Mental Fatigability and Heart Rate Variability in Mild Cognitive Impairment

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Objectives: *Adaptive physiological stress regulation is rarely studied in mild cognitive impairment (MCI). Here we targeted mental fatigability (MF) as a determinant of altered high frequency heart rate variability (HF-HRV) reactivity in individuals with MCI, and examined frontobasal ganglia circuitry as a neural basis supporting the link between MF and HF-HRV reactivity.* **Methods:** *We measured mental fatigability and HF-HRV during a 60-minute cognitive stress protocol in 19 individuals with MCI. HF-HRV responses were modeled using a quadratic equation. Resting state functional connectivity of intra- and inter-network frontobasal ganglia circuitry was assessed using blood-oxygen-level-dependent magnetic resonance imaging among seven of the participants.* **Results:** *Lower MF was associated with faster and greater rebound in U-shape HF-HRV reactivity, which linked to a stronger connectivity between right middle frontal gyrus and left putamen.* **Conclusions:** *Results suggest that MF may contribute to abnormal physiological stress regulation in MCI, and fronto basal ganglia circuitry may support the link.* (Am J Geriatr Psychiatry 2016; ■■:■■–■■■■–■■–■■)

Key Words: mild cognitive impairment, mental fatigability, cardiovascular reactivity, frontobasal ganglia circuitry, physiological stress regulation

Evidence suggests that the reduced capacity to physiologically adapt to environmental challenges may lead to neurodegeneration, although there has been little work examining physiological adaptation in individuals beginning to show early signs of cognitive deficits, such as mild cognitive impairment (MCI).[1] Cognitive impairment and maladaptive physiological responses to challenges may be signaling neurobiological alterations that underpin a downward spiral in overall health in MCI and accelerate the progression to dementia.[2] The parasympathetic branch of the autonomic nervous system, often measured by the high frequency (HF) domain of heart rate variability (HRV), sensitively and quickly responds to the changing environment, both withdrawing and activating as needed, which is a critical component of flexible physiological adaptation. Reduced capacity for flexible automatic regulation may reflect pending transition to dementia.[3] Among the small number of studies available, evidence is inconsistent regarding autonomic regulation in MCI, suggesting further study is needed of the factors that may predict HF-HRV alterations in MCI.

Here, we examined mental fatigability (MF; i.e., increased fatigue over acute but constant mental load), one of the most common neurological phenomena associated with aging, as a potential determinant of HF-HRV alteration. MF is associated with the alteration of activity in multiple peripheral homeostatic pathways in response to acute stressors in old age.[4,5] Importantly, MF and altered HF-HRV are both related to selective regions of prefrontal cortex (PFC), basal ganglia, insula, and anterior cingulate cortex,[6,7] which together build a functional circuit called the frontobasal ganglia circuitry. In this pilot study of MCI patients, we aimed to provide proof of concept of a shared central origin of MF and adaptive autonomic regulation. Specifically, we examined whether MF was indeed associated with altered HF-HRV during a cognitive stress task; in a small subgroup for whom resting-state functional connectivity (rsFC)

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data were collected, we also explored whether alterations in the frontobasal ganglia circuitry were associated with MF and HF-HRV.

METHODS

An exploratory cross-sectional study was conducted of 19 patients with amnestic MCI (mean age: 72.3 years; 11 men; mean education: 16.63 years; mean Montreal Cognitive Assessment [MOCA]: 24.5) who were referred by local memory clinics. Participants had no use (73.7%) or stable use (26.3%) of memantine or cholinesterase inhibitors, no treatment with antidepressants or anxiolytics, and no major cardiovascular conditions (e.g., stroke, congestive heart failure, myocardial infarction). Seven (36.8%) reported use of anti-hypertensive medications. Seven of the 19 participants without magnetic resonance imaging (MRI) contraindications attended MRI scans. The study was approved by the institutional research subject review board.

Stress Protocol

The stress protocol was conducted within a 2-hour window in the morning (9:00–11:00 A.M.). Participants were instructed to refrain from caffeine, exercise, and medications on the morning of testing to limit potential acute effects on outcomes. The stress protocol lasted for 70 minutes, including a 10-minute resting (baseline) period and a 60-minute cognitive tasks period. There were five computerized tasks sharing similar visual components and targeting sustained and divided attention, requiring fast reaction time.[8] The purpose of using five similar tasks instead of a single task was to balance the familiarity and novelty in stimuli, in order to simultaneously manipulate MF and induce HF-HRV reactivity.

MF

A six-item visual analog scale (items selected from a 18-item scale[9] based on content validity and understandability for individuals with MCI) was used to assess fatigue severity at the end of baseline and immediately after the cognitive tasks; Cronbach's α reliability was 0.91 and 0.97, respectively. The ratings

were summed for each period (baseline and post-tasks); there was a significant increase in fatigue rating from baseline to post-cognitive tasks (Wilcoxon signed ranks test: Z = −2.33, p = 0.020). MF was calculated using the discrepancy between the two sum scores, with higher scores indicating more fatigue.

