# Impact of Pharmacological and Non-Pharmacological Interventions on Sleep and Cognition in Older Adults with Insomnia

Loïc Barbaux

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By: Loïc Barbaux

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Signed by the final examining committee:

_____ Chair
Dr. Christophe Grova

_____ External Examiner
Dr. Christina Schmidt

_____ Examiner
Dr. Richard Courtemanche

_____ Examiner
Dr. Véronique Pépin

_____ Examiner
Dr. Nárlon C. Boa Sorte Silva

_____ Thesis Supervisor
Dr. Thien Thanh Dang-Vu

Approved by _____
Dr. Maryse Fortin, Graduate Program Director

/ /2025 _____
Dr. Pascale Sicotte, Dean of the Faculty of Arts and Sciences

## Abstract For PhD

Impact of pharmacological and non-pharmacological interventions on sleep and cognition in older adults with insomnia.

**Loïc Barbaux, Ph.D.**
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Sleep supports overall health and cognition, notably memory consolidation through NREM-related brain oscillations. Sleep architecture is disrupted by aging, with chronic insomnia further compounding these changes. Given its links to cognitive decline and adverse health outcomes, addressing chronic insomnia in older adults is critical for promoting healthy aging.

High insomnia prevalence in older adults contributes to widespread sedative-hypnotic use, yet its impact on sleep regulation remains unclear. We compared sleep architecture, EEG spectrum, and NREM brain oscillations related to memory consolidation across older adults with chronic insomnia, with and without chronic sedative-hypnotic use (benzodiazepines, BDZ, and benzodiazepine receptor agonists, BZRA), and good sleepers. Findings indicated that chronic BZD and BZRA use impairs sleep regulation at both macro- and micro levels, potentially mediating the association with cognitive decline in aging.

Cognitive behavioral therapy for insomnia (CBTi) is a non-pharmacological intervention that constitutes the first-line treatment for insomnia. This study assessed the combined impact of CBTi and sedative-hypnotic withdrawal on sleep and cognition in older adults with chronic insomnia. The combined intervention improved withdrawal success, reduced insomnia severity, and preserved sleep duration, while also enhancing subjective sleep quality. A concurrent reduction in sleep spindle density was observed. These findings highlight strategies for safer and more effective sedative-hypnotic discontinuation in aging populations.

Rocking bed stimulation represents a promising intervention to improve sleep and memory, although its long-term effects remain unclear. This study examined the impact of three consecutive nights of rocking apparatus stimulation in young good sleepers to replicate prior findings, intended for future application in older adults with insomnia. On the first night, rocking stimulation did not enhance sleep architecture, brain oscillations, or memory, likely due to suboptimal motion and noise-related disturbances. However, a second night rescued some effects, suggesting rapid habituation. These findings underscore the importance of refining stimulation parameters to optimize the potential benefits of rocking on sleep and memory.

This thesis presents new insights into pharmacological, behavioral, and rocking motion interventions, which may help design a comprehensive approach to enhancing sleep quality and cognitive health in aging populations.

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## Contribution of Authors

**Chapter 2: Effect of chronic sedative-hypnotic use on sleep architecture and brain oscillations in older adults with chronic insomnia.**
Loïc Barbaux, Aurore A. Perrault, Nathan E. Cross, Oren M. Weiner, Mehdi Es-sounni, Florence B. Pomares, Lukia Tarelli, Margaret McCarthy, Antonia Maltezos, Dylan Smith, Kirsten Gong, Jordan O'Byrne, Victoria Yue, Caroline Desrosiers, Doris Clerc, Francis Andriamampionona, David Lussier, Suzanne Gilbert, Cara Tannenbaum, Jean-Philippe Gouin, Thien Thanh Dang-Vu

Conceptualization: LB, AAP, TTDV, NEC
Recruitment: LB, ME, OMW, DC, CD, LT
Data collection: LB, ME, OMW, AAP, FBP, LT, MM, AM, DS, KG, JOB
Project coordination: LB, ME, AAP, OMW, LT, FBP
Data curation: LB, AAP, NEC, ME, OMW, LK, MM, AM, DS, VY, MM, KG
Formal analysis: LB
Methodology: NEC, AAP, JOB
Visualization: LB, AAP, NEC
Interpretation: LB, AAP, NEC, TTDV
Supervision: AAP, NEC, TTDV
Funding: TDV, JPG
Writing - original draft: LB, AAP, NEC, TTDV
Editing and reviewing: OMW, JPG, CT, SG, DL, CD, FA, JOB, FBP, ME, LT, MM, AM, DS, KG

**Chapter 3: Effects of cognitive-behavioral therapy for insomnia during sedative-hypnotics withdrawal on sleep and cognition in older adults.**
Loïc Barbaux, Nathan E. Cross, Aurore A. Perrault, Mehdi Es-sounni, Caroline Desrosiers, Doris Clerc, Francis Andriamampionona, David Lussier, Cara Tannenbaum, Anik Guimond, Sébastien Grenier, Jean-Philippe Gouin, Thien Thanh Dang-Vu

Conceptualization: LB, NEC, TTDV, AAP
Recruitment: ME, LB, DC, CD, FA, DL, SG, JPG, CT
Data collection: LB, ME
Project coordination: LB, ME
Data curation: LB, ME, NEC
Formal analysis: LB
Methodology: JOB, NEC, AAP
Visualization: LB, NEC, AAP
Interpretation: LB, NEC, AAP, TTDV
Supervision: AAP, NEC, TTDV
Funding: TTDV, JPG
Writing - original draft: LB, NEC, AAP, TTDV
Editing and reviewing: JPG, CT, SG, DL, CD, FA, ME, DC

**Chapter 4: Impact of rocking bed stimulation on sleep and memory over multiple nights.**
Loïc Barbaux, Emma-Maria Phillips, Ophélia Fontaine, Alireza Moezi, Nathan E. Cross, Ramin Sedaghati, Sylvie Belleville, Nathalie Bier, Shannon Hebblewaithe, Laurence Bayer, Thien Thanh Dang-Vu, Aurore A. Perrault

Conceptualization: AAP, TTDV
Recruitment: LB, EMP, OF
Project coordination: LB, EMP, OF
Data curation: LB, EMP, OF, AAP
Formal analysis: LB, EMP, OF, AAP
Methodology: AAP, NC, EM, RS, LBayer
Visualization: LB, EMP
Interpretation: LB, EMP, AAP, TTDV
Supervision: AAP, TTDV, RS
Funding: AAP, TTDV, RS, SB, NB, SH
Writing - original draft: LB, EMP, AAP, TTDV
Editing and reviewing: LB, EMP, OF, NC, EM, RS, LBayer, SB, NB, SH, AAP, TTDV

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# List of Abbreviations

**AASM**: American Academy of Sleep Medicine
**AD**: Alzheimer's disease
**AHI**: Apnea-hypopnea index
**ApoE**: Apolipoprotein E
**ARAS**: Ascending reticular activating system
**Aβ**: β-amyloid
**BZD**: Benzodiazepine
**BZRA**: Benzodiazepine Receptor Agonist or Z-drugs
**CBTi**: Cognitive-behavioral therapy for insomnia
**CP**: Absolute coupling phase distance from SO up-state
**CRIUGM**: Centre de recherche de l'Institut universitaire de gériatrie de Montréal
**DL**: Delayed recall
**DKEFS**: Delis-Kaplan Executive Function System
**DORAs**: Dual orexin receptor antagonists
**DSST**: Digit Symbol Substitution Test
**DSM-5**: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
**ECG**: Electrocardiogram
**EEG**: Electroencephalogram
**EMG**: Electromyogram
**EOG**: Electrooculogram
**ESS**: Epworth Sleepiness Scale
**FCSRT**: French adaptation of the 16-items Free and Cued Selective Reminding Test
**GABA**: Gamma-aminobutyric acid
**GABAA**: Gamma-aminobutyric acid type A
**GAI**: Geriatric Anxiety Inventory
**GDS**: Geriatric Depression Scale
**GS**: Group involving good sleepers
**HADS**: Hospital Anxiety and Depression Scale
**Hz**: Hertz
**ICD-11**: International Classification of Diseases, 11th edition
**ICSD-3**: International Classification of Sleep Disorder, 3rd edition
**IL-6**: Interleukin-6
**IMM**: Immediate recall
**INS**: Group involving participants with insomnia
**ISI**: Insomnia Severity Index
**ISO**: Symptoms of insomnia
**LC**: Locus coeruleus
**LDT**: Laterodorsal tegmental
**LH**: Lateral hypothalamus
**MED**: Group involving participants with insomnia and chronic sedative-hypnotic use
**MI**: Modulation index
**MINI**: Mini-International Neuropsychiatric Interview
**MMSE**: Mini-Mental State Examination
**MoCA**: Montreal Cognitive Assessment

**MRF**: Mesencephalic reticular formation
**MSLT**: Multiple Sleep Latency Test
**MSSQ**: Motion Sickness Susceptibility Questionnaire
**NBM**: Nucleus basalis of Meynert
**NIS**: No insomnia symptoms
**NREM**: Non-Rapid Eye Movement
**N1**: NREM Stage 1
**N2**: NREM Stage 2
**N3**: NREM Stage 3
**OSA**: Obstructive Sleep Apnea
**PETHs**: Peri-event time histograms
**PID**: Probable insomnia disorder
**PLM**: Periodic Limb Movement
**PLMI**: Periodic Limb Movement Index
**POMS**: Profile Of Mood States
**PPT**: Purdue Pegboard Test
**PSG**: Polysomnography
**PSQI**: Pittsburgh Sleep Quality Index
**RBD**: REM Sleep Behaviour Disorder
**RCT**: Randomised Controlled Trial
**REM**: Rapid Eye Movement
**RF**: Reticular formation
**RM-ANOVA**: Repeated Measures Analysis of Variance type ANOVA
**RMS**: Root-mean-square
**RN**: Raphe nuclei
**ROCK**: Rocking stimulation condition
**SCID**: Structured Clinical Interview
**SCN**: Suprachiasmatic nucleus
**SCT**: Stimulus control therapy
**SE**: Sleep Efficiency
**SES**: Sociodemographic variables (age, education level, and sex)
**SFI**: Sleep Fragmentation Index
**SL**: Sleep Latency
**SOL**: Sleep Onset Latency
**SO**: Slow Oscillation
**SRT**: Sleep Restriction Therapy
**SSI**: Stage Switch Index
**STAT**: Stationary condition
**SWA**: Slow Wave Activity
**SWS**: Slow Wave Sleep
**TC**: Thalamocortical neurons
**TIB**: Time in Bed
**TMT**: Trail Making Test
**TMN**: Tuberomammillary nucleus
**TNF-α**: Tumor Necrosis Factor-alpha
**TRN**: Thalamic Reticular Nucleus
**TSP**: Total Sleep Period

**TST**: Total Sleep Time
**VLPO**: Ventrolateral Preoptic Nucleus
**WASO**: Wake After Sleep Onset
**WP+CBTi**: Withdrawal Plan + CBTi Group
**WPo**: Withdrawal Plan alone Group
**µV**: Microvolts

# Chapter 1: General Introduction

## 1.1 What is sleep physiology ?

Sleep or sleep-like state is observed in all animal species despite the increased vulnerability and risk of predation associated with this resting behavior[1]. Throughout evolution, it has been preserved as a fundamental biological process[2]. Sleep composes one-third of our lives and is as essential as feeding and drinking. Sleep is defined as a reversible behavioral state of perceptual disengagement from/and unresponsiveness to the environment, generally characterized by a recumbent posture, closed eyes, and a quiescence state[3]. Although the brain is in an immobile body, it remains active during sleep with a dynamic activity responsible for several functions[4].

### 1.1.1 Measurement of sleep and wakefulness states

#### *1.1.1.1 Subjective sleep assessment*

Sleep is a multidimensional behavior that includes both objective physiological processes and subjective experiences and integrating both assessments is essential for a comprehensive understanding of sleep and its impact on health. A self-reported restorative night of sleep was associated with enhancement in well-being, daily functioning, positive mindset, that further increases confidence and productivity[5]. It was also associated with enhancement in reflexes and reaction time, leading to greater physical capabilities. Importantly, sleep was linked to positive effects on social interactions, enhancing empathy, communication skills and emotional well-being. Furthermore, the subjective sleep perception was found to influence sleep satisfaction and daytime functioning[6].

Subjective sleep assessment are constituted by standardized questionnaires related to sleep quality or insomnia complaints (e.g., Pittsburgh Sleep Quality Index (PSQI)[7], Insomnia Severity Index (ISI)[8], St Mary's questionnaire[9]). In addition, the sleep diary, used daily over several weeks, is the most commonly used tool for assessing subjective sleep[10,11]. Sleep diaries report how a person feels upon awakening, documenting their perception on time spent asleep and latency to fall asleep as well as the frequency and duration of nighttime awakenings (i.e. wake after sleep onset, WASO). They also assess whether their sleep was refreshing, and determine their level of sleepiness[12].

#### *1.1.1.2 Objective sleep assessment*

Polysomnography recordings (PSG) is widely acknowledged as the gold standard for objective sleep assessment[13]. PSG encompasses a comprehensive set of measurements, including electroencephalogram (EEG) for cerebral electrical activity, electromyogram (EMG) for muscle activity placed on the chin, electrooculogram (EOG) composed of bipolar electrodes for

electrical activity of ocular movement, according to the American Association of Sleep Medicine (AASM) guidelines[14]. EEG signal recorded from the scalp provides an indication of spontaneous electrical activity of the dendrites of cortical pyramidal neurons, specifically the synchronisation of their excitatory or inhibitory potentials. Additional measurements include electrocardiogram (ECG) for cardiac activity, and various respiratory measurements (i.e. abdominal/thoracic belts, pulse oximeter, thermistor) and assessing body movements (e.g. EMG electrodes on legs for periodic leg movements)[13].

Actigraphy is a non-invasive method for objectively measuring sleep using a wrist- or ankle-worn device[15]. These devices track body movement acceleration across three axes and ambient light to estimate sleep duration, fragmentation, and onset based on immobility and darkness. While actigraphy provides valuable insights into sleep patterns over multiple days, it remains an indirect measure and does not identify sleep stages[16,17].

#### 1.1.1.2.1 Vigilance states

Vigilance states are composed of wakefulness, and sleep, further categorised into NREM (Non Rapid Eye Movement) and sleep. From PSG recordings and according to the AASM guidelines, visual sleep scoring on 30-s epochs enables the characterisation of these vigilances states, according to the presence of specific grapho-elements, characterized by specific frequencies and amplitudes on the EEG signal[14]. In addition, EEG signal is used to perform power spectrum analysis, which decomposes EEG signal into its constituent frequencies bands and quantifies their respective power[18].

##### 1.1.1.2.1.1 Wakefulness

During wakefulness, the cortical acitivity is desynchronized, EEG signal is composed of fast frequency and low amplitude wave of mixed-voltage, ranging in the alpha, beta and gamma power spectrum, respectively from 8 to 11 Hz, 15 to 30 Hz and 30 to 120 Hz. Specifically during relaxed wakefulness and eyes closed, it is possible to measure alpha rhythm, a marker of reduced cerebral frequency[19].

Beyond the time spent awake (i.e. WASO), there are other markers of wakefulness or sleep fragmentation, such as the number of transitions between sleep stages (stage switch index; SSI) and number of transitions from deep to lighter sleep stages (sleep fragmentation index; SFI) per hour of sleep[20]. The density of micro-awakening also called arousals informs on the integrity of sleep. Arousals are characterized by sudden increases in spectral activity of high-frequency

bands (i.e., alpha, beta), without leading to complete wakefulness, and typically last from 3 to 15 seconds[21].

#### 1.1.1.2.1.2 Sleep

##### *1.1.1.2.1.2.1 NREM sleep*

NREM sleep is divided into three stages, respectively from falling asleep to deep sleep: N1, N2, and N3, usually described in percentage of the total sleep period (TSP), from sleep onset to the final awakenings. It is characterized by an overall low muscle tone and slow rapid eye movements[22] (See **Figure 1**).

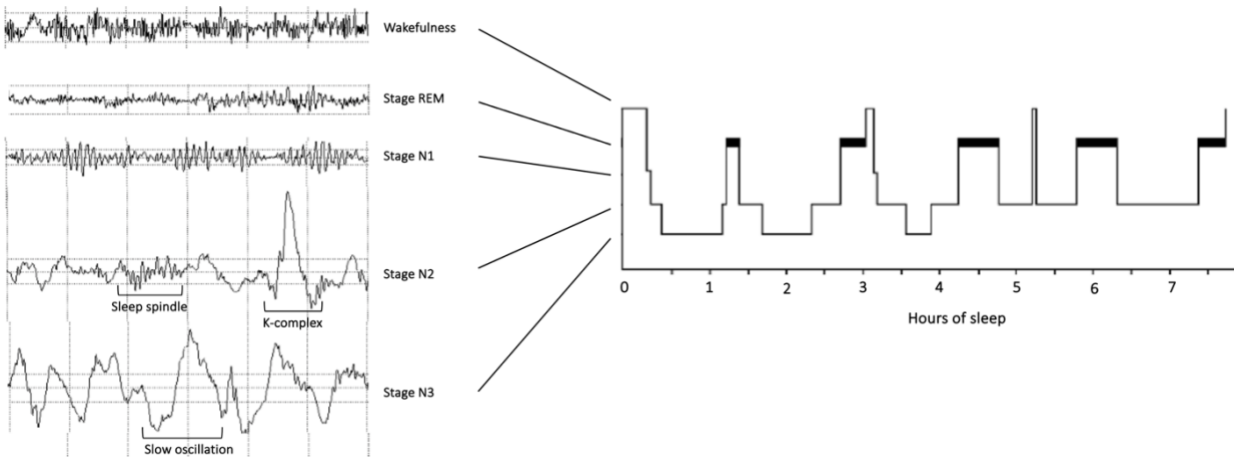


Figure 1: Distinctive EEG pattern of sleep stages and wakefulness

Adapted from Pandi-Perumal et al.[23] and Barbaux[24].

*Rapid Eye Movement, REM*

###### 1.1.1.2.1.2.1.1 Stage N1

The transition from wakefulness to sleep is represented by N1 stage. It is characterized by slow eye movement, low-amplitude waves and mixed frequency activity in the theta or alpha range[25].

###### 1.1.1.2.1.2.1.2 Stage N2

As sleep deepens and cortical activity becomes increasingly synchronized, the EEG signal becomes characterized by larger amplitude and slower frequencies in the N2 stage. This stage is characterized by the presence of specific brain oscillations, namely spindles (sigma frequency: 12-16 Hz) and K-complexes (0.5-1 Hz)[25].

*1.1.1.2.1.2.1.2.1 K-complex*

K-complexes are generated by the cortex and are characterized by a biphasic wave with a high amplitude positive peak followed by a low amplitude negative peak[26]. They last from 0.5 to 1 sec and can appear both spontaneously[27] or in response to sensory stimulation, such as auditory stimulation[28].

*1.1.1.2.1.2.1.2.2 Sleep spindles*

Sleep spindles are characterized as brief bursts of activity oscillating within the sigma frequency range (11-16 Hz) typically lasting between 0.5 to 3 sec, occurring more frequently in N2, but are also present in N3[29,30]. Spindles can be visually detected in the EEG signal or using algorithm[31]. Their generation involve a thalamo-cortical loop, further discussed in the chapter "1.1.2.2.1.1 Thalamo-cortical pathway". Spindles are categorized into slow or fast spindles according to their frequency with a threshold typically set at 13 Hz and based on their localization[29,30,32–34]. Fast spindles (>13 Hz) are predominantly found in posterior areas, while slow spindles (<13 Hz) are preferentially observed at the frontal site.

Spindle characteristics remain consistent within individuals across multiple nights between and appear as a stable trait in adults[30] and older adults[35]; although spindles have been found to be modulated by sensory stimulation[36,37], pharmacological intake[38] as well as aging processes[39]. Spindles have been functionally involved in sleep stability, as its density is a strong stable trait within individuals across nights[40,41], in sleep maintenance in the face of noise[42] and are heritable[43]. Sleep spindles are also associated with sleep-dependent memory consolidation processes, including declarative memory[44–49] and procedural memory[50–53], further discussed in the chapter "1.2.1.2 Active system consolidation process".

1.1.1.2.1.2.1.3 Stage N3

The N3 stage displays the greatest amplitude and lowest frequency waves. It is characterized by the dominance of slow wave activity (SWA), is prevalent in the early sleep period and declines thereafter[54]. This stage also known as deep sleep or slow wave sleep (SWS), including slow oscillations (SO; <1.25 Hz) and delta rhythm (0.5-4 Hz), known as slow wave activity (SWA).

*1.1.1.2.1.2.1.3.1 Slow oscillations*

Slow oscillations (SOs) are generated by the cortex and are recorded at a frequency from 0.5 to 1.25 Hz during N3. SO biphasic shape reflects the alternating pattern of cortical excitability

state, known as the down-state and the up-state[55]. The down-state is characterized by a cortical silence: cortical neurons are hyperpolarized, and their excitability decreases. This state is associated with a negative wave in EEG recording from cortical surface. Conversely, the up-state is characterized by a depolarization of cortical neurons, resulting in an increase in excitability, associated with a positive wave in EEG recording.

Both N3 duration and SOs has been found to provide beneficial effect on sleep-dependent memory consolidation. In addition, SOs synchronizes and bind other NREM rhythms (i.e., delta rhythm, thalamo-cortical spindles, hippocampal sharp-wave ripples) enabling sleep-dependent memory consolidation processes[56,57], see "1.2.1.2 Active system consolidation process". SWA is also essential for sleep homeostasis, see "1.1.3 Sleep-wake regulation".

#### *1.1.1.2.1.2.2 REM*

REM sleep is defined by muscle atonia, except for rapid eye movements, with an EEG activity similar to wakefulness or N1 stage[58], characterized by low amplitude and mixed-frequencies, in the gamma, and most prevalent in the theta frequency range[59,60]. Periods with no rapid eye movements refer to tonic REM, while in the presence of rapid eye movements, phasic REM[61].

### 1.1.1.2.1.3 Sleep architecture

During the night, sleep follows a cyclical pattern: first N1, then N2, followed by N3, and finally REM sleep. The combination of NREM and REM periods forms a sleep cycle, with each cycle lasting approximately 90 minutes and occurring 4 to 5 times throughout the night[62]. Furthermore, the proportion of time spent in N3 is highest early in the night and nearly absent later on, while REM sleep is most prevalent during the late night and absent during the early night. Additionally, the composition of sleep stages—N1, N2, N3, and REM—represents approximately 5%, 50%, 15%, and 25% of TSP in healthy adults[54].

The combination of SOL, WASO, and TST is represented by the time spent in bed (TIB), which reflects the duration of the lights-off period. In addition, sleep efficiency (SE) is calculated as the percentage of the TST/TIB ratio, which is considered ideal when it reaches 85% or higher.

### 1.1.2 Neurobiology of sleep-wake regulation

#### *1.1.2.1 Wakefulness promotion*

The reticular formation (RF) is essential for the regulation of wakefulness and sleep. An experiment conducted by Magoun and Moruzzi in 1949 demonstrated that electrical stimulation of the RF could awaken a cat from an anesthesia-induced state[63]. EEG recordings revealed low-amplitude, high-frequency waves characteristic of wakefulness. However, after sectioning the cat's brainstem, it was no longer possible to awaken the animal, and the EEG displayed a continuous coma state characterized by high-amplitude and low-frequency activity. The RF is a neural structure located along the brainstem, characterized both structurally and functionally into three columns: central, median, and lateral. The central reticular column includes the raphe nuclei (RN), which contain serotonergic neurons[22,64]. The median reticular column contains the mesencephalic reticular formation (MRF), a non-specific structure that includes two specific nuclei: the laterodorsal tegmental (LDT) and the pedunculopontine tegmental (PPT) nuclei, both consisting of cholinergic neurons. Anatomically and functionally connected to the RF, the locus coeruleus (LC) is a brainstem structure situated at the junction of the pons and midbrain, composed of noradrenergic neurons. Together, these structures form the ascending reticular activating system (ARAS).

Wakefulness, or cortical arousal, is sustained notably through direct excitatory projections to the frontal cortex through reciprocal excitatory interactions within the ARAS. Furthermore, the ARAS is continuously stimulated by incoming sensory information (both external and proprioceptive). The ARAS plays a crucial role in maintaining cortical arousal, or wakefulness, through two distinct pathways: the ventral pathway and the dorsal pathway.

The ventral pathway specifically describes the pathway through which projections from ARAS ascend via the hypothalamus and basal forebrain, influencing cortical arousal and promoting desynchronization, which is marked by the higher-frequency in EEG signal characteristic of wakefulness. The ascending projections of the ARAS depolarize neurons in the posterior hypothalamus, particularly within the tuberomammillary nucleus (TMN)[22,64]. The TMN contains histaminergic neurons, which release excitatory histamine projections to the cortex and the basal forebrain, specifically targeting the nucleus basalis of Meynert (NBM). The cholinergic neurons in the NBM then send excitatory projections to the cortex, leading to the cortical desynchronization observed similarly during wakefulness. Another crucial structure in maintaining wakefulness is the lateral hypothalamus (LH), which contains orexin (or hypocretin) neurons[22,64]. These neurons have excitatory projections that depolarize wake-

promoting structures such as the ARAS and the TMN, further enhancing cortical activation (See **Figure 2A**).

The dorsal pathway refers to the pathway that extends from ARAS to the thalamus and subsequently to the cortex, while also encompassing direct projections from ARAS to the cortex. The excitatory cholinergic neurons of both LDT and PPT are essential in depolarizing the thalamus and promote cortical excitation. During wakefulness, the thalamus functions as an information gateway, regulating the flow of sensory signals to and from various cortical regions[22,64].

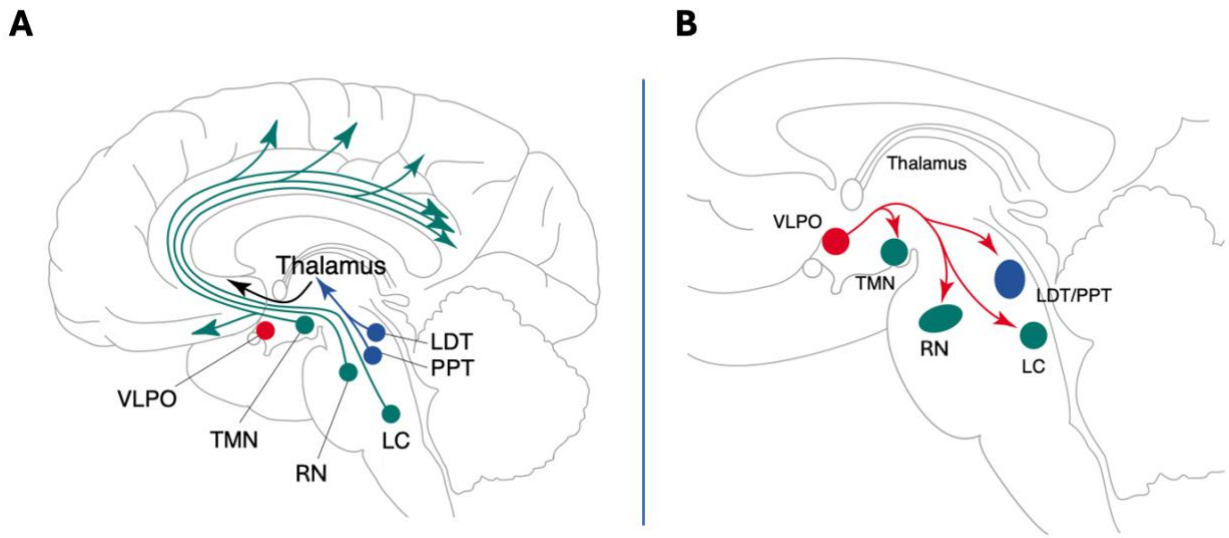


Figure 2: Wake and NREM promoting system

Adapted from Saper et al.[65].

*RN=raphe nuclei; LC=locus coeruleus; PPT=pedunculopontine tegmental; LDT=laterodorsal tegmental; VLPO=ventrolateral preoptic nucleus; TMN=tuberomammillary nucleus*

*(A) During wakefulness, the ascending reticular activating system send excitatory projections to the thalamus and the cortex.*

*(B) During NREM sleep, the VLPO send inhibitory projections to the ascending reticular activating system.*

### *1.1.2.2 Sleep promotion*

Sleep induction occurs through the activation of the anterior hypothalamus within the preoptic area and specifically involving the ventrolateral preoptic nucleus (VLPO). The VLPO consists of GABAergic and galaninergic inhibitory neurons that hyperpolarize neurons in structures responsible for sustaining wakefulness and cortical excitation, specifically the ARAS, the LH, the TMN, and LDT/PPT indirectly[22,64] (See **Figure 2B**).

The accumulation of adenosine, a marker of increasing sleep pressure, promotes sleep by activating the VLPO (see “1.1.3 Sleep-Wake Regulation”).

#### 1.1.2.2.1 NREM maintenance

##### 1.1.2.2.1.1 Thalamo-cortical pathway

As the excitatory cholinergic afferents to the thalamocortical neurons (TC) and the inhibitory inputs to the thalamic reticular nucleus (TRN) are progressively inhibited, cortical activity increasingly becomes influenced by the thalamic activity[66].

The thalamo-cortical pathway encompasses various thalamic structures that are essential for regulating sleep-wake cycles[22,64]. Neurons in the TRN release inhibitory GABAergic signals to TC neurons, which subsequently project excitatory glutamatergic signals to the cortex. In turn, the cortex sends excitatory projections back to the TRN, establishing a thalamo-cortical circuit. Additionally, TC neurons provide excitatory feedback to the TRN neurons, creating a local loop within this system.

During wakefulness, the TRN exhibits tonic inhibitory activity that filters and modulates sensory input from the environment as it passes through the thalamus to the cortex[22,64]. The TRN interacts closely with other neural networks to ensure an adaptive response to external stimuli. As sleep onset begins and the cholinergic activity is inhibited, TRN neurons shift to an intrinsic "burst" firing pattern. These neurons have distinct electrophysiological characteristics that allow the maintenance of a tonic firing during depolarization for sensory information relay, and an oscillatory pacemaker activity when hyperpolarized[30]. This TRN driven activity hyperpolarizes TC neurons, initiating an oscillatory state that synchronizes cortical rhythms, reaching its peak during SWA[22,30].

##### *1.1.2.2.1.2 Sleep spindle generation*

The initiation of spindle activity originates in the opening of low-threshold, voltage-dependent $Ca^{2+}$ channels (CaV3) in the TRN, which functions as a pacemaker[67,68]. Due to their low-threshold properties, TRN $Ca^{2+}$ channels can open during hyperpolarized states, which occur when the ARAS system weakens[22]. The TRN neurons dendrites express high levels of these low-threshold $Ca^{2+}$ channels[67,69], generate "burst" action potentials, involving rapid sequences of action potentials firing[30]. Cortico-reticular projections from cortical layer VI to TRN distal dendrites lead to excitatory postsynaptic potentials, thereby activating $Ca^{2+}$ channels[70] and

further activate $Ca^{2+}$-dependent potassium SK2-type, causing after-hyperpolarization, which limits burst duration[68]. Inhibitory influence from TRN neurons on TC neurons is enhanced notably by robust axon-dendrite connectivity[71], and the recruitment of extra synaptic GABAergic receptors[72]. Together, these mechanisms amplify TC neuron hyperpolarization through tonic TRN inhibition[30,73]. In response to inhibitory postsynaptic potentials from TRN, TC cells can initiate rebound burst firing through low-threshold $Ca^{2+}$ channels[74], driving thalamo-cortical oscillatory activity to the cortex[75]. This discharge mode is triggered when multiple inhibitory postsynaptic potentials from TRN neurons are received. Excited TC neurons then project excitatory glutamatergic outputs onto TRN neurons[76,77]. This feedback can occur in an "open-loop" format, where the TRN neurons excited are adjacent to those initially inhibiting the TC neurons, allowing lateral excitation within the TRN to propagate and synchronize spindle rhythms[30,73,78].

The synchronization of thalamic spindle rhythms is predominantly regulated by corticothalamic mechanisms that ensure spatial and temporal coordination[79]. Corticoreticular projections to the TRN are topographically organized, with terminal arborizations aligning with dense innervation areas, facilitating cortical-TRN communication and thalamic rhythm modulation[30]. The simultaneous activation of multiple sectors of the TRN also contributes to this coordination. Moreover, thalamic circuits are essensial for the synchronization of spindle rhythms. Open-loop feedback between TC neurons and the TRN facilitates the recruitment of additional TRN cells, allowing spindle activity to spread across larger thalamic territories[73]. Direct dendritic communication among TRN neurons through gap junctions further enhances synchronization, with functional coupling being particularly pronounced during the burst firing of TRN neurons[80]. In addition, several anti-synchronization mechanisms exist to modulate spindle rhythms, leading to hyperpolarisation, and further complete deactivation of TRN neurons[81–84].

The average duration of a spindle ranges from 0.5 to 3 sec, followed by a refractory period of 5 to 10 sec. This refractory period is primarily induced by cellular afterhyperpolarization, resulting from the activation of $Na^{+}$- and $Ca^{2+}$-dependent $K^{+}$ channels in TRN neurons[85]. Additionally, TC neurons experience cellular after-hyperpolarization induced by hyperpolarization-activated non-selective cation (HCN) channels, which contribute to the suppression of burst rebound activity in TC neurons[30,86].

#### 1.1.2.2.1.2 Slow oscillation generation

Slow oscillation is represented by an alternation between two states of stable membrane potentials recorded in EEG: the down-state and the up-state[55]. During up-state, a negative wave is measured by intracranial EEG in the deep cortical layers, and a positive wave is measured by EEG in the superficial cortical layers. As previously mentioned, TC neurons have afferents in all cortical layers, although majority of synapses are found between layers III to VI[87]. These glutamatergic excitatory afferents activate several types of neurons, including inhibitory parvalbumin interneurons, which lack GluA2 subunit at their postsynaptic AMPAR receptors[30]. This property induces a faster and more prolonged temporal summation of synaptic inputs than that induced directly by glutamatergic afferents, inducing an inhibitory dominance in deep cortical layers[88]. In superficial layers, parvalbumin interneurons inhibit dendrite-targeting somatostatin interneurons of pyramidal neurons, thus conducting to a disinhibition effect and neuronal discharge recorded in EEG.

During down-state or cortical silence, a positive wave is measured by intracranial EEG in the deep cortical layers and a negative wave is measured by EEG in the superficial cortical layers[55]. This time, somatostatin interneurons inhibits superficial layers leading to a surface cortical silence although deep pyramidal neurons soma is activated and can also activate TC neurons through their excitatory afferences. Thus, sleep spindles are time-locked to particular phase of SO, inducing a cross-frequency phase amplitude coupling[34].

#### 1.1.2.2.2 REM sleep

The regulation of REM sleep involves REM-on and REM-off neurons, and their interneurons localized in the brainstem[89]. While REM-on neurons are localized in the LDT/PPT, REM-off neurons are localized in the RN and the LC. REM-on neurons are inhibited by the ARAS system during wakefulness, and by the REM-off neurons during NREM sleep, preventing REM onset. The decrease in the REM-off neurons over time facilitates the activation of the REM-on neurons and REM onset. Termination of REM period is constituted by the activation of REM-off neurons by the REM-on neurons. This reciprocal innervation maintains the cyclic pattern of NREM and REM sleep across the night. REM sleep is not in the scope of the present thesis, and REM generation will not be discussed further.

### 1.1.3 Sleep-wake regulation

During wakefulness, the VLPO is inhibited by the ARAS system, while during NREM, in contrast, the ARAS is inhibited by the VLPO. The switch from one process to the other is known as the flip-flop switch model[64,90], regulated by two processes : the homeostatic processus S and the circadian processus C[91,92]. These two processes are closely associated in on the cellular and molecular level[93,94].

The process S, also known as sleep homeostasis, refers to the accumulation of sleep-promoting factors, such as adenosine, in the cortex and the brainstem during wakefulness due to neuronal activity. Adenosine was found associated with sleep pressure, the accumulation of which leads to VLPO activation for sleep promotion[95–97]. This increase in sleep pressure accumulated during wakefulness is gradually reduced during sleep, especially involving SWA, and reduces the need for sleep. Such process is influenced by the proportion of the prior wakefulness period[92]. Moreover, sleep homeostasis was observed to temporally and spatially reflects local cortical neuronal activity[98,99].

The process C is an endogenous biological clock that regulates the circadian rhythm. The circadian rhythm is mediated by clock genes, such as Period (Per3), which encode protein involved in generating circadian rhythmicity[100–103]. It is primarily driven by light, and to a lesser extent by daytime activities and food intake[104]. During wakefulness, light is detected by the reticular ganglion cells containing melanopsin, which activate the suprachiasmatic nucleus (SCN) of the hypothalamus via the retino-hypothalamic pathway. The SCN is the main synchroniser of the circadian rhythm in a 24-hours light-dark cycle, influencing various physiological processes (i.e. thermogenesis, metabolism, mood, sleep)[104,105]. This activation leads to the inhibition of melatonin production by the pineal gland. As light diminishes in the evening, melatonin production begins cyclically.

## 1.2 Why sleep is important ?

### 1.2.1 Function of sleep

Sleep is a behavior essential for health, ensuring physiological homeostasis and overall brain function[106–108]. This is particularly evident in the consequences of sleep disturbance, or deprivation, which manifests through a range of detrimental effects.

Both partial and total sleep deprivation leads to significant perturbation in physiologycal homeostasis. Animal studies demonstrated detrimental effect such as weight loss despite increased nutrient intake, skin lesions and impaired thermoregulation[109]. Notably, complete

sleep deprivation resulted in mortality within 2 to 3 weeks, whereas partial sleep deprivation led to death within 4 to 6 weeks. Research in human also indicated an association between sleep duration and mortality risk. A 22-year longitudinal study found correlations between both short (i.e. <6 hours) and long (i.e. >8 hours) sleep duration and increased mortality risk[110,111]. Furthermore, sleep regularity has been recognized as a stronger predictor of mortality risk compared to sleep duration[112].

The effect of sleep on the cardiovascular system was widely studied. One-night sleep deprivation induced sympathetic hyperactivity, evidenced by increased stress hormone secretion (i.e. cortisol, noradrenaline), and higher blood pressure and heart rate in healthy adults[113]. The discrepancy between chronological age and the heart's estimated biological age, determined based on cardiovascular risk factors (e.g., smoking, diabetes, hypertension) and referred to as excess heart age—was the lowest in individuals sleeping 7 hours per night and increased with both shorter and longer sleep durations[114]. Moreover, one-night sleep deprivation impaired cortical control of respiratory motor output (i.e. diaphragm), reducing inspiratory endurance in healthy adults[115].

The immune system is also impacted by sleep. In mice model, circadian rhythm disruption significantly altered cellular innate immune system[116]. Studies in healthy adults also reported that partial sleep deprivation activated cellular innate immune response, with increased levels of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)[117,118]. Additionally, evidence suggests a link between the gut microbiome and sleep regulation through the microbiota-gut-brain axis[119]. Certain bacterial taxa displayed associations with SE and IL-6 levels, while others are linked to sleep fragmentation[120]. Notably, self-reported sleep quality demonstrates a positive correlation with the Firmicutes-to-Bacteroidetes (F/B) ratio in healthy young adults[121]. Short sleep duration (i.e. <5 hours) also showed effect on the kidney function, with an increased risk of proteinuria, a marker of kidney disease progression[122].

Beyond its effect on physical health, sleep was also found essential in metabolism regulation, weight control and appetite. One night of sleep deprivation increased a hormone regulating appetite (i.e. ghrelin), while reducing hormones regulating satiety and metabolism (i.e. leptin, adiponectin), potentially facilitating weight gain in individuals with obesity[123]. Sleep deprivation contributed to fatigue, which may, in turn, reduce physical activity and energy expenditure, and encouraging sedentary behaviors and increased food intake[124,125]. Short sleep duration (i.e. <7 hours) was associated with an increased risk of obesity, adverse cardiovascular outcomes (i.e. cardiovascular diseases, hypertension, coronary heart diseases) and diabetes

mellitus[111]. The risk of type 2 diabetes incidence followed a U-shape, with the lowest incidence observed in individuals sleeping 7 to 8 hours per night[111,126].

Sleep is also essential for cognitive function. Sleep disturbance leads to vigilance and attention impairment[127], reduced driving performance[128] and further increases the risk of traffic accident[129]. Within the academic sphere, poor sleep quality and quantity was linked to worsening in performance, and neurocognitive impairment[130]. Moreover, sleep deprivation was associated with increased in anxiety levels[131]. Even moderate sleep loss induced increased aggressivity, anger in response to irritants (e.g. noise), and diminished enthusiasm[132,133]. Notably, lower N3 duration was associated with reduced positive mood following one-night sleep deprivation[134,135]. Sleep is also strongly associated with depression[136–138]. Approximately 80% of individuals with depression report sleep disturbances[139], which commonly include prolonged sleep latency, increased fragmentation, and reduced durations of both N3 and REM duration[140]. Furthermore, sleep disturbance not only constitutes as a symptom of depression but also represents a risk factor for its onset[141]. Notably, individuals with insomnia but no depression displayed a twofold increased risk of depression incidence compared to those without insomnia or depression[142]. Furthermore, sleep impacted nociception and pain sensibility. Studies shown that sleep restriction (i.e. 4 hours) increased vulnerability of having migraine[143], and pain sensibility specifically in healthy females[144].

Sleep also constitutes also a significant determinant of stroke risk[145,146]. A meta-analysis involving over 500.000 individuals found a U-shape association between sleep duration on stroke incidence[147]. Both short (i.e. 5 or 6 hours) and long (i.e. 8 or 9 hours) sleep duration increased stroke incidence, by respectively 15% and 45%[147]. Similarly, a U-shape effect was found for the risk of cardiovascular disease mortality[148].

#### *1.2.1.1 Sleep-dependent memory consolidation*

This thesis focuses on one important function of sleep: memory consolidation, which involves specific brain oscillatory activity.

##### 1.2.1.1.1 Memory processes

It is well established that sleep is crucial for the formation of memory[149]. Memory function is typically divided into three processes: encoding, consolidation, and retrieval[149]. The perception of a stimulus initially leads to the formation of a labile memory trace, susceptible to forgetting. Memory consolidation encompasses both short- and long-term memory process that stabilize

this trace, integrating the information into an accessible memory-related knowledge network. Retrieval characterises the reactivation and recall of memories. Given that sleep is characterized by a reduced responsiveness to external stimuli, it provides an optimal window for memory consolidation[149]. Memory formation in the hippocampus is characterized by change in neuronal connectivity, a process known as synaptic plasticity. This phenomenon involves modification in the synaptic strength, with either long-term potentiation (LTP), enhancing synaptic strength, or long-term depression (LTD), reduced synaptic connections within the memory-related neural network[150,151].

Memory can be classified into declarative and non-declarative memory, based on the type of information coded and the neural pathway involved[152]. Declarative memory involves the medial temporal lobe, the prefrontal cortex, and the hippocampus[153]. It refers to explicit memory, which can be consciously recalled and verbally expressed. Furthermore, this type of memory is divided into semantic memory, which includes knowledge of facts and concepts independent of the encoding context and requires repeated encoding for consolidation. Episodic memory refers to the recall of events contextualised in a specific temporal and spatial framework adapted to individuals' experience, characterized by fast encoding. Non-declarative memory involves motor areas, the striatum, and the cerebellum. It refers to implicit memory, which do not require conscious processes. This includes procedural memory, referred as motor memory, for motor skills, as well as conditioning such as Pavlovian reflexes.

Numerous studies have demonstrated the effect of sleep on stabilizing memory performance[154] and providing beneficial effect on sleep-dependent memory consolidation, across a large range of motor sequence learning tasks[155]. These benefits are influenced by the experimental design (i.e. varied delay design, nap versus overnight sleep, sleep deprivation), the type of memory assessment as well as age and clinical status[154,156–158]. A meta-analysis on sleep-dependent procedural memory consolidation revealed a significant improvement in younger adults (i.e., 18–35 years) but did not observe the similar effect in older adults (i.e., 60–85 years)[157]. In addition, individuals with insomnia did not display the same sleep-related memory benefits observed in healthy participant[156].

Extensive research demonstrated the role of sleep in procedural memory enhancement, particularly when using the finger-tapping task. Beneficial effect was found across various experimental designs, including varied time design[53,159–162], nap studies[163,164], sleep deprivation[165], and dimension transfer design assessing the ability to apply new learned skills to new tasks[166]. Notably, REM sleep was found to predict sleep-dependent improvements in procedural memory performance in healthy young adults[167–169]. Additionally, REM sleep is

closely linked to emotional memory consolidation[170]. Numerous studies also demonstrated the importance of sleep spindles, particularly fast spindles activity in the parietal region, with the improvement of procedural memory performance[50,171–174].

Moreover, the importance of sleep was also demonstrated for declarative memory in multiple studies[149,175]. Notably, N3 duration in early sleep was associated with improvement in declarative memory consolidation[47,176–179]. Furthermore, the greatest memory improvement was associated with the highest hippocampal reactivation during N3[180].

Studies also observed an association between improvement in declarative memory and increased in fast spindle in the parietal area[47,181–183].

#### *1.2.1.2 Active system consolidation process*

The active system consolidation process refers to the system in which the encoded the memory trace is transferred from the hippocampus to the neocortex (especially during N3) through repetitive reactivation, promoting long-term retention[184]. The active system consolidation process combines two hypotheses for sleep-dependent memory consolidation process. The dual process hypothesis suggests that N2-N3 benefits declarative memory, while REM improves procedural memory consolidation[149]. The sequential hypothesis assumes that, during N3, non-adaptive memories are weakened and adaptive ones strengthened, with consolidation occurs during REM[149].

Such hippocampal activity, known as sharp-wave ripples are temporally coupled with thalamo-cortical sleep spindles and cortical SOs and are beneficial for sleep-dependent memory consolidation[149,179,185–188]. Numerous studies investigated the coupling between SO and spindle, and observed that fast spindles were coupled around the SO up-phase, while slow spindles nested after the up-state in the up-to-down phase[34,37,189–194] (See **Figure 3**). Furthermore, the phase of SO at which spindles were coupled showed significant variation between individuals while maintaining consistency between consecutive nights within individuals[195]. Several studies have demonstrated the role of the coupling between SO and spindles in the consolidation of both procedural[50–52] and declarative memory[36,37,194,196–200]. Cross-frequency coupling between SO phases and sigma frequency can be assessed using the modulation index (MI) and the coupling preferred phase (CP)[201]. MI represents the coupling strength, specifically the average degree of modulation of the coupling between SO and sigma. CP reflects the average preferred phase (in a circular visual ranging from 0 to 360°) at which the amplitude of sigma is highest.

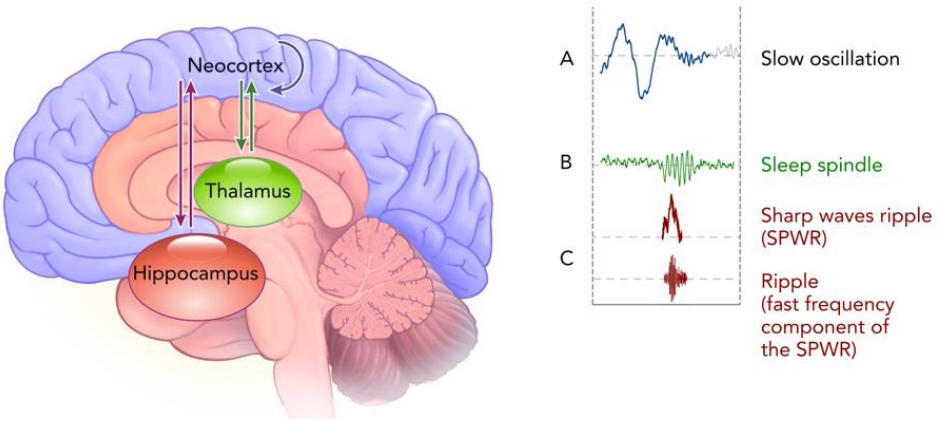


Figure 3: Neural interplay between hippocampal sharp wave ripples, thalamo-cortical spindle and cortical slow oscillation

Adapted from Marshall & Cross et al.[57].

### 1.2.2 Sleep disorders: chronic insomnia

Sleep disorders are common in the general population, represented by parasomnias (e.g. somnambulism), central disorders of hypersomnolence (e.g. narcolepsy), sleep-related breathing disorders (e.g. obstructive sleep apnea; OSA), sleep-related movement disorder (e.g. restress legs syndrome or periodic limb movement of sleep), or circadian rhythms sleep-wake disorders[202,203]. The present thesis focused only on the most prevalent sleep disturbance, represented by insomnia.

#### *1.2.2.1 Definition of insomnia*

Insomnia definitions changed over time, from a focus on symptomatology classification to an emphasis on treatment implications[204]. Insomnia used to be subdivided into different types: psychophysiological insomnia, paradoxical insomnia, idiopathic insomnia[205,206]. The most common form is constituted by psychophysiological insomnia, defined by somatic tension and negatives and excessive worry about pre-sleep routine or bedtime, leading to a hyperarousal cerebral state, further disrupting sleep. Insomnia is characterized as paradoxical when individuals reported complaints about sleep, while objective sleep assessment (PSG) did not provide any sleep perturbation[207,208]. Furthermore, a discrepancy of at least 15% between objective (i.e., PSG) and subjective (i.e., sleep diaries) sleep measures, known as sleep misperception, is common and occurs in approximately 50% of individuals with insomnia[207,209,210]. Individuals with insomnia disorder tend to overestimate their wakefulness

events, including sleep onset and nocturnal awakenings, while underestimating their sleep duration[207]. In addition, idiopathic insomnia referred to insomnia disorder with no apparent disrupting factors and starting since childhood.

Currently, insomnia disorder is classified based on the absence and presence of medical or psychiatric conditions (comorbid) into short-term (acute) or chronic insomnia, rather than classified into primary or secondary insomnia. Acute insomnia refers to sleep disturbances lasting less than three months, whereas chronic insomnia is defined by complaints occurring for at least three times per week for a minimum duration of three months. Insomnia is a complex and heterogeneous disorder, with significant inter-individual variability in the changes associated with it. Evidence based on objective sleep duration and spectral activity identified distinct insomnia subtypes[211]. Similarly, a high-dimensional data-driven subtyping of insomnia identified three profiles: highly distressed (low happiness, negative affect, pre-sleep arousal), moderately distressed (pre-sleep arousal with either negative affect and stress-induced insomnia or reduced positive impact and happiness), and low distressed (insomnia linked to life events, fatigue, and childhood trauma rather than rumination)[206]. Insomnia subtyping was also established from difference in subtype-specific brain structural connectivity[212]. There is currently no consensus on insomnia phenotyping, and the definition of insomnia subtypes is still a topic of intense research.

The third edition of the International Classification of Sleep Disorder (ICSD-3) of the AASM in 2014 defined insomnia disorder by self-reported sleep initiation or maintenance difficulties, despite having adequate opportunities and circumstances for sleep; leading to impaired daytime functioning[202]. In addition, the Diagnostic and Statistical Manuel of Mental Disorders, 5$^{th}$ edition (DSM-5)[213] in 2013 from the American Psychiatric Association and the International Classification of Diseases, 11$^{th}$ edition (ICD-11) in 2019 from the World Health Organization converged to provide the same definition for insomnia disorder[214].

#### *1.2.2.2 Prevalence and risk factors*

Multiples studies reported that insomnia disorder is commonly found in the worldwide population[215,216]: Europe[217,218], America[219,220], Asia and Africa[221]. According to these studies, insomnia disorder prevalence ranged from approximately 4 to 40 % of the general population, and even greater in the United States[216]. The estimated prevalence of insomnia disorder among a sample of 2000 Canadians (i.e., aged 18–99) was approximately 13% in 2007[222]. In 2023, a study involving a larger sample of 4000 Canadians (i.e., aged 18–102) estimated the prevalence of insomnia disorder at around 16%, while insomnia symptoms were reported in approximately

35% of participants[223]. The difference in the definition of insomnia[222,223], as the subjective questionnaires used (ISI[224]; PSQI[7] and the population demographics may account for the variation in insomnia prevalence[223,225,226].

The behavioral model proposed by Spielman is the most widely accepted framework for explaining both the development and chronic persistence of insomnia[227]. These "3P" model outlines the sequential interaction of three factors: predisposing, precipitating, and perpetuating factors. Predisposing factors account for biological, psychological, behavioural components that increase the susceptibility for insomnia. Insomnia complaints are associated with numerous risk factors as reported by multiples studies[108,228,229]. Insomnia disorder was found highly prevalent among female compared to male[223,230], among older adults compared to young adults[223,231,232], individuals from lower socioeconomic status, and lower self-reported quality of life and poorer overall health[233]. In addition, insomnia is associated with medical condition (i.e. genetic factors, cardiovascular disease, neurologic disease, breathing and urinary problem, chronic pain and gastrointestinal problems)[234], further worsened by medical care hospitalization[235]. Lifestyle factors (i.e. caffeine consumption[236], shift work[237]), sleep disorders such as OSA, and psychosocial factors (i.e. anxiety, depression[238], caregivers to a family member[239]) are also linked to a higher prevalence of insomnia. Precipitating factors refer to negative life events that disrupt sleep, including environmental disturbances, stress, racial discrimination or traumatic experiences. Over time, insomnia is reinforced as individuals attempt to adjust their sleep habits in response to persistent sleep disturbance, leading to chronic insomnia. Perpetuating factors encompass maladaptive behaviors that sustain insomnia, such as substance use to promote sleep, prolonged napping or excessive time spent in bed[229]. According to this model, insomnia become self-sustaining, regardless of its initial cause.

#### *1.2.2.3 Sleep and daytime functioning impairment*

Individuals with insomnia complaints demonstrate clinically significant distress, with detrimental consequences that significantly impact their daily functioning on physical health (diabetes, hypertension), mental well-being (depression, anxiety, suicide) and cognitive function (impaired concentration, attention, and memory)[6,240–242]. Sleep complaints also included frequent daytime napping[243,244].

A meta-analysis comparing individuals with insomnia disorder compared to healthy controls reported that insomnia disorders disrupts sleep continuity, with decreased sleep duration and SE, and increased sleep onset, fragmentation (i.e. WASO, arousal density). In addition, sleep

architecture was impacted, while both N3 and REM duration decreased, and both N1 and N2 duration increased in adults[245,246] and in older adults[228] with insomnia.

Regarding sleep spindles in individuals with insomnia disorder[247], studies did not report any significant difference regarding spindle density or frequency[248,249] or related sigma power activity[250,251] in adults and older adults[252]. In contrast, a decreased in delta power and increase in sigma power spectrum was observed in older adults with insomnia[253].

Furthermore, the hyperarousal hypothesis explained that insomnia is characterized by a 24-hour state of heightened activation with somatic, cognitive, and cortical arousal components[254,255]. Individuals with insomnia disorders exhibited increase sympathetic nervous system activity, with elevated heart rate, higher body temperature, and heightened alertness, and in contrast a reduction in parasympathetic nervous system activity[256–259]. Cognitive arousal refers to hyperactivity of specific cerebral area, associated with negative affect, rumination, and worry[260,261]. In addition, cortical arousal as investigated with power spectrum analysis reveals a decrease in low-frequency bands (e.g., delta and theta)[262,263] in individuals with insomnia, while high-frequency bands, (i.e. beta) show increased activity[253,264,265]. Given that insomnia is a complex and heterogeneous disorder with multiple subtypes, varying symptoms, and diverse assessment tools, this may explain the inconsistency in study findings[263]. Insomnia disorder has a substantial impact on Canada's healthcare system: the associated costs reached approximately $500 million in 2020, encompassing healthcare expenses and work productivity losses: insomnia complaints play a significant role in the economic burden of illness in Canada[266–268].

