Université de Montréal

# L'influence de la cécité sur le rythme circadien et le sommeil

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# Résumé

Le sommeil s'avère crucial pour le bien-être de l'organisme. En particulier, le sommeil est une période privilégiée pour le maintien et la plasticité du cortex. En outre, de nombreuses études ont démontré son importance dans les processus de mise à l'échelle des synapses neuronales, la consolidation mnésique, la régularisation des émotions ainsi que la performance cognitive. La période et la structure du sommeil sont gouvernées par deux processus, soit la pression homéostatique et le rythme circadien. Le rythme circadien endogène, généré par le noyau suprachiasmatique de l'hypothalamus, se maintient synchronisé au rythme jour-nuit environnemental par l'information photique provenant des cellules ganglionnaires intrinsèquement photoréceptrices de la rétine. Par conséquent, la lumière et le fonctionnement de la rétine s'avèrent importants pour le maintien du rythme circadien et, en conséquence, le sommeil. De ce fait, il n'est pas surprenant que la cécité soit reliée à une plus grande fréquence de troubles du sommeil. Ceux-ci proviennent, du moins en partie, de rythmes circadiens non-synchronisés ou en libre cours causé par l'absence d'information photique. La cécité induit aussi une modulation anatomique et fonctionnelle du cortex, en particulier dans les aires visuelles. Cette réorganisation corticale peut, donc, aussi moduler l'activité corticale lors de l'état de sommeil.

Les études, qui font l'objet de cette présente thèse, visent à investiguer les effets de la cécité sur la période et la structure du sommeil. En particulier, des données comportementales et physiologiques furent comparées entre un groupe de participants avec cécité, ne reportant aucune perception visuelle résiduelle, et un groupe contrôle de participants ayant une vision normale. La cécité était d'origine congénitale chez la moitié des participants et elle fut acquise plus tard dans la vie chez les autres participants aveugles. Les présentes études rapportent sur la

qualité de leur sommeil, le rythme éveil-sommeil, la phase du rythme circadien, ainsi que la macro- et microstructure de leur sommeil. En lien avec les études antérieures, les aveugles démontrent une plus grande fréquence de phases anormales du rythme circadien, de troubles du sommeil et de déstabilisation du rythme éveil-sommeil. De plus, bien que la structure du sommeil demeure généralement présente en absence de vision, certaines modulations électrophysiologiques furent observées. En particulier, des différences dans l'activité corticale lors du sommeil NREM observées entre les aveugles congénitaux et les aveugles tardifs suggèrent que la réorganisation corticale, provenant de la perte de vision, peut être observée lors du sommeil. De plus, la modulation des aires corticales visuelles associée avec la cécité résulte en une absence de certaines composantes caractéristiques des différents stades du sommeil. Notamment, l'oscillation occipitale de fréquence alpha observée lors d'un état de repos et lors de l'endormissement se voit absente chez les aveugles. Les résultats démontrent que la modulation du rythme circadien ainsi que la réorganisation corticale associée avec la cécité agissent sur la période et la structure caractéristique du sommeil.

**Mots-clés** : cécité, rythmes circadiens, sommeil NREM et REM, macrostructure, microstructure, plasticité corticale.

## Summary

Sleep is a crucial state for the wellbeing of humans. More specifically, sleep is a privileged period for cortical maintenance and plasticity. Accordingly, numerous studies have demonstrated the importance of sleep in synaptic downscaling processes, memory consolidation, emotional regulation, as well as cognitive performance. The timing and structure of sleep is shown to be governed by two main processes: the homeostatic pressure and the circadian rhythm. In turn, the endogenous circadian rhythm, produced by the suprachiasmatic nucleus of the hypothalamus, is entrained to the day-night environmental cycle by photic input from the intrinsically photoreceptive retinal ganglion cells. Thus, light is necessary for the proper entrainment of the circadian rhythm, and consequently, for sleep. It is, therefore, not surprising that blindness is associated with a greater incidence of sleep disturbances. Specifically, these disturbances can be, in part, explained by abnormal or free-running circadian rhythms resulting from the absence of photic input. Further, absence of visual input also induces anatomical and functional changes throughout the brain, and specifically in the visual cortical areas. Such cortical reorganisation could, potentially, also modulate the cortical activity of sleep.

The studies that compose the present thesis aim to expand upon the effects of blindness on the timing and structure of sleep. Specifically, both behavioural and physiological data were collected and compared between a group of blind participants, reporting no conscious light perception, and a control group of normal sighted participants. In the blind group, half of the participants were born blind, while the other half had acquired blindness later in life. The studies report on the various components of sleep, including its quality, the sleep-wake rhythm, the phase of the circadian rhythm, as well as its macro- and microstructure. In line with previous studies, a larger incidence of abnormal circadian phase, sleep disturbances, and reduced sleep-

wake stability were observed in the blind group. Further, although the macro- and microstructure of sleep remains generally present in the absence of vision, certain electrophysiological differences were, nevertheless, observed. Differences in NREM cortical activity observed between the congenitally and late blind participants suggest that the cortical reorganisation associated with the absence of vision may be detected through electrophysiological recordings of sleep. Further, modulations of cortical activity in blindness also resulted in the absence of certain characteristics of the different stages of sleep. Namely, occipital alpha oscillations, typically observed during a quiet resting state and in the transition from wake to sleep, are absent in blind individuals. These results, therefore, demonstrate that both the circadian rhythm abnormalities and the cortical reorganisation that is associated with the absence of vision can influence both the timing and the structure of sleep in blind individuals.

**Keywords**: blindness, circadian rhythms, NREM and REM sleep, macrostructure, microstructure, cortical plasticity

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# Liste des sigles et abréviations

| | |
|---|---|
| AASM | *American Academy of Sleep Medicine* |
| AHI | Index d'apnées et d'hypopnées |
| AUC | Aire sous la courbe |
| BDI | *Beck Depression Index* |
| BL | groupe aveugle |
| BRAINlab | *Brain Research and Integrative Neuroscience Laboratory* |
| CAR | *Cortisol awakening response* |
| CB | Groupe d'aveugles congénitaux |
| CRM | Dépistage cardiaque, respiratoire, et musculaire |
| Crx | *Cone-rod-homeobox* |
| CV | *Coefficient variation* |
| dLGN | Noyau géniculé dorsolatéral |
| DMH | Noyau hypothalamique dorsomédial |
| ECG | Électrocardiographie |
| ECLIA | *Electro-chemo-luminescence immunoassay* |
| EEG | Électroencéphalographie |
| ELISA | *Enzyme-linked immunosorbent assay* |
| EMG | Électromyographie |
| EOG | Électrooculographie |
| ESS | *Epworth Sleepiness Scale* |
| etc. | *Etcetera* |
| HADS | *Hospital Anxiety and Depression Scale* |
| ipRGCs | Cellules ganglionnaires de la rétine intrinsèquement photoréceptives |
| LB | Groupe d'aveugles tardif |
| LGN | Noyau géniculé latéral |
| LHA | Aire hypothalamique latérale |
| MEQ | *Morningness-Eveningness Questionnaire* |

| | |
|---|---|
| MO | Début de la sécrétion de mélatonine |
| N1 | Sommeil NREM de stade 1 |
| N2 | Sommeil NREM de stade 2 |
| N3 | Sommeil NREM de stade 3 |
| NREM | *Non-rapid eye movement* |
| p. ex. | Par exemple |
| PGO | Ponto-géniculo-occipital |
| PRC | Courbe phase-réponse |
| PSG | Polysomnographie |
| PSQI | *Pittsburgh Sleep Quality Index* |
| RBD | *REM Sleep Behaviour Disorder* |
| REM | *Rapid eye movement* |
| RHT | Voie rétinohypothalamique |
| SCN | Noyau suprachiasmatique |
| SC | Groupe contrôle d'individus avec vision |
| SE / SE% | Efficacité du sommeil |
| SPZ | Zone sous-paraventriculaire |
| STW | Ondes en dent-de-scie |
| SWA | Activité à ondes lentes |
| SWS | Sommeil d'ondes lentes |
| TIB | Période de temps passé au lit |
| TST | Temps total de sommeil |
| VLPO | Noyaux préoptiques ventrolatéraux |
| WASO | Éveil suite à l'endormissement |

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# INTRODUCTION

# Revue de la littérature

Le sommeil est un état physiologique nécessaire pour le maintien de l'organisme. Son importance peut être considérée par le fait que nous passons près d'un tiers de notre vie dans cet état. Bien que les fonctions du sommeil ne soient toujours pas bien identifiées, les conséquences négatives d'une déficience de sommeil sur les capacités physiologiques et psychologiques de l'individu sont bien connues [Everson, Bergmann, et Rechtschaffen, 1989]. Diverses études ont démontré le rôle important du sommeil dans la performance cognitive (p. ex. [Thomas et al., 2000]), la consolidation mnésique, incluant les mémoires implicites et explicites (p. ex. [Plihal et Born, 1997; Stickgold, 2005; Marshall et Born, 2007; Tamminen, Payne, Stickgold, Wamsley, et Gaskell, 2010; Diekelmann et Born, 2010]), la régularisation des émotions (p. ex. [Vandekerckhove et Cluydts, 2010]), et divers autres processus cognitifs. Ainsi, le sommeil s'avère être une période privilégiée du maintien de l'activité corticale et de neuroplasticité.

Vu l'importance du sommeil dans l'organisation de l'activité corticale, l'évaluation de celle-ci dans les populations présentant un risque d'un sommeil entravé, tels les aveugles, est essentielle. Comme le sera abordé dans les prochaines sections, la cécité, soit congénitale ou acquise au cours de la vie, engendre non seulement de grandes modulations corticales, mais aussi une plus grande incidence de troubles du sommeil [Léger, Guilleminault, Defrance, Domont, Paillard, 1999; Tabandeh et al., 1998]. Ces troubles de sommeil peuvent être, du moins en partie, en raison de rythmes circadiens non-synchronisés ou en libre cours causés par une absence d'information photique (p. ex. [Flynn-Evans, Tabandeh, Skene, et Lockley, 2014]). Ainsi, les études qui font l'objet de cette présente thèse visent à évaluer, de façon comparative, la régularisation du cycle éveil-sommeil, le rythme circadien, et la structure physiologique du

sommeil d'un groupe d'individus aveugles comparée aux individus avec une vision normale ou corrigée à la normale.

## Le sommeil : composition, neurobiologie et théorie fonctionnelle

L'intérêt scientifique de la physiologie du sommeil et des processus apparentés a pris ampleur suite à l'identification d'une période du sommeil particulière et cyclique qui se caractérise par une présence de mouvements oculaires rapides (*rapid eye movement (REM) sleep)*, ainsi nommée « sommeil REM ». [Aserinsky et Kleitman, 1955; Dement et Kleitman, 1957a]. En conséquence, et par l'absence d'activité oculaire, les autres phases du sommeil ont été nommées « sommeil NREM (non-REM) ». Le sommeil REM porte aussi le nom de sommeil paradoxal, décrit par Jouvet [1965], par la présence d'une activité électroencéphalographique similaire à l'éveil, d'une absence de tonus musculaire et un seuil d'éveil élevé résultant d'une inhibition thalamique. De plus, ce stade de sommeil s'avère aussi être une période riche en expérience onirique. Lorsqu'éveillé du sommeil REM, la probabilité de rappel d'un rêve est plus élevée et il contiendra un discours plus complexe et bizarre, comparativement au rappel de rêves lors des autres stades du sommeil [Nielsen, 2010].

De façon plus générale, le sommeil REM se caractérise par un cerveau actif dans un corps paralysé, tandis que le sommeil NREM se définit par un cerveau tranquille dans un corps mobile [Carskadon et Dement, 2005]. Plus particulièrement, une synchronisation neuronale se présente de façon progressive au cours du sommeil NREM, reflétée par un ralentissement de la fréquence du signal EEG. Le sommeil fût davantage défini par divers experts dans le domaine, notamment Rechtschaffen et Kales [1968] et, plus récemment, par l'*American Academy of Sleep Medicine* (AASM) [Iber, Ancoli-Israel, Chesson, Quan, 2007; Berry et al., 2015], incluant une sous-

catégorisation de différents stades de sommeil NREM. Les diverses études, qui ont découlé de la première classification des stades du sommeil, ont ainsi mené à une compréhension de la neurobiologie, de la physiologie et même des processus cognitifs impliqués dans ces différents stades de sommeil.

L'étude du sommeil et de ses différents stades se fait par la méthode de polysomnographie (PSG), qui comporte différentes mesures incluant l'électroencéphalographie (EEG), l'électrooculographie (EOG), l'électromyographie (EMG), l'électrocardiographie (ECG), ainsi que des mesures de l'activité respiratoire. Le sommeil peut être catégorisé en différents stades qui composent sa macrostructure, incluant le sommeil NREM de stade N1, N2 et N3, et le sommeil REM [Iber et al., 2007; Berry et al., 2015]. Tel que démontré à la Figure 1, au cours d'une période de sommeil, les stades du sommeil alternent de façon cyclique et ils forment la structure hypnographique de la période de sommeil. La composition des cycles diffère au cours d'une nuit typique, où le sommeil N3 est prépondérant lors de la première partie de la nuit, tandis que les périodes de sommeil REM deviennent plus longues au cours de la deuxième moitié de la nuit [Roehrs, 2010; Dement et Kleitman, 1957a].

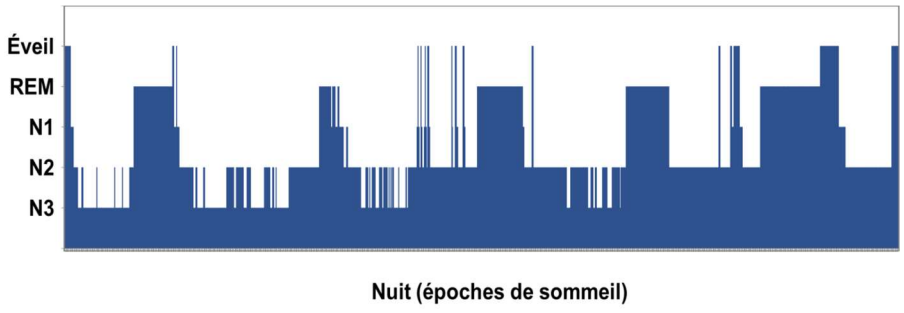


**Figure 1.** Représentation schématique de l'hypnogramme typique d'une nuit de sommeil illustrant la présence cyclique du sommeil NREM (incluant les stades N1, N2, et N3) et du sommeil REM. En plus d'une latence de sommeil dans les premières minutes de la nuit, des éveils brefs et spontanés peuvent être observés au cours de la nuit et un éveil final marquant la fin de la période de sommeil.

Les différents stades de sommeil comportent aussi une gamme de composantes électrophysiologiques qui composent la microstructure du sommeil (Figure 2). Notamment, les stades de sommeil NREM contiennent une présence de pointes vertex, observées lors du sommeil de stade N1, des fuseaux de sommeil et les complexes K, majoritairement observés lors du sommeil N2, et une activité d'ondes lentes lors du sommeil du stade N3. Ces composantes proviennent d'une interaction entre l'activité thalamique et corticale ([De Gennaro et Ferrara, 2003; Merica, 2000; McCormick, Nielsen, Nicolas, Ptito, et Montplaisir, 1997; Steriade, McCormick, et Sejnowski, 1993], etc.) et sont observées à des dérivations spécifiques du signal EEG [McCormick et al., 1997; Doran, 2003; Jobert, Poiseau, Jähnig, Schulz, et Hubicki, 1992; Zeitlhofer et al., 1997; Steriade, Gloor, Llinas, Da Silva, Mesulam, 1990]. La microstructure du sommeil NREM est associée à différents processus fonctionnels du sommeil. En particulier, il est suggéré que les complexes K reflètent une atténuation de l'activité corticale (*cortical down-state*) [Cash et al., 2009] qui survient en réponse à des stimuli internes et externes afin de préserver le sommeil (p. ex. [Wauquier, Aloe, et Declerck, 1995; Amzica et Steriade, 2002]). Les fuseaux de sommeil, ainsi que son activité de fréquence sigma (12-16 Hz), et l'activité d'ondes lentes sont fortement impliqués dans les processus de la consolidation mnésique du sommeil NREM, particulièrement les processus de mémoire hippocampo-dépendants [Schabus et al., 2004; Fogel et Smith, 2006; Clemens, Fabó, et Halász, 2005, 2006; Morin et al., 2008; Bang, Khalilzadeh, Hamalainen, Watanabe, et Sasaki, 2014; Walker, 2009; Peigneux et al., 2004; Marshall, Helgadottir, Molle, et Born, 2006]. De plus, l'activité d'ondes lentes est un indice de la pression homéostatique du sommeil, un processus qui sera détaillé dans la prochaine section [Finelli, Baumann, Borbély, et Achermann 2000].

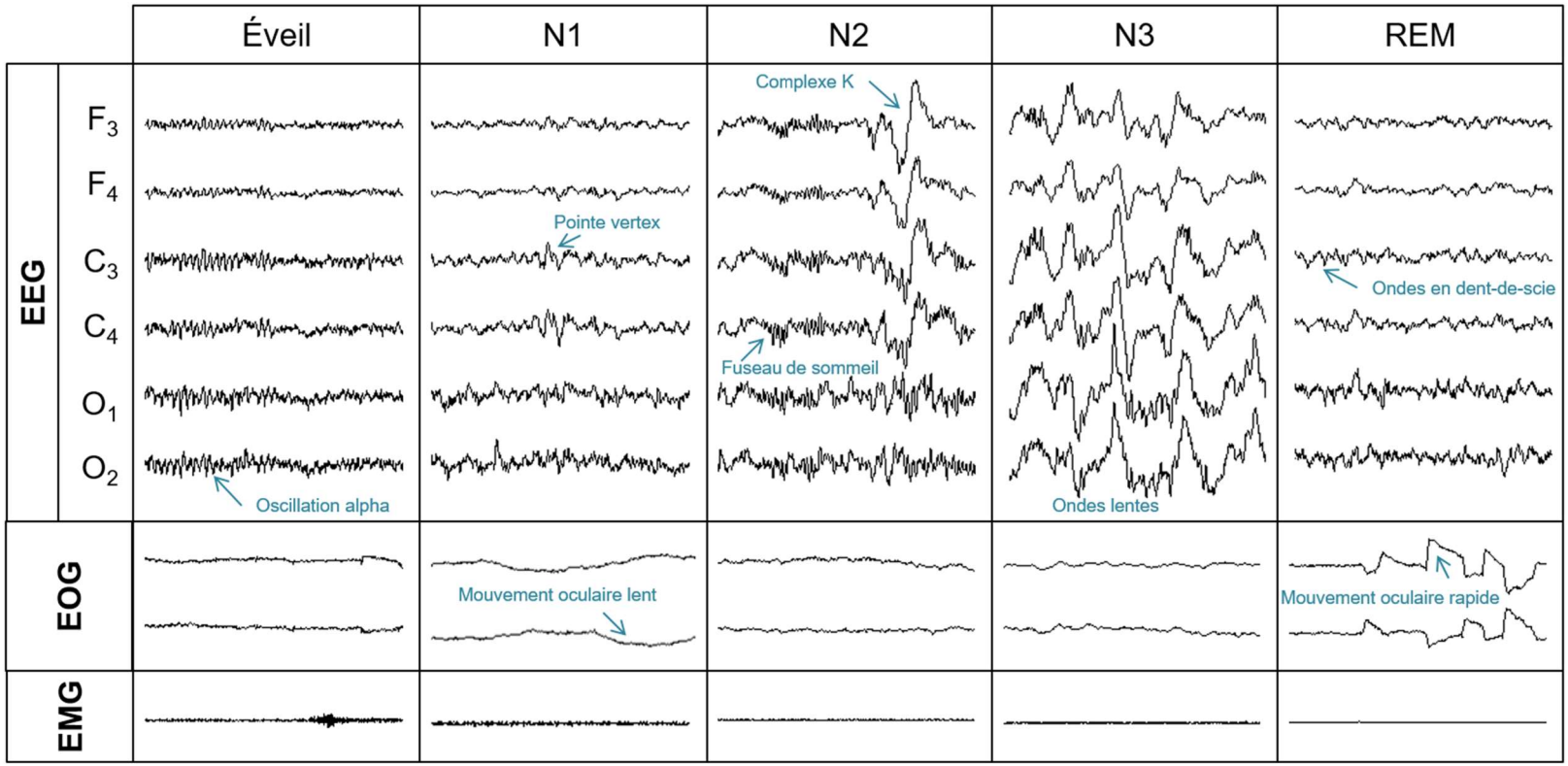


**Figure 2.** Illustration des différents stades de sommeil, ainsi que l'activité EEG, EOG et EMG associée. Les composantes particulières sont identifiées dans les stades de sommeil correspondant. L'activité électrophysiologique est représentée pour chacune des dérivations classiques de l'AASM.

Des éléments microstructuraux caractérisent aussi l'état d'éveil qui précède le sommeil et le sommeil REM. En particulier, tel son nom le décrit, le sommeil REM se démarque par la présence phasique de mouvements oculaires rapides. Une activité oculaire est aussi observée lors de la transition de l'éveil au sommeil, qui inclue le stade de sommeil N1, où l'on observe des mouvements oculaires lents et automatiques (*slow eye movements*) [Carskadon et Dement, 2011]. Au niveau des signaux EEG, une activité oscillatoire de fréquence alpha peut être typiquement observée dans les dérivations occipitales lors de l'éveil relax avec les yeux fermés [Niedermeyer, 2005; Carskadon et Dement, 2011], tel l'état d'éveil qui précède la transition au sommeil. De récentes études ont démontré que l'activité oscillatoire alpha reflèterait des processus d'inhibition fonctionnelle [Klimesch, Sauseng, et Hanslmayr, 2007; Jensen et Mazaheri, 2010] provenant de cellules GABAergiques pyramidales des couches granulaires et intragranulaires du cortex occipital [Jensen et Mazaheri, 2010; Bollimunta, Chen, Schroeder et Ding, 2008]. Lors du sommeil REM, une présence phasique d'ondes en dent-de-scie (*sawtooth waves*, ou STW) peuvent aussi être détectées [Sato et al., 1997]. Cette microstructure n'a, toutefois, fait sujet de plusieurs études. Conséquemment, très peu est présentement connu sur l'origine et la fonction des STWs. Certains auteurs proposent que les STW reflèteraient l'activité ponto-géniculo-occipitale (ondes PGO) observée dans les études animales (ex. [Takahara, Kanayama, et Hori, 2009]), mais ceci n'est encore confirmé chez l'humain. En particulier, contrairement aux ondes PGO, les STWs se présentent de façon maximale sur le vertex [Sato et al., 1997; Yasoshima et al., 1984]. Toutefois, certaines études ont démontré une association temporelle entre l'apparition des STWs et les autres composantes phasiques du sommeil REM. Spécifiquement, une apparition transitoire du tonus musculaire précède, typiquement, l'occurrence des STWs tandis que les mouvements oculaires rapides se présentent de façon

concurrente à cette composante [Sato et al., 1997; Berger et Oswald, 1962; Takahara et al., 2009].

Le sommeil peut donc être interprété comme une période d'activité corticale et physiologique distincte de l'éveil et qui possède une gamme de caractéristiques et fonctions particulières. Ainsi, le sommeil ne serait qu'une période passive où l'activité du corps, du cerveau, et l'état de conscience sont atténués. Au lieu, il joue un rôle actif dans le maintien et la santé du corps et du cortex. En particulier, le sommeil permettrait une mise à l'échelle des synapses neuronales (*synaptic downscaling*) et, ainsi, l'optimisation des réseaux et connexions corticales (p. ex. [Tononi et Cirelli, 2014]). De ce fait, tel énoncé par Tononi et Cirelli [2006, 2014], le sommeil serait le prix à payer pour la plasticité corticale.

## Modèle de deux processus du sommeil: Pression homéostatique et rythme circadien

Il est couramment accepté que le sommeil, autant sa période que sa structure, dépend de deux facteurs principaux, soit la pression homéostatique du sommeil et le rythme circadien de l'éveil (Figure 3a) [Borbély, 1982; Achermann, 2004; Borbély, Daan, Wirz-Justice, et Deboer, 2016]. Un troisième facteur, soit le processus ultradien, est parfois suggéré à titre de régulateur du cycle de sommeil NREM et REM. La pression homéostatique se définit d'une pression ou d'un besoin de sommeil qui s'accumule au cours de l'éveil et qui s'atténue lors du sommeil. La pression homéostatique est donc dépendante des périodes de sommeil et d'éveil antérieures. Un éveil prolongé génère, conséquemment, une augmentation du besoin de sommeil, tandis qu'une sieste au cours de la journée aiderait à atténuer temporairement cette pression (Figure 3b). De plus, une dette de sommeil peut être atteinte par un manque aigu ou continuel de sommeil qui a

pour but d'équilibrer la pression accumulée au cours des journées. Au niveau moléculaire, la pression homéostatique est liée à l'accumulation d'adénosine dans l'espace extracellulaire, particulièrement dans la région du prosencéphale basal (*basal forebrain*) [Landolt, 2008]. L'accumulation d'adénosine dans le cortex est le résultat de l'activité cellulaire, soit par l'hydrolisation de l'adénosine-tri-phosphate comme source d'énergie [Burnstock, 2007; Landolt, 2008]. Ainsi, la concentration d'adénosine, les inhibiteurs de sa recapture, les agonistes et les antagonistes d'adénosine ont tous des répercussions sur l'éveil, la vigilance et le sommeil (p. ex. [Bennington, Kodali, et Heller, 1995; Porkka-Heiskanen, et al., 1997; Landolt, 2008]. L'intensité de la pression homéostatique peut aussi être observée par la mesure de fréquence EEG lors de l'éveil et du sommeil. Spécifiquement, l'activité d'ondes lentes (*slow wave activity*, SWA) incluant l'activité de fréquence delta lors du sommeil, ainsi que l'activité de fréquence thêta lors de l'éveil sont fortement corrélées à la pression homéostatique [Finelli et al, 2000; Achermann, Dijk, Brunner, et Borbély, 1993; Dijk, Brunner, Beersma, et Borbély, 1990; Dijk, Beersma, et Daan, 1987]. Ainsi, plus la pression homéostatique est élevée, soit par une prolongation de l'éveil ou par une privation du sommeil, plus élevé sera l'activité thêta lors de l'éveil et l'activité delta lors du sommeil subséquent. De plus, l'activité de fréquence de fuseaux de sommeil (*spindle frequency activity*) démontre une relation inverse avec l'activité d'ondes lentes et la pression homéostatique. En conséquence, une hausse de pression homéostatique est associée avec une baisse d'activité de fuseaux de sommeil [Dijk, Hayes, et Czeisler, 1993]. Ces résultats démontrent, ainsi, que la pression homéostatique du sommeil affecte non-seulement la période du sommeil, mais aussi sa macro- et microstructure.

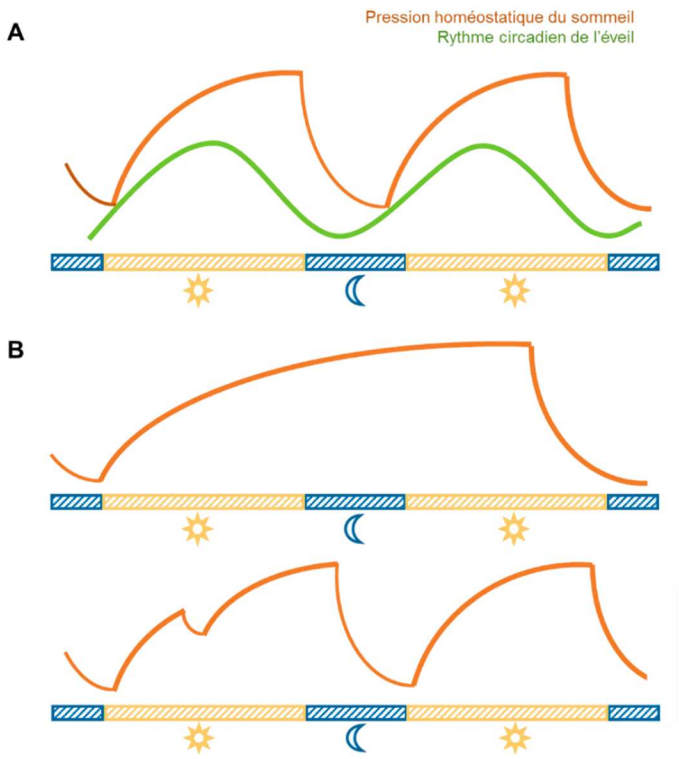


**Figure 3.** (A) Représentation schématique de la pression homéostatique du sommeil et du rythme circadien de l'éveil au cours d'une période de 24 heures jour/nuit. (B) illustration des variations de la pression homéostatique selon les circonstances du sommeil.

Le rythme circadien est un rythme biologique intrinsèque d'une période d'environ 24 heures (*circa* = environ, *dies* = jour), qui délimite, en partie, une période d'activité et de repos (Figure 3a). Cette activité circadienne se trouve parmi toutes les espèces vivantes, incluant les plantes, dont les premières observations furent reportées par De Mairan [1729]. Le rythme circadien dirige l'expression génétique, les processus physiologiques et endocriniens, ainsi que le comportement, incluant la période d'éveil et de sommeil [Gachon, Nagoshi, Brown, Ripperger, et Schibler, 2004; Stephan et Zucker, 1972]. Puisque le rythme circadien est un rythme intrinsèque, il ne dépend pas, du moins de façon significative, des périodes d'éveil et de sommeil

antérieures. Au lieu, le rythme circadien est une horloge biologique qui indique l'heure favorable des différents processus et il optimise la concordance entre les processus biologiques et le comportement. Quoique le rythme circadien se retrouve dans tous les cellules et organes du corps, l'ensemble de ces horloges, dites périphériques, est régularisé par l'horloge maître située dans les noyaux suprachiasmatiques de l'hypothalamus (*suprachiasmatic nucleus*, ou SCN) [Reppert et Weaver, 2002; Klein et Moore, 1991; Sujino et al., 2003]. Les SCN sont de petites structures bilatérales de l'hypothalamus composées d'environ 20 000 neurones fortement interconnectés, et sont composées de deux parties principales, soit la coquille ('*shell*') qui comporte les neurones dorsomédiales, soit le corps ('*core*') qui comporte les neurones ventrolatéraux [Moore, Speh, et Leak, 2002; Rosenwasser et Turek, 2005]. Bien que la fonction de ces deux parties ne puisse être complètement dissociée, les neurones de la coquille semblent être responsables du maintien et de la projection du rythme circadien, jouant ainsi un rôle de *pacemaker*. D'autre part, les neurones du corps du SCN semblent être principalement impliqués dans la synchronisation du rythme circadien aux stimuli internes et externes [Rosenwasser et Turek, 2005].

Les études d'isolation temporelle, telles les expériences avec un protocole de désynchronisation forcée [Kleitman, 1939], ont permis l'étude détaillée du rythme circadien et son influence sur le sommeil. Spécifiquement, la période de sommeil, incluant sa durée et son efficacité, est fortement modulée par la phase du rythme circadien (p. ex [Czeisler, Weitzman, Moore-Ede, Zimmerman et Knauer, 1980; Dijk et Czeisler, 1980]). Ainsi, un sommeil tenté lors d'une phase atypique du rythme sera de plus courte durée, aura une plus grande latence d'endormissement et sera plus fragmenté que le sommeil en phase normale. De plus, ces études ont aussi démontré que le sommeil REM est fortement modulé par la phase du rythme circadien

[Dijk et Czeisler, 1995]. Ainsi, lorsque l'horloge biologique est alignée au cycle jour-nuit, le sommeil REM est de plus longue durée lors des heures matinales subjectives, correspondant avec la fin de la période de sommeil nocturne. Le rythme circadien semble aussi agir sur la microstructure du sommeil. En particulier, une plus grande fréquence de fuseaux de sommeil et de l'activité de fréquence sigma sont observées lors des heures de la journée subjective et son nadir se présente lors de la fin de la nuit subjective [Dijk et Czeisler, 1995; Dijk, Shanahan, Duffy, Ronda, et Czeisler, 1997].

La pression homéostatique et le rythme circadien sont, ainsi, deux facteurs qui déterminent la période d'éveil et de sommeil au cours de la journée, ainsi que la structure intégrale du sommeil. Ces deux processus ne sont, toutefois, pas entièrement indépendants. De récentes études ont soulevé une influence réciproque mutuelle entre la pression homéostatique et le rythme circadien sur le sommeil, démontrant ainsi que ces deux processus n'agissent pas seulement de façon additive sur la période et structure du sommeil [Franken, Thomason, Heller, et O'Hara, 2007; Dijk et Archer, 2010; Borbély et Achermann, 1999].

## Les noyaux suprachiasmatiques et leur influence sur le sommeil

L'influence du rythme circadien sur le sommeil provient des connexions entre le SCN et les structures corticales clefs du sommeil, ainsi que l'influence de l'horloge biologique sur les processus physiologiques et endocriniens qui aident à promouvoir l'éveil et le sommeil. Comme illustré à la Figure 4, le SCN projette aux structures corticales associées au maintien de l'éveil et du sommeil. En particulier, la majorité des projections du SCN se fait sur la zone sous-paraventriculaire (SPZ) agissant comme un amplificateur des signaux efférents. Celles-ci projettent, en partie, aux noyaux hypothalamiques dorsomédiaux (DMH) qui envoient un signal

inhibiteur, soit GABAergique, aux noyaux préoptiques ventrolatéraux (VLPO) [Gooley et Saper, 2005]. Le VLPO est fortement connecté, par des projections inhibitrices, au système d'activation réticulaire ascendant qui gouverne le maintien de l'état d'éveil (p. ex. [Gaus, Strecker, Tate, Parker et Saper, 2002]). Les noyaux du DMH projettent aussi, d'autre part, aux neurones orexines de l'aire hypothalamique latérale (LHA) [Gooley et Saper, 2005], une structure jouant un rôle dans le contrôle circadien et homéostatique du sommeil [Deboer, Overeem, Visser, et Meijer, 2004]. Il est suggéré que les neurones du LHA soient, du moins en partie, responsables du contrôle circadien du sommeil REM [Kantor et al., 2009]. Quoiqu'en plus petite concentration, les neurones du DMH, VLPO et LHA reçoivent aussi des projections directes du SCN [Gooley et Saper, 2005]. De ce fait, les signaux efférents provenant du SCN contrôlent l'état d'éveil par l'entremise de l'inhibition du VLPO sur le système réticulaire ascendant et par l'activation des neurones orexines du LHA.

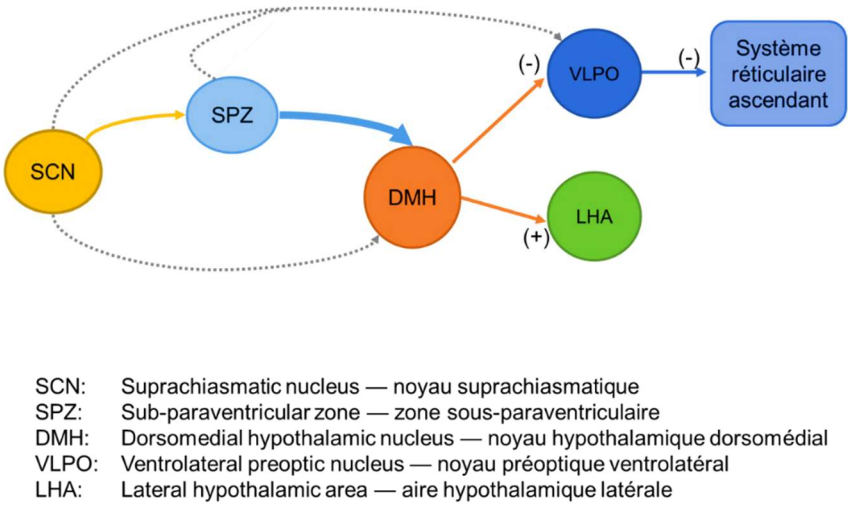


**Figure 4.** Illustration schématique des projections efférentes du SCN associée aux structures clés du maintien de l'éveil et du sommeil.

Le SCN contrôle aussi une gamme de processus physiologiques et endocriniens qui modulent l'état de vigilance et de somnolence [Gooley et Saper, 2005]. Trois facteurs rythmiques spécifiques, soit la mélatonine, le cortisol, et la température corporelle (illustrés à la Figure 5), jouent un rôle particulier dans la régularisation de l'éveil et du sommeil. La mélatonine, une hormone produite par la glande pituitaire, est sécrétée au cours de la nuit, en absence de la lumière (p. ex. [Brzezinski, 1997]). Celle-ci est ainsi considérée comme un indice intrinsèque de la période nocturne environnementale. En contrepartie, le cortisol est sécrété de façon accrue suite à l'éveil et il diminue graduellement au cours de la journée pour atteindre une concentration minimale lors de la nuit [Kreiger, Allen, Rizzo et Kreiger, 1971; Chan et Debono, 2010]. En dernier, la température corporelle est élevée au cours de la journée, elle diminue lors de la fin de la journée subjective et elle atteint son nadir au cours de la nuit subjective [Czeisler et Buxton, 2005]. Ainsi, lorsque ces facteurs sont proprement synchronisés au rythme environnemental, ils permettent le maintien de la vigilance au cours de la journée et de la somnolence au cours de la nuit. Les mesures de la température corporelle et de la mélatonine sont les mesures typiquement employées lors de l'étude du rythme circadien, car celles-ci reflètent vigoureusement l'activité du SCN et elles ne reçoivent peu, ou aucune influence modulatoire additionnelle [Czeisler et Buxton, 2005].

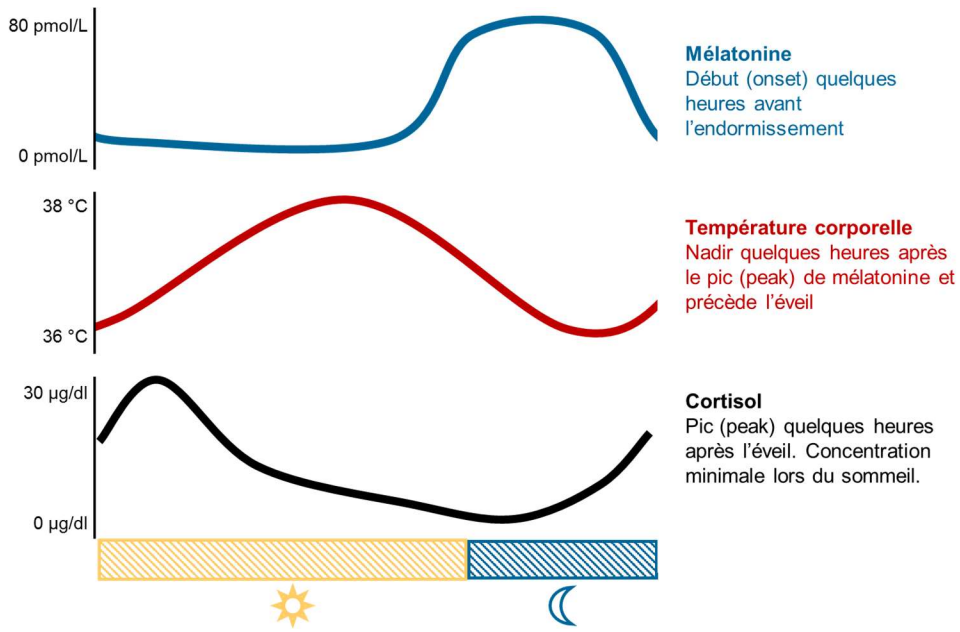


**Figure 5.** Représentation schématique du rythme circadien de la mélatonine, de la température corporelle et du cortisol.

## Synchronisation de l'horloge biologique: rôle de la rétine

Les études de désynchronisation forcée ont aussi révélé une caractéristique particulière du rythme circadien provenant du SCN : lorsque privée de l'information temporelle environnementale, l'horloge biologique exerce sa propre période intrinsèque, qui ne correspond pas exactement à celle de l'environnement, soit de 24 heures. La période circadienne intrinsèque possède une grande variabilité inter-sujet, mais se démontre stable lors de mesures intra-sujets. En moyenne, la période circadienne chez les humains est d'environ 24.2 heures [Czeisler et al., 1999]. La majorité de la population possède une période circadienne plus longue que la période environnementale, tandis qu'une plus petite proportion possède une période plus courte que 24 heures. Ces études soulignent, conséquemment, le besoin constant de synchroniser l'horloge biologique au rythme jour-nuit environnemental. En l'absence d'une telle synchronisation, le

rythme biologique en libre cours continuerait graduellement à se désynchroniser de son environnement. Le corps du SCN est essentiel à la synchronisation de l'horloge et il reçoit des projections afférentes nécessaires pour maintenir une telle synchronisation (Figure 6). Celles-ci incluent des projections glutamatergiques de cellules ganglionnaires de la rétine provenant de la voie rétinohypothalamique (RHT); des projections GABAergiques et de neuropeptides Y du feuillet intergéniculé de la voie géniculo-hypothalamique; et des projections sérotoninergiques des noyaux du raphé mésencéphalique (médial et dorsal) [Gooley et Saper, 2005]. La projection du RHT et des cellules ganglionnaires de la rétine s'avère être à la fois nécessaire et suffisante pour la synchronisation photique du rythme circadien [Johnson, Moore, et Morin, 1988]. Inversement, les projections des noyaux de raphé mésencéphaliques représentent les processus de synchronisation non-photiques qui proviennent du niveau de stimulation et de l'activité motrice [Mistlberger, Antle, Glass, et Miller, 2000; Penev, Turek, et Zee, 1993]. Ces projections sérotoninergiques jouent aussi un rôle dans la régularisation de l'information photique sur le SCN [Rosenwasser et Turek, 2005]. En dernier, le feuillet intergéniculé semble jouer un rôle secondaire dans le maintien du rythme circadien en recevant un agrégat d'informations incluant des projections de la rétine et du raphé mésencéphalique. De plus, la coquille du SCN reçoit, elle aussi, des projections afférentes pouvant aussi jouer un rôle secondaire dans la modulation du rythme circadien. Celles-ci incluent des projections norépinéphrines du locus coeruleus, des projections cholinergiques de prosencéphale basal et des projections histaminergiques de l'hypothalamus postérieur [Rosenwasser et Turek, 2005]. Toutefois, même en considérant toutes les projections afférentes du SCN, l'information photique captée par les yeux s'avère être le facteur principal dans la synchronisation du rythme circadien au cycle jour-nuit de 24-heures

[Duffy et Czeisler, 2009]. Ainsi, la lumière est considérée comme le principal *zeitgeber*, ou minuteur de l'horloge biologique du SCN.

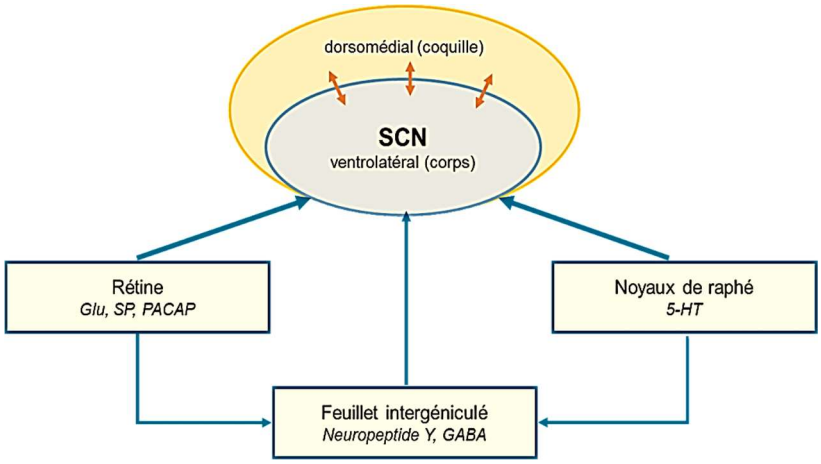


**Figure 6**. Représentation schématique des trois projections afférentes majeures au corps du SCN, soit les projections de la rétine (voie rétinohypothalamique), du feuillet intergéniculé (voie géniculohypothalamique) et des noyaux de raphé. Image basée de la figure 34-3 de Rossenwasser et Turek, 2005.

Les neurones, qui composent le RHT, proviennent d'une sous-catégorie de cellules ganglionnaires de la rétine qui projettent, en majorité, directement au SCN. Les cellules ganglionnaires, qui composent cette voie, se différencient des cellules ganglionnaires du nerf optique et du système visuel classique par leur capacité photoréceptrice. Ces cellules ganglionnaires de la rétine intrinsèquement photoréceptives (*intrinsic photoreceptive retinal ganglion cells*, ou ipRGCs) possèdent le photopigment de mélanopsine, présent dans l'entièreté de la cellule [Fu, Liao, Do et Yau, 2005; Hattar, Liao, Takao, Berson, et Yau, 2002]. La mélanopsine est un photopigment à base de vitamine A qui s'active lentement en réponse à l'irradiation photique et qui possède une affinité pour la longueur d'onde de fréquence de 480 nm, soit de couleur visuelle bleue [Hankins, Peirson, et Foster, 2008]. L'activité de la

mélanopsine s'avère être suffisante pour les capacités photiques de synchronisation du rythme circadien. Toutefois, les ipRGCs reçoivent aussi l'information des photorécepteurs classiques de l'œil, soit les cônes et les bâtonnets, qui jouent un rôle secondaire dans l'information photique projetée au SCN [Hattar et al., 2003].

