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At Heinrich-Heine-University Düsseldorf

The Long-Term Relationship Between Sleep, Glymphatic Function, and Alzheimer's Disease

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Jorik Daniël Elberse

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signed:

Dean: Prof. Dr. med. Nikolaj Klöcker

First examiner: Prof. Dr. med. Simon B. Eickhoff

Second examiner: Prof. Dr. phil. nat. Charlotte von Gall

For Oma Jo

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German Summary

Die Alzheimer-Krankheit (AD) ist eine fortschreitende neurodegenerative Erkrankung, gekennzeichnet durch die Ablagerung toxischer Proteine, Amyloid-Beta ($A\beta$) und Tau, was zu schweren kognitiven und Gedächtnisdefiziten führt. Schlaf spielt dabei eine zentrale Rolle: Schlechter Schlaf beschleunigt die Proteinablagerung, während AD-Pathologie die für den Schlaf zuständigen Netzwerke zusätzlich stört und so einen sich selbst verstärkenden Kreislauf erzeugt. Ein Fortschritt im Verständnis dieses Zusammenhangs war die Entdeckung des glymphatischen Systems, eines hirnweiten Netzwerks für flüssigkeitsvermittelte Abfallbeseitigung. Seine Aktivität, unterstützt durch infraslowe Oszillationen im Schlaf, bildet einen Hauptweg für die Entfernung von $A\beta$ und Tau und liefert eine mechanistische Erklärung für die Schutzwirkung des Schlafs vor Neurodegeneration.

Die Theorie in der Literatur stützt sich auf drei Annahmen: (1) Schlafstörung und AD-Pathologie beeinflussen sich wechselseitig, (2) Schlaf treibt die glymphatische Aktivität an, und (3) glymphatische Dysfunktion sagt Entstehung und Fortschreiten von AD voraus. Diese Dissertation prüft jede dieser Annahmen anhand gezielter Forschungsfragen: Erstens, wie interagiert Insomnie mit AD-Pathologie und beeinflusst Netzwerke für Schlaf, Gedächtnis und Kognition? Zweitens, wie wirken Schlafentzug und Schlafrestriktion auf die glymphatische Funktion? Drittens, kann frühe glymphatische Dysfunktion AD-Status und -Schwere vorhersagen?

Bildgebungsdaten wurden aus zwei großen Kohorten erhoben. Studie 1 nutzte ADNI-Daten, um den Einfluss von Insomnie und AD auf funktionelle Konnektivität, Degree Centrality, graue Substanz und strukturelle Kovarianz zu untersuchen. Studie 2 analysierte glymphatische Funktion im multi-site ENIGMA-Sleep-Schlafentzugsdatensatz mit MRI-Indizes wie Volumen perivaskulärer Räume, Plexus choroideus, Free-Water-Index und DTI-ALPS. Studie 3 prüfte diese Indizes zusammen mit der Brain Clearance Rate (BCR) in ADNI und nutzte maschinelles Lernen mit ablativen Vergleichen, um den Beitrag einzelner glymphatischer Marker zur Vorhersage des AD-Fortschreitens zu bestimmen.

Die Analysen zeigten, dass insomnieassoziierte Pathologie in drei zentralen Netzwerken zwischen prodromaler und klinischer AD deutlich variierte. Schlafentzug führte zu temporäre Reduktionen von MRI-Indizes der CSF, während Schlafrestriktion mit Erholungsschlaf diese wiederherstellte. Frühzeitige Reduktionen der BCR, nicht jedoch anderer glymphatischer Marker, erwiesen sich als signifikanter Prädiktor für späteren AD-Status und -Schwere.

Diese Ergebnisse stützen eine bidirektionale Beziehung zwischen Schlafstörungen und AD. Während Schlafentzug nur vorübergehende glymphatische Defizite verursacht, können wiederholte oder frühe Störungen zu systemischer Dysfunktion führen und die AD-Entwicklung verstärken. Da die Neurodegeneration einen kritischen Wendepunkt darstellt, sind frühe Interventionen zur Erhaltung von Schlaf und glymphatischer Funktion entscheidend, um diesen Kreislauf zu durchbrechen.

English Summary

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder marked by the accumulation of toxic proteins, amyloid beta ($A\beta$) and tau, leading to profound cognitive and memory deficits. Sleep plays a critical role in this process, as poor sleep accelerates protein accumulation, while AD pathology further disrupts brain networks regulating sleep, creating a self-reinforcing cycle. A key advancement in understanding this relationship came with the discovery of the glymphatic system, a brain-wide network for fluid-mediated waste clearance. Its activity, facilitated by infraslow oscillations during sleep, provides a major pathway for $A\beta$ and tau clearance and offers a mechanistic explanation for the protective role of sleep against neurodegeneration.

The theory advanced in the literature rests on three central assumptions: that sleep disturbance and AD pathology influence each other bidirectionally, that sleep drives glymphatic activity, and that glymphatic dysfunction predicts the development and progression of AD pathology. This dissertation systematically interrogates each of these assumptions through targeted research questions: first, how does insomnia interact with AD pathology to affect brain networks governing sleep, memory, and cognition? Second, how do sleep deprivation and sleep restriction impact glymphatic function? Third, can early glymphatic dysfunction predict AD status and severity?

Previously acquired imaging data were collected from two large cohorts. Study 1 used subjects from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) to examine the impact of insomnia and AD pathology on brain networks’ functional connectivity, degree centrality, gray matter volume, and structural covariance. Study 2 investigated glymphatic function in a multi-site ENIGMA-Sleep deprivation dataset using glymphatic MRI indices, including perivascular space volume, choroid plexus volume, free water index, and DTI-ALPS. Study 3 assessed these indices alongside the brain clearance rate (BCR) in ADNI, employing machine learning with ablative comparisons to determine the contribution of each glymphatic feature to predicting AD progression.

Analyses revealed that insomnia-related pathology within three main brain networks differed significantly between prodromal and clinical AD. Sleep deprivation was associated with transient reductions in MRI indices of CSF influx, whereas sleep restriction with subsequent recovery sleep restored these measures. Finally, early reductions in the BCR, but not other glymphatic metrics, emerged as a significant predictor of later AD status and severity.

These findings support a bidirectional relationship between sleep disturbances and AD. While sleep deprivation causes only temporary glymphatic deficits, repeated or early impairments may cascade into broader system-level dysfunction and exacerbate AD development. As neurodegeneration marks a critical turning point, interventions that preserve sleep and glymphatic function in preclinical stages will be essential in breaking the cycle.

List of Abbreviations

Clinical

AD	Alzheimer's Disease
(a)MCI	(Amnesic) Mild Cognitive Impairment
ATN	Amyloid-Tau-Neurodegeneration
BMI	Body Mass Index
CN	Cognitively Normal

Genetic

APOE4	Apolipoprotein E4
PSEN1-2	Presenilin 1 and 2
SNP	Single Nucleotide Polymorphism

Molecular

Aβ	Amyloid Beta
APP	Amyloid Precursor Protein
AQP4	Aquaporin-4
p-tau	Phosphorylated Tau
NE	Norepinephrine

Neuroanatomy

BG	Basal Ganglia
ChP(V)	Choroid Plexus (Volume)
Cing	Cingulate Cortex
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CSO	Centrum Semiovale
dmPFC	Dorsomedial Prefrontal Cortex
Fr	Frontal Cortex
FrOper	Frontal Operculum
GM(V)	Gray Matter (Volume)
HC(V)	Hippocampus (Volume)
ICV	Intracranial Volume
Ins	Insula
ISF	Interstitial Fluid
IPFC	Lateral Prefrontal Cortex
Med	Medial Cortex
mpPFC	Medial Posterior Prefrontal Cortex
Par	Parietal Cortex
ParOper	Parietal Operculum
pCun	Precuneus
PCC	Posterior Cingulate Cortex
PVS(V)	Perivascular Space (Volume)
SCN	Suprachiasmatic Nucleus
Temp	Temporal Cortex
vPFC	Ventral Prefrontal Cortex
WM	White Matter

Neuroimaging

ALPS	Along the Perivascular Space
AV45	¹⁸ F-Florbetapir
BCR	Brain Clearance Rate
BNM	Brain Network Metric
BOLD	Blood-Oxygenation-Level-Dependent
CEN	Central Executive Network
DC	Degrees Centrality
DMN	Default Mode Network

dMRI	Diffusion Magnetic Resonance Imaging
DTI	Diffusion Tensor Imaging
FC	Functional Connectivity
FLAIR	Fluid Attenuated Inversion Recovery
FWD	Framework Displacement
FWI	Free Water Index
GSI	Glymphatic System Index
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
RBM	Region-Based Morphometry
ROI	Region-Of-Interest
(rs-)fMRI	(Resting State) Functional Magnetic Resonance Imaging
SC	Structural Covariance
SN	Saliency Network
T1/T2w	T1/T2-Weighted
TNS	Three-Network System

Questionnaires

ADAS	Alzheimer's Disease Assessment Scale
CDR	Clinical Dementia Rating
FAQ	Functional Activity Questionnaire
GDS	Geriatric Depression Scale
KSS	Karolinska Sleepiness Scale
MCTQ	Munich Chronotype Questionnaire
MEQ	Morningness-Eveningness Questionnaire
MMSE	Mini-Mental State Examination
NPI	Neuropsychiatric Inventory
PSQI	Pittsburgh Sleep Quality Index

Sleep

N1-3	NREM Stage 1-3
(N)REM	(Non-)Rapid Eye Movement
NS	Normal Sleep
SD	Sleep Deprivation
SR	Sleep Restriction
SWS	Slow-Wave Sleep
TiB	Time in Bed

Statistics

AIC	Akaike Information Criterion
ANOVA	Analysis of Variance
AUC	Area Under the Curve
CLMM	Cumulative Link Mixed Model
CI	Confidence Interval
CV	Cross-Validation
EMM	Estimated Marginal Means
FDR	False Discovery Rate
MCC	Matthews Correlation Coefficient
ML	Machine Learning
(R)LME	(Robust) Linear Mixed Effects
ROC	Receiver-Operator Curve
SHAP	Shapley's Additive Explanations

Units

Hz	Herz
T	Tesla

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Chapter 1

Introduction

For much of modern neuroscience, the brain was believed to recycle its extracellular waste through internal mechanisms, including autophagy, protein ubiquitination, and phagocytosis by activated microglia [4]. This view was primarily influenced by the absence of lymphatic structures in the central nervous system (CNS) [5]. However, cerebrospinal fluid (CSF) tracer studies in the early 1980s challenged the notion of a “closed” waste clearance system by demonstrating that exogenous dyes consistently exited the CNS along perivascular pathways [6, 7]. Nevertheless, evidence for the active involvement of CSF in waste clearance remained elusive for nearly four decades.

In 2012, Iliff et al. [8] published their seminal study describing the glymphatic system, a fluid-mediated waste clearance pathway in the CNS. The name “glymphatic”, a portmanteau of “glia” and “lymphatic”, was chosen to reflect the system’s dependence on astroglial cells and its functional similarity to the body’s lymphatic system. In their study, Iliff and colleagues outline the trajectory of CSF through the CNS, as it enters the perivascular spaces (PVS) of penetrating arteries, then crosses the glia limitans into the neural parenchyma, and exits via the PVS of draining veins. They further demonstrate that this glymphatic flow facilitates the removal of metabolic waste from the interstitium and, crucially, that this is an active process regulated by astrocytic water channel aquaporin-4 (AQP4).

The introduction of the glymphatic model, discussed in greater detail below, recontextualized several longstanding views on brain homeostasis; most notably, the role of sleep in maintaining healthy brain function. In 2013, Xie and colleagues reported a threefold increase in glymphatic activity during sleep in mice, as well as a nearly 60% expansion of the interstitial space to facilitate fluid flow [9]. A follow-up study by Hablitz et al. demonstrated a strong circadian regulation of CSF influx and AQP4 localization [10]. Complementary studies in humans have shown that sleep deprivation severely impacts molecular clearance [11]. Collectively, these findings have prompted the hypothesis that waste clearance may represent one of the primary physiological functions of sleep [12].

The glymphatic system has not only contributed to solving the mystery of sleep, but it has also opened new avenues for understanding and potentially mitigating major neurological disorders [13]. Persistent disruption in waste clearance is now recognized as a key factor in the development of diseases such as Alzheimer’s dementia (AD), which is characterized by the accumulation of neurotoxic amyloid-beta ($A\beta$) and phosphorylated tau (p-tau) proteins [14]. Glymphatic activity was found to directly counteract AD biomarker aggregation [15, 16], whereas glymphatic dysfunction was found to precede the onset of clinical manifestations [17].

The widely observed relationship between sleep and glymphatic activity, coupled with the neuroprotective effects of sleep, has prompted theories that the glymphatic system may be the “missing link” between sleep disruption and neurological disorders such as AD [13]. However, this theory has not been without its detractors. A recent rodent study by Miao et al. reported reduced glymphatic clearance during sleep and anesthesia [18], leading some to question the validity of the glymphatic model altogether [19].

Yet, in spite of the substantial body of evidence supporting the glymphatic model, as well as novel findings questioning its validity, no study to date has attempted to synthesize a comprehensive framework connecting sleep, glymphatic function, and AD. This chapter presents a critical review of the current literature surrounding these interrelated subjects and outlines my aims to exhaustively explore the multifaceted relationships that form the basis of the glymphatic theory. Consequently, I hope to contribute meaningful insights to the ongoing discourse on the interplay between sleep, waste clearance, and dementia.

1.1 Why Do We Sleep?

At face value, sleep is an evolutionary death sentence. It monopolizes nearly one-third of the lifespan, time that could otherwise be dedicated to survival and reproduction, while rendering the subject vulnerable to existential threats. Yet, remarkably, sleep is one of the most highly conserved traits across phylogenetically diverse species [20]. What, then, makes sleep so indispensable to warrant several thousand years of preservation in the face of such steep competitive costs? In the following sections, I outline the neural substrates of sleep and highlight several of its key functions.

1.1.1 The Anatomy of Sleep

In humans, the initiation of sleep is primarily regulated by hypothalamic structures. The suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, functions as the body’s master circadian clock [21]. It receives direct input from the retina and adjusts the body’s circadian rhythm accordingly. As ambient light diminishes, the SCN prompts the pineal gland to release melatonin, signalling the brain to initiate the transition to sleep [22]. Concurrently, sleep-promoting regions of the hypothalamus, namely the ventrolateral preoptic nucleus, release inhibitory neurotransmitters such as GABA and galanin [23]. These neurotransmitters target wake-promoting regions in the hypothalamus and brainstem, suppressing the release of excitatory neuromodulators like histamine, orexin, and norepinephrine (NE). Once sleep is fully initiated, the thalamus plays a crucial role in maintaining it. Thalamic relay nuclei gate incoming sensory stimuli, reducing external input to the cortex, while the thalamic reticular nucleus generates rhythmic inhibitory firing patterns that produce the neural oscillations characteristic of sleep [24].

1.1.2 The Stages of Sleep

Sleep is structured into three distinct non-rapid eye movement (NREM) stages and one rapid eye movement (REM) stage, each defined by characteristic patterns of neural activity and linked to different functional outcomes [25]. NREM Stage 1 (N1)

represents the initial transition from wakefulness to sleep, characterized by diminished sensory awareness, slowed heart rate and respiration, muscle relaxation, and low-amplitude, mixed-frequency brain activity. This stage is brief, and it typically transitions quickly into NREM Stage 2 (N2), which is marked by further reductions in muscle tone and sensory awareness, as well as the appearance of brief bursts of neural activity known as sleep spindles and K-complexes. NREM Stage 3 (N3), also known as slow-wave sleep (SWS), is characterized by high-amplitude delta (0.5 – 4 Hz) oscillations and represents a state of maximal cortical synchronization and minimal sensory responsiveness. During NREM sleep, the brain frequently cycles into REM sleep episodes. These episodes are characterized by the eponymous rapid eye movements, generalized muscle atonia, autonomic dysregulation, and cortical desynchronization, including high-frequency neocortical activity and limbic theta (5 – 7 Hz) oscillations [26]. A majority of sleep functions occur during the SWS and REM stages, yet all stages are required to maintain a healthy sleep architecture [25].

1.1.3 Memory and Learning

One of the primary purposes of sleep is to consolidate recent experiences into long-lasting memory engrams (**Fig. 1.1**). While the waking brain is exposed to an unceasing stream of stimuli, sleep provides a critical window for the selective reactivation and strengthening of relevant information within neural networks. This reactivation reinforces synaptic connections (“fire together”), enhancing the stability of encoded memories (“wire together”) [27]. Newly formed memory engrams are initially stored in the hippocampus, where they are preferentially reactivated during SWS. Through repeated reactivation across sleep cycles, these engrams undergo systems consolidation, gradually becoming integrated into distributed, long-term representations in the neocortex [27, 28]. Myriad studies have shown that sleep after learning strengthens memory retention, whereas sleep disturbance impairs it [29–31].

1.1.4 Emotional Regulation

While we may sleep to remember, we also sleep to forget [32]. Reactivation of limbic circuits during REM sleep has been shown to facilitate the decoupling of emotional content from episodic memories [33]. Conversely, sleep disruption impairs this regulatory process, contributing to affective instability and increased susceptibility to stress. Chronic dysregulation of emotional processing may, in turn, play a role in the development of mood disorders or post-traumatic stress disorders [34].

1.1.5 Executive Function and Attention

The ability to sustain attention over prolonged intervals, often referred to as vigilant attention, is a fundamental component of many higher-order executive functions [35, 36]. Evidence from both behavioral and neurophysiological studies suggests that sleep deprivation impairs vigilant attention, resulting in attentional lapses and reaction time variability [35]. It also disrupts cognitive flexibility, diminishing the brain’s ability to efficiently switch between internally directed thought and goal-oriented cognition [37]. These deficits are thought to arise in part from reduced replenishment of excitatory neurotransmitters involved in attentional regulation [38].

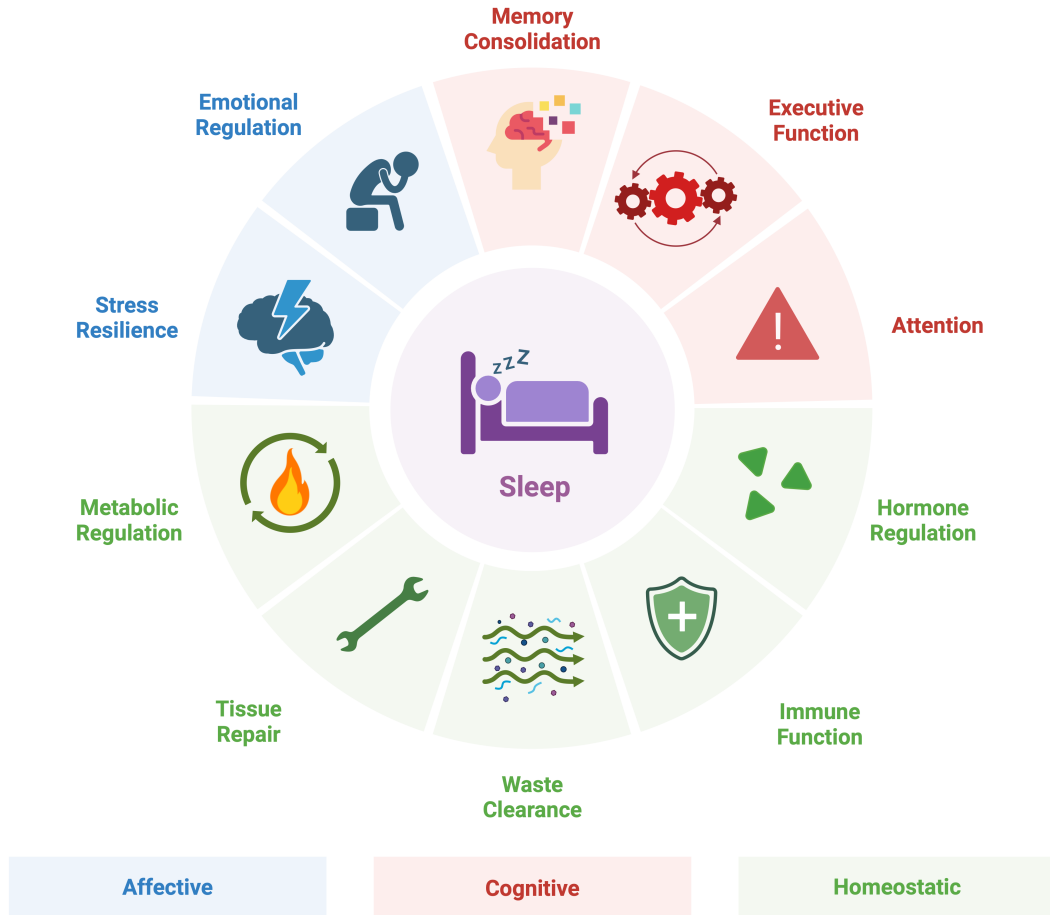


Fig. 1.1: The benefits of sleep. Sleep supports cognitive abilities such as memory, learning, attention, and executive function. It strengthens emotional regulation and stress resilience and sustains homeostatic processes, including immune function, tissue repair, metabolism, and clearance of brain waste.

1.1.6 Homeostasis

Neurochemical replenishment exemplifies one of the critical homeostatic functions performed by sleep. Indeed, attenuated brain activity provides the optimal environment for synaptic restoration [39]. In addition to supporting neural restoration, sleep is important for many aspects of peripheral homeostasis, including endocrine regulation of metabolic processes, suppression of pro-inflammatory activity, temperature modulation, and the facilitation of waste clearance mechanisms [8, 40, 41]. Notably, SWS is associated with large pulses of growth hormone secretion, which support tissue repair, metabolism, and immune function [40].

1.1.7 Waste Clearance

An equally vital counterpart to the restoration of neurotransmitters and metabolic resources is the clearance of neural waste. During wakefulness, neural activity generates metabolic byproducts such as CO_2 , lactate, and aggregation-prone proteins like amyloid beta ($\text{A}\beta$) [42, 43]. Sleep facilitates the removal of these extracellular waste products primarily through the glymphatic system, which promotes convective CSF flow to flush out toxins [8, 9]. This process is discussed in further detail in **Section 1.3**.

1.1.8 Sleep Disorders

Various sleep disorders are known to disrupt the processes outlined above. Among the most prevalent sources of sleep disturbance are insomnia symptoms, typically characterized by difficulty initiating sleep, maintaining sleep, or waking prematurely [44]. When such symptoms occur at least three times per week for a duration of three months or more, the condition is classified as insomnia disorder. This disorder is primarily associated with dysfunction in brain networks underlying attentional control, often manifesting as hyperarousal and persistent rumination [45–47]. Other common sleep disorders include obstructive sleep apnea, restless leg syndrome, REM sleep behavior disorder, and narcolepsy [48]. While each is linked to distinct pathophysiological mechanisms, all are associated with impairments in the restorative and regulatory functions of sleep.

1.1.9 Chronic Sleep Disturbance

Persistent sleep disturbance, especially in the context of sleep disorders, has been linked to elevated all-cause mortality [49] and increased susceptibility to both psychiatric and neurodegenerative conditions [50]. While dysregulation of emotional processing and synaptic neurochemistry might predict the onset of major depressive disorder or anxiety disorder [51, 52], compromised glymphatic clearance may promote the aggregation of $A\beta$, phosphorylated tau (p-tau) and α -synuclein, key pathological markers in Alzheimer’s disease, Parkinson’s disease, and related dementias [53–56]. Crucially, this relationship is reciprocal: as neurodegenerative disorders often compromise the very neural systems responsible for sleep initiation and maintenance, including the hypothalamic and brain stem circuits previously discussed [54].

1.2 The Neurobiology of Alzheimer’s Disease

Alzheimer’s dementia is the most common form of dementia in adults over the age of 65, with an estimated 33 million people affected worldwide [14]. Clinically, it is characterized by progressive memory loss, cognitive decline, aphasia, and behavioral disturbances. Neuroimaging evidence indicates that individuals along the AD continuum show features of accelerated brain aging, with structural alterations resembling those typically observed in individuals 10–15 years older than their chronological age [57]. The following sections review current insights into AD pathogenesis, with particular attention paid to its mutual relationship with chronic sleep disturbance.

1.2.1 Pathogenesis

The accumulation of $A\beta$ and p-tau proteins represents the defining pathological pathway of AD. $A\beta$ peptides, particularly $A\beta_{40}$ and $A\beta_{42}$, are produced from the amyloid precursor protein (APP) through enzymatic cleavage by β - and γ -secretases [14, 58, 59]. In AD, these peptides aggregate to form extracellular amyloid plaques, disrupting neuronal function and initiating neuroinflammatory responses [59, 60]. Concurrently, tau, a microtubule-associated protein, becomes hyperphosphorylated and forms intracellular neurofibrillary tangles, impairing axonal transport and contributing to neuronal death [14, 59]. While tau pathology can arise independently,

it frequently progresses alongside or is exacerbated by $A\beta$ accumulation [59, 61]. The combined presence of $A\beta$ plaques and tau tangles drives synaptic dysfunction and neurodegeneration, with pathology typically originating in the medial temporal lobe, primarily the entorhinal cortex and hippocampus (HC), and spreading along interconnected brain networks, progressively impairing the functional organization of regions involved in memory and cognition [62].

1.2.2 Network Degeneration

The propagation of pathology across neuronal networks is particularly evident in the default mode network (DMN), which supports internally directed cognition such as mind-wandering and self-referential thought, and is highly susceptible to early $A\beta$ deposition [63]. As the disease advances, networks closely linked to the DMN, including the central executive network (CEN), which governs working memory and goal-directed cognition, and the salience network (SN), which mediates salience detection and coordinates DMN and CEN activity, become increasingly affected [64, 65]. Alterations within these networks, collectively known as the three-network system (TNS) [66], represent some of the earliest functional manifestations of AD pathology [67, 68].

1.2.3 Clinical Trajectory

AD progresses along a continuum comprising preclinical, prodromal, and clinical stages. The preclinical stage is typically asymptomatic but may show early pathological changes such as $A\beta$ deposition, tau pathology, and alterations in functional brain networks [14, 69]. The prodromal stage, or mild cognitive impairment (MCI), is characterized by detectable biomarker accumulation and the emergence of cognitive deficits. MCI may be classified as amnesic, affecting primarily memory function, or non-amnesic, affecting other domains such as executive function, mood, language, or attention [14, 69, 70]. Furthermore, MCI may be progressive, with a high risk of conversion to clinical AD, or stable, with cognitive deficits remaining relatively constant [71]. Clinical AD then represents the terminal stage, characterized by high biomarker burden, extensive neurodegeneration, and profound cognitive deficits [14, 69]. Diagnoses along the AD continuum are generally based on clinical evaluation and standardized measures, including the AD Assessment Scale (ADAS) and the Mini-Mental State Examination (MMSE) [72, 73]. In addition to these clinical tools, many studies now also employ the amyloid-tau-neurodegeneration (ATN) method, which stages the AD continuum on the basis of biomarker-defined pathology [61, 74].

1.2.4 Genetic Risk Factors

Several risk factors contribute to the progression of AD from preclinical to clinical stages. Foremost among these is the apolipoprotein E4 (APOE4) allele, which encodes the E4 isoform of the APOE protein, a critical regulator of lipid transport and metabolism in the brain [75]. Possession of one copy of APOE4 confers a three- to fourfold increased risk of AD, while homozygosity may elevate risk more than tenfold [76, 77]. Other genetic risk factors include mutations in APP and in the presenilin genes (PSEN1, PSEN2), which enhance amyloidogenic processes, and variants of TREM2 and AQP4, which affect microglial function and glymphatic clearance [78–

81]. Overall, genetic factors are estimated to explain approximately 70% of AD risk, either by directly accelerating $A\beta$ and tau pathology or by attenuating clearance [78].

1.2.5 Modifiable Risk Factors

Progression along the AD continuum is also influenced by several modifiable factors, defined as conditions or behaviors that can be addressed through interventions to reduce susceptibility and mitigate symptoms [82, 83]. Metabolic and vascular disorders, including type 2 diabetes, obesity, dyslipidemia, and hypertension, promote oxidative stress and exacerbate $A\beta$ and tau pathology [83–86]. Preventable factors such as traumatic brain injury, chronic stress, and mood disorders often precede clinical onset and increase vulnerability [83, 87–89]. Finally, lifestyle-related behaviors, including physical inactivity, poor diet, irregular sleep, alcohol use, and smoking, further elevate risk, while interventions targeting these factors may provide protective benefits [82, 90, 91].

1.2.6 Bidirectional Relationship with Sleep

Sleep disturbances play a fundamental role in AD pathogenesis, both as a contributing factor to, and a consequence of, disease progression (**Fig. 1.2**). Epidemiological studies indicate that 40–70% of individuals on the AD continuum experience chronic disruptions in sleep, typically attributed to insomnia, circadian rhythm disruptions, or medication side-effects [54, 92]. In the preclinical and prodromal stages, sleep disturbances have been associated with significantly increased $A\beta$ and p-tau burden [4]. In the clinical stage, insomnia symptoms are nearly ubiquitous [93], in part due to significant degeneration of the TNS, which is essential for regulating arousal at sleep onset [37, 46]. Given that network degeneration represents an early feature of AD pathology, insomnia symptoms may appear as early as the preclinical stage and continue to serve as a meaningful clinical indicator across the AD continuum [94]. Nevertheless, comprehensive investigations of this bidirectional relationship have been limited, in part due to the lack of a unifying framework for insomnia pathology and the frequent under-reporting of symptoms, particularly within aging populations [95, 96]. Addressing this gap requires conceptual models that integrate sleep disturbance into the trajectory of AD pathophysiology. The glymphatic system has recently emerged as one such model, offering a novel perspective on how irregular sleep may contribute to disease progression.

1.3 The Glymphatic System

For decades, researchers have linked poor sleep to increased $A\beta$ and p-tau burden [4, 55, 93], though the underlying mechanisms of this relationship remained unclear. The 2012 discovery of the glymphatic system marked a major step toward establishing a unified framework linking sleep, waste clearance, and AD pathology. This section provides a comprehensive overview of the glymphatic system and highlights key unresolved questions in the field.

1.3.1 The Anatomy of "Brainwashing"

Although the glymphatic system has no single anatomical origin, its functional origin is arguably the production of CSF by the choroid plexus (ChP) in the bilateral

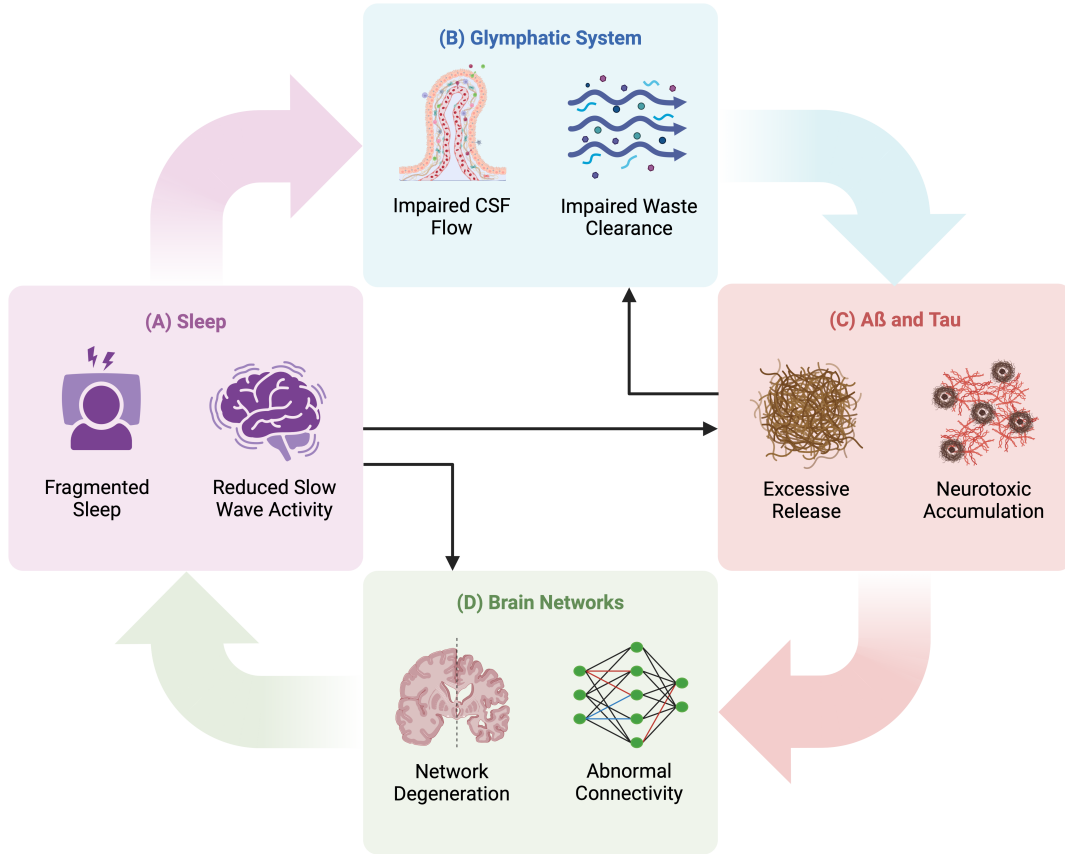


Fig. 1.2: The bidirectional relationship between sleep and Alzheimer's disease pathology. (A) Disrupted sleep from maladaptive routines or sleep disorders reduces slow wave activity and directly promotes $A\beta$ and p-tau release. (B) Impaired sleep also disrupts glymphatic clearance by lowering CSF inflow, altering NE tone, and mislocalizing AQP4. (C) These clearance impairments drive the accumulation of neurotoxic $A\beta$ plaques and p-tau tangles, which in turn further disrupt glymphatic function. (D) This pathology then propagates along brain networks, including networks that regulate sleep, creating a self-reinforcing cycle. $A\beta$ = Amyloid Beta, AQP4 = Aquaporin-4, CSF = Cerebrospinal Fluid, NE = Norepinephrine, p-tau = Phosphorylated Tau.

third ventricle (**Fig. 1.3A**). This CSF flows from the ventricles into the subarachnoid space surrounding the cortex and is then driven into the PVS of penetrating arteries by arterial pulsation (**Fig. 1.3B**). AQP4 water channels, located on astrocytic endfeet at the glia limitans, mediate the transfer of CSF into the brain parenchyma. Within the parenchyma, CSF exchanges with interstitial fluid (ISF) through diffusion and convective flow, facilitating the clearance of metabolic waste. Finally, a mixture of CSF, ISF, and metabolites is taken up by the PVS of large-caliber draining veins and directed towards the dural venous sinuses. From there, waste is transported out of the brain via meningeal lymphatic vessels to the cervical lymph nodes [8].

1.3.2 Imaging the Glymphatic System

Glymphatic physiology was first defined in rodents using fluorescent CSF tracer imaging and contrast-enhanced MRI [8, 97]. Contrast-enhanced MRI has also been applied in humans to visualize CSF movement throughout the brain [98]. Gadolinium-based contrast agents, which enhance T1-weighted MRI signal by shortening the longitudinal relaxation time, are the most common contrast agent used

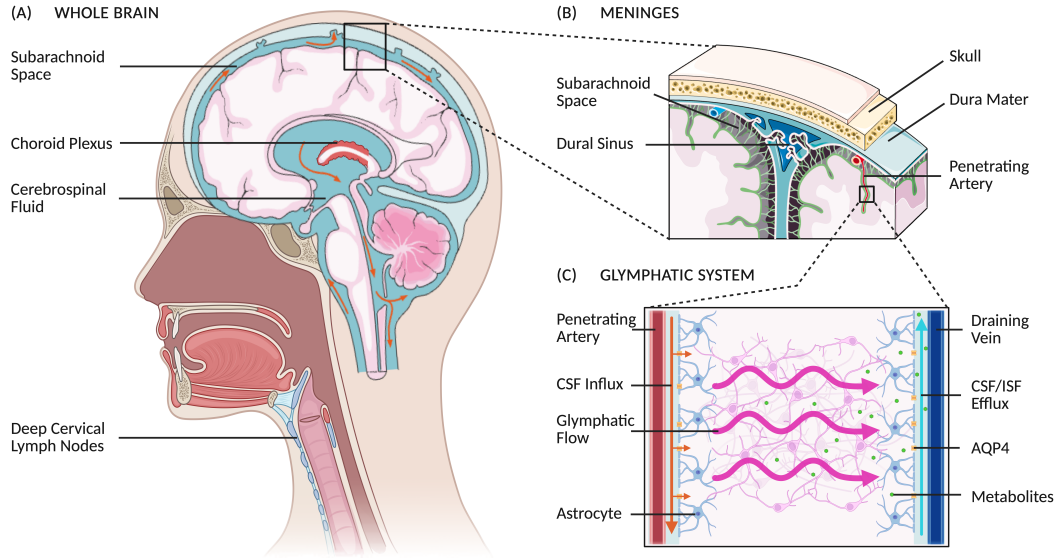


Fig. 1.3: Components of the glymphatic system. Several structures involved in glymphatic clearance are shown at the level of the (A) whole brain, (B) meninges, or (C) neural tissue. The choroid plexus is responsible for producing CSF, which disperses across the brain via the subarachnoid space. CSF is driven into the PVS of penetrating arteries by arterial pulsation and is transported into the parenchyma by AQP4. It diffuses through the parenchyma, picking up waste metabolites, and is taken up by the PVS of draining veins. Waste then flows into the dural sinuses and subsequently the deep cervical lymph nodes. *AQP4* = Aquaporin-4, *CSF* = Cerebrospinal Fluid, *ISF* = Interstitial Fluid.

in both murine and human studies [99]. In addition to these invasive methods, several non-invasive MRI techniques have been developed to assess glymphatic function. Anatomical MRI sequences such as T1-weighted (T1w), T2-weighted (T2w), and fluid-attenuated inversion recovery (FLAIR) can be employed to segment MRI-visible PVS, whose enlargement may indicate glymphatic impairment [100, 101]. Diffusion MRI (dMRI) enables the quantification of free water content within the brain parenchyma and the evaluation of water diffusivity along perivenous spaces, as assessed by the ALPS index [100, 102]. Furthermore, arterial spin labelling can be used to assess vascular water exchange [103], while functional MRI techniques like ultrafast fMRI and CSF-BOLD coupling can provide dynamic measurements of CSF and metabolite movement within the glymphatic system [101, 104].

1.3.3 The Role of Sleep

The glymphatic system is predominantly active during sleep [9, 11, 15, 99, 105, 106]. In murine models, glymphatic activity increases markedly under natural sleep conditions and anesthesia [9]. Studies have shown that extracellular space volume expands during sleep, facilitating enhanced fluid flow, while it contracts during wakefulness [9, 107]. Pharmacological inhibition of NE release enhances glymphatic activity by modulating slow vasomotion of cerebral blood vessels, which drives CSF flow through perivascular spaces during sleep [108]. Both CSF-ISF exchange and AQP4 localization exhibit circadian regulation [10, 42]. Additionally, stimulation of low-frequency neural rhythms enhances glymphatic clearance in mice [109]. In humans, CSF tracer studies reveal that solute clearance from the interstitium is significantly impaired following sleep deprivation, with dysfunction persisting for up to 48 hours post-deprivation [11].

1.3.4 Glymphatic Dysfunction in Alzheimer's Disease

Glymphatic clearance of $A\beta$ and p-tau has been demonstrated in both rodent and human studies. In murine models, targeted deletion of the *Aqp4* gene, which encodes AQP4 water channels, markedly reduced glymphatic clearance [110]. In human post-mortem brain tissue, histopathological analyses revealed a strong spatial correlation between $A\beta$ deposition and AQP4 mislocalization [111]. Furthermore, individuals along the AD continuum have been found to exhibit reduced perivascular AQP4 expression compared to cognitively normal controls [112]. Genetic association studies have identified AQP4 SNPs that modulate the rate of $A\beta$ accumulation and cognitive decline [79]. NE signaling is also disrupted in AD [113], with sleep deprivation suppressing NE oscillations in an APP/PSEN1 mouse model [106]. Several known risk factors for AD, such as aging, hypertension, physical inactivity, chronic sleep disruption, and traumatic brain injury, are strongly associated with impaired glymphatic function [112, 114, 115]. Additionally, a recent contrast-enhanced MRI study in humans linked delayed glymphatic clearance, as measured by intrathecal CSF tracer retention, to lower plasma p-tau concentrations [116]; however, the study's findings were limited by the inclusion of participants with preexisting disturbances in CSF dynamics. Taken together, glymphatic impairment may present a critical step in Alzheimer's pathogenesis and thus, an important target for investigative and therapeutic efforts.

1.3.5 Open Questions and Criticisms

In spite of the wealth of evidence suggesting a link between sleep, glymphatic function, and AD, causal evidence for this relationship has yet to be established. It remains uncertain whether reduced glymphatic activity during sleep precedes the accumulation of $A\beta$ pathology or whether it occurs concurrently. Although one recent study reported evidence supporting a temporal relationship in which impaired glymphatic function preceded $A\beta$ deposition [17], its conclusions were based solely on the analysis of the ALPS index, which may not fully capture global glymphatic dynamics [117]. Several studies have called into question some of the core assumptions of glymphatic system function [18, 99]. One of the most prominent is the study by Miao et al. [18], which reported findings that directly opposed those of the work by Xie et al. [9]. Using intrathecal administration of a fluorescent CSF tracer, the study measured its movement via optical fiber photometry in a target brain region across sleep, wakefulness, and anesthesia. The tracer was found to move more slowly during sleep and anesthesia compared to wakefulness [18]. However, the study has been criticized for key methodological issues [15, 99]: it measured tracer movement between brain regions rather than actual solute clearance; it did not observe naturalistic sleep conditions; and it conducted measurements at a delayed time point after anesthetic administration, which may have affected glymphatic dynamics. In spite of these limitations, the study raised some important questions regarding the need for structured, standardized methodologies to measure glymphatic function.