#### *1.2.2.4 Normative aging and its association with insomnia*

A study of over 6800 older adults diagnosed with insomnia disorder reported that nearly 90% presented at least one comorbid condition or risk factor known to disrupt sleep (i.e. depression, cancer, cardiovascular diseases, medication use)[269]. This finding suggests that sleep disturbances commonly observed in older adults are primarily attributable to comorbid conditions rather than being an inherent consequence of aging[270]. The increased prevalence of chronic conditions with advancing age may contribute to the higher incidence of insomnia complaints in this population. Notably, fewer than 7% of individuals with insomnia have no underlying chronic condition, further supporting the role of comorbidities in late-life sleep disturbances[271]. In addition to medical conditions, age-related psychosocial and lifestyle factors, such as social isolation, reduced mobility, and retirement, have also been associated with adverse effects on sleep quality, further exacerbating the risk of insomnia in older adults[272]. As sleep becomes more fragile with age, the risk of developing insomnia increases.

Regarding subjective sleep quality, insomnia complaints are the most common sleep disturbance among the elderly population[272–274]. It is well established that sleep maintenance decreases with aging[275,276]. Sleep duration was found to decrease from childhood to seniors in a linear manner, from 10 minutes every decade for males and 8 min for females[277], and reaches a plateau at 60 years[278]. Similarly, decrease in SE was observed[278]. Sleep onset latency was also observed to increase with aging, usually from the age of 50 years[277–279].

Sleep fragmentation, such as the arousal index[280], and WASO, increase with age[278]. These age-related changes in sleep pattern are accompanied by alterations in sleep architecture. Sleep stages proportion is also changed with aging: N1 and N2 are increased, while N3 and REM duration are decreased[278] (See **Figure 4**).

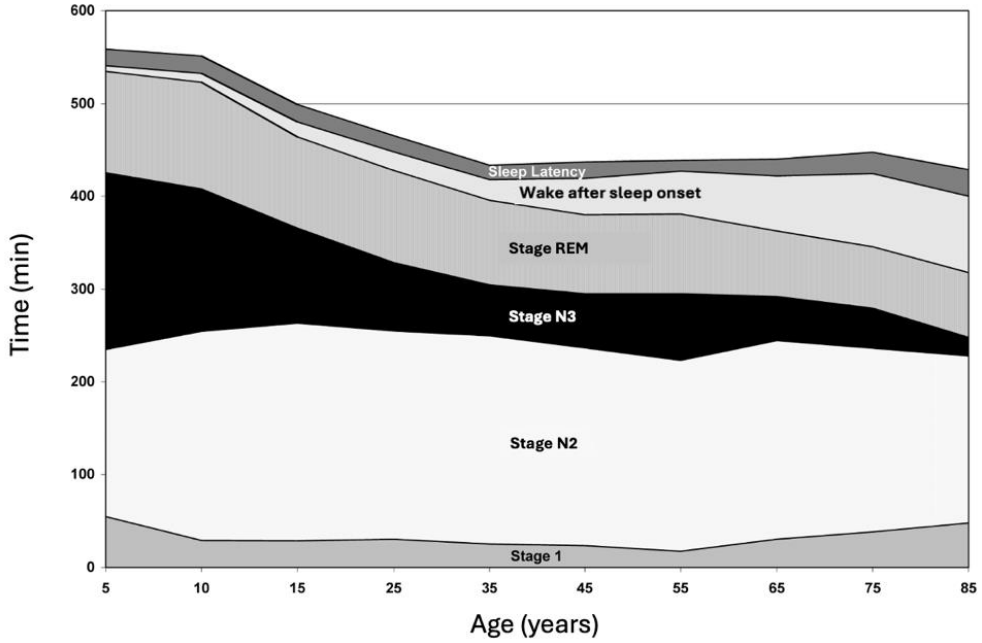


Figure 4: Age effect on sleep stages, nocturnal awakenings and sleep onset durations

Adapted from Ohayon et al.[278].

*REM= rapid eye movement*

In addition, spindle activity, specially fast spindle density was found decreased with aging[281–286], as well as SWA[276,287] and SO density and amplitude[283,288,289]. The changes in the characteristics of brain oscillation are associated with cognitive decline in the elderly[290]. In addition, SO and spindle coupling was found impaired with aging, and may contribute to the memory impairment experienced with aging[192,197,289,291–293], where the peak in fast spindle activity was not found at the SO up-state, but earlier.

### *1.2.2.5 Association with neurodegenerative pathways*

Sleep is essential for the clearance of metabolic waste accumulated during daytime through the glymphatic system[294], a process that evacuates proteins from the brain implicated in neurodegenerative diseases, including β-amyloid (Aβ), tau, and α-synuclein[295]. This mechanism is particularly relevant in carriers of the apolipoprotein E (ApoE) ε4 allele—the strongest genetic risk factor for Alzheimer's disease (AD) —who exhibit increased β-amyloid aggregation[296,297].

Evidence from cerebrospinal fluid tracer studies indicates that a single night of sleep deprivation significantly impairs molecular brain clearance[298]. In line with findings from animal models demonstrating Aβ accumulation following chronic sleep loss[299], sleep disruption has been associated with an increased Aβ burden in both middle-aged[300] and older healthy individuals[301]. Moreover, the proportion of SWA as well as SE were associated with the longitudinal trajectory of Aβ deposition in the cortex[302].

Findings from a large dataset gathered by the Canadian Longitudinal Study on Aging, middle-aged and older (i.e. >45 years) with probable insomnia disorder (PID) exhibit poorer lifestyle (tobacco and alcohol use, low incomes), medical condition (anxiety, depression, pain, fatigue, diabetes) when compared to individuals who solely report symptoms of insomnia (ISO) and with no insomnia symptoms (NIS)[303]. Furthermore, this study results revealed that middle-aged adults and older with PID showed cognitive impairment in comparison to those with ISO and NIS. Specifically, their declarative memory, as predicted by age, was significantly affected[303]. Accordingly, several studies have demonstrated that sleep complaints, such as insufficient sleep duration or symptoms of insomnia, are associated with a higher risk of developing cognitive decline or dementia[304–306]. Furthermore, it has been demonstrated that the development of insomnia disorder after 45 y.o is linked to an increased risk of developing subjective cognitive impairment[307]. Studies have shown that a range of 2% to 6% of older individuals with subjective cognitive impairment, specifically memory-related, will eventually develop mild cognitive impairment[308–310]. Subsequently, it has been demonstrated that over 60% of individuals with mild cognitive impairment will develop dementia or AD[311,312]. Therefore, early intervention in treating insomnia disorders could potentially prevent or slow down the onset of cognitive impairment.

## 1.3 How to improve sleep ?

### 1.3.1 Benzodiazepine and benzodiazepine receptor agonist

The introduction of benzodiazepines (BZD) dates back to the 1960s with Chlordiazepoxide and Diazepam, initially prescribed to treat sleep disorders and particularly insomnia complaints with their sedative-hypnotic properties[313,314]. By the 1970s, BZDs had become the most commonly prescribed class of drugs worldwide due to their rapid onset of action and efficacy in treating insomnia[315,316], as well as various psychiatric disorders such as anxiety, and obsessive-compulsive disorder[317–321]. However, by the 1980s, concerns emerged regarding tolerance, as well as diminished long-term efficacy, and dependence, as withdrawal symptoms were observed even at therapeutic doses upon discontinuation[322–324]. In response, the 1980s and 1990s saw the development of benzodiazepine receptor agonists (BZRA), commonly known as Z-drugs, which were designed as alternatives for insomnia treatment, offering a shorter onset and duration of action compared to traditional BZDs[325].

#### *1.3.1.1 Mechanism of action*

BZDs and BZRAs function as ligand for the gamma-aminobutyric acid type A ($GABA_A$) ionotropic receptor, a chloride-selective ion channel with four transmembrane domains, composed of five subunits for the most common subtype: two α, two $\beta$, and one γ[326–328] (See **Figure 5**). Both BZDs and BZRAs act as positive allosteric modulators, binding to their specific site at the α-γ subunit interface rather than directly to the $GABA_A$ binding site at the α-β interface[329,330]. The binding to the $GABA_A$ receptor induces a tridimensional conformational change that facilitates the $Cl^-$ channel opening. Specifically, BZDs/BZRAs enhance the opening frequency of the $GABA_A$ receptor $Cl^-$ channel, but only in the presence of GABA, while in absence of GABA, they have no impact on $GABA_A$ receptor function[331]. The influx of $Cl^-$ lead to the hyperpolarisation of the neuronal membrane and overall neuronal depression, accounting for the GABA inhibition effect[332,333].

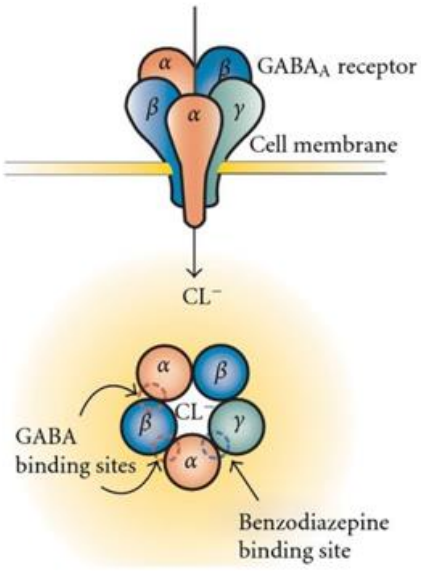


Figure 5: Structure of the GABA$_A$ receptor

Adapted from Vinkers et al.[334].

*The chloride-selective ion channel GABA$_A$ receptor, composed of five subunits: two α, two β, and one γ. The binding of specific ligands (GABA, BZD/BZRA) lead to an influx of Cl$^-$ and neuronal hyperpolarisation.*

### *1.3.1.2 Heterogeneity of the GABA$_A$ receptor and effect*

The GABA$_A$ receptor subunit isoforms and localisation heterogeneity account for their multiple properties and distinct clinical outcomes[335–338]. This especially concerns the GABA$_A$ receptor α isoform implicated in the effect of BZDs/BZRAs, and particularly the $\alpha_1$ isoform, which predominates in the brain[328,339], as well as the $\alpha_2$ and $\alpha_3$ isoforms. Pharmacological research strategies with genetically modified mice (i.e. knock-in and knock-out models) have proven to be a powerful methods for examining the role of specific GABA$_A$ receptor subtypes on sedative-hypnotic effects[337,340].

The GABA$_A$ receptors containing the $\alpha_1$ isoform is localised mainly in the thalamus, hippocampus, cerebellum, basal ganglia, and throughout the cortex[335,337,338]. The $\alpha_1$ isoform is essential for the sedative effect, as demonstrated by studies on genetically modified mice with a Diazepam-insensitive $\alpha_1$ isoform[337,341], and also involved in amnesic effect[328,338,341,342].

The GABA$_A$ receptor containing the $\alpha_2$ isoform is distributed in the cerebral cortex and the striatum[335,339], and largely distributed in the limbic system; hypothalamus, hippocampus, and amygdala[337,343]. The $\alpha_2$ subunit was found to mediate anxiolytic effect, also demonstrated in research in genetically modified mice[341,344]. Localised in the motoneurons of the spinal

cord[335,337], the $\alpha_2$ subunit displayed myorelaxant effect in mice[345]. Another study reported suppressed delta activity during NREM, typically induced by Diazepam in genetically modified mice with $\alpha_1$[346] and $\alpha_3$[347] Diazepam-insensitive $GABA_A$ receptors. Although the $\alpha_1$ and $\alpha_3$ subtypes are widely distributed in the thalamocortical network, BZDs/BZRAs effects extend beyond this system, suggesting a role for the $\alpha_2$ isoform in the EEG pattern during NREM[335,348]. Consistently, the $\alpha_2$ isoform, specifically localised in the hypothalamus and the ARAS was found associated with NREM sleep generation in mice[344]. Others isoform such as the $\alpha_3$ can also be found in the TRN, which effect on delta activity regulation[349], as well as in the amygdala, cortex, cerebellum, and both LC and RN, with hypnotic and anxiolytic effects[335,337,350]. The $GABA_A$ receptors containing the $\alpha_5$ are localised in the hippocampus[337,351], suggesting a link with sleep and memory[338,352,353].

#### *1.3.1.3 Pharmacodynamic and pharmacokinetic properties*

The heterogeneity of BZDs/BZRAs compounds and their clinical effects is driven by variations in their pharmacodynamic and pharmacokinetic properties. Based on pharmacokinetic BZD/BZRA elimination half-life, which represents the time needed for the plasma concentration of the drug to decrease by half, BZDs can be classified as short-acting (approximately up to 5 hours), intermediate-acting (approximately up to 24 hours) or long-acting (more than 24 and up to 100 hours)[314,315]. In contrast, BZRAs are usually shorter-acting (e.g., with a half-life of up to 6 hours).

Regarding pharmacodynamic, while BZDs binds on the $GABA_A$ receptor displaying $\alpha_1$, $\alpha_2$, $\alpha_3$, $\alpha_5$ isoforms with comparable affinity[354,355], BZRAs binds on the $GABA_A$ receptor with the $\alpha_1$ isoform with high potency, medium potency for $\alpha_2$, $\alpha_3$, and low binding affinity to $\alpha_5$ isoforms[338,356]. In addition, some BZRAs are selective to a specific isoform, as the $\alpha_1$ for Zaleplon or Zolpidem[357], while others as Zopiclone are less specific[338].

The use of BZDs in older adults was associated with improvement in subjective sleep quality, however with a small effect size[358]. Small improvement was found on greater TST and lower nocturnal awakenings compared to placebo[358]. Studies provide large evidence that BZDs altered sleep architecture[359], a decrease in N3 and REM duration, along with an increase in N2 duration, is commonly observed in healthy individuals[38,360–362]. The effect of BZDs on the transition from wakefulness to sleep, reflected in N1 duration, has been associated with a reduction in N1 duration[362,363], however a recent systematic review reported inconclusive findings[359]. When compared to older adults with and without insomnia disorder, older adults chronically using BZDs exhibited a higher arousal density[252]. These effects were observed across both short- and

long-acting BZDs, with prolonged duration in long-acting compounds leading to extended effects[359].

Regarding BZRAs, a recent systematic review suggested that Zopiclone may be an effective treatment for insomnia in older adults, both with and without comorbidities[364]. Compared to placebo, Zopiclone was associated with fewer nocturnal awakenings, increased TST, and improved subjective sleep quality[358]. Sleep architecture changes included reduced N1 duration[365] and prolonged N2 duration[366]. Additionally, Zopiclone use may influence REM sleep duration and density[364]. In addition, the use of BZRAs has been shown to reduce wake duration in placebo-controlled older adults with insomnia disorder when used for one month, concurrently extending their overall sleep duration[367,368].

#### *1.3.1.4 Adverse effects*

The use of BZDs/BZRAs entails certain adverse effects. Association was found between BZDs/BZRAs use and the development of comorbidities in older adults[369]. An association between the exposure to BZDs/BZRAs and increased cardiovascular mortality was found in women aged over 50 years[370]. Other adverse effects include daytime sleepiness and loss of motor coordination, which can lead to hip fracture for both BZDs[371] and BZRAs[372]. This is particularly concerning given that approximately 30% of them passed away in the subsequent year, and the quality of life for survivors exhibited a gradual decline[373]. In addition, such use is nevertheless accompanied by dependence and cognitive decline[374,375]. Moreover, the risk of developing dementia or Alzheimer's disease is also increased[376,377], although these results remain controversial[378]. In addition, age-related physiological change also increased the sensitivity to the $GABA_A$ receptors and reduced BZDs/BZRAs clearance, increasing BZDs/BZRAs effects[379,380]. The shorter half-life of BZRAs, along with their minimized residual daytime effects, and their properties to bind the $\alpha_1$ $GABA_A$ receptor involving in sedative effect specifically, makes them a more clinically appealing alternative to BZDs[350,355,381]. However, considering these adverse effects, the American Geriatrics Society strongly advises against the use of BZDs/BZRAs, regardless of the duration of use[382].

#### *1.3.1.5 Prevalence*

In 2008, approximately 5.2% of American adults aged 18 to 80 years reported using BZDs, with prevalence peaking at 8.7% among those aged 65 to 80 years[383]. Usage was twice as common in females as in males[383]. Among elderly individuals with BZDs use, one-third were

chronic consumers, defined as taking BZDs more than three times per week for over three months. Despite growing awareness of their risks, hypnotic prescriptions remain widespread, particularly among the elderly[384–386]. Between 1996 and 2013, the number of American adults receiving a BZDs prescription increased by 67%[387]. A similar pattern is observed in Canada, where by 2016, nearly one-quarter of seniors aged 65 and over in Quebec were chronic users, for at least three weeks within a four-month period[388,389]. A study of approximately 4000 Canadian adults (18 to 102 years) found that around 15% used prescribed sleep medication at least three times per week, with higher prevalence among females, older adults, and those with insomnia disorder[223]. This represents a 1.5- to 2-fold increase over the past 15 years[222,223]. In Europe, the widespread use of BZDs among older adults is also evident, with consumption exceeding 30% in countries such as Spain, Croatia, and Serbia between February 2019 and March 2020[390]. This extensive use is further illustrated by prescription rankings. In 2018, several BZDs (e.g., Clonazepam, Alprazolam) and BZRAs such as zolpidem were among the 50 most prescribed medications in the United States[391]. More generally, BZDs/BZRAs continue to be commonly used in aging populations[392].

### 1.3.2 Cognitive-behavioral therapy for insomnia (CBTi)

Several non-pharmacological strategies have been developed, including cognitive, behavioral, and educational approaches[393].

The cognitive approach for insomnia aims to identify and challenge misconceptions and negative beliefs that contribute to persistent sleep difficulties[229,394]. This process involves establishing realistic expectations regarding sleep duration and quality while addressing dysfunctional thoughts regarding the severity, frequency, or tolerability of symptoms and excessive concerns about sleep[395].

Behavioral strategies included sleep resctriction therapy (SRT), stimulus control therapy (SCT) and relaxation, both adressing circadian regulation and inhibitory factors and attitude related to sleep. The SRT consists in limiting the time in bed in order to improve the match between individuals's sleep needs, thus manipulating sleep homeostasis[395,396]. The average TST over one or two weeks generally obtained from sleep diaries is extracted and based on this, with TIB adjusted accordingly over time.

The SCT aims to reassociate bedtime and the sleep environment with successful sleep. To counteract behaviors that contribute to insomnia, individuals are encouraged to go to bed only when experiencing sleepiness, leave the bed if unable to fall asleep within a reasonable time, and maintain a consistent sleep schedule. The bedroom should be used exclusively for sleep

and intimacy, avoiding activities such as eating, reading, or watching television. Additionally, naps should remain short and be scheduled earlier in the day to minimize their impact on nighttime sleep[396].

Relaxation encompasses structured exercises that aim to reduce sleep-related physiological factors like muscle tension and cognitive arousal[397]. This includes progressive muscle relaxation, abdominal breathing, meditation, hypnosis or mindfulness techniques[398,399]. For instance, yoga, a discipline encompassing physical postures, breathing exercises, meditation, and mindfulness techniques was beneficial for fatigue and subjective quality of life[396,400].

The educational component includes sleep hygiene recommendations, to promote sleep, such as avoiding energy drinks, tea, coffee, alcohol, or nicotine before bedtime. It also advises against consuming heavy meals late in the evening, encourages regular physical activity, promotes morning light exposure while avoiding blue light exposition before bedtime and, maintaining an optimal sleep environment—characterized by darkness, quietness, comfort, and a cool temperature[396]. Additionnaly, education is provided regarding the characteristics of a normal sleep, as well as physiological sleep change with aging[397].

The combination of these various components is referred to as cognitive-behavioral therapy for insomnia (CBTi), which is strongly recommended as the first-line treatment for insomnia[397,401,402]. Indeed, multiple studies reported that CBTi is effective to reduce insomnia symptoms (i.e. ISI[208,403], the Insomnia Severity Questionnaire, ISQ[404]) and improve sleep quality[208,215,405–409]. Beneficial effects on sleep quality include reduced SOL, and sleep fragmentation (i.e. WASO[404]) and increase in SE. Furthermore, in addition to improving daytime functioning, CBTi was found beneficial to improve depression symptoms[410], and was associated with improvement in positive mental health and energy/vitality[411]. In addition, CBTi was found effective in the long-term[412]. CBTi also demonstrates beneficial effects in elderly individuals[402,413–416], including those with comorbid conditions such as psychiatric[417], medical, or cognitive disorders[418,419]. In addition, online CBTi format, as well as individual or group therapy also demonstrated beneficial effect on sleep and daytime functioning[402,420,421].

Nevertheless, the precise functions of each cognitive, behavior or educational remain undefined, and it is uncertain whether all aspects of CBTi are necessary to be effective[395]. Each of these components has individually been associated with benefits in improving sleep quality, except for sleep hygiene education, which may be ineffective or even detrimental[395,397,405]. Although relaxation therapy improved sleep latency, it did not address cognitive, homeostatic, or circadian sleep disturbances[396], and its effects were not sustained, as no subjective global

improvement was observed at the six-month follow-up[422]. Additionally, both the SCT and the SRT were the most effective procedures for sleep initiation and maintenance[405]. However, SCT did not adress homeostasic sleep disruptions, and did not restrict time spent in bed. For all these reasons, the AASM only recommends these various individual strategies on a conditional basis, as they may not be suitable for all patients[397].

One major point to considere is the access to CBTi. The Delphi consensus recommendations for managing chronic insomnia in Canada emphasize CBTi as the first-line treatment and highlight the need for awareness on improving access to CBTi[423].

### 1.3.3 Alternative interventions

Beyond pharmacological treatment and psychological interventions, researchers have investigated how change in lifestyle or alternative approach could improve sleep. Acupressure has been shown to improve subjective sleep quality in the elderly[424], however, there is currently no concrete evidence of its effectiveness in treating insomnia[425].

Exercise has been shown to improve subjective sleep quality and cognitive function[419,426–429], while also having a positive impact on objective sleep quality, although the findings across studies remain inconsistent[430]. Additionally, exercise effects on sleep can vary depending on factors such as intensity[431], and engaging in physical activity requires good physical condition, which can limit access for older individuals. Music therapy has been shown to improve sleep quality in middle-aged adults with insomnia based on subjective assessments[432], but no evidence demonstrates its effectiveness for chronic insomnia.

Furthermore, the positive impact of sensory stimulation on sleep quality has been extensively studied. Aromatherapy, especially before bedtime, has been shown to enhance subjective sleep quality in older adults[433]. However, no significant association was found in patients with comorbidities such as mild cognitive impairment or AD[434]. While olfactory stimulation has been linked to increased N3 duration, the effect size was small, and the findings were limited to healthy adults rather than individuals with insomnia[435].

Phase-locked auditory stimulation during sleep was associated with an increase in SWA, linked with increase in sleep-dependent memory improvement in healthy young[36] and older adults[436,437]. However, the results have shown inconsistency or may appear with delay[438].

Non-pharmacological strategies for improving sleep have gained interest, but evidence regarding their effectiveness and relevance to chronic insomnia remains limited. A stimulation that appears to be a promising alternative for insomnia and improving sleep quality in older individuals could be rocking.

### *1.3.3.1 Rocking motion*

Rocking babies to sleep has been a long-standing practice, the first rocking devices were designed for infants in the form of cradles, nearly 3000 years ago, into rhythmic motion with a string or suspended to promote sleep[439]. The relationship between sleep and rocking motion has only recently become a subject of scientific investigation.

Rocking therapy, designed to replicate *in utero* motion, was investigated on preterm infants to help them to maintain a regular breathing and decreased apnea. The effect of a gently oscillating waterbed (i.e., 12 to 14/min) on 8 premature infants with apnea resulted in less apnea under the rocking stimulation[440]. A similar reduction was observed using a rocking bed (i.e., 10 to 22 cycle/min) on 12 infants with recurrent apnea[441]. However, these findings were not considered as clinically significant to reduce important apnea (i.e., >20 sec)[442].

The use of hammocks has been tested on 20 preterm infants, showing that sleep-wake patterns after a stressful event such as diaper changes were more favorable with the hammock than without[443]. Similarly, an improvement in the sleep-wake state with hammock use has been observed in preterm infants, along with a reduction in both heart rate and respiratory rate[444]. Sleep quality was compared between hammock and bed users and displayed that hammock users had shorter sleep periods compare to bed users, as well as higher body mass index (BMI) and greater activity index[445].

A relaxation machine was design to reduce stress and induce sleep, through rocking vibration stimulating a mother's embrace and rocking motion of her baby[446]. While testing ten different motions, the most effective for inducing sleep in adults was the linear motion[447]. The rocking motion effect of a recliner chair on sleep was also investigated and revealed that sleep quality is improved in adults during a lateral rocking nap, with an increased in stage N3 duration and spindle density[448]. The human body perceives gravity through the vestibular system, which integrates gravitational and motion-related signals and is also thought to mediate the effects of rocking motion.

### *1.3.3.2 Vestibular stimulation*

#### 1.3.3.2.1 Neurophysiology of the vestibular system

The vestibular system is localised in the inner ear within the petrous portion of the temporal bone and consists in two main structures within the bony labyrinth: the vestibule and the

semicircular canals[449]. These structures are covered on their inner surface by the corresponding components of the membranous labyrinth, which is covered by a specialized sensory epithelium (See **Figure 6**). The inner ear is filled with the endolymph in the membranous labyrinth and the perilymph between the membranous and the bony labyrinths[450].

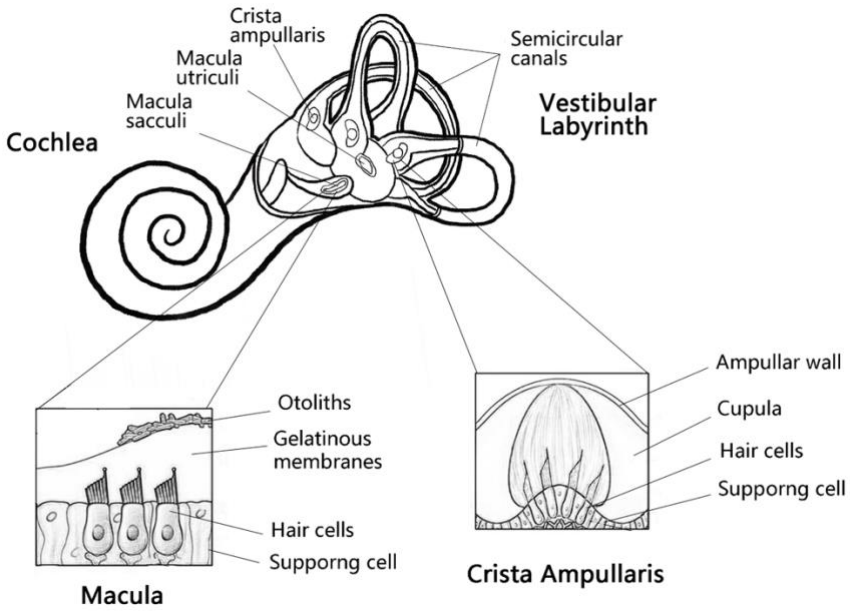


Figure 6: The vestibular system

Adapted from Huang et al.[451].

*The vestibular system includes the semicircular canals, the vestibule (saccule and utricle), and their corresponding membranous components within the bony labyrinth.*

#### 1.3.3.2.1.1 The semicircular canals

The semicircular canal comprise three membranous canals and at the base of each semicircular canal is an enlarged structure at one end called the ampulla[449]. Each ampulla contains an ampullary crest or crista structure, composed by nerve fiber, support cells, and hair cells, which are mechanoreceptors[450]. Hair cells are divided into type I and type II, referencing to the time interval between 2 action potentials. Type I hair cells provide rapid, phasic responses for acute motion detection, quickly adapting to changes, while Type II hair cells ensure sustained, tonic signaling for prolonged vestibular input, maintaining continuous transmission over time. Each hair cell is surrounded by hair bundle at their apical pole, composed by a single flexible kinocilium, larger and longer than the stereocilia, and by 100 non motile stereocilia. The stereocilia are arranged in a stepped pattern, with the tallest positioned nearest to the kinocilium and gradually decreasing in height as they extend further away. The kinocilium is connected to

the adjacent stereocilia, which are themselves interconnected by “tip-links”, initiates their coordinated displacement and defines the polarization axis of the hair bundle. Hair bundles are covered by the cupula, a flexible gel-like structure that extends the entire height of the ampulla, thus isolating hair cells from the endolymph.

During head movements, the semicircular canal localised in the same plan moves, and inertia leads the endolymph to move in the opposite direction. The endolymph exerts a pressure on the cupula, which in turn bends hair cells and induce tension in the “tip-links”, mechanically inducing the opening of ion $K^+$ channels. This influx leads to further facilitate $Ca^{2+}$ influx and generate an action potential. The bending direction influences neural signaling; when stereocilia deflect toward the kinocilium, membrane depolarization occurs, triggering an excitatory potential. In opposite, when stereocilia bend away from the kinocilium, this leads to a hyperpolarisation and an inhibitory signal. The anterior, lateral, and posterior semicircular canals are oriented in the sagittal, transverse, and frontal planes, respectively. Positioned at right angles to each other’s, semicircular canals respond to three plans or angular acceleration and deceleration. Because the vestibular system is present on both sides, a movement that elicits an excitatory potential on one side extends in a simultaneous inhibitory potential on the opposite side. Specifically, lateral semicircular canals on both sides function operate in pairs, while the anterior semicircular canal on the right side is paired with the posterior semicircular canals on the left side (RALP). Similarly, the posterior semicircular canal on the right side is paired with the anterior semicircular canals on the left side (LARP).

#### 1.3.3.2.1.2 The vestibule

The vestibule comprises two otolith organs, the utricle and the saccule[449]. The macula consisted in nerve fiber, supports cells, hair cells, and is covered by a gelatinous membrane, called the otolithic membrane and in which calcium carbonate crystals, known as otoliths or otoconia, are dispersed. The increased weight of the otolithic membrane, due to the presence of otoliths, makes it responsive to acceleration forces. Its motion exerts pressure on the sensory hair cells, causing their bending and generating a neural signal. Positioned perpendicularly, the otolith organs are pressured to the opposite side of the motion and respond to changes in movement: the utricle detects horizontal and the saccule vertical linear acceleration and deceleration.

#### 1.3.3.2.1.3 Vestibular pathway

The vestibular ganglion also known as the ganglion of Scarpa comprises bipolar neurons, receiving hair cells afference from the cristae and the macula[452]. Specifically, the superior division of the vestibular ganglion received afference from the utricular macula, and both the anterior and lateral ampullary cristae ducts. The inferior division received afference from the saccular macula, and the posterior lateral ampullary cristae ducts.

Axons from the superior and inferior divisions converge to form the primary vestibular nerve, whose cell bodies reside in the vestibular ganglion. This nerve then merges with the cochlear nerve, to form the vestibulocochlear nerve (cranial nerve VIII), which transmits sensory information through the internal auditory canal and enter to the brainstem at the pontomedullary junction.

#### 1.3.3.2.1.4 Central vestibular system

Central vestibular nuclei are localised in the posterior part of the brainstem and comprise the superior, lateral, inferior and medial vestibular nucleus[449]. These vestibular nuclei send projections through secondary vestibular neurons to the cerebellum, spinal cord, and thalamus while integrating multiple sensory inputs, including vestibular, somatosensory, and visual information. Secondary vestibular neurons project to multiple regions, contributing to gaze stabilization, postural control, and spatial cognition[453]. They connect to the extra-oculomotor cranial nerves: oculomotor (III), trochlear (IV), and abducens (VI), ensuring image stability on the retina during head movements through the vestibulo-ocular reflex. Projections to spinal motoneurons support balance via the vestibulo-cervical reflex, which stabilizes head position, and the vestibulo-spinal reflex, which adjusts posture in response to changes in orientation[453].

### 1.3.3.2.2 Vestibular system and sleep

The vestibular nuclei are connected to multiple cerebral structure involved in sleep regulation[453]. Studies in mice have demonstrated their connectivity with regions regulating sleep and wakefulness, including the LC, and both LDT/PPT[454], RN, and lateral preoptic area, as well as connectivity with the suprachiasmatic nucleus (SCN)[455]. The presence of melatonin and its receptors have been identified in the vestibular ganglion, and vestibular sensory cells[456], suggesting a potential link between vestibular function and circadian rhythm. Research in rats demonstrated that the circadian rhythms is disrupted after bilateral lesion of the vestibular hair cells[457], particularly in the regulation of body temperature and locomotor activity[458].

Furthermore, a study in mice demonstrated that the vestibular nuclei project through orexinergic neurons to the posterior nucleus of the hypothalamus[459]. Vestibular orexinergic afferents are thought to be involved in the pathophysiology of narcolepsy-cataplexy[460].

Clinical studies shown that patients with vestibular vertigo exhibit an increased risk of sleep disturbances[461]. An association was identified between self-reported sleep quality and the duration of vestibular symptoms in patients with vestibular disorders. Notably, those experiencing vertigo for two years or more reported significantly poorer sleep quality, particularly in terms of sleep latency and efficiency[462]. Space missions in microgravity environment lead to inhibition of the otolithic activity, and sleep disturbances are reported, due to space and motion sickness[23]. Similarly, research on patients with bilateral vestibular loss supports the vestibular system role in circadian regulation, particularly in temperature homeostasis[457]. However, objective assessments of sleep in vestibular disorders are lacking[453]. Anatomical and functional connections between the vestibular nuclei and thalamus have been established in both animal and clinical studies[463,464].

#### 1.3.3.2.3 Direct vestibular stimulation

Beneficial effects of sensory stimulation through vestibular system on sleep quality have been investigated.

Galvanic vestibular stimulation is a non-invasive technique that delivers electrical currents to the vestibular nerves, influencing postural control, spatial orientation, and more recently sleep quality[465]. A study found that repeated electrical vestibular stimulation delivered prior the sleep onset reduced ISI score and improve the perception of restful sleep[466], although effect of such long-term usage on sleep quality needs further investigation[467]. Direct electrical stimulation of the vestibular system has been associated with shorter sleep onset latency compared to sham conditions, but only in individuals who previously exhibited prolonged sleep latency during daytime naps and did not appear to have a therapeutic effect in a model of transient insomnia in healthy sleepers[468]. Although a promising method, other less invasive types of stimulation need to be investigated.

#### 1.3.3.2.3 Rocking bed stimulation

An easier form of vestibular stimulation can be achieved with a rocking bed, thus indirectly stimulating the vestibular as well as proprioceptive and somatosensory systems[464]. Research conducted using a rocking bed has demonstrated that rocking affects specific aspects of sleep

architecture and microstructure. However, findings vary across studies, likely due to multiple contributing factors. Most studies assessed the overnight effect of a continuous rocking bed stimulation in healthy young adults[37,469,470], and a few involved elderly[471], and some were conducted during nap[472,473]. The movement trajectory was purely linear head-to-toe[469,470] or up-down[470], as well as lateral parallel swing[37,470,472].

Following rocking bed stimulation, sleep latency was found shortened[37,469,472] as well as the combined sleep latency to N1 and N2[37], and sleep latency to N2[472]. Additionally, while delta power was found to increase during a nap, N3 duration remained unaffected[472]. During the nap study, N2 duration was found to increase, but this was not observed during overnight studies. During rocking overnight, N3 duration increased, as well as SO count, whereas delta power remained unchanged[37]. Sigma power was found to increase in N2[472], and N3[37], while spindle density was found greater in N3[37]. Furthermore, the entrainment of intrinsic spindles and SO was enhanced, leading to greater neuronal synchronization[37]. Effect of rocking stimulation on declarative memory revealed an increase in overnight memory accuracy in healthy young adults, correlated with an increase in sigma EEG power[37]. While no changed in overall sleep duration was observed after rocking bed stimulation in overall studies, sleep fragmentation was found to decreased, as shown by the arousal density in N3[37].

Using an otoconia-deficient mouse, a study demonstrated that the rocking effect is mediated through the otolithic organs of the vestibular system and driven by the maximal linear acceleration of lateral movement[474]. Further investigations into acceleration characteristics, using a fixed frequency with various amplitudes, revealed that the most beneficial acceleration for sleep architecture occurred at a frequency of 1 Hz, with an acceleration around 79 $cm.s^{-2}$. Given that vestibular afferences in mice are three or four times less developed than in humans[475–477], this corresponds to an acceleration of around 20-25 $cm.s^{-2}$ in humans. This value aligns with the beneficial effects on sleep architecture, spectral activity, brain oscillations and memory observed when the movement trajectory followed a linear parallel swing with a maximal linear acceleration of approximately 26 $cm.s^{-2}$ [37,472]. This may explain why alternative movement trajectories did not lead to improve sleep quality[469,470]. Moreover, no effects were observed in mice beyond an acceleration threshold of 32 $cm.s^{-2}$, which correspond to approximately 10 $cm.s^{-2}$ in humans. This could account for findings from a study assessing linear parallel swing that reported no beneficial effects of rocking when acceleration was set around 10 $cm.s^{-2}$ [470].

## 1.4 Main research questions & hypothesis

The literature demonstrates the importance of sleep in maintaining cognitive, physical, and psychological health, and its involvement in numerous physiological functions. An important function is sleep-dependent memory consolidation, which is supported during NREM by the synchronization of specific rhythms, such as spindles and SOs. However, as individuals age, sleep undergoes significant changes, including alterations at the macro and the micro levels, which can negatively affect overall health. These changes are often exacerbated in older adults suffering from insomnia, further compromising sleep quality. Chronic disruptions in sleep patterns are linked to cognitive decline and an increased risk of various health problems. Therefore, it is crucial to address insomnia in the aging population to support healthy aging and prevent the onset of cognitive disorders. Consequently, addressing chronic insomnia in this population is essential to support healthy aging and mitigate related risks to both cognitive and physical well-being.

"How can sleep quality be modulated in the aging population, and what is the impact of these modulations on cognitive functions such as memory?"

### 1.4.1 Chapter 2: effect of chronic sedative-hypnotic use on sleep architecture and brain oscillations in older adults with chronic insomnia.

First, the objective is to characterize the effect of chronic sedative-hypnotic use on sleep in older adults with insomnia. Chronic use of sedative-hypnotics, both short- and long-acting, is common due to their sedative effects, particularly in reducing sleep onset and nocturnal awakenings. However, evidence also suggests adverse effects on sleep quality, including reductions in both N3 and REM durations, as well as SWA. Further research is needed to better understand the long-term effects of sedative-hypnotics on sleep, particularly their relationship with cognitive decline and memory. Additionally, the influence of chronic sedative-hypnotic use on NREM brain oscillations linked to memory remains unclear, underscoring the need for investigation into the broader health consequences, particularly in relation to cognitive decline. The difference in the duration of action diversity between chronic sedative-hypnotic use also requires further characterization.

The impact of chronic sedative-hypnotic (BZDs/BZRAs) use in older adults will be examined, comparing three groups: healthy sleepers, individuals with insomnia disorder not using pharmacological treatments, and individuals with insomnia disorder who chronically use BZDs or BZRAs. A comprehensive analysis of sleep architecture will be conducted, including EEG spectral properties, with a specific focus on NREM brain oscillations associated with cognition and memory, such as SOs and spindles and their coupling.

Chronic sedative-hypnotic use is expected to have a more pronounced effect on sleep macrostructure than insomnia disorder without pharmacological intervention, leading to reduced N3 and REM durations, extended N2 duration, and increased sleep fragmentation. In terms of EEG spectrum, lower-frequency activity (e.g., delta and theta power) is anticipated to decrease, while higher-frequency bands, such as sigma power, are expected to show increased spindle activity. Furthermore, both spindle and SO characteristics are predicted to be altered, affecting their coupling.

### 1.4.2 Chapter 3: effects of cognitive-behavioral therapy for insomnia during sedative-hypnotics withdrawal on sleep and cognition in older adults.

Therefore, sedative-hypnotic withdrawal is commonly advised, although it may lead to the re-emergence of insomnia symptoms. Cognitive behavioral therapy for insomnia (CBTi) is considered the first-line treatment for chronic insomnia. The combined effects of CBTi and sedative-hypnotic withdrawal on sleep quality and cognitive function in older adults remain underexplored, representing a gap for understanding the broader cognitive implications for aging populations.

Secondly, the objective is to assess the effect of CBTi during a sedative-hypnotic withdrawal plan in older adults with insomnia disorder. A randomized-controlled trial will compare sedative-hypnotic plan alone with withdrawal combined with CBTi, focusing on sleep and cognitive function. Primary outcomes will include changes in self-reported insomnia severity, sleep quality, and objective measures of SE and spindle density. Secondary outcomes will include PSG, sleep diary-based measures, as well as neuropsychological assessments.

Greater improvements in sedative-hypnotic withdrawal success, as well as both objective and subjective sleep outcomes will be anticipated in the combined intervention group compared to the sedative-hypnotic withdrawal plan alone group. Additionally, neuropsychological performance would be improved in the combined intervention group compared to the sedative-hypnotic withdrawal plan alone.

However, access to CBTi remains limited, and alternative interventions should be provided to individuals who do not respond to the combined approach or for whom insomnia symptoms persists.

### 1.4.3 Chapter 4: impact of rocking bed stimulation on sleep and memory over multiple nights.

Rocking bed stimulation in a lateral parallel swing motion has been shown to improve sleep quality by reducing sleep onset, increasing N3 duration, and both spindles and SOs activities. Furthermore, rocking stimulation has been shown to improve sleep-dependent memory consolidation, particularly for declarative memory. However, only the overnight effect of rocking bed stimulation was investigated, and the long-term effects of such stimulation remain underexplored. In addition, its impact on procedural memory has not been investigated.

This pilot study will aim to assess the potential of the rocking bed apparatus in improving long-term sleep quality and its impact on memory in healthy adults. Conducted over five PSG-recorded nights, the study will include two conditions: two consecutive nights in a stationary bed followed by three consecutive nights in the rocking apparatus. Outcomes will measure through self-reported sleep quality, objective sleep measures including sleep architecture, NREM brain oscillations related to memory (such as spindles and SOs), and performance on declarative and procedural memory tasks.

Existing literature suggests that rocking apparatus stimulation may enhance both subjective and objective sleep quality while facilitating long-term memory consolidation.

# Chapter 2: Effect of chronic sedative-hypnotic use on sleep architecture and brain oscillations in older adults with chronic insomnia.

# Effect of chronic sedative-hypnotic use on sleep architecture and brain oscillations in older adults with chronic insomnia.

Authors:

Loïc Barbaux[1,2*], Aurore A. Perrault[1,2,3], Nathan E. Cross[1,2,4], Oren M. Weiner[1,2], Mehdi Essounni[1,2], Florence B. Pomares[1,2], Lukia Tarelli[1,2], Margaret McCarthy[1,2], Antonia Maltezos[1,2], Dylan Smith[1,2,6], Kirsten Gong[1,2], Jordan O'Byrne[1,2,7], Victoria Yue[1,2], Caroline Desrosiers[2], Doris Clerc[2], Francis Andriamampionona[2], David Lussier[2], Suzanne Gilbert[2], Cara Tannenbaum[2], Jean-Philippe Gouin[2,5], Thien Thanh Dang-Vu[1,2*]

Affiliations:

[1]Sleep, Cognition and Neuroimaging Lab, Department of Health, Kinesiology and Applied Physiology, School of Health & Center for Studies in Behavioural Neurobiology, Concordia University, Montreal, Quebec, Canada

[2]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, CIUSSS Centre-Sud-de-l'Ile-de-Montréal, Québec, Canada

[3]Sleep and Circadian Group, Woolcock Institute of Medical Research, Macquarie University, Sydney, NSW, Australia

[4]School of Psychology, University of Sydney, NSW, Australia

[5] Stress, Interpersonal Relationship and Health Lab, Department of Psychology & Centre for Clinical Research in Health, Concordia University, Quebec, Canada

[6] Statistics Canada Biobank, Statistics Canada, Ontario, Canada

[7] Department of Psychology, Université de Montréal, Montreal, Quebec, Canada

* corresponding authors

loicbrb@gmail.com; Department of Health, Kinesiology and Applied Physiology; Concordia University, 7141 Sherbrooke St W, H4B 1R6 Montreal, QC, Canada

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## 2.1 Abstract

**Study objectives**: High insomnia rates in older adults lead to widespread benzodiazepine (BZD) and benzodiazepine receptor agonist (BZRA) use, despite evidence that chronic use disrupts sleep regulation and impacts cognition. Little is known about sedative-hypnotic effects on NREM slow oscillations (SO) and spindles, including their coupling, which is crucial for memory, especially in the elderly. Our objective was to investigate the effect of chronic sedative-hypnotic use on sleep macro-architecture, EEG relative power, SO and spindle characteristics and coupling.

**Methods**: One hundred and one individuals (66.05 ± 5.84 years, age range: 55-80 years 73% female) completed a one-night study and were categorized into three groups: good sleepers (GS, n=28), individuals with insomnia (INS, n=26) or individuals with insomnia who chronically use BZD/BZRA (MED, n=47; Diazepam Equivalent: 6.1 ± 3.8 mg/week). We performed a comprehensive comparison of sleep architecture, EEG relative spectrum, and associated brain oscillatory activities, focusing on SO and spindles, and their temporal coupling.

**Results**: Chronic BZD/BZRAs use was associated with sleep architecture and spectral activity disruption compared to older adults with and without insomnia; as well as altered sleep-related brain oscillations characteristics, and their synchrony. An exploratory interaction model suggested that higher doses correlated with more pronounced disruptions in sleep micro-architecture and EEG spectrum.

**Conclusions:** Our results suggest that chronic sedative-hypnotic use is detrimental to sleep when compared to drug-free GS and INS. Such alteration of sleep regulation – at the macro and micro-architectural levels - may contribute to the reported association between sedative-hypnotic use and cognitive impairment in older adults.

**Keywords:** benzodiazepine, sleep, brain oscillations, aging

## 2.2 Introduction

Insomnia complaints are one of the most common sleep disturbances in the general population[478] and exhibit a higher prevalence among older individuals compared to young adults[479,480]. Insomnia disorder is defined by complaints of difficulties initiating and/or maintaining sleep, despite having adequate opportunities and circumstances for sleep, occurring at least three times per week for more than three months[213]. Insomnia disorder not only impairs quality of life and health but also increases the risk for cognitive decline and dementia[303–307], thereby representing a major health issue in the aging population.

While cognitive-behavioural therapy for insomnia (CBTi), a multimodal psychological intervention, is considered the gold standard management of insomnia, its access remains challenging[481–483]. Pharmacological treatment is still the most widely accessible and used treatment option for insomnia, with a higher prevalence in the elderly[387,390,484]. The prolonged use of sedative-hypnotics, defined as a duration of at least three months[485], is particularly common among seniors[486–489]. Benzodiazepines (BZDs, e.g., Diazepam, Clonazepam, Nitrazepam, Oxazepam, Lorazepam, Temazepam) or benzodiazepine receptor agonists (Z-drugs or BZRAs, e.g. Zopiclone) are among the most prescribed class of drugs to manage insomnia complaints. They enhance the inhibitory activity by acting as a gamma-aminobutyric acid (GABA) neurotransmitter $GABA_A$ receptor agonists and binding specifically to its **α** subunits[333]. They are used for their myorelaxant, anxiolytics and sedative-hypnotics properties (i.e., shorten sleep latency, promote sleep continuity)[490]. While BZDs range from short- to long-acting hypnotics (e.g., with a half-life of up to 100 hours), BZRAs are usually shorter-acting (e.g., Zopiclone has a half-life of up to 9 hours in older adults[491]), with fewer sedative and myorelaxant side effects[315,492,493]. Sedative-hypnotic use for one month has been shown to reduce wake after sleep onset in placebo-controlled studies of older adults with insomnia disorder, and extend their overall sleep duration[367,368]. However, when compared to older adults with and without insomnia disorder, older adults chronically using BZDs presented a higher sleep fragmentation[252], and changes in sleep architecture (including a reduction in time spent in deep sleep (N3) and REM sleep while increasing duration in N2 sleep)[359]. Despite their frequent prescription[25], the chronic use of sedative-hypnotics has been also associated with an accelerated decline in both cognitive and physical health[374–377].

Changes in sleep architecture are often associated with alterations in sleep electroencephalogram (EEG) rhythms. Indeed, compared to older adults with and without insomnia disorder, BZDs users exhibit less theta activity and increased beta and sigma power in NREM and overall across the night[252,494]. In terms of discrete oscillations, sedative-hypnotics increase spindle density[495], suppress slow wave activity (SWA)[495] and interfere with the intrinsic relationship between those NREM rhythms (i.e., temporal synchrony, phase-amplitude coupling (PAC)) [496,497].

However, further investigation is required to determine whether chronic use of sedative-hypnotics alters interactions between NREM rhythms, particularly in older adults. Given the diversity in acting duration among sedative-hypnotics, their effects on sleep architecture can vary significantly. Furthermore, sleep fragmentation and duration have been characterized only in a between-group design involving middle-aged (55-65 year-old) adults with insomnia complaints using BZDs for prolonged periods compared to healthy sleepers[495], or older adults with insomnia complaints using BZRAs in placebo-controlled studies[367,368]. Finally, the description of the intrinsic relationship between SO and spindle focused only on a single use of BZRAs and did not investigate the elderly population[496–498].

In summary, our comprehension of the chronic impact of BZDs and BZRAs on sleep macro- and micro-structure remains incomplete. Here, we aimed to further characterize the effect of chronic use of BZDs/BZRAs on sleep regulation in older adults using a between-group design involving good sleepers, individuals with insomnia disorder not taking any pharmacological treatment to manage their symptoms and individuals with insomnia disorder who chronically use either BZDs or BZRAs as sleep-aids. We performed a comprehensive comparison of sleep architecture, including EEG spectral properties and associated brain oscillations. Specifically, we focused on NREM brain oscillations associated with cognition and memory. We hypothesized that chronic use of sedative-hypnotics would have a more significant impact on sleep macrostructure compared to drug-free insomnia disorder, resulting in reduced N3 and REM duration, prolonged N2 duration, but greater sleep fragmentation. Regarding EEG spectrum, we anticipated reduced activity in low-frequency bands (i.e., delta and theta power) and greater activity in high-frequency bands such as sigma power indicative of increased spindle activity. We also expected that both spindle and SO characteristics would be impacted, thus altering their coupling.

## 2.3 Material and Methods

### 2.3.1 Participants

We investigated 3 groups of older adults: good sleepers (GS), individuals with insomnia disorder who do not use sleeping medication to manage their symptoms (INS) and individuals with insomnia disorder who are chronic sedative-hypnotics users (MED). The INS group were not under any type of sedative-hypnotic treatment at the time of assessment. The MED group was using at least one of the options listed, with only on type of BZDs or BZRAs prescribed for insomnia from the following: BZD (Diazepam, Clonazepam, Nitrazepam, Oxazepam, Lorazepam, Temazepam) or BZRA (Zopiclone) drugs. Data used in this dataset were collected in the scope of three different projects conducted in the laboratory and published[194,208] or registered (ISRCTN13983243, ISRCTN10037794) elsewhere. All groups had similar recruitment process through online advertisements published on social media, alongside printed advertisements in various public outlets, specifically targeting older adults (*Bel Âge* journal) and from physician referrals. Advertisements and physician guides for referrals outlined the inclusion and exclusion criteria specific to each group: the GS group consisted of older adults who were good sleepers, the INS and MED groups included older adults with chronic insomnia. The MED group was recruited as part of a trial on an intervention for BZDs/BZRAs discontinuation (ISRCTN10037794), and only baseline data collected prior to the intervention were analyzed in the present study.

Prospective participants underwent screening via a telephone-based checklist to assess inclusion and exclusion criteria, followed by a semi-structured individual interview.

Eligible participants underwent a screening polysomnographic (PSG) recording to exclude the presence of additional sleep disorders that could contribute to symptoms of insomnia (i.e. sleep apnea).

Older adults included in the GS group were self-defined good sleepers with no sleep complaints and no sleep dissatisfaction. The INS and MED groups consisted of participants meeting the DSM-5 diagnostic criteria for insomnia disorder for at least 3 months[213]. The DSM-5 diagnostic criteria for insomnia disorder are defined as self-reported difficulties initiating sleep, difficulties maintaining sleep, and/or early morning awakenings, for at least 3 times a week and for more than 3 months, combined with complaints of daytime functioning. Participants in the MED group had to meet a criterion of sedative-hypnotic use (regardless of the dosage): BZDs or BZRAs had to be prescribed for insomnia and to be used for more than 3 nights a week for more than 3 months. Averaged consumed doses of BZDs and BZRAs were converted into

Diazepam Equivalent Dose, according to the Equivalence Table of BZD in the Ashton Manuel Supplement[499].

For all groups, exclusion criteria were as follows: being under 55 y.o or over 80 y.o, major cardiovascular condition or intervention, recent severe infection, medical or unstable condition that could impair physical, psychological, or cognitive abilities (e.g., Parkinson's or AD), poor cognitive function (defined by a Mini Mental State Examination – score ≤ 24[500] or a Montreal Cognitive Assessment (MoCA) – < 23[501]), medical conditions likely to affect sleep (e.g., epilepsy, multiple sclerosis, chronic pain, stroke, active cancer), sleep disorders (e.g., moderate or severe sleep apnea (apnea-hypopnea index (AHI) greater than 15 events per hour), bruxism, restless legs syndrome or periodic limb movement (PLM) disorder defined by an index during sleep > 15/h), night shifts or a change in time zone in the last 6 weeks and history of alcoholism or drug abuse. Specifically for individuals in the GS and INS groups, exclusion criteria also included using any sleep-inducing medication (prescribed or over-the-counter) or having received any sleep-related intervention (e.g., cognitive-behavioral therapy for insomnia).

All participants signed a written informed consent form, which was approved by the Concordia University Human Research Ethics Committee and the Comité d'Éthique de la Recherche of the Institut Universitaire de Gériatrie de Montréal. One hundred and one participants were found eligible for the study and distributed as follows: twenty-eight participants in the GS group, twenty-six participants in the INS group as well as forty-seven included in the MED group. Participant demographics are presented in **Table 1**.

### 2.3.2 Study protocol

The three groups were drawn from studies containing three different protocols, however the data used in this analysis were all drawn from a single night of PSG. Upon recruitment into a study, all participants underwent a screening PSG, which also served as a habituation night. All participants in the MED group took their prescribed sedative-hypnotic medications during both the screening and experimental nights, ensuring their typical sleep patterns under medication. Depending on the specific projects they were recruited for, participants then completed at least one experimental night (baseline night), from which sleep characteristics were extracted to be used for this study and subsequently filled out the Insomnia Severity Index (ISI) questionnaire the following morning. For the present study, sleep characteristics were extracted from the first experimental night. The PSG night protocols varied between studies, particularly in terms of rise time. While the MED group had to wake up by 8 AM, other groups were instructed to wake up around 6 AM. The MED group had an average wake-up time of 7:22 AM.

### 2.3.3 Measures

#### *2.3.3.1 Insomnia Severity Index (ISI)*

Participants completed the ISI questionnaire, a 7 Likert-scale used to assess the nature, severity, and impact of current insomnia symptoms[8]. The total ISI score ranges from 0 to 28, with higher scores indicating more severe insomnia. Its overall Cronbach's **α** was 0.90.

#### *2.3.3.2 Polysomnographic (PSG) recording*

Whole-night PSG recordings were used for each night, including EEG, electromyogram (chin and legs EMG), electrooculogram (EOG), and electrocardiogram (ECG). During the screening night, the PSG setup included an oximeter, thoracic and abdominal belts, oral-nasal thermistor, and nasal cannula. From the habituation night, we computed the apnea-hypopnea index and periodic leg movement index to exclude potential sleep disorders. For the experimental night, the EEG montage included 13 electrodes (Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, O1, O2, M1, M2) positioned on the scalp according to the 10-20 system AASM guidelines. EEG signal was recorded by a Somnomedics amplifier (SomnoMedics, Germany) at a sampling rate of 512 Hz, referenced to Pz online for monitoring and to contralateral mastoids (M1 and M2) offline for analysis.

#### *2.3.3.3 EEG analysis*

All sleep scoring and analyses were conducted using the Wonambi python toolbox (https://wonambi-python.github.io) and the Seapipe python toolbox (https://github.com/nathanecross/seapipe). Sleep stages, arousal and artefact events were initially visually scored by multiple experts (AAP, OMW, LB), with a final review and revision conducted by a single expert scorer (LB) according to the AASM rules[14]. From the scoring, we computed the calculation of the following: total sleep period (TSP; from sleep onset to final awakening), total sleep time (TST; sum of the time spent in different sleep stages), sleep onset latency (SOL; from light off to the first epoch of sleep), time spent in bed (TIB; from light off to light on), sleep efficiency (SE; TST/TIB*100), arousal density (number per hour), sleep fragmentation index (SFI; number of transitions from deep to lighter sleep stages per hour) as well as the % of time spent in each sleep stage and wake (%TSP).

