

Locus coeruleus activity is related to sleep and 24-h rest-activity rhythms in the context of plasma Alzheimer's disease markers: a 7T MRI study of older individuals

Yuliya Patsyuk¹, Prokopis Prokopiou², Nicholas J. Ashton^{3,4,5}, Shorena Janelidze⁶, Kaj Blennow^{3,7}, Oskar Hansson^{6,8}, Henrik Zetterberg^{3,7,9,10,11,12,13}, Benedikt A. Poser^{14,15}, Heidi I.L. Jacobs^{1,2*}, Maxime Van Egroo^{1,2*}



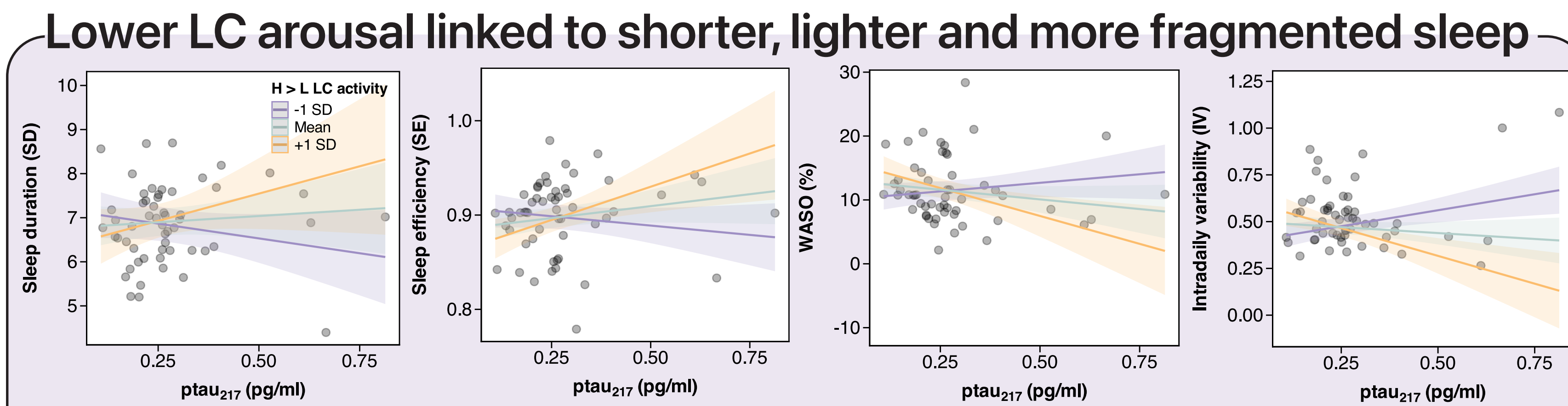
Background
The locus coeruleus (LC), an early tau pathology site¹ and key regulator of sleep-wake dynamics², may link sleep-wake disturbances to AD pathogenesis. Yet, the **interplay between LC functional metrics, sleep-wake regulation, and early AD pathology** remains poorly understood. Here, we investigated whether **daytime arousal-based LC activity relates to objective sleep-wake measures** in the context of **plasma AD-related biomarkers** in asymptomatic older individuals.

Methods
Imaging: Fifty-five cognitively unimpaired older adults (mean age 65.8 ± 8.6 y; 49% female) underwent a 7T MRI session including whole-brain MP2RAGE structural imaging and dedicated LC imaging using a high-resolution magnetization transfer-weighted turbo flash MRI sequence (0.4x0.4x0.5mm) sensitive to LC-related contrast, as well as an fMRI protocol (1.25x1.25x1.25mm) acquired during an affective task. A high-versus low-arousal (H > L) contrast, averaged across LC voxels, was computed as the index of daytime task-related LC activity.

