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Régulation de l'activité à ondes lentes en sommeil au cours du vieillissement et dans différentes pathologies du sommeil

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Régulation de l'activité à ondes lentes en sommeil au cours du vieillissement et dans différentes pathologies du sommeil

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SOMMAIRE

Le cycle éveil-sommeil est contrôlé par l'interaction entre deux processus indépendants : le processus circadien, qui correspond aux variations rythmiques de la propension au sommeil au cours des 24 heures et le processus homéostatique qui représente la dette de sommeil accumulée pendant l'éveil. Un marqueur physiologique important du processus homéostatique est la puissance spectrale de l'activité à ondes lentes (AOL) à l'EEG au cours du sommeil NREM. La présente thèse visait à étudier la puissance et la dynamique de l'AOL au cours du sommeil, chez des sujets normaux de divers groupes d'âge et des sujets atteints de différentes pathologies du sommeil.

La première partie de cette thèse est composée de deux volets. Le premier s'est intéressé aux modifications de l'architecture du sommeil et de l'EEG au cours du vieillissement. Le deuxième visait à mesurer les effets de l'âge sur la force de récupération du processus homéostatique, suite à une privation de sommeil de 25 heures. Dans la deuxième partie, nous avons étudié deux populations de patients qui présentent une hypersomnolence diurne, des sujets atteints du syndrome d'apnées du sommeil et des sujets souffrant d'hypersomnie idiopathique. Enfin, nous avons mesuré l'AOL dans une pathologie qui touche spécifiquement le sommeil à ondes lentes, le somnambulisme.

La baisse dramatique des stades profonds de sommeil au cours du vieillissement est associée à une diminution de la puissance de l'AOL. L'analyse spectrale de l'EEG nous a permis de démontrer qu'une baisse importante de l'AOL se produit entre l'enfance et le milieu de l'âge adulte. Il semble que la dynamique du déclin de l'AOL s'atténue et atteigne un plateau avec l'âge. Dans

le deuxième volet, nous avons noté que la consolidation du sommeil est gravement perturbée chez les sujets d'âge moyen pendant un épisode de sommeil de jour en dépit d'une privation de sommeil de 25 heures. Le rebond d'AOL lors du sommeil de récupération est significativement réduit chez les sujets d'âge moyen comparés aux sujets jeunes. Ces études suggèrent que le vieillissement soit associé à une atténuation de la force du processus de récupération homéostatique et à une augmentation de la sensibilité à un angle de phase anormal entre le signal circadien et l'épisode de sommeil.

Il existe des évidences croissantes à l'effet que des altérations de la régulation de l'AOL soient présentes dans plusieurs pathologies du sommeil. Les hypersomniaques présentent aussi une diminution de l'AOL au cours du sommeil. Cette observation pourrait refléter une baisse du processus de régulation homéostatique dans cette population. Chez les apnéiques, les éveils fréquents provoqués par les apnées, semblent affecter le niveau de l'AOL. Il semble que ces patients vivent en fragmentation chronique de sommeil. Chez les somnambules, la présence d'éveils répétés en SOL semble empêcher l'accumulation normale de l'AOL en début de nuit.

L'utilisation du modèle à deux processus a soulevé un grand intérêt en permettant d'étudier la régulation du sommeil à l'aide d'un cadre théorique. L'étude de l'AOL au cours du sommeil pourra améliorer notre compréhension des mécanismes responsables des modifications du cycle éveil-sommeil avec l'âge et dans différentes pathologies du sommeil.

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LISTE DES ABRÉVIATIONS

Français :

ANOVA :	Analyse de variance
AOL :	Activité à ondes lentes
EEG :	Electroencéphalogramme
EMG :	Electromyogramme
EOG :	Electrooculogramme
FFT :	Transformée rapide de Fourier
MOR :	Mouvement oculaire rapide
NSC :	Noyau suprachiasmatique
Processus C :	Processus circadien
Processus S :	Processus homéostatique
SAS :	Syndrome d'apnées du sommeil
SLP :	Sommeil lent profond
SOL :	Sommeil à ondes lentes
SP :	Sommeil paradoxal
TIDE :	Test itératif de délai d'endormissement

Anglais :

AHI:	apnea + hypopnea index
ANOVA:	analysis of variance
BMI:	body mass index
CPAP:	continuous positive airway pressure
EDS:	excessive daytime somnolence
EEG:	electroencephalogram
IH:	Idiopathic hypersomnia
KC:	K-complexe
MSLT:	multiple sleep latency test
PLSM:	Periodic leg movement in sleep
PSG:	polysomnography recording
REM:	rapid-eye-movement
SaO2:	oxygen saturation
SAS:	sleep apnea syndrome
SEM:	standard error of the mean
SWA:	slow wave activity
WASO :	wake time after sleep onset

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Je dédie cette thèse à mes parents, qui m'ont appris que pour réaliser nos rêves, il suffisait travailler fort et de croire en nous. À toi papa, je sais que de là-haut, tu m'accompagnes et me guides tous les jours. Tu m'as donné la force de caractère et la passion qui m'ont permis de mener ce projet à bien. Maman, tu m'a appris à me faire confiance et à faire confiance à la vie. Je tiens à vous remercier de tout mon cœur pour l'amour que vous m'avez toujours témoigné. Vous m'avez transmis les plus belles valeurs de la vie, celles du cœur. Je vous aime très fort.

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1. INTRODUCTION GÉNÉRALE

Les mystères entourant le sommeil ont toujours exercé une grande fascination. Au cours du sommeil, le cerveau s'isole du monde extérieur et la conscience du dormeur s'absente. Lors de l'endormissement, le cerveau qui était «ouvert» aux stimuli sensoriels, se désengage de son environnement afin de permettre la transition entre l'éveil et le sommeil. Par ailleurs, malgré l'absence de contact avec le monde extérieur, une activité interne très intense est maintenue dans notre cerveau pendant le sommeil.

Les états de vigilance et les transitions entre eux représentent un continuum, un processus dynamique. Pendant de nombreuses années, les chercheurs ont tenté d'établir un lien entre l'activité des neurones et les états de vigilance, afin de comprendre les mécanismes responsables du cycle éveil-sommeil. Les états d'éveil et de sommeil sont caractérisés par des patrons d'activité neuronale distincts qui leur sont propres. Il est maintenant connu que le sommeil est un état actif, il n'est pas uniquement le résultat de la fatigue des systèmes d'éveil. En effet, il existe des structures responsables du déclenchement et du maintien du sommeil à différents niveaux du système nerveux central.

1.1 Sommeil et activité électroencéphalographique (EEG)

L'électroencéphalogramme (EEG) représente l'enregistrement des fluctuations de l'activité électrique d'un ensemble de neurones. Lorsqu'on enregistre l'activité EEG, on mesure le courant généré par l'activité simultanée de milliers de neurones situés dans la région sous l'électrode. Comme les états d'éveil

et de sommeil sont marqués par des patrons d'activité neuronale distincts, l'activité EEG possède, elle aussi, des rythmes caractéristiques.

La transition entre l'éveil et le sommeil est signalée par plusieurs modifications tant au niveau de l'activité EEG, qu'aux niveaux moteur, somatique et viscéral. Le sommeil n'est pas un état homogène, mais est divisé en deux états distincts : le sommeil non-REM (NREM) et le sommeil paradoxal ou REM pour «rapid eye movement». Le sommeil NREM est subdivisé selon l'importance de l'activité EEG à ondes lentes. Le sommeil NREM comprend donc 4 stades identifiés à l'aide de critères visuels définis et standardisés (Rechtschaffen et coll., 1968). Le stade 1 marque la transition entre l'éveil et le sommeil et se reconnaît par la disparition des ondes alpha et un ralentissement de l'EEG. Le stade 2 se distingue du stade 1 par la présence d'événements phasiques caractéristiques : les fuseaux du sommeil et les complexes K. Avec la progression du sommeil, des ondes lentes et de grande amplitude apparaissent (0.1 à 4 Hz) (Rechtschaffen et coll., 1968; Steriade et coll., 1993). Ces ondes lentes marquent les stades 3 et 4, souvent regroupés pour parler du sommeil à ondes lentes (sommeil à ondes lentes : SOL; ou sommeil lent profond : SLP) au cours duquel l'EEG est «synchronisé». Le sommeil paradoxal ou REM tient son nom de ses caractéristiques paradoxales pour un état de sommeil. En effet, trois signes cardinaux permettent de distinguer le REM des autres états de vigilance : 1) une activation cérébrale similaire à celle de l'état d'éveil ; 2) une suppression complète de l'activité des muscles antigravitationnels (atonie) ; 3) des mouvements oculaires rapides (MOR). Le premier épisode de sommeil REM

survient généralement 80 minutes après l'endormissement et l'alternance entre les cycles NREM-REM survient environ toutes les 90 minutes au cours d'une nuit. Au cours du sommeil, le SOL est retrouvé principalement au début de la nuit, alors que la durée des épisodes de sommeil REM augmente avec la progression de la nuit.

1.2 Structures responsables de l'initiation et du maintien du sommeil

1.2.1 Transition éveil-sommeil

La transition entre la veille et le sommeil semble résulter de la modulation de l'excitabilité de divers groupes neuraux. Le thalamus est un relais très important dans la genèse du sommeil. Il contrôle l'entrée des informations sensorielles à destination du cortex. Afin de diminuer l'interaction avec notre environnement, les signaux provenant de l'extérieur sont bloqués par le thalamus au moment de l'endormissement. De plus, le noyau réticulaire du thalamus est responsable de la genèse des fuseaux du sommeil (Steriade et coll., 1984). Les neurones du noyau réticulaire exercent une inhibition étendue sur tout le thalamus. Par leurs propriétés intrinsèques, ces cellules vont permettre l'apparition des oscillations thalamo-corticales caractéristiques des premiers stades de sommeil : les fuseaux du sommeil. La progression du sommeil est marquée par une hyperpolarisation graduelle des neurones thalamiques et corticaux, qui vont passer d'un mode oscillatoire de la fréquence des fuseaux (7-14 Hz chez l'animal) jusqu'à la fréquence delta (0.1-4 Hz), fréquence à laquelle le potentiel membranaire est le plus hyperpolarisé (Steriade, 1996).

1.2.2 Sommeil à ondes lentes

Les sections suivantes de cette thèse, s'intéresseront principalement à un segment du continuum que représente le sommeil : le SOL. Le sommeil est caractérisé par une diminution du taux de décharge de la majorité des populations neuronales du prosencéphale. Par ailleurs, des groupes restreints de neurones augmentent leur activité au cours du SOL, notamment au niveau du tronc cérébral, du prosencéphale basal et de l'hypothalamus antérieur (Findlay et coll., 1969; McGinty et coll., 1974; Jones, 1994; Steriade, 1996).

La formation réticulée médullaire et le noyau de la voie solitaire, deux groupes de cellules situés dans la portion caudale du tronc cérébral semblent impliqués dans la genèse de la synchronisation corticale observée pendant le SOL. Ils envoient des projections vers des régions plus rostrales du tronc (Norgren, 1978; Saper et coll., 1980). Par la suite, les neurones de ces relais pontiques et mésencéphaliques envoient des projections directement au thalamus, à l'hypothalamus, à l'aire préoptique, au prosencéphale basal (noyau de la bande diagonale de Broca), à l'amygdale, au noyau «bed» de la strie terminale et aussi au cortex, notamment au cortex orbitofrontal.

L'hypothalamus antérieur, la région préoptique, le prosencéphale basal et le cortex lui-même, contiennent des groupes de neurones appelés «sleep facilitatory region» qui seraient importants dans la genèse du sommeil (Von Ecomo, 1931; Nauta, 1946). On retrouve donc, à tous les niveaux du système nerveux central, des neurones actifs au cours du SOL et qui jouent un rôle dans l'initiation et le maintien du sommeil.

Les substances chimiques impliquées dans la genèse et le maintien du SOL ont été identifiées à l'aide de différentes manipulations pharmacologiques. Les principaux neurotransmetteurs connus sont le GABA, la sérotonine, la norépinéphrine et l'adénosine (Jouvet, 1972; Jouvet, 1984; Mendelson, 1985; Radulovacki et coll., 1985). Plusieurs autres facteurs chimiques tels des peptides opiacés (enképhaline, endorphine), le peptide muramyl, l'interleukin-1, la somatostatine et le «delta sleep-inducing peptide» semblent aussi avoir un rôle facilitateur dans l'induction du sommeil (Pieron H, 1913; Havlicek et coll., 1979; Krueger et coll., 1982, 1989).

Un des mécanismes proposés pour la genèse du sommeil est une inhibition des neurones du système activateur ascendant (système d'éveil) par les cellules des systèmes responsables du sommeil (Hess, 1931; Lineberry et coll., 1971; Steriade et coll., 1990). D'autres travaux ont suggéré que les systèmes du sommeil aient une influence «synchronogénique» directe et étendue sur les systèmes du prosencéphale (Magnes et coll., 1961; Siegel et coll., 1974; Jones, 1994). On retrouve, dans chaque région du vaste réseau du sommeil, des cellules responsables des manifestations du sommeil entremêlées avec des neurones faisant partie du système activateur de l'éveil. Il doit donc exister des régions stratégiques du système activateur dont l'inhibition par les systèmes responsables du sommeil permettrait d'en contrôler l'excitation et de conduire au sommeil.

1.3 Mécanismes de régulation du sommeil

1.3.1 Fonctions récupératrices du SOL

La fonction la plus clairement rattachée au SOL et la mieux documentée dans la littérature concerne la récupération physiologique. Les premières évidences que le SOL soit relié à la récupération physiologique proviennent d'études de privation de sommeil. Dans une étude pionnière où des sujets étaient soumis à une privation de sommeil de 264 heures, l'épisode de sommeil de récupération n'était que de 14.4 heures (Gulevich et coll., 1966). Il est alors apparu que la relation entre la durée de l'éveil et celle du sommeil n'était pas linéaire. Il semble que la dette de sommeil soit plutôt compensée par une augmentation de l'intensité du sommeil. Depuis de nombreuses années, le SOL a d'ailleurs été identifié comme le reflet de l'intensité du sommeil et du besoin de récupération physiologique (Blake et coll., 1937). En effet, la quantité de SOL est beaucoup plus élevée dans la première partie de l'épisode de sommeil et diminue ensuite progressivement au cours de la nuit, à mesure que les heures de sommeil s'accumulent et que le besoin de récupération diminue (Dement et coll., 1957; Williams et coll., 1964; Webb et coll., 1971). De plus, suite à une privation de sommeil, on note une augmentation marquée du SOL au cours de l'épisode de sommeil subséquent (Williams et coll., 1964; Webb et coll., 1971; Borbely et coll., 1981). À l'opposé, lorsque des siestes diurnes sont permises ou si l'épisode de sommeil précédent est prolongé, la quantité de SOL est atténuée lors de la nuit suivante (Karacan et coll., 1970; Webb et coll., 1971; Feinberg et coll., 1980).

Il a aussi été suggéré que le SOL permette la restauration du métabolisme cérébral, en rétablissant les réserves de glycogène cérébral qui seraient épuisées pendant l'éveil (Steriade, 1996). D'ailleurs, il a été démontré récemment que la quantité de SOL et d'activité à ondes lentes (AOL: activité spectrale de l'EEG entre 0.75 et 4.5 Hz) semblait aussi dépendante de la «qualité» de l'éveil précédent. Par exemple, une activité cérébrale intense au cours de l'éveil entraînerait une augmentation du métabolisme cérébral (Horne, 1989). Cette augmentation du métabolisme pourrait être associée à la libération d'une substance neurochimique comme l'adénosine, qui provoquerait une augmentation du SOL et de l'AOL au cours de l'épisode de sommeil suivant (Benington et coll., 1995). Les régions du cerveau qui sont plus actives pendant l'éveil pourraient donc manifester une augmentation plus marquée de SOL et d'AOL au cours du sommeil. Une étude récente a d'ailleurs démontré qu'une stimulation unilatérale du cortex somatosensoriel pendant la journée, provoquait une augmentation locale de l'AOL au cours des premières heures de l'épisode de sommeil suivant (Kattler et coll., 1994). Une augmentation du SOL pendant le sommeil a été observée suite à un apprentissage intense, par exemple, suite à une stimulation visuelle riche pendant la journée (Horne et coll., 1985).

De plus, les fonctions du SOL ont été associées aux neurones qui sont les plus actifs pendant la veille. Les décharges neuronales caractéristiques du SOL pourraient permettre la réorganisation des circuits cérébraux et la stimulation des dendrites afin de consolider les traces de mémoire acquises au cours de l'éveil

(Steriade, 1996). Le renforcement des synapses *labiles* provoquerait la stabilisation de réseaux neuronaux impliqués dans les processus mnésiques.

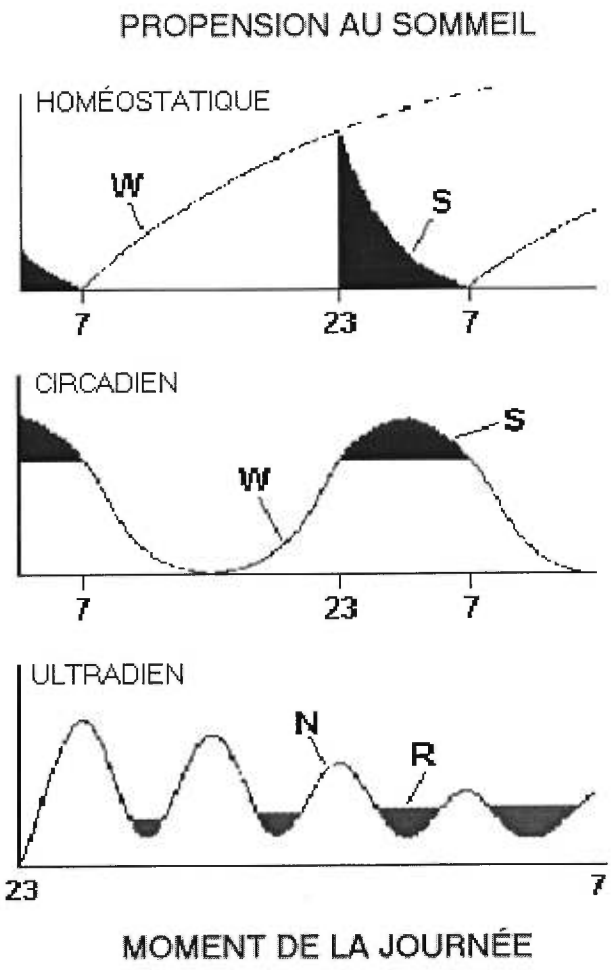
La diminution de la réponse neuronale aux stimuli extérieurs lors de l'endormissement a aussi permis de spéculer quant au rôle du SOL dans la récupération physiologique. Steriade a proposé que dans le réseau thalamo-cortical, les décharges neuronales caractéristiques lors des oscillations delta ou des fuseaux, préviennent l'inertie métabolique cérébrale et permettent le maintien des neurones dans un état d'activation biochimique afin de faciliter une transition rapide vers un état actif, que ce soit le REM ou l'éveil (Steriade, 1996).

1.3.2 Modèle de régulation du sommeil à deux processus

Il y a plus de vingt ans, le terme *homéostasie* a été proposé par Borbély (Borbely, 1980) afin de caractériser l'aspect de la régulation du sommeil qui est dépendante de la durée de l'éveil et du sommeil. Son équipe fût la première à proposer un modèle mathématique offrant un cadre conceptuel à l'étude des processus de régulation du sommeil en tenant compte de divers phénomènes tels : la privation de sommeil, la dépendance du sommeil de la phase circadienne, le sommeil durant le travail posté et la désynchronisation interne en absence d'indices temporels (Borbély, 1982; Daan et coll., 1984). Selon les postulats de base de ce modèle, deux processus indépendants sont responsables de la régulation du sommeil et donc de la distribution des épisodes d'éveil et de sommeil : le processus homéostatique (S) et le processus circadien (C) (voir figure 1). Le processus S est l'élément dépendant de la quantité d'éveil et d'heures de sommeil, alors que le processus C (indépendant du cycle éveil-sommeil) est

contrôlé par un oscillateur circadien. C'est l'interaction constante entre ces deux processus S et C qui semble définir exactement la propension et la durée du sommeil. Les épisodes de sommeil et d'éveil sont donc généralement consolidés à des moments spécifiques au cours d'une période de 24 heures.

Figure 1. Processus homéostatique, circadien et ultradien impliqués dans la régulation du sommeil



Selon le modèle, 2 processus jouent un rôle dominant dans la régulation du sommeil:
A) Un processus dépendant du sommeil ou processus homéostatique, qui augmente pendant l'éveil (W) et se dissipe au cours du sommeil (S).
B) Un processus indépendant du sommeil ou processus circadien, qui représente les variations de la propension au sommeil au cours des 24 heures.
L'interaction entre ces deux processus détermine la propension et la durée du sommeil.
C) La régulation du sommeil comporte aussi des rythmes ultradiens, ayant une période de moins de 24 heures, représentés sur la figure par l'alternance entre le sommeil NREM et REM au cours d'un épisode de sommeil.

Le processus C est indépendant du sommeil et de l'éveil et il correspond aux variations rythmiques de la propension au sommeil. Ce rythme endogène

présente une période d'environ 24 heures et il persiste en isolation temporelle. L'organisation circadienne (du latin *circa* ; environ et *dies*; jour) des fonctions biologiques est générée et contrôlée par une structure diencéphalique située dans la partie antérieure de l'hypothalamus : le noyau suprachiasmatique (NSC) (Moore et coll., 1972). Cet oscillateur est entraîné par le cycle lumière-obscurité, via la voie rétino-hypothalamique (Moore et coll., 1972). Deux fonctions principales sont attribuées au NSC: la genèse interne de rythmes circadiens et la synchronisation de ces rythmes avec le cycle lumière-obscurité. Son rôle serait donc crucial dans la détermination des moments d'initiation et de fin des épisodes d'éveil et de sommeil et dans leur consolidation. Il existe plusieurs marqueurs biologiques de ce processus, en particulier les variations circadiennes de la température corporelle et de la concentration plasmatique de la mélatonine. L'oscillateur circadien a donc une implication majeure dans l'organisation du sommeil. En effet, la propension au sommeil est modulée par la phase circadienne. Par exemple, la propension au sommeil augmente sur la partie descendante de la courbe de température corporelle et atteint son maximum près du minimum thermique. Sur la portion ascendante de la courbe de température, la propension au sommeil diminue pour atteindre un point minimal autour du maximum thermique. Plusieurs protocoles expérimentaux ont permis d'étudier la relation entre le signal émis par l'horloge biologique et l'organisation du sommeil (Wever, 1979; Carskadon et coll., 1980; Weitzman et coll., 1981; Akerstedt et coll., 1981; Daan et coll., 1984; Gillberg et coll., 1982; Lavie, 1986; Dijk et coll., 1999). La caractéristique commune de toutes ces études est qu'elles initiaient des

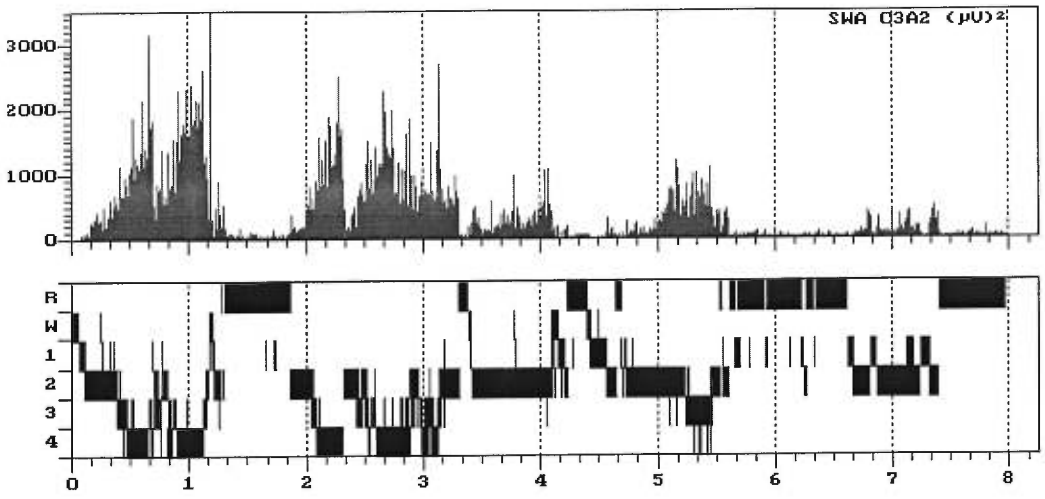
épisodes de sommeil à différentes phases circadiennes. Malgré les différences méthodologiques entre ces protocoles, leurs résultats corroborent une relation intime entre la propension au sommeil et la phase circadienne.

Le processus S représente la dette de sommeil qui résulte de la durée de la période d'éveil qui précède. Le processus S croît pendant l'éveil et se dissipe au cours du sommeil. Le SOL est considéré comme un marqueur physiologique de l'intensité du sommeil, et donc du processus S. Ainsi, le processus S contrôle l'intensité du sommeil. L'équipe de Borbely a montré que l'analyse spectrale de l'AOL à l'EEG était aussi un marqueur précis de l'activité du processus S. L'analyse spectrale de l'EEG est une mesure quantitative du signal EEG au cours du sommeil et une analyse continue plus fine que les stades conventionnels de sommeil. L'analyse spectrale permet donc de connaître la puissance (en μV^2) ainsi que le décours temporel des fréquences qui composent un signal EEG (Niedermeyer et coll., 1998). Elle est réalisée à l'aide de la transformée rapide de Fourier (FFT), qui calcule les différentes composantes fréquentielles de l'EEG (Nuwer, 1988). Par exemple, l'analyse spectrale de l'AOL permet la quantification des composantes lentes de l 'EEG, correspondant au SOL. L'AOL, comme le SOL, est plus élevée au début de l'épisode de sommeil et diminue de façon exponentielle avec la progression du sommeil (Borbély, 1982) (voir fig. 2).

Le processus S pourrait aussi être associé à un facteur endogène libéré de façon spécifique au cours du sommeil. En effet, des substances comme le peptide muramyl, le «delta sleep inducing factor» et l'interleukin 1 s'accumulent pendant

l'éveil et ont la capacité d'induire le sommeil lorsqu'elles sont injectées à des animaux (Pappenheimer et coll., 1975; Krueger et coll., 1982). Toutefois, aucune donnée expérimentale n'a permis de corréler directement un substrat neurochimique au processus S. Au niveau physiologique, Steriade a rapporté que l'hyperpolarisation des neurones thalamo-corticaux en sommeil NREM était associée aux oscillations du potentiel membranaire dans les fréquences de l'AOL (Steriade et coll., 1993). Ces résultats suggèrent un lien entre les processus neurophysiologiques et le concept d'homéostasie du sommeil.

Figure 2. Dynamique de l'AOL au cours d'un épisode de sommeil.



Suite à la proposition du modèle original, de nombreuses études ont tenté d'en vérifier les postulats de base, spécialement le volet homéostatique. L'analyse de siestes diurnes et de périodes d'éveil prolongées ont permis d'estimer la puissance de l'AOL après des durées d'éveil variables, et donc de vérifier la proposition voulant que le processus S augmente selon une fonction exponentielle

saturante au cours de l'éveil. La majorité de ces études ont utilisé l'analyse spectrale de l'AOL comme mesure du processus S.

La privation de sommeil est une approche classique afin d'étudier les mécanismes de régulation du sommeil. La proposition voulant que le processus S augmente graduellement avec la durée de l'éveil, a été corroborée par ces études de privation de sommeil. Lorsqu'un épisode de sommeil succède à une période d'éveil prolongée, le niveau initial de l'AOL est augmenté (Borbely et coll., 1981; Dijk et coll., 1990, 1991, 1993). Toutefois, comme le déclin de l'AOL est exponentiel, l'augmentation de la durée totale de l'épisode de sommeil de récupération n'est pas proportionnelle à la durée de l'éveil (Borbély, 1982). En plus d'un niveau accru d'AOL suite à une privation de sommeil, l'accumulation de l'AOL à l'intérieur des premiers cycles de sommeil NREM est accélérée (Borbely et coll., 1981; Dijk et coll., 1990).

Plus spécifiquement, lors d'une privation sélective de SOL pendant les trois premières heures d'un épisode de sommeil, on remarque une augmentation significative du SOL et de l'AOL aux cours des heures de sommeil suivantes (Dijk et coll., 1987). D'autres auteurs ont montré que lorsque la durée des épisodes de sommeil est limitée à 3 ou 4 heures pendant quelques nuits (privation partielle), une faible augmentation de l'AOL est observée au cours de l'épisode de sommeil de récupération. Cette observation s'explique par le fait que la dette ou la pression de sommeil, manifestée par le niveau de l'AOL, est en grande partie évacuée après un certain nombre d'heures de sommeil (Brunner et coll., 1990). Ces observations sont en accord avec les prédictions du modèle à deux processus.

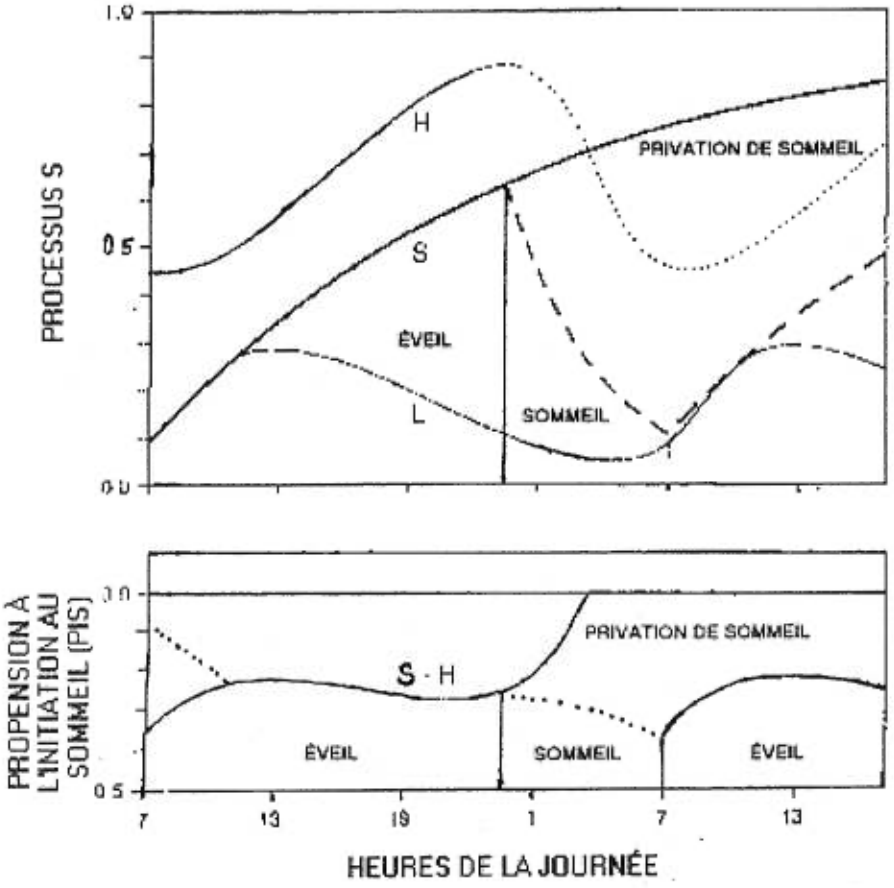
Des études de privation de sommeil chez l'animal ont rapporté des résultats similaires à ceux obtenus chez l'humain. En effet, une augmentation marquée du niveau initial de l'AOL était présente chez des rats ayant été privés de sommeil pendant 24 heures (Schwierin et coll., 1999).

Des études dans lesquelles des siestes diurnes étaient réalisées toutes les deux heures (entre 10h et 4h), en gardant un intervalle d'au moins 3 jours entre chaque sièste, ont montré une augmentation exponentielle de l'AOL avec la durée de l'éveil précédent la sièste (Beersma et coll., 1987; Dijk et coll., 1987b). De plus, lorsque des siestes sont permises au cours de la journée, des répercussions importantes sont observées sur l'intensité de l'AOL, qui diminue lors de l'épisode de sommeil suivant (Karacan et coll., 1970; Knowles et coll., 1990; Werth et coll., 1996). Une étude récente a rapporté que la réduction de la pression homéostatique était manifestée par une atténuation du déclin de l'AOL au cours de la nuit, en plus de la diminution de son niveau initial (Werth et coll., 1996). D'autres études ont montré que l'AOL au cours des siestes diurnes était influencée par la durée de l'épisode de sommeil précédent (Akerstedt et coll., 1986; Gillberg et coll., 1991).

Les constantes de temps du processus S ont été calculées à partir du taux de changement de la densité de puissance de l'EEG au cours du sommeil normal et suite à une privation de sommeil (Borbely et coll., 1981). Le modèle assume que la courbe du déclin du processus S est une asymptote qui s'approche de zéro pendant le sommeil, alors qu'au cours de l'éveil, le processus S approche une

asymptote supérieure. Le déclin de la puissance de l'AOL au cours du sommeil est exponentiel et monotone.

