clenching are common in pediatrics. However, in this study these oral parafunctions appeared to be two separate entities observed in different populations; SB was more prevalent in children ≤12 years old, while wake-time TC in adolescence ≥ 13 years old. The reduction in SB prevalence with aging has already been reported in the literature (4). In the present study, the lower SB frequency in older subjects may have been related to the fact that parents visit their children's bedroom less often after the age of twelve, which may influence SB reports. In any case, it has been demonstrated that more than 86% of adults with SB report having been bruxers in childhood (14). A genetic predisposition might explain the onset of SB in early ages and its probable lifelong persistency. Other environmental and development factors, however, may also influence the occurrence of SB and its consequences on the craniofacial apparatus. In contrast, wake-time TC seems to be more prevalent in adolescents and young adults, the same population in which a peak in TMD problems has been observed (35, 36). Longitudinal studies in both SB and TC samples may help clarify these issues.

Tooth wear is widely reported in literature as being the distinctive dental sign of bruxism (both awake and during sleep). Although tooth wear cannot be used as an absolute diagnostic criteria for SB (37), SB results as a significant risk factor for tooth wear in children and adolescents (AOR 8.8). However, in this study tooth wear was established only by questionnaire. Thus, the reliability of the finding, although significant, should be evaluated with caution.

SB subjects also seem to be more at risk of experiencing jaw muscle fatigue, difficulties in opening the jaw wide (i.e. yawning), and perceiving an uncomfortable dental

occlusion. Complaints concerning chewing performance and occlusal bite stability are frequently reported by TMD patients (38). Several studies have previously investigated SB as a sign/cause of TMD in pediatric populations (39). The present findings seem to support a potential role for SB mostly in the musculoskeletal/myogenous components of TMDs (muscle soreness or fatigue).

Interestingly, SB subjects had a lower prevalence of posterior crossbite compared to controls. Dental crossbite, especially if unilateral and posterior, has been considered as a potential risk factor for the development of TMD in children and adolescents (34), although its causal relationship with TMD remains highly debated, with some evidence suggesting no association (40, 41). The present results suggest that SB and crossbite are likely to be non-related risk factors for TMD signs and symptoms.

Subjects who reported TC during wake-time appeared to be more at risk of experiencing TMJ clicking, locking, jaw muscle fatigue, uncomfortable dental occlusion and difficulties in yawning. Moreover, they reported problems during sleep due to some form of pain. The presence of these TMD signs and symptoms suggests that wake-time TC is a harmful oral activity for the craniomandibular apparatus and may support its role as an etiological or contributing factor to the development of TMD (9, 42).

SB subjects reported frequent headaches three times more than controls with an AOR of 4.3. The association between SB and headache has already been observed in both adults and children (43, 44). Moreover, it has been shown in literature that children with headaches frequently have concomitant sleep problems, such as SDB and SB, and a higher incidence of TMD (45, 46). In the present study, information on headache characteristics (e.g. pain intensity, pain quality, time of onset, and duration) was not collected, thus speculation on the specific types of headaches (e.g. tension type) and potential causes cannot be made in this study population.

Both SB and TC groups reported more sleep complaints compared with the control group. Although the overall sleep quality was not judged as poor by either group, the feeling of non-refreshing sleep in the morning, daytime sleepiness, frequent awakenings

during sleep and a long sleep latency (>30 minutes to fall asleep), were frequently reported. These symptoms may suggest the presence of sleep disorders, especially of SDB. However, no significant association was found between SB and snoring or sleep apnea complaint-reports. This may be due to the small sample size and to the limits of the methodology used. Parents may not be aware of respiratory pauses during sleep, though they may hear snoring or tooth grinding sounds. Although snoring was reported with similar prevalence in the three groups, 23.3% of subjects in the SB group reported loud breathing during sleep (significantly higher than controls; AOR 3.1). These subjects may be at risk of developing habitual snoring or respiratory disturbances in the future, and predisposing or aggravating factors may be already present (47). However, this remains speculative since specific evaluations of nasal cavities or oropharyngeal structures were not performed (e.g. nasal fibroscopy). Thus, no conclusion can be drawn and further studies are recommended.

SDB signs and symptoms such as mouth breathing, snoring and daytime sleepiness, have been also related to long-face morphology (dolichofacial trait), maxillary transverse deficiency (narrow palate), and retrognathia (48, 49). In the study sample, 60.3 % of SB subjects presented a dental class II. However, they also showed a higher prevalence of brachyfacial phenotype when compared to controls. The retrognathic profile may be seen as a predisposing factor for SDB, while the brachyfacial phenotype (short and broad face) is known to be the typical characteristic face of a bruxer with hypertrophic masseter muscles. Although an association has been shown in the literature, there is not enough evidence to support a cause-effect relationship between specific craniofacial morphology and SDB. Whether the SDB is caused by abnormalities of the craniofacial structures, or the abnormal craniofacial development is due to functional limitations in the respiratory traits, remains to be established.

As reported in the literature, the present findings confirm the association between bruxism and some behavioral habits/complaints. In particular, both SB and TC subjects seem to be easily distracted and interrupt others more than twice as controls. These behaviors, suggestive of ADHD-like behaviors, may be the manifestation of specific

psychosocial factors or personality traits that have been suggested to be related to bruxism in children and adolescents. For example, the prevalence of thought disorders, conduct disorders and antisocial disorders has been found to be higher in bruxers compared to non-bruxers (50). Other characteristics, such as neuroticism, perfectionism, aggressiveness, higher sensitivity to stress and maladaptative coping strategies seem to be related to an increased risk of developing bruxism (51, 52).

The present study has some limitations. First of all, all subjects were seeking orthodontic treatment at the Orthodontic Clinic of the University of Montreal. Therefore, the present findings should be extrapolated with caution since the external validity is not yet established. Furthermore, the methodology is limited in its scope: intra-examiner error testing was not performed. The reliability of the findings is based on the parents and children reports. The eventual presence of false positive and false negative cases must be considered in all three groups. Finally, the small size of the SB and TC groups analyzed should be taken into account. Due to the limited sample studied, it is possible that existing differences between groups were not detected (type II errors). Based on the results of the present study, a post-hoc sample size estimation performed on the variable “sleep discomfort due to pain” revealed that over 1000 controls and 300 bruxers would be needed to have an 80% power to detect a difference of 4.2% between groups (4.6% of CTL and 8.8% of SB). For practical reasons, such sample sizes would be difficult to reach.

In conclusion, the present study supports, at least in a pediatric population seeking orthodontic treatment, that sleep bruxism and wake-time bruxism are two different conditions with little overlap. Whether this is due to age and developmental maturation factors is unknown at this time. Further research and clinical trials are required to better understand and define the relationship between oral parafunctions and TMD, SDB, and behavioral signs and symptoms. However, in each group, subjects reporting the presence of specific orofacial, sleep or behavioral complaints may be at risk for developing further health problems. It is therefore mandatory that dentists investigate children and adolescents with sleep bruxism and wake-time tooth clenching in the presence of sleep or behavioral

complaints or reports. The patient at risk should be referred to a specialist (i.e., orthodontist, sleep medicine expert, psychologist) in order to assess the presence of co-morbidity, to perform an early diagnosis (if indicated using polysomnographic tools), and to identify the best therapeutic approach for symptom management.

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Conflicts of Interest - G. Lavigne was an invited speaker to the congress by UCB, Belgium; he is a consultant and lecturer for Pfizer (Wyeth) Canada; he receives free or at reduced costs oral appliances, such as ORM-Narval, France-Canada, Silencer, Canada and Klearway, Canada, used for research purposes on sleep-disordered breathing. The other authors have indicated no financial conflicts of interest.

Table 3.3.1 Prevalence of variables in the study population (n=604).

Prevalence	% (95% CI)
Sleep bruxism	15 (12 – 18)
Wake-time bruxism (tooth clenching)	12.4 (9.6 – 15.2)
Tooth wear	5.3 (3.5 – 7.1)
TMJ clicking	2.8 (1.5 – 4.2)
Jaw muscle fatigue	5.1 (3.4 – 6.9)
Morning TMJ pain	4.8 (3.1 – 6.5)
Headache	5.6 (3.8 – 7.5)
Mouth breathing	34 (30.2 – 37.8)
Loud breathing (during sleep)	17.7 (14.7 – 20.8)
Snoring	25.6 (22.1 – 29.1)
Sleep apnea	1.8 (0.8 – 2.9)
Daytime sleepiness	7.3 (5.2 – 9.4)
Feeling unrefreshed in the morning	20.7 (17.9 – 23.3)
Easily distracted	26.7 (23.2 – 30.3)
Agitated	7.7 (5.5 – 9.8)
Interrupts or intrudes on others	11.8 (9.2 – 14.4)

Values are given as percentage (95% CI).

TMJ stands for temporomandibular joint.

Table 3.3.2 Craniofacial morphology and dental characteristics for control (CTL), sleep bruxism (SB) and wake-time tooth clenching (TC) subjects.

Craniofacial morphology variable	CTL (group 1) (%)	SB (group 2) (%)	TC (group 3) (%)	*P*-value*		
				1 vs. 2	1 vs. 3	2 vs. 3
Facial type						
Brachyfacial	9.7	28.1	12.2	0.001	0.65	0.16
Mesofacial	75.6	63.2	78			
Dolichofacial	14.7	8.8	9.8			
Dental class						
I	56.4	36.2	54.8	0.01	0.42	0.04
II	39.1	60.3	35.7			
III	4.5	3.4	9.5			
Posterior crossbite	33.8	15.5	23.8	0.006	0.28	0.31
Limited lateral movements	2.8	1.8	14.6	1	0.005	0.02
Hypertrophic tonsils	21.6	10.3	9.5	0.06	0.09	1

All variables were assessed by an experienced orthodontist during the clinical examination.
*Determined using the chi-square test.

Table 3.3.3 Temporomandibular (TMD) signs and symptoms, oral habits and parafunctions for control (CTL), sleep bruxism (SB) and wake-time tooth clenching (TC) subjects.

TMD Problems*	CTL (group 1) (%)	SB (group 2) (%)	TC (group 3) (%)	*P*-value†		
				1 vs. 2	1 vs. 3	2 vs. 3
Tooth wear	1.8	14	9.8	0.001	0.02	0.75
Reported TMJ clicking	2.3	5.2	14.3	0.4	0.003	0.2
Reported TMJ locking	0.5	3.4	7.3	0.1	0.01	0.6
Uncomfortable dental occlusion	17.5	32.8	35.7	0.02	0.01	0.8
Jaw muscle fatigue	1.4	10.3	16.7	0.003	< 0.0001	0.4
Frequent headache	4.1	12.1	4.8	0.05	0.7	0.3
Difficulties in yawning	1.9	8.8	17.1	0.02	< 0.0001	0.2
Gum chewing	75.5	89.7	83.3	0.02	0.3	0.4
Mouth breathing	24.2	31	66.7	0.3	< 0.0001	0.001

*Temporomandibular disorder (TMD) signs and symptoms, oral habits, and parafunctions.
†Determined using Fisher's exact test.
TMJ, temporomandibular joint.

Table 3.3.4 Sleep complaints for control (CTL), sleep bruxism (SB) and wake-time tooth clenching (TC) subjects.

Sleep complaints	CTL (group 1) (%)	SB (group 2) (%)	TC (group 3) (%)	*P*-value*		
				1 vs. 2	1 vs. 3	2 vs. 3
Loud breathing (during sleep)	9.2	23.2	16.7	0.009	0.2	0.5
Snoring	19.3	29.3	26.2	0.1	0.3	0.8
Sleep apnea	0.9	0.0	4.8	1	0.1	0.2
Dry mouth on awakening	28.3	39.7	57.1	0.1	0.001	0.1
Daytime sleepiness	1.8	7.1	19.0	0.05	< 0.0001	0.1
Feeling unrefreshed in the morning	10.0	22.4	52.4	0.02	< 0.0001	0.003
Difficulty waking up in the morning	10.5	27.6	50.0	0.002	< 0.0001	0.03
Unable to fall asleep within 30 min on more than three occasions per week	37.6	52.6	54.8	0.05	0.04	0.8
Frequent awakenings from sleep	27.6	35.1	54.8	0.3	0.001	0.06
Poor sleep quality	2.3	1.7	7.1	1	0.1	0.3
Sleep discomfort because of pain	4.6	8.8	14.3	0.2	0.03	0.5
Sleep discomfort because of feeling hot	12.9	12.3	42.9	1	< 0.0001	0.001
Nightmares	16.1	24.6	16.7	0.2	1	0.45
Nocturnal enuresis	5.5	0.0	4.9	0.08	1	0.2

*Determined using Fisher's exact test.

Table 3.3.5 Behavioral complaints for control (CTL), sleep bruxism (SB) and wake-time tooth clenching (TC) subjects.

Behavioral complaints	CTL (group 1) (%)	SB (group 2) (%)	TC (group 3) (%)	*P*-value*		
				1 vs. 2	1 vs. 3	2 vs. 3
Does not seem to listen when spoken to	9.5	19	23.8	0.06	0.02	0.6
Difficulties in organizing tasks and activities	10.5	21.1	14.3	0.04	0.4	0.4
Difficulties in maintaining enthusiasm throughout an activity	12	20.7	24.4	0.1	0.05	0.8
Easily distracted by external stimuli	16.8	37.9	33.3	0.001	0.02	0.7
Fidgets with hands or feet	16	24.1	38.1	0.2	0.002	0.2
Agitated	6.4	6.9	11.9	1	0.2	0.5
Interrupts or intrudes on others	6.4	15.5	19	0.03	0.01	0.8

*Determined using Fisher's exact test.

Table 3.3.6 Dental, temporomandibular disorders (TMD), sleep and behavioral complaints.

	SB vs. CTL		TC vs. CTL	
Complaint	AOR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Dental class II	2.0 (1.1–3.8)	0.02	NS	NS
Posterior crossbite	0.4 (0.2–0.9)	0.02	NS	NS
Limited lateral movements	NS	NS	5.2 (1.5–18.3)	0.01
Tooth wear	8.8 (2.5–30.8)	0.001	3.7 (0.8–16.1)	0.08
Reported TMJ clicking	NS	NS	5.0 (1.4–18.3)	0.01
Uncomfortable dental occlusion	2.5 (1.2–5)*	0.01	2.2 (1–4.7)*	0.04
Jaw muscle fatigue	10.5 (2.4–45.2)	0.002	13.5 (3–60)	0.001
Frequent headache	4.3 (1.4–12.9)*	0.009	NS	NS
Difficulties in yawning	2.2 (1.3–3.6)*	0.003	10.9 (2.5–47.5)*	0.001
Mouth breathing	NS	NS	5.6 (2.6–11.9)*	<0.0001
Loud breathing (during sleep)	3.1 (1.3–7.2)	0.009	NS	NS
Dry mouth on awakening	NS	NS	3.1 (1.5–6.3)	0.001
Daytime sleepiness	7.4 (1.6–33.6)	0.009	9.1 (2.5–33.6)	0.001
Feeling unrefreshed in the morning	3.4 (1.5–7.7)†	0.004	7.4 (3.3–16.4)†	<0.0001
Difficulty wakening in the morning	3.3 (1.5–7.2)	0.002	7.3 (3.4–15.9)	<0.0001
Unable to fall asleep within 30 min on more than three occasions each week	1.8 (1–3.4)†	0.06	1.6 (0.8–3.1)†	0.2
Frequent awakening from sleep	NS	NS	2.5 (1.2–5)	0.01
Sleep discomfort because of feeling hot	NS	NS	5.0 (2.3–11)	<0.001
Does not seem to listen when spoken to	NS	NS	3.2 (1.3–7.9)*	0.01
Easily distracted by external stimuli	2.8 (1.4–5.6)‡	0.002	3.3 (1.4–7.5)‡	0.004
Fidgets with hands or feet	NS	NS	3.4 (1.5–7.4)*	0.002
Interrupts or intrudes on others	2.4 (0.9–6.5)	0.08	5.1 (1.8–14.7)	0.003

The results are presented as adjusted OR (AOR) with the 95% CI and the *P*-value (binary logistic regression) for the sleep bruxism (SB) group vs. the control (CTL) group, and for the wake-time tooth-clenching (TC) group vs. the CTL group.
All AOR values are adjusted for the age factor.
*AOR adjusted for age and gender factors.
†AOR adjusted for age and body mass index factors.
‡AOR adjusted for age, gender and body mass index factors.
TMJ, temporomandibular joint; NS, non-significant variable.

References:

1. Petit D, Touchette E, Tremblay RE, Boivin M, Montplaisir J. *Dyssomnias and parasomnias in early childhood*. Pediatrics 2007;119:e1016-1025.

2. Simola P, Niskakangas M, Liukkonen K, Virkkula P, Pitkaranta A, Kirjavainen T, et al. *Sleep problems and daytime tiredness in Finnish preschool-aged children-a community survey*. Child Care Health Dev 2010;36:805-811.

3. Cheifetz AT, Osganian SK, Allred EN, Needleman HL. *Prevalence of bruxism and associated correlates in children as reported by parents*. J Dent Child (Chic) 2005;72:67-73.

4. Lavigne G, Manzini C, Huynh NT. *Sleep Bruxism* In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:1129-1139.

5. Glaros AG, Tabacchi KN, Glass EG. *Effect of parafunctional clenching on TMD pain*. J Orofac Pain 1998;12:145-152.

6. Gomez FM, Ortega JE, Horrillo I, Meana JJ. *Relationship between non-functional masticatory activity and central dopamine in stressed rats*. J Oral Rehabil 2010;37:827-833.

7. Kampe T, Edman G, Bader G, Tagdae T, Karlsson S. *Personality traits in a group of subjects with long-standing bruxing behaviour*. J Oral Rehabil 1997;24:588-593.

8. Svensson P, Burgaard A, Schlosser S. *Fatigue and pain in human jaw muscles during a sustained, low-intensity clenching task*. Arch Oral Biol 2001;46:773-777.

9. Farella M, Soneda K, Vilmann A, Thomsen CE, Bakke M. *Jaw muscle soreness after tooth-clenching depends on force level*. J Dent Res 2010;89:717-721.

10. Lund JP, Donga R, Widmer CG, Stohler CS. *The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity*. Can J Physiol Pharmacol 1991;69:683-694.

11. AASM. *Sleep Related Bruxism*. American Academy of Sleep Medicine (AASM) eds ICSD-2 International classification of sleep disorders, 2nd ed:Diagnosis and coding manual Westchester, Illinois 2005:189-192.

12. *The glossary of prosthodontic terms*. J Prosthet Dent 2005;94:10-92.

13. Lavigne GJ, Huynh N, Kato T, Okura K, Adachi K, Yao D, et al. *Genesis of sleep bruxism: motor and autonomic-cardiac interactions*. Arch Oral Biol 2007;52:381-384.

14. Hublin C, Kaprio J. *Genetic aspects and genetic epidemiology of parasomnias*. Sleep Med Rev 2003;7:413-421.

15. Manfredini D, Lobbezoo F. *Role of psychosocial factors in the etiology of bruxism*. J Orofac Pain 2009;23:153-166.

16. Bloomfield ER, Shatkin JP. *Parasomnias and movement disorders in children and adolescents*. Child Adolesc Psychiatr Clin N Am 2009;18:947-965.

17. Silvestri R, Gagliano A, Arico I, Calarese T, Cedro C, Bruni O, et al. *Sleep disorders in children with Attention-Deficit/Hyperactivity Disorder (ADHD) recorded overnight by video-polysomnography*. Sleep Med 2009;10:1132-1138.

18. Herrera M, Valencia I, Grant M, Metroka D, Chialastri A, Kothare SV. *Bruxism in children: effect on sleep architecture and daytime cognitive performance and behavior*. Sleep 2006;29:1143-1148.

19. Sheldon SH. *Obstructive Sleep Apnea and Bruxism in Children*. In: Clinics SM (ed). Dentistry's Role in Sleep Medicine, 2010:163-168.

20. Sjoholm TT, Lowe AA, Miyamoto K, Fleetham JA, Ryan CF. *Sleep bruxism in patients with sleep-disordered breathing*. Arch Oral Biol 2000;45:889-896.

21. Ohayon MM, Li KK, Guilleminault C. *Risk factors for sleep bruxism in the general population*. Chest 2001;119:53-61.

22. DiFrancesco RC, Junqueira PA, Trezza PM, de Faria ME, Frizzarini R, Zerati FE. *Improvement of bruxism after T & A surgery*. Int J Pediatr Otorhinolaryngol 2004;68:441-445.

23. Eftekharian A, Raad N, Gholami-Ghasri N. *Bruxism and adenotonsillectomy*. Int J Pediatr Otorhinolaryngol 2008;72:509-511.

24. Lam DJ, Jensen CC, Mueller BA, Starr JR, Cunningham ML, Weaver EM. *Pediatric sleep apnea and craniofacial anomalies: a population-based case-control study*. Laryngoscope 2010;120:2098-2105.

25. Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Spruyt K. *Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea*. Pediatrics 2010;126:e1161-1167.

26. Khoury S, Rouleau GA, Rompre PH, Mayer P, Montplaisir JY, Lavigne GJ. *A significant increase in breathing amplitude precedes sleep bruxism*. Chest 2008;134:332-337.

27. Koyano K, Tsukiyama Y, Ichiki R, Kuwata T. *Assessment of bruxism in the clinic*. J Oral Rehabil 2008;35:495-508.

28. Huynh N, Morton P, Rompré PH, Papadakis A, Remise A. *Associations between sleep-disordered breathing symptoms and facial/dental morphometry from screening exams*. American Journal of Orthodontics & Dentofacial Orthopedics 2011;in press.

29. Chervin RD, Hedger K, Dillon JE, Pituch KJ. *Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems*. Sleep Med 2000;1:21-32.

30. Blais FC, Gendron L, Mimeault V, Morin CM. *Evaluation of insomnia: validity of 3 questionnaires*. Encephale 1997;23:447-453.

31. Proffit WR, Fields HW, Sarver DM. *Orthodontic diagnosis: the development of a problem list* In: Mosby E (ed). Contemporary Orthodontics. St Louis, Missouri, 2007:167-233.

32. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. *CDC growth charts: United States*. Adv Data 2000;314:1-27.

