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Research Article

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Effects of spermidine supplementation on slow oscillation-spindle coupling and sleep-dependent memory consolidation in individuals with subjective cognitive decline or mild cognitive impairment: protocol for a randomized, double-blind, placebo-controlled trial

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Background: Sleep disturbances and alterations in sleep microstructure emerge early in the course of Alzheimer's disease (AD) and may contribute to cognitive decline. In particular, the temporal coupling of cortical slow oscillations (SOs) and sleep spindles during non-rapid eye movement sleep deteriorates with ageing and cognitive impairment. It is closely linked to sleep-dependent memory consolidation. Spermidine, a naturally occurring polyamine and autophagy inducer, has been proposed as a potential intervention to support brain health, but evidence from human studies remains inconclusive. However, no human intervention studies have investigated the effects of spermidine supplementation on sleep physiology, particularly SO-spindle coupling, in individuals at increased risk of AD.

Methods: This randomized, double-blind, placebo-controlled trial investigates the effects of spermidine supplementation over 12 weeks in adults aged 55-75 years with subjective cognitive decline (SCD) or mild cognitive impairment (MCI). Seventy-six participants with SCD or MCI are randomized 1:1 to receive either 6 mg/day spermidine or matched placebo. An additional 38 cognitively healthy

participants serve as a baseline reference group. The primary outcome is SO-spindle coupling during non-rapid eye movement sleep, assessed by overnight high-density polysomnography at baseline and post-intervention. Secondary outcomes include further electroencephalography (EEG)-derived measures of sleep macro- and microstructure and sleep-dependent memory consolidation assessed using verbal and visuospatial memory tasks. Exploratory outcomes include subjective and actigraphy-derived sleep measures, alertness, broader cognitive and functional measures, peripheral markers of polyamine metabolism, autophagy-related pathways, inflammation, metabolic regulation and AD pathology, as well as baseline structural and functional neuroimaging. Treatment effects will be evaluated by comparing changes from baseline to follow-up between the spermidine and placebo groups.

Conclusions: This trial will determine whether spermidine supplementation improves SO-spindle coupling in individuals with SCD or MCI and will further characterize potential effects on sleep physiology and sleep-dependent memory consolidation. By integrating neurophysiological, behavioural, molecular, and neuroimaging measures, the study may provide insight into biologically plausible pathways linking spermidine supplementation, sleep physiology, and cognitive function in early stages of cognitive decline.

Trial registration: ClinicalTrials.gov, NCT07383311. Initially registered on 17 September 2025. Prospectively registered, further updated.

Protocol version: Based on BB 129/22f, version 7 (8 September 2026).

Sponsor: University Medicine Greifswald

Keywords: Sleep physiology, PSG, memory consolidation, Subjective Cognitive Decline, Mild Cognitive Impairment, spermidine

Introduction

Alzheimer's disease (AD) is the leading cause of dementia and develops gradually from preclinical disease through subjective cognitive decline (SCD) and mild cognitive impairment (MCI) to dementia [1–3]. Despite recent advances (e.g., anti-amyloid antibodies [4,5]), disease-modifying therapies remain limited, highlighting the need for preventive strategies targeting early pathophysiological mechanisms.

Among the biological processes implicated in AD pathogenesis, autophagy has emerged as a promising therapeutic target. Hence, dietary supplements are being investigated as potential strategies to counteract cognitive decline by targeting cellular mechanisms underlying neurodegeneration. Autophagy is a lysosome-dependent degradation pathway that maintains cellular homeostasis and neuronal health by removing damaged cellular components and protein aggregates [6,7]. In AD, autophagic processes are impaired early in the disease course, leading to the accumulation of amyloid-β and hyperphosphorylated tau, which drive neurodegeneration and cognitive decline [8,9].

Spermidine, a naturally occurring polyamine present in all living cells and in dietary sources such as wheat germ and soybeans, has recently received attention for its role in promoting autophagy [10,11], thereby supporting brain health and potentially delaying AD progression.

Besides impaired autophagy, sleep disturbances are increasingly recognized as both a consequence and a contributing factor to AD pathology [12]. Sleep problems are common in AD, affecting both macro- and microstructural features [13], already detectable at the SCD and MCI stages [14,15]. Sleep deprivation, as well as weak slow oscillation-spindle couplings during non-rapid eye movement sleep (NREM), have been associated with increased amyloid-β levels and tau burden [16,17].

Beyond its association with AD pathology, sleep plays a critical role in memory consolidation, altered by a complex interplay of sleep oscillations. These include slow oscillations (SOs), spindles, and hippocampal ripples. During SO-spindle coupling events, hippocampal replay signals are optimally timed to coincide with cortical up-states, promoting synaptic plasticity and memory stabilization [18]. In aging and AD, disturbances in SO-spindle coupling are associated with poorer memory performance, while external stimulation that enhances SO activity can improve memory consolidation [19].