The EEG spectrum power density average (30 sec resolution with artefact excluded) was computed using a Fast Fourier Transformation and Welch's method (Overlapping: 50%;

Resolution: 0.25 Hz). Mean relative power for the following frequency ranges was calculated as absolute power divided by broad spectrum (0.5-35 Hz) total power: SO (0.25-1.25 Hz), delta (0.5-4 Hz), theta (4-7.75 Hz), alpha (8-11 Hz), sigma (11.25-16 Hz), beta (low: 16.25-19 Hz and high: 19.25-35 Hz). The delta/beta ratio index for NREM and REM sleep was also assessed as an electrophysiological index of cortical arousal[502].

For spindle detection, the highest center frequency peak (integral of the Gaussian fit) over the sigma range specific for each subject was obtained[503,504]. Using those participant-specific adapted sigma ranges, we determined with a 2Hz bandwidth the highest peak in the 10 to 13 Hz range for midline frontal (Fz – slow spindle) and the 13 to 16 Hz range for midline parietal (Pz - fast spindle) on artefact-free derivations accounting for spindle frequency gradient[505,506]. Spindles were automatically detected using a validated algorithm[507]. We performed sensitivity analyses using other published algorithms[508,509]. Results can be found in **Appendix A**.

SO events were detected on a fixed band-pass FIR filter from 0.16 to 1.25 Hz on artefact-free EEG recordings of Fz and Pz using a published algorithm[84]. We performed sensitivity analyses using another validated algorithm[510] also implemented in the Wonambi and Seapipe toolboxes.

For SOs and spindles detected in NREM (N2 + N3), we extracted the following characteristics: density (i.e., mean number of spindles/SOs per epoch of 30 s), amplitude (μV), duration (sec) and peak frequency (Hz).

Spindle and SO coupling was assessed using three complementary measures: event co-occurrence, preferred coupling phase, and the modulation index as we previously published[194,511].

SO-spindle temporal co-occurrence was determined via the intersection-union rule. SO+ is defined as the proportion of the SO that co-occurs with spindles. Spindle+ is defined as the count of spindles linked with SO divided by the total count of spindles. The intersection/union threshold was set at 10% overlap duration between SO and spindle.

We investigated SO (0.5 to 1.25 Hz) and participant-specific adapted sigma band (Fz: 10-13Hz; Pz: 13-15Hz) phase-amplitude coupling based on each SO event detected across the whole night, using an approach we have recently published[194]. The preferred coupling phase (CP) was used for the timing and the modulation index was used for the strength of SO-spindle coupling.

### 2.3.4 Statistical analyses

Statistical analyses were performed using RStudio 1.2.50 (RStudio, Inc., Boston, MA) and R package (ggplot2, sjstats, sjmisc, forcats, emmeans, rstatix). Normality of distribution was checked with Shapiro tests and homogeneity of variance was tested with Levene tests.

We first investigated differences in macro-architecture (including wake duration, SOL, duration in sleep stages, sleep efficiency and markers of sleep fragmentation). We used mixed-model analyses of variance (ANOVA), with Stage as within-subject factor (Wake vs N1 vs N2 vs N3 vs REM) and Group as between-subject factor (GS vs INS vs MED) to investigate the difference between groups on wake and sleep stages durations, as well as Group by Stage interaction. Analyses of variance (ANOVA) with Group as a between-subject factor (GS vs INS vs MED) and unpaired-posthoc test were computed to investigate the difference between groups on our sleep-derived measures. We performed non-parametric tests (Kruskal-Wallis test and Dunn test) only when the variance or normality of distribution was not homogeneous. Age was regressed out from all sleep measures prior to statistical group-level comparisons. For a complete assessment of how sedative-hypnotics impact sleep quality, all analyses were repeated with the use of other methods for spindle[508,509] detection and SO[510] detection. These are reported in the **Appendix A**. Between-group effect sizes were calculated using Hedge's g (which corrects for small sample sizes). Watson circular statistic test for non-uniformity of circular data was performed to test whether spindles had a to the SO phase[512].

As an exploratory analysis within the MED group, we tested the relationship between our sleep measures, and both treatment duration and medication equivalent dose in Diazepam using Spearman's correlation. Moreover, we investigated group differences in sleep measures between BZDs users and BZRAs users using parametrical (t-test) and non-parametrical (Wilcoxon) tests. Due to differences in dose between BZDs users and BZRAs users, sedative-hypnotics equivalent dose was regressed out from all sleep measures in this analysis.

The level of significance was set to a p-value of <.05 and p-values were adjusted for multiple comparisons (Benjamini-Hochberg/FDR correction) in a family-wise manner across the following domains: sleep architecture, spectral power, spindle and slow oscillation properties, and their coupling[513]. For significant results, both raw ($p$) and adjusted p-values ($q$) were reported when appropriate.

## 2.4 Results

One hundred and one individuals (66.05 ± 5.84 years, 73% female) were categorized into three groups: good sleepers (GS, n=28), individuals with insomnia (INS, n=26) or individuals with insomnia who chronically use sedative-hypnotics (either BZD or BZRA) to manage their insomnia difficulties (MED, n=47; dose equivalent in Diazepam: 6.1 ± 3.8 mg/week; minimum dose duration: 1 year, corresponding to approx. 200 individual doses); see **Table 1** for demographics and **Table S1** in **Appendix A** for the various sedative-hypnotics used. We found that participants in the MED group were older compared to both GS and INS groups (all $p<.02$), while no difference was found regarding sex ratio (Fisher, $p=.25$). The GS group displayed no clinically significant insomnia (ISI score: 3.6 ± 3.1), while both the INS and the MED groups exhibited higher insomnia severity (ISI score > 8) ($p<.001$; see **Figure S1** in **Appendix A**). The MED group reported a lower ISI score compared to the INS group (INS group: 17.5 ± 4.1; MED group: 13.6 ± 4.8; $p<.002$).

### 2.4.1 Chronic use of BZD and BZRA affects sleep architecture.

There was a Group effect for SE ($F(2,97)=12.8$, $p=.002$, $q=.004$), where both INS ($p=.001$, $q=.002$) and MED ($p=.005$, $q=.01$) displayed lower SE compared to the GS group (**Figure 1A**) (**Table 2**). Significant Group effect was found for TIB ($F(2,97)=7.3$; $p=.001$, $q=.005$), and TST ($F(2,97)=3.6$; $p=.03$, $q=.04$), where the MED group displayed greater TIB (all $p<.01$, all $q<.04$) than both GS and INS groups but also greater TST compared to the INS ($p=.01$, $q=.04$) but not the GS group ($p=.03$, $q=.09$). We also found a Group*Stage interaction ($F(8,400)=162.9$; $p<.001$) on the proportion of time spent in each sleep stage (% over TSP) with significant main effect of Stage ($F(4,400)=15.6$; $p=.004$) but not Group ($F(2,98)=.99$; $p=.60$). Specifically, the MED group was associated with spending more time in N1 and less time in N3 compared to both INS and GS groups (all $p<.001$, all $q<.001$) (**Table 2**). The MED group was associated with spending more time in N2 compared to the INS ($p<.001$, $q<.001$), but not the GS group. In addition, the GS group was also associated with spending more time in N2 compared to the INS ($p<.001$, $q<.001$) group. The MED group exhibited increased time spent awake compared to the GS ($p=.02$, $q<.001$) but not the INS group (**Figure 1B**). We also observed increased in time spent awake in the INS group compared to the GS ($p=.001$, $q=.003$) group. Meanwhile, no significant difference was observed between the three groups for REM duration (**Figure 1B**). We found a main effect of Group on latency to REM ($F(2,97)=7.3$, $p=.03$, $q=.10$) as MED was associated with longer latency to REM compared to the INS and GS groups (all $p=.004$, all

$q$=.01), although these did not pass corrections for multiple comparisons. We did not find any significant effect for SOL and sleep latency to other stages.

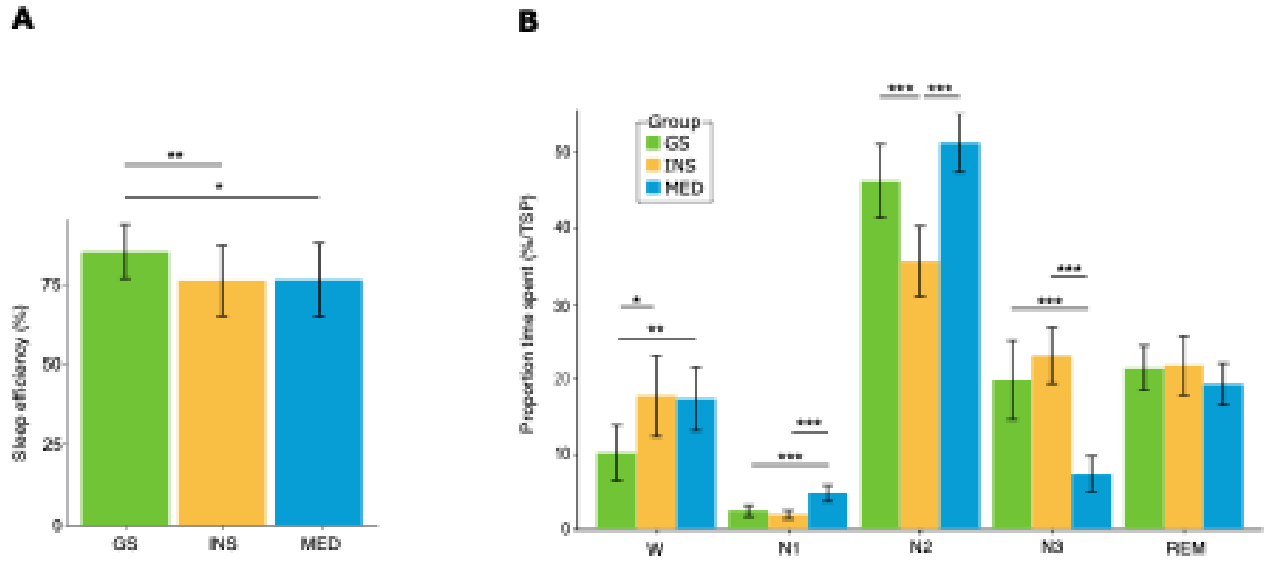


Figure 1: Chronic sedative-hypnotic use affects sleep architecture

*For the GS (green), the INS (orange), and the MED (blue) group:*

*(A) Mean sleep efficiency (%) (± SD)*

*(B) Mean proportion time spent in wake and sleep stages (% over TSP) (± SD)*

*Asterisks represent significance (p): *<0.05; **<0.01; ***<0.001*

In terms of sleep fragmentation, we found a Group effect for SFI ($F$(2,97)=14.3, $p$<.001) and total arousal density ($F$(2,97)=11.8, $p$=.003, $q$=.006). The INS group was associated with more arousal than the GS and MED groups (all $p$<.004, all $q$=.01) and lower SFI than the GS ($p$=.02, $q$=.05) and MED ($p$<.001) group (**Table 2**).

In summary, participants with insomnia (MED and INS) were associated with changes in sleep architecture, resulting in lower SE with or without chronic sedative-hypnotic use. Additionally, chronic sedatives-hypnotic use was linked to poorer sleep quality, characterized by prolonged light sleep duration and reduced deep sleep (N3).

### 2.4.2 Chronic use of BZD and BZRA alters spectral activity

Power analysis of sleep EEG revealed Group effects in specific spectral bands. Compared to the GS group only (Fz: $p$=.003, $q$=.01; Pz: $p$<.001, $q$=.002), the MED was associated with lower relative power in the theta band over the frontal (Fz; $F$(2,97)=9.2, $p$=.01 $q$=.02) and posterior

(Pz; $F(2,97)=12.3$, $p=.002$, $q=.02$) electrodes in both NREM sleep (N2 and N3 combined) and in REM sleep (Fz; $F(2,97)=12$, $p=.002$, $q=.02$) and posterior (Pz; $F(2,97)=12.9$, $p=.002$, $q=.02$) compared to both groups (**Figure 2, Table S2-S3** in **Appendix A**). There was an effect of Group on relative power in the frontal sigma (Fz; F(2,97)=9.10, $p=.01$, $q=.02$) and lower beta bands (Fz; F(2,97)=8.2, $p=.02$, $q=.03$), that were driven by MED group which displayed higher sigma power ($p=.009$, $q=.03$) and lower beta power ($p=.01$, $q=.04$) during NREM when compared to the GS group only (**Figure 2A**). There was also an effect of Group on high beta relative power in frontal regions only (Fz- F(2,97)=9.99, $p=.007$, $q=.02$ - **Figure 2A**) in NREM sleep, although post hoc analysis did not reveal a significant difference (**Table S2** in **Appendix A**). During REM, the MED group displayed less theta relative power than the two other groups (all $p\leq.01$, all $q\leq.04$) in both frontal (**Figure 2C**) and parietal (**Figure 2D**) regions (**Table S3** in **Appendix A**). We did not find any significant Group effects for relative power in the SO, delta and alpha frequencies. However, we found a reduction in the ratio between slower to higher EEG frequencies (i.e., delta/beta ratio) in the MED group compared to INS ($p=.01$, $q=.03$) and GS ($p=.007$, $q=.02$) ($F(2,97)=9.99$, $p=.007$; $q=.02$) in NREM; but not in REM (**Table S2** in **Appendix A**).

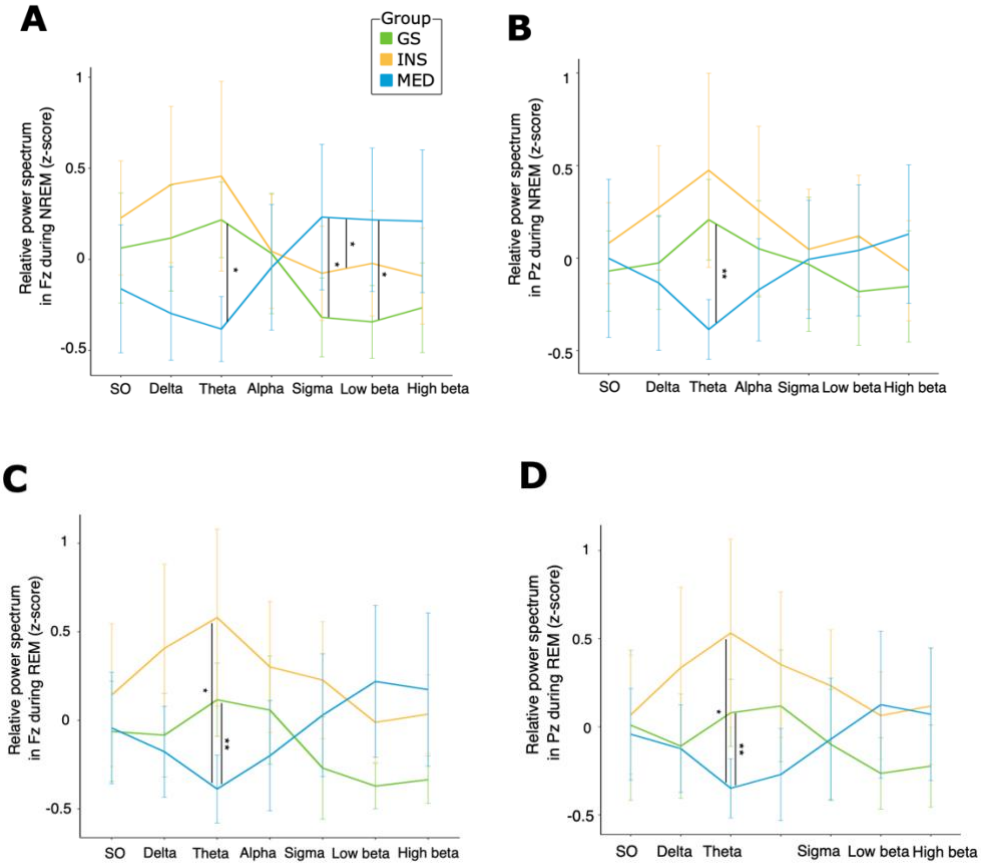

Figure 2: Chronic sedative-hypnotic use alters spectral activity

*For the GS group (green), the INS group (orange), and the MED (blue) group:*

*(A) Mean relative spectral activity in Fz during NREM (z-score)*

*(B) Mean relative spectral activity in Pz during NREM (z-score)*

*(C) Mean relative spectral activity in Fz during REM (z-score)*

*(D) Mean relative spectral activity in Pz during REM (z-score)*

*Asterisks represent significance (p): *<0.05; **<0.01; ***<0.001*

### 2.4.3 Spindles but not SOs are altered with chronic use of BZD and BZRA

During NREM sleep, a Group effect was observed on frontal spindle density ($F(2,97)=7.9$, $p=.02$, $q=.048$) with the MED group exhibiting greater spindle density compared to the INS group only ($p=.006$, $q=.02$). However, there was no significant Group effect on spindle density detection on the posterior channel (Pz – $F(2,97)=0.7$, $p=.50$). We found no significant effect of Group on other spindle characteristics (**Figure 3A** and **Table S4** in **Appendix A**). We observed similar findings using other published methods of spindle detections (see in **Appendix A, Table S5**).

**A**

SPINDLE

| | | Density (/30 s) | Duration (s) | Amplitude (µV) | Frequency (Hz) |
|---|---|---|---|---|---|
| Fz | GS | 1.19 ± 0.2 | 0.77 ± 0.04 | 92.7 ± 18.3 | 11.36 ± 0.5 |
| | INS | **1.1 ± 0.19** | 0.75 ± 0.03 | 94.92 ± 23.3 | 11.29 ± 0.5 |
| | MED | **1.29 ± 0.3** * | 0.77 ± 0.1 | 83.14 ± 21.6 | 11.35 ± 0.5 |
| Pz | GS | 1.45 ± 0.27 | 0.74 ± 0.04 | 71.25 ± 17.26 | 13.53 ± 0.56 |
| | INS | 1.38 ± 0.34 | 0.73 ± 0.04 | 77.08 ± 21.64 | 13.81 ± 0.46 |
| | MED | 1.48 ± 0.36 | 0.75 ± 0.06 | 65.21 ± 14.3 | 13.49 ± 0.59 |

SO

| | | Density (/30 s) | Duration (s) | Amplitude (µV) | Frequency (Hz) |
|---|---|---|---|---|---|
| Fz | GS | 3.83 ± 0.78 | 1.35 ± 0.06 | 122.26 ± 30.17 | 0.76 ± 0.06 |
| | INS | 3.98 ± 0.82 | 1.37 ± 0.05 | 124.16 ± 37.02 | 0.73 ± 0.05 |
| | MED | 3.82 ± 0.71 | 1.41 ± 0.08 | 104.61 ± 28.41 | 0.7 ± 0.07 |
| Pz | GS | 3.41 ± 0.73 | 1.43 ± 0.07 | 96.2 ± 26.29 | 0.68 ± 0.06 |
| | INS | 3.62 ± 0.86 | 1.43 ± 0.06 | 102.85 ± 32.2 | 0.67 ± 0.06 |
| | MED | 3.5 ± 0.67 | 1.46 ± 0.06 | 84.67 ± 21.39 | 0.65 ± 0.07 |

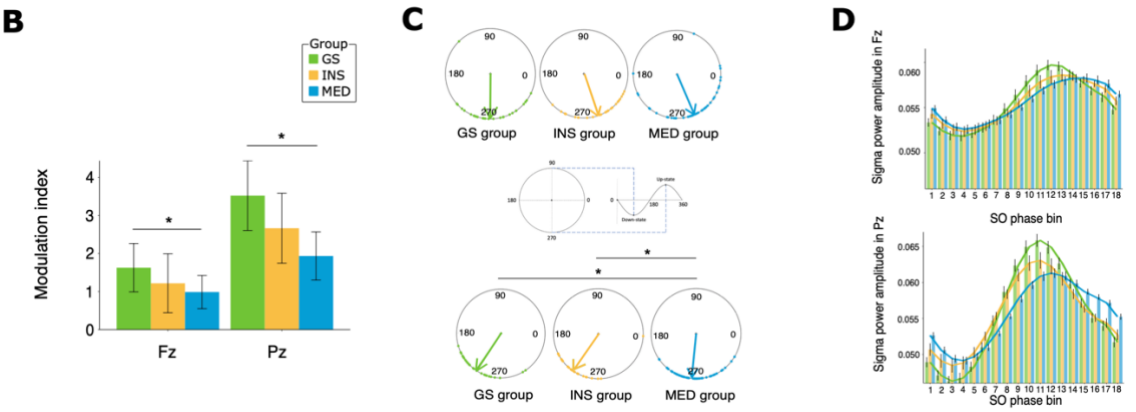


Figure 3: Chronic sedative-hypnotic use impact on SO-spindle and their association

*For the GS group (green), the INS group (orange), and the MED (blue) group:*

*(A) Mean spindle (left) and SO (right) characteristics (± SD)*

*(B) Mean Modulation index (± SD)*

*(C) Preferred-phase coupling polar plot for Fz (up) and Pz (down) during NREM. Arrows represents the average coupling preferred-phase for each group.*

*(D) Phase-amplitude histograms for Fz (up) and Pz (down). Each bar represent the average sigma power mean amplitude (µV) (± SD) across 18 bins, where each bin represent 20°.*

*Asterisks represent significance (p): *<0.05; **<0.01; ***<0.001*

We did not find any significant Group effect on SO density in both frontal and parietal regions (all $p$>.05). However, we found a Group effect on frontal SO frequency ($F$(2,97)=8.4, $p$=.02,

*q*=.08). The MED group exhibited a slower SO peak frequency compared to the GS (*p*=.004, *q*=.01) group only, although these did not pass corrections for multiple comparisons (**Table S4** in **Appendix A**).

Using a more rigid SO detection algorithm[510] based on fixed amplitude threshold (75µV), we did not observe any significant Group effect for SO characteristics either (all *p*>.05; see **Appendix A**, **Table S6**).

### 2.4.4 Chronic BZD and BZRA use affected SO-spindle association

We did not find any significant Group effect for the temporal co-occurrence of spindles and SOs in frontal and parietal regions (**Table S7** in **Appendix A**).

We found a Group effect in frontal on the PAC between SO and sigma (MI; $F(2,97)=6.8$, $p=.03$ – **Figure 3C**). Post-hoc tests revealed that the MED group displayed lower coupling strength (MI) compared to the GS group (*p*=.01, *q*=.03), but no difference was found between the MED and INS groups, as well as between the GS and the INS group. The same Group effect was observed in the parietal channel Pz ($F(2,97)=13.3$, $p=.001$, $q=.002$ – **Figure 3C**) driven again by differences between the MED and GS groups (*p*<.001).

Furthermore, we found a Group effect on the coupling phase in the parietal regions (**Figure 3D**) driven by the MED group which presented a greater (delayed) preferred coupling phase (CP) compared to both the GS (*W*= .3, *p*<.01) and INS (*W*= .3, *p*<.01) groups. Phase-amplitude histograms (**Figure 3E**) represent this delay in SO-sigma in the MED group.

In summary, the MED group displayed a weaker SOs and spindles coupling strength (MI) and a later preferred coupling phase when compared to GS.

### 2.4.5 Effect of the use and type of chronic sedative-hypnotic exposure on sleep.

A subgroup analysis was conducted within the MED group (N=47) to investigate the associations between dose and duration of sedative-hypnotic consumption on sleep measures. Significant associations were observed between higher sedative-hypnotic dosage and increased SOL (*p*=.003, *q*=.01, *r*=.45), as well as latency to reach stage N2 (*p*=.002, *q*=.01, *r*=.44), comparisons, decreased TST (*p*=.02, *q*=.07, *r*=-.33) and greater latency to REM (*p*=.04, *q*=.08, *r*=.31). Additionally, we observed a correlation between higher sedative-hypnotic dosage and increased relative power in high-frequency during NREM, including sigma (*p*=.004, *q*=.01, *r*=.41 – **Figure 4B**) and beta (*p*=.003, *q*=.01, *r*=.42 – **Figure 4C**) bands. We observed a correlation between a longer duration of sedative-hypnotic consumption and decreased

posterior spindle duration (Pz; $p$=.004, $q$=.02, $r$= -.41 – **Figure 4D**) but no other sleep variables were associated with dose or duration of use.

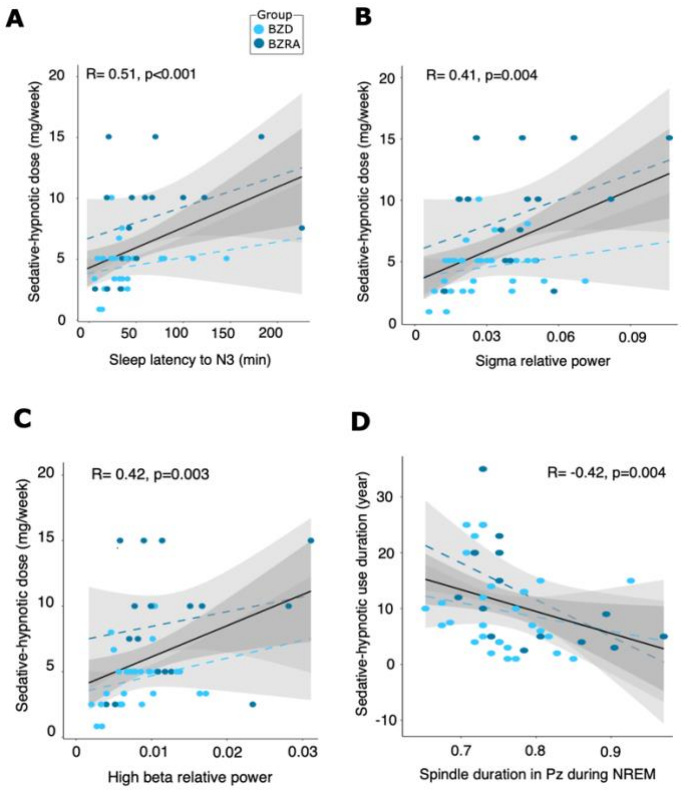


Figure 4: Impact of sedative-hypnotic dose and duration

For the BZD (darkblue) and the BZRA group (lightblue):

*(A) Scatterplot showing correlation between the change in the dosage and the change in the sleep latency to N3*

*(B) Scatterplot showing correlation between the change in the dosage and the change in the sigma relative power*

*(C) Scatterplot showing correlation between the change in the dosage and the change in the high beta relative power*

*(D) Scatterplot showing correlation between the change in the sedative-hypnotic use duration and the change in the spindle duration in Pz*

We then categorized participants in the MED group based on their type of sedative-hypnotic class, into either the BZD (n=18; dose equivalent in Diazepam: 8.75 ± 4.39 mg/week) or the BZRA (n=29; dose equivalent in Diazepam: 4.41 ± 2.01 mg/week) group. We did not find any significant difference on age, sex or duration of hypnotic consumption between the two groups (all $p$>.05), but we found a Group effect driven by BZD which displayed greater sedative-

hypnotics dose equivalent in diazepam ($p$=.002) compared to the BZRA group. Hence, we adjusted our analyses for sedative-hypnotic equivalent dose. We did not observe significant Group effect for all outcomes (**Table S8** in **Appendix A**).

In summary, the alteration in sleep architecture and spectral activity became more pronounced as the dosage of sedative-hypnotics increased. However, the characteristics of SOs and spindles, including their temporal co-occurrence and coupling strength, showed no association with medication dosage. The duration of sedative-hypnotic use was only associated with a decrease in posterior spindle duration (Pz).

## 2.5 Discussion

This study investigated the effect of chronic sedative-hypnotic use on sleep architecture in older adults, including good sleepers, individuals with insomnia who do not take any pharmacological treatment for sleep and individuals with insomnia who chronically use BZDs/BZRAs for insomnia management. We found that chronic use of use BZDs/BZRAs was associated with changes in sleep regulation without reducing its fragmentation or enhancing N3 duration. Alterations in relative spectral power were evident, particularly in the theta range and in sigma and beta activity. Chronic sedative-hypnotic use was also linked to increased spindles, and despite no changes in SOs characteristics, there was an association with weaker and delayed timing of SO-spindle phase-amplitude coupling. Finally, we found that higher doses of BZDs/BZRAs use correlated with worsened sleep parameters, but there was no difference between the types of drugs in terms of sleep measures.

Both insomnia groups (INS and MED) displayed lower sleep efficiency and greater wake duration compared to good sleepers (GS), which is consistent with typical insomnia complaints. Surprisingly, the use of chronic sedative-hypnotics (MED) was associated with more sleep fragmentation (i.e. more shifts to lighter stages[20]) but less arousal density compared to drug-free individuals with insomnia. Furthermore, the chronic use of BZDs/BZRAs was associated with further disruption in sleep architecture compared to insomnia alone: it was linked to increased N1 and N2 duration, with reduced N3 duration. These findings are comparable to previous studies with similar clinical groups[252,494] where the chronic use of BZDs alone greatly altered sleep architecture (especially N3 duration) compared to drug-free insomnia[494] or good sleepers[252,494]. Reduction in time spent in N3 has been linked to impaired cognitive performance[514], reduced cortical volume[515], as well as a reduction in cerebral metabolism and

altered brain clearance[516], suggesting that BZDs/BZRAs related-sleep architecture alterations may worsen brain health in older adults. While BZDs use is not associated with shorter sleep latency, it has been associated with greater time in bed, longer N1 duration, and shorter latency to REM[495]. In the present study, we only observed a trend in a shorter latency to REM.

Alterations in sleep architecture associated with chronic use of sedative hypnotics were also captured in the differences in EEG spectral power and brain oscillations. Consistent with the literature on BZDs/BZRAs use in middle-aged to older adults with and without insomnia, we observed a significant reduction in the relative theta power during both NREM[252] compared to GS, and REM[495] sleep compared to both groups. The inhibitory effects induced by sedative-hypnotics may result in a lack of theta activity as theta activity generation involves GABAergic neurons[517–519]. Moreover, in frontal regions, the increase in relative beta power and the reduction in delta/beta ratio (an index of cortical arousal[502]) observed in chronic users of sedative-hypnotics suggest an increased firing of arousal systems, which may prevent subjects from entering or spending a long time in N3 sleep[502,520]. In contrast, we did not observe any group differences in parameters of discrete SOs or SWA. A previous study found a reduction in overall SWA associated with chronic BZDs use in the elderly[252] but their use of absolute power rather than normalised relative power may have confounded the results[521]. However, we did find that chronic sedative-hypnotics were associated with an increase in slow (frontal) spindles. Previous studies have observed an increase in sigma activity as well as slow spindle density in healthy young adults following acute BZRA administration[522,523] and schizophrenia outpatients[524]. However, an increase in spindle amplitude has also been reported[522] , which we did not observe. This suggests that the pharmacological impact on spindle activity might differ between acute and chronic use in the elderly.

Given that communication between thalamocortical neurons and thalamic reticular neurons is crucial for spindle and SO synchronization[525], such chronic use of sedative-hypnotics may also disrupt the synchronization of NREM oscillations. Spindles temporally linked with SOs have been linked with memory consolidation[192,194]. In the present study, while we found that chronic use of sedative-hypnotics was linked to increased spindle density, it also weakened the temporal link between spindles and SOs, without affecting SO characteristics. Specifically, it delayed the SO-sigma phase-amplitude coupling and reduced the coupling strength in both the frontal and parietal regions. The present findings align with the existing literature showing that the consistency of SO phase locking with spindles is reduced following acute use of BZRA in

schizophrenia outpatients compared to healthy controls[523]. As synchronization between SOs and spindles is thought to mediate memory consolidation[57,84,195,526,527], this desynchronization between NREM oscillations induced by chronic use of sedative-hypnotic may have significant detrimental implications for plasticity and memory processes, which is especially concerning in an elderly population.

Our results suggest that chronic use of sedative-hypnotics seems detrimental to sleep compared to drug-free GS and INS. Such alteration of sleep regulation – at the macro and micro-level - may explain the reported strong link between sedative-hypnotic use and cognitive impairment in older adults[374]. Indeed, chronic use has been demonstrated to accelerate cognitive decline and morbidity[528–530]. Future studies should assess whether altered spindle characteristics and their coupling to SO, due to chronic use of sedative-hypnotics, might relate to memory performance. More importantly, other approaches, whether pharmacological[531–533] or non-pharmacological[37,397,437], need to be considered to address insomnia complaints while preserving the integrity of the intrinsic mechanisms related to cognitive functioning.

To our knowledge, no previous study has directly and systematically compared sleep macro- and micro-architecture between BZDs and BZRAs users. It would be expected that BZRAs might be less detrimental because of their usually shorter-acting pharmacokinetic effect. However, we found no differences in sleep architecture between BZDs and BZRAs users. Interestingly, we found that the dosage, not the duration of use per se, has an impact on sleep measures, which might increase the risk for neurodegeneration. Indeed, studies have found associations between sedative-hypnotic use and increased risk of developing dementia, increasing specifically with cumulative dose and exposure and when long-acting medication was used[376,534–537]. However, conflicting evidence exists at higher doses[377,538,539]. Future studies should further clarify the discrepancies in these findings and investigate the differing effects of these medications on sleep.

Some limitations of this study may affect the interpretability of the findings. First, our sample size was relatively limited, especially when comparing individuals using BZRAs and those using BZDs. Secondly, the use of BZDs/BZRAs was determined through self-reporting, which may not accurately represent actual medication consumption as measured by objective assessments. The potential discrepancy could result in inaccuracies in our analysis of the dosage and duration of sedative-hypnotic use. We were also unable to examine sex differences among our participants due to the predominance of females over males. Understanding these

differences is essential, as they can influence sleep needs and responses to treatments. Additionally, different wake time (lights on) protocols between the projects might have hindered Group effects on sleep duration. However, all sleep architecture measures were normalised to TSP (%), so that the effect of wake times (before sleep onset and after final awakening) on these measures were minimized. Relatedly, although our focus was on the objective assessment of sleep regulation, the retrospective design where sedative-hypnotic use was not randomly assigned, may have led to differences between the two groups of individuals with insomnia beyond the presence of BZDs/BZRAs. Studies employing randomized controlled designs would strengthen these findings but may be difficult to implement for ethical concerns given that long-term BZDs/BZRAs use is not recommended in older adults[540]. We were also not able to properly compare the effects of BZDs/BZRAs use on N2 and N3 stages separately as the MED group displayed too few epochs of N3, which is an inherent effect of BZDs/BZRAs use[38,495]. This study's analysis of sleep oscillations is constrained by the inherent low spatial resolution of EEG, which limits the precise characterization of their local dynamics. Finally, the data is cross-sectional, and future studies should investigate sleep both before and after the use of sedative-hypnotics.

In conclusion, chronic use of sedative-hypnotics in older adults was associated with disrupted sleep architecture and spectral activity compared to older adults both with and without insomnia disorder. The use of these drugs was also linked to the alteration of spindle activity and their synchrony to SOs. The current findings highlight the impact of chronic use of sedative-hypnotics on sleep and suggest these may have detrimental health outcomes, including for cognitive decline.

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## 2.6 Tables

### Table 1: Demographics

*Participant demographics across the GS, INS, and MED groups include age, sex, years of education, Insomnia Severity Index scores, and, for the MED group, sedative-hypnotic use (Diazepam-equivalent dosage and duration). Asterisks indicate statistically significant differences between groups (p<.05).*

| Characteristics | GS | | INS | | MED | | Kruskal-Wallis test | | | Wilcoxon test | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | GS vs INS vs MED | | | GS vs INS | | INS vs MED | | GS vs MED | |
| | range | Mean ± SD | range | Mean ± SD | range | Mean ± SD | F | df | *p* | t | p | t | p | t | p |
| N | 28 | | 26 | | 47 | | | | | | | | | | |
| Age | [56 - 77] | 64.5 ± 7.0 | [55 - 75] | 64.1 ± 5.3 | [61 - 80] | 68.1 ± 4.7 | 12.02 | 2 | **.002*** | 355 | .88 | 411 | **.01*** | 350 | **.01*** |
| Sex | | | | | | | | | | | | | | | |
| Female \| Male | 18 \| 10 | | 22 \| 4 | | 34 \| 13 | | Fisher test: *p=.25* | | | | | | | |
| % | 64.3 \| 35.7 | | 84.6 \| 15.4 | | 72.3 \| 27.7 | | | | | | | | | |
| Education years | [9 - 25] | 17 ± 3.5 | [10 - 25] | 16.8 ± 3.7 | [9 - 20] | 14.7 ± 2.4 | 11.9 | 2 | **.003*** | 339 | .61 | 891 | **.001*** | 749 | **.02*** |
| ISI score [/28] | [0 - 12] | 3.6 ± 3.1 | [12 - 27] | 17.5 ± 4.1 | [6 - 23] | 13.6 ± 4.8 | 60 | 2 | **<.001*** | .5 | **<.001*** | 882.5 | **.002*** | 55.5 | **<.001*** |
| Sedative-hypnotic consumption | | | | | | | | | | | | | | | |
| Duration [years] | | | | | [1 - 35] | 10.9 ± 8.2 | | | | | | | | | |
| Dose equivalent in Diazepam [mg/week] | | | | | [0.8 - 15] | 6.1 ± 3.8 | | | | | | | | | |

GS, good sleepers; INS, individuals with chronic insomnia; MED,individuals with chronic use of sedative hypnotics as treatment for chronic insomnia; ISI, Insomnia Severity Index

### Table 2: Effects of chronic sedative-hypnotic use on sleep architecture

*Mean (± SD) measures of sleep architecture across the GS, INS, and MED groups including measures of sleep duration, sleep initiation and sleep fragmentation. Asterisks indicate statistically significant differences between groups (p<.05).*

| Outcome measure | GS | | INS | | MED | | GS vs INS vs MED Kruskal-Wallis test or ANOVA | | | | | GS vs INS post hoc - Dunn test or t test | | effect size | INS vs MED post hoc - Dunn test or t test | | effect size | GS vs MED post hoc - Dunn test or t test | | effect size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | df | residual | *p* | *q* | *p* | *q* | g' | *p* | *q* | g' | *p* | *q* | g' |
| ***Sleep duration*** | | | | | | | | | | | | | | | | | | | | |
| TIB (min) | 460 | 50.29 | 472.22 | 54.39 | 504.51 | 54.15 | 7.27 | 2 | 97 | 0.001 | **0.005*** | 0.40 | - | -0.23 | 0.01 | **0.04*** | -0.60 | <0.001 | **0.002*** | -0.85 |
| TSP (min) | 434.91 | 50.05 | 435.6 | 57.72 | 464.78 | 60.04 | 8.96 | 2 | 97 | 0.01 | **0.02*** | 0.97 | - | -0.01 | 0.01 | **0.04*** | -0.54 | 0.01 | **0.04*** | -0.57 |
| TST (min) | 390.7 | 53.75 | 358.17 | 59.84 | 382.93 | 59.63 | 3.57 | 2 | 97 | 0.03 | **0.04*** | **0.03** | 0.09 | 0.62 | 0.01 | **0.04*** | -0.57 | 0.96 | - | -0.01 |
| SE (%) | 85.12 | 8.47 | 76.09 | 10.96 | 76.3 | 11.29 | 12.79 | 2 | 97 | 0.002 | **0.004*** | 0.001 | **0.002*** | 0.99 | 0.32 | - | -0.18 | 0.005 | **0.01*** | 0.71 |
| N1 (% TSP) | 2.49 | 1.32 | 1.98 | 0.95 | 4.81 | 2.46 | 29.00 | 2 | 97 | **< 0.001*** | - | 0.24 | - | 0.39 | **< 0.001*** | - | -1.12 | **< 0.001*** | - | -0.91 |
| N2 (% TSP) | 46.17 | 8.53 | 35.51 | 7.86 | 51.21 | 9.01 | 20.67 | 2 | 97 | **< 0.001*** | - | **< 0.001*** | - | 1.35 | **< 0.001*** | - | -1.49 | 0.19 | - | -0.30 |
| N3 (% TSP) | 19.8 | 9.2 | 23.05 | 6.28 | 7.39 | 5.39 | 35.31 | 2 | 97 | **< 0.001*** | - | 0.11 | - | -0.38 | **< 0.001*** | - | 1.98 | **< 0.001*** | - | 1.47 |
| REM (% TSP) | 21.37 | 5.24 | 21.76 | 6.69 | 19.27 | 6.28 | 0.39 | 2 | 97 | 0.82 | - | - | - | - | - | - | - | - | - | - |
| ***Sleep Initiation*** (min) | | | | | | | | | | | | | | | | | | | | |
| SOL | 15.46 | 15.25 | 21.47 | 33.17 | 26.99 | 36.99 | 0.09 | 2 | 97 | 0.95 | - | - | - | - | - | - | - | - | - | - |
| SL to N2 | 17.37 | 15.49 | 22.65 | 33.14 | 29.46 | 36.77 | 0.71 | 2 | 97 | 0.70 | - | - | - | - | - | - | - | - | - | - |
| SL to N3 | 32.41 | 25.13 | 41.3 | 39.29 | 56.56 | 46.13 | 5.16 | 2 | 97 | 0.08 | - | - | - | - | - | - | - | - | - | - |
| SL to REM | 90.79 | 33.53 | 94.53 | 42.02 | 138.84 | 78.22 | 7.31 | 2 | 97 | **0.025** | 0.10 | 0.99 | - | -0.1 | 0.004 | **0.01*** | -0.65 | 0.004 | **0.01*** | -0.73 |
| ***Sleep Fragmentation*** | | | | | | | | | | | | | | | | | | | | |
| Wake (% TSP) | 10.17 | 6.47 | 17.7 | 9.11 | 17.32 | 9.67 | 11.83 | 2 | 97 | 0.003 | **0.004*** | 0.001 | **0.003*** | -0.99 | 0.32 | - | 0.20 | 0.007 | **0.02*** | -0.69 |
| Arousal density (Nber/h) | | | | | | | | | | | | | | | | | | | | |
| all night | 14.7 | 5.52 | 20.66 | 7.4 | 14.66 | 6.72 | 11.79 | 2 | 97 | 0.003 | **0.006*** | 0.004 | **0.01*** | -0.9 | 0.003 | **0.01*** | 0.77 | 0.62 | - | 0.01 |
| NREM | 0.25 | 0.11 | 0.35 | 0.14 | 0.24 | 0.12 | 8.99 | 2 | 97 | **0.01*** | - | **0.03** | 0.08 | -0.77 | 0.001 | **0.003*** | 0.75 | 0.40 | - | 0.1 |
| REM | 0.21 | 0.09 | 0.32 | 0.13 | 0.24 | 0.15 | 10.64 | 2 | 97 | 0.005 | **0.007*** | 0.002 | **0.005*** | -0.91 | 0.01 | **0.04*** | 0.48 | 0.29 | - | -0.24 |
| SFI | 17.49 | 3.89 | 13.7 | 4.22 | 18.7 | 5.35 | 14.28 | 2 | 97 | **< 0.001*** | - | 0.02 | **0.05*** | 0.62 | **< 0.001*** | - | -0.77 | 0.27 | - | -0.27 |

TSP, total sleep period; TIB, time in bed; SOL, sleep onset latency; SL, sleep latency; WASO, wake after sleep onset; SE, sleep efficiency; SFI, sleep fragmentation index; SSI, stage switch index; NREM, non-rapid eye movement; REM, rapid eye movement

# Chapter 3: Effects of cognitive-behavioral therapy for insomnia during sedative-hypnotics withdrawal on sleep and cognition in older adults.

# Effects of cognitive-behavioral therapy for insomnia during sedative-hypnotics withdrawal on sleep and cognition in older adults.

Authors:

Loïc Barbaux[1,2*], Nathan E. Cross[1,2,4], Aurore A. Perrault[1,2,3], Mehdi Es-sounni[1,2], Caroline Desrosiers[2], Doris Clerc[2], Francis Andriamampionona[2], David Lussier[2], Cara Tannenbaum[2], Anik Guimond[2], Sébastien Grenier[2,6], Jean-Philippe Gouin[2], Thien Thanh Dang-Vu[1,2*]

Affiliations:

[1] Sleep, Cognition and Neuroimaging Lab, Department of Health, Kinesiology and Applied Physiology, School of Health & Center for Studies in Behavioural Neurobiology, Concordia University, Montreal, Quebec, Canada

[2] Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, CIUSSS Centre-Sud-de-l'Ile-de-Montréal, Québec, Canada

[3] Sleep and Circadian Group, Woolcock Institute of Medical Research and Macquarie University, Sydney, NSW, Australia

[4] School of Psychology, University of Sydney, NSW, Australia

[5] Stress, Interpersonal Relationship and Health Lab, Department of Psychology & Centre for Clinical Research in Health, Concordia University, Quebec, Canada

[6] Department of Psychology, University of Montreal, Quebec, Canada

* corresponding authors

loicbrb@gmail.com; tt.dangvu@concordia.ca

Department of Health, Kinesiology and Applied Physiology

Concordia University,

7141 Sherbrooke St W, H4B 1R6 Montreal, QC, Canada

Manuscript under review in Sleep Medicine

## 3.1 Abstract

**Objectives:** Our objective was to assess the effect of cognitive-behavioral therapy for insomnia (CBTi) on subjective and objective sleep quality (including sleep spindles) and cognition during a sedative-hypnotics withdrawal program in older adults with insomnia disorder.

**Methods**: We performed a two-arm randomised controlled trial (RCT) of a sedative-hypnotic withdrawal plan alone (WPo group) or combined with CBTi (WP+CBTi group) in 47 older adults with insomnia disorder over a sixteen-week period. Our primary outcomes were change in self-reported insomnia severity (Insomnia Severity Index (ISI)), sleep efficiency (SE) from sleep diaries, and change in SE and spindle density from polysomnographic (PSG) recordings collected at baseline and at post-intervention (16 weeks). Secondary outcomes included other sleep changes from PSG, actigraphy and sleep diaries, sleep and mood questionnaires and neuropsychological assessments (manual dexterity, attention/concentration, verbal inhibition, visuo-spatial abilities).

**Results**: The withdrawal program was effective in achieving discontinuation and reducing insomnia severity, with similar success with and without CBTi. The combined intervention additionally improved subjective sleep quality and prevented the decrease in subjective sleep duration induced by sedative-hypnotic discontinuation. Neither intervention significantly impacted objective sleep architecture or cognitive performance. Furthermore, reduction in sleep spindle density was observed with combined CBTi and withdrawal, but not with withdrawal alone.

**Conclusions**: Both withdrawal alone and sedative-hypnotic withdrawal combined with CBTi effectively facilitated discontinuation and reduced insomnia severity, with the combined intervention further enhancing subjective sleep quality and preserving sleep duration. Although neither approach significantly impacted objective sleep architecture or cognitive performance, the potential reduction in sleep spindle density linked to the combined intervention warrants further investigation.

**Keywords**: CBTi; sedative-hypnotics withdrawal; ageing; spindle; cognition, subjective sleep

## 3.2 Introduction

Insomnia disorder, defined by the complaints of difficulties falling and/or maintaining sleep more than 3 nights per week, and/or accompanied by early morning awakenings, despite adequate sleep opportunities[213], is highly prevalent in the older population. Insomnia symptoms are the most prevalent sleep disturbance among the elderly, with up to 50% experiencing of difficulty initiating or maintaining sleep[243,273,274,541]. Insufficient sleep has been linked to reduced grey matter volume, notably in the thalamus, hippocampus, and cortical areas such as the temporal and orbitofrontal cortices, leading to deficits in attention and working memory[542–545]. It is associated with poorer quality of life and health and increased risks for cognitive decline[303,307,546], thereby representing a major health issue.

The chronic consumption of prescribed sedative-hypnotics as a treatment for insomnia is common among the elderly[387,389,390,484,486–488]. Two major classes of sedative-hypnotics are benzodiazepines (BZDs) and benzodiazepine receptor agonist (BZRAs)[547]. While BZDs/BZRAs are effective in reducing subjective insomnia symptoms, many individuals develop tolerance over time[321]. Furthermore, long-term use of these sedative-hypnotics does not result in objective improvements in sleep quality already disrupted by insomnia. The long-term use of these sedative-hypnotics does not lead to objective improvements in the sleep quality already disrupted by insomnia. BZDs alter sleep architecture by reducing deep sleep[252,495] and disrupt the spectral properties of brain oscillations such as spindles and slow oscillations (SO)[548], which may contribute to impaired memory consolidation and cognitive issues[549]. For instance, both BZDs[252,522] and BZRAs[524,550] use have been shown to increase spindle activity and both sigma and beta power spectrum. In addition, chronic use of BZDs[375,551] and BZRAs[374] are accompanied with dependence and cognitive decline. Furthermore, associations has been found between BZDs/BZRAs use and the development of dementia[376–378], but also comorbidities in older adults, including daytime sleepiness and loss of motor coordination, which can increase risk for hip fractures[371]. This is particularly concerning given that approximately 30% of older adults who experienced hip fracture passed away in the subsequent year, while survivors exhibited a gradual decline in quality of life[373]. Considering this evidence, the American Geriatrics Society advises against the use of BZDs and BZRAs in older adults, regardless of the duration of use[382].

However, the use of BZDs[387,389,390,484,486,487] and BZRAs[488] in older adults remains high, and older adults can become dependent on these medications to be able to sleep, particularly after

chronic long-term use. Therefore, it is necessary to encourage withdrawal from BZDs/BZRAs in older adults to reduce the risk of adverse effects.

Several studies have investigated the impact of sedative-hypnotics withdrawal on sleep quality and cognitive function. BZDs/BZRAs discontinuation has been shown to improve self-reported sleep and quality of life outcomes in older adults[552]. Moreover, in a sample of 19 adults with insomnia and chronic use of BZDs, after a 15-day withdrawal period, they exhibited an improvement in slow wave sleep percentage 15 days after withdrawal[553]. Sleep efficiency declined following withdrawal but gradually improved, returning to levels comparable to pre-withdrawal 15 days post-withdrawal. Furthermore, improvements in attention, concentration, motor performance tasks, verbal and non-verbal memory, and visuo-spatial tasks have been observed after withdrawal in the elderly[554]. However, recovery effects are limited, as residual cognitive deficits remain in most cognitive functions compared to control subjects[554–556]. A major limitation is that BZDs/BZRAs withdrawal could be unsuccessful and accompanied by a worsening of insomnia symptoms called insomnia rebound[557]. Successful withdrawal is not always easy to achieve in chronic users, and approximately half of them will continue to use sedative-hypnotics after tapering[558,559]. Although withdrawal programs are effective in the short term, the beneficial effects on sleep are not sustained over time, with a gradual return of sleep quality indices to initial values following one year[560]. This is understandable as withdrawal alone is not focused on the fundamental issues associated with the hypnotic consumption, namely chronic insomnia. Therefore, effective withdrawal programs may benefit from implementing other therapeutic approaches to address chronic insomnia.

Cognitive-behavioral therapy for insomnia is considered the first line intervention for the management of insomnia in adults given its long-term efficacy[561,562]. CBTi is a multimodal psychological intervention aimed at modifying maladaptive thinking and behaviours that contribute to the perpetuation of insomnia[563] and is highly effective in reducing insomnia severity, improving subjective sleep quality and daytime functioning in diverse populations[208,408,564,565], including older adults[566–568]. Both BZDs[558,569,570] and BZRAs[569,570] withdrawal intervention combined to CBTi program has been shown to reinforce withdrawal success and be more successful in reducing insomnia severity, than standard sedative-hypnotics tapering alone[558,569,570]. However, few studies have assessed the effects of CBTi on both subjective and objective sleep quality during sedative-hypnotic withdrawal in older individuals with chronic insomnia. In addition to investigating subjective sleep quality, describing the

impact on objective sleep quality and brain oscillations is important for understanding the implications for cognitive function in older adults.

The objective of this study was to assess the effect of CBTi on sleep quality during a sedative-hypnotics (BZDs/BZRAs) withdrawal program in older adults with insomnia disorder. Using a RCT design of a sedative-hypnotic withdrawal plan alone (WPo group) or combined with CBTi (WP+CBTi group), our primary outcomes were change in self-reported insomnia severity and sleep quality as well as objective changes in sleep efficiency and spindle density. Secondary outcomes included PSG and sleep diaries-extracted measures of sleep as well as neuropsychological assessments. We expected to observe a greater improvement in sleep objective and subjective outcomes in the combined intervention group (WP+CBTi) than with a sedative-hypnotics withdrawal intervention alone (WPo). We also hypothesized that neuropsychological performances would be greater in the WP+CBTi group compared to the WPo group.

## 3.3 Materials and Methods

### 3.3.1 Participants

Older adults (≥60 years) chronically using sedative-hypnotics for the management of chronic insomnia were recruited from advertisements (both online and in newspapers), Centre de recherche de l'institut universitaire de gériatrie de Montréal (CRIUGM) participant databases, collaborations with primary care and sleep clinics at IUGM, as well as patient associations. Initially, participants underwent a phone screening to determine their eligibility based on inclusion and exclusion criteria.

Inclusion criteria were: participants aged 60 and older; French speaking; with insomnia disorder; and using sedative-hypnotics (either BZDs or BZRAs) to treat their insomnia. Participants meeting the DSM-5 diagnostic criteria for insomnia disorder for at least 3 months were included in the study[213]. The DSM-5 criteria for chronic insomnia disorder are defined as self-reported dissatisfaction with sleep associated with initiating sleep (i.e., sleep onset latency greater than 30 min), difficulties maintaining sleep (i.e., wake after sleep onset greater than 30 min), and/ or early morning awakenings (i.e., final awakening time earlier than desired by at least 30 min), for at least 3 times a week and for more than 3 months, combined with significant

distress or impairments of daytime functioning, despite adequate sleep opportunities. Participants also had to meet a criterion of sedative-hypnotic use (regardless of the dosage): BZDs (Diazepam, Clonazepam, Nitrazepam, Oxazepam, Lorazepam, Temazepam) or BZRAs (Zopiclone) drugs had to be prescribed for insomnia and to be used for more than 3 nights a week for more than 3 months. Averaged consumed doses of BZDs and BZRAs were converted into Diazepam Equivalent Dose, according to the Equivalence Table of BZD in the Ashton Manuel Supplement[499].

Exclusion criteria were as follows: medical conditions affecting cognition (e.g., AD or Parkinson's disease, epilepsy, fibromyalgia, stroke) or sleep (e.g., narcolepsy, sleep apnea with apnea-hypopnea index (AHI) > 15/h, periodic limb movement index (PLMI) during sleep > 15/h, both confirmed by PSG screening); cognitive deficits (dementia or Mini Mental State Examination[500] – MMSE score ≤ 23); sensorimotor deficits (including visual or auditory deficits); active major depression or psychotic disorders (assessed during a structured clinical interview following the Mini International Neuropsychiatric Interview guidelines[571]); active cancer; night shift work or changes in time zones over the past 2 months; alcohol consumption (> 10 drinks/week) or illicit drug use, currently in palliative care.

