

Cortical thickness is associated with altered autonomic function in cognitively impaired and non-impaired older adults

Feng Lin^{1,2,3,4} , Ping Ren¹ , Xixi Wang^{3,5}, Mia Anthony¹, Duje Tadin³ and Kathi L. Heffner^{1,2}

¹School of Nursing, University of Rochester Medical Center, Rochester, NY 14642, USA

²Department of Psychiatry, University of Rochester Medical Center, Rochester, NY 14642, USA

³Department of Brain and Cognitive Science, University of Rochester, Rochester, NY 14642, USA

⁴Department of Neuroscience, University of Rochester Medical Center, Rochester, NY 14642, USA

⁵Department of Biomedical Engineering, University of Rochester, Rochester, NY 14642, USA

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Key points

- The parasympathetic nervous system (PNS) is critical for adaptation to environment demands.
- Alzheimer's disease (AD), via frontal compensatory processes, may affect PNS regulation, thereby compromising older adults' capacity for adaptation, and increasing morbidity and mortality risk.
- Here we found that AD-associated neurodegeneration accompanied an overactive anterior cingulate cortex, which in turn resulted in a high level of PNS activity at rest, as well as strong PNS activity withdrawal in response to the mental effort.
- This discovery provides the first line of evidence to suggest that AD-associated neurodegeneration links to altered PNS regulation during mental effort in older adults, and that the compensatory processes accompanying frontal hyperactivation appear to be responsible for these alterations.

Abstract The parasympathetic nervous system (PNS) is critical for adaptation to environment demands. PNS can reflect an individual's regulatory capacity of frontal brain regions and has been linked to cognitive capacity. Yet, the relationship of PNS function to cognitive decline and abnormal frontal function that characterize preclinical progression toward Alzheimer's disease (AD) is unclear. Here, we aimed to elucidate the relationship between PNS function and AD-associated neurodegeneration by testing two competing hypotheses involving frontal regions' activity (neurodegeneration *vs.* compensation). In 38 older human adults with amnesic mild cognitive impairment (aMCI) or normative cognition, we measured AD-associated neurodegeneration (AD signature cortical thickness; ADSCT), resting-state functional magnetic resonance imaging of frontal regions' spontaneous activation, and an electrocardiography measure of PNS (high frequency heart rate variability; HF-HRV). HF-HRV was assessed at rest and during a cognitive task protocol designed to capture HF-HRV reactivity. Higher HF-HRV at rest was significantly related to both more severe AD-associated neurodegeneration (lower ADSCT scores) and worse cognitive ability. Cognitive impairments were also related to greater suppression of HF-HRV reactivity. High activities of the anterior cingulate cortex significantly mediated relationships between ADSCT and both HF-HRV at rest and HF-HRV reactivity. Notably, these relationships were not affected by the clinical phenotype. We show that AD-associated neurodegeneration is associated with altered PNS regulation and that compensatory processes linked to frontal overactivation might be responsible for those alterations. This finding provides the

first line of evidence in a new framework for understanding how early-stage AD-associated neurodegeneration affects autonomic regulation.

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Corresponding author F. Lin: University of Rochester, 601 Elmwood Ave, Rochester, NY 14642, USA.
Email: vankee_lin@urmc.rochester.edu

Abbreviations ACC, anterior cingulate cortex; AD, Alzheimer's disease; ADSCT, Alzheimer's disease signature cortical thickness; ALFF, amplitude of the low frequency fluctuation; aMCI, amnesic mild cognitive impairment; ANS, autonomic nervous system; BOLD, blood oxygen level dependent; ECG, electrocardiography; fMRI, functional magnetic resonance imaging; HC, healthy control; HF-HRV, high frequency heart rate variability; MNI, Montreal Neurological Institute; MOCA, Montreal Cognitive Assessment; PNS, parasympathetic nervous system.

Introduction

The autonomic nervous system (ANS), comprising the parasympathetic (PNS) and sympathetic (SNS) branches, is critical for adaptation to environmental demands. While the SNS has long been recognized as the predominant support for 'fight or flight' in the face of threat, more recent models emphasize the regulating role of the PNS in supporting flexible responses during adaptation to changing or demanding environments (Thayer *et al.* 2009). For instance, more active PNS, often indexed by higher high frequency heart rate variability (HF-HRV), is linked to greater cognitive capacity that can support mental efforts toward adaptation in younger and healthy adults (Hansen *et al.* 2003). Frontal brain regions (e.g. prefrontal cortex, anterior cingulate cortex (ACC)) play a direct role in regulating PNS. In individuals without cognitive impairment, greater neural efficiency in frontal regions links to higher PNS activity (i.e. higher HF-HRV). But, in response to cognitive challenges, activation of the frontal regions can lead to PNS withdrawal (i.e. decrease in HF-HRV) (Thayer *et al.* 2012). Both aspects reflect the frontal regions' top-down regulatory capacity (Thayer *et al.* 2009). This is of potential relevance for Alzheimer's disease (AD) as frontal regions' function in AD is compromised by neurodegeneration. Individuals at high risk for AD often have hyperactivation in the frontal regions, likely resulting from compensation for neural deficits of posterior brain regions or insufficient neural efficiency of frontal regions themselves (Li *et al.* 2014; Lin *et al.* 2017b). However, despite close links between frontal and PNS function, little is known about whether the early stage of neurodegeneration in AD affects frontal regions' regulation of PNS. For example, reduced PNS activation during rest is observed in the middle to late stages of AD compared to healthy older adults (Femminella *et al.* 2014), suggesting altered PNS regulation with more advanced neurodegeneration. However, there have been contradictory findings regarding the level of HF-HRV in individuals with the earliest clinical phenotype of AD – amnesic mild cognitive impairment (aMCI) (Zulli *et al.* 2005; Collins *et al.* 2012; Lin *et al.* 2014). Because