1.4 Aims of Thesis

The theory advanced in the literature rests on three key assumptions: that sleep disturbance and AD pathology influence each other bidirectionally, that sleep disturbance disrupts glymphatic system function, and that glymphatic dysfunction predicts the development and progression of AD pathology. This dissertation aims to systematically investigate each of these assumptions, addressing critical gaps in contemporary literature and integrating insights across the domains of sleep, neuroimaging, and machine learning.

Aim 1: Sleep and Alzheimer’s Disease

The bidirectional relationship between sleep and AD is exemplified by the TNS, which plays a central role in both early AD pathogenesis and insomnia symptomology [118, 119]. Yet, to date, no study has systematically characterized how insomnia symptoms influence TNS integrity across the AD continuum. **Chapter 3** aims to fill this gap by investigating differential effects of insomnia symptoms on TNS function and morphology at distinct disease stages, thereby advancing understanding of the mechanisms linking insomnia and AD. We hypothesize that insomnia in clinical AD will be associated with atypical functional and morphological TNS alterations indicative of an interaction between these pathologies.

Aim 2: Sleep and Glymphatic Function

Molecular clearance in humans is reduced following sleep deprivation, with impairments persisting for up to 48 hours despite subsequent restorative sleep [11]. Whether these effects indicate substantive disruption of glymphatic function, however, remains unclear. To address this question, **Chapter 4** conducts a multi-cohort glymphatic MRI analysis across nine experimental sleep disturbance datasets, aiming to clarify the impact of acute sleep loss on glymphatic function. We hypothesize that sleep deprivation will be associated with glymphatic impairments indicated by increased PVS and ChP volume, increased free water in the white matter (FWI), and reduced diffusion along the perivascular space (DTI-ALPS).

Aim 3: Glymphatic Function and Alzheimer’s Disease

A broad spectrum of genetic, clinical, metabolic, and lifestyle factors shapes the onset and progression of AD [82, 87, 88, 90]. Glymphatic dysfunction has been proposed as a marker of AD [120], yet its role relative to established risk factors remains to be elucidated. **Chapter 5** applies a machine learning framework to a large longitudinal AD dataset to quantify the contribution of glymphatic features such as PVS and ChP volume, DTI-ALPS, and the brain clearance rate (BCR) to predicting disease status and severity. We hypothesize that the inclusion of these glymphatic data will significantly enhance the performance of the models.

Chapter 2

Materials and Methods

This chapter provides a concise overview of the methods used to obtain the results presented in **Chapter 3**, **Chapter 4**, and **Chapter 5**. It contains text and figures from one publication [1] and two preregistrations [2, 3].

2.1 Data Collection

2.1.1 Alzheimer’s Disease Neuroimaging Initiative

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a collaboration of 63 research sites across the United States and Canada to collect, validate, and utilize AD data, including MRI and PET images, genetic assays, CSF and blood biomarkers, and cognitive assessments [121]. The ADNI database contains more than 5,000 individuals across various clinical groups, including elderly control, early mild cognitive impairment (MCI), late MCI, and clinical AD. **Chapter 3** and **Chapter 5** use data from the second and third phases of the initiative (ADNI-2 and ADNI-3), with collection dates ranging from 2011 to 2021.

Cohort 1

For the study presented in **Chapter 3**, a cohort of $n = 320$ ADNI subjects was created. All subjects underwent at least one session of 3T T1-weighted (T1w) MRI and resting-state functional MRI (rs-fMRI) acquisition. Additionally, they completed a test battery including the Neuropsychiatric Inventory (NPI) [122], Mini-Mental State Exam (MMSE) [72], and Geriatric Depression Scale (GDS) [123], within six months of this scanning session. These tests are summarized in **Section 2.6.2**. Subjects whose diagnoses changed, such as from MCI to AD, within this six-month period, were excluded. Additionally, subjects diagnosed with disorders affecting sleep quality, including generalized depression ($GDS > 8$), obstructive sleep apnea, restless leg syndrome, and narcolepsy, were excluded. The selected subjects were divided across three diagnostic groups: cognitively normal (CN), MCI, and AD. Domain K (“Sleep”) of the NPI was used to determine whether subjects were suffering from insomnia symptoms around the time of their scanning session (see **Section 2.5.1**). Individuals with insomnia symptoms were then matched to similar individuals without symptoms using propensity scores calculated from age, sex, handedness, education level, MMSE score, and GDS score. Finally, scans were screened for artefacts and visually inspected. These selection procedures are summarized in **Fig. 2.1**.

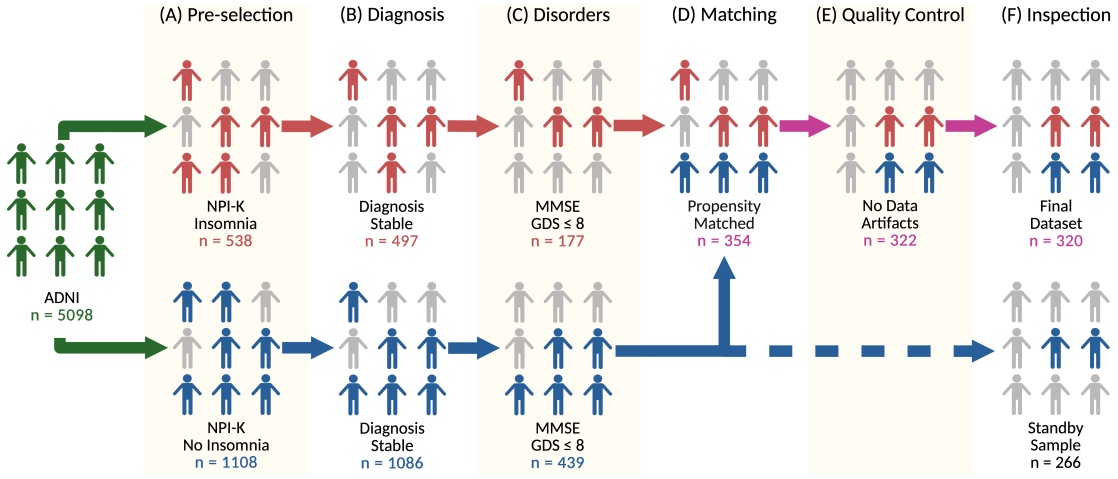


Fig. 2.1: Construction of the chapter 3 study cohort. (A) Subjects were pre-selected based on available MRI and NPI data and grouped by presence of insomnia symptoms. (B) Subjects with changes in AD diagnosis were excluded. (C) Subjects without MMSE or GDS data, or with GDS > 8, were excluded. (D) Subjects were propensity matched on demographic variables. (E) Scans were automatically screened for motion artefacts and data corruption. (F) All remaining scans were inspected, yielding the final cohort. *ADNI* = *Alzheimer’s Disease Neuroimaging Initiative*, *A/T Status* = *Amyloid/Tau Status*, *GDS* = *Geriatric Depression Scale*, *MMSE* = *Mini-Mental State Exame*, *MRI* = *Magnetic Resonance Imaging*, *NPI-K* = *Neuropsychiatric Inventory Domain K*

Cohort 2

For the study presented in **Chapter 5**, a cohort of $n = 337$ ADNI subjects was created. Subjects were required to have at least three scanning sessions at intervals of six months or more, including 3T T1w MRI, diffusion MRI (dMRI), and NPI domain K (NPI-K) data within six months of each session. All scans were quality controlled as described above. For model training, a weighted sampling strategy was applied to sample the three sessions with the highest data availability, prioritizing previously acquired ^{18}F -florbetapir (AV45) PET, and ^{18}F -flortuacipir or ^{18}F -MK-6420 PET data, as these were required for the calculation of the target variable (**Section 2.6.1**). The final sample was split 80% for training and 20% for testing. These selection procedures are summarized in **Fig. 2.2**.

2.1.2 ENIGMA-Sleep

The ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) consortium is a global initiative for data sharing in neuroimaging and genomics, encompassing over 400 institutions, 45 countries, and 50 specialized working groups [124]. The “Sleep” working group aims to address key questions in sleep research through collaborative data aggregation and analysis [125]. For the study presented in **Chapter 4**, previously acquired MRI, demographic, cognitive, and sleep health data of $n = 433$ subjects were collected from thirteen different studies across nine international sites [126–137]. All participants underwent two acquisitions of 3T T1w MRI and (optionally) dMRI: one after a night of habitual sleep and another following experimentally induced sleep disturbance. A small control sample ($n = 38$) maintained normal sleep across both nights. Participants were excluded if they reported any sleep disorders or any neurological or psychiatric disorders that typically affect sleep quality, or if they were under active treatment with psychiatric or hypnotic medications. An overview of the included datasets is shown in **Table 2.1**.

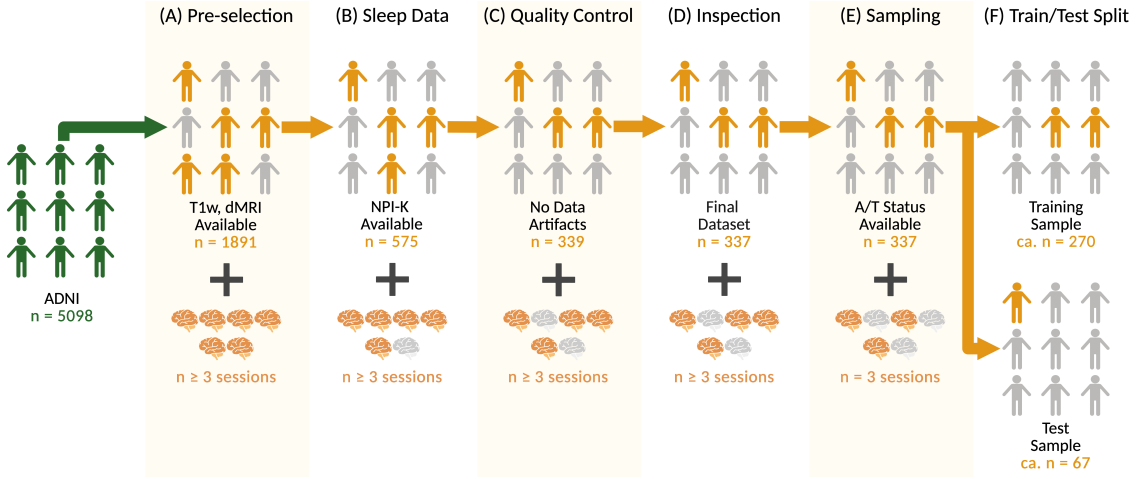


Fig. 2.2: Construction of the chapter 5 study cohort. (A) Subjects were pre-selected based on available T1w MRI and dMRI data. (B) Subjects without NPI-K scores within six months of MRI scans were excluded. (C) Scans were automatically screened for motion artefacts and data corruption. Subjects with fewer than three remaining scans were excluded. (D) All remaining scans were inspected, yielding the final cohort. (E) Weighted sampling was applied to select three sessions with the most data, prioritizing amyloid- and tau-PET. (F) The sample was split 80% to 20% for model training and evaluation. *AD* = Alzheimer’s Disease, *ADNI* = Alzheimer’s Disease Neuroimaging Initiative, *A/T Status* = Amyloid/Tau Status, *(d)MRI* = Diffusion Magnetic Resonance Imaging, *GDS* = Geriatric Depression Scale, *MMSE* = Mini-Mental State Examination, *NPI-K* = Neuropsychiatric Inventory Domain K, *T1w* = T1-Weighted

Sleep Restriction

The Juelich [128, 129], Melbourne [132], Singapore [131], Stockholm [130], and Trondheim [133] studies each employed a sleep restriction (SR) protocol. After several days of naturalistic, habitual sleep with ca. 6 to 8 hours time in bed (TiB), subjects were restricted to a 3 to 6-hour TiB for up to five days. This was achieved by delaying sleep onset to simulate realistic sleep deficits. MRI acquisition typically took place in the morning following the first night of sleep restriction. Exceptions to this protocol were [129] and [130], which collected MRI after the fifth night and on the first evening, respectively.

Sleep Deprivation

The Brussels [134], Juelich [128], Montreal [127], Oslo [135], Singapore [136, 137], and Zurich [126] studies each employed a total sleep deprivation (SD) protocol. Following several days of habitual sleep with a 6 to 8-hour TiB, subjects were kept awake for a period ranging from 22 to 40 hours. Subjects typically engaged in quiet activities such as reading, watching non-arousing movies, or playing board games, for the duration of their deprivation period. Wakefulness was maintained by supervisory staff, with intermittent testing used in certain protocols to prevent dozing. In all studies, MRI acquisition took place immediately following deprivation.

Dataset	Affiliation	Country	N	Protocol	Acquisition	Publications
Bruxelles	ULB Neurosciences Institute		25	SD (<i>22h</i>)	T1w, dMRI	Stee et al. [134]
Juelich	Forschungszentrum Juelich		87	SD (<i>24h</i>)	T1w, dMRI	Hennecke et al. [128]
				SR (<i>5h TiB</i>)		Lin et al. [129]
				SD (<i>24h</i>)		Elmenhorst (in prep)
Melbourne	Australian Catholic University		16	SR (<i>3h TiB</i>)	T1w	Poudel et al. [132]
Montreal	Concordia University		18	SD (<i>36h</i>)	T1w	Cross et al. [127]
Oslo	Oslo University Hospital		36	SD (<i>32h</i>)	T1w, dMRI	Voldsbekk et al. [135]
Singapore	National University of Singapore		66	SR (<i>5h TiB</i>)	T1w	Ong et al. [131]
				SD (<i>24h</i>)		Wee et al. [136]
				SD (<i>24h</i>)		Yeo et al. [137]
Stockholm	Karolinska Institutet		81	SR (<i>3h TiB</i>)	T1w, dMRI ^a	Nilsonne et al. [130]
Trondheim	Norwegian University of Science and Technology		73	SR (<i>4h TiB</i>)	T1w, dMRI	Saksvik-Lehouillier et al. [133]
Zurich	University of Zurich		31	SD (<i>40h</i>)	T1w	Adam et al. [126]

Table 2.1: Overview of the ENIGMA-Sleep datasets. This table summarizes the datasets referenced in Chapter 4, including dataset names, affiliated institutions, countries, acquired MRI data, and associated publications. Participant numbers are presented as total counts. Sleep deprivation is described in hours of wakefulness, while sleep restriction is described in hours permitted for time in bed (TiB). *h* = *Hours*, *(d)MRI* = *(Diffusion) Magnetic Resonance Imaging*, *SD* = *Sleep Deprivation*, *SR* = *Sleep Restriction*, *T1w* = *T1-Weighted*, *TiB* = *Time in Bed*. ^a dMRI collected only for the sleep-restricted condition.

2.2 Preprocessing

2.2.1 Data Management

Native DICOM files were converted into the BIDS format [138] using the `dcm2bids` library [139]. BIDS verification was done using the containerized validator included in ReproNim [140]. After verification, the raw data was stored as a DataLad dataset for easy management and version control [141].

2.2.2 Anatomical Preprocessing

All T1w images were preprocessed using the fMRIPrep pipeline [142]. This fully automated pipeline is part of the NiPreps suite, which is continuously updated with the most recent best-practice preprocessing methods for MRI scans [143]. The anatomical preprocessing steps performed by fMRIPrep are summarized below:

1. **Bias field correction:** Removes intensity inhomogeneities in the T1w image.
2. **Skull stripping:** Removes non-brain tissue, including the skull and surrounding anatomy.
3. **Tissue segmentation:** Classifies brain tissue into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF).
4. **Spatial normalization:** Warps the image into a standardized MNI template space.
5. **Surface reconstruction:** Estimates cortical surfaces, generates anatomical parcellations, and performs additional segmentations.

By default, fMRIPrep generates a single, subject-level T1w reference image by merging across sessions, which was used in **Chapter 3** for functional analyses. In contrast, **Chapter 4** and **Chapter 5** used a BIDS filter file to retain session-specific T1w images.

2.2.3 Functional Preprocessing

All rs-fMRI scans were preprocessed concurrently with the T1w images using the fMRIPrep pipeline. The key functional preprocessing steps are summarized as follows:

1. **Motion correction:** Estimates head motion and calculates motion parameters for confound regression.
2. **Slice timing correction:** Accounts for temporal differences in slice acquisition.
3. **Susceptibility distortion correction:** Corrects for B0 field inhomogeneities.
4. **Coregistration:** Aligns the BOLD reference image to the T1w reference image.
5. **Spatial normalization:** Warps functional images into a standardized template space.

Additionally, the optional ICA-AROMA step was applied to further remove motion artefacts using independent component analysis [144]. Using Nilearn as part of a custom script, the initial four BOLD volumes were discarded, temporal detrending and bandpass filtering (0.01–0.1 Hz) were applied, the 24 motion parameters obtained from fMRIPrep were regressed out, and the data was smoothed with a 5 mm full width at half maximum Gaussian kernel.

2.2.4 Diffusion Preprocessing

All dMRI scans were preprocessed with QSIPrep, a pipeline for diffusion-weighted data included in the NiPreps suite [145]. The following summarizes the preprocessing steps performed by QSIPrep:

1. **Denoising:** Reduces random noise and improves the signal-to-noise ratio.
2. **Unringing:** Removes artefacts near tissue boundaries.
3. **b=0 intensity harmonization:** Normalizes intensities across b0 reference images.
4. **Bias field correction:** Corrects for intensity inhomogeneities.
5. **Susceptibility distortion correction:** Corrects distortions caused by magnetic field inhomogeneities.
6. **Eddy-current distortion correction:** Realigns volumes to correct for head motion and eddy currents.
7. **Coregistration with T1w images:** Aligns diffusion images to the corresponding anatomical reference.
8. **Spatial normalization:** Warps images into a standardized template space.
9. **Tissue segmentation:** Classifies tissue types, if applicable for diffusion analyses.

2.2.5 Quality Assurance

As a final preprocessing step, all images underwent tool-assisted visual inspection. Subjects were excluded in the event of visible artefacts or data corruption. Furthermore, functional images that exhibited a framewise displacement (FWD) exceeding 2 degrees were excluded due to excessive motion. All exclusions made during the preprocessing phase have already been incorporated into the final subject counts reported above.

2.3 Brain Network Imaging

This section describes the computation of four brain network metrics (BNMs) used in the analyses reported in **Chapter 3**: the functional connectivity, degrees centrality, gray matter volume, and structural covariance. A summary of all BNMs is provided in **Table 2.2**.

2.3.1 Identification of Network Nodes

Nodes representing regions-of-interest (ROIs) within the three-network system (TNS) were identified using the 100-parcel, 7-network Schaefer atlas (**Fig. 3.1**) [146]. The bilateral nodes of the salience network (SN, $n = 12$), default mode network (DMN, $n = 24$), and central executive network (CEN, $n = 13$) were isolated. These nodes served as the basis for all subsequent BNM calculations.

2.3.2 Functional Connectivity

The whole-brain fMRI time series of each subject was extracted using Nilearn. Time series corresponding to the predefined TNS nodes were used to construct a 49×49 correlation matrix, containing the functional connectivity (FC) values of all within- and between-network edges. These values reflect the temporal synchronization of neural activity between TNS nodes.

2.3.3 Degree Centrality

The degrees centrality (DC) was calculated by binarizing the FC matrix using three absolute thresholds (0.2, 0.4, and 0.6) and counting the number of connections for each node. This metric reflects the relative importance of a node within the network, indicating how extensively it communicates with other nodes.

2.3.4 Gray Matter Volume

Voxelwise gray matter volume (GMV) within TNS nodes was extracted using Region-Based Morphometry (RBM) implemented in CAT12 on preprocessed T1w scans normalized to MNI space. This metric provides a measure of local anatomical structure, capturing nodewise variations in cortical volume.

2.3.5 Structural Covariance

Structural covariance (SC) matrices were constructed separately for each diagnostic group and for the two insomnia conditions within each group. For each participant, mean GMV values were extracted from the predefined TNS nodes, and pairwise Pearson correlations between nodes were computed to generate the SC matrices. These matrices capture patterns of coordinated GMV changes across nodes within the TNS.

Metric	Derived From	Level	Interpretation
FC	rs-fMRI	Edge	Temporal synchronization between nodes
DC	rs-fMRI	Node	Node importance within the network
GMV	T1w MRI	Node	Local gray matter structure
SC	T1w MRI	Edge	Coordinated anatomical variation

Table 2.2: Summary of brain network metrics used in Chapter 3. *DC = degrees centrality, FC = functional connectivity, GMV = gray matter volume, MRI = magnetic resonance imaging, rs-fMRI = resting-state functional magnetic resonance imaging, SC = structural covariance, T1w = T1-weighted*

2.4 Glymphatic System Imaging

This section details the calculation of five glymphatic system indices (GSIs) used across the analyses presented in **Chapter 4** and **Chapter 5**: the perivascular space volume, the choroid plexus volume, the free water index, and the DTI-ALPS index. A summary of all GSIs is provided in **Table 2.3**.

2.4.1 Perivascular Space Volume

The fully containerized ShiVAi pipeline was used to segment perivascular spaces (PVS) in T1w images [147]. This pipeline leverages the SHIVA-PVS model, a U-shaped neural network trained on the three-dimensional spatial features of PVS [148]. The pretrained weights for this model were obtained from [149]. The FreeSurfer Desikan-Killany parcellations were used to identify PVS clusters in the centrum semiovale (CSO), basal ganglia (BG), and hippocampus (HC). The total adjusted perivascular space volume (PVSV) was calculated by summing individual PVSVs and normalizing by intracranial volume (ICV) to account for interindividual differences in brain size. Model performance was evaluated by validating the adjusted PVSVs against volumes previously reported by Custer et al. [150] in the Stockholm dataset [130]. The final adjusted PVSVs were used as an index of glymphatic influx and aquaporin-4 (AQP4) function (see **Fig. 4.1**).

2.4.2 Choroid Plexus Volume

The choroid plexus (ChP) segmentation was performed by FreeSurfer’s automated segmentation module within the fMRIPrep workflow. Estimated ChP volumes (Ch-PVs) were extracted from the segmentation statistics and adjusted for brain size using the ICV. The resulting index was used to estimate global CSF production.

2.4.3 DTI-ALPS Index

The DTI-ALPS (Diffusion Tensor Imaging Along the Perivascular Space) index was calculated as in Taoka et al. [102], where the diffusivity in the x-direction along the projection and association fibers is divided by the diffusivity in the y-direction and z-direction of the projection and association fibers, respectively. The ALPS script developed by Liu, Barisano, et al. [151, 152] was used to perform this calculation in MNI space on preprocessed dMRI scans. This index served as a measure of diffusion within specific glymphatic efflux pathways.

2.4.4 Free Water Index

This index appears only in the **Chapter 4** analyses because it requires multishell dMRI data. The Dipy free water elimination model was used to obtain the free water-corrected fractional anisotropy and mean diffusivity, as well as a global free water estimate, from dMRI scans. Each of the scalar maps was then registered to standardized space using the native DWI-to-MNI transformation matrix obtained from QSIPrep. Finally, the free water index (FWI) was calculated by masking the global free water estimate with the WM segmentation obtained during anatomical preprocessing. This index provides a quantitative measure of free water content within the white matter, and is typically inversely correlated with glymphatic flow.

2.4.5 Brain Clearance Rate

This index appears only in the **Chapter 5** analyses because it requires positron emission tomography (PET) and CSF biomarker data. Previously acquired CSF A β 42 volumes were divided by AV45 standard uptake value ratios (SUVRs) [153] to obtain the brain clearance rate (BCR), a novel GSI reflecting the degree of A β burden in the brain relative to CSF collected in the lumbar region, with higher values indicating a higher rate of clearance (**Fig. 5.1**).

Index	Derived From	Interpretation	Used In
PVSV	T1w MRI	CSF inflow and AQP4 function	Chapter 4 & 5
ChPV	T1w MRI	CSF production	Chapter 4 & 5
DTI-ALPS	dMRI	Diffusion along efflux pathway	Chapter 4 & 5
FWI	T1w, dMRI	Diffusion in the parenchyma	Chapter 4
BCR	PET, CSF	A β clearance from the brain	Chapter 5

Table 2.3: Summary of glymphatic system indices used in Chapter 4 and Chapter 5. A β = amyloid beta, ALPS = along the perivascular space, AQP4 = aquaporin-4, ChPV = choroid plexus volume, CSF = cerebrospinal fluid, (d)MRI = (diffusion) magnetic resonance imaging, DTI = diffusion tensor imaging, FWI = free water index, BCR = Brain clearance rate, PET = positron emission tomography, PVSV = perivascular space volume, T1w = T1-weighted

2.5 Sleep Assessments

This section describes the assessment of four sleep-related measures used in the analyses reported in **Chapter 3**, **Chapter 4**, and **Chapter 5**. A summary of all assessments is provided in **Table 2.4**.

2.5.1 Insomnia Symptoms

Insomnia symptoms were identified using the Neuropsychiatric Inventory (NPI), a widely used clinical assessment tool designed to evaluate behavioral and psychological symptoms in individuals with neurodegenerative disorders such as AD [122]. It assesses 12 domains of neuropsychiatric disturbance, including delusions (NPI-A), hallucinations (NPI-B), agitation/aggression (NPI-C), depression/dysphoria (NPI-D), anxiety (NPI-E), elation/euphoria (NPI-F), apathy (NPI-G), disinhibition (NPI-H), irritability (NPI-I), aberrant motor behavior (NPI-J), sleep disturbances (NPI-K), and appetite changes (NPI-L), based on structured interviews with caregivers. Each domain is rated by both frequency and severity, yielding a composite score that reflects overall symptom burden (**Appendix A**). Subdomains 1, 2, and 6 of the NPI-K represent the diagnostic criteria of insomnia symptoms, that is, difficulty falling asleep, difficulty maintaining sleep, and early awakening [44]. In **Chapter 3**, subjects were included in the insomnia condition if they had answered "yes" to any of these three questions.

2.5.2 Long-Term Sleep Quality

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) [154] was used in **Chapter 4** to assess self-reported sleep quality of the last month. It consists of 19 items, which are

grouped into seven component scores: (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbances, (6) use of sleep medication, and (7) daytime dysfunction. These components are summed to yield a total score ranging from 0 to 21, with higher scores indicating poorer sleep quality (**Appendix B**).

Neuropsychiatric Inventory Domain K

The total NPI-K score was used in **Chapter 5** to assess sleep quality across the AD continuum. This score reflects both the frequency and severity of all-cause sleep disturbance in AD individuals.

2.5.3 Subjective Sleepiness

The Karolinska Sleepiness Scale (KSS) [155] was used in **Chapter 4** to assess subjective sleepiness after sleep deprivation (SD) and sleep restriction (SR). It consists of a single 9-point item, ranging from 1 (“extremely alert”) to 9 (“very sleepy, fighting sleep”) (**Appendix C**).

2.5.4 Chronotype

Chronotype, that is, an individual’s biologically driven preference for the timing of sleep and wakefulness within a 24-hour period, was determined in **Chapter 4** using the Morningness-Eveningness Questionnaire (MEQ) [156] or the Munich Chronotype Questionnaire (MCTQ) [157].

Morningness-Eveningness Questionnaire

The MEQ consists of 19 items that evaluate sleep-wake preferences, alertness, and optimal times for physical and mental performance. The total score classifies individuals into one of five chronotypes, ranging from “definite morning type” to “definite evening type.” (**Appendix D**). These five categories were further reduced to three: morning-types, evening-types, and intermediate types.

Munich Chronotype Questionnaire

The MCTQ gathers detailed information on sleep-wake behavior, including mid-sleep time, social jetlag, and sleep debt (**Appendix E**). The central chronotype measure is mid-sleep on free days corrected for sleep debt, which was thresholded at <3:30 a.m. for morning-types and >5:30 a.m. for evening-types.

Measures	Values	Derived From	Used In
Insomnia Symptoms	Yes/No	NPI-K	Chapter 3
Long-Term Sleep Quality	0 (Good) – 21 (Poor)	PSQI	Chapter 4
	0 (Good) – 12 (Poor)	NPI-K	Chapter 5
Subjective Sleepiness	0 (Alert) – 9 (Sleepy)	KSS	Chapter 4
Chronotype	Morning/Evening/Inter.	MEQ / MCTQ	Chapter 4

Table 2.4: Summary of sleep-related measures used in Chapter 3–Chapter 5. Abbreviations: KSS = Karolinska Sleepiness Scale, MEQ = Morningness-Eveningness Questionnaire, MCTQ = Munich Chronotype Questionnaire, NPI-K = Neuropsychiatric Inventory Domain K.

2.6 Clinical and Cognitive Assessments

This section details a range of assessments included in the ADNI dataset and used in the analyses of **Chapter 3** and **Chapter 5**. A summary of all assessments is provided in **Table 2.5**.

2.6.1 Amyloid-Tau-Neurodegeneration Status

In addition to the clinical diagnoses included in the ADNI dataset, **Chapter 5** assessed the status and severity of AD at specific time points using the amyloid-tau-neurodegeneration (ATN) framework [74]. This unbiased classification method, which is based on physiological measures instead of traditional clinical measures, consists of three binary values: amyloid (A), tau (T), and neurodegeneration (N). These values are either non-pathological (“-”) or pathological (“+”). Consistent with the amyloid cascade hypothesis [158], the ATN framework identifies discrete stages along the AD continuum, from physiologically normal (A-T-N-), to amyloid-positive (A+T-N-), amyloid and tau-positive (A+T+N-), and pathological AD (A+T+N+).

In the ADNI dataset, A status and T status were previously classified based on the AV45 and ^{18}F -flortaucipir or ^{18}F -MK-6420 SUVR values, respectively [153]. The N status was classified based on the hippocampal volume (HCV), obtained during the Freesurfer automated segmentation procedure (**Section 2.2.2**). As in Heininger et al. [58], individuals with an HCV below a threshold of 2821.1 mm³ were classified as N+.

2.6.2 Neuropsychological Assessments

The following subsections contain a range of neuropsychological questionnaires used for post-hoc correlations in **Chapter 3** and the training of the classifier model featured in **Chapter 5**

Neuropsychiatric Inventory

All NPI domains (NPI-A through NPI-L) were included in **Chapter 3** for post-hoc correlation analyses.

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a standardized screening instrument used to assess global cognitive function [72]. It evaluates orientation to time and place, immediate memory through word registration, attention and calculation via tasks such as serial subtraction, delayed recall of previously presented words, language abilities including naming, repetition, comprehension, reading, and writing, as well as visuospatial skills through figure copying. The total score ranges from 0 to 30, with higher scores reflecting better cognitive performance (**Appendix F**).

Geriatric Depression Scale

The Geriatric Depression Scale (GDS) is a self-report questionnaire designed to assess depressive symptoms in older adults[123]. It evaluates mood, feelings of satisfaction, energy, social engagement, and other affective and cognitive indicators of depression. Items are scored dichotomously (e.g., yes/no), and higher total scores indicate greater levels of depressive symptoms (**Appendix G**).

Alzheimer’s Disease Assessment Scale

The Alzheimer’s Disease Assessment Scale (ADAS) is a standard measurement tool for assessing cognitive dysfunction in Alzheimer’s disease, evaluating memory, language, praxis, orientation, and attention [73]. Both the 11-item (ADAS-Cog11) and 13-item (ADAS-Cog13) versions were used in **Chapter 5**, and scores from the two versions were combined for analysis. Higher scores indicate greater cognitive impairment **Appendix H**.

Clinical Dementia Rating

The Clinical Dementia Rating (CDR) is an assessment designed to stage the severity of dementia across multiple domains, including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care [159]. The global score represents overall dementia severity, with higher scores reflecting higher severity **Appendix I**.

Functional Activities Questionnaire

The Functional Activities Questionnaire (FAQ) is a caregiver report used to assess an individual’s ability to perform instrumental activities of daily living, such as managing finances, shopping, preparing meals, and keeping appointments [160]. Higher scores indicate greater functional impairment **Appendix J**.

2.6.3 Medical History

A set of self-reported questions on medical history was collected in the ADNI dataset and used for model training in **Chapter 5**. Participants provided yes/no responses regarding the presence of comorbidities across multiple domains, including:

1. **Psychiatric disorders** (e.g., depression, anxiety)
2. **Neurologic disorders** (e.g., stroke, epilepsy)
3. **Head, eyes, ears, nose, and throat conditions** (e.g., hearing loss, sinus disease)
4. **Cardiovascular disease** (e.g., hypertension, heart attack)
5. **Respiratory conditions** (e.g., asthma, chronic obstructive pulmonary disease)
6. **Hepatic disease** (e.g., hepatitis, cirrhosis)
7. **Dermatologic or connective tissue disorders** (e.g., eczema, rheumatoid arthritis)
8. **Musculoskeletal conditions** (e.g., osteoarthritis, osteoporosis)
9. **Endocrine or metabolic disorders** (e.g., diabetes, thyroid disease)
10. **Gastrointestinal disease** (e.g., ulcers, inflammatory bowel disease)
11. **Hematopoietic or lymphatic disorders** (e.g., anemia, lymphoma)

12. **Renal or genitourinary disease** (e.g., chronic kidney disease, urinary tract infection)
13. **Allergies**
14. **Alcohol abuse**
15. **Drug abuse**
16. **Smoking**

Assessment	Measures	Used In	For
ATN status	AD status and severity	Chapter 5	Prediction target
NPI	Neuropsychiatric symptoms	Chapter 3	Post-hoc correlation
		Chapter 5	Model training
MMSE	Cognitive function	Chapter 3	Post-hoc correlation
		Chapter 5	Model training
GDS	Depressive symptoms	Chapter 3	Post-hoc correlation
		Chapter 5	Model training
ADAS	Cognitive function	Chapter 5	Model training
CDR	Global dementia severity	Chapter 5	Model training
FAQ	Functional independence	Chapter 5	Model training
Medical History	Self-reported comorbidities	Chapter 5	Model training

Table 2.5: Summary of cognitive and clinical assessments used across Chapter 3 and Chapter 5. *AD = Alzheimer’s Disease, ADAS = Alzheimer’s Disease Assessment Scale, ATN = Amyloid-Tau-Neurodegeneration, CDR = Clinical Dementia Rating, FAQ = Functional Activities Questionnaire, GDS = Geriatric Depression Scale, MMSE = Mini-Mental State Examination.*

2.7 Statistical Analyses

2.7.1 Statistical Tests

Descriptive statistics are presented as means $\pm$ standard deviations for continuous variables, or as counts and percentages for categorical variables. Group differences were evaluated using independent-samples t-tests or analyses of variance (ANOVA) for continuous variables, and chi-square tests for categorical variables. All inferential analyses assumed significance at $p < .05$, with false discovery rate (FDR) correction applied to account for multiple comparisons.

2.7.2 Linear Regression Models

Main Linear Model for Brain Network Metrics

To investigate the interaction between insomnia symptoms and AD pathology on brain network function and morphology in **Chapter 3**, the following model was fitted:

$$\text{BNM} \sim \text{Insomnia} \times \text{Diagnosis} + \text{Age} + \text{Sex} + \text{FWD} + \text{GMV} \quad (2.1)$$

Where:

- **BNM**: Brain network metric (FC, SC, DC, or GMV)
- **Insomnia**: Binary variable indicating the presence (1) or absence (0) of insomnia symptoms
- **Diagnosis**: Categorical variable indicating the participant's diagnostic group (CN, MCI, AD)
- **Age**: Chronological age (in years) at the time of data collection
- **Sex**: Self-reported biological sex (male/female)
- **FWD**: Framewise displacement
- **GMV**: Total gray matter volume

Including the interaction term allowed the model to test whether the relationship between insomnia and brain network organization varied across diagnostic groups.

Edgewise Functional Connectivity Models

Building on the results of the model presented in **Eq. (2.1)**, we fit a series of linear regression models for each functional connectivity edge, stratified by diagnostic group:

$$\text{FC}_{ij} \sim \text{Insomnia} + \text{Age} + \text{Sex} + \text{FWD} + \text{GMV}, \quad \text{for each Diagnosis} \quad (2.2)$$

Where:

- **FC_{ij}**: Functional connectivity between nodes i and j
- **Insomnia, Diagnosis, Age, Sex, FWD, GMV**: Defined as in **Eq. (2.1)**

Nodes and their corresponding edges were defined at either the network level (e.g., DMN to SN) or the region-of-interest (ROI) level (e.g., left parietal DMN to right medial SN). Stratification by edge and diagnostic group resulted in a total of 960 models, each conforming to the structure outlined in **Eq. (2.2)**. The resulting parameter estimates were visualized as heat maps representing all ROI- and network-level edges within and between the DMN, SN, and CEN (**Fig. 3.2**).

Nodewise Degrees Centrality Models

An additional 196 models were fit to examine the relationship between insomnia symptoms and DC:

$$\text{DC}_i^{(t)} \sim \text{Insomnia} + \text{Age} + \text{Sex}, \quad \text{for each Diagnosis} \quad (2.3)$$

Where:

- **DC_i^(t)**: Degree centrality of node i at threshold $t \in \{0.2, 0.4, 0.6\}$
- **Insomnia, Diagnosis, Age, Sex**: Defined as in **Eq. (2.1)**

Model estimates were projected onto 2D brain maps to illustrate region-specific functional changes (**Fig. 3.3**).

Post-Hoc Correlational Models

Finally, the post hoc associations between FC alterations and cognitive and clinical outcomes, including MMSE, GDS, and NPI domain scores were explored:

$$\text{Outcome}_k \sim \text{FC}_{ij}^* + \text{Age} + \text{Sex}, \quad \text{for each Diagnosis} \quad (2.4)$$

Where:

- **Outcome_k**: Total score of assessment k (e.g., MMSE, GDS, or individual NPI domains)
- **FC_{ij}^{*}**: Categorical variable representing an edge between nodes i and j previously identified as significantly associated with insomnia symptoms
- **Diagnosis, Age, Sex**: Defined as in **Eq. (2.1)**

Edges with significant post hoc correlations were visualized using chord diagrams. The direction and strength of these associations were evaluated using volcano plots constructed from model estimates and $-\log_{10}(p)$ values (**Fig. 3.4 – Fig. 3.7**)

Assumptions

The model-specific assumption of linearity was met in the models presented in **Eq. (2.1)**, **Eq. (2.2)**, **Eq. (2.3)** on account of the binary and categorical classification of the IVs. Linearity in **Eq. (2.4)** was confirmed visually through the evaluation of partial residual plots. The assumptions of homoscedasticity and normality were met in 97.5% and 57.5% of models, respectively. These rates were considered acceptable, as heteroscedasticity was negligible and the minimum number of observation ($n = 320$) was sufficiently large to justify parametric inference under the Central Limit Theorem [161].

2.7.3 Cumulative Link Mixed Model

A cumulative link mixed model (CLMM) was applied in **Chapter 4** to assess the impact of experimental sleep disturbance on KSS scores:

$$\text{KSS}_{st} \sim \text{SleepCondition}_t + \text{Age} + \text{Sex} + \text{Site} + \text{Chronotype} + (1 \mid \text{ID}_s) \quad (2.5)$$

Where:

- **KSS_{st}**: Karolinska Sleepiness Scale score for subject s under sleep condition t
- **SleepCondition_t**: Categorical variable indicating the sleep condition ($t =$ normal sleep, sleep restriction, or sleep disturbance)
- **Age, Sex**: Defined as in **Eq. (2.1)**
- **Site**: Categorical variable indicating the scanning site
- **Chronotype**: Categorical variable indicating circadian preference (morning-type, evening-type, or intermediate)
- **ID_s**: Anonymous identifier assigned to each subject s

- $(1 \mid \text{ID}_s)$: Random intercept for each subject, accounting for repeated measures within individuals

The CLMM framework was chosen to accommodate the ordinal nature of KSS outcomes while modelling both subject-level variability and fixed predictors. Covariate selection was guided by ablative comparisons, in which age, sex, BMI, PSQI score, and chronotype were included in various iterations. The model presented in **Eq. (2.5)** yielded the lowest Akaike Information Criterion ($\text{AIC} = 2336.25$) among all candidates and was therefore selected as the final model. Scatter plots with fitted trend lines were used to visualize raw scores and estimates (**Fig. 4.2**).

Assumptions

The assumption of proportional odds for categorical predictors with >3 levels was tested by fitting two alternative models with **SleepCondition_t** and **Chronotype** included as nominal effects. Comparison of the AIC and log-likelihood values indicated no improvement in fit, validating this assumption. Multicollinearity was evaluated using the scaled Generalized Variance Inflation Factor, with all predictors showing minimal collinearity (< 2). Linearity of continuous predictors and normality of residuals were visually confirmed using effect plots and quantile-quantile plots, respectively.

2.7.4 Linear Mixed Effects Models

Main Linear Mixed Effects Model for Glymphatic System Indices

To assess the impact of experimental sleep disturbance on glymphatic function in **Chapter 4**, data were restructured into a long format with three aligned vectors: sleep condition, GSI, and corresponding z-scored values. DTI-ALPS values were sign-inverted to ensure that higher scores uniformly reflected greater glymphatic abnormality across indices. A linear mixed effects (LME) model was then fit:

$$\text{Value}_{stg} \sim \text{Index}_g \times \text{SleepCondition}_t + \text{Age}_s + \text{Sex}_s + (1 \mid \text{Site}_s) + (1 \mid \text{ID}_s) \quad (2.6)$$

Where:

- **Value_{stg}**: Z-scored value of glymphatic index g for subject s under sleep condition t
- **Index_g**: Categorical variable indicating the glymphatic index (ChPV, PVSV, FWI, DTI-ALPS)
- **SleepCondition_t**: Categorical variable indicating the sleep condition (normal sleep, sleep disturbance, sleep restriction)
- **Age_s, Sex_s**: Defined as in **Eq. (2.1)**
- $(1 \mid \text{Site}_s)$: Random intercept accounting for site-level variation
- $(1 \mid \text{ID}_s)$: Random intercept accounting for repeated measures within subjects

The site-corrected LME framework was selected to simultaneously model both within-subject and between-subject effects. Given the uneven distribution of dMRI data across datasets (**Table 2.1**), site was included as a random effect to account for nuisance variance while reducing the risk of false positives. Outcomes were evaluated using t-values, with $|t| > 1.96$ indicating significance. Approximate p -values from the LME were included to aid interpretation. Pairwise differences between sleep conditions were assessed for each index using estimated marginal means with confidence intervals, and visualized using violin plots (**Fig. 4.3**)

Baseline Variance Model

To verify that baseline GSI values were comparable across sites, an additional LME was fitted to quantify the variance attributable to scanning sites at baseline:

$$\text{Value}_s \sim 1 + (1 \mid \text{Site}_s), \quad \text{for each Index} \quad (2.7)$$

Where:

- **Value_s**: Z-scored value of the glymphatic index for subject s
- **1**: Fixed intercept term
- **(1 | Site_s), Index**: Defined as in **Eq. (2.6)**

The outcomes of this model were visualized in scatter plots (**Fig. 4.4**)

Assumptions

The model-specific assumptions of linearity and homoscedasticity were evaluated by plotting residuals against fitted values, with visual inspection indicating these assumptions were satisfied. However, a quantile-quantile plot of residuals revealed deviations from normality, which was statistically confirmed by a Shapiro–Wilk test ($p < .001$). To address this violation, the analysis was shifted to a robust linear mixed effects (RLME) framework. This method selectively downweights outlying observations to mitigate the influence of non-normal residuals and produce more stable estimates [162].