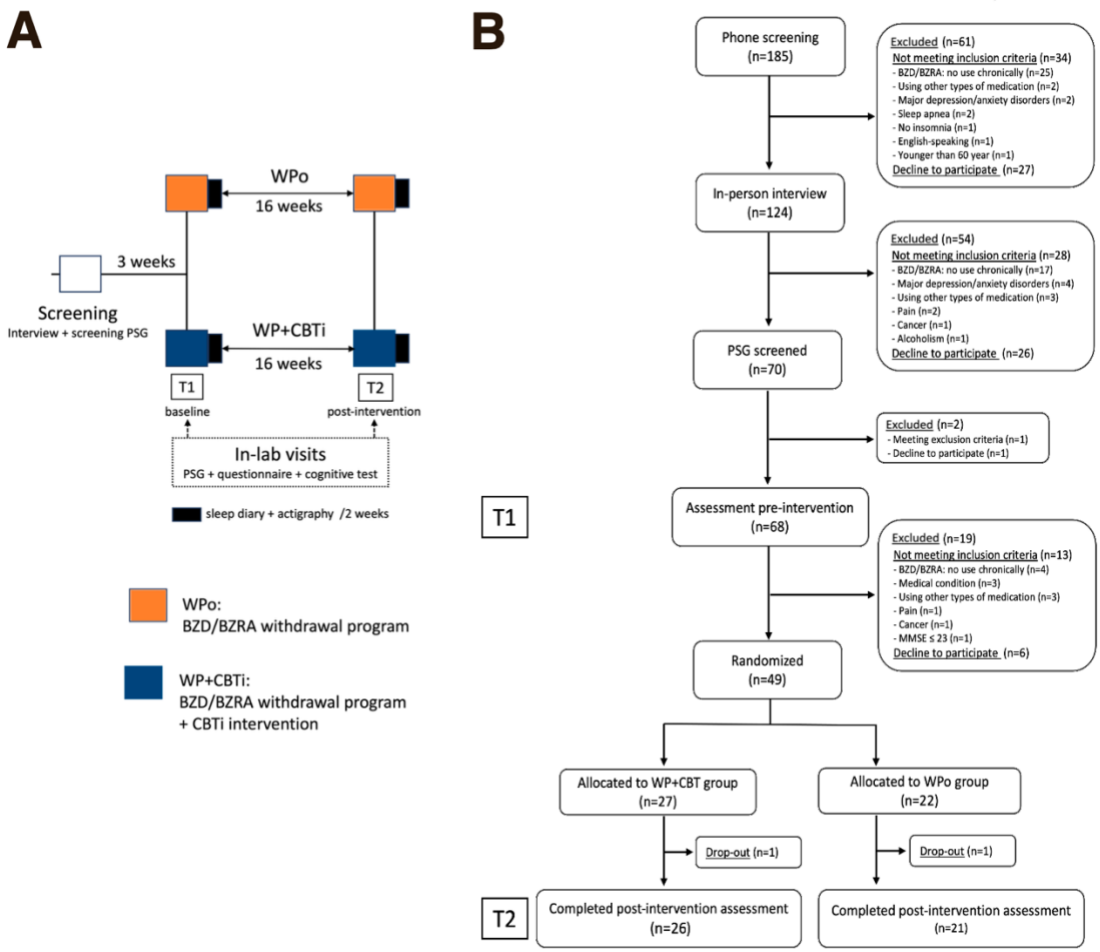


Figure 1: Study Design and participant flow chart

(A) Participant screening included a clinical interview and an overnight PSG to assess exclusion criteria. This first PSG also served as a habituation session to the sleep laboratory environment. At pre-intervention (T1), participants underwent an overnight PSG and the following morning, completed questionnaires and cognitive assessments. Starting from these baseline assessments and continuing over a two-week period, participants completed sleep diaries and wore a wrist actigraphy device. Subsequently, participants were then randomized into either the withdrawal plan combined with CBTi (WP+CBT group) or the withdrawal plan alone group (WPo group). After completing the interventions over a 16-week period (T2), participants underwent the same assessments as during the pre-intervention phase (T1).

(B) Participant consort flow chart

### 3.3.2 Study protocol

Eligible participants were enrolled in a randomised controlled trial comprised of a withdrawal program combined with CBTi-arm (WP+CBTi) and a withdrawal program only control arm

(WPo - see **Figure 1A** for the study design). Within a month after the initial PSG screening, which also served as an adaptation night, participants completed a baseline assessment (T1). The latter included a second PSG recording, and in the following morning, they completed questionnaires and participated in a neuropsychological assessment. Outside the sleep laboratory, participants completed a two-week sleep diary at home while continuously wearing an actigraphy device throughout this period. Participants were then randomized into two groups using a computer-generated randomisation to ensure balanced groups in terms of age, equivalent dose in Diazepam and the duration of hypnotics use. All participants were then enrolled in the withdrawal program. Participants who underwent CBTi simultaneously with the sedative-hypnotics withdrawal plan constituted the WP+CBTi group (n=26), whereas those who only underwent the withdrawal plan constituted the WPo group (n=21).

Sixteen-week post-randomization (T2), participants from both groups came back to the laboratory and underwent the same protocol as the baseline assessment (PSG, neuropsychological assessment, questionnaires) followed by a 2-week sleep diary and actigraphy (see **Figure 1A**).

Following post-interventions (T2), participants in the WPo group received the CBTi intervention. All participants signed a written informed consent form, which was approved by the Comité d'Éthique de la Recherche of the CRIUGM. This study was registered as a clinical trial (ISRCTN10037794), https://www.isrctn.com/ISRCTN10037794).

### 3.3.3 Withdrawal program

The withdrawal plan included an educational brochure, adapted from and tested in a previous RCT[572], providing information on the risks of sedative-hypnotic use and tapering, and recommendations for sleep hygiene. This plan was implemented over a sixteen-week period, during which participants received telephone follow-ups every two weeks. These follow-ups aimed to monitor insomnia progression using the ISI[8,573], assess withdrawal symptoms via the benzodiazepine withdrawal symptom questionnaire[574], and offer support and encouragement. Reported withdrawal symptoms included physical (e.g., tremors, sweating), emotional (e.g., heightened anxiety, irritability), and cognitive (e.g., concentration difficulties) domains. Symptoms were considered severe if the total score exceeded 20. A visual guide illustrated the gradual reduction of sedative-hypnotic intake, starting with whole tablets, then halving the dosage, followed by quarter-tablets, and alternating doses daily, ultimately leading to complete withdrawal. The achievement of complete or partial withdrawal was self-reported by

participants at the post-intervention assessment (T2), where they provided details on the dosage and frequency of sedative-hypnotic use.

### 3.3.4 CBTi intervention

The CBTi intervention was delivered to participants in the WP+CBTi group and to those in the WPo group after completing T2 assessments. It was structured over 16-weeks in 8 group sessions of 90-minutes conducted by a trained psychologist. The first four sessions were given every week, and the last four sessions were separated by two weeks apart. The CBTi program consisted of psychoeducation about sleep and circadian rhythms, stimulus control, sleep restriction, sleep hygiene, cognitive therapy, and relaxation based on Morin & Espie[562]. Each group included 3 to 5 participants, for a total of 7 groups. Randomization process employed non-stratified batches to evenly divided the number of participants from WP+CBTi and WPo. If a participant was unable to join one session, a catch-up session was proposed. All participants from the WP+CBTi completed the 8 sessions.

### 3.4.1 Measures

#### 3.4.1.1 Questionnaires

Participants completed the following sleep-related questionnaires at pre- and post-intervention (T1 and T2) :

*Insomnia Severity Index (ISI)*; the ISI is a 7 Likert-scale self-assessment questionnaire used to assess the nature, severity, and impact of current insomnia symptoms[8,573]. Each item is scored on a scale of 0 to 4, and the total score varies between 0 and 28 (with higher scores indicating more severe insomnia). It overall Cronbach's **α** was 0.82. The change in ISI score was one of our primary outcomes for this study. Participants with an ISI score below 8 post-intervention (T2) were classified as remitters, while those with a reduction of 7 or more in their ISI score were considered responders[575].

*Pittsburgh Sleep Quality Index (PSQI)*; the PSQI is a self-report measure of general sleep quality over the past month. It includes 18 items divided into seven sub- components assessing sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, medication use, and daytime dysfunction. The global score ranges from 0 to 21, with higher scores indicating poorer sleep quality[7]. It overall Cronbach's **α** was 0.65.

*Epworth sleepiness scale (ESS)*; the ESS is a self-administered questionnaire designed to measure an individual's general level of daytime sleepiness during common daily activities. It consists of eight questions, on a 4-point Likert scale. The total score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness[576]. The overall Cronbach's **α** was 0.71.

*Geriatric Anxiety Inventory (GAI)*; the GAI is a self-report measuring anxiety in older adults[577]. It consists of 20 items, covering various symptoms of anxiety, including worry, tension, and physical symptoms. The total score ranges from 0 to 20, with higher scores indicating more severe anxiety symptoms. The overall Cronbach's **α** was 0.89.

*Geriatric Depression Scale (GDS)*; the GDS is a self-report measure designed to assess depression in older adults[578]. It consists of 30 items, covering various symptoms of depression, including mood, and cognitive function. The total score ranges from 0 to 30, with higher scores indicating more severe depressive symptoms. The overall Cronbach's **α** was 0.58.

#### *3.4.1.2 Sleep Diary*

At pre- and post-intervention (T1, T2), participants completed the Consensus sleep diary[10] every morning over two weeks. They reported time spent in bed (TIB), total sleep time (TST), sleep onset latency (SOL), wake duration after sleep onset (WASO), sleep efficiency (TST/TIB*100) and sleep satisfaction (from 1: very bad sleep to 5: very good sleep). For each sleep variable, measures were averaged over 2 weeks at each time point. Only sleep diary data with more than 5 days completed per timepoint were included in the analyses.

#### *3.4.1.3 Actigraphy*

At each time point (T1, T2), participants wore a wrist-wearable accelerometer device (Philips Respironics, Murrysville, USA - Actiwatch) for a period of two weeks to extract TIB, TST, SOL, WASO, SE, by averaging the values over the whole period[15,579]. Bedtime and wake-up time estimates were determined visually by identifying periods of no motor activity and light exposure, cross-referenced with sleep schedules recorded in participant's sleep diaries. For each sleep variable, measures were averaged over 2 weeks at each time point. Only actigraphy data with more than 5 days completed per timepoint were included in the analyses.

### *3.4.1.4 Polysomnographic (PSG) recording*

Whole-night PSG recordings were used at each time point (T1, T2), including electroencephalography (EEG) montage with 15 electrodes (Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, T3, T4, O1, O2, M1, M2) positioned on the scalp according to the 10-20 system AASM guidelines, electromyogram (chin and legs EMG), electrooculogram (EOG), electrocardiogram (ECG). During screening night only, the PSG setup included an oximeter, thoracic and abdominal belts, oral-nasal thermistor, and nasal cannula, to compute the AHI and PLMI and exclude potential sleep disorders. EEG signal was recorded by a Somnomedics amplifier (SomnoMedics, Germany) at a sampling rate of 512 Hz, referenced to Pz online and to contralateral mastoids (M1 and M2) offline for analysis. Only PSG data with > 180min of sleep (TST) recorded per timepoint were included in the analyses.

### *3.4.1.5 EEG analysis*

All sleep scoring was conducted using the Wonambi python toolbox (https://wonambi-python.github.io). EEG analyses were conducted using the Seapipe python toolbox (https://github.com/nathanecross/seapipe). Sleep stages (N1, N2, N3, REM) and wake 30-s epochs scoring as well as the detection of arousal and artefact events were visually scored according to the AASM rules[54]. From the scoring, we computed the calculation at each time point (T1, T2) of: total sleep time (TST; sum of the time spent in different sleep stages), sleep onset latency (SOL; from light off to the first period of sleep), sleep latency to stages (SL), wake after sleep onset (WASO; sum of the nocturnal awakenings duration), time spent in bed (TIB; sum of TST, SOL and WASO), sleep efficiency (SE; TST/TIB*100), arousal density (per epoch of 30 s), sleep fragmentation index (SFI; number of transitions from deep to lighter sleep stages per hour).

Spindles were automatically detected using a validated algorithm[507] and implemented in the Seapipe toolbox. The spindle detection algorithm consisted of computing the root-mean-square (RMS) of the participant-adapted sigma band with a 0.5 s overlap window and smoothed with Gaussian filter[521,580]. For spindle detection, the highest center frequency peak (integral of the Gaussian fit) over the sigma range specific for each subject was obtained[503,504]. Using those participant-specific adapted sigma ranges, we determined with a 2Hz bandwidth the highest peak in the 10 to 13 Hz range for midline frontal (Fz – slow spindle) and the 13 to 16 Hz range for midline parietal (Pz - fast spindle), as well as the midline central electrode (Cz; 12-15 Hz), on artefact-free derivations accounting for spindle frequency gradient[505,506]. RMS were identified as a spindle event when values exceeded a threshold at 2 SD above the mean peak

amplitude. Detection criteria included a spindle duration ranging from 0.5 to 3 s. For spindles detected in NREM (N2 + N3), we extracted the following characteristics: density (i.e., mean number per epoch of 30 s), amplitude (µV), duration (s) and frequency (Hz).

#### *3.4.1.6 Neuropsychological assessment*

The neuropsychological assessment focused on cognitive functions usually impaired in chronic BZD users. Six cognitive dimensions were studied based on a previous study investigating partial improvement post-withdrawal[554]. The neuropsychologist was blinded to the participants' group assignments to avoid bias in evaluating cognitive performance. The neuropsychological assessment lasted approximately one hour and was conducted at pre- and post-intervention (T1, T2), one hour after waking up.

*Digit Symbol Substitution Test (DSST)*; the DSST involves a table with nine numbers, each associated with a geometric symbol[581]. A random series of 140 digits is presented to the participant who must complete it with the corresponding symbols within a maximum of 90 seconds. The number of completed symbols is obtained as a valid measure of attention and concentration, as a scaled score from the Wechsler Adult Intelligence Scale-Third Edition[582].

*Rey complex figure & modified Taylor complex figure tests (MTCF/ROCF);* the MTCF/ROCF assess visual-spatial abilities[583,584]. Both tests consist of two phases: a copy phase, where participants draw a complex figure based on a model, and an immediate recall phase, where they reproduce the figure from memory. For each phase, the time taken to complete each drawing is recorded in seconds, and scaled scores and z-scores are obtained. The z-scores are adjusted for sociodemographic variables (age, education level, and sex; z-score SES) and for the copy time, copy score, and immediate recall score (z-score All)[585]. The MCTF and the ROCF are respectively and randomly counterbalanced between each time point (T1, T2).

The Delis-Kaplan executive function system allows the evaluation of cognitive functions in older adults and combined the color/word interference test as the trail making test (TMT), both used to assess executive function[586].

*Trail making test (TMT)*; the TMT assesses digit and letter recognition alongside visual-motor skills[587]. In the first session (TMT-A), participants connect numbers from 1 to 25, randomly distributed on a sheet, in ascending order as quickly as possible. In the second session (TMT-B), participants alternate between connecting numbers (1 to 13) and letters (A to L) in ascending

and alphabetical order, respectively (1-A-2-B, etc.). Completion times in seconds are recorded, and z-scores are calculated, accounting for age and education level[588].

*Color/word interference test (Stroop)*; this test evaluates attention, verbal inhibition, and flexibility[589]. Initially, participants described the color of cells aloud as quickly as possible (condition 1). Next, they read a series of color names printed in black and white as quickly as possible (condition 2). Then, they were presented with color words printed in a different color (e.g., the word "red" printed in blue) and were asked to identify the color of the ink (condition 3). In the final component, participants stated the word itself when it was framed and the color of the ink when it was not framed (condition 4). For each condition, completion times were recorded in seconds, and scaled scores were obtained from Appendix D of the Examiner Manual.

*French adaptation of the 16-items free and cued selective reminding test (FCSRT)*; the FCSRT is used to measures difficulties in verbal episodic memory[590]. During the encoding phase, sixteen items were presented to the participant who must memorize and retrieved it over immediate and delayed recall, first cued and then free recall. Participant underwent three phases of free and cued recall. The number of words retrieved during the three phases of immediate free and cue recall (with a maximum of 48) and the delayed free and cue recall (with a maximum of 16) were reported. For the free score and the delayed free score recall score, z-score calculated controlling for age, sex and education level[591].

*Purdue Pegboard Test (PPT)*; the PPT measures manual dexterity and bimanual coordination[592]. Participants are presented with a perforated board containing two rows of twenty-five holes and are instructed to place as many sticks as possible into the holes within thirty seconds, using their dominant hand (condition 1), non-dominant hand (condition 2), and both hands (condition 3). For each condition, the total number of sticks placed is recorded, and z-scores are calculated to account for age and sex[593].

### 3.4.2 Statistical analyses

Statistical analyses were performed using RStudio 1.2.50 (RStudio, Inc., Boston, MA) and R package (ggplot2, sjstats, sjmisc, forcats, emmeans, rstatix, lme4, ltm).

Our primary outcomes were derived from questionnaires (ISI score), 2-week sleep diaries (SE), and PSG-derived measures (SE and spindle density). Secondary outcomes include changes in additional self-reported questionnaire scores, 2-week sleep diary and actigraphy averaged sleep

measures, other PSG-derived measures and neuropsychological performances. The sedative-hypnotics withdrawal success was also included, as the percentage decrease of self-reported sedative-hypnotics consumption from baseline (T1) to post-intervention (T2) for each participant, as well as the proportion of participants achieving completion of the withdrawal program in each group.

We used mixed-model analyses of variance (ANOVA), with Time as within-subject factor (T1 vs T2) and Group as between-subject factor (WPo vs WP+CBTi) on every outcome to assess the impact of both interventions. Per-protocol analyses were conducted considering variability in attrition depending on the measures completed. Non-parametric tests were used (WTS, Wald Test Statistic for small sample size) on variables with no homogeneous variance and anormal distribution.

Exploratory bivariate Spearman's Rho correlations were conducted between the change in sedative-hypnotics dose and changes in primary outcomes in each group to investigate the effects of CBTi in the relationship between change in sedative-hypnotics use and changes in subjective and objective sleep.

Normality of distribution was checked with Shapiro tests and homogeneity of variance was tested with Levene tests. Effect sizes were calculated using Hedges's g, indicating the degree of change over time (within-group effect) (corrects for small sample size). The level of significance was set to a p-value of <.05 and p-values were adjusted for multiple comparisons (Benjamini-Hochberg/FDR correction). For significant results, both raw ($p$) and adjusted p-values ($q$) were reported when necessary.

## 3.4 Results

Participant demographics are presented in **Table 1**. Forty-nine individuals with chronic use of sedative-hypnotics for chronic insomnia were randomized to either the withdrawal program combined to CBTi (WP+CBTi group – N= 27) or the withdrawal program only (WPo group – N= 22). Participants were older adults (69.1 ± 6.2 y.o) chronically using BZDs/BZRAs (dose equivalent in Diazepam: 7.1 ± 7.9 mg/week; duration: 9.7 ± 8.0 years). They were in majority female (70.2%) and most held a university diploma (mean 14.7 ± 2.4 education years). The majority of participants used BZRAs (Zopiclone: 68%), while a smaller proportion used BZDs, including Oxazepam: 13%, Lorazepam: 9%, Clonazepam: 4%, Nitrazepam: 4% and Temazepam: 2%.

We did not find any difference between the WP+CBTi and WPo groups regarding age, sex, education years, sedative-hypnotics dose and duration, as well as anxiety, depression and sleep quality (ISI, PSQI) levels (t-test, Wilcoxon test, Fisher test; all $p>.05$).

### 3.4.1 Participant adherence and primary outcome attrition

During the intervention, 2 participants (N=1 from WP+CBTi; N=1 from WPo) dropped out of their participation to the project (see **Figure 1B**). At 16 weeks post-randomization (T2), 26 participant (attrition rate 3.7%) from the WP+CBTi group and 21 participants (attrition rate 4.6%) from the WPo group filled the ISI questionnaire (primary outcome). Regarding self-reported SE, 25 participants (attrition rate 7.4%) from the WP+CBTi group and 19 participants (attrition rate 9.5%) from the WPo group filled sleep diaries at 16 weeks post-randomization (T2). Regarding objective SE and spindle density obtained from PSG recordings, 25 participants (attrition rate 7.4%) from the WP+CBTi group and 20 participants (attrition rate 9.1%) from the WPo group completed overnights at 16 weeks post-randomization (T2). Attrition rates of the secondary measures can be found in Supplemental materials.

### 3.4.2 Effect of both interventions on self-reported sedative-hypnotic discontinuation

A Time effect was found on the sedative-hypnotic dose ($F(2,47)=135$, $p<.001$), where the self-reported dose was significantly reduced in both the WPo (dose T2 - T1: -4.6 ± 3.4 mg/week; $p<.001$) and the WP+CBTi groups (dose T2-T1: -5.6 ± 5.8 mg/week; $p<.001$) (see **Figure 2A** and **Table 2**). We did not find significant differences between groups following sedative-hypnotic discontinuation (T2); and no interaction between Time and Group (all $p>.05$). We also did not find group differences in the percentage of reduction in sedative-hypnotic consumption (WPo: 82.8 ± 32.2 %; WP+CBTi: 81.7 ± 30.6 %; $p=.73$), or in the proportion of participants achieving complete tapering (WPo: 71.4 ± 4.6 %; WP+CBTi: 65.4 ± 4.9 %; $p=.76$).

In the WP+CBTi group, out of 27 participants, 1 (3.7%) was not successful at reducing their consumption of sedative-hypnotics, while 2 participants (9%) from the WPo group did not reduce their BZD/BZRA use. Additional analyses indicate that sedative-hypnotic dose at baseline is negatively associated with the percentage reduction in self-reported consumption after both interventions (WP+CBTi: $r=-.5$; $p<.001$ - **Figure S1** in **Appendix B**; WPo: $r=-.3$; $p=.04$). Furthermore, higher levels of depression (WP+CBTi: $r=.01$; $p=.97$; WPo: $r=-.5$; $p=.03$) and anxiety (WP+CBTi: $r=-.07$; $p=.75$; WPo: $r=-.6$; $p=.002$) at baseline (T1) were linked to a lower success rate in withdrawal in the WPo group only.

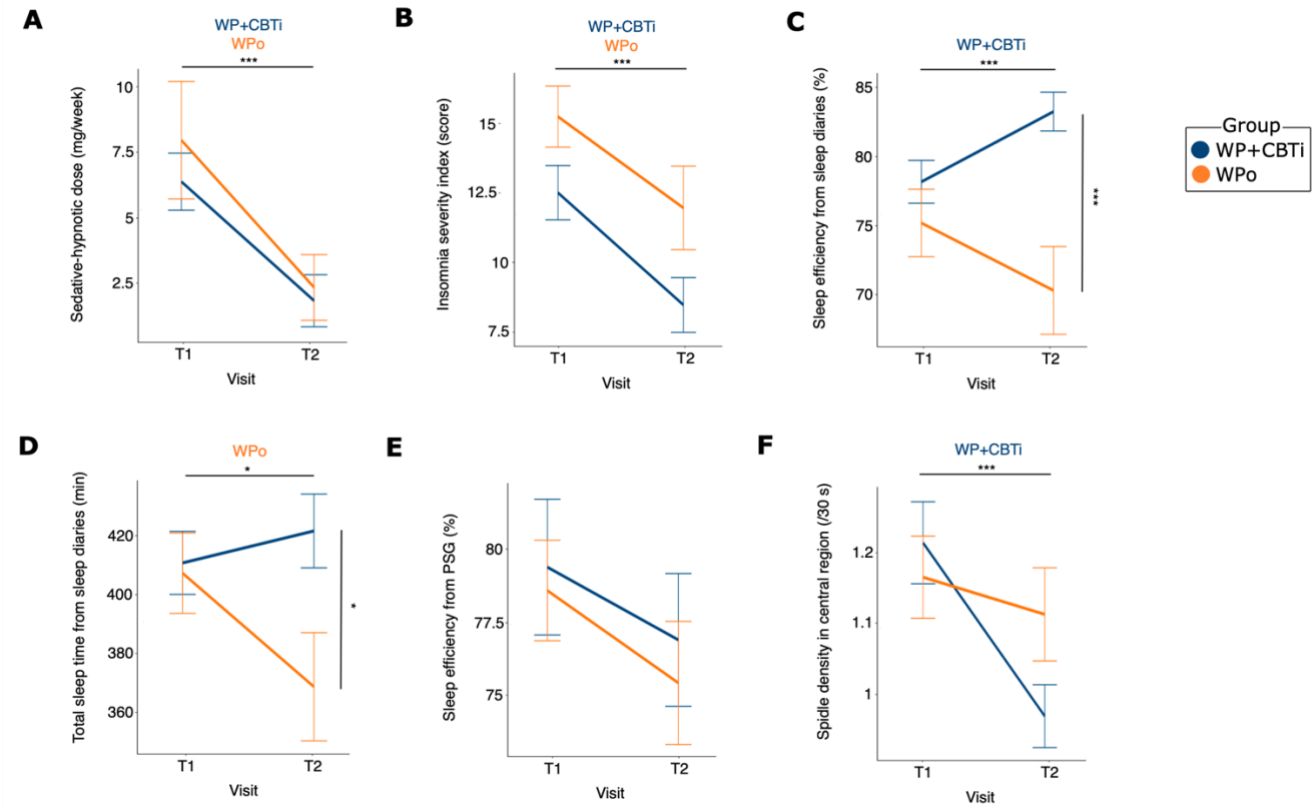


Figure 2: Sedative-hypnotic dose and sleep parameters changes at post-intervention

*(A) Sedative-hypnotic dose consumption was reduced post-intervention for both groups*

*(B) Insomnia severity was reduced post-intervention in both groups*

*(C) Sleep efficiency from sleep diaries increased in CBTi with difference between groups at T2 following withdrawal*

*(D) Total sleep time from sleep diaries decreased in withdrawal alone with difference between groups at T2*

*(E) Sleep efficiency from polysomnography (PSG) did not change post-intervention*

*(F) Spindle density in central region was reduced in CBTi following withdrawal*

*Asterisks represent significance (p): *<.05; **<.01; ***<.001*

### 3.4.3 Effect of both interventions on subjective sleep quality

At 16-week post-randomization, per-protocol analysis showed a Time effect for ISI score ($F(2,47)=31.1$, $p<.001$, $q=.004$ – **Figure 2B**), where both the WP+CBTi and the WPo groups displayed reduced insomnia severity at T2 compared to T1 (all $p<.001$) (see **Table 2**). The WPo group exhibited a moderate change in ISI scores (g'=.5), whereas the WP+CBTi group showed a large change (g'=.8). A Group effect ($F(2,47)=4.5$, $p=.04$, $q=.08$) was found, however, it did

not survive correction for multiple comparisons. No significant interaction between Time and Group was observed ($p$>.05). Post-hoc analyses did not show significant Group difference at T1 and T2 (all $p$<.05). In the WP+CBTi group, 7 out of 26 participants (26.9%) were considered as responders (ISI score reduced by at least 8 point at T2) and 12 (46.2%) were considered in remission (ISI score below 8 at T2). Meanwhile, in the WPo group, 3 out of 21 participants (14.3%) were considered as responders and 7 (33.3%) were considered in remission. There were no significant Group differences in the number of participants responders or in remission at T2 (all $p$>.05).

Concerning change in PSQI score (WP+CBTi N=26; WPo N=21), we found a Time effect ($F$(2,47)=9.8, $p$=.003, $q$=.01– **Table 2**) driven by a significant reduction in PSQI score in WP+CBTi group only (-23%, $p$=.003, g'=.6; WPo: -9% $p$>.05, g'=.2). However, we found no Time*Group interaction ($F$(2,47)=2.5, $p$>.05) or Group effect ($F$(2,47)=2.9, $p$>.05).

No associations were observed between change in sedative-hypnotic dosage and change in ISI or PSQI scores in both groups (all $p$>.05).

Regarding self-reported SE from sleep diary (WP+CBTi N=25; WPo N=19), per-protocol analysis revealed a significant Group*Time interaction ($F$(2,44)=11.4, $p$=.002, $q$=.008) as well as a Group effect ($F$(2,44)=9.4, $p$=.004, $q$=.02) (see **Figure 2C - Table 2**). The increase in SE was only observed in the WP+CBTi group (+6.5%; $p$=.004, g'=-.7; WPo: -6.5%, $p$>.05, g'=.4) with a significant difference between groups at T2 ($p$=.001). There was a significant Group*Time interaction ($F$(2,44)=8.5, $p$=.006, $q$=.03) but no Group or Time effect (all $p$>.05) for self-reported sleep duration due to a decrease in TST in the WPo group only (-9.5%; $p$=.02, g'=.5; WP+CBTi: +2.6%, $p$>.05, g'=-.2) with a significant difference between the groups at T2 ($p$=.02) (see **Figure 2D**). While we found no Time*Group interaction ($F$(2,44)=1.1, $p$>.05) or Time effect ($F$(2,44)=2.1, $p$>.05), we observed a significant Group effect ($F$(2,44)=14.1, $p$<.001, $q$=.005) on sleep satisfaction, where post-hoc tests indicated significant differences between groups at both T1 ($p$=.01) and T2 ($p$=.001). We found a significant Group*Time interaction on WASO, although it did not pass multiple comparison ($F$(2,44)=4.5, $p$=.03, $q$=.08), due to an increase WPo group only (-28.2%; $p$=.04, g'=-.3; WP+CBTi: -13.9%, $p$>.05, g'=.2) with a significant difference between groups at T2 ($p$=.02). Analyses of self-reported questionnaire scores (GAI, GDS, ESS) and other measures of sleep (e.g., wake duration, latency) using sleep diaries did not reveal any significant interaction or main effect of Time or Group (all $p$>.05) and displayed none-to-small effect size (g'<0.3; see **Table 2**). No association

was found between change in SE and change in sedative-hypnotic dosage at post-intervention in both groups (all $p>.05$).

### 3.4.4 Effect of both interventions on objective sleep

Per-protocol analysis from PSG-related measures (WP+CBTi N=15; WPo N=12) revealed no changes in the primary outcome SE ($p<.05$) (see **Figure 2E**). We also did not find any effects of Group and Time on additional sleep architecture measures or averaged sleep measure extracted from actigraphy (WP+CBTi group: n=25; WPo group: n=20) (all $p<.05$) (see **Table 2** and **Table S1** in **Appendix B**). Further analyses per sleep stage N2 and N3 separately, are also presented in **Appendix B**.

### 3.4.5 Effect of both interventions on sleep spindle characteristics

Regarding changes in sleep spindle density (primary outcome), per-protocol analysis (WP+CBTi N=23; WPo N=20) indicated a significant Time effect of spindles detected during NREM sleep in the central region ($F(2,43)=8.9$, $p=.005$, $q=.01$; see **Figure 2F**), primarily driven by a reduction in spindle density in the WP+CBTi group only (-19.8%, $p<.004$, g'=1; WPo: -5.1%, $p>.05$, g'=.2) (see **Table S3** in **Appendix B**). Similar results were found per stage (see **Appendix B**).

Further analyses revealed that the decrease in central spindle density in WPo correlated with the reduction in the sedative-hypnotic dose consumed ($r=.5$; $p=.04$ - **Figure S2** in **Appendix B**). However, similar correlation was not found in the WP+CBTi group ($p>.05$).

We observed no interaction or main effects of Group or Time on central spindle characteristics (i.e., duration, amplitude, peak frequency).

### 3.4.6 Effect of both interventions on cognitive performance

There were no significant interactions or main effects of Time or Group with none-to-small effect size on neuropsychological performance (all $p<.05$ and g'<.2) (see **Table S2** in **Appendix B**).

## 3.5 Discussion

This two-arm RCT investigated the effects of CBTi on both subjective and objective measures of sleep quality, as well as cognitive function, during sedative-hypnotic withdrawal in older individuals with chronic insomnia. Both groups resulted in a significant reduction in sedative-hypnotic dosage, with participants achieving an 80% decrease post-intervention. Both groups also decreased insomnia severity from baseline to follow-up. Additionally, the combination of CBTi intervention and sedative-hypnotic withdrawal enhanced self-reported sleep quality (SE) from sleep diaries and prevented a decline in sleep duration (TST) and the trend toward increased nocturnal awakenings (WASO) observed after withdrawal alone. Neither intervention resulted in changes to cognition or sleep architecture objective assessment. However, both interventions were associated with a reduction in spindle density.

The withdrawal program successfully achieved sedative-hypnotic withdrawal. Similarly, previous research showed that older adults with insomnia experienced equivalent success rates when discontinuing sedative-hypnotics, whether through withdrawal alone or combined with CBTi[594,595] or self-help CBTi[596] at post-intervention. Our findings demonstrate that gradual dose reduction is effective in reducing sedative-hypnotic use, with CBTi not appearing to enhance an already high withdrawal success rate. The high success rate in the withdrawal alone condition suggests a potential ceiling effect, limiting the impact of CBTi on further improvement[594–596]. The withdrawal intervention, without the inclusion of CBTi, likely benefited from regular telephone follow-ups, which provided support, reinforced motivation and contributed to the success of the withdrawal process. This could be due to the fact that CBTi is not primarily designed to target sedative-hypnotic consumption[91,92]. Other factors also contribute to withdrawal success. For instance, a lower dose of sedative-hypnotics at baseline was associated with a higher discontinuation rate post-intervention, which is consistent with previous findings[598]. In the present study, participants with higher baseline anxiety and depression showed the lowest withdrawal success in withdrawal alone. Psychological distress, readiness to change, and self-efficacy also influence sedative-hypnotic discontinuation in individuals with chronic insomnia[599]. However, motivation may still play a role in the challenges associated with withdrawal success[600].

We observed a reduced insomnia severity following sedative-hypnotic withdrawal, with a moderate effect for withdrawal alone and a large effect when combined with CBTi. In line with these findings, a prior study reported a similar reduction in ISI scores among older adults who

received CBTi, either alone or combined with sedative-hypnotic tapering, compared to withdrawal alone and sustained at the 12-month follow-up[96]. Other studies did measure insomnia severity and observed a reduction following sedative-hypnotic withdrawal, either alone or in combination with CBTi[97]. These findings challenge the long-term efficacy of BZD and BZRA in managing insomnia, as their discontinuation did not overall exacerbate symptoms in our participants. Instead, insomnia severity declined. Likewise, sedative-hypnotics withdrawal had no adverse impact on anxiety[601]. While in this study, insomnia severity improved post-withdrawal regardless of CBTi therapy, there was a stronger benefit after CBTi. The positive impact of combining CBTi and withdrawal on insomnia severity may become more apparent over time[601]. For example, in older adults receiving sedative-hypnotic withdrawal alone, the occurrence of rebound of insomnia symptoms was found at post-intervention; however, self-reported sleep quality improved at the follow-up six-months later[38]. However, our study design did not include a long-term follow-up assessment to determine whether CBTi could be more effective in managing insomnia and preventing relapse. Future studies should further describe the long-term effect of combined interventions on self-reported sleep quality and insomnia severity.

Nevertheless, the combination of CBTi and withdrawal showed benefits by improving self-reported sleep quality, as seen in the reduced PSQI score and increased SE from sleep diaries. No such improvements were observed with withdrawal alone. Another study found that both the combined intervention and CBTi intervention alone leaded to an increased SE from sleep diaries in older adults[32]. The beneficial effect of combined interventions on self-reported sleep quality was also reported in adult and middle-aged adults with chronic insomnia through questionnaire or sleep diaries[38]. Furthermore, the long-term benefits of CBTi were sustained at one- and two-year follow-ups, whether delivered independently or alongside sedative-hypnotic tapering, in older adults with chronic insomnia[603]. Yet, it has also been observed that sedative-hypnotic discontinuation in adults with chronic insomnia also leads to self-reported improvements in sleep quality, as recorded in sleep diaries two-weeks post-intervention[553]. However, sleep quality scores remained lower compared to those reported by controls without sleep disorders. Overall, the evidence suggests that CBTi interventions may improve various subjective sleep dimensions following withdrawal of sedative-hypnotics, enhancing both overall sleep quality (PSQI) and insomnia severity (ISI).

In addition, CBTi effectively prevented the decline in sleep duration typically observed with sedative-hypnotic withdrawal. However, the significant change in TST was observed only in withdrawal alone, despite no change in SE. Notably, sedative-hypnotic withdrawal, whether combined with CBTi or as a standalone intervention, has been reported to reduce TST while improving SE[558]. By including strategies to consolidate sleep by aligning TIB more closely with actual sleep needs, CBTi improves the quality of sleep rather than its duration, which explains why SE improves without a corresponding increase in TST. In contrast, older adults undergoing tapering, either alone or with CBTi, showed increased TST and SE[594], highlighting the need for further research on how combining CBTi with withdrawal affects sleep duration.

The withdrawal program combined with CBTi did not improve objective sleep quality, as measured by PSG recordings and actigraphy data post-intervention, nor did either intervention alone. Aligning with the general CBTi research, this finding is not surprising. CBTi interventions did not have an effect on objective PSG measures in middle-aged adults with chronic insomnia[208]. Meta-analyses suggest that improvements in sleep quality following CBTi are more consistently detected through self-reported assessments than through objective measures like actigraphy or PSG[393,604].

Objective assessment of sleep quality via PSG after a CBTi intervention are limited in the literature. Only small changes were found in PSG outcomes following sedative-hypnotic withdrawal, whether alone or combined with placebo biofeedback or CBTi. Specifically, reduced TST and SE were observed following all three interventions[594]. Another study involving older adults receiving a withdrawal plan with or without CBTi reported increased N3 and REM duration, while TST and N2 duration decreased post-intervention, although no significant group effect was observed[558]. Similar to subjective sleep, is possible that improvements in objective sleep quality may emerge with a delay, as one study showed that sleep quality could improve two weeks after sedative-hypnotic withdrawal[553]. However, these improvements were not sustained over time, as sleep quality returned to baseline after one-year follow-up[558,594].

The CBTi intervention combined to sedative-hypnotic withdrawal was effective in reducing spindle density in the central region. Chronic BZDs use has been found to increase spindle density in adults[522], which may explain the observed decrease in spindle density following discontinuation of long-term sedative-hypnotic use. Although such a reduction was not

observed following sedative-hypnotic withdrawal alone, the decrease in spindle density correlated with the reduction in the sedative-hypnotic dose consumed. This is the first study to report this effect, the clinical significance of which remains to be further investigated.

No effects on cognitive functioning were observed following sedative-hypnotics withdrawal combined to CBTi and withdrawal alone. In the short-term, CBTi has been shown to not change objective cognitive assessment[605]. In middle-aged adults with chronic insomnia, CBTi did not influence either the objective or subjective measures of cognitive functioning[208]. A study reported an increase in self-reported cognitive function following CBTi in middle-aged adults, while no improvement was captured through objective cognitive assessments[606]. Discrepancies exist between subjective reports of daytime impairment — commonly reported among individuals with chronic insomnia — and objective neuropsychological performance[607]. This may account for the lack of cognitive changes following both interventions. There is a lack of research investigating the ideal post-intervention assessment period that is necessary to capture cognitive improvements that may emerge over a longer timeframe. Literature is also lacking in describing the effects of combining CBTi with sedative-hypnotics withdrawal, as well as withdrawal alone, on cognition. Sedative-hypnotic withdrawal in older adults with chronic use improved information processing speed and accuracy at post-intervention[555]. A meta-analysis reported cognitive improvements following sedative-hypnotic withdrawal in chronic users[554,556]. However, impairments, particularly in verbal memory persisted when compared to controls or normative data. Furthermore, sedative-hypnotics withdrawal in older adults was found associated with prolonged impairment in attentional and psychomotor cognitive functions, sustained for at least six months post-intervention[559].

Following the withdrawal intervention, both groups showed equivalent outcomes, regardless of CBTi inclusion. While the response rate (>7-point reduction in the ISI) was low (26%), remission (ISI score <8 at post-intervention) was high (46%). This suggests that remission occurred even without reaching the typical score reduction threshold used to define treatment response. This likely reflects that many participants did not have severe insomnia at baseline (ISI < 22).

The findings may be influenced by several limitations. First, the sample size was limited and consisted of a majority of females (F = 70%), not allowing for sex differences analysis. Second, the description of the combined intervention's impact on outcomes may require adding a CBTi

intervention alone group, which was not included in this study. Third, the dosage of sedative-hypnotics was self-reported, and we did not conduct urine toxicology screening to objectively assess the dose used and could lead to inaccurate withdrawal success rate. Fourth, missing data limited complete observation. For example, discrepancies were noted between the changes in SE from self-report SE and actigraphy, limited analysis of sleep misperception—which has been shown to be significantly impact by CBTi[208]. Finally, the long-term effects of the combined intervention on sleep quality and cognition were not assessed here.

In conclusion, effective sedative-hypnotic withdrawal resulted in a reduction in insomnia severity. When combined with a CBTi intervention, this additionally improved subjective sleep quality and prevented decreases in sleep duration induced by sedative-hypnotic discontinuation. Neither intervention, however, significantly impacted objective sleep architecture or cognitive performance. Furthermore, reductions in sleep spindle density may be attributed to CBTi, but further investigation is needed to clarify these findings.

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## 3.6 Tables

### Table 1: Demographics

| | WP+CBTi group | | WPo group | |
|---|---|---|---|---|
| Characteristics | range | Mean ± SD | range | Mean ± SD |
| N | | 26 | | 21 |
| Age | [61-90] | 70.39 ± 6.4 | [61-84] | 67.52 ± 5.8 |
| Sex | | | | |
| Female \| Male | 18 \| 8 | | 15 \| 6 | |
| % | 69.2 | 30.8 | 71.4 | 28.8 |
| Education years | [8 - 19] | 14.5 ± 2.5 | [11 - 20] | 14.9 ± 2.3 |
| Sedative-hypnotic consumption | | | | |
| Duration [years] | [1 - 23] | 9.6 ± 7.1 | [1 - 35] | 9.8 ± 9.2 |
| Dose equivalent in Diazepam [mg/week] | [0.8 - 25] | 6.4 ± 5.7 | [2.5 - 59] | 8.0 ± 10.3 |
| Score at T1 | | | | |
| Psychiatric comorbidities | | | | |
| ESS [/24] | [0 - 18] | 4.8 ± 3.9 | [2 - 10] | 5.0 ± 2.7 |
| GAI [/20] | [0 - 17] | 7.4 ± 5.3 | [0 - 17] | 6.2 ± 5.2 |
| GDS [/30] | [0 - 18] | 7.4 ± 5.1 | [1 - 21] | 9.3 ± 5.8 |
| MMSE [/30] | [24 - 30] | 27.8 ± 1.9 | [25 - 30] | 28.3 ± 1.7 |
| ISI [/28] | [2 - 23] | 12.5 ± 5.0 | [7 - 26] | 15.2 ± 5.0 |
| PSQI [/21] | [4 - 18] | 10.7 ± 3.7 | [7 - 18] | 11.4 ± 3.3 |

ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; GAI, Geriatric Anxiety Inventory; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; WPo, sedative-hypnotics withdrawal plan group; WP+CBTi, CBTi combined to sedative-hypnotics withdrawal plan

Table 2: Self-reported sleep quality from diaries, questionnaires and PSG-related outcomes

| | | WP+CBTi group | | WPo group | | Cohen g' (T1 vs T2) | | Time*Group | | | Time | | | Group | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome measure | (N) | Mean | SD | Mean | SD | WP+CBTi | WPo | F | *p* | *q* | F | *p* | *q* | F | *p* | *q* |
| **Questionnaires** (26 WP+CBTi vs 21 WPo) | | | | | | | | | | | | | | | | |
| ISI [score/28] | T1 | 12.5 | 4.97 | 15.24 | 5.04 | 0.78 | 0.48 | 0.33 | 0.57 | - | 31.05 | <0.001 | **0.004*** | 4.5 | **0.04** | 0.08 |
| | T2 | 8.46 | 5.02 | 11.95 | 6.89 | | | | | | | | | | | |
| PSQI [score/21] | T1 | 10.69 | 3.66 | 11.43 | 3.34 | 0.64 | 0.22 | 2.5 | 0.12 | - | 9.82 | 0.003 | **0.01*** | 2.87 | 0.10 | - |
| | T2 | 8.23 | 3.79 | 10.62 | 3.58 | | | | | | | | | | | |
| ESS [score/24] | T1 | 4.81 | 3.87 | 5.05 | 2.65 | -0.07 | 0.04 | 0.62 | 0.43 | - | 0.01 | 0.91 | - | 0.13 | 0.72 | - |
| | T2 | 5.12 | 4.24 | 4.9 | 3.27 | | | | | | | | | | | |
| GAI [score/20] | T1 | 7.38 | 5.28 | 6.24 | 5.19 | 0.18 | 0.07 | 0.08 | 0.77 | - | 1.74 | 0.19 | - | 0.66 | 0.42 | - |
| | T2 | 6.46 | 4.67 | 5.81 | 6.33 | | | | | | | | | | | |
| GDS [score/30] | T1 | 7.04 | 5.09 | 9.33 | 5.8 | -0.01 | 0.32 | 2.89 | 0.09 | - | 3.64 | 0.06 | - | 0.48 | 0.49 | - |
| | T2 | 7.08 | 5.58 | 7.29 | 6.3 | | | | | | | | | | | |
| **Sleep diaries** (25 WP+CBTi vs 19 WPo) | | | | | | | | | | | | | | | | |
| Mean SE (%) | T1 | 78.18 | 7.75 | 75.2 | 10.64 | -0.66 | 0.37 | 11.36 | 0.002 | **0.01*** | <0.01 | 0.95 | - | 9.37 | 0.004 | **0.02*** |
| | T2 | 83.26 | 7.03 | 70.32 | 13.85 | | | | | | | | | | | |
| Mean TIB (min) | T1 | 526.45 | 51.51 | 546.49 | 62.37 | 0.36 | 0.34 | 0.01 | 0.90 | - | 6.72 | **0.01** | 0.05 | 1.59 | 0.21 | - |
| | T2 | 507.06 | 53.38 | 525.18 | 58.15 | | | | | | | | | | | |
| Mean TST (min) | T1 | 410.81 | 53.48 | 407.32 | 59.47 | -0.18 | 0.51 | 8.48 | 0.01 | **0.03*** | 2.66 | 0.11 | - | 2.61 | 0.11 | - |
| | T2 | 421.67 | 62.66 | 368.75 | 80.07 | | | | | | | | | | | |
| Mean SOL (min) | T1 | 32.07 | 27.08 | 31.14 | 25.84 | 0.25 | -0.27 | 3.53 | 0.06 | - | 0.07 | 0.79 | - | 1.15 | 0.28 | - |
| | T2 | 25.57 | 24.74 | 43.68 | 45.93 | | | | | | | | | | | |
| Mean WASO (min) | T1 | 32.06 | 21.39 | 42.76 | 30.21 | 0.22 | -0.3 | 4.52 | **0.03** | 0.08 | <0.01 | 0.98 | - | 3.19 | 0.07 | - |
| | T2 | 27.59 | 22.7 | 54.81 | 39.83 | | | | | | | | | | | |
| Mean Sleep satisfaction (/5) | T1 | 3.1 | 0.59 | 2.62 | 0.43 | -0.35 | -0.08 | 1.09 | 0.30 | - | 2.09 | 0.15 | - | 14.12 | <0.001* | **0.005*** |
| | T2 | 3.35 | 0.68 | 2.65 | 0.38 | | | | | | | | | | | |
| **Polysomnography** (25 WP+CBTi vs 20 WPo) | | | | | | | | | | | | | | | | |
| SE (%) | T1 | 79.36 | 11.74 | 78.55 | 7.78 | 0.21 | 0.35 | 0.04 | 0.84 | - | 3.09 | 0.08 | - | 0.18 | 0.67 | - |
| | T2 | 76.84 | 11.49 | 75.35 | 9.53 | | | | | | | | | | | |
| TIB (min) | T1 | 498.48 | 52.5 | 512.25 | 43.69 | -0.08 | 0.42 | 2.14 | 0.15 | - | 0.86 | 0.36 | - | 0.05 | 0.83 | - |
| | T2 | 502.6 | 48.55 | 493.95 | 38.81 | | | | | | | | | | | |
| TST (min) | T1 | 393.68 | 62.66 | 402.3 | 51.1 | 0.1 | 0.5 | 1.11 | 0.29 | - | 2.92 | 0.09 | - | 0.02 | 0.88 | - |
| | T2 | 386.84 | 73.39 | 373.4 | 59.62 | | | | | | | | | | | |
| WASO (min) | T1 | 77.2 | 58.76 | 82.6 | 42.42 | -0.23 | -0.15 | 0.55 | 0.46 | - | 3.59 | 0.06 | - | 0.47 | 0.49 | - |
| | T2 | 90.08 | 46.37 | 89.1 | 39.26 | | | | | | | | | | | |
| SOL (min) | T1 | 18.6 | 18.41 | 12.7 | 13.67 | -0.09 | -0.43 | 1.43 | 0.23 | - | 2.41 | 0.12 | - | 0.71 | 0.40 | - |
| | T2 | 20.28 | 19.62 | 20 | 18.08 | | | | | | | | | | | |
| SL to N2 (min) | T1 | 20.8 | 18.55 | 15.6 | 13.71 | -0.07 | -0.34 | 0.54 | 0.46 | - | 0.55 | 0.46 | - | 0.47 | 0.49 | - |
| | T2 | 22.16 | 20.15 | 21.45 | 18.33 | | | | | | | | | | | |
| SL to N3 (min) | T1 | 37.28 | 28.42 | 32.8 | 21.65 | -0.46 | -0.28 | 0.41 | 0.52 | - | 5.24 | **0.02** | 0.31 | 1.21 | 0.27 | - |
| | T2 | 52.6 | 35.43 | 43.1 | 44.28 | | | | | | | | | | | |
| SL to REM (min) | T1 | 128.32 | 61.8 | 132.85 | 70.19 | -0.09 | 0.37 | 1.44 | 0.23 | - | 0.27 | 0.60 | - | 0.19 | 0.66 | - |
| | T2 | 134.24 | 67.02 | 110.9 | 39.75 | | | | | | | | | | | |
| SL to NREM (min) | T1 | 24.04 | 18.46 | 16.95 | 13.65 | -0.23 | -0.4 | 0.79 | 0.38 | - | 1.04 | 0.31 | - | 1.15 | 0.28 | - |
| | T2 | 29.6 | 25.89 | 23.75 | 18.28 | | | | | | | | | | | |
| N1 (% TSP) | T1 | 2.12 | 1.56 | 2.55 | 1.36 | -0.12 | -0.12 | 0.02 | 0.90 | - | 0.16 | 0.69 | - | 1.61 | 0.21 | - |
| | T2 | 2.32 | 1.68 | 2.75 | 1.74 | | | | | | | | | | | |
| N2 (% TSP) | T1 | 37.44 | 8.6 | 38.8 | 8.99 | -0.02 | 0.45 | 2.27 | 0.14 | - | 1.91 | 0.17 | - | 0.2 | 0.65 | - |
| | T2 | 37.64 | 8.69 | 34.25 | 10.48 | | | | | | | | | | | |
| N3 (% TSP) | T1 | 27.96 | 8.06 | 25.3 | 6.58 | 0.32 | -0.14 | 1.39 | 0.25 | - | 0.24 | 0.63 | - | 0.2 | 0.66 | - |
| | T2 | 25.28 | 8.2 | 26.4 | 8.46 | | | | | | | | | | | |
| REM (% TSP) | T1 | 16.48 | 5.7 | 16.75 | 5.16 | 0.14 | -0.09 | 0.56 | 0.46 | - | 0.03 | 0.86 | - | 0.46 | 0.50 | - |
| | T2 | 15.68 | 5.08 | 17.25 | 5.58 | | | | | | | | | | | |
| Wake (% TSP) | T1 | 16.08 | 11.03 | 16.7 | 8.14 | -0.28 | -0.29 | 0.13 | 0.72 | - | 3.75 | 0.05 | - | 0.27 | 0.60 | - |
| | T2 | 19.2 | 10.33 | 19.35 | 9.15 | | | | | | | | | | | |
| SFI | T1 | 7.28 | 3.86 | 7.85 | 2.41 | -0.07 | -0.23 | 0.53 | 0.46 | - | 2.37 | 0.12 | - | 1.57 | 0.21 | - |
| | T2 | 7.52 | 2.31 | 8.65 | 3.47 | | | | | | | | | | | |
| Arousal density Total | T1 | 18.92 | 9.18 | 22.51 | 7.62 | -0.33 | 0.07 | 1.92 | 0.16 | - | 0.31 | 0.58 | - | 0.38 | 0.54 | - |
| | T2 | 21.83 | 7.72 | 21.91 | 8.6 | | | | | | | | | | | |
| Arousal density NREM | T1 | 0.33 | 0.16 | 0.39 | 0.13 | -0.38 | 0.04 | 2.23 | 0.14 | - | 0.28 | 0.60 | - | 0.37 | 0.54 | - |
| | T2 | 0.39 | 0.14 | 0.38 | 0.16 | | | | | | | | | | | |
| Arousal density REM | T1 | 0.27 | 0.17 | 0.32 | 0.2 | 0.08 | 0.09 | 0.06 | 0.81 | - | 0.01 | 0.90 | - | 0.47 | 0.49 | - |
| | T2 | 0.25 | 0.15 | 0.3 | 0.17 | | | | | | | | | | | |

ESS, Epworth Sleepiness Scale; GAI, Geriatric Anxiety Inventory; GDS, Geriatric Depression Scale; ISI, Insomnia Severity Index; NREM, non-rapid eye movement; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; SE, sleep efficiency; SFI, sleep fragmentation index; SOL, sleep onset latency; SL, sleep latency; TIB, time in bed; TSP, total sleep period; TST, total sleep time; WASO, wake after sleep onset; WPo, sedative-hypnotics withdrawal plan group; WP+CBTi, CBTi combined to sedative-hypnotics withdrawal plan.

# Chapter 4: Impact of rocking bed stimulation on sleep and memory over multiple nights.

# Impact of rocking bed stimulation on sleep and memory over multiple nights.

Authors:

Loïc Barbaux[1,2,10], Emma-Maria Phillips[1,2,10], Ophélia Fontaine[1,2], Alireza Moezi[3], Nathan E. Cross[1,2,4], Ramin Sedaghati[3], Sylvie Belleville[2,5], Nathalie Bier[2], Shannon Hebblewaithe[6], Laurence Bayer[7,8], Thien Thanh Dang-Vu[1,2,10], Aurore A. Perrault[1,2,9,10*]

Affiliations:

[1] Sleep, Cognition and Neuroimaging Lab, Department of Health, Kinesiology and Applied Physiology, School of Health & Center for Studies in Behavioural Neurobiology, Concordia University, Montreal, Quebec, Canada

[2] Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, CIUSSS Centre-Sud-de-l'Ile-de-Montréal, Quebec, Canada

[3] Department of Mechanical, Industrial and Aerospace Engineering, Concordia University, Montreal, Quebec, Canada

[4] School of Psychology, University of Sydney, NSW, Australia

[5] Department of Psychology, University of Montreal, Quebec, Canada

[6] Department of Applied Human Sciences, Concordia University, Montreal, Quebec, Canada

[7] Department of Neuroscience, Faculty of Medicine, University of Geneva, Switzerland

[8] Center for Sleep Medicine, Geneva University Hospital, Geneva, Switzerland

[9] Sleep and Circadian Group, Woolcock Institute of Medical Research and Macquarie University, Sydney, NSW, Australia

[10] Authors contributed equally

* corresponding authors

aurore.perrault@gmail.com

Sleep and Circadian Group,

Woolcock Institute of Medical Research and Macquarie University,

Sydney, NSW, Australia

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## 4.1 Abstract

**Study objectives**: Continuous overnight rocking stimulation appears to be a promising intervention for enhancing both sleep quality and memory, through the modulation of NREM oscillations such as sleep spindles and slow oscillations (SO) activity, associated with memory consolidation. This pilot study evaluated the efficacy of a rocking bed apparatus in healthy young adults on sleep and memory, with the long-term objective of applying this approach to older adults with insomnia.

**Methods**: Nineteen individuals (25 ± 3.6 years, age range: 21-31 years 53% female) completed three consecutive nights under the rocking condition (ROCK) as well as two stationary nights (STAT), counterbalanced and separated by one week. The rocking motion was delivered via a rail-based system inducing continuous back-and-forth movement, with a lateral displacement of 21 cm and a complete cycle every 4 seconds (0.25 Hz). Polysomnographic recordings (PSG) were used to compare sleep architecture, spindle activity, and SO characteristics using automated detection methods. Declarative and procedural memory performance, as well as subjective sleep quality, were also assessed.

**Results**: Sleep quality was disrupted during the first night under the ROCK condition, as evidenced by alterations in sleep architecture. However, a habituation effect was observed over the following two consecutive nights, leading to sleep quality recovery. The intervention did not affect spindles or SOs characteristics, nor did it impact either procedural or declarative memory performance. Nonetheless, neural entrainment appeared to emerge on the second night.

**Conclusions**: Our results suggest that the rocking bed apparatus negatively impacted sleep quality and memory during the first night, while participants exhibited habituation to this effect by the second night. These findings highlight the importance of optimizing rocking parameters to achieve potential benefits on both objective and subjective sleep quality, as well as memory performance.