33. Barlow SE. *Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report*. Pediatrics 2007;120 Suppl 4:S164-192.

34. Tecco S, Festa F. *Prevalence of Signs and Symptoms of Temporomandibular Disorders in Children and Adolescents with and without Crossbites*. World J Orthod 2010;11:37-42.

35. Magnusson T, Egermark I, Carlsson GE. *A longitudinal epidemiologic study of signs and symptoms of temporomandibular disorders from 15 to 35 years of age*. J Orofac Pain 2000;14:310-319.

36. Kohler AA, Helkimo AN, Magnusson T, Hugoson A. *Prevalence of symptoms and signs indicative of temporomandibular disorders in children and adolescents. A cross-sectional epidemiological investigation covering two decades*. Eur Arch Paediatr Dent 2009;10 Suppl 1:16-25.

37. Abe S, Yamaguchi T, Rompre PH, De Grandmont P, Chen YJ, Lavigne GJ. *Tooth wear in young subjects: a discriminator between sleep bruxers and controls?* Int J Prosthodont 2009;22:342-350.

38. Michelotti A, Iodice G. *The role of orthodontics in temporomandibular disorders*. J Oral Rehabil 2010;37:411-429.

39. Pereira LJ, Pereira-Cenci T, Del Bel Cury AA, Pereira SM, Pereira AC, Ambosano GM, et al. *Risk indicators of temporomandibular disorder incidences in early adolescence*. Pediatr Dent 2010;32:324-328.

40. Farella M, Michelotti A, Iodice G, Milani S, Martina R. *Unilateral posterior crossbite is not associated with TMJ clicking in young adolescents*. J Dent Res 2007;86:137-141.

41. Restrepo CC, Sforza C, Colombo A, Pelaez-Vargas A, Ferrario VF. *Palate morphology of bruxist children with mixed dentition. A pilot study*. J Oral Rehabil 2008;35:353-360.

42. Michelotti A, Cioffi I, Festa P, Scala G, Farella M. *Oral parafunctions as risk factors for diagnostic TMD subgroups*. J Oral Rehabil 2010;37:157-162.

43. Bruni O, Fabrizi P, Ottaviano S, Cortesi F, Giannotti F, Guidetti V. *Prevalence of sleep disorders in childhood and adolescence with headache: a case-control study*. Cephalalgia 1997;17:492-498.

44. Vendrame M, Kaleyias J, Valencia I, Legido A, Kothare SV. *Polysomnographic findings in children with headaches*. Pediatr Neurol 2008;39:6-11.

45. Isik U, Ersu RH, Ay P, Save D, Arman AR, Karakoc F, et al. *Prevalence of headache and its association with sleep disorders in children*. Pediatr Neurol 2007;36:146-151.

46. Liljestrom MR, Le Bell Y, Anttila P, Aromaa M, Jamsa T, Metsahonkala L, et al. *Headache children with temporomandibular disorders have several types of pain and other symptoms*. Cephalalgia 2005;25:1054-1060.

47. Gozal D, O'Brien LM. *Snoring and obstructive sleep apnoea in children: why should we treat?* Paediatr Respir Rev 2004;5 Suppl A:S371-376.

48. Marino A, Malagnino I, Ranieri R, Villa MP, Malagola C. *Craniofacial morphology in preschool children with obstructive sleep apnoea syndrome*. Eur J Paediatr Dent 2009;10:181-184.

49. Pirila-Parkkinen K, Pirttiniemi P, Nieminen P, Tolonen U, Pelttari U, Lopponen H. *Dental arch morphology in children with sleep-disordered breathing*. Eur J Orthod 2009;31:160-167.

50. Katayoun E, Sima F, Naser V, Anahita D. *Study of the relationship of psychosocial disorders to bruxism in adolescents*. J Indian Soc Pedod Prev Dent 2008;26 Suppl 3:S91-97.

51. Serra-Negra JM, Ramos-Jorge ML, Flores-Mendoza CE, Paiva SM, Pordeus IA. *Influence of psychosocial factors on the development of sleep bruxism among children*. Int J Paediatr Dent 2009;19:309-317.

52. Restrepo CC, Vasquez LM, Alvarez M, Valencia I. *Personality traits and temporomandibular disorders in a group of children with bruxing behaviour*. J Oral Rehabil 2008;35:585-593.

Annex 1. The questionnaire used in the study.

QUESTIONNAIRE MÉDICAL ET DENTAIRE

Notez que le genre masculin est utilisé uniquement pour alléger le texte et inclut le féminin.

Nom : _____ Prénom : _____ Sexe : F ☐ - M ☐

Date de naissance : jour ____ mois ____ année ____ Âge : ____

Histoire médicale :	**Oui**	**Non**
Actuellement sous les soins d'un médecin?	☐	☐
Si oui, la raison :		
Prend des médicaments régulièrement?	☐	☐
Si oui, lesquels?		
Problème de saignement prolongé?	☐	☐
Anémie?	☐	☐
Haute/basse pression?	☐	☐
Rhumes fréquents ou sinusites?	☐	☐
Problèmes pulmonaires?	☐	☐
Troubles digestifs?	☐	☐
Diabète?	☐	☐
Troubles thyroïdiens?	☐	☐
Arthrite?	☐	☐
Épilepsie?	☐	☐
Troubles nerveux?	☐	☐
Maux de tête fréquents?	☐	☐
Perte de conscience?	☐	☐
Maux ou limitation de mouvement au cou ou aux épaules?	☐	☐
Maux d'oreilles?	☐	☐
Chirurgie pour enlever les amygdales ou adénoïdes?	☐	☐
Déjà eu radiothérapie (tumeur)?	☐	☐
Allergies?	☐	☐
Fièvre des foins	☐	☐
Asthme	☐	☐
Poussière	☐	☐
Animaux	☐	☐
Autres	☐	☐

Histoire dentaire : Date du dernier examen dentaire : ____ mois ____ année		
Le patient a déjà eu :	**Oui**	**Non**
Traitements dentaires (gencives, traitement de canal, obturations)?	☐	☐
Traitements orthodontiques?	☐	☐
Extractions?	☐	☐
Respire surtout : Par la bouche?	☐	☐
Par le nez?	☐	☐
Moitié par la bouche, moitié par le nez?	☐	☐
Traumatisme : Sur les dents?	☐	☐
À la tête ou au cou?	☐	☐
Si oui, quel genre :		
Douleur : Aux gencives?	☐	☐
Aux dents?	☐	☐
Déjà sucé son pouce/ses doigts?	☐	☐
Suce encore son pouce/ses doigts?	☐	☐
Troubles de la langue?	☐	☐
Troubles de la parole?	☐	☐
À déjà vu un orthophoniste?	☐	☐
Le patient joue un instrument de musique? Si oui, lequel?	☐	☐

Habitudes :	**Oui**	**Non**
1. Est-ce que l'articulation de la mâchoire du patient craque (fait des bruits secs) en ouvrant ou en fermant ou en mastiquant?	☐	☐
2. Est-ce que l'articulation de la mâchoire du patient fait un bruit de grattement (frottement) en ouvrant ou en fermant ou en mastiquant?	☐	☐
3. Est-ce que la mâchoire du patient se bloque de sorte que l'ouverture normale n'est pas possible?	☐	☐
Si oui, est-ce que c'est possible de la débloquer toute seul?	☐	☐
Si non, combien de temps le blocage dure généralement?		
4. Est-ce que la mâchoire du patient bloque de sorte que la fermeture normale n'est pas possible?	☐	☐

5. Est-ce que le patient mastique ou suce :	**Jamais ou presque**	**Parfois**	**Souvent**	**Toujours ou presque**
Ses lèvres, sa langue ou ses joues?	☐	☐	☐	☐
Ses ongles?	☐	☐	☐	☐
De la gomme à mâcher?	☐	☐	☐	☐
Un crayon ou un stylo?	☐	☐	☐	☐

6. Est-ce que le patient serre les dents?	**Oui**	**Non**
	☐	☐

	Jamais ou presque	**Parfois**	**Souvent**	**Toujours ou presque**
Si oui,	☐	☐	☐	☐
Pendant la journée?	☐	☐	☐	☐
Pendant la nuit?	☐	☐	☐	☐

7. Est-ce que le patient grince des dents?	**Oui**	**Non**
	☐	☐

	Jamais ou presque	**Parfois**	**Souvent**	**Toujours ou presque**
Si oui,	☐	☐	☐	☐
Pendant la journée?	☐	☐	☐	☐
Pendant la nuit?	☐	☐	☐	☐
Est-ce que cela le dérange?	☐	☐	☐	☐
Si oui, pourquoi?				

	Oui	**Non**
8. Est-ce que ses dents sont usées?	☐	☐
9. Est-ce que le patient a déjà brisé des plombages ou couronnes?	☐	☐
10. Est-ce que la façon dont les dents ferment est inconfortable?	☐	☐

	Sur le ventre	**Sur le dos**	**Sur le côté**	**Variable ou ne sais pas**
11. En général, quelle est sa posture lors du sommeil?	☐	☐	☐	☐

	Jamais ou presque	**Parfois**	**Souvent**	**Toujours ou presque**
12. Est-ce que sa mâchoire est endolorie ou raide en se réveillant le matin?	☐	☐	☐	☐

13. Est-ce que le patient ressent de la fatigue au niveau des muscles du visage ou de la mastication?	**Oui**	**Non**
	☐	☐

	Jamais ou presque	**Parfois**	**Souvent**	**Toujours ou presque**
Lors de son réveil le matin?	☐	☐	☐	☐
Pendant la journée?	☐	☐	☐	☐
Pendant la nuit?	☐	☐	☐	☐
	Augmente	**Diminue**	**Stable**	**Variable**
Comment cette fatigue varie-t-elle?	☐	☐	☐	☐

14. Au cours du **dernier mois**, indiquez jusqu'à quel point son problème de mâchoire rend difficile :	**Pas du tout**	**Un peu**	**Modérément**	**Beaucoup**	**Extrêmement**
Mastiquer	☐	☐	☐	☐	☐
Boire	☐	☐	☐	☐	☐
Exercices physiques	☐	☐	☐	☐	☐
Manger des aliments durs	☐	☐	☐	☐	☐
Manger des aliments mous	☐	☐	☐	☐	☐
La digestion	☐	☐	☐	☐	☐
Nettoyer les dents	☐	☐	☐	☐	☐
Bâiller	☐	☐	☐	☐	☐
Avaler	☐	☐	☐	☐	☐
Parler	☐	☐	☐	☐	☐

Sommeil :	**Oui**	**Non**
1. Durant son sommeil, est-ce que le patient :		
Ronfle plus de la moitié du temps?	☐	☐
Ronfle toujours?	☐	☐
Ronfle bruyamment?	☐	☐
Respire fort ou bruyamment?	☐	☐
A des problèmes ou de la difficulté à respirer?	☐	☐
2. Avez-vous déjà vu le patient :		
Arrêter de respirer durant la nuit?	☐	☐
3. Est-ce que le patient :		
A tendance à respirer par la bouche durant le jour?	☐	☐
Se réveille avec la bouche sèche?	☐	☐
Mouille son lit occasionnellement?	☐	☐
4. Est-ce que le patient :		
Se réveille avec un sentiment de ne pas être reposé?	☐	☐
A un problème de somnolence durant le jour?	☐	☐
Est-ce qu'un professeur ou une autre personne vous a rapporté que le patient somnole durant le jour?	☐	☐
Est difficile à réveiller le matin?	☐	☐
Se réveille le matin avec des maux de tête?	☐	☐
Grandit de façon normale depuis sa naissance?	☐	☐
Est obèse?	☐	☐
5. Souvent, le patient :		
Ne semble pas écouter lorsqu'on lui parle directement.	☐	☐
A de la difficulté à organiser des tâches et des activités.	☐	☐
Est facilement distrait par des stimulis externes.	☐	☐
Gigote ses mains ou ses pieds ou se tortille lorsqu'il est assis.	☐	☐
Ne reste pas en place ou est agité.	☐	☐
Interrompt ou est intrusif avec les autres (exemple : se mêle d'une conversation ou d'un jeux sans y être invité)	☐	☐
6. À l'école, le patient :		
Réussit bien?	☐	☐

Qualité du sommeil :

Instructions : Les questions qui suivent font références aux habitudes de sommeil **du patient** au cours du **dernier mois seulement**. Vos réponses devraient correspondre aux meilleures estimations possibles **pour la majorité** des jours et des nuits du dernier mois. SVP veuillez répondre à toutes les questions.

1.	Durant le dernier mois, à quelle heure vous êtes-vous couché? _____				
2.	Durant le dernier mois, combien de minutes avez-vous pris pour vous endormir à chaque soir? _____ min				
3.	Durant le dernier mois, à quelle heure vous êtes-vous levé le matin? _____				
4.	Durant le dernier mois, combien d'heures de sommeil avez-vous eu par nuit? (ceci peut-être différent du nombre d'heures passées au lit) _____ heures				
5.	**Durant le dernier mois, combien de fois avez-vous eu de la difficulté à dormir parce que vous :**	**Pas durant le dernier mois**	**Moins 1 fois par semaine**	**1 ou 2 fois par semaine**	**3 fois ou plus par semaine**
5.a	Ne pouviez pas vous endormir à l'intérieur de 30 min?	☐	☐	☐	☐
5.b	Vous réveilliez au milieu de la nuit ou tôt le matin?	☐	☐	☐	☐
5.c	Deviez vous lever pour aller à la salle de bain?	☐	☐	☐	☐
5.d	Ne pouviez pas respirer facilement?	☐	☐	☐	☐
5.e	Toussiez ou ronfliez bruyamment?	☐	☐	☐	☐
5.f	Aviez froid?	☐	☐	☐	☐
5.g	Aviez trop chaud?	☐	☐	☐	☐
5.h	Aviez fait de mauvais rêves?	☐	☐	☐	☐
5.i	Ressentiez de la douleur?	☐	☐	☐	☐
5.j	Autres raisons. SVP décrivez et à quelle fréquence :	☐	☐	☐	☐
6.	**Durant le dernier mois, comment évalueriez-vous la qualité globale de votre sommeil?**	**Très bien** ☐	**Plutôt bien** ☐	**Plutôt mal** ☐	**Très mal** ☐
7.	**Durant le dernier mois, combien de fois avez-vous :**	**Pas durant le dernier mois**	**Moins 1 fois par semaine**	**1 ou 2 fois par semaine**	**3 fois ou plus par semaine**
7.a	Pris un médicament (avec ou sans ordonnance) pour vous aider à dormir?	☐	☐	☐	☐
7.b	Eu de la difficulté à rester éveillé pendant que vous conduisiez, mangiez, ou vous engagiez dans une activité sociale?	☐	☐	☐	☐
8.	**Durant le dernier mois, jusqu'à quel point avez-vous eu de la difficulté à maintenir suffisamment d'enthousiasme pour compléter vos activités?**	**Aucune** ☐	**Légère** ☐	**Quelque peu** ☐	**Beaucoup** ☐
9.	**Avez-vous un partenaire de lit ou de chambre?**				
9.a	Pas de partenaire de lit ou de chambre. ☐				
9.b	Partenaire ou colocataire dans une autre chambre. ☐				
9.c	Partenaire dans la même chambre, mais pas dans le même lit. ☐				
9.d	Partenaire dans le même lit. ☐				
10.	**Si vous avez un partenaire de lit ou de chambre, demandez-lui combien de fois dans le dernier mois vous avez :**	**Pas durant le dernier mois**	**Moins 1 fois par semaine**	**1 ou 2 fois par semaine**	**3 fois ou plus par semaine**
10.a	Ronflé bruyamment?	☐	☐	☐	☐
10.b	Eu de longues pauses entre les respirations pendant votre sommeil?	☐	☐	☐	☐
10.c	Eu des contractions ou secousses dans les jambes pendant votre sommeil?	☐	☐	☐	☐
10.d	Eu des épisodes de désorientation ou de confusion durant le sommeil?	☐	☐	☐	☐
10.e	Eu des agitations pendant que vous dormiez? SVP décrire et à quelle fréquence?	☐	☐	☐	☐

3.4 Fourth Article: "Sleep Bruxism, Snoring, and Headache in Adolescents: an Experimental Trial with a Mandibular Advancement Appliance"

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Abstract

Introduction: Sleep bruxism (SB) is a sleep-related movement disorder characterized by tooth grinding and/or clenching, frequently associated with snoring, sleep-disordered breathing, and headaches. This study assesses the efficacy of a mandibular advancement appliance (MAA) for SB management in symptomatic adolescents reporting frequent headache and snoring.

Methods: Sixteen adolescents (mean age 14.9±0.5) reporting SB, frequent headache (>1day/week), and/or snoring underwent four ambulatory polysomnographic recordings for baseline (BSL; 1 night) and wearing the MAA during sleep (3 nights). SB diagnosis was confirmed by BSL recordings. The MAA was worn in three different positions (free splints – FS; neutral position – NP; and advanced to 50% of maximum protrusion – A50) for one week each in random order (FS–NP–A50 or NP–A50–FS, in compliance with titration order NP–A50). Headache complaints were assessed with pain intensity questionnaires using a 0–100 visual analogue scale in the morning after each PSG recording.

Results: Overall, sleep variables did not differ across the four nights. SB index (episodes/h of sleep) decreased with use of the MAA, and up to 60% in A50 position ($p=0.004$; ANOVA). Snoring was measured as the % of sleep time spent snoring. The subgroup (n=8) with >3.7% snoring showed a significant improvement with the MAA: snoring decreased linearly (-93%; $p=0.002$). Prior to the MAA, headache intensity was reported (n= 16) at 42.7±5/100 mm. It showed a decreasing trend from 21 to 51% with the MAA ($p=0.07$).

Conclusion: Short-term use of an MAA appears to reduce SB as well as snoring and headache complaints in adolescents. However, interactions between SB, breathing during sleep, and headache as well as the long-term effectiveness and safety of the MAA in adolescents need further investigation.

Keywords: Sleep bruxism, headache, snoring, adolescents, mandibular advancement appliance.

Introduction

Sleep bruxism (SB) is a sleep-related movement disorder characterized by tooth grinding and clenching. It is frequently observed in pediatrics. Recent epidemiological studies have reported SB prevalence ranging from 13% to 38% in children and adolescents (1-5) The etiology of SB is still under investigation. Genetic, physiological, neurological, and psychosocial factors may be involved in the genesis of the rhythmic masticatory muscle activity (RMMA) that occurs frequently (at least >2 episodes/h of sleep) in patients with SB (6, 7).

Repeated and sustained masticatory muscle activity during sleep may have a number of clinical consequences on the stomatognatic system, such as tooth wear, tooth damage, muscle fatigue, orofacial pain, temporomandibular disorders (TMD), and headache (HA) (1, 6, 8-11). SB may be also concomitant with other medical disorders, particularly other sleep disorders. These include parasomnias (e.g., sleep walking, sleep talking, enuresis), periodic limb movements during sleep, restless leg syndrome (RLS), and sleep-disordered breathing (SDB) (12-18). All these conditions may share common pathophysiological factors. In particular, it has been hypothesized that co-activation of the jaw-opening and jaw-closing muscles during RMMA may re-open the upper airway in response to an obstructive respiratory event such as obstructive sleep apnea (6, 19, 20). However, the relationship between SB and these comorbidities remains to be assessed, and further research is needed to determine whether these are cases of intersecting prevalence or if one condition causes or exacerbates the other.

It is noteworthy that in clinical settings, subjects reporting SB in association with pain, HA, or sleep complaints need further clinical investigation, and treatments are usually required. This study assesses in adolescents reporting SB, HA, and snoring the effectiveness of a mandibular advancement appliance (MAA), which has previously been used to separately manage SB, HA, and SDB (21-25). We hypothesized that the MAA could improve breathing during sleep to the benefit of all concomitants complaints that may share common pathophysiological substrates.

Material and Methods

This study followed a randomized controlled cross-over experimental trial design. The protocol was approved by the Ethics Review Board of the *Hôpital du Sacré-Coeur de Montréal*, and was conducted in compliance with the hospital's clinical ethical standards. All participants and at least one of their parents signed a written consent form and received compensation for participating in the study.

Study sample

Participants were recruited through announcements (previously approved by the Ethics Review Board) posted on the university campus and in the dental clinics of the University of Montreal from winter 2009 to summer 2011. Volunteer participants were initially interviewed by the research staff by phone (either directly or through their parents). Participants with a positive history of SB with HA or snoring were invited to come to the university research lab for a clinical examination and an initial ambulatory polysomnographic (PSG) assessment.

The inclusion criteria were age from 12 to 19 years and a history of SB associated with frequent HA (>1/week) and/or snoring. Reports of SB and snoring were assessed in the first night of PSG recording (BSL). HA intensity was assessed using a questionnaire with a 0–100 mm visual analogue scale (VAS). Headache was self-reported, with no clinical diagnosis. HA criteria were based on the definition of probable episodic tension-type HA (International Classification of Headache Disorders, ICHD-II, by the International Headache Society (26)). Exclusion criteria were diagnosed migraine, cluster HA, orthodontic treatments, severe medical diseases, and regular medications use.

Study protocol

At the first visit, candidates filled out questionnaires to assess general health, sleep quality, pain, headache, and bruxism complaints.

The clinical examination (performed by MCC) included an assessment of dental, temporomandibular joint, and masticatory muscle status. Jaw movements, including maximal opening, laterality, and protrusion, were also measured.

The first ambulatory PSG was usually performed on the day of the clinical examination. It was used to both confirm the SB diagnosis and to establish a baseline (BSL) night. Because the ambulatory PSG system allowed the participants to sleep in their own bed at home, a habituation night was not required.

Candidates who met the inclusion criteria were invited to come to the dental clinic for dental impressions and radiograms. X-rays, including a panoramic view and a lateral cephalogram, were performed to rule out contraindications to MAA use and to assess craniofacial features.