2.8 Machine Learning Models

To predict ATN status in **Chapter 5**, three ML models were implemented: L1-regularized logistic regression, L2-regularized logistic regression, and an AutoGluon ensemble model [163]. The L1 and L2 logistic regressions served as baseline models, while the AutoGluon model was used as the primary predictive framework.

2.8.1 Feature Selection

Following previous longitudinal modeling in the ADNI dataset [164], a feature set spanning demographic, clinical, cognitive and physical domains was defined. In **Chapter 5**, this set was expanded with one sleep related feature (NPI-K score) and four glymphatic features (PVSF, ChPV, DTI ALPS, BCR). As in previous work, ordinal questionnaire scores were treated as continuous variables during model training. All continuous features were standardized to enhance model performance,

while categorical features were one-hot encoded for the baseline models. A weighted selection procedure was applied to identify three consecutive sessions with maximal participant data availability. The complete feature set is summarized in **Table 2.6**.

2.8.2 Regularized Logistic Regression

Logistic L1 (lasso) and L2 (ridge) regression models were implemented using the `scikit-learn` library. Data were partitioned into 80% training and 20% test sets, and regularization parameters were tuned via cross-validated grid search to minimize overfitting and enhance generalizability.

2.8.3 AutoGluon Ensemble Model

The AutoGluon model was used to construct an ensemble of multiple base learners, including gradient boosting machines, random forests, extra trees, k-nearest neighbors, multi-layer perceptrons, and neural networks. Hyperparameters were optimized automatically within the AutoGluon framework. The training consisted of two main stages: bootstrap aggregation ("bagging") with cross-validation (CV) and stacked ensembling.

Bootstrap Aggregation

First, the training data was split into $k = 8$ folds, in line with previous optimization experiments [163]. Subsequently, for each subset D_k , a bagged model M was trained on the union of the remaining subsets D/D_k , with D_k serving as the validation set. The predictions of the folds were then concatenated to generate the out-of-fold (OOF) predictions, which were evaluated against the target ground truth to calculate the CV score. Additionally, the predictions from the bagged model were averaged to yield a final predicted class. These steps were then repeated for the next model $M + 1$.

Stacked Ensembling

The stacked ensembling step combines multiple layers L of bagged models, each trained on both the original dataset and the predictions from preceding layers. For the final layer, a Greedy Weighted Ensemble algorithm was used to produce a meta-model from the weighted predictions of the second-to-last layer. Additionally, skip connections were used to connect this meta-model to all preceding layers. To prevent data leakage, OOF predictions were employed during training; during inference, the averaged predictions are used. The ultimate number of models trained was equal to $k \times M \times L + 1$, where k refers to the number of folds, M to the number of models in each layer, L to the number of layers, and 1 to the final ensemble model [163].

2.8.4 Model Evaluation

Baseline model performance was evaluated using k-fold cross-validation ($k = 8$). OOF predictions from each fold were compared to the true labels to calculate performance metrics, including accuracy, Matthews correlation coefficient (MCC), F1, precision, and recall. For the AutoGluon ensemble, predictions from bagged base learners were averaged, and stacked ensembles were evaluated using the same OOF

Domain	Feature	Type	Levels
Target	ATN Status	Categorical	A,T,N (-/+)
Demographics	Age	Continuous	Years
	Sex	Binary	Male / Female
	Education	Continuous	Years of education
	Marital	Categorical	Married, Single, Divorced, Widowed
	Ethnicity	Binary	Latino / Not Latino
Cognitive / Clinical	Diagnosis	Categorical	CN, MCI, AD
	MMSE	Continuous	0–30
	GDS	Continuous	0–30
	ADAS	Continuous	0–70
	CDR	Ordinal	0–3
	FAQ	Continuous	0–30
Genetic	APOE4	Categorical	0, 1, 2 alleles
Medical History	Psychiatric	Binary	Yes / No
	Neurological	Binary	Yes / No
	Head, Ear, Nose, Throat	Binary	Yes / No
	Cardiovascular	Binary	Yes / No
	Respiratory	Binary	Yes / No
	Hepatic	Binary	Yes / No
	Dermatologic	Binary	Yes / No
	Musculoskeletal	Binary	Yes / No
	Endocrine-Metabolic	Binary	Yes / No
	Gastrointestinal	Binary	Yes / No
	Hematopoietic-Lymphatic	Binary	Yes / No
	Renal-Genitourinary	Binary	Yes / No
	Allergies	Binary	Yes / No
	Alcohol	Binary	Yes / No
	Drug	Binary	Yes / No
	Smoking	Binary	Yes / No
Sleep / Glymphatic	NPI-K	Continuous	0–12
	Adjusted PVSV	Continuous	Unitless index
	Adjusted ChPV	Continuous	Unitless index
	DTI-ALPS	Continuous	Unitless index
	BCR	Continuous	Unitless index

Table 2.6: Features used in predictive modeling. Each feature was available for up to three sessions per participant. *AD* = Alzheimer’s Disease, *ADAS* = Alzheimer’s Disease Assessment Scale, *APOE4* = Apolipoprotein E4, *ATN* = Amyloid-Tau-Neurodegeneration, *BCR* = Brain Clearance Rate, *CDR* = Clinical Dementia Rating, *ChPV* = Choroid Plexus Volume, *CN* = Cognitively Normal, *DTI-ALPS* = Diffusion Tensor Imaging Along the Perivascular Space, *FAQ* = Functional Activities Questionnaire, *GDS* = Geriatric Depression Scale, *MCI* = Mild Cognitive Impairment, *MMSE* = Mini-Mental State Examination, *NPI-K* = Neuropsychiatric Inventory Domain K, *PVSV* = Perivascular Space Volume.

predictions. Ablation analyses examined the impact of including or excluding glymphatic features on model performance. All model performance metrics are summarized in **Table 5.3**.

2.8.5 Shapley Additive Explanations

To interpret the contributions of individual features to the ensemble model predictions, Shapley Additive Explanations (SHAP) values were computed [165]. SHAP quantifies the impact of each feature on a prediction by comparing the model output with and without the feature, averaging over all possible feature combinations. SHAP explanations were visualized using stacked bar charts (**Fig. 5.4-Fig. 5.8**).

2.9 Resources

2.9.1 Ethics Statement

All data used in this study were obtained from ADNI and ENIGMA. Procedures were approved by local institutional review boards at each participating site, and all participants or their legally authorized representatives provided written informed consent. Data were de-identified prior to sharing, and researchers accessed the data under a Data Use Agreement, in compliance with ethical guidelines for human research.

2.9.2 Software

All data collection and management tasks were performed using Python 3.11 and the `pandas` library. Dataset provenance was tracked in Bash using DataLad [141]. Preprocessing was conducted in Bash with prebuilt Apptainer containers obtained from ReproNim [140]. SHIVA inference was executed in a custom Python 3.8 virtual environment. L1 and L2 regression and AutoGluon models were trained within a custom Python 3.11 virtual environment. All preprocessing, inference, and machine learning steps were performed interactively on the Juseless cluster at Forschungszentrum Jülich, while all statistical analyses were conducted locally in RStudio 4.5. Data-driven figures were generated reproducibly in RStudio, while overview figures and schematics were created and refined using BioRender.com.

2.9.3 Data Availability

The ADNI and ENIGMA data presented in this study are publicly available to qualified researchers upon request through the Data Use Agreements. All analysis code, computational environments, and logs are publicly available on GitHub [166] and GitLab [167].

Chapter 3

The Interplay of Insomnia and Alzheimer’s Disease in the Three-Network System

This chapter explores the relationship between sleep and AD by examining how insomnia symptoms affect brain network integrity across different stages of the AD continuum. It contains text, data, and figures from [1]

3.1 Introduction

Sleep disturbances are a common catalyst and consequence of AD pathology. This relationship is clinically significant, as 40% to 70% of older adults at risk for AD report chronic sleep problems [92], and sleep impairments affect at least 24% of patients with mild to moderate AD and 39% with severe AD [168, 169]. Animal and human studies demonstrate that in the prodromal and preclinical stages of AD, sleep disturbances induce higher $A\beta$ levels in the brain [93, 170–172], enhance tau accumulation in the ISF and CSF [170], increase the risk of clinical diagnosis, [54], and accelerate cognitive decline [50, 53–55, 94, 168, 173, 174]. In the clinical stage, sleep disturbances may be exacerbated by tau-driven deterioration of brain networks involved in sleep and circadian rhythm [175], the emergence of abnormal sleep–wake behaviors, and certain types of medication [55]. This bidirectional relationship between sleep disturbances and AD pathophysiology [176] represents a mutually reinforcing cycle that warrants further investigation using large-scale clinical data.

Insomnia symptoms are one of the most prevalent sources of sleep disturbance in adults, affecting approximately 30% to 35% of the general population [177, 178]. This high prevalence is due in part to their comorbidity with neurological and affective disorders [179]. Insomnia symptoms are characterized by perceived difficulties in falling asleep, maintaining sleep, and early waking times, not attributable to sleep-disrupting external conditions and accompanied by subjective daily dysfunctions [44]. Chronic insomnia disorder, in turn, is defined by the occurrence of these symptoms at least thrice a week and for a period of at least 3 months [180]. Despite the high prevalence of both insomnia symptoms and chronic insomnia disorder in middle-aged and older participants, the neurobiological correlates of insomnia remain relatively poorly understood. Multimodal neuroimaging studies have suggested that insomnia may primarily be a functional brain disorder, that is to say, caused by aberrant connectivity of certain brain regions and networks [178].

A recent study based on 29,423 participants found that insomnia symptoms were

associated with increased FC within the DMN, SN, and CEN, alongside decreased FC between the DMN and both the SN and CEN [119]. These three intrinsic brain networks, hereafter the three-network system (TNS, **Fig. 3.1**), are broadly implicated in distinct yet interrelated cognitive functions: the DMN supports self-referential thought, mind-wandering, and rumination; the SN is critical for detecting salient stimuli and switching between mind-wandering and directed thought; and the CEN underlies working memory, decision making, and goal-oriented behavior [66].

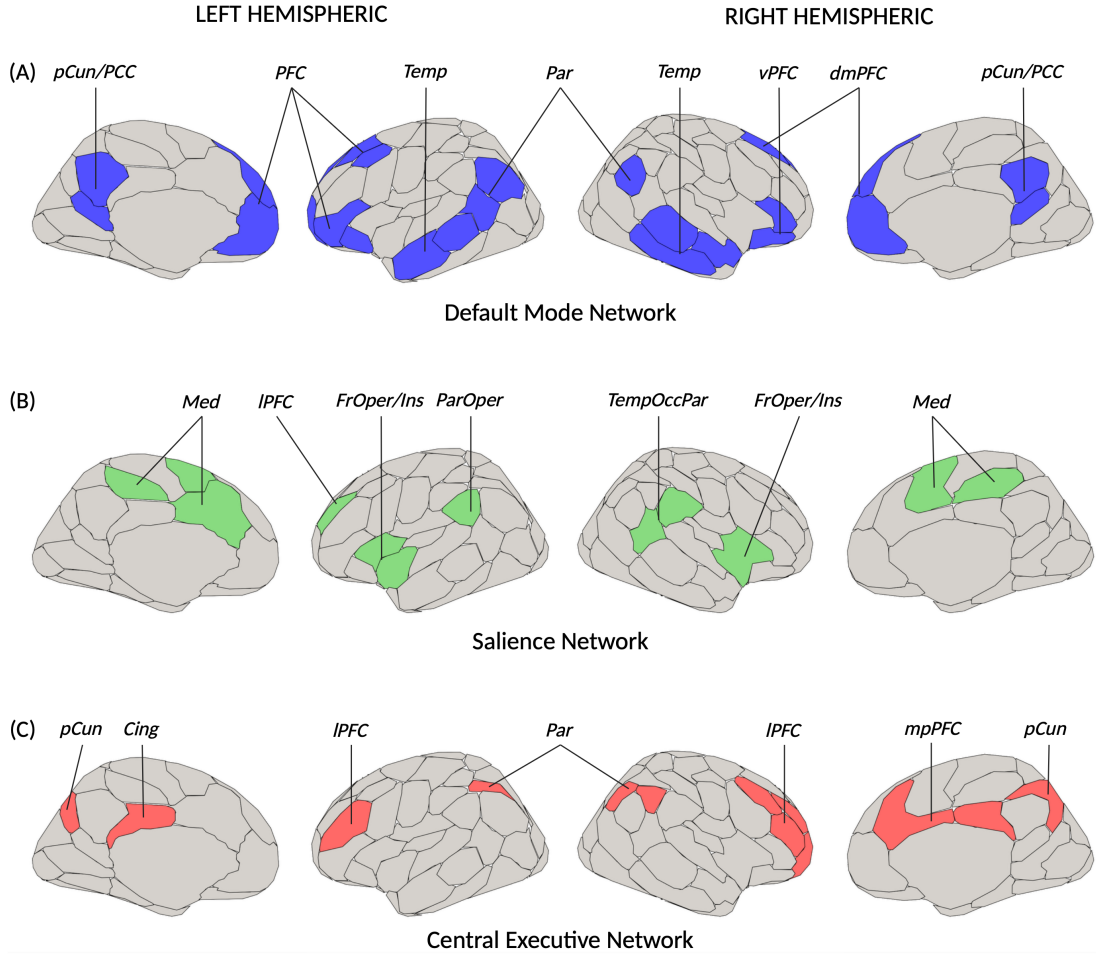


Fig. 3.1: Cortical parcellations of the three-network system (TNS). (A) The Default Mode Network (DMN), including the precuneus/posterior cingulate cortex (*pCun/PCC*), ventral and dorsomedial prefrontal cortices (*vPFC*, *dmPFC*), temporal cortex (*Temp*), and parietal cortex (*Par*). (B) The Salience Network (SN), including the medial cortex (*Med*), lateral prefrontal cortex (*lPFC*), frontal operculum/insula (*FrOper/Ins*), parietal operculum (*ParOper*), and temporal-occipital-parietal region (*TempOccPar*). (C) The Central Executive Network (CEN), including the precuneus (*pCun*), cingulate cortex (*Cing*), lateral and medial posterior prefrontal cortices (*lPFC*, *mpPFC*), and parietal cortex (*Par*).

Given that insomnia and AD both independently affect TNS connectivity and morphology, this chapter aims to investigate whether insomnia symptoms modulate the extant functional and structural alterations associated with AD progression, and whether such modulation is linked to particular cognitive and psycho-affective outcomes. Using clinical and MRI data from the ADNI cohort, we evaluated the relationship between the presence of insomnia symptoms and four brain network metrics: the FC, DC, SC, and GMV. These indices respectively reflect the degree of functional co-activation between network nodes, the involvement of individual nodes in co-activation pairs, the structural co-association of nodes via shared gray matter alterations, and volumetric changes in gray matter of individual nodes. Together,

they provide a comprehensive assessment of the functional and structural integrity of the TNS.

3.2 Results

3.2.1 Participant Demographics

The main sample ($n = 320$) consisted of 135 male and 185 female participants with a mean age of 74.0 ± 7.64 years. Of these participants, 148 were CN, 132 were diagnosed with MCI, and 40 with AD. Each diagnostic group was equally divided and matched across the -insomnia and +insomnia conditions. The sociodemographic and clinical differences between these matched groups are displayed in **Table 3.1-Table 3.3**

3.2.2 Functional Connectivity Alterations Associated With Insomnia Symptoms

Insomnia symptoms were associated with significant FC alterations across all nodes and diagnoses (all $ps < .01$). Moreover, there was a significant interaction between insomnia and diagnosis for AD individuals ($ps < .001$), but not CN and MCI individuals. Within diagnostic groups, insomnia symptoms were associated with varying patterns of FC abnormalities, both at the level of networks and ROIs. CN and MCI+insomnia were characterized by patterns of increased FC within networks, while AD+insomnia was characterized by patterns of decreased FC within and between networks (**Fig. 3.2**).

Within-CEN, CEN-SN, and CEN-DMN FC alterations were prevalent in the CN and AD groups, but not in MCI. As within the DMN, these CEN edges were hyperconnective in CN and hypoconnective in AD. In CN, increased FC was driven by enhanced co-activation of the right lateral PFC (lPFC) with various hubs of the TNS. In AD, decreased FC was associated with attenuated co-activation of the bilateral lPFC, right parietal CEN, and several hubs of the TNS. Overall, whereas the connectivity profile of the CN group showed increased modulation by the CEN, the findings in the AD group suggested a widespread dysconnectivity of the CEN from the other two networks. These FC alterations largely centered around the same ROIs, namely the lPFC.

Within-SN and SN-DMN alterations were a significant marker of insomnia symptoms in the MCI group and were present to a lesser extent in the CN and AD groups. Increased within-SN connectivity in MCI was driven by enhanced correlation of the frontal operculum, insula, and medial SN. These same ROIs exhibited various amounts of attenuation in their correlation with DMN hubs, including the precuneus and PFC, across all diagnostic groups. This reduction in SN-DMN FC was the only consistent correlate of insomnia symptoms that was evident across the entire trajectory of AD.

		-Insomnia	+Insomnia	Total	<i>p</i> -value
Cognitively Normal (CN)					
Total <i>N</i> (%)		74 (50)	74 (50)	148	
Age		73.54 (7.8)	74.41 (7.3)	73.97 (7.5)	.481
Sex	Male	21 (28)	20 (27)	41 (28)	1.000
	Female	53 (72)	54 (73)	107 (72)	
Education		16.27 (2.5)	16.43 (2.3)	16.35 (2.4)	.677
MMSE		28.91 (1.2)	29.08 (1.2)	28.99 (1.2)	.376
GDS		1.15 (1.4)	1.30 (1.4)	1.22 (1.4)	.520
Aβ status	Negative	43 (74)	39 (64)	82 (69)	.315
	Positive	15 (26)	22 (36)	37 (31)	
NPI domains	A (delusions)	0.000	0.000	0.000	n/a
	B (hallucinations)	0.000	0.000	0.000	n/a
	C (agitation/aggression)	0.027	0.189	0.109	.170
	D (depression/dysphoria)	0.178	0.824	0.503	.004**
	E (anxiety)	0.027	0.149	0.088	.069
	F (elation/euphoria)	0.000	0.000	0.000	n/a
	G (apathy/indifference)	0.041	0.216	0.129	.148
	H (disinhibition)	0.014	0.108	0.061	.391
	I (irritability/lability)	0.027	0.689	0.361	.001***
	J (motor behavior)	0.000	0.000	0.000	n/a
	K (sleep)	0.000	3.081	1.551	<.001****
	L (appetite)	0.041	0.459	0.252	.036*

Table 3.1: Participant demographics for the cognitively normal (CN) group. Comparisons between the -insomnia and +insomnia conditions were conducted using t-tests for continuous and chi-squared tests for categorical/ordinal variables. Significant differences are highlighted in bold. Adapted from [1]. *A β* = Amyloid Beta, *GDS* = Geriatric Depression Scale, *MMSE* = Mini-Mental State Examination, *NPI* = Neuropsychiatric Inventory.

		-Insomnia	+Insomnia	Total	<i>p</i> -value
Mild Cognitive Impairment (MCI)					
Total <i>N</i> (%)		66 (50)	66 (50)	132	
Age		72.56 (7.5)	73.62 (7.8)	73.09 (7.6)	.424
Sex	Male	43 (65)	31 (47)	74 (56)	.054
	Female	23 (35)	35 (53)	58 (44)	
Education		15.71 (2.8)	15.53 (2.6)	15.62 (2.7)	.704
MMSE		28.14 (1.7)	27.99 (1.8)	28.06 (1.7)	.619
GDS		2.03 (1.8)	2.29 (2.0)	2.16 (1.9)	.438
Aβ status	Negative	17 (41)	17 (42)	34 (42)	1.000
	Positive	24 (59)	23 (58)	47 (58)	
NPI domains	A (delusions)	0.000	0.000	0.000	n/a
	B (hallucinations)	0.000	0.000	0.000	n/a
	C (agitation/aggression)	0.333	0.508	0.420	.443
	D (depression/dysphoria)	0.333	0.848	0.591	.023*
	E (anxiety)	0.303	0.636	0.470	.181
	F (elation/euphoria)	0.015	0.061	0.038	.254
	G (apathy/indifference)	0.636	0.576	0.606	.832
	H (disinhibition)	0.242	0.212	0.227	.817
	I (irritability/lability)	0.394	0.864	0.629	.059
	J (motor behavior)	0.061	0.061	0.061	1.000
	K (sleep)	0.000	3.530	1.765	<.001****
	L (appetite)	0.167	0.338	0.252	.401

Table 3.2: Participant demographics for the mild cognitive impairment (MCI) group. Comparisons between the -insomnia and +insomnia conditions were conducted using t-tests for continuous and chi-squared tests for categorical/ordinal variables. Significant differences are highlighted in bold. Adapted from [1]. *A β* = Amyloid Beta, *GDS* = Geriatric Depression Scale, *MMSE* = Mini-Mental State Examination, *NPI* = Neuropsychiatric Inventory.

		-Insomnia	+Insomnia	Total	p-value
Alzheimer's Disease (AD)					
Total N (%)		20 (50)	20 (50)	40	
Age		77.24 (8.1)	77.69 (6.7)	77.46 (7.3)	.851
Sex	Male	10 (50)	10 (50)	20 (50)	1.000
	Female	10 (50)	10 (50)	20 (50)	
Education		15.40 (2.4)	15.70 (2.6)	15.55 (2.5)	.706
MMSE		21.65 (3.2)	21.05 (5.5)	21.35 (4.4)	.674
GDS		1.60 (1.7)	1.95 (1.7)	1.78 (1.7)	.523
Aβ status	Negative	1 (6)	2 (12)	3 (9)	1.000
	Positive	15 (94)	14 (88)	29 (91)	
NPI domains	A (delusions)	0.45	0.55	0.50	.799
	B (hallucinations)	0.00	0.45	0.23	.075
	C (agitation/aggression)	0.45	0.75	0.60	.434
	D (depression/dysphoria)	0.60	1.00	0.80	.433
	E (anxiety)	0.30	1.30	0.80	.127
	F (elation/euphoria)	0.20	0.00	0.10	.324
	G (apathy/indifference)	2.30	1.25	1.78	.298
	H (disinhibition)	0.45	0.00	0.23	.051
	I (irritability/lability)	0.80	1.30	1.05	.370
	J (motor behavior)	0.55	1.15	0.85	.391
	K (sleep)	0.00	4.05	2.03	<.001****
	L (appetite)	2.00	1.65	1.83	.727

Table 3.3: Participant demographics for the Alzheimer's disease (AD) group. Comparisons between the -insomnia and +insomnia conditions were conducted using t-tests for continuous and chi-squared tests for categorical/ordinal variables. Significant differences are highlighted in yellow. Adapted from [1]. *A β* = Amyloid Beta, *GDS* = Geriatric Depression Scale, *MMSE* = Mini-Mental State Examination, *NPI* = Neuropsychiatric Inventory.

3.2.3 Minor Degrees Centrality Alterations

Insomnia symptoms were associated with significant DC alterations across all diagnostic groups for .4 absolute threshold ($ps < .01$), but not the .2 and .6 thresholds, indicating a dependency on thresholding. Within-group analyses revealed non-significant DC changes of individual ROIs associated with insomnia symptoms for all thresholds (**Fig. 3.3**). Aggregate DC alterations at the network level were non-significant for the DMN and SN, but CEN DC values were reduced in AD+insomnia ($\beta s < 0$, $ps < .05$) at all thresholds. This aligns with the significant CEN dysconnectivity identified in AD in the within-group FC analyses.

3.2.4 No Morphological Alterations

The TNS SC did not significantly change between the insomnia conditions across diagnostic groups. Furthermore, the +insomnia condition was not associated with significant alterations in the GMV of the main nodes of the TNS.

3.2.5 Functional Connectivity Alterations Associated With Cognitive Decline

To investigate whether the observed FC abnormalities in CN, MCI, and AD individuals with insomnia symptoms were associated with cognitive decline, we conducted a post hoc analysis assessing the relationship between inter-ROI FC and MMSE scores. In the CN and MCI groups, within-DMN hyperconnectivity, especially increased FC between the PFC and precuneus, appeared to be the most significant correlate of reduced cognitive function ($\beta s < 0$, $ps < .01$). In AD, several hypoconnective within-DMN, DMN-SN, and SN-CEN edges were associated with reduced cognitive function ($\beta s > 0$, $ps < .05$). A single SN-CEN edge, between the medial SN and IPFC, was also associated with higher cognitive function ($\beta = -2.3$, $p = .04$). These findings, summarized in **Fig. 3.4**, suggest that major alterations in FC may underlie cognitive decline across clinical groups, and critically, that both hyper- and hypoconnectivity within key networks such as the DMN may have detrimental effects, depending on the stage of AD.

3.2.6 Functional Connectivity Alterations Associated With Depressive Symptoms

To further investigate whether FC abnormalities were associated with depressive symptoms, a post hoc analysis was conducted, modeling the relationship between altered inter-ROI FC and scores from the GDS and domain D ("Depression/Dysphoria") of the NPI. We found that a majority of FC alterations in CN individuals with insomnia symptoms correlated with a significant reduction of depressive symptoms reflected by decreased GDS scores ($\beta s < 0$, $ps < .05$), in contrast to the increased depressive symptoms/dysphoria suggested by NPI-D scores at baseline (**Table 3.1**).

In MCI individuals with insomnia symptoms, FC alterations predominantly correlated with reductions in the GDS and NPI-D scores ($\beta s < 0$, $ps < .05$), though some correlated with increased NPI-D scores ($\beta s > 0$, $ps < .05$), similar to the difference observed at baseline. In contrast, FC alterations in AD individuals with insomnia symptoms overwhelmingly correlated with increased GDS scores ($\beta s > 0$, $ps < .001$), with no GDS or NPI-D changes observed at baseline. Within DMN,

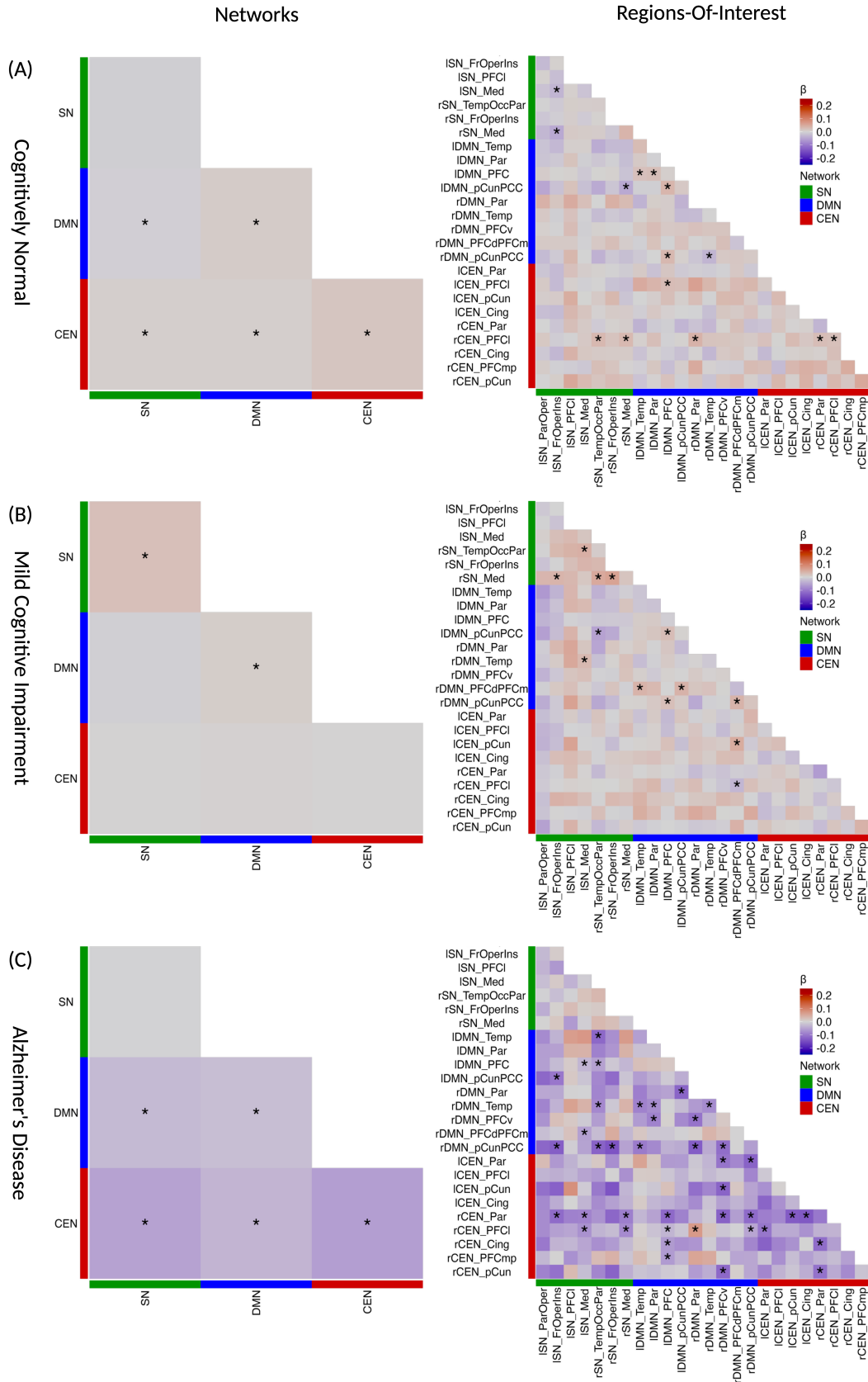


Fig. 3.2: Three-network functional connectivity changes in the presence of insomnia symptoms. (A) Network- and (B) ROI-level alterations in TNS connectivity associated with insomnia symptoms in the CN, MCI, and AD groups. $*p < .05$. β = estimate, AD = Alzheimer's disease, CN = cognitively normal, MCI = mild cognitive impairment, ROI = region-of-interest, TNS = three-network system. Adapted from [1].

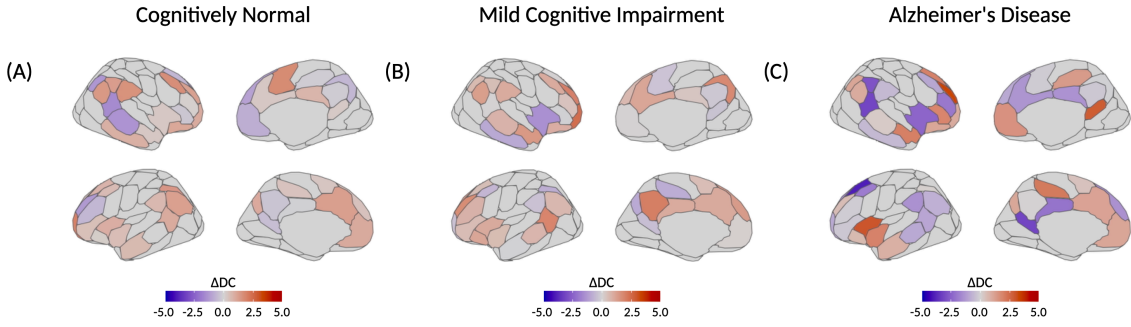


Fig. 3.3: Mean changes in ROI-level degree centrality in the presence of insomnia symptoms for (A) CN, (B) MCI, and (C) AD groups. Degree centrality was computed with an absolute threshold of .04. All changes shown were nonsignificant. Adapted from [1]

namely PFC-precuneus hyperconnectivity seemed to drive the negative correlations in CN and MCI, while widespread DMN-CEN dysconnectivity drove a majority of the negative correlations in AD. These findings are outlined in **Fig. 3.5**. It is important to note that these correlations reflect variability only within the mild range of depressive symptoms, as subjects with GDS scores higher than eight were excluded from the study.

3.2.7 Functional Connectivity Alterations Associated With Behavioral Symptoms

Numerous FC alterations, but in particular hyperconnective within-DMN edges, were correlated with increases in aggression (NPI-C), anxiety (NPI-E), sleep disturbances (NPI-K), and changes in appetite (NPI-L) in CN individuals with insomnia symptoms ($ps < .05$). They further exhibited small changes in apathy (NPI-G) and irritability (NPI-I) scores, though these scores were also typically higher for CN+insomnia individuals at baseline (**Table 3.1**). In MCI individuals with insomnia symptoms, FC alterations were predominantly associated with increased sleep disturbances alongside numerous smaller associations, including marginally reduced apathy, increased disinhibition, reduced irritability, and abnormal appetite ($ps < .05$). Finally, in AD individuals with insomnia symptoms, FC alterations within and between all three networks were associated with significant decreases in apathy ($ps < .05$). At a more discrete level, intra-PFC hypoconnectivity was associated with reduced depressive symptoms and anxiety, parietal-temporal DMN and medial SN-LPFC hypoconnectivity with, respectively, increased and reduced disinhibition and irritability, and various additional DMN-CEN edges with changes in appetite. As expected, reduced PFC-parietal CEN connectivity, a highly significant finding in AD+insomnia, was associated with stark reductions in sleep quality ($ps < .05$). These findings are displayed in **Fig. 3.6** and **Fig. 3.7**.

3.3 Discussion

This chapter investigated the effect of insomnia symptoms on four functional and structural indices of the TNS along the trajectory of AD. It found that FC was the only index significantly affected by insomnia symptoms across all diagnostic groups and all levels of analysis. It further discovered an interaction between the effect of insomnia symptoms and diagnosis in the AD group. Cross-sectional, within-group analyses of major components of the TNS revealed patterns of increased FC

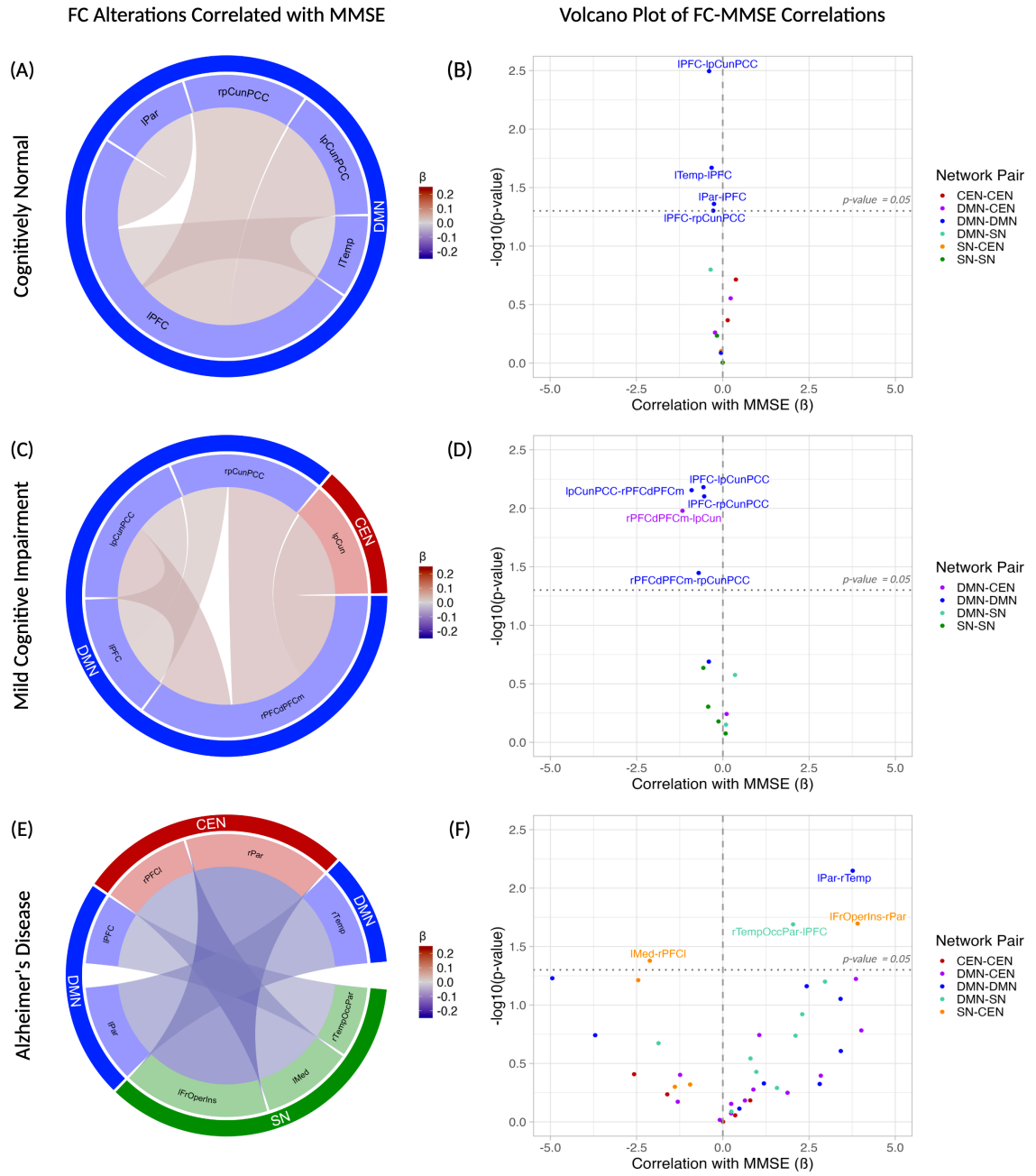


Fig. 3.4: Post hoc correlations between functional connectivity alterations and cognitive scores. Chord diagrams (A, C, E) highlight FC alterations that also correlated with MMSE score. Volcano plots (B, D, F) show correlation strength vs. significance, with significant negative associations in the top left and positive in the top right. In CN and MCI, increased within-DMN connectivity was associated with poorer cognitive performance. In AD, reduced connectivity across multiple networks correlated with lower MMSE scores. β = Estimate, AD = Alzheimer's Disease, CN = Cognitively Normal, DMN = Default Mode Network, FC = Functional Connectivity, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination.

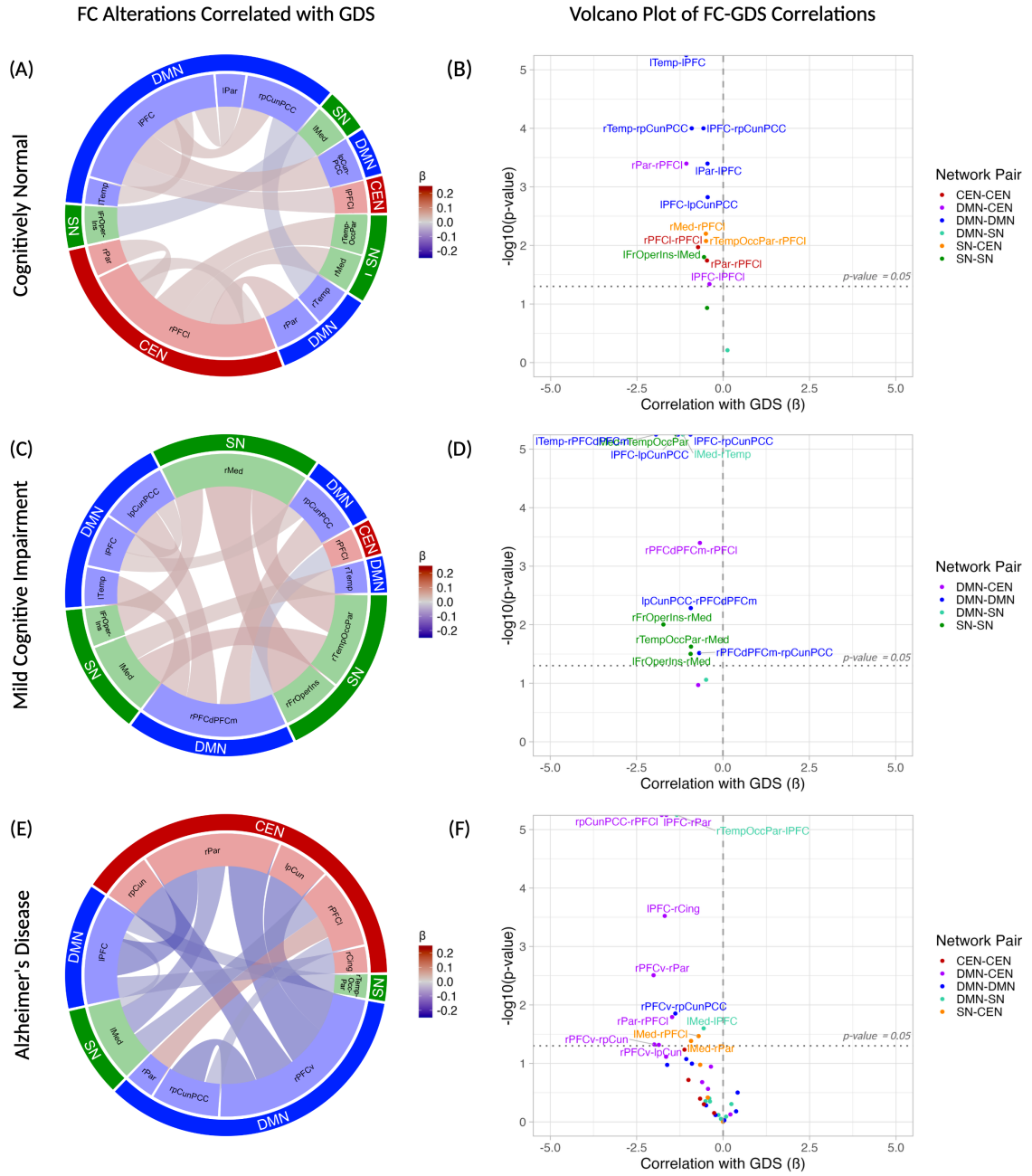


Fig. 3.5: Post hoc correlations between functional connectivity alterations and depressive symptoms. Chord diagrams (A, C, E) highlight FC alterations that also correlated with Geriatric Depression Scale (GDS) scores. Volcano plots (B, D, F) show correlation strength vs. significance, with significant negative associations in the top left and positive in the top right. Whereas most alterations in CN and MCI correlated with reduced depressive symptoms, most alterations in AD correlated with increased depressivity. β = Estimate, AD = Alzheimer's Disease, CN = Cognitively Normal, DMN = Default Mode Network, FC = Functional Connectivity, GDS = Geriatric Depression Scale, MCI = Mild Cognitive Impairment.

