



Sleep-Related Cerebral Hypoperfusion Across the Cognitive Continuum: From Normal Aging to Mild Cognitive Impairment

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Background

Sleep quality is increasingly recognized as a modifiable determinant of brain health and cognitive ageing. Sleep disturbance has been linked to altered cerebral perfusion, but whether these associations differ across the cognitive continuum—from cognitively normal (CN) to subjective cognitive decline (SCD) and mild cognitive impairment (MCI)—remains unclear. We examined associations between sleep quality and cerebral perfusion across CN, SCD, and MCI.

Methods and Materials

- Sample:** 1,698 BIOCIS participants were included and classified as CN, SCD, or MCI using NIA-AA criteria.
- Sleep assessment:** Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI).
- Neuroimaging:** Cerebral perfusion was quantified using arterial spin labelling MRI, deriving global and regional cerebral blood flow (CBF).
- Primary analysis:** Within-group linear regression examined associations between PSQI component scores and CBF, adjusting for age, sex, education, and APOE ε4 status, with false discovery rate correction.
- Moderation analysis:** For significant PSQI-CBF associations, plasma pTau181, Aβ42/40, GFAP, and NfL were tested as moderators of effect estimates.

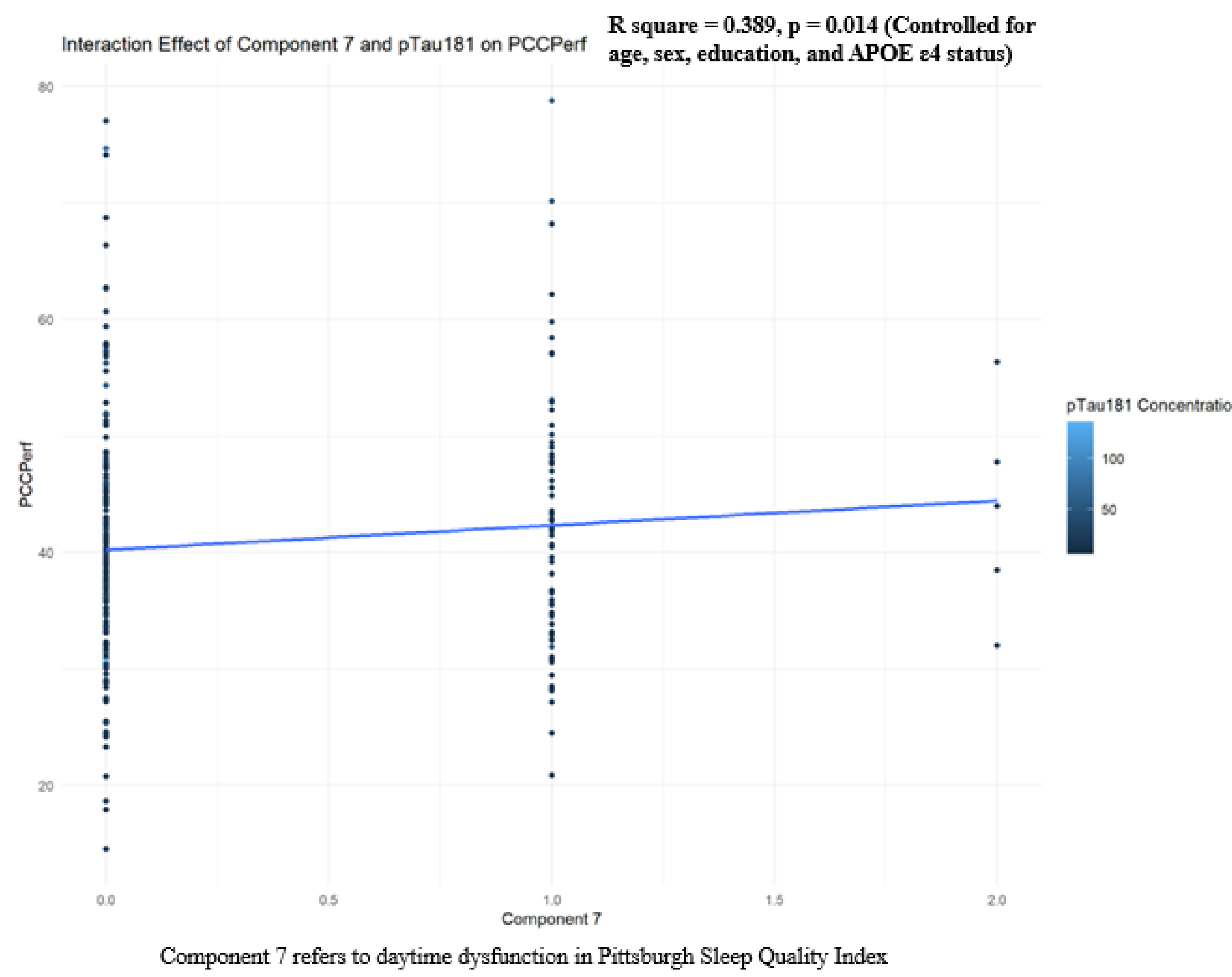
Variable	CN	SCD	MCI	P value
N	639	459	600	
Demographics and covariates				
Age, years	55.15 (9.93)	57.74 (9.33)	62.50 (10.24)	<0.001
Male sex, n (%)	420 (66.0%)	290 (63.6%)	351 (58.7%)	0.026
Education, years	15.78 (3.13)	15.29 (3.19)	14.02 (3.78)	<0.001
APOE ε4 carrier, n (%)	96 (18.9%)	70 (17.8%)	88 (16.3%)	0.540
Sleep (Pittsburgh Sleep Quality Index)				
PSQI total score	4.96 (2.81)	6.02 (3.08)	5.32 (2.97)	<0.001
PSQI component 1 (subjective sleep quality)	0.97 (0.70)	1.16 (0.72)	0.97 (0.71)	<0.001
PSQI component 2 (sleep latency)	0.83 (0.91)	1.04 (0.97)	0.94 (0.93)	0.001
PSQI component 3 (sleep duration)	1.13 (0.76)	1.30 (0.80)	1.19 (0.85)	0.003
PSQI component 4 (habitual sleep efficiency)	0.59 (0.91)	0.68 (0.95)	0.70 (0.94)	0.103
PSQI component 5 (sleep disturbances)	0.97 (0.46)	1.09 (0.48)	1.01 (0.45)	<0.001
PSQI component 6 (sleep medication use)	0.15 (0.57)	0.20 (0.63)	0.13 (0.55)	0.126
PSQI component 7 (daytime dysfunction)	0.35 (0.51)	0.59 (0.65)	0.39 (0.57)	<0.001
ASL-derived cerebral blood flow (CBF)				
Global grey matter CBF	28.09 (5.18)	28.58 (5.19)	27.77 (5.74)	0.212
Medial frontal CBF	30.83 (12.32)	31.53 (13.26)	32.60 (12.26)	0.350
Middle frontal CBF	36.19 (13.19)	37.30 (12.68)	36.94 (13.53)	0.686
Posterior cingulate CBF	40.72 (10.33)	42.11 (9.95)	41.02 (10.16)	0.257
Caudal pontine CBF	41.87 (10.13)	42.57 (11.27)	41.92 (10.73)	0.703
Left hippocampal CBF	31.76 (9.97)	31.97 (8.99)	32.25 (8.87)	0.864
Right hippocampal CBF	31.84 (8.93)	32.38 (8.19)	33.39 (9.16)	0.130
Blood-based biomarkers				
Plasma pTau181 (pg/mL)	15.35 [11.97, 19.52]	16.40 [12.40, 20.70]	18.00 [14.00, 22.30]	<0.001

