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CCA identifies a neurophysiological marker of adaptation capacity that is reliably linked to internal locus of control of cognition in amnestic MCI

Lizbeth Peralta-Malváez · Adam Turnbull · Mia Anthony · Ehsan Adeli · F. Vankee Lin

Abstract Locus of control (LOC) describes whether an individual thinks that they themselves (internal LOC) or external factors (external LOC) have more influence on their lives. LOC varies by domain, and a person's LOC for their intellectual capacities (LOC-Cognition) may be a marker of resilience in older adults at risk for dementia, with internal LOC-Cognition relating to better outcomes and improved treatment adherence. Vagal control, a key component of parasympathetic autonomic nervous system (ANS) regulation, may reflect a neurophysiological biomarker of internal LOC-Cognition. We used canonical correlation analysis (CCA) to identify a shared neurophysiological marker of ANS regulation from electrocardiogram (during auditory working memory) and functional connectivity (FC) data. A canonical variable from root mean square of successive differences (RMSSD) time series and between-network FC was significantly related to internal LOC-Cognition ($\beta = 0.266$, SE = 0.971, CI = [0.190, 4.073], $p = 0.031$) in 65 participants (mean age = 74.7, 32 female) with amnestic mild cognitive impairment (aMCI). Follow-up data from 55 of these individuals (mean age = 73.6, 22 females) was used to show reliability of this relationship ($\beta = 0.271$, SE = 0.971, CI = [0.033, 2.630], $p = 0.047$), and a second sample (40 participants with aMCI/healthy cognition, mean age = 72.7, 24 females) showed that the canonical vector biomarker generalized to visual working memory ($\beta = 0.36$, SE = 0.136, CI = [0.023, 0.574], $p = 0.037$), but not inhibition task RMSSD data ($\beta = 0.08$, SE = 1.486, CI = [−0.354, 0.657], $p = 0.685$). This canonical vector may represent a biomarker of autonomic regulation that explains how some older adults maintain internal LOC-Cognition as dementia progresses. Future work should further test the causality of this relationship and the modifiability of this biomarker.

Keywords Locus of control · Dementia · LOC-Cognition · Autonomic flexibility

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Introduction

Locus of control (LOC) describes a personality trait based on whether an individual thinks that they themselves (internal LOC) or external factors (external LOC) have more influence on their lives. Internal LOC has been theorized to enable better coping mechanisms and adjustment to chronic

diseases [34]. In addition to reflecting a personality trait, LOC has been shown to vary by domain, for example, the extent to which someone believes they are in control of their health (LOC-Health) or intellectual capacities (LOC-Cognition). Lachman [16] found that these domain-specific LOC measures show age-related differences and are stronger predictors of behavioral outcomes in older adults than overall LOC. Critically, our recent studies suggest that the early stages of dementia (specifically, mild cognitive impairment,MCI) are associated with a shift in LOC-Cognition, with a decrease in internal LOC-Cognition and an increase in external LOC-Cognition [32]. This is in line with research from other disorders showing that worsening depression symptoms predict a shift from internal to external LOC [15]. Additionally, one study suggested that internal LOC might be protective against cognitive decline and brain aging in older adults [31], and maintaining a belief that you are in control of your own cognition may be an essential driver of adherence to interventions in older adults at risk for dementia [44]. Not only do these findings imply that LOC-Cognition may be an indicator of dementia progression, but LOC-Cognition may also act as a feed-forward mechanism for the progression of dementia, leading to less resilience as individuals' cognition declines alongside their belief that they are in control of their cognition.

Identifying potentially modifiable mechanisms that underpin internal LOC-Cognition among older adults at risk for dementia is fundamental for developing effective interventions that can promote internal LOC-Cognition to potentially improve both adherence to interventions and general cognitive outcomes. Research has shown that individuals with strong internal LOC show altered stress response or better adaptation capacity [22, 31]. Of note, autonomic nervous system (ANS) regulation serves as the primary indicator of stress response or adaptation capacity [40]. Cumulative work, including ours, has shown that ANS regulation, and selected brain networks that are tightly interwoven via bidirectional communication, support "autonomic flexibility", regulating physiological and behavioral responses to threatening or challenging stimuli and influencing health [29]. Particularly, impaired vagal control capacity (an aspect of autonomic flexibility involving control over the parasympathetic, or "rest-and-digest" branch, of the ANS) at rest and during selected cognitively challenging tasks (e.g., working memory tasks) is related to neurodegeneration and cognitive deficits in individuals at risk for or with dementia [17, 20, 25]. Together, these findings suggest that the capacity to control autonomic flexibility via vagal nerve systems may be a mechanism explaining differences in internal LOC-Cognition in older adults at risk for dementia.