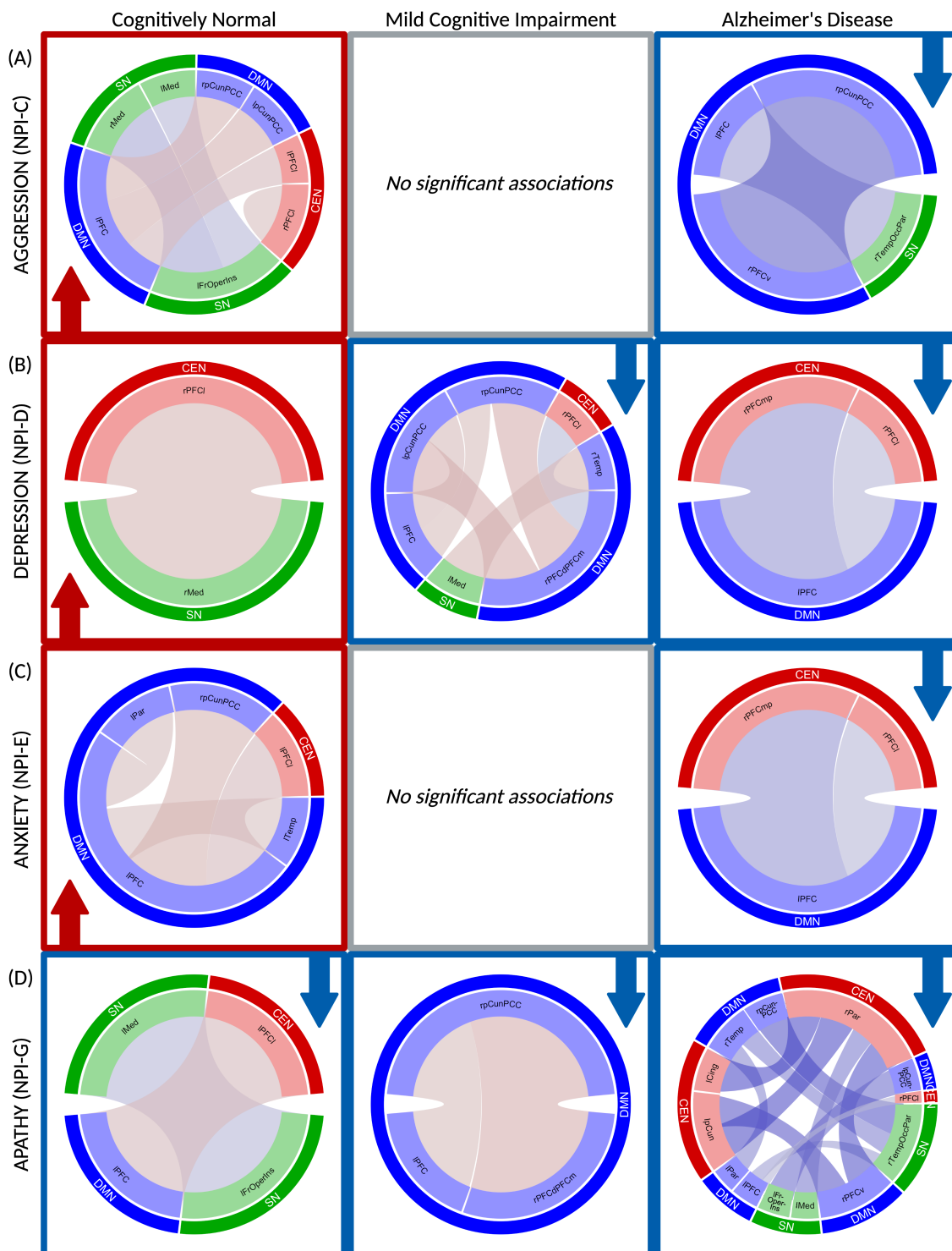


Fig. 3.6: Post hoc correlations between functional connectivity alterations and behavioral symptoms (NPI-C to NPI-G). Chord diagrams illustrate all FC changes that were also significantly associated with (A) aggression, (B) depression/dysphoria, (C) anxiety, and (D) apathy. Border colors indicate the direction of the association: red for increased scores, blue for decreased scores, and gray for no consistent trend. CN individuals with insomnia-related FC alterations showed increased aggression, dysphoria, and anxiety, while those with MCI or AD exhibited decreases in these domains. Apathy was reduced across all groups. AD = Alzheimer's Disease, CN = Cognitively Normal, FC = Functional Connectivity, NPI = Neuropsychiatric Inventory, MCI = Mild Cognitive Impairment.

associated with insomnia symptoms in the CN and MCI groups, and patterns of decreased FC in the AD group. The CN and MCI groups exhibited within-DMN, within-SN (MCI only), and CEN hyperconnectivity, whereas the AD group exhibited within-DMN and CEN hypoconnectivity. In contrast, all groups exhibited some degree of SN-DMN hypoconnectivity. These results were not reflected by similar DC alterations. Only the aggregate CEN DC of the AD group was significantly reduced at all thresholds. The SC and GMV were not significantly affected by insomnia symptoms across the trajectory of AD. A summary of the main findings of this study is depicted in **Fig. 3.8**.

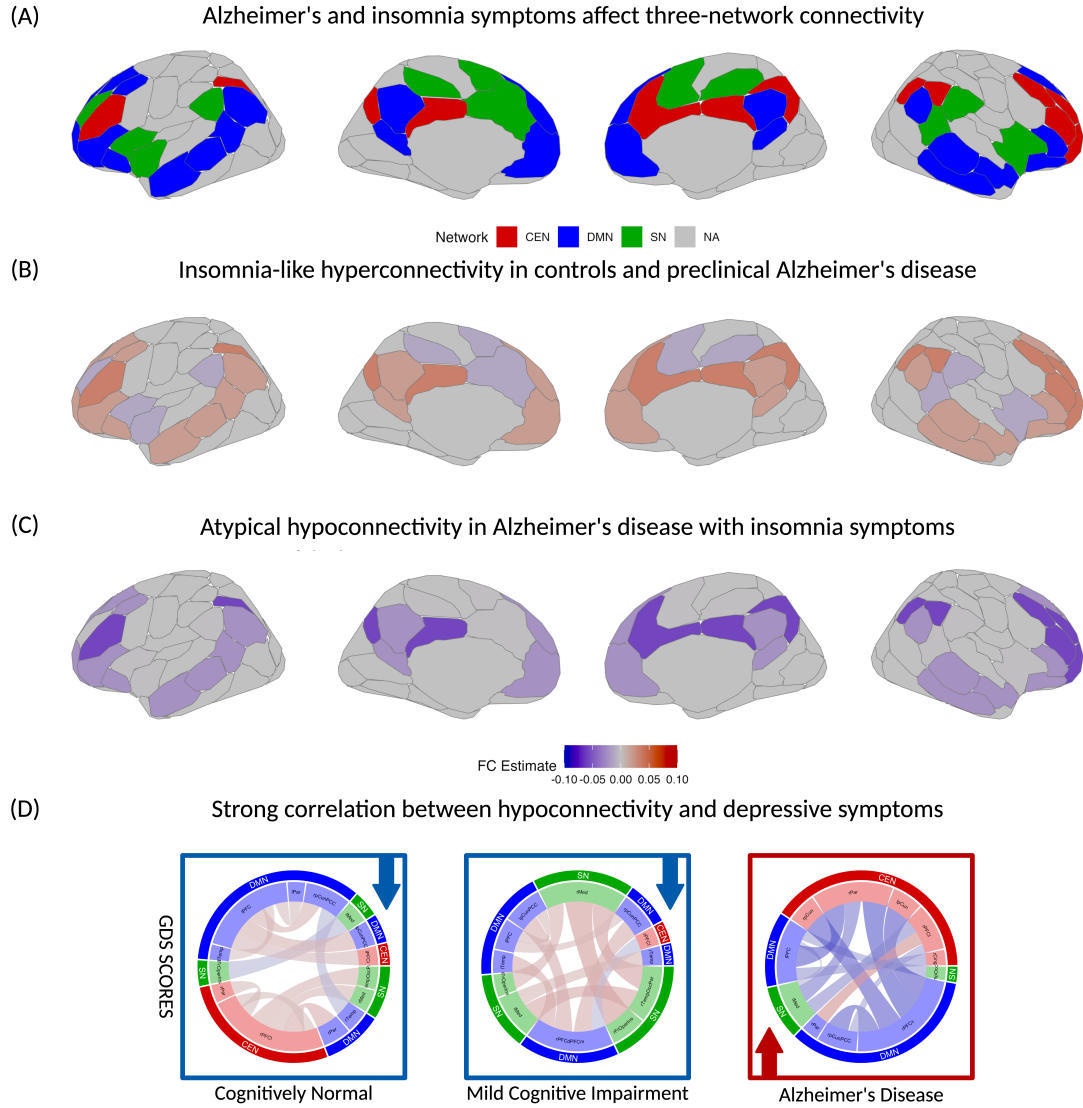


Fig. 3.8: Summary of main findings. (A) Three-network functional connectivity is significantly affected by AD pathology and insomnia symptoms. (B) CN and MCI subjects exhibit insomnia-like FC changes, including DMN and CEN hyperconnectivity and reduced DMN-SN coupling. (C) In contrast, AD subjects exhibit widespread hypoconnectivity not typical of insomnia. (D) FC changes in AD are strongly linked to increased depressive symptoms, which are reversed in CN and MCI. *AD* = Alzheimer's Disease, *CEN* = Central Executive Network, *CN* = Cognitively Normal, *DMN* = Default Mode Network, *FC* = Functional Connectivity, *MCI* = Mild Cognitive Impairment, *SN* = Salience Network.

3.3.1 Interaction Between Alzheimer's Disease and Insomnia Symptoms

AD pathophysiology is typically associated with both structural and functional alterations [181, 182] spreading along networks like the DMN, SN, and CEN [62, 67, 68]. In contrast, functional brain network alterations, but not structural alterations, are most often found to underlie insomnia symptoms [119, 183–185]. We hypothesized that insomnia symptoms modulated both the structural and functional integrity of the TNS in individuals along the AD continuum. However, we found that insomnia symptoms mainly affected FC, and to a lesser extent, DC of the TNS. Interestingly, the patterns of hyperconnectivity identified in the CN and MCI groups mimicked the connectivity alterations typically found in insomnia [119], whereas those in AD did not. To wit, within-DMN FC alterations are typically seen as a correlate of hyperarousal in insomnia, and precuneus-PFC hyperconnectivity was observed in individuals with insomnia symptoms in the CN and MCI groups. Insomnia symptoms in AD were instead associated with intra-temporal and temporal-parietal hypoconnectivity. However, both patterns of FC alterations were associated with decreased cognitive function and sleep quality. Similarly, IPFC connectivity, which reflects the degree of DMN regulation by the CEN, was increased in CN but decreased in AD in the presence of insomnia symptoms. Overall, the evidence supports an interdependent effect of insomnia symptoms and AD on the FC patterns within the TNS.

3.3.2 DMN Connectivity Alterations and Associated Symptoms

Current knowledge of the TNS suggests that even minor FC alterations of its closely associated components may be associated with major pathological manifestations [66]. In the context of both insomnia and AD, TNS dysfunctions are broadly correlated with deficits in attention and cognitive control, abnormal arousal states, and maladaptive thought and behavior [118, 119, 186]. Baseline DMN activity guides self-referential mental processes at rest, whereas hyperactivity may accompany more maladaptive forms of self-referential thought, such as rumination. Indeed, DMN hyperactivity is an important finding in insomnia, as it is frequently associated with hyperarousal states at the onset of sleep [46]. We identified a significant within-DMN hyperconnectivity in both CN and MCI, characterized by an increased FC between the precuneus/PCC and the PFC, two main hubs of the DMN [187]. DMN hyperactivity may sometimes be a result of inadequate downregulation by the SN, i.e., the inadequate suppression of mind wandering and rumination when required [65]. Indeed, we found signs of reduced DMN-SN connectivity in CN and MCI as well, intersecting at the precuneus/PCC.

Curiously, there was also evidence of reduced DMN-SN connectivity in AD not accompanied by DMN hyperconnectivity. A possible explanation for this could be the degeneration of precuneus-centric subnetworks, as these structures are prone to high levels of beta-amyloid accumulation [188]. This could lead to decreased baseline connectivity, meaning that, even in the case of inadequate regulation by the SN, the subnetwork would not become hyperconnective. Indeed, we do see that many hyperconnective edges in CN/MCI are nonsignificant in AD. However, this does not fully explain the prominent within-DMN hypoconnectivity we see in AD +insomnia. One explanation could be exacerbated functional disintegration of the DMN, as the

DMN is an early target of AD pathophysiology [63] and insomnia symptoms may increase the severity of neurodegeneration [189]. However, DMN hypoactivity has also been reported in insomnia as a correlate of emotional dysregulation and reduced daytime attentiveness as a consequence of poor quality of sleep [183, 190, 191]. We speculate that extant comorbidities of progressed AD may specifically exacerbate the affective symptoms of insomnia, leading to the significant link between DMN dysconnectivity and insomnia symptoms in this group. This speculation is somewhat supported by our post hoc correlations between the FC and GDS scores, which revealed that, despite a nonsignificant baseline difference, altered within-DMN, DMN-SN, and DMN-CEN connectivity in AD was associated with profound increases in depressive symptoms. Interestingly, we also saw a marked decrease in apathy for AD individuals with insomnia symptoms, which is distinct from depression and a strong correlate of neurodegenerative diseases [192, 193]. Taken together, the FC alterations of the DMN in AD+insomnia and the psycho-affective correlates of these alterations exhibit a pattern that could be considered atypical for both disorders.

3.3.3 SN Connectivity Alterations and Associated Symptoms

The SN is predominantly involved in salience detection and arousal, as well as regulating the activity of the DMN and CEN in concert [65]. In insomnia, SN hyperconnectivity may be correlated with increased arousal as a result of sustained processing of environmental and proprioceptive stimuli [183, 194]. Conversely, SN hypoconnectivity is not a common phenomenon in insomnia but has been found to correlate with negative affect and apathy in late-life depression [195]. We found that, in the MCI group, insomnia symptoms were associated with significantly increased connectivity of the medial SN with the bilateral frontal SN, the operculum, and the insula. Insular connectivity aberrations are consistently associated with various neuropsychiatric conditions, including insomnia [196]. Although within-SN hyperconnectivity has been implicated in many sleep studies as a correlate of emotional hyperarousal, many studies may have inadequately controlled depression and anxiety levels [37, 183, 197]. Crucially, we did not find that within-SN hyperconnectivity predicted changes in cognitive or affective scores in MCI +insomnia, suggesting these connectivity alterations are not as impactful on daytime function as the ones identified in the DMN.

3.3.4 CEN Connectivity Alterations and Associated Symptoms

The CEN is involved in working memory and goal-oriented action and is critically affected in anxiety disorders [65]. CEN hyperconnectivity has been suggested to reflect a compensatory mechanism for sleep disturbance, as it inhibits emotional dysregulation and facilitates simpler cognitive processes that are inhibited by poor sleep [198]. CEN hypoconnectivity, in contrast, is linked to depressive and anxiety symptoms and is often associated with the emotional distress experienced by individuals with long-term insomnia symptoms [183, 199]. In the CN+insomnia group, CEN FC alterations revealed an increase in the association of all networks with the right IPFC, a key area for the inhibitory control of emotional reactivity [200]. Persistent hyperconnectivity between the right LPFC and the right parietal DMN showed that this inhibitory control mechanism was still partially present in AD +insomnia; despite

a notable hypoconnectivity between the right IPFC and the medial SN, parietal CEN, ventral PFC, and precuneus/PCC. Interestingly, hypoconnectivity between the right IPFC and the left medial SN was also correlated with an increased MMSE score, suggesting perhaps that reduced inhibitory control may be beneficial to daytime cognitive performance. A more notable symptom of AD+insomnia, however, was the significant dysconnectivity of the right parietal CEN with numerous TNS hubs. This dysconnectivity was also reflected in the aggregate DC of the CEN in AD individuals. Decreased FC of the right parietal gyrus is thought to underlie symptomatic anxiety in late-life depression [199]. Thus, similarly to our findings in the DMN, this dysconnectivity may reflect an exacerbation of comorbid negative affect in AD individuals in the presence of insomnia symptoms.

3.3.5 The Absence of Morphological Alterations

The present study found no significant alterations in the SC or GMV of any TNS nodes. This finding is in line with current knowledge on (the absence of) morphological changes associated with insomnia symptoms [184]. However, it also suggests that insomnia symptoms do not significantly accelerate the structural decline present in AD. A possible reason for this could be that the present study investigated short-term insomnia symptoms rather than chronic insomnia disorder [201], and that significant structural changes might require persistent symptoms.

3.3.6 Correlations with Psycho-Affective Symptoms

Insomnia can come paired with a variety of symptoms that may reflect the mental inability to sleep (i.e., hyperarousal) or the cognitive and affective consequences of (perceived) poor quality sleep (i.e., post-insomnia emotional dysregulation). The present study identified correlates of predominantly the latter type in AD individuals with insomnia symptoms. Crucially, cognitive and depressive symptoms were strengthened when comparing AD individuals with and without insomnia symptoms. Whether this reflects an increased prevalence of particular insomnia subtypes could be a topic of future investigations. Phenotypic subtypes incorporating non-sleep characteristics, such as cognitive, psycho-affective, lifestyle, and genetic traits, have increasingly become a focal point in the nosology of insomnia [202, 203]. This investigation excluded individuals with high GDS scores to isolate the relationship between insomnia symptoms and AD. Future studies should strive to include depressive patients to investigate whether the prevalence of insomnia subtypes characterized by negative affect varies along the AD continuum. Cognitive decline and depressive episodes are common behavioral phenomena of AD. Thus, the significant contribution of insomnia symptoms to the severity of these phenomena may be easily overlooked. Unfortunately, AD individuals are still rarely screened for insomnia, making it difficult to assess whether providing treatments such as cognitive behavioral therapy could help to alleviate these concerns and substantially improve quality of life [204].

3.3.7 Limitations

The present study had some limitations. First, insomnia symptoms were broadly classified because of the limited availability of sleep assessments in the ADNI database. Indeed, the NPI is a more general cognitive well-being questionnaire that is not

specifically tailored toward assessing insomnia. It also does not assess the frequency of symptoms or daily dysfunction, which are diagnostic criteria for ID. In contrast, e.g., the Insomnia Severity Index [205] would be able to capture insomnia symptoms more accurately. Utilization of the ISI could also allow further studies to compare the effects of acute and chronic insomnia. Second, the limited availability of sleep assessments also made the present study unable to correct the effect of sleep deprivation and daytime sleepiness on wakeful FC, as well as cognitive function and affect. Questionnaires like the Epworth Sleepiness Scale [206], PSQI [154], or informant- or actigraphy-based reports of sleep length and quality could help further isolate the effect of insomnia symptoms while correcting for the myriad influences of general sleep disturbance. Third, the present study relied on the assumption that FC alterations are a key pathophysiological mechanism in insomnia, and underlie a majority of insomnia symptoms, which remains a point of contention in the literature [183]. Fourth, the present study investigated the interaction between insomnia symptoms and AD on cross-sectional data of individuals at distinct stages of the AD continuum. To better assess the long-term interrelationship between the two disorders, large-scale longitudinal datasets are required. Fifth, beyond assessing beta-amyloid status at baseline, the study could not control for variance explained by potential differences in biomarker impacts and neurodegeneration within diagnostic groups. Further studies should account for this by assessing AD pathogenesis at the statistical level. Finally, the present study suffered from low statistical power at the node level due to the large number of exclusions during selection and preprocessing, significantly reducing the a priori sample size, and the generally low power of multinodal rs-fMRI FC analyses [207].

3.4 Conclusion

This chapter presented evidence that insomnia symptoms significantly modulate the effect of AD pathophysiology on the three-network functional organization. Namely, within-network FC of the DMN and the CEN in individuals with clinical AD and insomnia symptoms differed significantly from CN individuals with insomnia symptoms. These findings suggest that insomnia may manifest atypically in AD patients, underscoring the need for enhanced screening and targeted treatment of insomnia in this population.

Chapter 4

Assessing Glymphatic Function After Sleep Deprivation and Sleep Restriction.

This chapter explores the impact of sleep deprivation and sleep restriction on the glymphatic system by assessing MRI-derived indices of glymphatic function in thirteen datasets shared under the ENIGMA-Sleep initiative. It contains text and data from [2].

4.1 Introduction

The glymphatic system hypothesis stands out as one of the most influential, if not controversial [19], theories in modern sleep research. Much of its prominence is owed to its explanatory potential, as it provides a robust framework for understanding the protective effects of sleep in the context of various neurological disorders [4, 13]. The established glymphatic model comprises four sequential steps: the influx of cerebrospinal fluid (CSF) into the CNS by way of the perivascular spaces (PVS) of penetrating arteries; the transposition of CSF across the glia limitans, mediated by aquaporin-4 (AQP4) water channels at the astrocytic endfeet; the diffusion and advection of CSF through the parenchyma, where it collects metabolic waste proteins and mixes with the interstitial fluid (ISF); and the subsequent uptake of this commixture into the perivenous spaces of large-caliber draining veins [8].

From the earliest formulation of the glymphatic model, sleep has been a prominent asterisk. A nominal study by Xie and colleagues [9] showed that sleep correlated with a surge in CSF influx, convective exchange, and A β clearance in rodents. Sleep deprivation, in turn, has been associated with reduced CSF tracer clearance and elevated AD biomarker levels in both human and rodent models [11, 12]. In some cases, the effect of disturbed sleep on molecular clearance was shown to persist in spite of restorative sleep for up to 48 hours [11].

A number of emergent findings have, however, begun to challenge the dominant framework. Leading this charge was a study by Miao and colleagues [18], which reported a reduction, rather than an increase, in glymphatic flow during sleep and anesthesia. This publication prompted various responses and replication efforts, bringing questions regarding sleep and glymphatic function to the forefront of the field [19]. This chapter aims to provide new insights into the relationship between sleep and glymphatic function by quantifying multiple MRI indices of the glymphatic system in a large, multi-site sleep deprivation dataset provided by the ENIGMA

consortium (**Table 2.1**) [124].

In lieu of invasive, tracer-based methods, glymphatic MRI has emerged as a reliable, non-invasive approach for evaluating glymphatic function in humans [100]. Here, we assess four indices: the adjusted choroid plexus volume (ChPV) and perivascular space volumes (PVSV), the free water index (FWI), and the DTI-ALPS index. These indices respectively reflect the degree of CSF generation and influx, glymphatic flow, and efflux [16, 208], offering a holistic evaluation of glymphatic activity post-sleep (**Fig. 4.1**).

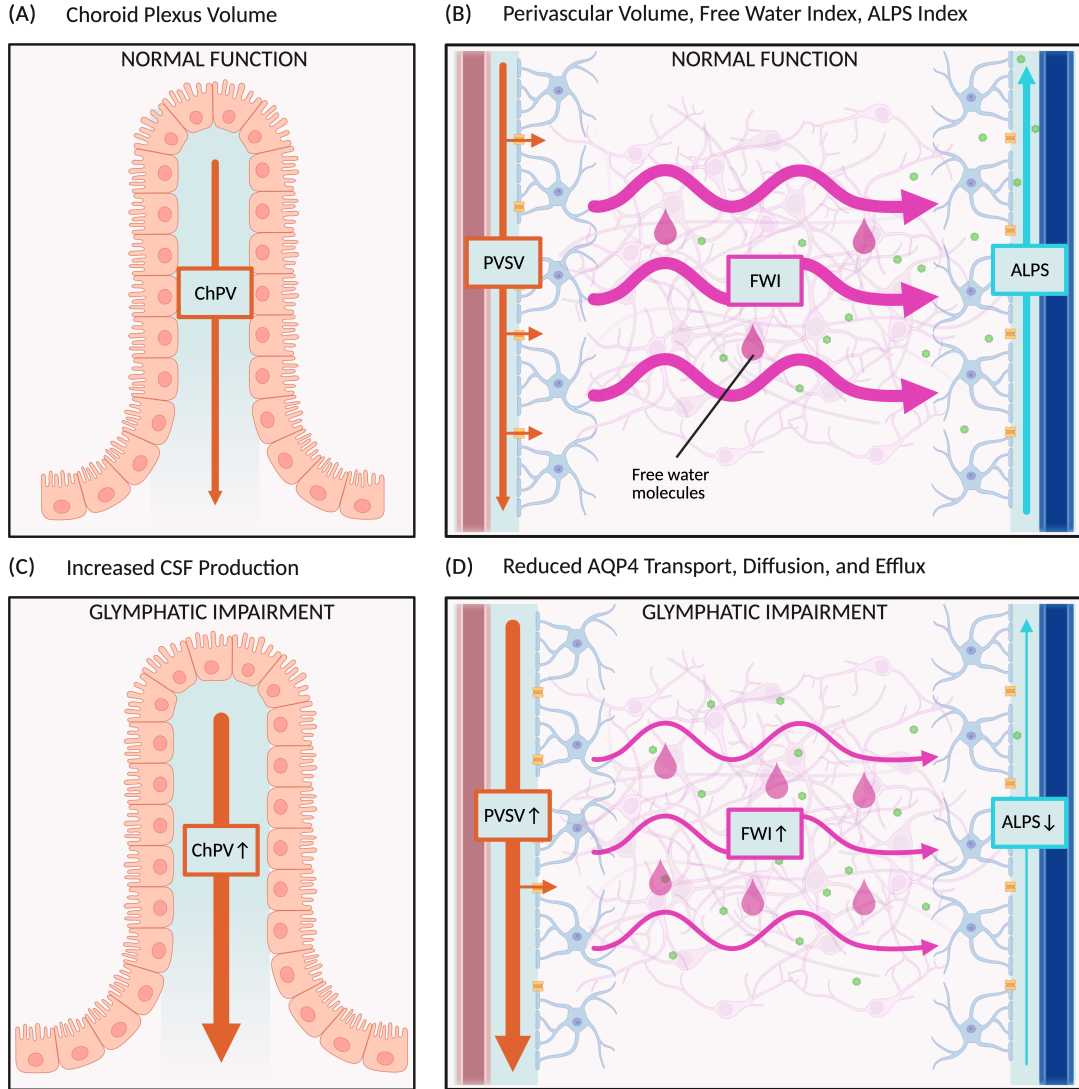


Fig. 4.1: Glymphatic MRI Indices. (A) Choroid Plexus Volume (ChPV) reflects CSF production during sleep. (B) Perivascular Space Volume (PVSV) reflects periarterial CSF influx and AQP4-mediated transport. The Free Water Index (FWI) inversely correlates with glymphatic flow, and the ALPS index reflects efflux. (C) In glymphatic impairment, ChPV typically enlarges to compensate for reduced clearance. (D) PVSV increases due to impaired AQP4 transport. The FWI increases with reduced glymphatic flow. The ALPS index decreases with reduced efflux. *ALPS = Diffusion Along the Perivascular Space, AQP4 = Aquaporin-4, CSF = Cerebrospinal Fluid, ChPV = Choroid Plexus Volume, FWI = Free Water Index, PVSV = Perivascular Space Volume.*

4.2 Results

4.2.1 Participant Demographics

The main sample ($n = 433$) consisted of 223 female and 210 male participants with a mean age of 30.1 ± 14.5 years. Of these participants, 38 were controls, 183 were in the sleep restriction (SR) group, and 212 were in the sleep deprivation (SD) group. Average sleep duration was 7.0 ± 1.0 hours in the control group and 4.0 ± 1.0 hours in the SR group. Subjects in the SD group were deprived of sleep for 28.3 ± 6.8 hours. The sociodemographic and clinical differences between these matched groups are displayed in **Table 4.1**.

There were significant differences in age, sex, and chronotype between all groups (all $ps < .05$). On average, SR subjects were the oldest (35.7 ± 18.1 years) and SD subjects the youngest (25.4 ± 9.5 years). Women were more prevalent in the control group (66%), and men in the SD group (57%). Additionally, morning-types were prevalent in the control and SR groups (32% and 28%) but were the least common chronotype in the SD group (21%). Intermediate chronotypes were most prevalent overall (75%).

4.2.2 Subjective Sleepiness After Sleep Disturbance

The efficacy of experimental sleep disturbance was assessed using a CLMM fitted on KSS scores. Participants reported significantly higher KSS scores after SR ($\beta = 3.00$, $SE = .28$, $z = 10.58$, $p < .001$) and SD ($\beta = 4.13$, $SE = .27$, $z = 15.23$, $p < .001$), indicating a steep increase in self-rated sleepiness. Interestingly, age was negatively associated with KSS scores ($\beta = -.044$, $SE = .014$, $z = 15.23$, $p < .001$), suggesting a slightly lower sleepiness in older participants. Several sites furthermore showed significantly higher self-rated sleepiness compared to the reference site (e.g., Montreal, $\beta = 1.83$, $p = .003$; Oslo, $\beta = 1.78$, $p < .001$; Stockholm, $\beta = 2.39$, $p = .001$). Finally, chronotype showed marginal effects, with morning-types reporting somewhat lower sleepiness compared to evening-types ($\beta = -.93$, $p = .052$). The main findings are illustrated in **Fig. 4.2**.

4.2.3 No Alterations in Choroid Plexus Volume

The estimated marginal means (EMMs) of ChPV were negative across all conditions; however, all corresponding confidence intervals (CIs) overlapped with zero, and none of the pairwise contrasts reached statistical significance (**Fig. 4.3A**).

4.2.4 Increased PVS Volume After Sleep Restriction

The EMMs of PVS were negative at baseline ($EMM = -.16$, 95% CI $[-.28, -.05]$), with further reduction after SD ($EMM = -.27$, 95% CI $[-.41, -.14]$), and near-zero values in SR ($EMM = .01$, 95% CI $[-.14, .15]$). Pairwise comparisons revealed a significant increase in PVS from NS to SR ($\Delta = .17$, $p = .012$), and a significant reduction when comparing SR to SD ($\Delta = -.28$, $p = .001$). The contrast between NS and SD approached significance after adjustment ($p = .062$). These findings are illustrated in (**Fig. 4.3B**).

		Control	SR	SD	Total	<i>p</i> -value
Total <i>N</i> (%)		38 (8.8)	183 (42.3)	212 (49.0)	433	
Age		28.5 (7.4)	35.7 (18.1)	25.4 (9.5)	30.1 (14.5)	<.001****
Sex	Female	25 (65.8)	93 (50.8)	92 (43.4)	210 (48.5)	.028*
	Male	13 (34.2)	90 (49.2)	120 (56.6)	223 (51.5)	
Chronotype	Morning	6 (31.6)	51 (27.9)	21 (16.3)	78 (23.6)	<.001****
	Evening	3 (15.8)	39 (21.3)	11 (8.5)	53 (16.0)	
	Intermediate	10 (52.6)	93 (50.8)	97 (75.2)	200 (60.4)	
PSQI score	0–5	11 (73.3)	67 (85.9)	52 (81.2)	130 (82.8)	0.549
	6–10	4 (26.7)	10 (12.8)	12 (18.8)	26 (16.6)	
	11–15		1 (1.3)		1 (0.6)	
	16–21					
BMI		24.7 (2.8)	23.6 (3.1)	23.2 (3.0)	23.6 (3.1)	0.182
Handedness	Left	3 (15.8)	5 (6.8)	7 (16.7)	15 (11.2)	0.217
	Right	16 (84.2)	68 (93.2)	35 (83.3)	119 (88.8)	
Site	Bruxelles			25 (11.8)	25 (5.8)	<.001****
	Juelich	19 (50.0)	13 (7.1)	55 (25.9)	87 (20.1)	
	Melbourne		16 (8.7)		16 (3.7)	
	Montreal			18 (8.5)	18 (4.2)	
	Oslo	19 (50.0)		17 (8.0)	36 (8.3)	
	Singapore			66 (31.1)	66 (15.2)	
	Stockholm		81 (44.3)		81 (18.7)	
	Trondheim		73 (39.9)		73 (16.9)	
	Zurich			31 (14.6)	31	

Table 4.1: Participant demographics. Continuous variables are presented as means with standard deviations. Categorical/ordinal variables are presented as counts with percentages. Comparisons between the control, sleep restriction (SR), and sleep deprivation (SD) groups were conducted using analysis of variance (ANOVA) for continuous and chi-squared tests for categorical/ordinal variables. Significant differences are highlighted in bold. *ANOVA = Analysis of Variance*, *BMI = Body Mass Index*, *PSQI = Pittsburgh Sleep Quality Index*, *SD = Sleep Deprivation*, *SR = Sleep Restriction*.

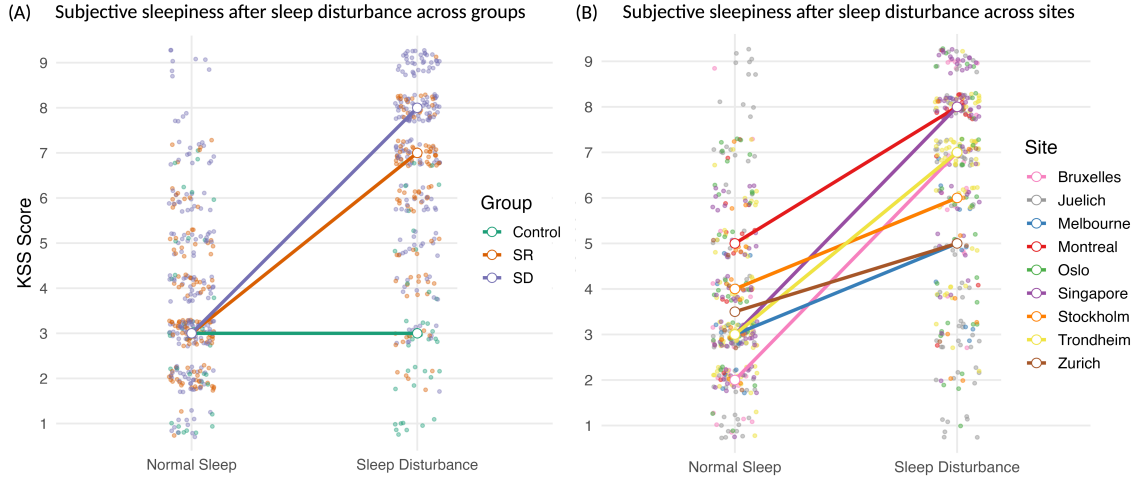


Fig. 4.2: KSS scores following sleep disturbance by (A) experimental group and (B) site. Individual scores are shown as scatter points; medians are indicated by white dots and connecting lines. Sleepiness after sleep disturbance was increased in both the SR and SD groups compared to controls. Sleepiness was consistently increased across sites, though the baseline levels differed significantly. *KSS = Karolinska Sleepiness Scale, SD = Sleep Deprivation, SR = Sleep Restriction.*

4.2.5 Decreased Free Water Index After Sleep Restriction

The SR group exhibited a significantly decreased FWI compared to baseline (EMM = $-.69$, 95% CI $[-.88, -.49]$; $\Delta = -.70$, $p < .001$), while the SD group showed no significant change from baseline. The contrast between SD and SR was also significant ($\Delta = -.28$, $p = .001$). These findings are illustrated in **Fig. 4.3C**. However, the baseline FWI demonstrated a large site-specific variance component ($\sigma^2 = 1.55$) in baseline variance analyses. This suggests considerable heterogeneity across scanning sites, complicating the interpretation of between-condition effects. Stratifying FWI comparisons by site resulted in all contrasts becoming non-significant after correction. This issue is examined further in **Section 4.2.8**.

4.2.6 ALPS Index Abnormalities After Sleep Deprivation and Sleep Restriction

To ensure consistency across indices in the RLME model, the ALPS index was previously sign-inverted so that higher values reflect greater abnormality. In this section, model estimates and confidence intervals are re-inverted for ease of interpretation. The ALPS index was significantly increased in the SR group relative to baseline (EMM = $.40$, 95% CI $[.21, .59]$; $\Delta = .33$, $p < .001$) and significantly decreased in the SD group (EMM = $-.36$, 95% CI $[-.56, -.16]$; $\Delta = -.43$, $p < .001$). The difference between SD and SR was also significant ($\Delta = -.76$, $p < .001$). These findings are illustrated in (**Fig. 4.3D**).

4.2.7 Quantifying Site Effects in the RLME Model

The RLME architecture provides a unified way to assess both within-subject and between-subject effects. However, interpreting the latter requires careful consideration of the variance attributed to site at baseline. The FWI exhibited a high site-related variance at baseline ($\sigma^2 = 1.55$), ALPS showed a moderate variance

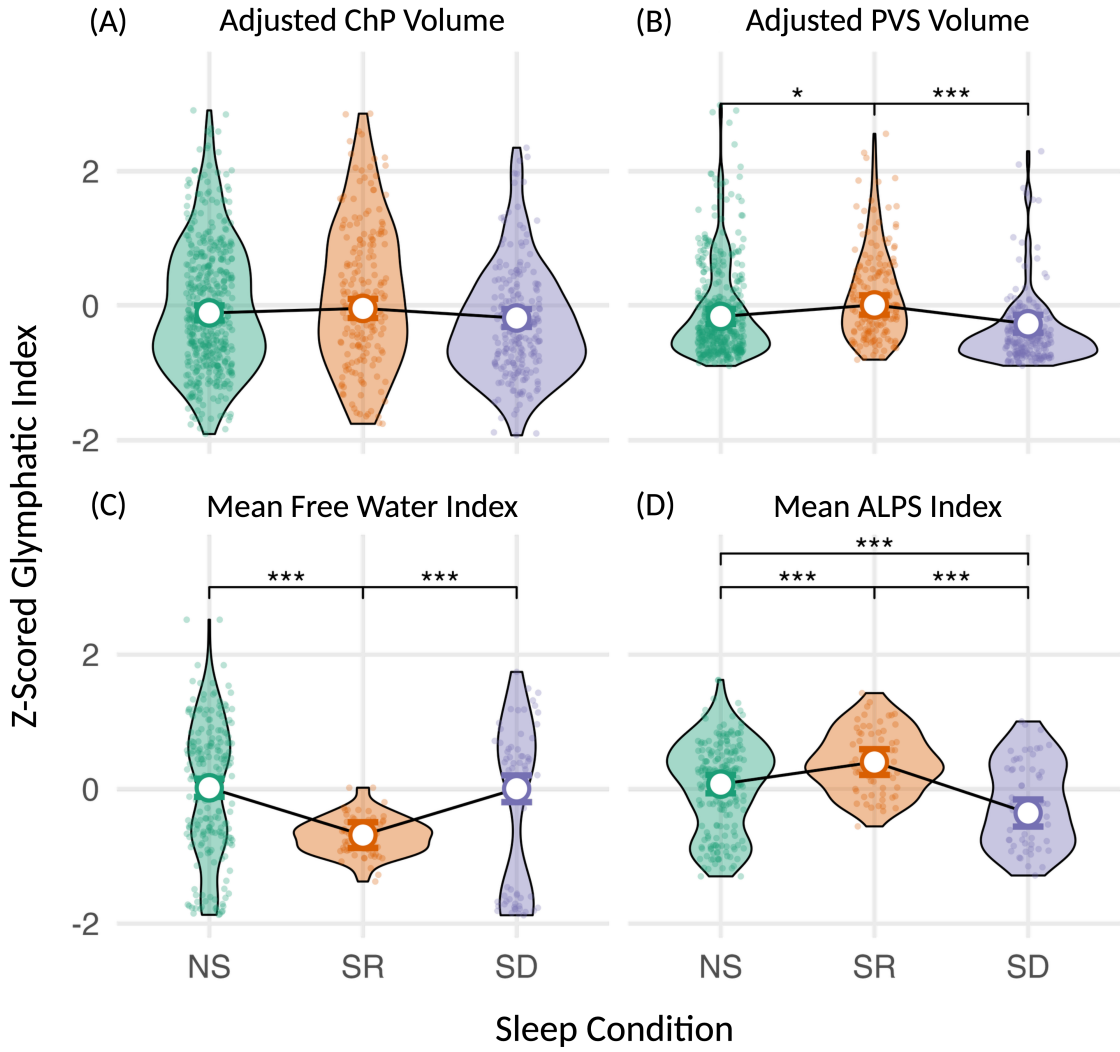


Fig. 4.3: Estimated marginal means of glymphatic indices after normal sleep (NS), sleep restriction (SR), or sleep deprivation (SD). (A) ChPV did not change across the NS, SR, and SD conditions. (B) PVSV was increased in SR compared to NS and SD. (C) The FWI was reduced in SR compared to NS and SD; however, this effect appeared to be partially driven by a strong site-dependent difference in the SD condition (see **Fig. 4.4**). (D) The ALPS index was increased in SR and decreased in SD. *ALPS = Diffusion Along the Perivascular Space, ChPV = Choroid Plexus Volume, FWI = Free Water Index, NS = Normal Sleep, PVSV = Perivascular Space Volume, SD = Sleep Deprivation, SR = Sleep Restriction.*

($\sigma^2 = 0.37$), and ChP and PVS volumes exhibited low variance ($\sigma^2 = 0.17$; $\sigma^2 = 0.10$). The difference between high and moderate variance is illustrated in **Fig. 4.4**. To confirm the robustness of the primary results, sensitivity analyses excluding the potential site confounder - namely, the Bruxelles dataset - were performed.