Figure 3. Représentation schématique de la version modifiée du modèle à deux processus au cours d'un épisode normal d'éveil et en privation de sommeil (*Tirée de Borbély et coll., 1989*).



Au cours de l'éveil, le processus S augmente de façon exponentielle. Le processus circadien, représenté par le seuil H, augmente lui aussi au cours de la journée jusqu'à l'heure habituelle du coucher et diminue par la suite. L'illustration du bas, représente la PIS résultant de l'intervalle entre le processus S et le seuil H (S-H). Au cours de la journée, PIS est à un niveau uniforme et peu élevé. Lorsque l'éveil est prolongé à l'extérieur des limites circadiennes, la PIS augmente rapidement, jusqu'à ce qu' elle atteigne un niveau plafond (correspondant à 0 sur le graphique du bas) étant donné l'action synergique du processus homéostatique qui continue à augmenter et du processus circadien qui lui, commence à diminuer.

Ainsi, le taux de décroissance instantané du processus S a été calculé à partir de la dynamique du déclin de l'AOL au cours du sommeil: $r = 0.238$/h. Le taux d'accumulation de l'AOL ($r = 0.055$/h) a été déterminé à l'aide de trois données expérimentales : la densité de puissance de l'AOL à la fin d'un épisode de sommeil normal, à la fin d'une journée d'éveil normal, et suite à 24 heures de privation de sommeil (Borbely et coll., 1981).

Le modèle a été élaboré à l'aide de données normatives et aussi suite à une privation de sommeil (Borbely et coll., 1981). Selon le modèle, le niveau du processus S augmente au cours de l'éveil selon une fonction exponentielle limitée par deux asymptotes («saturating exponential function»). Comme on peut voir à la figure 3, le processus C, sous la direction de l'oscillateur circadien, agirait en modulant deux seuils qui définissent ainsi le moment de l'initiation (seuil haut : H) et de la fin des épisodes de sommeil (seuil bas : L). Le seuil L (éveil) a été décrit à partir de données expérimentales dans lesquelles la durée du sommeil était calculée chez des sujets qui dormaient à différentes phases circadiennes (Akerstedt et coll., 1981; Daan et coll., 1984). Le seuil L a été défini comme une fonction sinusoïdale un peu étirée avec une portion ascendante plus rapide et une phase descendante plus lente.

Les auteurs ont ensuite défini le seuil H, qui détermine le moment de l'initiation du sommeil. Le seuil H a été défini en mesurant la propension à l'initiation du sommeil à différents moments de la journée (Borbély et coll., 1989). Le modèle assume qu'au cours de la période d'éveil habituelle, un processus circadien vienne contrecarrer la propension au sommeil croissante,

induite par le processus homéostatique. Le seuil H est en direction opposée au seuil L et possède une amplitude et une phase différentes. Cette relation inverse entre les deux seuils permettrait de maintenir un niveau d'éveil constant pendant la majeure partie de la période d'éveil.

De cette façon, le processus S augmenterait de façon exponentielle au cours de la période d'éveil, jusqu'à ce qu'il atteigne le seuil H et il déclinerait aussi de façon exponentielle pendant le sommeil, jusqu'à ce que le seuil bas (L) soit atteint et que l'épisode de sommeil soit complété. Ce système fonctionnerait comme un thermostat, aussi appelé «somnostat», qui oscillerait entre les deux seuils H et L. La fréquence de l'alternance éveil-sommeil dépend donc de l'intervalle entre les niveaux des deux seuils et du taux d'accumulation et de déclin du processus S. Le modèle assume que le niveau des seuils L et H est influencé de façon considérable par les conditions extérieures. Par exemple, la chaleur, la noirceur ou l'absence de stimulation sociale ou intellectuelle peut diminuer le seuil H et ainsi accélérer l'initiation du sommeil. Les stimuli environnementaux permettraient au contraire de retarder l'épisode de sommeil en augmentant le niveau du seuil H. Le seuil L, qui fonctionne au cours du sommeil, semble moins sensible à l'environnement que le seuil H, bien que la sonnerie d'un réveil-matin puisse simuler efficacement une montée subite du seuil L. Le modèle à deux processus permet de prédire le moment du sommeil sous divers horaires comme la désynchronisation interne en absence d'indices temporels, la fragmentation de sommeil pendant le repos-couché, la dépendance de phase de la durée du sommeil en absence d'indices temporels, la privation de sommeil et le

travail posté. Par exemple, on peut simuler une privation de sommeil, en suspendant le seuil H, ce qui permet au processus S d'augmenter sur une plus longue période.

La régulation du sommeil présente également des variations ultradiennes (< 24 heures). En effet, le modèle permet aussi de prédire le processus ultradien, observé au cours d'un épisode de sommeil et représenté par l'alternance entre les cycles NREM et REM (Achermann et coll., 1990, 1993). Cette élaboration du modèle tient compte non seulement du déclin de l'AOL ou du processus S pendant un épisode de sommeil, mais aussi de l'alternance ultradienne de l'AOL et de sa dynamique à l'intérieur des cycles NREM-REM. Cette variable a permis de démontrer que la durée de l'éveil et du sommeil précédant un épisode de sommeil influençait la tendance globale de l'AOL, mais aussi son taux d'accroissement à l'intérieur des épisodes de sommeil NREM. Le modèle assume que l'activation périodique d'un signal déclencheur du REM («REM trigger») soit responsable du déclin de l'AOL jusqu'au niveau observé en REM. Après un certain temps, l'inactivation de ce signal permettrait la montée de l'AOL au cours du cycle NREM suivant. Le signal déclencheur du REM serait activé avant le début de l'épisode de REM et provoquerait le déclin de l'AOL. Ce signal a été incorporé au modèle à partir de données expérimentales (Achermann et coll., 1987, 1990). Dans leur modèle d'interaction réciproque, McCarley et Hobson (McCarley et coll., 1975) ont proposé que l'alternance entre les cycles NREM-REM soit générée par l'interaction entre deux groupes de neurones (REM-on et

REM-off) dans le tronc cérébral. Il a été suggéré que l'interaction entre ces groupes de neurones puisse représenter l'homologue physiologique du signal déclencheur du REM proposé dans le modèle à deux processus.

1.4 Régulation de l'activité à ondes lentes dans différentes conditions physiologiques et expérimentales.

Première partie

1.4.1 Premier volet : Modifications de l'EEG de sommeil au cours du vieillissement.

D'importantes modifications dans la macrostructure du sommeil sont observées au cours du vieillissement. On note, entre autres, une augmentation des stades 1 et 2 de sommeil et de la fragmentation du sommeil et une avance des heures de lever et de coucher (Miles et Dement, 1980; Bliwise et coll., 1993; Carrier et coll., 1997). De toutes les composantes du sommeil, ce sont les stades 3 et 4 (ou SOL), qui subissent les plus profondes transformations avec l'âge. En effet, ces stades sont particulièrement abondants chez l'enfant, où ils occupent environ 20 % de la durée totale du sommeil, ils diminuent progressivement pendant l'adolescence et chez le jeune adulte pour atteindre des niveaux voisins de 5% vers l'âge de 50 ou 60 ans (Williams et coll., 1974). Ces stades de sommeil peuvent même disparaître à des âges très avancés (80 ans et plus). Les modifications marquées dans la macrostructure du sommeil reliées à l'âge sont donc principalement attribuables à la diminution substantielle du SOL.

Les changements considérables de la macrostructure du sommeil avec l'âge sont évidemment reflétés au niveau de l'EEG. En effet, la baisse dramatique des stades profonds de sommeil est associée à une diminution importante de la

puissance de l'AOL à l'EEG. La dynamique du déclin de l'AOL au cours du sommeil est un bon indicateur de l'intégrité du processus homéostatique. Quelques études ont rapporté une diminution de l'AOL entre des sujets jeunes et d'âge moyen (Dijk et coll., 1989; Landolt et coll., 1996; Carrier et coll., 2000). Selon les concepts d'homéostasie du sommeil, on pourrait associer le vieillissement à une atténuation de l'efficacité du processus S (Dijk et coll., 1989). Il a d'ailleurs été suggéré que les constantes de temps du processus S augmente avec l'âge (Borbely et coll., 1981; Daan et coll., 1984). Toutefois, le modèle à deux processus a été élaboré à partir de données normatives du sommeil de sujets jeunes (21-29 ans), et aucune étude n'a encore permis d'en déterminer tous les paramètres qui expliqueraient les modifications des mécanismes de régulation du sommeil avec l'âge. Les modifications de la structure sommeil et de l'EEG en sommeil NREM entre l'enfance et le milieu de l'âge adulte n'ont encore jamais été rapportées de façon systématique.

1.4.2 Deuxième volet : Manipulation du processus S: Privation de sommeil et effet d'âge.

Nos connaissances sur les altérations de la structure du sommeil et de l'EEG en sommeil avec l'âge proviennent principalement d'études descriptives. Plusieurs hypothèses ont été avancées afin d'expliquer les modifications du cycle éveil-sommeil avec l'âge. Il a été suggéré, entre autres, que ces changements soient causés par une diminution de la force du processus S et par une augmentation de la sensibilité à un angle de phase anormal entre l'épisode de

sommeil et le signal émis par l'horloge biologique (Moline et coll., 1992; Campbell, 1995; Duffy et coll., 1998; Dijk et coll., 1999).

La privation de sommeil est un outil permettant d'étudier la force de récupération du processus homéostatique. Très peu d'études ont rapporté les effets de l'âge sur le sommeil de récupération, suite à une privation de sommeil. Lorsque des sujets âgés étaient soumis à une privation de sommeil, un rebond de SOL était observé, toutefois le niveau de SOL demeurait réduit (Bonnet, 1986). Par ailleurs, le milieu de l'âge adulte, une période pendant laquelle surgissent de nombreuses plaintes de sommeil, a été négligé dans la littérature. En effet, à notre connaissance, une seule étude a évalué les différences dans l'architecture du sommeil entre des jeunes et des sujets d'âge moyen (Webb, 1981). Suite à une privation de sommeil, une augmentation du nombre de minutes de SOL était présente chez les deux groupes, les sujets d'âge moyen montraient néanmoins un rebond plus faible. Les effets différentiels d'une privation de sommeil sur l'EEG quantifié au milieu de l'âge adulte n'ont encore jamais été rapportés.

Il existe une interaction constante et une relation de phase privilégiée entre les processus S et C. Il a été proposé que dans des conditions normales, une augmentation de la tendance circadienne à l'éveil se produisait au cours de la journée et viendrait contrecarrer l'augmentation de la propension au sommeil. Ceci permettrait de maintenir un épisode d'éveil consolidé de 16 heures chaque jour. De la même façon, l'augmentation de la tendance circadienne au sommeil à mesure que la nuit progresse s'opposerait à la diminution de la propension homéostatique au sommeil qui résulte de la durée du sommeil qui précède. Cette

relation opposée entre les processus homéostatique et circadien permettrait un épisode de sommeil consolidé de 8 heures. Cette interaction peut être étudiée dans des protocoles dans lesquels on crée un conflit, c'est-à-dire que l'on modifie en laboratoire leur relation de phase endogène. Le protocole de désychronisation forcée a permis de séparer expérimentalement les influences circadiennes et homéostatiques, afin de comprendre leur rôle respectif dans les changements de la consolidation et de la durée du sommeil avec l'âge. La manipulation de cette relation de phase affecterait les personnes âgées de façon plus importante que les sujets jeunes (Webb, 1981). Le sommeil des personnes âgées contient une quantité plus importante d'éveil que celui des sujets jeunes, à n'importe quelle phase circadienne. Le nombre d'éveils chez les personnes âgées augmente principalement en fin de nuit, lorsque l'épisode de sommeil est initié sur la partie ascendante de la courbe de température (Dijk et coll., 1997, 1999; Duffy et coll., 1998). De plus, d'autres études ont montré que les sujets d'âge moyen présentent plus de difficultés d'adaptation dans des situations où le système est mis au défit, par exemple lors de simulation de décalage horaire en laboratoire ou lors de travail posté (Moline et coll., 1992; Campbell, 1995).

Aucune étude n'a tenté de déterminer les modifications des mécanismes circadien et homéostatique de régulation du sommeil au milieu de l'âge adulte. Comme mentionné précédemment, les effets de la privation de sommeil sur la force du processus de récupération homéostatique au cours du vieillissement sont peu connus, mais une atténuation de ce processus est envisagée. Il semble aussi

que le vieillissement soit associé à une plus grande sensibilité à un angle de phase anormal entre l'épisode de sommeil et la rythmicité circadienne.

Deuxième partie

1.4.3 AOL et troubles du sommeil: hypersomnie idiopathique, syndrome d'apnées du sommeil et somnambulisme

Il existe des évidences croissantes à l'effet que des altérations de la régulation de l'AOL soient présentes dans plusieurs pathologies du sommeil et maladies psychiatriques. En effet, des modifications du SOL ont été rapportées, entre autres, chez des populations dépressives, narcoleptiques, insomniaques et dans certains désordres psychiatriques comme la schizophrénie. Certains groupes ont d'ailleurs proposé que l'insomnie soit une maladie du SOL (Gaillard, 1976; Sewitch, 1987). Kupfer et Reynolds ont même suggéré que le SOL ait des effets bénéfiques et protecteurs contre les désordres psychiatriques et le vieillissement pathologique (Kupfer et coll., 1989). Par ailleurs, peu d'études ont tenté de déterminer les mécanismes de régulation du sommeil et les processus impliqués dans les modifications du sommeil retrouvées dans ces diverses pathologies. Certaines pathologies dans lesquelles on observe des perturbations du sommeil et de l'AOL fournissent des avenues de recherche pour l'étude des mécanismes de régulation du sommeil et des altérations possibles dans certaines conditions physiologiques.

Chez les sujets atteints d'hypersomnie idiopathique, le cycle éveil-sommeil est caractérisé par des épisodes de sommeil nocturne prolongés et

ininterrompus, une ivresse du sommeil au réveil, ainsi que par une somnolence diurne excessive (Roth et coll., 1972; Montplaisir et coll., 1982). Cette maladie dont la pathophysiologie demeure encore inconnue est diagnostiquée par l'exclusion d'autres pathologies causant une somnolence diurne comme la narcolepsie, le syndrome d'apnées du sommeil ou l'hypersomnie post-traumatique. Une caractéristique importante de ces patients est qu'ils rapportent une somnolence excessive en dépit d'un sommeil apparemment normal. En effet, la macrostructure du sommeil semble normale chez ces patients, malgré la durée prolongée des épisodes de sommeil. Une altération de la régulation de l'AOL pourrait expliquer la fatigue diurne excessive présente chez ces patients ainsi que leur besoin irrépressible de dormir.

Le syndrome d'apnées du sommeil (SAS) se distingue aussi par la présence de somnolence diurne excessive. Le sommeil des sujets apnéiques est perturbé par des arrêts respiratoires récurrents qui surviennent pendant toute la durée de l'épisode de sommeil (Dement et coll., 1978; Reimao et coll., 1985; Guilleminault et coll., 1988). Ces pauses respiratoires fragmentent le sommeil en provoquant des éveils répétés pendant la nuit. La macrostructure du sommeil est en général très perturbée chez les patients apnéiques. En effet, une privation de REM et de SOL a été rapportée chez ces patients, même si l'efficacité de sommeil semble plus ou moins modifiée (Reimao et coll., 1985; Guilleminault et coll., 1988). Le traitement par pression positive continue («CPAP») permet de rétablir le débit respiratoire et une structure de sommeil normale, et il supprime les épisodes d'hypoxie chez les patients SAS. Cet appareil améliore aussi la

somnolence diurne chez les patients SAS, telle que mesurée en laboratoire à l'aide du TIDE (test itératif de délai d'endormissement). On peut penser que la fragmentation du sommeil lors des apnées va nuire à la dynamique de l'AOL au cours de la nuit, et pourra influencer le niveau de vigilance au cours de la journée suivante.

Le somnambulisme est une parasomnie considérée comme un désordre de l'éveil du SOL («disorder of arousal from NREM sleep»), caractérisée par des déambulations nocturnes mais dont l'expression en laboratoire prend souvent la forme de comportements moteurs complexes (Jacobson et coll., 1965; Kales et coll., 1966; Broughton, 1968; Keefauver et coll., 1994). L'épisode de somnambulisme se manifeste en général comme un éveil soudain mais incomplet en SOL. La macrostructure du sommeil est normale chez les somnambules, mais on remarque toutefois une plus grande quantité d'éveils survenant en SOL, comparativement à des sujets contrôles (Blatt et coll., 1991). Ces éveils en SOL et leur distribution au cours de l'épisode de sommeil peuvent affecter l'accumulation de l'AOL, en fragmentant le SOL.

1.5 Buts et hypothèses

Le but général de la présente thèse est d'explorer les altérations du niveau et de la dynamique de l'AOL chez des sujets normaux de différents groupes d'âge et dans certaines pathologies du sommeil. Les hypothèses spécifiques pour chacun des deux volets de cette thèse sont les suivantes.

1.5.1 AOL et effets de l'âge

Nous avons premièrement étudié les effets de l'âge sur la macrostructure du sommeil, en nous intéressant aux modifications survenant entre l'enfance et le milieu de l'âge adulte. Dans le second volet de cette thèse, nous avons tenté de comprendre les causes de la détérioration du cycle veille-sommeil au milieu de l'âge adulte.

A) Nous avons mesuré les changements de la puissance et de la dynamique de l'EEG au cours du sommeil NREM pour quatre groupes d'âge : enfants, adolescents, jeunes adultes et âge moyen. Nous prévoyons que des modifications importantes des mécanismes de régulation du sommeil, manifestées entre autres par un déclin de la puissance et de la dynamique de l'AOL, seront présentes entre l'enfance et le début de l'âge adulte.

B) Nous avons ensuite évalué les effets de l'âge sur les mécanismes circadien et homéostatique de régulation du sommeil. Nous proposons que la force du processus de récupération homéostatique du sommeil, suite à une privation de sommeil de 25 heures, diminue avec l'âge. Nous pensons aussi que le vieillissement affectera la capacité à maintenir un sommeil consolidé à un angle de phase anormal entre le cycle éveil-sommeil et la rythmicité circadienne. En

résumé, nous avons évalué, suite à une privation de sommeil de 25 heures, comment l'organisation temporelle du sommeil et de l'EEG en sommeil NREM est modifiée chez des sujets jeunes et d'âge moyen, lors d'un épisode de sommeil de jour, un moment où la propension circadienne au sommeil diminue.

1.5.2 AOL et troubles du sommeil

Nous nous sommes ensuite intéressés à l'impact de différentes pathologies du sommeil, comme l'hypersomnie idiopathique, le syndrome d'apnées du sommeil et le somnambulisme, sur le niveau et le décours temporel du SOL et de l'AOL au cours du sommeil NREM.

A) Nous avons tout d'abord étudié l'hypersomnie idiopathique et le syndrome d'apnées du sommeil, deux pathologies du sommeil dans lesquelles les sujets se plaignent de somnolence diurne, afin de vérifier s'il existait une corrélation entre la présence de somnolence pathologique et l'AOL. La somnolence diurne pourrait être expliquée par une altération de la régulation de l'AOL au cours du sommeil.

Dans l'hypersomnie idiopathique, il est intéressant d'étudier la régulation de l'AOL, car le sommeil de ces sujets semble être consolidé et sans perturbation apparente. Nous proposons que les sujets hypersomniaques présentent une augmentation de l'AOL, reflétant peut-être une hypersensibilité à la durée de l'éveil. On peut imaginer par exemple, que la puissance de l'AOL lors du premier cycle de sommeil soit comparable à celle des sujets normaux mais que la baisse de l'AOL au cours des cycles subséquents soit beaucoup moins abrupte. Ces patients maintiendraient ainsi un niveau de pression homéostatique élevé lors d'une sieste

diurne, traduisant une augmentation persistante de l'activité du processus S au cours des 24 heures.

Dans le cas du syndrome d'apnées du sommeil, l'interruption fréquente du sommeil lors des pauses respiratoires ainsi que la somnolence diurne résultante amènent aussi l'hypothèse que chez ces sujets, le niveau et la dynamique du SOL et de l'AOL seront modifiés au cours de l'épisode de sommeil. On peut aussi penser que la somnolence diurne, mesurée en laboratoire par le TIDE, sera négativement corrélée au niveau de l'AOL au cours de la nuit précédente. Nous avons donc mesuré le niveau de l'AOL et son décours temporel au cours d'un épisode de sommeil chez des patients SAS et sujets contrôles lors d'une nuit de sommeil en laboratoire. De plus, nous avons vérifié s'il existait une corrélation entre le niveau de l'AOL pendant la nuit et la somnolence diurne au cours de la journée suivante, chez les patients SAS. Nous nous sommes aussi intéressés à l'effet du traitement par CPAP, afin de voir s'il permettait de rétablir une dynamique et un niveau normaux d'AOL chez les patients SAS.

B) Nous avons finalement étudié une pathologie connue dans laquelle des manifestations surviennent spécifiquement pendant le SOL. Les conséquences de ces phénomènes sur la régulation de l'AOL sont inconnues. Chez les somnambules, on peut penser que la présence d'éveils répétés au cours du sommeil aura des répercussions sur l'accumulation et le décours temporel de l'AOL. Comme ces éveils se produisent principalement pendant le SOL, les perturbations de l'AOL devraient être plus accentuées dans la première portion de l'épisode de sommeil. La dynamique de l'AOL au cours d'une nuit de sommeil

n'a jamais été rapportée dans cette population. Nous avons donc comparé la puissance ainsi que la dynamique de l'AOL chez des somnambules et des sujets contrôles, en relation avec le nombre d'éveils survenant en SOL et leur distribution à travers l'épisode de sommeil. Nous pensons que l'accumulation de l'AOL, particulièrement au cours du premier cycle NREM, sera diminuée chez les somnambules.

MÉTHODES ET RÉSULTATS

2. ARTICLES DE RECHERCHE

2.1. PREMIER ARTICLE

MODIFICATIONS DE L'EEG EN SOMMEIL NREM AU COURS DU VIEILLISSEMENT: DE L'ENFANCE AU MILIEU DE L'ÂGE ADULTE

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Article en révision: JOURNAL OF SLEEP RESEARCH

AGE-RELATED MODIFICATIONS OF NREM SLEEP EEG: FROM CHILDHOOD TO MIDDLE AGE

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RUNNING HEAD: **Alterations in NREM sleep EEG with age.**

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SUMMARY

This study investigated the modifications in NREM sleep EEG power in 54 subjects, from children to middle-aged adults. Spectral analyses were performed on 5 hours of NREM sleep. A marked decrease of absolute SWA was observed with increasing age; children and adolescent had significantly more SWA than young and middle-aged adults throughout the night. The decline of SWA across the night seems to level off with increasing age, suggesting an age-related attenuation of homeostatic sleep pressure. Absolute theta and alpha power were higher for children and adolescents compared to older subjects. Theta power was higher for young adults than for middle-aged adults. Adolescents had higher sigma power than the other three groups, and young adults had more sigma power than middle-aged adults. Absolute beta power was lower for middle-aged adults than for the other three groups. Therefore, the major alterations of NREM sleep EEG occurring between childhood and middle age are not restricted to SWA, but encompassed the theta, alpha, sigma and beta frequency bands.

Key words: Aging, sleep, maturation, spectral analysis, electroencephalogram.

INTRODUCTION

Polysomnographic sleep undergoes marked modifications from childhood through adolescence. The most obvious sleep change across the maturational process is the decrease in slow-wave sleep (SWS). Children's sleep pattern is characterized by important amounts of SWS, mostly in the first third of the night (Bes *et al.*, 1991; Coble *et al.*, 1984; Feinberg *et al.*, 1989; Williams et al., 1974). However, when the reduction in SWS first appears is still matter of controversy. A quantitative change in SWS occurs somewhere during puberty (Carskadon, 1982; Coble *et al.*, 1984; Feinberg, 1989; Williams *et al.*, 1972; 1974). Carskadon (1982) observed a reduction in SWS by almost 40 % during the second decade of life. Similarly, Coble *et al.* (1984) reported that, in 6 to 15 year-old children, NREM sleep was marked by a progressive decrease in the percentage of delta sleep (stages 3 and 4). Kahn *et al.*, (1996) described a gradual decline in SWS across the Tanner puberty stages, with approximately 35 % of decline from Tanner stages 1 to 5. An increased proportion of stage 2 sleep, a reduction of total sleep time and a phase delay of the sleep-wake cycle have also been reported between childhood and adolescence (Carskadon *et al.*, 1982; 1997; Coble *et al.*, 1984; Williams *et al.*, 1972; 1974). Some authors have observed that the transition between childhood and adolescence was characterized by the appearance of sleep complaints and an increase in daytime sleepiness (Carskadon, 1982; Williams *et al.*, 1974). It was thus suggested that most changes occurring between childhood and adolescence may be a consequence of pubertal or hormonal changes rather than a strict reflect of age

(Carskadon, 1982; Karacan *et al.*, 1975; Williams *et al.*, 1972). In a recent paper, Carskadon and collaborators (1997) indicated that sleep-phase delay, which is one of the most consistent modifications in sleep patterns between children and adolescents, may reflect developmental alterations in circadian timing mechanisms. They also proposed that sleep pressure during the day builds up more slowly, enabling individuals to stay awake longer as adolescence progresses. Carskadon *et al.* (1998) have suggested a possible maturational influence on sleep homeostatic regulation. Using preliminary data, they have demonstrated, following sleep deprivation, a greater reduction in the amount of slow-wave sleep over consecutive nights in more mature adolescents than in less mature ones.

During adulthood, SWS begins its sharpest decline across the twenties (Feinberg, 1982; 1989; Williams *et al.*, 1974). Young adults' sleep is also characterized by an increase in REM percent, a shorter latency to the first REM period, and a further decrease in sleep duration compared to adolescents (Williams *et al.*, 1974). As aging proceeds, sleep patterns become more disturbed, with more frequent awakenings across the night, increases in stages 1 and 2 sleep, and a significant and gradual decline in SWS (Bliwise, 1993; Carrier *et al.*, 1997; Feinberg, 1987; Miles *et al.*, 1980; Williams *et al.*, 1974).

Spectral analysis makes possible the quantitative description of the time course of sleep EEG across the night. Hence, it is a powerful tool to explore alterations in sleep regulation mechanisms. For instance, spectral analysis of slow-wave activity (SWA) is a quantitative measure of slow-wave sleep

dynamics, and represents a physiological marker of homeostatic regulation of sleep (Borbély, 1982; Daan *et al.*, 1984). The robustness of the homeostatic marker has been challenged in many protocols using total and partial sleep deprivations, or nap studies (Borbély *et al.*, 1981; Dijk *et al.*, 1987). Sleep deprivation not only increases SWA and theta activity but also reduces sleep spindle activity in the night following deprivation. The reverse effect is produced by a nap in the early evening, producing a decrease in sleep pressure.

Few studies have assessed the effect of age on quantitative measures of the sleep EEG. Most observations describe changes from young adulthood to middle age (Carrier *et al.*, 2000; Dijk *et al.*, 1989; Landolt *et al.*, 1996). These studies have mostly reported a decrease in NREM sleep EEG power density for SWA, theta and sigma activity in middle-aged subjects compared to young adults. Furthermore, the decay rate of EEG power density during NREM sleep is slower in middle-aged subjects than in young adults for SWA and theta bands, so that the between-group difference diminished over the course of sleep. In addition, the difference in sigma activity (frequency range of sleep spindles) increases with time-of-night. These results were interpreted as possibly reflecting an attenuation of the build-up of sleep pressure with increasing age. To our knowledge, no studies investigating alterations of the quantitative sleep EEG, especially SWA, between childhood and young adulthood have yet been undertaken. If EEG SWA power before adulthood is considered, important information may emerge on the appearance of modifications in NREM sleep EEG, reflecting homeostatic sleep regulation mechanisms.

The aim of the present study was to investigate age-related modifications of EEG power spectra in NREM sleep across the night, from childhood to middle age. Furthermore, we explored the alterations in the dynamics of SWA during NREM sleep with increasing age, representing the strength of the homeostatic process.

METHODS

Subjects

Fifty-four subjects between the ages of 6 and 60 years were studied. Four groups, with a female/male ratio of 1:2, were defined as: *children* (3 girls and 6 boys; mean age 7.11 yrs; range 6-10 yrs), *adolescents* (5 girls and 10 boys; mean age 15.33 yrs; range 14-16 yrs), *young adults* (5 women and 10 men; mean age 23.73 yrs; range 19-29 yrs) and *middle aged adults* (5 women and 10 men; mean age 45.4 yrs; range 36-60 yrs). All subjects reported to be in good health and to be free of sleep complaints. They did not abuse drugs or alcohol, and did not take medications known to influence sleep. Subjects were screened for the presence of sleep apneas (index > 10) and periodic limb movements during sleep (index > 10). All subjects with an index >10 were excluded. Sleep efficiency was set at a minimum of 85 % to obtain comparable sleep parameters for all groups. Bedtime and waketime for the difference groups were: 20h30 to 7h00 for the children group, 22h30 to 7h30 for the adolescents, 23h00 to 8h30 for the young adults and 23h00 to 7h00 for the middle-aged group.

Sleep recordings

All subjects underwent one night of polysomnographic recording in a sleep laboratory. Children and middle-aged adults were recorded at the Sacré-Cœur Hospital, whereas adolescents and young adults where studied at the Louis-H Lafontaine Research Center. The same staff elaborated the two laboratory settings according to identical specifications (polygraphs). This minimized the possibility of differences due to methodology. Experimental conditions such as EEG montages and data acquisition parameters were also strictly the same in the two laboratories. Electrodes were placed according to the international 10-20 system, using a referential montage with at least central and occipital EEG derivations, and left and right electrooculogram (EOG) and chin electromyogram (EMG). A Grass polygraph (sensitivity 7.0 μV/mm, bandpass 0.3-100 Hz) was used to amplify signals. The signals were also relayed to a PC computer where they were digitized at a sampling rate of 128 Hz and filtered with a digital filter having an upper cutoff frequency of 64 Hz. Only frequencies up to 31.0 Hz were considered for spectral analyses. Sleep stages were visually scored on screen by 20-second epochs using the C3/A2 lead, according to the standard criteria (Retchschaffen *et al.*, 1968).

EEG spectral analysis

To quantify the dynamics of NREM sleep EEG over the course of the night, spectral analyses were performed for the first 5 hours of NREM sleep (stages 2, 3 and 4 sleep). In order to obtain data which are equivalent with most studies investigating sleep regulatory mechanisms (Achermann *et al.*, 1993;

Aechbach *et al.*, 1993; Dijk *et al.*, 1989) and since it is the standard derivation for sleep scoring (Retchschaffen *et al.*, 1968), spectral analyses were performed on the C3/A2 derivation.

Power spectral analyses were performed with a commercial software package (Eclipse 3.0, Stellate Systems) which computes fast Fourier transforms (FFT) on 4-second epochs with a cosine window tapering. This yielded a spectral resolution of 0.25 Hz. Artifacts were rejected by visual inspection and analyses were performed on artifact-free epochs. Epochs with artifacts were considered as missing data in order to preserve sleep continuity. After spectral analyses, five 4-second epochs were averaged to keep a correspondence with the 20-second sleep scoring windows. Then, spectral activity was averaged per hour for the first five NREM hour of sleep. Five frequency bands were defined as: SWA (0.75 to 4.5 Hz), theta (4.0 to 7.75 Hz), alpha (8.0 to 12.0 Hz), sigma or spindle frequency activity (SFA: 12.25 to 15.0 Hz) and beta (15.25 to 31.0 Hz). Absolute power was used for all frequency bands.

Statistical analyses

To evaluate the differences in sleep architecture, one-way ANOVA with one independent variable (Age groups) and one dependent factor (individual sleep parameters) were performed. Significant F values were adjusted with Bonferroni correction for multiple testings. For a quantitative description of EEG power for each age group during the night, the first statistical analyses were performed on log-transformed power values, to normalize data distributions. Two-way ANOVAs with one independent factor (Age group) and

one repeated measure (NREM hour) were performed to illustrate the effects of age and time-of-night on EEG power in the various frequency bands during NREM sleep. *P*-levels (alpha) were adjusted with Huynh-Feldt correction for sphericity, and considered significant when ≤ 0.05. Contrast analyses and *post hoc* Tukey HSD (p-level ≤ 0.05) comparisons were used to decompose the interaction effects and identify the nature of significant results, or to locate the differences in main effects.

To assess the dynamic of SWA over the course of the night, further analyses were performed on percent of mean SWA during NREM sleep for the entire night. Two-way ANOVAs with one independent factor (Age group) and one repeated measure (NREM hour) were used to investigate the effects of age on the dynamics of changes in EEG during NREM sleep. Then, trend analyses were performed for each group with a between-groups comparison of the rates of change.