Les ipRGCs ne composent qu'une minorité (1-3%) des cellules ganglionnaires dans la rétine et ils sont disposés de façon dispersée dans la rétine [Hattar et al., 2002]. Leur arborisation dendritique permet, toutefois, la formation d'un réseau photorécepteur couvrant toute la rétine [Provencio, Rollag, et Castrucci, 2002]. La bifurcation des projections afférentes RHT fait en sorte que chaque rétine énerve les deux noyaux du SCN, avec une petite prédominance de projections controlatérales [Gooley et Saper, 2005]. Les projections du RHT sont glutamatergiques et, au niveau du SCN, modulent de façon directe et indirecte l'expression de la protéine PER (période), une composante cardinale dans la boucle de rétroaction (*feedback loop*) qui génère le rythme circadien [Reppert et Weaver, 2002]. Les neurones du RHT expriment aussi le neuropeptide de substance P et le peptide activant l'adénylate-cyclase hypophysaire qui jouent un rôle secondaire et de support de l'activité glutamatergique dans les neurones du SCN [Rosenwasser et Turek, 2005].

De ce fait, le système visuel classique, ainsi que les ipRGCs de la rétine jouent un rôle important dans le maintien de la synchronisation du rythme circadien au cycle jour-nuit environnemental. Tel qu'abordé dans les prochaines sections, une altération de l'information visuelle pourrait, en conséquence, avoir des répercussions sur le maintien du rythme circadien ainsi que sur la stabilité et la structure du sommeil de l'individu. De plus, un rythme circadien et un sommeil anormal peuvent aussi engendrer des répercussions sur la santé physique et mentale de l'individu. Puisque les aveugles subissent une perte de la perception visuelle, et

souvent une dégradation de la rétine, il s'avère nécessaire de bien comprendre les conséquences de la cécité sur le maintien du rythme circadien et la structure du sommeil.

## Rôle du rythme circadien dans la santé de l'individu

Telle que mentionnée ci-haut, une altération du rythme circadien peut avoir des conséquences sur la période, la qualité et même la structure du sommeil. La désynchronisation du rythme circadien a aussi des conséquences sur le maintien et la santé de l'individu. En particulier, tel que démontré par l'amplitude de la mélatonine, le profil hormonal de l'organisme est atténué lors de rythmes circadiens anormaux [Turner, van Someren, et Mainster, 2010]. La mélatonine, en addition à son rôle d'indicateur de la période nocturne, joue aussi diverses fonctions et possède divers avantages pour la santé [Pandi-Perumal, Srinivasan, Maestroni, Poeggeler, et Hardeland, 2006; Turner et al., 2010]. Par exemple, la mélatonine s'avère être un antioxydant endogène puissant [Benot et al., 1999]. Ainsi, une réduction de cette hormone est observée lors de diverses maladies et cancers [Mishima et al., 1999; Schernhammer et Hankinson, 2005; Turner et al., 2010].

Le rythme circadien influence aussi divers autres processus physiologiques et hormonaux, incluant le maintien du rythme métabolique de l'organisme de par son influence sur l'homéostasie du glucose et la sécrétion d'insuline [Sadacca, Lamia, de Lemos, Blum, et Weitz, 2011; Rudic et al., 2004]. Une perturbation du rythme circadien et du sommeil est, donc, un facteur de risque d'obésité et du syndrome métabolique. De ce fait, le maintien d'un rythme circadien synchronisé au rythme environnemental de 24 heures s'avère important non-seulement pour synchroniser l'éveil et le sommeil, mais nécessaire aussi pour le maintien de la santé de l'organisme.

## Rythmes circadiens chez les aveugles : absence de synchronisation photique

Étant donné le rôle de l'information lumineuse dans le maintien de la synchronisation du rythme circadien endogène au rythme environnemental de 24 heures, les troubles de rythmes circadiens sont fréquemment observés chez les aveugles (p. ex. [Skene et Arendt, 2007; Lewy et Newsome, 1983; Sack, Lewy, Blood, Keith, et Nakagawa, 1992]). Ces anormalités peuvent prendre différentes formes, tel un rythme circadien en libre cours, un rythme synchronisé, mais décalé de sa phase normale (soit un avancement ou un délai de phase), ou une absence de rythme circadien. L'anormalité des rythmes circadiens dans la population aveugle a fait l'objet de diverses études, toutefois, le taux d'incidence de ces anormalités circadiennes demeure imprécis. Il est estimé qu'environ 50-80% des individus avec une cécité présentera un trouble du rythme circadien. Par exemple, Lockley et collègues ont démontré que, dans un groupe de 59 aveugles, 29% avaient un rythme circadien en libre cours, 15% avec un rythme circadien décalé et 5% avec un rythme non-détectable. L'autre moitié, soit 51% des aveugles, présentaient un rythme circadien normal [Lockley, Skene, Butler, et Arendt, 1999]. Cependant, 80% de ces participants ont reporté la présence de troubles du sommeil, suggérant ainsi que le rythme circadien peut, en partie, influencer la qualité du sommeil de ces individus.

De plus, Skene et collègues ont mené une étude sur 67 aveugles, dont 37 avaient une cécité complète de la vision [Skene, Lockley, Thapan, et Arendt, 1999]. Les auteurs ont démontré que la majorité des individus ayant une perception visuelle résiduelle (soit 77%) maintenait un rythme circadien normal et synchronisé au rythme environnemental de 24 heures. Toutefois, l'incidence de rythmes circadiens anormaux était élevée chez les aveugles complets (soit 76%), et que 92% des individus énucléés présentaient un rythme circadien en libre cours. Ainsi, bien que l'étiologie et l'âge de la cécité ne contribuent pas de façon significative à l'occurrence d'un

rythme circadien anormal chez les aveugles, le degré de vision résiduel s'avère être un facteur fondamental dans le maintien du rythme circadien au rythme jour-nuit environnemental.

## Troubles de sommeil chez les aveugles

Puisque la mélanopsine, et non les photorécepteurs classiques, s'avère suffisante pour la synchronisation du rythme circadien, la perte de vision ne cause pas directement une perte de l'information photique transmise au SCN. Toutefois, comme plusieurs études le démontrent, les troubles de sommeil sont fréquemment reportés chez les aveugles. En particulier, Léger et collègues, ont démontré, parmi un grand nombre d'individus aveugles ($n$ = 1073), une plus grande incidence et fréquence de troubles du sommeil [Léger et al., 1999]. Les aveugles ont aussi fait rapport d'un sommeil plus court comparativement au groupe contrôle (ayant une vision normale). Bien que la majorité des troubles reportés sont des symptômes de dysosmie, incluant l'insomnie (voir aussi [Tabandeh et al., 1998]), Léger et collègues ont aussi démontré une plus grande fréquence de parasomnies chez les aveugles, incluant un plus grand nombre de cauchemars. Une telle plus grande fréquence de cauchemars fût aussi reportée par Meaidi, Jennum, Ptito et Kupers [2014]. Les résultats de Tabandeh et collègues [1998] complémentent l'étude de Léger et collègues en évaluant l'index de la qualité du sommeil (par l'emploi du *Pittsburgh Sleep Quality Index*, PSQI) de 384 aveugles, dont 54 n'avaient aucune perception lumineuse. L'index de la qualité du sommeil était plus élevé chez les aveugles que leur groupe contrôle, confirmant ainsi une plus grande fréquence de troubles de sommeil chez les aveugles. De plus, les auteurs ont aussi rapporté une corrélation entre l'intensité des troubles de sommeil, démontrée par le score du PSQI, et le degré de perte de vision, ce qui n'avait pas été significativement observé dans l'étude de Léger et collègues. Les résultats suggèrent, donc, que

les aveugles font état de plus de troubles de sommeil que la population normale. De plus, bien que l'étiologie et l'âge de la perte de vision n'ont peu d'influence sur la présence de troubles de sommeil, la présence résiduelle de vision s'avère être un facteur important, où une plus grande fréquence et intensité de troubles de sommeil sont observée chez les aveugles complets.

Les troubles de sommeil chez les aveugles peuvent être, du moins en partie, expliqués par un manque d'information photique provenant de la rétine et, en conséquence, l'occurrence de rythmes circadiens anormaux (p.ex. [Uchiyama et Lockley, 2015; Flynn-Evans, et al., 2014]). Toutefois, tel abordé dans des études antérieures, les rythmes circadiens anormaux et en libre cours peuvent justifier certains, mais non pas tous les troubles de sommeil reportés par la population aveugle [Moseley, Fouladi, Jones, et Tobin, 1996; Lockley, Skene, Arendt et al., 1997; Lockley, Skene, Tabandeh, et al., 1997; Léger et al., 1999]. En particulier, la présence de troubles de sommeil provient d'une origine multifactorielle. De plus, la présence de rythmes circadiens anormaux n'induit pas directement des répercussions comportementales, telle la modulation du cycle éveil-sommeil et la présence de troubles de sommeil.

## La perte de vision engendre une réorganisation corticale et plasticité compensatoire

La privation sensorielle, telle la cécité, induit aussi des changements anatomiques et fonctionnels au niveau du cerveau. En particulier, une réduction du volume de la matière grise des aires visuelles primaires et associatives ainsi qu'une atrophie de la matière blanche des voies associées au cortex visuel sont observées chez les aveugles congénitaux [Ptito, Schneider, Paulson, et Kupers, 2008; Park et al., 2009; Noppeney, Friston, Ashburner, Frackowiak, et Price, 2005]. Cependant, quoiqu'il y ait une réduction de la matière grise, une augmentation de

l'épaisseur corticale est aussi observée dans plusieurs aires corticales visuelles [Jiang et al., 2009; Wang et al, 2013; Voss et Zatorre, 2012; Park et al., 2009], suggérant ainsi une réduction de l'élagage du cortex visuel (*cortical prunning*) chez ces aveugles [Park et al., 2009]. De Volder et collègues [1997] ont aussi démontré une augmentation de l'activité métabolique en état de repos dans le cortex occipital des aveugles congénitaux. Ces résultats suggèrent que le cortex 'visuel' des aveugles demeure actif même en absence d'information visuelle rétinienne. En particulier, le cortex visuel contiendrait des propriétés amodales qui sont davantage recrutées en absence de l'information visuelle de la cécité ([Harrar, Aubin, Chebat, Kupers et Ptito, 2018], présenté en annexe). Ainsi, diverses études ont démontré une activation du cortex visuel chez les aveugles, en particulier les aveugles congénitaux, lors de tâches 'non-visuelles' qui incluent les autres modalités sensorielles ainsi que des processus cognitifs d'ordre supérieur, tels la lecture braille, le traitement de la parole et la mémoire (voir [Kupers et Ptito, 2014] pour une revue de littérature). Des permutations de l'activité corticale des aveugles furent aussi observées par voie de mesure de l'activité électrophysiologique. En particulier, l'activité de fréquence alpha des dérivations postérieures est notamment modulée chez les aveugles, à la fois lors de l'état de repos et lors de la complétion de tâches cognitives [Noebels, Roth, et Kopell, 1978; Kriegseis, Hennighausen, Rösler, et Röder, 2006; Schubert et al., 2015; Kober, Wood, Kampl, Neuper, et Ischebeck, 2014]. En addition à la modulation des aires corticales visuelles, des différences anatomiques peuvent aussi être détectées dans l'entièreté du cerveau des aveugles [Park et al., 2009; Chebat et al., 2007; Ptito et al., 2008; Fortin et al., 2008], démontrant, ainsi, une réorganisation corticale de grande échelle suite à la perte de vision, particulièrement lorsque celle-ci a lieu au cours des premières années de vie de l'individu.

## Effets de la cécité sur le sommeil : Études antérieures

Malgré la fréquence de troubles de sommeil et de rythmes circadiens anormaux, ainsi que la réorganisation corticale chez les individus avec cécité, le sommeil et sa structure physiologique n'ont été que peu étudiés. De plus, les quelques études relevées démontrent des résultats équivoques et inconsistants. Par exemple, Krieger et Glick [1971] furent les premiers à reporter une réduction, voire même une absence d'activité d'ondes lentes chez un groupe de 5 aveugles tardifs. La durée totale du sommeil, ainsi que les éveils nocturnes ont, toutefois, demeuré non-affectés par l'absence de vision. Des résultats similaires furent observés chez cinq individus avec une déficience visuelle [Hono, Hiroshige et Miyata, 1999] et aveugles [Hono, Hiroshige, et Miyata, 2000] et plus récemment chez un groupe de 10 aveugles avec aucune perception visuelle résiduelle [Ayala-Guerrero et Mexicano, 2015]. Ces résultats ne sont, cependant, pas observés dans toutes les études (p. ex. [Léger, Guilleminault, Santos, et Paillard, 2002]) ni parmi tous les participants d'une même étude.

L'étude de Hono et collègues [2000] a aussi démontré une réduction globale de la durée du sommeil de stade N2 ainsi qu'une réduction de la densité de fuseaux de sommeil au cours de la nuit. Toutefois, ces résultats contredisent les résultats de Scrofani et collègues [1996] qui ont démontré un plus grand nombre de fuseaux de sommeil lors du stade N2 chez des individus atteints de privation sensorielle, soit la perte de vision ($n = 4$) ou la surdité ($n = 4$). Ces auteurs ont suggéré que l'augmentation de la présence de fuseaux de sommeil serait le résultat d'une altération de l'interaction entre les neurones sensoriels ascendants et le système neuronal d'éveil et de sommeil au niveau du thalamus. Ainsi, la réduction de l'influx sensoriel ascendant, résultant de la cécité, permet une synchronisation thalamo-corticale plus stable ce qui, en conséquence, amplifie la présence de fuseaux lors du sommeil. Ces résultats suggèrent ainsi que

la cécité et les modulations corticales associées peuvent potentiellement altérer la physiologie du sommeil chez les aveugles. Toutefois, ces études ne font mention d'une mesure du rythme circadien sous-jacent. Plus particulièrement, tel que mentionné ci-haut, un rythme circadien anormal est fréquemment observé chez les aveugles (p. ex. [Lockley et al., 1999]), et celui-ci est un facteur affectant la durée et la structure du sommeil, particulièrement le sommeil REM [Czeisler et al., 1980].

Au début des années 1990, une étude de cas fut menée chez un aveugle tardif ayant un rythme circadien en libre cours, d'une période d'environ 24.25 heures, et qui tentait de maintenir un cycle éveil-sommeil et un rythme social de 24 heures [Klein et al., 1993]. L'étude a démontré une modulation de l'architecture du sommeil similaire aux études de désynchronisation forcée [Czeisler et al., 1980; Strogatz, Kronauer, et Czeisler, 1986]. Plus précisément, une variation de la latence du sommeil, du temps total de sommeil, ainsi que la latence et la quantité de sommeil REM furent déterminés par la phase du rythme circadien, tel que mesuré par la température corporelle. Léger et collègues [2002] ont aussi démontré une modulation du sommeil REM parmi un groupe de 26 aveugles n'ayant aucune perception lumineuse, un réflexe pupillaire et un électrorétinogramme négatif. De plus, les participants reportaient des troubles de sommeil, particulièrement des épisodes cycliques d'insomnie. Un cycle circadien en libre-cours fût confirmé chez ces individus par l'analyse de la sécrétion de mélatonine. Similairement aux résultats de Klein et collègues, mais contrairement à d'autres études [Krieger et Glick, 1971; Hono et al. 1999; 2000; Ayala-Guerrero et Mexicano, 2015], Léger et collègues ont démontré une réduction du temps total et de l'efficacité du sommeil chez les aveugles, comparativement au groupe contrôle. De plus, aucune différence significative ne fût observée entre les deux groupes pour la proportion de sommeil lent-profond. Une augmentation de la latence et une

diminution de la durée du sommeil REM furent, toutefois, démontrées en comparaison à un groupe contrôle ayant une vision normale. Les auteurs proposent que la réduction du sommeil REM observée chez les aveugles dérive de la désynchronisation du rythme éveil-sommeil et du cycle circadien sous-jacent, tel supporté par des études antérieures (p. ex. [Czeisler et al. 1980]). Cependant, l'absence d'une mesure de la concentration de la mélatonine lors de l'enregistrement des données PSG limite la confirmation d'une telle hypothèse.

Ces études, quoiqu'elles présentent une diversité de résultats, parfois même contradictoires, soulèvent deux mécanismes neuronaux, qui surviennent lors de la cécité, pouvant provoquer une altération de la physiologie du sommeil chez les aveugles; la réorganisation corticale suite à la perte de vision, et l'altération du rythme circadien. Ces études présentent, toutefois un nombre de facteurs limitants, notamment un petit nombre de participants, une absence d'un groupe contrôle, l'utilisation de techniques et de mesures datées, ainsi que le manque d'un marqueur de la phase du rythme circadien. Ainsi, les études de cette présente thèse visent à différencier l'impact de ces deux mécanismes neuronaux sur le sommeil des aveugles.

## Objectifs et hypothèses

L'objectif principal de cette présente thèse est d'évaluer les effets de la cécité sur le rythme circadien et la physiologie du sommeil. Spécifiquement, l'étude a pour but de confirmer la présence d'une plus grande fréquence de rythmes circadiens anormaux chez les personnes aveugles, et que celle-ci soit corrélée avec la présence de troubles du sommeil et la perturbation du cycle éveil-sommeil. De plus, la physiologie du sommeil, incluant sa macro- et microstructure fut examinée en contrôlant la phase du rythme circadien. Ceci permet ainsi de détecter les changements au niveau de l'activité corticale lors du sommeil qui seraient associés à la perte de vision en tant que telle, ainsi que les changements physiologiques du sommeil provenant d'une perturbation du rythme circadien. Ainsi, les différentes études qui font l'objet de cette présente thèse ont pour but de complémenter les résultats des études antérieures et d'approfondir les connaissances sur l'influence de la cécité sur le sommeil.

L'importance de cette étude est exprimée par l'augmentation de la déficience visuelle dans la population. En particulier, quoique les avancements en médecine réduisent l'incidence de la cécité à la naissance, la déficience visuelle tardive est à la hausse dans les sociétés occidentales de par le prolongement de l'espérance de vie et de l'accroissement du taux de diabète. Il est estimé que plus de 75% de la population aveugle, soit près de 156 millions de personnes, est âgée de plus de 50 ans [Gordois et al., 2012]. Tel que résumé dans la section précédente, les altérations du rythme circadien et la déficience du sommeil provoquent des séquelles sur le bien-être de la personne, autant au niveau physiologique que psychologique. Ainsi, il s'avère nécessaire de bien comprendre les effets de la cécité sur ces deux dimensions, afin de minimiser les séquelles chez ces individus ainsi que lors du vieillissement.

## Plan général de l'étude et inclusion de participants

Le projet de recherche se compose de différentes étapes permettant une étude comparative des différentes composantes du sommeil et du rythme circadien chez un groupe d'aveugles et un groupe contrôle, dont les participants ont une vision normale ou corrigée à la normale. Trois composantes principales de l'étude peuvent être soulignées, soit une analyse longitudinale du rythme éveil-sommeil au cours de 30 jours consécutifs, une analyse biochimique des marqueurs de la phase du rythme circadien et une investigation de l'électrophysiologie du sommeil. Ces analyses furent, de plus, complémentées par divers questionnaires permettant l'étude de facteurs connexes, tel le chronotype, ainsi qu'une mesure de la qualité de leur sommeil. Ces études furent menées sur un groupe de 11 aveugles et 11 sujets contrôle. Ces mêmes participants furent utilisés au travers de toutes les étapes du présent projet, permettant ainsi d'évaluer ceux-ci autant pour les mesures comportementales, que biochimiques et électrophysiologiques. Le groupe aveugle était composé d'un groupe d'individus dont l'origine de la cécité est mixte. Environ la moitié de ces participants, soit 5, sont aveugles depuis la naissance tandis que l'autre moitié, soit 6, ont atteint la cécité au cours de leur vie. Dans tous les cas, l'origine de la cécité provenait d'une source périphérique, soit de la rétine ou du nerf optique. De plus, tous les participants du groupe aveugle reportaient n'avoir aucune perception de lumière. Un critère important pour l'inclusion des participants, autant pour le groupe aveugle que pour le groupe contrôle, était une absence de perturbations médicales, psychiatriques, ou pharmacologiques. Cette pré-sélection fut accomplie par un processus de dépistage rigoureux, ayant pour but d'exclure tout facteur potentiel, telle la présence d'apnée du sommeil, pouvant altérer le rythme circadien et/ou la qualité du sommeil. Ainsi, autre que la perte de vision, les participants, qui constituent les deux groupes de ce projet, se présentaient en bonne santé.

## Hypothèses et justifications des méthodes

Les études, qui ont découlé de ce projet de recherche, ont ainsi permis l'investigation de diverses hypothèses portant sur le sommeil et les rythmes circadiens des personnes aveugles en comparaison avec un groupe contrôle dotée d'une vision normale. Ces études ont fait l'objet de diverses publications scientifiques qui seront présentées dans le prochain chapitre. Cette prochaine section décrit les quatre hypothèses de l'étude, résume la méthodologie employée et les articles connexes.

### *i. Une plus grande incidence de troubles de sommeil se voit chez les aveugles.*

Une plus grande fréquence de troubles de sommeil est typiquement reportée dans la population aveugle [Tabandeh et al., 1998; Léger et al., 1999]. L'étiologie ainsi que l'âge de la cécité ne semblent être des facteurs modulateurs pour la présence de ces troubles du sommeil. Toutefois, les troubles de sommeil sont plus fréquemment observés chez les individus avec une cécité complète [Tabandeh et al., 1998]. Le premier article de cette thèse, soit *Altered sleep-wake patterns in blindness: A combined actigraphy and psychometric study*, vise à confirmer l'incidence des troubles du sommeil dans notre groupe d'aveugles. La présence de troubles du sommeil fut mesurée par l'index de la qualité du sommeil, le *Pittsburgh Sleep Quality Index* (PSQI). De plus, la présente étude a pris en considération des facteurs autres pouvant aussi contribuer à une incidence plus élevée de troubles du sommeil, tel que le chronotype (*Morningness-Eveningness Questionnaire*, MEQ) et les conditions de vie des participants, incluant leur emploi, leur vie familiale, etc. Cette première investigation permettrait de corroborer les études antérieures qu'il y a, effectivement, une plus grande incidence de troubles du sommeil chez les personnes aveugles, mais que celle-ci n'est pas nécessairement observée

chez tous les individus ayant perdu la vision. Ainsi, une plus grande proportion et une plus grande sévérité d'un sommeil perturbé seront observées chez les participants aveugles, déterminés par le score PSQI, comparativement à l'échantillon d'individus ayant une vision normale ou corrigée à la normale.

### *ii. Les aveugles ont une plus grande variabilité dans leur période de sommeil.*

En lien avec une plus grande incidence de troubles de sommeil et de rythmes circadiens en libre cours chez les aveugles, il peut être attendu que la stabilité de la période de sommeil serait, elle aussi, altérée chez ces individus. Particulièrement, la période de sommeil, ainsi que son efficacité seront, en moyenne, réduite chez les individus aveugles, et ceci serait particulièrement présent chez ceux qui rapportent une présence de troubles de sommeil. De plus, en lien avec l'anormalité du rythme circadien, et en particulier pour les rythmes circadiens en libre cours, une plus grande variabilité de la période de sommeil serait observée et celle-ci serait corrélée avec l'incidence de siestes [Lockley, Skene, Tabandeh, et al., 1997]. Afin de confirmer une telle hypothèse, une mesure d'activité et de sommeil fut enregistrée par la méthode d'actigraphie pour une durée de 30 jours. Ces enregistrements furent complémentés avec des journaux de sommeil, complétés chaque jour par les participants pour indiquer la période et la qualité de leur sommeil. Les résultats de cette étude sont détaillés dans le premier article de cette thèse en concordance avec la première hypothèse. Ainsi, les tendances et la variabilité du cycle éveil-sommeil et de l'efficacité du sommeil furent examinées au cours d'une période de 30 jours. De plus, le lien entre la période moyenne du sommeil et le chronotype fut observé. La corrélation entre les troubles du sommeil reportée par le PSQI et la variabilité de la période et l'efficacité du sommeil au cours des 30-jours furent aussi examinées.

### *iii. L'incidence d'une phase anormale du rythme circadien est plus élevée chez les aveugles comparativement au groupe contrôle.*

La présence de rythmes circadiens en libres cours est fréquemment observée dans la population aveugle, en particulier ceux avec une cécité complète [Skene et Arendt, 2007]. En particulier, il est estimé qu'au moins la moitié des aveugles ont un rythme circadien anormal. Ainsi, une investigation des profils circadiens de la mélatonine et du cortisol a fait objet de la deuxième étude de cette présente thèse, soit *Melatonin and cortisol profiles in the absence of light perception*. Des échantillons de salive furent collectés à intervalle de 2 heures et la concentration de la mélatonine et du cortisol en furent dérivés afin de déterminer leur profil au cours d'une période de 24 heures. En particulier, le début de la sécrétion de mélatonine (*melatonin onset*), la réponse à l'éveil du cortisol (*cortisol awakening response*), la concentration moyenne de ces hormones, ainsi que l'interaction de ces deux hormones furent examinés. Telle suggérée par la littérature antérieure, une plus grande proportion de phase circadienne anormale, déterminée par la sécrétion de mélatonine, sera observée chez les aveugles, comparativement au groupe contrôle. De plus, il sera attendu que la réponse à l'éveil du cortisol sera, elle aussi, altérée chez les personnes aveugles. Ainsi, parmi les individus aveugles, il y aura une plus grande proportion de désynchronisation de la phase circadienne, mais que les deux marqueurs biologiques demeureront reliés.

### *iv. La macro- et microstructure du sommeil demeurent largement préservées chez les aveugles. Toutefois, l'activité corticale reflètera aussi la réorganisation corticale associée avec la cécité.*

Une étape importante de la présente étude est d'examiner la macrostructure et la microstructure du sommeil des aveugles tout en contrôlant pour la phase du rythme circadien. Une mesure de la phase du rythme circadien, soit le début de la sécrétion de mélatonine, telle

que décrite à la section précédente, fut déterminée pour chaque participant et classifiée en 4 catégories; soit une phase normale, un délai de phase, une phase décalée (*shifted phase*), ou une phase non-classifiée. La physiologie du sommeil fut examinée par l'enregistrement polysomnographique performé au laboratoire du Danish Center for Sleep Medicine à Glostrup (Danemark). Les données PSG ont été analysées suivant les critères de l'AASM [Iber et al., 2007; Berry et al., 2015] afin de quantifier la macrostructure du sommeil, incluant les stades de sommeil NREM (N1, N2, et N3) et le sommeil REM. Celle-ci est détaillée dans le troisième article, soit *Sleep structure in blindness is influenced by circadian desynchrony.* Il est attendu que la macrostructure du sommeil demeurera généralement préservée chez les participants aveugles, mais que la phase du rythme circadien aura une influence sur son architecture, notamment la proportion de sommeil REM. La microstructure du sommeil fut aussi examinée par l'emploi de méthodes d'analyses développées par le Danish Center for Sleep Medicine en collaboration avec le Danish Technical University. L'état de la microstructure du sommeil des aveugles fut sujet du quatrième et dernier article de la présente thèse, soit *Sleep microstructure is largely preserved in blind individuals.* Puisque l'absence de vision, particulièrement lorsque celle-ci a lieu tôt dans la vie, génère une réorganisation corticale, il est attendu que les composantes associées au système visuel, soit directement ou indirectement, seront modulées chez les aveugles.

## Contribution des auteurs

Le projet de recherche qui fait sujet de cette thèse fut réalisé en collaboration avec le Brain Research and Integrative Neuroscience Laboratory (BRAINlab) et le Danish Center for Sleep Medicine de l'Université de Copenhague. Cette prochaine section résume la contribution des

auteurs pour chacun des articles qui ont fait l'objet de cette thèse. Pour l'entièreté du projet de recherche, la mise au point du protocole a été faite par l'entremise d'une collaboration entre Sébrina Aubin, M.Sc.; Prof. Maurice Ptito, MD, PhD; Prof. Ron Kupers, PhD; Prof. Tore Nielsen, PhD; et Dr. Poul Jennum, MD, PhD. Les initiales du nom des auteurs sont utilisées au cours de cette prochaine section.

**Article 1.** ***Altered sleep-wake patterns in blindness: A combined actigraphy and psychometric study***

SA fut responsable du dépistage des participants, de la collecte de données, de l'analyse (avec l'assistance de CG, étudiante de stage de Grenoble INP), de l'interprétation des données ainsi que l'écriture du manuscrit. SA, RK, MP, et PJ ont fait la critique, la correction et la révision du manuscrit.

**Article 2.** ***Melatonin and cortisol profiles in the absence of light perception***

SA, avec l'assistance de 2 étudiants de l'École de médecine de l'Université de Copenhague, a collecté les échantillons de salive. L'analyse des concentrations moléculaires de la mélatonine et du cortisol fut complétée par une analyste du Département de biochimie clinique de l'Hôpital Glostrup-Rigshospitalet au Danemark. L'interprétation des résultats et l'écriture du manuscrit furent complétées par SA. Une critique et la révision du manuscrit furent complétées par SA, MP, RK, et PJ.

**Article 3.** ***Sleep structure in blindness is influenced by circadian desynchrony***

La collecte de données de polysomnographie fut complétée par SA avec l'assistance de deux étudiants de l'École de médecine de l'Université de Copenhague. L'analyse des données fut

complétée par SA, suivant les règles de l'AASM, et supervisée par une analyste en polysomnographie du Danish Center for Sleep Medicine. SA a interprétée les résultats et elle a écrit le manuscrit connexe, qui fut révisé et corrigé par TN, PJ, RK et MP.

**Article 4.** ***Sleep microstructure is largely preserved in blind individuals***

Les données de l'article 3 ont été utilisées à nouveau pour l'article 4. La microstructure du sommeil fut analysée par SA et JAEC et les résultats furent interprétés par SA. Le manuscrit fut écrit par SA, dont la méthodologie écrite avec l'assistance de JAEC. Une critique et la révision du manuscrit furent performées par MP, RK, PJ et TN.

**Autres contributions.** ***The multisensory blind brain***

Tel abordé dans la revue de littérature, l'auteur de cette présente thèse a aussi participé à des collaborations additionnelles quant au sujet de l'effet de la cécité sur divers processus cognitifs. En particulier, SA a collaboré à l'écriture du chapitre intitulé *The multisensory blind brain* dans le livre *Mobility of visually impaired people : Fundamentals and ICT assistive technologies*. Ce chapitre est présenté à l'Annexe I.

# CORPS DE L'OUVRAGE

# Article 1

# Altered sleep-wake patterns in blindness: A combined actigraphy and psychometric study

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# Altered sleep-wake patterns in blindness: A combined actigraphy and psychometric study

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**Abstract**

Objective: Light plays an important role in the synchronization of the internal biological clock and the environmental day/night pattern. Thus, absence of vision is often associated with both increases in reported sleep disturbances and incidence of free-running circadian rhythms. In this study, we discuss variability in the sleep–wake pattern between blind and normal-sighted individuals. Methods: Thirty-day actigraphy recordings were collected from 11 blind individuals without residual light perception and 11 age- and sex-matched normal-sighted controls. From these recordings, we extracted parameters of sleep and wake, including episodes of rest, day-time and night-time sleep periods, and the number of awakenings throughout sleep. A measure of sleep efficiency was derived from these measures for each night-time sleep episode. We also examined complementary measures of sleep quality, using the Pittsburgh Sleep Quality Index, and chronotype, using the Morningness-Eveningness Questionnaire. Results: Although no group differences were found when averaging over the entire recording period, we found a greater variability throughout the 30-days in both sleep efficiency and timing of the night-time sleep episode in blind participants as compared to sighted control participants. We also confirm previous reports of reduced sleep quality in blind individuals. Notably, the variability in sleep efficiency and in the timing of sleep correlated with the severity of sleep disturbances. Conclusion: The timing and physiology of sleep are strongly dependent on the endogenous circadian phase; therefore, observed findings support the hypothesis of free-running circadian rhythms as a dominant factor for the sleep disturbances experienced in blindness.

**Keywords** Blindness; Actigraphy; Circadian rhythms; Sleep efficiency; Sleep disturbances; Light perception; Chronotype; PSQI; MEQ

## 1. Introduction

Circadian control over sleep–wake patterns is a frequently studied phenomenon. Particularly, the use of a forced desynchrony protocol (originally defined by Kleitman [1]) has shown that, when sleep is attempted at an irregular phase of the circadian rhythm, sleep latency and awakenings are increased, and overall sleep time is decreased [2–4]. Additionally, the underlying sleep structure, such as rapid-eye movement (REM) sleep, and its microstructure, e.g., sleep spindles, are also dependent on the circadian phase [5–7].

The master biological clock, located in the suprachiasmatic nucleus (SCN) [8], and associated circadian rhythms are kept synchronized to the environmental 24-hour day/night cycle through various zeitgebers, or time cues. In humans, as with most mammalian species, light is the primary zeitgeber for circadian entrainment through the direct projections of the melanopsin containing retinal ganglion cells to the SCN via the retinohypothalamic tract [9,10]. In the absence of light, endogenous circadian rhythms become free-running, resulting in a temporal deregulation of the biological clock from the 24-hour environmental and social day-night schedule.

Therefore, it comes with no surprise that blind individuals report more sleep disturbances than their normal-sighted counterparts, particularly regarding symptoms of insomnia [11,12]. Moreover, the presence and intensity of sleep disturbances are dependent on the presence of residual vision; totally blind individuals, without residual light perception, report greater sleep disturbances than those with residual vision [13]. In addition, blind individuals also show a higher proportion of free-running circadian rhythms [14], as measured by changes in melatonin concentration and core body temperature. It is estimated that approximately half of the totally blind population has free-running circadian rhythms, while the remaining displays either

normally or abnormally (advanced or delayed) entrained rhythms [15]. Similar to overall sleep disturbances, free running circadian rhythms are more prevalent in blind individuals with no light perception [2,16,17]. Blind individuals in whom the non-photic retinohypothalamic tract is absent – as is the case of enucleated people – have a higher prevalence of free-running rhythms compared to non-enucleated blind individuals [18]. As most peripheral retinal diseases cause a degeneration of the optic nerve, including the optic chiasm (i.e., [19,20]), these may also be associated with an atrophy of the retinohypothalamic tract, with the exception of a few rare cases where this 'non-visual' tract is fully preserved [21]. Consequently, blindness from central origin, or lesions occurring posterior to the lateral geniculate nucleus, should have only limited influences on circadian rhythms.

These studies, both in blind and normal-sighted individuals, highlight the intrinsic relation between light input, sleep quality, and sleep–wake patterns. However, it is important to underscore some discrepancies between free-running circadian rhythms and reported sleep disturbances. Although persons with free-running circadian rhythms also tend to report more sleep disturbances, some do not express any complaints regarding their sleep quality [18,22]. On the other hand, the presence of sleep complaints in the blind population does not necessarily imply that they have free-running circadian rhythms [12].

The aim of the present study was to further examine how the sleep–wake pattern is altered in a well-characterized group of blind individuals without residual light perception. We focused on the variability in the sleep–wake pattern over an extended sampling period. Actigraphy and sleep diaries have been suggested as complementary measures to medical interviews; polysomnographic recordings are also suggested as complementary measures for the assessment of sleep disorders, particularly for the diagnosis of sleep– wake circadian rhythm disorders. Yet,

this method has seldom been utilized in sleep studies of blind individuals. In our study, we used continuous actigraphy (30 days) to isolate particularities of the sleep– wake pattern in blind individuals. More specifically, we examined both the average and the variability across the recording period. Actigraphy was complemented by measures of general sleep quality and chronotype to better understand and explain the sleep–wake patterns in blindness. To the best of our knowledge, this is the first study using actigraphy data collected over an extended period of time to investigate variability in sleep–wake patterns of blind individuals.

## 2. Methods

### 2.1. *Participants*

Data were collected from 11 blind individuals with no self reported conscious light perception ($M_{age}$: 44.5 ± 14.9; three males; all right-handed). In all cases, blindness was of peripheral origin (retina or optic tract). Approximately half of the group was born blind (5/11) while the remaining (6/11) became blind throughout life. Eleven age- and sex-matched individuals (normally sighted; $M_{age}$: 43.4 ± 14.2; four males; two left-handed) with normal or corrected to normal vision were also recruited. Table S1 (Supplementary file) reports the demographic information of the participants. Each participant provided written informed consent for participation. The Regional Capital Research Ethics Committee of Denmark (De Videnskabsetiske Komiteer, Region Hovedstaden, Denmark) approved the study (H-2-2014-081). None of the participants reported having neurological or psychiatric disorders. Purported presence of depression and anxiety was tested using the Beck Depression Index and the Hospital Anxiety and Depression Scale. Participant screening also included a structured medical interview and one night of cardiac, respiratory, and movement monitoring (CRM; similar to Level III sleep studies) in order

to rule out severe sleep apnea (apnea–hypopnea index, AHI > 15) or excessive limb movements that may interfere with sleep–wake patterns. Additionally, we screened for the presence of REM-Sleep Behavior Disorder (RBD) and excessive daytime sleepiness using the RBD screening questionnaire (RBDSQ) and the Epworth Sleepiness Scale, respectively. Participants also reported having regular sleep–wake schedules (i.e., no shift work), and had not been traveling across time zones in the month prior to the experimental trial. The participants taking sleep medication ($n = 4$) were asked to refrain from doing so, starting one week prior to the start of the trial until the end of the study period. This was done to ensure that the natural endogenous rhythm would be expressed throughout the trial. All participants were compliant with this constraint, except for one who resumed taking sleep medication during the last week of the trial. These days were excluded from the analysis for this participant. In addition to age and sex, additional factors of interest included work status and child care, because they contribute to the regularity and stability of sleep–wake patterns.

### 2.2. *Actigraphy*

In order to measure shifts in the sleep–wake cycle over time, participants wore an actigraph (Actiwatch Spectrum, Philips Respironics, Murrysville, PA, USA) for a period of 30 days. Watches were worn continuously throughout this period but were removed if there was a risk of getting the watch wet (e.g., taking a shower) or if it caused interference with daily activities (e.g., playing a sport). Actigraphy recordings were complemented by daily sleep and activity logs in which participants reported pertinent information about their sleep (such as the time they went to bed, the number and duration of night-time awakenings, etc.) and daily activities (e.g., napping and irregular activities, such as parties).

Activity and photic light recordings were sampled in one-minute epochs, for a total of 1440 samples per day. From these recordings, activity states (active, rest, and sleep) were automatically detected using the validated default settings of Respironics Actiware (version 5.70.1, Actiwatch Communication and Sleep Analysis Software, Philips Respironics). Default settings included an activity threshold-crossing zone method (40 activity counts) which was used to determine active epochs (for definition and comparison of activity count measures, we refer to Reference [23]). Sleep onset was marked following ten minutes of inactivity and sleep offset was marked when at least ten minutes of activity was detected within the non-active, rest period. Two investigators (SA and CG) crosschecked recordings for artifacts and correspondence with the daily sleep logs. Manual adjustments of the sleep–wake activity were based on event markers, activity patterns, photopic measures, and sleep diaries. Nights with missing data, or that were marked as irregular by the participant (travel, festivities, etc.) were excluded from analysis. The two nights spent at the sleep center during the experimental period were also excluded from the analysis. Recording malfunction occurred for one of the blind participants, resulting in only 12 days of recordings for this participant. In total, an average of 25.2 days was kept for blind participants and 26.3 days for sighted controls.

The various parameters that were extracted from the actigraphy data to assess sleep efficiency and sleep–wake patterns are listed in Table 1. We limited the parameters of interest to the timing of sleep (onset and offset), the occurrence of day-time naps, and the measure of night-time sleep efficiency, as well as its associated sub-measures: time in bed (TIB), total sleep time (TST), and awakenings throughout the sleep period (wake after sleep onset; WASO). Sleep efficiency (SE) represented the proportion of time spent sleeping during the period where the participant was resting, with 100% indicating complete sleep efficiency, meaning the individual

slept for the entire rest period. This measure therefore takes into account not only the number of awakenings during sleep but also the latency of sleep onset and morning awakenings. We compared both the average of these parameters as their variability over the entire recording period. As the timing and duration of sleep has previously been shown to vary with circadian phase [2], variability of the nighttime sleep parameters throughout the 30-day period is a useful measure of sleep quality. Measures of variability were calculated by taking the difference between the largest and smallest values (range) for each variable within the 30-day period. For example, the range of night-time awakenings refers to the difference between the night with the highest and the lowest WASO occurrences for each participant. We also tested for other measures of variability based upon the inter-quartile range, standard deviation, and variance (not reported), all of which yielded very similar results.

**Table 1.** Description of the various daily sleep parameters extracted from actigraphy recordings.

| Sleep Parameter | Description |
|---|---|
| Rest Period / Time in bed (TIB) | Period of reduced activity, reflecting the period where the individual was lying down |
| Sleep Onset | Time at which the individual fell asleep |
| Sleep Offset | Time at which the individual woke up |
| Total Sleep Time (TST) | Duration (min) between sleep onset and offset |
| Wake After Sleep Onset (WASO) | Duration (min) of awakenings during the sleep period |
| Nap | Frequency and duration of sleep activity occurring outside of the night-time sleep period |
| Sleep Efficiency (SE) | SE = [ (TST – WASO) / TIB ] * 100% |

### 2.3. *Questionnaires*

Chronotype was assessed using the Morningness-Eveningness Questionnaire (MEQ) [24]. This questionnaire consists of 19 items, containing both Likert and time-scale questions [25], in which the participant indicates his or her temporal preferences for undertaking various activities and overall feelings of sleepiness and alertness throughout the day. The resulting MEQ score (sum of each individual question) is used for classification within one of five chronotype categories: Definite Evening (DE), Moderate Evening (ME), Neither (N), Moderate Morning (MM), and Definite Morning (DM).

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) [26]. The PSQI consists of 19 self-rated questions to assess the general sleep quality (global PSQI score) derived from seven components of sleep quality: subjective sleep quality, duration, disturbances, latency, habitual efficiency, associated daytime dysfunctions, and use of sleep medication. Global PSQI scores were measured for each participant and compared between groups.

Both the MEQ and PSQI were completed at the sleep center during the experimental period. Questionnaires were verbally administered to blind participants, and completion of the questionnaires was supervised for the sighted participants.

### 2.4. *Statistical Analysis*

We used Welch's unequal variance *t*-tests to compare the blind and sighted groups for measures of sleep quality, sleep efficiency, timing of the night-time sleep episodes, and the occurrence of daytime naps. Mean and standard error of the mean (±SE) are also reported in summary of these comparisons. Multivariate analysis of variance was used to identify differences between the blind and sighted groups for the underlying sleep parameters used to

measure sleep efficiency, including TIB, TST, and WASO. Pearson's correlations were conducted to test for linear relationships between the various measures. All measures were compared against a 95% statistical significance threshold ($p < 0.05$).

## 3. Results

As no differences were detected between the congenitally and late blind participants for any of the outcome variables described below, the data of the two groups were pooled to increase statistical power. Thus, results reported below examine differences between blind (congenitally and late blind combined) and sighted controls. There were no demographic differences between the blind and sighted groups, either in age distribution [$t(20) = 0.09$, $p = 0.93$], sex, work status, or child care (Supplementary Table S1). Moreover, none of the participants had infant children (below three years of age) under their care.

Table 2 summarizes the mean value (±SE) of the components of the sleep–wake pattern, sleep quality, and chronotype for both the blind and sighted groups. Group differences and associated correlations are described below.

**Table 2.** Mean (± SE), and comparative statistical value for the various measures of characteristics of sleep between the blind and sighted sample.

| | | Blind | Sighted | *p* value |
|---|---|---|---|---|
| | **MEQ score** | 54.1 (± 3.6) | 54.2 (± 3.5) | *n.s.* |
| | **Global PSQI** | 7.9 (± 1.4) | 4.5 (± 0.8) | .03* |
| **Average** | **SE (%)** | 82.9 (± 1.4) | 82.8 (± 1.7) | *n.s.* |
| | **TIB (min)** | 488.4 (± 21.9) | 506.3 (± 2.8) | *n.s.* |
| | **TST (min)** | 402.5 (± 15.7) | 419.7 (± 19.3) | *n.s.* |
| | **WASO (min)** | 50.5 (± 7.0) | 57.9 (± 6.8) | *n.s.* |
| **Range** | **SE (%)** | 36.1 (± 5.5) | 20.6 (± 1.9) | .02 |
| | **TIB (min)** | 354.7 (± 36.3) | 265.7 (± 30.4) | *.08* |
| | **TST (min)** | 332.6 (± 30.3) | 251.4 (± 27.0) | *.06* |
| | **WASO (min)** | 123.4 (± 20.5) | 99.2 (± 11.4) | *n.s.* |
| | **Nap (#)** | 6.7 (± 1.5) | 6.7 (± 2.8) | *n.s.* |
| | **Nap (min)** | 351.4 (± 95.9) | 300.1 (± 123.5) | *n.s.* |
| **Range** | **Sleep Onset (min)** | 323.1 (± 43.5) | 238.5 (± 21.7) | *n.s.* |
| | **Sleep Offset (min)** | 355.0 (± 32.0) | 260.6 (± 25.5) | .03 |

* one-tailed statistical significance; *n.s.* non-significant statistical difference

3.1. *Sleep Quality – PSQI*

Fig. 1 illustrates the distribution of global PSQI scores for each group. In line with our expectations, the global PSQI scores of blind individuals were higher than those of normally sighted controls, $t(20) = 2.11$, $p = 0.03$ (Table 2). The majority of blind individuals (7/11) obtained a global PSQI above the clinical threshold for sleep disturbances (PSQI > 5), while this was only the case for a minority (3/11) for the sighted controls. Moreover, the blind group also showed a greater distribution in reported sleep disturbances. A mild level of sleep disturbance was observed in approximately one third (4/11) of the blind individuals (PSQI between six and eight), while approximately the same frequency of blind participants (3/11) reported severe sleep disturbances (PSQI > 12). Of the remaining blind individuals, the majority (3/4) fell just under the clinical threshold for disturbed sleep (PSQI = 5).