aMCI can be a pathophysiologically heterogeneous group (Jacquemont *et al.* 2017), these contradictory findings may be due to the examination of HF-HRV in the context of clinical phenotype instead of AD-associated neurodegeneration.

AD signature cortical thickness (ADSCT), including atrophy in several posterior brain regions (e.g. bilateral inferior and middle temporal lobes, entorhinal cortex, and fusiform gyrus) has been used as a common index for AD-associated neurodegeneration (Jack *et al.* 2015). Deficits in ADSCT are highly correlated to amyloid or tau pathology, disturb brain function, and occur much earlier than the symptomatic preclinical AD phenotype such as aMCI (Jack *et al.* 2015). In the present study, we enrolled a group of older adults without clinical diagnosis of AD or other types of dementia (healthy control (HC) and older adults with aMCI), and examined two types of relationships: (1) the associations between ADSCT and HF-HRV at rest and in response to cognitive tasks; (2) the mechanism linking ADSCT with HF-HRV by focusing on frontal regions' activity. The frontal regions' activity was indexed by the amplitude of the low frequency fluctuation (ALFF), measuring the resting-state regional spontaneous activity with functional magnetic resonance imaging (fMRI) (Hou *et al.* 2014; Ren *et al.* 2016). We tested two competing hypotheses that differ in whether the focus is on (A) *neurodegeneration per se* or (B) *compensatory* mechanisms that are pronounced in early stages of AD-associated neurodegeneration. (A) Based on the literature on cognitively normal people (discussed above), greater AD-associated neurodegeneration or worse cognitive performance would lead to reduced HF-HRV regardless of the level of frontal regions' activity. (B) Based on known frontal regions' compensatory mechanism in early stages of AD-associated neurodegeneration, greater AD-associated neurodegeneration would exaggerate the frontal regions' compensation, which, in turn, would lead to an abnormal increase in HF-HRV. Note that, in either circumstance, the hypothesized link is with AD-associated neurodegeneration instead of the clinical phenotype (aMCI vs. HC). In sum, our overarching aim is to test how frontal brain

activity interacts with PNS function, and how this differs between neurotypical individuals and those affected by AD-associated neurodegeneration.

Methods

Ethical approval

The study was approved by the university's research subject review board and all participants provided written informed consent (according to the latest revision of the Declaration of Helsinki).

Participants

Thirty-eight participants (20 HC and 18 aMCI) completed the study. Participants with aMCI were recruited from university-affiliated memory clinics using the clinical diagnosis of 'mild cognitive impairment due to Alzheimer's disease' (Albert *et al.* 2011); participants had deficits in memory based on a comprehensive neuropsychological battery but intact basic activities of daily living, in addition to the absence of dementia using NINCDS-ADRDA criteria per assessment. Participants had to be stable on AD medication (i.e. memantine or cholinesterase inhibitors; 5 participants from aMCI group (27.7%) were in these medications) for 3 months prior to enrolment. Age-, sex- and education-matched HC participants without self-reported history of dementia or aMCI were recruited from the community. In addition, all participants were required to be ≥ 60 years of age, English-speaking, community-dwelling, and had adequate visual and auditory acuity for testing, as well as the capacity to give consent based on the research team's assessment. Exclusion criteria included the presence of severe cardiovascular disease (e.g. chronic heart failure), inflammatory (e.g. irritable bowel syndrome), or uncontrollable psychiatric (e.g. major depression) diseases, uncontrollable hypertension, or MRI contraindications (e.g. pacemaker, claustrophobia).

Design and procedure

The present study was cross-sectional, consisting of two sessions within a 2-week window. The first session comprised a series of cognitive assessments and interview for demographic and health background. The second session was started in the morning (09.00–11.00 h) in a temperature-controlled room (20–25°C), and included a 10 min acclimation period with continuous electrocardiography (ECG) assessment followed by a 30 min fMRI (T1 structural imaging and resting-state fMRI), and then two 10 min cognitive tasks with ECG measured throughout. The tasks included two commonly used computerized executive function tasks: Stroop Color Word and Dual 1-back task. For the Stroop task, participants

were shown a series of coloured words on the screen, and asked to judge the colour of the word regardless of the meaning of the word as quickly and accurately as possible. For the Dual 1-back task, participants were shown an English letter on the screen, and asked to judge, as quickly and accurately as possible, if the current stimulus matched the letter and position of the previous one. For both tasks, feedback was displayed after the participant responded to an individual trial. Each of the tasks lasted 10 min, and the order of the two tasks was randomized across participants. Instructions and practice were provided before each of the formal tasks. The tasks targeted inhibition and working memory, two executive function domains compromised comparably early in both normal ageing and neurodegeneration (Suchy, 2009). Of note, before coming to the second session appointment, the participants were instructed to avoid caffeine, physical exercise, or taking a β -blocker in the same morning.