**Keywords**: sleep, sensory stimulation, brain oscillations, memory

## 4.2 Introduction

Sleep is a behavior characterized by a decrease in the responsiveness to external stimulus. However, the sleeping brain remains in a certain state of reactivity as noise can alter sleep quality[608,609]. Conversely, beneficial effect of sensory stimulation is widely investigated to improve sleep quality. Olfactory stimulation has been shown to boost delta power and slow spindle frequency[610,611], while phase-locked auditory stimulation increases SO activity and consolidates declarative memory; however, neither method has demonstrated objective changes in sleep architecture or improvements in sleep quality[36,437].

While rocking baby to sleep has been common practices for ages, the link between sleep and vestibular stimulation has only started to be uncovered. direct electrical stimulation of the vestibular system revealed shorten SOL[468]. Similarly, galvanic vestibular stimulation during nap improved sleep quality on both objective and subjective measures[612]. Although a promising method, other less invasive types of stimulation need to be investigated. An easier form of vestibular stimulation can be achieved with a rocking bed, thus indirectly stimulating the vestibule as well as proprioceptive and somatosensory system.

Overall, results showed that rocking affects specific aspects of sleep architecture and microstructure. Sleep latency is shortened[469], as the latency to N1 and N2 combined[37], even in mice[474]. Delta power was increased[472], as well as the time spend in N3[37] with reduction in sleep fragmentation (i.e., arousals). Effect of rocking stimulation on waking behavior like declarative memory revealed an increase in overnight memory accuracy in healthy young adults, correlated with an increase in sigma EEG power[37]. Sigma power was increased, as well as spindle density in N3[37,472]. Thus, Bayer et al.[472] and Perrault et al.[37] used the same type of bed (lateral movement, maximal linear acceleration at 25 $cm.s^{-2}$) and found the most beneficial effects on sleep architecture, spectral activity, brain oscillations and declarative memory improvement. Additionally, continuous rocking stimulation enhanced the entrainment of intrinsic spindles and SO, leading to greater neuronal synchronization[37].

However, this was not replicated by Omlin et al.[470] and Van Sluijs et al.[473] who used lateral movement but maximum accelerations below 25 $cm.s^{-2}$. Furthermore, there has been no significant improvement in sleep quality observed with head-to-toe[469,470], up-and-down[470], or rotational movement[473]. A study shown in mice that the rocking effect is conducted through the otolithic organs in the vestibular system and mediated by the maximal linear acceleration of the

movement when performed in lateral movement[474]. Future studies should explore alternative directions for movement in animals. The optimal maximal linear acceleration was funded around 25 $cm.s^{-2}$ in humans: higher value disrupted sleep, and lower value did not affect sleep.

For now, no study investigated the effect of a rocking stimulation on multiple nights, to characterize if the effect is acute (habituation effect)[37,469,470,472,473] or remains consistent across nights. Effect of a rocking bed stimulation on procedural memory improvement has never been investigated. There is a need to investigate whether such stimulation could yield long-term benefits, thereby enabling its utilization to enhance sleep quality and cognitive function as memory in clinical populations such as older adults with insomnia. These benefits could be particularly relevant for older adults who do not respond to therapeutic interventions as CBTi.

Therefore, the objective of this pilot study is to reproduce and evaluate the potential of the rocking bed prototype in enhancing long-term sleep quality among healthy adults, as reported by Bayer et al.[472] and Perrault et al.[37]. A secondary analysis was conducted to assess the impact of rocking stimulation on procedural memory, alongside its effects on declarative memory over three consecutive nights. The study employed a single-centre, within-subject, interventional randomized cross-over trial over five PSG-recorded nights under two conditions: stationary and rocking. After a screening night, participants experienced two consecutive nights in a stationary bed followed by three consecutive nights in a rocking apparatus, with the order of conditions counterbalanced (1:1 allocation ratio) and separated by a one-week washout period (see **Figure 1A** for study design). Primary outcomes were derived from self-reported sleep quality, PSG metrics (SE, N3 duration (%TSP)), and memory task performance (accuracy). Secondary outcomes included additional PSG-related metrics such as sleep architecture and brain oscillations (spindles and SOs), as well as supplementary memory task measures. Based on the literature, we hypothesized that the rocking apparatus stimulation would enhance both subjective and objective sleep quality and facilitate long-term memory consolidation.

## 4.3 Methodology

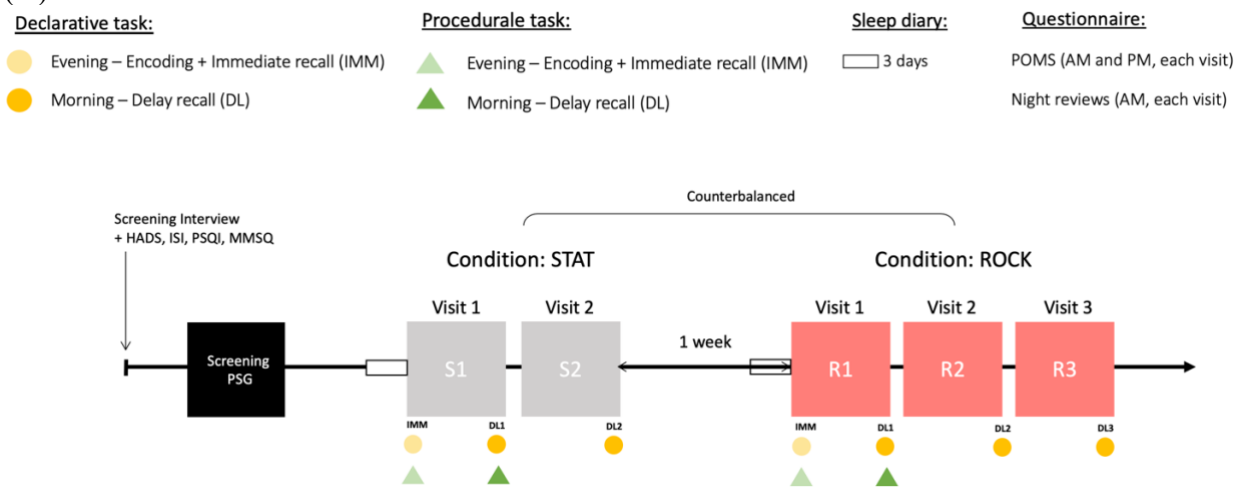
### 4.2.1 Participants

We examined young adults (N=19), self-defined as good sleepers with no sleep complaint, vestibular disorders or motion sickness, fluent in English or French, recruited through social media announcements and other means of communication (e.g., emails, interpersonal referral). Potential participants were initially screened through a telephone-based semi-structured interview, followed by a semi-structured diagnostic interview to confirm their eligibility by ensuring they met the inclusion criteria and did not exhibit any exclusion criteria. During this process, participants completed questionnaires covering demographics, sleep habits, and medical conditions. Eligible participants completed a screening polysomnographic (PSG) overnight at the Centre de Recherche of the Institut Universitaire de Gériatrie de Montréal (CRIUGM) sleep laboratory to exclude the presence of sleep disorders that could contribute to symptoms of insomnia and habituate participant to the experimental conditions in the rocking apparatus (stationary overnight).

Exclusion criteria were as follow: being under 18 y.o. or over 35 y.o.; medical conditions likely to affect sleep: neurological disorder (e.g., epilepsy, multiple sclerosis, concussion in the past 3 month, Parkinson's disease), brain lesion history, major brain surgery in the past 3 month, chronic pain, active cancer or treated for less than 2 years, general anxiety disorder, major depression disorder assessed using the Structured Clinical Interview for the DSM-V (SCID) and the Hospital Anxiety and Depression Scale (HADS) questionnaire with a score >10[613,614]; major cardiovascular events or interventions (e.g., stroke, myocardial infarct, angioplasty, pacemaker, heart failure causing limitation of ordinary physical activity); impaired cognitive function (e.g., diagnosed dementia); sleep-related conditions (e.g., insomnia disorders assed using the Pittsburg Sleep Quality Index (PSQI)[7] and the Insomnia Severity Index (ISI)[575] (cut-off > 7), sleep apnea (apnea-hypopnea index (AHI) > 5 events/hour both confirmed by PSG screening and using the STOP-Bang questionnaire score > 4[615]), bruxism, narcolepsy with cataplexy, REM-sleep behaviour disorder (RBD), restless legs syndrome or periodic limb movement (PLM) disorder during sleep with index >15/ hour confirmed by PSG screening), night shifts or a change in time zone in the last 6 weeks), alcohol consumption (>10 glasses/week), use of cannabis or illicit drugs, smoking (>10 cigarettes/days), pregnant or breastfeeding women, current use of psychoactive medications (e.g., antidepressant, anxiolytics, stimulants, sleep aids as sedative-hypnotics); vestibular system disorders and

sensitivity to motion sickness assessed with the Motion Sickness Susceptibility Questionnaire (MSSQ-short form)[616] (cut-off <19 used by Van Sluijs et al.[473]); motor impairment.

(A)




(B)

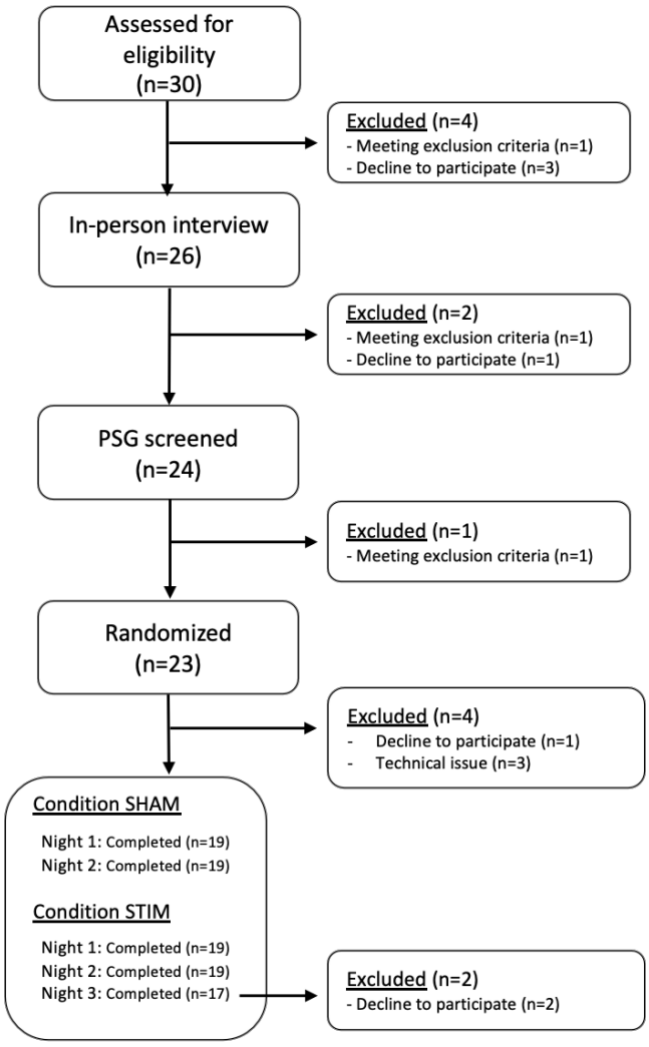


Figure 1: Study Design and participant flow chart

*(A) Participant screening included am semi-structured diagnosed interview and an overnight PSG to assess exclusion criteria. This first PSG also served as a habituation session to the sleep laboratory environment, especially the rocking apparatus. Eligible participants underwent two overnight PSG with the bed in the stationary condition (STAT) counterbalanced with three overnights under the rocking motion stimulation (ROCK). In a period of 3 days before the first overnight of each condition, participants were asked to completed sleep diaries. Declarative and procedural assessment comprised tasks in the evening and morning on the first night of each condition. Delayed recalls were also gathered the second and third visit on the rocking stimulation condition. For each experimental overnights, participant completed in the evening and the morning the POMS questionnaire, as a subjective night reviews.*

*(B) Participant consort flow chart*

### 4.2.2 Study protocol

One week after the initial PSG screening, eligible participants were enrolled in a single-centre within-subjects interventional randomized cross-over trial over five PSG overnights under two conditions (i.e. rocking and stationary): two consecutive stationary and three consecutive rocking; randomly counterbalanced (1:1 allocation ratio); separated by one week apart (see **Figure 1A** for the study design).

During the rocking condition, the bed motion was initiated in the evening at lights-off and ceased in the morning at lights-on. Participants were instructed to adhere to their normal sleep schedule throughout the study. To monitor sleep deprivation, they were required to complete a sleep diary for three days preceding the first night of each condition. Participants were instructed to refrain from consuming caffeine, alcohol, or energy drinks after 2PM on the afternoon preceding the overnight visits.

Each sleep assessment included an overnight PSG recording, and questionnaires filled in the morning regarding participant night of sleep. Participants completed a mood questionnaire before and after each overnight. Participants engaged in cognitive tasks assessing declarative and procedural memory every evening and morning of the first night's conditions. Additionally, declarative memory tasks were administered the morning after the second night under each condition.

All participants signed a written informed consent form, which was approved by the Comité d'Éthique de la Recherche of the CRIUGM. This study was registered as a clinical trial (ISRCTN12645581), https://www.isrctn.com/ISRCTN12645581).

Nineteen participants were found eligible for the study, with their demographics information presented in **Table 1**.

### 4.2.3 Rocking apparatus

The rocking apparatus was designed to replicate the motion described in published studies[37,472] with a lateral movement of 10.5 cm at a frequency of 0.25 Hz, completing one full cycle of back-and-forth motion every four seconds, with a peak linear acceleration of approximately 26 $cm.s^{-2}$ (see **Figure 2**). In the present study, the bed design was chosen following a focus group consensus (Maltezos et al., unpublished data), to ensure its suitability for at-home use, particularly by older populations. The current system generates longitudinal motion through a rail system with both acceleration and braking capabilities. This contrasts with the previously used crank-and-rod system, which converted continuous circular motion into back-and-forth linear motion[472]. The current rocking apparatus was positioned between the mattress and the frame and could be activated by the participant using a remote control. The motor and ventilation system of the rocking apparatus produced a sound level of about 43 dB. To control for any extraneous auditory stimuli, the motor and ventilation system operated throughout all experimental nights, regardless of whether the bed was in a rocking or stationary state. For the same reason, participants were given the option to use earplugs, starting from the first experimental night and continuing consistently for all subsequent nights.

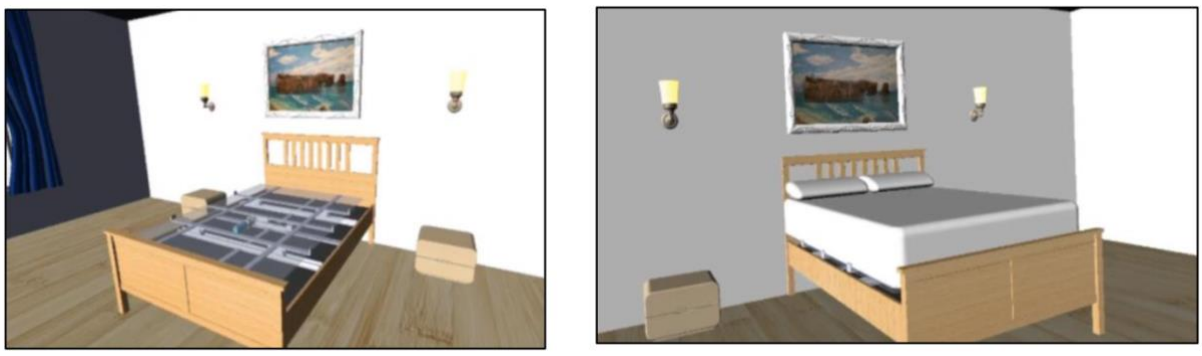


Figure 2: Design of the rocking apparatus

*Lateral movement at 0.25Hz – full cycle of 4s.*

### 4.2.4 Polysomnographic (PSG) recording

Whole-night PSG recordings were used for each night, including electroencephalogram (EEG), electromyogram (chin and legs EMG), electrooculogram (EOG), electrocardiogram (ECG). During the habituation night only (first night), the PSG setup included an oximeter, thoracic and abdominal belts, oral-nasal thermistor, and nasal cannula. From the habituation night we computed the apnea-hypopnea index (AHI) and periodic leg movement index (PLMI) to exclude potential sleep disorders. For the experimental night the EEG montage with 14 electrodes (Fpz, Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, O1, O2, M1, M2) disposed on the scalp according to the 10-20 system AASM guidelines. EEG signal was recorded by a Somnomedics amplifier (SomnoMedics, Germany) at a sampling rate of 512 Hz, referenced to Pz online and to contralateral mastoids (M1 and M2) offline for analysis.

### 4.2.5 EEG analysis

#### *4.2.5.1 Sleep architecture*

All sleep scoring and preprocessing (manual artefact and arousal detections) were conducted using the Wonambi python toolbox (https://wonambi-python.github.io). EEG analyses were conducted using the Seapipe python toolbox (https://github.com/nathanecross/seapipe). Sleep stages (N1, N2, N3, REM) and wake 30-second epochs, as well as the detection of arousal and artifact events, were visually scored by expert scorers according to AASM guidelines[25]. All analyses were conducted in a blinded manner and revised by one expert scorer to minimize interindividual variation. From the scoring, we computed the calculation at each time point (T1, T2) of: total sleep time (TST; sum of the time spent in different sleep stages), sleep onset latency (SOL; from light off to the first period of sleep), sleep latency to stages (SL), wake after sleep onset (WASO; sum of the nocturnal awakenings duration), time spent in bed (TIB; sum of TST, SOL and WASO), sleep efficiency (SE; TST/TIB*100), arousal density (per epoch of 30 s), sleep fragmentation index (SFI; number of transitions from deep to lighter sleep stages per hour).

#### *4.2.5.2 Sleep spindle*

Spindles were automatically detected using a validated algorithm[509] and implemented in the Seapipe toolbox. The spindle detection algorithm consisted of computing the root-mean-square (RMS) of the participant-adapted sigma band with a 0.5 s overlap window and smoothed with Gaussian filter[521,580]. For spindle detection, the highest center frequency peak (integral of the

Gaussian fit) over the sigma range specific for each subject was obtained[503,504]. Using those participant-specific adapted sigma ranges, we determined with a 2Hz bandwidth the highest peak in the 10 to 13 Hz range for midline frontal (Fz – slow spindle) and the 13 to 16 Hz range for midline parietal (Pz - fast spindle), as well as the midline central electrode (Cz; 12-15 Hz), on artefact-free derivations accounting for spindle frequency gradient[505,506]. RMS were identified as a spindle event when values exceeded a threshold at 2 SD above the mean peak amplitude. Detection criteria included a spindle duration ranging from 0.5 to 3 s. For spindles detected in NREM (N2 and N3), we extracted the following characteristics: density (i.e., mean number per epoch of 30 s), amplitude (μV), duration (s) and frequency (Hz).

#### *4.2.5.3 Slow oscillation*

SO events were detected on a fixed band-pass FIR filter from 0.16 to 1.25 Hz on artefact-free EEG recordings of Fz using a published algorithm[84] and implemented in the Wonambi and Seapipe toolboxes. SOs candidates were flagged using a duration criteria of two positive-to-negative zero crossings within 0.8 to 2 sec. Then, trough-to-peak amplitudes between two positive-to-negative zero crossings were computed on SO candidates and only the top 25% highest amplitudes were considered as SO in the study. The variables extracted from these detections were as follow: density (i.e., mean number of spindles/SO per epoch of 30 s), amplitude (μV), duration (sec) and frequency (Hz) and extracted for stages N2 and N3.

#### *4.2.5.4 Neural entrainment*

We examined whether the rocking apparatus at 0.25 Hz effectively entrained brain oscillations occurrence, using the method described by Perrault et al.[37]. An accelerometer was placed on the bed and coupled to the EEG recordings to detect horizontal displacements as the bed oscillated from left to right. Within these intervals, we analyzed the distribution of SOs and spindles occurrence around markers. For the rocking (ROCK) condition, markers were assigned each time the bed reached the extremity of a predetermined side, corresponding to a full cycle of 4 seconds (0.25 Hz), and for the stationary (STAT) condition, virtual markers were assigned every 4-second stationary periods. The average distribution of SOs and spindles occurrence was normalized for each EEG channel (Fz, Pz) in both N2 and N3 stages, graphically represented by computed peri-event time histograms (PETHs). The data were segmented into 8-second windows, divided into 80 bins of 100 ms, and centered around the virtual marker. To estimate positional variations, acceleration data were double-integrated over time.

### 4.2.6 Memory assessment

The memory tasks were conducted using the open-source software, PsychoPy[617].

#### *4.2.6.1 Procedural memory*

Procedural motor memory was assessed using the sequence finger tapping task (FTT)[53,159]. Participant were asked to tap with their non-dominant hand as quickly and accurately as possible a pre-determined sequence of keys: "4-1-3-2-4" or "1-4-2-3-1" in a 30 second period as published in a study investigating sleep-dependent procedural memory consolidation[618]. Each finger was associated with one number (e.g., “1” is linked to the index; “4” to the little finger). As digits sequences changed over condition, the first task component consisted in an evening (PM) encoding/training session, followed by a testing session of twelve 30-second practice blocks. On the next morning (AM), participants were asked to complete another three 30-second practice blocks. Sequence was presented on the screen for each testing session to avoid working memory involvement[53]. Each practice block was separated from the next by a 15 second rest period.

The total number of sequences completed in each 30-second block was recorded and categorized as either correct or incorrect. Accuracy was calculated as the ratio of correctly typed sequences to the total sequences performed.

The last three blocks of the evening testing session were compared to the three blocks performed the next morning testing session.

#### *4.2.6.2 Declarative memory*

Declarative memory was assessed with the word paired-associate learning task: participants were asked to memorize and then recalled semantically unrelated word-pairs[152]. The same two lists of 46 word-pairs than used by Perrault et al.[37] were given and counterbalanced between conditions: stationary or rocking. The task has three components: a memory encoding, an immediate recall in the evening (IMM) and delayed recall the next morning (DL). In the evening, participants were asked to memorize 46 word-pairs from one of the two lists. Each pair was presented on the screen for 4 s, with a 100 ms inter-stimulus interval. The encoding phase was followed by an immediate recall: one word per pair was presented to the participant, who was asked to type the associated word with no time limit. The number of correct answers (including those with spelling mistakes), incorrect answers, and unanswered questions (left blank or “unknown”) were recorded out of a maximum score of 46. We calculated the

percentage of correct, incorrect, and unanswered responses. Additionally, accuracy performance was assessed by subtracting the number of incorrect answers from the number of correct ones.

### 4.2.7 Questionnaire

#### *4.2.7.1 Profile Of Mood States (POMS)*

Participant mood was assessed using the short version of the Profile Of Mood States (POMS) questionnaire, administered both in the evening and the following morning after each experimental overnight visit[619]. We focused on specific dimensions: Tension-Anxiety (score out of 24), Vigor-Activity (score out of 24), and Fatigue-Inertia (score out of 20). Responses were rated on a 5-point Likert scale ranging from "not at all" to "extremely." We computed the overnight change for every experimental overnight.

#### *4.2.7.2 Subjective night reviews*

Participants were asked to report their sleep perception each morning following the experimental overnight by completing a night review. They reported time spent in bed (TIB), total sleep time (TST), sleep onset latency (SOL), wake duration after sleep onset (WASO), sleep efficiency (TST/TIB*100) and sleep satisfaction (from 1: very bad sleep to 5: very good sleep). Additional feedback from participants were asked to provide on their subjective experiences each morning following every overnight (rated from 1 to 10). This feedback assessed their perception of the comfort of the rocking apparatus (10: very comfortable), whether the bed motion was relaxing (10: very relaxing), pleasant (10: very pleasant), and noisy (10: silent).

### 4.2.8 Statistical analysis

The analysis was performed using RStudio version 1.2.50 (RStudio, Inc., Boston, MA) with various R packages, including sjstats, emmeans, rstatix, FSA, car, and effsize. Normality of distribution was checked with Shapiro tests and homogeneity of variance was tested with Levene tests.

For our primary objective, the main outcomes were derived from self-reported night review questionnaires (SE) and PSG measures, including SE and N3 duration (%TSP). Secondary outcomes encompassed additional PSG-related measures such as sleep architecture and brain oscillations, including spindles and SO characteristics.

For our secondary objective, the primary outcomes focused on the accuracy of both declarative and procedural tasks. Secondary outcomes included additional measures derived from these tasks.

To evaluate the potential of the rocking apparatus prototype in enhancing long-term sleep quality and memory, we conducted a three-step analysis. First, we examined the impact of the initial night of rocking apparatus stimulation, by using t-test to compare both condition: rocking (ROCK) and stationary (STAT), on outcomes acquired during the first overnight, or provided in the morning for memory outcomes. We also used ANOVA in a within (Condition: ROCK vs STAT) X within (Stage: Wake vs N1 vs N2 vs N3 vs REM) design for proportion of time spent in each stage, sleep latency to each stage, arousal density in each stage, and slow oscillations and spindle outcomes (N2 and N3), the factor stage was adapted to the outcomes. Specifically for declarative memory and POMS outcomes, we performed an ANOVA in a two-level within design (Condition: ROCK vs STAT X Session: Evening vs Morning).

Second, we assessed the consistency of this effect over two consecutive nights under both conditions, by using ANOVA, in a within (Visit: 1 vs 2) X within (Condition: ROCK vs STAT) design.

Finally, we investigated whether the rocking intervention had lasting effects over multiple nights, by using repeated measures analysis of variance type ANOVA (RM-ANOVA) in a within (visit: 1 vs 2 vs 3) X within (condition: ROCK vs STAT) design. In analyzing the previously mentioned variables that depend on the duration of specific sleep stages, we performed RM-ANOVA in a within (visit: 1 vs 2 vs 3) X within (Stage: Wake vs N1 vs N2 vs N3 vs REM) design.

Due to technical issues, sample sizes varied across analyses. For the POMS questionnaire, the first, second, and third analyses included 18, 17, and 15 participants, respectively. Night reviews involved 19 participants for the first two analyses and 16 for the third. Procedural memory assessment was conducted with 18 participants. For spindle and slow oscillation measures, the first and second analyses included 18 participants, while the third involved 16.

To assess neural entrainment, a Chi-square goodness-of-fit test was conducted to evaluate whether the average occurrence probability of brain oscillations was uniformly distributed in synchronization with the rocking motion. Due to technical constraints, neural entrainment was examined only at the end of data collection, and accelerometer data were available for only six participants.

For outcomes not normally or homogeneously distributed, we used non-parametric tests as follows: Wilcoxon test (t-test), Wald-Type Statistic (ANOVA), Friedman test (RM- ANOVA). Paired post-hoc test were used to specifically assess difference within groups. Effect sizes were calculated using Hedges's *g'* (corrects for small sample size). The level of significance was set to a p-value of <.05 and p-values were adjusted for multiple comparisons (Benjamini-Hochberg/FDR correction).

Control analyses were conducted to determine if the order of the first overnight condition (STAT vs ROCK) affected the results, using t-test or Wilcoxon test. Similarly, the effect of the order of the list assigned for declarative memory tasks, and the FTT sequence for procedural memory was examined.

A power analysis conducted based on Perrault et al.[37] indicated that 17 participants would be sufficient to detect an increase in N3 duration following rocking bed stimulation ($\eta 2 = .74$), with an $\alpha$ level of 0.05 and a power of $\beta = 0.8$, considering a tail two-tailed paired t-test.

## 4.4 Results

Participant demographics are presented in **Table 1**. Nineteen participants (mean age: 24.9 ± 3.6 years; 53% female) were enrolled in this interventional, randomized crossover trial under two distinct sleep conditions: three consecutive nights with rocking apparatus stimulation, followed by two consecutive nights on a stationary bed, with a one-week interval separating the conditions (see **Figure 1A** for study design). Participants did not exhibit insomnia symptoms, anxiety or depression disorders, vestibular system dysfunctions, or sensitivity to motion sickness.

Nineteen participants completed at least four of the five experimental overnights, allowing for the investigation of rocking stimulation effects after the first night (STAT1 vs ROCK1) and across two consecutive nights. Seventeen participants were included in the analysis of rocking effects over three nights, as two did not complete the final stimulation night (STIM3) (see **Figure 1B** for participant flow chart).

Control analysis did not show effect of the order or list assigned to the first overnight condition (all $p$>.05, **Table S1** in **Appendix C**).

### 4.3.1 Effect of the rocking apparatus stimulation on subjective report of sleep and mood

#### *4.3.1.1 Self-reported mood and sleep*

When comparing STAT1 versus ROCK1, while no Condition effect was found, a significant Session effect was observed only for the POMS component tension/anxiety ($F(1,17)=11.13$, $p<.001$, **Table 2A**), as well as a Condition by Session interaction ($F(1,17)=4.16$, $p=.04$), although it did not survive multiple comparison. Participant were less tensed/anxious in the morning compared to the evening only in ROCK1 ($p=.008$). In addition, no significant Condition effects was observed for subjective sleep from night review (all $p>.05$, **Table 2B**).

When investigating the rocking effect over two consecutive nights, no significant Condition or Visit effect was observed for the POMS questionnaire (all $p>.05$). Only a significant Condition effect was observed for SE ($F(1,18)=4.64$, $p=.03$), WASO ($F(1,18)=4.51$, $p=.03$) and sleep quality ($F(1,18)=6.32$, $p=.01$); however, there was no Visit effect and post hoc analysis did not reveal significant difference (all $p>.05$; **Table 3**).

Across the 3 rocking nights, significant Visit effect was observed for tension-anxiety ($F(2,28)=11.31$, $p=.003$) of the POMS questionnaire, where a greater reduction in morning-to-evening tension-anxiety differences from ROCK1 to ROCK2, and to ROCK3 (all $p=.02$; **Table 4**). There was no significant effect of Visit, Condition or Condition by Visit interaction on self-reported sleep measures from night review (all $p>.05$; **Table 4**).

#### *4.3.1.2 Report of rocking perception*

The only perception of the rocking apparatus that reached significance was relative to Condition effect observed for the noise component, where greater noise was reported in ROCK1 compared to STAT1 ($F(1,18)=130$, $p=.001$; **Table 2B**). Consistently, the rocking apparatus was found noisier ($F(1,18)=11.62$, $p=.001$; **Table 3**) in ROCK1 compared to STAT1 ($p=.001$); however no main effect of Condition or Visit was observed when comparing STAT2 versus ROCK2. Across the 3 rocking nights, a significant Visit effect was observed ($F(2,30)=4.48$, $p=.02$; **Table 4**), where the rocking apparatus was perceived less noisy from ROCK1 to ROCK3 ($p=.01$); however it did not survive correction for multiple comparison.

### 4.3.2 The rocking apparatus stimulation initially disrupted sleep architecture, but normalizes over time

#### *4.3.2.1 Sleep latencies*

When comparing STAT1 versus ROCK1, no significant difference was observed for the SOL ($p$>.05; **Table 2B**). No significant Condition or Condition by Stage interaction was observed for sleep latency to stages (all $p$>.05; **Table S2** in **Appendix C**).

Regarding the second-level analysis, no significant Condition, Visit or interaction effects were observed for the SOL, ($p$>.05; **Table 3**). A significant Visit effect was found for sleep latency to REM only (F(1,18)=7.06, $p$=.01), which decreased from STAT1 to STAT2 only ($p$=.01).

Across the 3 rocking nights, no significant Visit effect was noticed for SOL ($p$>.05) (**Table 4**). No Condition, Visit or interaction effects were found for sleep latency to stages (all $p$>.05; **Table S3** in **Appendix C**).

#### *4.3.2.2 Sleep and wake duration*

When comparing STAT1 versus ROCK1, no significant difference was observed for TST and SE (all $p$>.05; **Table 2B**). Despite the lack of a significant Condition effect, a significant Condition by Stage interaction emerged for the wake and sleep stages duration (%TSP) (F(1,18) = 28.95, $p$<.001; **Table S2** in **Appendix C**; **Figure 3**). Participants spent more time awake ($p$=.03), in N1 ($p$=.045) and N2 ($p$=.03) during ROCK1 compared to STAT1, as well as less time in N3 ($p$=.04) and REM ($p$=.01).

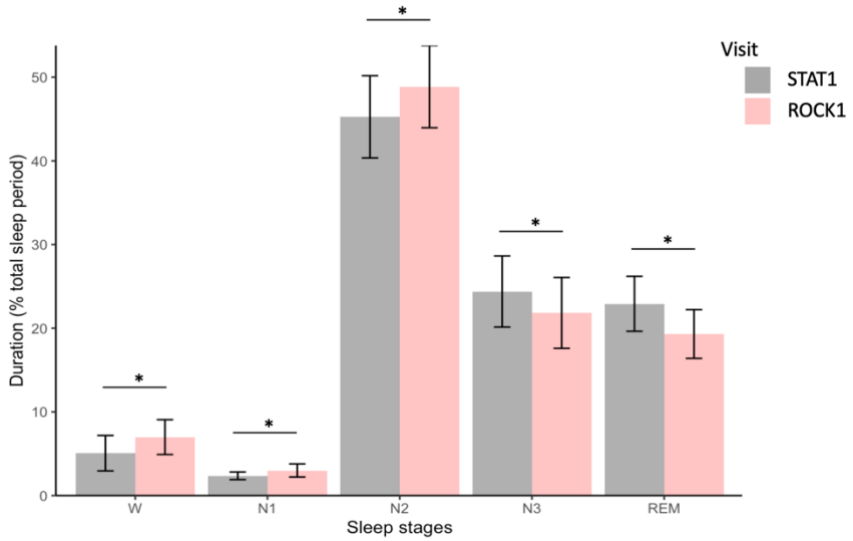



Figure 3: Impact of the first rocking apparatus stimulation overnight accounting for wake and sleep stages

*Asterisks represent significance (p): *<0.05*

Regarding the second-level analysis, no significant Condition, Visit or interaction effects were observed for TST and SE (all $p$>.05; **Table 3**). Significant Condition effect was observed for wake (F(1,18)=7.33, $p$=.007) and N1 duration (F(1,18)=5.51, $p$=.02), as well as main effect of Condition (N2: F(1,18)=5.51, $p$=.03; REM: F(1,18)=13.67, $p$=.002) and Visit (N2: F(1,18)=9.87, $p$=.01; REM: F(1,18)=26.7, $p$<.001) for both N2 and REM duration (**Table 3**). Mostly driven by difference between STAT1 and ROCK1 (see above), we found that REM duration was found to increase from STAT1 to STAT2, and from ROCK1 to ROCK2, as N2 duration decreased from ROCK1 to ROCK2 (**Figure 4**).

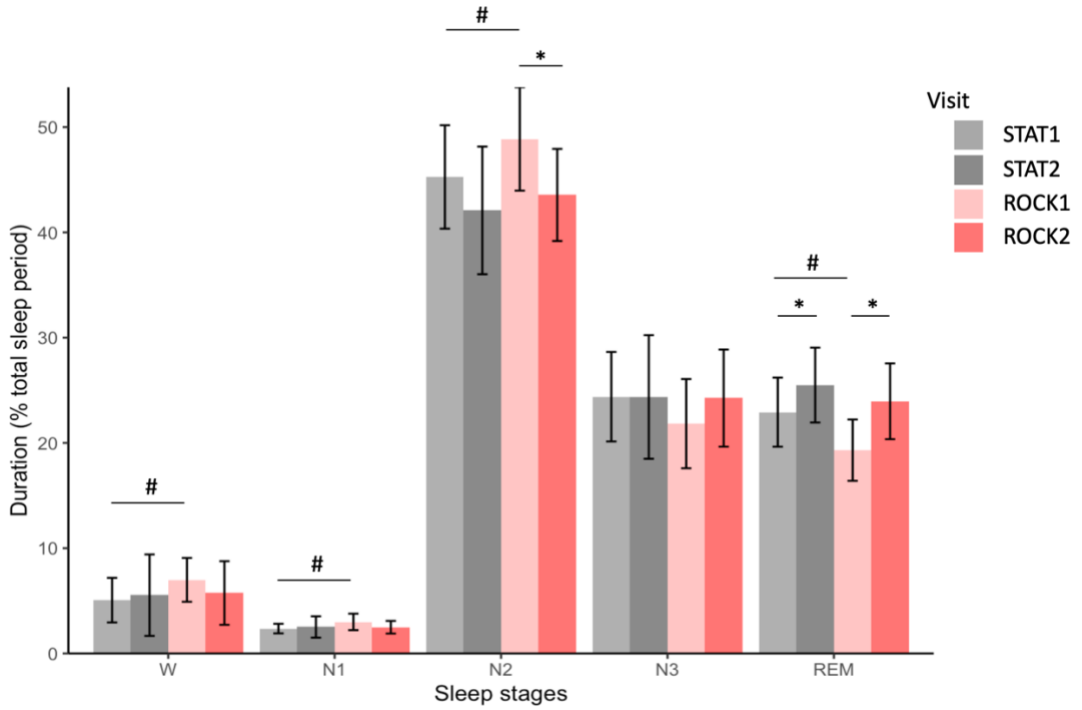



Figure 4: Impact of the rocking apparatus stimulation over two consecutive nights on wake and sleep stages duration

*Asterisks represent significance for Condition effect (p): *<0.05 and difference symbol represent significance for Visit effect (p): # <0.05.*

Across the 3 rocking nights, we found a significant Visit effect for SE (F(1,32)=8.82, $p$=.01), indicating an increase from ROCK1 to ROCK3; however no significant Condition effect was noticed for TST ($p$>.05; **Table 4**). While no significant Visit effect was observed, a significant Visit by Stage interaction was found for sleep and wake durations (%TSP) (F(1,32)=42.81, $p$<.001; **Table S3** in **Appendix C**). The rocking stimulation decreased N1 duration from ROCK1 to ROCK3 ($p$=.04), and decreased N2 duration from ROCK1 to ROCK2 ($p$=.01) and further to ROCK3 ($p$=.001; **Figure 5**). Conversely, N3 duration increased from ROCK1 to

ROCK3 ($p$=.02), as well as REM sleep from ROCK1 to ROCK2 ($p$=.001) and continued to lengthen by ROCK3 ($p$=.01). Wake duration was reduced from ROCK1 to ROCK2 ($p$=.045).

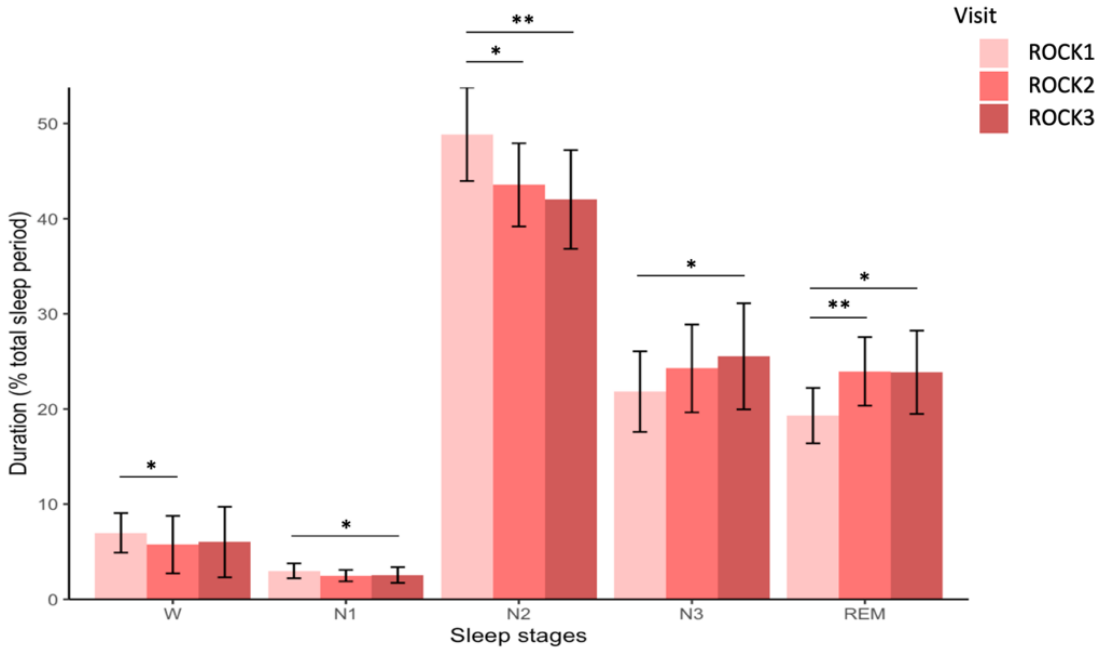



Figure 5: Impact of the rocking apparatus stimulation over three nights on wake and sleep stages duration

*Asterisks represent significance (p): *<0.05; **<0.01*

### *4.3.2.3 Sleep fragmentation*

When comparing STAT1 versus ROCK1, no significant Condition effect was observed for SFI and the arousal density (all $p$>.05; **Table 2B**). Concerning the arousal density in N2, N3 and REM, post hoc analysis on Condition by Stage interaction (F(1,18) = 14.69, $p$=.002) revealed no Condition effect (all $p$>.05; **Table S2** in **Appendix C**).

Regarding the second-level analysis, no significant Condition, Visit or interaction effects were observed for SFI and the arousal density (all $p$>.05; **Table 3**). A significant Visit (F(1,18)=14.26, $p$=.001) effect was observed for arousal density in N2, as well as a main effect of Condition (F(1,18)=13, $p$<.001) and Visit (F(1,18)=13.3, $p$<.001) for arousal density in REM (**Table 3**). Post hoc analysis revealed that arousal density in N2 decreased from ROCK1 to ROCK2 only ($p$=.01). Arousal density in REM increased from the first to the second night in both condition (STAT: $p$=.02; ROCK: $p$=.02), while no main Condition effect was found.

Across the 3 rocking nights, no significant Condition effect was noticed for SFI and the arousal density (all $p$>.05; **Table 4**). While no significant Visit effect was observed, a significant Visit

by Stage interaction was found for arousal density (F(1,32)=27.66, $p$<.001; **Table S3** in **Appendix C**). Arousal density in N2 was reduced from ROCK1 to ROCK3 ($p$=.01), and arousal density in REM increased from ROCK1 to ROCK2 ($p$=.02).

### 4.3.3 Effect of the rocking stimulation on NREM brain oscillations activity

#### *4.3.3.1 Spindles*

When comparing STAT1 and ROCK1, no significant Condition effect or Condition by Stage interaction was observed for both slow and fast spindle density (**Table 5**). A Condition by Stage interaction was observed for slow spindle duration (F(1,18) = 9.04, $p$=.003); however post hoc analysis shown no significant difference. No significant effect of Condition or Condition by Stage interaction was noticed for other spindle characteristics (all $p$>.05).

Over two consecutive nights, a Condition by Visit interaction was found only for fast spindle density in N2 (F(1,18)=8.46, $p$=.01), and N3 (F(1,18)=9.06, $p$=.01), although post hoc analyses show no significant difference for Condition (all $p$>0.05; **Table 6**). In addition, a significant Visit effect was found for slow spindle amplitude in N2 (F(1,18)=12.47, $p$=.003), and N3 (F(1,18)=10.03, $p$=.01). Similarly, post hoc analyses revealed no significant Visit effect (all $p$>0.05; **Table 6**).

Across the 3 rocking nights, a significant Visit effect was observed only for fast spindle density (F(1,18)=4.45, $p$=.02), where the density increased significantly from ROCK1 to ROCK2 in N2 ($p$=.01), and from ROCK1 to ROCK3 in both N2 ($p$=.01) and N3 ($p$=.02; **Figure 6**). Significant Visit effect (F(1,18)=4.75, $p$=.02), and Visit by Stage interaction (F(1,18)=8.04, $p$=.002) were found for fast spindle duration (**Table 7**). Fast spindle duration showed a significant increase from ROCK1 to ROCK2 in N2 ($p$=.02), and from ROCK1 to ROCK3 in both N2 ($p$=.005) and N3 ($p$=.03). In addition, a significant Visit by Stage interaction was observed for fast spindle amplitude (F(1,18)=12.11, $p$<.001), although post hac analysis did not show any significant difference.

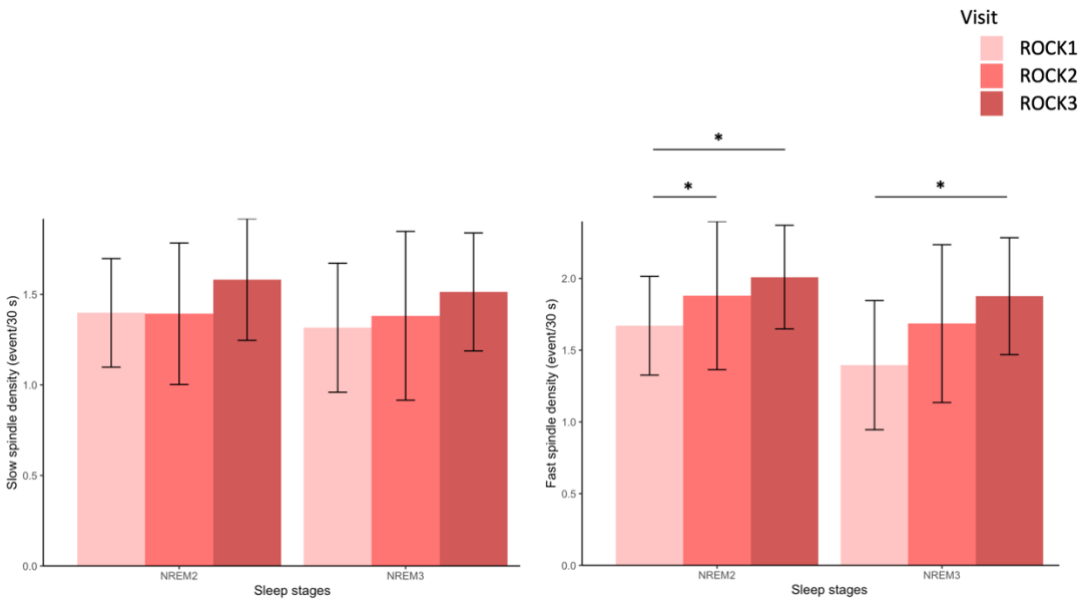



Figure 6: Effect of the rocking apparatus stimulation on fast and slow spindle density

*Asterisks represent significance (p): *<0.05*

#### *4.3.3.2 Slow oscillation*

When comparing SO characteristics in STAT1 and ROCK1 in the frontal area, significant Condition by Stage interaction was found for SO density ($F(1,18) = 8.29$, $p$=.004; **Table 5**), however post hoc analysis did not reveal any significant difference (all $p$>.05). In addition, significant Condition effect was observed for SO duration ($F(1,18) = 5.98$, $p$=.01), which was shorter in ROCK1 compared to STAT1 only during N3 ($p$=.01; **Table 5**). No significant Condition or Condition by Stage interaction was noticed for other SO characteristics (all $p$>0.05).

Over two consecutive nights, a significant Visit effect was found ($F(1,18)=11.42$, $p$=.001) for SO density, which increased from STAT1 to STAT2 ($p$=.003) (See **Figure 7**, **Table 6**). Significant main effect of Condition ($F(1,18)=9.80$, $p$=.002) and Visit (Fz: $F(1,18)=8.36$, $p$=.004) was observed for SO duration, where it decreased only from STAT1 to STAT2 ($p$=.002) and was shorter in ROCK1 compared to STAT1 ($p$=.002) in N3. No difference was found for STAT2 versus ROCK2. No other main effect of Condition or Condition by Stage interaction was noticed in N3 (all $p$>0.05). Analysis conducted during N2 displayed also significant Visit effect for SO density ($F(1,17)=17.68$, $p$<.001; **Figure 7**), duration ($F(1,17)=6.80$, $p$=.02) and amplitude ($F(1,17)=15.11$, $p$<.001).

Post hoc analysis revealed increase in SO density and a decrease in SO amplitude from both STAT1 to STAT2 ($p$=.004) and ROCK1 to ROCK2 ($p$=.04).

Across the 3 rocking nights, no significant Visit or Visit by Stage interaction was found for SO density ($p$>.05; **Table 7**). We found a Visit by Stage interaction for SO amplitude (F(2,30)=3.96, $p$=.03), although it did not survive multiple comparison.

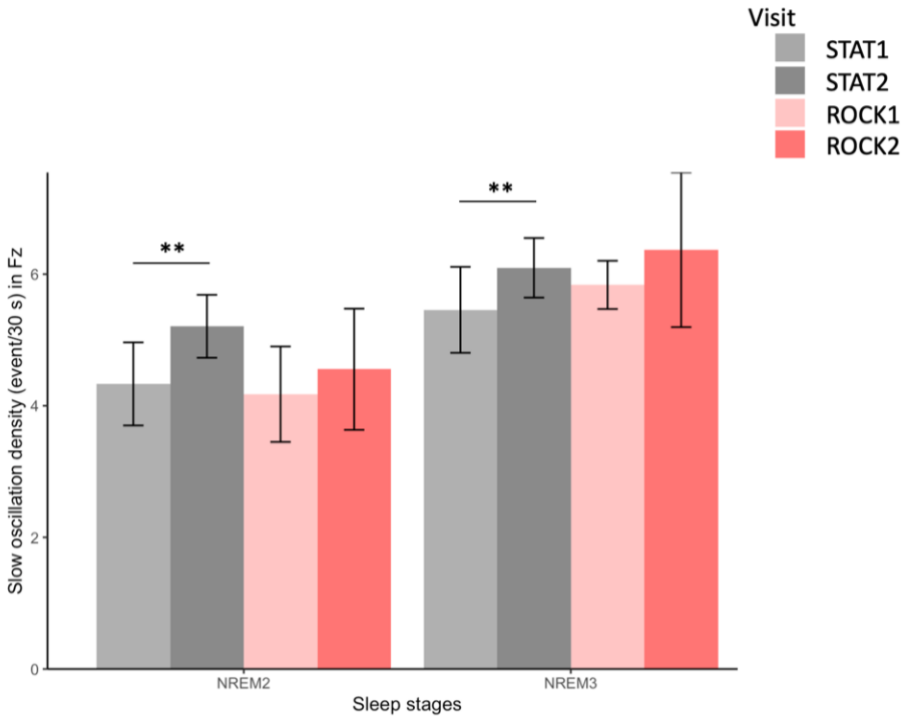



Figure 7: Effect of the rocking apparatus stimulation on frontal slow oscillation density

*Asterisks represent significance (p): *<0.05; **<0.01*

### *4.3.3.3 Neural entrainment*

We conducted Chi-square goodness-of-fit tests to demonstrate that the distribution of both SOs and spindles were uniform under all stationary visits (all $p$>.05; **Table 8**).

During the rocking condition, the average distribution of slow spindle occurrence was not uniform during both N2 ($\chi^2$=17.5, $p$=.03) and N3 ($\chi^2$=22.9, $p$=.01) only during ROCK3. In addition, the distribution of fast spindle occurrence was not uniform in both N2 ($\chi^2$=19.5, $p$=.02) and N3 ($\chi^2$=17.0, $p$=.03) during ROCK2 and ROCK3 (N2: $\chi^2$=37.7, $p$=.01; N3: $\chi^2$=18.3, $p$=.01), but not ROCK1. Moreover, the average distribution of frontal SOs was not uniform in N2 during ROCK1 ($\chi^2$=56.2, $p$=.01), ROCK2 ($\chi^2$=71.4, $p$=.01) and ROCK3 ($\chi^2$=105.5, $p$=.01). Similarly, it was also observed in N3 during ROCK3 ($\chi^2$=71.4, $p$=.01). The clustering of SOs and spindles at specific rocking motion time points are illustrated in **Figure 8**.

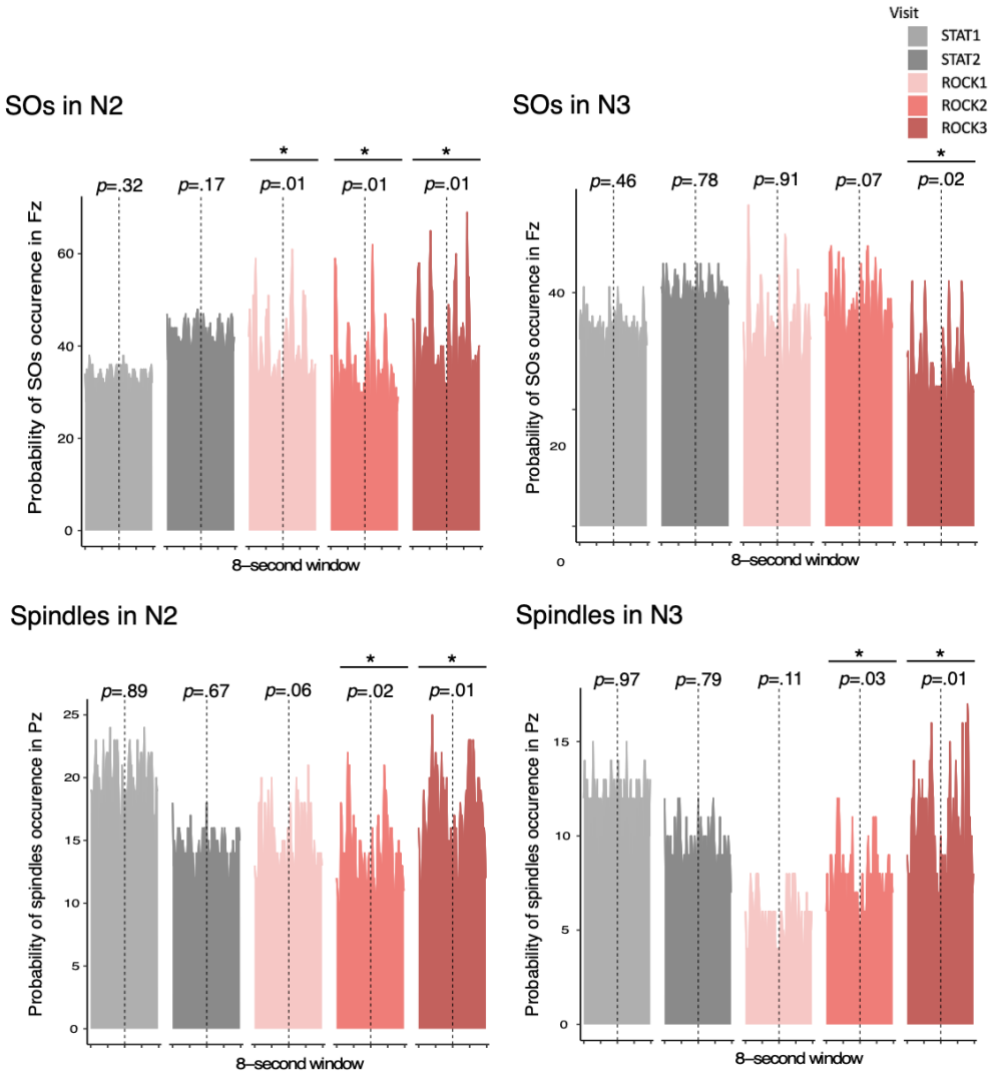



Figure 8: The rocking apparatus induce entrainment of frontal SOs and parietal spindles

*Graphical representation of the peri-event time histograms of observed SOs and fast spindles occurrence centered on virtual marker (dashed line). Peaks represents SOs and spindles cluster at specific period of the rocking motion.*

*Asterisks represent significance (p): *<0.05*

### 4.3.4 The rocking apparatus stimulation did not improve memory performance

#### *4.3.4.1 Declarative memory*

When comparing STAT1 versus ROCK1, we only observed a significant Session effect but no Condition or interaction effect for declarative memory performances (**Table 2A**). More specifically, we observed higher percentages of correct responses ($F(1,18)=48.1$, $p<.001$), greater accuracy ($F(1,18)=51.2$, $p<.001$; **Figure 9**), as well as less incorrect $F(1,18)=43.0$, $p<.001$) and unanswered responses $F(1,18)=6.7$, $p=.01$) in the morning compared to evening

performance, for both STAT1 and ROCK1, confirming overnight memory consolidation (all $p<.05$). Supplemental analyses revealed positive correlations with change in declarative overnight accuracy and change in fast spindle density during N2 only (N2: r=.49; $p=.03$) and duration (N2: r=.52 $p=.02$; N3: r=.49; $p=.03$), but no significant association with sleep architecture measures or SOs characteristics.