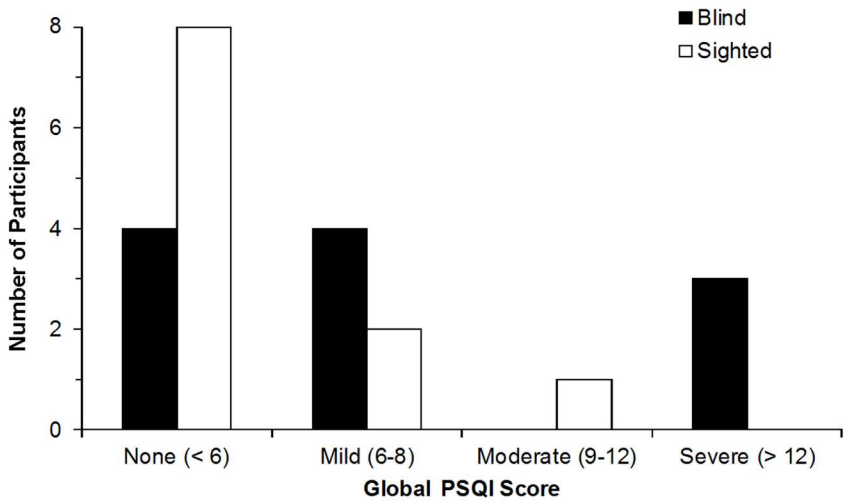


**Figure 1.** Distribution of global PSQI scores for the blind and the sighted group. Categorisation of sleep disturbance severity from the global PSQI score (none, mild, moderate, severe) is based on Tabandeh et al., 1998.

3.2. *Sleep Efficiency*

Table 2 reports the sleep parameter means for the blind and sighted groups. There were no significant group differences in the average measure of sleep efficiency, $t(20) = 0.04$, $p = 0.97$. Moreover, a multivariate analysis failed to reveal differences for any of the sub-measures of sleep efficiency [Pillai's Trace: 0.16, $F(3,18) = 1.16$, $p = 0.35$]. Correlations between the averaged sleep parameters: time in bed, total sleep time, duration of night-time awakenings, and night-time sleep efficiency, are shown in Table 3. None of the sleep parameters, averaged over the whole recording period, correlated with global PSQI scores (all $p$s > 0.33).

A greater variability in SE scores was observed in the blind compared to the sighted group [$t(20) = 2.69$, $p = 0.02$]. When looking at the underlying measures, a multivariate analysis failed to detect significant group differences [Pillai's Trace: 0.18, $F(3,18) = 1.29$, $p = 0.31$]. More specifically, only marginal differences were observed for the variability in time spent in bed (TIB) and duration of sleep (TST, both $p$s < 0.08), while no difference was detected for the duration of nighttime awakenings (WASO, $p > 0.11$). Additionally, like the averaged measures, the variability in night-time sleep parameters also showed strong inter-variable correlations (Table 3). Importantly, the range of the night-time sleep parameters (SE, TIB, TST, and WASO) all correlated with global PSQI scores (all $p < 0.01$). Given the significant group difference in PSQI scores, we examined these correlations for the blind and sighted groups separately. The SE variability was strongly correlated with the global PSQI in the blind (SE: $r = 0.70$, $p = 0.02$) but not in the sighted control (SE: $r = -0.24$, $p = 0.47$, shown in Fig. 2). Similar correlations were observed for the blind and sighted groups between global PSQI scores and the range of TIB (BL: $r = 0.53$, $p = 0.10$; SC: $r = 0.62$, $p = 0.04$), the range of TST (blind: $r = 0.39$, $p = 0.23$; controls: $r = 0.63$, $p = 0.04$), and the range of WASO (blind: $r = 0.61$, $p = 0.05$; controls: $r =$

0.16, $p = 0.64$), although none reached statistical significance when correcting for multiple comparisons ($p < 0.025$).

**Table 3**. Pearson correlation value ($r$) of average (white) and range (grey) measures of the global PSQI score and the sleep parameters: time in bed (TIB), total sleep time (TST), wake after sleep onset (WASO) and sleep efficiency (SE).

| | **TIB (min)** | **TST (min)** | **WASO (min)** | **SE (%)** | **Global PSQI** |
|---|---|---|---|---|---|
| **TIB (min)** | | **.87 **** | **.74 **** | **.57 *** | **.62 *** |
| **TST (min)** | **.90 **** | | **.71 **** | **.63 *** | **.56 *** |
| **WASO (min)** | **.51 *** | -.13 | | **.72 **** | **.59 *** |
| **SE (%)** | - .19 | .25 | **-.83 **** | | **.63 *** |
| **Global PSQI** | .22 | .13 | .10 | -.18 | |

* $p < .05$, ** $p < .001$

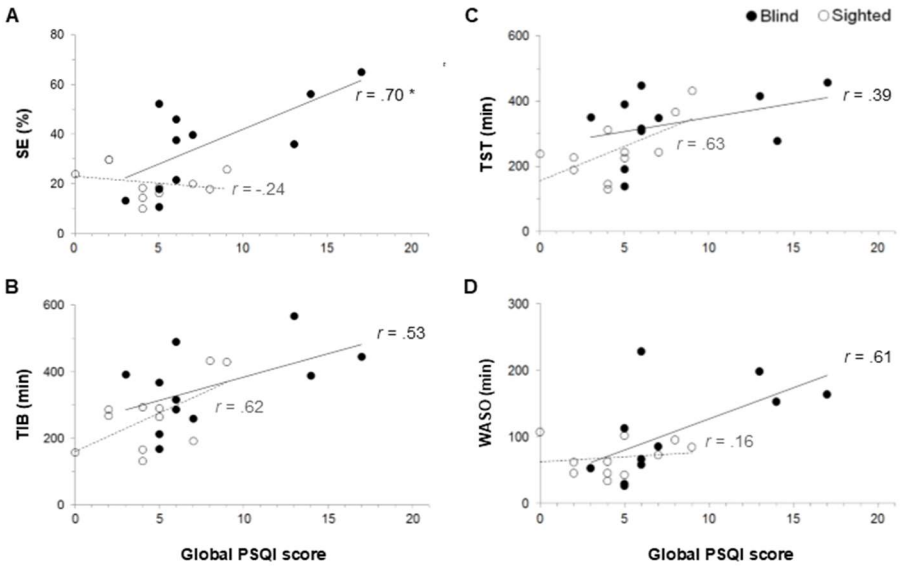


**Figure 2.** Correlation between global PSQI scores and the range of sleep parameters throughout the 30-day period for both the blind (black) and sighted (white) groups, separately. Sleep parameters include (A) sleep efficiency, (B) time in bed, (C) total sleep time, and (D) wake after sleep onset. Linear trends and Pearson's *r* value are indicated for both groups (blind: full line; sighted: dashed line). Statistically significant correlations are marked with an asterisk ($p < .05$).

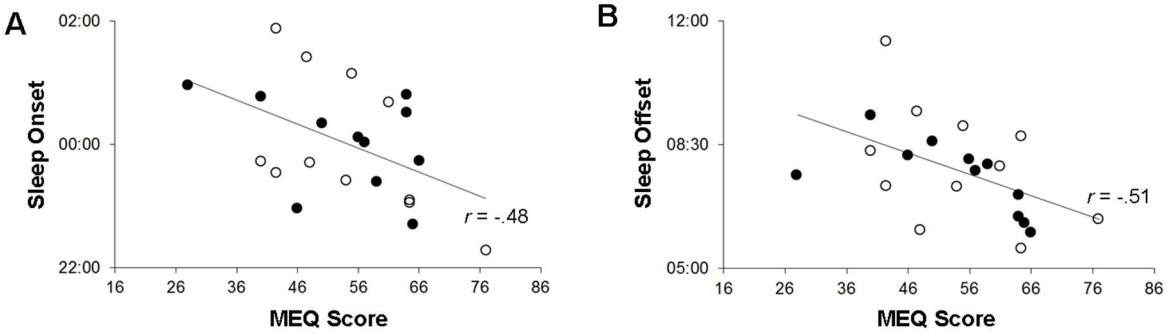


**Figure 3.** Scattering and correlation between the averaged sleep onset (A) and sleep offset (B) time to the MEQ score for both blind (black) and sighted sample (white).

3.3. *Chronotype*

MEQ scores did not differ significantly between the blind and sighted groups; $t(20) = -0.03$, $p = 0.98$ (Table 2). Furthermore, as shown in Fig. 3, MEQ scores were negatively correlated with both average sleep onset time ($r = -0.48$, $p = 0.02$) and average sleep offset time ($r = -0.51$, $p = 0.02$). Thus, early chronotypes, or morning types, fell asleep and woke up at an earlier time than late chronotypes, or evening-type individuals.

Fig. 4 illustrates the timing of the night-time sleep episode and the presence of daytime naps throughout the 30-day recording period for four participants: two congenitally blind individuals, showing high degrees of variability of their sleep–wake pattern, and two age- and sex-matched sighted controls.

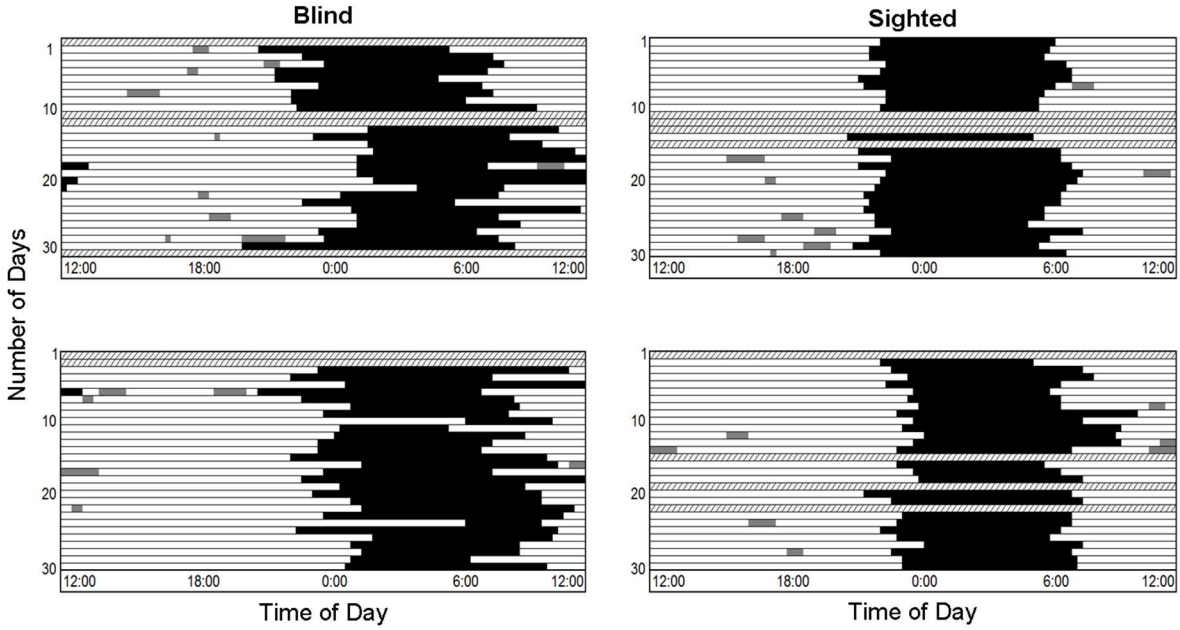


**Figure 4.** Illustration of the sleep-wake pattern of two congenitally blind (left) and two age- and sex-matched sighted controls (right) throughout the trial. Black segments mark the timing of the night-time sleep episode while grey segments highlight the presence of daytime napping throughout the 30-day period. Days for which the recording was excluded from analysis are marked by dashed bars.

3.4. *Daytime Naps*

No group differences were detected for either the number or the duration of day-time episodes [count: $t(20) = -0.14$, $p = 0.99$; duration: $t(20) = 0.33$, $p = 0.75$]. Expectedly, the number of naps and the sum of daytime sleep duration over the 30-day period were strongly correlated to each other ($r = 0.94$, $p < 0.001$).

3.5. *Sleep-Wake Stability*

There was no difference in the range of sleep onset time between the blind and sighted controls [$t(20) = 1.74$, $p = 0.10$; shown in Fig. 5A and Table 2]. In contrast, blind individuals showed greater variability in the timing of sleep offset: the time at which they awoke from their night-time sleep [$t(20) = 2.31$, $p = 0.03$; Fig. 5B and Table 2]. Furthermore, the variability in both sleep onset and sleep offset correlated with global PSQI scores [sleep onset: $r = 0.58$, $p < 0.01$ (Fig. 5C); sleep offset: $r = 0.50$, $p = 0.02$ (Fig. 5D)]. More specifically, a higher global PSQI score was associated with a larger range in the timing of sleep, both for the time falling asleep and waking up. Similar correlations were observed for blind (sleep onset: $r = 0.53$, $p = 0.09$; sleep offset: $r = 0.36$, $p = 0.28$) and sighted individuals (sleep onset: $r = 0.40$, $p = 0.22$; sleep offset: $r = 0.43$, $p = 0.19$) separately, although none reached statistical significance.

Finally, although the timing of night-time sleep is associated with the underlying chronotype, the variability in the timing of sleep was independent of chronotype as no correlations were found between the range of sleep timing (onset and offset) and MEQ scores ($p$s > 0.30). Thus, the range in the timing of night time sleep did not differ between morning-types and evening-types.

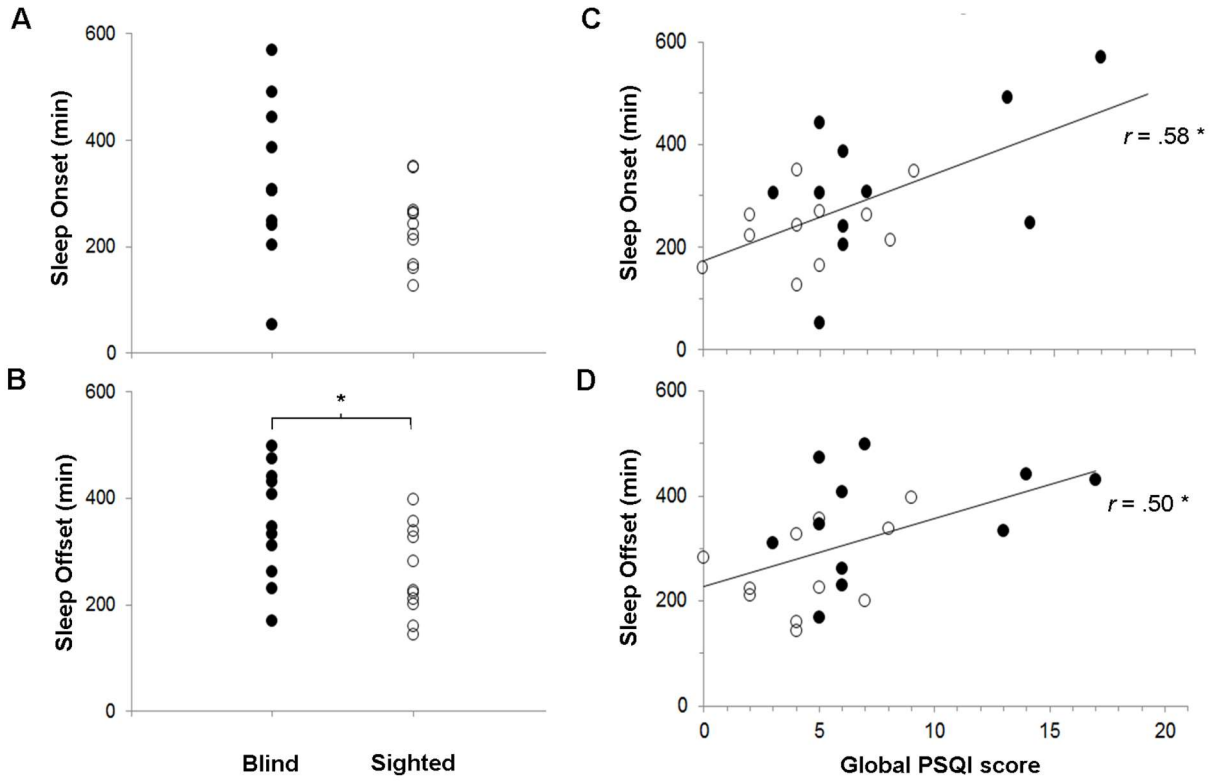


**Figure 5.** Distribution of the range of sleep onset and offset for blind (black) and sighted (white) individuals (panels A and B) and its correlation to the global PSQI score (panels C and D). Statistically significant results are marked with an asterisk ($p < .05$).

## 4. Discussion

Since light is an important source for the entrainment and synchrony of the biological clock to the 24-hour day/night cycle, we examined how the sleep–wake pattern is altered in blind individuals with no residual light perception, as compared to normal sighted individuals. We used actigraphy recordings to measure various sleep parameters of night-time sleep and the overall sleep–wake patterns over a period of 30-days. Moreover, chronotype and general sleep quality were assessed with the MEQ and the PSQI, respectively. Our data revealed a larger variability in sleep efficiency and in the timing of sleep and wake in blind individuals, supporting the hypothesis of increased presence of free-running circadian rhythms in blindness.

### 4.1. *General Sleep Quality*

As expected, blind participants had higher global PSQI scores than the matched sighted controls. These results are in line with previous studies that have examined PSQI scores in a blind population [13,27,28]. Notably, the global PSQI scores from the blind group had a sparse distribution, with a first cluster near the threshold score for disturbed sleep (>5), a second at a higher score range. A similar variability in the spectrum of sleep disturbances in blind individuals, and associated PSQI scores, was also reported in previous studies (e.g., [29]). Thus, although sleep disturbances are more prevalent in blind individuals, the severity of these disturbances is variable among individuals. Furthermore, the current results revealed a general increase in all the sub-components of the PSQI, as well as a greater use of prescribed sleep medication by blind individuals. Thirty-six percent of the blind participants used sleep medication – in most cases, melatonin – as a sleep aid for most or every night, while none of the sighted controls used any sleep medication.

4.2. *Timing and Efficiency of Night-Time Sleep*

From the continuous actigraphy recordings, we extracted various parameters from the night-time sleep episodes: time in bed, total sleep time, and the number of awakenings during the sleep episode. From this information, we derived a measure of sleep efficiency for each corresponding night. Notably, no differences were found between the blind and sighted groups when sleep parameters were averaged over the 30-day period. Nevertheless, a larger variability in sleep efficiency was observed for blind participants as compared to the sighted control participants. Thus, during the 30-day period, blind individuals had a larger mixture of both nights of good (high sleep efficiency) and poor (low sleep efficiency) sleep. Normal sighted individuals had more stable sleep efficiency throughout the recording period. Moreover, decreased overall sleep quality (as measured by the PSQI), correlated with increased variability of nighttime sleep in the blind but not in the sighted participants. Although this result seems to support the increased presence of sleep–wake circadian rhythm disorders in the blind, some caution is needed when interpreting this group difference, as high PSQI scores were absent in the normal-sighted sample.

The timing of the night-time sleep period, more specifically wake up time in the morning (sleep offset), was also more variable in the blind participants. A similar trend was observed for time falling asleep (sleep onset), although this failed to reach significance. Importantly, the variability of the sleep period correlated with the global PSQI scores. Thus, a higher PSQI score, suggesting lower sleep quality and greater sleep disturbances, was associated with greater variability in the timing of the night-time sleep period, both for sleep onset and offset.

The above findings corroborate previous results of the importance of circadian phase for both the timing and quality of sleep and wake [6,28,30]. Particularly, a recent study

demonstrated that both subjective and objective reports of poor sleep are associated with circadian phase. O'Donnell et al. showed that sleep quality was perceived as good when in synchrony with normal circadian phase, whereas it was judged as poor during forced desynchrony conditions, i.e., when circadian phase becomes desynchronized to the sleep–wake pattern [31]. Additionally, the timing and duration of the night-time sleep episode also varies with circadian phase. An increase in the duration of night-time sleep is observed when sleep occurs during its typical circadian phase, centered on the melatonin peak and the core body temperature nadir, as compared to when sleep occurs out of circadian phase [2,22,30]. Moreover, the timing of sleep onset and sleep offset also varies according to circadian phase [2,22,28]. Thus, the increased variability in the night-time sleep episode may underline a transitional shift in the endogenous circadian rhythm. We hypothesize that the sleep disturbances reported by blind individuals who also show larger variability in the timing and efficiency of their sleep may stem from a non-24-hour, free running circadian rhythm. The absence of a clear shifting phase within the 30-day period would further suggest that the drift rate between the 24-hour day/night and the endogenous free-running rhythm is rather small in these individuals. Thus, the free-running biological clock of these individuals would have a cycle beat close to 24-hours. However, in the absence of physiological circadian phase markers, such as the timing of melatonin onset throughout the study period, proper association between the findings of variability and endogenous circadian rhythms cannot be achieved, as discussed below.

### 4.3. *Day-Time Naps*

The lack of a group difference in the frequency and duration of the day-time nap episodes is at odds with previous studies [22,32,33]. These studies suggested that the occurrence and timing of daytime naps is a good behavioral indicator of circadian de-synchrony and free-running circadian rhythms. Possible confounding factors for the absence of this effect in the present experiment are discussed further below.

### 4.4. *Chronotype*

A person's chronotype is a determining factor for the time at which he/she feels most awake, alert, and also plays a role in the timing of sleep and wake. Chronotypes are modulated by a variety of factors, including age [34,35], sex [36], and the endogenous circadian rhythm [37]. Particularly, morning-types (larks) were found to have shorter than 24-hour circadian periods while longer circadian periods were associated with evening-types (owls) [38]. Moreover, the circadian phase angle of sleep – the phase of the circadian rhythm at which individuals preferably tend to fall asleep – also varies with the chronotype; an earlier phase angle for sleep onset occurs in morning-types as compared to evening-types [39–41].

We did not find group differences in the distribution in MEQ scores and associated MEQ type. However, average timing of nighttime sleep period, both onset and offset, correlated with MEQ score. Therefore, as demonstrated in previous studies [24,42,43], morning types go to bed and wake up earlier than evening types, highlighting the impact of the underlying chronotype on the overall behavioral sleep–wake pattern. We also assume that both blind and sighted individuals adopted daily rhythms that best matched with their chronotype. Moreover,

chronotype did not correlate with measures of sleep quality or sleep efficiency. Thus, increased sleep disturbances in the blind cannot be attributed to differences in underlying chronotypes.

### 4.5. *Differences Between Sleep Disturbance and Free-Running Circadian Rhythms*

Overall, the observed results corroborate previous findings that blind people experience more disturbed sleep and that, particularly in totally blind individuals, this may be associated with free running circadian rhythms [44]. However, some caution is needed. Although sleep is largely dependent on circadian phase and associated physiological rhythms, such as melatonin and core body temperature (e.g., [45,46]), it is also influenced by a multitude of other factors. Such factors include the homeostatic drive for sleep [6,47,48], environmental settings and social demands, consumption of psycho-stimulants and depressors (e.g., caffeine and alcohol), and levels of stress. Consequently, sleep disturbances may be attributed to factors other than a misalignment or a non-entrainment of the circadian rhythm. Likewise, the multitude of factors regulating the sleep–wake pattern can result in a masking effect, rendering abnormal or non-entrained circadian rhythms asymptomatic. Such a discrepancy between the underlying circadian rhythms and the associated diagnosis of non-24-hour sleep–wake rhythm disorder has previously been reported in blind individuals [28]. In general, the circadian period length is estimated to be shorter (closer to 24 hours) when assessed through behavioral sleep–wake reports in comparison to biological markers of circadian rhythms [28]. Furthermore, behavioral manifestations of free running circadian rhythms may be absent when rhythm period is close to 24-hours as daily circadian shifts may be compensated by other zeitgebers. Although light is the primary zeitgeber [49,50], other important sources of entrainment and daily regularity include environmental temperature, food consumption [51], and social zeitgebers [52,53]. This

multitude of sleep–wake regulators may help to explain why some blind individuals may exhibit sleep disturbances in the absence of variances in circadian rhythms, and how free-running circadian rhythms may not beget disturbances in sleep quality.

Social constraints, such as work, school, or small children are, therefore, crucial factors in regulating sleep–wake rhythms, particularly in the timing of wake. The majority of our participants, both blind and sighted, were not working on a regular basis. Consequently, most participants may have lacked daily work and other social obligations, allowing them to adopt a sleep–wake habit that best suited them. For example, some might have adopted a shifted sleep–wake pattern where they went to bed earlier or later, others might have elongated their sleep time by sleeping in the morning, while others could undertake daytime naps, all to compensate for disturbed sleep throughout the night. We can assume that selected methods would vary on an inter-subject basis, and that these could also vary in an intra-subject fashion throughout the recording period. This can explain, at least in part, why some average measures of sleep efficiency did not differ between the two groups of interest.

### 4.6. *Study Limitations*

A number of study limitations need to be addressed. First, there is the relatively small sample size of blind individuals ($n$ = 11). Blindness, specifically blindness without residual light perception, is a rare condition, and its incidence has decreased sharply in the past decades due to novel approaches in the handling of newborns that have led to a sharp decrease in cases of retinopathy of prematurity. Thus, recruitment of congenitally blind participants, particularly when excluding other common medical factors associated with aging, such as sleep apnea and medication, has become exceedingly difficult. Although participants reported that they had no

residual conscious light perception, this was not tested formally in an ophthalmological setting. We also did not test for retinal reactivity to blue light. Thus, it remains possible that, although the individuals reported no perceptual photic experiences, non-photic light information could remain functional and entrain the endogenous circadian rhythm of these blind individuals. Finally, studies have shown that actigraphy may lead to an over- or underestimation of sleep parameters, including the time of sleep onset and offset, nighttime awakening, and daytime naps, when compared to subjective measures such as daily activity journals [33], and objective measures such as PSG [23]. Therefore, although good overall coherence is found between actigraphy and PSG measures [54,55], actigraphy measures are limited to the detection of general changes in the sleep–wake pattern [23].

The current study only investigated sleep–wake patterns derived from continuous actigraphy recordings over a 30-day period. As described above, behavioral sleep–wake patterns are only weakly associated with the endogenous circadian rhythm. Therefore, the current study could not confirm whether blind individuals have free running circadian rhythms. A physiological marker of circadian rhythms, such as serial melatonin, cortisol, or core body temperature, for a minimum of two temporal intervals (see e.g., [46,56]) would render a better assessment of the underlying circadian period and phase. Nevertheless, blind individuals had significantly larger variability in the wake-up time and sleep efficiency. In addition, these measures correlated with higher PSQI scores. Moreover, sleep timing and quality are dependent on circadian phase [2,22,28,30], supporting the argument of increased incidence of free-running, non-24-hour circadian rhythms in blind individuals.

Furthermore, we collected actigraphy data over 30 consecutive days, which reduced noise in the extraction of average tendencies, and provided a sufficient number of days to observe

changes in the sleep–wake cycle. However, this time period may not be long enough for the observation of a full circadian cycle from free running, non-24-hour rhythms [18,57].

In conclusion, the present study confirms the presence of a higher prevalence of sleep disturbances in totally blind individuals. Additionally, blind individuals showed greater variability in both the timing of the night-time sleep episode, particularly for the time at which they awaken, as well as the efficiency of their sleep throughout the 30-day trial period. The findings suggest that an increased variability of night-time sleep may be a useful indicator of sleep disturbances and possibly the presence of a sleep–wake circadian rhythm disorder, most particularly in blind individuals.

**Supplementary Table 1.** Participant demographic information.

| Subject | Age | Sex | Work | Child Care | Blindness Onset (age) | Cause of Blindness | BDI |
|---|---|---|---|---|---|---|---|
| CB1 | 32 | F | Std. | No | 0 | Retinopathy of prematurity | 1 |
| CB2 | 62 | M | Yes | Yes | 0 | Retinopathy of prematurity (right eye); Retrolental fibroplasi (left eye) | 1 |
| CB3 | 27 | M | Yes | No | 0 | Retinopathy of prematurity | 1 |
| CB4 | 29 | F | Std. | No | 2 | Retinopathy of prematurity | 0.93 |
| CB5 | 54 | F | No | No | 0 | Retinopathy of prematurity | 1 |
| LB1 | 64 | F | No | No | 31 | Diabetes | 0.52 |
| LB2 | 47 | F | No | No | 8 | Retinopathy of prematurity (right eye); Retinal detachment (left eye) | 0.83 |
| LB3 | 51 | M | Occ. | No | 40 | Accident and glaucoma | 0.22 |
| LB4 | 62 | F | Occ. | No | 22 | Iris inflammation; cataract; ocular infection | 0.65 |
| LB5 | 29 | F | Yes | Yes | 12 | Iris inflammation; cataract; glaucoma | 0.59 |
| LB6 | 32 | F | No | No | 24-25 | Diabetes | 0.22 |
| SC1 | 36 | F | Yes | No | -- | -- | -- |
| SC2 | 59 | M | No | No | -- | -- | -- |
| SC3 | 25 | M | Std. | No | -- | -- | -- |
| SC4 | 27 | F | Std. | No | -- | -- | -- |
| SC5 | 57 | F | No | No | -- | -- | -- |
| SC6 | 61 | M | Yes | Yes | -- | -- | -- |
| SC7 | 47 | F | Yes | Yes | -- | -- | -- |
| SC8 | 53 | M | Occ. | Yes | -- | -- | -- |
| SC9 | 60 | F | No | No | -- | -- | -- |
| SC10 | 28 | F | Yes | No | -- | -- | -- |
| SC11 | 30 | F | Std. | No | -- | -- | -- |

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# Article 2

# Melatonin and cortisol profiles in the absence of light perception

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# Melatonin and Cortisol Profiles in the Absence of Light Perception

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**Short Title:** Melatonin and Cortisol in Blindness

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## Highlights

- Increased presence of abnormal timing of melatonin onset in blind individuals as compared to normal-sighted individuals.
- Increase in overall melatonin concentrations in blind individuals.
- Overall melatonin concentrations correlate with PSQI scores.
- No differences in cortisol profile between blind and normal-sighted individuals.


## Abstract

As light plays an important role in the synchronisation of the internal biological clock to the environmental day/night schedule, we compared the 24-h profiles of biological circadian markers in blind and normal sighted individuals. Salivary melatonin and cortisol concentrations were collected every two hours in eleven blind subjects, reporting no conscious light perception, and eleven age- and sex-matched normal sighted controls. Timing of melatonin onset and associated cortisol quiescence period confirm an increased incidence of abnormal circadian patterns in blindness. Additionally, blind subjects showed a greater overall melatonin concentration throughout the 24-h period. Cortisol profiles, including concentration and morning cortisol peaks, on the other hand, did not differ between blind and sighted individuals. These findings support previous reports of an increase in abnormal circadian rhythms and the absence of the entrainment properties of light in blindness.



**Keywords** Blindness; Cortisol; Melatonin; Circadian phase; Sleep

## 1. Introduction

Blindness, particularly complete blindness with no residual light perception, is associated with an increased incidence of free-running, or non-24-h, circadian rhythms [1–3]. The altered timing of the internal biological rhythms results from the loss of the 'non-visual' pathway of the visual system, that also originates from the retina. More specifically, melanopsin responsive retinal ganglion cells send direct projections, via the retinohypothalamic tract, to the suprachiasmatic nucleus (SCN) of the hypothalamus, an area identified as the master biological clock [4–6]. Light thus serves to coordinate and synchronise the internal biological rhythms to the external environmental day-night cycle. In the absence of light, the circadian rhythms enter a 'free-running' state, thereby following the natural endogenous rhythm of the SCN. Interestingly, the natural rhythm of the biological clock is near, but not precisely 24-h. Czeisler et al. [7] found that the average free-running circadian rhythm in humans is approximately 24.2-hrs. Moreover, there is a strong intra-individual stability of the endogenous rhythm, when measured repeatedly [7], although some changes are observed throughout child development, adulthood, and aging ([8,9] for examples). Interindividual variability in the endogenous circadian rhythm has also been associated with the underlying chronotype [10,11]. More particularly, morning-types (larks) tend to have shorter rhythms that are less than 24-h, while longer cycles are characteristic for evening-types (owls) [12].

Circadian rhythms are expressed throughout most physiological systems, from gene expression and hormonal regulation to core body temperature and metabolism. Behavioural manifestations of circadian rhythms can also be observed, most prominently in the sleep-wake pattern. Thus, it is of no surprise that blind individuals, in comparison to normal-sighted individuals, report more sleep disturbances [13,14]. More specifically, free-running circadian

rhythms have been suggested as a possible underlying source of some sleep disturbances experienced by blind individuals [15,16].

Although behavioural expressions of the endogenous circadian rhythms can be seen through the sleep-wake pattern, they are often masked by additional factors such as napping, caffeine ingestion, etc. (ex. [17]). Therefore, a more accurate measure of the circadian rhythm can be derived from hormonal and physiological markers. Particularly, melatonin concentrations and core body temperature are known to be reliable measures for the assessment of the endogenous circadian rhythm and have become a standard for chronobiology studies [18].

Here we examined melatonin and cortisol profiles over a 24-h observation period in blind individuals with no conscious light perception. As completely blind individuals report a greater incidence of abnormal circadian rhythms, we investigated how this translates to the associated circadian markers. Particularly, we expected a larger variability in the onset of the melatonin response. However, the diurnal time-profile of the melatonin and cortisol concentrations may also be altered in blind individuals, which has seldom been investigated.

## 2. Methods

### *2.1. Subjects*

Eleven blind individuals ($M_{age}$: 44.5 ± 14.9; 3 males, 8 females; all right-handed), reporting no residual light perception, and eleven age-and sex-matched sighted controls ($M_{age}$: 43.4 ± 14.2; 4 males, 7 females; 2 left-handed) with normal or corrected to normal vision, were recruited for a study of sleep patterns in which melatonin and cortisol samples were collected over a 24-h period. Each participant provided written informed consent for participation. The

Regional Capital Research Ethics Committee of Denmark (De Videnskabsetiske Komiteer, Region Hovedstaden, Denmark) approved the study (H-2-2014-081).

Table 1 summarises subject information. Age and sex were matched factors during the recruitment of subjects for both the blind and normal sighted groups as these are important modulating factors of melatonin and cortisol secretion profiles [19–21]. We ensured that no more than a four (4) year difference was present between grouping pairs.

In all cases, blindness was of peripheral origin, yet onset of blindness was variable with approximately half ($n$ = 5) of subjects acquiring blindness at birth or during the early years of life, while onset of blindness was later in life for the remaining subjects ($n$ = 6).

Each subject underwent a complete and detailed medical and sleep profile prior to the start of the study. This procedure included a detailed medical history interview, and the completion of the Beck Depression Index (BDI) and the Hospital Anxiety and Depression Scale (HADS) to exclude any medical or psychiatric disorders. Further, cardio-respiratory-movement monitoring (similar to Level III sleep monitoring) during one-night sleep, as well as the administration of the Epworth Sleepiness Scale (ESS) and the Rapid Eye Movement Sleep Behaviour Disorder Screening Questionnaire (RBD-SQ), were used to exclude any underlying sleep disorders, including severe apnea (AHI > 15). Subjects taking melatonin or other sleep aids ($n$ = 4 blind individuals) discontinued their medication one week (7 days) before the saliva sampling session. During their stay at the sleep center, participants also completed the Pittsburgh Sleep Quality Index (PSQI) questionnaire to determine their general sleep quality in the month preceding the saliva sampling period (scores shown in Table 1).

**Table 1**. Demographic information and PSQI scores of blind and normal sighted subjects.

| Blind Group | | | | | | Normal Sighted Group | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Subject** | **Sex** | **Age** | **Global PSQI** | **Onset** | **Cause** | **Subject** | **Sex** | **Age** | **Global PSQI** |
| BL1 | M | 27 | 5 | 0 | Retinopathy of prematurity | SC1 | M | 25 | 4 |
| BL2 | F | 29 | 13 | 2 | Retinopathy of prematurity | SC2 | F | 27 | 5 |
| BL3 | F | 29 | 6 | 12 | Iris inflammation; cataract; glaucoma | SC3 | F | 28 | 0 |
| BL4 | F | 32 | 3 | 24-25 | Diabetes | SC4 | F | 30 | 8 |
| BL5 | F | 32 | 5 | 0 | Retinopathy of prematurity | SC5 | F | 36 | 4 |
| BL6 | F | 47 | 6 | 8 | Retinopathy of prematurity (right eye); Retinal detachment (left eye) | SC6 | F | 47 | 2 |
| BL7 | M | 51 | 14 | 40 | Accident; glaucoma | SC7 | M | 53 | 9 |
| BL8 | F | 54 | 17 | 0 | Retinopathy of prematurity | SC8 | F | 57 | 4 |
| BL9 | M | 62 | 5 | 0 | Retinopathy of prematurity (right eye); Retrolental fibroplasi (left eye) | SC9 | M | 59 | 7 |
| BL10 | F | 62 | 7 | 22 | Iris inflammation; cataract; ocular infection | SC10 | F | 60 | 2 |
| BL11 | F | 64 | 6 | 31 | Diabetes | SC11 | M | 61 | 5 |

*2.2. Saliva Sampling and Analysis*

Samples were collected every 2 h starting at noon the day the subject was scheduled to arrive at the sleep center until noon the following day, for a total of 13 samples: 12:00 p.m., 2:00 p.m.,4:00 p.m., 6:00 p.m., 8:00 p.m., 10:00 p.m., 12:00 a.m., 2:00 a.m.,4:00 a.m., 6:00 a.m., 8:00 a.m., 10:00 a.m., 12:00 p.m. Saliva was collected using the Salivette (Sarstedt, Verona Italy) sampling system. To avoid contamination, subjects were instructed not to brush their teeth or consume any food or beverage 30 min before each sample. They were also advised to avoid any strenuous exercise during the sampling period. Daytime saliva samples were self-collected by the individual while samples collected during the night (from 20:00 until 8:00) were regulated by the research team present at the sleep center. Samples were kept refrigerated during the sampling period and were frozen at −20◦C once the 24-h sample collection period was complete. Samples from each subject were assayed in the same assay series, within the same batch. Melatonin concentrations were analysed by enzyme-linked immunosorbent assay (ELISA). Inter-assay coefficient variation (CV) was 13%, and an intra-assay CV was between 5 and 17% for low control, and 3–6% for high control. Cortisol was analysed by electro-chemo-luminescence immunoassay (ECLIA) with an inter-assay coefficient of variation of 5.2%.

Lighting conditions were only controlled during the sleep period of the sample collection. Subjects slept in light and sound-attenuated rooms. During the daytime hours, subjects were exposed to ordinary light conditions. Upon arrival at the sleep center, around 07:00 p.m., participants were exposed to standard hospital lighting until they went to sleep, between 10:00 and 12:00p.m., depending on their preference. Saliva samples were collected between 12:00 p.m. and 8:00 a.m. under a dim red light. Following the last saliva collection of the sleep period (8:00 a.m.), subjects were re-exposed to hospital and natural lighting conditions.

We compared the melatonin and cortisol profiles of blind and normal-sighted subjects. The timing of evening melatonin onset was used to determine if subjects were in synchrony ('in-phase') or not ('out-of-phase') with the environmental day-night rhythm. Based on a review by Pandi-Perumal and colleagues [22], and inline with the guidelines of the Dutch national referral center for sleep–wake disturbances and chronobiology, melatonin onset was determined as a rise in concentration (> 4 pg/ml) and was considered to be in a normal circadian phase if present between the 8:00 p.m. and 12:00 p.m. sampling period. This time window was adjusted from the proposed timing (between 7:00 p.m. and 10:00 p.m., [7]) to account for sampling time differences since we did not take samples at 7:00 p.m. Further, since participants were exposed to light until they retired to sleep (between 10:00 p.m. and mid-night), melatonin suppressing light effects may have been present. Melatonin onset was considered out-of-phase if the rise in melatonin occurred outside this time-window.

We also examined the overall profile of cortisol, including the presence of the cortisol awakening response (CAR) determined by the highest concentration measure following awakening. Waketime was scheduled for 8:00 a.m. in the morning for all subjects, thus a normal CAR response was expected either at the 8:00 or 10:00 a.m. sampling time.

Additionally, the area under the curve (AUC) and mean concentration of melatonin and cortisol throughout the 24-h sampling period were compared between blind and sighted groups. This allowed for a general measure of melatonin and cortisol concentrations throughout the sampling period. Lastly, correlations between these measures and reported general measure of sleep quality, assessed by global PSQI scores, were also examined.

*2.3. Statistical Analyses*

All data is reported as the mean (± SE) for the blind and sighted group separately. Chi-square tests (categorical variables) and Welch's t-test for unequal variance (continuous variables) were carried out for group comparisons. These findings were confirmed with a Mann-Whitney U test for non-Gaussian sample distributions. We also performed Spearman correlations between the melatonin and cortisol characteristics (mean and AUC) and the obtained global PSQI scores. Differences of $p < 0.05$ were considered as statistically significant. All analyses were done using IBM SPSS Statistics v20.0.3.

## 3. **Results**

*3.1. Melatonin*

In the blind group, melatonin onset occurred within the regular time window in 45% (5/11) of the cases, while 27% (3/11) showed a normal profile but an abnormal timing (shown in Fig. 1a). The remaining 27% (3/11) showed an abnormal or non-existent secretion pattern (shown in Fig. 1a). Missing data in one subject made it impossible to determine the proper circadian phase; however, the few data points available suggested that the circadian phase was abnormal. The other 2 abnormal patterns showed high melatonin concentration (< 25 pg/ml) throughout most or all of the 24- period.

Eighty-two percent (9/11) of the sighted group expressed a normal melatonin rhythm (Fig. 1a), whereas 9% (1/11) had a reduced pattern and delayed timing of melatonin onset (between 12:00 p.m. and 2:00 a.m., Fig. 1b). Lastly, one sighted subject showed a greatly reduced and abnormal timing of the melatonin secretion (Fig. 1b). Although a smaller number of blind individuals had a normal timing of melatonin secretion, as reported above, this failed to reach

statistical significance (Table 2; $\chi^2$= 3.14, $p$ = 0.08). Nevertheless, the area under the curve (AUC) and mean melatonin concentration were greater in blind compared to sighted individuals (AUC: $t(19) = 2.76$, $p = 0.01$; Mean: $t(19) = 2.71$, $p = 0.02$), as shown in Fig. 2. This holds true even when excluding the two blind subjects with abnormal continuous plateau effects of melatonin concentration (AUC: $t(17) = 2.42$, $p = 0.03$; Mean: $t(17) = 2.31$, $p = 0.04$). Although an overall greater melatonin concentration is observed for blind individuals, no differences were detected for the minimal and maximal values throughout the 24-h sample period (Min: $t(19) = 1.43$, $p = 0.19$; Max: $t(19) = 1.88$, $p = 0.09$). Lastly, none of the measures differed between congenital and late blind individuals (all $p$s > 0.18).

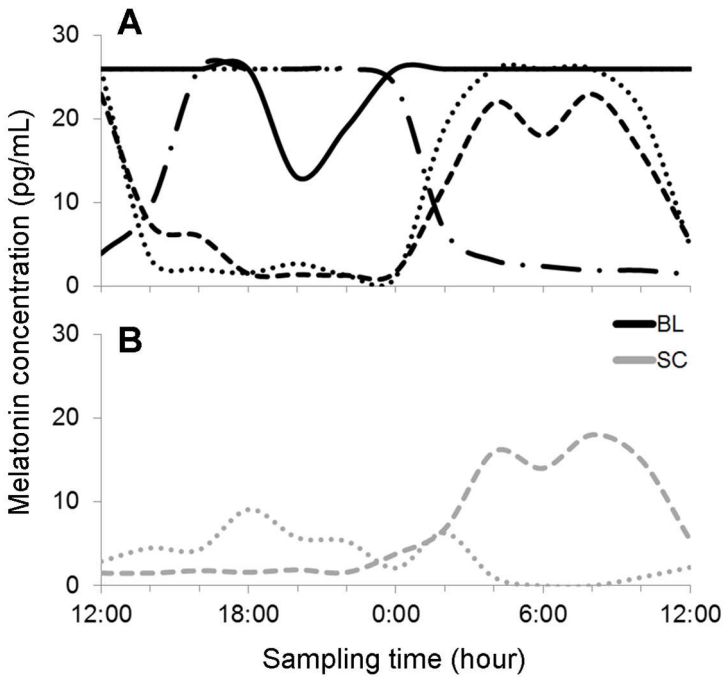


**Figure 1.** Abnormal melatonin patterns in blind (panel A, *n* = 5) and sighted (panel B, *n* = 2) subjects. Line styles (full, dotted, dashed) are used to depict the different subjects.

**Table 2.** Salivary melatonin and cortisol profiles in blind and sighted subjects.

| | **Blind (*n* = 10)** | **Sighted (*n* = 11)** | ***p*-value** |
|---|---|---|---|
| **Melatonin Onset (# in-phase)** | 5 | 9 | *.08* |
| **AUC (h x pg/mL)** | 169.79 (± 19.03) | 107.58 (± 12.13) | .02 |
| **24-hour mean (pg/mL)** | 14.34 (± 1.92) | 8.54 (± 0.95) | .01 |
| **Minimal value (pg/mL)** | 4.80 (± 2.65) | 1.00 (± 0.20) | *n.s.* |
| **Maximal value (pg/mL)** | 25.7 (± 0.30) | 22.19 (± 1.85) | *n.s.* |
| | **Blind (*n* = 9)** | **Sighted (*n* = 8)** | ***p*-value** |
| **Morning Cortisol Peak (#)** | 8 | 7 | *n.s.* |
| **AUC (h x nmol/L)** | 43.67 (± 4.07) | 46.32 (± 6.99) | *n.s.* |
| **24-hour mean (nmol/L)** | 3.66 (± 0.33) | 3.88 (± 0.69) | *n.s.* |
| **Minimal value (nmol/L)** | 1.14 (± 0.14) | 1.00 (± 0.00) | *n.s.* |
| **Maximal value (nmol/L)** | 11.44 (± 1.39) | 13.00 (± 2.33) | *n.s.* |

Abbreviations: *n.s.*: non-significant, AUC: area under the curve.