RESULTS

Sleep variables

Table 1 presents sleep parameters (Mean ± SD) derived from visual scoring. Children and adolescents had longer sleep latency than young adults and middle-aged subjects. REM sleep latency was longer for children than for young adults and middle-aged adults. REM latency was also longer for adolescents than the young adults. Sleep efficiency was higher only for the young adults compared to middle-aged subjects. Important differences with

regard to percentage of time spent in the various sleep stages were also observed between age groups. The middle-aged group had a higher percentage of wakefulness, stages 1 and 2 sleep, compared to children and adolescent group. Percent of stage 2 sleep was higher for adolescents and young adults than for children. In contrast, the percentage of SWS (stages 3 and 4 sleep) was more important for the children than for the other three groups. The percentage of SWS was also higher for adolescents, than for young adults or middle-aged subjects. There were main effects of gender and age for the percentage of stages 3+4, but no interaction. With age, the percentage of SWS decreased, and women had a higher percentage of SWS compared to men. Young adults presented a higher percentage of REM sleep than the three other groups.

Insert Table about here
(All-night sleep variables)

Spectral activity

NREM hours versus NREM-REM cycles

NREM hour timebase was chosen for spectral analysis in order to compensate for the differences between the groups in the duration of the first NREM period (REM latencies: Children: 163.52 ± 54.43; Adolescents: 124.98 ± 39.94; Young adults: 86.69 ± 26.30; Middle-aged: 100.89 ± 20.67 min ± SD; $p<0.0001$). Analyses per NREM hours allows for measurement of the intensity of EEG spectral power on the same averaging unit (e.g. 60 minutes) and for comparison of subjects who have different numbers of NREM-REM cycles that

vary in length. For illustrative purposes, we added a graph of absolute SWA across NREM-REM cycles. Further analyses were performed on the first 5 NREM hours of sleep.

Insert Figure 1 about here
(Fig.1 Absolute SWA power for 4 NREM cycles in four age groups.)

As illustrated in Figure 2, a marked decrease of SWA is observed with increasing age. In the four age groups, SWA declined over the first five NREM hours of sleep. A two-way ANOVA (on log transformed values) with Age group as the independent factor and NREM hour as a repeated measure revealed a significant interaction effect (F (12,200) = 1.93, $\varepsilon = 90$, $p = 0.04$), showing that the decay rate of SWA was not the same for the different groups; between-group differences in SWA power was larger at the beginning of the night and decreased over the five NREM hours. Contrast analyses were performed to evaluate the effects of age group at each NREM hour, and revealed significant between-group differences for each hour ($p< 0.001$). *Post hoc* Tukey HSD mean comparison tests demonstrated that SWA was significantly higher for children and adolescents (no significant difference between these two groups), compared to young adults and middle-aged subjects. Furthermore, young adults showed a significantly higher level of SWA than the middle-aged group. This pattern of difference was present for all NREM hours.

Insert Figure 2 about here
(Fig.1 Absolute SWA power for 5 NREM hours in four age groups.)

Absolute theta power was also significantly higher across the night for children and adolescents compared to young and middle-aged adults. It also showed a declining profile over consecutive NREM hours, as illustrated in Figure 3. A significant interaction between factors Age group and NREM hour was observed (F (12,200) = 8.16, ε = 0.85, p <0.0001). Significant between-groups differences were observed for each NREM hour (p <0.0001). In comparison to children and adolescents (no significant difference between these groups), theta power was lower for young adults and middle-aged subjects for all hours. Theta power was also higher for young adults compared to middle-aged adults for NREM hours 1, 2, 4 and 5. The interaction may be explained by the variations of the effect of age across the night. Between-group differences in absolute theta power were most important at the beginning of sleep and diminished over the course of the night. Children and adolescents showed, indeed, a steeper decline of theta power especially during the first two hours.

Insert Figure 3 about here
(Fig.2 Absolute theta for 5 NREM hours in four age groups.)

A significant Age group X NREM hour interaction was found for alpha power (F (12, 200) = 2.90, ε = 0.76, p = 0.003). Significant between-group differences in alpha power were noted for each hour (p <0.0001) (fig. 4). Alpha power was higher for children and adolescents than for middle-aged subjects at all hours. Adolescents had also more alpha power compared to young adults for the 5 NREM hours (Fig. 4).

Insert Figure 4 about here
(Fig.4 Absolute alpha power for 5 NREM hours in four age groups.)

For sigma power, a significant interaction between Age group and NREM hour was found (F (12,200) = 2.17, ε = 0.99, p =0.015). Sigma power was different between the four groups for each NREM hour (p <0.0001). Adolescents had a higher sigma power than the three other groups for the 5 NREM hours (Fig.5). Sigma power was significantly higher for young adults compared to children for hour 3. Young adults had also more sigma power than middle-aged subjects for all hours. Children had a higher sigma power than middle-aged subjects for hours 1 and 5.

Insert Figure 5 about here
(Fig.3 Absolute sigma power for 5 NREM hours in four age groups.)

For beta power, the ANOVA revealed significant main effects of both Age group and NREM hour (F (3, 50) = 9.69; p <0.0001; F (4, 200) = 10.55; ε = 0.92; p <0.0001), but no significant interaction. Beta power was significantly higher for the 3 younger groups compared to middle-aged subjects. Adolescents had higher beta power than young adults. Overall, beta power was higher for the first NREM hour compared to the next four hours (Fig. 6).

Insert Figure 6 about here
(Fig.6 Absolute beta power for 5 NREM hours in four age groups.)

Dynamics of SWA and theta power: Integrity of the homeostatic process

To study the individual profile of EEG power spectra within each group, spectral activity was expressed as a percentage of the mean power during NREM sleep for the entire night. Figure 7 a and b represent the percentage of SWA and theta band in the course of the night, and show that the effect of age on EEG power varied across the night. A significant Age X NREM hours interaction effect was noted for both frequency bands (F (12, 200) = 2.55, ε = 0.78, p = 0.008; F (12, 200) = 13.36, ε = 0.80, p <0.0001). Trend analysis revealed a linear component for the dynamics of SWA and theta decrease for the four groups ($p<0.002$), and a quadratic component ($p<0.002$, children and adolescents and $p<0.05$, young adults) for all but the middle-aged subjects. Between-group comparisons on linear trend showed that the rate of decline was different for the four groups. The decrease of SWA and theta during the night displayed a similar profile for children and adolescents The two younger groups had a higher rate of decline than did the two older groups. The SWA and theta decreases in young adults were steeper compared to the observed decreases in middle-aged participants. It is interesting to note that for children and adolescents, the build-up of SWA and theta power at the beginning of the night was higher than that of young adults and middle-aged adults. The decline of SWA and theta during the night seemed to approach a plateau value with increasing age.

Insert Figure 7 about here
(Fig.7 Percent of mean SWA and theta for 5 NREM hours in four age groups.)

DISCUSSION

To our knowledge, this study is the first to describe the age-related alterations of EEG SWA occurring from childhood to middle age. A marked reduction of absolute SWA was observed between adolescence and adulthood. The alterations in EEG power across age groups were not restricted to SWA, but encompassed the theta, alpha, sigma and beta frequency bands as well. The dynamics of the decline of SWA and theta across the night seems to approach a plateau with increasing age, suggesting an age-related attenuation of homeostatic sleep pressure.

The most important decline of absolute SWA occurred between the adolescent and the young adult groups. Theta power showed similar variations. It is known that theta, as SWA, is sensitive to sleep deprivation (Dijk *et al.*, 1993). Age-related differences in SWA and theta power were attenuated in the course of the night, as SWA and theta power declined. The higher amplitudes of SWA and theta for children and adolescents compared to that of older subject's highlight the possible maturational influences on sleep regulatory mechanisms. The precocious reduction in SWA between adolescents and young adults suggests that SWA may play a role in the intense physiological transformations occurring during maturation. As such, Church *et al.* (1975) have proposed that the changes of EEG during sleep could reflect the kinetics of the underlying metabolic processes. The higher EEG power of young subjects was also seen as a possible reflect of a higher level of synchronization of cortical neurons, compared to older individuals (Astrom *et al.*, 1992). Hormone secretion, which

undergoes rapid changes during puberty, could also be related to EEG modifications before the twenties. Our study indicates that the first modifications of SWA take place at the end of the maturational process.

This study also brings new data concerning the dynamics of NREM sleep EEG during childhood and adolescence. The build-up of SWA was similar for children and adolescents. However, children and adolescents had a higher build-up of SWA and its decay was steeper than for older subjects. A similar dynamics was present for theta activity across the night. These observations are not in the direction of the recent hypothesis of Carskadon and collaborators (1997) suggesting a possible reduction in the rate of accumulation of the "sleep drive" or sleep/wake homeostatic process in adolescents compared to children. However, further studies investigating the effects of different amount of wakefulness on sleep would be necessary to evaluate the hypothesis of an attenuation of the homeostatic drive during adolescence. The present results reveal that adolescents have a higher build-up and a steeper decay of SWA than young adults, suggesting that the strength of the homeostatic process might undergo major modifications between adolescence and young adulthood. Moreover, according to previous reports, the present study shows that the time course of the decline of SWA is slower and shallower across the night for middle-aged adults, compared to young adults (Carrier *et al.*, 2000; Dijk *et al.*, 1989; Landolt *et al.*, 1996). This support the suggested stronger build-up of sleep pressure in younger individuals as well as the attenuation of the homeostatic drive with advancing age. We extend this interpretation and suggest

that sleep regulatory mechanisms are more effective from childhood to adolescence, and then attenuate somewhere between the end of adolescence and young adulthood.

An important decrease in the percentage of SWS (stages 3 and 4 sleep) occurs across the process of aging. However, in the present study, the reduction in SWS between childhood and adolescence was not exactly paralleled by absolute SWA; the levels of SWA were similar in these two groups. This discrepancy may be due in part to the standard criteria of visual scoring (Retchschaffen *et al.*, 1968). More specifically, it has been demonstrated that children and adolescents possess high amplitude K-complexes (KCs), called giant KCs (Metcalf *et al.*, 1971; Rompré *et al.*, 1998). Isolated KCs are not included in the visual identification of sleep stages 3 and 4. These waves, described in stage 2 sleep, have been reported to be of markedly higher amplitude and density during adolescence, compared to childhood, young adulthood and the middle age (Rompré *et al.*, 1998). Theses giant KCs might have increased SWA power in the adolescent group, which can explain why they show a reduced amount of SWS but not of SWA compared to children. The electrophysiological substrate of KCs is still unknown, but seems related to some components of the slow oscillations described by Amzica and Steriade (1998). They stated that KCs reflect, at the level of the EEG, the slow oscillation (< 1 Hz) generated in the cortex. They suggested that KCs may play a role in synchronizing the thalamocortical network during sleep, and in triggering various oscillations, such as spindles and thalamic intrinsic delta. They also

reported that, through their shape, KCs contain spectral components belonging to the delta frequency band, so that delta waves result partially from the KC itself.

The age-related alterations of EEG power in this study also affected alpha, sigma and beta frequency bands. Overall, children and adolescents exhibited higher power for the alpha band than the two older groups. We, thus, corroborated the age-related reduction of power in frequencies up to 12 Hz for NREM sleep EEG, reported between young adults and middle-aged adults (Carrier *et al.*, 2000; Dijk *et al.*, 1989; Landolt *et al.*, 1996), and broaden the observations to children and adolescents.

Power in the sigma band displayed somewhat different variations between age groups. Absolute sigma power for the adolescent group was significantly higher than for the other three groups. It has been shown that the dynamic of spectral power in the sigma frequency band is a reliable indicator of sleep spindle activity (Dijk *et al.*, 1993). A peak in sleep spindles amplitude has been reported in subjects aged between 15 and 20, which then decreases with advancing age (Gibbs *et al.*, 1969; Nicolas *et al.*, 1998). Moreover, sleep spindles, as other components of the sleep EEG, undergo developmental changes (Jankel *et al.*, 1985). It has been shown that spindle frequency increased monotonically from childhood to middle age (Principe *et al.*, 1982). It is thus possible that the sigma frequency band (12.25-15.0 Hz) used in this study, does not include the spindle frequency range of children. This could further explain the lower absolute sigma power for children compared to adolescents. The

reduction of sigma power between young adults and middle-aged adults has already been reported (Carrier *et al.*, 2000; Dijk *et al.*, 1989; Landolt *et al.*, 1996). This may correspond to the decline in sleep spindle amplitude (Principe *et al.*, 1982) and density (Kubicki *et al.*, 1989; Nicolas *et al.*, 1998) reported in older subjects.

The lower beta activity for the middle-aged group, compared to the three younger groups, is a somewhat unexpected result. A recent report rather demonstrated an increased beta power with advancing age (Carrier *et al.*, 2000). On the other hand, spectral analyses performed on waking (Hartikainen *et al.*, 1992; Petit *et al.*, unpublished data) and REM sleep EEG (Petit *et al.*, unpublished data) showed a reduction of beta power with advancing age. Alterations of beta activity has also been reported in different conditions. More specifically, a high beta power has been suggested as a possible indicator of hyperarousal, mostly in depressed and insomniac populations (Armitage *et al.*, 1995; Merica *et al.*, 1998). An enhancement of beta power during sleep has been reported under the influence of benzodiazepine medication (Borbély *et al.*, 1985; Wagner *et al.*, 1997). However, few studies have proposed a functional significance of beta activity during normal sleep. Further research is needed to unify these observations concerning beta activity in different conditions and during normal sleep.

We can not rule out the possibility of a first-night effect on sleep architecture. Sleep latency and REM latency are reportedly longer in children and in adolescents during the first night of polysomnographic recordings. In our study, these variables for the child and adolescent groups appear to resemble

those previously reported (Benoit, 1981; Coble et al., 1987; Carskadon et al., 1987; Palm et al., 1989. However, sleep efficiency was very high in groups of both children and adolescents. This indicates that sleep quality after sleep onset was good.

CONCLUSIONS

The dynamics of NREM sleep EEG undergo important modifications, mostly between adolescence and young adulthood. The precocious changes in EEG SWA power suggest a peak associated with the end of maturation, followed by the already reported decline with advancing age. Aging seems to be linked to an attenuation of homeostatic sleep drive.

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Table 1. All-night sleep variables

Sleep variables	Children[1]		Adolescents		Young adults		Middle-aged Adults		*F*	*p*	Post-hoc Tukey HSD[2]
Sleep lat. (min.)	25.04	(12.74)	24.38	(13.91)	9.58	(6.11)	12.71	(6.22)	7.76	0.0002*	CH>YA, MA; AD>YA, MA
REM lat. (min.)	163.52	(54.43)	124.98	(39.94)	86.69	(26.30)	100.89	(20.67)	10.01	<0.0001*	CH>YA, MA; AD>YA
Sleep eff. (%)	95.39	(4.73)	94.38	(3.43)	96.55	(1.62)	91.12	(5.31)	5.08	0.004*	YA>MA
% stage 1	6.84	(3.5)	6.71	(3.05)	8.61	(2.97)	11.21	(4.16)	7.14	0.0004*	MA>CH, AD
% stage 2	41.26	(10.46)	53.47	(3.81)	54.78	(4.95)	62.40	(8.01)	17.45	<0.0001*	MA>AD>CH; YA>CH
% stages 3+4	34.18	(10.16)	23.63	(6.74)	14.48	(5.82)	7.75	(6.65)	30.73	<0.0001*	CH>AD>YA; CH>MA; AD>MA
% stage REM	17.72	(1.26)	18.17	(2.83)	22.13	(3.68)	18.64	(4.07)	5.32	0.003*	YA>CH, AD; YA>MA
% wakefulness	4.35	(4.81)	4.92	(3.29)	2.86	(1.74)	8.86	(5.30)	6.25	0.001	MA>CH; AD; YA
TST (min.)	528.63	(36.82)	494.24	(23.12)	502.53	(46.32)	439.49	(34.54)	13.44	<0.0001*	CH>MA; AD>MA; YA>MA

[1]Mean (Standard deviation). [2] CH=children; AD=adolescents; YA= young adults; MA= middle-aged adults. **P* values were considered significant when < 0.05.

Legends for figures.

Figure 1. Absolute SWA power across 4 NREM cycles for children (——), adolescents (- - - - -), young adults (— - —) and middle-aged adults (———).

Figure 2. Absolute SWA power across 5 NREM hours for children (black triangles), adolescents (black circles), young adults (open squares) and middle-aged (black diamond) adults.

Figure 3. Absolute theta power across 5 NREM hours for children (black triangles), adolescents (black circles), young adults (open squares) and middle-aged (black diamond) adults.

Figure 4. Absolute alpha power across 5 NREM hours for children (black triangles), adolescents (black circles), young adults (open squares) and middle-aged (black diamond) adults.

Figure 5. Absolute sigma power across 5 NREM hours for children (black triangles), adolescents (black circles), young adults (open squares) and middle-aged (black diamond) adults.

Figure 6. Absolute beta power across 5 NREM hours for children (black triangles), adolescents (black circles), young adults (open squares) and middle-aged (black diamond) adults.

Figure 7 a. Percentage of mean SWA power for the entire night across 5 NREM hours for children (black triangles), adolescents (black circles), young adults (open squares) and middle-aged (black diamond) adults. Dotted lines indicate 100 %.

Figure 7 b. Percentage of mean theta power for the entire night across 5 NREM hours for children (black triangles), adolescents (black circles), young adults (open squares) and middle-aged (black diamond) adults. Dotted lines indicate 100 %.

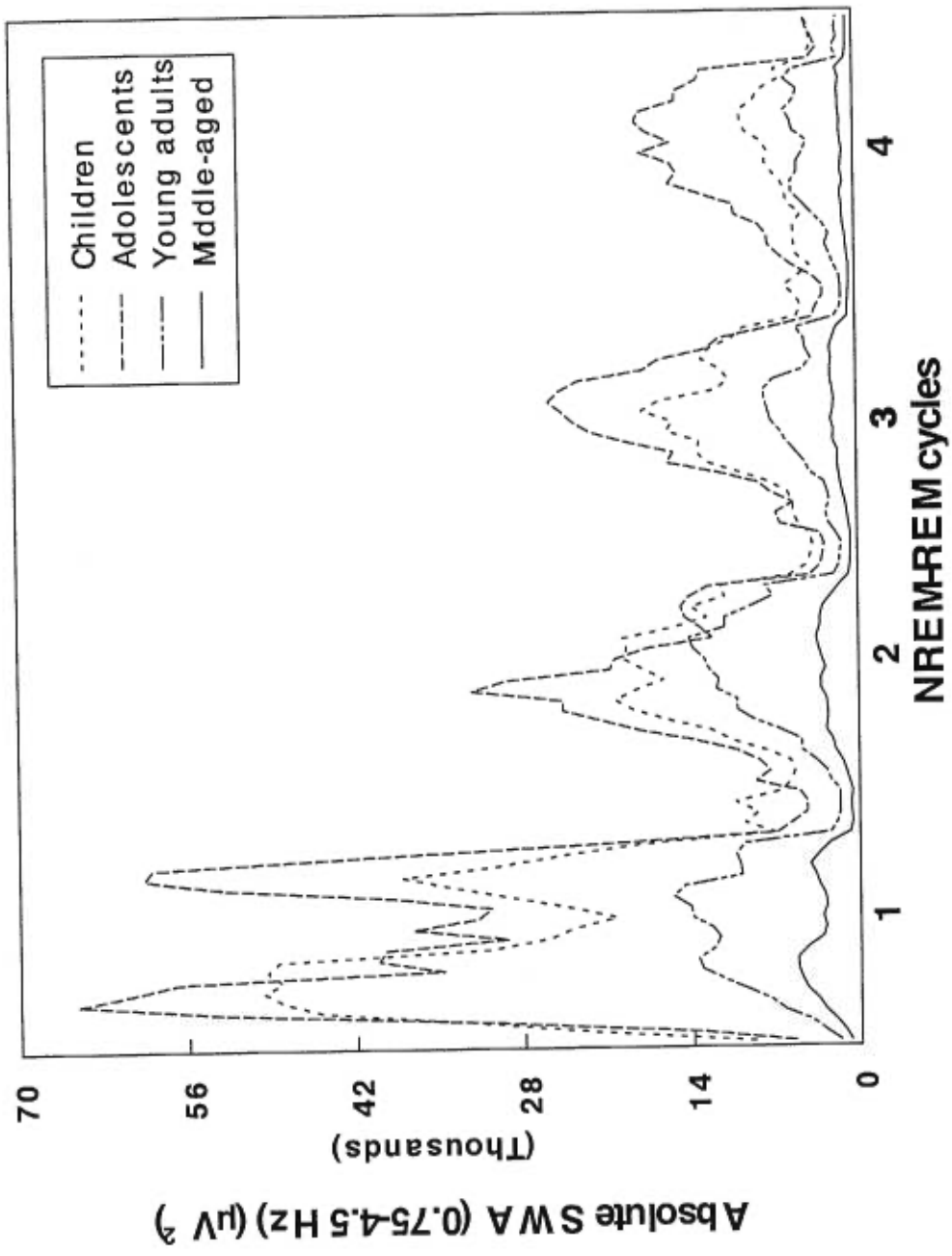

Children
Adolescents
Young adults
Middle-aged
Absolute SWA (0.75-4.5 Hz) (μV²)
(Thousands)
70
56
42
28
14
0
1
2
3
4
NREM-REM cycles

Figure 1.

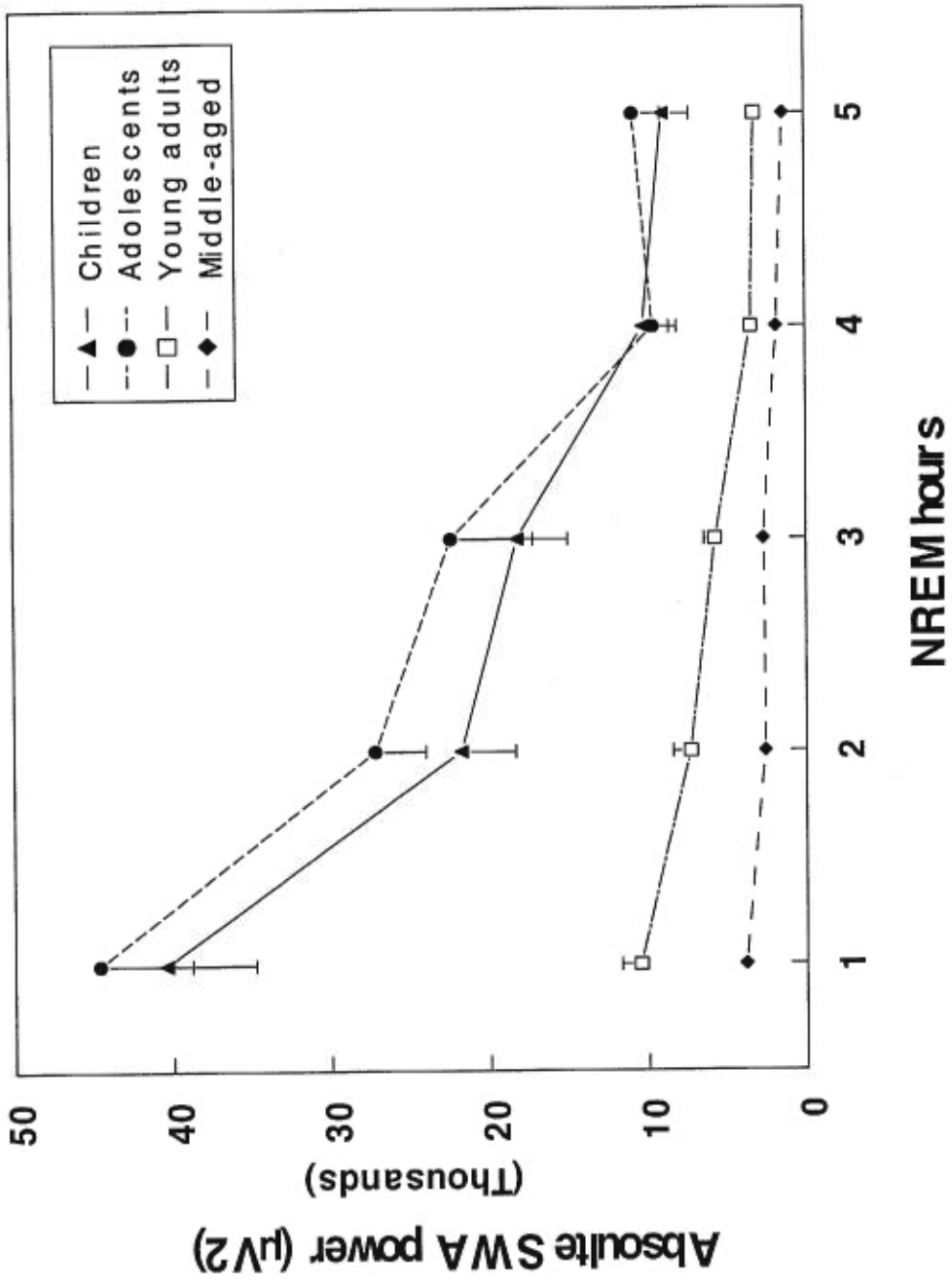

Children
Adolescents
Young adults
Middle-aged
Absolute SWA power (μV2)
(Thousands)
0
10
20
30
40
50
1
2
3
4
5
NREM hours

Figure 2.

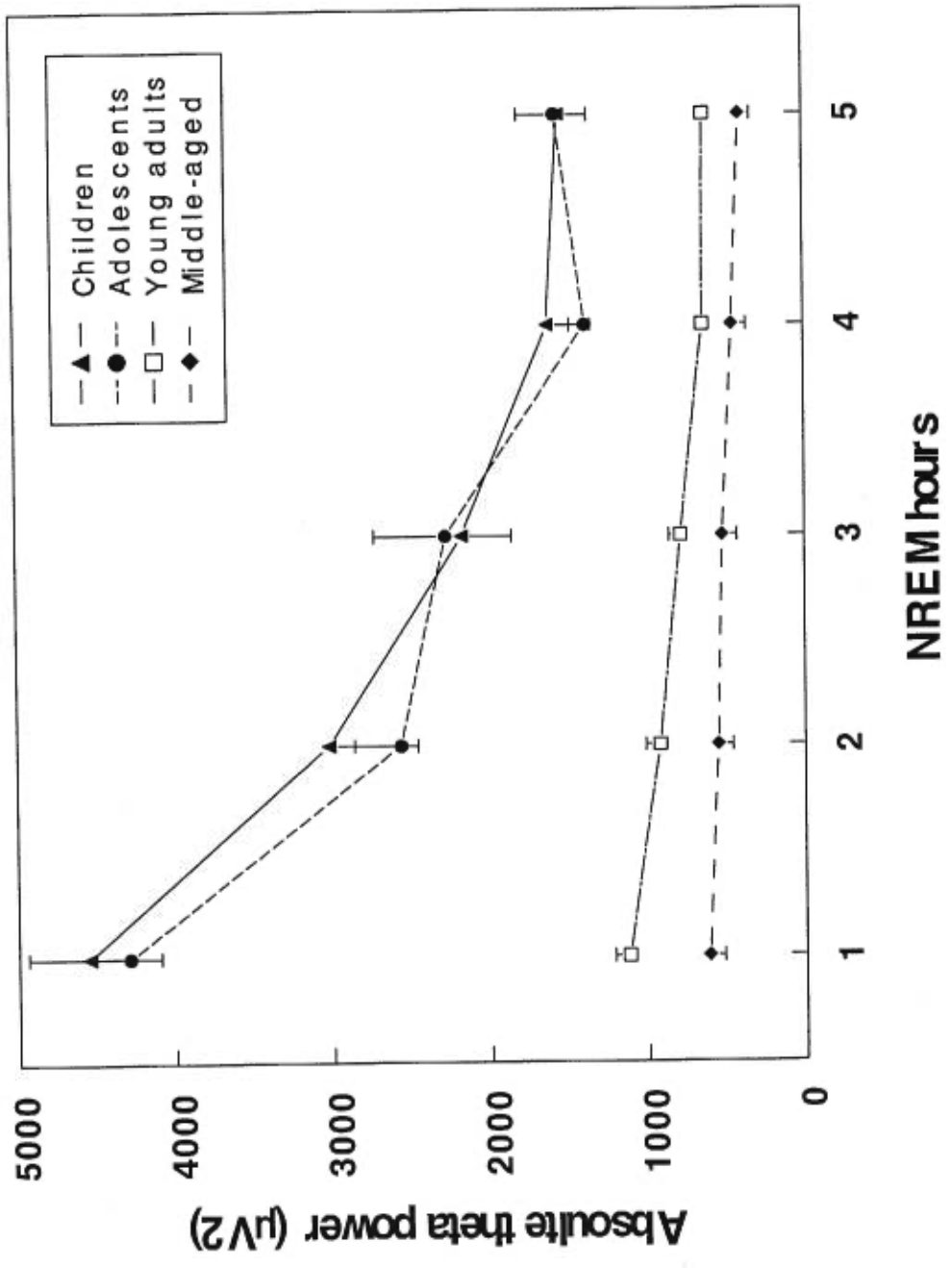

Children
Adolescents
Young adults
Middle-aged
Absolute theta power (μV2)
5000
4000
3000
2000
1000
0
1
2
3
4
5
NREM hours

Figure 3.

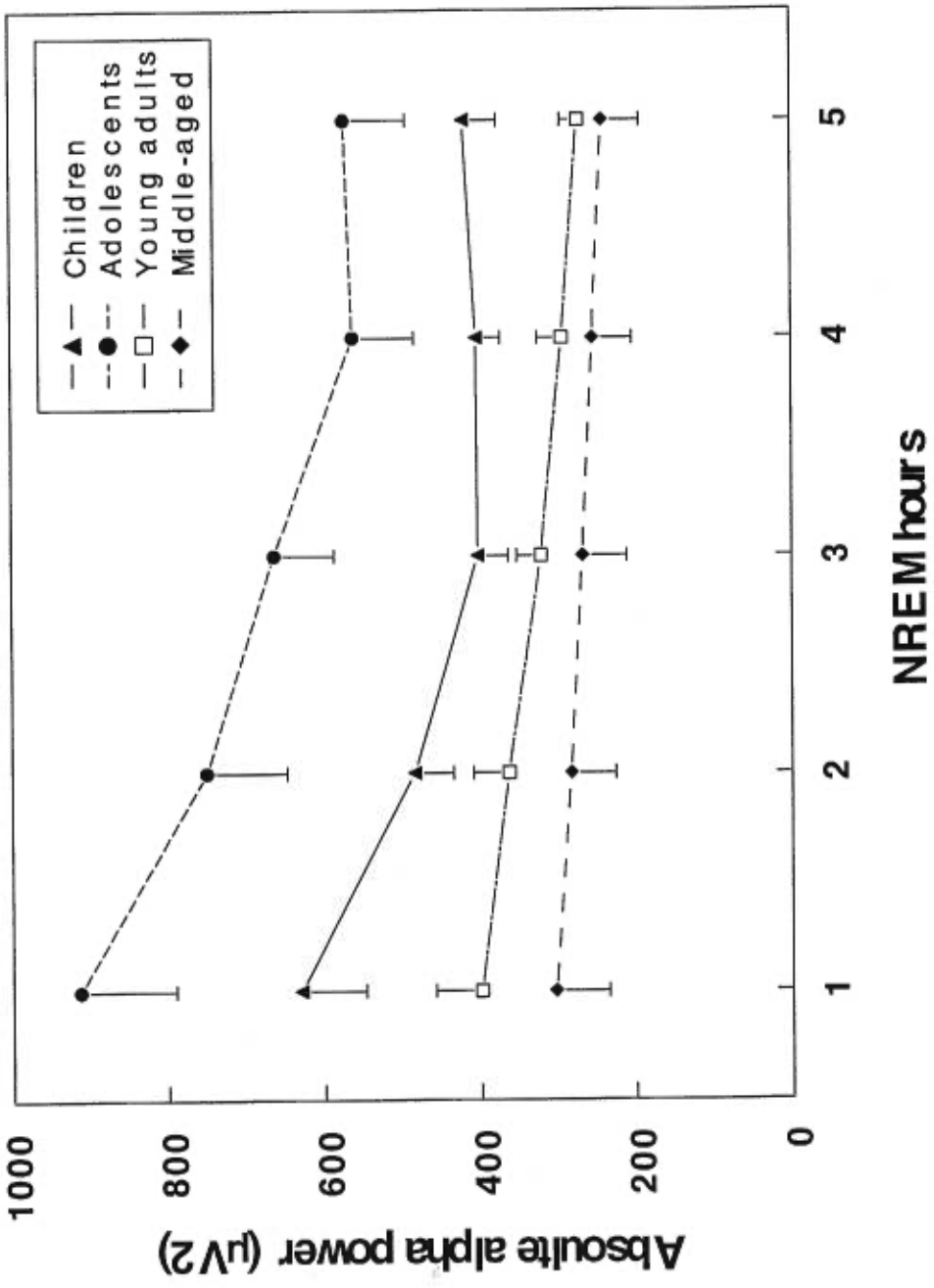

Children
Adolescents
Young adults
Middle-aged
Absolute alpha power (μV2)
1000
800
600
400
200
0
1
2
3
4
5
NREM hours

Figure 4.