Sleep & rest-activity pattern assessment: Within ~1.3 years of imaging, participants wore a wrist accelerometer (Axivity AX3) for ten days, from which intradaily variability (IV), interdaily stability (IS), sleep duration, sleep efficiency (SE) and wake after sleep onset (WASO%) were derived. Within ~4.5 years of the blood draw, three nights of at-home frontopolar EEG were recorded using the Sleep Profiler, yielding actigraphy-matching sleep-wake metrics and sleep macrostructure (N1%, N2%, N3%, REM%).

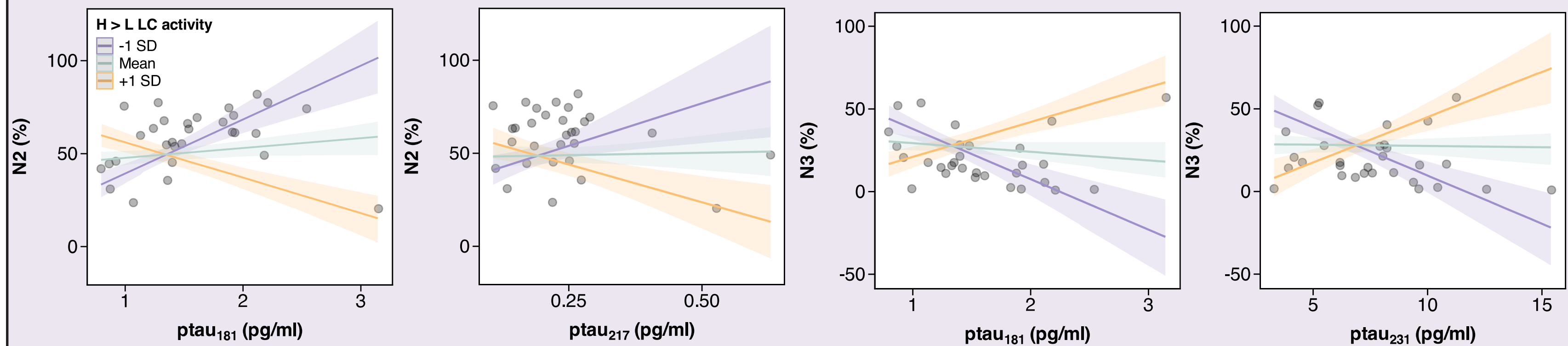
Plasma AD markers: Plasma levels of AD biomarkers including glial fibrillary acidic protein (GFAP), tau phosphorylated at threonine 181 (ptau₁₈₁), threonine 217 (ptau₂₁₇) and threonine 231 (ptau₂₃₁) were assessed using single-molecule array technology.

Statistical analyses: Robust multiple linear regression probed relationships between daytime LC activity (H > L) and sleep and rest-activity measures in the context of plasma AD biomarkers. All models were adjusted for age, sex, and BMI, and FDR corrected. Sensitivity analyses tested anatomical specificity using a shifted LC mask, controlled for LC structural integrity, and accounted for time lags between acquisitions.



At elevated ptau₂₁₇, lower LC arousal corresponded to lower SD ($p=.04$), lower SE ($p=.02$), higher WASO% ($p=.02$), lower IS ($p=.04$), and higher IV ($p=.003$). At elevated ptau₁₈₁*, lower LC arousal associated with higher WASO% ($p=.05$), lower IS ($p=.03$), and higher IV ($p<.001$). At elevated ptau₂₃₁*, lower LC activity linked to higher IV ($p<.001$). At higher GFAP*, lower LC activity linked to lower SE ($p=.006$), higher WASO% ($p=.004$), and higher IV ($p=.03$).

* Results not shown in figures.