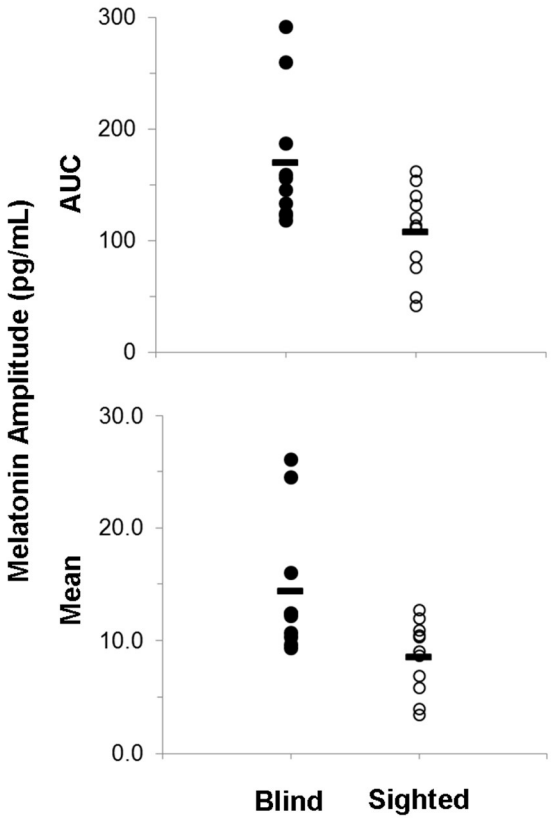


**Figure 2.** Dispersion of measures of melatonin concentration in blind (filled circles) and sighted (open circles) subjects. Top panel illustrates the area under the curve (AUC) and bottom panel the mean concentration measure over the 24-hour sample period.

*3.2. Cortisol*

Data points were missing for two blind and three sighted sub-jects, preventing to determine the timing and intensity of the cortisol profile. Thus, the following results are conducted on nine blind and eight sighted subjects. Table 2 and Fig. 3 depict the cortisol profiles. The majority of blind and sighted individuals showed a morning cortisol peak and an evening quiescence period and there was no significant group difference ($\chi^2$= 0.27, $p$ = 0.88). More specifically, 88.9% (8/9) of blind subjects and 87.5% (7/8) of sighted subjects had a morning cortisol peak, although two of the sighted subjects showed a slightly earlier morning peak. The remaining subjects ($n$ = 2) had abnormal cortisol patterns which included an overall rise in cortisol during sleep and an earlier occurring 'morning peak'. Nevertheless, the cortisol profile coincided with the melatonin profile. Particularly, the melatonin onset occurred during the quiescent period of the cortisol profile in the majority of the cases. The only exception was a normal-sighted subject with abnormal melatonin pattern, who also displayed an abnormal cortisol profile (shown in bottom panel of Fig. 3).

The AUC and mean cortisol concentration over the 24-h period did not differ between blind and sighted subjects (AUC: $t(15) = -0.33$, $p = 0.75$; Mean: $t(15) = -0.29$, $p = 0.78$) or between congenitally and late blind individuals (AUC: $t(7) = 0.73$, $p = 0.49$; Mean: $t(7) = 0.88$, $p = 0.41$).

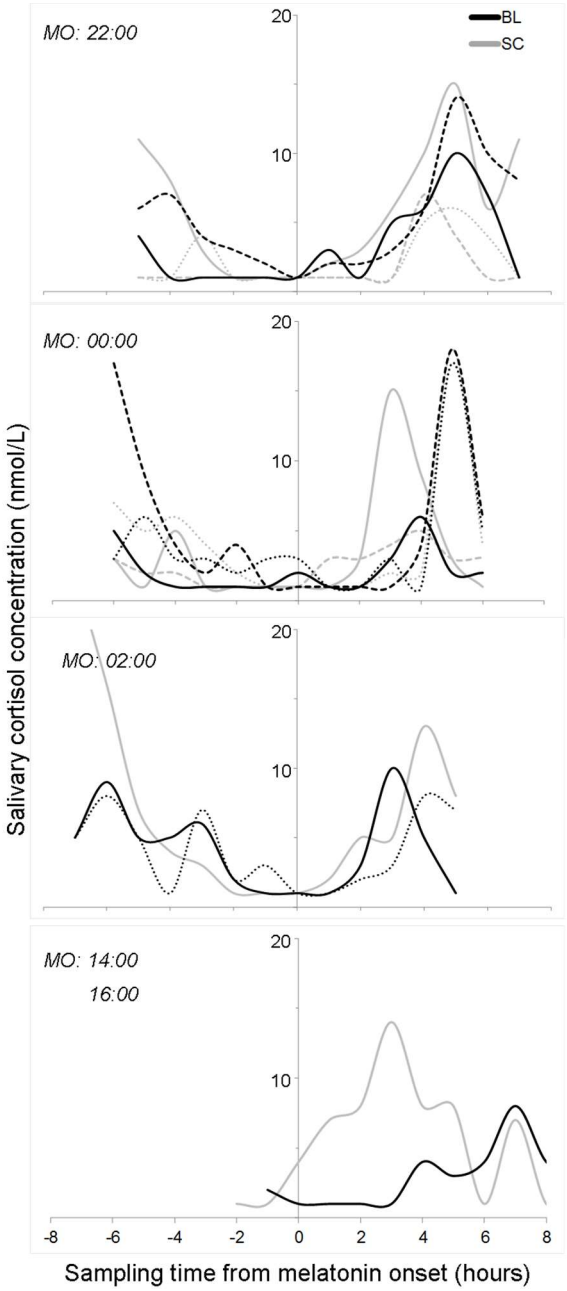


**Figure 3.** Cortisol concentration based on timing of melatonin onset for both blind (black, $n$ = 8) and sighted (grey, $n$ = 7) subjects. Line styles (full, dotted, dashed) are used to depict the different subjects. Each panel groups a different melatonin onset (MO) time. Top two panels contain MO times within the normal circadian window (MO at 22:00 and 00:00). Bottom two panels contain abnormal MO times at 2:00, 14:00 and 16:00. In most cases, MO occurred during the cortisol quiescence period.

*3.3. Correlation with Global PSQI*

Although a general trend for a lower global PSQI score was present for individuals showing a normal compared to abnormal circadian phase, based on melatonin onset timing (mean PSQI: 5.129 ± 0.89, $n$ = 13 and 8.29 ± 1.92, $n$ = 9, respectively), this failed to reach statistical significance, $t(20) = -1.42$, $p = 0.19$. However, we detected a monotonic correlation between global PSQI scores and melatonin concentrations (AUC: $\rho = 0.53$, $p = 0.01$; Mean: $\rho = 0.55$, $p = 0.01$). Cortisol measures did not correlate with global PSQI scores (AUC: $\rho = 0.20$, $p = 0.42$; Mean: $\rho = 0.22$, $p = 0.39$). Moreover, scores did not depend on the presence of normal morning cortisol response (present: 6.53 ± 1.06, $n$ = 15, abnormal: 4.50 ± 0.50, $n$ = 2, $t(15) = 1.74$, $p = 0.11$).

## 4. Discussion

The current study compared melatonin and cortisol profiles of blind and normal sighted individuals. Light is the primary zeitgeber, allowing for the synchronisation and maintenance of the internal biological clock to the external environmental day-night pattern. Consequently, a lack of visual input can result in the disruption of the endogenous circadian rhythm to the 24-h schedule. As melatonin and cortisol are biological markers of circadian rhythms, we expect a greater incidence of abnormal patterns in blind as compared to normal-sighted individuals. Since both age and gender can modulate the circadian pattern of melatonin and cortisol [19–21], we ensured that these factors did not differ between the two groups.

In line with our hypothesis, a greater number of abnormal melatonin patterns were observed in the blind group. These results are also in line with previous findings suggesting an increase in free-running circadian rhythms in blind individuals [15]. Previous studies have identified

various types of circadian patterns in blind individuals including normal entrained, abnormally entrained (advanced or delayed), free-running, and unclassified rhythms ([3,15,23,24] for examples). We found here a similar incidence of circadian rhythms: out of the 11 subjects, five had a normal timing of melatonin onset, two a delayed onset, one an advanced onset and three an abnormal or unclassified circadian phase.

Blind individuals also had larger melatonin concentration, as measured by the AUC and mean concentration over the collected sample times. Exposure to light in the evening, as well as in the early morning, can alter the timing and concentration of secreted melatonin [25–27]. Particularly, the phase-response-curve (PRC) of melatonin sensitivity to light exposure suggests that, under normal and entrained conditions, exposure to light in the evening hours delays the onset of melatonin secretion, while exposure to bright light in the early morning hours produces a forward melatonin shift [28,29]. Here, all subjects were exposed to normal hospital lighting conditions (minimum 300 lux illumination) before retiring for sleep, which may explain the reduced melatonin concentration and delayed melatonin onset. Interestingly, this effect is lacking in blind individuals, as suggested by higher mean and AUC melatonin values. As constant lighting protocols are associated with reduced plasma melatonin levels [26], we assume that the suppressive and shifting effects of light on the endogenous circadian phase, and consequently melatonin concentrations, are absent in totally blind individuals.

Moreover, increased melatonin correlated with reported sleep disturbances, as indicated by the global PSQI score. More specifically, results suggest a monotonic relationship between overall melatonin concentrations and sleep disturbances, rather than a direct linear one. These results are in line with previous studies demonstrating a trend between free-running circadian rhythms in blind individuals and their reported sleep disturbances [15,16]. However, disrupted

circadian rhythms cannot be considered as a singular underlying cause for the increased incidence of sleep disturbances recounted by blind people.

We also measured cortisol profiles over a 24-h period. The overall 24-h cortisol profile showed a coinciding circadian phase to the melatonin profile as melatonin onset occurred during the cortisol quiescence period. This was found for melatonin onsets that occurred in the normal time range, as well as during abnormal timing (outside the 8:00–12:00 p.m. time window). These results corroborate findings by Weibel and Brandenberger [30] of a relation between melatonin and cortisol profiles, even in altered circadian phases. Here, only one sighted individual showed an abnormal cortisol profile. This subject also had an abnormal melatonin profile despite reporting no issues with her sleep.

Cortisol peaks, corresponding to the cortisol awakening response, occurred either at the 8:00 or 10:00 a.m. sampling time. Although the cortisol morning response has been suggested as a circadian marker, particularly when sleep and wake time are unrestricted, studies have shown that CAR is tightly associated with awakening rather than an independent circadian rhythm [31,32]. Rather, circadian control of morning cortisol peak would manifest itself in the measured amplitude. In our study, all subjects were awakened at the same time (8:00) and it is reasonable to assume that the cortisol response would occur in the period following awakening. However, the presence of morning cortisol peak at this period may be due to an awakening before the scheduled wake time. Therefore, even though some individuals had an altered circadian phase, the physiological response of increased cortisol secretion following awakening remained present. Lastly, we did not find group differences in overall measures of the cortisol profile, determined by the AUC and averaging over all samples.

Cortisol is a pulsatile hormone that is strongly determined by environmental and circumstantial influences. For example, a rise in cortisol occurs following awakening [31,32] and cortisol concentrations are also altered following physical and mental stress, caffeine and food intake, etc. (e.g. [33–36]). Cortisol secretion is determined to a lesser extent by the circadian phase. In the present study, participants were awoken every second hour during the night in order to acquire the saliva samples. Although awakenings were kept brief, and completed in darkness, we cannot completely rule out the possibility of increased stress and augmented cortisol response. On most occasions, both blind and sighted subjects were able to re-engage in sleep following the awakening, and only few experienced prolonged wake periods between some of the sample times. Nevertheless, we cannot ignore the fact that purported stress induced by the scheduled awakenings and from being in a new environment (sleep center) may have limited the detection of circadian differences in the cortisol profiles.

Interestingly, only approximately half the blind individuals showed abnormal patterns of melatonin secretion. Although these results are in line with previous findings (e.g. [23,24]), one may wonder why not all blind individuals express altered circadian rhythms. Constant conditions and temporal isolation and forced desynchrony protocol studies suggest that the absence of retinal light input results in the absence of circadian rhythm entrainment, permeating the occurrence of free-running circadian rhythms (e.g. [37]). There are various possible explanations for the presence of normal circadian marker profiles in blind individuals. First, as the present study consisted only of one 24-h sample period, the presence of free-running circadian rhythms can go undetected. The natural endogenous rhythm runs at a non-24-h pace and, consequently, phases in and out of synchrony with the environmental 24-h period [38]. Therefore, the possibility remains that some of the observed normal melatonin patterns were

free-running but happened to be ‘in-phase’ during the sample period. This may hold particularly true for the blind individuals who were taking prescribed melatonin or other sleep aids. Although melatonin treatment was discontinued one week before the collection period, circadian desynchrony from the environmental 24-h rhythm may not have been detected during the sampling time, particularly if the endogenous circadian period is close to 24-h. Nevertheless, only two out of the four subjects who took melatonin showed abnormal plateaued melatonin concentrations. Of the others, one had a delayed melatonin onset, and the other a normal circadian rhythm throughout the sampling period.

Second, free-running circadian rhythms can be environmentally entrained by non-photic, secondary zeitgebers [39], such as food consumption [40], exercise [41], and other social zeitgebers [42,43]. Particularly, secondary zeitgebers may be sufficient for circadian entrainment when the endogenous circadian period length is close to 24-h. Thus, even in the absence of light input, a 24-h rhythm can be maintained.

A third explanation for the maintenance of normal circadian profiles in the absence of conscious vision results from the anatomical dissociation of the image-forming and non-image-forming pathways from the retina. Particularly, the image-forming central visual pathway has retinofugal projections through the dorso-lateral geniculate nuclei (dLGN) to the visual cortex, while the non-image-forming pathway primarily projects to the SCN, but also has projections to the LGN and other structures (e.g. [44,45]). Both pathways are also intrinsically related: melanopsin ganglion cells relay irradiance information to the image-forming system (e.g. [46,47]). Additionally, the photoreceptors, rods and cones and the conventional visual pathways play a modulatory role in the circadian response to light [48–50]. Both animal and human blindness studies have demonstrated the preservation, albeit atrophied, of the central visual

pathways and retinofugal structures, including the optic nerve, optic chiasm, dLGN, optic radiations and visual cortices [51,52]. Furthermore, although blindness may alter or reduce circadian functions, such as impaired pineal transcriptome enzymes in cone-rod-homeobox (Crx) deficient mice [53], there is an over-all preservation of circadian entrainment by light [52,54]. Similar results have also been reported in humans, where photic entrainment and melatonin suppression by light can be observed in some 'visually' blind individuals [55,56]. Thus, even in the absence of light and visual perception, the non-visual effects of light maybe preserved in blind individuals. Particularly, participants were selected on subjective reports of absence of light perception. Consequently, although the individuals are completely blind in the sense of conscious visual perception, 'non-visual' pathways may still be functional.

## 5. **Conclusion**

In this study, we report that blind subjects with no conscious light perception have larger melatonin, but not cortisol salivary concentrations throughout when measured over a 24-h period. Increased melatonin correlated with higher PSQI scores and may result from the absence of the suppressive effects of light on the master circadian clock in the suprachiasmatic nucleus of the hypothalamus. Our study also confirms previous findings of abnormal melatonin onset timing in blind individuals and supports the hypothesis of increased abnormal circadian rhythms in blindness.

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# Article 3

# Sleep structure in blindness is influenced by circadian desynchrony

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# Sleep structure in blindness is influenced by circadian desynchrony

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**Summary**

We examined the structure, duration and quality of sleep, including non-rapid eye movement sleep and rapid eye movement sleep, in 11 blind individuals without conscious light perception and 11 age- and sex-matched sighted controls. Because blindness is associated with a greater incidence of free-running circadian rhythms, we controlled for circadian phase by a measure of melatonin onset timing. When circadian rhythm was entrained, and melatonin onset occurred at normal times, sleep structure did not differ between blind and sighted individuals. On the other hand, an abnormal timing of the circadian phase, including delayed, shifted and unclassifiable melatonin onsets, led to larger rapid eye movement sleep latencies and increased wake times. No differences were observed for stages of non-rapid eye movement sleep, either between congenital and late blind and sighted individuals, or across the different circadian phases. Moreover, abnormal circadian phases were more common in the blind ($n$ = 5) than the sighted ($n$ = 2) sample. Our findings suggest that the sleep structure of blind individuals depends on entrainment of circadian phase, rather than on the absence of vision.

**Keywords** Circadian phase; melatonin; REM sleep; NREM sleep

## 1. Introduction

Visual deprivation, as in the case of total or partial blindness, induces structural and functional changes in visual cortical areas (Kupers and Ptito, 2014; Park et al., 2009; Ptito et al., 2008), and in other parts of the brain (Cecchetti et al., 2016; Chebat et al., 2007; Ptito et al., 2008; Tomaiuolo et al., 2014). Besides these changes, a number of electrophysiological changes have been reported. Particularly, resting state occipital alpha oscillations, when eyes are closed, are absent in blind individuals (Noebels et al., 1978). Various studies have shown these oscillations to be associated with activity of the visual cortex, thalamus and insula (Feige et al., 2005; Goldman et al., 2002; Larson et al., 1998; Sadato et al., 1998), although their nature and significance remain to be elucidated. Furthermore, reduced parieto-occipital alpha power has been reported in blind individuals during cognitive tasks (Kober et al., 2014; Kriegseis et al., 2006; Schubert et al., 2015), possibly reflecting alterations in the thalamocortical pathway (lateral geniculate nucleus and primary visual cortex; Cecchetti et al., 2016; Kupers and Ptito, 2014).

Given such severe anatomo-physiological changes (Kupers and Ptito, 2014), sleep states may also be modulated by the absence of visual input. Indeed, blind individuals report more sleep disturbances than do normal-sighted controls (Aubin et al., 2016; Leger et al., 1999; Tabandeh et al., 1998). In totally blind individuals, sleep disturbances may be partially explained by a free-running circadian rhythm that results from the absence of entrainment by light (Flynn-Evans et al., 2014; Uchiyama and Lockley, 2015). More specifically, sleep is mediated by two processes: a homeostatic drive for sleep and a circadian rhythm of wake (Borbély, et al., 1982; Borbély et al., 2016). Disruptions of either process generate disturbances in sleep and its underlying structure. Thus, the incidence of free-running circadian rhythms associated with

blindness can account for some, but not all, of the sleep disturbances reported by blind individuals (Leger et al., 1999; Lockley et al., 1997; Moseley et al., 1996).

Nevertheless, relatively little is known about the structure of sleep and its electrophysiological correlates in blind individuals. In addition, the few published studies investigating sleep electroencephalogram (EEG) in the blind report inconsistent or contradictory results with respect to both rapid eye movement (REM) and non-REM (NREM) sleep. Some early studies conducted in small cohorts ($n$ = 5) of blind participants with varying degrees of light perception suggest that deep sleep (N3 or NREM stages 3 and 4 in earlier terminology), characterised by slow-wave activity (SWA), may be reduced or absent in blindness (Hono et al., 1999; Krieger and Glick, 1971). This conclusion is corroborated by the results of a recent study in a larger group of 10 blind participants without conscious light perception (Ayala-Guerrero and Mexicano, 2015). None of these studies, however, reported any differences between blind and normal-sighted control groups for NREM sleep stage 2 (N2) or REM sleep. Leger et al. (2002) examined the structure of night-time sleep in a large sample ($n$ = 26) of totally blind individuals, with either congenital or acquired blindness, who all had free-running circadian rhythms. Blind participants had reduced sleep duration and lower sleep efficiency than did their age- and sex-matched sighted controls. Blind participants also had reduced REM sleep duration and increased REM sleep latency. The variations in timing and duration of REM sleep support the presence of free-running circadian rhythms, as REM sleep is strongly dependent on circadian phase (Czeisler et al., 1979, 1980).

The current knowledge on the sleep structure of blind individuals is, however, limited by studies consisting of small sample sizes and the absence of a circadian marker. Importantly, although abnormal phased and free-running circadian rhythms are more prevalent in totally

blind individuals (Flynn-Evans et al., 2014; Lewy and Newsome, 1983), circadian-phase markers were not concurrently measured in most previous studies examining the macro- and microstructure of sleep in this population.

Accordingly, our goal was to investigate the consequences of visual deprivation on sleep structure in a sample of blind individuals while controlling for underlying circadian phase. Particularly, we aimed to examine how the proportion and distribution of NREM and REM sleep are modulated by the absence of vision while also controlling for the phase of the circadian rhythm. We hypothesised that modulations in REM sleep are more dependent upon circadian phase, which is more variable in blind individuals, resulting in larger disturbances in sleep architecture when 'out-of-phase'.

## 2. Materials and Methods

### *2.1. Participants*

Eleven blind individuals (BL), reporting no conscious light perception ($M_{age}$: 44.5 ± 14.9 years; eight females; all right-handed) participated in the study. In all cases, blindness was of peripheral origin, affecting the retina or optic tract. Five participants were blind from birth (congenitally blind, or CB; $M_{age}$: 40.8 ± 16.1 years; three females), while the remaining six acquired blindness later in life (late blind, or LB; $M_{age}$: 47.5 ± 14.7 years; five females; range of blindness duration: 8–40 years). A group of 11 age- and sex-matched individuals with normal or corrected-to-normal vision (sighted controls, or SC; $M_{age}$: 43.4 ± 14.2 years; seven females; two left-handed) were recruited for controlled comparisons. Table 1 reports the demographic information of all participants, all of whom provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Regional

Capital Research Ethics Committee of Denmark (De Videnskabsetiske Komiteer, Region Hovedstaden, Denmark; H-2-2014-081).

### *2.2.Procedure*

Participants underwent extensive pre-screening to ensure that external influences (e.g. other sleep disorders) on the quality and quantity of their sleep were limited. Screening included a medical interview to exclude any neurological or psychiatric disorders, as well as medical disorders or treatments that might influence sleep and alertness. Depression and anxiety were assessed using the Beck Depression Index and the Hospital Anxiety and Depression Scale. Furthermore, all participants underwent 1 night of cardiac, respiratory and movement monitoring (similar to a Level III sleep study) in order to exclude cases of severe sleep apnea (apnea–hypopnea index >15) or excessive limb movement that may interfere with sleep quality. The presence of possible REM sleep behaviour disorder (RBD) and excessive daytime sleepiness were examined using the RBD screening questionnaire and the Epworth Sleepiness Scale, respectively. Participants were asked to refrain from taking sleep medication for 1 week before the scheduled experimental procedure.

**Table 1.** Demographic information and global Pittsburgh Sleep Quality Index (PSQI) scores from blind and age- and sex-matched normal sighted participants.

| Blind Group | | | | | | Normal Sighted Group | | | |
|---|---|---|---|---|---|---|---|---|---|
| Subject | Sex | Age | Global PSQI | Onset | Cause | Subject | Sex | Age | Global PSQI |
| BL1 | M | 27 | 5 | birth | Retinopathy of prematurity | SC1 | M | 25 | 4 |
| BL2 | F | 29 | 13 | 2 | Retinopathy of prematurity | SC2 | F | 27 | 5 |
| BL3 | F | 29 | 6 | 12 | Iris inflammation; cataract; glaucoma | SC3 | F | 28 | 0 |
| BL4 | F | 32 | 3 | 24-25 | Diabetes | SC4 | F | 30 | 8 |
| BL5 | F | 32 | 5 | birth | Retinopathy of prematurity | SC5 | F | 36 | 4 |
| BL6 | F | 47 | 6 | 8 | Retinopathy of prematurity (right eye); Retinal detachment (left eye) | SC6 | F | 47 | 2 |
| BL7 | M | 51 | 14 | 40 | Accident; glaucoma | SC7 | M | 53 | 9 |
| BL8 | F | 54 | 17 | birth | Retinopathy of prematurity | SC8 | F | 57 | 4 |
| BL9 | M | 62 | 5 | birth | Retinopathy of prematurity (right eye); Retrolental fibroplasi (left eye) | SC9 | M | 59 | 7 |
| BL10 | F | 62 | 7 | 22 | Iris inflammation; cataract; ocular infection | SC10 | F | 60 | 2 |
| BL11 | F | 64 | 6 | 31 | Diabetes | SC11 | M | 61 | 5 |

*2.3. Polysomnography (PSG)*

Participants spent two consecutive nights at the sleep centre. Nocturnal PSG recordings were collected for both nights; analyses were conducted on recordings collected only during the second night. On the second night, participants arrived at the sleep centre at about 19:00, and were exposed to ordinary hospital lighting conditions until they retired to sleep in a sound- and light-attenuated room. Participants were free to go to bed between 22:00 and 00:00 in the evening depending on personal preference. All participants were awakened at 06:00 the following morning.

Polysomnographic recordings were collected using the SOMNOscreen system and analyses were manually conducted using the DOMINO Analysis Software (SOMNOmedics GmbH, Randersacker Germany). Recordings included EEG (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1, derivations from the 10–20 electrode placement system), electrooculogram (EOGL/A2, EOGR/A2), electromyogram of the chin and legs, electrocardiogram, airflow thermistor, thoracic and abdominal respiratory bands, and pulse oximetry. EEG and EOG references, labelled A1 and A2, consisted of the left and right mastoid, respectively. PSG recordings and analyses were conducted in concordance with the American Academy of Sleep Medicine standard guidelines (AASM guidelines v2.2; Berry et al., 2015). Sleep staging, based on 30-s epochs, was completed by one investigator (SA) and cross-validated by a second member of the sleep centre (HL) to ensure inter-scorer reliability.

From the PSG recordings, various sleep parameters were extracted, including measures of sleep duration and latency, sleep efficiency, and proportions of sleep stages (N1, N2, N3 and REM sleep). Definitions of these parameters are provided in Table 2.

*2.4. Circadian phase and desynchrony*

Melatonin concentration, extracted from saliva samples collected every 2-h over a period of 24-h, was used to determine the underlying circadian phase for each participant. Samples were collected during the day prior and throughout the first night, the adaptation night, at the sleep centre. Details regarding collection, analysis and results are discussed in a related report (Aubin et al., 2017). Based on the review by Pandi-Perumal et al. (2007), circadian cycle was considered to be 'in-phase' if melatonin onset (MO; absolute value >4 pg $mL^{-1}$) occurred between 20:00 and 00:00 in the evening. The rhythm was considered to be 'out-of-phase' or abnormal if MO occurred outside this time period.

Beyond general 'normal, in-phase' and 'abnormal, out-of-phase' separation of circadian phases, we categorised four different MO timings: (1) 'Normal' circadian phase, if MO occurred between 20:00 and 00:00; (2) 'Delayed' circadian phase, when MO was detected before 04:00; (3) 'Shifted' circadian phase, if MO occurred at a time outside the normal and delayed phases; and (4) 'Unclassified' circadian phase if no clear MO was observed throughout the 24-h sampling time.

**Table 2.** Definitions of target sleep parameters.

| Parameter | Abbreviation | Unit | Definition |
|---|---|---|---|
| Sleep period | SP | Min | Time between 'lights off' (participant went to bed) and 'lights on' (participant was awakened) |
| Total sleep time | TST | Min | Time in any epoch marked as sleep (N1, N2, N3, REM) TST = SP – ($SL_{N1}$ + WASO)<br>TST = N1 + N2 + N3 + REM |
| Total wake time | TWT | Min | Time in epochs marked as Wake throughout SP<br>TWT = SP – TST<br>TWT = $SL_{N1}$ + WASO |
| Sleep latency | $SL_{N1}$ | Min | Time between 'lights off' and first epoch scored as N1 |
| Wake after sleep onset | WASO | Min | Time in epochs scored as Wake following $SL_{N1}$ |
| Sleep efficiency | SE | % | Proportion of SP in any sleep state<br>SE = TST / SP |
| Sustained sleep efficiency | $_{sus}$SE | % | Proportion of time in any sleep state between sleep onset ($SL_{N1}$) and 'lights on'<br>$_{sus}$SE = TST / (SP – $SL_{N1}$) |
| REM sleep latency | REM-SL | Min | Time between first epoch scored as REM sleep and start of SP |
| NREM 1 sleep | N1 | % | Proportion of SP scored N1 |
| NREM 2 sleep | N2 | % | Proportion of SP scored N2 |
| NREM 3 sleep | N3 | % | Proportion of SP scored N3 |
| REM sleep | REM | % | Proportion of SP scored REM |

*2.5. Statistical analysis*

Measures are expressed as means ± standard deviations. Student's *t*-tests for independent groups compared differences between BL and SC groups, and between CB and LB when applicable. One-way analysis of variance (ANOVA) with four levels of the independent variable (circadian phase categories) was conducted to examine differences between circadian phases. Bonferroni pairwise comparisons were conducted to determine the relationship between each circadian phase group. Pearson correlations were used to test for linear relationships between sleep parameters and timing of MO. Statistical significance was set to $p < 0.05$ for each analysis. All analyses were conducted using the SPSS v20 statistical software package (SPSS, Chicago, IL, USA).

## 3. **Results**

One blind participant was removed from the analysis due to an insufficient number of data points to determine circadian phase, therefore analysis was conducted on 10 blind and 11 normal-sighted participants. Overall, half of the blind sample (50%) showed a desynchronised, or 'out-of-phase', MO pattern, while an abnormal circadian phase was only found in a minority (18%) of the control group. More specifically, normal circadian phase occurred in five out of 10 (50%) blind individuals and nine out of 11 (82%) normal-sighted controls. Delayed circadian phase occurred in three out of the combined 21 cases, including in two blind and one sighted individual, where MO occurred at the 02:00 sampling time for all cases of this category. A shifted circadian phase was observed in both one blind and one sighted individual. For both cases, the shifted phase was characterised by an MO detected at the 14:00 sampling time. Lastly, unclassified circadian phase was observed in two blind individuals.

*3.1. Sleep architecture in blind individuals with normal MO timing*

To examine differences in sleep structure between blind and sighted individuals, the first set of comparisons was limited to individuals having normal MO timing, i.e. occurring between 20:00 and 00:00 (BL: $n = 5$; SC: $n = 9$). As illustrated in Fig. 1a and detailed in Table 3, sleep stage hypnograms were similar for both groups. A significant difference was detected for the duration of total sleep time ($t_{12} = 3.03$, $p = 0.01$) where, on average, sleep duration was shorter for blind than for sighted individuals. Blind individuals also had an overall shorter sleep period than did normal-sighted individuals ($t_{12} = 3.46$, $p < 0.01$). No other group differences were observed (all $p > 0.11$). Additionally, although small in sample size, we did not observe any differences between the sleep parameters of the congenitally and late blind individuals with a normal timing of MO onset (all $p > 0.19$). Importantly, therefore, blind individuals with a normal MO timing had the same sleep architecture as normal-sighted individuals (Fig. 2).

**Table 3**. Mean (± SD) of sleep parameters comparing blind and sighted groups with normal timing of melatonin onset; *p*-values for independent samples *t*-tests.

| Sleep parameter | Blind ($n = 5$) | Sighted ($n = 9$) | *t*-test (*p*) |
|---|---|---|---|
| Time in Bed (min) | 404.5 (± 34.3) | 458.1 (± 24.0) | < .01 |
| Total Sleep Time (min) | 347.1 (± 69.8) | 423.0 (± 24.1) | .01 |
| Total Wake Time (min) | 57.4 (± 42.5) | 35.1 (± 18.5) | .19 |
| Wake After Sleep Onset (min) | 45.9 (± 47.5) | 26.2 (± 19.1) | .28 |
| Sleep Latency (min) | 11.4 (± 9.0) | 8.9 (± 7.6) | .59 |
| REM Sleep Latency (min) | 66.8 (± 34.4) | 67.6 (± 18.6) | .96 |
| Sleep Efficiency (%) | 85.3 (± 11.7) | 92.4 (± 3.8) | .11 |
| Sustained Sleep Efficiency (%) | 87.8 (± 13.0) | 94.2 (± 4.0) | .19 |

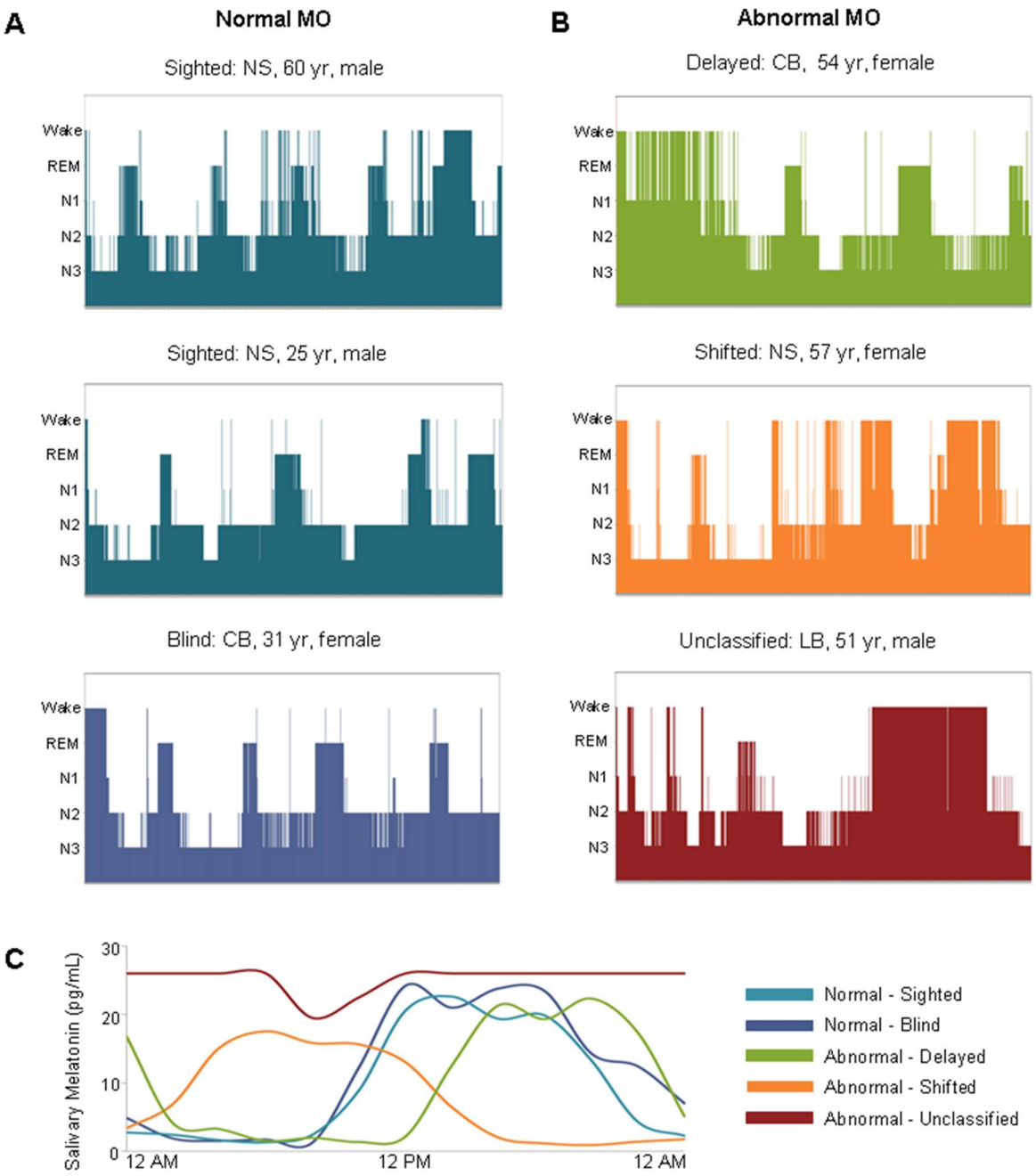


**Figure 1.** Hypnograms of sleep stages from sighted and blind participants with both normal and abnormal circadian timing. **A** represents the sleep structure of two normal-sighted and one blind participant. **B** represents the sleep structure of three participants with delayed, shifted, and unclassified timings of melatonin onset, respectively. **C** shows the averaged melatonin patterns over a 24-hour period, depicting the different timings of MO, with associated colour legend for the entire figure.

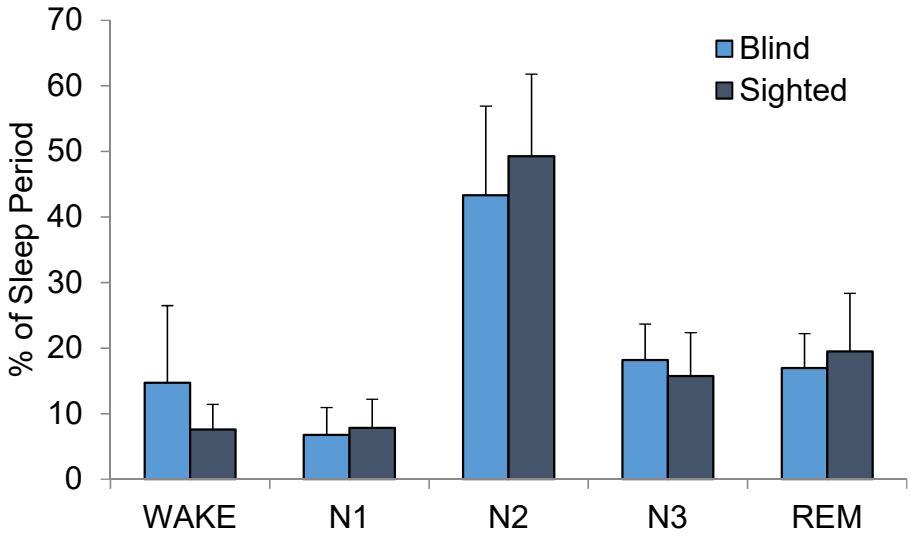


**Figure 2.** Percentage of time spent in each sleep stage for blind and sighted groups.

*3.2. Sleep structure in relation to MO*

Sleep structure was also investigated across the four circadian phases determined by MO timing (Fig. 1a,b; Table 4). Time to REM sleep onset was significantly different by circadian phase categories ($F_{3,17} = 5.42$, $p < 0.01$); a longer REM sleep latency was present for the circadian phase delayed group than it was for the normal and shifted groups (both $p = 0.03$). REM sleep latency did not differ between the delayed and unclassified groups, or between the normal and shifted groups (both $p > 0.99$). There was also a positive correlation between REM sleep latency and MO ($r = 0.49$, $p = 0.03$), indicating that increased desynchrony from an entrained circadian rhythm is associated with a larger latency in the appearance of REM sleep during the night-time sleep period.

**Table 4.** Mean (±SD) of sleep parameters across different circadian phases as determined by melatonin onset; *p*-values for one-way ANOVAs.

| | Circadian Phase | | | | |
|---|---|---|---|---|---|
| **Sleep parameter** | **Normal** | **Delayed** | **Shifted** | **Unclassified** | ***p*** |
| Total Sleep Time (min) | 395.9 (± 57.3) | 377.5 (± 54.8) | 341.4 (± 4.4) | 384.1 (± 52.7) | .47 |
| Total Wake Time (min) | 43.0 (± 29.8) | 48.9 (± 37.7) | 87.4 (± 60.2) | 109.8 (± 44.0) | .07 |
| Wake After Sleep Onset (min) | 33.2 (± 31.9) | 41.2 (± 36.0) | 79.5 (± 53.1) | 94.8 (± 63.3) | .11 |
| Sleep Latency (min) | 9.8 (± 7.9) | 7.6 (± 5.3) | 7.8 (± 7.2) | 14.9 (± 19.2) | .80 |
| REM Sleep Latency (min) | 67.3 (± 24.0) | 127.8 (± 50.8) | 41.0 (± 45.3) | 115.8 (± 24.4) | <.01 |
| Sleep Efficiency (%) | 89.9 (± 8.0) | 89.2 (± 7.4) | 80.5 (± 11.1) | 76.2 (± 10.0) | .13 |
| Sustained Sleep Efficiency (%) | 92.0 (± 8.5) | 90.9 (± 7.6) | 81.8 (± 10.2) | 79.0 (± 13.7) | .18 |

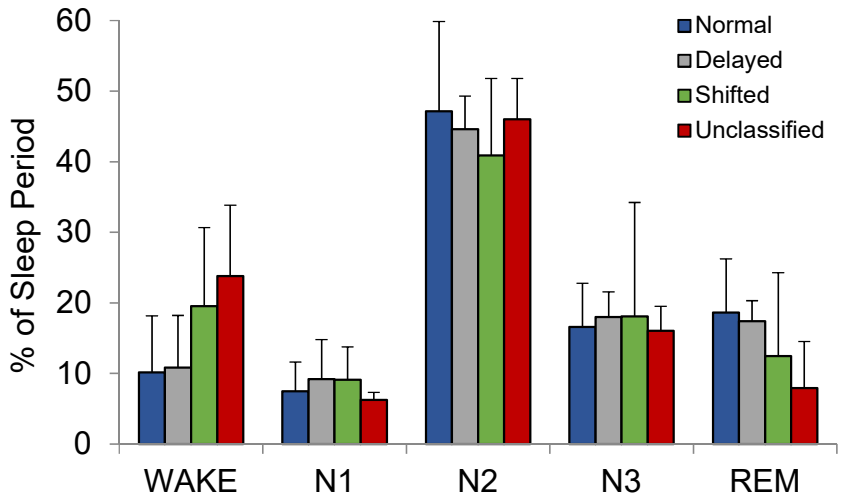


**Figure 3.** Percentage of time spent in each sleep stage across different circadian phases: normally entrained, delayed, shifted and unclassified.

We also observed a tendency for increased Wake across circadian phase groups ($F_{3,17}$ = 2.90, $p$ = 0.07). As shown in Fig. 3, both the shifted and unclassified circadian phase groups spent more time awake than did the normal and delayed circadian phase groups. Bonferroni pairwise comparisons, however, did not show significant differences between the four MO groups (all $p > 0.12$). Further, in contrast to the linear relationship observed between REM sleep latency and circadian phase, the proportion of time spent in each NREM sleep stage (N1, N2 and N3) remained relatively stable across all four circadian groups.

## 4. **Discussion**

The present study examined the sleep structure of blind individuals in relation to underlying circadian phase. Circadian phase was measured by MO timing derived from 24-h saliva samples, and was considered normal or in-phase if the rise in melatonin occurred between 20:00 and 00:00. In line with our expectations, a greater number of abnormal MO timings were observed in blind than in normal-sighted individuals. Abnormal circadian phases were observed in half of the blind sample, while only in a minority of the controls. Further, although sleep structure was normal for participants with normal circadian rhythms, it was disrupted when circadian rhythms were desynchronised, regardless of whether they were sighted or blind.

### *4.1. Sleep structure is normal in cases of 'in-phase' MO*

When comparing the sleep structure of blind and normal-sighted participants with a normal MO timing, a significant difference was observed for the total amount of sleep time. This effect originated from a difference in the length of the sleep period. Particularly, although the sleep period was partially controlled – all were awakened at 06:00 – blind participants went to bed,

on average, nearly 1-h later than normal-sighted individuals. Though interesting, we cannot provide a conclusive explanation for such an observation other than a general preference for these blind individuals to go to bed at a later time. Specifically, as shown in an associated report (Aubin et al., 2016), no differences were found between the blind and sighted groups for chronotype as measured with the Morningness–Eveningness Questionnaire. Importantly, no significant differences were found for the total time spent awake, or the latency to sleep, suggesting that the reduced sleep period, and consequently reduced total sleep time, were not the result of individuals being unable to engage in sleep.

Our results do not support the detrimental role of blindness on SWA and N3 sleep, as suggested in previous studies (Ayala-Guerrero and Mexicano, 2015; Hono et al., 1999; Krieger and Glick, 1971). Specifically, we did not find differences in the proportion of each sleep stage, including N1, N2, N3 and REM between the blind participants and the normal-sighted controls, particularly when circadian rhythm was 'in-phase'. It is important to note that the reduced or absent SWA and N3 sleep reported in previous studies were not detected in all participants (Ayala-Guerrero and Mexicano, 2015; Hono et al., 1999; Krieger and Glick, 1971). Further, this result was not consistently observed in all previous studies. Leger et al. (2002), for example, did not report differences in NREM sleep stages in their group of congenital and acquired blind individuals with free-running circadian rhythms. Moreover, a longitudinal case study spanning a 104-day follow-up period of one late blind individual with a non-24-h circadian rhythm (Klein et al., 1993) found not only the presence of slow-wave sleep, but also a minimal variability of this sleep stage across circadian phases. Thus, these results, along with the present ones, do not support the role of either blindness or circadian phase as a main modulator of slow-wave sleep (Dijk and Czeisler, 1995). Rather, the presence and amplitude of SWA is thought to be primarily

dependent upon homeostatic sleep processes (Finelli et al., 2000). In summary, when circadian rhythm is entrained and in normal phase, no differences were detected for the hypnogram structure of sleep between blind and normal-sighted individuals.