Enhancing autophagy in specific brain regions in Huntington’s disease Drosophila models improved sleep patterns and reduced sleep fragmentation [20]. In patients with obstructive sleep apnea, impaired autophagy was associated with increased oxidative stress, cell death, and clinical symptoms such as excessive daytime sleepiness and cognitive impairment. Interventions that enhanced autophagy reversed these negative effects, highlighting a potential therapeutic role for autophagy modulation in sleep disorders [21,22]. Together, these findings support the idea that autophagy-related mechanisms and sleep physiology may be functionally intertwined.

Human evidence regarding spermidine supplementation, however, remains heterogeneous. Observational studies have reported that higher dietary spermidine intake was associated with larger

hippocampal volume, greater mean cortical thickness, and increased cortical thickness in brain regions particularly vulnerable to AD, including parietal and temporal areas [23]. Tavares et al. found that higher dietary spermidine intake was associated with better global cognitive performance, processing speed, and episodic memory across a comprehensive battery of eight cognitive tests, but not with brain volumetric measures [24]. In contrast, higher circulating spermidine concentrations have been associated with lower hippocampal volume, reduced global cortical thickness, higher AD-related brain ageing scores [25], and reduced SO-spindle coupling during NREM sleep [26]. These contradicting findings support the hypothesis that dietary intake and circulating levels may capture different biological processes.

Evidence from interventional studies is similarly inconclusive. A 12-month supplementation trial using 0.9 mg/day spermidine in individuals with SCD did not improve memory performance [27]. Further, Senekowitsch et al. demonstrated that orally administered spermidine is largely pre-systemically converted to spermine, which then enters the systemic circulation, raising important questions about biological processes [28]. These findings may partly explain the heterogeneous results observed across previous human studies, e.g., due to unclear optimal dose, supplementation duration, and underlying biological mechanisms.

Taken together, current evidence indicates that the relationships between spermidine supplementation, autophagy, sleep physiology, and cognitive function remain incompletely understood. SO-spindle coupling is of particular interest because its temporal precision deteriorates with ageing and cognitive impairment and is closely linked to sleep-dependent memory consolidation [29–31]. We therefore hypothesize that spermidine supplementation may improve SO-spindle coupling in individuals with SCD or MCI. Controlled intervention studies examining this electrophysiological mechanism together with memory and biological measures remain scarce. This study protocol was prepared in accordance with the SPIRIT guidelines available at https://www.consort-spirit.org/.

Objectives and Hypotheses

Primary objective

The primary objective of this randomized, double-blind, placebo-controlled trial is to determine whether 12 weeks of spermidine supplementation improves SO-spindle coupling during NREM sleep compared with placebo in individuals with SCD or MCI.

Secondary objectives

Secondary objectives are:

- to determine whether spermidine supplementation affects further EEG-derived measures of sleep macro- and microstructure, including SO and spindle activity;
- to determine whether spermidine supplementation improves sleep-dependent memory consolidation assessed using verbal and visuospatial memory tasks.

Exploratory objectives

Exploratory objectives are:

- to explore intervention effects on subjective sleep quality, habitual sleep-wake behaviour, alertness, and broader cognitive and functional outcomes in SCD/MCI;
- to explore whether spermidine supplementation modulates peripheral markers of polyamine metabolism, autophagy-related pathways, inflammation, metabolic regulation, and AD pathology;
- to characterize baseline structural and functional neuroimaging measures and their associations with sleep physiology, sleep-dependent memory consolidation, cognition, and biological markers in healthy controls (HC) vs. SCD/MCI;
- to explore associations among intervention-related changes in sleep physiology, memory consolidation, cognitive performance, and peripheral biological markers within the SCD/MCI group.

Methods

Study Design and Setting

This clinical trial investigates whether 12 weeks of spermidine supplementation improves SO-spindle coupling in individuals with SCD or MCI. Further EEG-derived sleep measures and sleep-dependent memory consolidation constitute secondary outcomes, while biological, neuroimaging, actigraphic, subjective sleep, and broader cognitive measures are exploratory. Age- and sex-matched HC are included as a baseline reference group. The study is conducted at the University Medicine Greifswald.

Participants

Eligibility

Eligibility criteria for SCD/ MCI participants and HC are summarized in Table 1. In brief, all participants will be aged 55-75 years. Individuals in this age range represent a population in whom age-related alterations in sleep physiology, memory consolidation, and early AD-related pathology become increasingly prevalent, while many individuals remain in the pre-dementia stages of SCD or MCI [32]. It therefore provides an optimal window for investigating preventive interventions targeting potentially modifiable mechanisms.

SCD participants report a subjectively perceived decline in memory function despite average, unaffected performance on neuropsychological tests. MCI participants meet established clinical criteria for mild cognitive impairment, including subjective and objective cognitive decline, preserved functional independence, and the absence of dementia. HC must have no subjective or objective cognitive impairment and must meet the same exclusion criteria as SCD and MCI participants.