However, we did not observe any Condition effect for the first overnight change in accuracy (**Table 2B**). In addition, no significant Condition or Visit effect was observed over two consecutive nights, as well as in the 3 rocking nights (all $p>.05$; **Table 3-4**).

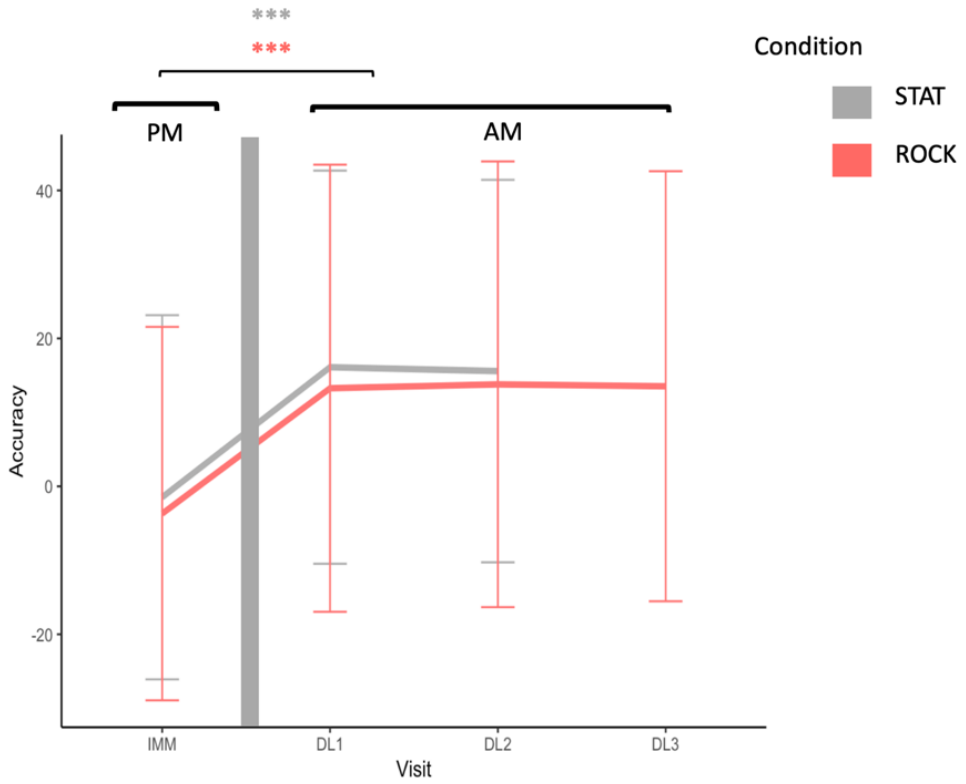



Figure 9: Change in declarative memory across evening and morning sessions

*For the STAT condition (grey) and the ROCK condition (red):*

*Mean accuracy of declarative performance across evening immediate recall (PM) and morning delayed recall (AM) (± SD). The dark grey vertical bar indicates the overnight period.*

*Asterisks denote significance after Bonferroni correction (*<.05).*

### *4.3.4.2 Procedural memory*

When comparing STAT1 versus ROCK1, while we did not find any Visit effect for procedural memory accuracy, significant Visit effect was observed for the total number of sequences performed ($F(1,17)=18.7$, $p<.001$) and the number of correct sequences performed

(F(1,17)=11.2, *p*=.004; **Figure 10**). Supplemental analysis did not reveal any significant correlations between overnight change in procedural memory performance and N2, N3, REM duration, as well as spindles and SOs characteristics.

We did not observe Condition or Visit effect for the second-level analysis, as well as in the 3 rocking nights (all *p*>.05; **Tables 3-4**).

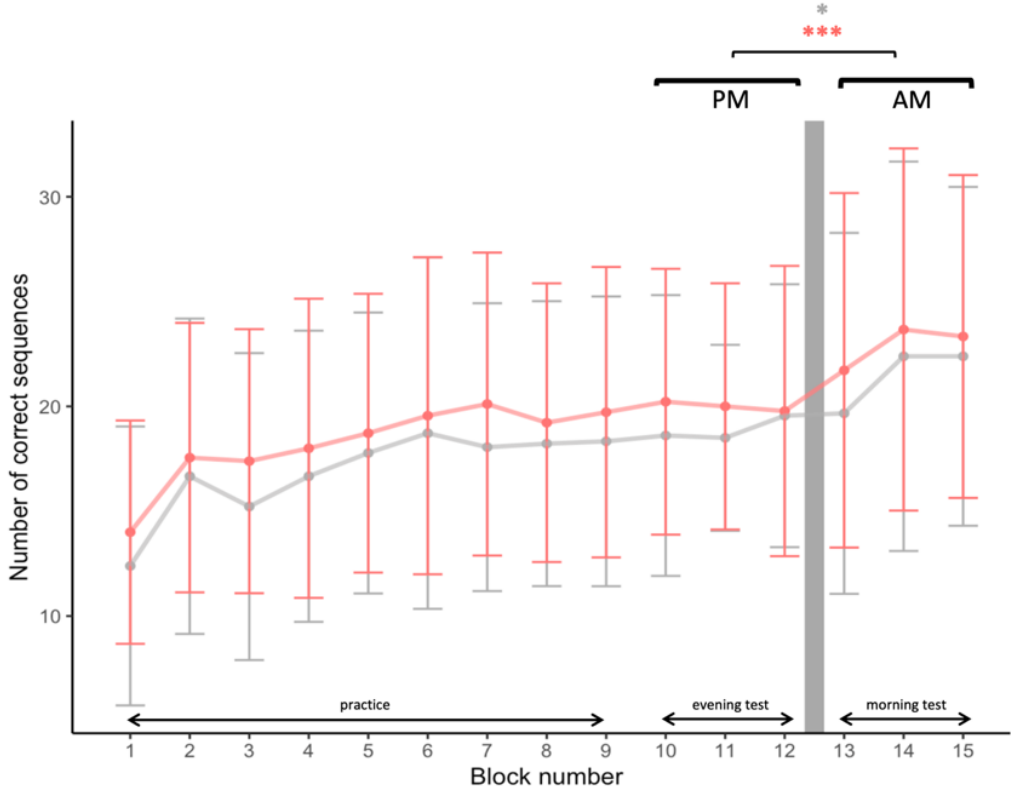



Figure 10: Overnight change in procedural memory

*For the STAT condition (grey) and the ROCK condition (red):*

*Mean of correct sequences across the 15 trials of 30-second blocks in the procedural memory task (± SD). Blocks 1 to 9 represent practice, 10 to 12 the evening test (PM), and 13 to 15 the morning test (AM). The dark grey vertical bar indicates the overnight period.*

*Asterisks denote significance after Bonferroni correction (*<.05).*

## 4.5 Discussion

Using an established rocking motion (0.25 Hz, lateral direction, with excursion over 21 cm) described by Bayer et al.[472] and Perrault et al.[37], this study examined the effects of multiple consecutive (3) nights of rocking stimulation on sleep parameters (i.e. sleep architecture, SOs and spindles characteristics and their neural entrainment, self-reported sleep quality), mood and memory performance (declarative, procedural), compared to two nights in stationary position.

First, we considered the effect of the first overnight under rocking stimulation on sleep. The rocking apparatus stimulation led to a worsening of sleep stage composition, with more awakenings, increased time spent in lighter stages (i.e. N1, N2) and reduced deep sleep and REM sleep. Overall, sleep duration, sleep latency, sleep fragmentation (i.e. SFI, arousal density) were not impacted by the motion and were found to be equivalent to the stationary condition.

Consistent with our results, studies did not report significant changes in overall sleep duration, latency or sleep efficiency under rocking condition[37,471–473] and noted that the effect of rocking motion on sleep mainly concerned sleep stages proportion[37,472]. However, our findings contrast with those of Bayer et al.[472] and Perrault et al.[37], who observed beneficial effects of rocking motion on sleep[37,472]. Specifically, these studies reported a reduction in sleep onset[469,472] and an increase in N3 duration[37], along with a decrease in arousal density[37]. Moreover, an increase in N2 duration under rocking motion was found, but it was associated with reduced sleep onset[472], rather than an increase in N1 duration as observed in our findings. It appears that the present rocking apparatus had the opposite effect, with a detrimental impact on sleep.

Brain oscillations characteristics remained largely unaffected by the rocking apparatus stimulation. Spindle characteristics were comparable to those observed in the stationary condition, and no significant entrainment with the rocking motion was detected following the first night under rocking apparatus stimulation. The reduction in SOs duration observed under rocking motion did not constitute a major change in SOs characteristics, however the bed motion did entrain frontal SOs in N2.

These findings contrast with studies using the same bed motion, which reported an increased in spindle density, concomitant with an increase in sigma power spectrum activity[37,472]. In addition, while no significant increase in SOs density was reported, an increased in SOs count was found[37]. Furthermore, both SOs and spindles were entrained and clustered at specific time points in the bed motion[37,472].

The reduction in the tension/anxiety level may explain the relaxing effect of the rocking motion, as reported by other studies[469,470,472]. Relaxation is typically characterized by a decrease in sympathetic system activity (i.e. respiratory and heart rate), although this was not investigated in this study[620]. Nevertheless, individual's preferred rocking motion settings did not influence sleep quality[473], highlighting that further studies are needed to clarify the relaxation effect of rocking motion.

Research has investigated the effects of rocking in healthy young adults using various motion parameters, such as rotational movements along the roll or pitch axis[470], back-and-forth oscillations in a recliner chair along the y-axis pitch[448], side-to-side pendulum movements[473], or parallel swing bed[469]. While no detrimental effects on sleep quality were identified in these studies, some effect of rocking bed on sleep were observed[448,469,470,473]. An increase in N2 duration, accompanied by a higher spindle count, was observed, although this was reported in minute and did not significantly alter spindle density, SOs characteristics or subjective sleep quality[470]. Napping under rocking motion resulted in accelerated delta power buildup and greater SOs density[473]. The parallel swing bed was associated with a reduction in sleep latency, although the findings were not statistically significant[469]. The recliner chair did not affect sleep duration, but N3 duration increased, along with a shorter SL to N3 under rocking motion[448]. In addition, both spindle count and density were increased.
The significant discrepancies between the results from our rocking apparatus and those in mentioned studies raise an important question: what could explain these differences? Inconsistencies between studies can be attributed to difference regarding the protocol; nap or overnight; but more importantly, the bed motion setting: direction, trajectory, and intensity or peak acceleration.

Rocking stimulation is dependent on the frequency (f) and back-and-forth amplitude ($A_{max}$) of the rocking apparatus, resulting in a specific peak acceleration, calculated as $\alpha_{peak}=(2\pi f)^2*A_{max}$. Evidence from an otoconia-deficient mouse model suggests that the sleep-promoting effects of rocking are mediated by the otolithic organs of the vestibular system and are driven by the maximal linear acceleration of lateral movement[474]. Investigations into acceleration parameters, using a fixed frequency while varying amplitude, have identified an optimal acceleration for sleep architecture at 1 Hz, corresponding to approximately 79 $cm.s^{-2}$. Given that vestibular afferences in mice are three to four times less developed than in humans[475–477], this translates to an estimated 20–25 $cm.s^{-2}$ in humans. Previous studies investigated rocking motion with

varying intensity parameters: approximately 10 to 15 cm.s$^{-2}$ [470], 22 cm.s$^{-2}$ [469], 26 cm.s$^{-2}$ [37,472]. Both animal and human studies have shown that rocking motion at and below 15 cm.s$^{-2}$ did not provide significant benefits for sleep[470,473,474]. Conversely, intensities at or above 35 cm.s$^{-2}$ were found to be detrimental to sleep in both mice[474] and human[473]. Studies using a linear parallel trajectory and a motion intensity of approximately 26 cm.s$^{-2}$ demonstrated improvements in sleep quality in both mice[474] and human (i.e. sleep architecture, spectral activity, brain oscillations, neural entrainment), and memory performance[37,472]. In the present study, the rocking apparatus operated at a frequency around 0.22 ± 0.1 Hz, resulting in a maximum linear acceleration of around 20 cm.s$^{-2}$. This contrasts with the expected acceleration intensity of approximately 26 cm.s$^{-2}$, based on theoretical parameters set at a frequency of 0.25 Hz and an amplitude of 10.5 cm, as used by Bayer et al.[472] and Perrault et al.[37]. The absence of beneficial effect on sleep in our study may therefore be attributable to suboptimal bed parameters, particularly the lower frequency, which likely result in an acceleration peak that did not sufficiently reach the optimal threshold of approximately 26 cm.s$^{-2}$, associated with improvements in sleep quality and memory.

Furthermore, the variation in gravitational force along the longitudinal axis induced by the rocking apparatus was recorded using an accelerometer and followed a sinusoidal trajectory, as illustrated in **Figure 11**. Distinct periods of pronounced positional variations were observed, occurring continuously at both the extremities and the midpoint of the motion cycle (**Figure 11A**). In contrast, the rocking motion employed by Bayer et al.[472] and Perrault et al.[37] appeared smoother and more consistent throughout the cycle (**Figure 11B**). This aligns with the system employed by Bayer et al.[472], where a circular motion was converted into a continuous linear oscillation in the longitudinal plane. In the present study, however, a linear rail-based system was used for back-and-forth movement. Moreover, some participants reported abrupt amplitude variations, describing a sensation of "jerk", particularly at the "motion extremities" and the midpoint, and expressed a preference for a "smoother" and more "continuous motion". These intrinsic characteristics of the rocking apparatus—marked by abrupt jerks—may account for the absence of a beneficial rocking effect in the present study. Conversely, a smoother and more continuous rocking trajectory, in addition to an optimal acceleration peak, appears to be essential for improving on sleep quality.

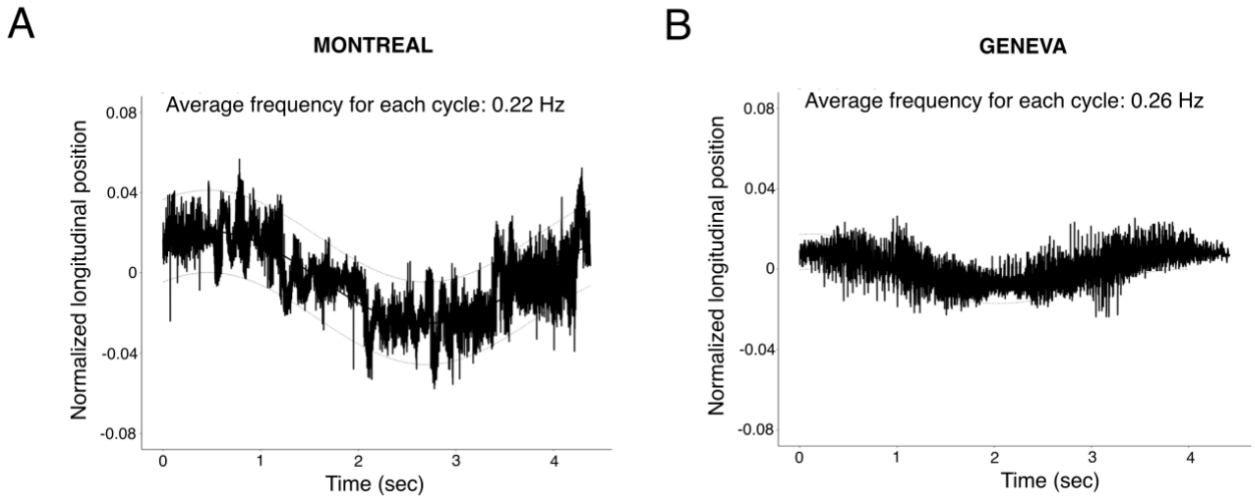



Figure 11: Profile of the rocking motion

*The peaks correspond to the extremities of the back-and-forth movement (left and right, in cm), whereas zero indicates the midpoint of the bed's displacement. Mean longitudinal position for each 4-second cycle over 5 minutes (sampling rate: 100 Hz). The black line shows the overall average trajectory, the smooth black curve represents the fitted sinusoidal model, and the dotted lines indicate ± standard deviation.*

*(A) From the rocking apparatus used in the present study in Montreal*

*(B) From the rocking bed used by Bayer, et al.*[472] *in Geneva obtained via correspondence*

Secondly, we examined the effect of consecutive nights of rocking apparatus stimulation on sleep. Overall, sleep stages that were altered after the first overnight under the rocking condition returned to levels comparable to the stationary condition by the second night, with an increased REM duration and a decreased in both N2 and wake time duration. Additionally, while both N1 and N3 duration were initially affected by rocking on the first night, both progressively increased across the three rocking nights. A similar pattern was observed for SE based on EEG recordings, whereas no significant changes occurred over time for sleep onset, duration, or fragmentation. Alongside this gradual improvement in sleep quality, a reduction in tension/anxiety levels was also observed across the three rocking nights.

Regarding brain oscillations, fast spindle density progressively increased over the three nights in both N2 and N3 under the rocking condition. Neural entrainment emerged on the second rocking night and was maintained on the third night for both slow and fast spindles. In contrast, SO density and duration did not improve on the second and third nights, and SO amplitude decreased on the second consecutive night in both conditions. However, SO entrainment was

evident from the first night in N2 and became more pronounced by the third night under the rocking condition.

Previous studies did not report improvements in sleep quality on the second consecutive overnight under motion[469], nor detrimental effects, except for reduced delta power spectrum in older adults[471]. The observed increase in REM duration may reflect a stress-induced REM sleep rebound, an adaptive strategy to a new sleep environment[621].

While the expected benefits on memory and sleep were not observed, the rocking apparatus demonstrate a potential positive effect on brain oscillations by gradually enhancing neural entrainment of both SOs and spindles, along with an increase in fast spindle density.

Furthermore, sound level measurements may help clarify both the detrimental effects on sleep and memory observed after the first night and the progressive adaptation over the three rocking overnights over the three rocking overnights. The present rocking apparatus generated approximately 40 dB, whereas the stationary condition with the motor turned off produced around 26 dB. In contrast, previous studies investigating rocking stimulation reported sound levels described as "barely detectable" level[469], below 30 dB[473,622], or not exceeding 37 dB[37,472], highlighting a notable difference with the present study. Given that the sleeping brain remains reactive to noise[42], the Night Noise Guidelines for Europe indicate that exposure in the 30–40 dB range can disrupt sleep, leading to increased body movements, more frequent awakenings, and reduced subjective sleep quality, with more pronounced effects at higher noise levels[623,624]. Noise-induced sleep disturbances have been associated with heightened cortical arousal, increased sleep fragmentation, and reduced N3 sleep duration[625–628], as well as an elevated risk of cardiovascular disease[629]. However, in the present study, rocking motion did not appear to affect arousal density. The adverse effects observed on the first rocking night may be attributed to noise exposure, as reported by participants, yet these effects were absent on the second night. This pattern aligns with findings on habituation to noise, as individuals exposed to repeated noise show a reduced likelihood of sleep disturbance over an 8-night period[628]. Nevertheless, interindividual differences in noise sensitivity and habituation remain insufficiently explored in the literature[624].

While an overnight improvement in declarative memory performance was observed in the rocking condition, no significant difference emerged compared to the stationary condition, aligning with previous findings[470,473]. In contrast, other studies have reported an improvement in declarative performance following rocking bed stimulation[37]. Additionally, a positive

association between greater declarative accuracy and increased fast spindle density has been reported[37]. Given that the rocking apparatus stimulation did not enhance spindles and SOs activity, no improvement in memory performance was expected[57,630,631].
Furthermore, rocking apparatus stimulation did not impact procedural memory consolidation, as performance remained equivalent between stationary and rocking conditions, and accuracy did not improve overnight, as would be expected in a typical consolidation process[53,159,632]. The procedural memory task was adapted from a published study on sleep-dependent motor skill learning[53], which involved young adults, similar to the present study. The discrepancy in findings may therefore be attributable to differences in the rocking stimulation parameters used in this study.

Some limitations may interfere with our findings interpretation. While neither procedural nor declarative memory improved under the rocking condition, a high degree of inter-individual variability was observed in memory performance. Approximately 10% of participants maintained high performance throughout the study, whereas around 20% exhibited generally lower scores, potentially indicating a ceiling effect[633]. Additionally, the statistical power of the study did not allow for the identification of responder subtypes, such as individuals with trained motor skills (i.e. gamers, or musician, particularly pianist), who have been shown to exhibit enhanced procedural memory consolidation[634]. Future studies should further characterize the impact of rocking bed stimulation on memory.
Our findings indicate that the brain responded to rocking stimulation, as evidenced by spindles and SOs entrainment. However, event-related potentials were not examined[37], which could have provided insights into whether the neural response to stimulation persisted across the three consecutive nights, similar to findings showing stable SO responses to auditory stimulation after ten consecutive nights[635].

Furthermore, the effects of rocking stimulation could be assessed over a longer duration to determine the latency of expecting effect. Phase-locked acoustic stimulation during SWS has been shown to improve memory retention over a week[437]. However, such improvements did not emerge immediately after the first night but instead developed progressively over three consecutive nights[438]. Similarly, studies on targeted memory reactivation have demonstrated that memory benefits peaks on the third night, suggesting that an adaptive period to auditory stimulation may be necessary[636]. The initial sleep disruption observed on the first night,

followed by a subsequent rescue effect, may reflect a habituation process to the new stimulation environment, potentially delaying the beneficial effects of rocking on sleep and memory.

In conclusion, the first night of rocking stimulation did not improve sleep architecture, brain oscillations, or memory performance and was either ineffective or had adverse effects on sleep and memory. This may be primarily attributed to abrupt movements and noise from the rocking apparatus, which disrupted sleep quality. However, these negative effects were transient, as a rescue effect emerged on the second night, suggesting habituation to the rocking stimulation. Our findings emphasize the necessity of ensuring smooth motion with precise acceleration peak settings to maximize the beneficial effects of rocking on sleep and memory.

**Acknowledgments**
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## 4.6 Tables

### Table 1: Participant demographics

| | Mean ± SD | range | | Mean ± SD | range |
|---|---|---|---|---|---|
| N | 19 | | ISI | | |
| | | | score (/28) | 2.2 ± 2.5 | [0 - 7] |
| Age | 24.9 ± 3.6 | [21 - 31] | PSQI | | |
| | | | score (/21) | 3.3 ± 1.7 | [1 - 7] |
| Sex (n\|%) | | | HADS-Anxiety | | |
| Female | 10 \| 52.6% | | score (/21) | 3.2 ± 2.8 | [0 - 7] |
| Male | 9 \| 47.4% | | HADS-Depression | | |
| | | | score (/21) | 1.5 ± 1.6 | [0 - 5] |
| BMI | 21.6 ± 2.5 | [17 - 27] | MMSQ | | |
| | | | score (/54) | 3.9 ± 4.2 | [0 - 7] |
| Education (n\|%) | | | | | |
| CEGEP (DEP) | 1 \| 5.3% | | Randomisation (n\|%) | | |
| CEGEP (DEC) | 3 \| 15.8% | | Start with ROCK | 9 \| 47.4% | |
| Bachelors | 7 \| 36.8% | | Start with STAT | 10 \| 52.6% | |
| Masters | 6 \| 31.6% | | | | |
| PhD | 2 \| 10.5% | | | | |

BMI, Body Mass Index; ISI, Insomnia Severity Index; HADS, Hospital Anxiety and Depression Scale; MMSQ, Motion Sickness Susceptibility Questionnaire; PSQI, Pittsburg Sleep Quality Index; ROCK, rocking condition; STAT, stationnary condition

### Table 2: Impact of the first rocking apparatus stimulation overnight on outcomes

(A) By comparing Condition (STAT1 versus ROCK1) and Visit (evening versus morning) effect

| Outcomes | STAT1 | | | | ROCK1 | | | | Condition | | | Session | | | Condition X Session | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Evening | | Morning | | Evening | | Morning | | Wald-type stat | | | Wald-type stat | | | Wald-type stat | | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | df | stat | *p* | df | stat | *p* | df | stat | *p* |
| DECLARATIVE MEMORY Answers (%) | | | | | | | | | | | | | | | | | |
| Correct | 48.4[a] | 26.75 | 67.51[a] | 28.88 | 46[b] | 27.43 | 64.42[b] | 32.84 | 1, 18 | 0.35 | 0.55 | 1, 18 | 46.11 | **< 0.001*** | 1, 18 | 0.08 | 0.77 |
| Incorrect | 34.44[a] | 26.68 | 19.91[a] | 24.81 | 33.52[b] | 26.99 | 20.48[b] | 27.12 | 1, 18 | 0.13 | 0.71 | 1, 18 | 42.95 | **< 0.001*** | 1, 18 | 0.26 | 0.60 |
| Unanswered | 17.16[a] | 23.89 | 12.58[a] | 20.92 | 20.48[b] | 21.62 | 15.1 | 24.93 | 1, 18 | 0.4 | 0.52 | 1, 18 | 6.68 | **0.01*** | 1, 18 | 0.79 | 0.37 |
| Accuracy | 6.42[a] | 21.98 | 21.89[a] | 22.82 | 5.74[b] | 22.98 | 20.21[b] | 25.22 | 1, 18 | 0.06 | 0.81 | 1, 18 | 56.17 | **< 0.001*** | 1, 18 | 0.64 | 0.42 |
| PROCEDURAL MEMORY | | | | | | | | | | | | | | | | | |
| Total sequence | 23.09[a] | 5.62 | 26.72[a] | 7.44 | 24.8[b] | 5.82 | 27.76[b] | 7.74 | 1, 17 | 2.77 | 0.11 | 1, 17 | 18.69 | **< 0.001*** | 1, 17 | 0.49 | 0.49 |
| Correct sequence | 18.89[a] | 5.37 | 21.48[a] | 8.14 | 20[b] | 6.07 | 22.91[b] | 8.02 | 1, 17 | 1.95 | 0.18 | 1, 17 | 11.22 | **0.004*** | 1, 17 | 0.1 | 0.75 |
| Accuracy | 81.28 | 7.77 | 78.89 | 14.74 | 80.17 | 11.94 | 81.83 | 13.44 | 1, 17 | 0.35 | 0.55 | 1, 17 | 1.23 | 0.26 | 1, 17 | 0.51 | 0.47 |
| POMS | | | | | | | | | | | | | | | | | |
| Vigor-Activity (/24) | 9.83 | 4.95 | 10.94 | 5.09 | 9.44 | 3.91 | 10.78 | 4.78 | 1, 17 | 0.16 | 0.69 | 1, 17 | 3 | 0.10 | 1, 17 | 0.1 | 0.75 |
| Tension-Anxiety (/24) | 1.33 | 2.72 | 1.06 | 2.24 | 1.33[b] | 1.85 | 0.17[b] | 0.38 | 1, 17 | 0.69 | 0.40 | 1, 17 | 11.13 | **< 0.001*** | 1, 17 | 4.16 | **0.04** |
| Fatigue-Inertia (/20) | 3.33 | 3.56 | 1.72 | 2.3 | 2.44 | 2.71 | 1.33 | 1.19 | 1, 17 | 0.82 | 0.36 | 1, 17 | 4.44 | **0.04** | 1, 17 | 1.05 | 0.30 |

POMS, Profile Of Mood States questionnaire; ROCK1, rocking condition at Visit 1; STAT1, stationnary condition at Visit 1
Declarative memory: n=19; Procedural memory: n=18; POMS: n=18
Asterisks represent significance (*p*) after Bonferonni correction
Significant post hoc analysis: a: Evening versus Morning in STAT1; b: Evening versus Morning in ROCK1

(B) By comparing STAT1 versus ROCK1 on overnight change

| Outcomes | STAT1 | | ROCK1 | | STAT1 vs ROCK1 Wilcoxon test or *t-test* | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | df | stat | *p* | *g'* |
| Difference Evening - Morning | | | | | | | | |
| DECLARATIVE MEMORY | | | | | | | | |
| Accuracy | 15.47 | 9.25 | 14.47 | 9.22 | 1, 18 | 0.52 | 0.61 | 0.10 |
| PROCEDURAL MEMORY | | | | | | | | |
| Total sequence | 3.63 | 4.5 | 2.97 | 2.95 | 1, 17 | 93.5 | 0.74 | 0.16 |
| Correct sequence | 2.59 | 4.78 | 2.91 | 3.19 | 1, 17 | *-0.32* | *0.75* | *-0.07* |
| Accuracy | -2.39 | 13.18 | 1.66 | 6.88 | 1, 17 | 65 | 0.39 | -0.37 |
| POMS | | | | | | | | |
| Vigor-Activity (/24) | 1.11 | 3.38 | 1.33 | 3.29 | 1, 17 | *-0.32* | *0.75* | -0.06 |
| Tension-Anxiety (/24) | -0.28 | 1.18 | -1.17 | 1.69 | 1, 17 | 37 | 0.09 | 0.59 |
| Fatigue-Inertia (/20) | -1.61 | 2.81 | -1.11 | 2.42 | 1, 17 | 52.5 | 0.68 | -0.18 |
| SUBJECTIVE NIGHT REVIEW | | | | | | | | |
| SE (%) | 103.47 | 5.97 | 104.88 | 5.86 | 1, 18 | 43 | 0.20 | -0.23 |
| SOL (min) | 16.53 | 8.69 | 19.63 | 9.53 | 1, 18 | 31.5 | 0.19 | -0.33 |
| TST (min) | 451.33 | 42.62 | 436.58 | 46.82 | 1, 18 | 87.5 | **0.03** | 0.31 |
| WASO (min) | 13.53 | 21.66 | 17.74 | 18.47 | 1, 18 | 44.5 | 0.23 | -0.2 |
| Sleep quality (/5) | 3.89 | 0.81 | 3.74 | 0.87 | 1, 18 | 30 | 0.35 | 0.18 |
| Rocking apparatus (/10) | | | | | | | | |
| Comfortable | 8.37 | 1.21 | 8 | 1.83 | 1, 18 | 28.5 | 0.15 | 0.2 |
| Relaxing | 7.79 | 1.44 | 7.42 | 1.68 | 1, 18 | 36.5 | 0.38 | 0.22 |
| Pleasant | 8.05 | 1.18 | 7.53 | 1.74 | 1, 18 | 70 | 0.08 | 0.32 |
| Noisy | 8.74 | 1.88 | 6 | 2.24 | 1, 18 | 130 | **0.001*** | 1.27 |
| SLEEP ARCHITECTURE | | | | | | | | |
| SE (%) | 90.22 | 4.04 | 88.44 | 4.23 | 1, 18 | *1.49* | *0.15* | 0.41 |
| SOL (min) | 18.25 | 13.45 | 17.54 | 11.07 | 1, 18 | *0.23* | *0.82* | 0.05 |
| TST (min) | 422.84 | 37.31 | 415.47 | 40.41 | 1, 18 | *0.96* | *0.35* | 0.18 |
| SFI | 6.81 | 1.53 | 6.92 | 1.52 | 1, 18 | *-0.45* | *0.66* | -0.07 |
| Arousal density (event/hour) | 14.87 | 4.56 | 16.13 | 5.46 | 1, 18 | *-1.33* | *0.2* | -0.24 |

POMS, Profile Of Mood States questionnaire; ROCK1, rocking condition at Visit 1; SE, sleep efficiency; SFI, sleep fragmentation index; SOL, sleep onset latency; STAT1, stationnary condition at Visit 1; TST, total sleep time; WASO, wake after sleep onset

Declarative memory: n=19; Procedural memory: n=18; POMS: n=18; Night review: n= 19; Sleep architecture: n=19

Asterisks represent significance (*p* ) after Bonferonni correction

Table 3: Consistency of the rocking apparatus stimulation effect over two consecutive nights

| Outcomes | STAT1 | | STAT2 | | ROCK1 | | ROCK2 | | Condition | | | Visit | | | Condition X Visit | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | *df* | stat | *p* | *df* | stat | *p* | *df* | stat | *p* |
| DECLARATIVE MEMORY | | | | | | | | | | | | | | | | | |
| Accuracy | 15.47 | 9.25 | 15.05 | 10.02 | 14.47 | 9.22 | 15.58 | 9.9 | 1, 18 | 0.01 | 0.91 | 1, 18 | 0.17 | 0.69 | 1, 18 | 1.62 | 0.22 |
| POMS | | | | | | | | | | | | | | | | | |
| Vigor-Activity (/24) | 0.76 | 3.13 | -0.65 | 5.59 | 1.06 | 3.17 | -0.06 | 7.03 | 1,16 | *0.34* | *0.56* | 1,16 | *0.85* | *0.37* | 1,16 | *0.04* | *0.84* |
| Tension-Anxiety (/24) | -0.12 | 0.99 | -0.29 | 0.69 | -1.18 | 1.74 | -0.47 | 1.07 | 1,16 | 3.67 | 0.06 | 1,16 | 5.49 | **0.02** | 1,16 | 1.6 | 0.20 |
| Fatigue-Inertia (/20) | -1.53 | 2.87 | -1.12 | 2.12 | -1.18 | 2.48 | -1.12 | 1.69 | 1,16 | 0.62 | 0.43 | 1,16 | 0.001 | 0.94 | 1,16 | 0.12 | 0.72 |
| SUBJECTIVE NIGHT REVIEW | | | | | | | | | | | | | | | | | |
| SE (%) | 103.47 | 5.97 | 102.28 | 3.86 | 104.88 | 5.86 | 104.69 | 8.36 | 1, 18 | 4.64 | **0.03*** | 1, 18 | 1.95 | 0.16 | 1, 18 | 0.13 | 0.71 |
| SOL (min) | 16.53 | 8.69 | 14.58 | 6.79 | 19.63 | 9.53 | 17.79 | 11.06 | 1, 18 | 2.48 | 0.11 | 1, 18 | 2.37 | 0.12 | 1, 18 | 0.001 | 0.97 |
| TST (min) | 451.33 | 42.62 | 457.36 | 45.02 | 436.58 | 46.82 | 457.39 | 51.9 | 1, 18 | 1.04 | 0.30 | 1, 18 | 1.99 | 0.15 | 1, 18 | 0.73 | 0.39 |
| WASO (min) | 13.53 | 21.66 | 9.32 | 13.96 | 17.74 | 18.47 | 16.24 | 23.27 | 1, 18 | 4.51 | **0.03*** | 1, 18 | 1.63 | 0.20 | 1, 18 | 0.11 | 0.74 |
| Sleep quality (/5) | 3.89 | 0.81 | 4.21 | 0.79 | 3.74 | 0.87 | 3.89 | 0.81 | 1, 18 | 6.32 | **0.01*** | 1, 18 | 4.81 | **0.03** | 1, 18 | 0.69 | 0.40 |
| Rocking apparatus (/10) | | | | | | | | | | | | | | | | | |
| Comfortable | 8.37 | 1.21 | 8.32 | 1.38 | 8 | 1.83 | 8.21 | 1.65 | 1, 18 | 0.26 | 0.60 | 1, 18 | 0.51 | 0.47 | 1, 18 | 0.45 | 0.50 |
| Relaxing | 7.79 | 1.44 | 7.95 | 1.27 | 7.42 | 1.68 | 7.89 | 1.63 | 1, 18 | 0.02 | 0.90 | 1, 18 | 5.01 | **0.03** | 1, 18 | 1.96 | 0.16 |
| Pleasant | 8.05 | 1.18 | 8.05 | 1.31 | 7.53 | 1.74 | 8 | 1.49 | 1, 18 | 0.34 | 0.55 | 1, 18 | 3.01 | 0.08 | 1, 18 | 2.29 | 0.13 |
| Noisy | 8.74[c] | 1.88 | 8.11 | 2.4 | 6[c] | 2.24 | 6.89 | 2.47 | 1, 18 | 11.62 | **< 0.001*** | 1, 18 | 0.45 | 0.50 | 1, 18 | 5.39 | **0.02** |
| SLEEP ARCHITECTURE | | | | | | | | | | | | | | | | | |
| SE (%) | 90.22 | 4.04 | 89.81 | 7.61 | 88.44 | 4.23 | 89.99 | 6.23 | 1, 18 | 2.58 | 0.10 | 1, 18 | 2.48 | 0.11 | 1, 18 | 0.66 | 0.41 |
| SOL (min) | 18.25 | 13.45 | 17.44 | 18.87 | 17.54 | 11.07 | 17.86 | 15.37 | 1, 18 | 0.07 | 0.79 | 1, 18 | 1.1 | 0.29 | 1, 18 | 0.01 | 0.93 |
| TST (min) | 422.84 | 37.31 | 426.21 | 49.46 | 415.47 | 40.41 | 434.45 | 51.58 | 1, 18 | 0.001 | 0.95 | 1, 18 | 0.75 | 0.39 | 1, 18 | 0.87 | 0.36 |
| SFI | 6.81 | 1.53 | 6.55 | 1.7 | 6.92 | 1.52 | 6.52 | 1.34 | 1, 18 | 0.04 | 0.85 | 1, 18 | 2.26 | 0.15 | 1, 18 | 0.12 | 0.73 |
| Arousal density (event/hour) | 14.87 | 4.56 | 14.54 | 4.67 | 16.13 | 5.46 | 14.61 | 4.75 | 1, 18 | 0.84 | 0.37 | 1, 18 | 1.49 | 0.23 | 1, 18 | 0.49 | 0.49 |
| Duration (%TSP) | | | | | | | | | | | | | | | | | |
| N1 | 2.36[c] | 0.66 | 2.52 | 1.47 | 3[c] | 1.14 | 2.49 | 0.87 | 1, 18 | 5.51 | **0.02*** | 1, 18 | 2.73 | 0.09 | 1, 18 | 0.66 | 0.41 |
| N2 | 45.26[c] | 7.14 | 42.09 | 8.81 | 48.87[b,c] | 7.13 | 43.55[b] | 6.35 | 1, 18 | 5.51 | **0.03*** | 1, 18 | 9.87 | **0.01*** | 1, 18 | 0.98 | 0.33 |
| N3 | 24.39 | 6.18 | 24.36 | 8.53 | 21.83 | 6.15 | 24.26 | 6.7 | 1, 18 | 3.82 | 0.05 | 1, 18 | 0.27 | 0.60 | 1, 18 | 1.99 | 0.15 |
| REM | 22.92[a,c] | 4.77 | 25.49[a] | 5.16 | 19.31[b,c] | 4.23 | 23.95[b] | 5.23 | 1, 18 | 13.67 | **0.002*** | 1, 18 | 26.7 | **< 0.001*** | 1, 18 | 1.93 | 0.18 |
| Wake | 5.06[c] | 3.08 | 5.54 | 5.62 | 6.99[c] | 3.02 | 5.74 | 4.39 | 1, 18 | 7.33 | **0.007*** | 1, 18 | 2.73 | 0.09 | 1, 18 | 3.44 | 0.06 |
| Arousal density (event/min) | | | | | | | | | | | | | | | | | |
| N1 | 0.52 | 0.2 | 0.53 | 0.29 | 0.69 | 0.3 | 0.63 | 0.35 | 1, 18 | 4.2 | 0.06 | 1, 18 | 0.3 | 0.59 | 1, 18 | 0.31 | 0.58 |
| N2 | 0.34 | 0.15 | 0.29 | 0.13 | 0.4 | 0.18 | 0.3 | 0.13 | 1, 18 | 2.4 | 0.13 | 1, 18 | 14.26 | **0.001*** | 1, 18 | 1.53 | 0.23 |
| N3 | 0.1 | 0.07 | 0.08 | 0.04 | 0.09 | 0.07 | 0.1 | 0.07 | 1, 18 | 0.02 | 0.90 | 1, 18 | 0.11 | 0.73 | 1, 18 | 1.42 | 0.23 |
| REM | 0.25 | 0.12 | 0.33 | 0.19 | 0.21 | 0.13 | 0.31 | 0.3 | 1, 18 | 13 | **< 0.001*** | 1, 18 | 13.3 | **< 0.001*** | 1, 18 | 0.03 | 0.86 |
| SL to stage (min) | | | | | | | | | | | | | | | | | |
| N2 | 20.75 | 13.7 | 19.42 | 18.87 | 20.41 | 11.47 | 20.23 | 15.92 | 1, 18 | 0.09 | 0.76 | 1, 18 | 1.85 | 0.17 | 1, 18 | 0.01 | 0.92 |
| N3 | 31.8 | 14.76 | 29.23 | 20.18 | 31.88 | 12.43 | 31.07 | 15.8 | 1, 18 | 0.46 | 0.49 | 1, 18 | 3.59 | 0.06 | 1, 18 | 0.71 | 0.39 |
| REM | 107.04[a] | 40.1 | 87.28[a] | 26.76 | 119.7 | 36.08 | 101.52 | 31.2 | 1, 18 | 5.82 | **0.02** | 1, 18 | 7.06 | **0.01*** | 1, 18 | 0.01 | 0.93 |

Declarative memory: n=19; POMS: n=17; Night review: n= 19; Sleep architecture: n=19

POMS, Profile Of Mood States questionnaire; ROCK, rocking condition; SE, sleep efficiency; SFI, sleep fragmentation index; SL, sleep latency; SOL, sleep onset latency; STAT, stationnary condition; TST, total sleep time; TSP, total sleep period; WASO, wake after sleep onset

ANOVA or Wald-type statistic: asterisks represent significance (p) after Bonferonni correction

Significant post hoc analysis: a: STAT1 versus STAT2; b: ROCK1 versus ROCK2; c: STAT1 versus ROCK1

Table 4: Effect of the rocking apparatus stimulation intervention over multiple nights

| Outcomes | ROCK1 | | ROCK2 | | ROCK3 | | Visit | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Friedman test or RM-ANOVA | | |
| | Mean | SD | Mean | SD | Mean | SD | df | stat | *p* |
| DECLARATIVE MEMORY | | | | | | | | | |
| Accuracy | 13.76 | 9.43 | 14.41 | 9.81 | 12.71 | 10.46 | 2, 32 | 1.45 | 0.25 |
| POMS | | | | | | | | | |
| Vigor-Activity (/24) | 1.33 | 3.2 | 0.33 | 7.34 | -0.4 | 5.46 | *2, 28* | *0.7* | *0.50* |
| Tension-Anxiety (/24) | -1.33[a,c] | 1.8 | -0.53[a] | 1.13 | 0[c] | 2.24 | 2, 28 | 11.31 | **0.003*** |
| Fatigue-Inertia (/20) | -1.4 | 2.56 | -1.27 | 1.75 | -1.13 | 1.68 | 2, 28 | 1.48 | 0.47 |
| SUBJECTIVE NIGHT REVIEW | | | | | | | | | |
| SE (%) | 104.54 | 5.21 | 104.92 | 9.03 | 103.28 | 5.01 | 2, 30 | 3 | 0.22 |
| SOL (min) | 19.56 | 9.78 | 17.69 | 11.93 | 17 | 10.8 | 2, 30 | 0.49 | 0.78 |
| TST (min) | 439.69 | 49.45 | 456.9 | 50.9 | 454.99 | 47.75 | 2, 30 | 5.15 | 0.07 |
| WASO (min) | 16.81 | 16.25 | 16.66 | 24.92 | 12.31 | 15.49 | 2, 30 | 2.39 | 0.30 |
| Sleep quality (/5) | 3.88 | 0.89 | 4 | 0.82 | 4 | 0.82 | 2, 30 | 1.12 | 0.57 |
| Rocking apparatus (/10) | | | | | | | | | |
| Comfortable | 7.94 | 1.98 | 8.19 | 1.8 | 8.38 | 1.45 | 2, 30 | 2.14 | 0.34 |
| Relaxing | 7.5 | 1.71 | 8 | 1.67 | 7.88 | 1.78 | 2, 30 | 3.66 | 0.16 |
| Pleasant | 7.62 | 1.86 | 8.12 | 1.5 | 8 | 1.75 | 2, 30 | 3.83 | 0.14 |
| Noisy | 6.25 | 2.35 | 6.81 | 2.64 | 7.31 | 2.06 | 2, 30 | *4.48* | ***0.02*** |
| SLEEP ARCHITECTURE | | | | | | | | | |
| SE (%) | 88.63[c] | 3.97 | 89.97 | 6.6 | 90.37[c] | 5.65 | 2, 32 | 8.82 | **0.01*** |
| SOL (min) | 18.47 | 11.2 | 18.58 | 16.09 | 17.24 | 13.5 | 2, 32 | 0.47 | 0.79 |
| TST (min) | 417.18 | 42.32 | 438.65 | 52.88 | 428.59 | 48.82 | 2, 32 | 0.87 | 0.43 |
| SFI | 6.85 | 1.56 | 6.51 | 1.37 | 6.6 | 1.62 | 2, 32 | 0.5 | 0.61 |
| Arousal density (event/hour) | 15.67 | 5.34 | 14.95 | 4.91 | 13.69 | 3.58 | 2, 32 | 1.54 | 0.23 |

Declarative memory: n=17; POMS: n=15; Night review: n= 16; Sleep architecture: n=17
POMS, Profile Of Mood States questionnaire; ROCK, rocking condition; SE, sleep efficiency; SFI, sleep fragmentation index; SL, sleep latency; SOL, sleep onset latency; TST, total sleep time; TSP, total sleep period; WASO, wake after sleep onset
Asterisks represent significance (*p*) after Bonferonni correction
Significant post hoc analysis: a: ROCK1 versus ROCK2; b: ROCK2 versus ROCK3; c: ROCK1 versus ROCK3

Table 5: Impact of the first rocking apparatus stimulation overnight on spindle and slow oscillation

| Outcomes | STAT1 | | | | ROCK1 | | | | Condition | | | Stage | | | Condition X Stage | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N2 | | N3 | | N2 | | N3 | | ANOVA or Wald-type statistic | | | ANOVA or Wald-type statistic | | | ANOVA or Wald-type statistic | | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | df | stat | *p* | df | stat | *p* | df | stat | *p* |
| SLEEP SPINDLE | | | | | | | | | | | | | | | | | |
| Channel: Fz | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 1.45 | 0.51 | 1.37 | 0.54 | 1.40 | 0.44 | 1.32 | 0.52 | 1, 18 | 0.67 | 0.40 | 1, 18 | 0.27 | 0.59 | 1, 18 | 0.004 | 0.94 |
| Duration (s) | 0.78 | 0.08 | 0.72 | 0.07 | 0.78 | 0.06 | 0.71 | 0.06 | 1, 18 | 0.16 | 0.68 | 1, 18 | 44.92 | **< 0.001*** | 1, 18 | 9.04 | **0.003*** |
| Amplitude (µV) | 130.51 | 32.76 | 153.37 | 41.58 | 136.68 | 38.94 | 152.92 | 41.96 | 1, 18 | 0.42 | 0.52 | 1, 18 | 16.42 | **0.001*** | 1, 18 | 4.66 | **0.045** |
| Frequency (Hz) | 11.26 | 1.69 | 10.91 | 1.59 | 11.47 | 1.48 | 11.05 | 1.49 | 1, 18 | 0.02 | 0.88 | 1, 18 | 18.08 | **< 0.001*** | 1, 18 | 0.49 | 0.48 |
| Channel: Pz | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 1.90 | 0.70 | 1.69 | 0.83 | 1.67 | 0.50 | 1.39 | 0.65 | 1, 18 | 5.33 | **0.03** | 1, 18 | 8.55 | **0.009*** | 1, 18 | 0.55 | 0.46 |
| Duration (s) | 0.82 | 0.09 | 0.72 | 0.07 | 0.79 | 0.08 | 0.69 | 0.04 | 1, 18 | 4.20 | 0.05 | 1, 18 | 128.86 | **< 0.001*** | 1, 18 | 0.01 | 0.89 |
| Amplitude (µV) | 87.98 | 21.15 | 106.36 | 31.84 | 94.53 | 34.45 | 107.03 | 28.06 | 1, 18 | 0.41 | 0.51 | 1, 18 | 48.03 | **< 0.001*** | 1, 18 | 0.15 | 0.69 |
| Frequency (Hz) | 12.64 | 1.82 | 13.08 | 0.65 | 12.48 | 1.82 | 13.03 | 0.66 | 1, 18 | 0.09 | 0.75 | 1, 18 | 0.13 | 0.72 | 1, 18 | 0.45 | 0.49 |
| SLOW OSCILLATION | | | | | | | | | | | | | | | | | |
| Channel: Fz | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 4.33 | 0.91 | 5.45 | 0.94 | 4.17 | 1.05 | 5.83 | 0.53 | 1, 18 | 0.70 | 0.40 | 1, 18 | 110.20 | **< 0.001*** | 1, 18 | 8.29 | **0.004*** |
| Duration (s) | 1.34 | 0.05 | 1.29[b] | 0.08 | 1.33 | 0.06 | 1.26[b] | 0.06 | 1, 18 | 5.98 | **0.01*** | 1, 18 | 18.32 | **< 0.001*** | 1, 18 | 4.53 | **0.03** |
| Amplitude (µV) | 149.88 | 38.58 | 233.73 | 68.25 | 167.75 | 67.40 | 242.05 | 69.67 | 1, 18 | 2.74 | 0.09 | 1, 18 | 216.96 | **< 0.001*** | 1, 18 | 0.94 | 0.33 |
| Frequency (Hz) | 12.43 | 0.18 | 12.16 | 0.22 | 12.43 | 0.18 | 12.15 | 0.21 | 1, 18 | 0.09 | 0.76 | 1, 18 | 57.17 | **< 0.001*** | 1, 18 | 0.67 | 0.42 |

N=19
ROCK1, rocking condition at Visit 1; STAT1, stationnary condition at Visit 1
Asterisks represent significance (*p*) after Bonferonni correction
Significant post hoc analysis: a: STAT1 versus ROCK1 during N2; b: STAT1 versus ROCK1 during N3

## Table 6: Consistency of the rocking apparatus stimulation effect over two consecutive nights on spindle and slow oscillation

| Outcome measures | STAT1 | | STAT2 | | ROCK1 | | ROCK2 | | Condition | | | Visit | | | Condition X Visit | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | df | stat | *p* | df | stat | *p* | df | stat | *p* |
| SLEEP SPINDLE | | | | | | | | | | | | | | | | | |
| Channel: Fz | | | | | | | | | | | | | | | | | |
| Stage: N2 | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 1.45 | 0.52 | 1.53 | 0.48 | 1.42 | 0.42 | 1.39 | 0.53 | 1, 17 | 1.36 | 0.26 | 1, 17 | 0.09 | 0.77 | 1, 17 | 0.53 | 0.47 |
| Duration (s) | 0.77 | 0.07 | 0.78 | 0.06 | 0.78 | 0.05 | 0.76 | 0.06 | 1, 17 | 0.18 | 0.67 | 1, 17 | 0.13 | 0.72 | 1, 17 | 1.69 | 0.21 |
| Amplitude (µV) | 132.44 | 32.56 | 122.77 | 32.93 | 136.44 | 40.05 | 124.8 | 35.93 | 1, 17 | 0.57 | 0.45 | 1, 17 | 12.47 | **0.003*** | 1, 17 | 0.12 | 0.72 |
| Frequency (Hz) | 11.22 | 1.72 | 11.54 | 1.67 | 11.56 | 1.45 | 11.46 | 1.57 | 1, 17 | 0.08 | 0.77 | 1, 17 | 0.40 | 0.52 | 1, 17 | 0.43 | 0.5 |
| Stage: N3 | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 1.37 | 0.55 | 1.45 | 0.51 | 1.35 | 0.5 | 1.38 | 0.64 | 1, 17 | 0.54 | 0.46 | 1, 17 | 0.71 | 0.39 | 1, 17 | 0.17 | 0.67 |
| Duration (s) | 0.72 | 0.06 | 0.72 | 0.06 | 0.7 | 0.06 | 0.7 | 0.06 | 1, 17 | 4.74 | 0.05 | 1, 17 | 0.09 | 0.76 | 1, 17 | 0.51 | 0.48 |
| Amplitude (µV) | 156.01 | 41.11 | 151.23 | 43.44 | 154.74 | 42.39 | 151.2 | 44.5 | 1, 17 | 0.16 | 0.69 | 1, 17 | 10.03 | **0.01*** | 1, 17 | 0.03 | 0.87 |
| Frequency (Hz) | 10.87 | 1.62 | 11.2 | 1.64 | 11.16 | 1.44 | 11.23 | 1.56 | 1, 17 | 0.07 | 0.78 | 1, 17 | 2.25 | 0.13 | 1, 17 | 0.1 | 0.75 |
| Channel: Pz | | | | | | | | | | | | | | | | | |
| Stage: N2 | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 1.89 | 0.71 | 1.75 | 0.79 | 1.65 | 0.51 | 1.88 | 0.71 | 1, 17 | 0.21 | 0.65 | 1, 17 | 0.13 | 0.71 | 1, 17 | 8.46 | **0.01*** |
| Duration (s) | 0.82 | 0.09 | 0.81 | 0.1 | 0.78 | 0.08 | 0.81 | 0.08 | 1, 17 | 0.76 | 0.39 | 1, 17 | 0.49 | 0.49 | 1, 17 | 2.43 | 0.13 |
| Amplitude (µV) | 89.81 | 20.15 | 89.65 | 21.77 | 96.28 | 34.56 | 88.98 | 20.13 | 1, 17 | 0.04 | 0.83 | 1, 17 | 0.81 | 0.36 | 1, 17 | 0.47 | 0.49 |
| Frequency (Hz) | 12.61 | 1.87 | 12.2 | 2.08 | 12.46 | 1.87 | 12.47 | 2.11 | 1, 17 | 0.12 | 0.71 | 1, 17 | 0.001 | 0.98 | 1, 17 | 1.46 | 0.22 |
| Stage: N3 | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 1.69 | 0.85 | 1.58 | 0.79 | 1.37 | 0.66 | 1.68 | 0.75 | 1, 17 | 1.22 | 0.28 | 1, 17 | 0.3 | 0.58 | 1, 17 | 9.06 | **0.01*** |
| Duration (s) | 0.72 | 0.07 | 0.7 | 0.06 | 0.69 | 0.04 | 0.69 | 0.04 | 1, 17 | 2.47 | 0.11 | 1, 17 | 0.35 | 0.55 | 1, 17 | 1.11 | 0.29 |
| Amplitude (µV) | 108.33 | 31.55 | 107.84 | 29.08 | 108.53 | 28.08 | 108.64 | 28.15 | 1, 17 | 0.01 | 0.94 | 1, 17 | 0.12 | 0.72 | 1, 17 | 0.005 | 0.94 |
| Frequency (Hz) | 13.09 | 0.67 | 13.03 | 0.73 | 13.04 | 0.68 | 13.21 | 0.72 | 1, 17 | 0.29 | 0.59 | 1, 17 | 0.43 | 0.51 | 1, 17 | 3.83 | 0.07 |
| SLOW OSCILLATION | | | | | | | | | | | | | | | | | |
| Channel: Fz | | | | | | | | | | | | | | | | | |
| Stage: N2 | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 4.36[a] | 0.93 | 5.22[a] | 0.7 | 4.17 | 1.08 | 4.55 | 1.3 | 1, 17 | 2.67 | 0.10 | 1, 17 | 17.68 | **< 0.001*** | 1, 17 | 1.03 | 0.3 |
| Duration (s) | 1.34 | 0.05 | 1.31 | 0.06 | 1.33 | 0.06 | 1.32 | 0.05 | 1, 17 | 0.06 | 0.81 | 1, 17 | 6.8 | **0.02*** | 1, 17 | 0.89 | 0.35 |
| Amplitude (µV) | 152.11[a] | 38.42 | 143.24[a] | 39.04 | 170.48[b] | 68.27 | 155.22[b] | 44.53 | 1, 17 | 2.50 | 0.11 | 1, 17 | 15.11 | **< 0.001*** | 1, 17 | 0.43 | 0.5 |
| Frequency (Hz) | 12.43 | 0.18 | 12.41 | 0.18 | 12.44 | 0.18 | 11.2 | 3.8 | 1, 17 | 1.20 | 0.27 | 1, 17 | 0.22 | 0.63 | 1, 17 | 0.75 | 0.38 |
| Stage: N3 | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 5.47[a] | 0.97 | 6.11[a] | 0.67 | 5.85 | 0.54 | 6.36 | 1.66 | 1, 17 | 0.53 | 0.46 | 1, 17 | 11.42 | **0.001*** | 1, 17 | 2.03 | 0.15 |
| Duration (s) | 1.28[a,c] | 0.08 | 1.26[a] | 0.07 | 1.26[c] | 0.06 | 1.26 | 0.06 | 1, 17 | 9.80 | **0.002*** | 1, 17 | 8.36 | **0.004*** | 1, 17 | 4.58 | **0.03** |
| Amplitude (µV) | 237.79 | 67.83 | 232.86 | 69.04 | 244.99 | 70.46 | 233.65 | 64.04 | 1, 17 | 0.06 | 0.79 | 1, 17 | 3.43 | 0.06 | 1, 17 | 0.17 | 0.67 |
| Frequency (Hz) | 12.17 | 0.23 | 12.18 | 0.24 | 12.16 | 0.22 | 10.94 | 3.7 | 1, 17 | 1.25 | 0.26 | 1, 17 | 0.02 | 0.88 | 1, 17 | < 0.001 | 0.98 |