The MAA was manufactured by a specialized dental laboratory (Dentec Laboratory, Quebec City, Canada) and was provided by ResMed (Narval O.R.M.™ CC, USA and France). The appliance is an optimized mandibular retainer device comprising upper and lower custom-made semi-rigid splints that are vacuum-pressed onto the patient's tooth molds. The two splints are linked by a tractable flexible joint designed to mimic the physiological articulation of the tempormandibular joint (TMJ). This enables jaw movement and allows setting and adjusting mandible protrusion according to the individual's advancement capability (Figure 3.4.1). This MAA is highly comfortable. The material is flexible and its minimal size means there is no invasion of tongue space and no contact with incisors. This prevents tooth tilting and minimizes post-wear dental sensitivity. Once the individually fitted MAA was customized, it was given to the participant and adjusted. Participants were instructed to wear it during sleep only. All participants wore the MAA in three different positions (one week each) in random order: free splints (FS),

neutral position (NP), and advanced to 50% of maximum protrusion (A50). FS position was obtained by removing the connectors between the upper and lower splints so that only the dental surfaces were covered, allowing a full range of jaw movement. In NP position, the mandible was retained in maximum intercuspidation (set as the participant's normal occlusion). Although no advancement is obtained, this setting prevents the jaw from moving backward during sleep. The A50 position was obtained by shortening the connectors to retain the mandible at 50% of the previously measured maximum protrusion.

Each MAA position was tested for one week followed by a washout period (5–7 days) to avoid a potential carry-over effect. The three positions were randomized into two sequences: 1) FS, NP, A50; or 2) NP, A50, FS, in compliance with a titration paradigm (NP–A50). Participants were randomly allocated to one of the two sequences. Appliance compliance was monitored using self-report questionnaires. After each week with the MAA, participants underwent PSG recordings while wearing the device during sleep. Participants underwent a total of four ambulatory PSGs: one baseline and three sleeping with the MAA.

Ambulatory PSG

An ambulatory PSG system (Siesta, Compumedics, Australia) was used to perform a full sleep study at the participant's home (level 2). Participants came to the research lab in the late afternoon. The research staff placed all the electrodes on the participants, who then left the lab. Participants returned the PSG system the following day. Participants and their parents were instructed to start PSG recording in the evening once everything was correctly set and the participants were lying in bed (corresponding to lights off). Participants were instructed to stop the system in the morning at awakening (lights on).

Sleep data were checked the next day. If any technical problems had compromised the data, recording was repeated the following day. The overall success rate of the ambulatory PSG recordings was 86%.

The following channels were recorded: EEG (F_3M_2, F_4M_1, C_3M_2, C_4M_1, O_1M_2, O_2M_1); EOG (right and left); ECG (3 derivations); and EMG from the suprahyoid muscles and the right and left masseter and temporalis muscles (essential for RMMA scoring). Respiratory parameters were assessed by recording abdominal and thoracic respiratory effort, airflow (oro-nasal cannula), and oxymetry. A microphone was used to measure snoring during the PSG recording at the participant's home.

For the offline analysis, data were visually scored according to the American Academy of Sleep Medicine Criteria (27). Despite the absence of audio-video recordings, RMMA was scored according to standard published rules (28, 29). In absence of an international consensus on which respiratory scoring criteria should be used in adolescents (i.e., pediatric vs. adult criteria), we decided to score breathing events according to the AASM criteria for children based on a recent publication that showed their greater sensitivity (27, 30). All nights were scored blind to the presence/absence and position (e.g. FS, NP, A50) of the MAA.

Statistical Analysis

Based upon Landry-Schönbeck *et al*.(23), a sample size of 16 subjects was estimated as sufficient to detect a decrease in RMMA index of 40% from baseline with the NP (effect size 0.77), with a power of 0.80 and at an alpha level of 0.05. Statistical comparisons between BSL, FS, NP, and A50 data were made using repeated measures ANOVA and pairwise tests (significant at $p \leq 0.05$). Abnormally distributed data (Shapiro-Wilk normality statistic < 0.05) were normalized by applying Log10. In the case of randomly missing data, a mixed model analysis was applied to include all participants in the analysis. Data were analyzed using SPSS (IBM SPSS Statistics, Version 17.0.0 for Macintosh, Chicago, IL, USA).

Results

Demographic, sleep, and dental characteristic of the sample at baseline

Of the many adolescents screened by phone interviews, 23 candidates were invited to the research lab to undergo a clinical examination and the first ambulatory PSG. Of these, 16 (8 F, 8 M; mean age 14.9±0.5 years) met the inclusion criteria and completed the study (no drop out).

At the clinical examination, all 16 participants reported tooth-grinding during sleep. Eleven of these were aware of SB because it was reported by their parents, whereas the remaining participants were told by other sources (e.g., friends, siblings, dentist). The majority (12/16) also reported daytime tooth clenching and other daytime oral parafunctions such as lip, nail, or cheek biting or gum chewing.

In the screening questionnaire, all participants reported frequent HA (>1/week) in the morning (11/16), during the day (10/16), and/or in the evening (11/16). HA pain was described as a feeling of tightening and pressing on the head without other associated symptoms (e.g., nausea, photophobia). The mean HA intensity assessed on a 0–10 mm visual analogue scale (VAS) was 42.75±5 on the screening questionnaire and 48±6.2 on clinical examination. Only six of the 16 participants reported occasional use of analgesics (e.g., ibuprofen or acetaminophen) for intense HA.

Seven participants reported nonrefreshing sleep. However, scores on the Epworth Sleepiness Scale and the Pittsburg Sleep Quality Index were within normal limits (mean value ± SEM of 7.3 ± 1.1 and 5.7 ± 0.6 respectively).

Mild to moderate snoring was reported by most participants (12/16), whereas none was aware of having sleep apnea. All participants were healthy (i.e., no medical or neurological diseases), and had a normal body mass index.

During the clinical examination, participants were also assessed for dental status, orthogantic profile, Mallampati score, and TMJ parameters (e.g., mandibular range of

motion, presence of muscular or TMJ pain) (Table 3.4.1). Only three participants presented mixed dentition (i.e., dentition containing both primary and secondary teeth). However, an adequate MAA retention and fit was obtained in all cases.

Sleep variables

The sleep variables recorded by the ambulatory PSG system in the BSL, FS, NP, and A50 nights are presented in Table 3.4.2. Overall, no significant difference was found between the four nights for sleep duration; wake time after sleep onset; sleep efficiency and percentage of sleep stages N1, N2, N3, and R; sleep cycles; number of awakenings; arousal index; or sleep stage shifts. However, in a pairwise comparison between nights, the % of stage N2 sleep significantly decreased between BSL and NP nights ($p=0.03$) and between BSL and A50 nights ($p=0.02$), and a trend was observed between BSL and FS nights ($p=0.06$).

A sequence effect (group with the sequence FS, NP–A50 vs. group with the sequence NP–A50, FS) was ruled out using t-tests for the following variables: sleep duration, arousal index, number of awakenings, and RMMA index. No differences between groups were observed.

Sleep bruxism

Data on RMMA and other masticatory muscular activity are presented in Table 3.4.2. Participants' reports of SB were confirmed by the first PSG recording (BSL night). RMMA episodes were identified and scored during sleep and wake epochs. SB was diagnosed and participants were included in the study if the RMMA index was greater than 2 episodes per h of sleep. However, for the statistical analysis, the RMMA index reported in Table 3.4.2 refers to episodes occurring during sleep only.

With the MAA, the RMMA index decreased significantly (overall $p=0.01$), linearly from BSL toward FS, NP, and A50 nights ($p=0.007$). Specifically, the RMMA index

decreased by 16.8% from BSL to FS night (p=0.02), 40% from BSL to NP night (p=0.02), and 60.5% from BSL to A50 night (p=0.004). However, no significant difference was observed between the three MAA positions. Only one participant showed an increase in RMMA index, and only in the night with the MAA in advanced position (A-50). In the BSL night, 69.7% of RMMA episodes were associated with sleep arousal (during a <5 sec time window). This association remained present in the MAA nights.

Parallel to the RMMA index, the burst index decreased linearly (p=0.01), with an overall significant decrease between BSL and FS, NP, and A50 nights (p=0.02), with no differences between the three MAA positions.

Conversely, the index of other muscular events recorded on the masseter and temporalis EMG channels increased significantly and linearly in the nights with the MAA (p=0.03). Because these muscular events involved the masticatory muscles but did not meet the RMMA scoring criteria, they were classified separately. In the absence of standard or validated criteria, we selected only episodes lasting from 0.5 to 10 sec during sleep (criteria derived from the AASM criteria for leg movements during sleep (27)). These other masticatory muscular activities increased by 20% with the MAA in the FS night (p=0.1), 35.7% in the NP night (p=0.01), and 34.3% in the A50 night (p=0.04).

Snoring and breathing during sleep

In the absence of a standard validated method to measure and report snoring, we quantified it as the % of sleep spent snoring. From the PSG recordings, overall snoring did not change (p=0.1; Table 3.4.2). However, using the median value of the BSL night as a cut-off, two groups of eight participants each were identified (above or below 3.7%). The ≥3.7% group showed a significant reduction in snoring (p=0.002), which decreased linearly (p=0.007) by 79% in the FS nights (p<0.001), 95.8% in the NP night (p=0.005), and 93% in the A50 night (p=0.008). However, no difference was observed between the three MAA positions. In the <3.7% group, no significant difference was found between nights.

Airflow and oxygen saturation were the only PSG variables with random missing data due to technical problems during the unattended recordings (2/64 nights for airflow, and 6/64 for oxymetry). We therefore performed a mixed model analysis to compare these variables across BSL, FS, NP, A50 nights. Results are presented in Table 3.4.2. The apnea-hypopnea index (AHI), at <1 episode/h of sleep at BSL, showed no significant difference between the four nights (p=0.5). Oxygen saturation levels were also within normal limits and showed no difference between nights.

Headache complaints

Headache complaints were assessed on a VAS scale the day after each PSG recording. Overall, HA intensity showed an improving trend, decreasing by 21-51% from the initial reported intensity (p=0.07). However, due to the heterogeneous nature of the HA (morning vs. daytime) in our sample and the methodology applied (morning questionnaire), no significant difference was detected between the four nights. For the six participants who reported HA in the morning only, a significant reduction of HA intensity (-57%) was observed between BSL and NP night (p=0.03).

In the morning questionnaire, participants were also asked to assess their sleep quality during PSG recording on a VAS scale (0–100 mm). They rated it at 58.2±5.2 at BSL, 56.5±6 with the MAA in FS position, 52.1±6.4 with the MAA in NP position, and 53.7±7.6 with the MAA in A50 position (overall p=0.9).

Subjective assessment of the mandibular advancement appliance

The MAA was subjectively assessed using another questionnaire filled out after each wearing period in FS, NP, and A50 position. Data are presented in Table 3.4.3. Comfort decreased significantly and linearly with position advancement (p=0.03). No change was found between the three MAA positions for all other assessed variables.

Discussion

The present study adds to the current literature new insights on the effectiveness and mechanisms of MAA. Our results suggest that short-term use of an MAA during sleep in symptomatic SB adolescents may help reduce RMMA and improve snoring and HA. We examined adolescents with comorbidities, which are frequently observed in daily clinical practice. However, these conditions rarely receive further attention or a confirmed diagnosis. In fact, SB incidence is usually underestimated, snoring is considered normal, and HA complaints are ignored. Yet early diagnosis and treatment are vital in this young population to prevent later consequences (e.g., damage to the stomatognatic system, the impact on academic performance of chronic pain and/or HA, risks of SDB-related cardiovascular and metabolic disorders).

Several types of oral appliances have been tested and have shown varied effectiveness in managing SB (21-23, 31-34). However, the actual mechanism of action remains unknown (35). Historically, the effectiveness of oral appliances in SB has been attributed to various factors, such as by covering tooth surfaces, modifying peripheral sensory inputs, and/or adjusting occlusal status. In the case of the MAA studied here, we hypothesize that the improved breathing during sleep could result in fewer SB episodes.

Consistent with previous studies in young adults (21-23), our findings confirm the short-term effectiveness of MAA in adolescents with SB, HA, and snoring. However, although progressive clinical improvement was achieved, no significant difference was found between the occlusal free splint position (control) and the neutral or advanced positions (active jaw retaining or repositioning). This finding suggests other possible explanations: decreased SB motor activity may be due to the appliance's restriction of jaw movements and/or its influence on masticatory muscle spindle input (e.g., information on muscle length, jaw position). However, although these peripheral sensory factors are known to influence the central generation pattern (CGP) of mastication during wakefulness (36, 37), their role in the genesis and regulation of RMMA during sleep remains unclear (20, 38).

As reported in the literature, oral appliances may also exacerbate SB (22). In our sample, only one participant showed a clear increase in RMMA with the MAA in advanced position. However, the uncontrolled PSG recording condition (at the participant's home) does not guarantee that the MAA was worn properly throughout the night. The appliance used in this study did not include an intra-device compliance chip, which would be very useful for objectively monitoring sleep time with the MAA.

During sleep, other motor activities may occur that involve the orofacial and masticatory muscles, such as lip sucking, swallowing, yawning, and head movements. These activities account for an estimated 40% of all muscular events in individuals with SB (39, 40). In contrast to previous findings (22), we recorded significant increases in other masticatory muscle activities when the MAA was worn. It remains to be demonstrated whether this result is related to the low classification specificity of these movements due to the absence of video recording, or whether the wearing of an MAA may have changed the observable EMG pattern instead of acting on the genesis of SB-related movements.

Of the many treatments that have been tested for the management of SB (e.g. oral appliances, medications, behavioral therapy), none has been demonstrated effective in curing the disorder (i.e., completely abolishing SB) (32). As for other spontaneous movements during sleep (e.g., periodic limb movements)(41, 42), it has been suggested that more than one type of RMMA episode occurs, e.g., isolated RMMAs, arousal related-RMMAs, breathing-related RMMAs, and leg- or body-movement-related RMMAs. These movements may vary in their response to different treatments that specifically address related factors.

Recent hypotheses about SB genesis include sleep-disordered breathing, in which the SB-related co-contraction of jaw-opening and jaw-closing muscles acts to reopen the airway after an obstructive respiratory event. This hypothesis needs to be tested in SB patients with concomitant SDB. In fact, our population was composed of SB adolescents with mild to moderate snoring only. Therefore, improved airflow and oxygen saturation during sleep may not have been detectable. However, the group of participants with higher snoring (arbitrarily set at >3.7% of sleep spent snoring) showed a significant improvement

with the MAA, as well as decreased RMMA. To our knowledge, an MAA is rarely applied to manage snoring or SDB in pediatrics, where more radical or definitive treatments, such as adenotonsillectomy or orthodontics, are preferred (43, 44). However, oral devices may be used as a temporary treatment, or when indicated, to mimic and test the potential effects of orthopedic therapy or orthognatic surgery, which are usually performed toward the end of adolescence (45).

Headache complaints, especially in the morning, have been related to both SB and SDB (11, 46, 47). Putative pathophysiological mechanisms include repeated and sustained muscle contractions in SB and recurrent hypoxia and hypercapnia in SDB. However, these hypotheses remain to be validated, and many other factors may be involved. In the present study, for example, the majority of participants were also aware of daytime oral parafunctions such as tooth clenching or nail and lip biting. These are recognized risk factors for the development and maintenance of forms of orofacial pain, including headache (1, 48). The coexistence of wake-time bruxism may explain the partial effect of the MAA on the subjectively assessed HA complaints, the only symptom to show an improvement trend in our study sample.

Due to the limitations of this study, our results need to be further investigated and confirmed in future studies. First, we were unable to determine the effects of airway opening and improved oxygenation during sleep on RMMA activity and HA complaints. According to the post-hoc sample size estimation, in order to show a statistically significant difference between the three MAA positions, more than 100 participants would be needed for the RMMA index and more than 200 for HA complaints. Note, however, that a more homogeneous sample (e.g., morning headache only) would probably have diminished the required sample size. Other limitations concern the methodology. Whereas the ambulatory PSG system ensured high participation and compliance, especially in adolescents (only 25% of our sample, i.e. four participants, all aged > 16 years old, would have participated if the study had been conducted in a hospital-based sleep center instead of at home), the lack of a sleep technician to attend the full recording increased the number of technical failures,

missing data, and uncontrolled conditions. Moreover, the absence of a concomitant audio-video recording reduced the scoring specificity for SB and other orofacial and masticatory movements. To subjectively assess headaches, an HA diary would have been more accurate to monitor variations in intensity and occurrence. Finally, the study protocol was designed to test the MAA effect in the short term only. Long-term treatment may be necessary to gain a significant improvement for signs and symptoms related to SB, HA, and SDB.

Conclusion

Short-term use of an MAA appeared to reduce SB and improve snoring and headache complaints in adolescents. However, the interactions between SB, breathing during sleep, and headache as well as the long-term effectiveness and safety of an MAA in adolescents need to be further investigated.

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Figure 3.4.1 The mandibular advancement device.

from ResMed Narval O.R.M® CC (www.resmed.com)

Table 3.4.1 Demographic, dental and oropharyngeal data for the study sample (n=10) assessed during the clinical examination.

Demographic Data			
Gender distribution: 8 F, 8 M			
Mean age: 14.9 ± 0.5 years			
Clinical Characteristics of Oropharyngeal Structures			
Mean maximum mouth opening: 50.2 ± 1.5 mm			
Mean maximum jaw protrusion: 8.1 ± 0.4 mm			
Dental and skeletal Class *(based on cephalometric assessment)*			
Class I	Class II	Class III	
3/16 (18.75%)	11/16 (68.75%)	2/16 (12.5%)	
Mallampati Score			
Type I	Type II	Type III	Type IV
3/16 (18.75%)	7/16 (43.75%)	4/16 (25%)	2/16 (12.5%)

Data are presented as mean ± SEM, or number and %.

Table 3.4.2 Polysomnographic variables for the baseline night and the three nights with the mandibular advancement appliance.

PSG Variables	BSL night (no device)	FS night (free splints)	NP night (neutral position)	A50 night (50% advanced)	P value
Sleep variables					
Total sleep time (min)	414.5 ± 14.4	396.6 ± 23.5	390.7 ± 21.3	398.3 ± 18.8	0.8
Wake time after sleep onset (min)	11 (2.7–46)	11.7 (1–74.7)	19.2 (2.3–101.3)	11.3 (11.3)	0.6
Sleep efficiency (%)	96.7 (91–99.3)	96.6 (82.1-99.6)	94.4 (76.4–99.2)	95.8 (86.8–98.7)	0.2
Sleep latency (min)	17.2 ± 2.5	23.4 ± 5.2	26.8 ± 6.5	23.2 ± 5.9	0.5
REM sleep latency (min)	136.1 ± 11.5	99.3 ± 8.9	136 ± 17.3	106.6 ± 11.7	0.1
Stage N1 (%)	3 (2–10)	3.1 (0.7–8.5)	4.9 (1.9–8.1)	3.4 (1.3–9.2)	0.2
Stage N2 (%)	42.5 ± 2.1	37.9 ± 2.2	38.9 ± 2	38.3 ± 1.6	0.1
Stage N3 (%)	36 ± 2.4	40.1 ± 2.9	38.5 ± 2.2	39.4 ± 2.3	0.3
Stage R (%)	17.1 ± 1	18.1 ± 1.3	17.8 ± 1.1	18.4 ± 1.1	0.7
NREM/REM sleep cycles (n)	4.5 (2–5)	4 (3–6)	4 (2–6)	4 (3–8)	0.5
Awakenings (n)	16 (6–52)	21 (2–53)	30.5 (5–75)	21 (7–62)	0.4
Arousals (n/h)	11.6 (4.8–27.5)	10.8 (3.4–40.2)	12.3 (4.5–22.3)	13.4 (3.3–26.4)	0.4
Sleep stage shifts (n/h)	28.6 ± 1.6	29.1 ± 1.7	30.5 ± 2	30.6 ± 2.3	0.6
Sleep-related masticatory movement variables					
RMMA index (n/h)	3.8 (1.8–7)	3.2 (0.1–6.4)	2.3 (0–7)	1.5 (0.1–15.5)	**0.01**
Burst index (n/h)	18.65 (8.9–51)	19.1 (0.6–46.8)	12.4 (0–41.6)	10.3 (1–116.1)	**0.02**
Other masticatory muscular activity (n/h)*	7 (3–12.6)	8.4 (2.3–18.7)	9.5 (2.9–20.6)	9.4 (3–18.8)	**0.03**
Sleep-related breathing variables					
Snoring (% of sleep spent snoring) (n=16)	3.7 (0.1–67.4)	3.9 (0.1–25.9)	1.5 (0–17.1)	2.3 (0.26.6)	0.1
Group ≥ 3.7% (n=8)	21.4 (3.8–67.4)	4.5 (0.2–19.9)	0.9 (0–13)	1.5 (0–14.7)	**0.002**
Group < 3.7% (n=8)	2.9 (0.1–3.5)	3.9 (0.2–25.9)	2.6 (0–17.1)	3.8 (0–26.6)	0.7
Apnea-hypopnea index §	(n=16) 0.7 ± 0.2	(n=14) 1 ± 0.4	(n=16) 1 ± 0.2	(n=16) 0.6 ± 0.1	0.5
Oxygen saturation level (%)§	(n=12)	(n=15)	(n=16)	(n=15)	
Overnight mean value	97.6 ± 0.2	97.4 ± 0.2	97.5 ± 0.1	97.7 ± 0.1	0.2
Overnight minimum value	94.4 ± 0.5	94.1 ± 0.5	94.5 ± 0.3	94.6 ± 0.4	0.8
Overnight maximum value	99.7 ± 0.1	99.6 ± 0.1	99.5 ± 0.1	99.8 ± 0.1	0.2

Data are presented as MEAN values ± SEM or MEDIAN (min–max). P values are calculated with ANOVA. If normality test (Shapiro–Wilk) < 0.05, data of that variable were normalized by applying Log10. Significant differences are in bold characters.

The mandibular advancement appliance (MAA) was worn in three different positions (free splints, FS; NP, neutral position; and A50, advanced to 50% of maximum jaw protrusion). After the first baseline night (BLS), to comply with a titration paradigm, the three positions were randomized into two sequences: 1) FS, NP, A50; or 2) NP, A50, FS. Participants were randomly allocated to one of two sequences. For table clarity, nights with the MAA are presented in order from active control to advanced, disregarding the two randomized sequences.

RMMA refers to rhythmic masticatory muscle activity.

*Other masticatory muscular activities are events recorded on the masseter and temporalis EMG channels that did not meet the RMMA scoring criteria and could not be classified due to the absence of a video recording (i.e., it was impossible to distinguish between swallowing, coughing, etc.). Only episodes occurring during sleep with duration of 0.5–10 sec were included in the analysis (extrapolated from AASM 2007, criteria for leg movements).