Depending on their biomarker status (primarily AD pathology; see Table 2), participants are reassessed and assigned to either the SCD or MCI group.

Table 1. Eligibility criteria for participants

Category	Healthy Controls	SCD participants	MCI participants
Age	55-75 years	55-75 years	55-75 years
Informed consent	Required	Required	Required
Cognitive status	No subjective or objective cognitive impairment	Subjectively reported decline in cognitive function (esp. memory) despite objectively normal cognitive performance	MCI (objective memory impairment ≥1.5 SD below norm; preserved independence)
Dementia (DSM-IV)	Excluded	Excluded	Excluded
CNS-active medication (esp. blood pressure medication)	Assessed	Assessed	Assessed
Neurological disease (e.g., stroke, epilepsy, Parkinson's disease)	Excluded	Excluded	Excluded
Psychiatric disorders (major depression, psychosis, bipolar disorder, substance abuse)	Excluded	Excluded	Excluded
Participation in other interventional studies	Excluded	Excluded	Excluded
Sleep disorders	Excluded	Excluded	Excluded
Dietary supplements (polyamine supplementation)	Excluded	Excluded	Excluded

Category	Healthy Controls	SCD participants	MCI participants
Allergies (wheat germ, gluten, histamine)	- (no intervention)	Excluded	Excluded

Abbreviations: CNS Central Nervous System, DSM-IV Diagnostic and Statistical Manual of Mental Disorders IV, MCI mild cognitive impairment, SCD subjective cognitive decline, SD Standard Deviation

Recruitment and Ethics

HC and SCD participants will be recruited from the Greifswald population through newspaper advertisements and flyers and screened via telephone before enrollment. MCI participants will be recruited via the memory clinic at the Department of Neurology, University Medicine Greifswald. All participants will receive financial compensation after study completion (€300 for SCD and MCI participants and €250 for HC due to shorter study participation).

The study has been approved by the Ethics Committee of University Medicine Greifswald (approval number BB 129/22b, first approved 20th October 2022), as well as the data security departments of University Medicine Greifswald and our cooperation partner for blood analysis, Freie Universität Berlin. It is registered at ClinicalTrials.gov (TRN: NCT07383311, 17th September 2025), and the German Clinical Trials Register (DRKS00038122). Written informed consent is obtained from all participants before study participation.

Sample Size and Power

An a priori power analysis was conducted using G*Power (Version 3.1.9.4). Assuming an anticipated effect size of 0.7 for SO-spindle coupling, a two-sided α of .05, and 80% power, the planned sample comprises 76 participants with SCD or MCI and 38 HC, including an anticipated dropout rate of 10%.

Intervention

Randomization and Blinding

Participants with SCD or MCI are randomly assigned in a 1:1 ratio to receive either spermidine or placebo. Randomization is performed through Study Randomizer (2017) [33], a web-based randomization service by an independent third party who is not involved in participant recruitment, assessment, or data analysis. Randomization is stratified by age and sex. The independent third party has access to participant ID, age, and sex and is responsible for treatment allocation and preparation of the corresponding study supplements. The allocation sequence is inaccessible to participants and study personnel involved in recruitment and outcome assessment.

Participants and investigators involved in study assessments remain blinded to treatment allocation throughout data collection. Treatment allocation will be revealed only after completion of data collection and prior to the prespecified stage of statistical analysis. Emergency unblinding of an individual participant is permissible only if knowledge of treatment allocation is considered medically necessary for participant safety or clinical management. In such cases, allocation will be disclosed by the independent third party only for the affected participant, and the reason and circumstances of unblinding will be documented.

Supplementation

The spermidine supplement is manufactured by The Longevity Labs (Graz, Austria) and consists of a wheat germ extract containing 2 mg of spermidine per sachet. Participants in the intervention group will ingest three sachets daily (6 mg total) for 12 weeks. This dose was selected based on previous clinical studies demonstrating good tolerability and safety while remaining below the no-observed-adverse-effects level (e.g., [28]). The placebo consists of microcrystalline cellulose and is identical in appearance, taste, and smell. Participants are instructed not to change their dietary habits during the study, monitored via food questionnaires (e.g., Mediterranean Dietary Adherence Scale [34], Food Frequency Questionnaires). Adherence is assessed using an adapted version of the MARS-10 questionnaire [35] and by counting remaining doses at the end of the study.

Safety Monitoring

Adverse events (AEs) are defined as any unfavorable medical occurrence arising during the study, irrespective of its causal relationship to the investigational product. This includes newly occurring medical conditions as well as worsening of pre-existing diseases or symptoms, such as increased severity or frequency of episodic conditions or deterioration of persistent baseline conditions following trial intervention.

Serious adverse events (SAEs) are defined as events that result in death, are life-threatening at the time of occurrence, require inpatient hospitalization or prolong an existing hospitalization, result in persistent or significant disability or incapacity, or involve a congenital anomaly or birth defect. In addition, medically important events that may not immediately meet these criteria but require intervention to prevent one of these outcomes are also classified as SAEs. Hospital admissions solely for elective procedures or stable pre-existing conditions are not considered SAEs.