In this study, we tested a novel hypothesis that patterns of autonomic regulation captured via neural and peripheral physiological measures would reflect an older person's internal LOC-Cognition. We assessed the vagal control of ANS activities (via root mean square of successive differences; RMSSD) of older adults with amnestic mild cognitive impairment (aMCI) during working memory tasks. Working memory is a critical component of cognitive decline during dementia that can be assessed in a single, short session, and has been shown to elicit reliable autonomic responses in older adults [28]. While resting-state HRV measures can also reflect parasympathetic adaptation capacity, there is evidence that there may be dissociable autonomic responses to specific environmental/cognitive stressors that relate to individual differences in participant traits [21, 39]. Given our focus on a population at risk for cognitive decline, particularly in executive functions such as working memory, and resilience markers related specifically to their cognition (LOC-Cognition), we chose to measure HRV data during a cognitive stressor to focus on autonomic signals that may specifically reflect vagal adaptation capacity related to at risk cognitive processes. We used canonical correlation analysis (CCA), which maximizes the linear correspondence between two sets of variables, to obtain correlated features from RMSSD time series and brain resting-state functional connectivity (FC) derived from fMRI data (see Fig. 1). Resting-state FC is a trait measure of brain function that has shown associations with HRV measures [7, 8]. By constraining the CCA using resting-state FC, we aimed to identify linear correspondences between FC and HRV measures to isolate aspects of autonomic regulation that are shared between the peripheral and central nervous systems. Given that dementia pathology predominantly affects the brain, we believe that these shared signals are critical for understanding individual differences in autonomic regulation in dementia. The identified canonical vector reflected a potential biomarker reflecting
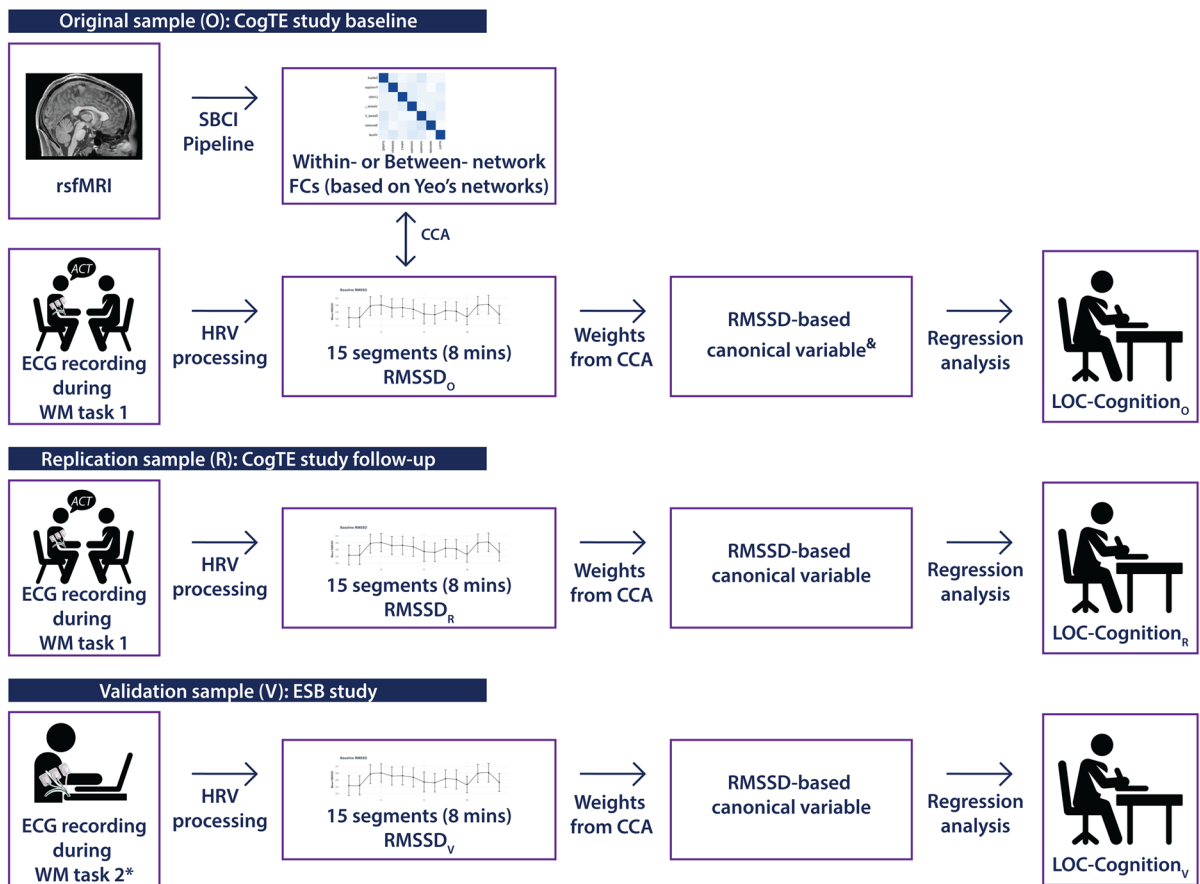
Fig. 1 Overview of the design and analytical flow throughout the original, replication and validation samples. We generated two sets of RMSSD based on CCA of within-networks FCs, as well as CCA of between-network FCs. Note: *we also included an inhibition task as comparison. "Weights from CCA" were all from CCA in Sample$_O$