Figure 5.

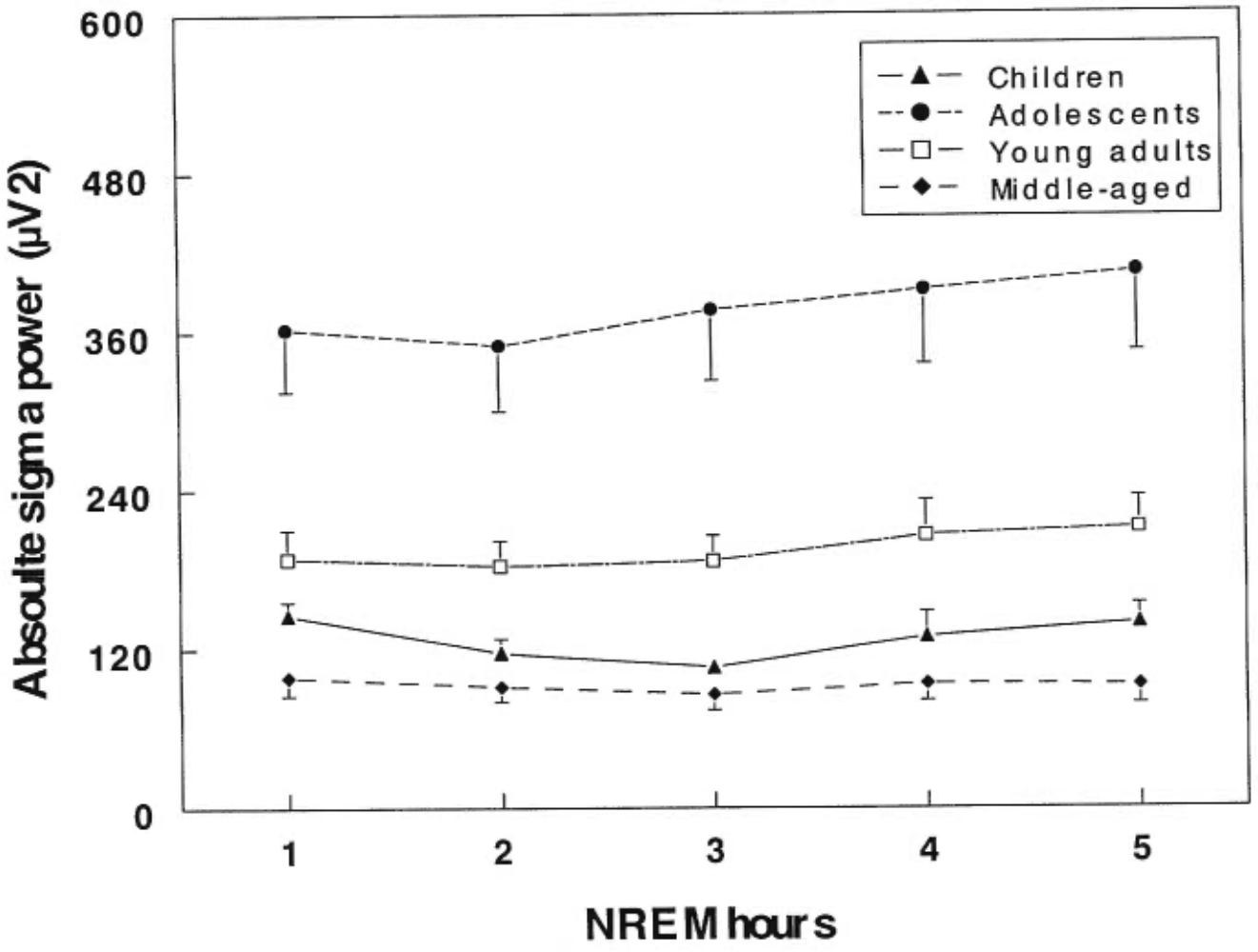

600
480
360
240
120
0
Absoulte sigma power (μV2)
1
2
3
4
5
NREM hours
Children
Adolescents
Young adults
Middle-aged

Figure 6.

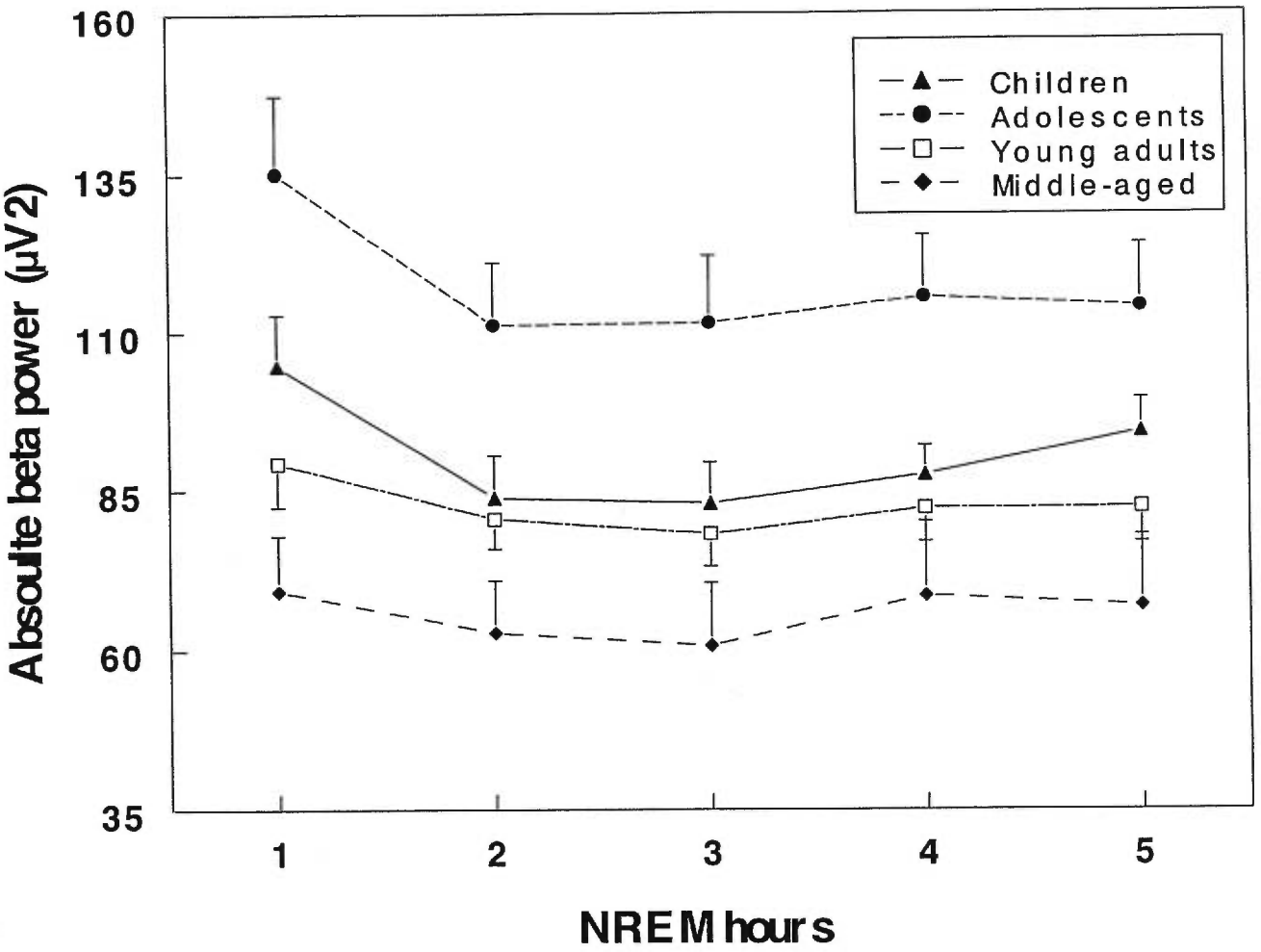
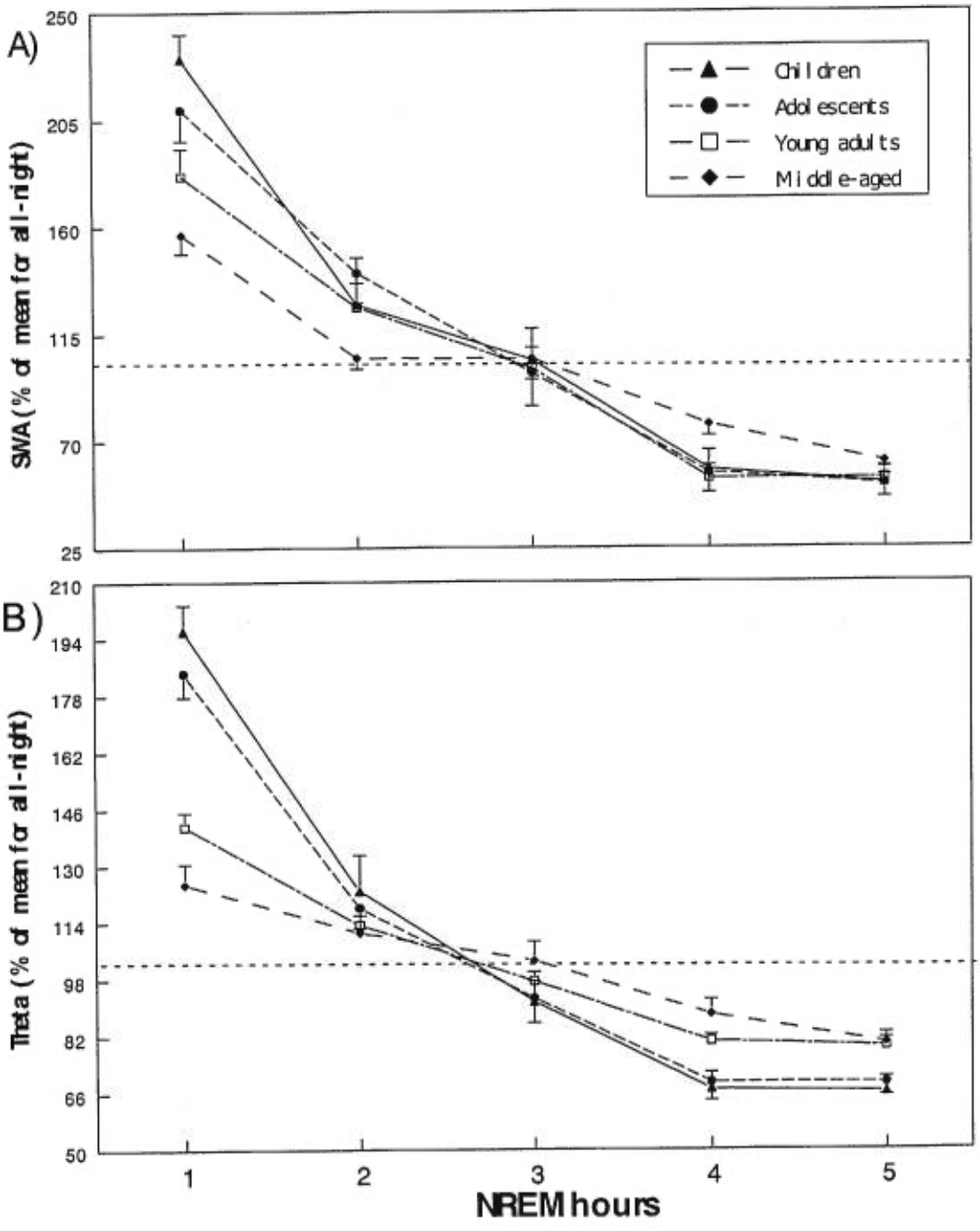

160
135
110
85
60
35
Absolute beta power (μV2)
1
2
3
4
5
NREM hours
Children
Adolescents
Young adults
Middle-aged

Figure 7.


A)
B)
Children
Adolescents
Young adults
Middle-aged
SWA (% of mean for all-night)
Theta (% of mean for all-night)
250
205
160
115
70
25
210
194
178
162
146
130
114
98
82
66
50
1
2
3
4
5
NREM hours

DEUXIÈME ARTICLE

EFFETS D'UNE PRIVATION DE SOMMEIL DE 25 HEURE SUR LE SOMMEIL DE RÉCUPÉRATION DE JOUR AU MILIEU DE L'ÂGE ADULTE

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EFFECTS OF A 25-HOUR SLEEP DEPRIVATION ON DAYTIME SLEEP IN THE MIDDLE-AGED

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RUNNING HEAD: RECOVERY DAYTIME SLEEP IN MIDDLE -AGED

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GAUDREAU, H., MORETTINI, J., LAVOIE, H., CARRIER, J. *Effects of a 25-hour sleep deprivation on daytime sleep in the middle-aged.* NEUROBIOL AGING. Our understanding of the mechanisms by which sleep deteriorates with age almost exclusively stems from comparisons of young and elderly subjects. The present study investigated the different effects of a 25-hour sleep deprivation on the recovery sleep initiated in the morning (when circadian sleep propensity decreases) of young (20-39y.) and middle-aged subjects (40-60y). Middle-aged subjects showed a steeper increase in the duration of wakefulness during daytime recovery sleep than the young subjects. Slow-wave sleep (SWS) and EEG slow-wave activity (SWA: spectral power between 0.5-4.5 Hz) were potentiated in both groups following sleep deprivation. However, the rebound of SWS and SWA was significantly less pronounced in the middle-aged than in the young. This reduction in homeostatic recuperative drive in middle-aged subjects might account for the decrease in their ability to maintain sleep when they have to recuperate at an abnormal circadian phase. These results helps to understand the increase in complaints related to shift work and jet lag in the middle years of life.

KEY WORDS: SLEEP, SLEEP DEPRIVATION, AGING, MIDDLE-AGE, HOMEOSTATIC, CIRCADIAN RHYTHMS

INTRODUCTION

The modification of sleep organization is a hallmark of the normal aging process. Until now, our understanding of the mechanisms by which sleep deteriorates with age has almost exclusively come from comparisons between young and elderly subjects. However subjective sleep complaints begin to increase significantly in the middle years of life (19) and almost all sleep parameters show significant effects of age between age 20 and age 60 (16; 20). The results of one study of 110 subjects between the ages of 20 and 60 years indicated that, at home, older subjects woke up earlier, went to bed earlier, spent less time in bed, and were more alert at waketime (11). In the laboratory, increasing age was associated with less time asleep, increased number of awakenings, increased amount of wakefulness during sleep, less slow-wave sleep (SWS) and Rapid-Eye Movement sleep (REM), higher percentages of stage 1 and stage 2 sleep, and shorter REM latency (11).

Results on quantitative sleep EEG also point out significant changes between 20 and 60 years of age (9; 16; 20). The most consistent of these modifications is a decrease in SWA (slow-wave activity: spectral power between 0.75 to 4.5 Hz) during NREM sleep with advancing age. These studies also report that the difference in SWA between young (20-39 y) and middle-aged (40-60y) subjects diminished across the sleep period, leading to a shallower decay rate of SWA throughout the night in the middle-aged subjects.

The interaction of homeostatic and circadian processes regulates the

sleep-wake cycle (1; 5). The homeostatic process represents the sleep debt accumulated during wakefulness. As a result, the homeostatic process increases exponentially during waking hours and decreases exponentially during sleep. The intensity and dynamic of SWS and SWA provide an estimate of the homeostatic process. Numerous studies have investigated the homeostatic process of sleep regulation in humans by measuring the effects of prior wakefulness and sleep on the sleep EEG. It has been shown that SWS and SWA are enhanced after an extension of prior wakefulness (1). The increase of SWA following sleep deprivation is more prominent at the beginning of the night. This leads to a steeper decline of SWA through the night following sleep deprivation (1).

The decrease in the amount of SWA and its more shallow decay rate across the night in older subjects may reflect an attenuation of sleep homeostatic pressure with increasing age (9; 16; 20). More information about the effects of differential amounts of wakefulness on sleep is necessary to support this suggestion. Very few studies to date have evaluated the effects of manipulations of the homeostatic process in aging. Studies in young and old rats have shown that aged rats exhibit reduced responses on SWS and on EEG delta power following sleep deprivation (26; 27). In studies of humans, elderly subjects have been subjected to one or two nights of sleep deprivation or to sleep fragmentation. Although elderly adults respond to sleep deprivation with an increase in SWS, they tend to show a lower rebound of SWS after this challenge than younger subjects (3; 4; 6). Therefore It appears that even though the

homeostatic process of elderly subjects has the ability to respond to major sleep deprivation challenges, its overall capacity to respond diminishes.

The circadian process of sleep regulation is controlled by an endogenous pacemaker, located in the suprachiasmatic nucleus of the hypothalamus. This circadian pacemaker is responsible for the rhythmic variations of sleep propensity throughout the 24-hour day. Sleep propensity increases on the falling limb of the circadian temperature curve and it maximizes near the trough of the curve. Sleep propensity decreases on the rising limb of the circadian curve and it minimizes near the peak of the curve (13; 17; 21; 30). When required to sleep at a circadian phase of low circadian sleep propensity both young and older subjects will show higher levels of wakefulness compared to baseline sleep (10; 17; 22; 23). However, it has been suggested that the sleep of aging subjects might be particularly vulnerable to a circadian phase misalignment (8; 22). A forced desynchrony protocol in which sleep episodes were initiated at all circadian phases and preceded by 18.33 hours of wakefulness indicated that elderly subjects show more wakefulness than young subjects at each phase. However, this difference between young and elderly subjects was more prominent when sleep occurred on the ascending limb of the circadian temperature rhythm, a point at which circadian sleep propensity is decreasing (15). These data supported the hypothesis of an increased susceptibility to a phase angle misalignment in elderly subjects.

The aim of the present study was to evaluate the different effects of a phase angle misalignment in young and middle-aged subjects in a situation of

enhanced sleep homeostatic pressure induced by an acute sleep deprivation. The study investigated the differences across young and middle-aged subjects in the effects of a 25-hour sleep deprivation on recovery sleep initiated in the morning, a time during which circadian sleep propensity decreases. We hypothesize that compared to the young, the strength of middle-aged subjects' homeostatic response will be less pronounced following sleep deprivation. The dynamics of SWS and SWA throughout the night will serve as measures of the homeostatic process recuperative drive. We predict a lower rebound of these sleep parameters following the sleep deprivation in the middle-aged subjects. We hypothesize further that the sleep of middle-aged subjects will be more vulnerable to an abnormal phase angle between the sleep-wake cycle and the circadian signal as measured by a steeper increase in wakefulness during daytime recovery sleep.

METHODS

Subjects

Thirty-three subjects between the ages of 20 and 60 completed the study. They were separated into two groups according to their age: young subjects (8 women and 8 men; 20-39 y.; mean age 30.0 y. sem=1.2) and middle-aged subjects (8 women and 9 men; 40-60 y.; mean age 50.2 y. sem 1.4). Subjects were screened to be in good health according to history, normal blood test and urinalysis (complete blood count, chemistry screen, thyroid function tests, prolactine, testosterone in men, and estrogens, FSH, LH. in women). Subjects were on no medications and they had no sleep complaints. They reported no history of psychiatric or neurological illnesses. Subjects who experienced night

work or transmeridian travel in the three months prior to the study were excluded from the sample. Obese individuals were also excluded (BMI >27). All subjects had a score lower than 4 on the short version of the Beck Depression Scale (2). Screening also included one-night sleep polysomnographic (PSG) evaluation. During the PSG screening, electroencephalogram (EEG), electromyogram (EMG) and electroculogram (EOG) were recorded. A nasal/oral thermistor and EMG leg electrodes were also used to screen for sleep apnea and for periodic leg movements respectively. Subjects with an apnea-hypopnea index >10 or a periodic limb movements index >10 were excluded from the study. Subjects were instructed to abstain from alcohol, caffeine, and medication during the laboratory experience. All subjects were required to be non-smokers because the study took place over an extended period of time in a confined environment.

Pre-menopausal and post-menopausal women were included in the study. Peri-menopausal women and women using hormonal contraceptives or receiving hormonal replacement therapy were excluded. Pre-menopausal women were required to have had a regular menstrual cycle (25-32 days) during the year preceding the study, no vasomotor complaints (hot flashes, night sweats), and low FSH levels (<20 iU/L). They were studied in the laboratory during the follicular phase of their menstrual cycle. Post-menopausal women had to have had no menstrual cycles during the past year and FSH levels above 20 iU/L. In the middle-aged group, four women were pre-menopausal and four women were post-menopausal. Subjects were asked to read and to sign a consent form that

provided detailed information about the nature, the purpose, and the risks of the study; they were paid for their participation. The ethical committee of the Hospital approved this project.

Procedure

Before the laboratory sleep study, subjects completed a French version of the "Pittsburgh Sleep Diary" (24) every day for 14 days, from which means for habitual waketimes, habitual bedtimes, and habitual time spent in bed were calculated. Subjects came to the chronobiology laboratory for 4 consecutive nights and for 2 days (see figure 1 for details). The first two sleep episodes (S1 and S2) were used as adaptation nights. For these two nights, subjects arrived at the chronobiology laboratory a few hours prior to their habitual bedtime and they left in the morning; they performed their habitual activities during the day. When subjects were admitted on the third night, they remained in the laboratory for the next 48 hours. Night 3 (S3) was used as the baseline sleep episode. The timing of bedtime and waketime for the laboratory sleep study was based on habitual bedtimes and waketimes averaged from the two-week sleep diaries. Participants were subject to a mini-constant routine for the 25 hours that immediately followed their habitual wake-up time on S3. During the mini-constant routine, subjects remained awake in bed in a semi-recumbent position with ambient lighting kept below 15 lux and they were given small snacks on a regular basis. A research assistant was present at all times to administer vigilance and performance evaluations, to collect saliva samples, and to make sure that subjects were not falling asleep. Rectal temperature was measured

continuously by a disposable rectal sensor (Yellowspring Inst.) that was inserted 10 cm into the rectum from bedtime of night 3 to the end of the experiment (Mini-Logger, Mini-Mitter). The mini-constant routine ended in the morning, one hour after habitual wake-up time. At the end of the mini-constant routine, lights were turned off and a daytime recovery sleep episode was recorded (S4). Subjects had to stay in bed for the habitual sleep length indicated in their sleep diaries.

Insert figure 1 about here

(Schema of the constant routine protocol)

Polysomnographic recordings

EEG electrodes were placed according to the international 10-20 system, using a referential montage with linked ears, a left and right electrooculogram (EOG) and a chin electromyogram (EMG). A Grass Model 15A54 amplifier system (gain 10000, bandpass 0.3-100 Hz) was used and signals were digitalized at a sampling rate of 256 Hz using a commercial software product (Harmonie, Stellate system). Sleep stages were scored visually on screen (LUNA, Stellate System) according to the standard criteria by 20-second epochs (25).

Quantitative EEG

Power spectral analyses were performed on the C3 derivation during NREM sleep with a commercial software package (Electrophysiological Recordings Analyser 2.0) that computes fast Fourier transforms (FFT) on 4-second epochs with a Hanning window tapering. This yielded a spectral resolution of 0.25 Hz. Automatic detection rejected artifacts and analyses were performed on artifact-

free epochs (7). Epochs containing artifacts were regarded as missing data in order to preserve sleep continuity. After spectral analyses, five 4-second epochs were averaged in order to maintain correspondence with the 20-second sleep scoring windows. Then, spectral activity was averaged per 60 minutes of NREM sleep for the first 180 NREM minutes. SWA was defined as absolute power (μV^2) for frequencies between 0.5 and 4.5 Hz. Values were expressed as a percentage of mean SWA during the first 180 minutes of N-REM sleep for the baseline sleep episode. Analyses on N-REM minutes received preference over N-REM periods because daytime recovery sleep disturbed the dynamic of sleep cycles.

Statistical analyses

Two-way ANOVAs with one independent factor (Group) and one repeated measure (Sleep episode) were performed in order to evaluate group (Young vs Middle-aged) differences in sleep architecture between baseline and daytime recovery sleep. Sleep parameters that did not distribute normally (Shapiro-Wilk test) were transformed prior to statistical analyses (see Table 1). A three-way ANOVA with one independent factor (Group) and two repeated measures (Sleep Episode and Half-hour) was performed to analyze group differences in the number of minutes of wakefulness for each half-hour during baseline and recovery sleep. Wakefulness values were log transformed prior to statistical analysis so that the variation could approximate a normal distribution. A three-way ANOVA with one independent factor (Group) and two repeated measures (Sleep episode and NREM minutes) was used to compare differential

effects of age on the SWA dynamic before and after sleep deprivation. *P*-levels (alpha) were adjusted with Huynh-Feldt correction for sphericity for repeated measures with more than two levels and they were considered significant when ≤ 0.05. Contrast analyses and post hoc Tukey HSD (p-level ≤ 0.05) comparisons were used either to decompose the interaction effects and to identify the nature of significant results or to locate the differences in main effects. Since no interaction was found between Group and Gender or between Group, Sleep Episode, and Gender on any sleep or SWA parameters, data from men and women were pooled together.

RESULTS

As shown in Table 1, a comparison of baseline sleep and daytime recovery sleep revealed that both groups of subjects showed reduced sleep latency and REM sleep latency along with a decrease in the number of minutes in stage 2 and of REM sleep (Sleep episode effect: $p \leq 0.02$, all cases). There was no interaction between Group and Sleep episode for these variables. There was a significant Group X Sleep episode interaction for the number of minutes of stage 1. Contrast analyses indicated a significant reduction of the length of stage 1 during daytime recovery sleep in the Young subjects ($p=0.0009$) but not in the Middle-aged subjects (ns).

There was also a significant Group X Sleep episode interaction for sleep efficiency. Contrast analyses revealed a significant decrease of sleep efficiency during daytime recovery sleep in both groups of subjects but that the Middle-

aged subjects had a more abrupt decline than did the Young subjects (see Figure 2; Middle-aged: $p<0.000001$; Young: $p=0.002$).

Insert Table 1 about here

Insert Figure 2 about here

The number of minutes of wakefulness per half-hour was averaged for the first six hours of the sleep episode for the purpose of evaluating the dynamic of wakefulness across the sleep episode (Fig. 3). A three-way ANOVA with one independent factor (Group) and two repeated measures (Sleep episode and Half-hour) revealed significant main effects of Group ($F_{1,31}=7.9$; $p=0.008$), Sleep episode ($F_{1,31}=53.7$; $p<0.001$), and Half-hour ($F_{7,207}=12.0$; $p<0.001$). There were also significant interactions between Group and Sleep episode ($F_{1,31}=5.3$; $p<0.03$) and between Sleep episode and Half-hour ($F_{7,248}=4.3$; $p<0.001$). Contrast analyses for the Sleep episode X Half-hour interaction indicated that the number of minutes of wakefulness was higher during daytime recovery sleep than during baseline sleep mostly after the first 120 minutes of the sleep episode (150 min, 180 min, 240 min, 360 min: $p<0.03$; 270 min, 300 min, 330 min: $p<0.0001$). Contrast analyses for the Group X Sleep episode interaction showed that both groups of subjects had a significant increase in wakefulness during daytime recovery sleep but that it was larger for the Middle-aged than for the Young subjects (Middle-aged: $p>0.000001$, Young $p=0.001$).

Insert Figure 3 about here

As show in Figure 4, SWS (stages 3+4 in min.) duration was significantly enhanced for both groups during recovery daytime sleep but

contrast analyses of the interaction revealed that SWS rebound was less pronounced in the Middle-aged group ($p=0.0003$) than in the Young group ($p>0.000001$).

Insert Figure 4 about here

Figure 5 illustrates mean SWA (expressed as percent of the mean of baseline) for the first 180 minutes of N-REM sleep. Three-way ANOVAs showed main significant effects of Group ($F_{1,31}=4.4$, $p<0.05$), Sleep episode ($F_{1,31}$:41.4; $p<0.001$), and NREM Hour ($F_{1.7,52.9}=30.8$; $p<0.001$) as well as a significant Group X Sleep episode interaction ($F_{1,31} = 4.3$, $p<0.05$). SWA was potentiated for both groups of subjects during daytime recovery sleep. However, contrast analyses of the Group X Sleep episode interaction indicated that SWA rebound was lower for the Middle-aged subjects ($p<0.004$) compared to the Young ones ($p<0.000002$). Post hoc analyses on the main N-REM hour effect exposed a declining profile of SWA across the sleep episode ($p<0.003$ for all N-REM hour comparisons).

Insert Figure 5 about here

DISCUSSION

To our knowledge, this is the first report of differential effects of sleep deprivation on sleep and on sleep EEG spectral power in young and middle-aged adults. Following 25 hours of sleep deprivation, there was more disruption in sleep consolidation in middle-aged than in young adults when recovery sleep was initiated in the morning, a time of decreased circadian sleep propensity. A

rebound of SWS and SWA was observed during recovery sleep for both groups of subjects but the increase was significantly less in the middle-aged than in the young subjects. These results suggest that the middle years of life are associated with important modifications in sleep regulatory processes.

It has been reported that the circadian phase strongly modulates sleep propensity and REM sleep propensity (12-14). In this study, the daytime recovery sleep episode was initiated one hour following habitual waketime, a circadian time that is usually associated with high sleep propensity and high REM sleep propensity. The increase in homeostatic sleep pressure following sleep deprivation in conjunction with the still high circadian sleep propensity at the beginning of the daytime sleep episode may account for the reduction in sleep latency observed in both groups of subjects. High circadian REM pressure may explain the significant reduction of REM sleep latency.

The forced desynchrony protocol is one of the techniques often proposed to separate the homeostatic influence from the drive of the circadian timing system. A nonlinear interaction of the circadian and the sleep-dependent components of sleep propensity has been reported in forced desynchrony studies (17). For instance, the amplitude of the circadian modulation for the amount of wakefulness during sleep has been shown to increase with the number of hours asleep. In the present study, a daytime recovery sleep episode occurred at a circadian time of decreasing sleep propensity. Not surprisingly, sleep efficiency was lower during daytime recovery sleep than during baseline sleep, at the expense of stages 1, 2 and REM sleep. The duration of wakefulness during

daytime recovery sleep was more prominent for both groups at the end of the sleep episode, when homeostatic sleep drive decreased. This probably reflects the combined influence of decreasing circadian sleep propensity drive and the evacuation of homeostatic sleep pressure.

It has been suggested that the sleep-wake cycle of older subjects might be particularly vulnerable to an abnormal phase angle between the sleep episode and the circadian timing system (8; 22). In our study, the more important reduction of sleep efficiency in the middle-aged group during daytime recovery sleep shows that the increased vulnerability to an abnormal phase angle is already apparent in the middle years of life. This higher vulnerability is observed despite an increased homeostatic sleep pressure at sleep onset induced by 25 hours of sleep deprivation.

SWS was significantly enhanced for both age groups during daytime recovery sleep but SWS rebound was less pronounced in the middle-aged group than in the young group. This corroborates the observation that older subjects preserve the ability to respond to sleep deprivation with a SWS rebound (22; 28). The only study to date that examined the effects of sleep deprivation on daytime sleep architecture in young and in middle-aged men reported a longer latency to stage 4 during recovery sleep in the middle-aged compared to the young subjects. However, no difference in the amounts of stages 3 and 4 was found (28). This previous study did not evaluate quantitative EEG parameters and used a more acute sleep deprivation (two days). In the present study, the rebound of SWS and SWA during recovery sleep was significantly lower for the

middle-aged than for the younger group. During the extended waking period, the build-up of sleep pressure appears to be weaker in middle-aged individuals than in young adults. The observed reduction of SWA following sleep deprivation in middle-aged subjects suggests that the homeostatic recuperative drive is already attenuated in the middle years of life. However, future research will need to address the effects of homeostatic challenges when sleep is initiated at a normal phase relationship with the circadian signal. This would verify that the smaller rebound of SWA in the middle-aged adults is not directly caused by the steeper increase of wakefulness during daytime recovery sleep.

Knowing the non-additive interaction between the homeostatic and the circadian processes, it is quite possible that the observed reduction in homeostatic recuperative drive following sleep deprivation in the middle-aged subjects may account for their reduced ability to maintain sleep when they have to recuperate at an abnormal circadian phase. In the middle-aged subjects, the shallower homeostatic sleep response following the sleep derivation may not have been able to "overide" the high circadian propensity for wakefulness at this time of day.

CONCLUSION

Results of this study suggest that people in their forties and fifties already show a heightened vulnerability to an abnormal phase angle between sleep and the circadian signal in addition to an attenuation of the homeostatic recuperative drive. These results help to understand why middle-aged individuals

demonstrate more difficulties than younger individuals adapting to challenges to the sleep-wake cycle such as shift work and jet lag (18; 22; 29).

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FIGURE LEGENDS

Figure 1. Schematic representation of the research protocol for a subject with habitual bedtime at midnight and habitual waketime at 08:00. Hours are from midnight to midnight on the horizontal axis. Each line represents one day of the research protocol. Dashed areas represent sleep episodes. S3 is the baseline sleep episode and S4 is the daytime recovery sleep episode. Vertical lines indicate admission (continuous) and departure (dotted) from the chronobiology laboratory.