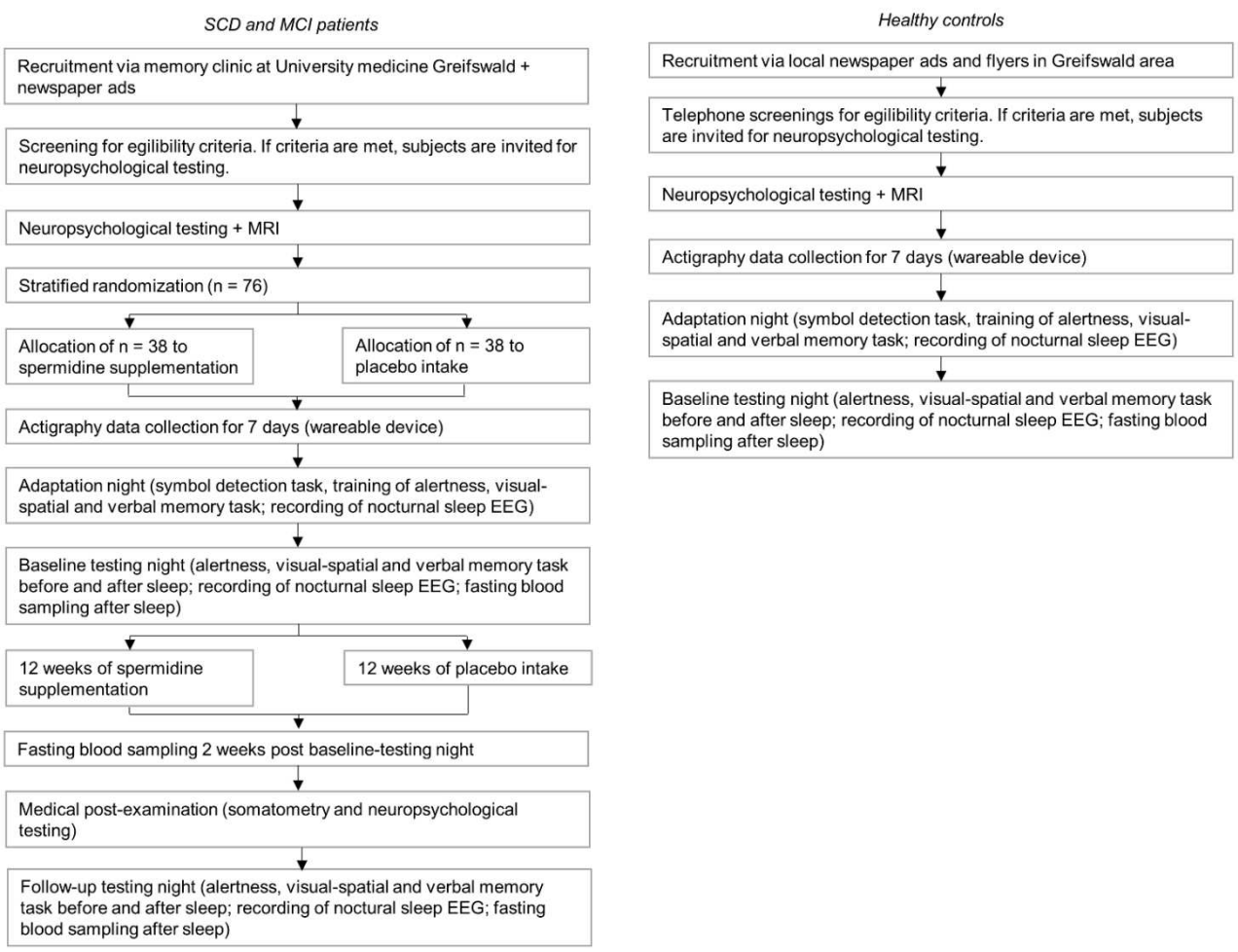
AEs and SAEs are monitored throughout the study. In the event of an SAE, the study physician assesses potential causality. If more than three SAEs likely related to the intervention occur, the trial will be discontinued.

Procedure

An overview of the study procedure is provided in Figure 1. All participants undergo baseline assessments, including medical history, somatometry, questionnaires, neuropsychological testing, and magnetic resonance imaging (MRI). Following baseline assessments, participants complete an adaptation night and a testing night, including overnight EEG and computerized cognitive tasks, and a blood draw the morning after a testing night.

SCD and MCI participants subsequently undergo a 12-week supplementation period, after which they complete follow-up assessments identical to baseline (except for a second MRI), including a second testing night. HC participate only in baseline assessments.

Figure 1. Study procedure for each subject group.



