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Regional grey matter volume links rest-activity rhythm fragmentation with past cognitive decline

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Abstract

Objectives—We examined the extent to which measures of neurodegeneration and cerebrovascular disease explain the rest-activity rhythm (RAR)-cognition link.

Methods—Seventy participants (mean age at MRI=86, standard deviation (SD)=2.6; 53% female) had cognitive, MRI, and accelerometer data. The slope of cognitive decline was defined applying a mixed model to 10 repeated Modified Mini Mental Status Test (3MS) measures over 14 years. Regional grey matter volume (GMV), white matter hyperintensities, and RARs were measured around year 12.

Results—Past 3MS decline was related to RAR fragmentation (per SD $\beta=-0.43$, 95% confidence interval (CI): $-0.73, -0.14$) and lower posterior parietal GMV (per standard deviation $\beta=0.47$, 95% CI: $0.14, 0.79$). Higher RAR fragmentation was related to lower posterior parietal GMV (Pearson $r=-0.39$, $n=70$, $p=0.0007$), which attenuated the association of RAR fragmentation and past cognitive decline by 17%.

Conclusions—Longitudinal studies are warranted to understand the temporal relations and mechanisms linking RAR fragmentation and neurodegeneration.

Introduction

Human activity follows 24-hour cycles known as the rest-activity rhythm (RAR). Early research found greater RAR fragmentation in people with dementia¹. Since RARs are measured non-invasively and are potentially modifiable, understanding the neurobiology of their relationship with cognition is a step towards biologically-informed screening and

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prevention. Neurodegenerative (amyloid-related²) and cerebrovascular³ processes have been implicated. However, to our knowledge, no prior studies have evaluated whether grey matter and/or cerebrovascular measures explain statistical correlations between RAR fragmentation and cognition.

Methods

Analytic sample

The parent study, the Health, Aging, and Body Composition Study, began in 1997. In 2010–2012, participants in substudies at the Pittsburgh site had MRI and accelerometry. Of 163 participants who had MRI, 138 had usable MRI data, and 74 also had adequate accelerometer data (>3 days of recording without periods of removal >3 hours) and were included in the analytic sample. Four of these participants were excluded based on evidence of likely cognitive impairment (3MS scores < 80) at the parent study's baseline.

Cognitive measure

Cognitive decline was defined using Teng's Mini-Mental Status Examination (3MS)⁴ measures from the parent study's year 1, 3, 5, 7, 9, 10, 11, 12, 13, and 14. As in previous published work⁵, a mixed model was used to define subject-specific slopes over the study period (among participants without baseline cognitive impairment). The distribution of 3MS slopes was normal and is shown in the Supplemental Figure. In secondary analyses, we classified participants with slopes of less than 0 defined as "decliners" (the rest were defined as cognitive "maintainers").

MRI-based measures

T1- and T2-weighted fluid-attenuated inversion recovery sequences were entered into automated pipelines using standard atlases to segment grey matter and white matter hyperintensity (WMH) volumes (as described⁵). Regional volumes were extracted in areas selected based on their relations with dementia as described previously⁵: grey matter volume (GMV) in the medial temporal lobe, middle frontal gyrus, posterior parietal, and cingulate cortex; and WMH volumes in the uncinate fasciculus, cingulum, and superior longitudinal fasciculus. GMVs were divided by total intracranial volume to standardize for head size.

Rest-activity rhythm measures

Participants wore a SenseWear Armband (BodyMedia, Pittsburgh, Pennsylvania) for seven 24-hour period (mean wear time=7.1 days, standard deviation (SD)=1). We used nonparametric methods⁶ to assess: (1) relative amplitude (RA), (2) inter-daily stability (IS), and (3) intra-daily variability (IV; a measure of RAR fragmentation).