4.2.8 Site-Adjusted Sensitivity Analyses

A sensitivity analysis was conducted, excluding data from the Bruxelles site, to ensure that the main findings were not site-driven. The main effects and interaction terms for SR and SD remained significant ($|t|s > 2$, $ps \leq 0.05$) and the direction and magnitude of the estimates were unchanged. Namely, as in prior analyses, SD was associated with increased and SR with decreased glymphatic impairment. As expected, excluding the site did result in a significant main effect of FWI ($\beta = .36$, $t = 5.53$, $p < .001$), which had not reached significance in prior analyses.

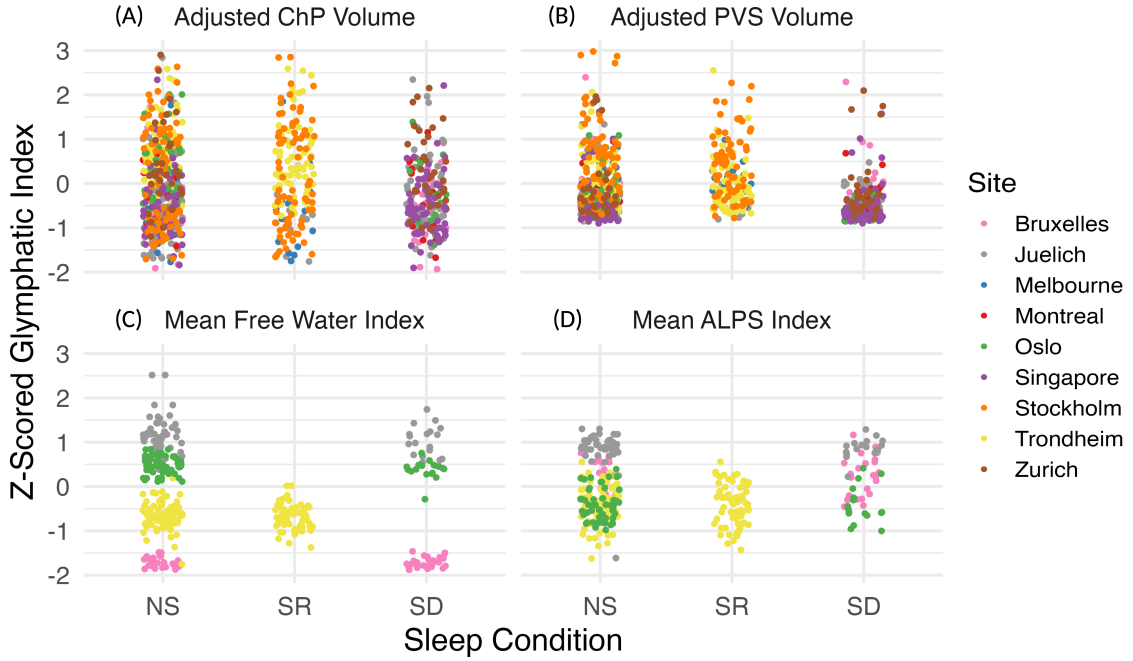


Fig. 4.4: Site-based effects in the RLME model across the (A) ChPV, (B) PVSV, (C) FWI, and (D) ALPS indices. Among the metrics examined, only the FWI displayed pronounced site-related stratification ($\sigma^2 = 1.55$). The Bruxelles dataset in particular appeared to be a significant outlier group relative to the Juelich and Oslo datasets. *ALPS* = *Diffusion Along the Perivascular Space*, *ChPV* = *Choroid Plexus Volume*, *FWI* = *Free Water Index*, *NS* = *Normal Sleep*, *PVSV* = *Perivascular Space Volume*, *SD* = *Sleep Deprivation*, *SR* = *Sleep Restriction*.

Pairwise comparisons of the EMMs showed no substantial change in significance or direction for ChPV and the ALPS index. A modest shift was observed in the PVSV, where the contrast between NS and SD, previously marginally significant, became fully significant ($\Delta = -.33$, $p < .001$). The most notable change occurred in FWI, where all pairwise contrasts reached high significance: SR vs. BL ($\Delta = -.87$, $p < .001$), SD vs. BL ($\Delta = .48$, $p < .001$), and SD vs. SR ($\Delta = -.33$, $p < .001$). These changes are likely confounded by site and should thus be interpreted with caution. All findings are summarized in **Fig. 4.5**.

4.2.9 Glymphatic Impairment Increases with Age

The RLME model further revealed a strong, positive relationship between age and glymphatic impairment ($\beta = .03$, $t = -3.44$, $p < .001$), suggesting that older participants tended to exhibit greater alterations across glymphatic indices. This relationship remained robust in sensitivity analyses.

4.2.10 No Sex Differences in Glymphatic Impairment

In spite of the observed sex imbalance at baseline (**Table 4.1**), sex was not associated with significant glymphatic alterations at any level of analysis.

4.2.11 Site-Specific Differences in Glymphatic Changes

To evaluate site-level differences in vulnerability to glymphatic disruption following sleep disturbance, we conducted a post hoc analysis of variance (ANOVA) with change in glymphatic system index (ΔGSI) as the DV and both scanning site and

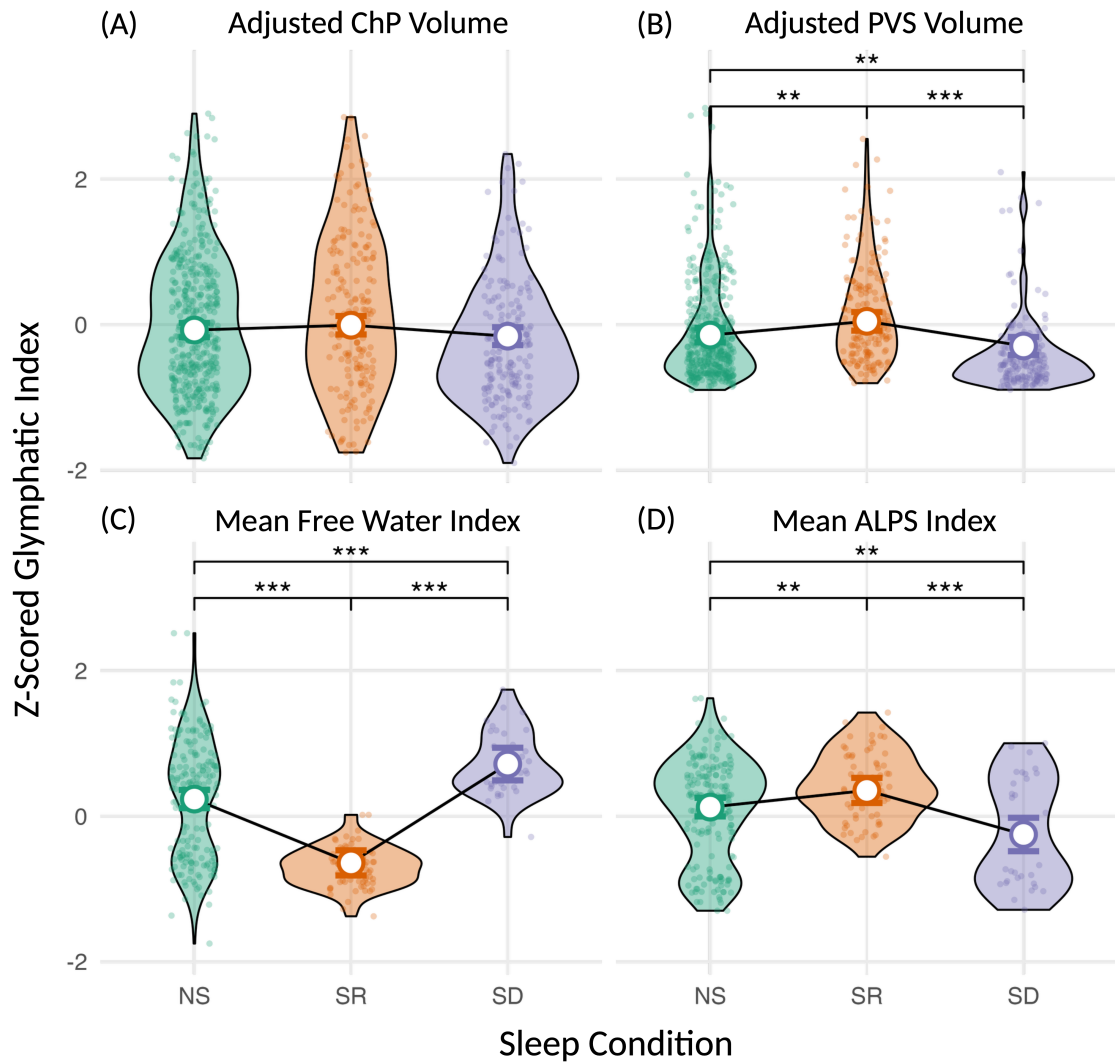


Fig. 4.5: Sensitivity Analyses. Estimated marginal means of glymphatic indices at NS, SR, and SD after excluding the outlier site (Bruxelles). **(A)** ChPV results did not change. **(B)** PVSV increases in SR and reductions in SD became more pronounced. **(C)** FWI remained reduced in SR, but showed a marked increase in SD. **(D)** ALPS increases in SR and reductions in SD became more pronounced. *ALPS = Diffusion Along the Perivascular Space*, *ChPV = Choroid Plexus Volume*, *FWI = Free Water Index*, *NS = Normal Sleep*, *PVSV = Perivascular Space Volume*, *SD = Sleep Deprivation*, *SR = Sleep Restriction*.

index type as the IVs. The analysis revealed a significant main effect of site ($F(8, 1023) = 2.21$, $p = .025$), indicating that the magnitude of observed glymphatic change was not uniform across datasets. A significant main effect of index type ($F(3, 1023) = 3.92$, $p = .008$) further confirmed that glymphatic indices differed in their perturbation after sleep disturbance.

As illustrated in **Fig. 4.6**, these effects reflected a gradient across sites, with some (e.g., Montreal) showing positive mean Δ GSI values consistent with glymphatic impairment, while others (e.g., Oslo) showed mean decreases suggestive of increased glymphatic activity or alternative, non-glymphatic sources of structural changes, such as microstructural or vascular alterations. These findings broadly align with outcomes of the site-corrected RLME model.

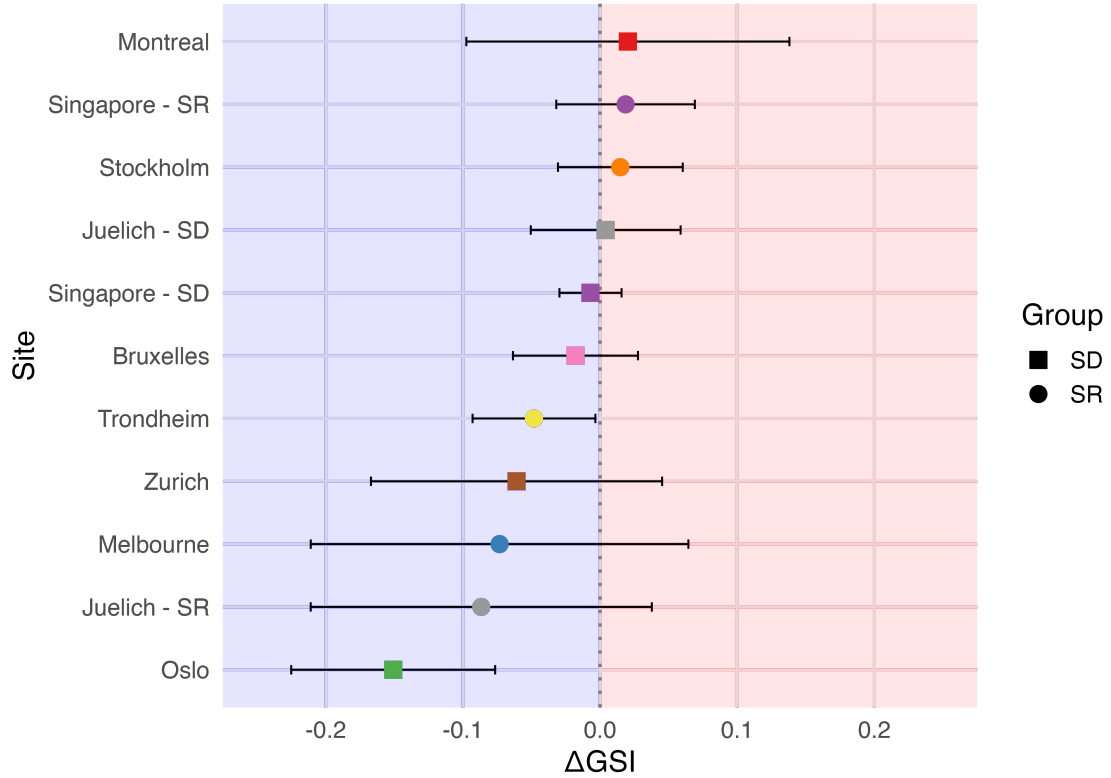


Fig. 4.6: Site-specific glymphatic changes. Mean changes in glymphatic system indices (ΔGSI) are shown for each scanning site. Positive ΔGSI values, interpreted as indicative of glymphatic impairment, are highlighted in red. Negative ΔGSI values are highlighted in blue. Sites differed significantly in ΔGSI ($p = .025$). Non-overlapping CIs indicate significance. $\Delta GSI = \text{Change in Normalized Glymphatic System Index}$, $SD = \text{Sleep Deprivation}$, $SR = \text{Sleep Restriction}$.

4.2.12 No Association Between Deprivation Length and Glymphatic Impairment

To assess whether the duration of sleep disturbance was associated with increased glymphatic abnormality, we fit a post hoc linear model taking ΔGSI as the DV and sleep deprivation duration (see **Table 4.1**) as the IV. Although some trends were observed between sites, the relationship was ultimately non-significant. More complex models might better predict the relationship between sleep disturbance duration and glymphatic index changes.

4.3 Discussion

This chapter investigated the effect of experimental sleep disturbance on four glymphatic indices: the ChPV, PVS_V, FWI, and ALPS index. It found that total sleep deprivation was linked to increased glymphatic system dysfunction, whereas partial sleep restriction exhibited equal and opposite effects. To wit, SD was primarily associated with reduced ALPS and PVS_V, while SR instead exhibited increased ALPS and reduced FWI. The following section examines each of these findings in detail and considers their implications in the context of existing literature.

4.3.1 Glymphatic Impairment

The defining feature of glymphatic function is arguably AQP4-mediated transport of CSF across the glia limitans [8]. Indeed, most well-known examples of glymphatic impairment are characterized by a loss or reduction of AQP4 function [110, 209]. Genetic risk factors for waste clearance impairments commonly affect the structure or localization of AQP4 channels [79, 210, 211]. A study by Simon et al. [110] found that in AQP4 knockout mouse models, the absence of AQP4-mediated transposition leads to PVS enlargement and reduced diffusion within the parenchyma and along large-caliber draining veins. These findings parallel observations in humans with neurological disorders marked by impaired waste clearance, such as AD [16, 17, 212]. Recent work by Li et al. [213] further suggests that such impairments are often accompanied by compensatory increases in ChPV to offset reduced glymphatic flow and efflux. Together, these findings support a model of glymphatic impairment in which ChP and PVS enlargement, alongside white matter and perivenous diffusion alterations, serve as important indicators of dysfunction.

The present study constructed a composite index from four key MRI-derived markers to capture glymphatic dysfunction non-invasively along a unified axis. It found that SD participants trended towards elevated values suggestive of glymphatic impairment, while SR participants trended towards values suggestive of heightened glymphatic activity. Sensitivity analyses confirmed the robustness of these findings. Moreover, the strong positive correlation between age and the composite index aligns with established evidence regarding age-related changes in glymphatic function [120]. Nevertheless, the lack of consistent alterations across all indices indicates that the observed effects are unlikely to represent systemic glymphatic dysfunction.

4.3.2 PVS Volume Alterations and Implications

The PVS surrounding cerebral arteries play a critical role in central nervous system immune surveillance and the regulation of CSF dynamics [214]. PVS enlargement is a well-established marker of aging and is frequently observed in disorders characterized by waste clearance impairments, such as small vessel disease and neurodegenerative disorders [60, 215]. Factors hypothesized to contribute to PVS enlargement include arterial stiffening, accumulation of waste proteins, and CSF/ISF imbalances [214]. Although PVS enlargement is typically considered a marker of chronic neurovascular dysfunction, recent work by Brendstrup-Brix et al. [105] and Richmond et al. [216] suggests that PVSV may respond acutely to changes in CSF circulation and astrocytic AQP4 distribution, both which are sensitive to sleep states and circadian regulation [10, 217]. As such, the present study assessed PVSV as a marker of glymphatic dysfunction after experimental sleep disturbance.

Analyses within and between groups revealed a significant increase in PVSV following SR when compared to both NS and SD. Despite this, the estimated marginal mean of PVSV remained near-zero, implying the observed increase may be driven by unusually low volumes at baseline and in the SD group. Several explanations may account for this. One possibility is that reductions in AQP4-mediated transposition, which may increase PVSV, are counteracted by decreased CSF production and inflow during sleep deprivation, as these phenomena are driven by rhythmic neural activity and arterial pulsatility characteristic of slow-wave sleep [8, 218]. Another explanation may be the overall reduction in brain volume typically associated with prolonged SD. Although PVSV in our study was normalized using the average ICV across sessions, this adjustment was applied after segmentation. A reduced ICV

may lower the detectability of smaller PVS clusters on MRI scans, thus contributing to a lower total PVSV [219]. Future studies should correct for within-subject ICV differences at the statistical level when comparing PVS metrics across conditions.

It is also possible that reduced PVSV simply reflects efficient fluid exchange between the PVS and brain parenchyma. In the NS condition, this is consistent with the literature. In the SD group, this pattern might point to compensatory glymphatic activity. While some functions of sleep can be delayed or reduced, the need to clear metabolic waste persists even throughout sustained wakefulness. Indeed, the glymphatic system may remain active during wakefulness, especially during restful activities that encourage slow, rhythmic brain activity [220]. However, abnormalities observed in the diffusion indices appear incompatible with this theory.

4.3.3 Free Water Level Alterations and Implications

In dMRI, free water refers to extracellular water molecules that are not restricted by neural tissue and are able to diffuse freely, predominantly in the white matter. These isotropic components are typically corrected for in conventional diffusion tensor imaging, as they affect the accuracy of diffusion metrics [221]. Free water levels are often inversely correlated with fractional anisotropy, with both serving as important markers of aging and neurodegeneration [222, 223]. Recent studies suggest that elevated FWI values may be associated with reduced glymphatic activity [16, 224]. This hypothesis is conceptually sound, given that enhanced glymphatic flow would be expected to reduce extracellular free water content within the parenchyma. However, the relationship between glymphatic function and FWI, particularly in the context of sleep, remains to be fully elucidated.

The present study found a significantly lower FWI in the SR condition relative to the NS and SD conditions. This finding was complicated by considerable baseline variability across sites but remained robust in sensitivity analyses. FWI reductions are generally associated with enhanced glymphatic activity, which aligns with the elevated ALPS scores also observed in the SR condition. At the same time, significant FWI reductions may point to microstructural changes in the white matter, a possible consequence of acute sleep disruption [225]. As with PVS, FWI is responsive to fluctuations in CSF influx and ICV, although no notable changes in PVSV or ChPV were observed following SR. Since FWI incorporates data from two imaging modalities, it may be more vulnerable to scanner variability than single-modality indices. Future studies should employ more rigorous strategies to reduce scanner-related variance to ensure the reliability of FWI comparisons across sites.

4.3.4 ALPS Index Alterations and Implications

The ALPS index is a widely used MRI-derived measure of glymphatic function, based on water diffusion along perivenous pathways near the lateral ventricles [102]. Although it has frequently been associated with impaired waste clearance [16, 117, 152, 226], its localized nature limits its ability to capture system-wide glymphatic impairments. Moreover, it has been shown to be sensitive to white matter microstructural changes, which may confound its interpretation in the context of sleep disturbance [117]. In order to support inferences about glymphatic function, the current study assessed the ALPS index alongside multiple other glymphatic indices.

In accordance with recent findings by Saito et al. [227], subjects overwhelmingly demonstrated reduced ALPS values following SD. However, corresponding FWI in-

creases were only seen in sensitivity analyses. Although these findings may reflect glymphatic dysfunction, reduced CSF inflow remains a plausible alternative explanation and could likewise account for the diminished PVSV and marginally reduced ChPV observed in the SD group. Conversely, participants in the SR group showed elevated ALPS values accompanied by decreased FWI. While these metrics may remain sensitive to microstructural alterations, their combination with near-baseline PVSV reliably points to elevated glymphatic activity. Given that SR was implemented through delayed sleep onset, this pattern may represent a “sleep rebound” effect, where glymphatic clearance intensifies during sleep to compensate for earlier deficits. This theory is discussed in further detail below.

4.3.5 CSF Inflow and Glymphatic Impairment

In the SD group, the convergence of reduced ALPS and PVS metrics appears consistent with an acute reduction in CSF inflow. This theory remains plausible despite the lack of significant ChPV changes, as ChP enlargement typically only occurs in longer-term or pathological alterations, not acute shifts in CSF dynamics [228, 229]. Attenuated CSF inflow has frequently been used as a proxy of glymphatic dysfunction, given that it comprises the first step of the glymphatic system [9, 10, 230]. However, transient reductions in CSF inflow do not inherently imply a breakdown of glymphatic activity. Indeed, CSF exchange may still proceed via AQP4 channels and parenchymal transport mechanisms in spite of reduced volume. These transient decreases could even elicit later rebound effects, as potentially evidenced in the SR group. While long-term reductions in CSF inflow could lead to the buildup of neurotoxic waste proteins and eventually impair glymphatic function, the present study suggests that even after 40 hours of deprivation, symptoms of such a systemic shift are not apparent.

4.3.6 “Glymphatic Rebound”

Rebound effects are a common finding in sleep deprivation studies. Subjects often exhibit rebounds both in sleep length, with longer recovery sleep compared to baseline, and in sleep architecture, including slow-wave and REM activity [231, 232]. Importantly, REM rebound may occur even within the same night, after only a few hours of sleep restriction [233]. The SR group exhibited decreased FWI and increased ALPS alongside stable PVS and ChPV, indicating improved glymphatic function. Yet, prolonged wakefulness may not explain these changes, as the SD group did not exhibit comparable effects. Instead, we theorize that the brief period of sleep following restriction accounts for the observed increases in glymphatic activity. Similar to REM sleep, the glymphatic system plays a crucial role in maintaining brain homeostasis. It stands to reason, then, that it would exhibit similar rebounds after periods of sleep deprivation. Follow-up studies should investigate this hypothetical “glymphatic rebound” using direct assessments of glymphatic efflux, including dynamic contrast-enhanced MRI and CSF tracers.

4.3.7 Limitations

The present study had limitations. First, it featured a multi-site dataset with high variability across methodologies and outcomes. Although these differences were corrected for at the statistical level, some results were shown to remain sensitive to

site-based variability. Future studies could consider more rigorous methods of site correction, such as data harmonization [234], though such approaches may present with additional limitations [235]. Second, the study employed only indirect metrics of glymphatic function, which are more prone to confounding and artifacts. These limitations notwithstanding, such metrics remain useful, as they can be derived from standard clinical images and do not require the administration of invasive materials. Third, the present study did not incorporate objective measures of sleep quality, relying solely on subjective self-reports collected upon awakening. Including methods such as polysomnography or actigraphy could enhance the assessment of sleep quality and help rationalize the observed changes in glymphatic activity. Fourth, the present study did not include a recovery sleep condition to bolster between-subject comparisons. Finally, the present study did not control for time-of-day effects in the evaluation of glymphatic indices, as this aspect was beyond the scope of the current investigation. Future studies could use MRI metadata to account for circadian fluctuations in glymphatic activity.

4.4 Conclusion

This chapter presented evidence that glymphatic function was reduced following sleep deprivation, likely due to transient decreases in CSF influx associated with diminished slow-wave sleep. Conversely, it found that sleep restriction was linked to increased glymphatic function, possibly reflecting a rebound effect compensating for delayed sleep onset. Importantly, both phenomena appeared to be acute phenomena and did not indicate significant impairment of the glymphatic system.

Chapter 5

Predicting Longitudinal Alzheimer’s Disease Progression Using Sleep and Glymphatic Features.

This chapter explores the relationship between the glymphatic system and AD by investigating how glymphatic features can predict AD progression in a large, longitudinal dataset. It contains text from [3].

5.1 Introduction

Despite making up 2% of the average human body mass, the brain is responsible for 20% of its metabolic demands [236]. This astronomical rate of energy consumption is only offset by its corresponding waste production [43]. Many of these waste products are neurotoxic in large quantities, making waste clearance an essential component of brain homeostasis [17, 41, 43].

Alzheimer’s disease (AD) remains one of the most prevalent examples of waste clearance impairments leading to significant neurological dysfunction [14]. AD pathogenesis identifies two key biomarkers: the accumulation of $A\beta$ proteins leading to extraneuronal plaque formation, and the accumulation of p-tau proteins leading to the formation of neurofibrillary tangles. Crucially, this pathogenesis is directly counteracted by waste clearance processes, which remove the waste molecules from the CNS before they can aggregate and induce neuroinflammation [8].

A cavalcade of cognitive, genetic, and behavioral factors is known to contribute to the onset and progression of AD [14, 82, 83]. Poor sleep quality is one such factor, as it has been associated with increased biomarker burden, neurodegeneration, and reduced cognitive function in individuals along the AD continuum [53, 54]. Sleep is also a key driver of glymphatic activity and waste clearance [10, 11, 113]. As such, it has been hypothesized that sleep disturbances influence AD pathogenesis primarily through impairments in glymphatic function [120].

While several studies have shown that glymphatic impairments are flush along the AD continuum [15, 16, 99, 109], and some evidence has even been found of glymphatic impairments preceding AD pathological changes [17], the exact onset and role of glymphatic impairment in AD pathogenesis remains unclear. Consequently, predictive modeling approaches that integrate multiple glymphatic indices

and longitudinal AD biomarkers may be particularly well-suited to disentangle these complex interactions.

Machine learning (ML) has emerged as an invaluable tool for prognostic predictions within chronic disorders [237–239]. Indeed, these models have the capability to detect subtle effects that might otherwise go unnoticed by conventional analyses [239]. What is more, ML models trained on subject data may forecast the future trajectory of disorders, allowing for targeted interventions [164]. Automated ensemble models like AutoGluon improve predictive performance by integrating outputs from a variety of ML frameworks, which allows for more robust modeling of complex, multi-feature clinical datasets [163].

In this chapter, neuroimaging, biomarker, clinical, and demographic data were collected from a large longitudinal AD sample ($n = 337$; sessions = 3) comprised of subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Six linear and ensemble ML models were trained on these data to predict ATN status at the final visit [74] and evaluate the role of sleep and glymphatic features through ablative comparisons and SHapley Additive exPlanations (SHAP) [165].

5.2 Results

5.2.1 Participant Demographics

The main sample ($n = 337$) consisted of 154 female and 183 male participants with a mean age of 75.3 ± 7.0 years at baseline. Of these participants, 162 were cognitively normal (CN), 151 had mild cognitive impairment (MCI), and 24 had clinical AD. Comparing between the CN, MCI, and AD groups, individuals further along the AD continuum were generally older, more likely to be male, had fewer years of education, carried more APOE4 alleles, and exhibited a greater number of comorbidities (all $ps \leq .028$) (**Table 5.1**). Additionally, these individuals scored significantly worse on all clinical and cognitive assessments ($ps < .001$), and presented with higher Choroid Plexus Volumes (ChPV, $p < .001$), lower DTI-ALPS indices ($p < .012$), and lower Brain Clearance Rates (BCR, $p < .001$) (**Table 5.2**). Interestingly, no participants in the cohort had a Clinical Dementia Rating (CDR) of 2 (“Moderate Dementia”) or 3 (“Severe Dementia”), suggesting that individuals with more advanced AD were underrepresented. This pattern is consistent with the general distribution of ATN (amyloid-tau-neurodegeneration) categories, with a majority of cases being A β - and/or tau-positive but showing minimal neurodegeneration.

5.2.2 Brain Clearance Rate Marks Glymphatic Impairment

Given the lack of glymphatic indices measuring glymphatic clearance directly, the present study introduced the BCR, a novel index representing the rate of amyloid clearance from the central nervous system (CNS) to peripheral regions (**Fig. 5.1**). The BCR showed robust agreement with established predictors of glymphatic dysfunction, including age, adjusted PVSF, and adjusted ChPV (**Fig. 5.2A**). Furthermore, it showed a strong negative correlation with AD pathogenesis, declining sharply in the preclinical stage (**Fig. 5.2B**). In contrast, the largest alterations in ChPV and DTI-ALPS occurred later, between the prodromal and clinical stages. Taken together, these results support the BCR as both a potential marker of glymphatic dysfunction and a predictor of cognitive decline.

Label	Levels	CN	MCI	AD	Total	p-value
Total N (%)		162 (48.1)	151 (44.8)	24 (7.1)	337 (100)	
Age		74.6 (6.4)	75.5 (7.6)	78.8 (6.8)	75.3 (7.0)	0.022*
Sex	Male	75 (46.3)	94 (62.3)	14 (58.3)	183 (54.3)	0.017*
	Female	87 (53.7)	57 (37.7)	10 (41.7)	154 (45.7)	
Education		16.6 (2.3)	16.3 (2.7)	15.1 (2.9)	16.3 (2.6)	0.028*
Marital Status	Married	129 (79.6)	117 (77.5)	19 (79.2)	265 (78.6)	0.124
	Widowed	9 (5.6)	11 (7.3)	5 (20.8)	25 (7.4)	
	Never Married	6 (3.7)	6 (4.0)	0 (0.0)	12 (3.6)	
	Divorced	18 (11.1)	15 (9.9)	0 (0.0)	33 (9.8)	
Ethnicity	Not Hispanic	149 (92.0)	144 (95.4)	21 (87.5)	314 (93.2)	0.117
	Hispanic	12 (7.4)	7 (4.6)	2 (8.3)	21 (6.2)	
APOE4 Status	Non-Carrier	102 (63.0)	79 (53.7)	10 (45.5)	191 (57.7)	<.001****
	Heterozygous	58 (35.8)	52 (35.4)	7 (31.8)	117 (35.3)	
	Homozygous	2 (1.2)	16 (10.9)	5 (22.7)	23 (6.9)	
Medical History	Psychiatric	4 (2.5)	15 (9.9)	3 (12.5)	22 (6.5)	<.001****
	Neurological	4 (2.5)	16 (10.6)	1 (4.2)	21 (6.2)	
	Head/Ears/Nose/Throat	8 (4.9)	21 (13.9)	3 (12.5)	32 (9.5)	
	Cardiovascular	7 (4.3)	27 (17.9)	2 (8.3)	36 (10.7)	
	Respiratory	4 (2.5)	14 (9.3)	1 (4.2)	19 (5.6)	
	Hepatic	2 (1.2)	2 (1.3)	0 (0.0)	4 (1.2)	
	Dermatologic	5 (3.1)	13 (8.6)	3 (12.5)	21 (6.2)	
	Musculoskeletal	8 (4.9)	29 (19.2)	3 (12.5)	40 (11.9)	
	Endocrine	7 (4.3)	28 (18.5)	0 (0.0)	35 (10.4)	
	Gastrointestinal	9 (5.6)	23 (15.2)	3 (12.5)	35 (10.4)	
	Hematologic	4 (2.5)	4 (2.6)	1 (4.2)	9 (2.7)	
	Renal-Genitourinary	6 (3.7)	18 (11.9)	2 (8.3)	26 (7.7)	
	Alcohol	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	
	Drug Use	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.6)	
	Smoking	3 (1.9)	17 (11.3)	2 (8.3)	22 (6.5)	

Table 5.1: Demographics stratified by diagnosis. Values were averaged across sessions and presented as means with standard deviations or counts with percentages. Comparisons were conducted using t-tests for continuous and chi-squared tests for categorical/ordinal variables. Significant differences are highlighted in bold. *AD = Alzheimer's Disease, APOE4 = Apolipoprotein E4, CN = Cognitively Normal, MCI = Mild Cognitive Impairment.*

		CN	MCI	AD	Total	<i>p</i> -value
Total N (%)		162 (100)	151 (100)	24 (100)	337 (100)	
ADAS		8.7 (5.0)	16.8 (8.0)	29.8 (7.9)	13.8 (8.9)	<.001****
CDR	No Dementia	39 (86.7)	10 (18.5)	0 (0.0)	49 (46.2)	<.001****
	Very Mild Dementia	6 (13.3)	42 (77.8)	2 (28.6)	50 (47.2)	
	Mild Dementia	0 (0.0)	2 (3.7)	5 (71.4)	7 (6.6)	
FAQ		0.5 (1.2)	3.7 (4.5)	15.6 (7.7)	3.0 (5.3)	<.001****
GDS		1.3 (1.6)	2.0 (1.7)	3.5 (3.3)	1.8 (1.9)	<.001****
MMSE		29.0 (1.2)	27.2 (2.5)	22.2 (3.7)	27.7 (2.7)	<.001****
NPI-K		0.5 (1.2)	1.0 (1.5)	1.5 (2.2)	0.8 (1.5)	<.001****
ATN Status	A-T-N- (Normal)	106 (65.8)	76 (50.3)	7 (30.4)	189 (56.4)	<.001****
	A+T-N- (Preclinical AD)	32 (19.9)	22 (14.6)	5 (21.7)	59 (17.6)	
	A-T+N- (Non-AD Pathology)	9 (5.6)	14 (9.3)	0 (0.0)	23 (6.9)	
	A-T-N+ (Non-AD Pathology)	1 (0.6)	7 (4.6)	3 (13.0)	11 (3.3)	
	A+T+N- (Prodromal AD)	11 (6.8)	31 (20.5)	5 (21.7)	47 (14.0)	
	A-T+N+ (Non-AD Pathology)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	A+T-N+ (AD/Concomitant Non-AD)	1 (0.6)	0 (0.0)	1 (4.3)	2 (0.6)	
	A+T+N+ (Clinical AD)	1 (0.6)	1 (0.7)	2 (8.7)	4 (1.2)	
PVSV		3303.5 (1871.9)	3321.7 (1960.2)	3022.2 (1854.2)	3291.6 (1906.7)	0.771
ChPV		793.8 (200.7)	863.9 (203.9)	923.5 (174.9)	834.5 (204.2)	<.001****
DTI-ALPS		1.3 (0.1)	1.3 (0.2)	1.2 (0.1)	1.3 (0.2)	0.012*
CSF Aβ42		1121.8 (331.6)	835.2 (307.4)	706.5 (394.5)	923.2 (354.0)	<.001****
AV45 SUVR		1.1 (0.2)	1.2 (0.2)	1.3 (0.2)	1.2 (0.2)	<.001****
BCR		1255.8 (441.1)	856.0 (505.8)	591.9 (465.8)	996.9 (523.7)	<.001****

Table 5.2: Clinical outcomes stratified by diagnosis. Values were averaged across sessions and presented as means with standard deviations or counts with percentages. Comparisons were conducted using t-tests for continuous and chi-squared tests for categorical/ordinal variables. Significant differences are highlighted in bold. $A\beta 42$ = Amyloid Beta 42, AD = Alzheimer's Disease, ADAS = Alzheimer's Disease Assessment Scale, ATN = Amyloid-Tau-Neurodegeneration, AV45 = ^{18}F -Florbetapir, BCR = Brain Clearance Rate, CDR = Clinical Dementia Rating, ChPV = Choroid Plexus Volume, CN = Cognitively Normal, CSF = Cerebrospinal Fluid, FAQ = Functional Activities Questionnaire, GDS = Geriatric Depression Scale, MMSE = Mini-Mental State Examination, MCI = Mild Cognitive Impairment, NPI = Neuropsychiatric Inventory, PVSV = Perivascular Space Volume, SUVR = Standardized Uptake Value Ratio.

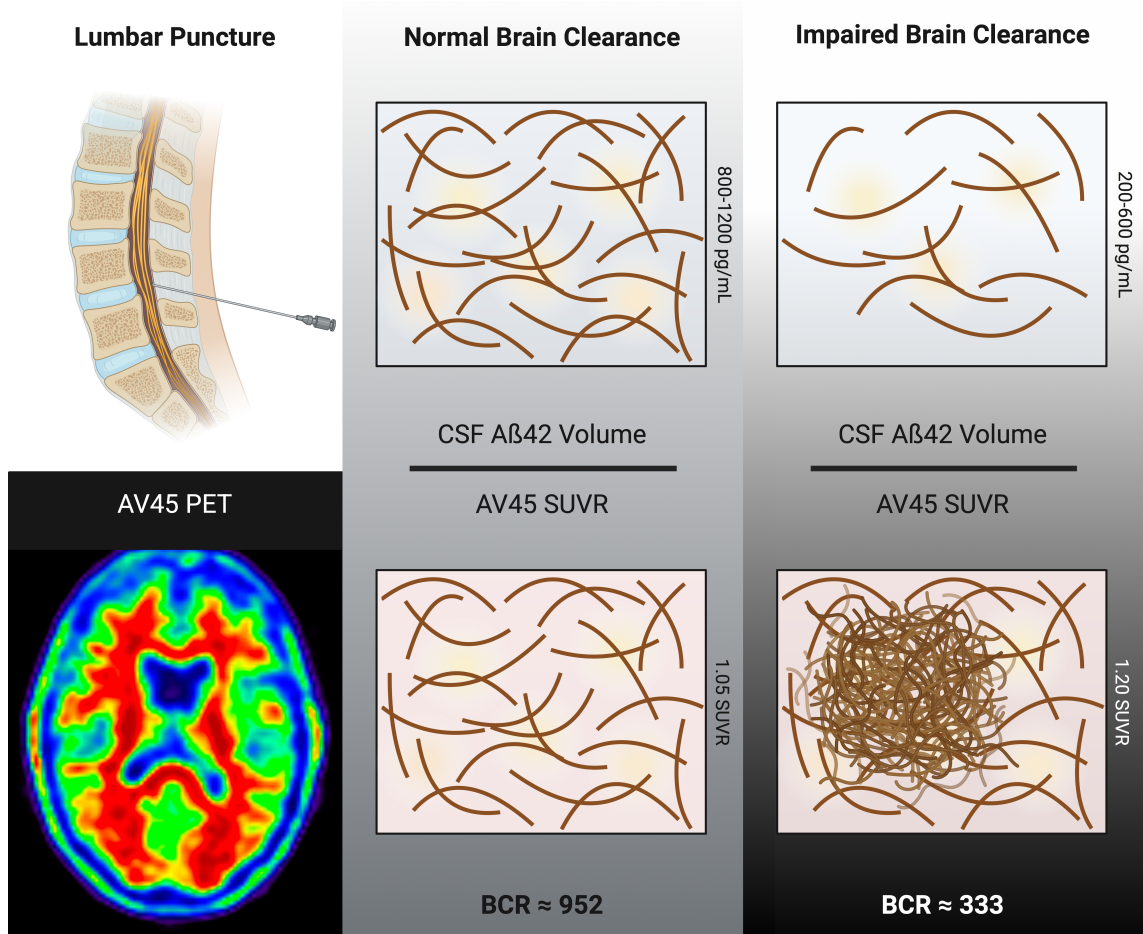


Fig. 5.1: Calculation of the BCR, defined as the ratio of CSF Aβ42 volume in the lumbar region to AV45 SUVR in the brain, reflecting glymphatic clearance efficiency. Reduced BCR indicates impaired clearance due to plaque deposition and glymphatic dysfunction in AD. Reference values for CSF Aβ42 and AV45 SUVR were taken from [240] and [241]. The PET image shown is from ADNI subject 002S0413. *Aβ42* = Amyloid Beta 42, *AD* = Alzheimer's Disease, *ADNI* = Alzheimer's Disease Neuroimaging Initiative, *AV45* = ¹⁸F-Florbetapir, *BCR* = Brain Clearance Rate, *CSF* = Cerebrospinal Fluid, *PET* = Positron Emission Tomography

5.2.3 AutoGluon Outperforms Baseline Models

The present study initially trained six multiclass prediction models, comprising L1 and L2 logistic regressions as well as AutoGluon ensembles, each evaluated with and without glymphatic features. The full feature set is shown in **Table 2.6**. L2 logistic regression demonstrated superior performance relative to L1 across all evaluation metrics, while AutoGluon further exceeded L2 performance (**Table 5.3**). The best-performing model was **Model 5**, the AutoGluon ensemble without glymphatic features (Accuracy = 0.87, MCC = 0.79). Within the AutoGluon framework, a bagged L2 NeuralNetFastAI and an L3 weighted ensemble achieved the strongest validation scores, whereas L1 XGBoost models ranked slightly lower, indicating that cross-model stacking outperforms single-algorithm ensembles (**Table 5.4**). Inclusion of NPI-K, PVSF, ChPV, DTI-ALPS, and BCR features resulted in a marginal decline in performance for L2 and AutoGluon models, but caused a substantial drop in performance in the L1 model.