Abbreviations: EEG electroencephalography, MRI Magnetic Resonance Imaging

Outcome Measures

Primary Outcome

The primary outcome is SO-spindle coupling during NREM sleep, assessed by overnight polysomnography (PSG). Coupling between the phase of cortical SOs and spindle activity will be quantified using an established phase-amplitude coupling approach based on Ladenbauer et al. [36]. The primary treatment effect will be defined as the between-group difference in change in SO-spindle coupling from baseline to follow-up.

Objective nocturnal sleep physiology is assessed by overnight PSG. EEG is continuously recorded using a 64-channel ActiCAP system with BrainAmp amplifiers (Brain Products GmbH, Gilching, Germany), complemented by four electrooculography and two chin electromyography electrodes. EEG electrodes are positioned according to the extended international 10-20 system and referenced to the right mastoid. Signals are acquired at 1000 Hz, with electrode impedances maintained below 10 kΩ whenever possible.

Secondary Outcomes

Further EEG-derived sleep measures

Secondary EEG-derived outcomes include sleep macrostructure and microstructure, including SO characteristics, spindle activity and density, and spectral sleep measures.

Sleep stages will be automatically classified in 30-s epochs using the YASA sleep-staging algorithm [37]. Automated classifications will undergo predefined quality-control procedures, including visual review of low-confidence or physiologically implausible epochs. Spectral power will additionally be quantified across predefined frequency bands. Detailed pre-processing procedures, frequency-band definitions, artefact-rejection criteria, and signal-detection parameters will be prespecified in the Statistical Analysis Plan before unblinding.

Sleep-dependent memory consolidation

This secondary measure is operationalized by overnight retention in two computerized verbal and visuospatial memory tasks administered before sleep and after awakening (see Figure 2).

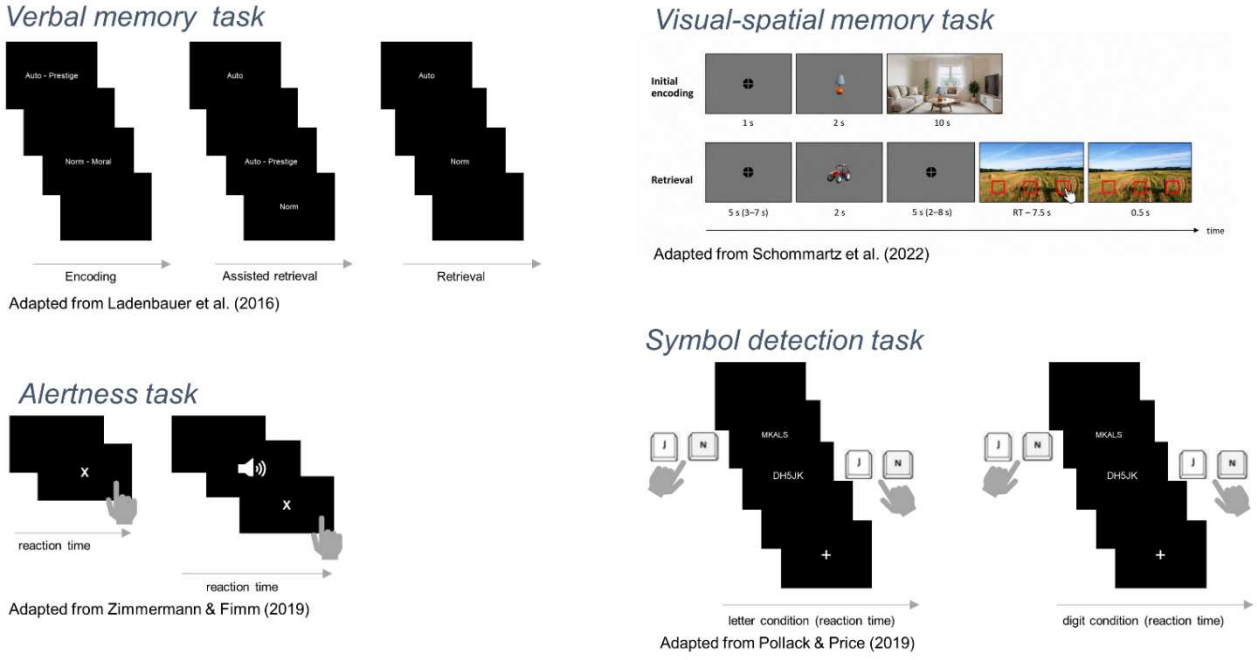
Visuospatial Memory Task

Visuospatial memory is assessed using an object-location association task adapted from Schommartz et al. [38]. Participants complete a practice session with feedback during the adaptation night. At baseline and follow-up, 60 object-location associations are encoded by presenting objects at predefined locations within semantically congruent scenes. Memory is assessed without feedback using a three-alternative forced-choice procedure, with 30 randomly selected associations tested before sleep and the remaining 30 after sleep. Performance is quantified by retrieval accuracy and reaction time.