Measures

Imaging data acquisition. A 3T Siemens TrioTIM scanner (Erlangen, Germany) equipped with a 32-channel receive-only head coil was used. The session began with a magnetization prepared rapid acquisition gradient echo (MPRAGE) scan (TR/TE = 2530 ms/3.44 ms, TI = 1100 ms, FA = 7, matrix = 256 \times 256, resolution 1 mm \times 1 mm \times 1 mm, slice thickness = 1 mm, 192 slices), which provides high-resolution T1 structural-weighted anatomical images for image-registration purposes. A 2-D axial fast gradient-recalled echo pulse sequence was used to generate field maps and correct for field inhomogeneity distortions in echo-planar imaging sequences. The resting-state fMRI data were collected using a blood oxygen level-dependent (BOLD) fMRI protocol with a gradient echo-planar imaging sequence (TE/TR = 30 ms/2500 ms, FA = 90, slice thickness = 4 mm, matrix = 64 \times 64, 4 mm \times 4 mm in-plane resolution, 30 axial slices, 100 volumes).

Cortical thickness. The structural images were processed using FreeSurfer image analysis suite v5.1.0 (<http://surfer.nmr.mgh.harvard.edu/>). These well-validated and fully automated procedures have been described previously (Fischl & Dale, 2000). Briefly, all the images were automatically processed with skull stripping, spatial transforms, atlas registration and spherical surface maps. After tessellating the grey–white boundary and locating the grey–pial boundary in FreeSurfer, cortical thickness is calculated as the closest distance between the grey–white matter boundary and the pial mesh at each vertex on the tessellated surface (Fischl & Dale, 2000). Automated cortical parcellation and region of interest (ROI) definition were performed using the Desikan–Killiany Atlas which manually labelled 34 cortical ROIs in each

hemisphere (Desikan *et al.* 2006). Of note, the results of Freesurfer segmentation were examined visually for topological defects, with manual editing performed to correct the defects. ADSCT was defined by averaging cortical thickness of bilateral inferior and middle temporal lobes, entorhinal cortex and fusiform gyrus, a lower value indicating worse AD pathology (Jack *et al.* 2015) (Fig. 1A).

Resting-state fMRI data preprocessing and analysis. For each participant, the first five volumes of resting-state fMRI scan were excluded, avoiding the noise related to the equilibrium of the scanner and participants' adaptation to the scanner. The remaining 95 volumes were slice-timing and head-motion corrected, coregistered to their own structure image, and normalized to Montreal Neurological Institute (MNI) standard space, and resampled ($3 \text{ mm} \times 3 \text{ mm} \times 3 \text{ mm}$). Data were subsequently

smoothed using Gaussian kernel (full width at half maximum (FWHM) 4 mm), and the linear trend, white matter, cerebrospinal fluid and head motion were regressed out using the general linear model. We also removed one participant's data due to the head movement being larger than 2 mm and 2 deg. The preprocessed data were filtered using band pass (0.01–0.08 Hz) to calculate ALFF values. Briefly, the BOLD time courses were converted to the frequency domain using the fast Fourier transform. Then the square root of the power spectrum was calculated, averaged across 0.01–0.08 Hz for each voxel, and defined as the ALFF at the given voxel (Zang *et al.* 2007). All preprocessing was conducted using the Data Processing Assistant for the resting state-fMRI package (Chao-Gan & Yu-Feng, 2010). For each participant, the ALFF of each voxel was divided by the global mean ALFF value. To determine the frontal regions

