

Circadian rest activity rhythm disruption as early marker of AD vulnerability in DS population

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BACKGROUND:

Sleep and circadian rest-activity rhythm (RAR) disruption may bidirectionally relate to Alzheimer's disease (AD). Down syndrome (DS), the most frequent genetic cause of AD, is characterized by a high burden of sleep disorders. Circadian RAR evolution across the AD clinical continuum in DS remains poorly characterized.

METHODS:

7-day wrist actigraphy in **140** adults with **DS** (**108** asymptomatic; **32** AD dementia) and 41 cognitively unimpaired controls. Group differences were tested with general linear models, including interaction terms for group-specific associations. Models were adjusted for age, sex, sleep efficiency, and OSA severity.

DABNI and SPIN cohorts

RESULTS:

- Adults with DS exhibited reduced relative amplitude and increased nocturnal motor activity, already detectable in asymptomatic individuals. Circadian amplitude showed a stepwise decline with advancing AD stage, whereas rhythm stability and timing were largely maintained, with significant phase delays emerging only at the dementia stage **Figure 1**.
- Age-related shifts in circadian timing were observed exclusively in individuals with DS and dementia, including delayed acrophase and postponed nighttime inactivity **Figure 2**.
- These associations persisted after accounting for sleep efficiency, sleep stage distribution, and OSA severity, suggesting that circadian dysregulation reflects AD-related pathophysiology rather than secondary effects of sleep disruption.
- No sex-specific differences were identified.

CONCLUSION:

- Adults with DS show early, progressive weakening of circadian RAR across the AD continuum, paralleling sporadic AD.
- Longitudinal multimodal studies should evaluate RAR as scalable biomarkers of AD progression.



- Circadian disruption is already **detectable in asymptomatic individuals?**
- RAR disturbances **worsen along the AD continuum?**
- These alterations **persist independently of nocturnal sleep disturbances**, such as OSA severity and sleep efficiency?
- The **age** and **sex** influences on circadian RAR profiles in DS?

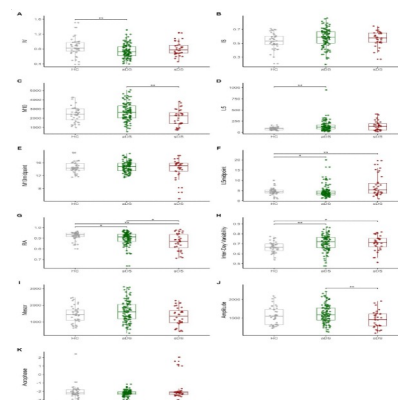


Figure 1. Boxplots for RAR measures by group. Values for (A) IV, (B) IS, (C) M10, (D) L5, (E) M10midpoint, (F) L5midpoint, (G) RA, (H) Inter-Day Variability (I) Mesor, (J) Amplitude, (K) Acrophase are shown by group of diagnosis. Jittered points display individual data within each group: HC (gray), aDS (green), sDS (red). The star (*) indicates significant values ($p < .05$).

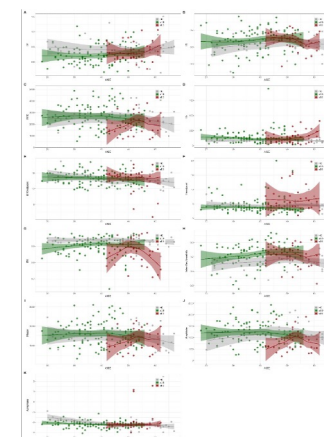


Figure 2. Group interactions across RAR measures and age. Scatter plots showing the association between (A) IV, (B) IS, (C) M10, (D) L5, (E) M10midpoint, (F) L5midpoint, (G) RA, (H) Inter-Day Variability (I) Mesor, (J) Amplitude, (K) Acrophase with age, by group. aDS, asymptomatic Down syndrome; HC, euploid cognitively unimpaired healthy controls.