autonomic regulation, and was significantly associated with internal LOC-Cognition at two separate time points within an aging sample at risk for dementia, as well as in a separate validation sample consisting both cognitively healthy older adults and those with aMCI.

Methods

Design overview

Figure 1 displays an overview of the study procedure. Briefly, we used a sample of 65 older adults (mean age = 74.72 ± 7.64) from the "CogTE" study [19] as the original sample set (Sample$_O$) where we collected measures of resting-state fMRI (rsfMRI), working memory-based task electrocardiogram (ECG), and LOC-Cognition. In Sample$_O$, we extracted RMSSD-based canonical variables (RMSSD-betweenFC-var$_O$ and RMSSD-withinFC-var$_O$) based on CCA of RMSSD and FC (separating averages of all within-network connections for withinFC and all between-network connections for between FC) and analyzed the relationship between autonomic flexibility and LOC-Cognition (see below for more details). As part of this analysis, CCA on Sample$_O$ also generates canonical vectors (RMSSD-betweenFC-vec$_O$ and RMSSD-withinFC-vec$_O$), which reflect a series of weights that can be applied to other RMSSD data. We used two samples—the 6-week follow-up data of the original sample set (Sample$_R$) and a sample set of 40 older adults (mean age = 72.83 ± 10.10) (Sample$_V$,

ESB study [32])—for replication and validation of canonical vectors that showed a significant relationship to LOC-Cognition in Sample$_O$. We directly developed RMSSD canonical variables (RMSSD-betweenFC-var$_R$ and RMSSD-betweenFC-var$_V$) using the canonical vector (RMSSD-betweenFC-vec$_O$) identified as significantly related to LOC-Cognition in in Sample$_O$ (rsfMRI data were not included in the replication samples). These variables were used to replicate and validate the relationship between RMSSD-betweenFC-var$_O$ and LOC-Cognition$_O$ using RMSSD canonical variables (RMSSD-betweenFC-var$_R$ and RMSSD-betweenFC-var$_V$) and LOC-Cognition scores (LOC-Cognition$_R$ and LOC-Cognition$_V$) from each sample.

Participants

Sample from CogTE study

Older adults with aMCI were recruited from university affiliated clinics. Description of the inclusion and exclusion criteria is available from the original report [19]. Out of the original 84 participants, 19 were excluded from the analyses due to the incomplete ECG recordings, leaving 65 participants as Sample$_O$. The original CogTE study included intervention and control groups. Sample$_O$ was baseline data from both groups. Replication sample$_R$ was from the 6-week follow-up data (post-intervention) from both groups, further excluding 10 participants missing valid RMSSD data.

Sample from ESB study

Older adults with aMCI or age-, sex-, and education-matched healthy cognition (HC) were recruited from local community or university affiliated clinics. Description of the inclusion and exclusion criteria is available from the original report [32]. We will refer to this validation sample as Sample$_V$. Description of all samples is available in Table 1.

Measures

LOC-Cognition

As in previous studies in our lab [32, 33], LOC-Cognition was assessed with the Personality in Intellectual Aging Contexts (PIC) Inventory Control Scales-Short Form [16]. The scale includes three 12-item subscales: internal (reflecting internal LOC-Cognition), chance, and powerful others. Internal LOC-Cognition assesses perceived control over one's intellectual competence. The other two subscales assess the perception that environment (chance) or other individuals (powerful others) are responsible for one's cognitive capabilities. Responses were made on a 6-point scale, from 1 (strongly agree) to 6 (strongly disagree). Items of a subscale were averaged so that higher scores in all subscales indicated higher levels of LOC-Cognition. In the following analyses, we focused on internal LOC,Cronbach's alpha was 0.75 for Sample$_O$, 0.67 for Sample$_R$, and 0.83 for Sample$_V$. As a comparison to internal LOC-Cognition, we used averaged scores of chance and powerful others to reflect external LOC-Cognition [32, 47].