Figure 2. Mean sleep efficiency (and sem) for young and middle-aged subjects during baseline and daytime recovery sleep.

Figure 3. Mean number of minutes of wakefulness per 30 minute of the sleep episode (and sem) for young and middle-aged subjects.

Figure 4. Mean number of minutes of SWS (and sem) for young and middle-aged subjects.

Figure 5. Hourly mean SWA (and sem) for the first 180 minutes of N-REM sleep for young and middle-aged subjects. Values are expressed as a percentage of mean SWA during the first 180 minutes of N-REM sleep for the baseline sleep episode.

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Table 1. All-night sleep parameters : mean and SEM. P value were considered significant when <0.05.

Sleep variables	Young		Middle-Aged		Main Group effects		Main Sleep Episode Effects		Group X Sleep episode Interactions	
	S3	S4	S3	N4	F	p	F	p	F	p
Sleep latency (min)[1]	11.2 (1.6)	4.4 (1.1)	10.9 (1.7)	5.5 (0.9)	0.5	0.51	**28.8**	**<0.001**	1.5	0.22
REM latency (min)[2]	81.1 (8.7)	67.7 (6.8)	79.2 (8.4)	54.4 (5.1)	1.3	0.26	**5.97**	**0.02**	0.5	0.49
Sleep efficiency (%)[3]	90.7 (1.9)	83.3 (3.7)	88.4 (2.0)	70.5 (2.7)	**6.8**	**0.01**	**52.1**	**<0.001**	**5.9**	**0.02**
Stage 1 (min)[2]	38.8 (3.8)	26.3 (3.5)	33.6 (3.8)	31.5 (3.5)	0	0.96	**9.8**	**0.004**	4.6	**0.04**
Stage 2 (min)	267 (8.1)	222 (13.1)	269 (9.1)	212 (10.2)	0.1	0.79	**31.9**	**<0.001**	0.4	0.52
SWS (min)[2]	32.0 (6.3)	54.1 (7.5)	12.8 (3.0)	23.4 (5.0)	**10.5**	**<0.03**	**63.1**	**<0.001**	**5.2**	**0.03**
REM (min)	97.0 (6.6)	68.7 (9.2)	93.9 (4.8)	54.3 (5.7)	1.02	0.32	**70.7**	**<0.001**	1.9	0.18

1. Log transformation Ln (var +1) performed before analyses. Mean values presented in original units.
2. Square root transformation performed before analyses. Mean values presented in original units.
3. Log transformation Ln (100 - var + 1) performed before analyses. Mean values presented in original units.

Figure 1.

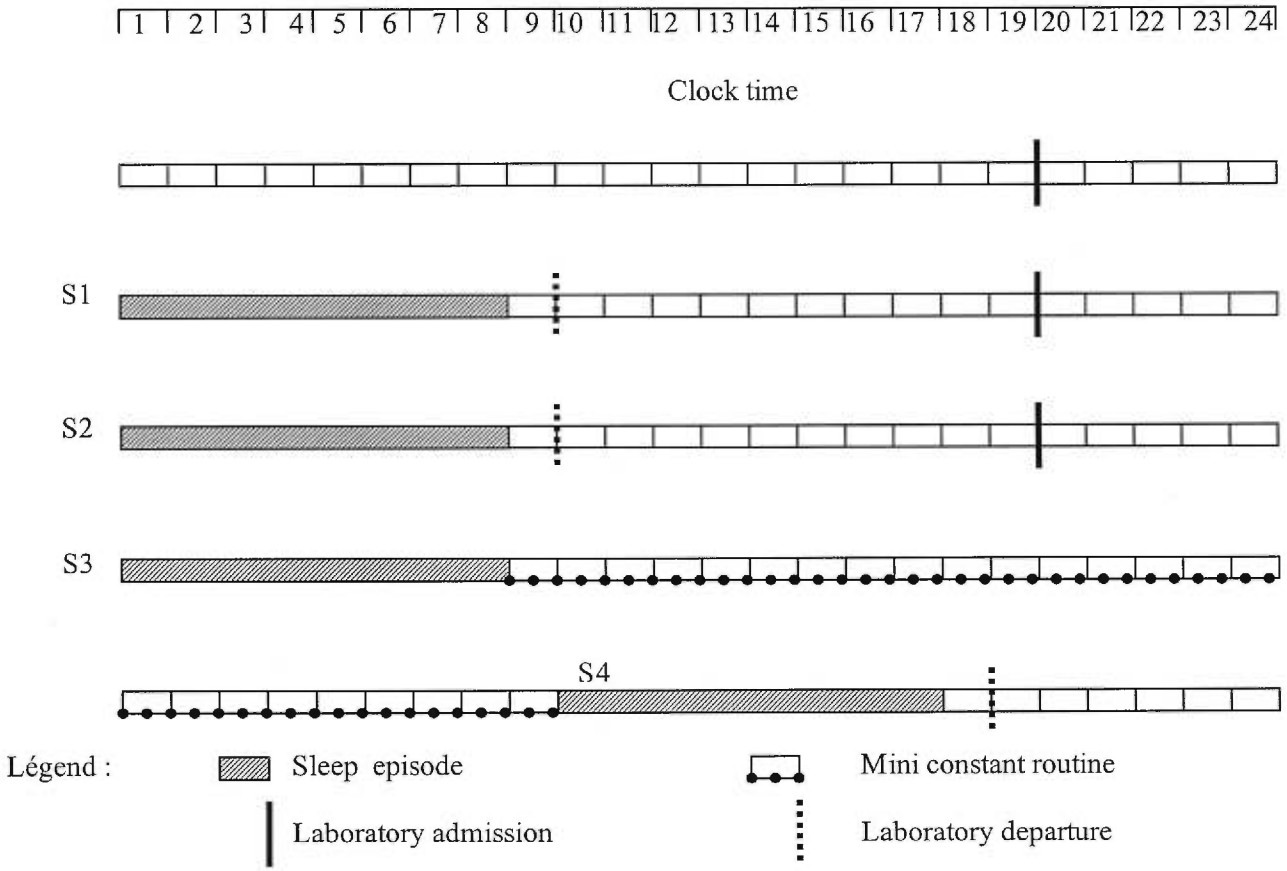

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Clock time
S1
S2
S3
S4
Légend :
Sleep episode
Mini constant routine
Laboratory admission
Laboratory departure

Figure 2.

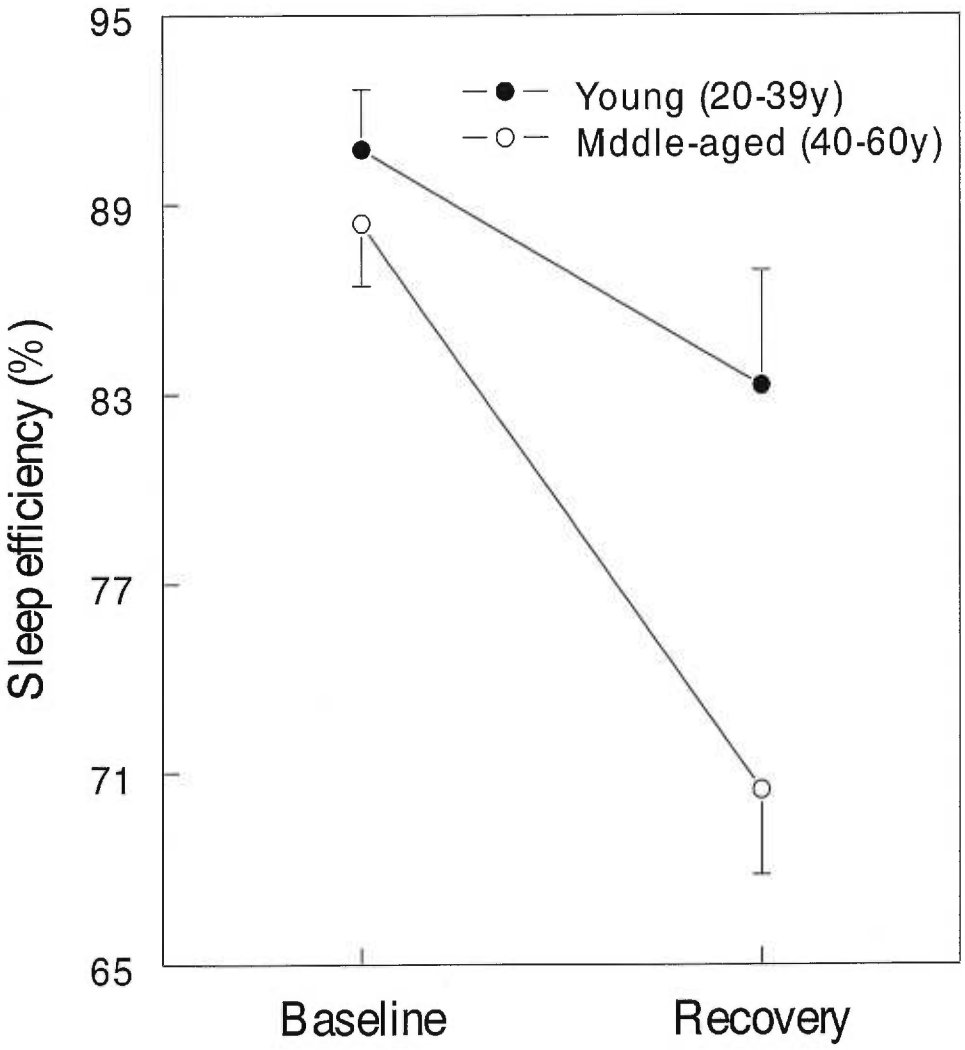

95
89
83
77
71
65
Sleep efficiency (%)
Young (20-39y)
Mddle-aged (40-60y)
Baseline
Recovery

Figure 3.

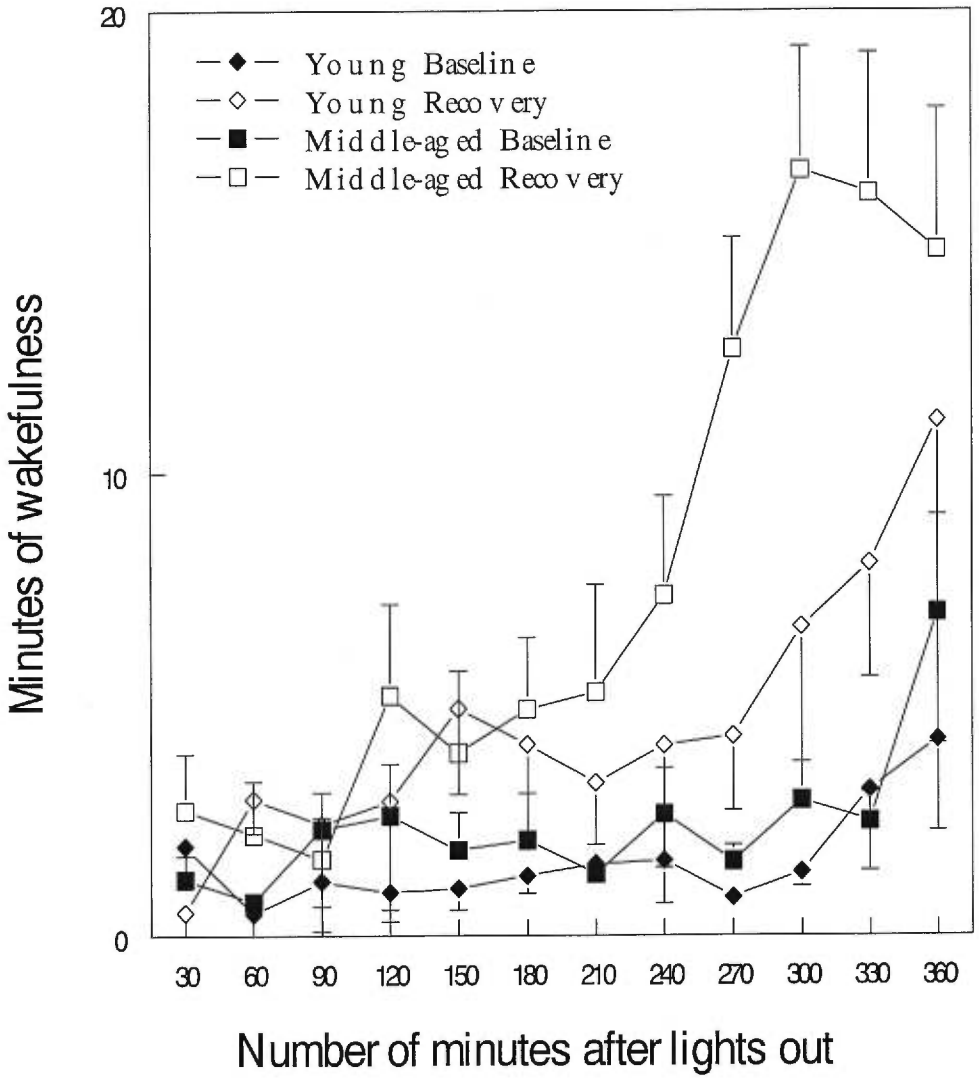

Young Baseline
Young Recovery
Middle-aged Baseline
Middle-aged Recovery
Minutes of wakefulness
20
10
0
30
60
90
120
150
180
210
240
270
300
330
360
Number of minutes after lights out

Figure 4.

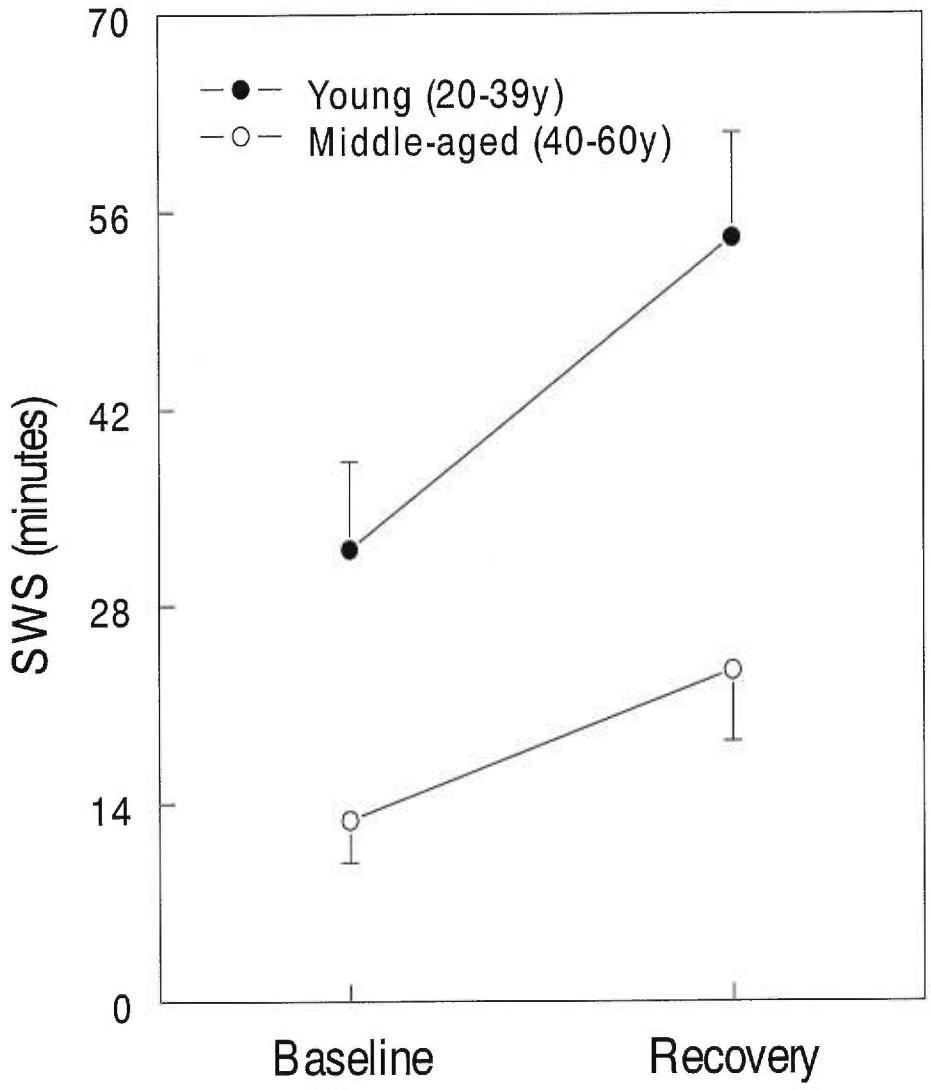
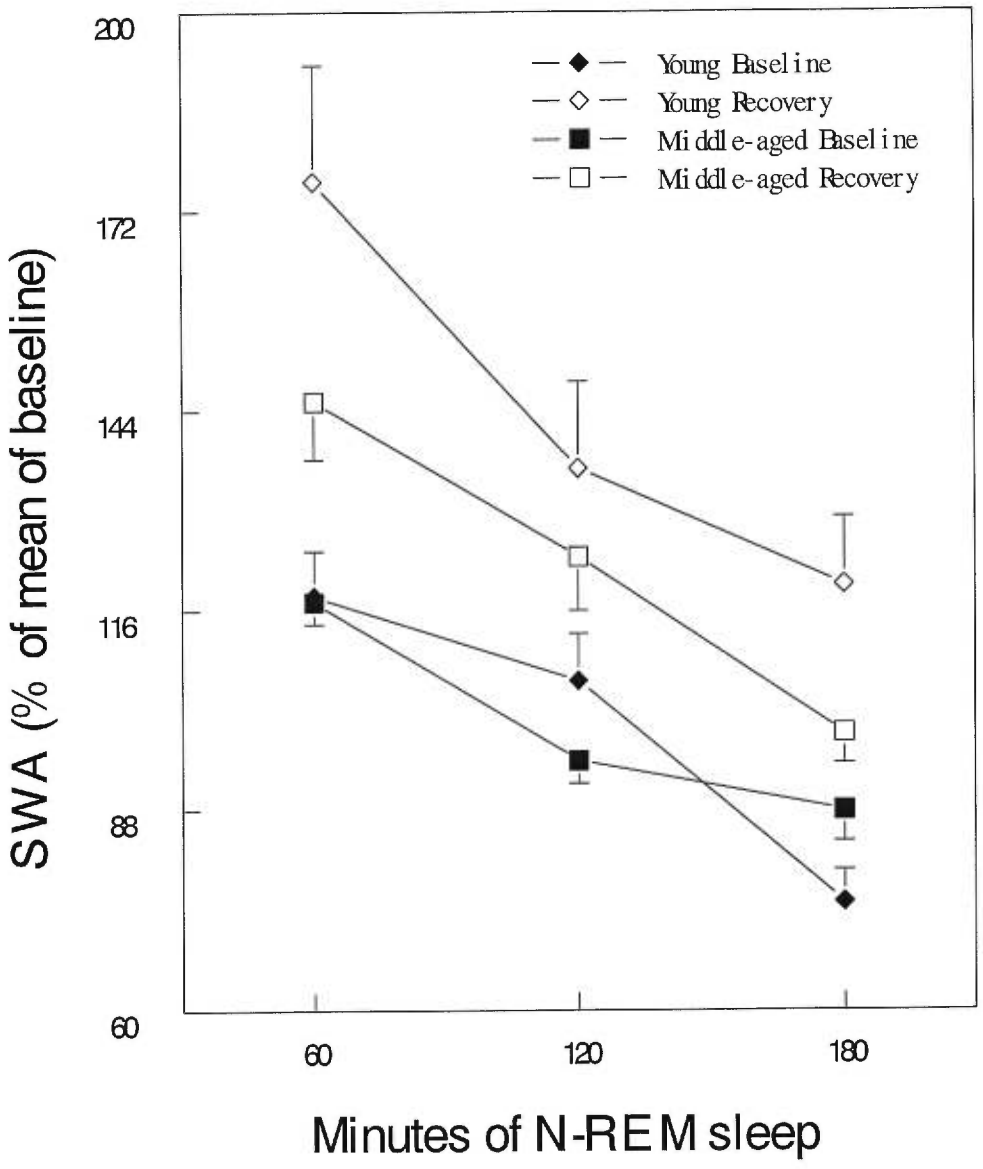

70
56
42
28
14
0
SWS (minutes)
Young (20-39y)
Middle-aged (40-60y)
Baseline
Recovery

Figure 5.


Young Baseline
Young Recovery
Middle-aged Baseline
Middle-aged Recovery
SWA (% of mean of baseline)
200
172
144
116
88
60
60
120
180
Minutes of N-REM sleep

TROISIÈME ARTICLE

RÉGULATION HOMÉOSTATIQUE DU SOMMEIL CHEZ DES PATIENTS SOUFFRANT D'HYPERSOMNIE IDIOPATHIQUE

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HOMEOSTATIC SLEEP REGULATION IN PATIENTS WITH IDIOPATHIC HYPERSOMNIA

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Clinical Neurophysiology

Abstract: 170 words, Main text: 2695 words, 3 Tables, 2 Figures, 28 References

Key words: Idiopathic hypersomnia, quantitative EEG, sleep homeostasis, sleepiness, SWA, SWS.

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ABSTRACT

Objective: To determine whether the spectral activity during sleep of patients with idiopathic hypersomnia (IH) differs from that of healthy subjects. **Methods**: Spectral analysis of the electroencephalogram (EEG) was performed in 10 patients with IH and in 10 age-matched control subjects. We compared the time course of absolute power for slow wave activity (SWA:0.75-4.5 Hz), and for theta, alpha, sigma and beta bands for the first four non-rapid-eye movement (NREM) episodes. **Results**: Compared to controls, IH patients had less SWA across the night though the exponential decay was preserved. The fall in SWA was statistically significant for the first two NREM episodes only. The lower power of SWA was related to lower amounts of stages 3 and 4 of NREM sleep during the sleep episodes. No correlation was found between SWA during the night and the mean sleep latency on the multiple sleep latency test (MSLT). **Conclusions**: These results showed that, in IH patients, the homeostatic sleep regulatory mechanisms are preserved but the sleep pressure, indicated by SWA, is lower.

INTRODUCTION

Idiopathic hypersomnia (IH) is a rare condition estimated to represent 5% of patients consulting for excessive daytime sleepiness (EDS). These patients experience EDS but they report sleeping soundly at night. They frequently experience sleep drunkenness upon awakening in the morning (Roth et al., 1972) and they usually have no difficulty sleeping for a long period of time if they allow themselves to do so (Billiard, 1994).

The diagnosis of IH is only made after the exclusion of other conditions known to cause EDS. For a differential diagnosis with narcolepsy, none of the patients should complain of cataplexy, sleep paralysis and hypnagogic hallucinations and they should not have any sleep onset REM periods during the multiple sleep latency test (MSLT). They should not have any clinical evidence of sleep apnea syndrome and the polygraphic recording should not reveal an index of respiratory events (apneas+hypopneas) exceeding five per hour of sleep. The investigation should also rule out upper airway resistance syndrome. Although the differential diagnosis can only be definitively made by recording the esophageal pressure, the absence of snoring and the reduced microarousal number during the polysomnographic study considerably limit the possibility of upper airway resistance syndrome (Guilleminault et al., 1993). The diagnosis of IH also requires the exclusion of a hypersomnia associated with periodic leg movements syndrome (PLMS). However, there are major controversies with regard to contribution of PLMS to hypersomnia since two studies (Mendelson,

1996; Nicolas et al., 1998) have shown that in patients complaining of hypersomnia who also have elevated PLMS index at night, there is no correlation between the severity of EDS and the number of PLMS associated or not with microarousals. Other conditions should also be ruled out in these patients such as the presence of any neurological condition including a past history of head trauma and psychiatric conditions especially affective disorders, the use of psychotropic medications or any other conditions known to be associated with EDS (ASDA, 1990).

The physiopathology of IH is largely unknown (Montplaisir et al., 1982; Roth et al., 1972). One characteristic of these patients is that they report EDS despite a seemingly normal sleep albeit prolonged. Borbely (1982) has shown that the quantification of slow wave activity (SWA: 0.75-4.5 Hz), especially during the first two sleep cycles, is a marker of the functioning of process S, an homeostatic process of sleep regulation which increases in relation to the duration of prior wakefulness and that is affected by different physiological (Dijk et al., 1990) or experimental conditions (Dijk et al., 1989). Although no systematic study has been undertaken to assess the functional significance of SWA, several observations suggest that it has a role in the restorative function of sleep. One series of evidence is the robustness of the relationship between increase duration of wakefulness and the power of SWA. Other evidence come from studies showing that sleep deprivation (which is most likely associated with decreased SWA) leads to a sensation of fatigue and unrecuperative sleep.

It may be postulated that these patients have a dysfunction of process S and that this type dysfunction could lead to daytime somnolence. The first hypothesis is that these patients have a decreased activity of the homeostatic process leading to unrecuperative sleep and EDS. Another hypothesis would be, on the contrary, that these patients have an hyperfunctioning process S, that is to say that the process S would be very active with a slow decay of SWA across the night. According to this hypothesis, IH patients would have high levels of SWA in every sleep cycles during the night and perhaps also during diurnal sleep.

The aim of the present study was to test these two hypotheses by looking at the spectral composition of nocturnal sleep, and in particular the all-night SWA distribution, in patients with IH compared to a group of age-matched normal controls.

METHODS

Subjects

Ten patients (4 men and 6 women) aged 25.4 ± 6.6 yrs (range 18-40) and 10 normal controls matched for age and sex (mean age: 25.2 ± 6.3, range 19-40) entered in the study. The controls reported to be in good health, they did not regularly take medication and they were free of sleep complaints. All subjects underwent one all-night polygraphic recording with a time in bed of at least seven hours. A MSLT was also administered to the IH patients only on the following day according to the standard procedure (Carskadon et al., 1986). Four

naps were recorded at 10.00, 12.00, 14.00 and 16.00. The mean sleep latency on the MSLT was defined as the mean time from light-off to the first 3 epochs of stage 1 sleep or one epoch of stage 2 or any other sleep stage.

The inclusion criteria for IH patients were: a) the presence of severe EDS for at least 1 year prior to entering the study; b) a sleep efficiency >90% during the all-night polygraphic recording; and c) a mean sleep latency on the MSLT ≤8 min without any sleep onset REM period. Exclusion criteria were: a) the presence or a history of cataplexy, sleep paralysis or hypnagogic hallucinations; b) a history of snoring or sleep-related breathing disorders; c) the presence of any other neurological disorder (including a history of head trauma or mononucleosis; d) the presence of any psychiatric or sleep disorders. All patients were examined by a certified psychiatrist specifically to rule out the presence of an affective disorder. None of these patients fulfilled the DSM-IV criteria for any psychiatric disorder; e) an index of respiratory events (apneas+hypopneas) ≥5, an index of microarousals ≥ 10 and an index of PLMS ≥10; and f) the use of medication likely to affect the central nervous system including psychostimulants for at least two weeks before the study. Nine of the ten patients were never treated for hypersomnia; one patient had been received Ritalin for 2 weeks and stopped it for one month prior to the recordings.

Demographic data on IH patients appear in Table 1. The mean age of onset of hypersomnia was 17.0 ± 3.1 yrs and the mean duration of the sysmptoms was

8.4 ± 5.7 yrs. There was no obvious cause for the hypersomnia in any patient. They were all DR2-negative; the complete HLA typing was avalaible for 6 patients only. Patients appeared to have normal body mass indexes. However, patients all had problems driving and staying awake in monotonous conditions. They fell asleep very quickly and their nocturnal sleep generally lasted more than 7 hours during weekdays (mean sleep duration: 8.1 ± 0.9 hours, range 7 to 9.5). They usually slept more during weekends and holidays.

Table 1 approximately here

All subjects were instructed not to nap or drink alcohol or caffeinated beverage during the day preceding the polygraphic study and alcohol or caffeinated beverages were prohibited during the MSLT day. Seven subjects reported not usually drinking caffeinated beverage while the other three subjects reported drinking two, three and five caffeinated beverages daily, respectively. Informed consent was obtained from all subjects. A questionnaire administered upon their arrival to the sleep laboratory verified whether the subjects complied or not with these instructions. Only one IH patient had a short nap of 15 minutes during the previous day.

Polygraphic studies

Sleep was recorded and scored according to Rechtschaffen and Kales' (1986) criteria using 20-second epochs. The recording montage was comprised

of left and right EOG, chin EMG and of central and occipital leads. Nasal and oral airflow were recorded with thermistors and thoracic and abdominal respiratory movements with strain gauges. Oxygen saturation (SaO_2) was measured continuously with a finger oxymeter (Biox III; Ohmeda, Boulder, CO). Surface EMGs of the anterior tibialis muscle of both legs were recorded to detect periodic leg movements.

Slow wave sleep (SWS) represents stages 3+4 of non-REM (NREM) sleep. A microarousal was defined as a return to alpha or theta frequency well differentiated from the background EEG activity lasting at least 3 sec but less than 10 sec. It had to be associated with an increase in chin EMG amplitude during REM sleep. Awakenings were defined as a shift to alpha activity lasting more than 10 seconds. The following sleep parameters were computed: total sleep time, sleep efficiency (SE: total sleep time/ total sleep period x 100), percentage of stages 1, 2, SWS and REM sleep, sleep latency (time from light off to the first occurrence of 3 successive epochs of stage 1 sleep or one epoch of any other sleep stage) and wake time after sleep onset (WASO). Periodic leg movements in sleep were scored using Coleman's (1982) criteria, i.e., movements lasting 0.5 to 5 sec with inter-movement intervals of 4 to 90 seconds and occurring in series of at least four consecutive movements. The index (number of events per hour of sleep) of respiratory events (apneas+hypopneas) and of periodic leg movements (PLMS) were computed.

EEG spectral analysis

EEGs were low-pass filtered and digitized on-line at a sampling rate of 128 Hz. Spectral analysis was performed by fast Fourier transform (FFT) for 4-sec mini-epochs on the signal from the C3/A2 lead. Mini-epochs with artifacts were rejected by visual inspection and were considered as missing data to preserve sleep continuity. Five consecutive 4-sec epochs were then smoothed and averaged to give 20-sec epochs corresponding to the 20 sec of sleep scoring. Five frequency bands were defined: SWA (0.75-4.50 Hz), theta (4.0-7.75 Hz), alpha (8-12 Hz), sigma (12.25-15.0 Hz) and beta (15.25-31Hz). The power spectra were expressed as absolute values. For the analysis of NREM-REM sleep cycles, cycles were defined according to Feinberg and Floyd's (1979) criteria as a succession of a NREM sleep episode lasting at least 15 minutes followed by a REM episode of at least 5 minutes. A NREM episode was defined as the time interval between the first occurrence of stage 1 sleep and the first occurrence of REM within a cycle.

To take into account the individual variation in cycle length, the dynamics of SWA (Figure 2) were analyzed by subdividing each NREM episode into 20 equal intervals and each REM episode into 5 intervals for seven hours of sleep, according to the method described by Achermann et al. (1993). The first four complete NREM-REM cycles in all subjects were retained for the study. To statistically assess the between-group difference on SWA, data for the 20 intervals were then averaged to calculate the one mean value for each NREM episode per subject.

Statistical analyses

Mann-Whitney U tests were used to determine differences between IH patients and controls. A repeated measure ANOVA was performed to test whether SWA changed across the night and whether these changes were different for the two groups. Pearson's correlation coefficients were calculated to evaluate the relationship between SWA, mean sleep latency on the MSLT and sleep parameters. Significance was reached at a p value ≤ 0.05. Results in the text and in the Tables are reported as means ± SEM.

RESULTS

Polygraphic sleep recordings

The polygraphic nocturnal parameters are given in Table 2. As expected, the IH patients had a longer total sleep time (487.6±8.7 min) compared to controls (458±13.1 min) and reduced sleep latency but the differences did not reach statistical significance (p=0.07). In addition, IH patients showed a significant decrease in SWS amount and an increase in REM sleep percent. There was no between-group difference for duration of sleep stage within any of the four cycles except for amount of SWS in the second cycle that was significantly lower in IH patients compared to controls (13.9±4.5 min vs 28.1±4.9 min, p=0.04). The mean sleep latency on the MSLT for the IH patients was 5.7 ± 0.7 min.

Table 2 approximately here

Spectral activity

Statistically significant between-group differences were found for SWA with controls showing greater level of SWA in NREM sleep for the entire night (Table 2). The mean SWA was 4939.8 ± 719 μV^2 for controls and 2533.7 ± 306 μV^2 for patients (p=0.007). Individual values of SWA for controls and IH patients are presented in Figure 1. The low dispersion of SWA values in IH patients is striking and illustrates well that the significant between-group #difference was not due to a few abnormal patients. No significant between-group differences were seen for other EEG frequencies although IH patients tended to have also lower levels in alpha, theta and sigma activities (Table 3).

Table 3 and Figure 1 approximately here

The SWA in each NREM-REM cycle is presented in Figure 2. An ANOVA with one independent factor (group) and one repeated measure (SWA in successive NREM episodes) yielded significant interaction between these two factors (F(3,54)=2.91, p=0.04). Contrast analysis showed a group difference for the two first NREM episodes only (p=0.04 and p=0.005, respectively).