Statistical analysis

The primary analysis examined age, sex, race, and education adjusted linear regression models for each set of measures (RAR, grey matter, and white matter hyperintensities) with 3MS slopes as the dependent variable. We next examined associations between the RAR and MRI variables that were related to the 3MS slopes using Pearson correlations. We entered

the selected variables into a final multivariable linear regression to assess whether the association of RARs with past cognitive decline were attenuated when adjusting for the MRI-measures. Secondary analyses followed the same methods except for using logistic instead of linear regression.

Results

RAR fragmentation (higher IV) and posterior parietal GMV were the only variables associated with the slope of past cognitive decline (Table). IV was also higher in people with categorically defined past cognitive decline (Supplemental Table). Higher IV was related to lower posterior parietal GMV (Pearson $r=-0.39$, $n=70$, $p=0.0007$). Adjusting for posterior parietal GMV attenuated the association between RAR fragmentation and past cognitive decline by 17%.

Discussion

Our findings extend prior literature^{1,2} with new evidence that neurodegenerative processes affecting posterior parietal GMV explain some of the statistical correlation between RAR fragmentation and past cognitive decline. Since amyloid deposition is frequently found in the posterior parietal region⁷, our findings guide future longitudinal research to focus on the temporal sequencing of these factors in dementia pathogenesis. Previous work reported smaller associations of RAR fragmentation with cerebrovascular disease³; therefore, larger samples or more specific vascular measures (e.g., of microbleeds) may be required to understand potential relations between RAR fragmentation and cerebrovascular disease.

Limitations of this study include potential effects of selection bias on our association estimates, because participants with poor health may have been less likely to participate in the accelerometer measurements taken at Year 12. Furthermore, we had no measures of RARs at baseline or throughout most of the follow-up period; therefore, we cannot tell when RAR fragmentation emerged or if it contributed to worsening brain health. In addition, the present report does not address the specific processes linking RARs and cognition, or the specific aspects of cognition involved. Longitudinal studies are warranted to understand how mechanisms linking RAR fragmentation and cognition play out over time, whether measuring RARs can help improve risk stratification, and if modifying RARs helps prevent dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Several studies link rest-activity rhythm (RAR) fragmentation and cognition, but the extent to which neurodegenerative and cerebrovascular processes explain this link is not known.
- We found posterior parietal grey matter explained a substantial portion of the RAR fragmentation-cognition link.
- Future work is needed to understand the temporal relations and mechanisms linking RAR fragmentation and neurodegeneration.

Table.

Association between each variable and the slope of decline (n=70)

	β (95% Confidence Interval)	t-value	p-value
<u>Model 1: Rest-activity rhythm variables</u>			
Relative amplitude (RA)	0.00 (−0.30, 0.30)	−0.01	0.99
Inter-daily stability (IS)	−0.13 (−0.50, 0.24)	−0.70	0.49
Intra-daily variability (IV)	−0.43 (−0.73, −0.14)	−2.91	0.01
<u>Model 2: Grey matter volumes</u>			
Medial temporal lobe	−0.28 (−0.59, 0.03)	−1.80	0.08
Middle frontal gyrus	0.10 (−0.21, 0.41)	0.63	0.53
Posterior parietal	0.47 (0.14, 0.79)	2.83	0.01
Cingulate	−0.17 (−0.45, 0.11)	−1.20	0.23
<u>Model 3: White matter hyperintensities</u>			
Uncinate fasciculus	−0.08 (−0.40, 0.25)	−0.46	0.64
Cingulum	0.11 (−0.16, 0.38)	0.81	0.42
Superior longitudinal fasciculus	0.11 (−0.25, 0.47)	0.63	0.53
<u>Model 4: IV and posterior parietal volume*</u>			
IV	−0.36 (−0.69, −0.03)	−2.5	0.04
Posterior parietal	0.12 (−0.13, 0.39)	0.98	0.33

Models are adjusted for age, sex, race, and education. Model degrees of freedom for error are all 61.

* Also include IS and RA for comparability with Model 1. Note that a Bonferroni correction would multiply the above-listed p-values by the number of tests, e.g., for Model 1 the p-value for IV would be 0.03.