HF-HRV

Electrocardiography was continuously monitored during the stress protocol. Series of intervals between consecutive R waves (every 20 seconds) were analyzed to generate HF-HRV data (0.15–0.50 Hz) with log-transformation applied and averaged by minute. Consistent with models of HRV as an index of flexible, adaptive responding to the environment (e.g., Porges[10]) our recent work suggests an early decline followed by an increase in HF-HRV in response to acute cognitive stress (i.e., a U-shape pattern).[11] Therefore, we modeled HF-HRV responses over the last minute of baseline and 60 minutes of cognitive tasks, a total of 61 time points, using the statistical mixed-effects model with

$$Y_{HF-HRV} = aX_{Time}^2 + bX_{Time} + c + \varepsilon$$

where parameters (*a, b, c*) were modeled as random effects at the individual level with an AR(1) covariance matrix. All parameters were significant (*a*: B [SE] = 2.25 [0.22], t [df] = 10.24 [20], p < 0.001; *b*: B [SE] = −8.03e⁻³[0.004], t [df] = −2.07 [133], p = 0.041; *c*: B [SE] = 1.60e⁻⁴ [0.62e⁻⁶], t [df] = 2.59 [86], p = 0.011). We next calculated four indices using the parameter coefficient: vertex (i.e., −*b*/2*a*, the length of time when HF-HRV starts rebounding), change (i.e., *a* × 60² + *b* × 60, change of HF-HRV over the tasks), and bottom (i.e., *a* × vertex² + *b* × vertex + *c*) and initial level (i.e., *c*) of HF-HRV.

rsFC

rsFC data were collected using a research dedicated 3T Siemens TrioTIM scanner equipped with a 32-channel receive-only head and body coil transmission (functional images: gradient echo-planar imaging sequence, TR = 2000 msec, TE = 30 msec, FA = 90, matrix = 64 × 64, resolution 4 × 4 × 4 mm³), preprocessed using Data Processing Assistant for Resting-state functional MRI (fMRI), and analyzed using

independent component analysis to identify resting networks using GIFT v3.0a (icatb.sourceforge.net). Details were described elsewhere.[8]

RESULTS

We first determined the covariates that should be included in understanding the relationship between MF and HF-HRV. None of the candidate covariates (i.e., sex, anti-hypertensive use, memantine or cholinesterase inhibitors use, education, or MOCA) influenced MF or HF-HRV (all p > 0.30). Using Spearman's correlation (r_s), MF was significantly related to vertex ($r_s = 0.44$, N = 19, p = 0.030) and change ($r_s = -0.41$, N = 19, p = 0.039), but not the bottom or initial level of HF-HRV model (see Figure 1). We also calculated the average HRV over the 60 minutes of the cognitive stress task; its correlation with MF was not significant

($r_s = -0.15$, N = 19, p = 0.27). In the following imaging-related analyses, we only included the vertex and change as indices for HF-HRV response.

Independent component analysis generated two networks related to frontobasal ganglia circuitry: the basal ganglia network (BGN) and the central executive network (CEN) (see Supplemental Figure 1). The level of MF was significantly related to the intra-network connectivity of BGN ($r_s = -0.67$, N = 7, p = 0.049) but not CEN ($r_s = -0.56$, N = 7, p = 0.10) using Spearman's correlation. Neither intra-network related to HF-HRV indices ($|r_s| = 0.39–0.54$, p > 0.10).

We also analyzed the four pairs of regions of interest as inter-network connectivity using relevant peak coordinates: bilateral putamen from the BGN and bilateral middle frontal gyrus (MFG) from the CEN (see Supplemental Figure S1). The level of MF ($r_s = -0.73$, N = 7, p = 0.031), as well as vertex ($r_s = -0.79$, N = 7, p = 0.018) and change ($r_s = 0.79$, N = 7, p = 0.018) of the