§ Mixed general model for the presence of random missing data. Sample size is indicated for each variable and each night.

Table 3.4.3 Self-report results from the questionnaire assessing the mandibular advancement appliance (MAA).

Variable	FS night (free splints)	NP night (neutral position)	A50 night (50% advanced)	P value
Appliance adaptation period (days)	3.6 ± 0.7	3.5 ± 0.5	5.4 ± 1.6	0.2
Time wearing the appliance (h/night)	7.6 ± 0.3	7.6 ± 0.3	7.5 ± 0.4	0.4
Nights per week with the appliance (n)	5.5 ± 0.4	6 ± 0.6	5.3 ± 0.3	0.7
MAA Comfort (VAS)	57.8 ± 5.6	48.1 ± 5.3	40.7 ± 6.8	**0.03**
Overall MAA satisfaction (VAS)	63.9 ± 5.8	68.2 ± 5	58.9 ± 5.6	0.3
Overall MAA effectiveness (VAS)	65.7 ± 5.6	73.6 ± 4.4	60 ± 7.6	0.1
Sleep quality with the appliance (VAS)	57.1 ± 6.3	62.9 ± 6.1	53.9 ± 6.5	0.6

Data are presented as mean ± SEM. VAS stands for visual analog scale (0–100 mm). P values are calculated with ANOVA. Significant differences are in bold characters.

References:

1. Carra MC, Huynh N, Morton P, Rompre PH, Papadakis A, Remise C, et al. *Prevalence and risk factors of sleep bruxism and wake-time tooth clenching in a 7- to 17-yr-old population*. Eur J Oral Sci 2011;119:386-394.
2. Cheifetz AT, Osganian SK, Allred EN, Needleman HL. *Prevalence of bruxism and associated correlates in children as reported by parents*. J Dent Child (Chic) 2005;72:67-73.
3. Nekora-Azak A, Yengin E, Evlioglu G, Ceyhan A, Ocak O, Issever H. *Prevalence of bruxism awareness in Istanbul, Turkey*. Cranio 2010;28:122-127.
4. Serra-Negra JM, Paiva SM, Seabra AP, Dorella C, Lemos BF, Pordeus IA. *Prevalence of sleep bruxism in a group of Brazilian schoolchildren*. Eur Arch Paediatr Dent 2010;11:192-195.
5. Strausz T, Ahlberg J, Lobbezoo F, Restrepo CC, Hublin C, Ahlberg K, et al. *Awareness of tooth grinding and clenching from adolescence to young adulthood: a nine-year follow-up*. J Oral Rehabil 2010;37:497-500.
6. Lavigne G, Manzini C, Huynh NT. *Sleep Bruxism* In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:1129-1139.
7. Rompre PH, Daigle-Landry D, Guitard F, Montplaisir JY, Lavigne GJ. *Identification of a sleep bruxism subgroup with a higher risk of pain*. J Dent Res 2007;86:837-842.
8. Bruni O, Fabrizi P, Ottaviano S, Cortesi F, Giannotti F, Guidetti V. *Prevalence of sleep disorders in childhood and adolescence with headache: a case-control study*. Cephalalgia 1997;17:492-498.
9. Pereira LJ, Costa RC, Franca JP, Pereira SM, Castelo PM. *Risk indicators for signs and symptoms of temporomandibular dysfunction in children*. J Clin Pediatr Dent 2009;34:81-86.
10. Pereira LJ, Pereira-Cenci T, Del Bel Cury AA, Pereira SM, Pereira AC, Ambosano GM, et al. *Risk indicators of temporomandibular disorder incidences in early adolescence*. Pediatr Dent 2010;32:324-328.
11. Vendrame M, Kaleyias J, Valencia I, Legido A, Kothare SV. *Polysomnographic findings in children with headaches*. Pediatr Neurol 2008;39:6-11.
12. Ohayon MM, Li KK, Guilleminault C. *Risk factors for sleep bruxism in the general population*. Chest 2001;119:53-61.
13. Sheldon SH. *Obstructive Sleep Apnea and Bruxism in Children*. Dentistry's Role in Sleep Medicine 2010;5:163-168.
14. Sjoholm TT, Lowe AA, Miyamoto K, Fleetham JA, Ryan CF. *Sleep bruxism in patients with sleep-disordered breathing*. Arch Oral Biol 2000;45:889-896.
15. Lavigne GL, Lobbezoo F, Rompre PH, Nielsen TA, Montplaisir J. *Cigarette smoking as a risk factor or an exacerbating factor for restless legs syndrome and sleep bruxism*. Sleep 1997;20:290-293.

16. Petit D, Touchette E, Tremblay RE, Boivin M, Montplaisir J. *Dyssomnias and parasomnias in early childhood*. Pediatrics 2007;119:e1016-1025.
17. Ng DK, Kwok KL, Poon G, Chau KW. *Habitual snoring and sleep bruxism in a paediatric outpatient population in Hong Kong*. Singapore Med J 2002;43:554-556.
18. Agargun MY, Cilli AS, Sener S, Bilici M, Ozer OA, Selvi Y, et al. *The prevalence of parasomnias in preadolescent school-aged children: a Turkish sample*. Sleep 2004;27:701-705.
19. Khoury S, Rouleau GA, Rompre PH, Mayer P, Montplaisir JY, Lavigne GJ. *A significant increase in breathing amplitude precedes sleep bruxism*. Chest 2008;134:332-337.
20. Lavigne GJ, Kato T, Kolta A, Sessle BJ. *Neurobiological mechanisms involved in sleep bruxism*. Crit Rev Oral Biol Med 2003;14:30-46.
21. Franco L, Rompre PH, de Grandmont P, Abe S, Lavigne GJ. *A mandibular advancement appliance reduces pain and rhythmic masticatory muscle activity in patients with morning headache*. J Orofac Pain 2011;25:240-249.
22. Landry ML, Rompre PH, Manzini C, Guitard F, de Grandmont P, Lavigne GJ. *Reduction of sleep bruxism using a mandibular advancement device: an experimental controlled study*. Int J Prosthodont 2006;19:549-556.
23. Landry-Schonbeck A, de Grandmont P, Rompre PH, Lavigne GJ. *Effect of an adjustable mandibular advancement appliance on sleep bruxism: a crossover sleep laboratory study*. Int J Prosthodont 2009;22:251-259.
24. Gauthier L, Laberge L, Beaudry M, Laforte M, Rompre PH, Lavigne GJ. *Mandibular advancement appliances remain effective in lowering respiratory disturbance index for 2.5-4.5 years*. Sleep Med 2011;12:844-849.
25. Gauthier L, Laberge L, Beaudry M, Laforte M, Rompre PH, Lavigne GJ. *Efficacy of two mandibular advancement appliances in the management of snoring and mild-moderate sleep apnea: a cross-over randomized study*. Sleep Med 2009;10:329-336.
26. *The International Classification of Headache Disorders: 2nd edition*. Cephalalgia 2004;24 Suppl 1:9-160.
27. AASM. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specificiations*. Westchester, Illinois: American Academy of Sleep Medicine, 2007.
28. Lavigne GJ, Rompre PH, Montplaisir JY. *Sleep bruxism: validity of clinical research diagnostic criteria in a controlled polysomnographic study*. J Dent Res 1996;75:546-552.
29. Doering S, Boeckmann JA, Hugger S, Young P. *Ambulatory polysomnography for the assessment of sleep bruxism*. J Oral Rehabil 2008;35:572-576.
30. Accardo JA, Shults J, Leonard MB, Traylor J, Marcus CL. *Differences in overnight polysomnography scores using the adult and pediatric criteria for respiratory events in adolescents*. Sleep 2010;33:1333-1339.
31. Dube C, Rompre PH, Manzini C, Guitard F, de Grandmont P, Lavigne GJ. *Quantitative polygraphic controlled study on efficacy and safety of oral splint devices in tooth-grinding subjects*. J Dent Res 2004;83:398-403.

32. Huynh N, Manzini C, Rompre PH, Lavigne GJ. *Weighing the potential effectiveness of various treatments for sleep bruxism*. J Can Dent Assoc 2007;73:727-730.
33. Nascimento LL, Amorim CF, Giannasi LC, Oliveira CS, Nacif SR, Silva Ade M, et al. *Occlusal splint for sleep bruxism: an electromyographic associated to Helkimo Index evaluation*. Sleep Breath 2008;12:275-280.
34. Ommerborn MA, Schneider C, Giraki M, Schafer R, Handschel J, Franz M, et al. *Effects of an occlusal splint compared with cognitive-behavioral treatment on sleep bruxism activity*. Eur J Oral Sci 2007;115:7-14.
35. Klasser GD, Greene CS, Lavigne GJ. *Oral appliances and the management of sleep bruxism in adults: a century of clinical applications and search for mechanisms*. Int J Prosthodont 2010;23:453-462.
36. Lund JP, Kolta A, Westberg KG, Scott G. *Brainstem mechanisms underlying feeding behaviors*. Curr Opin Neurobiol 1998;8:718-724.
37. Kolta A, Lund JP, Westberg KG, Clavelou P. *Do muscle-spindle afferents act as interneurons during mastication?* Trends Neurosci 1995;18:441.
38. Kato T, Thie NM, Huynh N, Miyawaki S, Lavigne GJ. *Topical review: sleep bruxism and the role of peripheral sensory influences*. J Orofac Pain 2003;17:191-213.
39. Dutra KM, Pereira FJ, Jr., Rompre PH, Huynh N, Fleming N, Lavigne GJ. *Oro-facial activities in sleep bruxism patients and in normal subjects: a controlled polygraphic and audio-video study*. J Oral Rehabil 2009;36:86-92.
40. Kato T, Thie NM, Montplaisir JY, Lavigne GJ. *Bruxism and orofacial movements during sleep*. Dent Clin North Am 2001;45:657-684.
41. Zucconi M, Ferri R, Allen R, Baier PC, Bruni O, Chokroverty S, et al. *The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG)*. Sleep Med 2006;7:175-183.
42. Manconi M, Vitale G, Ferri R, Zucconi M, Ferini-Strambi L. *Periodic leg movements in Cheyne-Stokes respiration*. Eur Respir J 2008;32:1656-1662.
43. Guilleminault C, Monteyrol PJ, Huynh NT, Pirelli P, Quo S, Li K. *Adeno-tonsillectomy and rapid maxillary distraction in pre-pubertal children, a pilot study*. Sleep Breath 2011;15:173-177.
44. Pirelli P, Saponara M, Guilleminault C. *Rapid maxillary expansion in children with obstructive sleep apnea syndrome*. Sleep 2004;27:761-766.
45. Villa MP, Miano S, Rizzoli A. *Mandibular advancement devices are an alternative and valid treatment for pediatric obstructive sleep apnea syndrome*. Sleep Breath 2011.
46. Neau JP, Paquereau J, Bailbe M, Meurice JC, Ingrand P, Gil R. *Relationship between sleep apnoea syndrome, snoring and headaches*. Cephalalgia 2002;22:333-339.
47. Paiva T, Batista A, Martins P, Martins A. *The relationship between headaches and sleep disturbances*. Headache 1995;35:590-596.
48. Farella M, Soneda K, Vilmann A, Thomsen CE, Bakke M. *Jaw muscle soreness after tooth-clenching depends on force level*. J Dent Res 2010;89:717-721.

Chapter 4: General Discussion

The following pages will be dedicated to discuss the main findings of the four research articles included in this thesis. In accordance with the structure of this work, the first section will focus on the etiology and pathophysiology of RMMA during sleep, as supported by our new results (Section 4.1). The second section will summarize the epidemiological and clinical features of SB in pediatrics, and it will discuss the putative mechanisms that may explain the effect of MAA on RMMA during sleep (Section 4.2). Finally, the scientific and clinical relevance of the findings, the study limitations, and the future research directions will be considered (Sections 4.3 and 4.4).

4.1 CAP Phase A as the "Permissive Window" for Rhythmic Masticatory Muscle Activity during Sleep

The first two research articles included in this thesis aimed at further investigating the nature of the relationship between RMMA and sleep arousal. To achieve this objective, cyclic alternating pattern (CAP), a scoring method used to assess sleep instability (82), was analyzed in two different experimental protocols.

Previous studies have described RMMA as a motor activity secondary to sleep arousal (61, 63, 64, 66), and have made an association between RMMA and phase A of CAP (61, 252). Moreover, the majority of RMMA episodes were shown to occur in clusters, with the most frequent interval between 20 and 30 seconds (64), a periodicity that recalls the physiological arousal rhythm described as CAP (83).

The present data confirm the time-correlation between RMMA and CAP phase A, albeit with marked differences between phases A1, A2, and A3. For example, phase A1, which appears to reflect the cyclic homeostatic fluctuation of delta power (253, 254), reaches the highest frequency during the first NREM/REM sleep cycle and progressively declines across the successive sleep cycles. Conversely, arousal subtypes A2 and A3 are lower in relation to NREM deep sleep and increase before REM sleep onset. The RMMA

pattern of occurrence reflects CAP phase A2 and A3 modulation, reaching a peak during the pre-REM intervals of the sleep cycle (see Figure 3.1.1 page 53, and Figure 3.2.2 page 74).

The association between RMMA occurrence and CAP phase A was preserved even when external disturbing factors were applied and sleep instability was experimentally enhanced (either with clonidine or sensory stimulations). As expected in these conditions, CAP variables increased in both SB and control subjects. At the contrary, RMMA frequency was either decreased (under clonidine) or unchanged (under sensory stimulations). Taking these results together, we concluded that CAP phase A (i.e., sleep arousal) is not the generator or trigger of RMMA during sleep, rather the "permissive window" that facilitates, in period of unstable sleep, the occurrence of these motor events.

4.1.1 Evidence from the Experimental Trial with Clonidine

In a previous study conducted in our laboratory, a single dose of clonidine was shown to reduce RMMA by approximately 60% in SB subjects (240). This major effect has been used as a proof of concept to support the hypothesis that RMMA is the consequence of a cascade of physiological phenomena starting with the activation of sympathetic nervous system (See Figure 1.3 page 22). In fact, by shifting the balance between sympathetic and parasympathetic tone toward this latter one, clonidine blocks the cascade of autonomic events that seem to precede RMMA onset, thus preventing RMMA occurrence during sleep. However, the modulation of sleep arousal and sleep instability under clonidine was not evaluated earlier.

Clonidine is a potent sympathetic drug known to alter the NREM/REM sleep structure (255, 256). In our study, the most evident change was the marked suppression or complete abolishment of REM sleep. Based on the standard sleep scoring criteria (18, 257), REM sleep is identified when specific low amplitude, mixed frequency EEG patterns (e.g., sawtooth waves), rapid eye movements, and muscle hypotonia occur. A quantitative

analysis performed on the EEG, EOG and EMG channels confirmed that clonidine suppressed REM sleep in all SB subjects. In particular, significant difference in the EEG spectral analysis − mostly affecting slow wave activity and spindles − minor rapid eye movements, and higher levels of EMG activity were observed under clonidine (*Carra et al. article in preparation. Abstracts (258, 259)*). The suppression of REM sleep is a sensitive indicator of the drug effect on the central noradrenergic cells that regulate the NREM/REM switch. The homeostatic and circadian drives naturally push the sleeping individual toward REM sleep but clonidine blunts the occurrence of this sleep phase.

According to the reciprocal-interaction model (260, 261), the NREM/REM sleep cycle is generated by a finely regulated discharge of two brainstem cell groups that have self-excitatory and self-inhibitory connections and reciprocal firing pattern. In particular, the cholinergic REM-ON neurons, located in the laterodorsal-peducolopontine tegmentum, fire immediately before and during REM sleep, whereas the noradrenergic REM-OFF neurons, sited in the locus coeruleus, operate during NREM sleep and stop firing during REM sleep. The cessation of firing of the REM-OFF neurons seems to be a pre-requisite for the generation of REM sleep (107, 262). Therefore, the REM sleep suppression observed under clonidine may be related to the drug action on the postsynaptic α_2-adrenoceptors in the brainstem (263).

Under clonidine, the drastic alteration of the NREM/REM sleep cycle was paralleled by the alteration of the cyclic rise of CAP phase A2 and A3 in the pre-REM periods. It has been hypothesized that the abundance of CAP phase A1 in the descending phase of the sleep cycle is the EEG expression of the cerebral mechanisms involved in the build-up and maintenance of deep NREM sleep and may reflect the REM-OFF cell activity. Conversely, CAP phases A2 and A3 are predominant in the period preceding the onset of REM sleep (ascending phase) and may express the REM-ON drive (83). Thus, the increase in CAP variables (e.g., CAP time, CAP sequence, number and percentage of CAP phase A3) observed under clonidine may be related, among others, to its adrenergic action in the brainstem.

In the brainstem, the arousal system acts as a control mechanism that paces the progression of NREM/REM sleep cycle and protects sleep architecture against destabilizing stimulations. Arousals are active adaptative responses of the sleep regulatory mechanisms, which tend to remove the stimulus-disturbance effect and re-establish an internal equilibrium (75). The analysis of CAP enriches the neurophysiological information on phasic arousals and supplies an appropriate framework for investigating periodic phenomena such as movements disorders, like periodic limb movements during sleep (PLMS) or sleep bruxism. Physiologic, paraphysiologic and pathologic motor activities during NREM sleep are almost always associated with a stereotyped arousal pattern characterized by an initial increase in EEG delta power and heart rate, followed by a progressive activation of faster EEG frequencies (91, 92). These findings suggest that motor patterns are already written in brain codes (central pattern generator) embraced with autonomic sequence of EEG events, but require a certain degree of activation (i.e., arousal) to become visibly apparent. Whether the outcome is a physiologic movement, a muscle jerk or a major epileptic attack will depend on a number of ongoing factors but all events share the common trait of arousal-activated phenomena (93). However, CAP is not the generator of sleep-related movements, rather it operates as a gating-control rhythm that set the pace of their periodic appearance. In particular, CAP phase A offers a permissive window for the activation of motor episodes, while CAP phase B provides the refractory background for their occurrence (91, 264).

Despite the increased sleep instability, RMMA were reduced under clonidine. This paradox may be explained by the fact that clonidine strongly disrupted the NREM/REM sleep cycles. It is noteworthy, however, that clonidine acts on multiple sites, in the central nervous system as well as in the periphery, influencing the autonomic nervous system, the sleep-wake cycles, the arousal processes and the muscle tone (258, 265-269). It is therefore arduous to establish the precise mechanism by which clonidine reduces RMMA during sleep. Nonetheless, its effect could be linked to the alteration observed in the pattern of occurrence of CAP phases A2 and A3. In facts, the well-demonstrated peak during the pre-REM periods is blunted under clonidine (See Figure 3.1.1 page 53). The loss of the

ultradian NREM/REM sleep cycle and the parallel physiological fluctuation of CAP A phases may possibly explain the effect of clonidine on RMMA occurrence.

Finally, the cross-correlation analysis performed to assess the temporal association between RMMA episodes and CAP phase A, showed a positive correlation for RMMA onset and A2 and A3 phases in both placebo and clonidine nights. These data suggest that whenever an RMMA event occurs, it is likely to be associated with the more powerful and facilitatory arousal phases (264).

4.1.2 Evidence from the Experimental Trial applying Sensory Stimulations during Sleep

Data derived from the sleep recordings of SB and control subjects during the arousal-eliciting protocol (Chapter 3, Section 3.2) corroborate the "permissive window" interpretation (270).

Overall, SB subjects did not differ from controls for sleep variables and quantitative EEG spectral analysis. Conversely, SB subjects showed a higher number of CAP phase A3 than controls. In the experimental night, when the VT/AD stimulations were applied, both groups of subjects showed greater sleep instability (i.e., increased CAP variables) without major changes in sleep homeostasis (e.g., delta activity). However, notwithstanding the increased number of phases A2 and A3, RMMA occurrence was neither augmented nor induced in SB subjects or controls. This result may be explained by the fact that CAP phase A does not switch on the generator of movements during sleep, but rather provides the facilitatory background for the periodic occurrence RMMA in predisposed individuals.

Other considerations should also be pointed out. First of all, it appears that young and otherwise healthy SB subjects have a normal sleep structure, physiologic sleep homeostatic processes, and sleep instability within normal range. The only variable that differ between SB and control subjects in baseline conditions is the distribution between the differ subtypes of CAP phase A. In particular, SB subjects have a greater number per hour

of phase A3, the most powerful arousal phase. It seems, therefore, that what distinguish SB subjects from control is not the incidence of arousal, rather the magnitude of it (61, 66, 270). As arousals are a physiological structural component of sleep that ensures its reversibility in response to sensory inputs, noisy environment and movements (75), this increased number of CAP phase A3 may be also related to the higher number of RMMA during sleep that characterized SB subjects.

A range of variable arousal phenomena has been described in the literature according to the different combinations of associated EEG, behavioral, and autonomic activities (75, 271). Cortical arousal is distinguished from subcortical arousal, which is identified when autonomic activation is associated with a transient EEG patterns different from the conventional AASM arousal, and from behavioral arousal (also called movement arousal), which is described as any increase in EMG activity accompanied by a change in any other EEG channel (257). Cortical arousal can be generated directly by the cortex under the impulse of the physiologic evolution of sleep (e.g., the transition from NREM to REM sleep), or in response to a sensory perturbation, such as respiratory interruption (e.g., respiratory effort-related arousal, RERA), noisy environment, alteration of blood pressure or heart rate, painful stimuli, and motor activities (91, 134, 272, 273). The filter that gates the information to the cortex is situated in the thalamo-cortical connections where the incoming signals are blocked or attenuated via synaptic inhibition. In any case, the involvement of the brain makes arousal a unitary phenomenon, in which activation is modulated through a hierarchy of phasic responses ranging from slow high-amplitude (i.e., CAP subtypes A1) to fast low voltage EEG patterns (i.e., CAP subtypes A3) (82). In fact, the differentiation between CAP phases A1, A2, and A3 reflects theses differences, in which A1 corresponds to the “synchronization arousal” associated with only mild autonomic and muscular activation, whereas A3 is characterized by desynchronized EEG, and more powerful autonomic and behavioral activations (75, 82).