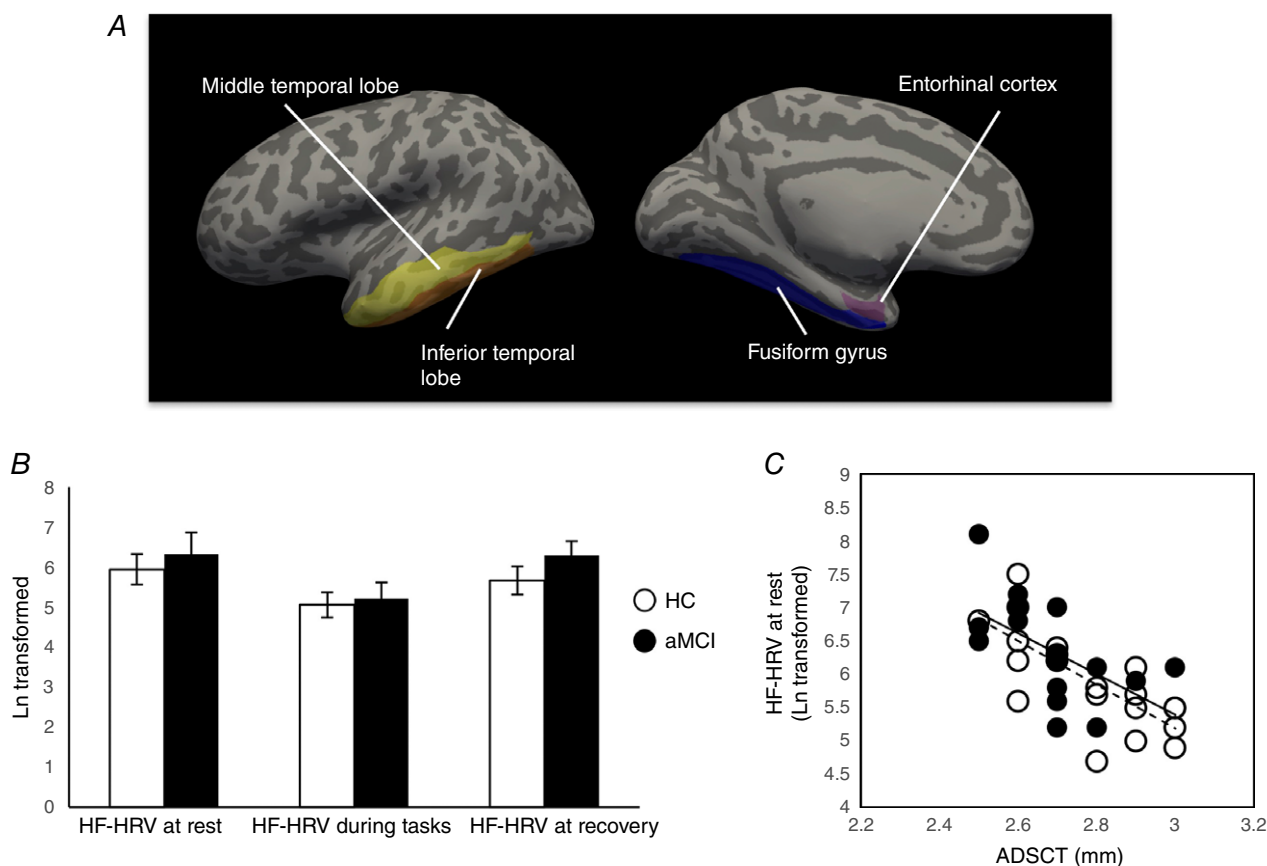


Figure 1. AD-related neurodegeneration and HF-HRV

A, AD-related neurodegeneration was indexed by ADSCT, which was defined by averaging cortical thickness of bilateral inferior and middle temporal lobes, entorhinal cortex and fusiform gyrus. Here, lower value indicated more severe AD pathology. B, mean and SEM of HF-HRV at rest, during tasks and at recovery by group. There was a significant quadratic pattern for HF-HRV (i.e. declined from at rest to tasks, and rebounded after recovery) in both groups, but there was no group by status interaction effect. C, there was a significant association between ADSCT and HF-HRV at rest but not HF-HRV reactivity (calculated as the difference between HF-HRV at tasks and rest) controlled for age and sex. The dashed line represents the correlation in HC group, and the continuous line represents the correlation in aMCI group. Similarity is observed relationships for the two groups. [Colour figure can be viewed at wileyonlinelibrary.com]

that were related to HRV at rest and reactivity, separate linear regression was applied to calculate the correlations between ALFF and HF-HRV at rest, as well as HF-HRV reactivity, in a voxel-by-voxel manner. A threshold of AlphaSim-corrected $P < 0.05$ (synthesizing uncorrected individual $P < 0.005$ and voxel size >22) was applied to all statistical maps (Ledberg *et al.* 1998).

Because the BOLD signal may be influenced by cardiac pulses that may confound with HRV examined in the study, we also conducted a secondary control analysis where we used slightly different preprocessing steps, regressing out pulse that was simultaneously recorded with the pulse oximetry in the resting-state fMRI, in addition to white matter, cerebrospinal fluid and head motion. Due to some technical problems (lack of synchronization of physiological and BOLD data, or failure in recording the physiological data), there were only 29 participants (aMCI: 11 and HC: 18, no significant demographic difference from the main sample) in this analysis. As in the main analysis, we identified brain regions within ACC (related to HF-HRV at rest: ACC1, MNI co-ordinate: 3, 33, 15, voxel size: 41; and related to HF-HRV reactivity: ACC2, MNI co-ordinate: 0, 24, 21, voxel size: 41). Correlations among key variables remained similar, as did indirect effects of ACC for mediating the relationships between ADCST and HF-HRV at rest (ACC1: $B = -5.55$, $SE = 1.94$, $Z = -2.86$, $P = 0.004$) or HF-HRV reactivity controlling for HF-HRV at rest (ACC2: $B = 2.13$, $SE = 1.17$, $Z = 1.82$, $P = 0.068$).

HF-HRV. HF-HRV was assessed using Biopac electrocardiography of a standard lead-II electrode configuration. Electrocardiography was continuously monitored at acclimation and during the cognitive tasks in the second session of the study. HRV software (MindWare) was used to process data as described previously (Berntson *et al.* 1997). Briefly, a series of intervals between consecutive R waves (every 20 s) was preprocessed to remove ectopic beats and artifact. Power spectral analysis was conducted to generate HF-HRV (0.12–0.40 Hz). HF-HRV data were expressed in absolute units and then natural log transformed for normalization. HF-HRV is generally accepted as an index for PNS (Cacioppo *et al.* 2007). Data at rest and during cognitive tasks (based on the order instead of the specific type of task) were averaged respectively (excluding the first and last minute to avoid noise). HF-HRV reactivity was then calculated as the discrepancy (HF-HRV during task – HF-HRV at rest) with larger positive values indicating greater increases in response to the tasks and larger negative values indicating greater suppression. Of note, in the second session, immediately after the two cognitive tasks we also had 40 min relaxation with ECG applied for the last 13 min. We calculated HF-HRV during recovery (excluding the first and last minute). In Fig. 1B, we showed the trajectory of HF-HRV at rest, during the task, and during recovery by group. The

pattern suggests a decline of HF-HRV during the cognitive tasks, with a return to baseline levels during recovery.

