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Rest-activity rhythm characteristics associated with depression symptoms in stroke survivors

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Abstract

Objective: To examine which 24-hour rest-activity rhythm (RAR) characteristics are associated with depression symptoms in stroke survivors.

Design: Cross-sectional observational study examining associations of RAR characteristics with the presence of depression symptoms adjusting for age, sex, race, and medical comorbidity.

Setting: Community setting.

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Participants: Stroke survivors: (1) recruited locally (N women = 35, N men = 28) and (2) a nationally representative probability sample (the National Health and Nutrition Examination Survey; NHANES; N women = 156, N men = 124).

Interventions: None.

Measurements: Objective RAR characteristics derived from accelerometer recordings including activity onset/offset times and non-parametric measures of RAR strength (relative amplitude), stability (interdaily stability), and fragmentation (intradaily variability). The presence of depression symptoms was categorized using Patient Health Questionnaire scores.

Results: In both samples, the only RAR characteristic associated with depression symptoms was intradaily variability (fragmentation): local sample, OR=1.96 [95% CI=1.05–3.63]; NHANES sample, OR=1.34, [95% CI = 1.01–1.78]). In the NHANES sample, which included both mild and moderate/severe depression, the association between 24-hour sleep-wake fragmentation and depression symptoms was driven by moderate-to-severe cases.

Conclusions: Stroke survivors with higher levels of RAR fragmentation were more likely to have depression symptoms in both samples. These findings have implications, given prior studies in general samples linking RAR fragmentation with future depression and dementia risk. Research is needed to establish the potential consequences, mechanisms, and modifiability of RAR fragmentation in stroke survivors.

Keywords

Depression; stroke; actigraphy; accelerometer; rest-activity rhythms

Poststroke depression (PSD) is a common consequence of stroke that can directly or indirectly lead to more disability with daily living [1]. Depression is also a risk factor for poor outcomes like dementia [2] especially when combined with stroke [3,4]. Although pharmacologic and psychological treatments significantly reduce depressive symptoms in stroke survivors (relative to control conditions in trials), non- and incomplete treatment responses remain very common [5]. Furthermore, reductions in depressive symptoms do not always translate to reductions in disability [6,7]. Thus, research is needed to identify novel intervention targets that plausibly underlie both PSD and related consequences such as dementia risk.

One plausible contributor to the likelihood that stroke survivors will experience depression symptoms (and related consequences) is disruption to healthy 24-hour rest-activity rhythms (RARs). In humans, main periods of rest and activity follow a 24-hour pattern that is known as the RAR. Several characteristics of the RAR can be measured objectively and unobtrusively assessed using accelerometer-based devices. For example, RAR measures reflect how stable activity patterns are across days (interdaily stability) or how fragmented 24-hour activity patterns are within days (intradaily variability). Prior research in general (not stroke specific) samples has shown that certain RAR disturbances predict future depression symptoms such as later activity onset timing [8], less robust or “modellable” 24-hour patterns [9], and more fragmented RARs [10].

Establishing which RAR characteristics relate to depression symptoms in stroke survivors has potential translational significance, because sleep-wake patterns can be passively monitored and are potentially modifiable. As pointed out previously, popular accelerometer-based wearable devices could be leveraged to screen for RAR characteristics that are associated with disease [11,12]. Moreover, since RARs are exogenously modifiable behaviors [13,14], mechanism and intervention studies could can be developed that modify RARs and test for potential effects on related factors like depression and its sequelae.

Based on prior literature, several RAR characteristics that were previously linked with depression symptoms [8–10] are likely to occur in stroke survivors. For example, post-mortem measures of cerebrovascular disease (higher burden of atherosclerosis and subcortical infarcts) have been shown to correlate with weak, unstable, and fragmented RARs [15]. Circadian rhythm abnormalities can also occur after a stroke [16]. Fragmented RARs are also plausible in stroke survivors, given two factors that can fragment RARs are common after stroke: sedentary behavior [1718] and subjective sleep disturbance [19].

However, we are unaware of prior evidence identifying objectively measurable RAR correlates of post-stroke depression symptoms in humans. Past studies have linked low physical activity levels with depression symptoms in stroke survivors[20], but we are unaware of prior evidence regarding which 24-hour RAR characteristics are associated with depression symptoms in stroke survivors. Given their plausible relevance, we sought to isolate specific RAR characteristics that related to depression symptoms among stroke survivors. To do so, we analyzed data from two independent samples of stroke survivors. We evaluated if standard measures of RAR timing, strength, stability, and fragmentation were associated with a higher likelihood that stroke survivors had depression symptoms.