Other sleep-related movement disorders, such as PLMS, have been observed in association with CAP phases A2 and A3, supporting the facilitatory role of arousal phase A

(91). As in PLMS subjects (91, 273), the greater arousal instability found in SB subjects may be due to RMMA motor events *per se* or to the effects of external disrupting factors, such as VT/AD stimuli (or clonidine) in experimental conditions. Furthermore, these results support the hypothesis that RMMA is probably initiated and regulated by different mechanisms, such as the autonomic sympathetic cardiac activity (64, 94), the hypothalamic-adrenal axis (32, 115, 116), genetic factors (68), or complex neurochemical influences (20, 51), rather than sleep arousal alone.

In fact, the strong association and time-correlation between RMMA and CAP phase A3 do not establish a cause-and-effect relationship between these two phenomena. Indeed, in the experimental condition in which sub-threshold sensory stimulations were applied, the increased sleep instability was not associated with the development of RMMA in controls, or the increase of RMMA in SB subjects. Thus, arousal and sleep instability seem to be facilitating but not sufficient factors for RMMA occurrence during sleep. Other predisposing factors that distinguish controls from SB subjects, and possible triggers still need to be identified.

4.2 Sleep Bruxism, Snoring, and Headache: a Triad that Needs Further Investigations

A more clinical perspective characterized the last two research articles included in this thesis. In particular, they were aimed to study SB as a common sleep disorders frequently associated with other orofacial, sleep, and behavioral problems. Taking into account the methodology applied, new evidence has been provided to support the comorbidity between SB and HA, sleep problems and behavioral complaints. Conversely, further research will be needed to support the complex, and still unclear, relationship between SB and breathing during sleep.

4.2.1 Evidence from the Epidemiological Survey on a Pediatric Population

The cross-sectional investigation was conducted on a 7 to 17 years old population seeking orthodontic treatment (Chapter 3, Section 3.3). Based on questionnaires, the prevalence of SB was 15%, falling into the range of prevalence already reported in the literature. Interestingly, the prevalence of wake-time bruxism (i.e., tooth clenching, TC) was also assessed. More than 12% of the population reported to have TC habit during the day. The identification of these subgroups allowed calculating the risk for SB subjects and TC subjects compared to controls. The design of the study and the statistical approach do not allow establishing a cause-effect relationship between two conditions, rather they describe the strength of the association between independent variables.

SB and TC appear to be two distinct disorders; not only they occur in two different physical state (during sleep vs. during wakefulness), but they seem to affect two different populations. SB in fact, was more prevalent among children aged less than 12 years, whereas TC was predominantly reported by adolescents. Although this finding needs to be replicated and further investigated, some interpretations could be advanced. SB is a sleep-related movement disorders in which a genetic predisposition may play an important role. Little evidence is already available, although no specific genes, polymorphisms, or pattern of inheritance have been yet identified (68). On the other hand, TC during wake-time seems to be a learned behavior, an adaptive response or a coping strategy that an individual develops a bit later in life, when psychosocial factors and stressful events begin to be involved. It is not excluded, however, that SB and TC also share common risk factors, and coexist in the same individual. Longitudinal studies could help clarifying this aspect.

Focusing on SB only, the results of this cross-sectional investigation showed that children with SB are at increased risk of having a dental class II, tooth wear, jaw muscle fatigue, uncomfortable dental occlusion, frequent headache, loud breathing during sleep, and several sleep-related complaints (e.g., unrefreshing sleep, daytime sleepiness). Some of these findings deserve to be further discussed. First of all, the relationship between SB, headache, and sleep.

It has been already reported that children suffering from migraine and tension-type headache may have shorter sleep duration, longer sleep latency, difficulties to get asleep, and frequent awakenings. Migraine children frequently present parasomnias (e.g., sleep talking, sleepwalking, nightmares), sleep bruxism, snoring, sleep-disordered breathing and daytime sleepiness (148, 174, 274). Therefore, headache can be the presenting symptom of several sleep disorders, which could be misdiagnosed: in several cases of adult migraine, the polysomnographic study revealed the presence of a primary sleep disorder, and the treatment of the underlying clinical condition (e.g., PLMS, obstructive sleep apnea) greatly improved the symptom headache (275). This could be the case also in some SB children. In fact, in our study SB children were at higher risk for loud breathing during sleep, possibly a precursor of SDB. However, the report of sleep apnea was not different between SB subjects and controls. These data could be explained by the limits of the methodology used. Children and their parents may not be aware of breathing pauses during sleep, while they may hear tooth-grinding noises even from a separate room.

SDB and particularly obstructive sleep apnea (OSA) may cause headaches, with up to 70% of OSA patients suffering from headaches (275-277). Although this head pain seems to be a non-specific symptom (277), the types of headache in OSA have mainly features of tension-type headache, migraine or chronic migraine (278) often reported in the morning. The pathophysiology of morning headache in OSA patients is not clearly understood: the role of intermittent hypoxemia is controversial and only a weak relationship has been found with sleep parameters. However, treatment with continuous positive airway pressure (CPAP) devices may improve or resolve headache in a subset of OSA patients (279).

In a more recent study on 90 children with headache, it was showed that SDB were more frequent in children with migraine (56.6%) and nonspecific headache (54%) compared to chronic migraine (27%). Moreover, 50% of children with tension-type headache manifested SB vs. 2.4% of children with non-tension headache (175).

Literature data on a particular form of headache, cluster headache (CH), also showed that OSA can trigger CH attacks. Furthermore, CH has been reported as an associated disorder of OSA with comorbidity between 31% and 80% of the cases (280).

Considering the high prevalence of comorbid SB, headaches, and SDB putative underlying mechanisms may be suggested: headache could be either related to the musculoskeletal tension in the masseter and temporalis areas following excessive activation during sleep (i.e., SB), or to the concomitant obstructive respiratory events associated with oxygen desaturation and sleep fragmentation (i.e., upper airway resistance syndrome, SDB) (See Figure 1.4 page 28). Lastly, the possibility of intersecting epidemics cannot not be excluded.

Data collected in this cross-sectional investigation were the rationale to design an experimental trial using specific EMG recordings and breathing monitoring during sleep in order to investigate the aforementioned hypotheses.

4.2.2 New Insights on the Role of Mandibular Advancement Appliances

Based on recent reviews on the available treatments for SB, the use of mandibular advancement appliances (MAA) appears to be the most effective in reducing RMMA during sleep (203, 204). These data have been confirmed in two experimental polysomnographic trials conducted in our laboratory, which tested different designs of MAA in a short-term treatment for SB subjects. RMMA index was decreased by 47 to 83% when the mandible was in the advanced position (reaching 75% of the maximum jaw protrusion)(229, 230).

MAA are also used in the treatment of snoring and mild to moderate case of obstructive sleep apnea (281-283), and they have been recently found effective in the management of morning headache in non-apnea patients (231). Although promising, all these findings rely on short-term experimental trial performed on small samples of adult

subjects. There is a need to systematically evaluate the efficacy of oral appliances using follow-up polysomnograms (also a long-term), and to develop more objective measures of real-time compliance and efficacy of MAA (e.g., an intra-device thermal chip to monitor the duration of use).

Our study (Chapter 3, Section 3.4) confirms the short-term effectiveness of MAA also in adolescents with SB, snoring, and HA. However, although progressive clinical improvement was achieved, no significant difference was found between the free splints (control position), and the neutral or advanced positions (active jaw retaining or repositioning). Moreover, residual RMMA episodes and increase of other muscular activities involving the masticatory muscles were observed.

From a clinical point of view, the use of MAA did not cause any side effects, pain or intolerable discomfort in our sample of adolescents. We selected a group of subjects aged between 12 and 19 years to avoid the primary dentition. Only three subjects presented a mixed dentition, which, however, did not hamper the MAA fitting. All our participants adapted easily to the MAA and did not report any worsening of their sleep quality while sleeping with the appliance. None of the MAA broke during the trial, suggesting a good resistance of this device also in subjects with SB. However, it must notice that the MAA was used only for a short-term treatment. MAA safety and longevity, as well as patient's compliance need to be re-assessed in long-term trials.

The present findings also suggest new explanations on the putative mechanisms of action by which MAAs would act on RMMA occurrence. The different hypotheses will be examined in the following sections.

4.2.2.1 Mandibular advancement appliances and breathing

During sleep, a general reduction in airflow (i.e., hypoventilation) and a decreased respiratory rate are physiologically observed. These are the consequences of the loss of the wakefulness respiratory control, and the sleep-related decrease in the ventilatory responses

to hypoxemia and hypercapnia (59, 284). Moreover, at sleep onset the activity of respiratory muscles falls, with a predominant effect on those muscles that combine respiratory and non-respiratory (e.g., postural and behavioral) functions, such as the pharyngeal muscles (285). This causes a transient decrease in ventilation and increased upper airway resistance even in healthy individuals (286). The pharynx is a highly collapsible and most vulnerable structure of the upper airway, since it lacks substantial bony or rigid support. Most frequently, the airway obstruction involves the velopharynx or retropalatal area, which presents the minimum caliber of the upper airway, and the oropharynx or retroglossal area, where soft tissue structures like the soft palate, tongue and tonsils promote airway obstruction (285, 287). The patency of the pharynx during respiration is almost completely dependent on the activity of the pharyngeal dilator muscles, such as the palatoglossus, the levator and tensor veli palatini, the genioglossus, the geniohyoideus, the pharyngeal constrictors, and also the masseter and pterygoid muscles, which contraction influences the position of the mandible and contributes to the maintenance of upper airway patency (288).

When a partial or complete obstruction of the upper airway takes place, the subsequent hypoxia and hypercapnia may elicit an arousal from sleep. Arousals are efficient physiological protective mechanism that contributes in removing the precipitating cause of collapse and reestablishing upper airway patency. Indeed, arousal is generally associated with a substantial increase in the activity of pharyngeal dilator muscles and sympathetic nervous system. Although effective, sleep arousal does not prevent episodes of obstructive apnea/hypopnea to cyclically reoccur and, on the other hand, it may have detrimental effects on sleep continuity and sleep quality.

The primary mechanism of action of an MAA seems to be mechanical. Despite the slight differences related to the MAA design, it keeps the jaw in a more anterior position, thus the tongue and the related soft tissues, resulting in an increased anterior-posterior and lateral dimensions of both the velopharynx and oropharynx (289, 290). These changes are thought to be mediated by mechanical stretching of the palatoglossal and palatopharyngeal

arches, through which exist intricate linkages with the muscle of the tongue, soft palate, lateral pharyngeal walls, and mandibular attachments. By increasing and stabilizing the upper airway space, the MAA prevents the collapse of the pharyngeal structures and improves respiration during sleep. The progressive advancement of the mandible, which can be reached in dependence on the individual jaw range of motion and MAA design, is an important factor that can influence the effectiveness of the treatment in SDB.

Our hypothesis was that the improved breathing during sleep with an MAA might be also responsible for the reduction of RMMA episodes, which occur as a "reaction" to slight upper airway obstruction or upper airway resistance. This explanation is supported by the superior efficacy of MAA compared to stabilization splints, and by the progressive improvement achieved when the MAA was in the advanced position. However, no significant difference was found in our study between the three tested MAA positions. If SB is a response to sleep-related hypoventilation or upper airway resistance, also in the absence of frank episodes of obstructive sleep apnea, remains to be demonstrated.

4.2.2.2 Mandibular advancement appliances and the masticatory system

By repositioning the jaw, the MAA may also exert some actions on the masticatory system. The masticatory muscles, including the masseter and the temporalis, are involved in many functions, such as chewing, swallowing, talking, and breathing. Chewing is a repetitive motor activity driven by the central pattern generator (CPG) within the central nervous system (45). The CPG is responsible of initiating and maintaining the pattern and the pace of this motor activity. The integration of peripheral influences from sensory inputs, such as those from muscle spindles, temporomandibular joint, oral mucosal, and periodontal mechanoreceptors, is necessary to control or fine-tune the rhythmic jaw movements. In particular, the trigeminal motoneuron activities are influenced by jaw muscle spindle afferents that carry information about muscle length, jaw position, and, to certain extent, tension (45). It cannot be excluded that the use of an MAA changes these

inputs. However, jaw muscle spindle activity has not yet been studied during sleep, and the role of peripheral sensory information, as well as the masticatory and respiratory CPG interactions on the onset and regulation of RMMA is still unknown (50, 291).

Alternatively, the reduction of SB-related motor activity observed with an MAA may be due to use of a semi-rigid oral appliance composed by two linked splints, which markedly restrict the range of jaw movements. However, we reported, in contrast to previous findings (230), that other orofacial muscular activities were increased with the MAA. These activities may include lip sucking, talking, swallowing, yawning, head movements, which are accounted for 40% of the muscular events in SB subjects in normal conditions (13, 14). Their increase (approximately by 35%) may be related to the lower scoring specificity and sensitivity of the study, since it was carried out with an ambulatory PSG system in absence of audio-video recordings. However, it could also been explained by the hypothesis that the use of a MAA would influence and change the observable EMG pattern of movement, rather that altering the efferent inputs to the CPG. In other words, the trigger of RMMA during sleep is preserved, but the bulky appliance does not allow scoring it since the characteristic EMG features (e.g., rhythmic bursts of 0.25-2 seconds) are not recognizable. This hypothesis might also be supported by a recent article, which studied masticatory muscle EMG activity during sleep in SB subjects wearing different designs of oral appliances, i.e., occusal splint vs. free maxillary-mandibular appliance vs. connected maxillary-mandibular appliance (design very similar to a MAA)(292). The authors found that the restriction of mandibular movements due to the connected maxillary-mandibular appliance do not exert a major influence on jaw-muscle activity compared to the other designs. However, they interestingly found that there was a specific suppression of phasic EMG episodes no matter the type of oral device. Conversely, the jaw muscles tonic activity was not modified by the use of such devices (292). Although these recent supporting data, further analyses on the periodicity and occurrence (e.g., in relation to sleep arousal) of orofacial motor activities, and further research on the effect of oral appliance on EMG activities during sleep would be extremely useful to elucidate this issue.

Finally, it remains to be assessed whether the effectiveness of MAA on headache complaints is linked to the improvement of breathing (i.e., oxygen saturation, sleep fragmentation), to the reduction of masticatory muscular activity during sleep, to both, or it may be attributed to other mechanisms, e.g., a placebo effect. These hypotheses remain possible, and the questions remain open.

4.2.2.3 More than one type of RMMA?

Of the many treatment approaches tested for SB, none completely abolished RMMA episodes during sleep (203). Based on this refractory effect, it may be suggested, as for other spontaneous movements during sleep (e.g., period limb movements), that there is more than one type of RMMA.

In the case of PLMS, for example, leg movements are frequently observed in association of cortical arousals and/or breathing events. In patients with OSA, PLMS typically occur synchronously with breathing resumption at the end of the apnea event, and are often suppressed by continuous positive airway pressure (CPAP) treatment (293-296). These PLMS may have a different pathogenesis compared to PLMS in other sleep disorders, (e.g., insomnia, narcolepsy), in terms of neurotransmitter or nervous pathways implicated in their generation.

In parallel, isolated or idiopathic RMMA, arousal related-RMMA, breathing-related RMMA, and leg or body movement-related RMMA could be distinguished. These events may all share common etiologic factors, but their occurrence may be regulated and paced by different related phenomena during sleep. Moreover, each type of RMMA may be more responsive to the specific treatment that particularly addresses the different related factors. The scientific and clinical relevance of the aforementioned theory need to be assessed in future investigations.

4.3 Scientific and Clinical Relevance of the Findings

The findings of this thesis added to the current literature new insights on the etiology, pathophysiology, and management of SB. A better understanding of the pathogenesis and regulation of rhythmic masticatory muscle activity during sleep is essential to identify evidence-based treatments that will improve the quality of care provided in clinical settings. This was in fact the two-folds objective of the thesis (from the title: "*Rhythmic Masticatory Muscle Activity during Sleep: Etiology and Clinical Perspectives*").

From a scientific perspective, the analysis of CAP allowed defining the role of sleep arousal, which had been considered a potential trigger or cause of RMMA for many years. Based on our data, sleep arousal is not the generator of motor events during sleep, rather the "permissive window" in which these events become manifest. Classical polysomnographic measures used to assess sleep quality (e.g., sleep efficiency, sleep latency, sleep arousal) were not able to finely describe the micro-structural components of sleep. As in a hierarchy of PSG measures, CAP variables appear to be the most sensitive scoring method to any source of internal and external perturbation during sleep, even in young healthy individual affected by SB only (our study population).

We reported for the first time the effect of a widely known medication, clonidine, on the macro- and micro-structure of sleep. This may provide evidence for other medical disorders in which clonidine is administered (e.g., menopause symptoms; opioid withdrawal syndrome), and support further research in the field. Moreover, the scoring and analysis of CAP will be extremely useful to assess the manifold deterioration of sleep in case of SB patients affected by other sleep disorders, such as insomnia, SDB, and RLS. In case of concomitant pain syndrome (e.g., TMD) as well, CAP can be used to investigate the source of sleep perturbation that is clinically manifest with varying symptoms, like fatigue, sleepiness, and neuro-cognitive dysfunction. Not lastly, it would be interesting to analyze

CAP in order to assess the effect of different treatments for SB, and other sleep disorders, on sleep stability and arousal pressure.

From a clinical perspective, our research provides scientific evidence to support the clinical impression that SB is often concomitant with other sleep and medical disorders. In the knowledge transfer process, we tried to increase the awareness that SB, a well-known burden for dentists, is much more than tooth wear, as it is frequently associated with orofacial pain, TMD, headaches, behavioral problems, and sleep complaints, including more severe sleep disorders, like sleep-disordered breathing. Dentists are responsible for the detection and prevention of SB detrimental consequences on patients' oral health. However, they are also called to be part of a multidisciplinary team of sleep specialists (e.g., pulmonologists, neurologists, psychologists), which represents the most efficient approach in the field of sleep medicine.

In particular, our research attempts to offer guidance to dentists and orthodontics in the diagnostic and therapeutic processes of SB and comorbid conditions. Their role could be cardinal in screening sleep disorders and identify risk factors in dental patients.

It has been proven that a wide range of craniofacial anatomical abnormalities contributes to airway collapsibility during sleep and predisposes individuals to develop SDB (297, 298). These include the reduced size of craniofacial bony structures (e.g. micrognatia, reduced mandibular body length, skeletal class II), and the retro-positioning of the maxilla-mandibular complex, which compromise the pharyngeal airspace. These craniofacial abnormalities are primarily inherited, but many environmental and functional factors can also influence the craniofacial development towards conditions of airspace narrowing (299, 300). Also the pediatric SB subjects in our epidemiological study (Section 3.3) have been found to be a skeletal/dental class II (i.e., retrognathic profile) with a frequency significantly higher than controls, suggesting a possible predisposing conditions to SDB that deserves further investigations (301).

An increasing amount of literature is nowadays dedicated at identifying preventing procedures or treatments that can act on craniofacial structures. Firstly, the orthodontic and orthopedic treatments have a great influence on these structures, by guiding the craniofacial growth during childhood and correcting eventual abnormalities in youth (302). The great importance of screening pediatric patients, identifying risk factors, and promote early diagnosis and treatment is related to the severe consequences that untreated SDB or OSA can cause during childhood and later in life. These include: very poor sleep quality, sleepiness, behavioral disturbances, learning deficits, cardiovascular morbidity, metabolic disturbances, and failure to thrive (303-307). This long list of medical problems highlights the clinical relevance of pursuing research in the objective of identifying preventive procedures and effective treatments.

We also reported for the first time in the literature the use of an MAA in adolescents in the management of symptomatic SB. Our results demonstrated that in a short-term basis, this treatment approach seems to be effective, well-tolerated, and safe even in this population. No side effect was recorded and high compliance was reported. Moreover, sleep quality was not affected by the use of MAA in any tested position. These results on the positive short-term effect of MAA may serve as pilot data for new long-term clinical trials. In fact, the use of MAA represents a non-pharmacologic treatment option that deserves high consideration in the management of sleep disorders, such as SB, HA pain, and SDB, especially in pediatrics. In the perspective of a multifactor etiology, it could also be suggested to study the effect of a combined therapy, i.e., MAA + CBT, for the treatment of SB and other sleep disorders (e.g., insomnia comorbid with SDB or snoring). This approach may have high clinical relevance, considering its characteristics of being conservative, reversible, and safe.

Finally, the use of an ambulatory PSG system to study sleep bruxism has never been applied before in adolescents. Although this methodology needs to be validated, it seems to be a powerful and advantageous tool that should be considered in future experimental and epidemiological studies (See Section 4.4.2).

4.4 Study Limitations and Future Directions

Study limitations, present in all the four research articles, should be considered when interpreting the present results.

Concerning the first two articles (Sections 3.1 and 3.2), the major limitation is related to the small sample of subjects recruited (due to the strict recruitment criteria applied), and the highly experimental settings. Although significant and reciprocally confirmatory, these results cannot be generalized without caution. Other pharmacological or physical manipulation of sleep physiology (e.g., REM sleep deprivation or induction) may assist in determining the role of other arousal-related factors that participate in RMMA occurrence.

The epidemiological survey instead (Section 3.3) was conducted on a large pediatric population. However, all subjects included in the study were seeking orthodontic treatment at the Orthodontic Clinic of the University of Montreal. Since the external validity of the present results has not yet been proven, these findings cannot be extrapolated to the general population. Moreover, the survey was mainly based on questionnaires, whose reliability is always limited, and which was missing questions to investigate stress and anxiety related complaints that may also be involved in the genesis of both sleep and wake-time bruxism.

Finally, the experimental trial with the MAA in adolescents (Section 3.4) suffers from some limitations related to the methodology applied. For example, the headache complaint was studied though questionnaires that were filled by the subjects the day of each PSG recording (i.e., after 1 week of MAA treatment). Since our sample was selected based on the report of frequent headache (>1/week) disregarding the time of the day, we may have not intercepted neither the actual benefit of the MAA nor a potential worsening. A different subject selection (e.g., subjects reporting frequent HA only in the morning), or a different assessment tool (e.g., HA diary), would have helped minimize at these problems. Moreover, although the sample size was estimated *a priori*, the number of subjects enrolled in the study was not sufficient to show significant differences between the three MAA

positions tested during the protocol. Thus, we could not confirm or deny the main hypothesis on the role of opening the airway and improving breathing during sleep on RMMA and headache complaints.