Cognitive assessment. We assessed global cognition, episodic memory and executive function in the first session. Global cognition was assessed using Montreal Cognitive Assessment (MOCA) (Rossetti *et al.* 2011). Episodic memory was the mean score of standardized values of learning and delayed recall from Rey's Auditory Verbal Learning Test (Estevez-Gonzalez *et al.* 2003). Executive function was a composite score using the algorithm provided by the EXAMINER package (Kramer *et al.* 2014). We used four computerized tasks: 1-back (different from the cognitively demanding tasks in the second session), dot counting, set shifting and flanker.

Other data analysis

SPSS 22.0 was used for the data analysis. Group comparisons on sample characteristics were conducted using the independent Student's t test and χ^2 tests for categorical and continuous variables, respectively. Repeated measures ANOVA was used to examine HF-HRV across time. Partial Pearson's correlations were conducted for the relationship between HF-HRV, ADCST and cognitive assessments controlling for age, sex and group. Mediation models were then estimated to test whether function of frontal regions mediated the effect of the ADCST on HF-HRV at rest and in response to tasks (reactivity) (Preacher & Hayes, 2008). Mediation models of HF-HRV reactivity controlled for resting levels (Benjamin, 1967). Bootstrapping of standard errors (5000 bootstrap draws) was used for indirect effect estimates using the INDIRECT macro from SPSS.

Results

A link between AD-associated neurodegeneration, HF-HRV and cognitive function

The aMCI group had significantly worse ADCST and worse performance on MOCA and episodic memory (but not executive function) than the HC group (Table 1). There were no group differences in HF-HRV at rest or for task reactivity. Both groups showed significant HF-HRV decline from rest during the tasks, and with recovery to resting levels following the tasks (quadratic model: HC: $F = 8.68$, $P = 0.008$; aMCI: $F = 12.33$, $P = 0.003$) without a time by group interaction effect ($F = 0.71$, $P = 0.41$) (Fig. 1B). Although clinically defined groups did not differ on HF-HRV, as noted in the Introduction, our primary aim was to examine associations between AD-associated neurodegeneration and HF-HRV and cognitive function. Indeed, lower ADCST was significantly related to higher HF-HRV at rest (Fig. 1C) and worse cognitive performance; and

Table 1. Demographics and clinical characteristics of aMCI and HC groups

	aMCI (n = 18)	HC (n = 20)	t or χ^2 test (P value), d.f.
Age, mean (SD)	74.44 (10.60)	70.95 (9.13)	1.09 (0.28), 36
Education, mean (SD)	15.39 (2.87)	15.75 (2.34)	-0.43 (0.67), 36
Male, n (%)	8 (44.4)	8 (40.0)	0.08 (0.78), 1
Geriatric depression scale, mean (SD)	3.00 (2.74)	1.60 (2.01)	1.81 (0.08), 36
Hypertension, n (%)	7 (38.9)	10 (50.0)	0.47 (0.53), 1
MOCA, mean (SD)	24.17 (2.55)	26.10 (2.73)	-2.25 (0.031), 36
Episodic memory, mean (SD)	-0.45 (0.97)	0.40 (0.72)	-3.07 (0.004), 36
Executive function, mean (SD)	0.05 (0.69)	0.39 (0.55)	-1.71 (0.10), 36
HF-HRV at rest (ms ²), mean (SD)	6.32 (2.29)	5.95 (1.70)	0.57 (0.57), 36
HF-HRV reactivity (ms ²), mean (SD)	-1.11 (2.10)	-0.90 (1.72)	-0.34 (0.74), 36
ADSCCT (mm ³), mean (SD)	2.67 (0.14)	2.79 (0.16)	-2.46 (0.019), 36
ALFF in ACC1, mean (SD)	1.26 (0.48)	1.09 (0.29)	1.30 (0.20), 35
ALFF in ACC2, mean (SD)	1.26 (0.47)	1.10 (0.37)	1.17 (0.25), 35

Table 2. Relationships between ADSCCT, HF-HRV and cognition

	Pearson's correlation (P value)				
	ADSCCT	HF-HRV at rest	HF-HRV reactivity	ACC1	ACC2
ADSCCT					
HF-HRV at rest	-0.37 (0.025) [#]				
HF-HRV reactivity	0.27 (0.12)	—			
ACC1	-0.60 (<0.001) [#]	0.70 (<0.001) [#]	—		
ACC2	-0.52 (0.001) [#]	—	-0.74 (<0.001) [#]		
MOCA	0.32 (0.059)	-0.38 (0.024) [#]	0.39 (0.022) [#]	-0.48 (0.004) [#]	-0.44 (0.009) [#]
Episodic memory	0.25 (0.15)	-0.46 (0.006) [#]	0.48 (0.004)	-0.39 (0.019) [#]	-0.44 (0.008) [#]
Executive function	0.23 (0.19)	-0.34 (0.049) [#]	0.29 (0.087)	-0.43 (0.011) [#]	-0.38 (0.024) [#]

Note: correlations controlled for age and sex.