METHODS

Study Design

This report is based on secondary analysis of data collected locally at an academic research institution and nationally via the National Health and Nutrition Examination Survey (NHANES). We utilized two samples to in order to evaluate if consistent results were obtained, i.e., if any findings were generalizable across these samples or sample specific. The local dataset combined baseline measures from two clinical trials and one observational study for adults who experienced a stroke: Engage Pilot Study (2019–2022, NCT04019275), Activating Behavior for Lasting Engagement (ABLE, NCT03305731, 2017–2019), and Monitoring Activating Behavior for Lasting Engagement (MABLE, 2017–2019). The methods of these studies have been described elsewhere [21,22]. Institutional Review Board approval was obtained, and all participants provided written informed consent. Both clinical trials included assessments of depression and actigraphy during the pre-intervention assessment.

The NHANES is a national program of studies designed to assess population level health and nutritional status of children and adults in the United States. The NHANES interview includes self-report assessments of health as well as medical and physiological measurements from a physical examination. In 1999, the survey became a continuous

program examining a nationally-representative sample of about 5,000 persons per year. We examined data from the 2011–2012 and 2013–2014 cycles because they included accelerometer-based assessments of 24-hour activity patterns. The sample was derived using probability-based sampling [23].

Participants

Participants in the local dataset experienced an ischemic or hemorrhagic stroke within the last 3 – 24 months. Exclusion criteria included severe aphasia (Boston Diagnostic Aphasia Examination score ≤1), currently receiving rehabilitation serves, and diagnoses of neurodegenerative disorder (i.e., dementia), major depressive disorder, psychiatric condition(s), and/or substance abuse. Sixty-nine participants wore an activPAL™ (PAL Technologies Ltd., Glasgow UK) for 7 days during the pre-intervention assessment. Of those, 5 failed accelerometer data quality control/could not produce valid measures, and 1 had missing clinical data. This resulted in an analytic sample size of 63 local stroke survivors.

In the NHANES dataset, valid accelerometer data was collected from 8,200 adults, of whom 342 (4.2%) reported a prior stroke [24]. Unlike the previously described local sample, there were no exclusions for the NHANES sample such as aphasia or major depressive disorder. Instead, the NHANES was designed to be a general population sample of non-institutionalized adults in the United States. Depression or covariate data was not available for 62 of these individuals resulting in an NHANES sample size of 280 stroke survivors.

Measures

Accelerometer and RAR measures.—In the local sample, activPAL™ monitors were worn continuously over 7 days on their unaffected thigh. In the NHANES, ActiGraph GT3X+ (Pensacola, FL) accelerometers were worn on non-dominant wrists continuously for seven consecutive days. For both studies we extracted five sleep-wake pattern measures from the time series of activity counts. Note that the accelerometer types and physical placement of these devices differed across these two samples. This may result in differences in the scales/ranges of activity levels detected. As such, we chose measures that, by virtue of how they are calculated, have ranges that do not depend on the scale of the accelerometer counts or overall intensity of activity. In other words, due to potential differences in activity detection across the two samples, any measures that depend on the scale of the activity count could not be compared across samples, and were therefore not considered in this analysis (e.g., overall activity level during the day or night).

We used sigmoidally transformed cosine models[25] to estimate (1) the “up-mesor” or time when activity passes up through mesor approximating when participant “gets going” in the morning; and (2) the “down-mesor” or time when activity passes down through mesor approximating when the participant “settles down” for the night. We used the non-parametric approach to calculate (3) relative amplitude (reflecting rhythm strength), (4) inter-daily stability (reflecting the degree of activity pattern consistency across days); and (5) intra-daily variability (within-daily fragmentation indicated as the magnitude and frequency o hourly transitions in activity levels across days).

Depression symptoms: In the local sample, depression symptoms were assessed with two different scales. One group of local participants completed the Patient Health Questionnaire-9 [26], whereas another group completed the PROMIS Depression Scale which was subsequently converted to PHQ-9 scores for analysis (following published conversion tables) [27]. We dichotomized total PHQ-9 scores of 5 or greater to reflect the presence of at least "mild" depression symptoms. In the NHANES sample, the PHQ-9 was also dichotomized to indicate the presence of at least mild depression symptoms (PHQ-9 scores of ≥5). The NHANES did not exclude individuals with major depressive disorder as the local study did, and therefore had a greater range of symptom severity. As such, we performed additional analyses in the NHANES examining PHQ-9 scores as none/minimal (PHQ-9 scores <5), mild (PHQ-9 scores 5–9), and clinically significant depression (PHQ-9 scores of ≥10 which has been validated as an optimal cut-point for detecting a diagnosis of major depression) [28].