Verbal Memory Task

Declarative verbal memory is assessed using an established cued word-pair association task adapted from Ladenbauer et al. [39]. Following a practice session during the adaptation night, participants encode 40 semantically related German category-instance word pairs at baseline and follow-up. Encoding is followed by an initial cued-recall test with feedback to provide an additional learning opportunity. Recall is subsequently assessed without feedback before sleep and again the following morning. Performance is quantified by recall accuracy and overnight retention.

Figure 2. Computerized cognitive tasks.



Verbal and visual-spatial memory and alertness are assessed at baseline and, in patients with SCD/MCI, after three months of supplementation. The symbol detection task is assessed at baseline only.

Exploratory Outcomes

Subjective sleep quality

Subjective sleep quality is assessed using standardized questionnaires: Pittsburgh Sleep Quality Index [40], Epworth Sleepiness Scale [41], Morningness-Eveningness Questionnaire [42], Essen Questionnaire on Age and Sleepiness [43], and the Berlin Questionnaire [44] .

Habitual sleep-wake behavior (actigraphy)

Actigraphy is a method for continuously measuring movement data, allowing estimation of sleep-wake patterns, rest-activity rhythms, and overall physical activity.

Each participant will be provided with an actigraph (ActiGraph wGT3X BT by ProCare B.V., Netherlands), worn continuously for one week to collect individualized activity data. For device initialization, the following parameters will be entered: participant identification number, sex, height (cm), weight (kg), date of birth, ethnicity, and wearing position (non-dominant upper arm). Data acquisition starts and ends automatically at predefined times (e.g., after the MRI appointment until the end of the adaptation night). Activity data are recorded at a sampling rate of 30 Hz using the device's idle sleep mode. Actigraphy data will be used to determine overall physical activity (standing, lying, sitting, and "off" in hours and percentage per day) and several sleep measures: in-bed and out-of-bed time, sleep latency (in min), total time in bed (in min), total sleep time (in min), wake after sleep onset, number of awakenings, average awakening (in min), as well as sleep efficiency (in percent), based on the Cole-Kripke algorithm.

Alertness

The alertness task, computerized via TAP 2.3.1 [45], is trained on the adaptation night and assessed at baseline (and follow-up) before and after sleep. It comprises two runs without a prior warning tone and two runs with one. Subjects must react to a cross in the middle of the screen by pressing a button. In the warning tone condition, subjects should not be distracted by the warning tone, but react to the

cross in the middle of the screen. Task performance is measured by speed (in ms) and hit or miss (see Figure 2).

Biological Measures

Blood samples are collected at baseline (HC and SCD / MCI participants), two weeks after baseline (SCD / MCI only), and follow-up (SCD / MCI only). Measures include polyamine concentrations and eIF5A hypusination assessed in peripheral blood mononuclear cells (PBMCs), neuropeptide Y levels, AD-related blood biomarkers, and standard clinical chemistry and inflammatory markers (for a full overview, see Table 2 and Table S1). Samples are collected, preprocessed, and stored at -80 °C until analyses at the Neuroimmunology Lab of the University Medicine Greifswald, or are directly analyzed by the Institute for Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald. Autophagy and polyamine-related markers will be analyzed at the Institute of Biology, Freie Universität Berlin, Germany.

Table 2. Blood-based biomarkers and sampling schedule

Biomarker domain	Analytes	Sample type	Time points	Scientific rationale
Autophagy & polyamine metabolism	Autophagy markers (e.g., LC3-II, p62/SQSTM1)*	PBMCs (CPT tube)	Baseline, follow-up	Assessment of autophagic activity and target engagement
	Spermidine and other polyamines	PBMCs (CPT tube)	Baseline, follow-up	Assessment of systemic polyamine availability
	eIF5A hypusination	PBMCs (CPT tube)	Baseline, 2 weeks post baseline, follow-up	Molecular marker of autophagy-related translation
Alzheimer's disease pathology	p-tau181, p-tau217, p-tau231	Plasma (EDTA)	Baseline, follow-up	Tau phosphorylation and neurodegeneration
	Aβ40, Aβ42	Plasma (EDTA)	Baseline, follow-up	Amyloid pathology
	Total tau, neurofilament light chain (NfL)	Plasma (EDTA)	Baseline, follow-up	Neuroaxonal injury
Neuroendocrine & metabolic markers	Neuropeptide Y	Serum	Baseline, follow-up	Sleep–stress–metabolism interactions
	Insulin, IGF-1	Serum	Baseline, follow-up	Metabolic and growth factor signaling
Inflammation & cardiovascular risk	hsCRP, IL-6, TNF-α, IL-1	Plasma (Li-heparin)	Baseline, follow-up	Neuroinflammation
	Homocysteine	Plasma (EDTA)	Baseline, follow-up	Cardiovascular risk factor

	Clinical safety parameters	Blood count, liver and kidney function, lipids, coagulation	Serum / plasma	Baseline, follow-up	Safety monitoring

*Final marker panel depending on assay validation.