Table 1 Characteristics of original, replication, and validation samples

	CogTE study		ESB study (Sample$_V$)		
	Sample$_O$ aMCI ($n=65$)	Sample$_R$ aMCI ($n=55$)	Total ($n=40$)	HC ($n=22$)	aMCI ($n=18$)
Age, mean (SD)	74.72 (7.64)	73.65 (7.08)	72.67 (10.06)	71.23 (9.61)	74.44 (10.60)
Years of education, mean (SD)	16.44 (2.44)	16.30 (2.50)	15.52 (2.64)	15.64 (2.50)	15.39 (2.87)
Male, n (%)	33 (50.7)	33 (60)	16 (40)	8 (36.4)	8 (44.4)
MoCA, mean (SD)	23.92 (2.59)	24.21 (2.88)	25.23 (2.76)	26.14 (2.67)	24.17 (2.55)
Internal LOC, mean (SD)	5.09 (0.65)	5.19 (0.58)	5.01 (0.81)	5.33 (0.52)	4.64 (0.96)
External LOC, mean (SD)	2.42 (0.63)	2.35 (0.61)	2.47 (0.87)	2.09 (0.72)	2.95 (0.82)

aMCI amnesic mild cognitive impairment, *SD* standard deviation, *n* number of participants, *MoCA* Montreal cognitive assessment, *LOC* locus of control (cognition)

Brain network FC measures

Data acquisition

Imaging data were collected using a research-dedicated 3 T Siemens TrioTIM scanner (Erlangen, Germany) with a 32-channel head coil in Sample$_O$. Each magnetic resonance session began with a scout image, followed by an MPRAGE scan (TI = 1100 ms, TE/TR = 3.44 ms/2530 ms, 1-mm isotropic resolution, 256 × 256 matrix, FA = 7, 1-mm slice thickness, 192 slices), which provides high-resolution structural-weighted anatomical images for image-registration purposes. A 2D axial fast gradient-recalled echo pulse sequence was used to generate field maps to correct for field inhomogeneity distortions in echo-planar imaging sequences. Blood-oxygen-level-dependent (BOLD) functional data were collected using a gradient echo-planar imaging sequence (TE/TR = 30 ms/2500 ms, 4-mm isotropic resolution, 64 × 64 matrix, FA = 90, 4-mm slice thickness, 37 contiguous axial slices). Participants were instructed to relax with their eyes open without falling asleep. An in-scanner camera was used to ensure compliance.

Data preprocessing

Resting-state fMRI data were preprocessed using scripts from a pipeline developed in our lab [6]. The script used for preprocessing is available at: https://github.com/sbci-brain/SBCI_Pipeline/blob/master/integrated_pipeline/preproc_step5_fmri.sh, and was carried out using FreeSurfer. Preprocessing included these steps: motion correction, slice-time correction, intensity normalization, and co-registration and normalization to the cortical surface (fsaverage). Additionally, motion, the first five components of the signal from the ventricular cerebrospinal fluid and white matter, the global signal, and a linear trend were regressed out alongside temporal filtering (0.009–0.08 Hz). Images were spatially smoothed using a kernel with 5 mm FWHM. Images were projected onto the gray-white matter boundary, and time series were extracted and correlated to generate a functional connectivity matrix (https://github.com/sbci-brain/SBCI_Pipeline/blob/master/integrated_pipeline/sbci_step6_functional.sh). Edges were averaged both within and between the 7 large-scale cortical networks (visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal, and default mode) and identified by Yeo and Krienen et al. [46] to give 7 average within-network functional connectivity and 21 between-network functional connectivity values per participant.

RMSSD measures

Data acquisition

ECG data in both CogTE and ESB studies were acquired with Mindware and BioLab software. Heart rate variability (HRV) was monitored continuously using a standard lead-II electrode configuration, while participants performed an auditory working memory (i.e., auditory consonant trigrams) task in CogTE, or Stroop (inhibition) and Dual 1-back (visual working memory) tasks in a random order across participants in ESB. The same protocol was used to collect ECG data for all three samples. Across both studies and subjects, the same environmental control was applied, including a fixed time window and room temperature for conducting ECG recording, and restricting from beta-blocker and caffeine intake on the day before ECG recording.