Figure 2 approximately here

Changes in SWA for NREM sleep was positively correlated with the amount of SWS for the entire night (r=0.73, p=0.018) and especially for the first

sleep cycle (r=0.75, p=0.01). No significant relationship was noted between the SWA and the amount of SWS in the other cycles. There was no significant correlation between the SWA for the entire night and the mean sleep latency on the MSLT in the IH group.

DISCUSSION

The present study showed that patients with IH have a lower level of SWA -- especially in the two first NREM episodes -- without alteration of its temporal evolution across sleep cycles. This is associated with lower levels in alpha, theta and sigma activities, even though the difference with normal controls did not reach statistical significance. These results are in agreement with the first hypothesis formulated proposing that patients with IH have a decrease in the level of process S, as indicated by the lower amount of SWA, even if the temporal decline of SWA during the night is preserved.

These alterations found in sleep EEG spectral activity may explain some of the symptoms commonly reported by patients. It may be speculated that the increased sleep time in IH patients may be a failed attempt to obtain normal SWA levels: IH patients have to sleep more to make up for the lower intensity of their sleep. Another hypothesis is that the decrease in SWA is the consequence of EDS and of increased duration of sleep at night. If found to be statisticaly significant in a larger popilation of IH patients, the decrease of fast activity (alpha and beta) may support the hypothesis of a defect in the arousal system in

IH, as suggested by Bonnet and Arand (1994). Long-term monitoring of sleep duration and napping by means of actigraphy and quantitative EEG analysis during wakefulness will be needed to further document the hypothesis of an arousal defect in IH.

Several hypotheses may be brought forward with regard to the mechanism responsible for the decrease SWA in IH. A first hypothesis is that IH represents an intensification of normal sleep mechanisms similar to those seen in long sleepers. However, there are major differences between the nocturnal sleep of IH patients and that of long sleepers. Unlike what was found for IH patients in the present study, long sleepers have a prolonged sleep latency, a reduced sleep efficiency and a lower amount of SWS in the first cycle without any change in REM sleep parameters (Aeschbach et al., 1996; Benoit et al., 1983).

Another possiblity is that IH patients have a decreased amplitude of their circadian rhythms. However, to our knowledge, there is not much evidence in the literature to support this hypothesis apart from the finding of a decrease temperature rhythm amplitude in somnolence associated with aging (Weitzman et al., 1982). Also, excessive sleepiness in the absence of any medical or psychiatric cause has been listed as a common feature of low amplitude circadian rhythms or the so-called irregular sleep-wake pattern (ASDA, 1990). The hypothesis of a decreased amplitude of circadian rhythms should be tested directly in IH patients in future studies.

A controversial point in the physiopathology of IH is the presence of psychiatric components since 50% of patients with IH report symptoms of anxiety or depression (Aldrich, 1996; Bassetti and Aldrich, 1997). There are, however, major differences between polygraphic characteristics of IH and depressed patients. Depressed patients frequently complain of insomnia and polysomnography shows longer sleep latency, altered sleep continuity (Benca, 1994) and reduced REM latency (Gresham et al., 1965) compared to controls. Furthemore, despite the fact that some depressed patients may complain of prolonged nocturnal sleep and daytime somnolence, polygraphic studies have documented a prolonged time in bed without increase in total sleep time (Billiard and Carlander, 1998). A study using EEG spectral analysis demonstrated a reduction in SWA primarily during the first 100 min of sleep associated with an increase in alpha and beta activity in depressed patients, indicating an excessive cortical arousal level (Armitage, 1995). REM latency was not shorter in our patients compared to controls and the alterations in sleep macro-structure and EEG spectral activity differed from those generally described in depressed patients.

In our patients, there was no significant relationship between SWA during the night and the mean sleep latency on the MSLT. The lack of correlation may be due to the fact that only patients with a mean sleep latency lower than 9 minutes on the MSLT were selected for the study; this probably caused a floor effect. Another fact that has to be taken into consideration is that the MSLT may

not be the most appropriate tool to accurately measure sleepiness in these patients (Chervin et al., 1995). As suggested by other investigators (Billiard, 1994; Voderholzer et al. 1998), other measures of EDS should be used in IH, especially total sleep time under an *ad libitum* condition.

Based on the present results, EEG spectral analysis may be helpful in differentiating IH from other types of hypersomnias. As aforementioned, the alterations in SWA in IH patients are different from that of normal long sleepers. Moreover, SWA differentiates IH patients from narcoleptics for whom either an increase (rather than a decrease) in SWA was found (Tafti et al., 1992) or an absence of SWA decay across the night was observed (Guilleminault et al., 1998). Therefore, changes in SWA may have a diagnostic value. Studies on sleep deprivation or in an *ad libitum* condition would help increasing the sensitivity of this measure.

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Table 1. Demographic data (mean±SEM) for idiopathic hypersomnia (IH) patients

Pts	Age	Age at onset	IH duration	Previous Treatment	HLA typing
1	24	14	10	None	A2 A30 B5 B18 Bw4 Bw6 C5 DR1 DR3 DQ1 DQ2
2	22	12	10	None	A30 Ax B13 B18 Bw4 Bw6 C5 C6 DR7DRx DQ2
3	24	16	8	None	A1 A2 B22 B35 Bw6 C4 DR7 DRx DQ2 DQ3
4	22	14	8	None	Complete HLA typing not available
5	34	20	14	None	A2 A3 B12 B40 Bw4 C5 DR4 DR7 DQ3
6	18	16	2	Ritalin 2 weeks	A3 A11 B7 B35 Cw4 Cx DR4 DR7 DQ2 DQ3
7	40	20	20	None	A2 A10 B14 B17 Bw4 Bw6 DR3 DR4 DQ2 DQ3
8	24	17	7	None	Complete HLA typing not available
9	22	20	2	None	Complete HLA typing not available
10	23	21	2	None	Complete HLA typing not available

Table 2. Nocturnal polygraphic data (mean±SEM) for controls and idiopathic hypersomnia (IH) patients

	IH patients	**Controls**	**p**
Total sleep time (min)	487.7 (8.7)	458.9 (13.1)	Ns
Sleep latency (min)	9.1 (2.9)	17.2 (3.1)	Ns
Sleep efficiency (%)	96.1 (0.8)	96.7 (0.5)	Ns
WASO (min)	18.9.7 (3.9)	13.9 (2.2)	Ns
MA index (n/h)	6.8 (0.6)	5.8 (1.4)	Ns
Stage 1 (%)	7.98 (0.8)	6.8 (0.9)	Ns
Stage 2 (%)	54.5 (1.8)	54.7 (2.0)	Ns
Stages 3-4 (%)	12.8 (1.3)	18.2 (1.5)	0.03
REM sleep (%)	24.8 (1.5)	20.3 (0.7)	0.02
REM latency (min)	85.3 (8.9)	87.6 (8.6)	Ns
PLMS index (number/hr)	0.5 (0.3)	1.0 (0.2)	Ns
AHI (number/hr)	1.0 (0.5)	0.3 (0.2)	Ns
MSLT (min)	5.7 (0.7)	--	--

Legend: WASO: wake time after sleep onset; **PLMS**: periodic leg movements; **REM**: rapid-eye-movement sleep; **MA**: microarousal; **AHI**: apnea/hypopnea index.

Table 3. Absolute power in the five frequency bands (mean ±SEM) for NREM sleep in controls and IH patients

NREM sleep	Controls	IH Patients	p [a]
SWA power (μV^2)	4939.8 (718.7)	2533.7 (306.1)	0.007
Theta power (μV^2)	813.7 (112.8)	482.2 (54.1)	Ns
Alpha power (μV^2)	303.6 (54.0)	179.8 (22.1)	Ns
Sigma power (μV^2)	182.0 (31.4)	115.5 (20.8)	Ns
Beta power (μV^2)	79.2 (8.5)	56.2 (7.1)	Ns

[a]**Mann-Whitney U test**

Legend for figures.

Figure 1. Individual SWA in NREM sleep for IH patients (triangles) and controls (circles). SWA is significantly lower in the IH patient group.

Figure 2. Dynamics of the SWA over four consecutive sleep cycles in controls (straight line) and IH patients (dotted line). In the patient group SWA was significantly lower during the first two NREM episodes but its temporal decay was preserved.

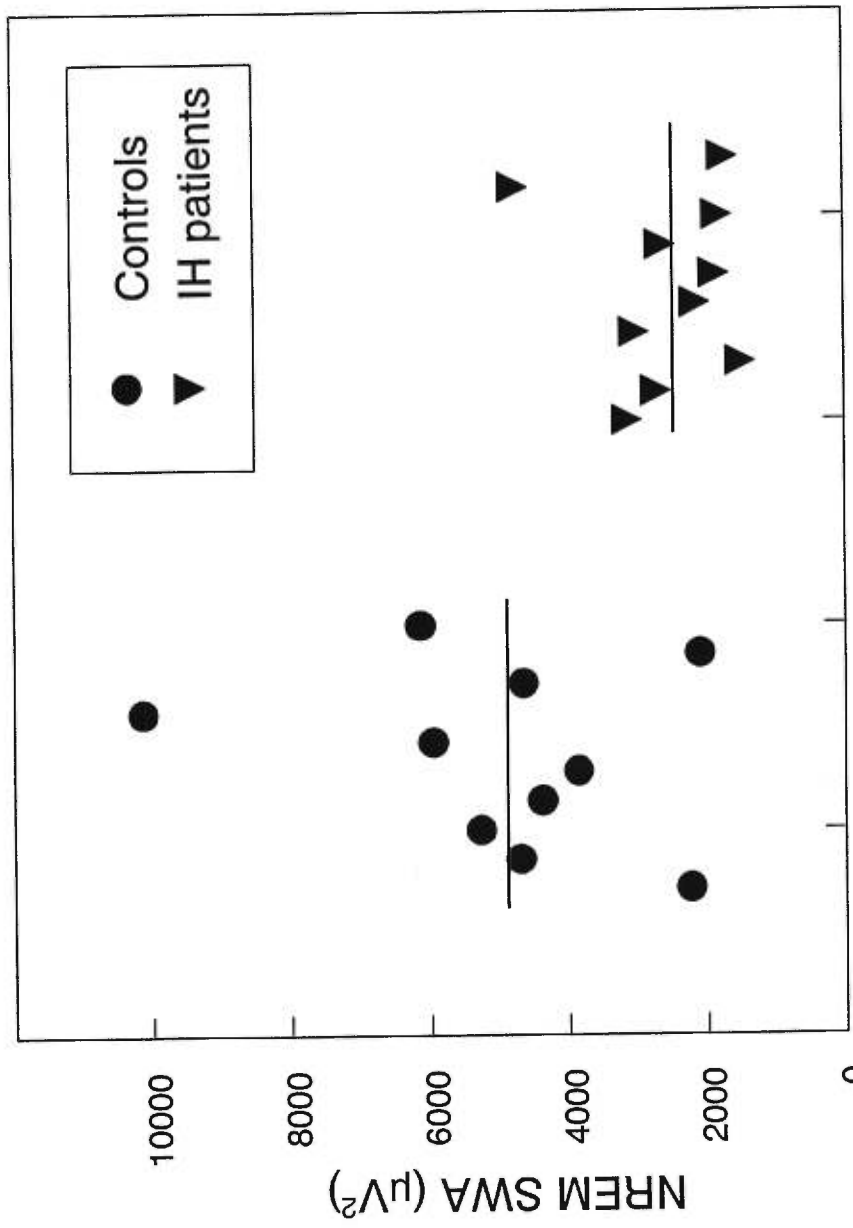
Controls
IH patients
NREM SWA (μV²)
0
2000
4000
6000
8000
10000

Figure 1.

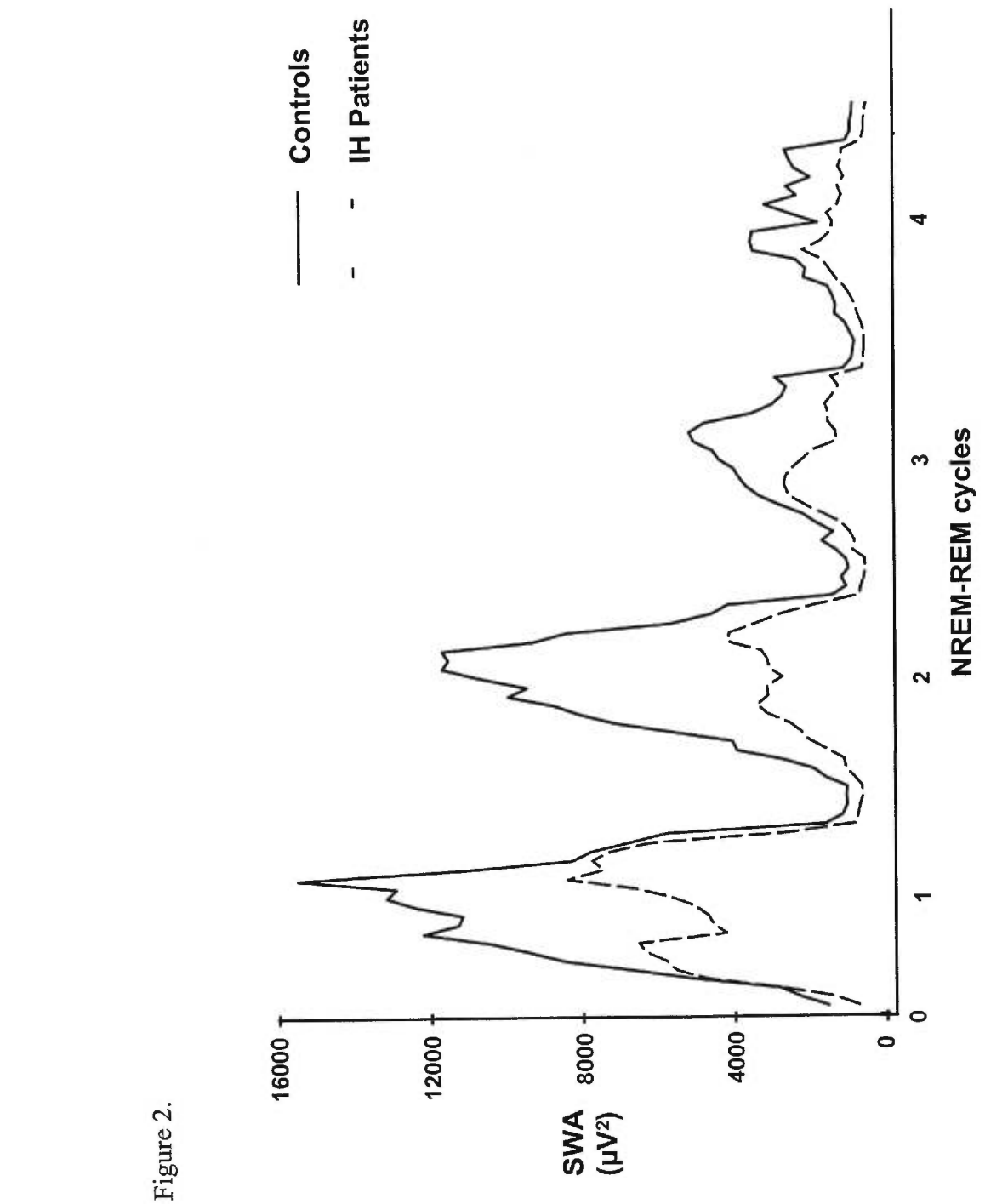
Controls
IH Patients
16000
12000
8000
4000
0
SWA
(μV²)
0
1
2
3
4
NREM-REM cycles

Figure 2.

QUATRIÈME ARTICLE

ACTIVITÉ À ONDES LENTES EN SOMMEIL CHEZ DES PATIENTS SOUFFRANT DU SYNDROME D'APNÉE DU SOMMEIL AVANT ET APRÈS TRAITEMENT AU CPAP: CONTRIBUTION À LA SOMNOLENCE DIURNE

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Article accepté: CHEST

SLOW-WAVE ACTIVITY IN SLEEP APNEA PATIENTS BEFORE AND AFTER CPAP TREATMENT: CONTRIBUTION TO DAYTIME SLEEPINESS

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CHEST, accepted

Title: 94 spaces, Abstract: 247 words, Text: 2989 words 40 references, 2 Tables, 2 Figures

RUNNING HEAD: SWA in SAS patients

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Abstract

Study Objectives: The aim of the present study was to estimate the course of slow wave activity (SWA), its amount during the night and its correlation with daytime sleepiness in sleep apnea syndrome (SAS) patients. This study also verified whether CPAP treatment also restores a normal pattern of SWA in severe SAS patients.

Participants: Ten patients diagnosed with severe SAS who showed a good clinical response to CPAP after approximately 9 months of treatment were included in this study. These patients were matched for sex and age with ten controls.

Design: All subjects had one night of polysomnographic recording (PSG) followed by the multiple sleep latency test (MSLT), the next day. For the SAS patients only, the same procedure was repeated after 9 ± 0.7 months of CPAP treatment. In addition to traditional scoring of sleep stages, apneas, hypopneas and microarousals, the SWA, defined as the power in the 0.75 to 4.5 Hz frequency band, was evaluated.

Results: A positive correlation between SWA of the first cycle and the MSLT ($r=0.58$ $p=0.04$) was found before treatment. Moreover, SAS patients significantly increased their mean SWA after CPAP treatment in the first (0.005) and second (0.04) sleep cycles and restored a more physiological decay of SWA across the night.

Conclusions: These results suggest that daytime sleepiness in SAS patients may be the result of a lack of SWA during the first part of the night and show that CPAP restores a more physiological pattern of SWA across the night.

Key words: Sleep apnea syndrome, CPAP, sleepiness, quantitative EEG, slow wave activity

Abbreviations

AHI: apnea + hypopnea index
ANOVA: analysis of variance
BMI: body mass index
CPAP: continuous positive airway pressure
EDS: excessive daytime somnolence
EEG: electroencephalogram
MSLT: multiple sleep latency test
NREM: non rapid-eye-movement
PSG: polysomnography recording
REM: rapid-eye-movement
SaO2: oxygen saturation
SAS: sleep apnea syndrome
SEM: standard error of the mean
SWA: slow wave activity

INTRODUCTION

Sleep apnea syndrome (SAS) is a chronic illness characterized by recurrent apneas and hypopneas during sleep, resulting in repetitive arousals and disruption of normal sleep architecture. Several studies have shown a strong deprivation of rapid-eye-movement (REM) sleep and of stages 3 and 4 non rapid-eye-movement (NREM) sleep in SAS patients, even though their sleep efficiency seems to be preserved[1,2] or minimally changed.[3,4] Among the various symptoms associated with this condition, the most prevalent is excessive daytime sleepiness (EDS).[5]

SAS is commonly treated with nasal continuous positive airway pressure (CPAP). It was found to restore normal airflow and sleep architecture and to suppress episodes of nocturnal hypoxemia.[6-8] CPAP also improves daytime sleepiness as measured by the multiple sleep latency test (MSLT),[8] especially with long-term use,[9] although some degree of daytime somnolence remains.

According to a proposed model of sleep regulation, sleep and vigilance are regulated by two processes: a circadian process (process C) and a homeostatic process (process S).[10-11] Slow-wave activity (SWA) is considered a marker or an objective measure of process S[12] and has been shown, in normal subjects, to increase with the duration of prior wakefulness and to decline exponentially during the night from the first to the last sleep cycle.[11,13,14] Unlike the quantification of slow-wave sleep which requires an amplitude criterion (> 75

μV) and a minimum quantity of these slow waves (20% of the epoch), SWA has no such criteria (thus also takes into account lower amplitude slow waves and slow waves present in stage 2 sleep) and has a broader frequency definition (0.75 to 4.5 Hz).

Few studies have looked at the functioning of process S in various medical conditions except in narcolepsy for which it was found to be enhanced.[15] To our knowledge, the dynamics of SWA have never been studied across the night in SAS patients. It is expected that SWA will be decreased in SAS patients and the habitual dynamic of SWA decline across the night will be disrupted. We will also verify whether the EDS of untreated SAS patients is related to the decrease in SWA and whether CPAP treatment will restore a normal amount and pattern of SWA.

METHODS

Subjects

Ten men (mean age: 42.7 ± 1.87; age range: 36 to 57; mean BMI: 37.54 ± 1.98) diagnosed with severe SAS who showed a good clinical and PSG response to CPAP after 9 months (±0.7) of treatment were included in the study. Inclusion criteria were: 1) an apnea + hypopnea index (AHI) of 30 or more during the diagnosis night; 2) a good response to CPAP treatment defined as an AHI below 10; and 3) an index of periodic limb movements during sleep below 10 per hour of sleep. Exclusion criteria were the presence of any other sleep

disorder or pulmonary disease and the use of any medication likely to affect sleep, EEG or respiratory functions in the month prior to entering the study. Ten normal male subjects (mean age: 43.9 ± 2.2; age range: 36 to 55; mean BMI: 26.9 ±1.15) were used as controls and were studied with the same procedure. None of the control subjects had a AHI greater than 5. Exclusion criteria were the same as those of the SAS group. All subjects signed a consent form prior to starting the experiment and the study was approved by the ethics committee of the hospital/university.

Nocturnal sleep studies

All subjects had one night of polysomnographic recording (PSG) followed by a modified MSLT the next day; for the SAS patients the same procedure was repeated after 9 ± 0.7 months of CPAP treatment (Tranquility Plus 7100, Healthdyne, Marietta, GA). Sleep was monitored using two EEG leads (C3-A2, 02-A1), right and left electrooculogram, chin electromyogram and electrocardiogram. To asses apneas and hypopneas, nasal and oral airflow were recorded with thermistors and respiratory movements with abdorminal and thoracic strain gauges. An apnea was defined as a cessation of the respiratory airflow of at least 10 sec duration and an hypopnea as reduction of the airflow exceeding 50% (lasting 10 sec or more). The AHI represents the number of apneas + hypopneas per hour of sleep. Oxygen saturation (Sa02) was measured continuously with a finger oxymeter (Biox III; Ohmeda, boulder CO); both time below 90% and minimum SaO2 were calculated. Surface electro-myogram of

anterior tibialis muscles was recorded to quantify periodic leg movements during sleep.

Sleep was recorded and scored manually according to Rechtschaffen and Kales' criteria[16] using 20-second epochs. The use of the 20-second epoch is essential, when performing all-night quantitative EEG analysis on signals recorded at 128Hz (analysis window of 4 seconds), to keep the time course of sleep staging and quantitative EEG values aligned. The following variables were calculated: total sleep time, sleep efficiency, number and index of microarousals, percentage of stages 1, 2, 3 + 4 and REM sleep, mean and lowest oxygen saturation levels. Sleep efficiency was defined as the percentage of time spent asleep over the total recording time from sleep onset to the last awakening. A microarousal was defined as a return to alpha or theta frequency well differentiated from the background EEG activity lasting at least 3 sec but less than 10 sec.[17]

MSLT

The MSLT consists of five opportunities to nap administered at 10h00, 12h00, 14h00, 16h00 and 18h00.[18] As for PSG, sleep onset in the modified MSLT was defined as 3 consecutive epochs (1 minute) of stage 1 sleep or 1 epoch (20 sec) of any other sleep stage. Participants were awakened after 10 minutes of sleep or the test was stopped after 20 minutes if they did not fall sleep. Participants were not allowed to drink alcohol or beverages containing caffeine nor to sleep between the 5 tests.

EEG spectral analysis

EEGs were low-pass filtered and digitized on-line at a sampling rate of 128 Hz. Quantitative analysis of the EEG was performed by fast Fourier transform calculated on 4-sec mini-epochs for the nights preceding the MSLT. SWA was defined as the power (in microvolts) in the 0.75 to 4.5 Hz frequency band. The 4-second mini-epochs containing an artifact were rejected and were considered as missing data to preserve sleep continuity. Two visual inspections were performed according to two different criteria. First, "classical artifacts" such as movement, ocular or muscle artifacts were removed. The second time, "pre-arousal" slow waves distinguishable from the background activity that occurred from 4 seconds prior, to 8 seconds after the end of the respiratory events were also removed. An example of these pre-arousal slow waves is shown in Figure 1. Inter-rater reliability between two experienced scorer was tested for the two patients with the highest AHI. To do so, a homemade computer program compares the scorings of the 2 scorers epoch by epoch and determines the percentage of similarly scored epoch. A between-scorer correlation rate of 98% and 93% was obtained for the first and the second patients, respectively.

Insert Figure 1 about here

Total SWA was calculated by adding the power of all valid NREM sleep epochs for the entire night. The time course of SWA was standardized for each subject by subdividing each NREM episode into 20 equal intervals and each REM episode into 5 intervals. Data were then averaged per subject to also obtain

the mean SWA per sleep cycle. Sleep cycles were scored according to Feinberg and Floyd's criteria.[19] A cycle was defined by the succession of a NREM sleep episode lasting at least 15 minutes followed by a REM episode of at least 5 minute duration. A NREM episode was defined as the time interval between the first occurrence of stage 1 sleep and the first occurrence of REM within a cycle. It has to be followed by a REM episode to be considered complete. Only the first three completed NREM episodes were included in the calculations.

Statistical analyses

Between-group differences in sleep variables and in total SWA was assessed by either Mann-Whitney U tests (controls versus SAS patients) or Wilcoxon matched-pair tests (treated versus untreated SAS patients). A two-way ANOVA with one independent and one repeated measure was used to compare SWA between SAS patients and controls for three successive NREM episodes. A two-way ANOVA with two repeated measures was used to compare SAS patients before and after treatment for three successive NREM episodes. The degrees of freedom were corrected according to Huynh-Felt adjustments for sphericity violation. Post-hoc comparisons were performed for the three episodes. Because 3 untreated patients did not complete their third cycle, the ANOVA were performed using only 7 patients (before and after treatment and for all cycles) and 10 controls.

In order to assess the relationship between the MSLT and different sleep parameters including SWA, Spearman's rank order tests (unilateral) were used.

Wilcoxon matched pair tests were performed to compare sleep parameters and MSLT results before and after CPAP treatment, and Mann-Whitney U tests to compare controls with SAS patients before treatment and with patients after CPAP treatment. Data are presented as mean ± standard error of the mean (SEM). All stastistics have been performed using the Statistica 5.1 software package (Statsoft Inc., Oklahoma, USA).

RESULTS

Results of PSG recordings are shown in Table 1. A shorter total sleep time was seen in SAS patients before treatment compared to normal controls. SAS patients also had more stage 1 sleep and less stage REM sleep; they also fell asleep more rapidly on the MSLT. Stage 2 sleep, stages 3 and 4 sleep and sleep efficiency were not statistically different between groups. SAS patients presented respiratory impairments (a mean AHI over 50; a mean time spent with SaO2 below 90% of 115 minutes and a mean minimum of SaO2 of 63.9%) obviously not present in the control group. After CPAP treatment, both respiratory and sleep variables returned to normal values; there was no significant difference between post-treatment values and those of controls (Table 1).

Insert Table 1 about here

The accumulation of all SWA during NREM sleep for the entire night was not statistically different for controls and untreated SAS patients. A statistically

significant difference in total SWA was found, however, between pre- and post-treatment values in SAS patients (9,219,644 ± 4,501,536 μV^2 vs 9,796,728 ± 3,902,393 μV^2; Wilcoxon, p=0.03).

The distributions of SWA for three sleep cycles for controls versus untreated SAS patients and for treated versus untreated patients are presented in Figure 2 A and B, respectively. There was no interaction effect between Group (controls and untreated patients) and NREM episode (1, 2, 3). However, an effect of NREM episode (F(2,30)=13.7; Huynh-Feldt p=0.00006) was found as can be seen in Figure 2A.

Insert Figure 2 about here

A second ANOVA with two repeated measures (SAS patients before and after CPAP treatment and SWA in successive NREM episodes) showed an interaction between the two factors (F(2,12)= 5.29; Huynh-Feldt p=0.023). To decompose this interaction effect, an analysis of simple effects was performed and showed a significant pre to post-treatment difference for the first (p=0.005) and second NREM episodes (p=0.04); the difference for the third NREM episode was not significant.

As shown in Table 2, the mean sleep latency on the MSLT was significantly correlated with SWA in the first NREM cycle (r=0.58, p=0.04) before treatment. The microarousal index was significantly correlated

(negatively) with the SWA in first NREM episode and the total accumulation of SWA for the entire night. There was no significant correlation between the MSLT and either the percentage of REM sleep, the AHI, the SaO2 minimum or the time spent with SaO2 under 90%.

Insert Table 2 about here

DISCUSSION

One of the major difficulties in studying SWA in SAS patients results from the numerous artifacts associated with repetitive microarousals or awakenings closely related to respiratory impairments. To our knowledge, this is the first study of all-night SWA in patients with SAS and there is no easy way and no validated or standard method to reject artifacts in this population.

We decided to exclude bursts of delta activity occurring at the end of the apneic episodes in close association with microarousals, since it was previously reported that these bursts are part of an arousal response[20,21] rather than physiological SWA associated with the restorative functional sleep as SWA seen during SWS. One may question whether the criteria used for artifact rejection, including the rejection of "pre-arousal delta waves" occurring at the end of apneic episodes, may have influenced the calculation of the total SWA across the night. To assess this possibility, we also calculated SWA across sleep cycles without rejecting these bursts of SWA. We obtained the same results.

Correlations between EDS, as measured by the MSLT, and SWA in the first NREM-REM sleep cycle also remained significant when the calculations were made without rejection of bursts of delta activity occurring at the end of the apneic episodes.

Results of the present study show that there is a lower amount of SWA across the night, and especially in the first two NREM episodes, before treatment compared to post-treatment values. Comparison between controls and untreated apneics did not reach the significance even though controls had values that were even higher than those of treated apneic patients. This result can first be explained by the small sample size and large standard deviations in SWA values for each group. The latter could be related to the large age range of subjects selected for the study since it is known that SWA varies greatly with age.[22,23] The lack of statistically significant differences is also due to the different statistical tests used to assess the differences between conditions in apneic patients (within-group test) on one hand and between controls and untreated patients (between-group test) on the other hand. Nonetheless, these results showed that SWA is a more sensitive index of change in slow wave sleep organization throughout the night than is the proportion of stages 3 and 4 sleep, which was not different from pre- to post-treatment recordings. These results show that the general pattern of SWA distribution across the night is normal in CPAP treated apneic patients. These results also suggest that the decrease in SWA found in untreated apneic patients is at least partly reversible with CPAP

treatment. This is consistent with previous findings of an increase in SWS with CPAP treatment.[24-26] Similarly, a slowing of the EEG during wakefulness had been found in untreated apneics[27] in frontal, central, parietal, occipital and temporal regions which was corrected after CPAP (Morisson et al., submitted).

One question that is often raised, with regard to SAS is the identification of factors responsible for EDS. Many studies on SAS patients have shown a correlation between the number of arousals due to respiratory events during the night and the severity of EDS measured with the MSLT.[28,29] One study (n=1146) showed recently that the AHI was positively correlated with daytime sleepiness but AHI explained only 11% of the variance in MSLT results.[30] A study of 466 patients showed that arousals resulting from respiratory disturbances was a good predictor of daytime sleepiness explaining 13% of the variance in MSLT results.[31] Daytime sleepiness was also positively correlated with oxygen desaturation,[32] increased respiratory efforts,[33] and para-sympathetic activation.[34] However, another study (n=100) failed to show any correlation between MSLT and AHI, or oxygen desaturation.[35] It has also been shown that oxygen desaturation induced experimentally by CO_2 inhalation in apneic patients treated with CPAP did not decrease sleep latency at the MSLT.[36] However, experimentally induced microarousals in healthy subjects resulted in daytime sleepiness.[37,38] In the present study, although the microarousal index was highly correlated (negatively) with the total amount of SWA ($r = -.75$; $p= 0.007$), it was not significantly correlated with the MSLT ($r= -.04$; ns). No correlation was

found neither between the number of respiratory events (AHI) and the severity of EDS. The MSLT test could have indeed been more sensitive to drowsiness if 30 sec instead of 1 minute (3 epochs of 20 sec) would have been used as the sleep onset criterion and if subjects had not been allowed to sleep for 10 minutes when they fell asleep. These points may have had an effect on the lack of correlation between the MSLT and the microarousal index or the AHI. Despite the low percentage of REM sleep found in untreated patients, which is restored after CPAP treatment, it does not appear that REM sleep percent play a role in EDS. On the other hand, a significant correlation was found between results of the MSLT and SWA during the first sleep cycle. These results suggest that SWA may have a major predictive value of EDS as measured by the MSLT in SAS patients. Since it was not possible to match the controls for body-mass index to the apneic patients, one should keep in mind that obesity might be a confounding factor. However, this had no bearing on the fact that both MSLT and SWA values improved post-treatment compared to pre-treatment in the apneic group, irrespective of a weight change.