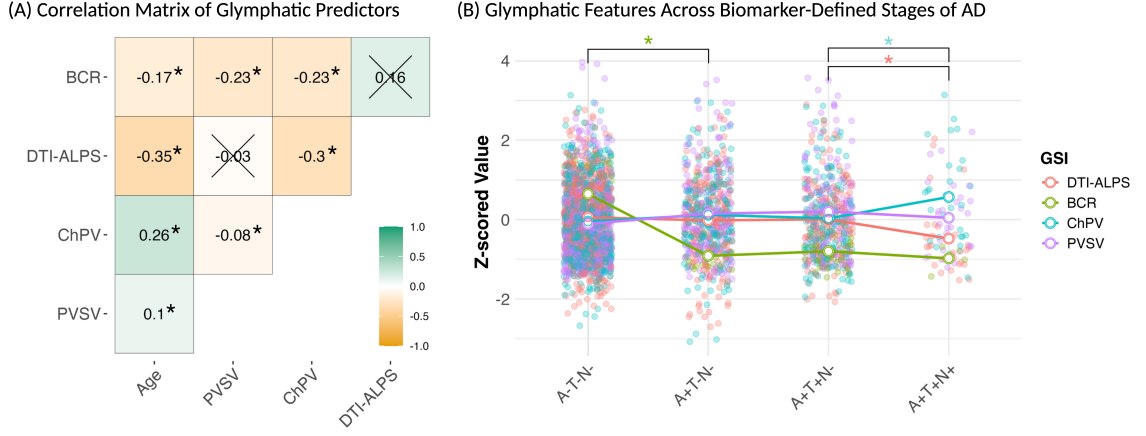


Fig. 5.2: Glymphatic Dysfunction Across Alzheimer's Disease Stages. (A) Correlation matrix of glymphatic markers, including the BCR. The BCR negatively correlated with PVSV, ChPV, and age, but not with DTI-ALPS; PVS and DTI-ALPS also showed no association. (B) Z-scored glymphatic indices across ATN-defined AD stages. The BCR declined significantly in the preclinical stage, while other indices decreased mainly between the prodromal and clinical stages. $*p < .05$. AD = Alzheimer's Disease, ATN = Amyloid-Tau-Neurodegeneration, BCR = Brain Clearance Rate, ChPV = Choroid Plexus Volume, DTI-ALPS = Diffusion Tensor Imaging Along the Perivascular Space, PVSV = Perivascular Space Volume

5.2.4 AD Stage Prediction Across Models

All six models were evaluated on their ability to classify key AD stages: biologically normal (A-T-N-), preclinical (A+T-N-), prodromal (A+T+N-), and clinical (A+T+N+). One-vs-rest ROC curves showed consistently high areas under the curve (AUCs) for all models and classes (AUCs ≥ 0.91), except for **Model 2**, whose performance trended lower (AUCs ≥ 0.71) but remained above chance (**Fig. 5.3**). Inclusion of glymphatic features boosted AutoGluon's performance for the biologically normal and preclinical stages (**Model 5**: AUCs ≥ 0.91 , **Model 6**: AUCs ≥ 0.95). Several baseline models, however, outperformed it on preclinical predictions (AUCs ≥ 0.97). Prodromal and clinical classes were consistently predicted with near-perfect accuracy, possibly due to class imbalances in the dataset, as seen in **Table 5.2**.

5.2.5 Explaining Model Classifications

SHAP was used to quantify the relative contribution of features across scanning sessions (s_1 , s_2 , s_3) to ATN status prediction at the final session. For the baseline logistic models, ADAS scores from s_2 and s_3 yielded the highest mean absolute SHAP values, followed by participant age (s_1 , s_2) and FAQ scores (s_2). **Model 2**, which demonstrated reduced classification performance overall, assigned disproportionately high attribution to BCR at s_1 and s_2 . In stark contrast, AutoGluon ensembles demonstrated a concentrated attribution pattern dominated by ATN status (s_1 , s_2), indicative of a heavy dependence on prior biomarker states rather than cognitive or clinical features. Medical history of neurological disorders (s_1), participant age (s_3), and BCR (s_1) provided marginal contributions to predictions, with the latter primarily informing the classification of prodromal ATN subtypes (A+T+N-). Of all other sleep-related and glymphatic features, only the total NPI-K score had a noticeable impact on predictions. These findings are summarized in **Fig. 5.4-Fig. 5.6**.

Model	Type	Feature Set	Accuracy	MCC	F1	Precision	Recall
Baseline							
Model 1	Logistic Regression (L1)	Control	0.83	0.74	0.82	0.84	0.83
Model 2	Logistic Regression (L1)	+Glymphatic	0.58	0.28	0.51	0.50	0.58
Model 3	Logistic Regression (L2)	Control	0.84	0.74	0.82	0.82	0.84
Model 4	Logistic Regression (L2)	+Glymphatic	0.82	0.72	0.81	0.83	0.82
Main							
Model 5	AutoGluon Ensemble	Control	0.87	0.79	0.86	0.88	0.87
Model 6	AutoGluon Ensemble	+Glymphatic	0.86	0.79	0.86	0.86	0.87
Post Hoc							
Model 7	AutoGluon Ensemble	-ATN1/2	0.45	0.10	0.41	0.38	0.45
Model 8	AutoGluon Ensemble	-ATN1/2, +Glymphatic	0.63	0.39	0.53	0.58	0.63
Model 9	AutoGluon Ensemble	+BCR	0.88	0.80	0.86	0.87	0.87

Table 5.3: Classification model performance metrics. Six models were trained on the feature set in **Table 2.6**. Baselines included L1- and L2-regularized logistic regressions with 8-fold CV. AutoGluon ensembles formed the main predictive framework. Ablation tests compared models with and without glymphatic features. Two additional models excluded session 1 and 2 ATN status for post hoc analysis. The final post hoc model only included the BCR. Best metrics for each category are highlighted in bold. *ATN = Amyloid-Tau-Neurodegeneration, ATN1/2 = ATN status for sessions 1 and 2, BCR = Brain Clearance Rate, CV = Cross-Validation, MCC = Matthews Correlation Coefficient.*

Model	Score	Evaluation Metric	Prediction Time	Fit Time	Stack Level	Fit Order
<i>NeuralNetFastAI r37 BAG L2</i>	0.950382	Accuracy	0.627800	24.341146	2	160
<i>WeightedEnsemble L3</i>	0.950382	Accuracy	0.628314	24.397050	3	218
<i>XGBoost r31 BAG L1</i>	0.946565	Accuracy	0.038726	1.156838	1	75
<i>WeightedEnsemble L2</i>	0.946565	Accuracy	0.039238	1.212169	2	109
<i>NeuralNetFastAI r160 BAG L2</i>	0.946565	Accuracy	0.611999	22.392167	2	186
<i>XGBoost r98 BAG L1</i>	0.942748	Accuracy	0.039518	1.206582	1	47
<i>NeuralNetTorch r89 BAG L1</i>	0.942748	Accuracy	0.133171	4.197195	1	108
<i>NeuralNetTorch r135 BAG L1</i>	0.942748	Accuracy	0.133312	3.969885	1	95
<i>NeuralNetTorch r158 BAG L1</i>	0.942748	Accuracy	0.133600	4.113188	1	49
<i>NeuralNetTorch r30 BAG L1</i>	0.942748	Accuracy	0.135560	3.936125	1	28
<i>NeuralNetTorch r143 BAG L1</i>	0.942748	Accuracy	0.138313	4.400857	1	60
<i>LightGBM r143 BAG L2</i>	0.942748	Accuracy	0.552602	21.466810	2	164
<i>LightGBM r15 BAG L2</i>	0.942748	Accuracy	0.557988	21.652953	2	157
<i>NeuralNetFastAI r102 BAG L2</i>	0.942748	Accuracy	0.618231	23.128461	2	131
<i>NeuralNetFastAI BAG L2</i>	0.942748	Accuracy	0.619349	23.347825	2	110
<i>NeuralNetFastAI r145 BAG L2</i>	0.942748	Accuracy	0.620282	22.367144	2	135
<i>NeuralNetFastAI r187 BAG L2</i>	0.942748	Accuracy	0.625400	23.858509	2	211
<i>NeuralNetTorch r79 BAG L2</i>	0.942748	Accuracy	0.742058	22.926588	2	122
<i>XGBoost r22 BAG L1</i>	0.938931	Accuracy	0.038546	0.591995	1	81
<i>XGBoost r194 BAG L1</i>	0.938931	Accuracy	0.038791	0.712145	1	33

Table 5.4: AutoGluon leaderboard for ATN classification from **Model 6**. Stacked ensembles (BAG L2/L3; WeightedEnsemble) achieved the highest validation scores, whereas L1 XGBoost models performed slightly worse. This highlights the advantage of heterogeneous stacking over single-algorithm tree ensembles. *BAG = bagged model; L1–L3 = stacking levels.*

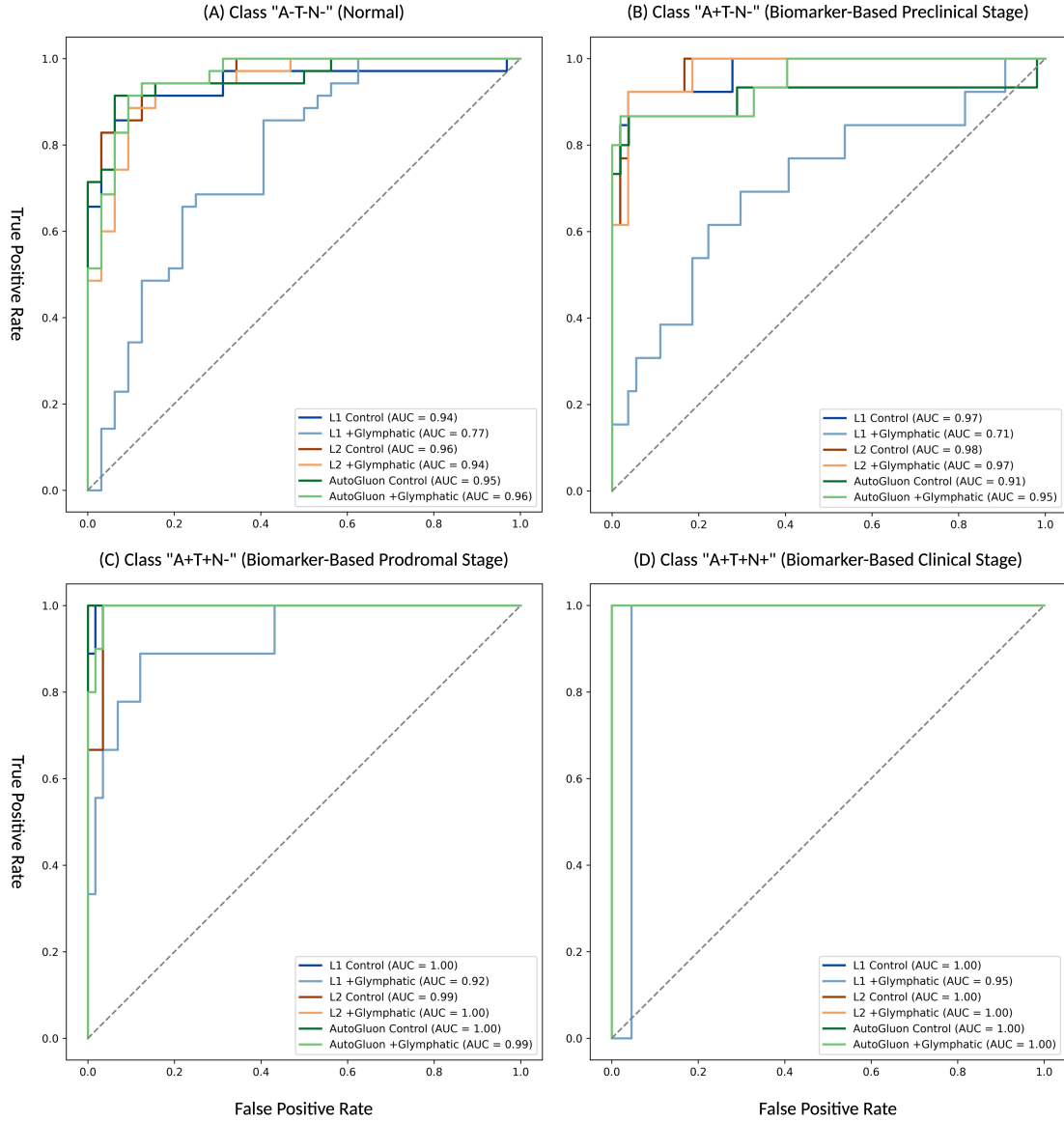


Fig. 5.3: One-vs-Rest ROC Curves for ATN Class Prediction. Each panel shows the performance of six models in predicting (A) A-T-N-, (B) A+T-N-, (C) A+T+N-, and (D) A+T+N+ status. AUCs are listed in the legend. AutoGluon outperformed baseline models for biologically normal classes, while baseline models exceeded AutoGluon for preclinical predictions. Predictions were near-perfect for prodromal and clinical stages. Glymphatic features generally improved AutoGluon performance. *ATN = Amyloid-Tau-Neurodegeneration, AUC = Area Under the Curve*

5.2.6 Post Hoc Models Excluding ATN Features

Given the finding that AutoGluon predictions relied almost entirely on earlier ATN measures, we trained two post hoc models (**Model 7** and **Model 8**) without ATN status at s_1 and s_2 . As expected, this restriction considerably reduced accuracy relative to both the baseline and main models (**Table 5.3**). However, the inclusion of glymphatic features produced a comparatively larger improvement, raising the prediction accuracy from 0.45 to 0.63. SHAP analysis highlighted strong contributions from APOE4 status, age, GDS scores, and MMSE scores in predicting ATN classes (**Fig. 5.7**). Including glymphatic measures shifted model reliance towards the BCR, particularly for classifying preclinical and prodromal stages.

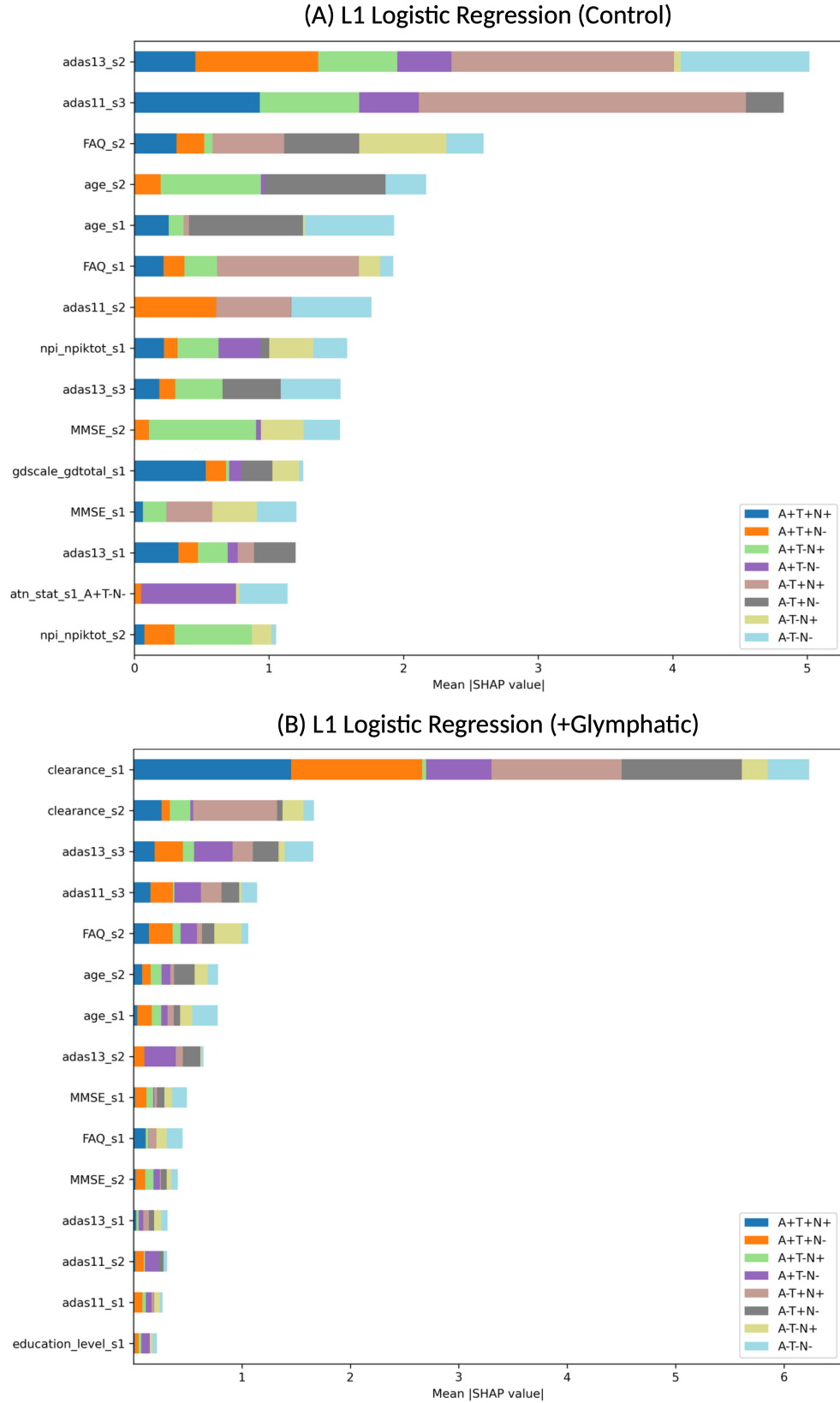


Fig. 5.4: Shapley's Additive Explanations of Model 1 & 2. Stacked bar plots of mean absolute SHAP values for ATN prediction at s_3 . Bars show the top 15 features ranked by average importance, with colors indicating class-specific contributions. L1 models prioritized ADAS, FAQ, and age, with the weaker +Glymphatic model additionally placing more weight on BCR. *ADAS11/13* = (11/13-point) Alzheimer's Disease Assessment Scale, *APOE4* = Apolipoprotein E4, *ATN* = Amyloid-Tau-Neurodegeneration, *FAQ* = Functional Activities Questionnaire, *GDS* = Geriatric Depression Scale Score, *MMSE* = Mini-Mental State Examination, *NPI-K* = Neuropsychiatric Inventory Domain K, $s_{1/2/3}$ = Session 1/2/3

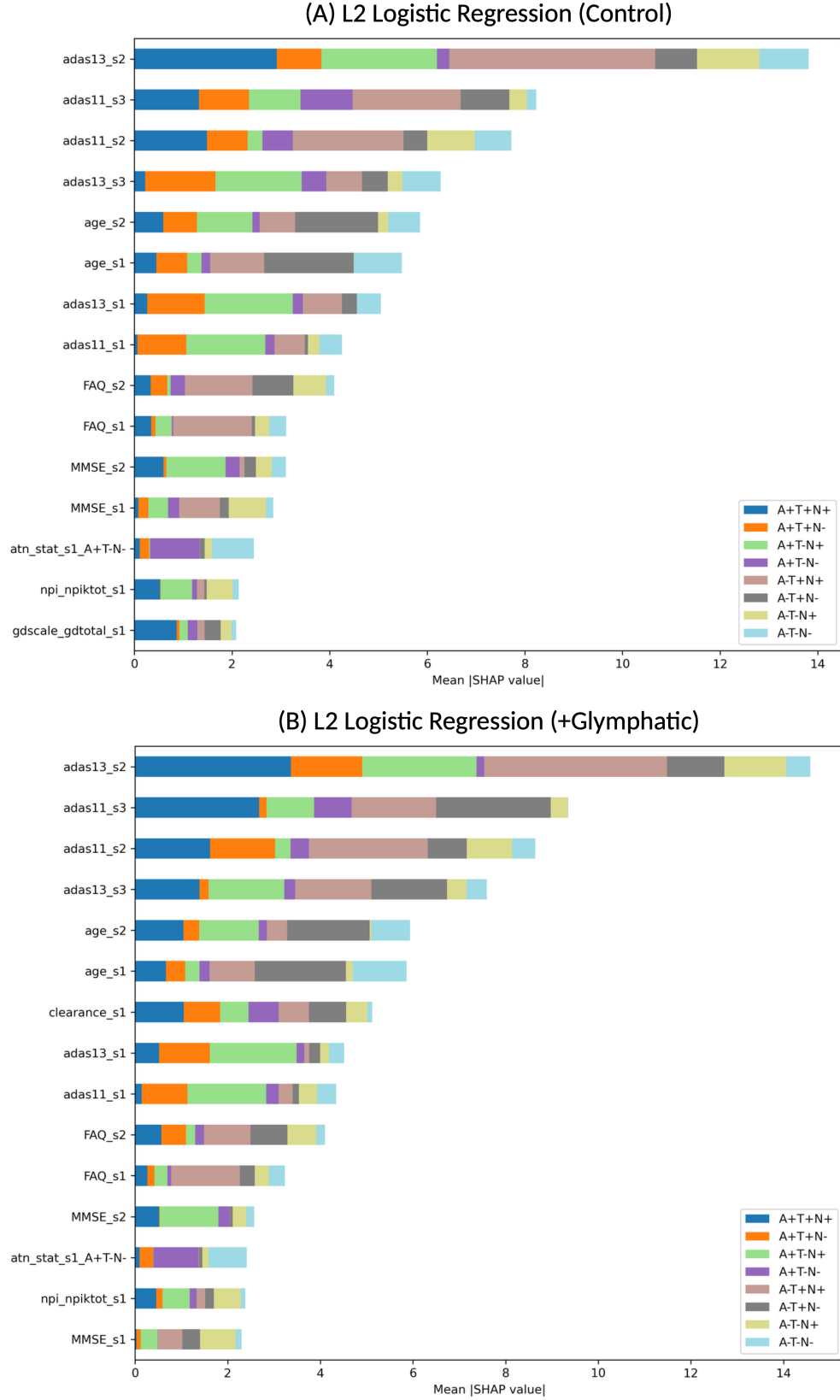


Fig. 5.5: Shapley's Additive Explanations of Model 3 & 4. Stacked bar plots of mean absolute SHAP values for ATN prediction at s_3 . L2 models prioritized ADAS, as well as age, FAQ, and BCR. *ADAS11/13 = (11/13-point) Alzheimer's Disease Assessment Scale*, *ATN = Amyloid-Tau-Neurodegeneration*, *FAQ = Functional Activities Questionnaire*, *GDS = Geriatric Depression Scale Score*, *MMSE = Mini-Mental State Examination*, *NPI-K = Neuropsychiatric Inventory Domain K*, $s_{1/2/3}$ = Session 1/2/3

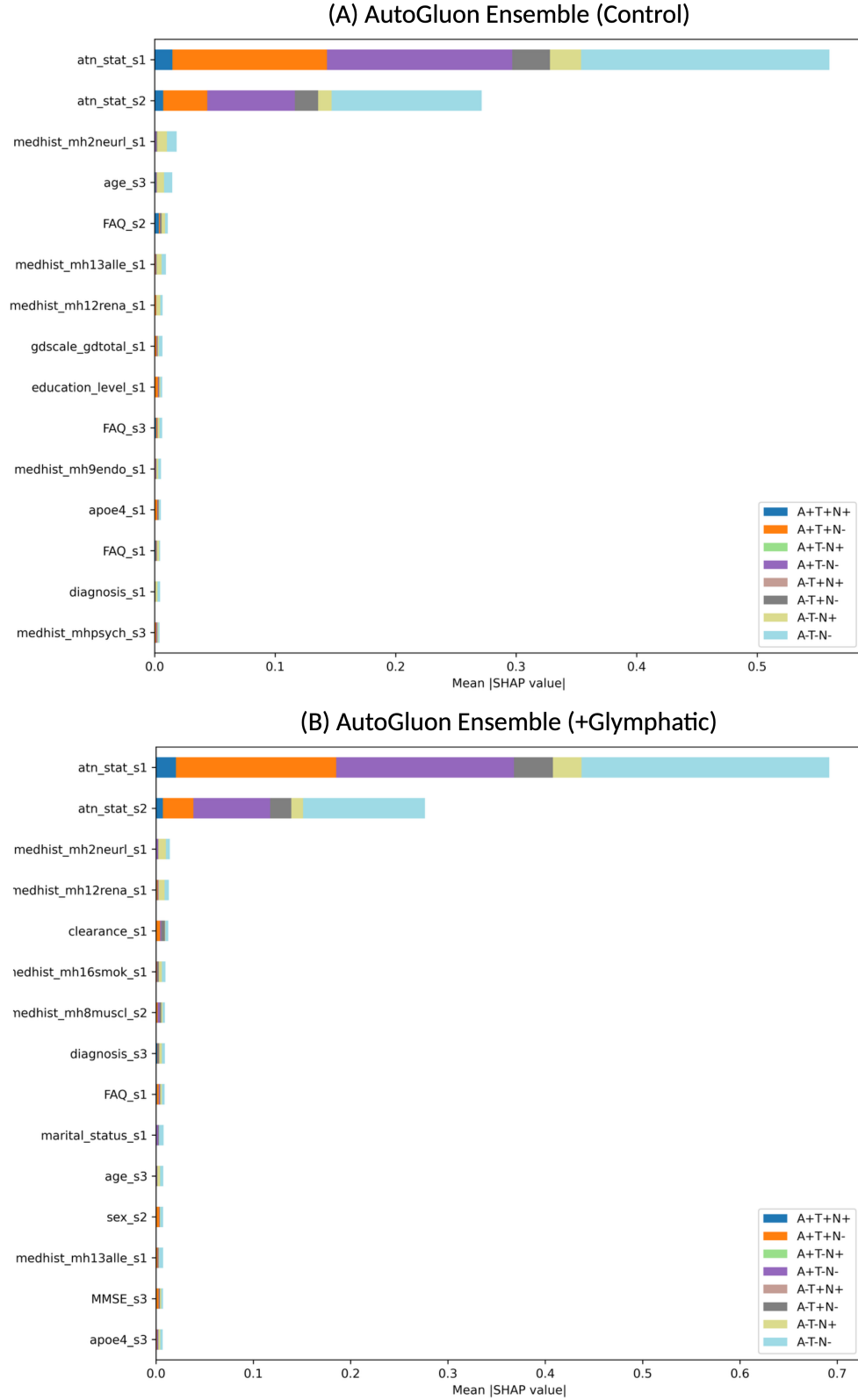


Fig. 5.6: Shapley's Additive Explanations of Model 5 & 6. Stacked bar plots of mean absolute SHAP values showing feature contributions to ATN status prediction at s_3 . AutoGluon placed substantial weight on earlier ATN status when forecasting later states. *APOE4* = Apolipoprotein E4, ATN = Amyloid-Tau-Neurodegeneration, FAQ = Functional Activities Questionnaire, GDS = Geriatric Depression Scale, MEDHIST = Medical History, MHPSYCH = Psychiatric Disorders, MH2NEURL = Neurological Disorders, MH8MUSCL = Musculoskeletal Disorders, MH9ENDO = Endocrine Disorders, MH12RENA = Renal-Genitourinary Disorders, MH13ALLE = Allergies, MH16SMOK = Smoking, MMSE = Mini-Mental State Examination, NPI-K = Neuropsychiatric Inventory Domain K, $s_{1/2/3}$ = Session 1/2/3

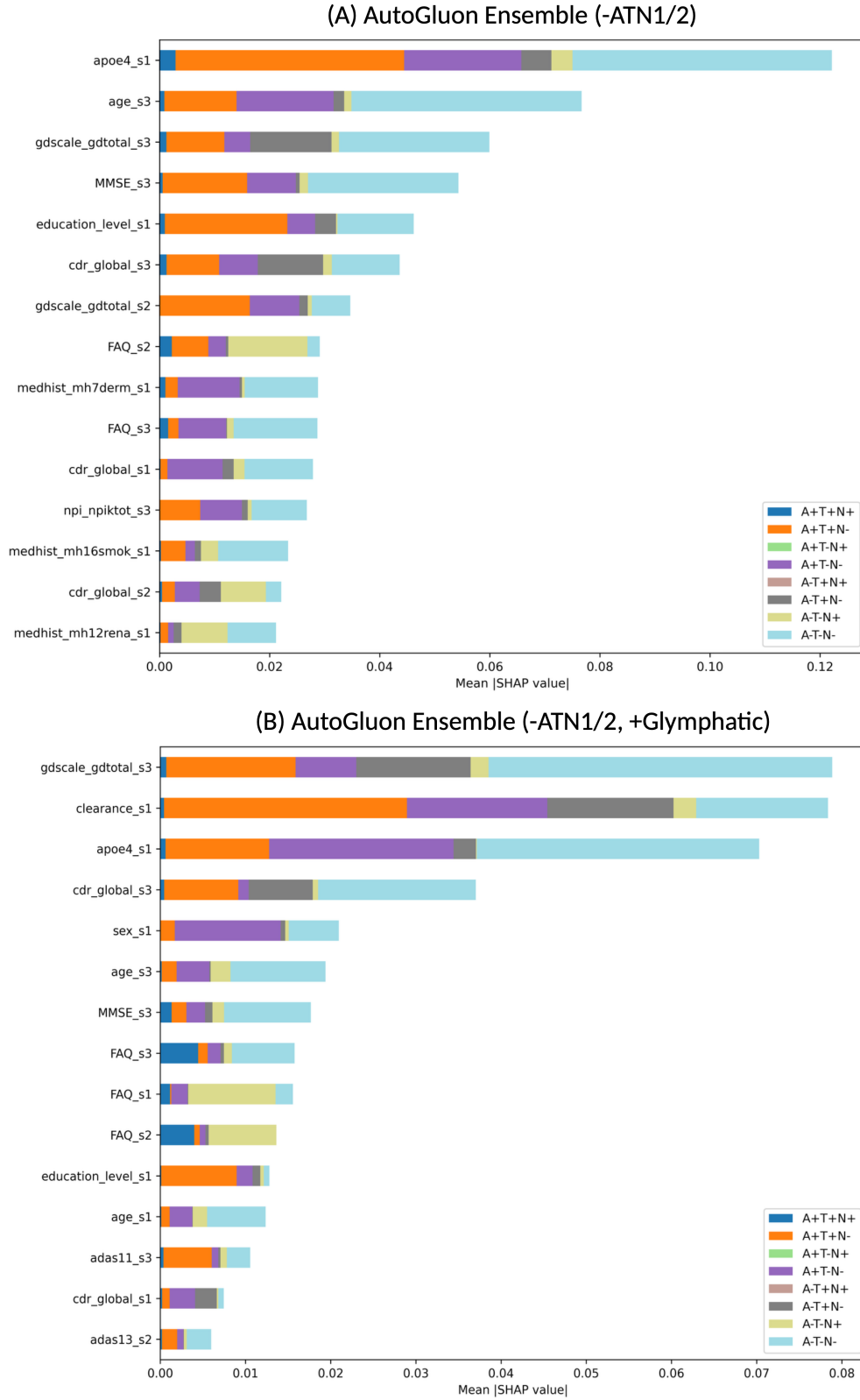


Fig. 5.7: Shapley's Additive Explanations of Model 7 & 8. Stacked bar plots of mean absolute SHAP values showing feature contributions to ATN status prediction at s_3 . The glymphatic model, which outperformed the non-glymphatic version, relied heavily on BCR for classifying preclinical and prodromal cases. *APOE4* = Apolipoprotein E4, *ATN* = Amyloid-Tau-Neurodegeneration, *FAQ* = Functional Activities Questionnaire, *GDS* = Geriatric Depression Scale, *MEDHIST* = Medical History, *MH7DERM* = Dermatological Disorders, *MH12RENA* = Renal-Genitourinary Disorders, *MH16SMOK* = Smoking, *MMSE* = Mini-Mental State Examination, *NPI-K* = Neuropsychiatric Inventory Domain K, $s_{1/2/3}$ = Session 1/2/3

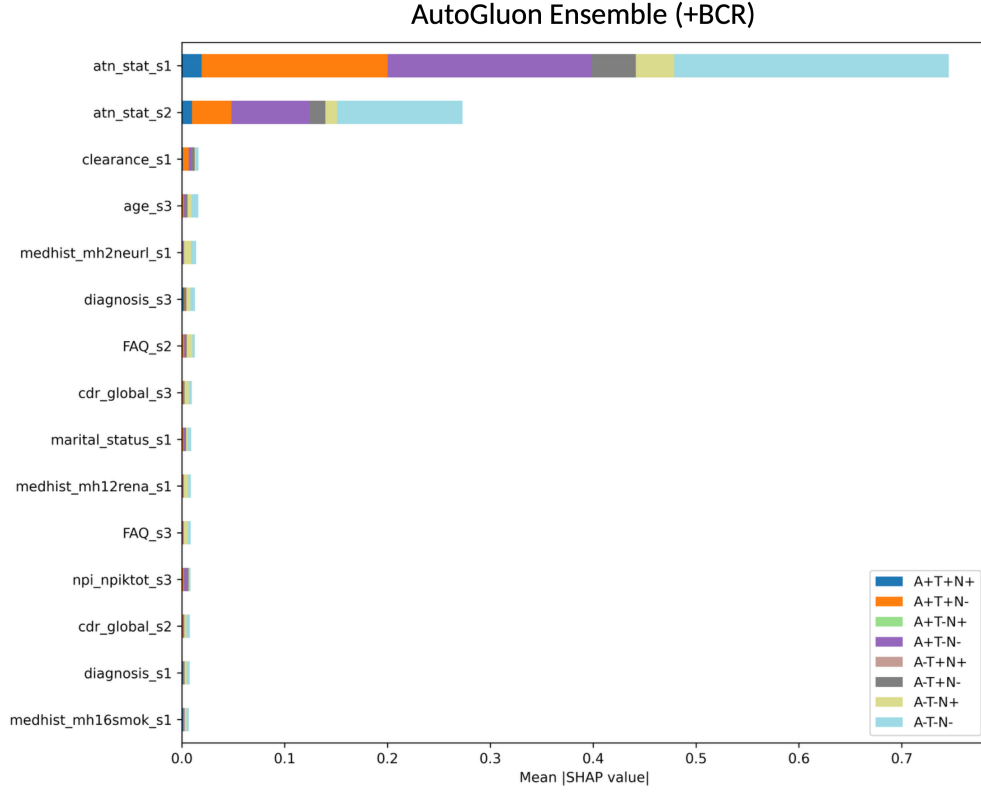


Fig. 5.8: Shapley’s Additive Explanations of Model 9. Stacked bar plots of mean absolute SHAP values showing feature contributions to ATN status prediction at s_3 . Although this model remained primarily dependent on ATN status, BCR contributed meaningfully to a subset of predictions. *APOE4* = Apolipoprotein E4, *ATN* = Amyloid-Tau-Neurodegeneration, *FAQ* = Functional Activities Questionnaire, *GDS* = Geriatric Depression Scale, *MEDHIST* = Medical History, *MH2NEURL* = Neurological Disorders, *MH12RENA* = Renal-Genitourinary Disorders, *MH16SMOK* = Smoking, *MMSE* = Mini-Mental State Examination, *NPI-K* = Neuropsychiatric Inventory Domain K, $s_{1/2/3}$ = Session 1/2/3

5.2.7 Post Hoc Model Excluding Glymphatic MRI Indices

Noting the consistent contribution of the BCR across models, a final post hoc model (**Model 9**) was trained with BCR as the sole glymphatic feature. Remarkably, this model outperformed all previous models (Accuracy = 0.88, MCC = 0.80). SHAP analysis indicated that ATN status remained the primary predictor, although BCR contributed meaningfully to classifying prodromal and preclinical cases (**Fig. 5.8**).

5.3 Discussion

This chapter investigated the impact of integrating glymphatic information, including the novel BCR index, into a set of predictors commonly used for modeling AD trajectories. It found that baseline linear models did not appreciably benefit from this data, while complex, ensemble approaches exhibited modest performance gains for classifying preclinical stages. The following sections examine each of these findings in detail and discuss their implications in the context of existing literature.

5.3.1 Glymphatic Impairment in AD

Glymphatic dysfunction is a robust finding in AD [16, 99]. However, the stage at which this dysfunction arises, as well as the role it plays in pathogenesis, remains

to be determined. This study found evidence of significant glymphatic impairment, represented by increased ChPV, decreased DTI-ALPS index, and decreased BCR, across clinical diagnoses and biomarker-defined disease stages. To wit, reductions in BCR were found to coincide with the onset of AD pathology in the preclinical stage, whereas alterations in ChPV and DTI-ALPS primarily occurred between the prodromal and clinical stages. This pattern is largely consistent with Huang et al. [17], who reported that early glymphatic changes preceded amyloid accumulation in preclinical AD. However, it appears to contradict findings by Kamagata et al. [16], who observed a more gradual decline of glymphatic indices across clinical diagnoses. This discrepancy could stem from differences in the operationalization of AD stages: indeed, our study observed more gradual changes across clinical stages, and more abrupt shifts across biomarker-defined stages.

The present study did not find any significant changes in the adjusted PVSV along the trajectory of AD. This finding contrasts prior work, where PVS enlargement is frequently described as a hallmark of AD pathology [16, 60, 99, 120, 242, 243]. A likely factor contributing to this inconsistency is the relative underrepresentation of participants with advanced AD in our sample. Indeed, the maximum CDR of our samples was 1, and prodromal (A+T+N-) and clinical biomarker profiles (A+T+N+) were substantially outnumbered by preclinical (A+T-N-) profiles. A recent longitudinal study by Menze et al. [242] demonstrated that individuals with an A+T+N- profile at baseline experienced significant PVS enlargement over successive follow-up sessions relative to individuals with an A+T-N- profile. Despite the lack of overall PVS enlargement, we identified a positive correlation between PVSV and ChPV, as well as negative correlations with DTI-ALPS and BCR, findings consistent with glymphatic theory [16, 99].

5.3.2 Glymphatic Predictors of AD Severity

Among the glymphatic indices examined, only BCR showed modest-to-strong contributions to predictions across all models, whereas PVSV, ChPV, and DTI-ALPS did not. As mentioned previously, the observed differences may be partially explained by the timing of glymphatic alterations: here, ChPV and DTI-ALPS emerged in the advanced stages of AD, while BCR exhibited measurable declines earlier in the disease continuum. Given the relatively consistent trajectory of ATN status, predictors that change early may hold greater value for classification [61]. Importantly, the predictive influence of BCR was comparable to established markers of AD severity, including age, cognitive performance, daytime activity, and neurological comorbidities [82, 164, 244]. Nevertheless, overreliance on BCR in the L1 multiclass model led to decreased accuracy, highlighting that it is not a holistic predictor of AD progression or other non-AD pathologies. Taken together, these results suggest that clearance impairments, particularly in early AD, may help predict the emergence of subsequent pathology.

5.3.3 Cognitive and Clinical Predictors of AD Severity

Consistent with prior longitudinal modeling efforts [164], cognitive and clinical scores, especially ADAS, FAQ, MMSE, and GDS, emerged as principal predictive factors in the linear models as well as the post hoc ensemble models. All models additionally incorporated age and, in some cases, APOE4 status. Sleep quality, as measured by the NPI-K, was impaired across diagnoses and offered marginal contri-

butions to predicting clinical AD (A+T+N+) and AD with concomitant pathology (A+T-N+). This finding suggests that sleep may have a limited detectable role in the development of preclinical and prodromal biomarkers. However, because the NPI-K relies on caregiver reports, its sensitivity may be constrained in early-stage participants, who are generally independent and may experience subtle sleep disturbances that go unobserved. Future studies incorporating dedicated sleep assessments, such as the PSQI [154], and/or actigraphy, are needed to more fully evaluate the relationship between sleep and early biomarker changes.

5.3.4 Biomarker-Based Predictors of AD Severity

The amyloid cascade, like the AD continuum itself, progresses through distinct, well-characterized stages [61, 74]. Prior longitudinal modeling by Ezzati et al. [61] demonstrated that biomarker-defined ATN stages align closely with clinical progression, allowing accurate prediction of conversion to symptomatic AD. In the present study, linear models required glymphatic, cognitive, and clinical features to accurately predict ATN status. In contrast, the ensemble model relied almost entirely on prior ATN measurements to forecast subsequent changes, effectively capturing general progression trends even when ATN status shifted across sessions. When prior ATN status was removed from the feature set, the ensemble model shifted to rely on glymphatic, cognitive, and medical history data, but this came at the cost of prediction accuracy. This behavior reflects AutoGluon’s ensemble-based architecture, which allows it to prioritize the most informative features directly, efficiently leveraging dominant longitudinal signals without the constraints of linear combination or regularization imposed in L1 and L2 models [163]. While such predictions are valuable for forecasting pathological changes, they provide limited insight into how biomarker profiles relate to clinical symptoms.

5.3.5 Multi-Domain Predictors

The strong predictive performance of ATN status and BCR may partially stem from their capacity to integrate information across multiple feature domains. ATN combines PET imaging of A β and p-tau with morphological assessment of hippocampal volume, while BCR incorporates both A β -PET and CSF-A β biomarker assays. Consistent with this notion, a meta-analysis of 116 ML studies on AD progression reported that models combining data from multiple imaging modalities achieved superior performance compared with models relying on uniform datasets [239]. The glymphatic system is increasingly recognized as being affected in AD [16, 99, 120], but its contributions to pathogenesis are complex and cannot be captured by a single measure [99, 117]. Integrating information across multiple domains may be essential for achieving the most informative and robust predictions in future studies.

5.3.6 Limitations

The present study had limitations. First, as previously discussed, the study sample did not cover the full AD continuum, with later-stage individuals being relatively underrepresented. This was partly due to the limited availability of follow-up dMRI and NPI-K data for these participants. Second, sleep was assessed using the NPI, a caregiver-reported behavioral questionnaire, which may have limited sensitivity. Future studies should aim to replicate these analyses in other longitudinal AD cohorts

that include more advanced cases and more comprehensive sleep assessments, such as the UK Biobank or the Wisconsin Registry of Alzheimer’s Prevention. Third, the study relied on the assumption that ATN status reflects AD severity, which has been supported by prior studies but remains theoretical. While biomarker burden underlies AD pathology, cognitive assessments are required to assess clinical status. Cognitive and behavioral function ultimately dictates whether biomarker-positive individuals qualify for MCI or AD diagnoses. Fourth, several established indices of glymphatic function, including the free water index and CSF-BOLD coupling [99, 101], were not incorporated in this study. This decision was made because of data limitations and to ensure that all participants were evaluated using a uniform feature set. Finally, the study did not evaluate standalone non-linear models, as this was outside its scope. Although the ensemble model incorporated several non-linear frameworks internally, assessing these models individually as baseline predictors could potentially reveal different patterns or trends.