Results

Associations between PSQI components and cerebral perfusion (ASL CBF)

Outcome (CBF region)	PSQI component	β	SD	p
CN				
Medial frontal	Habitual sleep efficiency	3.308708	0.945943	0.000589
Medial frontal	Sleep duration	3.108156	1.165064	0.008284
Posterior cingulate	Daytime dysfunction	2.852997	1.209747	0.019065
Left hippocampal	Sleep medication use	2.439686	1.086118	0.025739
Caudal pontine	Daytime dysfunction	2.461304	1.142051	0.032027
SCD				
Left hippocampal	Sleep duration	1.712416	0.773509	0.028246
MCI				
Posterior cingulate	Sleep latency	1.505959	0.654449	0.022168
Global grey matter	Habitual sleep efficiency	0.747804	0.336706	0.027245

pTau181-moderated association between daytime dysfunction and posterior cingulate hypoperfusion in CN



- CN:** Poorer sleep efficiency and shorter sleep duration were associated with medial frontal hypoperfusion ($\beta=3.31$, $p=0.0006$; $\beta=3.11$, $p=0.0083$). Greater daytime dysfunction was associated with posterior cingulate ($\beta=2.85$, $p=0.0191$) and caudal pontine hypoperfusion ($\beta=2.46$, $p=0.0320$), while sleep medication use was associated with left hippocampal hypoperfusion ($\beta=2.44$, $p=0.0257$).
- SCD:** Shorter sleep duration was associated with left hippocampal hypoperfusion ($\beta=1.71$, $p=0.0285$).
- MCI:** Longer sleep latency was associated with posterior cingulate hypoperfusion ($\beta=1.51$, $p=0.0222$), while poorer sleep efficiency was associated with global grey matter hypoperfusion ($\beta=0.748$, $p=0.0272$).
- Moderation:** Plasma pTau181 moderated the association between daytime dysfunction and posterior cingulate hypoperfusion in CN participants (interaction $\beta=0.3888$, $SE=0.1570$, $p=0.0139$).

Discussion

- Sleep disturbance was associated with hypoperfusion in social cognition (medial frontal), default-mode function (posterior cingulate), memory (hippocampus), and arousal/brainstem networks (pons).
- Associations were more widespread in cognitively normal adults, suggesting diffuse and potentially modifiable neurovascular vulnerability before cognitive decline..
- pTau181 × daytime dysfunction interaction supports a preclinical neurovascular–tau phenotype, highlighting the value of integrating sleep, biomarker, and imaging assessments for risk stratification