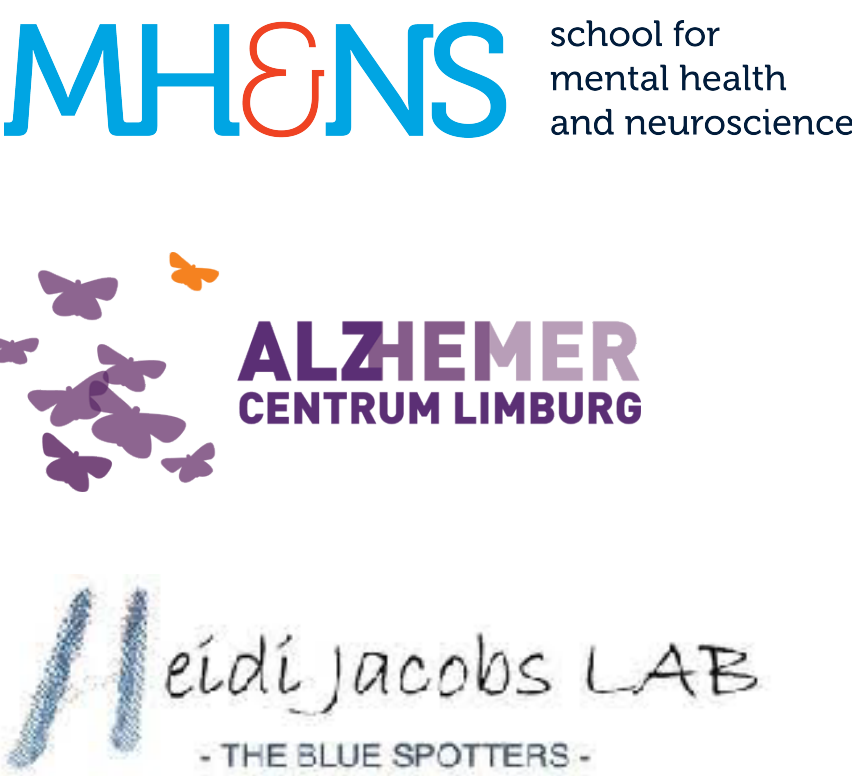
At elevated ptau₁₈₁, lower LC activity corresponded to more time spent in N2 ($p<.001$) and less N3 ($p<.001$). At elevated ptau₂₁₇, lower LC activity was associated with more N2 ($p=.007$). At elevated ptau₂₃₁, lower LC activity was linked to less N3 ($p=.001$).

Discussion
Lower daytime LC arousal is linked to worse sleep and 24-hour rest-activity pattern fragmentation. Drawing on animal evidence³, we propose that reduced daytime LC engagement may prevent the "functional fatigue" needed for healthy nocturnal sleep and impair LC-mediated processes such as glymphatic clearance⁴, contributing to poorer sleep amid emerging AD pathology.

Summary
Lower daytime task-related LC activity is related to shorter, lighter, and more fragmented sleep as well as to disruption of circadian rest-activity patterns in the presence of biomarker evidence of early AD pathology in asymptomatic older individuals. These findings suggest an aggravating or protective effect of, respectively, impaired or preserved LC function in early AD-related sleep-wake disturbances.

References
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¹ Faculty of Health, Medicine and Life Sciences, Mental Health and Neuroscience Research Institute, Alzheimer Centre Limburg, Maastricht University, Maastricht, Netherlands
² Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
³ Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
⁴ Banner Alzheimer's Institute and University of Arizona, Phoenix, AZ, USA
⁵ Banner Sun Health Research Institute, Sun City, AZ 85351, USA
⁶ Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden
⁷ Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
⁸ Memory Clinic, Skåne University Hospital, Malmö, Sweden
⁹ Department of Neurodegenerative Disease, UCL, Institute of Neurology, Queen Square, London, UK
¹⁰ UK Dementia Research Institute at UCL, London, UK
¹¹ Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
¹² Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA
¹³ Centre for Brain Research, Indian Institute of Science, Bangalore, India
¹⁴ Max Planck Institute for Human Development, Max Planck Research Group MR Physics, Berlin, Germany
¹⁵ Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, Netherlands



Contact: yuliya.patsyuk@maastrichtuniversity.nl