5.4 Conclusion

This chapter presented evidence that early reductions in glymphatic clearance can serve as reliable predictors of pathological changes in later stages of AD. However, the inclusion of glymphatic features alone was insufficient to consistently strengthen classification models. A composite approach that integrates multiple glymphatic indices may offer the most informative framework for understanding how clearance impairment contributes to AD progression.

Chapter 6

Discussion

This chapter reviews the key findings of the dissertation and evaluates the initial hypotheses against the evidence presented, and outlines future perspectives.

6.1 Sleep and AD

Sleep disturbance increases the risk for Alzheimer’s disease (AD) [4, 94, 173, 176], and vice versa [53, 93, 168, 175]. Despite this apparent reciprocity, the bidirectional relationship between sleep and AD remains largely theoretical. This dissertation advanced the hypothesis that the three-network system (TNS), implicated in insomnia pathology and sensitive to AD biomarker deposition, could provide empirical evidence for this relationship. Our findings revealed that AD individuals presenting with insomnia symptoms demonstrated distinctive functional alterations of the TNS, which diverged both from AD individuals without insomnia and from CN and MCI individuals with insomnia. This finding suggests that insomnia and AD are not merely correlated; AD pathology fundamentally alters the way that insomnia pathology manifests itself within the TNS. These changes were further associated with pronounced cognitive deficits and affective symptoms.

Network degeneration appears to be the most likely culprit of this drastic shift [62, 175]. To wit, insomnia-related functional connectivity alterations changed significantly from MCI to AD, a transition associated on the physiological level by the onset of neurodegeneration [14]. A study by O’Callaghan et al. [245] found that atrophy in brain networks may impair spontaneous cognitive processes such as mind-wandering. By extrapolation, TNS degeneration may similarly attenuate the hyperactive versions of such thoughts, like rumination and hyperarousal, leading to an overemphasis on the affective components of insomnia. This theory would be consistent with our findings, as many hyperconnective edges in MCI were preserved in AD, yet were largely overshadowed by different hypoconnective edges. Although it might be tempting to attribute this hypoconnectivity to neurodegeneration itself [246], our analysis revealed no morphological changes associated with insomnia symptoms.

The emergence of these abnormal patterns during neurodegeneration highlights a key limitation of this study: it provides little insight into how insomnia interacts with AD prior to the onset of clinical symptoms. One possible explanation is that insomnia, and more broadly sleep disturbances, act as a driving factor in AD pathology until the disease progresses to a stage where sleep is itself directly affected [54]. The validity of this theory remains to be tested through longitudinal analyses that track the interaction between insomnia and AD, particularly during the transition

from MCI to AD. Moreover, although insomnia represents one of the major forms of sleep disturbances [48], its specific relationship with AD pathology should not be assumed to extend to other sleep disorders. Indeed, conditions like obstructive sleep apnea and periodic limb movements have distinct pathologies [53] and warrant investigation in dedicated studies.

6.2 Sleep and Glymphatic Function

Sleep facilitates glymphatic clearance [9, 10, 12, 15, 108], while sleep disturbance impairs it [11, 12, 106]. Where invasive approaches are not feasible, such as in retrospective clinical samples, glymphatic function can be evaluated with MRI using several indices, including choroid plexus volume (ChPV), perivascular space volume (PVSV), free water levels in the parenchyma (FWI), and diffusion along the perivascular space (DTI-ALPS) [99, 101]. Individually, these indices target specific components of the glymphatic system, such as CSF influx, parenchymal diffusion, or efflux; together, they offer a sensitive measure of system-wide dysfunction [16]. Building on previous work by Eide et al. [11], we hypothesized that sleep deprivation and sleep restriction would lead to glymphatic dysfunction, as evidenced by increased ChPV, PVSV, and FWI, as well as decreased DTI-ALPS. Contrary to our hypothesis, sleep deprivation was primarily associated with reductions in PVSV and DTI-ALPS, whereas sleep restriction showed the opposite pattern.

In our discussion, we proposed that an acute reduction in slow-wave sleep (SWS) could account for these findings. Indeed, SWS drives brain fluid movement [247] and supports glymphatic activity through infraslow norepinephrine (NE) oscillations [108]. PVSV is known to respond dynamically to changes in sleep behavior and brain fluid content [248]. This could account for the observed reductions in DTI-ALPS and increases in FWI, as such diffusion metrics are generally sensitive to changes in global CSF dynamics [101, 117]. It could furthermore explain the contrasting observations in the sleep restriction group, as restorative sleep immediately following restriction could hypothetically lead to both a recovery of SWS [249] and a rebound in glymphatic activity. Future research incorporating polysomnographic measurements may be required to establish whether such a phenomenon is present.

A critical takeaway of this study is that single indices are not sufficient to assess the glymphatic system as a whole. Whereas previous studies have equated reductions in DTI-ALPS to glymphatic dysfunction [17, 60, 227], our findings highlight the need to evaluate these indices in their broader context. Additionally, recent debates about glymphatic function and sleep [19] underscore the importance of assessing not only glymphatic flow within the brain but also clearance from it when drawing inferences about glymphatic system function. Studies employing noninvasive glymphatic MRI techniques should strive to replicate their findings with methods that directly measure fluid flow, such as contrast-enhanced MRI [250] or dynamic BOLD-CSF coupling [251].

6.3 Glymphatic Function and AD

Sleep maintains glymphatic function [9, 10, 12, 15, 108], and glymphatic function maintains brain health [4, 8, 13, 99, 209]. Yet, attempts to model AD progression using machine learning (ML) methods have largely overlooked sleep and glymphatic data [164, 239, 244], leaving a potential source of early risk information unconsid-

ered. We therefore hypothesized that incorporating these data would improve model performance in predicting amyloid–tau–neurodegeneration (ATN) status across the AD continuum. Interestingly, our results showed that while the brain clearance rate (BCR), defined as the ratio of CSF- $A\beta$ to PET- $A\beta$, generally enhanced predictive performance, MRI indices such as ChPV, PVSV, and DTI-ALPS reduced it. These results may reflect the distinct timing of changes across glymphatic indices. To wit, while all indices became more impaired as AD progressed, the BCR showed significant changes early in the continuum, whereas MRI indices deteriorated only at later stages. This aligns with the observation that models drew heavily on early-changing features to forecast ATN status.

These findings provide some of the first evidence that reductions in glymphatic clearance may precede and predict subsequent AD pathology in humans. Although prior studies reported similar associations using the DTI-ALPS index [17], we were unable to replicate those results. Acute reductions in brain clearance may result from sleep deprivation [116] and/or aquaporin-4 (AQP4) dysfunction [211]. We hypothesize that if such clearance impairments persist over time, they may contribute to the development of AD pathology, which in turn could further disrupt sleep (as shown in Chapter 3) and impair glymphatic function through lasting alterations of the perivascular spaces and parenchyma, driven by $A\beta$ plaque accumulation, neuroinflammation, and loss or mislocalization of AQP4 [16, 99, 243].

Part of the predictive potential of the BCR may stem from its multimodality. Indeed, multimodal features, which integrate information across diverse domains, can greatly enhance model performance [239, 252, 253]. However, they also increase dataset dimensionality and computational demands, and their effectiveness can vary considerably depending on the framework applied [253]. Accordingly, we observed that while BCR enhanced performance in complex ensemble models, it strongly reduced performance in a baseline linear model. Nevertheless, multimodal ML may offer a promising avenue for modeling glymphatic function by integrating multiple indices and their temporal patterns into robust predictions. Future studies should investigate whether early changes in BCR can explain later abnormalities in ChPV, PVSV, FWI, and DTI-ALPS.

6.4 Acute vs. Chronic Glymphatic Impairment

The findings of this dissertation invite a brief reflection on the ontology of glymphatic impairment. Broadly, the literature distinguishes two types of impairment: first, a direct reduction in AQP4-mediated flow and clearance, typically measured invasively in murine models [8, 9, 11, 110]; and second, a longitudinal degradation of glymphatic structures, often assessed noninvasively using MRI-based indices [16, 17, 102, 243]. Although both phenomena are commonly described as "glymphatic impairment", our results imply that they correspond to distinct processes that are nevertheless closely related. In Chapter 4, we observed that sleep deprivation was associated with acute abnormal changes across glymphatic indices, yet these did not translate into an MRI profile indicative of systemic glymphatic impairment. In Chapter 5, we found that reductions in the BCR, which occurred early along the AD continuum, correlated with abnormal changes across all glymphatic indices; however, these changes did not manifest until the later stages of the continuum. Classifying glymphatic impairment as either "acute" or "chronic", for example, could help explain these findings and resolve several inconsistencies in the literature, including the observations that molecular clearance [116], but not

perivascular morphology [150], is affected by sleep deprivation, and that glymphatic impairment can both precede [17] and evolve alongside [16] AD pathology. To fully delineate this relationship, comparative studies integrating results from various invasive and noninvasive modalities are necessary.

6.5 The Long-Term Relationship Between Sleep, Glymphatic Function, and AD

Collectively, the findings of this dissertation support a temporally dynamic, bidirectional relationship between sleep, glymphatic function, and AD pathology. Acute reductions in fluid-mediated clearance, observed as transient CSF influx decreases (Chapter 4) and early BCR decline (Chapter 5), may represent the earliest perturbations. Repeated occurrences, such as those seen in sleep disorders, can then promote the accumulation of AD pathology. Over time, systemic glymphatic dysfunction emerges during the transition from prodromal to clinical AD (Chapter 5), compounded by network degeneration (Chapter 3), which disrupts neuronal and vascular coordination. This degeneration contributes to additional clinical manifestations, including insomnia-related changes (Chapter 3). Together, these processes establish a self-reinforcing cycle in which impaired sleep, declining glymphatic function, and AD pathology mutually exacerbate one another, *ad infinitum*.

6.6 "Breaking the Cycle"

This begs one final question: how can the cycle be broken? Our findings suggest that significant network and glymphatic alterations arise alongside neurodegeneration, the terminal stage of AD pathology [14, 74]. To prevent a cascade of clinical manifestations, the primary objective, as emphasized in prior studies [83, 254], should be to delay clinical conversion for as long as possible. To this end, therapeutics should focus on the mechanisms that underlie early pathology. This involves enhanced screening for sleep disturbances in the aging population using standardized questionnaires and actigraphy, alongside targeted interventions such as cognitive behavioral therapy for insomnia [255] and light therapy for circadian dysrhythmia [256]. Multidomain lifestyle interventions, including dietary adjustments, physical activity, and cognitive and social engagement, may present another critical avenue of early prevention [257, 258]. Transcranial and (remote) auditory stimulation of slow-wave activity offers a potentially powerful method to reinforce glymphatic clearance [259, 260]. Conversely, pharmacological sleep aids should be used with caution, as they may improve subjective sleep quality but attenuate glymphatic activity [108]. Finally, multimodal ML models trained on a spectrum of risk factors could support individualized predictions and inform targeted prevention efforts [164, 252]. Taken together, these interventions offer a mechanistically informed strategy to delay clinical conversion, mitigate downstream pathology, and provide a framework for personalized prevention in at-risk populations.

Conclusion

The present dissertation provides evidence that sleep deprivation induces acute glymphatic disruptions, which in turn strongly predict Alzheimer's pathogenesis. The resulting pathology further disrupts brain network activity, leading to additional clinical manifestations, including insomnia, negative affect, and alterations of glymphatic system integrity. To interrupt this cascade, the study proposes multimodal, risk-factor-informed interventions aimed at addressing early sleep disturbances and clearance impairments.

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Appendix A

Neuropsychiatric Inventory

A. DELUSIONS**(NA)**

Does the patient have beliefs that you know are not true (for example, insisting that people are trying to harm him/her or steal from him/her)? Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her.

☐ Yes (If yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient believe that he/she is in danger - that others are planning to hurt him/her? | ☐ Yes | ☐ No |
| 2. Does the patient believe that others are stealing from him/her? | ☐ Yes | ☐ No |
| 3. Does the patient believe that his/her spouse is having an affair? | ☐ Yes | ☐ No |
| 4. Does the patient believe that unwelcome guests are living in his/her house? | ☐ Yes | ☐ No |
| 5. Does the patient believe that his/her spouse or others are not who they claim to be? | ☐ Yes | ☐ No |
| 6. Does the patient believe that his/her house is not his/her home? | ☐ Yes | ☐ No |
| 7. Does the patient believe that family members plan to abandon him/her? | ☐ Yes | ☐ No |
| 8. Does the patient believe that television or magazine figures are actually present in the home?
(Does he/she try to talk or interact with them?) | ☐ Yes | ☐ No |
| 9. Does the patient believe any other unusual things that I haven't asked about? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency:

- ☐ 1. Rarely – less than once per week
- ☐ 2. Sometimes – about once per week
- ☐ 3. Often – several times per week but less than every day
- ☐ 4. Very often – once or more per day

Severity:

- ☐ 1. Mild – delusions present but seem harmless and produce little distress in the patient.
- ☐ 2. Moderate – delusions are distressing and disruptive.
- ☐ 3. Severe – delusions are very disruptive and are a major source of behavioral disruption. (If PRN medications are prescribed, their use signals that the delusions are of marked severity.)

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

B. HALLUCINAIONS**(NA)**

Does the patient have hallucinations such as seeing false visions or hearing false voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive; rather we are asking if the patient actually has abnormal experiences of sounds or visions.

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient describe hearing voices or act as if he/she hears voices? | ☐ Yes | ☐ No |
| 2. Does the patient talk to people who are not there? | ☐ Yes | ☐ No |
| 3. Does he/she describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc)? | ☐ Yes | ☐ No |
| 4. Does he/she report smelling odors not smelled by others? | ☐ Yes | ☐ No |
| 5. Does he/she describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her? | ☐ Yes | ☐ No |
| 6. Does he/she describe tastes that are without any known cause? | ☐ Yes | ☐ No |
| 7. Does he/she describe any other unusual sensory experiences? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Frequency:

- ☐ 1. Rarely – less than once per week.
- ☐ 2. Sometimes – about once per week.
- ☐ 3. Often – several times per week but less than every day.
- ☐ 4. Very often – once or more per day.

Severity:

- ☐ 1. Mild – hallucinations are present but harmless and cause little distress for the patient.
- ☐ 2. Moderate – hallucinations are distressing and are disruptive to the patient.
- ☐ 3. Severe – hallucinations are very disruptive and are a major source of behavioral disturbance. PRN medications may be required to control them.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

C. AGITATION/AGGRESSION**(NA)**

Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

- ☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes? | ☐ Yes | ☐ No |
| 2. Is the patient stubborn, having to have things his/her way? | ☐ Yes | ☐ No |
| 3. Is the patient uncooperative, resistive to help from others? | ☐ Yes | ☐ No |
| 4. Does the patient have any other behaviors that make him/her hard to handle? | ☐ Yes | ☐ No |
| 5. Does the patient shout or curse angrily? | ☐ Yes | ☐ No |
| 6. Does the patient slam doors, kick furniture, throw things? | ☐ Yes | ☐ No |
| 7. Does the patient attempt to hurt or hit others? | ☐ Yes | ☐ No |
| 8. Does the patient have any other aggressive or agitated behaviors? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the agitation/aggression.

Frequency:

- ☐ 1. Rarely – less than once per week.
☐ 2. Sometimes – about once per week.
☐ 3. Often – several times per week but less than every day.
☐ 4. Very often – once or more per day.

Severity:

- ☐ 1. Mild – agitation is disruptive but can be managed with redirection or reassurance.
☐ 2. Moderate – agitation is disruptive and difficult to redirect or control.
☐ 3. Severe – agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

D. DEPRESSION/DYSPHORIA**(NA)**

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|--|------------------------------|-----------------------------|
| 1. Does the patient have periods of tearfulness or sobbing that seem to indicate sadness? | ☐ Yes | ☐ No |
| 2. Does the patient say, or act as if, he/she is sad or in low spirits? | ☐ Yes | ☐ No |
| 3. Does the patient put him/herself down or say that he/she feels like a failure? | ☐ Yes | ☐ No |
| 4. Does the patient say that he/she is a bad person or deserves to be punished? | ☐ Yes | ☐ No |
| 5. Does the patient seem very discouraged or say that he/she has no future? | ☐ Yes | ☐ No |
| 6. Does the patient say he/she is a burden to the family or that the family would be better off without him/her? | ☐ Yes | ☐ No |
| 7. Does the patient express a wish for death or talk about killing himself/herself? | ☐ Yes | ☐ No |
| 8. Does the patient show any other signs of depression or sadness? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the depression/dysphoria.

Frequency:

- ☐ 1. Rarely – less than once per week.
- ☐ 2. Sometimes – about once per week.
- ☐ 3. Often – several times per week but less than every day.
- ☐ 4. Very often – essentially continuously present.

Severity:

- ☐ 1. Mild – depression is distressing but usually responds to redirection or reassurance.
- ☐ 2. Moderate – depression is distressing; depressive symptoms are spontaneously voiced by the patient and difficult to alleviate.
- ☐ 3. Severe – depression is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

E. ANXIETY**(NA)**

Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient say that he/she is worried about planned events? | ☐ Yes | ☐ No |
| 2. Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense? | ☐ Yes | ☐ No |
| 3. Does the patient have periods of [or complain of] shortness of breath, gasping, or sighing for no apparent reason other than nervousness? | ☐ Yes | ☐ No |
| 4. Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? (Symptoms not explained by ill health) | ☐ Yes | ☐ No |
| 5. Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds? | ☐ Yes | ☐ No |
| 6. Does the patient become nervous and upset when separated from you (or his/her caregiver)? (Does he/she cling to you to keep from being separated?) | ☐ Yes | ☐ No |
| 7. Does the patient show any other signs of anxiety? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the anxiety.

Frequency:

- ☐ 1. Rarely – less than once per week.
- ☐ 2. Sometimes – about once per week.
- ☐ 3. Often – several times per week but less than every day.
- ☐ 4. Very often – once or more per day.

Severity:

- ☐ 1. Mild – anxiety is distressing but usually responds to redirection or reassurance.
- ☐ 2. Moderate – anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate.
- ☐ 3. Severe – anxiety is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

F. ELATION/EUPHORIA**(NA)**

Does the patient seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the patient has a persistent and abnormally good mood or finds humor where others do not.

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient appear to feel too good or to be too happy, different from his/her usual self? | ☐ Yes | ☐ No |
| 2. Does the patient find humor and laugh at things that others do not find funny? | ☐ Yes | ☐ No |
| 3. Does the patient seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)? | ☐ Yes | ☐ No |
| 4. Does the patient tell jokes or make remarks that are not funny to others but seem funny to him/her? | ☐ Yes | ☐ No |
| 5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it? | ☐ Yes | ☐ No |
| 6. Does the patient "talk big" or claim to have more abilities or wealth than is true? | ☐ Yes | ☐ No |
| 7. Does the patient show any other signs of feeling too good or being too happy? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

Frequency:

- ☐ 1. Rarely – less than once per week.
- ☐ 2. Sometimes – about once per week.
- ☐ 3. Often – several times per week but less than every day.
- ☐ 4. Very often – essentially continuously present.

Severity:

- ☐ 1. Mild – elation is notable to friends and family but is not disruptive.
- ☐ 2. Moderate – elation is notably abnormal.
- ☐ 3. Severe – elation is very pronounced; patient is euphoric and finds nearly everything to be humorous.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

G. APATHY/INDIFFERENCE**(NA)**

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or does he/she lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient seem less spontaneous and less active than usual? | ☐ Yes | ☐ No |
| 2. Is the patient less likely to initiate a conversation? | ☐ Yes | ☐ No |
| 3. Is the patient less affectionate or lacking in emotions when compared to his/her usual self? | ☐ Yes | ☐ No |
| 4. Does the patient contribute less to household chores? | ☐ Yes | ☐ No |
| 5. Does the patient seem less interested in the activities and plans of others? | ☐ Yes | ☐ No |
| 6. Has the patient lost interest in friends and family members? | ☐ Yes | ☐ No |
| 7. Is the patient less enthusiastic about his/her usual interests? | ☐ Yes | ☐ No |
| 8. Does the patient show any other signs that he/she doesn't care about doing new things? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

Frequency:

- ☐ 1. Rarely – less than once per week.
- ☐ 2. Sometimes – about once per week.
- ☐ 3. Often – several times per week but less than every day.
- ☐ 4. Very often – nearly always present.

Severity:

- ☐ 1. Mild – apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behavior; patient responds to suggestions to engage in activities.
- ☐ 2. Moderate – apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
- ☐ 3. Severe – apathy is very evident and usually fails to respond to any encouragement or external events.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

H. DISINHIBITION**(NA)**

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

- ☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient act impulsively without appearing to consider the consequences? | ☐ Yes | ☐ No |
| 2. Does the patient talk to total strangers as if he/she knew them? | ☐ Yes | ☐ No |
| 3. Does the patient say things to people that are insensitive or hurt their feelings? | ☐ Yes | ☐ No |
| 4. Does the patient say crude things or make sexual remarks that he/she would not usually have said? | ☐ Yes | ☐ No |
| 5. Does the patient talk openly about very personal or private matters not usually discussed in public? | ☐ Yes | ☐ No |
| 6. Does the patient take liberties or touch or hug others in way that is out of character for him/her? | ☐ Yes | ☐ No |
| 7. Does the patient show any other signs of loss of control of his/her impulses? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

Frequency:

- ☐ 1. Rarely – less than once per week.
☐ 2. Sometimes – about once per week.
☐ 3. Often – several times per week but less than every day.
☐ 4. Very often – essentially continuously present.

Severity:

- ☐ 1. Mild – disinhibition is notable but usually responds to redirection and guidance.
☐ 2. Moderate – disinhibition is very evident and difficult to overcome by the caregiver.
☐ 3. Severe – disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

I. IRRITABILITY/LABILITY**(NA)**

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient have a bad temper, "flying off the handle" easily over little things? | ☐ Yes | ☐ No |
| 2. Does the patient rapidly change moods from one to another, being fine one minute and angry the next? | ☐ Yes | ☐ No |
| 3. Does the patient have sudden flashes of anger? | ☐ Yes | ☐ No |
| 4. Is the patient impatient, having trouble coping with delays or waiting for planned activities? | ☐ Yes | ☐ No |
| 5. Is the patient cranky and irritable? | ☐ Yes | ☐ No |
| 6. Is the patient argumentative and difficult to get along with? | ☐ Yes | ☐ No |
| 7. Does the patient show any other signs of irritability? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the irritability /lability.

Frequency:

- ☐ 1. Rarely – less than once per week.
- ☐ 2. Sometimes – about once per week.
- ☐ 3. Often – several times per week but less than every day.
- ☐ 4. Very often – essentially continuously present.

Severity:

- ☐ 1. Mild – irritability or lability is notable but usually responds to redirection and reassurance.
- ☐ 2. Moderate – irritability and lability are very evident and difficult to overcome by the caregiver.
- ☐ 3. Severe – irritability and lability are very evident; they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

J. ABERRANT MOTOR BEHAVIOR**(NA)**

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

- ☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

- | | | |
|--|------------------------------|-----------------------------|
| 1. Does the patient pace around the house without apparent purpose? | ☐ Yes | ☐ No |
| 2. Does the patient rummage around opening and unpacking drawers or closets? | ☐ Yes | ☐ No |
| 3. Does the patient repeatedly put on and take off clothing? | ☐ Yes | ☐ No |
| 4. Does the patient have repetitive activities or "habits" that he/she performs over and over? | ☐ Yes | ☐ No |
| 5. Does the patient engage in repetitive activities such as handling buttons, picking, wrapping string, etc? | ☐ Yes | ☐ No |
| 6. Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot? | ☐ Yes | ☐ No |
| 7. Does the patient do any other activities over and over? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

Frequency:

- ☐ 1. Rarely – less than once per week.
☐ 2. Sometimes – about once per week.
☐ 3. Often – several times per week but less than every day.
☐ 4. Very often – essentially continuously present.

Severity:

- ☐ 1. Mild – abnormal motor activity is notable but produces little interference with daily routines.
☐ 2. Moderate – abnormal motor activity is very evident; can be overcome by the caregiver.
☐ 3. Severe – abnormal motor activity is very evident, usually fails to respond to any intervention by the caregiver and is a major source of distress.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

K. SLEEP AND NIGHTTIME BEHAVIOR DISORDERS**(NA)**

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Does the patient have difficulty falling asleep? | ☐ Yes | ☐ No |
| 2. Does the patient get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? | ☐ Yes | ☐ No |
| 3. Does the patient wander, pace, or get involved in inappropriate activities at night? | ☐ Yes | ☐ No |
| 4. Does the patient awaken you during the night? | ☐ Yes | ☐ No |
| 5. Does the patient wake up at night, dress, and plan to go out, thinking that it is morning and time to start the day? | ☐ Yes | ☐ No |
| 6. Does the patient awaken too early in the morning (earlier than was his/her habit)? | ☐ Yes | ☐ No |
| 7. Does the patient sleep excessively during the day? | ☐ Yes | ☐ No |
| 8. Does the patient have any other nighttime behaviors that bother you that we haven't talked about? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the nighttime behavior.

Frequency:

- ☐ 1. Rarely – less than once per week.
- ☐ 2. Sometimes – about once per week.
- ☐ 3. Often – several times per week but less than every day.
- ☐ 4. Very often – once or more per day (every night).

Severity:

- ☐ 1. Mild – nighttime behaviors occur but they are not particularly disruptive.
- ☐ 2. Moderate – nighttime behaviors occur and disturb the patient and the sleep of the caregiver; more than one type of nighttime behavior may be present.
- ☐ 3. Severe – nighttime behaviors occur; several types of nighttime behavior may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

L. APPETITE AND EATING CHANGES**(NA)**

Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

☐ Yes (if yes, please proceed to subquestions)

☐ No (if no, please proceed to next screening question)

☐ N/A

- | | | |
|---|------------------------------|-----------------------------|
| 1. Has he/she had a loss of appetite? | ☐ Yes | ☐ No |
| 2. Has he/she had an increase in appetite? | ☐ Yes | ☐ No |
| 3. Has he/she had a loss of weight? | ☐ Yes | ☐ No |
| 4. Has he/she gained weight? | ☐ Yes | ☐ No |
| 5. Has he/she had a change in eating behavior such as putting too much food in his/her mouth at once? | ☐ Yes | ☐ No |
| 6. Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food? | ☐ Yes | ☐ No |
| 7. Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order? | ☐ Yes | ☐ No |
| 8. Have there been any other changes in appetite or eating that I haven't asked about? | ☐ Yes | ☐ No |

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

Frequency:

- ☐ 1. Rarely – less than once per week.
- ☐ 2. Sometimes – about once per week.
- ☐ 3. Often – several times per week but less than every day.
- ☐ 4. Very often – once or more per day or continuously.

Severity:

- ☐ 1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.
- ☐ 2. Moderate – changes in appetite or eating are present and cause minor fluctuations in weight.
- ☐ 3. Severe – obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient.

Distress: How emotionally distressing do you find this behavior?

- ☐ 0. Not at all
- ☐ 1. Minimally (almost no change in work routine)
- ☐ 2. Mildly (almost no change in work routine but little time rebudgeting required)
- ☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
- ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
- ☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

(05/27/09: JLC)

NPI	Neuropsychiatric Inventory Scoring Summary
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CENTER #	SCREENING #	PATIENT #	PATIENT INITIALS	VISIT	DATE
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F M L

M D Y

Please transcribe appropriate categories from the NPI Worksheet into the boxes provided. For each domain: - If symptoms of a domain did not apply, check the "N/A" box. - If symptoms of a domain were absent, check the "0" box. - If symptoms of a domain were present, check one score each for Frequency and Severity. - Multiply Frequency score x Severity score and enter the product in the space provided. - Total all Frequency x Severity scores and record the Total Score below. - If symptoms of a domain were present, check one score for Distress; total all distress scores for a summary score.	Rater's Initials:
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DOMAIN	N/A ¹	ABSENT	FREQUENCY	SEVERITY	FREQUENCY X SEVERITY	CAREGIVER DISTRESS
		0	1 2 3 4	1 2 3		0 1 2 3 4 5
A. Delusions	☐	☐				
B. Hallucinations	☐	☐				
C. Agitation/Aggression	☐	☐				
D. Depression/Dysphoria	☐	☐				
E. Anxiety	☐	☐				
F. Elation/Euphoria	☐	☐				
G. Apathy/Indifference	☐	☐				
H. Disinhibition	☐	☐				
I. Irritability/Lability	☐	☐				
J. Aberrant Motor Behavior	☐	☐				
TOTAL SCORE:						
K. Sleep and Nighttime Behavior Disorders	☐	☐				
L. Appetite/Eating Changes	☐	☐				

NPI	Neuropsychiatric Inventory
	Worksheet

Directions: Read all items from the NPI "Instructions for Administration of the NPI". Mark Caregiver's responses on this worksheet before scoring the Frequency, Severity, and Caregiver Distress for each item.

A. DELUSIONS: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Fear of harm ☐ 2. Fear of theft ☐ 3. Spousal affair ☐ 4. Phantom boarder ☐ 5. Spouse imposter ☐ 6. House not home ☐ 7. Fear of abandonment ☐ 8. Talks to TV, etc. ☐ 9. Other _____	B. HALLUCINATIONS: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Hears voices ☐ 2. Talks to people not there ☐ 3. Sees things not there ☐ 4. Smells things not there ☐ 5. Feels things not there ☐ 6. Unusual taste sensations ☐ 7. Other _____
C. AGITATION/AGGRESSION: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Upset with caregiver; resists ADL's ☐ 2. Stubbornness ☐ 3. Uncooperative; resists help ☐ 4. Hard to handle ☐ 5. Cursing or shouting angrily ☐ 6. Slams doors; kicks, throws things ☐ 7. Hits, harms others ☐ 8. Other _____	D. DEPRESSION/DYSPHORIA: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Tearful and sobbing ☐ 2. States, acts as if sad ☐ 3. Puts self down, feels like failure ☐ 4. "Bad person", deserves punishment ☐ 5. Discouraged, no future ☐ 6. Burden to family ☐ 7. Talks about dying, killing self ☐ 8. Other _____
E. ANXIETY: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Worries about planned events ☐ 2. Feels shaky, tense ☐ 3. Sobs, sighs, gasps ☐ 4. Racing heart, "butterflies" ☐ 5. Phobic avoidance ☐ 6. Separation anxiety ☐ 7. Other _____	F. ELATION/EUPHORIA: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Feels too good, too happy ☐ 2. Abnormal humor ☐ 3. Childish, laughs inappropriately ☐ 4. Jokes or remarks not funny to others ☐ 5. Childish pranks ☐ 6. Talks "big", grandiose ☐ 7. Other _____

CONTINUES ON NEXT PAGE

NPI	Neuropsychiatric Inventory
	Worksheet

G. APATHY/INDIFFERENCE: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Less spontaneous or active ☐ 2. Less likely to initiate conversation ☐ 3. Less affectionate, lacking emotions ☐ 4. Contributes less to household chores ☐ 5. Less interested in others ☐ 6. Lost interest in friends or family ☐ 7. Less enthusiastic about interests ☐ 8. Other _____	H. DISINHIBITION: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Acts impulsively ☐ 2. Excessively familiar with strangers ☐ 3. Insensitive or hurtful remarks ☐ 4. Crude or sexual remarks ☐ 5. Talks openly of private matters ☐ 6. Inappropriate touching of others ☐ 7. Other _____
I. IRRITABILITY/LIBILITY: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Bad temper, “flies off handle” easily ☐ 2. Rapid changes in mood ☐ 3. Sudden flashes of anger ☐ 4. Impatient, trouble coping with delays ☐ 5. Cranky, irritable ☐ 6. Argues, difficult to get along with ☐ 7. Other _____	J. ABERRANT MOTOR BEHAVIOR: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Paces without purpose ☐ 2. Opens or unpacks closets or drawers ☐ 3. Repeatedly dresses and undresses ☐ 4. Repetitive activities or “habits” ☐ 5. Handling, picking, wrapping behavior ☐ 6. Excessively fidgety ☐ 7. Other _____
K. SLEEP AND NIGHTTIME BEHAVIOR DISORDERS: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Difficulty falling asleep ☐ 2. Up during the night ☐ 3. Wanders, paces, inappropriate activity ☐ 4. Awakens others at night ☐ 5. Wakes and dresses to go out at night ☐ 6. Early morning awakening ☐ 7. Sleeps excessively during the day ☐ 8. Other _____	L. APPETITE/EATING CHANGES: ☐Yes ☐No ☐N/A Frequency_____ Severity_____ Distress _____ ☐ 1. Loss of appetite ☐ 2. Increased appetite ☐ 3. Weight loss ☐ 4. Weight gain ☐ 5. Change in eating habits ☐ 6. Change in food preferences ☐ 7. Eating rituals ☐ 8. Other _____

Appendix B

Pittsburgh Sleep Quality Index

Name: _____

Date: _____

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night? _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____
3. During the past month, what time have you usually gotten up in the morning? _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the <u>past month</u> , how often have you had trouble sleeping because you...	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a room mate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

Scoring the PSQI

The order of the PSQI items has been modified from the original order in order to fit the first 9 items (which are the only items that contribute to the total score) on a single page. Item 10, which is the second page of the scale, does not contribute to the PSQI score.

In scoring the PSQI, seven component scores are derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality.

Component 1: Subjective sleep quality—question 9

<u>Response to Q9</u>	<u>Component 1 score</u>
Very good	0
Fairly good	1
Fairly bad	2
Very bad	3

Component 1 score: _____

Component 2: Sleep latency—questions 2 and 5a

<u>Response to Q2</u>	<u>Component 2/Q2 subscore</u>
≤ 15 minutes	0
16-30 minutes	1
31-60 minutes	2
> 60 minutes	3

<u>Response to Q5a</u>	<u>Component 2/Q5a subscore</u>
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

<u>Sum of Q2 and Q5a subscores</u>	<u>Component 2 score</u>
0	0
1-2	1
3-4	2
5-6	3

Component 2 score: _____

Component 3: Sleep duration—question 4

<u>Response to Q4</u>	<u>Component 3 score</u>
> 7 hours	0
6-7 hours	1
5-6 hours	2
< 5 hours	3

Component 3 score: _____

Component 4: Sleep efficiency—questions 1, 3, and 4

Sleep efficiency = (# hours slept/# hours in bed) X 100%

hours slept—question 4

hours in bed—calculated from responses to questions 1 and 3

<u>Sleep efficiency</u>	<u>Component 4 score</u>
> 85%	0
75-84%	1
65-74%	2
< 65%	3

Component 4 score: _____

Component 5: Sleep disturbance—questions 5b-5j

Questions 5b to 5j should be scored as follows:

Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

<u>Sum of 5b to 5j scores</u>	<u>Component 5 score</u>
0	0
1-9	1
10-18	2
19-27	3

Component 5 score:_____

Component 6: Use of sleep medication—question 6

<u>Response to Q6</u>	<u>Component 6 score</u>
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Component 6 score:_____

Component 7: Daytime dysfunction—questions 7 and 8

<u>Response to Q7</u>	<u>Component 7/Q7 subscore</u>
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

<u>Response to Q8</u>	<u>Component 7/Q8 subscore</u>
No problem at all	0
Only a very slight problem	1
Somewhat of a problem	2
A very big problem	3

<u>Sum of Q7 and Q8 subscores</u>	<u>Component 7 score</u>
0	0
1-2	1
3-4	2
5-6	3

Component 7 score:_____

Global PSQI Score: Sum of seven component scores:_____

Copyright notice: The Pittsburgh Sleep Quality Index (PSQI) is copyrighted by Daniel J. Buysse, M.D. Permission has been granted to reproduce the scale on this website for clinicians to use in their practice and for researchers to use in non-industry studies. For other uses of the scale, the owner of the copyright should be contacted.

Citation: Buysse, DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. *Psychiatry Research* 28:193-213, 1989

Appendix C

Karolinska Sleepiness Scale

Purpose This scale [1] measures the subjective level of sleepiness at a particular time during the day. On this scale subjects indicate which level best reflects the psycho-physical state experienced in the last 10 min. The KSS is a measure of situational sleepiness. It is sensitive to fluctuations.

Population for Testing It has been used in studies of shift work, jetlag, for driving abilities [2], attention and performance, and in clinical settings. It is used for both males and females.

It is helpful in assessing the changes in response to environmental factors, circadian rhythm, and effects of drugs. Because the KSS is not a measure of ‘Trait’ sleepiness, it has not been widely used for clinical purposes.

Administration This is self-report measure. It takes 5 min to complete.

Reliability and Validity In a study conducted by Kaida et al. [3], the authors investigated the validity of the KSS and found that it was highly correlated to EEG and behavioral variables. The results

show that KSS has a high validity. However, because the scores of the KSS vary according to earlier sleep, time of day, and other parameters, it is difficult to deduce its test–retest reliability.

Scoring This is a 9-point scale (1=extremely alert, 3=alert, 5=neither alert nor sleepy, 7=sleepy – but no difficulty remaining awake, and 9=extremely sleepy – fighting sleep). There is a modified KSS that contains one other item: 10=extremely sleepy, falls asleep all the time. Scores on the KSS increase with longer periods of wakefulness and it strongly correlate with the time of the day.

Obtaining a Copy A copy can be obtained from the authors.

Direct correspondence:

Torbjörn Åkerstedt

IPM & Karolinska Institutet

Box 230

17177 Stockholm, Sweden

Email: Torbjorn.Akerstedt@ki.se

Karolinska Sleepiness Scale (KSS)

Extremely alert	1
Very alert	2
Alert	3
Rather alert	4
Neither alert nor sleepy	5
Some signs of sleepiness	6
Sleepy, but no effort to keep awake	7
Sleepy, but some effort to keep awake	8
Very sleepy, great effort to keep awake, fighting sleep	9
Extremely sleepy, can't keep awake	10

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Representative Studies Using Scale

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Appendix D

Morningness-Eveningness Questionnaire

MORNINGNESS-EVENINGNESS QUESTIONNAIRE (MEQ)

Instructions:

- Please read each question very carefully before answering.
- Please answer each question as honestly as possible.
- Answer ALL questions.
- Each question should be answered independently of others. Do NOT go back and check your answers.

1. What time would you get up if you were entirely free to plan your day?

5:00 – 6:30 AM	5
6:30 – 7:45 AM	4
7:45 – 9:45 AM	3
9:45 – 11:00 AM	2
11:00 AM – 12 NOON	1
12 NOON – 5:00 AM	0

2. What time would you go to bed if you were entirely free to plan your evening?

8:00 – 9:00 PM	5
9:00 – 10:15 PM	4
10:15 PM – 12:30 AM	3
12:30 – 1:45 AM	2
1:45 – 3:00 AM	1
3:00 AM – 8:00 PM	0

3. If there is a specific time at which you have to get up in the morning, to what extent do you depend on being woken up by an alarm clock?

Not at all dependent	4
Slightly dependent	3
Fairly dependent	2
Very dependent	1

4. How easy do you find it to get up in the morning (when you are not woken up unexpectedly)?

Not at all easy	1
Not very easy	2
Fairly easy	3
Very easy	4

5. How alert do you feel during the first half hour after you wake up in the morning?

Not at all alert	1
Slightly alert	2
Fairly alert	3
Very alert	4

6. How hungry do you feel during the first half-hour after you wake up in the morning?

Not at all hungry	1
Slightly hungry	2
Fairly hungry	3
Very hungry	4

7. During the first half-hour after you wake up in the morning, how tired do you feel?

Very tired	1
Fairly tired	2
Fairly refreshed	3
Very refreshed	4

8. If you have no commitments the next day, what time would you go to bed compared to your usual bedtime?

Seldom or never later	4
Less than one hour later	3
1-2 hours later	2
More than two hours later	1

9. You have decided to engage in some physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him is between 7:00 – 8:00 am. Bearing in mind nothing but your own internal “clock”, how do you think you would perform?

Would be in good form	4
Would be in reasonable form	3
Would find it difficult	2
Would find it very difficult	1

10. At what time of day do you feel you become tired as a result of need for sleep?

8:00 – 9:00 PM	5
9:00 – 10:15 PM	4
10:15 PM – 12:45 AM	3
12:45 – 2:00 AM	2
2:00 – 3:00 AM	1

- 11. You want to be at your peak performance for a test that you know is going to be mentally exhausting and will last for two hours. You are entirely free to plan your day. Considering only your own internal “clock”, which ONE of the four testing times would you choose?**

8:00 AM – 10:00 AM	4
11:00 AM – 1:00 PM	3
3:00 PM – 5:00 PM	2
7:00 PM – 9:00 PM	1

- 12. If you got into bed at 11:00 PM, how tired would you be?**

Not at all tired	1
A little tired	2
Fairly tired	3
Very tired	4

- 13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following are you most likely to do?**

Will wake up at usual time, but will NOT fall back asleep	4
Will wake up at usual time and will doze thereafter	3
Will wake up at usual time but will fall asleep again	2
Will NOT wake up until later than usual	1

- 14. One night you have to remain awake between 4:00 – 6:00 AM in order to carry out a night watch. You have no commitments the next day. Which ONE of the alternatives will suite you best?**

Would NOT go to bed until watch was over	1
Would take a nap before and sleep after	2
Would take a good sleep before and nap after	3
Would sleep only before watch	4

- 15. You have to do two hours of hard physical work. You are entirely free to plan your day and considering only your own internal “clock” which ONE of the following time would you choose?**

8:00 AM – 10:00 AM	4
11:00 AM – 1:00 PM	3
3:00 PM – 5:00 PM	2
7:00 PM – 9:00 PM	1

- 16. You have decided to engage in hard physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him is between 10:00 – 11:00 PM. Bearing in mind nothing else but your own internal “clock” how well do you think you would perform?**

Would be in good form	1
Would be in reasonable form	2
Would find it difficult	3
Would find it very difficult	4

- 17. Suppose that you can choose your own work hours. Assume that you worked a FIVE hour day (including breaks) and that your job was interesting and paid by results). Which FIVE CONSECUTIVE HOURS would you select?**

5 hours starting between 4:00 AM and 8:00 AM	5
5 hours starting between 8:00 AM and 9:00 AM	4
5 hours starting between 9:00 AM and 2:00 PM	3
5 hours starting between 2:00 PM and 5:00 PM	2
5 hours starting between 5:00 PM and 4:00 AM	1

- 18. At what time of the day do you think that you reach your “feeling best” peak?**

5:00 – 8:00 AM	5
8:00 – 10:00 AM	4
10:00 AM – 5:00 PM	3
5:00 – 10:00 PM	2
10:00 PM – 5:00 AM	1

- 19. One hears about “morning” and “evening” types of people. Which ONE of these types do you consider yourself to be?**

Definitely a “morning” type	6
Rather more a “morning” than an “evening” type	4
Rather more an “evening” than a “morning” type	2
Definitely an “evening” type	0

Appendix E

Munich Chronotype Questionnaire

Purpose The instrument was developed in order to assess individuals' chronotypes – diurnal preferences that manifest in personal sleep-wake rhythms. Consisting of 19 questions, the scale examines wake and sleep schedules (on both work and free days), energy levels throughout the day, sleep latency and inertia, and exposure to daylight. Individuals are also asked to subjectively rate themselves as one of seven possible chronotypes ranging from extreme early (preferring to rise much earlier than others) to extreme late. This information is combined to determine the time of day at which the respondent is likely to feel most alert, placing them objectively in a chronotype category. Though potentially a valuable tool for clinical purposes, the instrument has primarily been used in research to investigate how chronotype relates to age, sex, and external environment (e.g., exposure to daylight, community).