N=18
ROCK, rocking condition; STAT, stationnary condition
ANOVA or Wald-type statistic: Asterisks represent significance (*p* ) after Bonferonni correction
Significant post hoc analysis: a: STAT1 versus STAT2; b: ROCK1 versus ROCK2; c: STAT1 versus ROCK1; d: STAT2 versus ROCK2

## Table 7: Effect of the rocking apparatus stimulation intervention over multiple nights on spindle and slow oscillation

| Outcome measures | stage N2 | | | | | | stage N3 | | | | | | Visit | | | Stage | | | Visit X Stage | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ROCK1 | | ROCK2 | | ROCK3 | | ROCK1 | | ROCK2 | | ROCK3 | | Friedman test or RM-ANOVA | | | Friedman test or RM-ANOVA | | | Friedman test or RM-ANOVA | | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | df | stat | *p* | df | stat | *p* | df | stat | *p* |
| SLEEP SPINDLE | | | | | | | | | | | | | | | | | | | | | |
| Channel: Fz | | | | | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 1.47 | 0.4 | 1.43 | 0.52 | 1.62 | 0.44 | 1.43 | 0.47 | 1.42 | 0.64 | 1.56 | 0.4 | 2, 30 | 1.77 | 0.41 | 2, 30 | < 0.001 | 0.97 | 2, 30 | 1.4 | 0.49 |
| Duration (s) | 0.78 | 0.06 | 0.77 | 0.06 | 0.79 | 0.05 | 0.71 | 0.05 | 0.7 | 0.07 | 0.7 | 0.05 | 2, 30 | 1.64 | 0.2 | 2, 30 | 38.27 | **< 0.001*** | 2, 30 | 0.43 | 0.65 |
| Amplitude (µV) | 132.65 | 36 | 122.61 | 35.93 | 122.52 | 35.95 | 154.08 | 44.22 | 150.96 | 45.94 | 151.72 | 45.72 | 2, 30 | 2.48 | 0.1 | 2, 30 | 51.47 | **< 0.001*** | 2, 30 | 3.14 | 0.06 |
| Frequency (Hz) | 11.69 | 1.4 | 11.63 | 1.46 | 11.84 | 1.48 | 11.33 | 1.36 | 11.41 | 1.44 | 11.52 | 1.46 | 2, 30 | 1.08 | 0.58 | 2, 30 | 10.46 | **0.001*** | 2, 30 | 4.75 | 0.09 |
| Channel: Pz | | | | | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 1.62[a,e] | 0.52 | 1.95[a] | 0.66 | 2.02[e] | 0.51 | 1.42[f] | 0.68 | 1.74 | 0.74 | 1.88[f] | 0.57 | 2, 30 | 4.45 | **0.02*** | 2, 30 | 12.64 | **0.003*** | 2, 30 | 0.44 | 0.64 |
| Duration (s) | 0.78[a,e] | 0.08 | 0.82[a] | 0.08 | 0.84[e] | 0.08 | 0.69[f] | 0.04 | 0.7 | 0.04 | 0.72[f] | 0.04 | 2, 30 | 4.75 | **0.02*** | 2, 30 | 85.63 | **< 0.001*** | 2, 30 | 8.04 | **0.002*** |
| Amplitude (µV) | 89.5 | 19.53 | 88 | 20.36 | 86.31 | 19.01 | 105.15 | 23.59 | 109.84 | 28.62 | 109.57 | 27.3 | 2, 30 | 0.4 | 0.67 | 2, 30 | 63.89 | **< 0.001*** | 2, 30 | 12.11 | **< 0.001*** |
| Frequency (Hz) | 12.44 | 1.99 | 12.71 | 1.93 | 13.11 | 1.37 | 13.07 | 0.72 | 13.28 | 0.7 | 13.29 | 0.64 | 2, 30 | 5.5 | 0.06 | 2, 30 | 0.1 | 0.74 | 2, 30 | 0.23 | 0.88 |
| SLOW OSCILLATION | | | | | | | | | | | | | | | | | | | | | |
| Channel: Fz | | | | | | | | | | | | | | | | | | | | | |
| Density (event/30 s) | 4.34 | 1.03 | 4.91 | 0.8 | 5.15 | 0.71 | 5.83 | 0.57 | 5.84 | 0.7 | 5.94 | 0.79 | 2, 30 | 4.65 | 0.09 | 2, 30 | 117.75 | **< 0.001*** | 2, 30 | 4.57 | 0.1 |
| Duration (s) | 1.32 | 0.06 | 1.31 | 0.05 | 1.31 | 0.05 | 1.26 | 0.07 | 1.26 | 0.06 | 1.26 | 0.08 | 2, 30 | 2.2 | 0.33 | 2, 30 | 12.5 | **< 0.001*** | 2, 30 | 1.51 | 0.47 |
| Amplitude (µV) | 157.61 | 46.64 | 147.66 | 39.57 | 144.45 | 39.09 | 240.83 | 70.12 | 238.86 | 66.17 | 238.7 | 66.12 | 2, 30 | 2.82 | 0.08 | 2, 30 | 117.94 | **< 0.001*** | 2, 30 | 3.96 | **0.03** |
| Frequency (Hz) | 12.46 | 0.18 | 12.5 | 0.21 | 12.46 | 0.2 | 12.16 | 0.23 | 12.21 | 0.27 | 12.17 | 0.24 | 2, 30 | 1.54 | 0.23 | 2, 30 | 53.31 | **< 0.001*** | 2, 30 | 0.14 | 0.87 |

N=16
ROCK, rocking condition
Asterisks represent significance (p) after Bonferonni correction
Significant post hoc : a: ROCK1 versus ROCK2 in N2; b: ROCK1 versus ROCK2 in N3; c: ROCK2 versus ROCK3 in N2; d: ROCK2 versus ROCK3 in N3; e: ROCK1 versus ROCK3 in N2; f: ROCK1 versus ROCK3 in N3

Table 8: Neural entrainment

| Neural entrainment | STAT1 | | STAT2 | | ROCK1 | | ROCK2 | | ROCK3 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $\chi^2$ | *p* | $\chi^2$ | *p* | $\chi^2$ | *p* | $\chi^2$ | *p* | $\chi^2$ | *p* |
| SLEEP SPINDLE | | | | | | | | | | |
| Channel: Fz | | | | | | | | | | |
| Stage N2 | 4.50 | 0.65 | 4.69 | 0.68 | 8.17 | 0.40 | 13.29 | 0.06 | 17.46 | **0.03*** |
| Stage N3 | 7.03 | 0.51 | 1.29 | 0.99 | 3.59 | 0.87 | 3.05 | 0.85 | 22.94 | **0.01*** |
| Channel: Pz | | | | | | | | | | |
| Stage N2 | 3.33 | 0.89 | 4.82 | 0.67 | 13.50 | 0.06 | 19.53 | **0.02*** | 37.69 | **0.01*** |
| Stage N3 | 1.94 | 0.97 | 4.29 | 0.79 | 11.76 | 0.11 | 16.99 | **0.03*** | 18.34 | **0.01*** |
| SLOW OSCILLATION | | | | | | | | | | |
| Channel: Fz | | | | | | | | | | |
| Stage N2 | 7.55 | 0.32 | 10.03 | 0.17 | 56.19 | **0.01*** | 71.44 | **0.01*** | 105.46 | **0.01*** |
| Stage N3 | 6.52 | 0.46 | 4.70 | 0.78 | 2.70 | 0.91 | 13.40 | 0.07 | 19.70 | **0.02*** |

N=6

ROCK, rocking condition; STAT, stationnary condition

Asterisks represent significance (p) after Bonferonni correction

# Chapter 5: Discussion

## 5.1 Thesis overview

Sleep is an essential component for the maintenance of numerous physiological functions, as described in the Chapter 1. Specifically, sleep is important for cognition, as memory consolidation[149], including both procedural[50,53,159,171–174,637] and declarative memory[47,181–183]. Particularly, studies observed associations with the coupling between spindles and SOs with an improvement in both procedural[50–52] and declarative memory consolidation[36,37,194,196–200].
Sleep quality decreases over the lifespan[278]. Insomnia symptoms are common in older adults, such as insomnia disorder prevalence. In addition, sleep complaints are associated with increased risk of cognitive decline[304–306]. Specifically, middle-aged adults and over (i.e. 45 year and over) with probable insomnia disorders displayed cognitive impairment compared to individuals with insomnia symptoms only[303]. In addition, insomnia disorder has been associated with subjective cognitive impairment[307]. This could lead to a worsening of mild cognitive impairment or even AD[311,312]. Addressing sleep disturbance, especially insomnia complaints, is essential for promoting overall health and preventing any cognitive decline. This major challenge represents a public health issue worldwide, as the World Health Organization indicates that the elderly population (i.e. 60 years and older) represents around 18% of the worldwide population, and projects an increase to 38% by 2050, representing 1.5 to 2 billion individuals[638,639].

This thesis focuses on the impact of pharmacological and non-pharmacological interventions on sleep and cognition in older adults with insomnia. Chapter 2 observed that chronic use of sedative-hypnotic was detrimental for sleep quality and may be associated with cognitive decline. Chapter 3 evaluated the effect of sedative-hypnotic withdrawal combined to CBTi and found that subjective sleep quality was improved with CBTi. Chapter 3 investigated the novel effect of a rocking bed apparatus on three consecutive nights and highlighted the importance of optimal rocking motion parameters.

## 5.2 Subjective sleep quality

This thesis underscores that it is essential to consider the subjective component of sleep quality when assessing overall sleep health. Subjective sleep complaints of insomnia are highly prevalent worldwide[216–218,220,221,640]. As presented in this thesis, subjective sleep quality is

usually assessed using self-report questionnaires or sleep diaries, which capture individuals' perceptions of their sleep experience.

The present thesis findings highlighted that subjective sleep quality and insomnia complaints can be improved in older adults with insomnia through pharmacological approaches, behavioral interventions such as CBTi, and potentially through non-traditional strategies like rocking bed stimulation.

In Chapter 2, only one measure of subjective sleep quality was employed, represented by insomnia severity. Although this provided important information, it would have been valuable to complement these data with a more comprehensive assessment of subjective sleep quality, particularly among older adults with insomnia. The inclusion of the PSQI would have enabled a more comprehensive assessment of insomnia severity by accounting for factors such as the use of sleep medication and the impact of daytime impairment, including excessive sleepiness. Additionally, the use of sleep diaries could have provided an average estimate of nightly sleep patterns over a two-week period, thereby improving the reliability of self-reported sleep data. Indeed, Chapter 3 included both sleep diaries and insomnia severity questionnaires, enabling a more detailed characterization of subjective sleep quality. However, the integration of data from three distinct research projects limited the comparability of subjective measures, as few questionnaires were shared across studies. Despite this limitation, population-level differences have been identified in older adults, specifically between good sleepers and those with insomnia, as well as between those insomnia individuals with and without chronic use of sedative-hypnotics. Interestingly, older insomnia individuals treated with benzodiazepines had a lower insomnia severity compared to those without pharmacological treatment. This positive effect on subjective insomnia severity likely contributes to the difficulties in withdrawing those treatments, and contrasts with the disruptions observed with objective sleep architecture (see below).

Findings from Chapter 3 showed that among individuals with insomnia and benzodiazepine use, combining sedative-hypnotic discontinuation with CBTi was associated with improved sleep quality compared to withdrawal alone. Nevertheless, collecting daily subjective sleep data in older adults remains challenging due to inconsistencies in reporting. Despite these challenges, the findings presented in Chapter 3 reveal consistent trends, suggesting that meaningful subjective data can still be captured in this population. When sedative-hypnotic

withdrawal was not paired with CBTi, participants reported a deterioration in subjective sleep quality, with increased insomnia complaints. Similar to the present findings, the combined effect of CBTi and sedative-withdrawal program was beneficial for increasing self-reported sleep quality compared to the withdrawal program alone[558,569,570,596]. Literature also reported improvement in sleep quality, especially insomnia severity following CBTi in adults with insomnia but not using sedative-hypnotic[208,397,408,641]. Thus, these results provide new evidence that CBTi combined to withdrawal program is an effective intervention for improving subjective sleep quality in older adults

Additionally, no improvement in subjective sleep quality was observed following rocking bed stimulation in a sample of young, healthy sleepers. However, as previously discussed, optimized rocking parameters have shown potential for enhancing sleep quality[37,472], suggesting that this intervention could hold promise for older adults experiencing subjective complaints of insomnia.

It is therefore essential to assess sleep quality by considering its subjective component, especially regarding insomnia disorder. The findings of this thesis highlighted the benefits of sedative hypnotic use, cognitive behavioral therapy and potentially rocking bed stimulation on subjective sleep quality. By enhancing self-reported sleep quality, these pharmacological and non-pharmacological interventions may help mitigate the negative impact of aging and insomnia disorder on sleep among older individuals. However, this remains to be clarified, given the association between sedative-hypnotic use and dementia.

## 5.3 Objective sleep quality

Our findings further emphasized the importance of considering both objective and subjective aspects of sleep quality. Objective sleep quality was negatively affected by chronic sedative-hypnotic use. However, it remained unchanged following sedative-hypnotic withdrawal combined with CBTi but may potentially emerge with a certain delay. Lastly, while the rocking bed intervention did not yield significant improvements in objective sleep quality, further studies are needed to fully determine its impact on sleep quality, particularly through the inclusion of novel rocking parameters.

These results underscored that addressing sleep quality should not focus solely on alleviating subjective complaints at the expense of silently compromising objective sleep parameters.

Notably, chronic use of sedative-hypnotics, while reducing subjective sleep complaints, was associated with alterations in objective sleep quality architecture—particularly a reduction in deep sleep duration. Moreover, sleep efficiency in older adults with insomnia was found to be comparable regardless of sedative-hypnotic use.

Compared to subjective sleep quality, improving objective sleep quality appears to be more challenging. Both pharmacological and non-pharmacological interventions seem to induce changes that do not necessarily align with improvements in objective sleep metrics. This was observed in Chapter 2 and 4, where chronic use of sedative-hypnotic and the rocking stimulation initially had a detrimental effect on objective sleep quality. Furthermore, behavioral interventions do not appear to be an effective means of improving objective sleep quality immediately after treatment as presented in chapter 3. Studies displayed that objective sleep quality may appear with some delay following CBTi[558,603].
Moreover, the findings from Chapter 3 did not provide evidence that CBTi effectively improves objective sleep quality in the context of sedative-hypnotic withdrawal among older adults with insomnia. However, CBTi is primarily designed to target the subjective aspects of sleep rather than its objective features. Indeed, no improvement in objective sleep quality was observed following CBTi in adults with insomnia and no sedative-hypnotic use[208,397,642]. However, the absence of prolonged follow-up period may limit the ability to detect potential delayed improvements in objective sleep quality.

In the pursuit of improving sleep quality, both pharmacological interventions—such as chronic sedative-hypnotic use—and non-pharmacological approaches—such as rocking bed stimulation—were associated with alterations in sleep architecture. Specifically, these interventions led to a reduction in N3 sleep duration, as well as a worsened transition from wakefulness to sleep, reflected by increased N1 duration and prolonged wake periods. These sleep disturbances are associated with activation of inflammatory processes[643], which are associated with the accumulation of Aβ burden. In turn, this may lead to the development of mild cognitive impairment[644], AD or dementia[645,646]. The impact of cognition will be further discussed in section “5.4, Impact on cognition”.
Additional research emphasizes the importance of objective sleep metrics for understanding and monitoring neurodegenerative disorders. Sleep disturbances, such as insomnia complaints, predicted the risk of developing dementia[647]. A systematic review and meta-analysis study found that objective sleep measurement using PSG showed increased nocturnal awakenings

(WASO), reduced SE, and also a decrease in N3 duration[648] in individuals with AD, compared to controls. In addition, while not reported in the present thesis and in previous studies[494,649], decrease in SWA was also associated with tau pathology in the early phase of AD[650].
Efforts to improve subjective sleep quality should not come at the expense of alterations in its objective components, as such changes may have detrimental consequences on cognitive function and potentially contribute to neurodegenerative processes.

Studies examining spectral activities further underscore the importance of objective sleep measures. This is particularly critical when such interventions target individuals already experiencing sleep disturbances, such as insomnia disorder, as they may further exacerbate insomnia symptoms. Individuals with insomnia displayed increase in beta power[253,264,265,651], and this was linked with hyperarousal cortical state[307]. Similar to the present findings, older adults with insomnia and chronic use of sedative-hypnotic displayed an increased beta power. This suggests that chronic use of sedative-hypnotic further increased change in EEG spectrum induced by insomnia, leading to worsened sleep quality. However, findings remain inconsistent across studies[252,263,495], highlighting the need for further research to clarify the relationship between beta power and insomnia complaints. Current discrepancies in findings related to sleep architecture may be explained by factors such as the duration of sedative-hypnotic use, the heterogeneity of drug types, and the characteristics of the studied population.
Findings from the Chapter 2 showed that chronic use of sedative-hypnotic use induced a theta suppression effect in both NREM and REM. Theta power is associated with declarative memory, whereas the greatest reduction found in theta power was linked to worse memory performance[497]. Furthermore, theta power seems implicated in the regulation of emotional memory during REM[60,652]. Research on animal models observed that the subunits of the $GABA_A$ receptor containing the $\alpha_1$ subunits may underline the theta suppressive effect of sedative-hypnotics[344,653]. Future pharmacological research could investigate specific manipulation to adapt medication to this theta suppression effect. Chronic use of sedative-hypnotic could thus worsen the decrease of theta power during REM observed in both aging[654] and in insomnia[263]. In addition, the impact of the theta suppression effect induced by the chronic use of sedative-hypnotics could be clarified by investigating the coupling between both SO and spindle with hippocampal ripples in older adults with insomnia disorder.

Sensory modulation during sleep represents a potential mechanism for enhancing objective sleep quality. In particular, indirect vestibular stimulation through rocking bed motion has been

identified as a promising intervention, with evidence suggesting its potential to facilitate sleep consolidation and improve sleep quality. While using the same rocking motion parameters than studies previously published[37,472] (0.25 Hz; lateral direction; excursion over 21 cm), the present findings in the Chapter 4 were in the opposite direction of the beneficial effect on sleep and memory reported[37,472]. Findings revealed a deterioration in sleep architecture following the first night, likely induced by motion jolts and noise from the rocking apparatus, followed by a habituation effect to these disturbances on the second consecutive night. Furthermore, the intervention showed no beneficial effect on either spindles or SOs density, nor any impact on both declarative and procedural memory performance.

## 5.4 Impact on cognition

Similarly, the findings of this thesis underscored the potential impact of sleep interventions on cognitive functioning.

Both short and long self-reported sleep duration have been associated with an increased risk of cognitive decline in older adults[655]. Specific cognitive domains, such as executive function and verbal memory, are more severely impaired with extreme values of both short and long self-reported sleep duration[655]. While findings in Chapter 2 showed that chronic insomnia complaints were reduced through the use of sedative-hypnotics—suggesting a potentially beneficial effect on cognitive performance for older adults with insomnia—such improvements should be interpreted with caution. Indeed, chronic use of sedative-hypnotics has been concurrently associated with objective alterations in sleep quality, both at the macro- and micro-levels, with increased N1 duration and decreased N3 duration.

Studies have also reported associations between increased risk of cognitive decline and objective sleep parameters. An increase in N1 duration was associated with increased risk of rapid cognitive decline in older males[656]. A deficit in N3 duration as a consequence of aging[278] has been associated with age-related deficit in declarative memory in older adults, as well as the accumulation of Aβ burden in the cortex, marker of neurodegeneration[149]. Brain clearance occurs during N3 to reduce Aβ burden[646,650,656]. Aβ burden was associated with impairment of SWA, related to N3 stage, and further with cognitive decline such as memory consolidation in healthy older adults[657].

In line with the present findings, studies observed that sedative-hypnotic use increase N2 duration, as well as spindle density, and its related sigma power[30,497,522], but did not affect

spindle frequency, duration, amplitude[524,658]. Studies found that the increased spindle density induced by sedative-hypnotic use was associated with improvement in declarative memory performance[496,497,658]. In addition, sedative-hypnotic use improved SO-spindle coupling and this was associated with verbal memory improvement[496,497].

The present findings reported an increase in spindle density, but an alteration of the SO-spindle coupling. Inconsistencies in the findings may be attributed to factors such as the duration of sedative-hypnotic use and the characteristics of the study populations, which often consist of healthy young adults and acute use of medication[496,497,658]. While Chapter 2 did not include cognitive assessment, it is more likely that a decrease in the temporal association with spindle and SO leads to neurodegeneration in older adult. Impairment in the SO and spindle coupling was found predictive to tau pathology, but not the Aβ burden and in opposite, SWA was associated with the Aβ burden but not the tau pathology[659]. This was notably attributed to the hippocampal ripple affected by tau pathology as evidenced in animal model[660].

The present findings offer novel insights into the relationship between sleep and memory processes, particularly the effect of chronic sedative-hypnotic use on spindles and SO–spindle coupling in older adults with insomnia. As SO–spindle coupling is considered a key marker of active systems consolidation during sleep, future studies should incorporate cognitive assessments to clarify how memory performance relates to both spindle density and SO–spindle coupling in this population. Although chronic sedative-hypnotic use appears to increase spindle density, this effect does not necessarily translate into cognitive benefit, given the concurrent impairments observed in N3 sleep duration and SO–spindle coupling. While spindle density has been associated with enhanced memory performance, the disruption of spindle–SO coupling may, on the contrary, have detrimental consequences. This decoupling could contribute to cognitive decline in older adults with insomnia, underscoring the need for further investigation into the long-term cognitive effects of sedative-hypnotic use.

In addition, although some studies have reported a higher risk of developing cognitive impairments, such as dementia[376,536,661], with long-acting BZDs/BZRAs compared to short-acting medication[662,663], others have found increased risk associated with short-acting sedative-hypnotics, particularly at higher doses and among females[377]. While certain studies did not observe a significant association[376], the overall evidence suggests that both short- and long-acting BZDs/BZRAs may contribute to cognitive decline, reinforcing concerns about their prolonged use in older adults.

Furthermore, findings from both Chapter 3 and 4 did not display any improvement in cognition. Since both the sedative-hypnotic withdrawal combined to CBTi and rocking stimulation did not improve objective sleep quality, such findings were expected[664].

While CBTi intervention was found to improved sleep quality in adults with insomnia, it did not improve attention and working memory performance[208]. CBTi did not also improve subjective cognitive assessment, however, the changes in self-reported cognitive function observed following CBTi was associated with change in ISI score[208]. In addition, CBTi intervention improved concentration in middle-aged adults with insomnia[420]. Overall, CBTi did not greatly improve subjective cognitive function, with small to moderate effects[605], especially regarding attention function[665]. Inconsistency exists between studies[606], and may be explained by the diversity in studies protocol, and cognitive domains assessed, and by a lack in literature in describing the effect of CBTi on cognitive function, especially using objective cognitive assessment[605]. Furthermore, literature is lacking to characterize association between CBTi and Aβ burden[666].

In addition, effect of sedative-hypnotic use on cognition are lacking and remain inconsistent[554]. Studies observed declarative memory impairment[667] or no effect on it following sedative-hypnotic use[668]. The inconsistency in these findings may be explained by the difference between studies in the half-life of the sedative-hypnotic use. Memory improvement was observed at the maximum drug effect, the first half of the night, but not observed during the second half of the night[498]. Moreover, sedative-hypnotic with a half-life ranging around 7 hours induced memory impairment[667], while sedative-hypnotic with a half-life not exceeding 3 hours study led to memory improvement[497]. Studies using similar half-life sedative-hypnotic observed contradictory findings on memory performance, using different memory tasks[497,668]. In addition, the variability in the memory tasks may also explain the difference in memory performance underlying different memory type mechanism and may explain why sedative-hypnotic improved declarative but not procedural memory performance[497]. The present thesis did not observe any change in cognition, and this may be related to the fact that that participants at baseline did not present any cognitive deficits (exclusion criteria with a MMSE score $\leq 23$).

Sedative-hypnotics withdrawal effects on cognition in older adults have been investigated and remain unclear[556]. Multiple factors can confound the results, such as the cognitive domain evaluated, tasks employed, or the population of interest. Nevertheless, some other aspects of cognition remained impaired at 42 month following sedative-hypnotic discontinuation, such as verbal memory[669], while others, such as visuospatial abilities or attention and concentration, were improved[556,670]. This suggests that the effect of sedative-hypnotic withdrawal, combined

to CBTi may take some delay for proving beneficial effects on cognitive performance. The present thesis did not include follow-up, which may have shown more cognitive effect.

Since other studies reported memory improvement following rocking stimulation[37,472], further studies need to clarify the impact of rocking stimulation on declarative memory consolidation. Moreover, the effect of rocking stimulation on procedural memory also warrants further investigation, as it had not been previously characterized before. In addition, except for declarative and procedural memory, no others cognitive domains were explored after rocking stimulation.

## 5.5 Clinical implications

### 5.5.1 Sensory stimulation

The present thesis highlighted the importance of applying optimal parameters to rocking motion stimulation in order to achieve beneficial effects on both sleep quality and cognitive function.
Multiple studies reported connection between the vestibular nuclei and neuronal structure involved in the sleep-wake regulation[453]. This includes the connectivity to the ARAS[454], the SCN[455], the thalamus[463,464], potentially implicated in melatonin regulation[456], while further studies need to clarify such association. In addition, alteration in the vestibular function was associated with sleep disturbances[23,461,462]. However, objective assessments of sleep in vestibular disorders are lacking[453].
Rocking bed stimulation restricted to a two-dimensional, longitudinal trajectory appears to minimize the risk of motion sickness. Notably, motion sickness has also been associated with increased autonomic responses, such as elevated heart rate[671]. Moreover, the trajectory of the rocking bed movement has been found to influence autonomic functions, increasing the respiratory frequency and decreasing the heart rate[672]. Rocking bed movement in a longitudinal trajectory may enhance relaxation and support the transition from wakefulness to sleep, although its effect on autonomic system needs to be clarified. This intervention could thus have a protective role in improving the cardiovascular health in older adults. This could also be beneficial for individuals with insomnia disorder, who display a high prevalence of cardiovascular conditions[113].

A transient insomnia model was used to investigate the potential of direct electrical vestibular stimulation for sleep promotion, though no conclusive results were found[468]. While the majority

of studies have focused on healthy young adults, this remains the only study to explore the effects of vestibular stimulation in adults using an insomnia model. Although further studies are needed to clarify the potential benefits of rocking stimulation on sleep and memory in individuals with insomnia, the positive effects observed in previous research suggest that this approach could prove beneficial for individuals with insomnia[37,472]. One of the objectives of this thesis was to develop a rocking bed apparatus adaptable to various beds for at-home usage. While the present prototype seems not adequate for such use, once achieved, the beneficial effect of rocking stimulation on sleep and memory may extend beyond older adults with insomnia, potentially benefiting older adults more broadly, and especially those hospitalized following neurovascular events. Rocking bed stimulation could be implemented in hospital settings as a non-invasive intervention to enhance sleep quality, particularly by promoting brain oscillations such as spindles and slow oscillations, which may contribute to improved clinical recovery. Implementing rocking beds in hospital settings could represent a promising strategy to enhance sleep quality and cognitive performance in older patients, particularly in the context of neurovascular events. Improving sleep quality appears particularly critical in the context of neurological disorders—especially stroke, which represent a major public health as well as a leading causes of disability and premature mortality[673–675]. Patients recovering from stroke experiences significant sleep disturbances, and sleep architecture disruption[676–681], which may further altered recovery and cognitive function. In line with sleep architecture impairments, studies reported alteration in spindle and SO activity in both hemispheres as a consequence of stroke[676,677,681–683]. Furthermore, sleep underscores a crucial role in the processus of brain recovery following a stroke event, particularly through the increase of both spindles and SOs, and their coupling[684,685].

Other forms of sensory stimulation have also been investigated as potential strategies to enhance sleep. While olfactive stimulation was associated with the consolidation of targeted memory using specific cues[686,687], such sensorial stimulation did provide great change in objective sleep quality, such as sleep architecture[435,610,688]. Auditory stimulation is a promising intervention for improving sleep and memory in adults[36]. While displaying beneficial effect in older adults[436,689], results remain inconsistent and can be attributed to the diminished responsiveness to acoustic stimulation occurring during aging[291,438].

### 5.5.2 Alternative for pharmacological intervention

Chapter 2 displayed that chronic sedative-use was detrimental for sleep architecture, EEG spectrum power, and brain oscillation coupling. These changes may be associated with a worsening of both insomnia and age effect and lead to further accelerated cognitive decline in older adults with insomnia. While the increased of N2 duration was linked with the use of sedative-hypnotic use in older males, it was, however, also associated with higher risk of hypertension and myocardial infection in both females and males[370,656]. Thus, the impact of chronic use of sedative-hypnotic on cardiovascular disease need to be clarified. In addition, the use of BZDs was associated with adverse effect such as drowsiness, increased risk of car accident, increased risk of fall, potentially leading to hip fracture[369]. Furthermore, sedative-hypnotics are associated with abuse and dependence, even for short-acting[551]. Chronic use of sedative-hypnotics does not appear to be an effective strategy for improving sleep quality, particularly in older adults. Thus, since the chronic use of sedative-hypnotics is highly prevalent in older adults[222,223,384–386,389] and considering the detrimental impact on sleep and adverse effects of chronic sedative-hypnotic use in older adults with insomnia, withdrawal from chronic sedative-use is encourage[600].

Off-label medications such as anti-depressant, represented by mirtazapine and trazodone, or anti-psychotics, such as quetiapine, are also used for treating insomnia. However, their efficacity and safety remains inconsistent[423]. Mirtazapine and quetiapine were associated with improvement in sleep duration[690–692], but in concomitance with adverse effect such as daytime sleepiness and evidence of efficacity and safety at lower dose are lacking and need further investigations[423,692–694].

In addition, the beneficial effects of melatonin for insomnia are not strong, and studies need to further investigate its effect on safety and evidence for benefits[423,695,696].

In addition, the combination of sedative-hypnotic discontinuation to additional pharmacological intervention, such as melatonin, was widely investigated for improving withdrawal success[697]. While effect on sleep quality was not conclusive, contribution of melatonin displayed inconsistent findings, either observed to be beneficial for sedative-hypnotic withdrawal[698,699] or had no effect[700,701]. In addition, the use of melatonin medication or placebo, combined with psychological support for sedative-hypnotic withdrawal was investigated in older adults with insomnia[696]. Controlled release melatonin compared to placebo did not provide any benefit for increasing the withdrawal success, where withdrawal symptoms were observed equivalent in the combined group compared to withdrawal with placebo[696].

A class of medication also used for the management of insomnia disorder is represented by dual orexin receptor antagonists (DORAs). Daridorexant was safer than benzodiazepines, with no tolerance observed at one year follow up[423]. Such medication provided beneficial effects on sleep architecture, increasing sleep duration, and reducing sleep fragmentation[702] . Furthermore, beneficial effects of lemborexant on subjective sleep quality and lower insomnia complaint were sustained over one year in older adults with insomnia[703]. In addition, such use was associated with few side effects in older adults with insomnia[704]. The Delphi consensus recommendations for the management of chronic insomnia in Canada suggest that DORAs could be a promising pharmacological treatment for insomnia[423].

### 5.5.3 Need to account for psychological factors

Pharmacological treatment—particularly sedative-hypnotic —may not be equally suitable for all individuals. Before initiating pharmacological treatment, clinicians should consider the patient's overall psychological profile. Several psychological factors have been found to influence the success of sedative-hypnotic withdrawal. For instance, high fear of insomnia recurrence[600], high levels of psychological distress, and high behavioral inhibition at baseline have been associated with lower withdrawal success[705]. Moreover, stronger baseline motivation to discontinue use was also shown to facilitate successful tapering[706], possibly explaining the observed link between lower initial dosage and greater withdrawal success. In contrast, alcohol consumption has been associated with poorer withdrawal outcomes[706], a finding that particularly concern males[223], although sex differences in withdrawal success have not been consistently observed[706]. These findings suggest that a gradual dose reduction alone may be insufficient to ensure successful withdrawal, and that psychological assessment should be integrated into the discontinuation process. Given that sedative-hypnotic withdrawal can be accompanied by increased stress and anxiety, while CBTi is known to reduce both, the combination of CBTi with a tapering protocol appears especially beneficial[707]. This is particularly relevant for individuals initially prescribed sedative-hypnotics for anxiety-related symptoms[708]. However, findings from the Chapter 3 did not demonstrate any beneficial effect of combining the sedative-hypnotic withdrawal and CBTi on withdrawal success, this may be explained by the low level of anxiety and depression at baseline, as exclusion criterion. In addition, further studies need to clarify the impact of the combined intervention on both anxiety and depression levels.

## 5.6 Limitations and future perspectives

### 5.6.1 Sample characteristics

#### *5.6.1.1 Biological sex*

This thesis did not take into account the effect of biological sex or gender on pharmacological and non-pharmacological interventions. At the subjective level of sleep quality: as reported in Chapter 1, females are more prone to sleep disturbances, especially insomnia disorder, compared to males in adults and in older adults[223,233,709–711]. In addition, the greater prevalence of insomnia symptoms, including psychiatric disorders, such as anxiety and depression, is higher in females compared to males[712]. However, the causal link between depression and insomnia symptoms regarding sex-difference needs further investigations as difference in symptomatology and coping style between males and females may lead to under-diagnosed depression, and insomnia complaints[712].

At the objective level of sleep quality (i.e. PSG), biological sex difference between females and males, referring to biological and physiological difference, were observed[713]. Studies investigating sex effect on sleep reported difference at the macro level with a greater sleep quality in females compared to males[713]. This was evidenced by a longer sleep duration, reflected by an increase in SE, as well as a reduced N1 duration, and increased N3 duration in females compared to males in healthy adults[714–717]. In addition, the reduction of N3 duration over the lifespan was more important in males compared to females in healthy individuals[278]. However, studies did not observe significant biological sex difference in older adults regarding sleep architecture[263,281]. Furthermore, biological sex difference was observed at the micro level. Spindle activity was found greater in females compared to males in a population of healthy adults[718]. Moreover, the variability in spindle density was found greater in females compared to males[719]. In addition, spindle density was higher in females compared to males in older adults, especially fast spindles were associated with improvement in declarative memory performance, where sleep at the micro level seems more protective and could contribute to reduce cognitive decline in females[720].

In addition, literature needs future investigations to better diagnose insomnia disorder considering factors such as biological sex and gender, thereby facilitating more targeted and effective strategies to improve sleep quality in older adults. Older adults with insomnia and chronic use of sedative-hypnotic involved in Chapter 2 were overrepresented by females, with a majority of 72%, which may potentially bias the findings. Specifically, future studies also need to consider biological sex difference in sedative hypnotic use. Widely used[364,721,722],

Zopiclone represents the first drug for which the recommended dosage differs between males and females. In 2013, the American Food and Drug Administration decreased the recommended dose from 10mg to 5mg in females specifically for immediate-release and from 12.5 to 6.25 mg for extended-release[717,723,724]. Difference in biological sex regarding the elimination rate in the body, pharmacokinetic parameters, such as absorption, metabolism and elimination may explain those differences[717,723,724]. The post-menopausal period in females aged from 50 to 65 years displayed an increased risk of osteoporosis and fracture risk with BZD use[725]. In addition, when comparing pre-menopause and post-menopause, the low levels of progesterone at post menopause contributed to the increase rate of insomnia observed at this period[726]. Low progesterone levels are also observed during the follicular phase of the menstruation cycle, and are associated with change in spindle activity[727–729] and in sleep-dependent memory consolidation in females[730].

Furthermore, a recent study in 2023 in Canada identified age and sex difference in the choice of sleep aids, where females in the elderly were more able to use prescribed medication compared to males in the youth, using more alcohol[223].

#### *5.6.1.2 Ethnicity*

Ethnic diversity was not assessed in Chapters 1 and 2, as differences in sedative-hypnotic use may exist among participants from diverse ethnical backgrounds. In 2020, in America, non-Hispanic White adults were found to use sleep medication more frequently (10%) compared to non-Hispanic Black (6%), non-Hispanic White (5%) and non-Hispanic Asian (<2%)[731]. In 2023, in Canada, the prevalence of insomnia disorder was found around 29% for Indigenous people[223]. In addition, adults speaking "French only" at home less frequently reported feeling unrefreshing sleep, and those speaking a language other than French and English less frequently reported insomnia symptoms[732]. Nighttime insomnia symptoms were the lowest among those who reported speaking a language other than French or English at home (9.5%).

### 5.6.3 Rocking bed stimulation as a promising intervention

#### *5.6.3.1 Rocking bed optimal stimulation*

The trajectory of the rocking motion appears also critical for providing beneficial effect on sleep and memory. Among the various movement trajectories explored, such as rotational[470] or pendular motion[473], the most consistent improvements in both sleep quality and memory

consolidation were observed with longitudinal linear movements[37,472,474]. This preferential trajectory effect may reflect the specific vestibular system neuroanatomy, where longitudinal motion specifically involves the utricle, sensitive to horizontal linear acceleration, leading to promote sleep without triggering discomfort. In contrast, more complex or rotational movements stimulate the semicircular canals, notably involved in motion sickness—characterized by nausea or dizziness and arising from conflict between visual, vestibular, and proprioceptive information[733,734]. Longitudinal rocking motion may be beneficial by reducing the risk of motion sickness, which involves autonomic nervous system dysregulation. Further studies need to clarify its effect in older adults with insomnia.

In addition, most beneficial effect on sleep and memory were observed with an acceleration intensity of approximatively 26 $cm \cdot s^{-2}$ [37,472], while lower[469,470,474] and greater[470,473,474] values did not provide any beneficial effect.

Findings from Chapter 4 did not reveal any beneficial effects induced by the rocking stimulation, potentially due to the motion intrinsic properties, such as jolts.

#### *5.6.3.1 Implication for older adults with insomnia*

Technical factors may explain the present thesis results regarding the rocking effect on sleep and memory, as the noise of the rocking bed apparatus and disruptive movement in the motion, altering its smoothness. In addition, although the rocking bed apparatus was originally designed for home-based experiments in older adults with insomnia, it did not prove to be a practical solution due to several limitations, including excessive noise, substantial weight, and irregularities in the rocking motion. Further rocking bed device needs to be designed for a feasible at-home study.

Moreover, aging is associated with a decline in vestibular function[735]. This was evidenced with disruption of the vestibulo-ocular reflex during wakefulness[736]. In addition, the utricular function was found impaired with aging[737,738]. A rocking bed with a linear acceleration intensity at 15 $cm.s^{-2}$ did not provide any beneficial effect on sleep onset, N3 duration or NREM brain oscillations associated with memory in older adults[471]. In contrast, a decrease in SWA was observed. This highlights the need to further characterize the optimal acceleration intensity for older adults[739]. As the utricle is specific to linear acceleration, this suggests that rocking effect in older adults may also lead to differential effect sleep and memory than those observed in healthy young adults.

### 5.6.4 Association between chronic use of sedative-hypnotic and cognitive decline in older adults with insomnia

Although PSG provides high reliability in assessing sleep architecture, it would have been valuable to complement it with a measure of daytime sleepiness, such as the Multiple Sleep Latency Test (MSLT)[740], since daytime sleepiness is a common complaint among sedative-hypnotic users[741]. While the findings from Chapter 2 highlighted the potential risks associated with the chronic use of sedative-hypnotics, it would have been informative to explore a potential association with objective measures of daytime sleepiness.

Future studies need to clarify the impact of N3 reduction in chronic user of sedative-hypnotic use. N3 duration was not found associated with cognitive decline in older males[656,742] nor with older adults with AD[743]. However, the diversity in studies protocol, demographic factors, psychological conditions and sleep-aid medications may explain the discrepancy in the results. In addition, some findings were based on PSG data and may be biased by the first night effect[656]. This suggests that N3 alteration by sedative-hypnotic use could worsen the N3 deficit induced by age, and lead to neurodegeneration.

In addition, the present findings did not report any detrimental effect on REM duration, with only a trend to increased sleep latency to REM. In contrast, findings reported a reduction of REM duration caused by sedative-hypnotics[38,359,362,363,744]. The diversity in the sedative-hypnotic types may contribute to these findings, as short-acting sedative-hypnotics were observed more frequently to affect N3 than REM duration[359]. This also suggests that acute use of sedative-hypnotics induced a REM suppression effect, and chronic use may induce a change in the $GABA_A$ receptor affinity, leading to maintain REM in older adults. Thus, future studies need to clarify the impact of the REM suppression effect and its association with memory, induced by chronic sedative-hypnotic use in older adults with insomnia.

### 5.6.5 Challenge with CBTi

CBTi remains difficult to access and is still largely unavailable to many individuals[397,423]. Its potential benefits may only emerge over the long term[558,603], emphasizing the need to include follow-up assessments to determine whether improvements in sleep quality and cognitive functions are sustained. While improvement in subjective sleep quality was not observed at post intervention in the chapter 3, it may also appear with some delay. This was evident in a 3-month follow-up in older adults, where sleep onset, SE and sleep duration were improved over time[558].

In the long-term, the beneficial effects of sedative-hypnotic withdrawal combined to CBTi were not sustained, as sleep disturbances persisted[596]. An explanation reported was the decrease in the adherence[558], and CBTi booster sessions could further improve the maintenance of participant compliance[745]. The present thesis did not include follow-up assessment, and further studies need to clarify the delay of appearance of any beneficial effect of combining CBTi to sedative-hypnotic withdrawal on subjective sleep quality in older adult.

It is also essential to carefully assess anxiety and depression when evaluating sleep quality, as these factors can significantly influence both subjective and objective measures and are highly associated with insomnia[238,746,747].

Moreover, the volume of information derived from CBTi guidelines, and the withdrawal program may be overwhelming to implement in practice in older adults[596,600], highlighting the challenges associated with delivering this combined intervention for treating insomnia.

## 5.6 Conclusion

The present thesis investigated the effects of chronic sedative-hypnotic use in older adults with insomnia. This pharmacological exposure was found to negatively impact overall sleep quality, affecting both sleep architecture and EEG spectral activity. Moreover, the coupling between SO and spindles was disrupted, which may explain the observed association between long-term sedative-hypnotic use and cognitive decline in this population. The impact of sedative-hypnotic withdrawal combined with CBTi was also examined. Although this combined intervention improved subjective sleep quality, no significant changes were observed in objective sleep measures or cognitive performance following treatment. Lastly, the effects of three consecutive nights of rocking bed apparatus stimulation were explored in relation to sleep and memory. While this approach shows promise as a non-pharmacological intervention to enhance sleep and memory, the findings highlighted the need to optimize the rocking motion parameters to maximize its efficacy.

Taken together, these findings underscore the importance of addressing sleep quality in its entirety—not only reducing insomnia symptoms, but also as a strategy to protect against the adverse effects of aging on the brain. Insomnia, particularly in older adults, increases the risk of cognitive decline and neurodegeneration, highlighting the need for comprehensive interventions. While improvements in subjective sleep quality may be more readily achieved, enhancing objective sleep parameters remains essential to ensure long-term cognitive health.

This thesis offers novel insights into both pharmacological and non-pharmacological strategies for managing chronic insomnia and clarifies their distinct effect on sleep and memory. By advancing our understanding of how sleep modulation interfaces with brain aging, these findings pave the way for more targeted and effective interventions aimed at promoting healthy cognitive aging.

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# Appendices

## Appendix A: supplementary materials for Chapter 2

### Supplemental results

#### Table S1: Dosage and type of sedative-hypnotic used

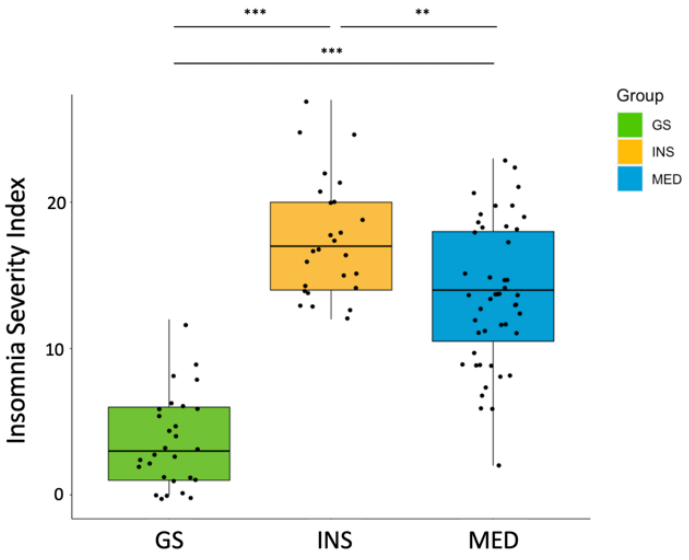
*Sedative-hypnotic use within the MED group. The MED group was using at least one of the options listed, with only one type of BZD or BZRA prescribed for insomnia: BZD (Diazepam, Clonazepam, Nitrazepam, Oxazepam, Lorazepam, Temazepam) or BZRA (Zopiclone) drugs.*

| Medication type | Dose equivalent in Diazepam (mg/ week) | N |
|---|---|---|
| BZD | | 18 |
| **Diazepam** | **10** | 1 |
| Clonazepam | 0.5 | 2 |
| Nitrazepam | 10 | 2 |
| Oxazepam | 20 | 6 |
| Lorazepam | 1 | 6 |
| Temazepam | 20 | 1 |
| BZRA | | 29 |
| Zopiclone | 15 | 29 |

BZD, benzodiazepine; BZRA, benzodiazepine receptor agonist

#### Figure S1: Insomnia Severity Index Score

*Mean and individual-specific self-reported insomnia severity score across the groups: GS (green), INS (yellow) and MED (blue). Asterisks represent significance (p): *<0.05; **<0.01; ***<0.001*



## Impact of chronic sedative-hypnotic use on spectral activity during NREM

### Table S2: Chronic sedative-hypnotic use affects spectral activity during NREM

*Mean (± SD) relative spectral power activity and delta/beta ratio in the frontal and parietal areas during NREM across the GS, INS, and MED groups. Asterisks indicate statistically significant differences between groups (p<.05).*

| Outcome measure | GS | | INS | | MED | | GS vs INS vs MED Kruskal-Wallis test or ANOVA | | | | | GS vs INS post hoc - Dunn test or t test | | | INS vs MED post hoc - Dunn test or t test | | | GS vs MED post hoc - Dunn test or t test | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | df | residual | p | q | p | q | effect size g' | p | q | effect size g' | p | q | effect size g' |
| ***Relative spectrum*** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| SO | 0.59 | 0.1 | 0.59 | 0.1 | 0.61 | 0.1 | 1.23 | 2 | 97 | 0.54 | - | - | - | - | - | - | - | - | - | - |
| Delta | 0.76 | 0.07 | 0.78 | 0.08 | 0.74 | 0.08 | 2.35 | 2 | 97 | 0.31 | - | - | - | - | - | - | - | - | - | - |
| Index Delta/Beta | 97.15 | 49.52 | 98.81 | 52.13 | 62.88 | 38.31 | 9.99 | 2 | 97 | 0.007 | **0.02*** | 0.96 | - | -0.01 | 0.01 | **0.03*** | 0.61 | 0.007 | **0.02*** | 0.60 |
| Theta | 0.08 | 0.03 | 0.07 | 0.03 | 0.06 | 0.03 | 9.16 | 2 | 97 | 0.01 | **0.02*** | 0.29 | - | 0.21 | 0.09 | - | 0.22 | 0.003 | **0.01*** | 0.69 |
| Alpha | 0.04 | 0.02 | 0.03 | 0.02 | 0.05 | 0.03 | 1.37 | 2 | 97 | 0.50 | - | - | - | - | - | - | - | - | - | - |
| Sigma | 0.02 | 0.01 | 0.02 | 0.01 | 0.03 | 0.02 | 9.10 | 2 | 97 | 0.01 | **0.02*** | 0.84 | - | -0.13 | **0.02** | 0.06 | -0.67 | 0.009 | **0.03*** | -0.73 |
| Low Beta | 0.02 | 0.008 | 0.018 | 0.009 | 0.03 | 0.025 | 8.24 | 2 | 97 | 0.02 | **0.03*** | 0.88 | - | -0.12 | **0.02** | 0.07 | -0.50 | 0.01 | **0.04*** | -0.57 |
| High Beta | 0.03 | 0.017 | 0.033 | 0.017 | 0.045 | 0.04 | 9.99 | 2 | 97 | 0.007 | **0.02*** | 0.66 | - | 0.04 | **0.02** | 0.07 | -0.56 | 0.07 | - | -0.53 |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| SO | 0.56 | 0.12 | 0.57 | 0.11 | 0.6 | 0.12 | *1.24* | 2 | 97 | *0.29* | - | - | - | - | - | - | - | - | - | - |
| Delta | 0.69 | 0.08 | 0.72 | 0.1 | 0.69 | 0.08 | *0.73* | 2 | 97 | *0.48* | - | - | - | - | - | - | - | - | - | - |
| Index Delta/Beta | 65.86 | 33.86 | 73.26 | 34.67 | 54.8 | 35.6 | 3.9 | 2 | 97 | 0.14 | - | - | - | - | - | - | - | - | - | - |
| Theta | 0.11 | 0.05 | 0.1 | 0.05 | 0.07 | 0.04 | 12.26 | 2 | 97 | 0.002 | **0.02*** | 0.23 | - | 0.32 | 0.05 | - | 0.51 | <0.001 | **0.002*** | 0.90 |
| Alpha | 0.05 | 0.02 | 0.04 | 0.03 | 0.04 | 0.03 | 1.26 | 2 | 97 | 0.53 | - | - | - | - | - | - | - | - | - | - |
| Sigma | 0.04 | 0.02 | 0.04 | 0.02 | 0.05 | 0.04 | 1.16 | 2 | 97 | 0.56 | - | - | - | - | - | - | - | - | - | - |
| Low Beta | 0.004 | 0.002 | 0.004 | 0.002 | 0.006 | 0.004 | 1.84 | 2 | 97 | 0.38 | - | - | - | - | - | - | - | - | - | - |
| High Beta | 0.009 | 0.004 | 0.007 | 0.007 | 0.01 | 0.007 | 4.55 | 2 | 97 | 0.10 | - | - | - | - | - | - | - | - | - | - |

SO, slow oscillation

### Table S3: Chronic sedative-hypnotic use affects spectral activity during REM

*Mean (± SD) relative spectral power activity and delta/beta ratio in the frontal and parietal areas during NREM across the GS, INS, and MED groups. Asterisks indicate statistically significant differences between groups (p<.05).*

| Outcome measure | GS | | INS | | MED | | GS vs INS vs MED Kruskal-Wallis test or ANOVA | | | | | GS vs INS post hoc - Dunn test or t test | | | INS vs MED post hoc - Dunn test or t test | | | GS vs MED post hoc - Dunn test or t test | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | df | residual | p | q | p | q | effect size g' | p | q | effect size g' | p | q | effect size g' |
| ***Relative power spectrum*** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| SO | 0.44 | 0.13 | 0.4 | 0.1 | 0.46 | 0.14 | 0.95 | 2 | 97 | 0.39 | - | - | - | - | - | - | - | - | - | - |
| Delta | 0.57 | 0.06 | 0.59 | 0.09 | 0.57 | 0.1 | 0.16 | 2 | 97 | 0.86 | - | - | - | - | - | - | - | - | - | - |
| Index Delta/Beta | 13.64 | 6.74 | 12.45 | 5.58 | 11.75 | 10.14 | 3.58 | 2 | 97 | 0.17 | - | - | - | - | - | - | - | - | - | - |
| Theta | 0.15 | 0.05 | 0.15 | 0.06 | 0.1 | 0.05 | 12.04 | 2 | 97 | 0.002 | **0.02*** | 0.60 | - | 0.07 | 0.01 | **0.04*** | 0.67 | 0.002 | **0.005*** | 0.82 |
| Alpha | 0.07 | 0.03 | 0.06 | 0.03 | 0.06 | 0.03 | 0.77 | 2 | 97 | 0.68 | - | - | - | - | - | - | - | - | - | - |
| Sigma | 0.04 | 0.02 | 0.04 | 0.02 | 0.05 | 0.02 | 1.80 | 2 | 97 | 0.17 | - | - | - | - | - | - | - | - | - | - |
| Low Beta | 0.01 | 0.01 | 0.02 | 0.01 | 0.03 | 0.03 | 1.91 | 2 | 97 | 0.39 | - | - | - | - | - | - | - | - | - | - |
| High Beta | 0.04 | 0.02 | 0.04 | 0.03 | 0.06 | 0.05 | 1.25 | 2 | 97 | 0.53 | - | - | - | - | - | - | - | - | - | - |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| SO | 0.42 | 0.16 | 0.4 | 0.13 | 0.47 | 0.15 | 2.51 | 2 | 97 | 0.29 | - | - | - | - | - | - | - | - | - | - |
| Delta | 0.5 | 0.08 | 0.54 | 0.1 | 0.55 | 0.11 | 1.65 | 2 | 97 | 0.20 | - | - | - | - | - | - | - | - | - | - |
| Index Delta/Beta | 13.66 | 11.6 | 13.11 | 6.02 | 13.38 | 13.1 | 3.75 | 2 | 97 | 0.15 | - | - | - | - | - | - | - | - | - | - |
| Theta | 0.16 | 0.05 | 0.15 | 0.07 | 0.1 | 0.05 | 12.92 | 2 | 97 | 0.002 | **0.02*** | 0.76 | - | -0.01 | 0.006 | **0.02*** | 0.74 | 0.002 | **0.005*** | 0.83 |
| Alpha | 0.1 | 0.06 | 0.09 | 0.05 | 0.07 | 0.05 | 2.10 | 2 | 97 | 0.35 | - | - | - | - | - | - | - | - | - | - |
| Sigma | 0.06 | 0.03 | 0.06 | 0.02 | 0.07 | 0.03 | 0.69 | 2 | 97 | 0.51 | - | - | - | - | - | - | - | - | - | - |
| Low Beta | 0.02 | 0.01 | 0.02 | 0.01 | 0.02 | 0.03 | 0.96 | 2 | 97 | 0.62 | - | - | - | - | - | - | - | - | - | - |
| High Beta | 0.03 | 0.02 | 0.03 | 0.02 | 0.05 | 0.04 | 0.33 | 2 | 97 | 0.15 | - | - | - | - | - | - | - | - | - | - |

SO, slow oscillation

## Table S4: Chronic sedative-hypnotic use affects SOs and spindles characteristics

*Mean (± SD) spindles and slow oscillations' characteristics in the frontal and parietal regions during NREM across the GS, INS, and MED groups. Asterisks denote statistically significant differences between groups (p<.05).*

| Outcome measure | GS | | INS | | MED | | GS vs INS vs MED Kruskal-Wallis test or ANOVA | | | | | GS vs INS post hoc - Dunn test or t test | | effect size | INS vs MED post hoc - Dunn test or t test | | effect size | GS vs MED post hoc - Dunn test or t test | | effect size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | df | residual | p | q | p | q | g' | p | q | g' | p | q | g' |
| ***Spindle characteristics*** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| Count | 678.54 | 149.6 | 563,0 | 145.9 | 688.53 | 152.7 | 9.02 | 2 | 97 | 0.01 | **0.048*** | **0.04** | 0.11 | 0.79 | 0.003 | **0.009*** | -0.89 | 0.53 | - | -0.12 |
| Density (Nber/30 sec) | 1.19 | 0.2 | 1.1 | 0.19 | 1.29 | 0.3 | 7.89 | 2 | 97 | 0.02 | **0.048*** | 0.24 | - | 0.40 | 0.006 | **0.02*** | -0.77 | 0.14 | - | -0.39 |
| Duration (sec) | 0.77 | 0.04 | 0.75 | 0.03 | 0.77 | 0.1 | 2.71 | 2 | 97 | 0.26 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 92.7 | 18.3 | 94.92 | 23.3 | 83.14 | 21.6 | 0.84 | 2 | 97 | 0.43 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 11.36 | 0.5 | 11.29 | 0.5 | 11.35 | 0.5 | 0.21 | 2 | 97 | 0.81 | - | - | - | - | - | - | - | - | - | - |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| Count | 826.68 | 177.15 | 703.12 | 207.86 | 796.6 | 222.7 | 5.34 | 2 | 97 | 0.07 | - | | | | | | | | | |
| Density (Nber/30 sec) | 1.45 | 0.27 | 1.38 | 0.34 | 1.48 | 0.36 | 0.69 | 2 | 97 | 0.50 | - | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 0.74 | 0.04 | 0.73 | 0.04 | 0.75 | 0.06 | 0.61 | 2 | 97 | 0.73 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 71.25 | 17.26 | 77.08 | 21.64 | 65.21 | 14.3 | 1.62 | 2 | 97 | 0.20 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 13.53 | 0.56 | 13.81 | 0.46 | 13.49 | 0.59 | 2.08 | 2 | 97 | 0.13 | - | - | - | - | - | - | - | - | - | - |
| ***SO characteristics*** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| Count | 2181.89 | 455.25 | 2029.5 | 571.38 | 2061 | 513.33 | *0.76* | 2 | 97 | *0.47* | - | | | | | | | | | |
| Density (Nber/30 sec) | 3.83 | 0.78 | 3.98 | 0.82 | 3.82 | 0.71 | 0.86 | 2 | 97 | 0.65 | - | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 1.35 | 0.06 | 1.37 | 0.05 | 1.41 | 0.08 | 2.23 | 2 | 97 | 0.33 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 122.26 | 30.17 | 124.16 | 37.02 | 104.61 | 28.41 | 1.27 | 2 | 97 | 0.29 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 0.76 | 0.06 | 0.73 | 0.05 | 0.7 | 0.07 | 8.39 | 2 | 97 | **0.02** | 0.08 | 0.07 | - | 0.46 | 0.40 | - | 0.57 | 0.004 | **0.01*** | 0.92 |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| Count | 1954.36 | 446.47 | 1840.65 | 566.78 | 1891.49 | 487.88 | *0.61* | 2 | 97 | *0.55* | - | | | | | | | | | |
| Density (Nber/30 sec) | 3.41 | 0.73 | 3.62 | 0.86 | 3.5 | 0.67 | 1.98 | 2 | 97 | 0.37 | - | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 1.43 | 0.07 | 1.43 | 0.06 | 1.46 | 0.06 | 0.31 | 2 | 97 | 0.86 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 96.2 | 26.29 | 102.85 | 32.2 | 84.67 | 21.39 | 1.54 | 2 | 97 | 0.22 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 0.68 | 0.06 | 0.67 | 0.06 | 0.65 | 0.07 | 1.05 | 2 | 97 | 0.59 | - | - | - | - | - | - | - | - | - | - |

SO, slow oscillation

### *Sensitivity analyses on methods of detection*

Spindle automatic detection: Lacourse et al., 2019[508]; Ray et al., 2015[509]

Similar to the detection algorithm used in the main manuscript (Moelle et al., 2011[507]), Ray and Lacourse detection algorithm applied over NREM revealed a Group effect in the frontal region for spindle amplitude. Moreover, all detections failed to reveal any Group effects in the characteristics of the parietal spindle. Both the Moelle and Lacourse detection revealed an increase in spindle density in the frontal region but not when using the Ray algorithm (**Table S5**).