[#]Statistical significance remained when also controlling for group and education.

lower HF-HRV reactivity (i.e. greater depression in HF-HRV) was also significantly related to worse cognitive performance (Table 2). These results were unaffected when controlling for group (clinical phenotype).

Mediating effect of frontal regions' function on the relationship between ADSCCT and HF-HRV

Applying the whole brain voxel-wise analysis of ALFF to HF-HRV at rest and reactivity, we consistently generated a region located in the ACC in which higher ALFF was significantly related to higher HF-HRV at rest (ACC1: MNI co-ordinate: 0, 33, 18, voxel size: 48) and lower HF-HRV reactivity (ACC2: MNI co-ordinate: 0, 24, 21, voxel size: 41; Fig. 2A). Of note, there was also a region generated in the brainstem area. Although ANS is known to be related to brainstem (Femminella *et al.* 2014), brainstem was not part of our frontal function hypothesis and thus it was not included in the subsequent analyses. There were no group differences in ALFF in either ACC, meaning that the clinical phenotype may not affect frontal activities

(Table 1). Controlling for age and sex, lower ALFF in ACC1 and ACC2 was significantly related to higher ADSCCT and better cognitive performance. Significant relationships remained when controlling for group (Table 2 and Fig. 2).

Next, we built a mediation model examining whether ACC mediated the relationship between ADSCCT and HF-HRV (Fig. 3A). Since we had a relatively small sample size for a well-controlled mediation analysis, age and sex were not controlled. The results showed that ALFF in ACC1 significantly mediated the association between ADSCCT and HF-HRV at rest (Indirect effect: $B = -4.90$, $SE = 1.69$, $Z = -2.90$, $P = 0.004$, Fig. 3B shows all direct effects). Although the correlation between ADSCCT and HF-HRV reactivity did not meet statistical significance ($P = 0.12$), the coefficient ($r = 0.27$) suggested a non-trivial association that warranted testing of the mediational model proposed (Frazier *et al.* 2004). ALFF in ACC2 also significantly mediated the association between ADSCCT and HF-HRV reactivity, controlling for HF-HRV at rest (Indirect effect: $B = 2.26$, $SE = 1.08$, $Z = 2.10$, $P = 0.036$, Fig. 3C shows all direct effects). When controlling for

the group effect, the indirect effects of the two models remained significant.

Discussion

Here we combined structural MRI, resting-state fMRI, and a peripheral physiological measure to elucidate the effect of AD-associated neurodegeneration on PNS. Unlike

previous studies of cognitively normal or healthy younger adults where higher HF-HRV at rest was linked to younger age and better cognitive regulation (e.g. Kemp *et al.* 2016; Williams *et al.* 2016), the present study found that more severe AD-associated neurodegeneration (indexed by lower scores in ADSCt), along with worse cognitive function, was linked to higher HF-HRV at rest among older adults. Worse cognitive function was also