Covariates: We examined covariates that might confound the association between sleep-wake pattern variables and depression: age, sex, race, and medical comorbidity. While the larger NHANES sample would have allowed further detailed characterizations, race was categorized as White compared with other racial status based on the limited of number of non-white participants in the local sample. Medical comorbidity was measured in the local sample with the Self-reported Comorbidity Questionnaire (SCQ) [29]; in the NHANES medical comorbidity was categorized as a count of the following self-reported chronic diseases (zero, one, two, or three or more): congestive heart failure; coronary heart disease, angina, heart attack, emphysema, thyroid problems, chronic bronchitis, or any liver condition.

Statistical analyses

Analyses used separate multivariable logistic regression models to evaluate associations of RAR variables (the independent variables) with depression symptom outcomes. All RAR variables and continuous covariates were standardized to a sample mean of zero and standard deviation of one to facilitate effect size comparisons. Local and NHANES data sets were analyzed separately. Age, sex, race, and medical comorbidity were included in regression models as covariates due to their established relationships with depression. Separate regression models were fitted for each activity pattern variable. For all analyses, p values smaller than 0.05 were statistically significant. All NHANES results were weighted following published guidance [30].

RESULTS

In both samples, the average age was approximately 65 years old (Table 1). Slightly more than half of the sample were women and approximately 70% were White/Caucasian. Consistent with the local study sample excluding cases of major depression, more participants met criteria for at least mild depression symptoms in the NHANES sample (32% in the local sample and 40% in the NHANES sample).

In both samples, greater intra-daily variability (indicating more fragmented 24-hour patterns) was associated with statistically higher odds of depression symptoms (Table 2).

None of the other activity pattern characteristics were statistically associated with the likelihood of having depression symptoms. These estimates come from models that included comorbidity as a covariate, and consistent results were observed without this adjustment.

Further analyses in the NHANES sample used multi-nominal logistic regressions to three-level depression symptom outcome: none/minimal symptoms; mild symptoms; and clinically significant depression symptoms. These models produced similar results, but additionally specified that greater intra-daily variability (RAR fragmentation) was associated with higher odds of clinically significant (odds ratio = 1.66, 95% confidence interval: 1.21–2.27) but not mild (odds ratio = 1.20, 95% confidence interval: 0.85–1.69) depression symptoms (compared with the reference group of none/minimal symptoms).

DISCUSSION

We found consistent evidence across two samples of stroke survivors that RAR fragmentation, but not timing, stability, or strength, was statistically associated with having depression symptoms. Higher RAR fragmentation was defined here as intra-daily variability which measures the frequency and extent of transitions in activity levels throughout the 24-hour day. Thus, in these samples stroke survivors having less sustained activity/rest periods was associated with having depression symptoms. In the context of the literature reviewed below that also links RAR fragmentation with dementia risk, our novel findings support the importance of determining the mechanisms, consequences, and modifiability of sleep-wake pattern fragmentation in stroke survivors.

Several plausible mechanisms could underlie the observed relationship between RAR fragmentation and depression symptoms in stroke survivors. First, differences in stroke characteristics, the presence of neurodegenerative pathology, or cognitive impairment may causally lead to both fragmented sleep-wake patterns and depression. Indeed, recent studies found that higher RAR fragmentation related to greater levels of amyloid deposition in the brain [31] and lower medial temporal lobe volumes [32]. Furthermore, higher RAR fragmentation correlates with greater levels of cerebrovascular disease determined upon autopsy including, most markedly, a higher number of subcortical infarcts [15]. Second, pre-existing cognitive impairment or depression may entail dysfunctions/deficits that lead to fragmented RARs. For example, dysfunctional reward processing, attentional deficits, pain, perceived stress, and/or alterations in circadian physiology might cause individuals to have more fragmented daytime activity engagement and less sustained sleep at night. In addition, a lack of environmental opportunities to sustain engagement in meaningful activity (e.g., lack of accessibility in their home, neighborhood, and social system(s) to support long-term participation upon return home) could contribute to fragmented activity patterns.