Population for Testing The scale has been validated in adults of college age and older.

Administration Requiring between 5 and 10 min for completion, developers have created a Web site where individuals can take the self-report questionnaire and have their results sent to them by email. A second version of the questionnaire designed specifically for shift workers is also available.

Reliability and Validity Zavada and colleagues [1] conducted a large-scale study in which

they compared the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ; (Chap. 54) to the MCTQ. They found that MEQ scores correlated highly with the midpoint of sleep on free days reported on the MCTQ ($r = .70$), and that a respondent's sleep schedule on free days is a good predictor of that individual's chronotype.

Obtaining a Copy The questionnaire is available online at: <http://chrono.biol.rug.nl/mctq-en.html>

Direct correspondence to:

Dr. M.C.M. Gordijn
P.O. Box 14, 9750 AA
Haren, the Netherlands.
Email: tvrbiol@rug.nl

Scoring The scale is scored electronically by the Web site at which it is available. Total scores can range from 16 to 86, with the lowest values representing extreme-late chronotypes. However, personal scores are not available through the questionnaire's Web site, which has been constructed for the sole purpose of the authors' research. Rather, individuals completing questionnaires at the site receive an email providing statistical comparisons of themselves to others in their subjective chronotype. Thus, the Web site itself is of limited clinical or diagnostic utility and arrangements must be made with developers in order to make further use of the instrument.

Munich ChronoType Questionnaire (MCTQ)

Please enter your age, gender, etc. This information is important for our evaluations

Age: _____ female male Height: _____ Weight: _____

On work days...

I have to get up at... _____ o'clock
 I need... _____ min to wake up
 I regularly wake up... _____ before the alarm with the alarm
 From... _____ o'clock I am fully awake
 At around... _____ o'clock, I have an energy dip
 On nights before workdays, I go to bed at _____ o'clock...
 ...and it then takes me... _____ min to fall asleep
 If I get the chance, I like to take a siesta/nap...
 Correct I then sleep for... _____ min
 Not correct I would feel terrible afterwards

On free days (please only judge normal free days, i.e., without parties etc)...

My dream would be to sleep until... _____ o'clock
 I normally wake up at... _____ o'clock
 If I wake up at around the normal (workday) alarm time, I try to get back to sleep...
 Correct Not correct

If I get back to sleep, I sleep for another... _____ min
 I need... _____ min to wake up
 From... _____ o'clock I am fully awake
 At around... _____ o'clock, I have an energy dip
 On nights before free days, I go to bed at _____ o'clock...
 ...and it then takes me... _____ min to fall asleep
 If I get the chance, I like to take a siesta/nap...
 Correct I then sleep for... _____ min
 Not correct I would feel terrible afterwards

Once I am in bed, I would like to read for... _____ min...
 ...but I generally fall asleep after no more than... _____ min

I prefer to sleep in a completely dark room Correct Not Correct
 I wake up more easily when morning light shines into my room Correct Not Correct
 How long per day do you spend on average outside (really outside) exposed to daylight?
 On work days: _____ hrs. _____ min On free days: _____ hrs _____ min

Self Assessment

After you have answered the preceding questions, you should have a feeling to which chronotype (time-of-day-type) you belong to. If, for example, you like (and manage) to sleep quite a bit longer on free days than on workdays, or if you cannot get out of bed on Monday mornings, even without a Sunday-night-party, then you are more a late go to bed early type. If, however, you regularly wake up and feel perky once you jump out of bed, and if you would rather than to an evening concert then you are an early type. In the following questions, you should categorise yourself and your family members.

Please tick only one possibility!

Description of categories: extreme early type = 0
 Moderate early type = 1
 Slight early type = 2
 Normal type = 3
 Slight late type = 4
 Moderate late type = 5
 Extreme late type = 6

I am...	0	1	2	3	4	5	6
As a child, I was...	0	1	2	3	4	5	6
As a teenager, I was...	0	1	2	3	4	5	6
In case you are older than 65: in the middle of my life, I was...	0	1	2	3	4	5	6

My parents are/were...							
Mother...	0	1	2	3	4	5	6
Father...	0	1	2	3	4	5	6

My siblings are/were ... (please underline Brother or Sister)							
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6
Brother/Sister	0	1	2	3	4	5	6

My partner (girl/boy friend, spouse, significant other) is/was...							
	0	1	2	3	4	5	6

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Representative Studies Using Scale

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Appendix F

Mini-Mental State Exam

The Mini Mental State Examination (MMSE)

By: Lenore Kurlowicz, PhD, RN, CS and Meredith Wallace, PhD, RN, MSN

WHY: Cognitive impairment is no longer considered a normal and inevitable change of aging. Although older adults are at higher risk than the rest of the population, changes in cognitive function often call for prompt and aggressive action. In older patients, cognitive functioning is especially likely to decline during illness or injury. The nurses' assessment of an older adult's cognitive status is instrumental in identifying early changes in physiological status, ability to learn, and evaluating responses to treatment.

BEST TOOL: The Mini Mental State Examination (MMSE) is a tool that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE takes only 5-10 minutes to administer and is therefore practical to use repeatedly and routinely.

TARGET POPULATION: The MMSE is effective as a screening tool for cognitive impairment with older, community dwelling, hospitalized and institutionalized adults. Assessment of an older adult's cognitive function is best achieved when it is done routinely, systematically and thoroughly.

VALIDITY/RELIABILITY: Since its creation in 1975, the MMSE has been validated and extensively used in both clinical practice and research.

STRENGTHS AND LIMITATIONS: The MMSE is effective as a screening instrument to separate patients with cognitive impairment from those without it. In addition, when used repeatedly the instrument is able to measure changes in cognitive status that may benefit from intervention. However, the tool is not able to diagnose the cause for changes in cognitive function and should not replace a complete clinical assessment of mental status. In addition, the instrument relies heavily on verbal response and reading and writing. Therefore, patients that are hearing and visually impaired, intubated, have low English literacy, or those with other communication disorders may perform poorly even when cognitively intact.

MORE ON THE TOPIC:

- Folstein, M., Folstein, S.E., McHugh, P.R. (1975). "Mini-Mental State" a Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research*, 12(3); 189-198.
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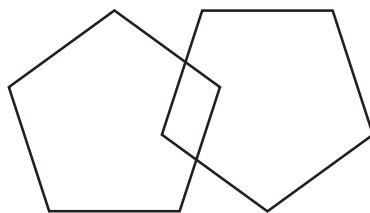
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The Mini-Mental State Exam

Patient _____ Examiner _____ Date _____

Maximum Score

- Orientation**
- 5 () What is the (year) (season) (date) (day) (month)?
- 5 () Where are we (state) (country) (town) (hospital) (floor)?
- Registration**
- 3 () Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
- Attention and Calculation**
- 5 () Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
- Recall**
- 3 () Ask for the 3 objects repeated above. Give 1 point for each correct answer.
- Language**
- 2 () Name a pencil and watch.
- 1 () Repeat the following "No ifs, ands, or buts"
- 3 () Follow a 3-stage command:
"Take a paper in your hand, fold it in half, and put it on the floor."
- 1 () Read and obey the following: CLOSE YOUR EYES
- 1 () Write a sentence.
- 1 () Copy the design shown.



_____ Total Score
ASSESS level of consciousness along a continuum _____
Alert Drowsy Stupor Coma

"MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used by permission.



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Appendix G

Geriatric Depression Scale

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

- | | | |
|---|-----|----|
| 1. Are you basically satisfied with your life? | yes | no |
| 2. Have you dropped many of your activities and interests? | yes | no |
| 3. Do you feel that your life is empty? | yes | no |
| 4. Do you often get bored? | yes | no |
| 5. Are you in good spirits most of the time? | yes | no |
| 6. Are you afraid that something bad is going to happen to you? | yes | no |
| 7. Do you feel happy most of the time? | yes | no |
| 8. Do you often feel helpless? | yes | no |
| 9. Do you prefer to stay at home, rather than going out and doing things? | yes | no |
| 10. Do you feel that you have more problems with memory than most? | yes | no |
| 11. Do you think it is wonderful to be alive now? | yes | no |
| 12. Do you feel worthless the way you are now? | yes | no |
| 13. Do you feel full of energy? | yes | no |
| 14. Do you feel that your situation is hopeless? | yes | no |
| 15. Do you think that most people are better off than you are? | yes | no |

Total Score _____

Geriatric Depression Scale (GDS)

Scoring Instructions

Instructions: Score 1 point for each bolded answer. A score of 5 or more suggests depression.

- | | | |
|---|------------|-----------|
| 1. Are you basically satisfied with your life? | yes | no |
| 2. Have you dropped many of your activities and interests? | yes | no |
| 3. Do you feel that your life is empty? | yes | no |
| 4. Do you often get bored? | yes | no |
| 5. Are you in good spirits most of the time? | yes | no |
| 6. Are you afraid that something bad is going to happen to you? | yes | no |
| 7. Do you feel happy most of the time? | yes | no |
| 8. Do you often feel helpless? | yes | no |
| 9. Do you prefer to stay at home, rather than going out and doing things? | yes | no |
| 10. Do you feel that you have more problems with memory than most? | yes | no |
| 11. Do you think it is wonderful to be alive now? | yes | no |
| 12. Do you feel worthless the way you are now? | yes | no |
| 13. Do you feel full of energy? | yes | no |
| 14. Do you feel that your situation is hopeless? | yes | no |
| 15. Do you think that most people are better off than you are? | yes | no |

A score of ≥ 5 suggests depression

Total Score _____

Ref. Yes average: The use of Rating Depression Series in the Elderly, in Poon (ed.): Clinical Memory Assessment of Older Adults, American Psychological Association, 1986

Appendix H

Alzheimer's Disease Assessment Scale

ADAS

Administration Manual for the Alzheimer's Disease Assessment Scale

Adapted from the Administration and Scoring Manual for the
Alzheimer's Disease Assessment Scale,
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Present manual modified by:
Donald Connor, Ph.D
Kimberly Schafer, MS
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INTRODUCTION

The test items on the cognitive part of the **ADAS** should be given in the order indicated.

**The WORD RECALL test is given first
and the
WORD RECOGNITION task is given last
with the
other cognitive tests given in-between.**

Separating the two word memory tasks in this way minimizes the chance that a subject will confuse the words from the two tasks.

At the start of a test session, before giving the **WORD RECALL** test, the tester should have a short conversation with the subject about neutral topics such as the weather, the subject's trip to the clinic, or what the subject had for breakfast. This conversation will help to put the subject at ease before the testing begins and will give the tester an opportunity to observe how the subject can use and understand language.

- There are three clinical ratings of language ability on the cognitive part of the **ADAS**.

The **ADAS** is not a timed test and the subject's score does not depend upon how rapidly the test is completed. The cognitive items should be given so that the session moves smoothly and quickly, but not so that the subject feels pressured to respond rapidly.

Feedback to the subject should be neutral and, usually, should not indicate whether or not the response was correct. Comments such as, "**That's fine**" or "**You're doing well**" are appropriate as long as the subject is trying. If the subject specifically asks whether or not they were correct, feedback can be given.

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INSTRUCTIONS for WORD RECALL TASK

On this task, the subject is given three trials to learn a list of high-frequency, high-imagery nouns. The 10 words are printed in block letters on white cards.

Use the appropriate word list for each visit as indicated on the study worksheet, and record the subject's responses on the study worksheet.

At the start of the first trial, the tester gives instructions similar to the following:	"I am going to show you some words printed on these white cards one at a time. Please read each word out loud and try to remember it, because later I will ask you to try to remember all of the words I have shown you. Ready, read the word and try to remember it."
The examiner can prompt with:	"Read it out loud and try to remember it" as necessary.
If the subject cannot read the word or is slow, the examiner can say the word out loud and have the subject repeat it. Note this and continue with this procedure at each testing. In some cases, the examiner may have to say all of the words and have the subject repeat them. Regardless, make sure the subject looks at each word while repeating it.	
After the presentation, the tester asks the subject to try to recall as many of the words as possible by saying:	"Good, now tell me all the words you remember that were on the list."
Two more learning and recall trials follow.	
For trials 2 and 3, say to the subject:	"Now I'm going to show you that same list again. Read each word out loud and try to remember it."
Encouragement can be given if the subject is nervous or giving up.	

SCORING:

The subject's score is the mean number of words *not* recalled on three trials (maximum score = 10)

Enter the subject's score on the study worksheet



INSTRUCTIONS for NAMING TASK

For this task, the subject is asked to name the 12 randomly presented real objects, with
high (Flower, Bed, Whistle, Pencil),
medium (Rattle, Mask, Scissors, Comb), and
low (Wallet, Harmonica, Stethoscope, Tongs) **frequency values**.

The subject is also asked to name the fingers on his/her dominant hand.

- Use the study worksheet to record the subject's responses.
- Objects should be presented in random order. Do not allow the subject to touch the objects.

Give the subject instructions similar to the following:	"Now I am going to show you some objects. I want you to tell me what their names are. What is this called?" (present object)
Continue to present objects in random order. The first question about each object should be:	"What is this called?" or "What is the name of this thing?"
If the subject responds with the object's function say:	"Yes, that's what it does, but what is its name?"

- If the subject does not respond, the examiner should give the clue for that item provided below. If the subject still does not respond or makes an error, go on to the next object.

ITEM	CLUES
Flower	grows in a garden
Bed	used for sleeping in
Whistle	makes a sound when you blow on it
Pencil	used for writing
Rattle	a baby's toy
Mask	hides your face
Scissors	cuts paper
Comb	used on hair
Wallet	holds your money
Harmonica	a musical instrument
Stethoscope	doctor uses it to listen to your heart
Tongs	picks up food



INSTRUCTIONS for NAMING TASK (Cont'd.)

- The subject is also asked to name the fingers of his/her dominant hand (e.g., thumb, index [pointer/forefinger], middle, ring finger, and pinky).

Give the subject instructions similar to the following:	“Now I am going to point to a part of your hand and I want you to tell me what it’s called. What is this?”
For the 4 fingers, if a query is necessary, say:	“What is another name for this finger?”

ITEM
Thumb
Index/forefinger/pointer
Middle
Ring
Pinky

The hardest part of scoring the naming task is determination of the range of correct responses based on the subject’s cultural and geographical background. A response other than the name given on the response form should be scored as correct if it is a name that would be used by a non-demented person with the same cultural background as the subject.

FOR EXAMPLE: the **Mask** might be called a **“false face”** in some parts of the U.S.; the **Wallet** might be called a **“billfold”** or the **Harmonica** might be called a **“mouth organ”**.

- Descriptions of the object, semantic or phonemic paraphasias should not be scored as correct.

EXAMPLES OF INCORRECT RESPONSES ARE: **“listening thing”** for **Stethoscope**, **“cutter”** for **Scissors**, and **“prongs”** for **Tongs**.

SCORING

0 = 0-2	items (objects and fingers) named incorrectly
1 = 3-5	items (objects and fingers) named incorrectly
2 = 6-8	items (objects and fingers) named incorrectly
3 = 9-11	items (objects and fingers) named incorrectly
4 = 12-14	items (objects and fingers) named incorrectly
5 = 15-17	items (objects and fingers) named incorrectly

Enter the subject’s score on the study worksheet.



INSTRUCTIONS for COMMANDS

This task is designed to assess receptive speech. The subject is asked to carry out 5 separate commands with 1 to 5 steps per command.

- Each command should be read once. If the subject does not respond or makes an error, the tester should give the **ENTIRE** command one more time.
- All commands should be given to every subject.
- If the subject demonstrates hearing or attentional difficulties, orient them by saying, “**Ready?**” or “**Now I want you to...**” prior to giving the command. Do **NOT** give the command more than twice.
- There should be no other materials near the pencil, watch and card (pens, paper, etc.)
- Each underlined element represents a single step.
- Each command is scored as a whole (no partial credit). All components must be correct for the response to be scored as correct.
- Use the study worksheet to record the subject’s responses.

Give the subject instructions similar to the following:	“Now I am going to ask you to do a few things. First, ... “Make a FIST .” (“Relax it” if needed) “Point to the CEILING and then to the FLOOR .”
Line up a Pencil, Watch, and Card on the table. Say:	“Put the PENCIL ON TOP OF THE CARD and then PUT IT BACK .” “Put the WATCH on the OTHER SIDE OF THE PENCIL and then TURN OVER THE CARD .”
Remove the Pencil, Watch, and Card from the table. Say:	“ TAP EACH SHOULDER TWICE with TWO FINGERS keeping your EYES SHUT .”

SCORING

0 =	All commands correct
1 =	1 command incorrect, 4 commands correct
2 =	2 commands incorrect, 3 commands correct
3 =	3 commands incorrect, 2 commands correct
4 =	4 commands incorrect, 1 command correct
5 =	All 5 commands correct

Enter the subject’s score on the study worksheet



INSTRUCTIONS for CONSTRUCTIONAL PRAXIS

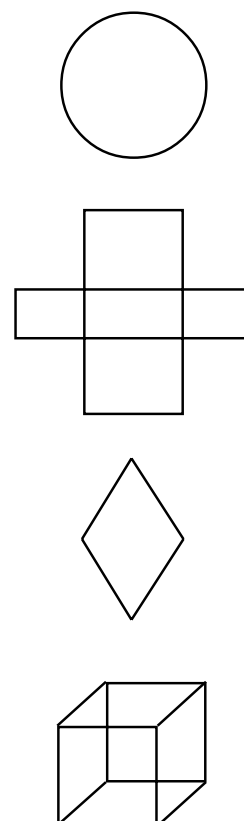
This test assesses the subject's ability to copy 4 geometric forms ranging from a very simple one (circle) to a fairly difficult one (cube).

- Use the study worksheet to score the subject's responses.
- The forms provided should be presented one at a time.
- The tester should give the subject a lead pencil with an eraser along with the drawing.

The instructions to the subject should be similar to the following:	"On this piece of paper is a shape. Try to draw another one that looks just like this, somewhere on the page." (Examiner may point to shape)
---	--

If the subject's response is quick or sloppy, prompt with:	"Take your time and try to draw it just like this one."
--	--

- The subject should be allowed **two attempts** for each shape. Allow a second attempt only if the subject asks or indicates a problem with their drawing. The subject may erase if they need to. If the subject draws on top of the printed design, count this as one attempt and indicate that they should try on an empty part of the page. If the subjects says the reproduction is poor, query if the subject wants another try. When two attempts are made, ask the subject to indicate which one is the best, and then score that attempt.
- If the subject cannot reproduce the figure in two attempts, the tester should go on to the next item.
- A drawing should be scored as correct if the subject has reproduced all of the essential features of the original. Changes in size do not count as errors. Small gaps between lines do not indicate an error, as long as the shape has been reproduced.



INSTRUCTIONS for CONSTRUCTIONAL PRAXIS (cont'd)

The forms should be presented in the following order:

Circle
Two Overlapping Rectangles
Diamond (Rhombus)
Cube

SCORING GUIDELINES:

Circle: A closed curved figure

Two Overlapping Rectangles: Forms must be four-sided, and overlap must be similar to presented form. Changes in size are not scored.

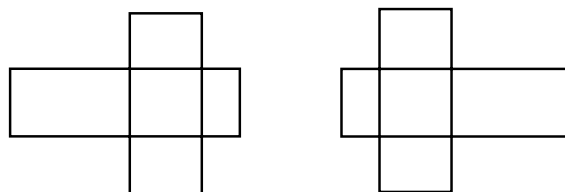
Diamond (Rhombus): Figure must be four-sided, oriented so that the points are at the top and bottom, and the sides are approximately equal length (e.g., longest side is not ≥ 1.5 times the length of the shortest side).

Cube: The form is 3-dimensional, with front face in the correct orientation, internal lines drawn correctly between corners. Opposite sides of faces should be approximately parallel.

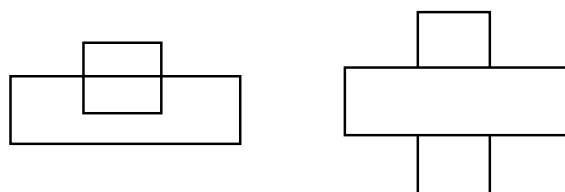
Examples of Correct and Incorrect Drawings:

Overlapping Rectangles

Correct

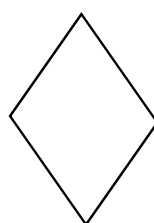


Incorrect



Diamond

Correct

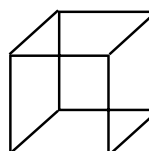


Incorrect

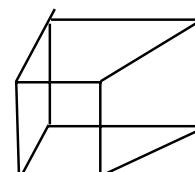
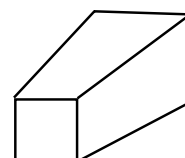


Cube

Correct



Incorrect



SCORING

0 =	All 4 drawings correct
1 =	1 form drawn incorrectly
2 =	2 forms drawn incorrectly
3 =	3 forms drawn incorrectly
4 =	4 forms drawn incorrectly
5 =	No figures drawn, scribbles; parts of forms; words instead of forms

Enter the subject's score on the study worksheet



INSTRUCTIONS for IDEATIONAL PRAXIS

This task is designed to determine whether the subject can perform a familiar but complex sequence sequence of actions.

➡ Use the study worksheet to record the subject's responses.

➡ A long envelope, an 8.5" x 11" sheet of paper and a pencil are placed in front of the subject.

Give the subject instructions similar to the following:

"I want you to pretend you have written yourself a letter. Take this piece of paper, fold it so that it will fit into the envelope, and then put it into the envelope. Then, seal the envelope, address the envelope to yourself, and show me where the stamp goes."

- ➡ There are 5 components to this task and each one is underlined in the instruction.
- ➡ If the subject forgets part of the task, or is having difficulty, the tester should repeat the instruction for the component of the task where the subject is having difficulty.

FOR EXAMPLE: If the subject stops after folding the paper and putting it in the envelope, the tester should give **one reminder** on the next component: **"Now seal the envelope."** If the subject cannot do this part, move on and give one reminder on the next component: **"Now address the envelope to yourself."**

After the first complete instruction only one additional reminder should be given for each component.

- ➡ Impairment on this item should reflect dysfunction in executing an overlearned task only and not recall difficulty.
- ➡ Any address which would enable a postal worker to deliver the envelope is counted as correct, even though it might not contain the subject's current address. The address should contain: name, street, city, and state. Zip code is not required.
- ➡ Have the subject indicate where the stamp goes by placing an "X" on the envelope.

SCORING

0 =	All components performed correctly
1 =	Failure to perform 1 component
2 =	Failure to perform 2 components
3 =	Failure to perform 3 components
4 =	Failure to perform 4 components
5 =	Failure to perform 5 components

Enter the subject's score on the study worksheet



INSTRUCTIONS for ORIENTATION

This task is designed to determine how well oriented the subject is with regard to time and place.

➔ Use the study worksheet to record the subject's responses.

➔ The components of orientation are:

Person
Day of the Week
Date, Month, Year
Season
Time of Day
Place

➔ The tester should ask the subject for each of these pieces of information one at a time.

➔ Make sure no watches, clocks, calendars, etc. are visible to the subject.

➔ One restatement of question is allowed (e.g., if subject confuses day and date).

➔ Acceptable range for answers include:

Date:	+ one day
Time:	+ one hour
Place:	Partial name acceptable (e.g., name of hospital, clinic or professional building)
Season:	Within one week prior to onset or within two weeks of termination

➔ **Month, Year, Day of the Week**, and the **subject's first and last name** must be **exact**.

SCORING: One point is given for each incorrect response (maximum = 8)

➔ Enter the subject's score on the study worksheet.



INSTRUCTIONS for WORD RECOGNITION

On this task the subject is given one trial to learn a list of 12 words.

- | | |
|---|--|
| <ul style="list-style-type: none"> ➤ Use the appropriate word list as indicated on the study worksheet, and record the subject's responses on the study worksheet. ➤ The learning part of this trial is similar to the learning part of the WORD RECALL TEST since the subject is asked to read each word aloud and try to remember it. | <ul style="list-style-type: none"> ➤ For the one test trial, the 12 studied words are mixed with 12 new words matched to the studied words for frequency and imagery and the subject is asked to decide for each word whether or not it was one of the studied words. |
|---|--|

At the start of the Learning Trial, give the subject instructions similar to the following:

"I am going to show you some words printed on these white cards. I want you to read each word out loud and try to remember it."

Some of the words on the WORD RECOGNITION TASK may not be familiar to the subject and the subject may have difficulty reading them. If the subject cannot read a word, the tester should say the word out loud. However, it is important for the subject to actually look at each word and try to read it.

At the end of the learning portion of a trial the tester should say something to the subject similar to the following:

"Now I'm going to show you another set of words. Some of the words were on the list I just showed you and others are new. For each word I want you to tell me whether it is one of the words I just showed you."

The tester shows the first word and says either:
or:

"Is this one of the words I showed you before, yes or no?"
"Did I show you this word before?"

The same instruction is given before the second test word. For the remaining test words the tester should say:

"How about this one?"



INSTRUCTIONS for WORD RECOGNITION (cont'd)

- If the subject does not remember the task (e.g., reads the word rather than responding **“Yes”** or **“No”**) then the tester should repeat or rephrase the entire question and make a note in the appropriate column on the worksheet that the subject had to be reminded of the task instructions. Likewise, if the subject appears to have fallen into a response set (i.e., saying **“Yes”** to every word or saying **“No”** to every word), then the test instructions should be repeated.



INSTRUCTIONS for REMEMBERING TEST INSTRUCTIONS

This item evaluates the subject's ability to remember the requirements of the WORD RECOGNITION TASK.

On each recognition trial, the subject is asked prior to presentation of the first two words:	"Did I show you this word before, or is this a new word?"
For the third word, the subject is asked:	"How about this one?"

- ➡ If the subject responds accurately, i.e., **"Yes"** or **"No"**, then memory for the instructions is accurate.
- ➡ If the subject fails to respond, this signifies that the instructions have been forgotten and the instruction is repeated.
- ➡ The procedure used for the third word is repeated for words 4-24. Each instance of memory failure for the test instructions is noted.

SCORING

0 =	Subject never needs extra reminders of instructions
1 =	Very mild – forgets once
2 =	Mild – must be reminded 2 times
3 =	Moderate – must be reminded 3 or 4 times
4 =	Moderately severe – must be reminded 5 or 6 times
5 =	Severe – must be reminded 7 or more times

Enter the subject's score on the study worksheet



INSTRUCTIONS for SPOKEN LANGUAGE ABILITY

This item is a global rating of the quality of speech, i.e., clarity, difficulty in making oneself understood.

- In rating this item the tester should consider all of the speech produced by the subject during the test session.
- Quantity of speech and word finding difficulty are not rated on this item.
- It should be noted that the higher scores (4-5) on this item are reserved for subjects whose expressive language abilities are impaired to such an extent that they seldom communicate without difficulty.

SCORING

0 =	No instances when it is difficult to understand the subject
1 =	Very mild – one instance of lack of understandability
2 =	Mild – subject has difficulty less than 25% of the time
3 =	Moderate – subject has difficulty 25-50% of the time
4 =	Moderately severe – subject has difficulty 50% of the time
5 =	Severe – one or two word utterance; fluent, but empty speech; mute

Enter the subject's score on the study worksheet



INSTRUCTIONS for WORD-FINDING DIFFICULTY AND COMPREHENSION

Word-Finding Difficulty in Spontaneous Speech

Along with Spoken Language Ability, this item rates impairment in expressive speech, but it rates **only word finding difficulty**, whereas Spoken Language Ability is a more global rating of the extent to which the subject can communicate verbally.

- ➡ To rate this item, the tester must determine whether the subject has difficulty in finding the desired word in spontaneous speech. The problem may be overcome by circumlocution, *i.e.*, giving explanatory phrases or nearly satisfactory synonyms.
- ➡ Do not include finger and object naming in this rating.

SCORING

0 =	No evidence of word finding difficulty in spontaneous speech
1 =	Very mild – 1 or 2 instances, not clinically significant
2 =	Mild – noticeable circumlocution or synonym substitution
3 =	Moderate – loss of words without comprehension on occasion
4 =	Moderately severe – frequent loss of words without comprehension
5 =	Severe – near total loss of content of words; speech sounds empty; 1 – 2 word utterances

Enter the subject's score on the study worksheet

Comprehension This item rates the subject's ability to understand speech

- ➡ To rate this item, the tester should consider how well the subject was able to understand the tester's speech during the opening discussion and during the test session
- ➡ Do not include responses to commands

SCORING

0 =	No evidence of poor comprehension
1 =	Very mild – 1 or 2 instances of misunderstanding
2 =	Mild – 3-5 instances of misunderstanding
3 =	Moderate – requires several repetitions and rephrasing
4 =	Moderately severe – subject only occasionally responds correctly, <i>i.e.</i> , yes/no questions
5 =	Severe – subject rarely responds to questions appropriately, not due to poverty of speech

Enter the subject's score on the study worksheet

Appendix I

Clinical Dementia Rating

Clinical Dementia Rating Worksheet

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's Clinical Dementia Rating (CDR). Please note information from the additional questions.

Memory Questions for the person close to the subject:

1. Does he/she have a problem with his/her memory or thinking? ☐ Yes ☐ No
- 1a. If yes, is this a consistent problem (as opposed to inconsistent)? ☐ Yes ☐ No
2. Can he/she recall recent events? ☐ Usually ☐ Sometimes ☐ Rarely
3. Can he/she remember a short list of items (shopping)? ☐ Usually ☐ Sometimes ☐ Rarely
4. Has there been some decline in memory during the past year? ☐ Yes ☐ No
5. Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (in the opinion of family and friends) ☐ Yes ☐ No
6. Does he/she completely forget a major event (e.g., trip, social function, family wedding) within a few weeks of the event? ☐ Usually ☐ Sometimes ☐ Rarely
7. Does he/she forget pertinent details of the major event? ☐ Usually ☐ Sometimes ☐ Rarely
8. Does he/she completely forget important information of the distant past (e.g., birthdate, wedding date, place of employment)? ☐ Usually ☐ Sometimes ☐ Rarely
9. Tell me about some recent event in his/her life that he/she should remember. (For later comparison with the subject's responses, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week:

Within 1 month:

10. When was he/she born?

11. Where was he/she born?

12. What was the last school he/she attended?

- Name

- Town/City

- Highest level achieved

13. What was his/her main occupation/job (or spouse's job if subject was not employed)?

14. What was his/her last major job (or spouse's job if subject was not employed)?

15. When did he/she (or spouse) retire and why?

Clinical Dementia Rating Worksheet

Orientation Questions for the person close to the subject:

How often does he/she know of the exact:

1. Date of the Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

2. Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

3. Year?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

4. Day of the Week?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Can he/she find his/her way about familiar streets?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighbourhood?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

8. How often can he/she find his/her way about indoors?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

Clinical Dementia Rating Worksheet

Judgment and Problem Solving Questions for the person close to the subject:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them:

- ☐ As good as they have ever been
☐ Good, but not as good as before
☐ Fair
☐ Poor
☐ No ability at all

2. Rate his/her ability to cope with small sums of money (e.g., give change, calculate the cost of groceries sold by weight):

- ☐ No loss
☐ Some loss
☐ Severe loss

3. Rate his/her ability to handle complicated financial or business transactions (e.g., balance check-book, pay bills):

- ☐ No loss
☐ Some loss
☐ Severe loss

4. Can he/she handle a household emergency (e.g., plumbing leak, small fire)?

- ☐ As well as before
☐ Worse than before because of trouble thinking
☐ Worse than before, another reason (why) _____

5. Can he/she understand situations or explanations?

- ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Does he/she behave* appropriately [i.e., in his/her usual (premorbid) manner] in social situations and interactions with other people?

- ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

*This item rates behaviour, not appearance.

Clinical Dementia Rating Worksheet

Community Participation Questions for the person close to the subject:

Occupational

1. Is the subject still working? ☐ Yes ☐ No ☐ N/A
If not applicable, proceed to item 4
If yes, proceed to item 3
If no, proceed to item 2
2. Did memory or thinking problems contribute to the subject's decision to retire? (Question 4 is next) ☐ Yes ☐ No ☐ D/K
3. Does the subject have significant difficulty in his/her job because of problems with memory or thinking?
☐ Rarely or Never ☐ Sometimes ☐ Usually ☐ Don't Know

Social life

4. Did he/she ever drive a car? ☐ Yes ☐ No
Does the subject drive a car now? ☐ Yes ☐ No
If no, is this because of memory or thinking problems? ☐ Yes ☐ No
5. If he/she is still driving, are there problems or risks because of poor thinking? ☐ Yes ☐ No
- *6. Is he/she able to independently shop for needs?
☐ Rarely or Never (Needs to be accompanied on any shopping trip) ☐ Sometimes (Shops for limited number of items; buys duplicate items or forgets needed items) ☐ Usually ☐ Don't Know
7. Is he/she able to independently carry out activities outside the home?
☐ Rarely or Never (Generally unable to perform activities without help) ☐ Sometimes (Limited and/or routine, e.g., superficial participation in church or meetings; going to the hairdresser's) ☐ Usually (Meaningful participation in activities, e.g., voting) ☐ Don't Know
8. Is he/she taken to social functions outside a family home? ☐ Yes ☐ No
If no, why not? _____
9. Would a casual observer of the subject's behaviour think the subject was ill? ☐ Yes ☐ No
10. If in nursing home, does he/she participate appropriately in social functions (thinking)? ☐ Yes ☐ No

IMPORTANT:

Is there enough information available to rate the subject's level of impairment in community participation?

If not, please probe further.

Community Participation: Such as going to church, visiting with friends or family, political activities, professional organisations such as associations of lawyers, other professional groups, social clubs, service organisations, educational programmes.

***Please add notes if needed to clarify subject's level of functioning in this area.**

Clinical Dementia Rating Worksheet

Questions on Housework and Hobbies for the person close to the subject:

- 1a. What changes have occurred in his/her abilities to perform household tasks? _____

- 1b. What can he/she still do well? _____

- 2a. What changes have occurred in his/her abilities to perform hobbies? _____

- 2b. What can he/she still do well? _____

3. If in nursing home, what can he/she no longer do well (Housework and Hobbies)? _____

Everyday Activities (the Dementia Scale of Blessed):

- | | No Loss | | Severe Loss |
|---------------------------------------|---------|-----|-------------|
| 4. Ability to perform household tasks | 0 | 0.5 | 1 |

Please describe: _____

5. Is he/she able to perform household tasks at the level of:
(Pick one. The person close to the subject does not need to be asked directly).

- ☐ No meaningful function.
(Performs simple activities, such as making a bed, only with much supervision)
- ☐ Functions in limited activities only.
(With some supervision, washes dishes with acceptable cleanliness; sets table)
- ☐ Functions independently in some activities.
(Operates appliances, such as a vacuum cleaner; prepares simple meals)
- ☐ Functions in usual activities but not at usual level.
- ☐ Normal function in usual activities.

IMPORTANT:

Is there enough information available to rate the subject's level of impairment in HOME & HOBBIES?

If not, please probe further.

Household Tasks: Such as cooking, laundry, cleaning, grocery shopping, taking out the rubbish, gardening, and basic home care.

Hobbies: Sewing, painting, handicrafts, reading, entertaining, photography, gardening, going to theatre or symphony, woodworking, participation in sports.

Clinical Dementia Rating Worksheet

Personal Care Questions for the person close to the subject:

*What is your estimate of his/her mental ability in the following areas:

	Unaided	Occasionally misplaced buttons, etc.	Wrong sequence, commonly forgotten items	Unable to dress
A. Dressing (the Dementia Scale of Blessed)	0	1	2	3
	Unaided	Needs prompting	Sometimes needs help	Always or nearly always needs help
B. Washing, grooming	0	1	2	3
	Cleanly; proper utensils	Messily; spoon	Simple solids	Has to be fed completely
C. Eating habits	0	1	2	3
	Normal complete control	Occasionally wets bed	Frequently wets bed	Doubly incontinent
D. Control of bladder and bowel (the Dementia Scale of Blessed)	0	1	2	3

* A box-score of 1 can be considered if the subject's personal care is improved compared with before, even if they do not receive prompting.

Clinical Dementia Rating Worksheet

Memory Questions for Subject:

1. Do you have problems with memory or thinking? ☐ Yes ☐ No
2. A few moments ago your (spouse, etc.) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details, if needed such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week

1.0 – Largely correct _____

0.5 _____

0.0 – Largely incorrect _____

Within 1 month

1.0 – Largely correct _____

0.5 _____

0.0 – Largely incorrect _____

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three trials).

Elements	1	2	3	4	5
	John	Brown,	42	Queen Street,	Auckland
	John	Brown,	42	Queen Street,	Auckland
	John	Brown,	42	Queen Street,	Auckland

(Underline elements repeated correctly in each trial).

4. When were you born? _____
5. Where were you born? _____
6. What was the last school you attended?
Name _____
Town/City _____ Highest level achieved _____
7. What was your main occupation/job (or spouse if not employed)? _____
8. What was your last major job (or spouse if not employed)? _____
9. When did you (or spouse) retire and why? _____

10. Repeat the name and address I asked you to remember:

Elements	1	2	3	4	5
	John	Brown,	42	Queen Street,	Auckland

(Underline elements repeated correctly).

Clinical Dementia Rating Worksheet

Orientation Questions for Subject:

Record the subject's answer verbatim for each question

1. What is the date today?

☐ Correct ☐ Incorrect

2. What day of the week is it?

☐ Correct ☐ Incorrect

3. What is the month?

☐ Correct ☐ Incorrect

4. What is the year?

☐ Correct ☐ Incorrect

5. What is the name of this place?

☐ Correct ☐ Incorrect

6. What town or city are we in?

☐ Correct ☐ Incorrect

7. What time is it?

☐ Correct ☐ Incorrect

8. Does the subject know who the person close to the subject is
(in your judgment)?

☐ Correct ☐ Incorrect

Clinical Dementia Rating Worksheet

Judgment and Problem Solving Questions for Subject:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the subject's best understanding of the problem. Circle nearest response.

Similarities:

Example: "How are a pencil and pen alike? (writing instruments)

How are these things alike?" Subject's Response

1. carrot.....cauliflower _____
(0 = vegetables)
(1 = edible foods, living things, can be cooked, etc.)
(2 = answers not pertinent; differences; buy them)

2. desk.....bookcase _____
(0 = furniture, office furniture; both hold books)
(1 = wooden, legs)
(2 = not pertinent, differences)

Differences:

Example: "What is the difference between sugar and vinegar? (sweet vs. sour)

What is the difference between these things?"

3. lie.....mistake _____
(0 = one deliberate, one unintentional)
(1 = one bad the other good – or explains only one)
(2 = anything else, similarities)

4. river.....canal (lake.....dam) _____
(0 = natural - artificial)
(2 = anything else)

Calculations:

5. How many 5 cent pieces in a dollar? ☐ Correct ☐ Incorrect
6. How many 20 cent pieces in \$5.40? ☐ Correct ☐ Incorrect
7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down. ☐ Correct ☐ Incorrect

Judgment:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?
(0 = try the telephone book, go to the city council for a directory; call a mutual friend)
(1 = call the police, call directory service (usually will not give address))
(2 = no clear response)
9. Subject's assessment of disability and social position and understanding of why he/she is present at the examination (perhaps already mentioned, but make your own judgment here):

☐ Good Insight ☐ Partial Insight ☐ Little Insight

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3
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	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal at first glance	No possibility of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult tasks abandoned; more complicated hobbies and interests abandoned	Only simple tasks preserved; very restricted interests, poorly maintained	No significant ability to do things in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal belongings	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Appendix J

Functional Activities Questionnaire

Functional Activities Questionnaire

Administration

Ask informant to rate patient's ability using the following scoring system:

- Dependent = 3
- Requires assistance = 2
- Has difficulty but does by self = 1
- Normal = 0
- Never did [the activity] but could do now = 0
- Never did and would have difficulty now = 1

Writing checks, paying bills, balancing checkbook	
Assembling tax records, business affairs, or papers	
Shopping alone for clothes, household necessities, or groceries	
Playing a game of skill, working on a hobby	
Heating water, making a cup of coffee, turning off stove after use	
Preparing a balanced meal	
Keeping track of current events	
Paying attention to, understanding, discussing TV, book, magazine	
Remembering appointments, family occasions, holidays, medications	
Traveling out of neighborhood, driving, arranging to take buses	
TOTAL SCORE:	

Evaluation

Sum scores (range 0-30). Cutpoint of 9 (dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment.

Pfeffer RI et al. Measurement of functional activities in older adults in the community. J Gerontol 1982; 37(3):323-329. Reprinted with permission of The Gerontological Society of America, 1030 15th Street NW, Suite 250, Washington, DC 20005 via Copyright Clearance Center, Inc.

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