This study also shows the importance of the nocturnal distribution of SWA across the night. It is not the total amount of SWA that was best correlated with the daytime vigilance, but rather the peak of SWA noted in the first part of the night. Indeed, the first NREM episode probably has a special role in sleep physiology since it is the period most affected by age,[23] sleep loss[39] or sleep extension.[40]

Taken altogether, these results suggest that the occurrence of respiratory events at night, associated with repetitive microarousals, decreases the amount of SWA across the night in patients with SAS. As a consequence of the decreased SWA, patients experience more EDS during the day. However, there was a lack of correlation between SWA and the MSLT after treatment with nasal CPAP. The MSLT value increased remarkably after successful CPAP treatment to a near normal value (mean = 9.97 ± 1.43). This result suggests that SWA may not be a major determinant of the mean sleep latency on the MSLT when there is no major residual somnolence.

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Table 1- Sleep Parameters for A: SAS patients (pre-treatment), B: CPAP treated SAS patients and C: Controls.

	SAS	CPAP	Controls	SAS vs CPAP	SAS vs Controls	CPAP vs Controls
	Mean ± SEM	Mean ± SEM	Mean ± SEM	Wilcoxon	Mann-Whitney	Mann-Whitney
TST (min)	426 ± 11.8	420 ± 12.0	465 ± 9.7	Ns	.02	.02
Sleep efficiency (%)	88.68 ± 1.58	91.22 ± 0.92	90.3 ± 1.43	Ns	Ns	Ns
Stage 1 (%)	21.71 ± 2.88	10.42 ± 0.85	11.9 ± 1.19	.005	.008	Ns
Stage 2 (%)	64.40 ± 2.15	65.43 ± 1.64	63.3 ± 2.56	Ns	Ns	Ns
Stage 3+4 (%)	3.21 ± 1.05	4.82 ± 1.22	4.86 ± 1.88	Ns	Ns	Ns
Stage REM (%)	10.66 ± 1.06	19.33 ± 1.36	19.39 ± 1.41	.005	.0003	Ns
Microarousals Index	43.50 ± 7.34	9.0 ± 1.35	10.6 ± 1.82	.005	.0007	Ns
AHI	54.65 ± 7.18	1.68 ± 0.81	0.66 ± 0.33	.005	.0004	Ns
SaO2 < 90% (min)	115.6 ± 33.8	0.12 ± 0.12	0.07 ± 0.05	.005	.001	Ns
Minimum SaO2 (%)	63.8 ± 4.4	90.8 ± 0.5	91.8 ± 0.6	.005	.001	Ns
MSLT (min)	3.99 ± 0.54	9.97 ± 1.43	12.71 ± 0.79	.005	.0006	Ns

Table 2- Spearman Rank Order Correlations between MSLT, SWA and sleep disruption indexes in 10 SAS patients

Correlations	SAS patients (pre-treatment)		SAS patients (post-treatment)	
	r	p	r	p
MSLT & Total SWA	0.29	Ns	-0.21	Ns
MSLT & NREM 1 SWA	0.58	0.04	0.09	Ns
MSLT & stage REM%	0.29	Ns	0.27	Ns
MSLT & AHI	0.09	Ns	0.15	Ns
MSLT & SaO2 minimum	-0.39	Ns	0.05	Ns
MSLT & Time with SaO2 <90%	0.38	Ns	-0.06	Ns
MSLT & Microarousal index	-0.04	Ns	0.04	Ns
Microarousal index & Total SWA	-0.75	0.007	-0.26	Ns
Microarousal index & NREM 1 SWA	-0.61	0.03	-0.32	Ns

FIGURE LEGENDS:

Figure 1. Examples of pre-arousal slow waves following apneas (marked by gray boxes) rejected as artifacts before computation of SWA.

Figure 2. Mean standardized time course of SWA across three NREM-REM cycles for : A) 10 controls and 10 SAS patients before treatment and B) for 10 SAS patients before and after treatment. There was a significant improvement in the level of SWA with CPAP treatment for the first and second NREM episodes. Note that for the before treatment condition 3 SAS patients had not completed their third cycle. However, it appears here for descriptive purposes.

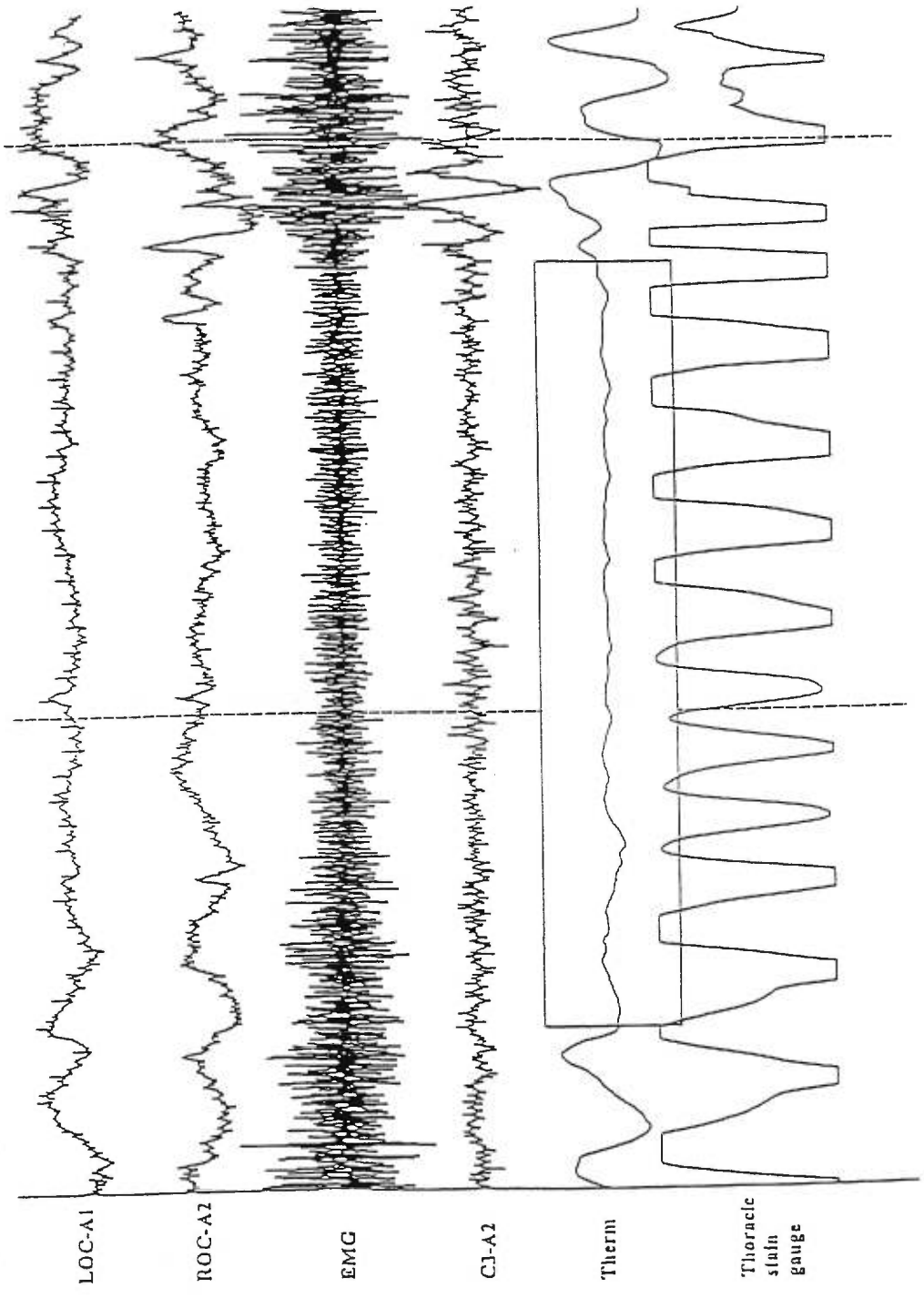

Figure 1.

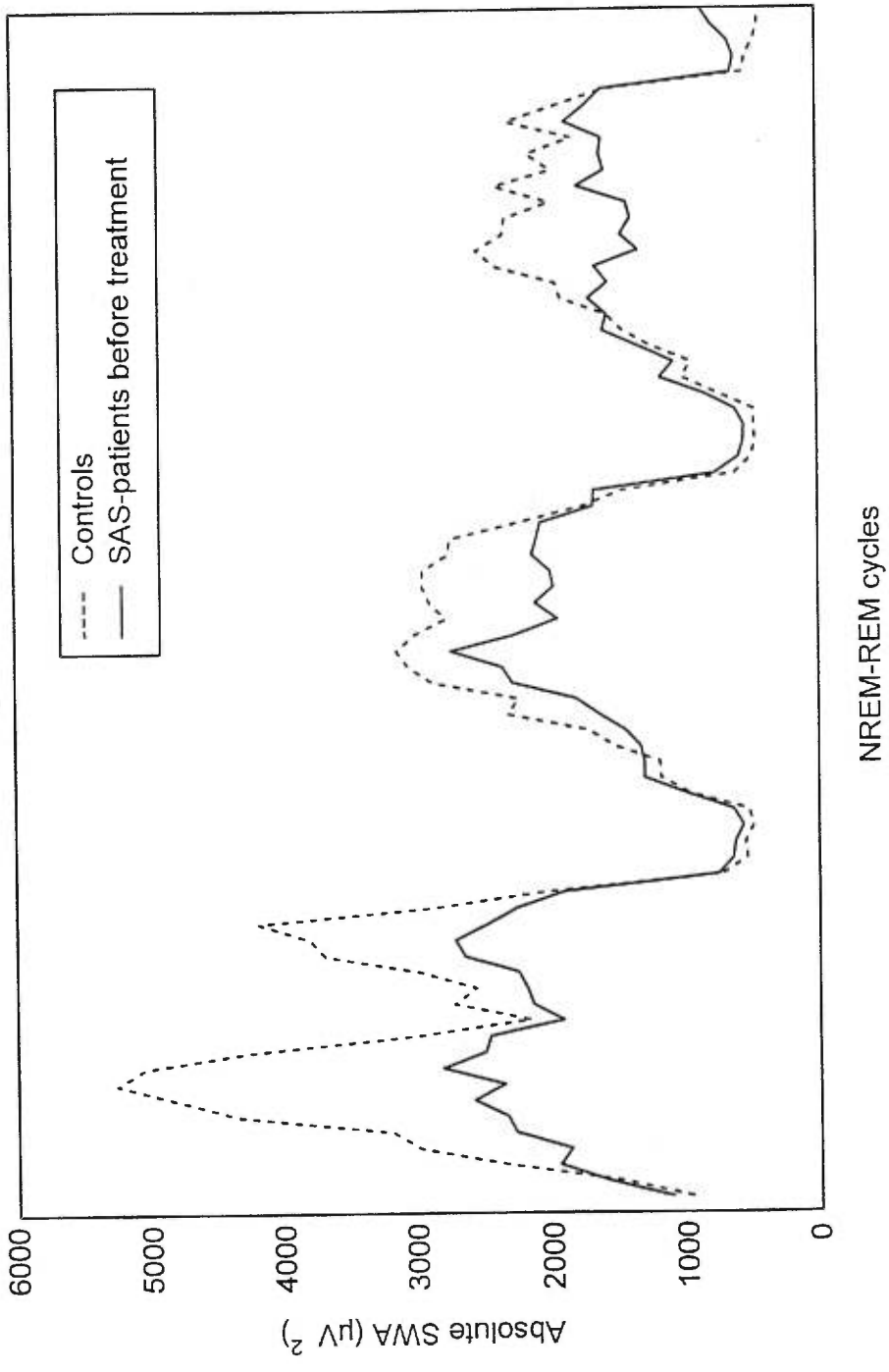
Controls
SAS-patients before treatment
Absolute SWA (μV ²)
6000
5000
4000
3000
2000
1000
0
NREM-REM cycles

Figure 2.A.

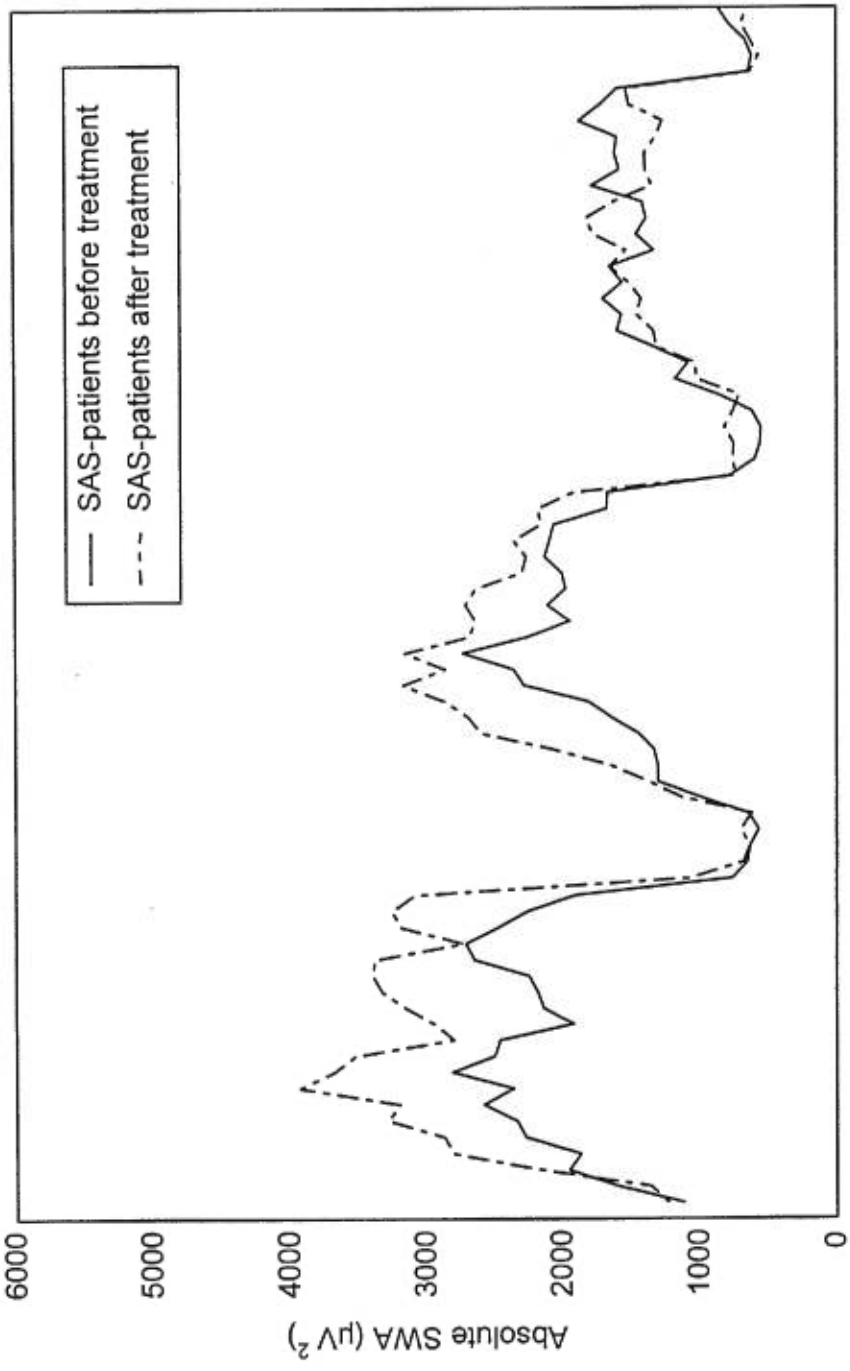
SAS-patients before treatment
SAS-patients after treatment
Absolute SWA (μV²)
6000
5000
4000
3000
2000
1000
0
NREM-REM cycles

Figure 2.B.

CINQUIÈME ARTICLE

DYNAMIQUE DE L'ACTIVITÉ À ONDES LENTES AU COURS DU SOMMEIL NREM DE SUJETS SOMNAMBULES ET CONTRÔLES

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DYNAMICS OF SLOW-WAVE ACTIVITY DURING THE NREM SLEEP OF SLEEPWALKERS AND CONTROL SUBJECTS

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SLEEP

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RUNNING HEAD: Slow-wave activity in sleepwalkers

SUMMARY

Objective: To compare the number and distribution of awakenings from slow wave sleep (SWS) and both the power and dynamics of EEG slow-wave activity (SWA) in sleepwalkers and controls.

Background: Somnambulism is considered to be a disorder of arousal from NREM sleep and related to anomalous SWS and SWA. Power spectral analyses have never been used to quantify patients' SWA across sleep cycles.

Methods: A polysomnographic study was performed on 15 adult sleepwalkers and 15 age- and sex-matched controls.

Results: Sleepwalkers had a significantly greater number of awakenings from SWS than did control subjects. Controls showed a greater decrease in SWA across NREM cycles. Sleepwalkers had a significantly lower level of SWA during the first NREM period, where most awakenings take place.

Conclusion: Sleepwalkers appear to suffer from an abnormality in the neural mechanisms responsible for the regulation of SWS.

KEY WORDS: Sleepwalking, parasomnias, EEG, slow-wave sleep, slow-wave activity

INTRODUCTION

Sleepwalking (somnambulism) is one of the parasomnias, a group of clinical disorders characterized by abnormal motor, verbal, or experiential events that occur during sleep. Although sleepwalking may occurs from lighter sleep stages, behavioral manifestations almost always arise from a sudden but incomplete arousal from slow wave sleep (SWS; stages 3 and 4 sleep), and is considered to be a "disorder of arousal" from non-rapid eye movement (NREM) sleep (1,2,3,4). Somnambulistic episodes tend to occur in the first third of the night and are usually characterized by confusion, automatic behaviors, decreased responsiveness to external stimuli, and amnesia of the event in the following morning (4,5,6,7). The actual behavioral manifestations can range from relatively simple movements (eg, sitting up in bed, picking at the bed covers, quiet walking about) to more complex acts (eg, getting dressed, climbing ladders, driving motor vehicles) including frantic, agitated attempts to run or escape (8,9,10,11,12,13,14).

Sleepwalking occurs in 1 to 15 % of the general population (15,16) and is more frequent in children and young adolescents (4% to 17%) than in adults (1% to 4%) (15,17,18,19,20 21). Since full blown episodes of somnambulism rarely occur in the sleep laboratory (3,8,22), the diagnosis of sleepwalking is largely based on the individual's history.

Analyses of sleep macrostructure (eg, sleep architecture, cyclic patterns of sleep stages) show no significant differences between adult somnambulistic patients and control subjects (11,22,23,24,25), except for one study showing a

METHODS

Subjects were 15 sleepwalkers (5 males/ 10 females; mean age = 25.1 ± 4.6 yrs; age range: 19-39 yrs) and 15 age- and sex-matched controls (mean age = 24.7 ± 5.3 yrs; age range: 18-37 yrs) . Table 1 presents a description of each sleepwalker's patient. All patients underwent a standard psychiatric and neurological investigation and none of the patients reported a history of psychiatric disorders, severe head trauma, diurnal or nocturnal seizures, current use of psychotropic medications or of other medications known to influence sleep recordings. Participants were screened for the presence of sleep apneas and periodic limb movements during sleep (PLMS). Subjects with an index of respiratory events (apneas, hypopneas/hour of sleep) greater than 10 or a PLMS index greater than 10 were excluded from the study. For both groups, only subjects with comparable sleep parameters entered the study.

Polysomnography

Subjects underwent one night of continuous polysomnographic recording in the sleep laboratory. Electrodes were placed according to the international 10-20 system for the following montage: C3/A2, O2/A1, left and right electrooculogram (EOG) and chin electromyogram (EMG). A Grass polygraph (sensitivity 7.0 μV/mm, bandpass 0.3-100 Hz) was used to amplify signals. The signals were also relayed to a PC computer where they were digitized at a sampling rate of 128 Hz and filtered with a digital filter having an upper cutoff frequency of 64 Hz. Twenty-second epochs from the C3/A2 lead were used to visually score sleep stages according to established criteria (33). Awakenings

were scored when sleep stages were interrupted by stage 0 (33) and were tabulated separately for each sleep stage.

EEG spectral analyses

In order to obtain data which are comparable with most studies investigating sleep regulatory mechanisms (29,32,34) and since it is the standard derivation for sleep scoring (33), spectral analyses were performed on the C3/A2 derivation using a commercial software package (Eclipse 3.0, Stellate Systems). Fast Fourier transforms (FFTs) were computed on 4-second mini-epochs with a cosine window tapering yielding a spectral resolution of 0.25 Hz. Mini-epochs containing artifacts were rejected by visual inspection and treated as missing data in order to preserve sleep continuity. Five consecutive 4-second epochs were averaged to maintain a correspondence with the 20-second epochs of sleep scoring. Power spectral analysis of SWA (0.75 - 4.50 Hz) was performed for the first four NREM cycles. In order to investigate EEG SWA dynamics and to compare sleep cycles between subjects, each NREM episode was divided into 20 equal intervals, and each REM episode into five equal intervals.

Statistical analyses

T-tests for independent samples were used to compare sleep variables and awakenings from each sleep stages between the two groups. A two-way analysis of variance (ANOVA) with one independent factor (Group) and one repeated measure (NREM cycle) was performed to evaluate the time course of SWA across NREM cycles. Alpha levels were adjusted with Huynh-Feldt correction

for sphericity, and results considered significant when $p \leq 0.05$. Contrast analyses were used to decompose the interaction effects and identify the nature of significant results. A two-way ANOVA with one independent factor (Group) and one repeated measure (each half of NREM cycle 1) was performed to investigate SWA dynamics during the first NREM cycle.

----Insert Table 2 About Here----

RESULTS

All-night sleep parameters

In the sleepwalker group, of the 5 behavioral manifestations that occurred during the laboratory sleep study, only one occurred out of stage 2, the other four arised out of SWS. The polysomnographic data for the adult sleepwalkers and controls are summarized in Table 2. Sleepwalkers had a higher percentage of stage 2 sleep ($t(28)=2.27$; $p=0.03$). No other significant difference was found on any of the other sleep variables indicating that both groups had comparable sleep architecture.

----Insert Table 2 About Here----

The number of awakenings from each sleep stage for the somnambulistic and control groups are presented in Table 3. Overall, both groups of subjects experienced more awakenings from stages 1 and 2, compared to stages 3 and 4. However, sleepwalkers had a significantly greater number of awakenings from SWS (stage 3 and 4 sleep) than did controls ($t(20.96)=2.74$; $p=0.01$). There were no significant differences between sleepwalkers and controls for the number of

awakenings from other sleep stages indicating that group differences were limited to SWS.

----Insert Table 3 About Here----

Spectral analyses

The absolute SWA power for sleepwalkers' and controls' four NREM cycles is presented in Figure 1. Both groups evinced a global decline in SWA across each NREM cycle. A two-way ANOVA showed a significant Group X NREM cycle interaction ($F_{3,84} = 2.90$, $\varepsilon = 0.84$, $p < 0.05$), indicating that the decrease in SWA across NREM cycles was greater in controls than in sleepwalkers. Contrast analyses revealed a significant between-group difference for the first NREM cycle ($p < 0.03$), indicating a greater level of SWA in the control group than in sleepwalkers at the beginning of the night. There were no statistically significant differences between the two groups on the remaining three NREM cycles.

----Insert Figure 1 About Here----

The dynamics of the SWA across the first four NREM cycles are illustrated in Figure 2. Since the most important difference between sleepwalkers' and controls' SWA occurred within the first NREM cycle, the intra-cycle dynamics of SWA was further investigated. A two-way ANOVA revealed a significant Group by Half of NREM cycle 1 interaction effect ($F_{1,18} = 6.75$, $p < 0.02$). Contrast analyses highlighted the different dynamics of SWA for both groups. Specifically, SWA power was similar for sleepwalkers and controls during the first half of NREM cycle 1 ($p = 0.43$), but was significantly

higher in the control group during the second half of the first NREM cycle ($p < 0.001$).

----Insert Figure 2 About Here----

DISCUSSION

The adult somnambulistic patients in this study were found to have a significantly higher number of awakenings from SWS than did age and sex matched control subjects. No significant differences were found between the two groups for number of awakenings from other sleep stages. These results indicate that the relatively high occurrence of awakenings in sleepwalkers is mainly confined to stages 3 and 4 sleep.

Consistent with most previous reports (11,22,23,24,25), we found no major differences between sleepwalkers and controls in their overall sleep architecture. Only one of the eight traditional sleep parameters investigated was significantly different between the two groups; sleepwalkers had a greater percentage of stage 2 sleep. One study showed a selective decrease in SWS for a subgroup of sleepwalkers with « serious violence toward others » compared to other subgroups (34). Although people with a history of somnambulism are sometimes described as having excessively deep sleep (5), our polysomnographic results confirm that they do not have more slow-wave sleep than controls (see Table 2).

Consistent with our hypothesis, somnambulistic patients were found to have significantly lower SWA power than control subjects during the first NREM cycle. As a result, the rate of decrease in SWA across NREM cycles was

greater in control subjects than in sleepwalkers. These results suggest that sleepwalkers' frequent awakenings from SWS interfere with the normal buildup of their SWA. Consequently, somnambulistic patients have lower EEG SWA than controls, especially during the first NREM cycle. The buildup of SWA at the beginning of the first NREM cycle was similar for both groups, but SWA fell prematurely in sleepwalkers (see Figure 2). In fact, SWA power was significantly lower among sleepwalkers during the second half of the first NREM cycle; the period during which most awakenings from SWS occur. The interruption of somnambulistic patients' SWS thus interferes with the buildup of their SWA. In subsequent NREM cycles, however, awakenings from SWS are less frequent and SWA can resume its buildup. This would account for the absence of significant differences in the two groups' SWA across the three other NREM cycles. The pattern of SWA observed during the first NREM cycle may reflect a general trend among adult sleepwalkers and suggests a lack of integrity in the homeostatic process underlying the regulation of slow wave sleep. Whether or not significant disruptions in SWA also occur in younger populations of sleepwalkers remains an open question.

Our results suggest that spectral analyses of SWA across NREM cycles can contribute to our understanding of the disorders of arousal. Delineating patterns of SWA associated with various parasomnias could help clarify their underlying pathophysiology. Given the likelihood that results of our study could be used in medico-legal settings, it is worth noting that the presence or absence of these findings in a given individual does not conclusively establish or refute a

tendency toward sleepwalking. The diagnostic value of SWA and awakenings from SWS could be further assessed by submitting them to manipulations influencing homeostatic features of sleep regulation. For instance, sleep deprivation is a factor which augments SWA (26,27,35) as well as the frequency and intensity of somnambulistic episodes (36,37,38). Assessing the differential effects of such a challenge on sleepwalkers' SWS and SWA could help determine these variables' diagnostic and theoretical utility. Taken together, the results suggest an abnormality in the neural mechanisms responsible for the regulation of SWS in somnambulistic patients. To what extent this presumed dysfunction in the regulation of SWS is similar to what has been found in other types of sleep disorders (39) and whether or not is related to the genetic predisposition to somnambulism (20,40,41) remains an open question.

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Table 1. **Patients characteristics**

Patient	Gender	Age at Consultation	Episode frequency	Self-injurious or aggressive behavior	Association with sleep terrors
FD	F	37	1-2/month	No	No
BS	F	25	Few times a week	No	No
SD	M	27	Few times/month	Purposeless aggres-ssion, minor injuries	No
PL	M	22	Five times a week	No	No
SB	F	22	2/month	No	Yes
KW	F	24	2 times a week	Minor injuries	Yes
ER	M	18	Few times a year	Minor injuries	Yes
NH	F	23	1-3 times a week	No	No
CH	F	26	Few times a month	No	No
AH	M	30	1-4 times a night, 5 nights a week	Aggressive behavior toward objects, minor injuries	Yes
BG	M	27	Few times a week	No	No
CG	F	21	Few nights a week, more than one episode within one night is frequent	No	No
GF	F	21	Few times a month	No	No
IP	F	23	3-4 times a week	No	No
CC	F	20	1-2 times a month	No	No

Table 2. **Polysomnographic data for sleepwalkers and controls.**

Sleep variables	Sleepwalkers		Controls		t-value	P
	Mean	S.D.	Mean	S.D.		
Sleep latency (min)	12.8	14.5	13.5	8.5	-0.16	0.88
REM latency (min.)	103.2	43.6	94.7	27.8	0.63	0.53
Sleep effiency (%)	93.3	5.7	95.1	3.2	-1.08	0.29
% stage 1	8.0	3.9	9.3	2.9	-1.08	0.29
% stage 2	59.2	6.0	54.8	4.4	2.27	**0.03**
% stage 3+4	12.6	5.6	15.1	4.7	-1.30	0.20
% stage REM	20.3	4.6	20.8	2.9	-0.40	0.69
Total sleep time (min)	459.2	45.8	470.3	53.4	-0.61	0.55

Table 3. **Arousals from different sleep stages in sleepwalkers and controls.**

	Sleepwalkers		**Controls**		**t-value**	**P**
	Mean	S.D	Mean	S.D		
Stage 1	8.4	4.9	8.5	4.8	-0.07	0.94
Stage 2	10.3	5.7	9.3	6.6	0.41	0.68
Stages 3 + 4	2.4	1.9	0.9	1.0	2.75	**0.01**
REM	3.0	2.1	4.3	3.5	-1.20	0.24

Legends for figures.

Figure 1.

Absolute SWA power across four NREM cycles for sleepwalkers and controls subjects.

Figure 2.

Dynamics of SWA over four consecutive sleep cycles in sleepwalkers and control subjects. The distribution of awakenings from stages 3 and 4 are represented by vertical marks on a line corresponding to the time course of the four NREM cycles.