*4.2. Sleep structure is disrupted in case of 'out-of-phase' MO*

On the other hand, when sleep was examined across circadian phase, we found group differences in sleep structure, particularly in the proportions of wake and REM sleep. REM sleep was the most variable of sleep stages across the different circadian phase categories. Specifically, REM sleep latency was significantly modulated by the timing of MO. The shortest latency for REM sleep was observed when MO occurred in the afternoon, while the longest latency was observed when the circadian phase was delayed and MO occurred later in the night (02:00). These results corroborate many previous findings associating circadian phase with the structure and propensity of sleep (Czeisler et al., 1979, 1980; Dijk and Czeisler, 1995; Dijk et al., 1997; Zulley, 1980). Similar results were also observed in two longitudinal studies in blind individuals with free-running circadian rhythms (Klein et al., 1993; Miles et al., 1977). Further, although only a trend ($p = 0.07$), the time spent awake was increased when strong abnormalities in melatonin secretion were observed. The time awake increased 13.2% to 155.3% when MO was out-of-phase as compared with in-phase; increases were particularly noteworthy in the groups with shifted and unclassified timing of MO.

The present study, therefore, found no differences in hypnogram sleep parameters between blind and normal-sighted groups when individuals had normal synchronised circadian rhythms. On the other hand, when circadian rhythms became desynchronised, as characterised by abnormal MO timings, REM sleep latency and, to a smaller degree, the duration of wake were

modulated by circadian phase. Similarly, the study by Leger and colleagues in 26 blind individuals with free-running circadian rhythms reported an overall decrease in the duration and latency of REM sleep in blind compared with sighted individuals (Leger et al., 2002). Nevertheless, in the absence of an associated measure of circadian phase, it was not possible to determine if the differences in REM sleep were due to dissociated circadian phases in the blind group, as suggested by the authors. The present study, therefore, expands upon these findings by examining the sleep structure of blind individuals while controlling for circadian phase. Indeed, when sleep occurred at an abnormal circadian phase, shown by the timing of MO, REM sleep latency was significantly altered.

However, we did not detect differences in desynchronised circadian rhythms between blind and normal-sighted individuals. Specifically, as abnormal and non-detectable (unclassified) phases of the circadian rhythm were found for only a subset of participants (seven out of 21), group comparisons could not be performed. Nevertheless, despite the small sample size, our results on the effects of circadian rhythm on the hypnographic structure of sleep are in line with reports showing that circadian rhythm modulates both wake and REM sleep (Czeisler et al., 1979, 1980). These results therefore support the robustness of the phase of circadian rhythm on the structure of sleep and we can propose that these effects are the same for both blind and sighted individuals.

## 5. **Conclusion**

In line with previous studies, abnormal circadian phase modulates the timing of REM sleep and the proportion of wake during night sleep. Furthermore, blindness is associated with a greater incidence of abnormal circadian rhythms, as measured by the timing of MO.

Nevertheless, when circadian phase is synchronised to the environmental day/night, sleep structure does not differ between blind and normal-sighted individuals. Our findings therefore suggest that, although sleep structure is influenced by the circadian phase, blindness *per se* does not modulate the structure of sleep, including the proportion of NREM and REM sleep.

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**Author contribution**

Sébrina Aubin: conceptualisation of study, data acquisition, data analysis, writing of manuscript; Poul Jennum: conceptualisation of study, provided study materials, review of manuscript; Tore Nielsen: conceptualisation of study, review of manuscript; Ron Kupers: conceptualisation of study, provided study materials and financial support, review of manuscript; Maurice Ptito: conceptualisation of study, provided study materials and financial support, review of manuscript.

**Conflicts of interest**

All authors report no conflicts of interest.

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# Article 4

# Sleep microstructure is largely preserved in blind individuals

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# Preserved sleep microstructure in blind individuals

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**Summary**

The loss of vision, particularly when it occurs early in life, is associated with compensatory cortical plasticity not only in the visual cortical areas, but throughout the entire brain. The absence of visual input to the retina can also induce changes in entrainment of the circadian rhythm, as light is the primary zeitgeber of the master biological clock found in the suprachiasmatic nucleus of the hypothalamus. In addition, a greater number of sleep disturbances is often reported in blind individuals. Here, we examined various electroencephalographic microstructural components of sleep, both during rapid-eye-movement (REM) sleep and non-REM (NREM) sleep, between blind individuals, including both of early and late onset, and normal-sighted controls. During wakefulness, occipital alpha oscillations were lower, or absent in blind individuals. During sleep, differences were observed across electrode derivations between the early and late blind samples, which may reflect altered cortical networking in early blindness. Despite these differences in power spectra density, the electroencephalography microstructure of sleep, including sleep spindles, slow wave activity, and sawtooth waves, were shown to remain present in the absence of vision.

**Keywords:** Blindness; Spectral Power, Alpha Oscillation, Sawtooth Waves; Sleep Spindles; Slow Waves

## Introduction

Besides its role in visual perception and cognitive processes, the visual system is also critically involved in various 'non-image-forming' processes. Light, captured by the retina, plays a central role in the entrainment of body rhythms to the external day/night cycle [1-3]. It might therefore not be surprising that blind individuals report more sleep disturbances than normal-sighted ones [4-6]. Increases in sleep disturbances in visually impaired individuals are also associated with lower health-related quality of life [7]. In complete blindness, sleep disturbances may be, in part, the result of free-running circadian rhythms due to the absence of light input from the retina [8,9]. Specifically, the timing and structure of sleep - notably rapid eye movement (REM) sleep – are strongly dependent on the underlying circadian phase [10,11]. However, free-running circadian rhythms cannot account for all sleep disturbances in blind individuals [12-14; see also 5].

Further, loss or deprivation of a sensory modality, particularly from birth, induces both structural and functional changes in the brain [15-17]. The visual cortex of blind individuals has been shown to contribute to the processing of sensory input from other modalities [18-20], as well to higher order cognitive processes such as language [21,22] and memory [23-25]. Additionally, blindness-related anatomical and functional changes are not only limited to sensory areas, but have been shown to occur throughout the brain [15, 16, 26, 27]. In a previous report, we have shown that the macrostructure of sleep, including the proportion of each sleep stage, is not directly modulated by blindness itself. Specifically, no differences were observed in the macrostructure of sleep between the blind and sighted participants when the circadian rhythm, as measured by the timing of melatonin onset, was normal, or 'in-phase' [28]. On the

other hand, an abnormal circadian phase led to differences in sleep structure, particularly in the proportion of wakefulness and REM sleep, as also shown by others [10,11,29].

As cortical rewiring occurs following the loss of a sensory modality, we sought to examine if the loss of vision modulates the underlying components of REM and non-REM (NREM) sleep. The microstructure of sleep in blindness has not been studied in-depth, and has produced conflicting results, e.g. some reporting a reduction or absence of NREM slow wave activity in blind individuals [30-32], whereas others did not observe these changes [29]. Furthermore, only two studies described sleep spindle density during NREM sleep in blind individuals; one reporting an increase of spindling activity [33], the other a decrease compared to the expected density measures in age-matched adults [34]. Mixed results have also been reported for EEG characteristics of REM sleep. Of the studies that have reported on the presence of sawtooth waves, some have shown that they are preserved [32,35], while others reported that they are altered in blind individuals [36].

The aim of the present study was, therefore, to examine purported alterations in EEG and sleep microstructure in visually-deprived individuals. Thereto, we included groups of completely blind individuals without residual light perception, both of early and late onset, and normal-sighted controls. Based on previous literature, we sought to determine if microstructural hallmarks of sleep, including sleep spindles and slow wave activity, as well as components that may be associated with visual cortical specific activity during sleep, including occipital alpha oscillations and sawtooth waves, would be altered in blind individuals. Absolute spectral power of classical frequency bands was also compared for each sleep stage. Further, as the phase of the circadian rhythm is known to modulate some of these features, and because abnormal

circadian phases are more prevalent in our blind sample [37], this variable was controlled throughout the analyses.

## Methods

**Participants.** Eleven blind participants (BL, $M_{age}$: 44.5 ± 14.9 years; 8 females; all right-handed) were recruited through the laboratory databases and word-of-mouth. None of the blind participants reported any conscious light perception. Eleven individuals with normal or corrected to normal vision (sighted controls, or SC; $M_{age}$: 43.4 ± 14.2 years; 7 females; 2 left-handed) were recruited as an age- and sex-matched control group through web advertisement and word-of-mouth. Additional demographic information of all participants can be found in a previous report [28]. Of the blind participants, five were blind within the early years of life (4 from birth and 1 from 2 years of age; termed early blind, or EB; $M_{age}$: 40.8 ± 16.1 years; 3 females) and the remaining 6 had acquired blindness (late blind, or LB; $M_{age}$: 47.5 ± 14.7 years; 5 females). In the LB group, blindness onset in this group was between 8 and 40 years of age. In all cases, blindness was of peripheral origin, affecting the retina or optic tract. No significant differences were found in demographic characteristics between the blind and sighted groups, nor between the early and late blind participants (see [4] for more information). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Capital Research Ethics Committee of Denmark. Written informed consent was provided by all participants and they received financial compensation for their participation.

**Screening.** Both blind and sighted participants underwent extensive screening to limit external influences on the quality and quantity of their sleep, apart from potential circadian

rhythm-based sleep-wake disorders (e.g., other sleep disorders such as sleep apnea, chronic pain with medication known to affect sleep, etc.). Screening included a medical interview to exclude neurological or psychiatric disorders, medical problems, and treatments that may influence sleep and alertness. Depression and anxiety were assessed using the Beck Depression Index [38] and the Hospital Anxiety and Depression Scale [39]. Furthermore, all participants underwent one night of cardiac, respiratory and movement monitoring (CRM; comparable to a Level III sleep study) to exclude cases of moderate or severe sleep apnea (apnea-hypopnea index, AHI > 15) or excessive limb movement. Moreover, participants taking sleep medication ($n = 4$) were asked to abstain from taking their sleep aids for at least one week before beginning participation.

**Measure of the circadian rhythm.** The phase of the circadian rhythm was determined by the timing of melatonin onset. Salivary concentrations of melatonin were extracted from samples collected every 2 hours over a 24-hour period (see [37] for additional details). The phase of the circadian rhythm was considered normal if melatonin onset (> 4pg/mL) occurred between the 8:00 PM and midnight sample. Otherwise, the phase of the circadian rhythm was considered to be abnormal (advanced or delayed) or non-detectable. The classification of normal and abnormal circadian phase was used as a covariate in the statistical analyses.

**Polysomnography.** Participants spent two consecutive nights at the sleep center where nocturnal polysomnographic (PSG) recordings were collected on both nights. The first night served mainly for habituation purposes, during which saliva samples were collected for determining the phase of the circadian rhythm. PSG analyses were conducted on recordings collected on the second night. During this night, participants were free to go to sleep at anytime

between 10:00 PM and midnight, depending on their preference. They were left to sleep undisturbed until they were awoken at 6:00 AM the following morning to mark the end of the sleep period. Further details on the participant's stay at the sleep center and the associated PSG recordings are summarized in an associated report [28]. PSG recordings and scoring procedures followed the American Academy of Sleep Medicine standard guidelines (AASM guidelines v2.2 [40]) dividing each sleep epoch of 30 s into wakefulness (W), REM sleep, and NREM sleep stage 1 (N1), 2 (N2) and 3 (N3). Recordings were collected using the SOMNOscreen system and PSG recordings were manually scored using the DOMINO Analysis Software (SOMNOmedics GmbH, Randersacker Germany). Based on the 10-20 electrode placement system, bilateral frontal, central and occipital EEG derivations were recorded. For the reported analyses, only left EEG derivations (F3/A2, C3/A2, O1/A2) were used and collected data was limited between 'lights off' and 'lights on' markers. Nevertheless, similar results were obtained for left and right electrode derivations (shown in Supplementary File 1).

**Microstructure analysis.** From the PSG recordings, various characteristics of each sleep stage were examined across groups. These characteristics included occipital alpha oscillations during wake and N1 sleep, sleep spindles and slow wave activity during N2 and N3 sleep, and sawtooth waves during REM sleep. Power spectra of four classical frequency bands, delta (0.5 – 4Hz), theta (4 – 8Hz), alpha (8 – 14 Hz), and beta (14 – 35 Hz), were also examined across sleep stages and electrode derivations.

*Artifact exclusion.* Prior to the analyses, EEG signals were filtered forward and backward with Butterworth filters: a notch filter for the removal of power-line noise (50 Hz) and a band-

pass filter to center the analyses on sleep-related activity (0.3-35 Hz). An automatic electromyographic (EMG) artifact detection and exclusion algorithm was applied [41]. In brief, this widely used method compares high frequency activity in each 4-s window to the background activity level in a surrounding local 3-min window. If the value in the 4-s window exceeded the local background activity by a factor of four, the 4-s window is detected as an EMG artifact and is removed from further analysis. For power spectrum computations, artifacts such as electrode pop (any sample in a 4-s EEG segment with a spectrum above 1000 $\mu V^2/Hz$) and flat-lines (all samples in the segment with a spectrum below 0.1 $\mu V^2/Hz$) were also removed. Overall, an average of 9.93 % ± 1.17 % of the signal was artefactual and removed from further analysis.

*Frequency Power Density.* Power spectra of the sleep EEG were computed using the Welch method [42]. Specifically, the periodogram function in MATLAB was used to estimate EEG Power Spectra Density (PSD) of each 4-s Hanning-weighted segment, with 50 % overlap and zero-padding of the time-domain signal resulting in a frequency resolution of 0.125 Hz. The power spectra for each 4-s segment were averaged for each sleep stage and for the 3 electrode derivations, separately. Transition epochs – epochs that are preceded or followed by an epoch of a different sleep stage - were excluded from analysis to minimise cross-stage contamination of EEG frequency power. Transition epochs accounted for an average of 27.04 % ± 2.13 % of all epochs between lights off and lights on. No differences in the number of transition epochs were found between BL and SC ($p = .95$), nor between EB and LB ($p = .30$). Frequencies were grouped into standard bands: delta: 0.5 Hz ≤ f < 4 Hz, theta: 4 Hz ≤ f < 8 Hz, alpha: 8 Hz ≤ f < 14 Hz, and beta: 14 Hz ≤ f < 35 Hz. All power densities were log transformed prior to statistical analysis to approximate the variation to a normal distribution.

*Occipital Alpha Oscillation.* Alpha oscillatory activity typically dominates the EEG activity of the occipital derivations of a sighted individual in a relaxed state with eyes closed. This oscillatory activity is thought to be associated with idling of the visual cortex [43]. Accordingly, we examined relative power for each frequency band in the occipital derivation during both wakefulness and N1 sleep. Power ratios were computed based on the same 4-s segments as for calculation of absolute power density. Power ratios were obtained by computing the power in each band normalized to total power in the 0.3-35 Hz frequency range. Power ratios are reported as a proportion of the overall signal power with a value between 0 and 1, where 1 indicates a complete dominance of the frequency band and all other bands absent.

*Sleep Spindles.* Sleep spindles (SS) were automatically detected during EMG-free N2 and N3 sleep epochs using a procedure inspired by previous studies [44-46], and conducted using Matlab. This analysis has previously been used in a previous study [47] EEG signals were bandpass filtered separately for slow (11 to 13 Hz) and fast (13 to 15 Hz) spindle frequencies using a $4^{th}$ order Butterworth filter (-3 dB at 11.1 Hz and 12.9 Hz for slow SS and 13.1 and 14.9 Hz for fast SS). Signals were forward and reverse filtered to obtain zero-phase distortion and to double the filter order. Using a time window of 0.25 s, the root mean square of the filtered signal was calculated. A SS was identified when at least two consecutive root mean square time points exceeded the $95^{th}$ percentile threshold. SS density (number per minute) were calculated for both N2 and N3 sleep, separately.

*Slow Wave Activity.* Average percentage of slow wave activity (SWA) per sleep epoch was computed based on automatically detected slow waves in EMG-free NREM sleep. For this

analysis, a 4th order band-pass Butterworth filter with cut-offs (-3 dB) at 0.3 and 4 Hz was used to forward and reverse filter the signal. SWA was automatically detected on the left frontal derivation (F3/A2) from artifact-free epochs using criteria described in the literature [48,49], and conducted using Matlab. Slow waves were characterised by a negative peak with < -40 μV amplitude and a duration of 125 – 1500 ms, a positive peak with a duration > 1000 ms, a peak to peak amplitude > 75μV, and a minimal SW duration of 425 ms. Slow wave activity percentage was computed for periods of N2 sleep ($SWA\%_{N2}$) and N3 sleep ($SWA\%_{N3}$) separately.

*Sawtooth Waves.* Sawtooth waves (STW) were identified manually and only in epochs of REM sleep. Detection followed criteria defined in earlier studies [50], including 1) a fronto-central, bilaterally synchronous event with maximal amplitude at the central derivation; 2) a minimum of at least 3 consecutive waves with a frequency between 2 - 5 Hz and an amplitude between 20 and 100 μV; and 3) waves characterised by a slow incline to a negative peak followed by a fast decline to a positive peak. Following manual identification, two STW characteristics were examined across groups: STW density (the number of STW per minute of REM sleep) and STW mean duration.

**Statistical Analysis.** Greenhouse-Geisser corrected one-way ANCOVAs were computed for each microstructural measure of interest. Group comparisons were performed separately between blind and normal-sighted samples (*group*) and between early and late blind samples (*blindness onset*). In all analyses of variance, a dichotomous measure of the phase of the circadian rhythm, either 'in-phase' or 'out-of-phase', was controlled as a covariate (refer to [37]

for details). As absolute spectral power was computed for all 3 electrode derivations (*derivation*), mixed two-way ANCOVAs were computed for this measure, with derivations (F3/A2, C3/A2, O1/A2) as a repeated measure factor. Separate ANCOVAs were computed for each microstructural measure of interest (e.g., slow and fast SS density) and for each frequency band (delta, theta, alpha, and beta). Further, each sleep stage (W, N1, N2, N3, REM) was examined separately. *Post-hoc* univariate ANCOVAs with a Holm-Bonferroni correction for multiple comparisons were used for the breakdown of interactions between groups and electrode derivations. In such cases, group differences were examined across the 3 derivations separately. Additional comparative analyses (ANCOVA) between the early blind, the late blind, and sighted groups were also performed for the absolute spectral power. These supporting results are reported in Supplementary File 2. Results are reported in mean and standard error of the mean (SEM) values and, unless otherwise specified, the significance level was maintained at $p = .05$ for all comparisons.

We confirm that all measures, conditions and data exclusions have been reported, either directly or indirectly through references to the associated published work pertaining to this study. Statistical measures were determined based on the study's aim and participant sample. The small sample size is due to the difficulty of finding completely blind individuals with no comorbid conditions. Although this may limit the generalisability of our conclusions, it serves as hypothesis-generating findings for the basis of future studies.

## Results

As provided in a previous report, there was a higher proportion of abnormal phases of the circadian rhythm in the blind sample, as measured by the onset of melatonin secretion [37]. No differences were observed, however, between EB and LB participants. For technical reasons, the melatonin profile could not be measured for one early blind participant, who was consequently removed from the analyses. Therefore, microstructural components of sleep were reported for a group of 10 blind and 11 normal-sighted individuals.

Overall, the sleep macrostructure including the proportion of each sleep stage within the sleep period did not differ significantly between the blind and sighted samples (all *p*s > .177), or between the early and late blind participants (all *p*s > .478), as illustrated in Figure 1.

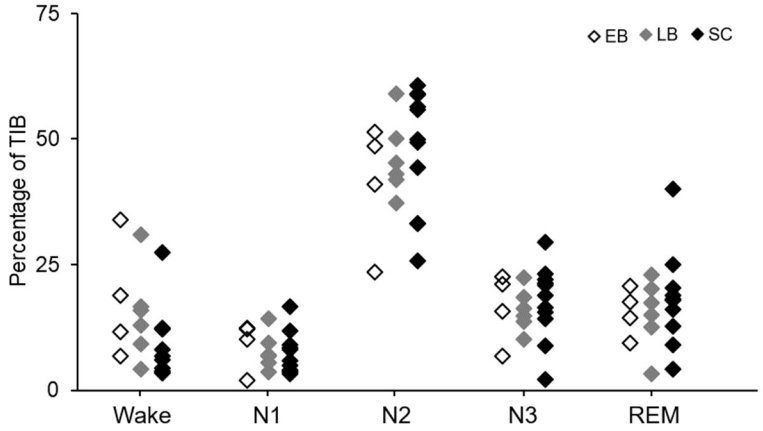


**Figure 1.** Proportion of time spent in the various sleep stages throughout the night for early blind (white), late blind (grey) and sighted participants (black). Abbreviations: EB = early blind, LB = late blind and SC = normal-sighted controls.

**Power spectra density across sleep stages**

Spectral power of the groups (BL vs SC) and blindness onset (EB vs LB) for each of the sleep stages are shown in Figure 2 and Table 1. Differences between each group pair and their interaction with electrode derivation were measured in separate ANCOVAs for each frequency band and sleep state. Statistically significant results are summarized in Table 2 and are further detailed below.

Wake state

A significant group x derivation interaction was detected for the delta power during the wake epochs within the sleep period ($F(2, 36) = 6.164$, $p = .012$). Overall, a lower delta power was found for BL as compared to SC ($F(1, 18) = 10.583$, $p = .004$). Further, *post-hoc* Holm-Bonferroni corrected analyses reveal that this difference was significant for the frontal ($F(1, 18) = 20.288$ $p < .001$), but not the central or occipital derivations ($F(1, 18) = 3.695$, $p = .071$ and $F(1, 18) = 0.921$, $p = .350$, respectively). Wake epochs were also marked by a lower alpha power in BL ($F(1, 18) = 4.975$, $p = .039$). This effect did not interact with electrode derivation, suggesting an overall decrease in alpha power in blind participants.

No main effects or interactions were detected between EB and LB participants for any of the frequency bands during epochs of wakefulness (all $p$s > .114).

NREM sleep stages

There were no significant differences in either N1, N2 and N3 sleep stages detected between BL and SC (shown in Table 1 and 2). However, significant blindness onset x derivation interactions were observed for the delta, alpha, and theta frequency bands throughout NREM

sleep stages between congenitally and late blind participants. The following section details the observed effects between EB and LB for each of the frequency bands, separately, as common patterns were observed for the power spectra across the stages of NREM sleep.

Specifically, an interaction was found for the delta frequency in N3 sleep ($F(2, 14) = 5.638$, $p = .024$), where *post-hoc* pairwise comparisons revealed a trend for lower delta power in EB in the occipital derivation, although this failed to reach significance during *post-hoc* comparisons (all $p$s > .161). A similar, but marginal, pattern was also detected for the delta frequency in N2 sleep ($F(2, 14) = 3.836$, $p = .065$).

Significant blindness onset x derivation interactions were also detected for the theta frequency band during both N1 sleep ($F(2, 14) = 4.795$, $p = .048$) and N2 sleep stages ($F(2, 14) = 7.823$, $p = .021$). A similar trend was also observed during N3 sleep ($F(2, 14) = 4.203$, $p = .077$). In all cases, occipital theta power appeared to be lower in EB as compared to LB. *Post-hoc* comparisons, however, failed to show significant differences between the two groups for each electrode separately (all $p$s > .131).

Alpha power also showed a significant blindness onset x derivation interactions for both N2 sleep ($F(2, 14) = 7.596$, $p = .020$) and N3 sleep ($F(2, 14) = 5.747$, $p = .042$). Holm-Bonferroni corrected *post-hoc* comparisons revealed that, in N3 sleep, alpha power was significantly higher for EB than LB in the frontal derivation ($F(1, 7) = 11.565$, $p = .011$) and central derivation ($F(1, 7) = 10.076$, $p = .016$), while no differences were found for the occipital derivation ($F(1, 7) = 0.369$, $p = .563$). A similar pattern was observed for N2 sleep, although *post-hoc* comparisons failed to reveal significant differences between the two groups for each derivation separately (all $p$s > .065). Likewise, a marginal interaction, showing the same trend between EB and LB, was also detected for epochs of N1 sleep ($F(2, 14) = 4.015$, $p = .063$).

REM sleep

A group x derivation interaction for delta power was found between BL and SC ($F(2, 36) = 5.305$, $p = .029$). *Post-hoc* analysis revealed that delta power was lower in the blind participants in the frontal derivation ($F(1, 18) = 9.817$, $p = .006$), while no group differences were detected for the central or occipital derivations ($F(1, 18) = 0.113$, $p = .740$ and $F(1, 18) = 0.163$, $p = .691$, respectively). No other differences were detected, either between the BL and SC groups, or between EB and LB, apart from a marginal blindness onset x derivation interaction for theta power ($F(2, 14) = 4.723$, $p = .060$).

Wake and REM sleep frontal delta power results from ocular activity

As shown in Supplementary File 3, lower frontal delta activity in blind individuals during epochs of wakefulness and REM sleep are likely the result of reduced ocular activity in this population. Specifically, when segments containing eye movements were removed from analysis, no differences were found for the delta power between the blind and sighted participants in either wake or REM sleep.

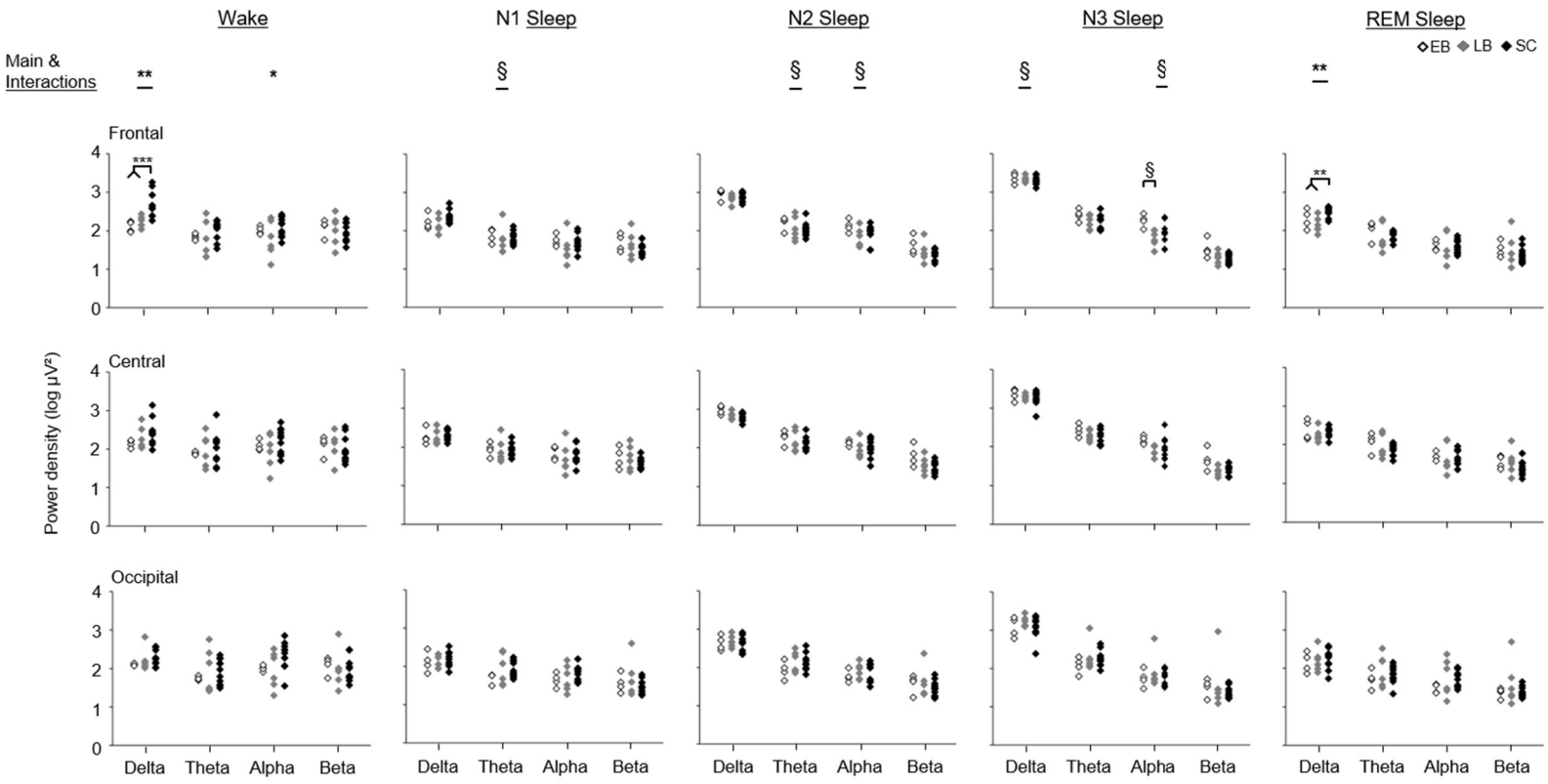


**Figure 2.** Spectral power density for the different frequency bands in the frontal (top panels), central (middle panels) and occipital (lower panels) derivation across the different sleep stages. Statistically significant differences between the blind and sighted and between the early and late blind participants are marked by '*' and '§', respectively. Statistical significance of each effect is marked by the number of symbols, such as */§ $p < .05$, **/§§ $p < .01$, ***/§§§ $p < .001$. Main effects and interactions with electrode derivations (underlined) are depicted in the top row, while derivation-specific effects are marked within the corresponding panels. See Figure 1 for abbreviations.

**Table 1.** Mean and SEM power spectra of each frequency band are reported for early blind ($n$ = 4), late blind ($n$ = 6), blind ($n$ = 10) and normal-sighted groups ($n$ = 11). Both overall and derivation specific values are reported. Epochs of wakefulness, N1, N2, N3, and REM sleep are reported in separate tables. ANCOVA p-values are reported for blindness (EB vs. LB) and group (BL vs. SC) effects. Statistical significance of the main group effects are reported in rows of 'overall' measures for all frequencies. Interactions between groups and derivations are reported in the electrode (frontal, central, and occipital) row for each frequency.

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **Wake** | Delta | Overall | 2.111 (0.059) | 2.249 (0.048) | .114 | 2.182 (0.065) | 2.483 (0.062) | .004 |
| | | Frontal | 2.103 (0.077) | 2.228 (0.063) | | 2.168 (0.086) | 2.718 (0.082) | |
| | | Central | 2.140 (0.108) | 2.286 (0.088) | .974 | 2.203 (0.094) | 2.459 (0.089) | .012 |
| | | Occipital | 2.090 (0.120) | 2.232 (0.098) | | 2.176 (0.071) | 2.273 (0.068) | |
| | Theta | Overall | 1.832 (0.180) | 1.897 (0.147) | .787 | 1.852 (0.102) | 2.007 (0.097) | .297 |
| | | Frontal | 1.839 (0.205) | 1.770 (0.167) | | 1.780 (0.102) | 2.036 (0.097) | |
| | | Central | 1.899 (0.169) | 1.975 (0.138) | .500 | 1.912 (0.117) | 2.054 (0.111) | .390 |
| | | Occipital | 1.758 (0.238) | 1.946 (0.194) | | 1.863 (0.128) | 1.931 (0.122) | |
| | Alpha | Overall | 2.034 (0.188) | 1.901 (0.153) | .600 | 1.922 (0.102) | 2.244 (0.097) | .039 |
| | | Frontal | 2.011 (0.201) | 1.781 (0.164) | | 1.841 (0.103) | 2.130 (0.097) | |
| | | Central | 2.088 (0.189) | 1.957 (0.154) | .407 | 1.969 (0.109) | 2.244 (0.104) | .386 |
| | | Occipital | 2.004 (0.205) | 1.966 (0.168) | | 1.955 (0.118) | 2.359 (0.112) | |
| | Beta | Overall | 2.087 (0.183) | 2.038 (0.150) | .841 | 2.038 (0.100) | 1.974 (0.095) | .655 |
| | | Frontal | 2.084 (0.181) | 2.021 (0.148) | | 2.035 (0.094) | 1.940 (0.090) | |
| | | Central | 2.098 (0.171) | 2.097 (0.140) | .785 | 2.067 (0.103) | 2.008 (0.098) | .799 |
| | | Occipital | 2.080 (0.221) | 1.995 (0.181) | | 2.012 (0.117) | 1.972 (0.111) | |

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **N1 Sleep** | Delta | Overall | 2.051 (0.100) | 2.182 (0.082) | .863 | 2.198 (0.052) | 2.288 (0.049) | .239 |
| | | Frontal | 2.241 (0.108) | 2.156 (0.088) | | 2.196 (0.060) | 2.353 (0.057) | |
| | | Central | 2.263 (0.106) | 2.252 (0.087) | .260 | 2.262 (0.054) | 2.310 (0.051) | .288 |
| | | Occipital | 2.112 (0.099) | 2.139 (0.081) | | 2.135 (0.065) | 2.200 (0.062) | |
| | Theta | Overall | 1.840 (0.140) | 1.865 (0.114) | .892 | 1.863 (0.075) | 1.872 (0.071) | .937 |
| | | Frontal | 1.876 (0.152) | 1.761 (0.124) | | 1.815 (0.078) | 1.809 (0.074) | |
| | | Central | 1.938 (0.132) | 1.902 (0.108) | .048 | 1.925 (0.071) | 1.897 (0.067) | .441 |
| | | Occipital | 1.705 (0.161) | 1.932 (0.132) | | 1.849 (0.092) | 1.909 (0.088) | |
| | Alpha | Overall | 1.742 (0.160) | 1.644 (0.130) | .652 | 1.674 (0.083) | 1.783 (0.079) | .369 |
| | | Frontal | 1.742 (0.173) | 1.533 (0.136) | | 1.613 (0.088) | 1.698 (0.084) | |
| | | Central | 1.839 (0.173) | 1.699 (0.141) | .063 | 1.741 (0.091) | 1.795 (0.086) | .169 |
| | | Occipital | 1.644 (0.157) | 1.702 (0.128) | | 1.667 (0.084) | 1.855 (0.080) | |
| | Beta | Overall | 1.658 (0.175) | 1.693 (0.143) | .879 | 1.682 (0.078) | 1.526 (0.075) | .179 |
| | | Frontal | 1.690 (0.160) | 1.637 (0.130) | | 1.663 (0.077) | 1.533 (0.073) | |
| | | Central | 1.725 (0.162) | 1.736 (0.132) | .188 | 1.728 (0.075) | 1.570 (0.071) | .718 |
| | | Occipital | 1.558 (0.215) | 1.706 (0.175) | | 1.655 (0.099) | 1.475 (0.094) | |

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **N2 Sleep** | Delta | Overall | 2.858 (0.058) | 2.785 (0.048) | .367 | 2.810 (0.041) | 2.788 (0.039) | .705 |
| | | Frontal | 2.953 (0.069) | 2.845 (0.057) | | 2.876 (0.040) | 2.886 (0.038) | |
| | | Central | 2.982 (0.055) | 2.830 (0.045) | .065 | 2.885 (0.038) | 2.831 (0.036) | .528 |
| | | Occipital | 2.638 (0.075) | 2.682 (0.062) | | 2.670 (0.061) | 2.648 (0.058) | |
| | Theta | Overall | 2.138 (0.119) | 2.123 (0.097) | .924 | 2.122 (0.067) | 2.099 (0.063) | .809 |
| | | Frontal | 2.197 (0.137) | 2.056 (0.112) | | 2.103 (0.073) | 2.041 (0.070) | |
| | | Central | 2.281 (0.122) | 2.167 (0.099) | .021 | 2.208 (0.066) | 2.124 (0.063) | .119 |
| | | Occipital | 1.936 (0.121) | 2.146 (0.99) | | 2.056 (0.081) | 2.132 (0.077) | |
| | Alpha | Overall | 2.007 (0.077) | 1.894 (0.063) | .297 | 1.945 (0.066) | 1.938 (0.063) | .942 |
| | | Frontal | 2.124 (0.108) | 1.818 (0.088) | | 1.949 (0.081) | 1.917 (0.077) | |
| | | Central | 2.132 (0.093) | 1.958 (0.076) | .020 | 2.034 (0.073) | 1.999 (0.069) | .510 |
| | | Occipital | 1.766 (0.078) | 1.907 (0.063) | | 1.853 (0.074) | 1.899 (0.070) | |
| | Beta | Overall | 1.670 (0.133) | 1.530 (0.108) | .441 | 1.582 (0.066) | 1.449 (0.063) | .172 |
| | | Frontal | 1.628 (0.135) | 1.446 (0.110) | | 1.503 (0.066) | 1.385 (0.063) | |
| | | Central | 1.799 (0.129) | 1.559 (0.105) | .289 | 1.651 (0.071) | 1.510 (0.067) | .868 |
| | | Occipital | 1.583 (0.181) | 1.586 (0.148) | | 1.593 (0.090) | 1.451 (0.086) | |

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **N3 Sleep** | Delta | Overall | 3.264 (0.048) | 3.286 (0.039) | .730 | 3.281 (0.052) | 3.220 (0.050) | .419 |
| | | Frontal | 3.367 (0.049) | 3.343 (0.040) | | 3.351 (0.038) | 3.341 (0.036) | |
| | | Central | 3.351 (0.043) | 3.296 (0.035) | .024 | 3.321 (0.051) | 3.256 (0.048) | .333 |
| | | Occipital | 3.072 (0.072) | 3.219 (0.059) | | 3.172 (0.080) | 3.063 (0.076) | |
| | Theta | Overall | 2.305 (0.078) | 2.268 (0.064) | .729 | 2.279 (0.060) | 2.247 (0.057) | .718 |
| | | Frontal | 2.407 (0.087) | 2.215 (0.071) | | 2.280 (0.064) | 2.224 (0.061) | |
| | | Central | 2.433 (0.067) | 2.295 (0.055) | .077 | 2.343 (0.058) | 2.260 (0.055) | .340 |
| | | Occipital | 2.074 (0.144) | 2.295 (0.117) | | 2.213 (0.090) | 2.258 (0.085) | |
| | Alpha | Overall | 2.060 (0.098) | 1.866 (0.080) | .169 | 1.947 (0.076) | 1.887 (0.072) | .586 |
| | | Frontal | 2.258 (0.104) | 1.804 (0.085) | | 1.984 (0.095) | 1.931 (0.090) | |
| | | Central | 2.177 (0.066) | 1.907 (0.054) | .042 | 2.014 (0.083) | 1.945 (0.079) | .953 |
| | | Occipital | 1.743 (0.182) | 1.886 (0.149) | | 1.842 (0.098) | 1.786 (0.093) | |
| | Beta | Overall | 1.568 (0.142) | 1.427 (0.116) | .466 | 1.487 (0.068) | 1.338 (0.065) | .142 |
| | | Frontal | 1.527 (0.103) | 1.301 (0.084) | | 1.383 (0.054) | 1.291 (0.054) | |
| | | Central | 1.671 (0.106) | 1.389 (0.086) | .326 | 1.498 (0.064) | 1.379 (0.061) | .445 |
| | | Occipital | 1.507 (0.283) | 1.592 (0.231) | | 1.580 (0.126) | 1.344 (0.120) | |

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **REM Sleep** | Delta | Overall | 2.285 (0.101) | 2.201 (0.082) | .539 | 2.241 (0.060) | 2.355 (0.057) | .196 |
| | | Frontal | 2.309 (0.114) | 2.148 (0.093) | | 2.217 (0.060) | 2.485 (0.057) | |
| | | Central | 2.398 (0.107) | 2.250 (0.088) | .168 | 2.310 (0.057) | 2.337 (0.054) | .029 |
| | | Occipital | 2.150 (0.117) | 2.205 (0.095) | | 2.194 (0.085) | 2.243 (0.081) | |
| | Theta | Overall | 1.938 (0.152) | 1.910 (0.124) | .888 | 1.923 (0.074) | 1.858 (0.071) | .546 |
| | | Frontal | 2.020 (0.171) | 1.828 (0.139) | | 1.903 (0.080) | 1.859 (0.076) | |
| | | Central | 2.071 (0.149) | 1.947 (0.122) | .060 | 1.998 (0.074) | 1.883 (0.070) | .581 |
| | | Occipital | 1.723 (0.175) | 1.954 (0.143) | | 1.867 (0.100) | 1.830 (0.095) | |
| | Alpha | Overall | 1.594 (0.165) | 1.653 (0.135) | .790 | 1.620 (0.081) | 1.678 (0.077) | .618 |
| | | Frontal | 1.607 (0.166) | 1.542 (0.136) | | 1.557 (0.079) | 1.595 (0.075) | |
| | | Central | 1.702 (0.161) | 1.656 (0.136) | .110 | 1.661 (0.081) | 1.677 (0.077) | .416 |
| | | Occipital | 1.473 (0.206) | 1.761 (0.168) | | 1.641 (0.105) | 1.762 (0.100) | |
| | Beta | Overall | 1.479 (0.169) | 1.553 (0.138) | .744 | 1.518 (0.079) | 1.391 (0.075) | .274 |
| | | Frontal | 1.516 (0.186) | 1.500 (0.152) | | 1.494 (0.091) | 1.388 (0.086) | |
| | | Central | 1.553 (0.141) | 1.560 (0.115) | .418 | 1.545 (0.073) | 1.420 (0.070) | .836 |
| | | Occipital | 1.367 (0.244) | 1.598 (0.200) | | 1.514 (0.110) | 1.366 (0.104) | |

Means and SEMs are corrected for covariate value of circadian phase (normal phase vs abnormal phases).
Abbr.: EB: early blind, LB: late blind, BL: blind, SC: sighted control.

**Table 2.** Summary of power spectra density differences between the blind (BL) and the sighted (SC) samples, and between the early (EB) and late (LB) blind samples. Summary includes the main effects for each frequency band, their interaction with electrode derivations, and electrode specific differences. Asterisks denote the statistical significance of these effects. The statistical significance of each effect is marked by asterisks: * $p < .05$, ** $p < .01$, *** $p < .001$.

| | | | Main effect | Interaction with derivations | Electrode derivation | | |
|---|---|---|---|---|---|---|---|
| | | | | | Frontal | Central | Occipital |
| **Wake** | | Delta | BL < SC *** | BL vs. SC ** | BL < SC * | | |
| | | Theta | | | | | |
| | | Alpha | BL < SC * | | | | [§]BL < SC ** |
| | | Beta | | | | | |
| **NREM** | **N1** | Delta | | | | | |
| | | Theta | | EB vs. LB * | | | |
| | | Alpha | | | | | |
| | | Beta | | | | | |
| | **N2** | Delta | | | | | |
| | | Theta | | EB vs. LB * | | | |
| | | Alpha | | EB vs. LB * | | | |
| | | Beta | | | | | |
| | **N3** | Delta | | EB vs. LB * | | | |
| | | Theta | | | | | |
| | | Alpha | | EB vs. LB * | EB > LB * | | |
| | | Beta | | | | | |
| **REM** | | Delta | | BL vs. SC ** | BL < SC * | | |
| | | Theta | | | | | |
| | | Alpha | | | | | |
| | | Beta | | | | | |

[§] Wake occipital alpha group differences are shown by relative power spectra analysis.

**Wake microstructure: occipital alpha oscillations**

Relative power ratios for each frequency band (delta, theta, alpha and beta) were examined both between BL and SC, and between EB and LB for stages of wakefulness and N1 sleep, separately. These power ratios are depicted in Figure 3. Expectedly, in SC individuals, alpha is the dominant frequency in the occipital derivation during epochs of wake. As sleep onset occurs, alpha power is reduced and delta power increases in N1 sleep. This dominance changes over to the delta frequency band during N1 sleep. Importantly, as compared to SC, wakefulness in BL was not characterized by a dominance in occipital alpha power. More specifically, alpha power during epochs of wakefulness was significantly lower in BL and SC ($F(1, 18) = 11.975$, $p = .003$). Conversely, greater beta power was observed in the wake epochs of the blind participants ($F(1, 18) = 10.945$, $p = .004$). No differences were detected between BL and SC for the relative delta power ($F(1, 18) = 0.036$, $p = .851$) and the relative theta power ($F(1, 18) = 0.997$ $p = .331$). Further, during N1 sleep, relative power did not differ between BL and SC for delta power ($F(1, 18) = 0.008$, $p = .928$), theta power ($F(1, 18) = 0.506$, $p = .486$), and alpha power ($F(1, 18) = 2.813$, $p = .111$). Relative beta power, however, remained greater in BL and SC during the N1 sleep stage ($F(1, 18) = 5.931$, $p = .026$).

No differences were found between EB and LB for any of the frequency bands, in both wake and N1 sleep stages (all $p$s > .098). In summary, occipital alpha dominance during wakefulness was reduced in blind individuals, with no differences detected between the early and the late blind samples. Reduced alpha activity was accompanied with increase beta power in occipital derivation, which also extended into the N1 sleep stage.

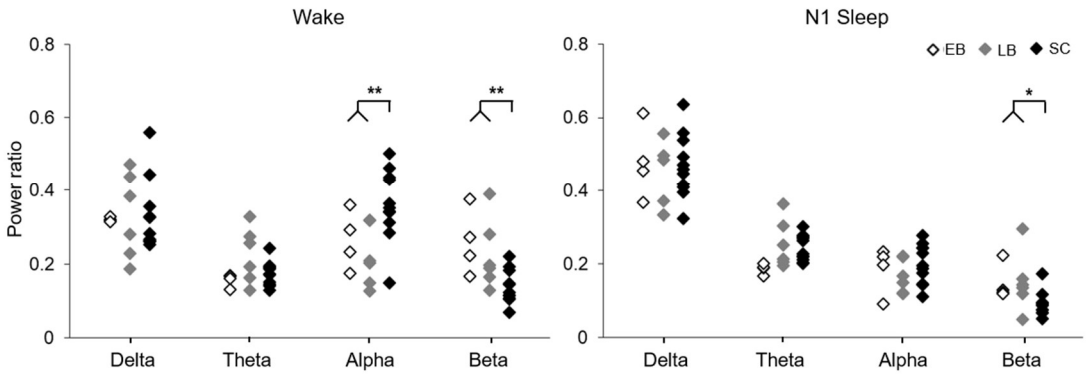


**Figure 3.** Power ratio of each frequency band in the occipital derivation within the wake (left) and N1 sleep (right) stages of the sleep period. * $p < .05$, ** $p < .01$. See Figure 1 for abbreviations.