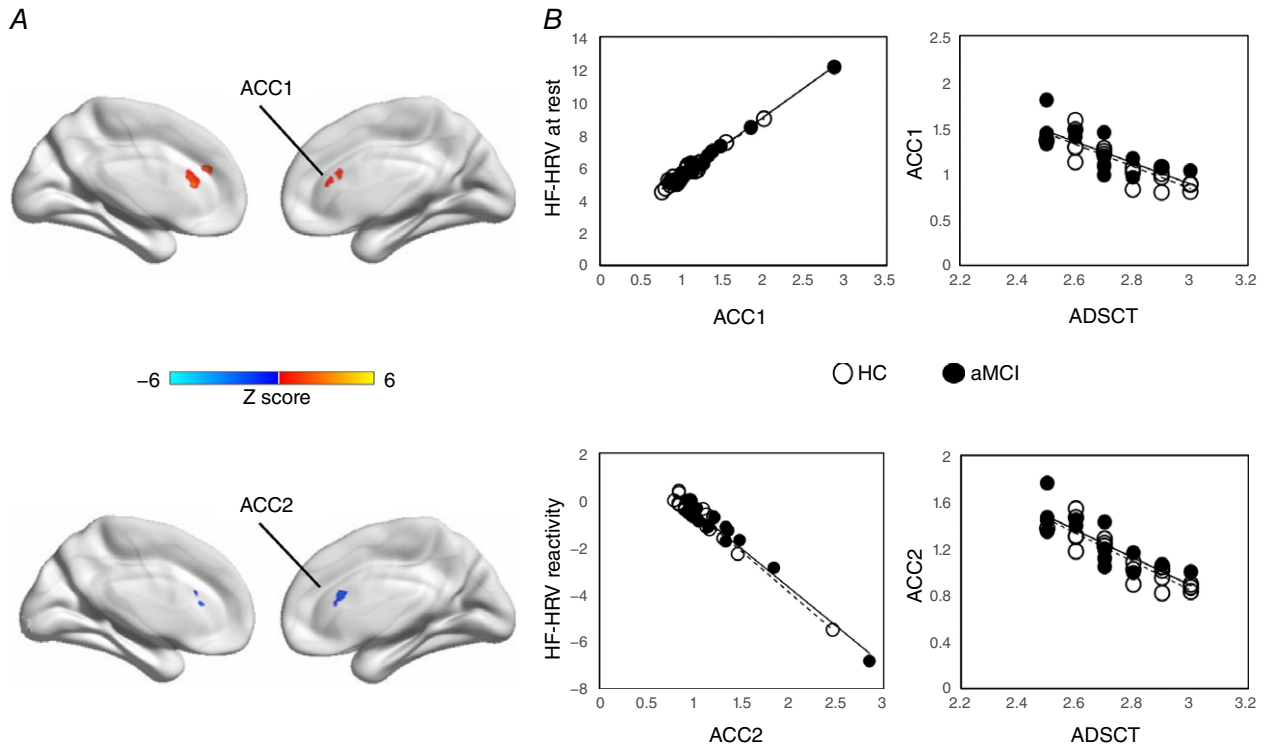


Figure 2. Frontal regions' function and HF-HRV
 A, with AlphaSim correction at $P < 0.05$, there was a region located in the anterior cingulate cortex (ACC) in which higher ALFF was significantly related to higher HF-HRV at rest (ACC1: MNI co-ordinate: 0, 33, 18, voxel size: 41) and lower HF-HRV reactivity (ACC2: MNI co-ordinate: 0, 24, 21, voxel size: 40). B, associations between ACC and HF-HRV at rest and reactivity controlled for age and sex. The dashed line represents the correlation in HC group, and the continuous line represents the correlation in aMCI group. Similarity is observed relationships for the two groups. [Colour figure can be viewed at wileyonlinelibrary.com]

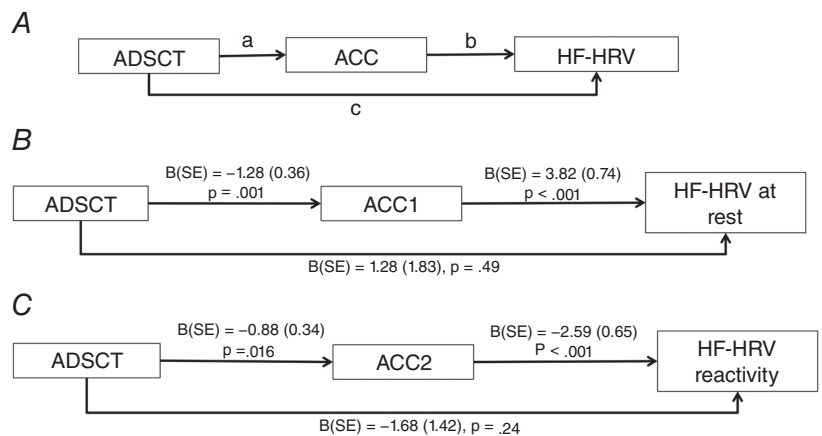


Figure 3. Mediation models examining ACC as a mediator for the relationship between ADSCt and HF-HRV
 A, conceptual model; B, ALFF in ACC1 significantly mediated the association between ADSCt and HF-HRV at rest; C, ALFF in ACC2 also significantly mediated the association between ADSCt and HF-HRV reactivity, controlling for HF-HRV at rest. Results reported in B and C are direct effects.

related to larger decline in HF-HRV, suggesting greater withdrawal of PNS, during the cognitive tasks. Notably, the relationships between ADSCT and HF-HRV were explained by ACC spontaneous activity level. That is, AD-associated neurodegeneration accompanied a hyperactive ACC, which, in turn, resulted in a high level of HF-HRV at rest, as well as stronger HF decline to the tasks. None of these relationships were affected by the clinical phenotype (i.e. HC vs. aMCI). This discovery provides the first line of evidence to suggest that AD-associated neurodegeneration is associated with altered PNS regulation during mental effort in older adults, and that the compensatory processes accompanying frontal hyperactivation appear to be responsible for these alterations.

The relationship between more severe AD-associated neurodegeneration and higher HF-HRV at rest is notable. Studies in healthy adults suggest that lower capacity of frontal regions, including ACC, is associated with reduced HF-HRV (Thayer *et al.* 2012). We suggest, however, that the well-established neural compensatory processes in early AD-neurodegeneration may help explain these seemingly inconsistent findings. As indicated in the literature, hyperactive ACC often comes from insufficient neural efficiency of frontal regions or the compensatory mechanism for neural loss of posterior regions (Li *et al.* 2014). Either process can lead to a correspondingly enhanced HF-HRV at rest or greater suppression of HF-HRV when engaging in cognitive tasks. It is possible that the positive relationship between HF-HRV and activity of frontal regions may only be applicable to healthy younger adults when neural efficiency and activity level of frontal regions are in the same direction (McEwen & Gianaros, 2010; Taylor *et al.* 2010). Given the common phenomenon of compensatory neural mechanisms in ageing and in the early stage of AD-associated neurodegeneration, simply increasing the frontal activities may not be useful. Instead, enhancing the 'efficiency' of the frontal regions may be warranted. Notably, in our recent cognitive training study, cognitive training strengthened such efficiency in older adults with aMCI (Lin *et al.* 2017a). The intervention approach may provide a viable pathway to determine the causal relationship between neural efficiency and HF-HRV. After all, adequate PNS function is critical for adaptation to cognitively challenging environments (Thayer *et al.* 2009). For older adults, including those at risk for AD, strengthening pathways regulating PNS may be efficacious for maintaining functional health in later life.