In order to confirm and further investigate the main research hypotheses of this thesis, further analyses need to be done.

4.4.1 What I Would Do Differently

In order to test the hypothesis that a common underlying pathogenetic mechanism links SB, HA, and breathing during sleep, I would suggest the followings:

- The relationship between SB and SDB should have been studied in a population of adolescents with frank OSA (AHI >2). The high incidence of obstructive apnea/hypopnea events would have allowed performing time-correlation analyses between RMMA and OSA, also in respect to sleep arousal and oxygen saturation levels. Then, the use of an MAA would have helped teasing out the role of breathing in the genesis of RMMA during sleep.
- To understand the role of respiration in SB, the monitoring of CO_2 levels would have been very useful to investigate possible oscillation in the hypoxia and hypercapnia levels, which may be responsible of arousal and RMMA, even in absence of frank episodes of obstructive sleep apnea.
- To understand the pathophysiology of HA in relation of SB, I should have included and compared two groups: a group of SB subjects reporting frequent HA in the morning (upon awakening), and a group of SB subjects reporting frequent HA during the day (toward the evening). The first group is suspected to be a sleep-breathing type of HA, whereas the latter one is more probably a form of tension-type HA secondary to wake-time bruxism, sleep bruxism, or TMD. There is a need to finely define the

overlap and the different characteristics of these forms of HA, which may also coexist in the same patient.

4.4.2 What Needs to Be Done

Based on the present findings, my future research agenda could be:

- The validity of ambulatory PSG recordings to diagnose SB needs to be assessed. To date, the published scoring criteria for RMMA are based on in-lab PSG data combined with an audio-video recording (level I). The highly controlled setting (e.g., sleep lab with sleep technicians attending the PSG) and the presence of a video camera zoomed on the face of the sleeping individual, ensure very good level of specificity and sensitivity in identifying RMMA episodes during sleep. These factors are obviously lost in a home PSG recording. However, other advantages are present, such as the more comfortable and natural sleep environment, and the higher participant's compliance in the study.

  We therefore designed a study to validate this promising tool for both research and clinical purposes. Ten subjects slept with the ambulatory PSG system while an audio-video recording was performed. Their nights will be scored with and without video, and concordance tests will be applied in order to define the specificity and sensitivity associated with the scoring of RMMA in absence of the standard required criteria (i.e., video). Preliminary analyses suggest a mean concordance rate of 68% (*Carra et al., article in preparation*).

- The epidemiology of SB needs to be studied with tools that allow an objective assessment of this sleep disorders. In this case, sophisticated although simplified recording methods (PSG level III and IV) could be applied in large populations in order to have a confirmed diagnosis of SB and related sleep disorders, which are frequently unreported by the subjects since they all occur during sleep (e.g., snoring or

sleep apnea). Moreover, confounding factors and differential diagnosis (e.g., with wake-time bruxism) could be more reliably assessed.

- Longitudinal cohort studies are also needed to identify the predisposing and risk factors that differentiate children with SB from controls. In particular, anatomical (e.g., craniofacial morphology and development), functional (e.g., mouth vs. nasal breathing), and psychosocial factors (e.g., personality traits and stressors) are the major candidates that should be assessed with objective and quantitative measures (e.g., 3D imaging, psychological questionnaires/interview) in children with and without SB.
- Sleep instability and CAP should be analyzed in adolescents with SB and comorbidities (e.g., snoring and headache), and the effect of an MAA on CAP variables should be evaluated (it has not yet been done). As for rapid maxillary expansion done in SDB children (308), it would be interesting to show that an effective treatment with an MAA would normalize sleep instability by reducing RMMA and improving breathing during sleep. I plan to realize this project as my first research study once I will be back in my own town Parma, Italy.
- Finally, new research avenues should be explored to elucidate the etiological hypotheses on the genesis of RMMA during sleep. The role of many mechanisms involved in sleep regulation, homeostatic process, circadian rhythm, and neuroendocrine systems remains unknown.

  Recently discovered hormones responsible of appetite and feeding behaviors, like ghrelin and leptin, may be implicated in the genesis of sleep-related rhythmic motor activities, like RMMA. There is evidence, in fact, that ghrelin has a physiological role in meal initiation in humans, whereas leptin suppresses appetite (309). Ghrelin levels rise in the first hours after sleep onset and progressively decrease toward the end of the night. Leptin levels during sleep counteract ghrelin ones, maintaining a relatively steady high level throughout the night. A hypothetical unbalance in the ghrelin/leptin ratio or specific ghrelin fluctuations during sleep may initiate abnormal behaviors related to feeding, such as rhythmic jaw muscle activities, at an incorrect time (e.g.

during sleep). Furthermore, the unconsumed feeding would not inhibit ghrelin secretion, thus allowing the "chewing" event to reoccur. Ghrelin secretion also appears to be directly stimulated by the sympathetic nervous system in rats (310). This finding is also clinically supported in sleep apnea patients, who have high sympathetic nervous activity and increased ghrelin levels (311).

The episodic and transient autonomic reactivations, considered the permissive window for the activity of trigeminal motorneurons, may also provide excitatory or disinhibitory mechanisms in ghrelin secretion regulation. Hypocretin system as well may be involved, activating brainstem arousal centers, increasing sympathetic tone and promoting feeding behaviors (312). This unexplored research field may be proposed as a new interesting perspective to elucidate the multiple mechanisms associated with the genesis of SB. Clinical trials could be designed to define the 24 h profile of leptin and ghrelin in sleep bruxism subjects and to challenge ghrelin secretion and sleep bruxism activity, for example in conditions of sleep restriction.

Conclusion

Sleep bruxism (SB) is a common sleep disorder characterized by recurrent rhythmic masticatory muscle activity (RMMA), which occurs in periods of sleep instability mostly associated with sleep arousal. Sleep arousal is coupled with surges of sympathetic nervous system activity, heart rate, and blood pressure, which may prelude to the RMMA. In fact, sleep arousal is considered the "permissive window" for the occurrence of motor events during sleep that follow a periodic fluctuation over the NREM/REM sleep cycle. Conversely, the trigger or cause, as well as the function, of RMMA are still unknown; the hypothetic role in physiologic functions, such as breathing, needs further investigations.

There is evidence, however, that SB is frequently concomitant with other medical problems or complaints (e.g., headache, sleep disorders), which should be taken into account in the clinical assessment and management of this sleep disorder. The use of mandibular advancement appliances could be an effective treatment option in cases of SB associated with snoring and headache. More research should be dedicated at studying the long-term effectiveness, compliance, and side effects of this treatment in both adult and pediatric populations.

This thesis represents just a little step forward in the research field of sleep bruxism. When I began my PhD, I felt it was like a mountain to climb, and once reaching the top I would have found the answer. I learnt that a researcher never stops climbing. New findings are immediately followed by new questions, in a never-ending process that feeds our interest and curiosity every day. I hope to pursue this path with the same motivation that drove me to this achievement.

References

1. Marie M, Pietkiewicz M. *La Bruxomanie*. Rev De Stomat 1907;14:107-116.
2. Frohman B. *The application of psychotherapy to dental problems.* Dent Cosmos 1931;73:1117-1122.
3. Faulkner KD. *Bruxism: a review of the literature. Part II.* Aust Dent J 1990;35:355-361.
4. Faulkner KD. *Bruxism: a review of the literature. Part I.* Aust Dent J 1990;35:266-276.
5. Miller S. *Oral diagnosis and treatment planning.* Philadelphia: P. Blakiston, 1936.
6. Ramfjord SP, Ash MM, Jr. *Centric and eccentric bruxism*. Occlusion. Philadelphia: Saunders, 1971.
7. Lavigne G, Manzini C, Huynh NT. *Sleep Bruxism* In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:1129-1139.
8. *The glossary of prosthodontic terms*. J Prosthet Dent 2005;94:10-92.
9. De Leeuw R. *Orofacial Pain. Guidelines for Assessment, Diagnosis and Management.* Chicago: Quintessence Publishing, 2008.
10. AASM. *International classification of sleep disorders, 2nd ed.: Diagnosis and coding manual. (ICSD-2)*. Westchester, Illinois.: American Academy of Sleep Medicine (AASM) eds. , 2005.
11. De Laat A, Macaluso GM. *Sleep bruxism as a motor disorder*. Mov Disord 2002;17 Suppl 2:S67-69.
12. Lavigne GJ, Rompre PH, Poirier G, Huard H, Kato T, Montplaisir JY. *Rhythmic masticatory muscle activity during sleep in humans*. J Dent Res 2001;80:443-448.
13. Kato T, Thie NM, Montplaisir JY, Lavigne GJ. *Bruxism and orofacial movements during sleep*. Dent Clin North Am 2001;45:657-684.
14. Dutra KM, Pereira FJ, Jr., Rompre PH, Huynh N, Fleming N, Lavigne GJ. *Oro-facial activities in sleep bruxism patients and in normal subjects: a controlled polygraphic and audio-video study*. J Oral Rehabil 2009;36:86-92.
15. Lavigne GJ, Rompre PH, Montplaisir JY. *Sleep bruxism: validity of clinical research diagnostic criteria in a controlled polysomnographic study*. J Dent Res 1996;75:546-552.
16. Walters AS, Lavigne G, Hening W, Picchietti DL, Allen RP, Chokroverty S, et al. *The scoring of movements in sleep*. J Clin Sleep Med 2007;3:155-167.
17. Hirshkowitz M, Kryger MH. *Monitoring Techniques for Evaluating Suspected Sleep-Disordered Breathing*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:1610-1623.
18. Iber C, Anacoli-Israel S, Chesson A, Quan SF. *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications.* Westchester, IL: American Academy of Sleep Medicine (AASM) 2007.

19. Koyano K, Tsukiyama Y, Ichiki R, Kuwata T. *Assessment of bruxism in the clinic*. J Oral Rehabil 2008;35:495-508.
20. Lavigne GJ, Khoury S, Abe S, Yamaguchi T, Raphael K. *Bruxism physiology and pathology: an overview for clinicians*. J Oral Rehabil 2008;35:476-494.
21. Abe S, Yamaguchi T, Rompre PH, De Grandmont P, Chen YJ, Lavigne GJ. *Tooth wear in young subjects: a discriminator between sleep bruxers and controls?* Int J Prosthodont 2009;22:342-350.
22. Johansson A, Johansson AK, Omar R, Carlsson GE. *Rehabilitation of the worn dentition*. J Oral Rehabil 2008;35:548-566.
23. Pergamalian A, Rudy TE, Zaki HS, Greco CM. *The association between wear facets, bruxism, and severity of facial pain in patients with temporomandibular disorders*. J Prosthet Dent 2003;90:194-200.
24. Chan ASL, Lee RWW, Cistulli PA. *Sleep-related Breathing Disorders*. In: Lavigne GJ, Cistulli PA, Smith MT (eds). Sleep Medicine For Dentists A Practical Overview. Hanover Park, Illinois: Quintessence Publishing Co, nc, 2009:35-40.
25. Philip P, Sagaspe P, Moore N, Taillard J, Charles A, Guilleminault C, et al. *Fatigue, sleep restriction and driving performance*. Accid Anal Prev 2005;37:473-478.
26. Rompre PH, Daigle-Landry D, Guitard F, Montplaisir JY, Lavigne GJ. *Identification of a sleep bruxism subgroup with a higher risk of pain*. J Dent Res 2007;86:837-842.
27. Ikeda T, Nishigawa K, Kondo K, Takeuchi H, Clark GT. *Criteria for the detection of sleep-associated bruxism in humans*. J Orofac Pain 1996;10:270-282.
28. Gallo LM, Lavigne G, Rompre P, Palla S. *Reliability of scoring EMG orofacial events: polysomnography compared with ambulatory recordings*. J Sleep Res 1997;6:259-263.
29. van der Zaag J, Lobbezoo F, Wicks DJ, Visscher CM, Hamburger HL, Naeije M. *Controlled assessment of the efficacy of occlusal stabilization splints on sleep bruxism*. J Orofac Pain 2005;19:151-158.
30. Koyano K, Tsukiyama Y. *Clinical Approach to Diagnosis of Sleep Bruxism*. In: Lavigne GJ, Cistulli PA, Smith MT (eds). Sleep Medicine For Dentists A Practical Overview. Hanover Park: Quintessence Publishing Co, nc, 2009:109-116.
31. Lavigne GJ, Montplaisir JY. *Restless legs syndrome and sleep bruxism: prevalence and association among Canadians*. Sleep 1994;17:739-743.
32. Ohayon MM, Li KK, Guilleminault C. *Risk factors for sleep bruxism in the general population*. Chest 2001;119:53-61.
33. Cheifetz AT, Osganian SK, Allred EN, Needleman HL. *Prevalence of bruxism and associated correlates in children as reported by parents*. J Dent Child (Chic) 2005;72:67-73.
34. Laberge L, Tremblay RE, Vitaro F, Montplaisir J. *Development of parasomnias from childhood to early adolescence*. Pediatrics 2000;106:67-74.
35. Petit D, Touchette E, Tremblay RE, Boivin M, Montplaisir J. *Dyssomnias and parasomnias in early childhood*. Pediatrics 2007;119:e1016-1025.

36. Serra-Negra JM, Paiva SM, Seabra AP, Dorella C, Lemos BF, Pordeus IA. *Prevalence of sleep bruxism in a group of Brazilian schoolchildren*. Eur Arch Paediatr Dent 2010;11:192-195.
37. Simola P, Niskakangas M, Liukkonen K, Virkkula P, Pitkaranta A, Kirjavainen T, et al. *Sleep problems and daytime tiredness in Finnish preschool-aged children-a community survey*. Child Care Health Dev 2010;36:805-811.
38. Strausz T, Ahlberg J, Lobbezoo F, Restrepo CC, Hublin C, Ahlberg K, et al. *Awareness of tooth grinding and clenching from adolescence to young adulthood: a nine-year follow-up*. J Oral Rehabil 2010;37:497-500.
39. Ng DK, Kwok KL, Cheung JM, Leung SY, Chow PY, Wong WH, et al. *Prevalence of sleep problems in Hong Kong primary school children: a community-based telephone survey*. Chest 2005;128:1315-1323.
40. Carlsson GE, Egermark I, Magnusson T. *Predictors of bruxism, other oral parafunctions, and tooth wear over a 20-year follow-up period*. J Orofac Pain 2003;17:50-57.
41. Glaros AG. *Incidence of diurnal and nocturnal bruxism*. J Prosthet Dent 1981;45:545-549.
42. Mobilio N, Casetta I, Cesnik E, Catapano S. *Prevalence of self-reported symptoms related to temporomandibular disorders in an Italian population*. J Oral Rehabil 2011.
43. Nekora-Azak A, Yengin E, Evlioglu G, Ceyhan A, Ocak O, Issever H. *Prevalence of bruxism awareness in Istanbul, Turkey*. Cranio 2010;28:122-127.
44. Miles TS. *Mastication*. In: Miles TS, Nauntofte B, Svensson P (eds). Clinical Oral Physiology: Quintessence Pub Co, 2004:219-243.
45. Lund JP. *Mastication and its control by the brain stem*. Crit Rev Oral Biol Med 1991;2:33-64.
46. Turker KS. *Reflex control of human jaw muscles*. Crit Rev Oral Biol Med 2002;13:85-104.
47. Lund JP, Kolta A, Westberg KG, Scott G. *Brainstem mechanisms underlying feeding behaviors*. Curr Opin Neurobiol 1998;8:718-724.
48. Huang CS, Hiraba H, Murray GM, Sessle BJ. *Topographical distribution and functional properties of cortically induced rhythmical jaw movements in the monkey (Macaca fascicularis)*. J Neurophysiol 1989;61:635-650.
49. Gastaldo E, Quatrale R, Graziani A, Eleopra R, Tugnoli V, Tola MR, et al. *The excitability of the trigeminal motor system in sleep bruxism: a transcranial magnetic stimulation and brainstem reflex study*. J Orofac Pain 2006;20:145-155.
50. Kato T, Thie NM, Huynh N, Miyawaki S, Lavigne GJ. *Topical review: sleep bruxism and the role of peripheral sensory influences*. J Orofac Pain 2003;17:191-213.
51. Lavigne GJ, Kato T, Kolta A, Sessle BJ. *Neurobiological mechanisms involved in sleep bruxism*. Crit Rev Oral Biol Med 2003;14:30-46.
52. Kato T, Dal-Fabbro C, Lavigne GJ. *Current knowledge on awake and sleep bruxism: overview*. Alpha Omegan 2003;96:24-32.
53. Lobbezoo F, Naeije M. *Bruxism is mainly regulated centrally, not peripherally*. J Oral Rehabil 2001;28:1085-1091.

54. Nakamura Y, Katakura N, Nakajima M. *Generation of rhythmical ingestive activities of the trigeminal, facial, and hypoglossal motoneurons in in vitro CNS preparations isolated from rats and mice*. J Med Dent Sci 1999;46:63-73.
55. Steriade M, Timofeev I, Grenier F. *Natural waking and sleep states: a view from inside neocortical neurons*. J Neurophysiol 2001;85:1969-1985.
56. Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. *Breakdown of cortical effective connectivity during sleep*. Science 2005;309:2228-2232.
57. Saper CB, Scammell TE, Lu J. *Hypothalamic regulation of sleep and circadian rhythms*. Nature 2005;437:1257-1263.
58. Saper CB, Cano G, Scammell TE. *Homeostatic, circadian, and emotional regulation of sleep*. J Comp Neurol 2005;493:92-98.
59. Horner RL, Kozar LF, Kimoff RJ, Phillipson EA. *Effects of sleep on the tonic drive to respiratory muscle and the threshold for rhythm generation in the dog*. J Physiol 1994;474:525-537.
60. Lavigne GJ, Huynh N, Kato T, Okura K, Adachi K, Yao D, et al. *Genesis of sleep bruxism: motor and autonomic-cardiac interactions*. Arch Oral Biol 2007;52:381-384.
61. Macaluso GM, Guerra P, Di Giovanni G, Boselli M, Parrino L, Terzano MG. *Sleep bruxism is a disorder related to periodic arousals during sleep*. J Dent Res 1998;77:565-573.
62. Reding GR, Zepelin H, Robinson JE, Jr., Zimmerman SO, Smith VH. *Nocturnal teeth-grinding: all-night psychophysiologic studies*. Int J Orthod 1968;6:111.
63. Satoh T, Harada Y. *Tooth-grinding During Sleep as an Arousal Reaction*. Experientia 1971;27:785-786.
64. Huynh N, Kato T, Rompre PH, Okura K, Saber M, Lanfranchi PA, et al. *Sleep bruxism is associated to micro-arousals and an increase in cardiac sympathetic activity*. J Sleep Res 2006;15:339-346.
65. Kato T, Montplaisir JY, Guitard F, Sessle BJ, Lund JP, Lavigne GJ. *Evidence that experimentally induced sleep bruxism is a consequence of transient arousal*. J Dent Res 2003;82:284-288.
66. Kato T, Rompre P, Montplaisir JY, Sessle BJ, Lavigne GJ. *Sleep bruxism: an oromotor activity secondary to micro-arousal*. J Dent Res 2001;80:1940-1944.
67. Satoh T, Harada Y. *Electrophysiological study on tooth-grinding during sleep*. Electroencephalogr Clin Neurophysiol 1973;35:267-275.
68. Hublin C, Kaprio J. *Genetic aspects and genetic epidemiology of parasomnias*. Sleep Med Rev 2003;7:413-421.
69. Khoury S, Rouleau GA, Rompre PH, Mayer P, Montplaisir JY, Lavigne GJ. *A significant increase in breathing amplitude precedes sleep bruxism*. Chest 2008;134:332-337.
70. Lindqvist B. *Bruxism in twins*. Acta Odontol Scand 1974;32:177-187.
71. Madrid G, Madrid S, Vranesh JG, Hicks RA. *Cigarette smoking and bruxism*. Percept Mot Skills 1998;87:898.
72. Manfredini D, Lobbezoo F. *Role of psychosocial factors in the etiology of bruxism*. J Orofac Pain 2009;23:153-166.

73. Schneider C, Schaefer R, Ommerborn MA, Giraki M, Goertz A, Raab WH, et al. *Maladaptive coping strategies in patients with bruxism compared to non-bruxing controls*. Int J Behav Med 2007;14:257-261.
74. Sjoholm TT, Lowe AA, Miyamoto K, Fleetham JA, Ryan CF. *Sleep bruxism in patients with sleep-disordered breathing*. Arch Oral Biol 2000;45:889-896.
75. Halasz P, Terzano M, Parrino L, Bodizs R. *The nature of arousal in sleep*. J Sleep Res 2004;13:1-23.
76. Moruzzi G, Magoun HW. *Brain stem reticular formation and activation of the EEG*. Electroencephalogr Clin Neurophysiol 1949;1:455-473.
77. Siegel JM. *Clues to the functions of mammalian sleep*. Nature 2005;437:1264-1271.
78. Ermis U, Krakow K, Voss U. *Arousal thresholds during human tonic and phasic REM sleep*. J Sleep Res 2010;19:400-406.
79. Kato T, Montplaisir JY, Lavigne GJ. *Experimentally induced arousals during sleep: a cross-modality matching paradigm*. J Sleep Res 2004;13:229-238.
80. Terzano MG, Mancia D, Salati MR, Costani G, Decembrino A, Parrino L. *The cyclic alternating pattern as a physiologic component of normal NREM sleep*. Sleep 1985;8:137-145.
81. Terzano MG, Parrino L, Smerieri A, Carli F, Nobili L, Donadio S, et al. *CAP and arousals are involved in the homeostatic and ultradian sleep processes*. J Sleep Res 2005;14:359-368.
82. Parrino L, Ferri R, Bruni O, Terzano MG. *Cyclic alternating pattern (CAP): The marker of sleep instability*. Sleep Med Rev 2012;16:27-45.
83. Terzano MG, Parrino L. *Origin and Significance of the Cyclic Alternating Pattern (CAP). REVIEW ARTICLE*. Sleep Med Rev 2000;4:101-123.
84. Terzano MG, Gatti PL, Manzoni GC, Formentini E, Mancia D. *Is the EEG cyclic alternating pattern a true autonomous entity? Analytic study in a case of post-traumatic coma with good prognosis*. Eur Neurol 1982;21:324-334.
85. Terzano MG, Parrino L, Smerieri A, Chervin R, Chokroverty S, Guilleminault C, et al. *Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep*. Sleep Med 2002;3:187-199.
86. Bruni O, Ferri R, Miano S, Verrillo E, Vittori E, Farina B, et al. *Sleep cyclic alternating pattern in normal preschool-aged children*. Sleep 2005;28:220-230.
87. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. *Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age groups*. Electroencephalogr Clin Neurophysiol 1998;107:439-450.
88. Bruni O, Novelli L, Miano S, Parrino L, Terzano MG, Ferri R. *Cyclic alternating pattern: A window into pediatric sleep*. Sleep Med 2010;11:628-636.
89. Ferri R, Huber R, Arico D, Drago V, Rundo F, Ghilardi MF, et al. *The slow-wave components of the cyclic alternating pattern (CAP) have a role in sleep-related learning processes*. Neurosci Lett 2008;432:228-231.
90. Ferri R, Bruni O, Miano S, Terzano MG. *Topographic mapping of the spectral components of the cyclic alternating pattern (CAP)*. Sleep Med 2005;6:29-36.