Abbreviations: Aβ Amyloid beta, CPT Cell Preparation Tube, EDTA Ethylenediaminetetraacetic Acid, eIF5A eukaryotic translation initiation factor 5A , hsCRP high-sensitivity C-reactive protein, IGF-1 Insulin-like Growth Factor 1, IL-1/6 Interleukin, Li-heparin lithium heparin, NfL neurofilament light chain, PBMC Peripheral Blood Mononuclear Cells, p-tau phosphorylated tau, TNF-α Tumor Necrosis Factor-alpha

MRI Measures

Structural and functional MRI is performed at the Baltic Imaging Center (Department of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald) using a 3 Tesla Siemens Skyra scanner equipped with a 32-channel head coil. MRI acquisition takes place approximately one week before baseline sleep EEG. During the resting-state functional MRI acquisition, participants are instructed to keep their eyes closed while remaining awake.

MRI serves two purposes within the present study. First, it is used to exclude clinically relevant structural brain abnormalities and neurological comorbidities. Second, baseline neuroimaging data provide exploratory measures of brain morphology, white matter microstructure, and functional brain organization that may be associated with sleep physiology, sleep-dependent memory consolidation, and biological markers.

The imaging protocol includes high-resolution T1-weighted structural imaging, resting-state blood oxygenation level-dependent (BOLD) functional MRI, diffusion tensor imaging (DTI), and three-dimensional fluid-attenuated inversion recovery (3D FLAIR). Acquisition parameters are summarized in Table 3.

Structural MRI will be used to derive cortical and subcortical brain measures, DTI will be used to characterize white matter microstructure, and resting-state fMRI will be used to investigate functional connectivity within large-scale brain networks relevant to cognitive function. 3D FLAIR images will be used to characterize white matter lesions and other structural abnormalities relevant to cognitive aging. Image preprocessing and analysis will be performed using standardized and validated neuroimaging pipelines. Details of image preprocessing, quality control, and statistical analyses will be specified in the Statistical Analysis Plan prior to unblinding.

Table 3. Neuroimaging data acquisition parameters.

Sequence	Main Parameters
Resting-state fMRI	TR = 2000 ms, TE = 30 ms, FOV = 192 × 192 mm², 34 slices, 360 volumes, descending acquisition, 3.0×3.0×3.0 mm³, flip angle 90°
T1 MPRAGE	TR = 1690 ms, TE = 2.52 ms, TI = 900 ms, 176 slices, 1.0 × 1.0 × 1.0mm³, flip angle 9°
DTI	TR = 11100 ms, TE = 107 ms, 70 slices, 1.8 × 1.8 × 2.0 mm³, 64 directions (b = 1000 s/mm²)
3D FLAIR	TR = 5000 ms, TE = 386 ms, 176 slices, 1.0×1.0×1.0 mm³

Abbreviations: TR repetition time, TE echo time, TI inversion time, FOV field of view, fMRI functional magnetic resonance imaging, DTI diffusion tensor imaging, FLAIR fluid-attenuated inversion recovery, MPRAGE magnetization prepared rapid acquisition gradient echo

Cognitive, Functional and Psychological Assessments

Cognitive performance will be assessed using standardized neuropsychological tests: CERAD-plus (Consortium to Establish a Registry for Alzheimer's Disease) [46], multiple-choice vocabulary intelligence test [47], and Digit Span Test [48]. Moreover, numerical and mathematical measures will be assessed via the Numerical Activities of Daily Living (short version) [49], the Subjective Numeracy Scale [50], and the Berlin Numeracy Test [51]. Functional abilities will be evaluated using the self-report version of the Everyday Cognition Questionnaire [52], and the extended Instrumental Activities of Daily Living scale [53].

Furthermore, the following affective measures will be assessed: Dia-X Depression and Anxiety Screening [54], the Geriatric Depression Scale [55], the Mathematics Anxiety Scale [56], the Headache Impact Test [57], and Migraine Disability Assessment [58].

The Mediterranean Diet Adherence Screener [34], a semi-quantitative food-frequency and a lifestyle questionnaire regarding physical activity, nicotine, and alcohol consumption, will be assessed.

Symbol Detection Task

Only at baseline, participants complete an adapted, shortened version of the digit and letter detection task described by Pollack and Price [59]. Participants are presented with strings of five symbols and, depending on the condition, indicate by key press whether the string contains a digit or a letter. Each condition comprises two blocks, with the order of conditions randomized across participants (see Figure 2).

Data Management and Retention

All study data are pseudonymized and stored in accordance with institutional data protection and security regulations, with personally identifiable information stored separately and accessible only to authorized personnel. Paper-based data are digitized and independently verified, and digital data are stored on secure institutional servers. Study data will be retained for at least 10 years in accordance with good scientific practice.