FIGURE 1. HF-HRV response over 60 minutes of cognitive tasks by dividing MF to high (N = 6) versus low (N = 13) level using a cutoff score of 12 for display purposes.
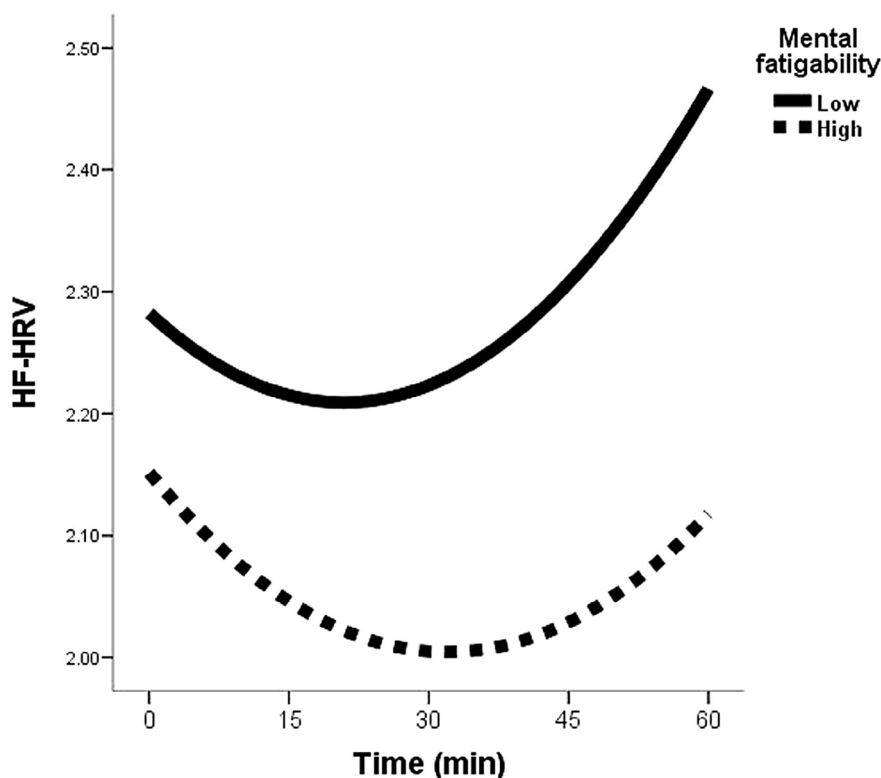
HF-HRV model, were significantly correlated to the connectivity of left putamen–right MFG.

Finally, we present two cases with lowest (i.e., 0, ID_L) and highest (i.e., 42, ID_H) MF scores, their frontobasal ganglia circuitry (taking left putamen as the seed) and HF-HRV response. Qualitatively, ID_L had stronger network connectivity than ID_H (Supplemental Figure S2A), and the HF-HRV response patterns (Supplemental Figure S2B) are similar to those for the high versus low MF levels in Figure 1.

DISCUSSION

To our knowledge, this is the first study to demonstrate a relationship between MF and HF-HRV reactivity, and does so in a group at high risk for dementia. MF and HF-HRV reactivity were both significantly inducible over the 60-minute cognitive stress task in individuals with MCI. Next, MF was associated with dynamic change in the HF-HRV U-shape response. More specifically, individuals with lower fatigability presented a faster (i.e., seen in smaller vertex) and greater (i.e., seen in larger change) rebound of HF-HRV, regardless of the initial or lowest level or average of HF-HRV response. Finally, consistent with our hypothetical model, the inter-network between left putamen and right MFG was linked to both MF and the HF-HRV U-shape response.

Consistent with a previous study in healthy adults,[5] the current study confirmed that individuals with lower MF tended to have a faster rebound from HF-HRV suppression over the task to an even higher ending level, reflecting a more flexible autonomic response to environmental challenge. More flexible autonomic responses, indexed by HRV, are associated with enhanced PFC function and better cognition,[12,13] and insufficient autonomic flexibility predicts incident Alzheimer disease.[3] Intriguingly, by examining the functional connectivity of both intra- and inter-networks related to PFC and basal ganglia, the findings here suggest a common neural support explaining the link between MF and HF-HRV reactivity. Although MF, broadly, may be linked to BGN, MF and HF-HRV reactivity seemed to share a more selective inter-network between right MFG at CEN and left putamen at BGN. The results are consistent with a recent meta-analysis

suggesting that left putamen may play a selective role in regulating HF-HRV reactivity during acute stressor tasks, particularly when the tasks primarily engage cognitive resources.[7]

Study limitations include the lack of a cognitively healthy comparison group and the small number of participants that precluded more refined models with multiple covariate adjustment (e.g., specific medication classes, medical conditions, progress in the neurodegenerative process). The lack of relationship between resting HF-HRV and MF may be due to the small sample size. Further, more complex dynamics of HF-HRV are worth considering in future studies,[14,15] as these dynamics may help clarify links between the autonomic nervous system, fatigability, and neural connectivity. We could not examine the causal relations among the frontobasal ganglia network, MF, and HF-HRV reactivity. Thus, whether the frontobasal ganglia network mediates the association between MF and HF-HRV reactivity remains to be determined, as does the etiology of altered frontobasal ganglia network activity in MCI, should larger scale studies support the current findings. Despite these limitations, our intriguing pilot findings suggest that MF may index susceptibility to the pernicious effects of stress in individuals at risk for dementia. Thus, MF may be a critically useful clinical target to slow progression to dementia and promote well-being in MCI.

APPENDIX: SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at doi:10.1016/j.jagp.2015.12.012.

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