It is notable that the level of HF-HRV, ACC activation, and the relationships between ADSCT, ACC activation and HF-HRV were not differentiated by clinical phenotype. The two groups did differ in ADSCT. This indicates that individuals with aMCI may still have the capacity to rely on frontal regions' compensation, thus maintaining PNS regardless of AD pathology.

Therefore, focusing on the clinical phenotype as a predictor of neuropathological-related effects in physiological regulation is not sufficient to understand the true effects of neurodegenerative disease. However, regarding the insignificant relationship between clinical phenotype and HF-HRV, we could not fully exclude the limitation of the small sample size, or lack of power (Quintana, 2017). Also, the participants' history of attending therapeutic programmes (e.g. physical exercise) that can affect HF-HRV (Albinet *et al.* 2010) was not assessed in the present study while physical exercise may be a common activity for older adults with cognitive deficits given its potential for cognitive maintenance. It should also be acknowledged that neurodegeneration is just one of the factors that likely drives pathophysiological heterogeneity in AD risk or aMCI, with others including amyloidosis or tau pathology (Jacquemont *et al.* 2017). The observed link between neurodegeneration and PNS warrants future exploration of AD-specific neuropathology and its effect on frontal activation and autonomic regulation.

In sum, our data support a new framework suggesting that early stage AD-associated neurodegeneration is linked to autonomic dysregulation via the involvement of neural inefficiency in frontal regions. A new profile for PNS should be carefully redefined in relation to AD (see Fig. 4 for a proposed preliminary framework). That is, as AD-associated neurodegeneration initiates, an abnormally active PNS may reflect compensation mechanisms in the frontal regions. However, PNS function eventually worsens as neurodegeneration progresses and starts affecting frontal regions, ultimately decreasing to the levels below normal ageing-associated PNS activity (Jack *et al.* 2010; Femminella *et al.* 2014). Several limitations of this framework need to be acknowledged. First, although we excluded the cardiac pulsation's influence on fMRI to clarify the relationship between fMRI and

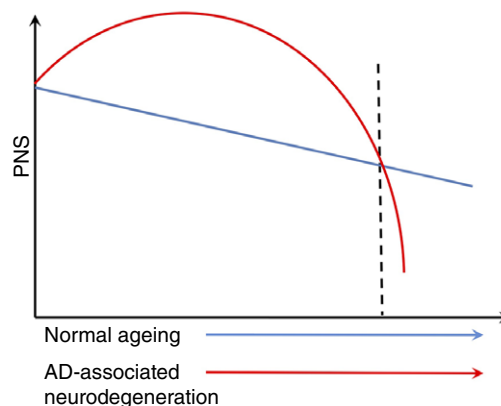


Figure 4. Conceptual framework of the relationship among PNS, age and AD-associated neurodegeneration

Blue line indicates PNS trajectory in the normal ageing; red line indicates PNS trajectory when AD-associated neurodegeneration occurs. [Colour figure can be viewed at wileyonlinelibrary.com]

PNS, other PNS indicators that are less sensitive to the influence of respirations (e.g. root mean square of successive differences) should also be examined. Also, other peripheral haemostatic processes (e.g. immune system, hypothalamic–pituitary–adrenal axis) may interact with the ANS as they are all centrally regulated by the frontal regions (Taylor *et al.* 2010). A more comprehensive, integrative framework is needed to fully explain the interplay of central and peripheral physiological regulation in AD-associated neurodegeneration. Second, using a cross-sectional design, the causal relationships between AD pathology, frontal activation and PNS cannot be confirmed. The next step will be to modify AD pathology or frontal neural efficiency (Lin *et al.* 2017a), and examine the consequential changes in PNS as discussed above. Third, using voxel-wise analysis, ACC was the only frontal region associated with HF-HRV. In the literature, in addition to ACC, striatum and prefrontal cortex play a role in HF-HRV (Thayer *et al.* 2012). Region of interest type analysis may be conducted to further confirm the current model with a relatively large sample. Finally, these findings are limited to a cognitively demanding situation, but it is unknown whether the observed alterations in PNS regulation would manifest in response to more metabolically or subjectively demanding situations (e.g. physical, psychological, or social stress) that activate multiple, co-ordinated systems to support stress adaptation (Segerstrom & Miller, 2004). Contemporary models of ageing underscore the role of stress adaptation in morbidity and mortality outcomes (Epel & Lithgow, 2014). Thus, these findings may have implications for advancing understanding of the role of neurodegeneration in multiple facets of older adults' function and health.

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Additional information

Competing interests

None declared.

Author contributions

F.L., D.T. and K.L.H. designed and drafted the work; P.R., X.W. and M.A. collected, analysed and interpreted the data, and revised the paper for important intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed. The work was conducted at the CogT Lab, University of Rochester.

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