Statistical Analysis

A detailed Statistical Analysis Plan (SAP) specifying preprocessing procedures, statistical models, handling of missing data, sensitivity analyses, and approaches to multiplicity will be finalized before database lock and unblinding.

Confirmatory analysis will focus on the primary outcome, SO-spindle coupling. The primary treatment effect will be evaluated by comparing the change from baseline to follow-up between the spermidine and placebo groups within the randomized SCD/MCI cohort using an appropriate repeated-measures regression model, including treatment group, time, and their interaction. Diagnostic status (SCD vs. MCI) will be included as a predefined covariate or stratification factor where appropriate.

Secondary analyses will evaluate intervention effects on further EEG-derived sleep parameters and sleep-dependent memory consolidation. Exploratory analyses will investigate effects on subjective sleep, actigraphy, alertness, cognitive and functional measures, peripheral biomarkers, and associations involving baseline MRI measures.

Primary analyses will follow the intention-to-treat principle. Missing outcome data will be handled according to procedures prespecified in the SAP, with per-protocol analyses conducted as sensitivity analyses. HC will not be included in confirmatory treatment-effect analyses but will serve as an exploratory baseline reference group.

Discussion

The present study describes a randomized, double-blind, placebo-controlled trial investigating whether spermidine supplementation improves SO-spindle coupling in individuals with SCD or MCI. Further EEG-derived sleep parameters and sleep-dependent memory consolidation will be assessed as secondary outcomes, while peripheral biological, cognitive, actigraphic, and neuroimaging measures provide exploratory characterization of potential treatment-related pathways.

Human evidence on the effects of spermidine remains heterogeneous. Observational studies have associated higher dietary spermidine intake with favorable cognitive and structural brain outcomes, whereas circulating spermidine concentrations have been associated with markers of brain aging and altered sleep microstructure [23–26]. Intervention studies have likewise yielded inconclusive results, and the presystemic conversion of orally administered spermidine to spermine introduces additional uncertainty regarding the biological mechanisms underlying its potential effects [27,28]. The present trial addresses these uncertainties by jointly assessing objective sleep physiology and sleep-dependent memory consolidation while incorporating peripheral molecular measures to characterize potential biological responses to supplementation. Major strengths of the study include its randomized, double-blind, placebo-controlled design and the multimodal characterization of individuals at increased risk of AD. In particular, high-density PSG enables detailed assessment of sleep macro- and microstructure, with SO-spindle coupling constituting the primary electrophysiological outcome. Given that the temporal coordination of SO and spindles deteriorates with ageing and cognitive impairment and is closely related to memory consolidation, this measure provides a biologically plausible target for spermidine supplementation [18,19]. Peripheral measures of polyamine metabolism, autophagy-related processes, and AD pathology complement these neurophysiological and behavioral outcomes. Baseline multimodal MRI further characterizes brain morphology, white matter integrity, cerebrovascular burden, and functional connectivity and enables exploratory investigation of their relationships with sleep, cognition, and biological markers.

Conclusion

Overall, this trial will determine whether spermidine supplementation improves SO-spindle coupling in individuals with SCD or MCI and will further characterize its effects on sleep physiology and sleep-dependent memory consolidation. Integrating neurophysiological, behavioral, and peripheral molecular measures may provide insight into biologically plausible pathways underlying potential treatment effects in early cognitive decline.

Trial status

The recruitment of participants started in June 2026.

The last follow-up is expected in December 2028.

Acknowledgements

None.

Protocol amendments

Any substantial amendment to the study protocol will be submitted to the institutional Ethics Committee for review and approval.

Consent or assent

A member of the investigational team will obtain written informed consent during study enrollment after reviewing the participant information sheet, the participant's questions, and the study inclusion and exclusion criteria.

Confidentiality

The collected data will be treated as confidential. Direct access to personal information and source data documentation will only be given to study monitors, study assessors, and the research team.

Authors' contributions

AF and SMW conceptualized and designed this trial. AF is supervising its implementation. SMW and AF are implementing the trial and supervising its conduct. MFS is performing recruitment and assessments. MFS, SMW, and AF drafted the study protocol. MFS will be performing statistical analyses. JR assists with patient recruitment through the memory clinic, which is part of the Department of Neurology. RM is responsible for the EEG setup, assists with task programming, and provides technical support. AV is supervising blood test analyses. All authors will be contributing to the interpretation of the data. All authors read and revised the original draft and subsequent versions of the manuscript. All authors read and approved the final version of the study protocol.

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Availability of data and materials

The data underlying this study cannot be made publicly available in order to protect participant privacy and comply with ethical approval guidelines regarding vulnerable populations. De-identified data sets may be requested upon reasonable application to the corresponding author for researchers who meet criteria for access to confidential data.

Ethics approval and consent to participate

The study was approved by the ethics committee of the University Medicine Greifswald, Germany (B 129/22e, date of first approval: **20.10.2022**). All procedures conducted during the trial will be carried out in compliance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no actual or potential conflicts of interest.

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