91. Parrino L, Boselli M, Buccino GP, Spaggiari MC, Di Giovanni G, Terzano MG. *The cyclic alternating pattern plays a gate-control on periodic limb movements during non-rapid eye movement sleep*. J Clin Neurophysiol 1996;13:314-323.
92. Parrino L, Smerieri A, Spaggiari MC, Terzano MG. *Cyclic alternating pattern (CAP) and epilepsy during sleep: how a physiological rhythm modulates a pathological event*. Clin Neurophysiol 2000;111 Suppl 2:S39-46.
93. Parrino L, Halasz P, Tassinari CA, Terzano MG. *CAP, epilepsy and motor events during sleep: the unifying role of arousal*. Sleep Med Rev 2006;10:267-285.
94. Marthol H, Reich S, Jacke J, Lechner KH, Wichmann M, Hilz MJ. *Enhanced sympathetic cardiac modulation in bruxism patients*. Clin Auton Res 2006;16:276-280.
95. Nashed A, Lanfranchi P, Rompré P, Carra MC, Mayer P, Huyhn N, et al. *Sleep Bruxism is Associated with a Rise in Arterial Blood Pressure*. Sleep 2012;35:529-536.
96. Miyawaki S, Lavigne GJ, Pierre M, Guitard F, Montplaisir JY, Kato T. *Association between sleep bruxism, swallowing-related laryngeal movement, and sleep positions*. Sleep 2003;26:461-465.
97. Verrier RL, Harper RM. *Cardiovascolar Physiology: Central and autonomic Regulation*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:215-225.
98. Lanfranchi P, Somers VK. *Cardiovascolar Physiology: Autonomic Control in Health and Sleep Disorders*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:226-236.
99. Bonnet MH, Arand DL. *Heart rate variability: sleep stage, time of night, and arousal influences*. Electroencephalogr Clin Neurophysiol 1997;102:390-396.
100. *Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use*. Circulation 1996;93:1043-1065.
101. Brandenberger G, Ehrhart J, Piquard F, Simon C. *Inverse coupling between ultradian oscillations in delta wave activity and heart rate variability during sleep*. Clin Neurophysiol 2001;112:992-996.
102. Magee KR. *Bruxisma related to levodopa therapy*. JAMA 1970;214:147.
103. Lavigne GJ, Soucy JP, Lobbezoo F, Manzini C, Blanchet PJ, Montplaisir JY. *Double-blind, crossover, placebo-controlled trial of bromocriptine in patients with sleep bruxism*. Clin Neuropharmacol 2001;24:145-149.
104. Lobbezoo F, Soucy JP, Hartman NG, Montplaisir JY, Lavigne GJ. *Effects of the D2 receptor agonist bromocriptine on sleep bruxism: report of two single-patient clinical trials*. J Dent Res 1997;76:1610-1614.
105. Lobbezoo F, Soucy JP, Montplaisir JY, Lavigne GJ. *Striatal D2 receptor binding in sleep bruxism: a controlled study with iodine-123-iodobenzamide and single-photon-emission computed tomography*. J Dent Res 1996;75:1804-1810.
106. McCarley RW. *Neurobiology of REM and NREM sleep*. Sleep Med 2007;8:302-330.
107. Pal D, Mallick BN. *Neural mechanism of rapid eye movement sleep generation with reference to REM-OFF neurons in locus coeruleus*. Indian J Med Res 2007;125:721-739.

108. Reding GR, Rubright WC, Zimmerman SO. *Incidence of bruxism*. J Dent Res 1966;45:1198-1204.
109. Hublin C, Kaprio J, Partinen M, Koskenvuo M. *Sleep bruxism based on self-report in a nationwide twin cohort*. J Sleep Res 1998;7:61-67.
110. Faraco J, Mignot E. *Genetics of Sleep and Sleep Disorders in Humans*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:184-198.
111. Landolt H, Dijk DJ. *Genetic Basis of Sleep in Healthy Humans*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:175-183.
112. Winocur E, Uziel N, Lisha T, Goldsmith C, Eli I. *Self-reported bruxism - associations with perceived stress, motivation for control, dental anxiety and gagging*. J Oral Rehabil 2011;38:3-11.
113. Pingitore G, Chrobak V, Petrie J. *The social and psychologic factors of bruxism*. J Prosthet Dent 1991;65:443-446.
114. Sato C, Sato S, Takashina H, Ishii H, Onozuka M, Sasaguri K. *Bruxism affects stress responses in stressed rats*. Clin Oral Investig 2010;14:153-160.
115. Seraidarian P, Seraidarian PI, das Neves Cavalcanti B, Marchini L, Claro Neves AC. *Urinary levels of catecholamines among individuals with and without sleep bruxism*. Sleep Breath 2009;13:85-88.
116. Vanderas AP, Menenakou M, Kouimtzis T, Papagiannoulis L. *Urinary catecholamine levels and bruxism in children*. J Oral Rehabil 1999;26:103-110.
117. Clark GT, Rugh JD, Handelman SL. *Nocturnal masseter muscle activity and urinary catecholamine levels in bruxers*. J Dent Res 1980;59:1571-1576.
118. Major M, Rompre PH, Guitard F, Tenbokum L, O'Connor K, Nielsen T, et al. *A controlled daytime challenge of motor performance and vigilance in sleep bruxers*. J Dent Res 1999;78:1754-1762.
119. Giraki M, Schneider C, Schafer R, Singh P, Franz M, Raab WH, et al. *Correlation between stress, stress-coping and current sleep bruxism*. Head Face Med 2010;6:2.
120. Katayoun E, Sima F, Naser V, Anahita D. *Study of the relationship of psychosocial disorders to bruxism in adolescents*. J Indian Soc Pedod Prev Dent 2008;26 Suppl 3:S91-97.
121. Restrepo CC, Vasquez LM, Alvarez M, Valencia I. *Personality traits and temporomandibular disorders in a group of children with bruxing behaviour*. J Oral Rehabil 2008;35:585-593.
122. Serra-Negra JM, Ramos-Jorge ML, Flores-Mendoza CE, Paiva SM, Pordeus IA. *Influence of psychosocial factors on the development of sleep bruxism among children*. Int J Paediatr Dent 2009;19:309-317.
123. Adams RD, Victor M. *Principle of Neurology*. New York: McGraw-Hill, Inc., 1993:348.
124. Winocur E, Gavish A, Voikovitch M, Emodi-Perlman A, Eli I. *Drugs and bruxism: a critical review*. J Orofac Pain 2003;17:99-111.

125. Winocur E, Gavish A, Volfin G, Halachmi M, Gazit E. *Oral motor parafunctions among heavy drug addicts and their effects on signs and symptoms of temporomandibular disorders*. J Orofac Pain 2001;15:56-63.
126. Dinis-Oliveira RJ, Caldas I, Carvalho F, Magalhaes T. *Bruxism after 3,4-methylenedioxymethamphetamine (ecstasy) abuse*. Clin Toxicol (Phila) 2010;48:863-864.
127. Sabuncuoglu O, Ekinci O, Berkem M. *Fluoxetine-induced sleep bruxism in an adolescent treated with buspirone: a case report*. Spec Care Dentist 2009;29:215-217.
128. Gerber PE, Lynd LD. *Selective serotonin-reuptake inhibitor-induced movement disorders*. Ann Pharmacother 1998;32:692-698.
129. Romanelli F, Adler DA, Bungay KM. *Possible paroxetine-induced bruxism*. Ann Pharmacother 1996;30:1246-1248.
130. Ellison JM, Stanziani P. *SSRI-associated nocturnal bruxism in four patients*. J Clin Psychiatry 1993;54:432-434.
131. Lavigne GL, Lobbezoo F, Rompre PH, Nielsen TA, Montplaisir J. *Cigarette smoking as a risk factor or an exacerbating factor for restless legs syndrome and sleep bruxism*. Sleep 1997;20:290-293.
132. Amir I, Hermesh H, Gavish A. *Bruxism secondary to antipsychotic drug exposure: a positive response to propranolol*. Clin Neuropharmacol 1997;20:86-89.
133. Rintakoski K, Ahlberg J, Hublin C, Broms U, Madden PA, Kononen M, et al. *Bruxism is associated with nicotine dependence: a nationwide Finnish twin cohort study*. Nicotine Tob Res 2010;12:1254-1260.
134. Lavigne G, Zucconi M, Castronovo C, Manzini C, Marchettini P, Smirne S. *Sleep arousal response to experimental thermal stimulation during sleep in human subjects free of pain and sleep problems*. Pain 2000;84:283-290.
135. Lavigne GJ, Zucconi M, Castronovo V, Manzini C, Veglia F, Smirne S, et al. *Heart rate changes during sleep in response to experimental thermal (nociceptive) stimulations in healthy subjects*. Clin Neurophysiol 2001;112:532-535.
136. Silvestri R, Gagliano A, Arico I, Calarese T, Cedro C, Bruni O, et al. *Sleep disorders in children with Attention-Deficit/Hyperactivity Disorder (ADHD) recorded overnight by video-polysomnography*. Sleep Med 2009;10:1132-1138.
137. Herrera M, Valencia I, Grant M, Metroka D, Chialastri A, Kothare SV. *Bruxism in children: effect on sleep architecture and daytime cognitive performance and behavior*. Sleep 2006;29:1143-1148.
138. Tan EK, Jankovic J, Ondo W. *Bruxism in Huntington's disease*. Mov Disord 2000;15:171-173.
139. Srivastava T, Ahuja M, Srivastava M, Trivedi A. *Bruxism as presenting feature of Parkinson's disease*. J Assoc Physicians India 2002;50:457.
140. Kwak YT, Han IW, Lee PH, Yoon JK, Suk SH. *Associated conditions and clinical significance of awake bruxism*. Geriatr Gerontol Int 2009;9:382-390.
141. Stewart JT, Thomas JE, Williams LS. *Severe bruxism in a demented patient*. South Med J 1993;86:476-477.
142. Trevathan E, Naidu S. *The clinical recognition and differential diagnosis of Rett syndrome*. J Child Neurol 1988;3 Suppl:S6-16.

143. Meletti S, Cantalupo G, Volpi L, Rubboli G, Magaudda A, Tassinari CA. *Rhythmic teeth grinding induced by temporal lobe seizures*. Neurology 2004;62:2306-2309.
144. Bisulli F, Vignatelli L, Naldi I, Licchetta L, Provini F, Plazzi G, et al. *Increased frequency of arousal parasomnias in families with nocturnal frontal lobe epilepsy: a common mechanism?* Epilepsia 2010;51:1852-1860.
145. Tinuper P, Provini F, Bisulli F, Vignatelli L, Plazzi G, Vetrugno R, et al. *Movement disorders in sleep: guidelines for differentiating epileptic from non-epileptic motor phenomena arising from sleep*. Sleep Med Rev 2007;11:255-267.
146. Lucchesi LM, Speciali JG, Santos-Silva R, Taddei JA, Tufik S, Bittencourt LR. *Nocturnal awakening with headache and its relationship with sleep disorders in a population-based sample of adult inhabitants of Sao Paulo City, Brazil*. Cephalalgia 2010;30:1477-1485.
147. Montplaisir J, Lapierre O, Lavigne G. *The restless leg syndrome: a condition associated with periodic or aperiodic slowing of the EEG*. Neurophysiol Clin 1994;24:131-140.
148. Miller VA, Palermo TM, Powers SW, Scher MS, Hershey AD. *Migraine headaches and sleep disturbances in children*. Headache 2003;43:362-368.
149. Sforza E, Zucconi M, Petronelli R, Lugaresi E, Cirignotta F. *REM sleep behavioral disorders*. Eur Neurol 1988;28:295-300.
150. Reutens S, Sachdev PS. *Periodic limb movements and other movement disorders in sleep: neuropsychiatric dimensions*. Int Rev Psychiatry 2005;17:283-292.
151. Lavigne G, Toumilehto H, Macaluso GM. *Pathophysiology of Sleep Bruxism*. In: Lavigne GJ, Cistulli PA, Smith MT (eds). Sleep Medicine For Dentists A Practical Overview. Hanover Park, Illinois: Quintessence Publishing Co, nc, 2009:117-124.
152. Michelotti A, Farella M, Gallo LM, Veltri A, Palla S, Martina R. *Effect of occlusal interference on habitual activity of human masseter*. J Dent Res 2005;84:644-648.
153. Bader G, Lavigne G. *Sleep bruxism; an overview of an oromandibular sleep movement disorder. REVIEW ARTICLE*. Sleep Med Rev 2000;4:27-43.
154. Camparis CM, Siqueira JT. *Sleep bruxism: clinical aspects and characteristics in patients with and without chronic orofacial pain*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:188-193.
155. Nagamatsu-Sakaguchi C, Minakuchi H, Clark GT, Kuboki T. *Relationship between the frequency of sleep bruxism and the prevalence of signs and symptoms of temporomandibular disorders in an adolescent population*. Int J Prosthodont 2008;21:292-298.
156. Rossetti LM, Pereira de Araujo Cdos R, Rossetti PH, Conti PC. *Association between rhythmic masticatory muscle activity during sleep and masticatory myofascial pain: a polysomnographic study*. J Orofac Pain 2008;22:190-200.
157. Huynh N, Khoury S, Rompré PH, Montplaisir JY, Lavigne GJ. *Prevalence of headache and neck pain in a sleep bruxism population investigated in a sleep laboratory*. Sleep 2006;29:A282.
158. Svensson P, Burgaard A, Schlosser S. *Fatigue and pain in human jaw muscles during a sustained, low-intensity clenching task*. Arch Oral Biol 2001;46:773-777.

159. Glaros AG, Burton E. *Parafunctional clenching, pain, and effort in temporomandibular disorders*. J Behav Med 2004;27:91-100.
160. McMillan AS, Lawson ET. *Effect of tooth clenching and jaw opening on pain-pressure thresholds in the human jaw muscles*. J Orofac Pain 1994;8:250-257.
161. Magnusson T, Egermark I, Carlsson GE. *A longitudinal epidemiologic study of signs and symptoms of temporomandibular disorders from 15 to 35 years of age*. J Orofac Pain 2000;14:310-319.
162. Velly AM, Gornitsky M, Philippe P. *Contributing factors to chronic myofascial pain: a case-control study*. Pain 2003;104:491-499.
163. Macfarlane TV, Kenealy P, Kingdon HA, Mohlin B, Pilley JR, Mwangi CW, et al. *Orofacial pain in young adults and associated childhood and adulthood factors: results of the population study, Wales, United Kingdom*. Community Dent Oral Epidemiol 2009;37:438-450.
164. Pereira LJ, Costa RC, Franca JP, Pereira SM, Castelo PM. *Risk indicators for signs and symptoms of temporomandibular dysfunction in children*. J Clin Pediatr Dent 2009;34:81-86.
165. Pereira LJ, Pereira-Cenci T, Del Bel Cury AA, Pereira SM, Pereira AC, Ambosano GM, et al. *Risk indicators of temporomandibular disorder incidences in early adolescence*. Pediatr Dent 2010;32:324-328.
166. Rugh JD, Harlan J. *Nocturnal bruxism and temporomandibular disorders*. Adv Neurol 1988;49:329-341.
167. Goulet JP, Clark GT, Flack VF, Liu C. *The reproducibility of muscle and joint tenderness detection methods and maximum mandibular movement measurement for the temporomandibular system*. J Orofac Pain 1998;12:17-26.
168. Barbosa Tde S, Miyakoda LS, Pocztaruk Rde L, Rocha CP, Gaviao MB. *Temporomandibular disorders and bruxism in childhood and adolescence: review of the literature*. Int J Pediatr Otorhinolaryngol 2008;72:299-314.
169. Miyake R, Ohkubo R, Takehara J, Morita M. *Oral parafunctions and association with symptoms of temporomandibular disorders in Japanese university students*. J Oral Rehabil 2004;31:518-523.
170. Dao TT, Lund JP, Lavigne GJ. *Comparison of pain and quality of life in bruxers and patients with myofascial pain of the masticatory muscles*. J Orofac Pain 1994;8:350-356.
171. Glaros AG, Williams K, Lausten L. *Diurnal variation in pain reports in temporomandibular disorder patients and control subjects*. J Orofac Pain 2008;22:115-121.
172. Rossetti LM, Rossetti PH, Conti PC, de Araujo Cdos R. *Association between sleep bruxism and temporomandibular disorders: a polysomnographic pilot study*. Cranio 2008;26:16-24.
173. Camparis CM, Formigoni G, Teixeira MJ, Bittencourt LR, Tufik S, de Siqueira JT. *Sleep bruxism and temporomandibular disorder: Clinical and polysomnographic evaluation*. Arch Oral Biol 2006;51:721-728.

174. Bruni O, Fabrizi P, Ottaviano S, Cortesi F, Giannotti F, Guidetti V. *Prevalence of sleep disorders in childhood and adolescence with headache: a case-control study*. Cephalalgia 1997;17:492-498.
175. Vendrame M, Kaleyias J, Valencia I, Legido A, Kothare SV. *Polysomnographic findings in children with headaches*. Pediatr Neurol 2008;39:6-11.
176. Lavigne G, Palla S. *Transient morning headache: recognizing the role of sleep bruxism and sleep-disordered breathing*. J Am Dent Assoc 2010;141:297-299.
177. Zarowski M, Mlodzikowska-Albrecht J, Steinborn B. *The sleep habits and sleep disorders in children with headache*. Adv Med Sci 2007;52 Suppl 1:194-196.
178. Biondi DM. *Headaches and their relationship to sleep*. Dent Clin North Am 2001;45:685-700.
179. Bailey DR. *Tension headache and bruxism in the sleep disordered patient*. Cranio 1990;8:174-182.
180. Macfarlane TV, Gray RJM, Kincey J, Worthington HV. *Factors associated with the temporomandibular disorder, pain dysfunction syndrome (PDS): Manchester case-control study*. Oral Dis 2001;7:321-330.
181. Olesen J, Lipton RB. *Headache classification update 2004*. Curr Opin Neurol 2004;17:275-282.
182. Isik U, Ersu RH, Ay P, Save D, Arman AR, Karakoc F, et al. *Prevalence of headache and its association with sleep disorders in children*. Pediatr Neurol 2007;36:146-151.
183. Liljestrom MR, Le Bell Y, Anttila P, Aromaa M, Jamsa T, Metsahonkala L, et al. *Headache children with temporomandibular disorders have several types of pain and other symptoms*. Cephalalgia 2005;25:1054-1060.
184. Sheldon SH. *Obstructive Sleep Apnea and Bruxism in Children*. In: Bailey D (ed). Sleep Medicine Clinics Dentistry's Role in Sleep Medicine: Elsevier. The Clinics, 2010:163-168.
185. Eitner S, Urschitz MS, Guenther A, Urschitz-Duprat PM, Bohnhorst B, Schlaud M, et al. *Sleep problems and daytime somnolence in a German population-based sample of snoring school-aged children*. J Sleep Res 2007;16:96-101.
186. Grechi TH, Trawitzki LV, de Felicio CM, Valera FC, Alnselmo-Lima WT. *Bruxism in children with nasal obstruction*. Int J Pediatr Otorhinolaryngol 2008;72:391-396.
187. DiFrancesco RC, Junqueira PA, Trezza PM, de Faria ME, Frizzarini R, Zerati FE. *Improvement of bruxism after T & A surgery*. Int J Pediatr Otorhinolaryngol 2004;68:441-445.
188. Eftekharian A, Raad N, Gholami-Ghasri N. *Bruxism and adenotonsillectomy*. Int J Pediatr Otorhinolaryngol 2008;72:509-511.
189. Oksenberg A, Arons E. *Sleep bruxism related to obstructive sleep apnea: the effect of continuous positive airway pressure*. Sleep Med 2002;3:513-515.
190. Thie NM, Kato T, Bader G, Montplaisir JY, Lavigne GJ. *The significance of saliva during sleep and the relevance of oromotor movements*. Sleep Med Rev 2002;6:213-227.