**Sleep microstructure: sleep spindles, slow wave activity, and sawtooth waves**

Average measures of sleep spindle density, percentage of slow wave activity and sawtooth wave density and mean length are summarized in Table 3. Group differences between the blind and sighted sample, and between the early and late blind participants were examined through univariate ANCOVA measures for each microstructure component, separately, in their respective stages sleep.

For components of NREM sleep, no differences were found BL and SC for either slow or fast spindles during N2 sleep ($SS_{SLOW}$: $F(1, 18) = 0.035$, $p = .854$; $SS_{FAST}$: $F(1, 18) = 0.017$, $p = .898$) or N3 sleep ($SS_{SLOW}$: $F(1, 18) = 2.505$, $p = .131$; $SS_{FAST}$: $F(1, 18) = 0.184$, $p = .673$). Further, no statistical differences were detected between the groups for the percentage of slow wave activity during epochs of N2 sleep ($F(1, 18) = 0.141$, $p = .712$) and N3 sleep ($F(1, 18) = 0.005$, $p = .947$).

Similar results were observed for comparisons between EB and LB. Specifically, SS density, either fast or slow, showed no significant difference in either sleep stage (N2 sleep: $SS_{SLOW}$:

$F(1, 7) = 1.903$, $p = .210$; $SS_{FAST}$: $F(1, 7) = 2.238$, $p = .178$; N3 Sleep: $SS_{SLOW}$: $F(1, 7) = 0.063$, $p = .809$; $SS_{FAST}$: $F(1, 7) = 1.237$, $p = .303$). A marginal difference in $SWA_{\%}$, however, was detected between the two blind samples during epochs of N2 sleep ($F(1, 7) = 3.890$, $p = .089$), where EB tended to have, on average, a higher percentage of slow wave activity during this sleep stage. No such difference was found for the $SWA_{\%}$ in N3 sleep ($F(1, 7) = 0.311$, $p = .595$).

REM sleep sawtooth waves (STW) were detected in all sample groups with no differences detected in either their density or mean length between BL and SC (STW density: $F(1, 18) = 0.052$, $p = .822$; STW length: $F(1, 18) = 0.016$, $p = .901$). Similarly, no difference was detected between EB and LB participants (STW density: ($F(1, 7) = 2.664$, $p = .147$; STW length: $F(1, 7) = 2.731$, $p = .142$).

**Table 3.** Mean (± SEM) of NREM and REM sleep microstructure components, including sleep spindles (SS) density, slow wave activity (SWA), and sawtooth waves (STW) density and mean length, across blindness groups.

| | | | EB | LB | BL (CB + LB) | SC |
|---|---|---|---|---|---|---|
| $SS_{SLOW}$ | N2 Sleep | Frontal | 4.818 (0.469) | 3.916 (0.383) | 4.407 (0.358) | 4.462 (0.340) |
| | | Central | 5.047 (0.496) | 3.990 (0.405) | 4.610 (0.386) | 4.404 (0.367) |
| | | Occipital | 4.314 (0.695) | 3.360 (0.567) | 3.863 (0.402) | 3.718 (0.382) |
| | N3 Sleep | Frontal | 4.809 (1.099) | 3.705 (0.898) | 4.251 (0.579) | 3.234 (0.551) |
| | | Central | 3.931 (0.972) | 3.751 (0.794) | 3.896 (0.522) | 2.788 (0.496) |
| | | Occipital | 2.954 (0.810) | 3.332 (0.662) | 3.362 (0.446) | 2.199 (0.424) |
| $SS_{FAST}$ | N2 Sleep | Frontal | 4.854 (0.485) | 3.622 (0.396) | 4.265 (0.417) | 4.205 (0.396) |
| | | Central | 5.228 (0.522) | 4.063 (0.426) | 4.685 (0.389) | 4.555 (0.370) |
| | | Occipital | 4.636 (0.823) | 3.716 (0.672) | 4.228 (0.466) | 4.193 (0.443) |
| | N3 Sleep | Frontal | 3.581 (0.997) | 1.473 (0.814) | 2.435 (0.579) | 2.109 (0.550) |
| | | Central | 4.076 (0.987) | 1.986 (0.806) | 2.843 (0.565) | 2.750 (0.537) |
| | | Occipital | 4.565 (1.322) | 3.156 (1.079) | 3.370 (0.664) | 2.740 (0.631) |
| SWA(%) | | N2 Sleep | 7.463 (1.152) | 4.530 (0.940) | 5.597 (0.775) | 6.010 (0.737) |
| | | N3 Sleep | 27.845 (5.080) | 24.178 (4.148) | 25.924 (3.767) | 25.562 (3.582) |
| STW | | Density | 2.081 (0.279) | 1.493 (0.228) | 1.714 (0.265) | 1.800 (0.252) |
| | | Mean length | 2.708 (0.279) | 2.113 (0.228) | 2.374 (0.197) | 2.339 (0.188) |

EB: Early blind ($n$ = 4), LB: Late blind ($n$ = 6), BL: Blind ($n$ = 10), SC: Sighted controls ($n$ = 11)
Mean length measures of STW are reported in seconds. Reported means include covariate correction for circadian phase.

## Discussion

The present study examined if the absence of vision, either of early or late onset, has any impact on the microstructural EEG components of NREM and REM sleep. Although blind and sighted groups differed in occipital alpha and beta power during wakefulness, the present study did not find significant differences between the blind and the sighted samples for the microstructural components of sleep. In contrast, however, differences were observed for the EEG power spectral density between early and late blind individuals across the derivations throughout NREM, but not REM sleep.

### Lower occipital alpha activity in the blind during wake

Both early and late blind subjects showed significantly lower relative alpha power in the occipital area during the wake epochs within the sleep period. This finding is in line with previous studies that have shown that occipital alpha oscillations are absent in early blind individuals during resting state [51] or while performing non-visual sensory tasks [52-54]. A prospective study in late onset blindness reported a gradual decrease of occipital alpha oscillations within the first months of blindness onset [55]. The fact that we did not find a difference between early and late blind individuals can be most likely attributed to the fact that all late blind participants in this study had been blind for at least 8 years.

The occipital alpha rhythm is a common EEG characteristic that is present during resting state with eyes closed [43] and was initially suggested to reflect the idling of the visual cortex in the absence of visual input [56,57]. Recent studies, however, suggest that alpha rhythms may rather reflect functional inhibition [58] originating from GABAergic granular and infragranular pyramidal cells [59,60]. In congenitally blind individuals, the occipital cortex has a higher

resting-state metabolic rate, and is involved in the processing of non-visual sensory modalities and cognitive functions [17,61]. Interestingly, blind individuals showed a dominance of the beta frequency band during wake and N1 sleep, suggesting increased cortical activity of the occipital 'visual' cortex even during a relaxed wakeful state.

Preserved sleep microstructure in blindness

Sleep microstructure, including sleep spindles and slow wave activity in NREM sleep stages, and sawtooth waves in REM sleep, we detected in all participants, both blind and normal-sighted. Thus, it can be suggested that the absence vision does not lead to the abolishment of these microstructural components of sleep. Moreover, the current study failed to detect significant differences in the density of slow and fast sleep spindles during N2 and N3 sleep. This finding is at odds with earlier studies reporting either an increase [33] or a decrease of sleep spindles [34] in blind individuals. Although the function of sleep spindles remains to be elucidated, spindle density and frequency have been associated with sleep-gating and memory consolidation ([62-64] for examples), and are modulated by homeostatic and circadian influences [65,66]. In the present study, we controlled for the phase of the circadian rhythm by a dichotomic grouping of participants per the timing of their evening melatonin onset. Free-running circadian rhythms are more prevalent in complete blind individuals, which may indirectly modulate sleep spindle density.

Further, no significant differences were found for the percentage of slow wave activity, nor in delta power. The occurrence of slow wave activity is strongly dependent on the homeostatic drive for sleep [67], and has also been shown to play a role in memory consolidation, particularly hippocampal dependent processes, such as declarative memory [68,69]. There are conflicting

reports regarding the occurrence of slow wave activity during sleep in blindness. Whereas a few studies reported reduced slow wave activity in blind individuals [30-32], other studies did not find changes in either N3 sleep or in slow waves [28,29]. The present findings, as well as a previous report on the hypnographic structure of sleep in these same participants [28], suggest that slow wave activity and N3 sleep is, generally, preserved in healthy blind individuals.

Nevertheless, a marginal difference was found for $SWA_{\%}$ between the early and the late blind participants during N2 sleep, but not during N3 sleep. Associatively, the two blindness onsets were also differentiated by a small but significant interaction with the electrode derivations for the delta power in N3 sleep, and a marginal interaction in N2 sleep. These results, along with previous literature, can therefore suggest that, in a sub-group of blind individuals, the absence of vision may affect, either directly or indirectly, slow wave activity during sleep. However, further studies are needed to better understand this effect. For example, it may be that blindness is associated with medical or sleep associated disorders, such as sleep apnea, that affect the occurrence of slow wave sleep throughout the night.

Sawtooth waves, occurring during epochs of REM sleep, were observed in all participants. The present study failed to detect significant differences in either the density or the mean length of this component between groups andor blindness onset. Although their exact nature and function remains to be elucidated, sawtooth waves are correlated with other phasic events of REM sleep, notably transient muscle tone activity and rapid eye movements (REMs). Specifically, transient muscle tone typically precedes the occurrence of sawtooth waves, while REMs typically occur concurrently, or within a 5-s window from a sawtooth event [50,70]. Although rapid eye movements are reduced or absent in blind individuals [35,36], we here show that the associated sawtooth waves remain present in the absence of vision.

Thus, the study did not detect significant differences between the blind and sighted participants for any of the microstructural components of NREM and REM sleep. However, for the following reasons we cannot draw conclusion in confirming that these components are not affected by blindness and, therefore, are equivalent to that of normal-sighted individuals. First, the study is based on a relatively small group of blind and normal-sighted individuals, limiting the propensity to detect more subtle group differences. Second, most of these microstructural components of sleep are known to be dependent and modulated by various factors of demographical, medical and psychological nature. Therefore, although we did not detect significant group differences in the microstructural components of sleep, further studies are needed to further parse out any potential effects of the loss of vision on the mechanisms of sleep.

Altered EEG power in the blind

Power spectra density only showed few differences between blind and normal-sighted individuals. In particular, absolute alpha power was lower in blind than in sighted individuals during epochs of wakefulness. As we did not detect an interaction with electrode derivation, our results suggest a general reduction in absolute alpha power, although the strongest reduction is observed over the visual cortex. Frontal delta power was also found to be lower in blind individuals, both during periods of wake and REM sleep. However, such differences in frontal delta power may be attributed to eye movement artifacts, which are especially prominent in frontal channels. No other differences were observed in power spectral density between the blind and the sighted individuals.

On the other hand, small but significant interactions were observed between blindness type and electrode derivation for the delta, theta and alpha frequency bands throughout stages of

NREM sleep. Moreover, when comparing absolute power densities, shown in Table 1, late blind individuals tended to be more similar to the sighted controls than those born blind. Differences in spectral power may reflect differences in the underlying thalamo-cortical and cortico-cortical networks [71] associated with early and late blindness onset. Specifically, congenital blindness is associated with cortical reorganisation of visual as well as non-visual areas [16, 61, 72,73]. Moreover, blindness alters whole brain networking, and particularly the connections between the 'visual' cortex and other functional networks [74]. Importantly, however, these cortical changes are much less pronounced in late onset blindness [ex. 15,75,76]. Thus, differences in power density between early and late blind individuals across electrodes derivations may reflect differences in the underlying cortical networking. Nevertheless, we would like to stress the preliminary nature of these findings. Further studies using large sample sizes are needed to better understand changes in cortical activity during the sleep in blind individuals.

In summary, we examined various aspects of the microstructure of sleep between blind, including early and late blind, and normal-sighted individuals. Results show that, during wakefulness within the sleep period, the blind group had lower occipital alpha activity, as compared to the sighted group. In contrast, no differences were detected for the microstructure of both NREM and REM sleep, including sleep spindles, slow wave activity and sawtooth waves. Thus, the present results may suggest that the underlying processes of sleep, including sleep-gating and cortical plasticity events of memory formation, may be preserved in blindness. Differences between early and late blind individuals were, however, detected in the power spectral density across the frequency bands of NREM sleep. Such differences may reflect the cortical network reorganisation that is associated with the absence of vision.

**Supplementary File 1**

Comparison of power spectral densities between left and right hemispheres

## Methods

An analysis of variance was performed for each frequency band (delta, theta, alpha, and beta) and sleep stage. Analyses examined differences between power spectral densities from the left and right hemisphere electrodes, with hemisphere (left and right) and electrodes (frontal, central, and occipital) as within-subject factors. When a significant hemisphere effect or interaction with electrode derivations was detected, results were further examined across groups (blind vs sighted) or blindness (early vs late blind), with a covariance for circadian phase. Mean and standard error of means (SEM) are reported in associated tables for each of the sleep stages of interest: Wake, N1 sleep, N2 sleep, N3 sleep, and REM sleep.

## Result Summary

Overall, spectral power density was similar between the left and right hemispheres. Some significant differences were nevertheless observed between the hemispheres for the spectral power in the delta and alpha frequency bands of N1 sleep and alpha frequency during REM sleep. Further, interactions between hemisphere and electrode derivation for the beta power was also detected for stages of N1 and N2 sleep. In all cases, differences in hemispheres did not interact with participant samples, including groups (blind vs sighted) or blindness (early vs late blind), suggesting that these effects are similar for all participants.

## Results

**Table 1.** Summary of ANOVA results for the power spectra density between the left and right hemisphere, and interaction with electrode derivations.

| | Main hemisphere effect (Left vs. Right) | | | | Interaction with derivations (Frontal, Central, Occipital) | | | |
|---|---|---|---|---|---|---|---|---|
| | **Delta** | **Theta** | **Alpha** | **Beta** | **Delta** | **Theta** | **Alpha** | **Beta** |
| **Wake** | .309 | .165 | .456 | .703 | .769 | .463 | .536 | .492 |
| **N1** | >.001 | .177 | .016 | .608 | .898 | .100 | .387 | .028 |
| **N2** | .259 | .169 | .126 | .236 | .720 | .259 | .354 | .045 |
| **N3** | .191 | .760 | .622 | .290 | .367 | .119 | .205 | .058 |
| **REM** | .229 | .576 | .048 | .352 | .511 | .347 | .464 | .083 |

In N1 sleep, significant hemisphere effects were observed for the delta ($F(1, 20) = 18.801$, $p < .001$) and alpha frequency bands ($F(1, 20) = 6.924$, $p = .016$). Both delta and alpha spectral power were lower in the left hemisphere (delta: 2.237 ± 0.034 $\mu V^2$; alpha: 1.721 ± 0.054 $\mu V^2$) as compared to the right hemisphere (delta: 2.293 ± 0.032 $\mu V^2$; alpha: 1.753 ± 0.056 $\mu V^2$). Hemisphere differences in delta spectral power did not significantly interact with group ($F(1, 17) = 0.939$, $p = .346$) or blindness ($F(1, 6) = 0.445$, $p = .529$) participant samples. Likewise, no interaction was detected between hemisphere and group ($F(1, 17) = 0.658$, $p = .428$) nor between hemispheres and blindness ($F(1, 6) = 0.506$, $p = .503$) for the alpha frequency. Additionally, a significant interaction between hemisphere and derivations was detected for the beta power during N1 sleep ($F(2, 40) = 4.966$, $p = .028$). Beta power was greater in the right hemisphere for the frontal (right: 1.627 ± 0.043 $\mu V^2$; left: 1.585 ± 0.049 $\mu V^2$) and central derivations (right: 1.665 ± 0.041 $\mu V^2$; left: 1.628 ± 0.047 $\mu V^2$) while dominant in the left hemisphere for the occipital derivation (right: 1.500 ± 0.038 $\mu V^2$; left: 1.539 ± 0.065 $\mu V^2$). This effect did not interact with group ($F(2, 34) = 1.358$, $p = .267$) nor blindness ($F(2, 12) = 0.473$, $p = .557$).

A significant interaction between hemisphere and electrode derivation was also detected for the beta frequency band in the N2 sleep stage ($F(2, 42) = 4.254$, $p = .045$). Like N1 sleep, beta power was greater for in the right hemisphere for the frontal (right: $1.507 \pm 0.044\ \mu V^2$; left: $1.445 \pm 0.044\ \mu V^2$) and central derivations (right: $1.624 \pm 0.046\ \mu V^2$; left: $1.576 \pm 0.046\ \mu V^2$) but dominant in the left hemisphere in the occipital derivation (right: $1.470 \pm 0.039\ \mu V^2$; left: $1.506 \pm 0.058\ \mu V^2$). Furthermore, this effect did not interact with group ($F(2, 36) = 0.904$, $p = .369$) nor blindness ($F(2, 14) = 0.412$, $p = .551$).

Lastly, a significant hemisphere effects was observed for the alpha frequency ($F(1, 21) = 4.398$, $p < .048$), where alpha power was lower in the left ($1.636 \pm 0.051\ \mu V^2$) than the right hemisphere ($1.665 \pm 0.048\ \mu V^2$). This effect did not interact with group ($F(1, 18) = 0.752$, $p = .392$) or blindness ($F(1, 7) = 0.668$, $p = .441$) participant samples.

**Table 2.** Right hemisphere mean and SEM power spectra (log $\mu V^2$) of each frequency band are reported for early blind ($n$ = 4), late blind ($n$ = 6), blind ($n$ = 10) and normal-sighted groups (n = 11). Both overall and derivation specific values are reported. Epochs of wakefulness, N1, N2, N3, and REM sleep are reported in separate tables. ANCOVA p-values are reported for blindness (EB vs. LB) and group (BL vs. SC) effects. Statistical significance of the main group effects are reported in rows of 'overall' measures for all frequencies. Interactions between groups and derivations are reported in the electrode (frontal, central, and occipital) row for each frequency.

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **Wake** | Delta | Overall | 2.174 (0.042) | 2.249 (0.035) | .213 | 2.185 (0.060) | 2.511 (0.057) | .001 |
| | | Frontal | 2.212 (0.058) | 2.242 (0.047) | | 2.198 (0.077) | 2.751 (0.074) | |
| | | Central | 2.185 (0.095) | 2.310 (0.078) | .694 | 2.220 (0.081) | 2.487 (0.077) | .005 |
| | | Occipital | 2.124 (0.053) | 2.194 (0.043) | | 2.138 (0.067) | 2.294 (0.064) | |
| | Theta | Overall | 1.896 (0.147) | 1.904 (0.120) | .967 | 1.869 (0.088) | 2.047 (0.084) | .171 |
| | | Frontal | 1.928 (0.163) | 1.845 (0.133) | | 1.851 (0.086) | 2.067 (0.082) | |
| | | Central | 1.962 (0.159) | 2.012 (0.130) | .497 | 1.949 (0.102) | 2.097 (0.097) | .794 |
| | | Occipital | 1.798 (0.164) | 1.856 (0.134) | | 1.807 (0.103) | 1.978 (0.098) | |
| | Alpha | Overall | 2.014 (0.178) | 1.931 (0.145) | .728 | 1.916 (0.090) | 2.290 (0.086) | .009 |
| | | Frontal | 2.008 (0.163) | 1.817 (0.133) | | 1.851 (0.081) | 2.151 (0.077) | |
| | | Central | 2.087 (0.182) | 2.015 (0.149) | .305 | 1.987 (0.094) | 2.299 (0.089) | .061 |
| | | Occipital | 1.947 (0.213) | 1.959 (0.174) | | 1.909 (0.116) | 2.419 (0.110) | |
| | Beta | Overall | 2.050 (0.112) | 2.037 (0.091) | .928 | 2.008 (0.076) | 1.969 (0.072) | .717 |
| | | Frontal | 2.064 (0.109) | 2.036 (0.089) | | 2.023 (0.077) | 1.935 (0.073) | |
| | | Central | 2.103 (0.105) | 2.122 (0.085) | .799 | 2.073 (0.079) | 1.990 (0.075) | .202 |
| | | Occipital | 1.983 (0.145) | 1.952 (0.118) | | 1.929 (0.093) | 1.981 (0.088) | |

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **N1 Sleep** | Delta | Overall | 2.275 (0.069) | 2.174 (0.062) | .316 | 2.220 (0.048) | 2.353 (0.043) | .058 |
| | | Frontal | 2.324 (0.092) | 2.165 (0.082) | | 2.242 (0.063) | 2.408 (0.056) | |
| | | Central | 2.326 (0.073) | 2.231 (0.065) | .290 | 2.273 (0.052) | 2.389 (0.047) | .583 |
| | | Occipital | 2.175 (0.055) | 2.125 (0.049) | | 2.146 (0.051) | 2.262 (0.046) | |
| | Theta | Overall | 1.910 (0.129) | 1.830 (0.115) | .658 | 1.866 (0.075) | 1.900 (0.068) | .750 |
| | | Frontal | 1.977 (0.133) | 1.807 (0.199) | | 1.888 (0.076) | 1.853 (0.069) | |
| | | Central | 1.999 (0.118) | 1.888 (0.105) | .064 | 1.937 (0.074) | 1.953 (0.067) | .052 |
| | | Occipital | 1.754 (0.146) | 1.794 (0.130) | | 1.773 (0.087) | 1.894 (0.078) | |
| | Alpha | Overall | 1.814 (0.164) | 1.659 (0.147) | .511 | 1.713 (0.090) | 1.806 (0.081) | .464 |
| | | Frontal | 1.825 (0.154) | 1.590 (0.137) | | 1.688 (0.091) | 1.721 (0.082) | |
| | | Central | 1.909 (0.176) | 1.724 (0.157) | .099 | 1.788 (0.099) | 1.830 (0.089) | .046 |
| | | Occipital | 1.707 (0.173) | 1.664 (0.154) | | 1.663 (0.093) | 1.866 (0.084) | |
| | Beta | Overall | 1.710 (0.120) | 1.630 (0.107) | .636 | 1.666 (0.059) | 1.552 (0.053) | .179 |
| | | Frontal | 1.767 (0.116) | 1.634 (0.103) | | 1.700 (0.068) | 1.576 (0.062) | |
| | | Central | 1.803 (0.122) | 1.705 (0.109) | .416 | 1.746 (0.064) | 1.611 (0.058) | .653 |
| | | Occipital | 1.559 (0.141) | 1.549 (0.126) | | 1.551 (0.062) | 1.469 (0.056) | |

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **N2 Sleep** | Delta | Overall | 2.870 (0.052) | 2.779 (0.042) | .217 | 2.808 (0.041) | 2.806 (0.039) | .982 |
| | | Frontal | 2.973 (0.067) | 2.838 (0.055) | | 2.883 (0.043) | 2.886 (0.041) | |
| | | Central | 2.989 (0.045) | 2.812 (0.037) | .025 | 2.874 (0.043) | 2.861 (0.041) | .888 |
| | | Occipital | 2.647 (0.068) | 2.688 (0.056) | | 2.666 (0.055) | 2.672 (0.052) | |
| | Theta | Overall | 2.180 | 2.114 | .638 | 2.127 (0.064) | 2.127 (0.061) | .989 |
| | | Frontal | 2.253 (0.113) | 2.071 (0.093) | | 2.135 (0.066) | 2.073 (0.063) | |
| | | Central | 2.322 (0.098) | 2.173 (0.080) | .001 | 2.221 (0.064) | 2.172 (0.061) | .037 |
| | | Occipital | 1.967 (0.110) | 2.098 (0.090) | | 2.024 (0.074) | 2.131 (0.071) | |
| | Alpha | Overall | 2.038 (0.064) | 1.903 (0.052) | .149 | 1.956 (0.064) | 1.963 (0.061) | .937 |
| | | Frontal | 2.152 (0.078) | 1.847 (0.064) | | 1.978 (0.074) | 1.952 (0.070) | |
| | | Central | 2.163 (0.076) | 1.980 (0.062) | .015 | 2.054 (0.072) | 2.037 (0.068) | .422 |
| | | Occipital | 1.798 (0.081) | 1.883 (0.066) | | 1.835 (0.072) | 1.900 (0.068) | |
| | Beta | Overall | 1.762 (0.086) | 1.534 (0.070) | .077 | 1.607 (0.55) | 1.481 (0.052) | .121 |
| | | Frontal | 1.751 (0.103) | 1.513 (0.084) | | 1.589 (0.061) | 1.443 (0.058) | |
| | | Central | 1.900 (0.102) | 1.610 (0.083) | .373 | 1.715 (0.066) | 1.558 (0.063) | .408 |
| | | Occipital | 1.636 (0.079) | 1.477 (0.065) | | 1.518 (0.055) | 1.442 (0.052) | |

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **N3 Sleep** | Delta | Overall | 3.277 (0.039) | 3.288 (0.032) | .821 | 3.286 (0.052) | 3.234 (0.049) | .489 |
| | | Frontal | 3.389 (0.042) | 3.334 (0.034) | | 3.355 (0.043) | 3.333 (0.041) | |
| | | Central | 3.371 (0.037) | 3.302 (0.030) | .009 | 3.332 (0.054) | 3.276 (0.051) | .561 |
| | | Occipital | 3.069 (0.063) | 3.230 (0.052) | | 3.171 (0.071) | 3.093 (0.067) | |
| | Theta | Overall | 2.338 (0.053) | 2.235 (0.043) | .173 | 2.264 (0.056) | 2.267 (0.053) | .974 |
| | | Frontal | 2.446 (0.069) | 2.232 (0.056) | | 2.308 (0.057) | 2.265 (0.054) | |
| | | Central | 2.463 (0.051) | 2.296 (0.042) | .003 | 2.354 (0.057) | 2.304 (0.054) | .063 |
| | | Occipital | 2.105 (0.053) | 2.178 (0.043) | | 2.131 (0.069) | 2.232 (0.066) | |
| | Alpha | Overall | 2.089 (0.053) | 1.839 (0.043) | .008 | 1.935 (0.073) | 1.916 (0.069) | .862 |
| | | Frontal | 2.285 (0.089) | 1.837 (0.073) | | 2.019 (0.093) | 1.969 (0.088) | |
| | | Central | 2.203 (0.059) | 1.922 (0.048) | .018 | 2.033 (0.084) | 1.991 (0.080) | .523 |
| | | Occipital | 1.779 (0.064) | 1.758 (0.053) | | 1.752 (0.067) | 1.789 (0.064) | |
| | Beta | Overall | 1.650 (0.085) | 1.402 (0.069) | .058 | 1.497 (0.054) | 1.389 (0.051) | .180 |
| | | Frontal | 1.649 (0.092) | 1.400 (0.075) | | 1.496 (0.057) | 1.373 (0.054) | |
| | | Central | 1.750 (0.101) | 1.447 (0.083) | .347 | 1.570 (0.065) | 1.442 (0.062) | .507 |
| | | Occipital | 1.550 (0.080) | 1.360 (0.065) | | 1.424 (0.054) | 1.353 (0.051) | |

| | | Electrode | EB | LB | *sig.* | BL | SC | *sig.* |
|---|---|---|---|---|---|---|---|---|
| **REM Sleep** | Delta | Overall | 2.345 (0.070) | 2.195 (0.057) | .143 | 2.254 (0.053) | 2.375 (0.050) | .126 |
| | | Frontal | 2.394 (0.080) | 2.171 (0.065) | | 2.261 (0.054) | 2.503 (0.051) | |
| | | Central | 2.436 (0.067) | 2.246 (0.055) | .017 | 2.321 (0.054) | 2.376 (0.051) | .001 |
| | | Occipital | 2.205 (0.076) | 2.168 (0.062) | | 2.180 (0.061) | 2.246 (0.058) | |
| | Theta | Overall | 1.980 (0.125) | 1.893 (0.102) | .606 | 1.921 (0.065) | 1.881 (0.062) | .667 |
| | | Frontal | 2.085 (0.130) | 1.857 (0.106) | | 1.946 (0.068) | 1.877 (0.065) | |
| | | Central | 2.096 (0.109) | 1.940 (0.089) | .002 | 1.996 (0.064) | 1.935 (0.061) | .439 |
| | | Occipital | 1.760 (0.146) | 1.881 (0.119) | | 1.821 (0.080) | 1.830 (0.077) | |
| | Alpha | Overall | 1.645 (0.139) | 1.657 (0.113) | .951 | 1.637 (0.072) | 1.722 (0.069) | .418 |
| | | Frontal | 1.666 (0.126) | 1.571 (0.103) | | 1.602 (0.068) | 1.633 (0.065) | |
| | | Central | 1.750 (0.138) | 1.695 (0.112) | .031 | 1.701 (0.072) | 1.726 (0.069) | .087 |
| | | Occipital | 1.520 (0.165) | 1.704 (0.135) | | 1.607 (0.095) | 1.807 (0.090) | |
| | Beta | Overall | 1.554 (0.113) | 1.539 (0.092) | .925 | 1.530 (0.059) | 1.426 (0.056) | .237 |
| | | Frontal | 1.615 (0.149) | 1.571 (0.121) | | 1.581 (0.082) | 1.437 (0.078) | |
| | | Central | 1.635 (0.105) | 1.600 (0.086) | .657 | 1.597 (0.060) | 1.482 (0.057) | .357 |
| | | Occipital | 1.412 (0.103) | 1.447 (0.084) | | 1.411 (0.052) | 1.361 (0.049) | |

**Supplementary File 2**

Analysis of power spectral density across early blind, late blind and normal-sighted participants.

## Methods

An analysis of variance (ANCOVA) was performed for each frequency band (delta, theta, alpha, and beta) and sleep stage. Analyses examined group effects (independent factor), including early blind (EB, $n = 4$), late blind (LB, $n = 6$) and normal-sighted samples (SC, $n = 11$), and their interaction with electrode derivations (frontal, central and occipital; repeated measures) while covarying for the phase of the circadian rhythm. Mean and standard error of means (SEM) are reported in associated tables for each of the sleep stages of interest: Wake, N1 sleep, N2 sleep, N3 sleep, and REM sleep.

## Results

**Wake.** A significant group effect was detected for the delta frequency band ($F(2, 17) = 5.918$, $p = .011$). Bonferroni pairwise comparisons revealed significantly lower delta power in EB as compared to SC ($p = .016$). LB also tended to be lower than SC ($p = .097$) but did not differ from EB ($p = .890$). Further, a marginal group x derivation interaction was found for the delta frequency band ($F(4 , 34) = 2.915$, $p = .057$). Specifically, although differences between the blind and sighted groups was greatest in the frontal derivation, delta power was lower in EB throughout all derivations.

| | | Electrode | EB | LB | SC | *sig.* |
|---|---|---|---|---|---|---|
| **Wake** | Delta | Overall | 2.100 (0.101) | 2.238 (0.083) | 2.483 (0.062) | .011 |
| | | Frontal | 2.093 (0.135) | 2.218 (0.111) | 2.718 (0.082) | |
| | | Central | 2.115 (0.147) | 2.262 (0.121) | 2.459 (0.089) | .057 |
| | | Occipital | 2.091 (0.110) | 2.233 (0.091) | 2.273 (0.068) | |
| | Theta | Overall | 1.813 (0.162) | 1.878 (0.133) | 2.007 (0.097) | .561 |
| | | Frontal | 1.822 (0.162) | 1.753 (0.133) | 2.036 (0.097) | |
| | | Central | 1.866 (0.186) | 1.942 (0.153) | 2.054 (0.111) | .454 |
| | | Occipital | 1.755 (0.201) | 1.938 (0.165) | 1.931 (0.122) | |
| | Alpha | Overall | 2.002 (0.160) | 1.869 (0.132) | 2.244 (0.097) | .102 |
| | | Frontal | 1.979 (0.158) | 1.749 (0.130) | 2.130 (0.097) | |
| | | Central | 2.048 (0.172) | 1.917 (0.141) | 2.244 (0.104) | .449 |
| | | Occipital | 1.978 (0.188) | 1.940 (0.154) | 2.359 (0.112) | |
| | Beta | Overall | 2.067 (0.159) | 2.018 (0.131) | 1.974 (0.095) | .881 |
| | | Frontal | 2.072 (0.150) | 2.010 (0.123) | 1.940 (0.090) | |
| | | Central | 2.068 (0.165) | 2.067 (0.135) | 2.008 (0.098) | .910 |
| | | Occipital | 2.063 (0.186) | 1.978 (0.153) | 1.972 (0.111) | |

**N1 Sleep.** A significant group x derivation interaction was detected for the theta frequency band ($F(4, 34) = 4.506$, $p = .012$), where theta power appeared lower for EB in the occipital derivation. However, breakdown of this interaction failed to reveal electrode specific differences between the three groups (Frontal: $F(2, 17) = 0.275$, $p = .763$; Central: $F(2, 17) = 0.070$, $p = .933$; Occipital: $F(2, 17) = 0.914$, $p = .42$). A significant group x derivation was also found for the alpha frequency ($F(4, 34) = 3.717$, $p = .031$), where alpha power tends to be overall lower in LB, and is particularly lower in both blind groups in the occipital derivation, as compared to SC. However, univariate comparisons for each derivation separately, failed to reveal significant differences between the three groups (Frontal: $F(2, 17) = 0.977$, $p = .40$; Central: $F(2, 17) = 0.387$, $p = .685$; Occipital: $F(2, 17) = 1.220$, $p = .320$).

| | | Electrode | EB | LB | SC | *sig.* |
|---|---|---|---|---|---|---|
| **N1 Sleep** | Delta | Overall | 2.212 (0.083) | 2.188 (0.068) | 2.288 (0.049) | .498 |
| | | Frontal | 2.247 (0.094) | 2.162 (0.077) | 2.353 (0.057) | |
| | | Central | 2.268 (0.086) | 2.257 (0.071) | 2.310 (0.051) | .439 |
| | | Occipital | 2.120 (0.104) | 2.146 (0.086) | 2.200 (0.062) | |
| | Theta | Overall | 1.848 (0.119) | 1.873 (0.098) | 1.872 (0.071) | .983 |
| | | Frontal | 1.884 (0.123) | 1.769 (0.101) | 1.809 (0.074) | |
| | | Central | 1.947 (0.113) | 1.911 (0.093) | 1.897 (0.067) | .012 |
| | | Occipital | 1.713 (0.141) | 1.941 (0.116) | 1.909 (0.088) | |
| | Alpha | Overall | 1.732 (0.131) | 1.635 (0.108) | 1.783 (0.079) | .571 |
| | | Frontal | 1.738 (0.135) | 1.529 (0.110) | 1.698 (0.084) | |
| | | Central | 1.826 (0.142) | 1.685 (0.117) | 1.795 (0.086) | .031 |
| | | Occipital | 1.633 (0.134) | 1.691 (0.111) | 1.855 (0.080) | |
| | Beta | Overall | 1.661 (0.125) | 1.696 (0.103) | 1.526 (0.075) | .405 |
| | | Frontal | 1.694 (0.122) | 1.642 (0.100) | 1.533 (0.073) | |
| | | Central | 1.722 (0.119) | 1.733 (0.098) | 1.570 (0.071) | .361 |
| | | Occipital | 1.566 (0.156) | 1.714 (0.128) | 1.475 (0.094) | |

**N2 Sleep.** Significant group x derivation interactions were observed for theta ($F(4, 34) = 7.168$, $p = .003$) and alpha power ($F(4, 34) = 5.378$, $p = .008$). Theta power appeared to be lower in the occipital derivation for EB, as compared to LB and SC groups, although separate analyses for each derivation failed to show significant differences (Frontal: $F(2, 17) = 0.660$, $p = .529$; Central: $F(2, 17) = 0.761$, $p = .483$; Occipital: $F(2, 17) = 1.142$, $p = .342$). Likewise, although no significant differences were found for each electrode derivation separately, EB tended to have higher frontal alpha power, and slightly lower occipital alpha power (Frontal: $F(2, 17) = 2.216$, $p = .140$; Central: $F(2, 17) = 0.801$, $p = .465$; Occipital: $F(2, 17) = 0.566$, $p = .578$).

| | | Electrode | EB | LB | SC | *sig.* |
|---|---|---|---|---|---|---|
| **N2 Sleep** | Delta | Overall | 2.854 (0.064) | 2.781 (0.052) | 2.788 (0.039) | .631 |
| | | Frontal | 2.941 (0.060) | 2.833 (0.049) | 2.886 (0.038) | |
| | | Central | 2.976 (0.053) | 2.824 (0.044) | 2.831 (0.036) | .139 |
| | | Occipital | 2.644 (0.098) | 2.687 (0.080) | 2.648 (0.058) | |
| | Theta | Overall | 2.131 (0.107) | 2.116 (0.088) | 2.099 (0.063) | .966 |
| | | Frontal | 2.188 (0.114) | 2.047 (0.093) | 2.041 (0.070) | |
| | | Central | 2.276 (0.104) | 2.162 (0.085) | 2.124 (0.063) | .003 |
| | | Occipital | 1.929 (0.122) | 2.140 (0.100) | 2.132 (0.077) | |
| | Alpha | Overall | 2.013 (0.104) | 1.900 (0.085) | 1.938 (0.063) | .699 |
| | | Frontal | 2.132 (0.115) | 1.827 (0.095) | 1.917 (0.077) | |
| | | Central | 2.137 (0.112) | 1.966 (0.092) | 1.999 (0.069) | .008 |
| | | Occipital | 1.768 (0.114) | 1.909 (0.094) | 1.899 (0.070) | |
| | Beta | Overall | 1.666 (0.102) | 1.526 (0.084) | 1.449 (0.063) | .231 |
| | | Frontal | 1.612 (0.100) | 1.430 (0.082) | 1.385 (0.063) | |
| | | Central | 1.795 (0.103) | 1.555 (0.085) | 1.510 (0.067) | .393 |
| | | Occipital | 1.591 (0.144) | 1.594 (0.119) | 1.451 (0.086) | |

**N3 Sleep.** Similar patterns to N2 sleep were observed in N3 sleep including significant group x derivation interactions for the theta ($F(4, 34) = 4.459$, $p = .024$) and the alpha frequency bands ($F(4, 34) = 4.064$, $p = .026$). Overall, EB tended to have higher frontal but lower occipital theta power as compared to both LB and SC, although separate group effects failed to reach significance (Frontal: $F(2, 17) = 1.438$, $p = .265$; Central: $F(2, 17) = 1.255$, $p = .310$; Occipital: $F(2, 17) = 0.868$, $p = .438$). On the other hand, a significant group effect was found for the alpha power in the frontal derivation ($F(2, 17) = 4.222$, $p = .032$), where EB had significantly higher alpha power as compared to LB ($p = .032$) and tended to have higher levels than SC ($p = .126$). The LB group did not significantly differ from SC for frontal alpha power ($p > .999$). Further, no significant group differences were detected for the central ($F(2, 17) = 1.706$, $p = .211$) or occipital electrode derivation ($F(2, 17) = 0.346$, $p = .713$).

| | | Electrode | EB | LB | SC | *sig.* |
|---|---|---|---|---|---|---|
| **N3 Sleep** | Delta | Overall | 3.268 (0.084) | 3.290 (0.069) | 3.220 (0.050) | .713 |
| | | Frontal | 3.366 (0.060) | 3.341 (0.049) | 3.341 (0.036) | |
| | | Central | 3.355 (0.081) | 3.299 (0.066) | 3.256 (0.048) | .131 |
| | | Occipital | 3.084 (0.125) | 3.230 (0.103) | 3.063 (0.076) | |
| | Theta | Overall | 2.301 (0.096) | 2.264 (0.079) | 2.247 (0.057) | .898 |
| | | Frontal | 2.395 (0.096) | 2.203 (0.079) | 2.224 (0.061) | |
| | | Central | 2.426 (0.089) | 2.288 (0.073) | 2.260 (0.055) | .024 |
| | | Occipital | 2.080 (0.137) | 2.301 (0.112) | 2.258 (0.085) | |
| | Alpha | Overall | 2.063 (0.115) | 1.869 (0.095) | 1.887 (0.072) | .377 |
| | | Frontal | 2.257 (0.124) | 1.803 (0.102) | 1.931 (0.090) | |
| | | Central | 2.176 (0.122) | 1.906 (0.100) | 1.945 (0.079) | .026 |
| | | Occipital | 1.756 (0.154) | 1.899 (0.126) | 1.786 (0.093) | |
| | Beta | Overall | 1.571 (0.105) | 1.430 (0.087) | 1.338 (0.065) | .206 |
| | | Frontal | 1.518 (0.080) | 1.292 (0.066) | 1.291 (0.054) | |
| | | Central | 1.667 (0.087) | 1.386 (0.072) | 1.379 (0.061) | .255 |
| | | Occipital | 1.529 (0.201) | 1.614 (0.165) | 1.344 (0.120) | |

**REM Sleep**. A significant group x derivation interaction was detected for the delta frequency ($F(4, 34) = 4.086$, $p = .029$). More specifically, group differences in the delta power were observed for the frontal electrode derivation ($F(2, 17) = 6.111$, $p = .010$) but not for central ($F(2, 17) = 0.961$, $p = .40$) or occipital derivation ($F(2, 17) = 0.128$, $p = .88$). Bonferroni pairwise comparisons revealed lower delta power in the LB group as compared to SC ($p = .009$), but not between EB and LB ($p = .555$) nor EB and SC ($p = .398$). Further, a significant group x electrode derivation was observed for theta power ($F(4, 34) = 3.648$, $p = .038$). Theta power tended to be lower in the EB group in the occipital derivation, as compared to the LB and SC groups, however, no group differences were detected for any of the electrodes derivations separately (Frontal: $F(2, 17) = 0.848$, $p = .446$; Central: $F(2, 17) = 0.952$, $p = .405$; Occipital: $F(2, 17) = 0.738$, $p = .493$). Lastly, a significant group x derivation interaction was also observed for the alpha frequency band ($F(4, 34) = 3.527$, $p = .047$). Although group differences for each electrode

derivations separately failed to show significant effects, occipital alpha power appeared to be lowest in EB as compared to both LB and SC (Frontal: $F(2, 17) = 0.136$, $p = .874$; Central: $F(2, 17) = 0.049$, $p = .953$; Occipital: $F(2, 17) = 1.358$, $p = .284$).

| | | Electrode | EB | LB | SC | *sig.* |
|---|---|---|---|---|---|---|
| **REM Sleep** | Delta | Overall | 2.291 (0.095) | 2.207 (0.078) | 2.355 (0.057) | .349 |
| | | Frontal | 2.314 (0.091) | 2.153 (0.075) | 2.485 (0.057) | |
| | | Central | 2.399 (0.086) | 2.251 (0.071) | 2.337 (0.054) | 0.029 |
| | | Occipital | 2.161 (0.136) | 2.216 (0.112) | 2.243 (0.081) | |
| | Theta | Overall | 1.940 (0.12) | 1.911 (0.10) | 1.858 (0.071) | .823 |
| | | Frontal | 2.018 (0.122) | 1.825 (0.100) | 1.859 (0.076) | |
| | | Central | 2.072 (0.115) | 1.949 (0.094) | 1.883 (0.070) | .038 |
| | | Occipital | 1.729 (0.153) | 1.960 (0.126) | 1.830 (0.095) | |
| | Alpha | Overall | 1.584 (0.129) | 1.643 (0.106) | 1.678 (0.077) | .831 |
| | | Frontal | 1.596 (0.126) | 1.531 (0.104) | 1.595 (0.075) | |
| | | Central | 1.688 (0.128) | 1.642 (0.106) | 1.677 (0.077) | .047 |
| | | Occipital | 1.468 (0.159) | 1.756 (0.130) | 1.762 (0.100) | |
| | Beta | Overall | 1.473 (0.125) | 1.547 (0.103) | 1.391 (0.075) | .503 |
| | | Frontal | 1.504 (0.144) | 1.439 (0.119) | 1.388 (0.086) | |
| | | Central | 1.540 (0.117) | 1.548 (0.096) | 1.420 (0.070) | .509 |
| | | Occipital | 1.376 (0.169) | 1.607 (0.139) | 1.366 (0.104) | |

**Supplementary File 3**

Frontal delta power during epochs of Wakefulness and REM sleep in the presence or absence eye movements.

## Objective

Demonstrate that differences in frontal delta power during Wake and REM sleep between the blind and the sighted group is, at least in part, the result of the absence of ocular activity (eye movements, or EM) in blind individuals.

## Results Summary

- Lower frontal delta power in blind individuals, in both Wake and REM sleep.
- Removal of EM segments resulted in reduced frontal delta power in the normal-sighted group, while no changes were found for the blind group.
- No differences detected between the early and the late blind groups.

## Methods and Statistical Analysis

We used an automatic detector to identify epochs (4 s segments) containing EMs in the sleep stages of interest: Wake and REM sleep. Details on the automatic EM detection can be found in an associated report [S1]. Two EM conditions were created: one where EM-containing segments were included (EM included, same as main analysis), and the other where, EM-containing segments were removed from the data (EM removed).

Greenhouse-Geisser mixed ANCOVAs were computed to measure the influence of EMs on frontal delta power during both Wake and REM sleep, separately. EM condition (EM included vs EM removed) was measured as a repeated measure factor, while blindness (blind vs normal-sighted or early blind vs late blind) was kept as a between subject factor. Circadian phase

(normal phase or abnormal phase) was controlled as a covariate factor. Paired *t*-tests were used to breakdown significant ANCOVA interactions. Mean and SEM values of the EM and blindness conditions are reported below.