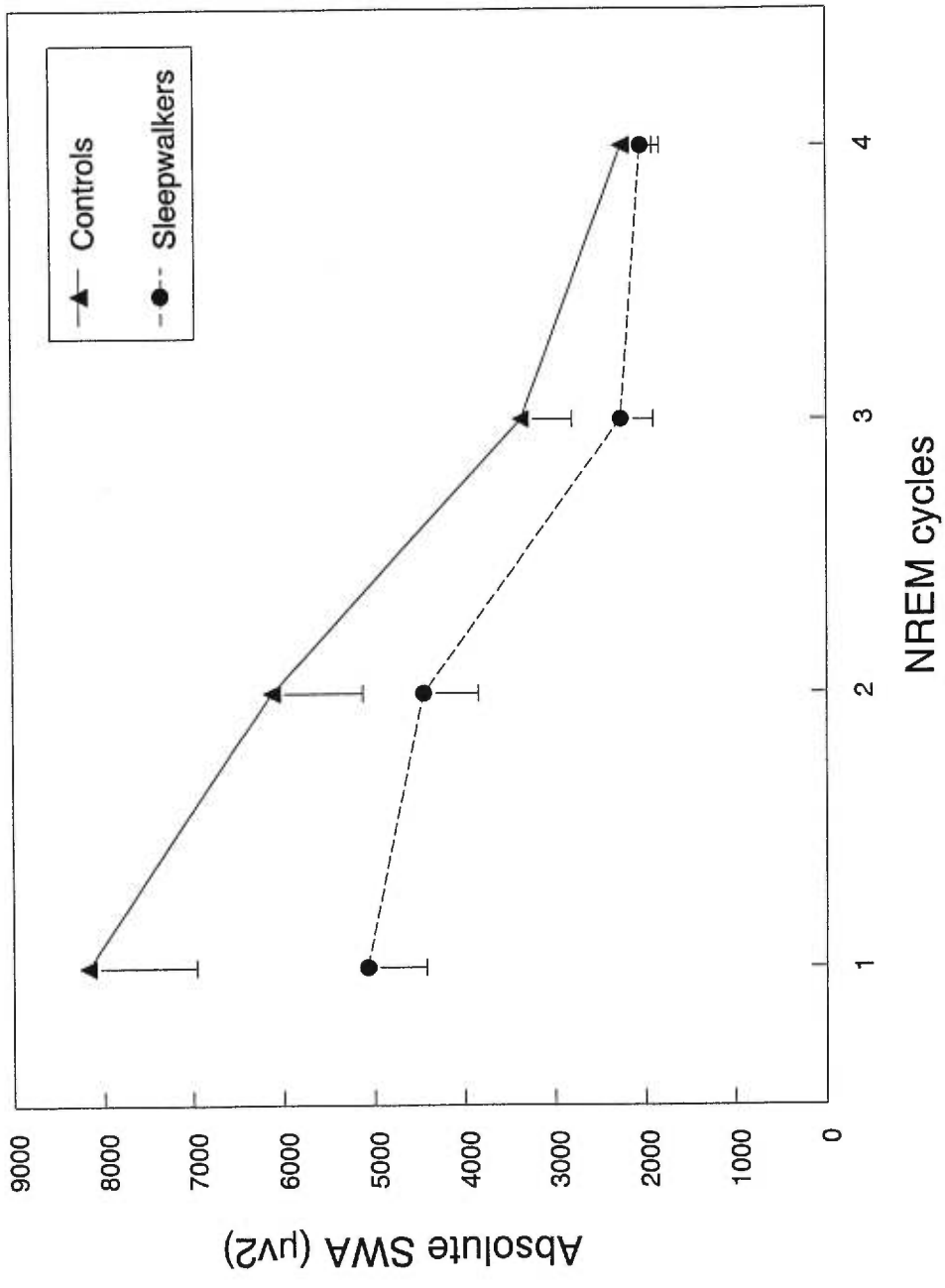
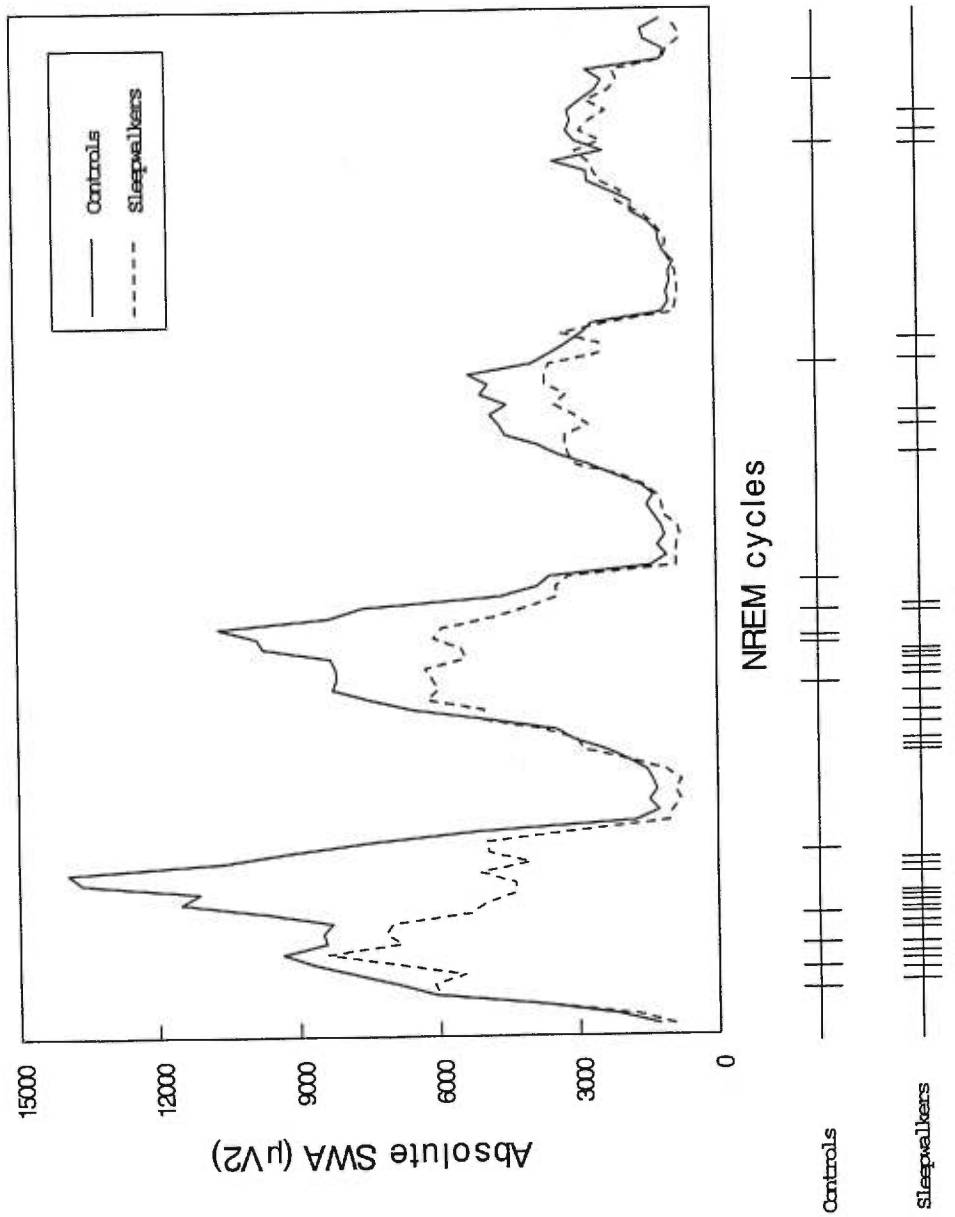

Controls
Sleepwalkers
Absolute SWA (μV2)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1
2
3
4
NREM cycles

Figure 1.

Figure 2.


Controls
Sleepwalkers
15000
12000
9000
6000
3000
0
Absolute SWA (μV2)
NREM cycles
Controls
Sleepwalkers

DISCUSSION

Le premier objectif de cette thèse était d'étudier les modifications de l'architecture du sommeil et de l'EEG en sommeil NREM qui surviennent au cours du vieillissement. Plus particulièrement, nous nous sommes intéressés aux altérations des mécanismes de régulation homéostatique du sommeil. Le marqueur du processus homéostatique utilisé dans les études présentées était la puissance spectrale de l'activité à ondes lentes à l'EEG (AOL: 0.75 à 4.5 Hz) au cours du sommeil NREM. Le premier volet comprenait tout d'abord une étude descriptive de l'évolution de l'AOL au cours du sommeil NREM chez l'enfant, l'adolescent, le jeune adulte et le sujet d'âge moyen. Le deuxième volet consistait en une étude des effets différentiels de l'âge sur la force du processus de récupération homéostatique, suite à une privation de sommeil de 25 heures. Parallèlement à ces études de populations normales, nous avons voulu explorer les modifications de la puissance spectrale de l'AOL dans différentes populations cliniques et l'impact de ces changements sur le fonctionnement diurne. L'intérêt principal de ces différents projets était d'étudier comment différentes conditions physiologiques et expérimentales influencent le niveau de l'AOL ainsi que sa dynamique au cours du sommeil.

Activité à ondes lentes et vieillissement

Notre première étude a révélé que l'architecture du sommeil et l'EEG en sommeil NREM subissent des changements majeurs entre l'enfance et le milieu de l'âge adulte. En effet, nous avons noté une baisse importante de la puissance de

l'AOL entre l'enfance et le milieu de l'âge adulte. De plus, des modifications de l'EEG étaient présentes dans toutes les bandes de fréquence étudiées.

La baisse la plus marquée de l'AOL semble se produire entre l'adolescence et le début de l'âge adulte. L'étude détaillée de l'évolution de l'AOL au cours d'un épisode de sommeil a révélé que la dynamique du déclin de l'AOL semble s'atténuer et atteindre un plateau avec l'âge. Les résultats de notre étude corrobore les travaux antérieurs ayant proposé qu'une atténuation du processus homéostatique se produise au cours du vieillissement (Dijk et coll., 1989; Landolt et coll., 1996; Carrier et coll., 2000). De plus, notre étude suggère que les changements de l'EEG au cours du sommeil soient très précoces et surviennent avant le début de l'âge adulte.

Les modifications de la puissance de l'AOL entre l'enfance et le milieu de l'âge adulte suggèrent une influence importante du processus de maturation dans les changements de l'EEG au cours du sommeil. Il a été proposé que le SOL atteigne un pic ontogénétique pendant l'enfance, puis diminue dramatiquement jusqu'au début de la vingtaine pour ensuite décliner plus graduellement au cours de la vie adulte (Blois et coll., 1983; Feinberg, 1990). Feinberg a amené certaines hypothèses concernant les processus biologiques associés à cette diminution du SOL. Il prétend qu'elle est le reflet d'un processus normal de maturation, représentant les modifications de la densité synaptique corticale qui surviennent pendant le développement. (Feinberg, 1982). En effet, le nombre de synapses corticales attendrait un maximum pendant l'enfance et serait suivit d'une réorganisation neuronale substantielle au cours de la seconde décade

(Huttenlocher, 1979). Un «élagage» ou d'une mort neuronale programmée qui permettrait une meilleure spécialisation corticale succéderait à une surproduction d'éléments neuronaux (Feinberg, 1982). Après les grands bouleversements entourant la période de maturation, la diminution de l'amplitude de l'AOL à l'EEG au cours de la vie adulte serait aussi causée par une perte synaptique (Huttenlocher, 1979). Il est connu que l'EEG est le reflet de la somme des potentiels post-synaptiques donc, la baisse de la densité synaptique résulterait en une diminution de l'amplitude du signal EEG. Le déclin du SOL avec l'âge pourrait refléter le vieillissement du système nerveux central. Il a aussi été proposé qu'au cours du vieillissement, les réseaux neuronaux présentent une capacité diminuée à maintenir un certain niveau de synchronisation entre les neurones (Feinberg et coll., 1967; Miles et coll., 1980; Astrom et coll., 1992). D'autres ont suggéré que les changements du SOL représentent un marqueur biologique extrêmement précoce du vieillissement du système nerveux central (Bliwise, 1993). Il a aussi été démontré qu'une diminution du métabolisme se produit au cours du vieillissement, en parallèle avec la baisse progressive des ondes lentes (Feinberg, 1968, 1982).

Des bouleversements importants surviennent aux niveaux biologique et psychologique au cours de l'adolescence. Pendant de cette période, règne une activité physiologique très intense. Le SOL et l'AOL au cours du sommeil pourraient donc supporter les transformations physiologiques nécessitant une activité métabolique accrue. Feinberg a suggéré que l'activité métabolique et

l'intégrité neuronale soient intimement reliées aux patrons de sommeil (Feinberg et coll., 1967). Certains auteurs ont rapporté une augmentation des stades 3 et 4 de sommeil pendant la deuxième année de la puberté (selon les stades de puberté de Tanner) (Karacan et coll., 1975). D'importantes modifications hormonales surviennent pendant la période de l'adolescence. On connaît toutefois mal l'impact des ces changements hormonaux sur d'autres systèmes, comme le sommeil par exemple. Il semble que le SOL ait des implications au niveau neuroendocrinien, entre autres, dans la régulation de la sécrétion de l'hormone de croissance (growth hormone: GH). La sécrétion de la GH est grandement modulée avec l'âge et atteint des valeurs maximales pendant la puberté (Rose et coll., 1991). Par la suite, la sécrétion de la GH pendant le sommeil diminue, en parallèle avec le déclin du SOL et de l'AOL. La diminution de la sécrétion de la GH serait particulièrement rapide entre 15 et 30 ans (Platt et coll., 1994). Même si le rôle stimulant du SOL dans la sécrétion de la GH n'est pas clairement défini, la relation mutuelle entre ces deux phénomènes a été démontrée dans de nombreuses études.

La diminution du métabolisme, ainsi que la perte progressive des ondes lentes (reflétant l'atténuation du processus homéostatique) au cours du vieillissement suggère que le besoin de récupération physiologique diminue avec l'âge. Les sujets plus âgés semblent plus tolérants ou moins sensibles à la durée de l'éveil, car malgré la baisse des ondes lentes, de la durée de l'épisode de sommeil principal et l'augmentation des éveils nocturnes, ces sujets conservent apparemment un niveau de vigilance diurne adéquat. Le SOL serait donc essentiel

aux transformations physiologiques accompagnant la maturation, et diminuerait ensuite avec l'entrée dans la vie adulte. Les transformations du sommeil et de l'EEG au cours du processus de maturation observées dans notre étude, apportent de nouvelles informations qui pourront aider à notre compréhension des processus de vieillissement.

Les résultats de notre étude descriptive corroborent l'hypothèse voulant que vieillissement soit associé à une atténuation du processus homéostatique. Dans le deuxième volet de ce projet, nous avons voulu vérifier expérimentalement cette hypothèse chez des sujets jeunes et d'âge moyen, en les soumettant à une privation de sommeil de 25 heures. Ceci nous a permis de mesurer les altérations possibles de la force de récupération du processus homéostatique avec l'âge. Il est connu que le vieillissement est associé à une désorganisation progressive du cycle éveil-sommeil. Dans cette deuxième étude, nous avons montré que la consolidation du sommeil est gravement perturbée dès le milieu de l'âge adulte pendant un épisode de sommeil de jour et ce, en dépit d'une privation de sommeil de 25 heures.

Le protocole de désynchronisation forcée permet d'étudier séparément les influences homéostatique et circadienne. Le cycle éveil-sommeil imposé dans ce protocole est d'une durée de 28 heures, i.e. au-delà des capacités d'entraînement de notre horloge biologique. De cette façon, des épisodes de sommeil sont initiés à toutes les phases circadiennes, tout en gardant la durée d'éveil constante. Ce protocole a permis de montrer qu'il existait une relation non-linéaire entre ces

deux processus (Dijk et coll., 1994). En effet, l'influence circadienne est de plus en plus importante au cours du sommeil, à mesure que le processus homéostatique diminue. Notre étude corrobore aussi l'importance de l'interaction entre les processus homéostatique et circadien. La quantité d'éveil augmentait chez les deux groupes de sujets vers la fin de l'épisode de sommeil de récupération, avec la dissipation du processus homéostatique et la baisse de la propension circadienne au sommeil.

Les études de désynchronisation forcée comparant des sujets jeunes et âgés ont montré une plus grande tendance aux éveils en fin de nuit chez les sujets âgés, peu importe la phase circadienne où l'épisode de sommeil était initié (Dijk et coll., 1994, 1995, 1997). Par contre, la proportion des éveils augmentait de façon dramatique chez les sujets âgés lorsque le sommeil était initié le matin, près du minimum de température (Dijk et coll., 1999). Dans notre étude, nous avons observé chez les sujets d'âge moyen, une augmentation notable des éveils au cours du sommeil de récupération, comparativement aux sujets jeunes. Ces résultats appuient la proposition voulant que les sujets vieillissants montrent une sensibilité accrue à un angle de phase anormal entre le signal circadien et le cycle éveil-sommeil. Il a été démontré lors d'expériences simulant le travail de nuit et un décalage horaire, que la capacité d'adaptation est réduite chez les personnes d'âge moyen (Moline et coll., 1992; Campbell, 1995). En effet, la sévérité des symptômes du décalage horaire et du travail de nuit augmente avec l'âge, due à l'incapacité à maintenir un épisode de sommeil consolidé à une mauvaise phase circadienne.

Suite à la privation de sommeil, les deux groupes de sujets ont montré un rebond d'AOL pendant le sommeil de récupération. Toutefois, cette augmentation de l'AOL était significativement réduite chez les sujets d'âge moyen comparés aux jeunes adultes. Cette baisse apparente de la force du processus de récupération homéostatique chez les sujets d'âge moyen suite à une privation de sommeil, pourrait expliquer la difficulté à maintenir un épisode de sommeil consolidé à une mauvaise phase circadienne. La baisse de l'AOL et donc du processus homéostatique pendant l'épisode de sommeil de récupération ne semble pas être un artéfact causé par les éveils. La diminution de l'AOL chez les sujets d'âge moyen est manifeste dès le début de l'épisode de sommeil, alors que l'intrusion des éveils due à la mauvaise phase circadienne n'est évidente que vers la fin du sommeil de récupération, lorsque le processus homéostatique est presque entièrement dissipé.

Notre étude suggère que la détérioration du sommeil chez les sujets d'âge moyen lors d'un épisode de sommeil de récupération de jour soit reliée à un déficit homéostatique qui fait en sorte que l'impact du processus circadien est de plus en plus important avec la progression du sommeil et l'évacuation du processus homéostatique.

On peut se questionner à savoir ce que l'on aurait observé si l'épisode de sommeil de récupération avait été initié à la bonne phase circadienne, après 40 heures de privation de sommeil. Si on propose une diminution de la force du processus de récupération homéostatique avec l'âge, des effets similaires seraient

attendus sur l'AOL et le SOL et non sur l'augmentation des éveils. Cette théorie demeure donc à vérifier afin de pouvoir confirmer et renforcer l'hypothèse de la baisse de la force du processus de récupération homéostatique au cours du vieillissement.

Des substances chimiques stimulant le SOL représenterait peut-être une nouvelle approche afin d'augmenter la sécrétion de GH chez les personnes vieillissantes (Van Cauter et coll., 1998). Une étude récente a d'ailleurs montré que le GHB (Υ-hydroxybutyrate), un stimulant efficace du SOL, administré au moment du coucher, doublait la sécrétion de la GH au cours du sommeil (Van Cauter et coll., 1997). Cette observation ouvre la voie à de futures recherches qui permettront peut-être de vérifier si l'administration de GHB constitue une stratégie nouvelle pour le traitement du déficit de GH ou de la perte de SOL chez les personnes vieillissantes.

Activité à ondes lentes et pathologies du sommeil

Dans la dernière partie de cette thèse, nous avons tout d'abord étudié deux populations de patients qui présentent une hypersomnolence au cours de la journée, des sujets atteints du syndrome d'apnées obstructives au cours du sommeil (SAS) et des sujets souffrant d'hypersomnie idiopathique. Le SAS se caractérise par des pauses respiratoires répétées au cours de la nuit associées à une augmentation importante des micro-éveils. Dans l'hypersomnie idiopathique, on note une hypersomnolence diurne mais sans anomalies de la structure du sommeil pendant la nuit.

Hypersomnie idiopathique

Nous avons étudié le sommeil de patients qui souffrent d'hypersomnie idiopathique. Ces sujets présentent une somnolence diurne semblable à celle observée dans le syndrome d'apnées du sommeil, mais une efficacité du sommeil normale (> 90%) et un taux normal de micro-éveils au cours de la nuit (index < 10). Chez les sujets hypersomniaques, l'analyse spectrale de l'EEG a montré que le niveau de l'AOL était significativement réduit par rapport aux sujets contrôles au cours des deux premiers cycles de sommeil NREM. Toutefois, la dynamique du déclin de l'AOL pendant l'épisode de sommeil semblait préservée chez les hypersomniaques.

Ces résultats ne corroborent pas notre hypothèse voulant que les sujets hypersomniaques présentent une augmentation de l'AOL. Au contraire, nous avons noté une diminution de l'AOL au cours du sommeil NREM chez les hypersomniaques. Cette observation pourrait refléter une baisse du processus de régulation homéostatique du sommeil dans cette population. On peut penser que la durée excessive de sommeil chez les hypersomniaques représenterait une incapacité à atteindre un certain niveau d'AOL au cours de la nuit, reflétant un sommeil moins intense. Cette diminution de l'intensité du sommeil serait alors compensée par une durée de sommeil prolongée.

Certaines caractéristiques de l'hypersomnie idiopathique ressemblent à une exacerbation du sommeil des longs dormeurs, comme par exemple la durée prolongée des épisodes de sommeil, et la répartition du SOL et de l'AOL pendant le sommeil. Une étude dans laquelle on s'intéressait à la régulation homéostatique

du sommeil chez des longs et des courts dormeurs, a montré au cours d'une nuit de sommeil normale, que la quantité de SOL était similaire entre les deux groupes malgré une différence de 3 heures dans la durée totale du sommeil (Aeschbach et coll., 1996). Il semble donc que le processus de récupération et la dynamique de l'AOL diffèrent considérablement, même entre des individus dits " normaux ". Dans notre étude, le niveau de l'AOL était plus faible chez les hypersomniaques que chez les sujets contrôles, et à la fin de la nuit, son accumulation totale demeure inférieure à celle des contrôles. Toutefois, il est important de noter que la durée de sommeil imposée dans cette étude était de 8 heures.

On peut imaginer que pour une majorité d'hypersomniaques, la récupération physiologique est incomplète, les obligations professionnelles nécessitant d'interrompre leur sommeil. Ces personnes vivent peut-être en privation chronique de sommeil, par rapport à leur besoin physiologique, à ce que leur système demande afin de maintenir un niveau de vigilance adéquat. Afin de vérifier ces hypothèses, il serait intéressait d'étudier une population d'hypersomniaques lors d'expériences où on les laisserait dormir à satiété, pour ensuite mesurer le niveau de l'AOL dans ces conditions. Atteindraient-ils alors des valeurs «normales» d'AOL?

Syndrome d'apnées du sommeil

Dans le cas du syndrome d'apnées du sommeil, nous avons notamment observé une diminution de l'AOL au cours du sommeil NREM. En comparant l'AOL chez les apnéiques avant et après le traitement par pression positive continue, nous avons noté une augmentation significative de la puissance de

l'AOL suite au traitement. Cette différence était particulièrement marquée pour les deux premiers cycles de sommeil NREM. Le rétablissement du niveau de l'AOL et de sa dynamique par le traitement par pression positive continue suggère que le déficit d'AOL chez les apnéiques soit réversible.

Chez les apnéiques, une corrélation était présente entre la baisse de l'AOL au cours des premiers cycles du sommeil et le degré de somnolence au cours de la journée, mesuré à l'aide du test itératif de délai d'endormissement (TIDE). La baisse de l'AOL permettait d'expliquer 10% de la somnolence diurne. L'hypersomnolence chez les apnéiques semble être engendrée par un ensemble de facteurs (désaturation en oxygène, effort respiratoire, obésité, éveils et micro-éveils, activation parasympathique). De plus, les éveils provoqués par les apnées ont pour effet de fragmenter le sommeil et d'entraîner ainsi une dette de sommeil. La fragmentation du sommeil provoquée par les apnées affecte donc le niveau de l'AOL. L'index de micro-éveils était significativement corrélé (négativement) avec le niveau d'AOL au cours du premier cycle de sommeil et avec l'accumulation totale d'AOL pendant la nuit. Il semble donc que les apnéiques vivent une fragmentation chronique de sommeil.

Conclusion : Hypersomnolence et AOL

Cette première étude des processus de régulation du sommeil chez des sujets apnéiques ou souffrant d'hypersomnie idiopathique pose un certain nombre de difficultés du point de vue de l'interprétation. Tout d'abord, on peut s'interroger sur la pertinence des mesures de vigilance qui ont été effectuées dans ces deux études. En effet, le niveau de vigilance a été mesuré principalement par

le TIDE. Ce test évalue la propension au sommeil, toutefois, plusieurs études ont remis en question la valeur du TIDE comme mesure générale du niveau de vigilance des sujets au cours de la journée. Cette mesure de somnolence n'est peut-être pas assez fine pour déterminer la somnolence pathologique de nos populations de sujets. Des mesures subjectives seraient peut-être plus sensibles à la somnolence diurne de ces sujets. Le TIDE mesure la capacité à s'endormir et non à rester éveillé, la latence au sommeil ne représente peut-être pas adéquatement l'intensité de la somnolence subjective ressentie par ces sujets. Ces études préliminaires montrent une diminution de la valeur absolue de l'AOL au cours des premiers cycles de sommeil. Toutefois, afin de vérifier si les processus homéostatiques sont véritablement perturbés, il serait nécessaire dans des études ultérieures de regarder la réponse de l'AOL à une privation de sommeil dans ces populations cliniques. Il faudrait aussi vérifier comment les mécanismes de régulation du sommeil et les niveaux de vigilance réagissent à une privation de sommeil dans une population d'hypersomniaques ou d'apnéiques. On peut penser que la force de récupération homéostatique et la dynamique de l'accumulation de l'AOL seront altérées dans ces populations. Ces sujets présenteront peut-être une sensibilité extrême ou un niveau de tolérance diminué à l'accumulation de la pression du sommeil.

Les résultats de ces études nous amènent à réfléchir sur la relation entre l'AOL et la vigilance. Existe-t-il un lien direct entre l'AOL et la vigilance? Aucune réponse définitive n'a été obtenue quant à la signification fonctionnelle des ondes lentes. En effet, seulement quelques études se sont penchées sur cette

question et nos connaissances à ce sujet demeurent encore limitées. Par exemple, la privation sélective de SOL ne semble pas avoir d'effets dramatiques sur la vigilance et la performance pendant la journée suivante (Johnson et coll., 1973, 1974; Gillberg et coll., 1994). Il semble que la durée totale de la privation de sommeil a un impact plus important sur le niveau de vigilance et la performance, que la privation sélective d'un ou l'autre des stades de sommeil (Johnson et coll., 1973, 1974). Malheureusement, ces études ont évalué visuellement les stades de sommeil et n'ont pas mesuré l'intensité de l'AOL à l'EEG. Des mesures plus fines auraient peut-être révélé des modifications de la puissance de l'EEG après une privation sélective de SOL. Il reste donc beaucoup à faire afin de comprendre le pourquoi du sommeil.

Somnambulisme

Enfin, nous avons étudié l'AOL dans une autre pathologie qui touche spécifiquement le sommeil à ondes lentes. Il s'agit du somnambulisme, dont les accès surviennent spécifiquement lors d'éveils en SOL. Nous avons voulu vérifier si ces éveils répétés au cours de la nuit s'accompagnaient de modifications dans l'évolution de l'AOL au cours du sommeil NREM. Notre étude a montré effectivement une diminution importante de l'AOL au cours des premiers cycles du sommeil chez les somnambules comparés aux sujets contrôles. De plus, le déclin de l'AOL au cours de l'épisode de sommeil était plus abrupt chez les sujets contrôles que chez les somnambules.

Lorsque nous nous sommes intéressés à la présence des éveils et à leur distribution au cours de l'épisode de sommeil, nous avons noté que chez les

somnambules, la grande majorité d'entre eux était confinée aux deux premiers cycles de sommeil NREM. Plus encore, ces éveils se produisaient principalement au cours des stades 3 et 4 de sommeil (ou SOL). Le nombre d'éveils au cours des autres stades de sommeil était similaire à celui des sujets contrôles. En raffinant les analyses, nous avons remarqué que la dynamique de l'AOL à l'intérieur du premier cycle NREM était perturbée chez les somnambules. En effet, l'accumulation de l'AOL est normale pour la première moitié du cycle. Toutefois, chez les somnambules, une baisse dramatique du niveau de l'AOL se produit dans la seconde portion du cycle. Cette observation suggère que la présence d'éveils répétés en SOL empêche l'accumulation normale de l'AOL, principalement en début de nuit. Comme les éveils sont moins fréquents au cours des cycles subséquents, l'accumulation de l'AOL peut alors recommencer, ce qui pourrait expliquer l'absence de différence entre les groupes pour les autres cycles de sommeil NREM.

Les accès somnambuliques se produisent lors d'un éveil (Broughton, 1968). Pour quelles raisons le somnambule s'éveille-t-il pendant le SOL? Certaines observations ont mené à la proposition que le somnambulisme soit une pathologie des ondes lentes (Denesle et Montplaisir, La recherche, 2000). Il est maintenant connu que les ondes lentes sont issues de la synchronisation corticale entre de larges populations de neurones (Amzica et coll., 1998). Ces oscillations sont le résultat de l'interaction constante entre le thalamus et le cortex et des propriétés intrinsèques des neurones corticaux. Les oscillations lentes dans la boucle thalamo-corticale sont très intenses. Steriade a proposé que si des

processus inhibiteurs puissants n'existaient pas pour maintenir ces oscillations dans certaines limites, elles pourraient déclencher des états d'excitabilité anormale et même des crises d'épilepsie, provoquées par l'activation synchronisée de larges populations de neurones corticaux. Il a été suggéré que lorsqu'un certain niveau de synchronisation est atteint entre les neurones chez les somnambules, il y aurait déclenchement d'un éveil. Le somnambulisme semble donc être associé à un déficit des mécanismes responsables de la synchronisation corticale, et non pas directement lié à un problème homéostatique. Le phénomène responsable du déclenchement des éveils en SOL apparaît être similaire dans le somnambulisme et dans l'épilepsie. Les crises de somnambulisme ressemblent aux manifestations de l'épilepsie psychomotrice. La privation de sommeil augmente l'apparition de crises d'épilepsie et l'activité anormale à l'EEG. La privation de sommeil est d'ailleurs une méthode diagnostique couramment utilisée dans les cas d'épilepsie.

Les accès somnambuliques semblent également être précipités par la privation sommeil ou un exercice physique intense. En parallèle, la privation de sommeil et l'exercice (ou plutôt l'augmentation de température cérébrale pendant un exercice) augmentent le SOL et l'AOL pendant l'épisode de sommeil suivant, ce qui favorise le déclenchement des épisodes de somnambulisme. Une étude présentement en cours au laboratoire du Centre d'étude du sommeil de l'hôpital du Sacré-Coeur, vise à mesurer les effets d'une privation de sommeil de 40 heures sur la prévalence des épisodes de somnambulisme, des éveils nocturnes et sur la dynamique de l'AOL pendant l'épisode de récupération. Jusqu'à présent, aucune étude n'a rapporté les conséquences fonctionnelles des éveils nocturnes sur le

niveau de vigilance des sujets somnambules pendant la journée. Une deuxième étude en cours a pour but de vérifier si la baisse de l'AOL au cours de la nuit s'accompagne d'une diminution de la vigilance au cours de la journée. Ces deux études permettront de déterminer, d'une part, l'intégrité du processus homéostatique en mesurant la réponse à une privation de sommeil et deuxièmement, d'évaluer l'impact d'une baisse de l'AOL au cours de la nuit sur le fonctionnement diurne.

L'étude de l'AOL et des processus homéostatiques dans ces différentes pathologies représente des données préliminaires basées essentiellement sur des données cliniques recueillies au cours des dernières années. Ces hypothèses de recherche devront faire l'objet de nombreux autres projets où seront utilisés des manipulations expérimentales ayant pour but de tester plus spécifiquement l'intégrité du processus homéostatique.

CONCLUSION GÉNÉRALE

Cette thèse avait pour but d'étudier les modifications de l'architecture du sommeil et de l'AOL à l'EEG en sommeil qui surviennent au cours du vieillissement et dans différentes pathologies du sommeil.

Activité à ondes lentes et vieillissement

Nous avons observé une baisse importante de la puissance de l'AOL à l'EEG entre l'enfance et le milieu de l'âge adulte, et de façon plus marquée entre l'adolescence et le début de l'âge adulte. Notre étude propose que les changements de l'EEG au cours du sommeil soient très précoces et surviennent avant le début de l'âge adulte. Les modifications de la puissance de l'AOL entre l'enfance et le milieu de l'âge adulte suggère une influence importante du processus de maturation dans les changements de l'EEG au cours du sommeil. L'analyse détaillée de l'AOL au cours d'un épisode de sommeil, a révélé que la dynamique du déclin de l'AOL semble s'atténuer et atteindre un plateau avec l'âge.

La privation de sommeil nous a permis de mesurer les altérations possibles de la force de récupération du processus homéostatique avec l'âge. Dans notre deuxième étude, nous avons montré que la consolidation du sommeil est gravement perturbée dès le milieu de l'âge adulte pendant un épisode de sommeil de jour, malgré une privation de sommeil de 25 heures. Ceci suggère que le vieillissement soit associé à des changements importants dans l'organisation du sommeil et dans sa capacité d'adaptation lors d'une manipulation du cycle éveil-

sommeil. Suite à la privation de sommeil, le rebond de l'AOL au cours du sommeil NREM est significativement diminué chez les sujets d'âge moyen comparés aux jeunes adultes. Cette baisse apparente de la force du processus de récupération homéostatique chez les sujets d'âge moyen suite à une privation de sommeil, pourrait expliquer leur difficulté à maintenir un épisode de sommeil consolidé à une mauvaise phase circadienne. Les résultats de notre étude appuient la proposition voulant que les sujets vieillissants montrent une sensibilité accrue à un angle de phase anormal entre le signal circadien et le cycle éveil-sommeil. Ces deux études s'intéressant aux effets de l'âge sur le sommeil corroborent aussi les travaux antérieurs ayant suggéré qu'une atténuation du processus homéostatique se produise au cours du vieillissement.

Activité à ondes lentes et pathologies du sommeil

Chez les sujets hypersomniaques, l'analyse spectrale de l'EEG a montré que le niveau de l'AOL était significativement réduit par rapport aux sujets contrôles au cours des deux premiers cycles de sommeil NREM, malgré un sommeil apparement consolidé. Toutefois, la dynamique du déclin de l'AOL pendant l'épisode de sommeil semble préservée chez les hypersomniaques. La diminution de l'AOL au cours du sommeil NREM pourrait refléter une baisse du processus de régulation homéostatique du sommeil dans cette population.

Nous avons noté que les sujets apnéiques ont un niveau réduit d'AOL au cours du sommeil NREM. De plus, la puissance de l'AOL augmente de façon significative chez ces sujets suite au traitement au CPAP. Le rétablissement du

niveau de l'AOL par le traitement avec CPAP suggère que le déficit d'AOL chez les apnéiques soit réversible. Les éveils provoqués par les apnées ont pour effet de fragmenter le sommeil, d'entraîner une dette de sommeil et en conséquence, une baisse du niveau de l'AOL. Il semble que les apnéiques vivent en fragmentation chronique de sommeil.

Chez les somnambules, nous avons constaté une diminution importante de l'AOL pour les premiers cycles de sommeil comparé aux sujets contrôles. De plus, des éveils en SOL étaient retrouvés principalement au cours des deux premiers cycles. Chez les somnambules, une baisse dramatique du niveau de l'AOL se produit dans la seconde portion du premier cycle NREM. Cette observation suggère que la présence d'éveils répétés en SOL empêche l'accumulation normale de l'AOL, principalement en début de nuit.

L'AOL, comme marqueur du processus homéostatique, semble contrôler l'intensité du sommeil. D'ailleurs, la baisse de l'AOL serait impliquée dans la désorganisation du cycle éveil-sommeil observée au cours du vieillissement et dans certaines pathologies du sommeil. L'AOL est un outil de travail nous permettant d'évaluer les altérations possibles du sommeil dans différentes conditions, et surtout, d'améliorer nos connaissances des mécanismes responsables de la régulation du cycle éveil-sommeil.

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