191. Campbell IG, Darchia N, Higgins LM, Dykan IV, Davis NM, de Bie E, et al. *Adolescent changes in homeostatic regulation of EEG activity in the delta and theta frequency bands during NREM sleep*. Sleep 2011;34:83-91.
192. Gaudreau H, Carrier J, Montplaisir J. *Age-related modifications of NREM sleep EEG: from childhood to middle age*. J Sleep Res 2001;10:165-172.
193. Jenni OG, Achermann P, Carskadon MA. *Homeostatic sleep regulation in adolescents*. Sleep 2005;28:1446-1454.
194. Jenni OG, Carskadon MA. *Spectral analysis of the sleep electroencephalogram during adolescence*. Sleep 2004;27:774-783.
195. Feinberg I, Higgins LM, Khaw WY, Campbell IG. *The adolescent decline of NREM delta, an indicator of brain maturation, is linked to age and sex but not to pubertal stage*. Am J Physiol Regul Integr Comp Physiol 2006;291:R1724-1729.
196. Achermann P, Borbely AA. *Sleep Homeostasis and Models of Sleep Regulation*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:431-444.
197. Laberge L, Petit D, Simard C, Vitaro F, Tremblay RE, Montplaisir J. *Development of sleep patterns in early adolescence*. J Sleep Res 2001;10:59-67.
198. Sadeh A, Dahl RE, Shahar G, Rosenblat-Stein S. *Sleep and the transition to adolescence: a longitudinal study*. Sleep 2009;32:1602-1609.
199. Carskadon MA, Acebo C, Jenni OG. *Regulation of adolescent sleep: implications for behavior*. Ann N Y Acad Sci 2004;1021:276-291.
200. Hagenauer MH, Perryman JI, Lee TM, Carskadon MA. *Adolescent changes in the homeostatic and circadian regulation of sleep*. Dev Neurosci 2009;31:276-284.
201. Huynh N, Guilleminault C. *Sleep Bruxism in Children*. In: Lavigne GJ, Cistulli PA, Smith MT (eds). Sleep Medicine For Dentists A Practical Overview. Hanover Park, Illinois: Quintessence Publishing Co, nc, 2009:125-131.
202. Lam MH, Zhang J, Li AM, Wing YK. *A community study of sleep bruxism in Hong Kong children: association with comorbid sleep disorders and neurobehavioral consequences*. Sleep Med 2011;12:641-645.
203. Huynh N, Manzini C, Rompre PH, Lavigne GJ. *Weighing the potential effectiveness of various treatments for sleep bruxism*. J Can Dent Assoc 2007;73:727-730.
204. Klasser GD, Greene CS, Lavigne GJ. *Oral appliances and the management of sleep bruxism in adults: a century of clinical applications and search for mechanisms*. Int J Prosthodont 2010;23:453-462.
205. Jadidi F, Castrillon E, Svensson P. *Effect of conditioning electrical stimuli on temporalis electromyographic activity during sleep*. J Oral Rehabil 2008;35:171-183.
206. Lobbezoo F, van der Zaag J, van Selms MK, Hamburger HL, Naeije M. *Principles for the management of bruxism*. J Oral Rehabil 2008;35:509-523.
207. Ommerborn MA, Schneider C, Giraki M, Schafer R, Handschel J, Franz M, et al. *Effects of an occlusal splint compared with cognitive-behavioral treatment on sleep bruxism activity*. Eur J Oral Sci 2007;115:7-14.
208. Shulman J. *Teaching patients how to stop bruxing habits*. J Am Dent Assoc 2001;132:1275-1277.

209. Wieselmann-Penkner K, Janda M, Lorenzoni M, Polansky R. *A comparison of the muscular relaxation effect of TENS and EMG-biofeedback in patients with bruxism*. J Oral Rehabil 2001;28:849-853.
210. Jadidi F, Norregaard O, Baad-Hansen L, Arendt-Nielsen L, Svensson P. *Assessment of sleep parameters during contingent electrical stimulation in subjects with jaw muscle activity during sleep: a polysomnographic study*. Eur J Oral Sci 2011;119:211-218.
211. Macedo CR, Silva AB, Machado MA, Saconato H, Prado GF. *Occlusal splints for treating sleep bruxism (tooth grinding)*. Cochrane Database Syst Rev 2007:CD005514.
212. Nascimento LL, Amorim CF, Giannasi LC, Oliveira CS, Nacif SR, Silva Ade M, et al. *Occlusal splint for sleep bruxism: an electromyographic associated to Helkimo Index evaluation*. Sleep Breath 2008;12:275-280.
213. Harada T, Ichiki R, Tsukiyama Y, Koyano K. *The effect of oral splint devices on sleep bruxism: a 6-week observation with an ambulatory electromyographic recording device*. J Oral Rehabil 2006;33:482-488.
214. Dube C, Rompre PH, Manzini C, Guitard F, de Grandmont P, Lavigne GJ. *Quantitative polygraphic controlled study on efficacy and safety of oral splint devices in tooth-grinding subjects*. J Dent Res 2004;83:398-403.
215. Okeson JP. *The effects of hard and soft occlusal splints on nocturnal bruxism*. J Am Dent Assoc 1987;114:788-791.
216. Clark GT, Beemsterboer PL, Solberg WK, Rugh JD. *Nocturnal electromyographic evaluation of myofascial pain dysfunction in patients undergoing occlusal splint therapy*. J Am Dent Assoc 1979;99:607-611.
217. Daif ET. *Correlation of splint therapy outcome with the electromyography of masticatory muscles in temporomandibular disorder with myofascial pain*. Acta Odontol Scand 2011.
218. Stapelmann H, Turp JC. *The NTI-tss device for the therapy of bruxism, temporomandibular disorders, and headache - where do we stand? A qualitative systematic review of the literature*. BMC Oral Health 2008;8:22.
219. Jokstad A, Mo A, Krogstad BS. *Clinical comparison between two different splint designs for temporomandibular disorder therapy*. Acta Odontol Scand 2005;63:218-226.
220. Jokstad A. *The NTI-tss device may be used successfully in the management of bruxism and TMD*. Evid Based Dent 2009;10:23.
221. Scrivani SJ, Keith DA, Kaban LB. *Temporomandibular disorders*. N Engl J Med 2008;359:2693-2705.
222. Al-Ani MZ, Davies SJ, Gray RJ, Sloan P, Glenny AM. *Stabilisation splint therapy for temporomandibular pain dysfunction syndrome*. Cochrane Database Syst Rev 2004:CD002778.
223. Fricton J. *Myogenous temporomandibular disorders: diagnostic and management considerations*. Dent Clin North Am 2007;51:61-83, vi.
224. Dao TT, Lavigne GJ. *Oral splints: the crutches for temporomandibular disorders and bruxism?* Crit Rev Oral Biol Med 1998;9:345-361.

225. Fricton J. *Current evidence providing clarity in management of temporomandibular disorders: summary of a systematic review of randomized clinical trials for intra-oral appliances and occlusal therapies*. J Evid Based Dent Pract 2006;6:48-52.
226. de Felicio CM, de Oliveira MM, da Silva MA. *Effects of orofacial myofunctional therapy on temporomandibular disorders*. Cranio 2010;28:249-259.
227. De Boever JA, Nilner M, Orthlieb JD, Steenks MH. *Recommendations by the EACD for examination, diagnosis, and management of patients with temporomandibular disorders and orofacial pain by the general dental practitioner*. J Orofac Pain 2008;22:268-278.
228. Gagnon Y, Mayer P, Morisson F, Rompre PH, Lavigne GJ. *Aggravation of respiratory disturbances by the use of an occlusal splint in apneic patients: a pilot study*. Int J Prosthodont 2004;17:447-453.
229. Landry-Schonbeck A, de Grandmont P, Rompre PH, Lavigne GJ. *Effect of an adjustable mandibular advancement appliance on sleep bruxism: a crossover sleep laboratory study*. Int J Prosthodont 2009;22:251-259.
230. Landry ML, Rompre PH, Manzini C, Guitard F, de Grandmont P, Lavigne GJ. *Reduction of sleep bruxism using a mandibular advancement device: an experimental controlled study*. Int J Prosthodont 2006;19:549-556.
231. Franco L, Rompre PH, de Grandmont P, Abe S, Lavigne GJ. *A mandibular advancement appliance reduces pain and rhythmic masticatory muscle activity in patients with morning headache*. J Orofac Pain 2011;25:240-249.
232. Martinez-Gomis J, Willaert E, Nogues L, Pascual M, Somoza M, Monasterio C. *Five years of sleep apnea treatment with a mandibular advancement device. Side effects and technical complications*. Angle Orthod 2010;80:30-36.
233. de Almeida FR, Lowe AA, Tsuiki S, Otsuka R, Wong M, Fastlicht S, et al. *Long-term compliance and side effects of oral appliances used for the treatment of snoring and obstructive sleep apnea syndrome*. J Clin Sleep Med 2005;1:143-152.
234. Saletu A, Parapatics S, Saletu B, Anderer P, Prause W, Putz H, et al. *On the pharmacotherapy of sleep bruxism: placebo-controlled polysomnographic and psychometric studies with clonazepam*. Neuropsychobiology 2005;51:214-225.
235. Saletu A, Parapatics S, Anderer P, Matejka M, Saletu B. *Controlled clinical, polysomnographic and psychometric studies on differences between sleep bruxers and controls and acute effects of clonazepam as compared with placebo*. Eur Arch Psychiatry Clin Neurosci 2010;260:163-174.
236. Raigrodski AJ, Christensen LV, Mohamed SE, Gardiner DM. *The effect of four-week administration of amitriptyline on sleep bruxism. A double-blind crossover clinical study*. Cranio 2001;19:21-25.
237. Mohamed SE, Christensen LV, Penchas J. *A randomized double-blind clinical trial of the effect of amitriptyline on nocturnal masseteric motor activity (sleep bruxism)*. Cranio 1997;15:326-332.
238. Stein DJ, Van Greunen G, Niehaus D. *Can bruxism respond to serotonin reuptake inhibitors?* J Clin Psychiatry 1998;59:133.

239. Van der Zaag J, Lobbezoo F, Van der Avoort PG, Wicks DJ, Hamburger HL, Naeije M. *Effects of pergolide on severe sleep bruxism in a patient experiencing oral implant failure*. J Oral Rehabil 2007;34:317-322.
240. Huynh N, Lavigne GJ, Lanfranchi PA, Montplaisir JY, de Champlain J. *The effect of 2 sympatholytic medications--propranolol and clonidine--on sleep bruxism: experimental randomized controlled studies*. Sleep 2006;29:307-316.
241. Brown ES, Hong SC. *Antidepressant-induced bruxism successfully treated with gabapentin*. J Am Dent Assoc 1999;130:1467-1469.
242. Kast RE. *Tiagabine may reduce bruxism and associated temporomandibular joint pain*. Anesth Prog 2005;52:102-104.
243. Bostwick JM, Jaffee MS. *Buspirone as an antidote to SSRI-induced bruxism in 4 cases*. J Clin Psychiatry 1999;60:857-860.
244. Mowla A, Sabayan B. *Topiramate for bruxism: report of 2 cases*. J Clin Psychopharmacol 2010;30:346-347.
245. Tan EK, Jankovic J. *Treating severe bruxism with botulinum toxin*. J Am Dent Assoc 2000;131:211-216.
246. Lee SJ, McCall WD, Jr., Kim YK, Chung SC, Chung JW. *Effect of botulinum toxin injection on nocturnal bruxism: a randomized controlled trial*. Am J Phys Med Rehabil 2010;89:16-23.
247. Lobbezoo F, Lavigne GJ, Tanguay R, Montplaisir JY. *The effect of catecholamine precursor L-dopa on sleep bruxism: a controlled clinical trial*. Mov Disord 1997;12:73-78.
248. Stohler CS. *Craniofacial pain and motor function: pathogenesis, clinical correlates, and implications*. Crit Rev Oral Biol Med 1999;10:504-518.
249. Ghanizadeh A. *ADHD, bruxism and psychiatric disorders: does bruxism increase the chance of a comorbid psychiatric disorder in children with ADHD and their parents?* Sleep Breath 2008;12:375-380.
250. O'Brien LM, Gozal D. *Sleep in children with attention deficit/hyperactivity disorder*. Minerva Pediatr 2004;56:585-601.
251. Shur-Fen Gau S. *Prevalence of sleep problems and their association with inattention/hyperactivity among children aged 6-15 in Taiwan*. J Sleep Res 2006;15:403-414.
252. Zucconi M, Oldani A, Ferini-Strambi L, Smirne S. *Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability*. J Clin Neurophysiol 1995;12:147-154.
253. Borbely AA, Achermann P. *Concepts and models of sleep regulation: an overview*. J Sleep Res 1992;1:63-79.
254. Terzano MG, Parrino L, Rosa A, Palomba V, Smerieri A. *CAP and arousals in the structural development of sleep: an integrative perspective*. Sleep Med 2002;3:221-229.
255. Miyazaki S, Uchida S, Mukai J, Nishihara K. *Clonidine effects on all-night human sleep: opposite action of low- and medium-dose clonidine on human NREM-REM sleep proportion*. Psychiatry Clin Neurosci 2004;58:138-144.

256. Gentili A, Godschalk MF, Gheorghiu D, Nelson K, Julius DA, Mulligan T. *Effect of clonidine and yohimbine on sleep in healthy men: a double-blind, randomized, controlled trial*. Eur J Clin Pharmacol 1996;50:463-465.
257. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects.* Los Angeles: Brain Information Service/Brain Research Institute 1968.
258. Carra MC, Huynh N, Lavigne GJ, Amzica F. *Clonidine suppresses REM sleep: new evidence from combined EMG, EOG, and EEG analyses*. J Sleep Res 2010;19.
259. Amzica F, Carra MC, Huynh N, Lavigne GJ. *Modulation of sleep homeostasis by clonidine*. J Sleep Res 2010;19.
260. McCarley RW, Massaquoi SG. *Neurobiological structure of the revised limit cycle reciprocal interaction model of REM cycle control*. J Sleep Res 1992;1:132-137.
261. Hobson JA, McCarley RW, Wyzinski PW. *Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups*. Science 1975;189:55-58.
262. Pace-Schott EF, Hobson JA. *The neurobiology of sleep: genetics, cellular physiology and subcortical networks*. Nat Rev Neurosci 2002;3:591-605.
263. Crochet S, Sakai K. *Alpha-2 adrenoceptor mediated paradoxical (REM) sleep inhibition in the cat*. Neuroreport 1999;10:2199-2204.
264. Carra MC, Macaluso GM, Rompre PH, Huynh N, Parrino L, Terzano MG, et al. *Clonidine has a paradoxical effect on cyclic arousal and sleep bruxism during NREM sleep*. Sleep 2010;33:1711-1716.
265. Szabo B. *Imidazoline antihypertensive drugs: a critical review on their mechanism of action*. Pharmacol Ther 2002;93:1-35.
266. Autret A, Minz M, Beillevaire T, Cathala HP, Schmitt H. *Effect of clonidine on sleep patterns in man*. Eur J Clin Pharmacol 1977;12:319-322.
267. Grenhoff J, Svensson TH. *Clonidine regularizes substantia nigra dopamine cell firing*. Life Sci 1988;42:2003-2009.
268. Katakura N, Chandler SH. *Iontophoretic analysis of the pharmacologic mechanisms responsible for initiation and modulation of trigeminal motoneuronal discharge evoked by intra-oral afferent stimulation*. Brain Res 1991;549:66-77.
269. Morilak DA, Jacobs BL. *Noradrenergic modulation of sensorimotor processes in intact rats: the masseteric reflex as a model system*. J Neurosci 1985;5:1300-1306.
270. Carra MC, Rompre PH, Kato T, Parrino L, Terzano MG, Lavigne GJ, et al. *Sleep bruxism and sleep arousal: an experimental challenge to assess the role of cyclic alternating pattern*. J Oral Rehabil 2011;38:635-642.
271. Togo F, Cherniack NS, Natelson BH. *Electroencephalogram characteristics of autonomic arousals during sleep in healthy men*. Clin Neurophysiol 2006;117:2597-2603.
272. Douglas NJ. *Respiratory physiology: understanding the control of ventilation*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:250-258.
273. Karadeniz D, Ondze B, Besset A, Billiard M. *EEG arousals and awakenings in relation with periodic leg movements during sleep*. J Sleep Res 2000;9:273-277.

274. Luc ME, Gupta A, Birnberg JM, Reddick D, Kohrman MH. *Characterization of symptoms of sleep disorders in children with headache*. Pediatr Neurol 2006;34:7-12.
275. Paiva T, Batista A, Martins P, Martins A. *The relationship between headaches and sleep disturbances*. Headache 1995;35:590-596.
276. Kudrow L, McGinty DJ, Phillips ER, Stevenson M. *Sleep apnea in cluster headache*. Cephalalgia 1984;4:33-38.
277. Neau JP, Paquereau J, Bailbe M, Meurice JC, Ingrand P, Gil R. *Relationship between sleep apnoea syndrome, snoring and headaches*. Cephalalgia 2002;22:333-339.
278. Mitsikostas DD, Viskos A, Papadopoulos D. *Sleep and headache: the clinical relationship*. Headache 2010;50:1233-1245.
279. Goksan B, Gunduz A, Karadeniz D, Agan K, Tascilar FN, Tan F, et al. *Morning headache in sleep apnoea: clinical and polysomnographic evaluation and response to nasal continuous positive airway pressure*. Cephalalgia 2009;29:635-641.
280. Chervin RD, Zallek SN, Lin X, Hall JM, Sharma N, Hedger KM. *Sleep disordered breathing in patients with cluster headache*. Neurology 2000;54:2302-2306.
281. Kushida CA, Morgenthaler TI, Littner MR, Alessi CA, Bailey D, Coleman J, Jr., et al. *Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005*. Sleep 2006;29:240-243.
282. Chan AS, Cistulli PA. *Oral appliance treatment of obstructive sleep apnea: an update*. Curr Opin Pulm Med 2009.
283. Gauthier L, Laberge L, Beaudry M, Laforte M, Rompre PH, Lavigne GJ. *Efficacy of two mandibular advancement appliances in the management of snoring and mild-moderate sleep apnea: a cross-over randomized study*. Sleep Med 2009;10:329-336.
284. Douglas NJ. *Respiratory Physiology: Understand the Control of Ventilation*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:250-258.
285. Horner RL. *Respiratory Physiology: Central Neural Control of Respiratory Neurons and Motoneurons during Sleep*. In: Kryger MH, Roth T, Dement WC (eds). Principles and Practice of Sleep Medicine. St. Louis: Elsevier Saunders, 2011:237-249.
286. Mezzanotte WS, Tangel DJ, White DP. *Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls*. Am J Respir Crit Care Med 1996;153:1880-1887.
287. Ayappa I, Rapoport DM. *The upper airway in sleep: physiology of the pharynx*. Sleep Med Rev 2003;7:9-33.
288. Jordan AS, White DP. *Pharyngeal motor control and the pathogenesis of obstructive sleep apnea*. Respir Physiol Neurobiol 2008;160:1-7.
289. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. *Oral appliances for snoring and obstructive sleep apnea: a review*. Sleep 2006;29:244-262.
290. Hoekema A, Stegenga B, De Bont LG. *Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review*. Crit Rev Oral Biol Med 2004;15:137-155.
291. McFarland DH, Lund JP. *Modification of mastication and respiration during swallowing in the adult human*. J Neurophysiol 1995;74:1509-1517.

292. Arima T, Tomonaga A, Toyota M, Inoue SI, Ohata N, Svensson P. *Does restriction of mandibular movements during sleep influence jaw-muscle activity?* J Oral Rehabil 2012.
293. Manconi M, Vitale G, Ferri R, Zucconi M, Ferini-Strambi L. *Periodic leg movements in Cheyne-Stokes respiration*. Eur Respir J 2008;32:1656-1662.
294. Zucconi M, Ferri R, Allen R, Baier PC, Bruni O, Chokroverty S, et al. *The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG)*. Sleep Med 2006;7:175-183.
295. Baran AS, Richert AC, Douglass AB, May W, Ansarin K. *Change in periodic limb movement index during treatment of obstructive sleep apnea with continuous positive airway pressure*. Sleep 2003;26:717-720.
296. Exar EN, Collop NA. *The association of upper airway resistance with periodic limb movements*. Sleep 2001;24:188-192.
297. Okubo M, Suzuki M, Horiuchi A, Okabe S, Ikeda K, Higano S, et al. *Morphologic analyses of mandible and upper airway soft tissue by MRI of patients with obstructive sleep apnea hypopnea syndrome*. Sleep 2006;29:909-915.
298. Lee RW, Sutherland K, Chan AS, Zeng B, Grunstein RR, Darendeliler MA, et al. *Relationship between surface facial dimensions and upper airway structures in obstructive sleep apnea*. Sleep 2010;33:1249-1254.
299. Harari D, Redlich M, Miri S, Hamud T, Gross M. *The effect of mouth breathing versus nasal breathing on dentofacial and craniofacial development in orthodontic patients*. Laryngoscope 2010;120:2089-2093.
300. Peltomaki T. *The effect of mode of breathing on craniofacial growth--revisited*. Eur J Orthod 2007;29:426-429.
301. Carra MC, Huynh N, Morton P, Rompre PH, Papadakis A, Remise C, et al. *Prevalence and risk factors of sleep bruxism and wake-time tooth clenching in a 7- to 17-yr-old population*. Eur J Oral Sci 2011;119:386-394.
302. Guilleminault C, Monteyrol PJ, Huynh NT, Pirelli P, Quo S, Li K. *Adeno-tonsillectomy and rapid maxillary distraction in pre-pubertal children, a pilot study*. Sleep Breath 2011;15:173-177.
303. Beebe DW. *Neural and neurobehavioral dysfunction in children with obstructive sleep apnea*. PLoS Med 2006;3:e323.
304. Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Spruyt K. *Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea*. Pediatrics 2010;126:e1161-1167.
305. Gozal D, O'Brien LM. *Snoring and obstructive sleep apnoea in children: why should we treat?* Paediatr Respir Rev 2004;5 Suppl A:S371-376.
306. Guilleminault C, Lee JH, Chan A. *Pediatric obstructive sleep apnea syndrome*. Arch Pediatr Adolesc Med 2005;159:775-785.
307. Montgomery-Downs HE, Young ME, Ross MA, Polak MJ, Ritchie SK, Lynch SK. *Sleep-disordered breathing symptoms frequency and growth among prematurely born infants*. Sleep Med 2010;11:263-267.

308. Miano S, Rizzoli A, Evangelisti M, Bruni O, Ferri R, Pagani J, et al. *NREM sleep instability changes following rapid maxillary expansion in children with obstructive apnea sleep syndrome*. Sleep Med 2009;10:471-478.
309. Cummings DE, Frayo RS, Marmonier C, Aubert R, Chapelot D. *Plasma ghrelin levels and hunger scores in humans initiating meals voluntarily without time- and food-related cues*. Am J Physiol Endocrinol Metab 2004;287:E297-304.
310. Mundinger TO, Cummings DE, Taborsky GJ, Jr. *Direct stimulation of ghrelin secretion by sympathetic nerves*. Endocrinology 2006;147:2893-2901.
311. Takahashi K, Chin K, Akamizu T, Morita S, Sumi K, Oga T, et al. *Acylated ghrelin level in patients with OSA before and after nasal CPAP treatment*. Respirology 2008;13:810-816.
312. Sakurai T. *The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness*. Nat Rev Neurosci 2007;8:171-181.