**Results**

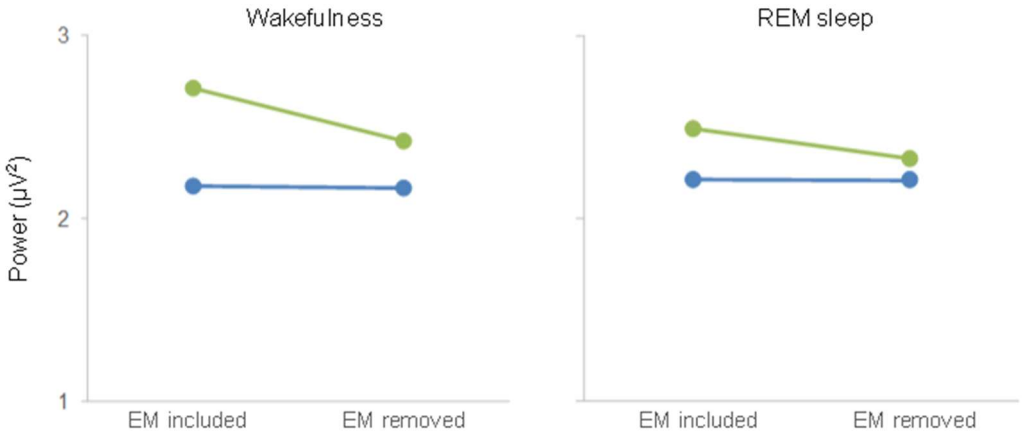


**Figure.** Differences in delta power in the blind (blue) and the sighted (green) groups for stages of wakefulness and REM sleep where eye movement activity was included or removed from the data.

Expectedly, significant overall group differences were found between blind and sighted individuals for both Wake ($F(1, 18) = 15.706$, $p = .001$) and REM Sleep ($F(1, 18) = 5.001$, $p = .038$). Further, as reported in the main study, no main effect of the onset of blindness, either early or late, was detected (Wake: $F(1, 7) = 1.387$, $p = .277$; REM sleep: $F(1, 7) = 1.199$, $p = .310$). Importantly, a significant interaction between groups (blind and normal-sighted) and EM removal was observed for both Wake ($F(1, 18) = 23.604$, $p < .001$) and REM sleep ($F(1, 18) = 11.659$, $p = .003$). Specifically, as shown in the figure below, EM removal did not affect the frontal delta power in blind individuals (Wake: $t(9) = 1.563$, $p = .153$; REM: $t(9) = 1.167$, $p =$

.273), but reduced delta activity in the normal sighted group (Wake: $t(10) = 5.659$, $p < .001$ ; REM: $t(10) = 4.126$, $p = .002$). This interaction was absent when comparing early and late blind individuals (Wake: $F(1, 18) = 1.073$, $p = .335$; REM sleep: $F(1, 18) = 1.256$, $p = .299$).

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# DISCUSSION GÉNÉRALE

Les études, qui composent cette présente thèse, ont examiné diverses facettes du sommeil chez un groupe d'aveugles ayant une cécité complète. La qualité et la structure du sommeil, ainsi qu'une mesure du rythme circadien furent évaluées de façon comparative à un groupe contrôle de participants ayant une vision normale ou corrigée à la normale. Les résultats confirment la majorité des hypothèses et démontrent une plus grande fréquence de troubles du sommeil et de rythmes circadiens chez le groupe avec cécité. De plus, certaines différences sont observées entre les aveugles et le groupe contrôle quant à la macro- et microstructure du sommeil, particulièrement en lien avec les composantes associées à la vision et le cortex visuel. Les résultats et les hypothèses associés sont résumés au cours des prochaines sections.

## Un lien entre la cécité, les troubles du sommeil et les rythmes circadiens anormaux

À titre de première étape, la présence de troubles du sommeil chez le groupe aveugle fut mesurée par le *Pittsburg Sleep Quality Index*. Le score global du questionnaire est un indice clinique d'un sommeil dérangé, ainsi que la sévérité de ce trouble de sommeil. En lien avec les études préalables, ainsi que la première hypothèse de la présente thèse, les résultats du questionnaire confirment une incidence plus élevée de troubles du sommeil chez les aveugles comparés aux individus ayant une vision normale. Cet effet n'est, toutefois, pas observé de façon uniforme parmi tous les participants avec cécité. Environ 1/3 des participants aveugles rapportent un trouble de sommeil sévère, 1/3 rapportent un trouble de sommeil léger, alors que le dernier 1/3 ne présentent pas de symptômes d'un sommeil troublé (score global PSQI < 5). Contrairement, la majorité des participants du groupe contrôle démontrent une bonne qualité de

leur sommeil. De plus, l'absence de différences entre les aveugles congénitaux et tardifs supporte les études antérieures démontrant que le degré de cécité, plutôt que l'étiologie ou l'âge de la perte de vision, serait un facteur déterminant pour la présence de troubles du sommeil parmi la population aveugle [Tabandeh et al., 1998]. Les résultats du questionnaire PSQI corroborent, donc, la présence d'une plus grande fréquence de troubles du sommeil chez les individus aveugles comparativement à la population avec une vision normale (p. ex. [Tabandeh et al., 1998; Lockley et al., 1999; Léger et al., 2002; Meaidi et al., 2014]). La présence de troubles de sommeil chez les aveugles fut originellement rapportée par Migeon et collègues en 1958 et fut, depuis, confirmée par diverses études. Les troubles du sommeil possèdent une origine multifactorielle. Toutefois, plusieurs études démontrent que chez la population aveugle, en particulier celle n'ayant aucune perception résiduelle de la lumière, les troubles du sommeil proviennent, du moins en partie, d'une altération du rythme circadien par l'absence de vision [Uchiyama & Lockley, 2015; Flynn-Evans, et al., 2014].

Ainsi, pour une deuxième partie de l'étude, le profil de deux marqueurs biologiques du rythme circadien, soit la mélatonine et le cortisol, fut examiné pour tous les participants. La période de sécrétion de mélatonine (*melatonin onset*), le pic matinal de cortisol (*cortisol awakening response*), ainsi que leur concentration moyenne au cours de 24-heures furent déterminés à partir d'échantillons de salive collectés à un intervalle de 2-heures. Tel présenté dans l'hypothèse originale, et mesuré par la période de sécrétion de la mélatonine, une plus grande fréquence de phase anormale du rythme circadien fut observée chez le groupe aveugle comparé aux participants avec une vision normale ou corrigée à la normale. Contrairement, aucune différence ne fut détectée entre les deux groupes pour le profil du cortisol. Ces résultats, quoiqu'ils aillent à l'encontre de l'hypothèse originale, ne sont, toutefois, pas entièrement

inattendus. La sécrétion du cortisol est dépendante de divers facteurs non-circadiens, tels le niveau de stress et la nutrition [Lovallo, Farag, Vincent, Thomas, et Wilson, 2006]. En particulier, la réponse matinale de cortisol s'avère être une réponse naturelle suite à l'éveil [Wilhelm, Born, Kudielka, Schlotz, et Wüst, 2007] et dépend peu de l'influence circadienne. Cependant, quoique la période du pic matinal de cortisol ne fut différente entre les deux groupes, l'occurrence de la période de quiescence du cortisol demeure, dans la majorité des cas, en lien avec la période de sécrétion de la mélatonine. Ceci suggère, ainsi, que ces deux marqueurs biologiques demeurent synchronisés même lors d'une phase anormale du rythme circadien. De plus, une mesure de l'aire sous la courbe a démontré une plus grande concentration de mélatonine au cours des 24 heures chez les participants avec cécité. Ce résultat semble contradictoire aux études démontrant qu'une perturbation du rythme circadien provoque une baisse de l'amplitude des marqueurs biologiques associés, telle la mélatonine [Turner, van Someren, et Mainster, 2010; Dijk et al., 2012]. En particulier, chez les participants aveugles possédant une phase anormale du rythme circadien, une telle atténuation de l'amplitude de la concentration de mélatonine ou de cortisol fut observée. Ainsi, il est possible que la sécrétion de la mélatonine demeure élevée chez les aveugles, même dans les cas de désynchronisation du rythme circadien endogène, par l'absence de l'effet suppressif de la lumière dû à la cécité.

Les résultats confirment, donc, les études antérieures démontrant que la cécité peut engendrer une anormalité du rythme circadien, qui peut se traduire en un décalage de phase, un rythme circadien non-détectable ou un rythme circadien en libre cours (p. ex. [Lockley et al., 1999; Skene et al., 1999]). Ainsi, tel démontré dans la présente étude, et dans diverses études antérieures (ex. [Lockley et al., 1999]), la perte de vision résulte en une altération du rythme circadien chez certains (environ 50%), mais pas tous les aveugles. En particulier, une altération

du rythme circadien sous-jacent se voit plus élevée chez les aveugles ayant une perte complète de vision [Tabandeh et al., 1998]. L'absence d'une relation directe entre la perte de vision et la présence de rythmes circadiens en libre cours peut avoir différentes origines. D'abord, la transmission de l'information photique par les cellules ganglionnaires intrinsèquement photoréceptrices de la rétine au SCN, par la voie rétinohypothalamique, se diffère du système visuel classique, où l'information captée par les cônes et les bâtonnets de la rétine est transmise au cortex visuel, en passant par les noyaux géniculés latéraux dorsaux (*dorsal lateral geniculate nucleus*) de l'hypothalamus. Ainsi, une perte de la vision, soit au niveau perceptuel, n'est directement associée à une perte de la projection de l'information photique au SCN. Ainsi, tel démontré par les souris déficientes du *cone-rod-homeobox* (*Crx -/-*) qui, même en absence de photorécepteurs cônes et bâtonnets fonctionnels, peuvent maintenir une synchronicité de leur rythme circadien par l'activité des photorécepteurs de mélanopsine des cellules ganglionnaires de la rétine [Rovsing, Rath, Lund-Andersen, Klein et Møller, 2010]. Une telle préservation de la synchronisation de l'horloge biologique à l'environnement par l'information photique fut aussi démontrée chez les humains avec cécité [Czeisler et al., 1995; Klerman et al., 2002]. Une seconde possibilité pour le maintien d'un rythme circadien stable est que, même en absence d'un système visuel 'non-perceptif' fonctionnel, le rythme circadien peut maintenir une synchronicité à l'environnement par l'entremise de zeitgebers secondaires, telle la régularité de repas et de consommation de nourriture, d'exercice et autres sources sociales [Mistlberger et Skene, 2004; Stephan, 2002; Miyazaki, Hashimoto, Masubuchi, Honma, et Honma, 2001]. Ceci est particulièrement vrai pour un rythme circadien endogène dont la période est près de 24-heures. Ainsi, quoique la vision et l'information photique jouent un rôle principal dans le maintien du rythme circadien à l'environnement, d'autres sources environnementales et sociales permettent

un support additionnel, parfois même suffisant pour le maintien d'une synchronicité au rythme jour-nuit de 24-heures.

Dans la présente étude, la rythmicité du cycle éveil-sommeil fut aussi examinée par des enregistrements d'actigraphie et ceux-ci complémentés par des journaux de sommeil. Ainsi, l'éveil et le sommeil de chaque participant furent examinés au cours d'une période de 30-jours, où une mesure de la période et de l'efficacité du sommeil en furent dérivées pour chacune des journées. Contrairement à l'hypothèse de base, il n'y a pas eu de différences observées entre les participants aveugles et avec une vision normale pour les mesures moyennées de la période d'enregistrement. Toutefois, les aveugles démontrent une plus grande variabilité de l'efficacité et de la période du sommeil, en particulier pour l'heure de leur réveil matinal. De plus, la perturbation du sommeil, telle mesurée par le PSQI, corrèle avec la variabilité des données d'actigraphie, incluant l'efficacité du sommeil (*sleep efficiency*), ainsi que l'heure d'endormissement (*sleep onset*) et d'éveil (*sleep offset*). Ainsi, les participants, qui reportèrent une plus grande sévérité de troubles du sommeil, démontrent une plus grande variabilité de leur sommeil au cours des 30 jours de l'étude. Ces individus ont donc vécu des nuits de bon sommeil et des nuits avec un sommeil perturbé. Au contraire, les individus qui ne présentèrent des troubles de sommeil (soit un score PSQI < 5) avaient une période et une qualité éveil-sommeil plus stable. De façon intéressante, puisque la période et la qualité du sommeil sont associées à la phase du rythme circadien [Lockley et al., 1999; O'Donnell et al., 2009], la variabilité de ceux-ci chez le groupe avec une cécité pourrait donc sous-tendre la présence d'un changement transitoire du rythme circadien chez ces individus.

Ainsi, les résultats de cette première étape de l'étude confirment une incidence plus élevée de troubles du sommeil reportés chez les aveugles comparativement à ceux avec une vision

normale ou corrigée à la normale. Ceci fut davantage associé à une plus grande variabilité du rythme éveil-sommeil chez les aveugles, incluant l'efficacité de leur sommeil au cours d'une période de 30-jours. En lien avec ces résultats, une plus grande proportion de phases anormales du rythme circadien fut observée chez le groupe aveugle. Ces résultats suggèrent ainsi que la perte de vision peut, chez certains individus aveugles, influencer considérablement la qualité de leur sommeil, et que ceci est, du moins en partie, le résultat d'une altération du rythme circadien sous-jacent.

## La structure du sommeil demeure, en général, préservée en absence de vision.

En addition à une fréquence plus élevée de troubles du sommeil et de rythmes circadiens anormaux chez les individus avec cécité, diverses études ont aussi démontré que la cécité, surtout lorsqu'elle survient lors des premières années de vie, engendre une réorganisation corticale non seulement dans les aires visuelles, mais dans l'entièreté du cerveau [Kupers and Ptito, 2014; Cecchetti et al., 2016; Park et al., 2009; Ptito et al., 2008]. Ainsi, il est d'intérêt de déterminer si les composantes de la structure physiologique du sommeil sont sujettes à des altérations par l'absence de vision. Jusqu'à présent, la structure du sommeil des personnes aveugles n'a fait l'objet d'un grand intérêt scientifique. La présente étude fournit donc des données originales sur la macrostructure et la microstructure du sommeil chez un groupe d'aveugles congénitaux et tardifs. La mesure de la phase du rythme circadien, par la période de sécrétion de mélatonine, a permis un contrôle, du moins en partie, pour l'influence circadienne sur la physiologie du sommeil. En particulier, plusieurs études antérieures ont démontré que le

rythme circadien module la structure du sommeil particulièrement au niveau de sa fragmentation et la proportion du sommeil REM (ex. [Dijk et Czeisler, 1995]). Le rythme circadien influence aussi la microstructure du sommeil, telle l'occurrence de fuseaux de sommeil lors du sommeil NREM [Dijk, et al., 1997]. Les résultats de la présente étude supportent une telle influence du rythme circadien sur la structure du sommeil. En particulier, lorsque la phase du rythme circadien est normale, aucune différence n'est observée entre les participants aveugles, soit congénitaux ou tardifs, et les participants avec une vision normale. Ainsi, en lien avec les hypothèses de base, les résultats suggèrent que la perte de vision ne serait directement un facteur modulatoire de la macrostructure du sommeil. Toutefois, la macrostructure du sommeil s'avère modulée par une phase anormale du rythme circadien, une condition qui se voit plus fréquente en absence de vision.

Les études antérieures reportent des résultats équivoques quant à la microstructure du sommeil, particulièrement pour la présence d'ondes lentes et des fuseaux de sommeil. En général, certains suggèrent une altération du sommeil d'ondes lentes en absence de vision [Krieger et Glick, 1971; Hono et al. 1999; 2000; Ayala-Guerrero et Mexicano, 2015], tandis que d'autres (p. ex. [Léger et al., 2002]) n'ont reporté de différence pour cette composante du sommeil. Pour les fuseaux de sommeil, une étude suggère une réduction [Hono et al., 2000] chez les individus avec cécité. Cependant, une seconde étude démontre une augmentation de l'occurrence de fuseaux de sommeil suite à la cécité par la réduction de l'information sensorielle ascendante lors du sommeil, permettant une meilleure stabilité et synchronisation de l'activité thalamo-corticale lors du sommeil NREM [Scrofani et al., 1996]. Les résultats de la présente étude démontrent que la microstructure du sommeil demeure, en général, préservée en absence de vision. Aucune différence ne fut observée entre les participants aveugles et ceux avec une

vision normale pour la présence de l'activité d'ondes lentes et de fuseaux de sommeil lors du sommeil NREM et la présence d'ondes en dents-de-scie lors du sommeil REM. Spécifiquement, ces composantes du sommeil furent détectées chez tous les participants. Des différences furent, par contre, observées entre les deux groupes pour l'oscillation occipitale de la bande de fréquence alpha lors des périodes d'éveil qui précèdent l'endormissement. Cette activité occipitale est une caractéristique typique d'un état de repos où les yeux sont fermés [Niedermeyer, 2005] et reflète l'activité inhibitrice des neurones GABAergiques de cellules pyramidales granulaires et infragranulaires des aires visuelles [Jensen & Mazaheri, 2010; Bollimunta et al., 2008]. Particulièrement, cette activité se voit réduite chez les aveugles. En contrepartie, chez ces individus, les dérivations occipitales se démarquent plutôt par une dominance de l'activité de la bande de fréquence bêta lors des époques d'éveil et de sommeil de stade N1. Ces résultats supportent ainsi une augmentation de l'activité métabolique de base du cortex occipital des aveugles [De Volder et al., 1997], par son implication dans le traitement d'informations provenant des autres modalités sensorielles et fonctions cognitives [Kupers et Ptito, 2014].

L'étude sur la microstructure du sommeil a aussi relevé des petites différences dans l'activité spectrale de la bande de fréquence delta, thêta et alpha lors des stades du sommeil NREM entre les aveugles congénitaux et les aveugles tardifs. En particulier, l'activité corticale de ceux ayant perdu leur vision plus tard dans la vie était plus similaire à celle du groupe avec une vision normale. Ces résultats sont en ligne avec les études précédentes qui démontrent des différences entre les aveugles congénitaux et tardifs (p. ex. [Noppeney, 2007; Sadato, Okada, Honda, et Yonekura, 2002]), et proposent que les différences observées reflèteraient une réorganisation du réseau cortical lorsque la cécité a lieu tôt dans la vie.

En résumé, les résultats de cette présente thèse démontrent que la perturbation du rythme circadien peut engendrer une altération de la période et la composition des différents stades du sommeil. De plus, bien que le sommeil et l'activité thalamo-corticale, qui sous-tend ses différents stades, se voient présents même en absence de vision, la réorganisation corticale qui provient de la cécité module certaines composantes caractéristiques du sommeil, particulièrement celles associées à l'activité visuelle, telle l'activité oscillatoire occipitale de la bande de fréquence alpha.

## Avantages et originalité de l'étude

La présente étude a examiné diverses variables comportementales et physiologiques du sommeil et du rythme circadien afin de déterminer les effets de la cécité sur celles-ci. Spécifiquement, il s'agit d'une étude comparative entre un groupe de participants aveugles, soit congénitaux, soit qui ont développé une cécité complète au cours de leur vie, et un groupe de participants avec une vision normale ou corrigée à la normale. L'avantage principal de cette présente thèse est que chaque facette de l'étude fut effectuée sur les mêmes groupes de participants. Ceci permet ainsi d'explorer davantage les liens entre la présence de troubles du sommeil, le cycle éveil-sommeil, la phase du rythme circadien, ainsi que les données électrophysiologiques du sommeil.

Cette étude a ainsi permis de confirmer plusieurs liens entre la perte de vision et la qualité et la composition du sommeil. De plus, la présente étude démontre de nombreux résultats originaux permettant de mieux approfondir les connaissances sur la relation entre la vision, les rythmes circadiens et le sommeil. En particulier, la présente fut la première à utiliser des données longitudinales d'actigraphie pour démontrer une plus grande variabilité de la période et de

l'efficacité du sommeil chez les individus avec cécité, et que celles-ci soient associées à la perturbation du sommeil de ces individus. De plus, les résultats du deuxième article ont, non-seulement, confirmés une incidence plus élevée de phases anormales du rythme circadien chez les aveugles, mais aussi une plus grande sécrétion de mélatonine au cours d'une période de 24-heures. De plus, la concentration de mélatonine au cours des 24-heures corrèle avec les perturbations de sommeil rapportées par les participants. Ces résultats suggèrent ainsi que, chez les individus aveugles, il y a une absence de l'effet suppressif de la lumière sur la sécrétion de mélatonine. En conséquence, il se peut que le potentiel de synchronisation de l'horloge biologique par la lumière soit aussi altéré chez ces individus. Les articles 3 et 4 ont abordé diverses composantes physiologiques du sommeil, incluant sa macrostructure et diverses composantes microstructurales. En particulier, ces mesures PSG furent associées à une mesure concomitante de la phase du rythme circadien, un aspect important qui n'a été que peu abordé dans les études antérieures. Ainsi, ceci a permis d'identifier l'influence directe ainsi qu'indirecte de la cécité sur la structure physiologique du sommeil.

# Limites de l'étude

Bien que les résultats de cette étude supportent et enrichissent les connaissances sur les effets de la perte de vision sur le sommeil et les rythmes circadiens, il importe de souligner quelques facteurs limitants et considérations additionnelles de la présente étude.

### 1. Taille de l'échantillon

En particulier, la présente étude fut menée sur un échantillon limité, soit de 11 individus aveugles et 11 individus avec une vision normale ou corrigée à la normale. Les participants

aveugles furent principalement recrutés à partir d'une base de données du *Brain Research and Integrative Neuroscience Laboratory* (BRAINlab). Néanmoins, le nombre d'individus aveugles disponibles et conformes aux critères de l'étude demeure limité. Spécifiquement, le recrutement fut limité à des individus reportant une cécité complète de la vision, soit une sous-catégorie des individus aveugles. De plus, afin de réduire la présence de facteurs potentiels pouvant influencer et corrompre les données, de stricts critères d'inclusion ont été mis en place lors de la sélection des participants. Ce dépistage avait pour but d'exclure toute source médicale et psychiatrique pouvant influencer la qualité et la structure du sommeil. Le style de vie fut aussi pris en considération, particulièrement lors de la première partie de l'étude où le rythme éveil-sommeil et la stabilité du rythme circadien furent examinés. Ainsi, tous les participants représentés dans cette étude étaient en bonne santé et ne présentaient pas de facteurs médicaux comorbides. Toutefois, cet échantillon ne s'avère, en conséquence, pas entièrement représentatif de la population générale, autant pour les participants aveugles que ceux ayant une vision normale ou corrigée à la normale. En particulier, les individus ayant perdu leur vision présentent parfois des troubles, symptômes, ou maladies connexes. Par exemple, la rétinopathie de la prématurité est aussi associée à un sous-développement des voies respiratoires ainsi qu'un neurodéveloppement compromis suite à une naissance prématurée [D'Angio et Maniscalco, 2004]. De plus, la cécité engendre souvent un style de vie plus sédentaire qui peut avoir des conséquences néfastes sur l'humeur et le sommeil [Sherrill, Kotchou, Quan, 1998; Fox, 1999]. Ainsi, il est fort probable que le nombre de troubles du sommeil soit plus élevé dans la population générale, comparativement à l'échantillon de la présente étude, où les participants sont relativement en bonne santé. Néanmoins, malgré une exclusion active de facteurs pouvant affecter la qualité du sommeil, une plus grande fréquence de troubles du sommeil et de rythmes circadiens anormaux

fut observée parmi l'échantillon aveugle, suggérant ainsi que la cécité peut moduler, chez environ la moitié des individus, leur rythme circadien et, en conséquence, leur sommeil.

Les difficultés de trouver des participants aveugles remplissant les critères d'inclusion, tels que mentionnés ci-dessus, présentent des limites statistiques pour les études cliniques d'une telle nature. Ainsi, la puissance statistique observée fut calculée pour les comparaisons générales entre le groupe aveugle et le groupe contrôle ayant une vision normale. Une telle analyse *post hoc* révèle une probabilité de 43.1% de détecter de grandes tailles d'effets entre les deux groupes. Ainsi, une grande probabilité d'erreurs de type II, où l'on ne réussit à détecter une vraie différence entre les deux groupes, est à considérer dans la présente étude particulièrement lorsque celle-ci est d'une plus petite taille d'effet. En conséquence, quoique nous n'avons pas détecté des différences significatives entre les deux groupes pour certaines des composantes d'intérêt, on ne peut confirmer une similarité entre les aveugles et avec une vision normale. En particulier, la petite taille de l'échantillon ne nous permet pas de confirmer une équivalence statistique entre les deux groupes.

Étant donnée une forte probabilité d'erreurs de types II par la petite taille de l'échantillon, ainsi qu'une présence *a priori* d'hypothèses pour la majorité des facettes du sommeil et du rythme circadien abordées dans la présente étude, les corrections pour comparaisons multiples au cours des 4 articles furent limitées. Ceci augmente, en conséquence, la probabilité d'erreur de type I. Toutefois, les résultats obtenus sont en ligne avec les études antérieures, supportant davantage que les différences détectées soient robustes et détectables même lors d'un petit échantillon. Pour les 'nouveaux' résultats, telles les différences dans l'activité spectrale des stades du sommeil NREM entre les aveugles congénitaux et tardifs, une attention particulière fut faite pour identifier ces résultats comme étant préliminaires pour lesquels d'autres recherches

sont nécessaires. Ces limites dans l'interprétation des résultats furent particulièrement adressées dans la section de Discussion de chacun des articles.

### 2. L'hétérogénéité des participants : effets de l'âge et du sexe sur le sommeil

Un autre point important dans la présente étude est l'âge et le sexe des participants. Une grande variabilité de l'âge des participants, ainsi qu'une prédominance de participants féminins composent à la fois le groupe de participants aveugles et le groupe de partiicpants ayant une vision normale. Certaines composantes électrophysiologiques, notamment la densité spectrale de la puissance de l'activité corticale des stades de sommeil NREM et REM sont influencés par le sexe [Dijk, Beersma, et Bloem, 1989]. De plus, divers changements dans la structure et l'activité corticale du sommeil sont observés avec l'âge. Notamment, au cours du vieillissement on observe une diminution progressive de l'activité d'ondes lentes, une diminution de l'activité de fréquence delta, thêta, et sigma, ainsi qu'une diminution de la présence homéostatique et circadienne de fuseaux de sommeils [Carrier, Land, Buysse, Kupfer, et Monk, 2001; Landolt, Dijk, Achermann, et Borbély; 1996; Wei, Riel, Czeisler, Dijk, 1999]. Ainsi, le vieillissement est associé avec une baisse de l'influence du rythme circadien sur le sommeil [Carrier et al., 2001; Wei et al., 1999]. De plus, les changements de l'activité d'onde lente associés avec l'âge seraient plus rapidement atténués chez les hommes que les femmes [Ehlers et Kupfer, 1997], suggérant ainsi que l'âge et le sexe jouent des rôles importants et interactionnels dans la composition et les caractéristiques du sommeil. Ainsi, il importe de noter que ces deux variables font source de variabilité, particulièrement pour la mesure de la microstructure du sommeil. Un échantillon de plus grande taille, ou l'inclusion de participants avec des caractéristiques démographiques spécifiques permettrait on contrôle plus optimal des effets de l'âge et du sexe sur la composition

du sommeil. Toutefois, puisque le recrutement de participants avec une cécité complète présente déjà de fortes limites, les effets de l'âge et du sexe dans la présente étude furent partiellement contrôlés par l'appareillement de l'âge et le sexe des participants entre le groupe aveugle et le groupe contrôle.

### 3. Mesure du rythme circadien et l'influence de la mélatonine exogène

La présente étude démontre une plus grande fréquence de rythmes circadiens anormaux dans le groupe aveugle, où la moitié des aveugles avaient un profil atypique de sécrétion de la mélatonine. Ces résultats corroborent les études antérieures démontrant une plus grande fréquence de rythmes circadiens anormaux chez les aveugles, particulièrement ceux dont la cécité est complète (p. ex. [Sack et Lewy, 2001]). Cependant, la présente étude ne peut directement conclure sur la présence de rythmes circadiens en libres cours parmi l'échantillon d'individus aveugles. Pour confirmer ceci, les échantillons des marqueurs biologiques du rythme circadien devront être collectés de façon répétée afin de détecter un déplacement linéaire de la sécrétion de mélatonine dans le temps. Toutefois, les résultats de la présente étude supportent l'hypothèse d'une incidence plus élevée de rythmes circadiens anormaux parmi les individus aveugles, telle que reporté dans les études antérieures (p. ex [Lewy et Newsome, 1983; Lockley, Skene, Arendt et al., 1997]).

Dans la présente étude, quatre participants prenaient, de façon régulière, des suppléments de mélatonine comme aide-sommeil. Ces participants ont cessé de prendre ce supplément pour la durée de l'étude, incluant une semaine avant le début de la phase longitudinale de 30-jours. Ainsi, nous pouvons assumer que leur rythme circadien fut synchronisé jusqu'à l'arrêt de la prise de mélatonine. Ainsi, si ces individus, en absence de la prise de mélatonine, possèdent un

rythme circadien en libre cours, la phase de celui-ci, tel démontré dans le deuxième article, dépend entièrement de la période endogène de leur horloge biologique. Toutefois, une phase anormale du rythme circadien ne serait potentiellement détectée si la période endogène est près de 24-heures. Néanmoins, de ces quatre participants, un délai de leur phase circadienne fut détecté chez deux individus et un effet plateau du profil de sécrétion de mélatonine fut observé pour un participant. Ceci suggère, ainsi, une anormalité circadienne chez les participants aveugles qui furent prescrits de la mélatonine pour améliorer leur sommeil.

### 4. L'absence de perception visuelle chez les participants aveugles

Dans la présente étude, tous les participants aveugles de l'étude ne rapportaient aucune perception lumineuse résiduelle. Une investigation objective, soit par une mesure du réflexe pupillaire, soit par l'électrorétinographie, soit par une mesure de potentiels évoqués, cependant, n'a pu être obtenue lors de l'étude. Ainsi, le niveau de cécité se base sur une mesure subjective et supportée par l'information disponible dans la base de données du BRAINlab. L'absence d'une mesure objective, en conséquence, limite la confirmation que les participants aveugles n'avaient aucune réaction visuelle, même s'ils ne percevaient pas, de façon consciente, la lumière. Toutefois, une étude par Czeisler et collègues [1995] ont démontré que, même en absence de perception visuelle subjective, l'influence de la lumière sur le rythme circadien peut être maintenue. Cette étude suggère, ainsi, que même avec une absence consciente de la vision, certains aveugles peuvent être sujets à une modulation du rythme circadien par l'exposition à la lumière lors de périodes atypiques. Ainsi, une mesure de la suppression de la mélatonine serait une étape importante dans les prochaines investigations, afin de mieux comprendre les effets de l'illumination sur le rythme circadien et, conséquemment, le sommeil de ces individus.

### 5. Le groupe contrôle

En dernier, par la nature et la complexité de l'étude, certaines limites doivent être notées pour le groupe contrôle, soit les individus avec une vision normale ou corrigée à la normale. Afin de mieux dissocier les effets directs de la cécité et indirects, par l'altération du rythme circadien, sur la physiologie du sommeil, il serait davantage nécessaire de comparer ceux-ci à un groupe d'individus avec une vision normale, mais qui présentent un rythme circadien altéré ou en libre cours. Ainsi, un groupe contrôle optimal serait composé d'individus avec une vision normale, mais privés d'information photique, soit par le port d'un bandage sur les yeux (*blindfolding*), tout en maintenant un style de vie régulier. Un tel groupe contrôle permettrait, en conséquence, de comparer les deux groupes dans une condition où l'influence de la vision sur le rythme circadien est davantage contrôlée. Un second alternatif serait l'utilisation d'un protocole de désynchronisation forcée pour les deux groupes de participants. Ce protocole permettrait ainsi de comparer le sommeil des aveugles et du groupe contrôle au travers des différentes phases du rythme circadien. Cependant, bien que ces deux conditions du groupe contrôle optimiseraient la comparaison du sommeil des individus avec cécité à un groupe d'individus avec une vision normale ou corrigée à la normale, la plausibilité de telles conditions et les protocoles de recherches associées sont fortement limités, voire même être impossible. De façon importante, cependant, les résultats de la présente étude corroborent à la fois les résultats d'une réorganisation corticale associée à la cécité, qui s'étend à des différences physiologiques au niveau de la microstructure du sommeil (ex. [De Volder et al., 1997; Noebels et al., 1978; Kriegseis et al., 2006]. De plus, les études reported sur des changements dans la macro- et microstructure du sommeil causés par l'altération de la phase circadienne, telle antérieurement

démontrée chez les individus avec cécité et avec une vision normale [Léger et al., 2002; Klein et al., 1993; Czeisler et al., 1980; Strogatz et al., 1986].

## Importance clinique des résultats

Les résultats de la présente thèse démontrent que la cécité module, à la fois directement et indirectement la structure physiologique du sommeil. Notamment, la perte de vision peut engendrer une réduction de la stabilité et l'efficacité du sommeil de l'individu, et ceci peut être, en partie, le résultat d'une anormalité du rythme circadien par le manque d'information photique provenant de la rétine. Toutefois, les altérations du rythme circadien ne sont la cause unique des troubles du sommeil présents chez les individus aveugles [Léger et al., 1999; Lockley et al., 1997; Moseley et al., 1996]. Il est raisonnable de supposer que le style de vie associé à la cécité, tel un taux d'activité plus sédentaire, ainsi que les répercussions psychologiques de la perte de vision sont aussi des facteurs de risque pour le développement de troubles du sommeil dans cette population tout comme dans la population générale. La perturbation de leur sommeil peut aussi avoir des répercussions sur le bien-être de l'individu. En particulier, une récente étude démontre que la présence de troubles du sommeil chez les personnes avec une déficience visuelle est associée à une plus basse qualité de vie [Tamura et al., 2016]. De plus, de nombreuses études ont démontré l'importance du sommeil dans la performance cognitive, la stabilité mentale, ainsi que le bien-être de l'individu (p. ex. [Vandekerckhove et Cluydts, 2010; Thomas et al., 2000; Everson et al., 1989]). Ainsi, comme l'étude le démontre, la population aveugle serait à un risque plus élevé de perturbations de leur sommeil. En conséquence, il importe d'éduquer ces

individus, tout comme le public général, sur des techniques d'hygiène de sommeil afin d'optimiser la présence d'une bonne nuit de sommeil.

Ainsi, la lumière joue un rôle essentiel dans le maintien de la synchronicité du rythme circadien endogène. Comme démontré dans la présente thèse, la perte de vision entraine une plus grande fréquence de rythmes circadiens anormaux. Cependant, cette relation n'est pas complète. En particulier, quoique les troubles du rythme circadien sont plus présents chez les individus avec cécité complète [Tabandeh et al., 1998], il est possible que l'effet 'non-visuel' de la lumière sur le rythme circadien persiste même en absence d'une perception consciente de la lumière [Czeisler et al., 1995]. Ainsi, il importe d'examiner, cas par cas, si les individus avec cécité, même en absence de perception visuelle, peuvent maintenir une synchronisation du rythme circadien endogène à l'environnement par l'activité des cellules ganglionnaires intrinsèquement photoréceptives de la rétine. Cette évaluation permettrait de réduire les répercussions de la perte de vision chez les individus aveugles. L'effet indirect de la lumière sur le rythme circadien devient particulièrement important lors de l'évaluation d'un patient pour énucléation. De plus, dans les cas où les effets 'non-perceptuels' de la lumière persistent, il devient également important d'éduquer ces individus sur l'importance d'une exposition appropriée de leurs yeux à la lumière, même en absence de son utilité perceptive.

L'influence de la vision sur le sommeil se voit particulièrement importante puisque la déficience acquise au cours de la vie est à la hausse dans les sociétés occidentales (ex. [Gordois et al., 2012]). Cette augmentation provient, principalement, du prolongement de l'espérance de vie et de l'accroissement du taux de diabète dans la population. De plus, le vieillissement est associé avec une détérioration de la santé de la rétine, soit le jaunissement de la lentille et le développement de cataractes. Bien que ces déficiences ne soient toujours complètes et qu'un

degré de vision est souvent résiduel, diverses études démontrent que même une altération partielle dans la qualité de l'information photique provenant de la rétine peut avoir des répercussions sur le rythme circadien et la qualité du sommeil de ces individus (p. ex. [Alexander et al., 2014; Ayaki, Kawashima, Negishi et Tsubota, 2015]). Tel que soulevé par la présente thèse, l'interaction entre les rythmes circadiens, le sommeil et le bien-être de l'individu, ainsi que le rôle important de la vision dans le maintien direct et indirect de ceux-ci, démontre l'importance du maintien d'une bonne santé de la rétine ainsi qu'une exposition appropriée à la lumière autant chez les personnes aveugles que la population générale, et en particulier la population âgée.

Ainsi les résultats de la présente thèse confirment l'importance de la vision dans le maintien de la stabilité, l'efficacité, et même la structure physiologique du sommeil. Quoique les présents résultats sont basés sur une comparaison entre un groupe d'individus aveugles et un groupe contrôle où les participants avaient une vision normale ou corrigée à la normale, le lien entre la vision et le sommeil peut s'appliquer de façon générale à la population. Notamment, les résultats confirment davantage la nécessité d'une exposition adéquate à la lumière lors de la journée et l'évitement de fortes sources de lumière, particulière de la lumière bleue, au cours de la nuit afin de maintenir une synchronisation de son rythme biologique endogène au rythme jour-nuit de son environnement et, en conséquence, optimiser son sommeil.

## Pistes futures de recherche

La présente étude se marque comme une première étape dans l'investigation du sommeil chez les personnes avec cécité. En particulier, de nombreuses études antérieures ont démontré que la cécité, surtout lorsqu'elle a lieu tôt dans la vie, résulte en une réorganisation corticale,

notamment dans le cortex visuel [Kupers et Ptito, 2014; Park et al., 2009; De Volder et al., 1997] ainsi que les connexions entre les aires corticales dites ‘visuelles’ et le reste du cerveau [Heine, Bahri, Cavaliere, Soddu, Laureys, et Ptito, 2015; Ptito et al., 2008]. Comme le soulèvent les présents résultats, certaines différences peuvent aussi être observées lors de l’état du sommeil. Tel décrit dans les sections précédentes, ces résultats ne sont que préliminaires, et plus d’études, particulièrement sur un plus grand échantillon, seront nécessaire.

Tel que sera abordé dans la prochaine et dernière section, une investigation continue des différentes facettes du sommeil des aveugles peut non seulement contribuer davantage aux connaissances de la réorganisation corticale associée à la perte de la vision, mais aussi approfondir les connaissances sur l’activité corticale, et sa fonction, qui caractérise les différents stades du sommeil. En particulier, le sommeil REM est caractérisé par une activité corticale globale plus élevée que le sommeil NREM. L’activité globale du sommeil REM se voit similaire à celle de l’éveil [Buchsbaum et al., 1989; Buchsbaum, Hazlett, Wu, et Bunney, 2001]. Toutefois, cette activité provient d’une réactivation sélective des aires corticales. Spécifiquement, l’activité des aires frontales est atténuée lors du sommeil REM, tandis que les aires visuelles extrastriées sont très actives lors de ce stade de sommeil [Braun et al., 1997; 1998; Maquet, 2000; Buchsbaum et al., 2001]. Certains auteurs ont même suggéré une association entre l’activité du cortex visuel et les éléments visuels du contenu onirique [Braun et al., 1998; Maquet et al., 2005; Ogawa, Nittono, et Hori, 2005]. Chez les aveugles, la perte de vision engendre des changements anatomiques et fonctionnels des aires corticales visuelles (p.ex. [Kupers Ptito, 2014; Park et al., 2009; Ptito et al., 2008]), particulièrement lorsque la cécité a lieu en début de vie. Plus spécifiquement, le cortex visuel des aveugles est recruté par les autres modalités et processus cognitifs [Kupers et Ptito, 2014] et possède une activité métabolique de

base plus élevée [De Volder et al., 1997]. Une étude de neuroimagerie des stades du sommeil NREM et REM chez les individus aveugles permettrait d'examiner l'activité corticale des aires visuelles de ces individus lors du sommeil. Plus spécifiquement, il serait intéressant de déterminer si l'activité des aires corticales extrastriées lors du sommeil est similaire ou différente par l'absence de vision.

De plus, la cécité s'avère un état particulier pour l'étude de la relation entre l'activité corticale, les mouvements oculaires et le contenu onirique. Tel décrit par Meaidi et collègues [2014], les rêves des individus aveugles ne contiennent peu ou pas d'éléments visuels. Spécifiquement, ceux avec une cécité complète depuis l'âge de 5-7 ans [Kerr, Foulkes, et Schmidt, 1982; Kirtley, 1975], ne rapporteront de rêves contenant des éléments visuels. Toutefois, lorsque la perte de vision a lieu plus tard dans la vie, des éléments visuels peuvent persister, de façon assez fréquente, dans leurs rêves [Meaidi et al., 2014]. La présence d'éléments visuels dans les rêves serait particulièrement associée au potentiel d'imagerie visuelle de l'individu [Meaidi et al., 2014]. Donc, les individus qui maintiennent une imagerie visuelle suite à la cécité rapportent plus d'éléments visuels dans leurs rêves. Ainsi, il peut être d'intérêt d'examiner davantage le contenu onirique de ces individus, en particulier relatifs à l'activité corticale ainsi que l'activité oculaire lors du sommeil REM, par l'entremise de méthodes d'électrophysiologie et de neuroimagerie. De telles études pourraient permettre d'éclaircir le rôle du cortex visuel, ainsi que l'activité corticale en général, dans le contenu onirique (p. ex. [Bókkon et Mallick, 2012]). De plus, elles pourraient aussi élaborer sur le débat, qui existe depuis plus de 50 ans, portant sur la relation entre mouvements oculaires du sommeil REM et le contenu onirique de celui-ci (p. ex. [Dement et Kleitman, 1957b; Hobson, Pace-Schott, et Stickgold, 2000; Eiser, 2005; Miyauchi, Misaki, Kan, Fukunaga, et Koike, 2009;

Leclair-Visonneau, Oudiette, Gaymard, Leu-Semenescu, et Arnulf, 2010]). Ainsi les aveugles s'avèrent un échantillon particulier pour l'étude du sommeil pouvant porter fruit sur différents aspects de la physiologie du sommeil et des processus cognitifs associés.

# CONCLUSION

Les études, qui constituent cette présente thèse, avaient pour objectifs d'examiner les répercussions de la cécité sur la stabilité périodique, la qualité, et la structure physiologique du sommeil. Les résultats démontrent que les stades du sommeil, ainsi que la majorité des composantes microstructurales typiques du sommeil demeurent présents chez les aveugles. Une réduction des caractéristiques du sommeil associées à l'activité corticale visuelle et de l'activité oculaire fut cependant détectée chez le groupe aveugle. De plus, des petites différences dans l'activité corticale lors du sommeil NREM furent détectées entre les aveugles congénitaux et les aveugles tardifs, suggérant que la réorganisation corticale associée à la cécité pourrait être observée lors de l'état de sommeil.

Les résultats supportent, aussi, l'influence du rythme circadien sur le sommeil, particulièrement au niveau de sa consolidation ainsi que la proportion et la latence du sommeil REM. Une anormalité du rythme circadien à l'environnement fut plus fréquemment observée chez les individus avec cécité. Les résultats suggèrent ainsi que la perte perceptuelle de la vision peut aussi engendrer une altération the la transmission de l'information photique de la rétine au noyau suprachiasmatique pour la synchronisation de l'horloge biologique endogène à l'environnement. De plus, la perte de vision fut associée à une plus grande fréquence de troubles du sommeil et une plus grande variabilité de la période et de l'efficacité de leur sommeil. Les présents résultats et les études antérieures démontrent ainsi un rôle important de la vision dans le maintien et la qualité du sommeil. Tel démontré par une panoplie d'études, les troubles du sommeil peuvent avoir des conséquences sur la qualité de vie, le bien-être de l'individu, ainsi que sur divers processus cognitifs. Ainsi, les résultats de la présente thèse soutiennent l'importance d'examiner chez les individus aveugles, cas par cas, l'influence de la cécité sur leur rythme circadien et leur sommeil.

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# Annexe I

# The multisensory blind brain

# The Multisensory Blind Brain

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# 1 Introduction

The brain is a fascinating organ. It has the incredible ability to turn electrical, mechanical, and chemical energy into multisensory knowledge about the world. Neuroscientists are taught that the brain is divided into regions—each responsible for interpreting information from a single sense, except a few integrative multisensory areas whose role is to combine information from the different senses (Fig. 1). For example, the posterior part of the brain, the occipital cortex, interprets visual information; the area above the ears, the temporal cortex, interprets auditory information; above from that towards the middle of the head is the somatosensory sulcus, which interprets tactile stimulation and generates motor actions. This idea that the mind is composed of distinct faculties, with separate seats in the brain, took origin from same kind of categorical location-based ideology as sixteenth century phrenology. Yet, we now know that this specificity hypothesis is largely incomplete and a fallacy. Studies into the plasticity in the blind brain have revealed that the occipital cortex is not solely reserved for visual functions. In fact, blind people trained in spatial tasks, such as braille reading, or on sensory substitution devices, need the occipital cortex to interpret these non-visual stimulations.