There are also plausible mechanisms by which higher RAR fragmentation could lead to depression and/or cognitive impairment over time. A recent longitudinal study demonstrated that sleep-wake pattern fragmentation and depression symptom levels were bi-directionally related over time [10]. Higher RAR fragmentation has also been related to the incidence of cognitive impairment as shown in some [33,34] but not all [35] studies. While the mechanisms behind these apparent prospective effects of RAR fragmentation are unknown, several

processes are plausible. Failure to sustain activity during the day may reduce the amount and quality of engagement with physical, social, and recreational activities that are important to maintaining emotional and brain health. Failure to sustain activity levels throughout the day may also reduce the build-up of homeostatic sleep drive and thus lead to reduced slow wave sleep [36]. Others have suggested that fragmented sleep-wake patterns may lead to physiological changes including alterations in autonomic, immunologic, and neurologic functions [15,31].

Study limitations.

Future studies will be required to determine which of the above mentioned (or other) processes/pathways explain the observed association between higher RAR fragmentation and depression symptoms in stroke survivors. This secondary data analysis was cross-sectional and limited by not including measures of the potential mechanisms and not being able to evaluate temporal relations between the factors examined. There were not adequate measures of potential contributing factors like sedentary behavior, napping, and sleep architecture/insomnia symptoms across both studies to fully parse the sources of RAR fragmentation observed here. Additionally, the local sample is possibly not representative of other regions and did not include cases of severe depression; notably, however, these two concerns are somewhat mitigated by including the larger NHANES sample that was designed to be representative and included a wide range of depression severity. This range of depression severity in the NHANES sample allowed us to demonstrate that RAR fragmentation was most strongly associated with moderate-to-severe than mild depression symptoms in stroke survivors.

Conclusions

From a panel of 24-hour RAR characteristics, we identified higher intra-daily variability as a correlate of depression symptoms in stroke survivors. This finding has public health relevance especially given that prior literature links both sleep-wake pattern fragmentation and post-stroke depression with cognitive decline/dementia risk. [37–41] As such, stroke survivors with both RAR fragmentation and depression may be at particularly high risk for dementia. Whether, and if so how, RAR fragmentation contributes to the mechanisms that influence post-stroke trajectories of cognitive function, including dementia risk, remains to be seen. The observations reported here support the need for future research to evaluate these mechanistic questions and the potential implications for behavioral health and goal-directed activity interventions. Specifically, behavioral activation and sleep medicine approaches could be combined to treatment fragmentation in stroke survivors by increasing sustained engagement with activity, decreasing napping/sedentary behavior, and improving sleep maintenance. However, future experimental intervention studies will be needed to evaluate if RAR fragmentation is modifiable in stroke survivors, and if doing so results in clinically meaningful reductions in depression symptoms and related sequalae.

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Abbreviations:

RAR	rest-activity rhythm
PSD	post-stroke depression

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Table 1.

Characteristics of Stroke Survivors

Characteristic	Local sample (n=63)	NHANES (n=280*)
Age, years	66.3 (11.7)	64.6 (18.4)
Female, % (n)	55.6 (35)	59.7 (156)
White race, % (n)	74.6 (47)	72.1 (146)
Medical comorbidity (SCQ)	7.0 (4.0)	-
Number of chronic diseases, % (n)		
0	-	44.5 (129)
1	-	23.1 (69)
2	-	16.1 (42)
3+	-	16.3 (40)
Depression symptoms (at least mild), % (n)	31.8 (20)	39.9 (123)

Notes. Means (standard deviations) shown unless otherwise noted. See text for additional details regarding variable definitions. SCQ = Self-Administered Comorbidity Questionnaire.

*Numbers reported are actual sample sizes whereas percentages are weighted to reflect the target sample in the United States per NHANES recommendations.

Table 2.

Adjusted odds of having mild depression symptoms for each rest-activity rhythm variable by study

Sleep-wake characteristic	Local sample (n=63)		NHANES (n=280*)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
"Get going" time (up-mesor)	0.80 (0.44-1.45)	0.55	1.33 (0.89-2.00)	0.17
"Settle down" time (down-mesor)	0.86 (0.47-1.59)	0.22	0.93 (0.70-1.22)	0.58
Rhythm strength (relative amplitude)	0.93 (0.53-1.65)	0.81	0.91 (0.63-1.32)	0.62
Inter-daily stability (activity pattern consistency across days)	1.07 (0.56-2.05)	0.84	0.92 (0.69-1.23)	0.56
Intra-daily variability (within-daily fragmentation)	1.96 (1.05-3.63)	0.03	1.34 (1.01-1.78)	0.03

Notes. Odds ratios all come from separate models adjusted for age, gender, race, and comorbidity measures.

*280 is the actual sample size but results are weighted to reflect the target sample in the United States per NHANES recommendations

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