To note, spindle count was lower using the Lacourse detection compared to Moelle and Ray algorithms, which produced relatively similar results. Overall, we found similar results on spindle characteristics using alternative spindle detections.

SO automatic detection: Massimini et al., 2004[510]

Compared to the detection algorithm used in the main manuscript (Staresina et al., 2015[84]), the Massimini detection algorithm identified a substantially lower SO count in the frontal region compared to the Staresina algorithm, and decreased following a frontal-to-parietal gradient. Using the Staresina algorithm, approximately 2150 SO were detected in the frontal area, compared to 1950 in the parietal region. In contrast, Massimini algorithm identified only 350 SO in the frontal area, and 80 in parietal region (**Table S6**). Massimini algorithm is a very

conservative detection with a fixed amplitude threshold of 75uV which appears inappropriate for the senior populations known to display reduced SO amplitude compared to young adults[285]. These results indicate that the Staresina algorithm is an effective tool for detecting SO in older adults.

## Table S5: Effect of chronic sedative-hypnotic use on spindles using Moelle, Ray and Lacourse detection algorithms during NREM

*Mean (± SD) spindles characteristics using Moelle, Ray and Lacourse detection algorithms in the frontal and parietal regions during NREM across the GS, INS, and MED groups. Asterisks denote statistically significant differences between groups (p<.05).*

| Spindle characteristics | GS | | INS | | MED | | GS vs INS vs MED Kruskal-Wallis test or ANOVA | | | | | GS vs INS post hoc - Dunn test or t test | | effect size | INS vs MED post hoc - Dunn test or t test | | effect size | GS vs MED post hoc - Dunn test or t test | | effect size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | df | residual | *p* | *q* | *p* | *q* | g' | *p* | *q* | g' | *p* | *q* | g' |
| **Mölle et al.** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| Count | 678.54 | 149.6 | 563,0 | 145.9 | 688.53 | 152.7 | 9.02 | 2 | 97 | 0.01 | **0.048*** | **0.04** | 0.11 | 0.79 | 0.003 | **0.009*** | -0.89 | 0.53 | - | -0.12 |
| Density (Nber/30 sec) | 1.19 | 0.2 | 1.1 | 0.19 | 1.29 | 0.3 | 7.89 | 2 | 97 | 0.02 | **0.048*** | 0.24 | - | 0.40 | 0.006 | **0.02** | -0.77 | 0.14 | - | -0.39 |
| Duration (sec) | 0.77 | 0.04 | 0.75 | 0.03 | 0.77 | 0.1 | 2.71 | 2 | 97 | 0.26 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 92.7 | 18.3 | 94.92 | 23.3 | 83.14 | 21.6 | 0.84 | 2 | 97 | 0.43 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 11.36 | 0.5 | 11.29 | 0.5 | 11.35 | 0.5 | 0.21 | 2 | 97 | 0.81 | - | - | - | - | - | - | - | - | - | - |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| Count | 826.68 | 177.15 | 703.12 | 207.86 | 796.6 | 222.7 | 5.34 | 2 | 97 | 0.07 | - | - | - | - | - | - | - | - | - | - |
| Density (Nber/30 sec) | 1.45 | 0.27 | 1.38 | 0.34 | 1.48 | 0.36 | 0.69 | 2 | 97 | 0.50 | - | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 0.74 | 0.04 | 0.73 | 0.04 | 0.75 | 0.06 | 0.61 | 2 | 97 | 0.73 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 71.25 | 17.26 | 77.08 | 21.64 | 65.21 | 14.3 | 1.62 | 2 | 97 | 0.20 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 13.53 | 0.56 | 13.81 | 0.46 | 13.49 | 0.59 | 2.08 | 2 | 97 | 0.13 | - | - | - | - | - | - | - | - | - | - |
| **Ray et al.** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| Count | 743.29 | 275.05 | 608.42 | 187.16 | 789.79 | 294.37 | 8.27 | 2 | 97 | **0.02** | 0.06 | 0.06 | - | 0.57 | 0.004 | **0.01*** | -0.72 | 0.41 | - | -0.19 |
| Density (Nber/30 sec) | 1.29 | 0.44 | 1.2 | 0.31 | 1.48 | 0.5 | 3.48 | 2 | 97 | **0.04** | 0.06 | 0.42 | - | 0.25 | 0.01 | **0.04*** | -0.61 | 0.10 | - | -0.36 |
| Duration (sec) | 0.73 | 0.05 | 0.71 | 0.04 | 0.75 | 0.07 | 6.56 | 2 | 97 | **0.04** | 0.06 | 0.05 | - | 0.50 | 0.01 | **0.04*** | -0.56 | 0.73 | - | -0.20 |
| Amplitude (µV) | 89.35 | 18.03 | 90.76 | 22.43 | 79.37 | 21.11 | 0.93 | 2 | 97 | 0.40 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 11.32 | 0.55 | 11.4 | 0.54 | 11.45 | 0.5 | 0.44 | 2 | 97 | 0.64 | - | - | - | - | - | - | - | - | - | - |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| Count | 805.93 | 292.41 | 678.85 | 266.21 | 841.51 | 298.53 | 4.02 | 2 | 97 | 0.13 | - | - | - | - | - | - | - | - | - | - |
| Density (Nber/30 sec) | 1.41 | 0.48 | 1.32 | 0.48 | 1.58 | 0.52 | 3.88 | 2 | 97 | 0.14 | - | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 0.73 | 0.06 | 0.72 | 0.05 | 0.76 | 0.09 | 2.06 | 2 | 97 | 0.36 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 71.07 | 17.48 | 76.06 | 20.01 | 64.81 | 12.88 | 7.19 | 2 | 97 | **0.03** | 0.14 | 0.49 | - | -0.26 | 0.01 | **0.04*** | 0.71 | 0.07 | - | 0.42 |
| Frequency (Hz) | 12.91 | 0.66 | 13.04 | 0.84 | 12.9 | 0.87 | 2.47 | 2 | 97 | 0.29 | - | - | - | - | - | - | - | - | - | - |
| **Lacourse et al.** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| Count | 426.07 | 242.93 | 393.08 | 233.96 | 636.62 | 382.33 | 6.28 | 2 | 97 | 0.003 | **0.008*** | 0.69 | - | 0.14 | 0.005 | **0.02*** | -0.71 | 0.02 | **0.048*** | -0.62 |
| Density (Nber/30 sec) | 0.74 | 0.41 | 0.77 | 0.45 | 1.22 | 0.75 | 6.54 | 2 | 97 | 0.002 | **0.008*** | 0.80 | - | -0.07 | 0.013 | **0.04*** | -0.67 | 0.005 | **0.01*** | -0.73 |
| Duration (sec) | 0.91 | 0.08 | 0.91 | 0.08 | 0.93 | 0.09 | 1.29 | 2 | 97 | 0.28 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 78.65 | 12.18 | 78.44 | 14.38 | 71.98 | 15.99 | 0.79 | 2 | 97 | 0.46 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 11.74 | 0.5 | 11.94 | 0.55 | 11.85 | 0.4 | 1.40 | 2 | 97 | 0.25 | - | - | - | - | - | - | - | - | - | - |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| Count | 736.86 | 425.57 | 626.42 | 392.33 | 777.94 | 447.74 | 2.24 | 2 | 97 | 0.33 | - | - | - | - | - | - | - | - | - | - |
| Density (Nber/30 sec) | 1.29 | 0.72 | 1.22 | 0.75 | 1.47 | 0.84 | 1.91 | 2 | 97 | 0.38 | - | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 0.88 | 0.07 | 0.89 | 0.07 | 0.9 | 0.1 | 1.16 | 2 | 97 | 0.32 | - | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 67.77 | 14.9 | 70.98 | 15.9 | 62.65 | 10.34 | 2.55 | 2 | 97 | 0.28 | - | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 13.23 | 0.55 | 13.42 | 0.64 | 13.16 | 0.68 | 4.83 | 2 | 97 | 0.09 | - | - | - | - | - | - | - | - | - | - |

Table S6: Effect of chronic sedative-hypnotic use on SOs using Staresina and Massimini detection algorithms during NREM

*Mean (± SD) SOs characteristics using Staresina and Massimini detection algorithms in the frontal and parietal regions during NREM across the GS, INS, and MED groups. Asterisks denote statistically significant differences between groups (p<.05).*

| SO characteristics | GS | | INS | | MED | | GS vs INS vs MED Kruskal-Wallis test or ANOVA | | | | | GS vs INS post hoc - Dunn test or t test | | | INS vs MED post hoc - Dunn test or t test | | | GS vs MED post hoc - Dunn test or t test | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | df residual | p | q | | p | q | effect size g' | p | q | effect size g' | p | q | effect size g' |
| **Staresina et al.** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| Count | 2181.89 | 455.25 | 2029.5 | 571.38 | 2061 | 513.33 | *0.76* | 2 97 | *0.47* | - | | - | - | - | - | - | - | - | - | - |
| Density (Nber/30 sec) | 3.83 | 0.78 | 3.98 | 0.82 | 3.82 | 0.71 | 0.86 | 2 97 | 0.65 | - | | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 1.35 | 0.06 | 1.37 | 0.05 | 1.41 | 0.08 | 2.23 | 2 97 | 0.33 | - | | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 122.26 | 30.17 | 124.16 | 37.02 | 104.61 | 28.41 | 1.27 | 2 97 | 0.29 | - | | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 0.76 | 0.06 | 0.73 | 0.05 | 0.7 | 0.07 | 8.39 | 2 97 | **0.02** | 0.08 | | 0.07 | - | 0.46 | 0.40 | - | 0.57 | 0.004 | **0.01*** | 0.92 |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| Count | 1954.36 | 446.47 | 1840.65 | 566.78 | 1891.49 | 487.88 | *0.61* | 2 97 | *0.55* | - | | - | - | - | - | - | - | - | - | - |
| Density (Nber/30 sec) | 3.41 | 0.73 | 3.62 | 0.86 | 3.5 | 0.67 | 1.98 | 2 97 | 0.37 | - | | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 1.43 | 0.07 | 1.43 | 0.06 | 1.46 | 0.06 | 0.31 | 2 97 | 0.86 | - | | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 96.2 | 26.29 | 102.85 | 32.2 | 84.67 | 21.39 | 1.54 | 2 97 | 0.22 | - | | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 0.68 | 0.06 | 0.67 | 0.06 | 0.65 | 0.07 | 1.05 | 2 97 | 0.59 | - | | - | - | - | - | - | - | - | - | - |
| **Massimini et al.** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| Count | 341.14 | 306.52 | 316.15 | 342.08 | 170.79 | 220.54 | 2.62 | 2 97 | 0.27 | - | | - | - | - | - | - | - | - | - | - |
| Density (Nber/30 sec) | 0.58 | 0.52 | 0.66 | 0.79 | 0.29 | 0.38 | 1.72 | 2 97 | 0.42 | - | | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 1.19 | 0.13 | 1.176 | 0.11 | 1.3 | 0.19 | 3.12 | 2 97 | 0.21 | - | | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 209.48 | 20.18 | 217 | 32.16 | 204.44 | 21.83 | 0.28 | 2 97 | 0.87 | - | | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 0.75 | 0.09 | 0.76 | 0.08 | 0.71 | 0.11 | 0.3 | 2 97 | 0.74 | - | | - | - | - | - | - | - | - | - | - |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| Count | 82.68 | 121.32 | 122.5 | 234.63 | 30.87 | 54.8 | 0.18 | 2 97 | 0.91 | - | | - | - | - | - | - | - | - | - | - |
| Density (Nber/30 sec) | 0.14 | 0.23 | 0.25 | 0.49 | 0.04 | 0.09 | 0.08 | 2 97 | 0.96 | - | | - | - | - | - | - | - | - | - | - |
| Duration (sec) | 1.29 | 0.16 | 1.31 | 0.17 | 1.42 | 0.17 | 5.97 | 2 97 | 0.05 | - | | - | - | - | - | - | - | - | - | - |
| Amplitude (µV) | 188.79 | 13.91 | 198.73 | 49.94 | 194.97 | 29.80 | 1.49 | 2 97 | 0.48 | - | | - | - | - | - | - | - | - | - | - |
| Frequency (Hz) | 0.69 | 0.11 | 0.67 | 0.10 | 0.62 | 0.095 | 3.2 | 2 97 | 0.20 | - | | - | - | - | - | - | - | - | - | - |

SO, slow oscillation

## Impact of chronic sedative-hypnotic use on SO-spindle association and SO-sigma PAC during NREM

Table S7: Chronic sedative-hypnotic use affects SO-spindle association and SO-sigma PAC during NREM

*Participant spindle/slow oscillation temporal association and SO-spindle phase-amplitude coupling parameters during NREM in the frontal and parietal areas across the GS, INS, and MED groups. Asterisks indicate statistically significant differences between groups (p<.05).*

| Outcome measure | GS | | INS | | MED | | GS vs INS vs MED Kruskal-Wallis test or ANOVA | | | | | GS vs INS post hoc - Dunn test or t test | | | INS vs MED post hoc - Dunn test or t te | | | GS vs MED post hoc - Dunn test or t test | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | F | df residual | p | q | | p | q | effect size g' | p | q | effect size g' | p | q | effect size g' |
| ***Temporal association*** | | | | | | | | | | | | | | | | | | | | |
| **Fz** | | | | | | | | | | | | | | | | | | | | |
| Recall | 0.12 | 0.03 | 0.11 | 0.03 | 0.12 | 0.04 | 4.68 | 2 97 | 0.10 | - | | - | - | - | - | - | - | - | - | - |
| Precision | 0.39 | 0.10 | 0.37 | 0.07 | 0.35 | 0.11 | 1.22 | 2 97 | 0.30 | - | | - | - | - | - | - | - | - | - | - |
| **Pz** | | | | | | | | | | | | | | | | | | | | |
| Recall | 0.1 | 0.02 | 0.09 | 0.03 | 0.09 | 0.03 | 5.40 | 2 97 | 0.07 | - | | - | - | - | - | - | - | - | - | - |
| Precision | 0.24 | 0.05 | 0.24 | 0.07 | 0.21 | 0.07 | 3.27 | 2 97 | 0.20 | - | | - | - | - | - | - | - | - | - | - |
| ***SO-sigma PAC*** | | | | | | | | | | | | | | | | | | | | |
| Modulation Index | | | | | | | | | | | | | | | | | | | | |
| Fz | 1.63 | 1.12 | 1.22 | 1.32 | 0.99 | 1 | 6.83 | 2 97 | 0.03 | **0.03*** | | 0.09 | - | 0.33 | 0.64 | - | 0.23 | 0.01 | **0.03*** | 0.63 |
| Pz | 3.52 | 1.62 | 2.67 | 1.56 | 1.94 | 1.45 | 13.32 | 2 97 | 0.001 | **0.002*** | | **0.02** | 0.07 | 0.55 | 0.99 | - | 0.26 | < 0.001 | **< 0.001*** | 0.85 |
| Coupling preferred-phase (degree) | | | | | | | | | | | | Watson's Two-Sample Test GS vs INS | | | Watson's Two-Sample Test INS vs MED | | | Watson's Two-Sample Test GS vs MED | | |
| | | | | | | | | | | | | stat | p | | stat | p | | stat | p | |
| Fz | 279 | 53 | 288 | 34 | 301 | 55 | - | - - | - | - | | 0.07 | $p > 0.10$ | | 0.07 | $p > 0.10$ | | 0.18 | $0.05 < p < 0.10$ | |
| Pz | 236 | 27 | 238 | 31 | 265 | 27 | - | - - | - | - | | 0.06 | $p > 0.10$ | | 0.33 | $p < 0.01$* | | 0.28 | $p < 0.01$* | |

SO, slow oscillation; PAC, phase-amplitude coupling

## MED subgroup analyses

### Table S8: Effect of chronic sedative-hypnotic exposure on sleep architecture

*Mean (± SD) measures of sleep architecture, spectral activity and brain oscillations characteristics between BZD users and BZRA users within the MED group. Asterisks indicate statistically significant differences between groups (p<.05).*

| Outcome measure | BZD n=18 | | BZRA n=29 | | MEDICATION TYPE (BZD vs BZRA) ANOVA or *Wilcoxon test* | | | | effect size |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | F | df | *p* | *q* | g' |
| ***Sleep duration*** | | | | | | | | | |
| TIB (min) | 494.61 | 67.63 | 510.66 | 44.03 | 0.01 | 1, 45 | 0.93 | - | - |
| TSP (min) | 440.17 | 68.2 | 480.05 | 49.66 | 0.22 | 1, 45 | 0.64 | - | - |
| TST (min) | 342.36 | 56.21 | 408.1 | 47.01 | 4.03 | 1, 45 | 0.05 | - | - |
| SE (%) | 70.41 | 14.5 | 79.96 | 6.76 | 2.95 | 1, 45 | 0.09 | - | - |
| N1 (% TSP) | 5.01 | 3.16 | 4.68 | 1.96 | *266* | 1, 45 | *0.92* | - | - |
| N2 (% TSP) | 50.79 | 11.78 | 51.47 | 6.99 | 0.01 | 1, 45 | 0.92 | - | - |
| N3 (% TSP) | 5.31 | 4.65 | 8.69 | 5.49 | 198 | 1, 45 | 0.17 | - | - |
| REM (% TSP) | 17.7 | 6.95 | 20.25 | 5.73 | 1.83 | 1, 45 | 0.18 | - | - |
| ***Sleep Initiation*** (min) | | | | | | | | | |
| SOL | 40.47 | 51.08 | 18.62 | 21.77 | *277* | 1, 45 | *0.73* | - | - |
| SL to N2 | 42.83 | 50.8 | 21.16 | 21.63 | *272* | 1, 45 | *0.82* | - | - |
| SL to N3 | 75.21 | 59.93 | 45.23 | 31.42 | *246* | 1, 45 | *0.86* | - | - |
| SL to REM | 167.39 | 101.5 | 121.12 | 54.29 | *300* | 1, 45 | *0.40* | - | - |
| ***Sleep Fragmentation*** | | | | | | | | | |
| Wake (% TSP) | 21.19 | 13.21 | 14.91 | 5.66 | 2.58 | 1, 45 | 0.12 | - | - |
| Arousal density (Nber/h) | | | | | | | | | |
| all night | 14.92 | 6.68 | 14.51 | 6.86 | 0.04 | 1, 45 | 0.85 | - | - |
| NREM | 0.23 | 0.1 | 0.25 | 0.13 | 0.10 | 1, 45 | 0.75 | - | - |
| REM | 0.28 | 0.19 | 0.21 | 0.12 | *0.05* | 1, 45 | *0.82* | - | - |
| SFI | 9.64 | 4.2 | 9.16 | 1.85 | *253* | 1, 45 | *0.87* | - | - |
| ***Relative power spectrum*** | | | | | | | | | |
| **Fz** | | | | | | | | | |
| SO | 0.6 | 0.1 | 0.61 | 0.1 | 0.05 | 1, 45 | 0.83 | - | - |
| Delta | 0.73 | 0.08 | 0.74 | 0.09 | 267 | 1, 45 | 0.90 | - | - |
| Index Delta/Beta | 48.89 | 32.01 | 71.57 | 39.8 | 261 | 1, 45 | 0.99 | - | - |
| Theta | 0.06 | 0.02 | 0.06 | 0.03 | 0.74 | 1, 45 | 0.40 | - | - |
| Alpha | 0.05 | 0.03 | 0.05 | 0.03 | 219 | 1, 45 | 0.36 | - | - |
| Sigma | 0.04 | 0.02 | 0.03 | 0.02 | 287 | 1, 45 | 0.58 | - | - |
| Low Beta | 0.01 | 0.01 | 0 | 0 | 260 | 1, 45 | 0.99 | - | - |
| High Beta | 0.01 | 0.01 | 0.01 | 0 | 269 | 1, 45 | 0.87 | - | - |
| **Pz** | | | | | | | | | |
| SO | 0.61 | 0.13 | 0.59 | 0.11 | 293 | 1, 45 | 0.49 | - | - |
| Delta | 0.68 | 0.07 | 0.69 | 0.09 | 0.16 | 1, 45 | 0.69 | - | - |
| Index Delta/Beta | 49.22 | 33.32 | 58.26 | 37.09 | 276 | 1, 45 | 0.75 | - | - |
| Theta | 0.06 | 0.02 | 0.08 | 0.04 | 1.37 | 1, 45 | 0.25 | - | - |
| Alpha | 0.04 | 0.03 | 0.05 | 0.03 | 194 | 1, 45 | 0.15 | - | - |
| Sigma | 0.06 | 0.05 | 0.04 | 0.03 | 274 | 1, 45 | 0.78 | - | - |
| Low Beta | 0.01 | 0.01 | 0.01 | 0 | 0.04 | 1, 45 | 0.84 | - | - |
| High Beta | 0.01 | 0.01 | 0.01 | 0.01 | 245 | 1, 45 | 0.73 | - | - |
| ***SO characteristics*** | | | | | | | | | |
| **Fz** | | | | | | | | | |
| Density (Nber/30 sec) | 3.88 | 0.45 | 3.79 | 0.84 | 0.39 | 1, 45 | 0.54 | - | - |
| Duration (sec) | 1.43 | 0.07 | 1.39 | 0.08 | 292 | 1, 45 | 0.50 | - | - |
| Amplitude (µV) | 95.63 | 31.23 | 110.19 | 25.5 | 211 | 1, 45 | 0.28 | - | - |
| Frequency (Hz) | 0.67 | 0.05 | 0.71 | 0.08 | 242 | 1, 45 | 0.68 | - | - |
| **Pz** | | | | | | | | | |
| Density (Nber/30 sec) | 3.53 | 0.56 | 3.48 | 0.74 | 270 | 1, 45 | 0.86 | - | - |
| Duration (sec) | 1.47 | 0.05 | 1.44 | 0.07 | 264 | 1, 45 | 0.97 | - | - |
| Amplitude (µV) | 80.44 | 27.02 | 87.29 | 17.03 | 207 | 1, 45 | 0.24 | - | - |
| Frequency (Hz) | 0.62 | 0.04 | 0.66 | 0.07 | 229 | 1, 45 | 0.49 | - | - |
| ***Spindle characteristics*** | | | | | | | | | |
| **Fz** | | | | | | | | | |
| Density (Nber/30 sec) | 1.36 | 0.28 | 1.24 | 0.23 | 0.04 | 1, 45 | 0.85 | - | - |
| Duration (sec) | 0.78 | 0.05 | 0.76 | 0.05 | 302 | 1, 45 | 0.38 | - | - |
| Amplitude (µV) | 77.27 | 20.93 | 86.78 | 21.53 | 199 | 1, 45 | 0.18 | - | - |
| Frequency (Hz) | 11.42 | 0.49 | 11.32 | 0.42 | 0.74 | 1, 45 | 0.40 | - | - |
| **Pz** | | | | | | | | | |
| Density (Nber/30 sec) | 1.6 | 0.36 | 1.41 | 0.34 | 1.40 | 1, 45 | 0.24 | - | - |
| Duration (sec) | 0.77 | 0.07 | 0.74 | 0.05 | 287 | 1, 45 | 0.58 | - | - |
| Amplitude (µV) | 62.75 | 16.48 | 66.73 | 12.83 | 212 | 1, 45 | 0.29 | - | - |
| Frequency (Hz) | 13.63 | 0.67 | 13.4 | 0.53 | 293 | 1, 45 | 0.49 | - | - |
| ***Temporal association*** | | | | | | | | | |
| **Fz** | | | | | | | | | |
| Recall ($SO^+$) | 0.12 | 0.04 | 0.11 | 0.04 | 0.01 | 1, 45 | 0.93 | - | - |
| Precision ($Spindle^+$) | 0.34 | 0.08 | 0.35 | 0.12 | 0.01 | 1, 45 | 0.91 | - | - |
| **Pz** | | | | | | | | | |
| Recall ($SO^+$) | 0.1 | 0.04 | 0.08 | 0.02 | 317 | 1, 45 | 0.22 | - | - |
| Precision ($Spindle^+$) | 0.21 | 0.08 | 0.2 | 0.07 | 0.42 | 1, 45 | 0.52 | - | - |
| ***Phase-Amplitude coupling*** Modulation Index | | | | | | | | | |
| Fz | 0.71 | 0.87 | 1.16 | 1.04 | 239 | 1, 45 | 0.64 | - | - |
| Pz | 1.74 | 1.55 | 2.06 | 1.39 | 240 | 1, 45 | 0.65 | - | - |

TSP, total sleep period; TIB, time in bed; TST, total sleep time; SOL, sleep onset latency; SL, sleep latency; WASO, wake after sleep onset; SE, sleep efficiency; SFI, sleep fragmentation index; SO, slow oscillation; SSI, stage switch index; NREM, non-rapid eye movement; REM, rapid eye movement

# Appendix B: supplementary materials for Chapter 3

## Tables

### Table S1: Actigraphy-derived outcomes

*Regarding actigraphy measures, at 16 weeks post-randomization (T2), 15 participants (attrition rate 44.4%) from the WP+CBTi group and 12 participants (attrition rate 45.5%) from the WPo group.*

| | | WP+CBT group | | WPo group | | Cohen g' (V1 vs V2) | | Time*Group | | | Time | | | Group | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome measure | (N) | Mean | SD | Mean | SD | WP+CBT | Wpo | F | *p* | *q* | F | *p* | *q* | F | *p* | *q* |
| **Actigraphy** (15 WP+CBT vs 12 WPo) | | | | | | | | | | | | | | | | |
| Mean TIB (min) | V1 | 516.54 | 40.57 | 513.63 | 51.99 | 0.08 | -0.01 | 0.71 | 0.40 | - | 0.14 | 0.71 | - | 0.01 | 0.91 | |
| | V2 | 510.27 | 74.03 | 514.03 | 41.09 | | | | | | | | | | | |
| Mean TST (min) | V1 | 446.89 | 42.7 | 446.74 | 49.48 | 0.38 | 0.35 | 0.19 | 0.66 | - | 4.8 | **0.03** | 0.15 | 0.01 | 0.93 | - |
| | V2 | 414.75 | 92.06 | 413.82 | 98.16 | | | | | | | | | | | |
| Mean SOL (min) | V1 | 15.95 | 18.85 | 13.18 | 11.35 | 0.01 | -0.21 | 0.12 | 0.73 | - | 1.29 | 0.26 | - | <0.01 | 0.98 | - |
| | V2 | 15.81 | 11.2 | 17.71 | 19.68 | | | | | | | | | | | |
| Mean WASO (min) | V1 | 48.92 | 20.3 | 44.22 | 16.26 | 0.37 | -0.06 | 0.99 | 0.32 | - | 0.54 | 0.47 | - | <0.01 | 0.97 | - |
| | V2 | 41.18 | 19.34 | 45.4 | 20.66 | | | | | | | | | | | |
| Mean SE (%) | V1 | 86.01 | 5.98 | 87.08 | 4.44 | 0.38 | 0.32 | 0 | 0.95 | - | 2.79 | 0.10 | - | 0.01 | 0.92 | - |
| | V2 | 82.17 | 11.97 | 79.97 | 18.27 | | | | | | | | | | | |

TIB, time in bed; TST, total sleep time; SOL, sleep onset latency; WASO, wake after sleep onset; SE, sleep efficiency; WPo, sedative-hypnotics withdrawal plan group; WP+CBT, CBTi combined to sedative-hypnotics withdrawal plan

### Table S2: Cognitive assessment performance

Regarding cognitive evaluation, 25 participants (attrition rate 7.4%) from the WP+CBTi group and 21 participants (attrition rate 4.6%) from the WPo group completed overnights at 16 weeks post-randomization (T2).

| | | WP+CBTi group | | WPo group | | Cohen g' (T1 vs T2) | | Time*Group | | | Time | | | Group | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome measure | (N) | Mean | SD | Mean | SD | WP+CBT | WPo | F | *p* | *q* | F | *p* | *q* | F | *p* | *q* |
| **Cognitive functioning** (25 WP+CBTi vs 21 Wpo) | | | | | | | | | | | | | | | | |
| *Manual dexterity* | | | | | | | | | | | | | | | | |
| PPT - Condition 1 (z-score) | T1 | -0.11 | 1.11 | -0.11 | 1.07 | 0.15 | -0.4 | 1.04 | 0.31 | - | 0.83 | 0.36 | - | 0.82 | 0.37 | - |
| | T2 | -0.3 | 1.34 | 0.33 | 1.07 | | | | | | | | | | | |
| PPT - Condition 2 (z-score) | T1 | -0.12 | 0.99 | -0.17 | 0.71 | -0.23 | -0.65 | 1.25 | 0.27 | - | 7.53 | **0.01** | 0.16 | 0.24 | 0.63 | - |
| | T2 | 0.12 | 1.03 | 0.4 | 0.95 | | | | | | | | | | | |
| PPT - Condition 3 (z-score) | T1 | 0.21 | 1.36 | 0.15 | 0.93 | 0.01 | -0.43 | 0.03 | 0.87 | - | 2.43 | 0.12 | - | 0.51 | 0.47 | - |
| | T2 | 0.19 | 1.27 | 0.61 | 1.13 | | | | | | | | | | | |
| *Attention/concentration* | | | | | | | | | | | | | | | | |
| DSST (scaled score) | T1 | 8.36 | 2.12 | 8.48 | 1.91 | <0.01 | -0.36 | 2.28 | 0.13 | - | 3.78 | 0.05 | - | 2.47 | 0.12 | - |
| | T2 | 8.36 | 1.93 | 9.19 | 1.86 | | | | | | | | | | | |
| *Visual-motor skills* | | | | | | | | | | | | | | | | |
| TMT-A (z-score) | T1 | 0.36 | 1.05 | 0.33 | 1.42 | 0.16 | 0.15 | 0.11 | 0.74 | - | 0.03 | 0.87 | - | 0.42 | 0.51 | - |
| | T2 | 0.19 | 0.89 | 0.13 | 1.01 | | | | | | | | | | | |
| TMT-B (z-score) | T1 | 0.86 | 1.43 | 0.87 | 2.25 | 0.01 | 0.15 | 0 | 0.99 | - | 0.11 | 0.74 | - | 0.6 | 0.44 | - |
| | T2 | 0.83 | 1.65 | 0.57 | 1.63 | | | | | | | | | | | |
| *Verbal inhibition and flexibility* | | | | | | | | | | | | | | | | |
| DKEFS - Condition 1 (scaled score) | T1 | 10.44 | 3.08 | 11.33 | 1.91 | -0.01 | -0.25 | 1.75 | 0.19 | - | 3.64 | 0.06 | - | 1.46 | 0.23 | - |
| | T2 | 10.48 | 3.24 | 11.86 | 2.13 | | | | | | | | | | | |
| DKEFS - Condition 2 (scaled score) | T1 | 10.76 | 2.44 | 11.9 | 1.84 | 0.03 | 0.03 | 0.03 | 0.85 | - | 0.08 | 0.78 | - | 3.51 | 0.06 | - |
| | T2 | 10.68 | 2.41 | 11.86 | 1.68 | | | | | | | | | | | |
| DKEFS - Condition 3 (scaled score) | T1 | 10.76 | 2.57 | 12.1 | 1.84 | 0.04 | -0.07 | 0.12 | 0.73 | - | 1.09 | 0.30 | - | 4 | 0.05 | - |
| | T2 | 10.64 | 3.17 | 12.24 | 2.07 | | | | | | | | | | | |
| DKEFS - Condition 4 (scaled score) | T1 | 10.96 | 3.21 | 11.52 | 3.09 | -0.11 | -0.12 | 0.01 | 0.92 | - | 1.46 | 0.23 | - | 0.86 | 0.35 | - |
| | T2 | 11.32 | 3.12 | 11.9 | 2.79 | | | | | | | | | | | |
| *Verbal memory* | | | | | | | | | | | | | | | | |
| Free Recall (z-score) | T1 | -0.51 | 1.26 | -0.24 | 1.13 | -0.46 | -0.07 | 2.4 | 0.13 | - | 4.29 | 0.05 | - | 0.01 | 0.92 | - |
| | T2 | 0.03 | 0.96 | -0.17 | 1.11 | | | | | | | | | | | |
| Delayed Free Recall (z-score) | T1 | 0.05 | 1.45 | 0.15 | 1.47 | 0.03 | -0.22 | 1.43 | 0.23 | - | 0.89 | 0.35 | - | 0.37 | 0.54 | - |
| | T2 | 0 | 1.75 | 0.48 | 1.44 | | | | | | | | | | | |
| *Visual-spatial abilities* | | | | | | | | | | | | | | | | |
| MCTF - Copy (scaled score) | T1 | 31.69 | 3.92 | 31.17 | 3.68 | 0.18 | -0.62 | 6.02 | **0.01** | 0.16 | 1.08 | 0.30 | - | 0.72 | 0.39 | - |
| | T2 | 31.02 | 3.71 | 33.21 | 2.22 | | | | | | | | | | | |
| MCTF - Copy (z-score SES) | T1 | 0.11 | 0.98 | -0.06 | 1 | 0.17 | -0.62 | 5.86 | **0.02** | 0.16 | 1.49 | 0.22 | - | 0.71 | 0.40 | - |
| | T2 | -0.06 | 0.99 | 0.5 | 0.61 | | | | | | | | | | | |
| MCTF - Copy (z-score All) | T1 | -0.01 | 0.97 | -0.18 | 1 | 0.16 | -0.6 | 5.27 | **0.03** | 0.16 | 1.55 | 0.22 | - | 0.29 | 0.59 | - |
| | T2 | -0.16 | 0.98 | 0.37 | 0.64 | | | | | | | | | | | |
| MCTF - Recall (scaled score) | T1 | 15.1 | 5.12 | 16.52 | 5.84 | -0.1 | -0.2 | 0.28 | 0.60 | - | 1.42 | 0.24 | - | 1.44 | 0.24 | - |
| | T2 | 15.96 | 4.81 | 17.83 | 6.47 | | | | | | | | | | | |
| MCTF - Recall (z-score SES) | T1 | -0.02 | 0.91 | 0.17 | 1.08 | -0.11 | -0.2 | 0.27 | 0.61 | - | 1.49 | 0.23 | - | 0.98 | 0.33 | - |
| | T2 | 0.15 | 0.88 | 0.4 | 1.19 | | | | | | | | | | | |
| MCTF - Recall (z-score All) | T1 | -0.2 | 1.15 | -0.2 | 1.18 | -0.05 | 0.02 | 0.04 | 0.84 | - | 0.01 | 0.92 | - | 0.02 | 0.89 | - |
| | T2 | -0.12 | 1.12 | -0.22 | 1.21 | | | | | | | | | | | |

DSST, Digit Symbol Substitution Test; DKEFS, Delis-Kaplan executive function system (Stroop); FCSRT, French adaptation of the 16-items free and cued selective reminding test; MMSE, Mini Mental State Examination; MTCF/ROCF, Rey complex figure & modified Taylor complex figure tests; PPT, Purdue Pegboard Test; SES, sociodemographic variables (age, education level, and sex); TMT,Trail making test; WPo, sedative-hypnotics withdrawal plan group; WP+CBTi, CBTi combined to sedative-hypnotics withdrawal plan

Table S3: Spindle characteristics in central region

| | | WP+CBTi group | | WPo group | | Cohen g' (T1 vs T2) | | Time*Group | | | Time | | | Group | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome measure | (N) | Mean | SD | Mean | SD | WP+CBTi | WPo | F | *p* | *q* | F | *p* | *q* | F | *p* | *q* |
| **Spindles adapted characteristics** | | | | | | | | | | | | | | | | |
| (23 WP+CBTi vs 20 WPo) | | | | | | | | | | | | | | | | |
| ***NREM*** | | | | | | | | | | | | | | | | |
| Density | T1 | 1.19 | 0.24 | 1.15 | 0.18 | 0.21 | 0.41 | 0.02 | 0.88 | - | 5.97 | **0.02** | 0.06 | 0.1 | 0.74 | - |
| | T2 | 1.13 | 0.36 | 1.07 | 0.22 | | | | | | | | | | | |
| Duration | T1 | 0.76 | 0.05 | 0.76 | 0.04 | 0.48 | 0.72 | 0.36 | 0.54 | - | 9.72 | 0.002 | **0.04*** | 0.25 | 0.61 | - |
| | T2 | 0.74 | 0.03 | 0.73 | 0.03 | | | | | | | | | | | |
| Amplitude | T1 | 84.03 | 25.71 | 75.66 | 16.89 | 0.13 | -0.28 | 2.72 | 0.11 | - | 0.19 | 0.66 | - | 0.45 | 0.51 | - |
| | T2 | 80.89 | 21.81 | 81.09 | 20.07 | | | | | | | | | | | |
| Frequency | T1 | 11.4 | 1.15 | 11.3 | 1.19 | -0.25 | -0.27 | 0.03 | 0.86 | - | 2.09 | 0.16 | - | 0.03 | 0.87 | - |
| | T2 | 11.75 | 1.48 | 11.74 | 1.86 | | | | | | | | | | | |
| ***NREM2*** | | | | | | | | | | | | | | | | |
| Density | T1 | 1.13 | 0.25 | 1.09 | 0.19 | 0.2 | 0.3 | 0.36 | 0.55 | - | 4.25 | **0.04** | 0.13 | 0.1 | 0.76 | - |
| | T2 | 1.07 | 0.33 | 1.02 | 0.23 | | | | | | | | | | | |
| Duration | T1 | 0.77 | 0.06 | 0.76 | 0.03 | 0.47 | 0.63 | 0.07 | 0.79 | - | 6.18 | **0.01** | 0.06 | 0.27 | 0.60 | - |
| | T2 | 0.75 | 0.04 | 0.74 | 0.03 | | | | | | | | | | | |
| Amplitude | T1 | 79.69 | 24.92 | 72.38 | 15.11 | 0.1 | -0.32 | 2.48 | 0.12 | - | 0.47 | 0.49 | - | 0.25 | 0.62 | - |
| | T2 | 77.21 | 21.16 | 78.66 | 21.01 | | | | | | | | | | | |
| Frequency | T1 | 11.58 | 1.16 | 11.39 | 1.27 | -0.21 | -0.25 | 0.06 | 0.81 | - | 1.68 | 0.20 | - | 0.11 | 0.74 | - |
| | T2 | 11.87 | 1.52 | 11.82 | 1.89 | | | | | | | | | | | |
| ***NREM3*** | | | | | | | | | | | | | | | | |
| Density | T1 | 1.29 | 0.32 | 1.24 | 0.21 | 0.16 | 0.45 | 0.03 | 0.85 | - | 4.85 | **0.03** | 0.10 | 0.18 | 0.67 | - |
| | T2 | 1.23 | 0.43 | 1.13 | 0.29 | | | | | | | | | | | |
| Duration | T1 | 0.74 | 0.04 | 0.75 | 0.06 | 0.4 | 0.67 | 0.76 | 0.38 | - | 8.68 | 0.003 | **0.04*** | 1.14 | 0.29 | - |
| | T2 | 0.73 | 0.04 | 0.72 | 0.03 | | | | | | | | | | | |
| Amplitude | T1 | 89.08 | 28.92 | 79.51 | 19.33 | 0.07 | -0.13 | 0.6 | 0.44 | - | 0.02 | 0.90 | - | 1.07 | 0.31 | - |
| | T2 | 87.17 | 27.35 | 82.16 | 21.11 | | | | | | | | | | | |
| Frequency | T1 | 11.18 | 1.15 | 11.13 | 1.14 | -0.32 | -0.3 | 0.01 | 0.90 | - | 2.83 | 0.1 | - | <0.01 | 0.96 | - |
| | T2 | 11.6 | 1.4 | 11.62 | 1.85 | | | | | | | | | | | |

WPo, sedative-hypnotics withdrawal plan group; WP+CBTi, CBTi combined to sedative-hypnotics withdrawal plan

## Figures

Figure S1: Lower sedative-hypnotic dosage at baseline were associated with withdrawal success following intervention

*Sedative-hypnotic dose at baseline is negatively associated with the percentage reduction in self-reported consumption in the WP+CBTi group only.*

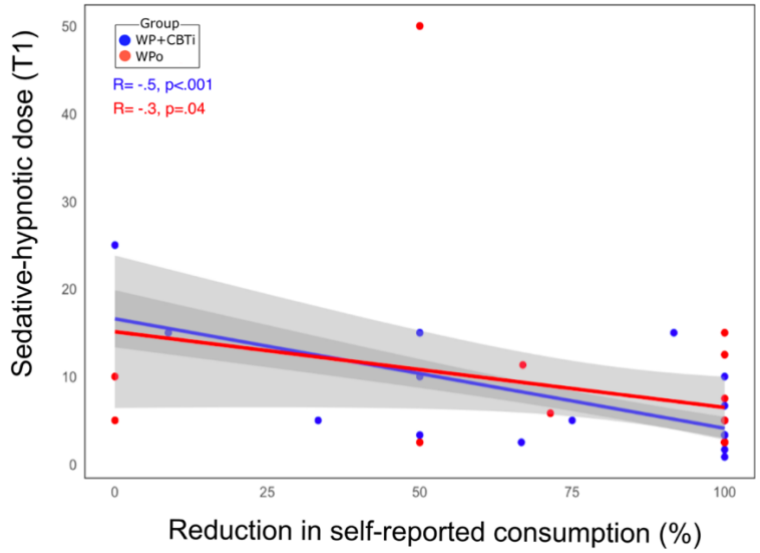
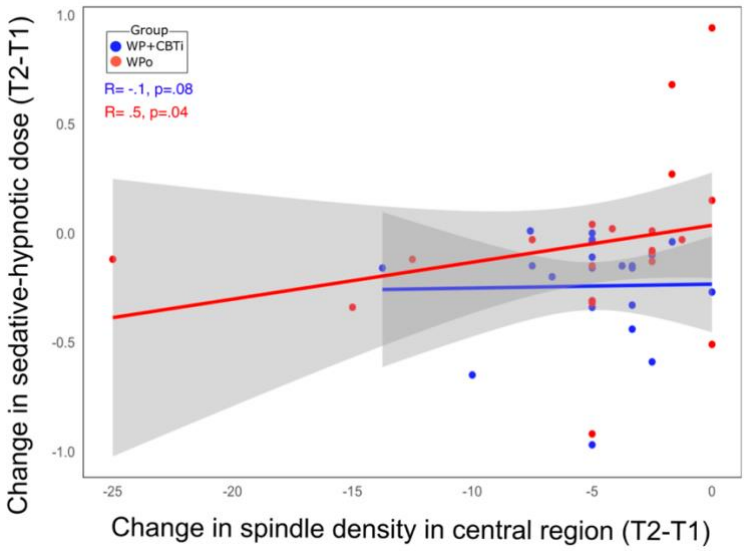


Figure S2: Association between spindle density reduction in central region and decreased sedative-hypnotic dose

*The decrease in central spindle density in WPo correlated with the reduction in the sedative-hypnotic dose consumed. However, similar correlation was not found in the WP+CBTi group.*



## Appendix C: supplementary materials for Chapter 4

### Table S1: Impact of the order of the first overnight assigned condition

| Outcomes | Order effect | |
|---|---|---|
| | stat | *p* |
| SLEEP ARCHITECTURE | | |
| SE (%) | 0.42 | 0.67 |
| SOL (min) | 0.61 | 0.54 |
| TST (min) | -0.1 | 0.91 |
| SFI | -0.63 | 0.53 |
| Duration (%TSP) | | |
| N1 | 191 | 0.77 |
| N2 | 0.67 | 0.50 |
| N3 | 0.47 | 0.63 |
| REM | -0.77 | 0.44 |
| Wake | 153 | 0.43 |
| Arousal density (event/min) | | |
| N1 | -0.39 | 0.69 |
| N2 | 202.5 | 0.53 |
| N3 | 190 | 0.79 |
| REM | 171 | 0.79 |
| SL to stage (min) | | |
| N2 | 0.69 | 0.49 |
| N3 | 0.2 | 0.84 |
| REM | 243.5 | 0.07 |
| SLEEP SPINDLE | | |
| Channel: Fz | | |
| Density (event/30 s) | 0.11 | 0.91 |
| Duration (s) | 0.62 | 0.54 |
| Amplitude (µV) | 0.2 | 0.84 |
| Frequency (Hz) | 182 | 0.97 |
| Channel: Pz | | |
| Density (event/30 s) | 0.52 | 0.61 |
| Duration (s) | 0.42 | 0.68 |
| Amplitude (µV) | 177 | 0.93 |
| Frequency (Hz) | 190 | 0.79 |
| SLOW OSCILLATION | | |
| Channel: Fz | | |
| Density (event/30 s) | 0.13 | 0.89 |
| Duration (s) | -0.03 | 0.97 |
| Amplitude (µV) | -0.75 | 0.45 |
| Frequency (Hz) | 171 | 0.79 |
| POMS (overnight change) | | |
| Vigor-Activity (/24) | -0.7 | 0.48 |
| Tension-Anxiety (/24) | 114 | 0.09 |
| Fatigue-Inertia (/20) | 145.5 | 0.60 |
| SUBJECTIVE NIGHT REVIEW | | |
| SE (%) | 152 | 0.41 |
| SOL (min) | 161.5 | 0.58 |
| TST (min) | -0.14 | 0.88 |
| WASO (min) | 148.5 | 0.35 |

| | Order effect | | List effect | |
|---|---|---|---|---|
| DECLARATIVE MEMORY | stat | *p* | stat | *p* |
| Answers (%) | | | | |
| Correct | 132 | 0.16 | 155 | 0.46 |
| Incorrect | 225 | 0.19 | 208 | 0.43 |
| Unanswered | 199 | 0.59 | 210 | 0.39 |
| Accuracy | 134.5 | 0.18 | 156 | 0.47 |
| PROCEDURAL MEMORY | | | | |
| Total sequence | -0.04 | 0.96 | 172 | 0.76 |
| Correct sequence | 0.09 | 0.93 | 175 | 0.70 |
| Accuracy | 164 | 0.96 | 164 | 0.96 |

## Table S2: Impact of the first rocking apparatus stimulation overnight accounting for wake and sleep stages

| Outcomes at Visit 1 | STAT | | | | | | | | | | ROCK | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N1 | | N2 | | N3 | | REM | | Wake | | N1 | | N2 | | N3 | | REM | | Wake | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Duration (%TSP) | 2.36 | 0.66 | 45.26 | 7.14 | 24.39 | 6.18 | 22.92 | 4.77 | 5.06 | 3.08 | 3 | 1.14 | 48.87 | 7.13 | 21.83 | 6.15 | 19.31 | 4.23 | 6.99 | 3.02 |
| Arousal density (event/min) | 0.52 | 0.2 | 0.34 | 0.15 | 0.1 | 0.07 | 0.25 | 0.12 | - | - | 0.69 | 0.3 | 0.4 | 0.18 | 0.09 | 0.07 | 0.21 | 0.13 | - | - |
| SL to stage (min) | - | - | 20.75 | 13.7 | 31.8 | 14.76 | 107.04 | 40.1 | - | - | - | - | 20.41 | 11.47 | 31.88 | 12.43 | 119.7 | 36.08 | - | - |

| Effect | Condition | | | Stage | | | Condition X Stage | | |
|---|---|---|---|---|---|---|---|---|---|
| | df | stat | *p* | df | stat | *p* | df | stat | *p* |
| Duration (%TSP) | 1, 18 | 0.05 | 0.82 | 1, 18 | 1850.31 | **< 0.001*** | 1, 18 | 28.95 | **< 0.001*** |
| Arousal density (event/min) | 1, 18 | 0.39 | 0.53 | 1, 18 | 126.08 | **< 0.001*** | 1, 18 | 14.69 | **0.002*** |
| SL to stage (min) | 1, 18 | 0.32 | 0.57 | 1, 18 | 379.08 | **< 0.001*** | 1, 18 | 1.41 | 0.49 |

| Post hocs | Condition: STAT vs ROCK | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N1 | | | N2 | | | N3 | | | REM | | | Wake | | |
| | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* |
| Duration (%TSP) | 45 | **0.045*** | -0.63 | 40.5 | **0.03*** | **-0.48** | 146 | **0.04*** | **0.4** | 163 | **0.01*** | 0.77 | 40 | **0.03*** | -0.6 |
| Arousal density (event/min) | 43.5 | 0.07 | -0.63 | 43 | 0.12 | **-0.36** | 95 | 0.39 | **0.17** | 102 | 0.08 | 0.3 | - | - | - |
| SL to stage (min) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

ROCK, rocking condition; SL, sleep latency; STAT, stationnary condition; TSP, total sleep period

Asterisks represent significance (*p* ) after Bonferonni correction

## Table S3: Effect of the rocking apparatus stimulation intervention over multiple nights accounting for wake and sleep stages

| Condition: ROCK | Visit 1 | | | | | | | | | | Visit 2 | | | | | | | | | | Visit 3 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N1 | | N2 | | N3 | | REM | | Wake | | N1 | | N2 | | N3 | | REM | | Wake | | N1 | | N2 | | N3 | | REM | | Wake | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Duration (%TSP) | 2.94 | 1.1 | 48.64 | 6.45 | 22.1 | 6.27 | 19.69 | 4.28 | 6.64 | 2.75 | 2.5 | 0.9 | 43.92 | 5.7 | 23.3 | 6.35 | 24.52 | 4.66 | 5.76 | 4.65 | 2.56 | 1.14 | 42.02 | 7.13 | 25.54 | 7.66 | 23.86 | 6.02 | 6.02 | 5.09 |
| Arousal density (event/min) | 0.66 | 0.28 | 0.37 | 0.16 | 0.1 | 0.07 | 0.22 | 0.14 | - | - | 0.64 | 0.36 | 0.3 | 0.13 | 0.11 | 0.07 | 0.34 | 0.31 | - | - | 0.54 | 0.28 | 0.29 | 0.1 | 0.08 | 0.05 | 0.26 | 0.1 | - | - |
| SL to stage (min) | - | - | 21.41 | 11.54 | 32.18 | 13.09 | 122.35 | 37.3 | - | - | - | - | 21.08 | 16.63 | 32.17 | 16.39 | 101.61 | 31.77 | - | - | - | - | 19.65 | 13.02 | 29.36 | 15.35 | 91.33 | 20.76 | - | - |

| Condition: ROCK | Visit | | Stage | | Visit X Stage | |
|---|---|---|---|---|---|---|
| | stat | *p* | stat | *p* | stat | *p* |
| Duration (%TSP) | 1.64 | 0.44 | 2207.15 | **< 0.001*** | 42.81 | **< 0.001*** |
| Arousal density (event/min) | 1.23 | 0.54 | 150.52 | **< 0.001*** | 27.66 | **< 0.001*** |
| SL to stage (min) | 4.82 | 0.09 | 312.05 | **< 0.001*** | 3.96 | 0.41 |

| Post hocs: Visit 1 vs 2 | N1 | | | N2 | | | N3 | | | REM | | | Wake | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* |
| Duration (%TSP) | 95 | 0.17 | 0.42 | 131 | **0.01*** | 0.74 | 73 | 0.89 | -0.18 | 1 | **< 0.001*** | -1.03 | 119 | **0.045*** | 0.22 |
| Arousal density (event/min) | 70 | 0.93 | 0.06 | 117 | 0.06 | 0.47 | 48 | 0.51 | -0.14 | 22.5 | **0.02*** | -0.33 | - | - | - |
| SL to stage (min) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

| Post hocs: Visit 2 vs 3 | N1 | | | N2 | | | N3 | | | REM | | | Wake | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* |
| Duration (%TSP) | 92 | 0.48 | -0.06 | 109 | 0.13 | 0.27 | 48 | 0.19 | -0.3 | 71 | 0.81 | 0.12 | 72 | 0.85 | -0.05 |
| Arousal density (event/min) | 78 | 0.32 | 0.31 | 65 | 0.79 | 0.11 | 90 | 0.26 | 0.34 | 80 | 0.55 | 0.26 | - | - | - |
| SL to stage (min) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

| Post hocs: Visit 1 vs 3 | N1 | | | N2 | | | N3 | | | REM | | | Wake | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | stat | pval | N1 | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* | stat | *p* | *g'* |
| Duration (%TSP) | 120 | **0.04*** | 0.33 | 141 | **0.001*** | 0.92 | 26 | **0.02*** | -0.46 | 23 | **0.01*** | -0.74 | 110 | 0.12 | 0.14 |
| Arousal density (event/min) | 84 | 0.18 | 0.43 | 116.5 | **0.01*** | 0.57 | 93.5 | 0.43 | 0.2 | 37 | 0.20 | -0.27 | - | - | - |
| SL to stage (min) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

ROCK, rocking condition; TSP, total sleep period

Asterisks represent significance (*p* ) after Bonferonni correction