In the second and third sections of this chapter, we will review the literature on the traditional multisensory brain areas. We argue that multisensory integration is a core aspect of human survival. In the fourth and fifth sections, we will review the literature on multisensory integration in areas of the brain that were classically considered to be modality-specific, and demonstrate that these areas are also active in the integration of information from multiple modal sources. We will debunk the myth that the visual areas of the brain are strictly visual. In the final section of this chapter, we argue in favour of the idea that the brain is divided according to function rather than modality. Information is, therefore, represented in an amodal manner, i.e. in a way

that it is abstracted from its modal source. We further argue that cognitive processes of memory and even mental imagery can be amodal in nature.

The impressive multisensory plasticity of the blind brain can, therefore, be capitalised on in order to improve high-tech rehabilitation devices for people with decreased visual abilities. Further, this evidence for cross-modal and cross-cortical plasticity suggest possibilities of rehabilitating patients with brain trauma (e.g. stroke) by accessing the latent multisensory pathways within the brain.

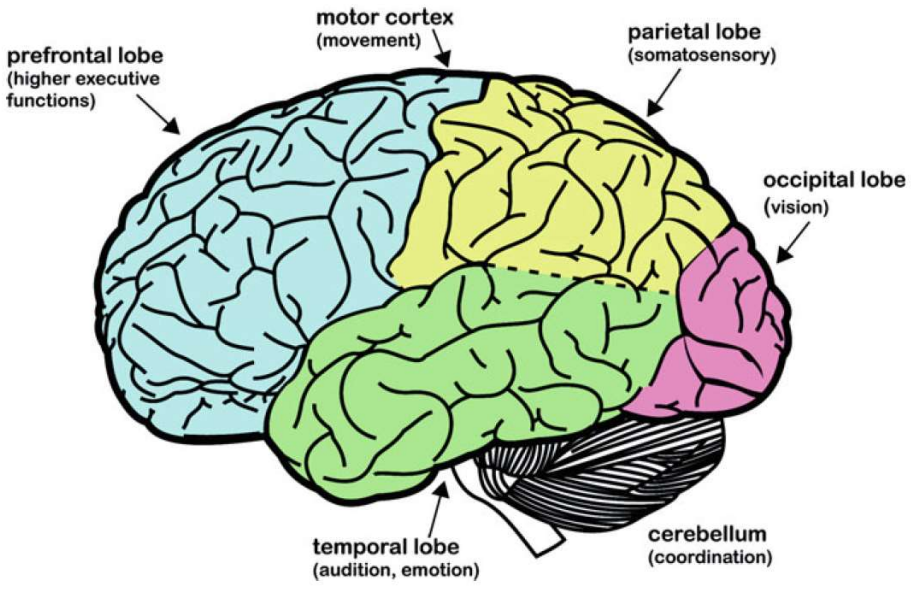


Fig. 1 Lateral view of the human brain indicating the various lobes and their primary functions. Modified from Anatomy of the Human Body, Gray H, Fig. 728 (1918)

## 2 What Is Multisensory?

There are a few areas of the brain that have been labelled as multisensory areas, and appear to be particularly important for integrating the information from multiple senses. Multisensory areas are composed of multisensory neurons—meaning neurons that respond to stimuli from multiple modalities. For example, neurons in the deep layers of the cat's superior colliculus (SC) respond to visual, auditory, and somatosensory stimuli [92, 134], and with overlapping receptive fields [131]. Thus, a stimulus located on the bottom left of the cat's sensory field could activate the same neuron in the SC whether the stimulus is visual, auditory, or a brush of the whisker. What makes these neurons particularly interesting is that they fire more frequently when stimulation come from two modalities, as compared to only one modality [132, 135]. These superadditive responses exceed the strongest unisensory response, and often exceed even the sum of the unisensory responses.

Investigations into superadditive neurons have revealed the principles of multisensory integration. The conditions that lead to increased neuronal activity also lead to behavioural improvements; an enhanced signal would, thus, improve detection (and lower threshold), allowing for faster responses with less variability— especially for eye movements [30, 31, 37, 133]. The conditions under which superadditivity and thus multisensory integration are likely to occur include: spatial and temporal proximity [44], and inverse effectiveness [93]. That is, for stimuli to be combined into a single event, they must occur in the same location (spatial proximity), at the same time (temporal proximity), and should be relatively weak (inverse effectiveness) in order to enable a substantial superadditive enhancement effect. Of course, without boundaries (space and time) all stimuli would collapse together. The question then becomes, how do multisensory neurons learn which stimuli go together?

Multisensory integration is thought to have developed to maximise our chance of survival by minimising the unisensory limitations of each sensory system. For example, the eye transduces light at a rather slow rate and has a coarse perception of time. In contrast, the auditory system has a mechanical transduction, which is relatively fast and temporally precise, but is limited in the spatial plane. Thus, our ability to spatially locate sounds is much less precise than our ability to locate visual stimuli. When we are faced with danger, the survival predicament dictates that we need to immediately detect the origin of the growling animal and either run away or prepare to fight. Many studies have demonstrated that the multisensory integration within the SC allows us to orient our eyes to a sound. The theory is that the sound is used to detect a rough location of the threat, and vision is used to determine what is threatening. In less dangerous conditions, tested in laboratory settings, it has been established that multisensory integration can sometimes be "optimal"—our perception is a weighted sum of the total information available, with more weight afforded to the sense with the least variability [1, 39]. Multisensory integration, thus, optimises all four f's necessary for our survival: fight, flight, feeding, and fertility.

Eating is an important multisensory activity [7]. Chefs have known this intuitively by making food that not only taste good but is also visually and texturally appealing. The influence of vision on flavour has been empirically tested; for example the effect of colour—be it the colour of the food itself [130], or the colour of the plate and tableware [61, 62] is known to greatly influence the feeding experience (for a review see [129]). The sound a food makes in the mouth is also important in our overall liking [147]. We will return to this idea of multisensory experience in nourishment when we discuss taste and smell perception in blind individuals

(Sect. 4.4). It is already clear, however, that multisensory integration is a crucial aspect of the human experience and is closely linked to many survival responses.

## 3 Multisensory Areas in the Brain

In this section we review all the classical multisensory areas of the brain. We argue that these multisensory areas are crucial for the development of body reference frames and spatial representations, for interacting with objects, accomplishing complex motor movements, and for determining one's self-representation within the world. These brain areas are capable of integrating information from multiple modalities, rather than only a specific sensory modality. We argue that these areas are organised according to functional specificity and combine multiple input sources to create an amodal reference frame.

The posterior parietal cortex (PPC) has been identified as an important multisensory area within the brain, converging visual, auditory, and tactile information for planning and executing movements. The PPC appears to be important for reference frame transformations between the senses [19]. For example, when we hear something, the perceived sound is encoded according to head-centred coordinates (because our ears are fixed on the head). In order to look at the source of the sound, its location needs to be coded in an eye-centred frame of reference (relative to the current eye position). Lewald and colleagues suggested that the PPC relates azimuth angles of sounds to body coordinates, in order to convert the information to different modality-specific reference frames [83]. To make a hand movement to the seen/heard object, it would then need to be coded in a hand-centred reference frame. Rather than undergoing arduous computations each time we move towards a sensed object, the PPC appears to maintain a common eye-centred reference frame, modulated by eye-, head-, body-, or limb position signals

[26]. Indeed, even a touch on the arm appears to be coded in the common eye-centred reference frame [59, 60, 109]. Further evidence of that the PPC is involved in integration comes from studies using brain stimulation. Transcranial magnetic stimulation (TMS) over this region disrupts multisensory visual–tactile integration [101], while transcranial direct current stimulation (tDCS) over this area enhances multisensory spatial orienting [14]. A common multisensory reference frame would facilitate communication between the modalities (with regards to spatial location) and the PPC is, therefore, considered an important multisensory area in the brain—particularly in spatial coding, though it may also play a role in temporal perception [152]. The anterior intraparietal sulcus (aIPS), from the postcentral to the superior parietal sulcus, is another known multisensory brain area with a particular role in the integration of visual and haptic signals (for a review, see [64]). For example, multisensory location information is needed to reach towards and pick up an object that is seen on the table. Current understanding is that the proprioceptive knowledge of the hand converges with the visual information for hand position in this area of the cortex. While the posterior IPS and some visual areas (discussion to follow) represent the hand in a predominantly visual manner, the aIPS converges multisensory information (vision and an important proprioceptive contribution) to build hand position representations for peripersonal hand space [50, 89].

The superior temporal polysensory (STP) region, in the posterior bank of the superior temporal sulcus (STS), has been a labelled as and "association" area because it receives auditory, visual, and somatosensory stimulation and is composed of unimodal, bimodal, and even trimodal neurons [18]. Its receptive fields are generally large, including both visual fields and bilateral somesthetic and auditory receptive fields [65]. In particular, peripheral vision and motion perception appear to be supported by projections from the STP and STS to the primary

visual cortex [41]. These parietal areas project to primary visual cortex (V1 and V2) [117]. This same region, but a little higher at the temporoparietal junction (TPJ), has been demonstrated in humans to be responsive to visual–tactile stimulation [68]. Once again, this multisensory cortex is associated with spatial perception—more specifically the feeling of being localised at a position in space, from a first-person perspective [13].

The anterior Ectosylvian Sulcus (AEC) in cats is an important anatomical area because of its wealth of cortico-cortico as well as cortico-subcortical projections. In many cases, neurons in the AEC respond to multisensory stimuli [96, 113]. In one of the first studies to demonstrate trisensory neuronal response (Fig. 2), Jiang and colleagues reported that of the cells in the AEC, recorded with the single-unit technique, *60% were unimodal, *30% were bimodal, and *10% were trimodal [71].

Depending on how multisensory neurons are defined, or tested, some studies report as much as 66% of neurons in the AEC to be multisensory [35] with projections to the SC, which likely underlies the latter's multisensory nature [70, 71]. While neurons in the SC always demonstrate maximum enhancement when their unimodal discharges overlap [143], the relationship in the AEC appears to be more complex. While some neurons in the AEC prefer auditory stimulation to precede the visual stimulation, other neurons have peak responses when the auditory stimulus trails the visual by as much as 200 ms [70]. Each neuron appears to have a preferred temporal relationship between stimuli (see also [11]). Moreover, depending on the temporal interval between the modalities, the same neuron can be excitatory or inhibitory [70].

Given the already multisensory nature of this region, cross-modal plasticity following sensory deprivation might be expected, where visually specific neurons may become responsive to stimuli in other modalities after a lack of visual stimulation. Indeed, a significant cross-modal

plasticity of the AEC was observed in cats that were visually deprived at birth [114]. Areas that were normally visual (the ventral bank and fundus of the AES) underwent a cross-modal intrusion, becoming primarily responsive to auditory and/or somatosensory stimulation.

These results in the cat provide a model for the intermodal compensatory plasticity that is observed following sensory loss; an area that is primarily visual, but demonstrates some measure of integration of auditory and somatosensory information with vision, will undergo considerable plasticity when vision is not available, becoming more responsive to auditory and tactile stimuli. Multisensory areas therefore allow for cross-modal plasticity following loss of a particular sensory modality. This transition from bimodal (or trimodal) into unimodal (or bimodal) specificity is likely mediated by GABAergic neurons [36], with a corresponding expansion of the remaining unisensory receptive fields into the area previously occupied by the modality that has been eliminated. Thus, the cross-modal abilities following sensory loss are maintained and strengthened, rather than completely novel. Following up on this point, the subsequent sections of this chapter will discuss cross-modal abilities in cortical areas that are traditionally considered unisensory.

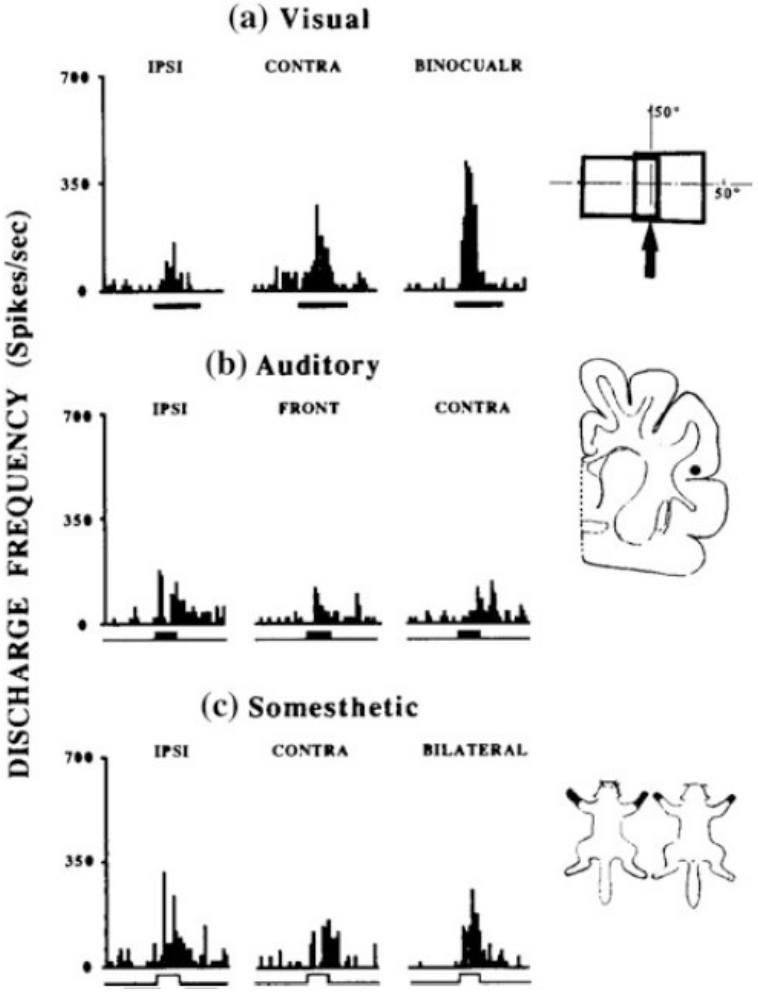


Fig. 2 Responses of a trimodal unit to a visual (a), an auditory (b), and a somatosensory (c) stimulus. Visual stimulus: a light bar (3° x 10°) moving upwards through the RFs at a speed of 300°/s; somatosensory stimulus: an air puff (100 ms); auditory stimulus: a burst of white noise (100 ms, 70 dB). Black bars, visual stimuli; thin line with filled bars, auditory stimuli; "up bars", air puff stimuli. Binwidth 10 ms. Insets show positions of RFs. The black dot in the schematic coronal section of the cat's brain represents approximate position of the cell within anterior ectosylvian cortex. Adapted from [70], Copyright (1994)

## 4 Primary Visual Cortex

Visual information from the retina is projected from the eye through the optic tract (including the optic chiasm) to the Lateral Geniculate Nucleus (LGN) before arriving to the occipital cortex. Neurons in this part of the brain, combined with other neurons 'devoted' to vision throughout the cortex, are said to take up about 30% of the cortex [54]. In comparison, approximately 8% of the cortex is estimated to be devoted to tactile information processing, and 3% for auditory processing. What, then, happens to these neurons when vision is restricted or completely eliminated? Over the last ten years, neuroimaging studies have demonstrated a considerable amount of neural plasticity in the "visual cortex" of blind people. This plasticity has been used to explain the superior abilities of blind people in auditory, tactile, proprioceptive and motion tasks (for a review, see [82]). We propose that this plasticity potentially arises from the presence of multisensory neurons within the primary visual cortex. These neurons would remain latent and largely immature in the normal "visual" brain, but would become active in the blind brain as a result of the absence of visual input.

### *4.1 Auditory Activation of Visual Areas*

Auditory stimuli have repeatedly been demonstrated to activate the visual cortex in early blind (EB) individuals, but not necessarily in sighted controls. The initial findings that EBs have neural activity within the occipital cortex was a novel insight and an explanation for anecdotal evidence of heightened auditory abilities in blind people [33, 144]. Several studies have demonstrated superior performance of EBs in auditory tasks as compared to sighted controls (SC), which has been attributed to an increased metabolic activity in the visual cortex of CB during the performance of these auditory tasks [6, 122]. Sensory substitution devices (SSD),

such as the PSVA (prosthesis substituting vision with audition), have also been used to demonstrate the fact that auditory stimulation can activate the occipital cortex [34]. The activity in the "visual cortex" is critical for interpreting the auditory information from PSVA devices [28], for localising simple sounds [27], and for interpreting auditory motion [106]. Moreover, the activation of the visual cortex from auditory stimulation led to the functional specialisation hypothesis [29], which suggests that the occipital cortex is specialised for spatial processing—rather than being strictly associated to visual processing (this will be further discussed in Sect. 6). While this plasticity in blind people is remarkable, and can be used to explain their often superior auditory abilities, activation of the occipital cortex by auditory stimuli is not always dependent on visual deprivation.

Auditory stimuli can activate the visual cortex, even in a brain that developed "normally" (see review in [52]; Fig. 3). Half a century ago, studies in the cat demonstrated that as many as 41% of "visual neurons" also responded to auditory stimuli [97]. In support of the functional specialisation hypothesis, these multisensory neurons in the visual cortex were thought to be spatially specific [97]. With spatially and temporally precise neuroimaging techniques, a recent study has confirmed that auditory stimuli evoke spatial-specific activity in the visual cortex of normally developed sighted individuals [17], even in the absence of simultaneous visual stimuli. The activation of the visual cortex by auditory stimuli is likely to originate from early projections from the auditory cortex and the superior temporal sulcus (STS) [117].

Taken together, we can conclude that a pathway for auditory stimuli to the occipital cortex is present even in brains that have developed with visual input. While these pathways are not completely pruned over the course of normal development, they remain largely undeveloped. These multisensory connections appear significantly strengthened and have expanded cortical

representation when visual input is unavailable, for example in the blind brain, and become apparent following training and experiences with non-visual stimuli [29].

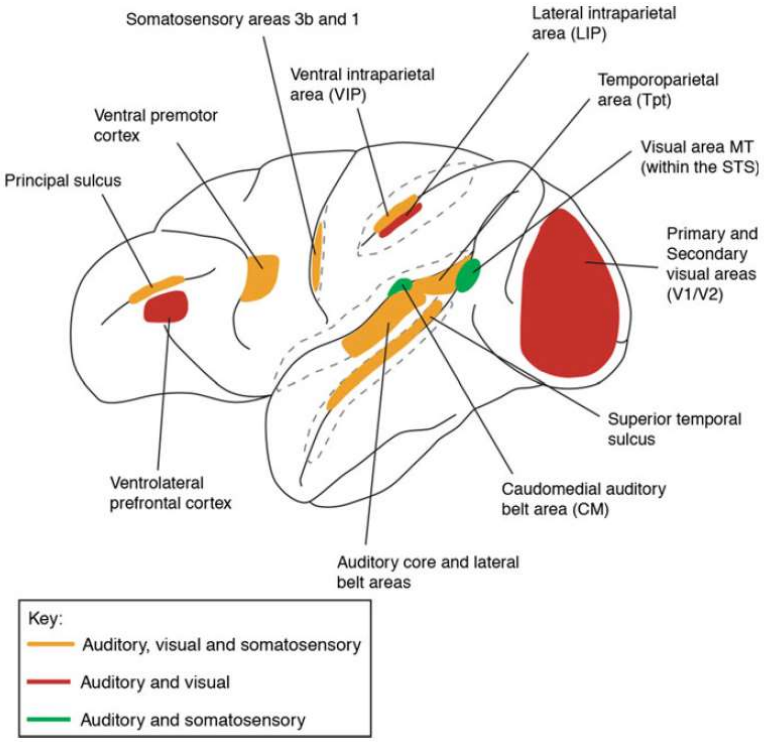


Fig. 3 The more modern scheme of the cortical anatomy of multisensory areas. Coloured areas represent regions where there have been anatomical and/or electrophysiological data demonstrating multisensory interactions. In primary and secondary visual areas (V1 and V2), the multisensory interactions seem to be restricted to the representation of the peripheral visual field. Dashed gray outlines represent opened sulci. Reprinted from [52], Copyright (2006), with permission from Elsevier

### *4.2 Tactile and Proprioceptive Activation of Visual Areas*

In the same vein as auditory stimuli, tactile devices that provide a complex touch stimulus also activate the visual cortex in blind people, but not necessarily in sighted controls. For example, in addition to somatosensory cortex response, blind people's occipital cortex is activated during braille reading but not for simple tactile detection tasks [124]. This activation appears to be critical for interpreting and understanding the tactile Braille stimulus, since Braille reading is impaired when the occipital cortex is damaged [57] or disrupted with TMS [25]. While reading was impaired, simple tactile detection was not when TMS was applied to the occipital cortex [25], but tactile detection was disrupted when TMS was applied to the parietal cortex [58]. Therefore, the visual cortex is actively involved in the representation of Braille letters, but not their detection. It could, thus, be argued that the visual cortex is actively involved in an amodal representation of text. The fact that text is represented in such an amodal fashion could explain why the visual word form area (VWFA), located within the visual cortex (in the ventral visual stream), is activated when blind individuals read a braille text (tactile) and when sighted individuals read a visual text [116].

Early blind people who are trained with the tongue display unit (TDU) also activate the occipital cortex when determining the orientation of a letter presented with the device [112] (Fig. 4a). Moreover, activation of the visual cortex, using TMS stimulation, induces phosphenes in sighed controls but refereed sensations on the tongue of practised TDU users [79], and tactile sensations in the fingers of practised Braille readers [110] (Fig. 4b). The activation of the occipital cortex during both Braille reading and TDU tasks in blind people is thought to be a result of the fact that these tasks demand a high degree of spatial acuity—they are both spatial perception tasks. The spatial layout of the neurons in the occipital cortex enables the

development of a retinotopic map, which provides vision with a high degree of spatial acuity. The particular characteristics of the neurons in this region appear to be an important factor for its recruitment in non-visual spatial tasks during blindness.[1]

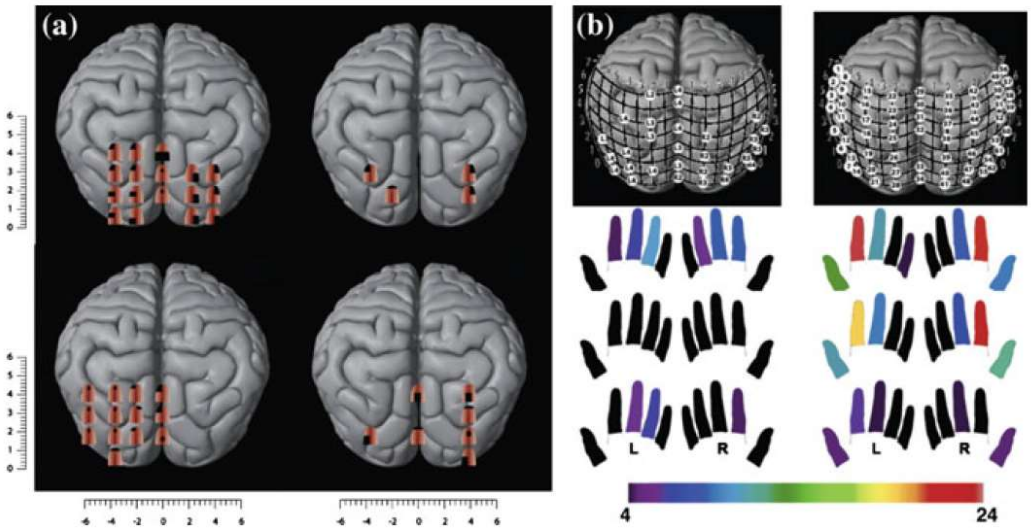


Fig. 4 TMS of the visual cortex in congenitally blind subjects can induce tactile sensations. a Somatotopically organised tactile sensations in the tongue induced by TMS over occipital cortex in four blind subjects who were trained to use their tongue to perform a motion discrimination task. The figure shows the areas of the tongue where tactile sensations were felt (indicated in black) after TMS stimulation of the occipital cortex. The numbers on the scales refer to the distance (in cm) from the inion. b TMS-induced tactile sensations referred to the fingertips in two congenitally blind proficient Braille readers. The number of visual cortex sites from which paresthesiae could be induced in a particular finger is colour-coded (see colour map), with red indicating the highest number of cortical sites that induced paresthesiae in a particular finger and purple the lowest number. Reprinted from [82], Copyright (2014) with permission from Elsevier

[1] Further discussions on cross-modal plasticity elicited by the stimulation of the tongue (TDU), and amodal representation of space, can be found in Chap. 6 by Chebat et al.

Under some conditions, early visual impairment appears to lead to better tactile performance in blind people as compared to sighted controls, as discussed in [82]. For example, in the "crossed hands paradigm", where people cross their arms and then have to determine which hand (left or right) was touched first, early blinds outperform sighted people [120]. Sighted people typically have difficulty determining which hand was touched first but blinds can report the temporal order of touches equally well with their hands in any posture. These results support the hypothesis that when vision develops normally, touch on the body is coded in a visual reference frame [59], both for perception and to guide actions [60]. The visual reference frame is an externally defined coordinate system that is automatically used by sighted controls. Blind people, on the other hand, only use an externally defined coordinate system when specifically instructed [94, 95]. Thus, guiding actions towards external objects is based on an external reference frames in sighted, but is based on an internal reference frame in blind people [118]. Much like the visual system, online corrections for hand orientation are made with proprioceptive inputs in the blind [55]. In addition to the increased neural plasticity in the blind brain, the ability of blind people to use either reference frame can also partially explain certain behavioural advantages compared to sighted controls.

The cortical networks associated with movement control are fairly similar for sighted and blind people, leading researchers to conclude that a multisensory network develops with a sensorimotor feedback system, rather than a visual feedback system [42]. While visual feedback primarily supports the system in adults with normal visual development, they hypothesise that such a system originates from a multisensory framework. Thus, this same network can be used regardless of the modality feeding the system in people with sensory deficits. Similarly, several perceptual tasks have demonstrated the role of the occipital cortex in decrypting highly spatial,

non-visual information. While the visual cortex is shown to be active when blind people, but not sighted controls, are highly trained in tactile tasks [112], there are now a handful of studies that demonstrate exceptions to this rule, even for certain simple tactile stimuli.

Despite popular belief, the occipital cortex can be recruited for tactile spatial tasks even in people with intact visual systems [148]. In this study they demonstrated that applying TMS to the occipital cortex disrupts tactile orientation discrimination (a spatial-based task) but not the ability to detect the stimulus, or to perceive texture (detection or discrimination tasks). Further, a subregion of the lateral occipital cortex, known as the lateral occipital tactile–visual area (LOtv) is activated by tactile stimuli (see discussion in [64]), for both 3D haptic perception [5], and less complex haptic stimuli [74, 108]. It remains a controversial point whether the activity in the LOtv represents amodal shape perception [5], or is attributed to mental imagery [149]—which can also be amodal (see Sect. 6.2). As was suggested for auditory-based studies, the multisensory cortical connections in the occipital lobe likely underpin the activity in the occipital cortex of blind people elicited by tactile stimuli; these stimuli likely become transduced into amodal representations in the multisensory blind brain.

### *4.3 Pain Activation of Visual Areas*

The relationship between vision and pain is well known, even intuitive [63]. We almost always look at the site of injury, and what we see will gauge our response. If the skin appears unharmed there is a "visual analgesic" effect and we feel less pain. If the skin is broken and bleeding, we will have an increase in pain perception. Experimentally, the effect of short-term visual deprivation (one week), causes otherwise normal people to experience increased tactile

and thermal acuity [153]. This early empirical data also demonstrated that blindfolding causes a drop in heat pain thresholds, indicating that lack of vision is related to hypersensitivity to pain.

In our pioneering study of pain and temperature perception in a blind population, we demonstrated that blind subjects had significantly lower heat pain and cold pain thresholds than matched controls [127]. We demonstrated that hypersensitivity to pain is specific to noxious thermal stimulation, rather than to thermal stimulation in general, and the effect is not culturally based. Taken together with findings of augmented responses to threatening auditory stimuli in blind subjects [75], these data provide compelling evidence that early blindness might cause an increased attentiveness to external threats.

In order to determine if the hypersensitivity to threatening stimuli arises from a compensatory neural plasticity that is rooted in the critical period of development, we compared the pain sensitivity in early and late blind subjects. While early blind individuals were quite different, data from late blind subjects was very similar to that of sighted individuals, including both responses to painful heat stimuli and questionnaires assessing awareness and anxiety towards pain [126]. This suggests that visual deprivation, per se, does not alone determine the development of pain hypersensitivity—the time at which the visual system is deprived is equally important.

Two competing hypotheses have been proposed to explain pain hypersensitivity in congenital blindness [126, 127]. According to the first hypothesis, pain hypersensitivity reflects cross-modal plasticity of brain circuits as a result of the lack of visual input. The absence of inhibitory effects of vision on pain perception in the visually deprived blind brain (i.e. a lack of inhibitory feedback from the visual analgesia effect) might leave the neural circuitry associated with nociceptive inputs particularly sensitive [86, 87, 153]. Alternatively, a second hypothesis

suggests that the pain hypersensitivity results from a hypervigilance to threatening stimuli in early blind individuals. Vision, when present, can signal potential threats to the body (e.g., a red hot stove) so that individuals can remain carefree until they see a dangerous stimulant. In the absence of the visual warning function, blind individuals might instead adopt a chronic state of hypervigilance as a way to avoid tissue damage. This more integrative interpretation of the pain hypersensitivity, combining both the psychological and biological aspects of pain, can also account for the observations that early blind individuals show increased responses to auditory threats [75], and are better at identifying body odours with a negative emotional valence [69]. Indeed, as shown in recent brain imaging studies, salient visual and noxious stimuli activate a partly overlapping cortical network [98], supporting the hypothesis that there is an intricate integration of vision and pain processing.

### *4.4 Chemical Senses*

The relationship between vision and taste is often automatic. Chefs will naturally devote significant amounts of time making their food look good, in addition to making it taste good. There is also empirical evidence that colour affects flavour perception [61, 62, 130].

Behavioural evidence has demonstrated that EB is associated with increased odour awareness [9] and increased ability to correctly name odours from everyday life [32, 99, 123]. We have replicated this enhanced detection of odours when blind participants sniffed the odorants (orthonasal route), but when they smelled them retronasally (through the mouth) the sighted controls tended to outperform the blind participants. Similarly, blind people appear to have a reduced taste sensitivity [47].

There are a few studies that have investigated the neural plasticity and behavioural differences associated with smell and taste in blindness (see review in [48]). BOLD responses recently demonstrated the important difference between taste and smell in blindness. While odours activate the visual cortex in blind participants, but not sighted participants [78], taste processing does not demonstrate this multisensory plasticity [49], see discussion in [81]. These studies have suggested that experience with food is an important predictor of performance in chemosensory experiments.

In the absence of vision, blind people face several obstacles when searching for food, buying food in impervious packaging, preparing food, and eating in restaurants [12], which might limit the diet of many blind people. While their diet may be limited, their exposure to odours is not, since most odours are not food-related. The limited variety in a blind person's diet would provide them with fewer flavour experiences causing poorer sensitivity to stimuli presented through the mouth, but normal (or heightened) sensitivity when stimuli are sensed orthonasally. Thus, the difference of experience between taste and odour appears to underlie the neural activation and behavioural performance differences reported between blind and sighted controls [48].

## 5 Primary Auditory and Somatosensory Cortex

In addition to the mounting evidence presented above of other sensory modalities activating the primary visual cortex, here we present evidence of the reverse— visual, and other types of stimuli, activating the primary auditory and somatosensory cortices in sensory deprived and normally developed brains.

In the auditory cortex, despite it being primarily an auditory processing centre, single electrode recordings have demonstrated the presence of trisensory neurons, responding to auditory, visual, and somatosensory stimuli [45]. This multisensory facilitation in the auditory cortex appears to be particularly responsive to voices and faces [22, 105, 139], i.e. multisensory integration for communication [52]. These multisensory neurons for communication are more likely to be enhanced when audio-visual delays are short, whereas longer delays between stimuli are associated with response suppression [51]. These neurons, therefore, support the hypothesis that temporal proximity is an important modulator of the activity in multisensory neurons. In addition to communication, multisensory neurons in the auditory cortex also play an important role in eye positioning [46, 146], and somatosensory processing [72]. Further, these multisensory pathways within the primary auditory cortex are present even after normal auditory development. However, as was the case for blind processing, these multisensory pathways appear to be particularly well developed in deaf individuals, as evidenced by cortical plasticity, and may underpin the selectively enhanced visual abilities of the deaf [8, 85].

Similarly, the primary somatosensory cortex is also responsive to non-tactile stimulation, in particular auditory and visual stimulation. Multisensory convergence on a single neuron in the somatosensory cortex has been demonstrated through single-unit recordings [150, 151], and tracer studies [23]. These kinds of multisensory neurons would likely support the cortical plasticity associated with early somatosensory deprivation [53].

In somewhat of a resistance to accept multisensory activity in primary cortices, this was thought to occur only after the stimuli had been processed in multisensory regions (presumably after an initial processing in the unisensory areas). That is, evidence for multisensory convergence in the “unisensory” cortices was thought to be the result of “top-down” feedback

from multisensory areas to the primary sensory areas [21, 38, 88, 102]. However, tracer studies have shown direct projections of auditory neurons to V1 and V2 [117]. In addition, damage to higher order "multisensory regions" does not necessarily hinder multisensory integration abilities (for a review see Ettlinger and Wilson [40]). Further, the timing of some integration activity (occurring 40 and 50 ms after stimulus) are too early to arise from feedback pathways [43]. Thus, multisensory activity in the primary sensory cortices results from a combination of feedback, feedforward, and lateral connections [43].

## 6 The Amodal Cortex

It is now becoming particularly clear that the view of a modality-specific divided brain is inappropriate, or at least incomplete. Although this might mostly hold true of primary cortices, where only about 10% of neurons respond to "inappropriate sensory" stimuli, even the boundaries of these divisions are unclear (i.e. multisensory [142]). Instead of sensory delineations, sensory deprivation studies have suggested a functional delineation for certain cortices [3, 136]. For example, the motion sensitive middle temporal cortex (hMT+) responds to any kind of motion, be it visual, auditory, or tactile in origin, and this is true for both sighted and blind individuals [91]. A common hypothesis suggests that the occipital cortex is, thus, spatially arranged, providing spatial information regardless of the modality (for a review see [125], see also Chebat et al., Chap. 6).

While vision might be used to localise objects for sighted individuals, auditory and proprioceptive localisation cues are utilised by the blind [145], and as such, both might rely on the same brain areas to interpret spatial information. In particular, the retinotopic arrangement of the visual cortex seen in sighted individuals is maintained in blind individuals when this

cortical region is recruited for tactile tasks, conserving a topographic representation of space [79, 110], see Fig. 4. Visual experience is, therefore, not a mandatory prerequisite for the topographically organised, functionally related, representations in the extrastriate visual cortex— these appear to be supramodal neural response patterns in the human brain [80]. In the same vein, the dorsal stream appears to be shaped by non-visual spatial information during early development [42].

Theoretically it is easy to fathom that the representation of spatial information in the brain is amodal: the structures supporting mental and spatial representations in the blind and sighted are often the same and the cortex maintains its functional organisation despite the absence of vision from birth. Demonstrating such a thing is very difficult, however. For example, auditory activation of the "visual cortex" can be interpreted as an attentional recruitment by auditory stimuli rather than attributing the activity to the auditory stimulus (e.g. [24, 84]). Similarly, in the case where a sound of a dog barking activates the visual cortex, the classic criticism has been that the sound invokes imagery, and the imagery is what then activates the visual cortex. Since all modalities can initiate mental imagery, might imagery be amodal?

### *6.1 Amodal Imagery*

While imagery is a highly visual construct in normal-sighted individuals, mental imagery also expands to the other sensory modalities [76]. In this more broad use of the term, mental imagery refers to the construct or representation of a quasi-perceptual experience in the absence of perceptual sensory input. It is also commonly referred to as "seeing with the mind's eye". Thus, imagery refers to a particular aspect of memory in which a mental "image" of a stimulus is maintained. Various neuroimaging studies have demonstrated that mental imagery activates

similar neuronal patterns as processes related to sensory perception. For example, visual imagery will activate the visual cortex, particularly the extrastriate and associate visual cortices; while auditory imagery will be associated with the activation of secondary auditory cortices [76].

Mental imagery in the blind appears to be a construct of the remaining sensory modalities. While blind people have limited mental imagery capabilities restricted to non-visual modalities, they often outperform sighted individuals in mental imagery tasks. For example, Paivio and Okovita [100] found that congenitally blind people were better than sighted individuals at recalling item pairs with a high-auditory imagery component, whereas the inverse was found for items with a high-visual imagery component [100]. Moreover, as imagery has been shown to facilitate encoding, learning and memory recall, Marchant and Malloy [90] demonstrated that congenitally blind and deaf individuals were able to recall as many paired words as sighted control individual, when these words contained multi-modal imagery (e.g. a train) [90]. More specifically, recall was only impaired for congenitally blind individuals when items possessed unimodal visual imagery (e.g. a rainbow). As such, the mental imagery of blind individuals is limited to, but also compensated by, non-visual sensory modalities. Moreover, some particularities of object representation that, in sighted individuals, are strongly visual-based, such as shape, contours and textures, are acquired in the blind through the other modalities, such as touch. Vision is, therefore, neither necessary nor sufficient for mental imagery, and as such can be equally experienced even by early blind individuals.

Mental imagery in the blind may also be limited to sequential processing, as simultaneous processing is thought to be purely visual [141]. This recent revelation might partially explain the impaired performance (i.e. slower response times) of blind individuals in some, but not all,

visuospatial imagery tasks [2, 73, 141]. Therefore, although mental imagery is possible, even when reared in the absence of visual input, it is limited to non-visual sequential imagery.

In support of the amodal mental imagery hypothesis, the visual cortical areas are activated when blind people perform mental imagery tasks. For example, the ventral stream is known to play an essential role in object representation [56, 138] and, consequently, is an important locus for imagery. In sighted individuals, the occipitotemporal (OCT) cortex of the ventral stream seems to be equally active for visual and haptic shape representation [4, 5, 77, 104]. Although sighted individuals can resort to visual characteristics of the stimulus for mental shape representation, blind individuals can also generate a mental image of an object's shape through tactile sensory information. A recent study by Peelen et al. [104] demonstrated that, in the blind, the OCT cortex, and particularly the object-selective cortex (OSC) is active during tactile shape mental imagery, prompted by having blind people think about and compare the shape of different objects [104]. Object representation was prompted by a verbal (auditory) stimulus, by which the name of a common object was given. The activation of the OCT in both sighted and blind individuals, for visual and tactile shape processing, supports the notion that this cortical area is associated with amodal shape representation [111].

Likewise, the dorsal stream, associated with spatial localisation, also plays a role in imagery, particularly in imagery of visuospatial information. As revealed through studies in the blind, this cortical stream is associated with amodal spatial processing; spatial imagery prompted from verbal instructions has been shown to activate parieto-occipital areas of the dorsal stream in both blind and sighted individuals [16, 140]. Similarly, in an experiment where participants discriminated and compared the size of the angle between a clock's hands, blind and sighted participants both activated the posterior parietal cortical areas [16]. Thus, both the dorsal and

ventral streams (see Fig. 5) normally associated with visual imagery also have a supramodal functional nature and are recruited for tactile and auditory mental imagery.

In summary, findings suggest that the multisensory plasticity following blindness extends beyond sensory perception, to processes of mental imagery. While there are some limitations in the imagery capabilities of the blind, namely the absence of certain, purely visual, characteristics (e.g. colour), and their inability to perform simultaneous processing of mentally generated images, blind people often outperform visual controls in non-visual mental imagery tasks. These multisensory processes suggest that it is possible that different forms of mental imagery can be represented simultaneously in the brain.

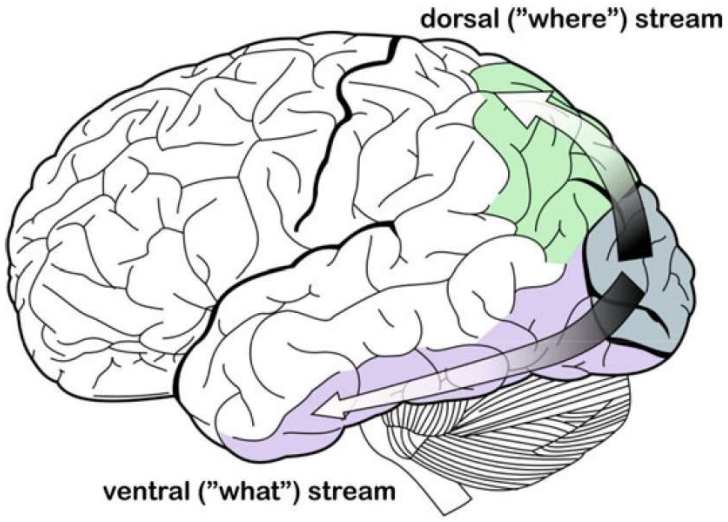


Fig. 5 The dorsal stream (green) and ventral stream (purple) are shown. They originate from a common source in the primary visual cortex. Modified by Selket from Anatomy of the Human Body, Gray H, Fig. 728 (1918)

### *6.2 Amodal Memory*

Although mental imagery refers to a particular aspect of memory, memory encompasses various other dimensions, including declarative, semantic, episodic, and procedural memory. Early blindness seems to result in an advantage for many of these aspects of memory leading several researchers to conclude that the primary visual cortex is recruited for higher order cognitive processes, such as verbal memory. In blind individuals, while the anterior region of the occipital cortex is associated with Braille reading, the posterior region is active during verbal memory and verb generation tasks [6]. It has been suggested that, in the absence of visual input from birth, the typical visual system hierarchy is inverted: in the blind, extrastriate areas become associated with amodal (or multisensory) processing, while the primary "visual" cortex is recruited for processing higher order cognitive functions, such as verbal memory [3, 6].

Verbal memory tasks yield different activation patterns for blind and sighted controls. Comparative BOLD fMRI measurements have revealed that, while the primary visual cortex is active during verbal memory and verb generation tasks in blind individuals, this activation is absent in sighted controls [6]. Furthermore, the magnitude of V1 activation is strongly correlated with verbal memory performance in blind participants [6]. Similarly, disrupting activity in the occipital pole by application of rTMS induces greater errors—particularly semantic errors—in an associative verb generation task in blind but not sighted individuals [3]. These results, thus, further support the role of the visual cortex in verbal processes of early blind individuals (see also auditory verb generation [20], speech comprehension [121], and language processing [10]). The visual cortex is not reserved for low-level visual processing, it can also be critical for processing higher order cognitive functions. Furthermore, in a follow-up study, long-term recall performance was assessed by recalling blind participants one year after initial testing, and

retesting them with the words used during the initial verbal memory tasks [115]. Raz and colleagues reiterated the correlation between activation in the occipital cortex and performance in verbal memory. The occipital cortex also plays an active role in episodic and semantic memory processes in early blind people.

More generally, memory capacity and fidelity appear to be enhanced with early visual deprivation. Blind individuals, particularly early blind people, are often reported to have superior memory [6, 67, 103, 107, 119, 128, 137]. Moreover, superior memory abilities associated with blindness depend on both the degree and timing of the visual impairment [67]. While memory appears to not be different between the late blinds and sighted individuals, it is considerably better in early blind populations [103]. Early blind individuals were found to, not only report more correct words (words from the original list), but also report fewer "false memories" (words that were semantically similar to, but not part of, the original word list) and fewer unrelated words [103]. This enhancement in memory suggests that blind individuals may rely more heavily on working and episodic memory in the absence of visual input.

## 7 Conclusions

While it was originally thought that the brain was parcelled into several specific subregions, each responsible for interpreting the information from a given sensory modality, along with a few "multisensory" areas that work to combine information across the senses, this idea has been largely debunked. A more recent view of the brain suggests that, instead of being sensory specific, cortical regions are functionally specific, likely based on their neuronal arrangement (e.g. striate cortex is best for interpreting spatial information, while the LOtv interprets shapes). Much of the evidence for non-visual activation of the "visual" cortex has come from blind

individuals who demonstrate considerable multisensory neural plasticity. Blinds trained in tactile and auditory tasks or on high-tech devices recruit their visual cortex to interpret the complex material. While this now classic example of neural plasticity was surprising and confusing at first, it fits with the evidence from several papers demonstrating that, even under normal visual development, activity in the occipital cortex can be elicited from tactile, auditory, olfactory, pain, and proprioceptive stimulation. Thus, the multisensory circuitry to the visual cortex is fastidious but certainly present, and becomes particularly robust when visual development is irregular.

Perhaps, vision plays a pivotal role in establishing multisensory functions during ontogeny, which would explain why visual pathways extend across to nearly all areas of the brain [66]. Vision, during development, might calibrate the senses to each other (so that size can be understood visually or haptically; so that speed can be understood visually and auditorally, enabling reference frame conversion between the modalities, etc.). In conditions of poor vision, the senses would be calibrated by another modality. Thus, while multisensory cortical areas have the primary role of integrating information, the evidence of multisensory activity in primary sensory cortices might be primarily related to the role of vision in ontogeny. After normal development of the senses, vision would be less relevant for primary cortical functions, and should eventually be pruned.

Understanding the multisensory nature of the brain enables us to develop better rehabilitation schemes and technologies. Rehabilitation schemes following brain damage (e.g. stroke related) have already benefitted from the knowledge of automatic audio–visual interactions when performing visual search tasks [15]. Moreover, understanding the role of vision within the brain, and the extensive plasticity in the blind brain, can improve technologies

built for the blind. Sensory substitution devices are developed with the knowledge that objects can be represented in multiple senses. These same devices can be further improved with a better understanding of the multisensory blind brain. Rather than devices that represent vision, we must remember that vision is in itself a representation of the outside world. The kinds of information that could enrich blind people's environments do not necessarily have a strictly "visual" component. Instead, thinking about the amodal functions of the occipital cortex might provide insight into the technological developments that should be pursued in the future.

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