

Aquaporin-4 haplotype-dependent modulation of the association between sleep microarousals and pontine grey matter myelin

P. Talwar¹; M. Zubkov¹; A. Gasparello¹; E. Seret¹; L. Wagner¹; N. Mortazavi¹; F. Collette¹; G. Hammad¹, C. Schmidt¹, G. Vandewalle¹

¹GIGA-CRC Human Imaging, Université de Liège

Background: Aquaporin-4 (AQP4) plays a central role in glymphatic function by facilitating clearance of neurotoxic waste products such as amyloid- β . Glymphatic activity is highest during sleep and engages brain regions where myelin integrity and AQP4-mediated water transport appear interrelated. The pons is critical for sleep regulation and may locally influence glymphatic clearance. However, it remains unclear how AQP4-mediated clearance relates to objective sleep measures and regional pontine myelin. We therefore examined whether sleep metrics are associated with pontine grey matter myelin (GMmP) and modulated by *AQP4* haplotypes.

Methods: In this prospective study, 335 young (18–31 years) and 101 older adults (50–70 years) underwent in-lab EEG recordings of habitual sleep. Automated pipelines were used for sleep staging and detection of microarousals during slow wave sleep (SWS). Quantitative MRI data were processed to derive magnetization transfer saturation (MTsat), a proxy for myelin content, within pontine grey matter. Genome-wide genotyping identified *AQP4* haplotypes (H1, H3). Associations between sleep parameters and GMmP were examined using generalized additive models (GAMLSS), adjusting for relevant covariates.

Results: In the combined cohort (N=401), a significant negative interaction was observed between SWS microarousals associated with sleep-stage transitions (without increased muscle tone) and GMmP among *AQP4* H3 carriers ($p=0.007$). Age-stratified analyses were not significant, though higher-order interactions with age and BMI showed trend-level effects ($p\approx 0.06$).

Conclusions: SWS microarousals interrupting stage continuity without triggering muscular activation are associated with lower pontine myelin in *AQP4* H3 carriers, linked to impaired glymphatic clearance, suggesting a role for *AQP4* in linking sleep physiology to regional myelin integrity.

Disclosure: Support: EU JPND (IRONSLEEP & HISTOPARK), WELBIO, ULIEGE, FNRS (Belgium), Wallonia-Brussels Federation