Data preprocessing

We filtered the ECG raw signal using a bandpass Butterworth filter of 4th order in the range [0.1, 100] Hz and preprocessed RMSSD data using the Heartpy library of Python [43]. The frequency range is recommended by the American Heart Association [1]. RMSSD, a vagal regulation capacity measure from HRV, was used as the outcome measure. The advantage of using RMSSD, compared to HF-HRV, is that RMSSD is less affected by the respiration frequency. Across all ECG data, we used the first 8-min data. The ECG data was processed in segments of 60 s with a 30-s sliding window. From 15 segments generated, we extracted the RMSSD and calculated the natural log. If there were missing values in four segments or less, we used interpolation (mean of the previous and the following variables). Of note, we only included participants with at least 11/15 segments across samples.

Data analysis

CCA is a statistical method that identifies and quantifies the associations between two linearly combined sets of variables *X* and *Y* (without assuming any particular form of precedence or directionality) [14]. The main goal is to find coefficient vectors (or canonical vectors) *a* and *b*, such that the correlation (ρ) between the sets is as large as possible:

$$\rho = max_{a,b} corr(aX, bY) \tag{1}$$

where *X* and *Y* come from the same number of observations *n* and have dimensions *n x p* and *n x q*, respectively, a ϵ R^p, and b ϵ R^q. With this, we obtained the canonical weights for the canonical variable explaining the highest correlation between the two sets of variables.

We examined CCA between RMSSD segments and FC measures in Sample$_O$. To understand whether within- or between-network FC played different roles in adaptation capacity related to internal LOC-Cognition, we separated FC into within-network features ($n = 7$) and between-network features ($n = 21$) and ran two sets of CCA. CCA was only performed on the data from Sample$_O$; to generate the RMSSD canonical variables for the replication and validation data (RMSSD-betweenFC-var$_R$ and RMSSD-betweenFC-var$_V$), we used Sample$_O$'s CCA weights/canonical vector (RMSSD-betweenFC-vec$_O$, representing a series of weights for each RMSSD segment). We did not use RMSSD-withinFC-vec$_O$ in later canonical variable calculation due to the insignificant findings between RMSSD-withinFC-var$_O$ and internal LOC-cognition (see results). To obtain values of the corresponding canonical variable (cv_n), which is RMSSD-betweenFC-var$_R$ for Sample$_R$ and RMSSD-betweenFC-var$_V$ for Sample$_V$, respectively), we used the following formula described earlier [45]:

$$cv_n = \sum_{k=1}^{s} a_k X_{i,k} \ \forall i = 1, \dots n \tag{2}$$

where *a* is RMSSD-betweenFC-vec$_O$, *X* is the matrix containing RMSSD segment values, *n* is the number of participants according to the sample used (65, 55, or 40), and *s* is the number of RMSSD segments (15). CCA was conducted in R with the *cancor()* function of CCA package.

Linear regression

To determine the correlation between LOC-Cognition and RMSSD canonical variables, we used linear regression (*stats* package) in R.

Using Sample$_O$, we calculated the correlation between RMSSD canonical variables (RMSSD-betweenFC-var$_O$ based on RMSSD-betweenFC-vec$_O$ and RMSSD-withinFC-var$_O$ based on RMSSD-withinFC-vec$_O$, respectively) and internal LOC-Cognition$_O$, with alpha set at 0.05. These analyses were also performed with external LOC-Cognition, for comparison purposes.

To assess the reproducibility of our findings, we performed two additional sets of linear regression: (1) using Sample$_R$, we examined the relationship between RMSSD-betweenFC-var$_R$ and internal LOC-Cognition$_R$. Sample$_R$ consisted both groups' post-intervention data (from CogTE study); therefore, we controlled for the group to remove intervention effect confounds; (2) using Sample$_V$, we examined the relationship between RMSSD-betweenFC-var$_V$ and internal LOC-Cognition$_V$. For Sample$_V$, we used RMSSD data during a visual working memory task and an inhibition task to test the generalizability of RMSSD-betweenFC-vec$_O$. We controlled for MOCA as Sample$_V$ included both HC and aMCI.

Results

Canonical correlation analysis

First, we attempted to extract an HRV biomarker reflecting adaptation capacity during an auditory working memory task by performing a CCA on the RMSSD time series constrained by either within- or between-network FC. CCA on Sample$_O$ identified a shared component characterized by a correlation of 86.9% and 66.23% between features from the RMSSD time series and between- and within-Yeo network FC, respectively. Figure 2A and B display the weights of RMSSD segments and brain networks contributing to the correlation. The CCA weights in both RMSSD canonical vectors (RMSSD-betweenFC-vec$_O$ and RMSSD-withinFC-vec$_O$) are highest for segments 5, 6, 12, 13, 14, and 15 in both scenarios, meaning these segments contribute the most to the canonical variables
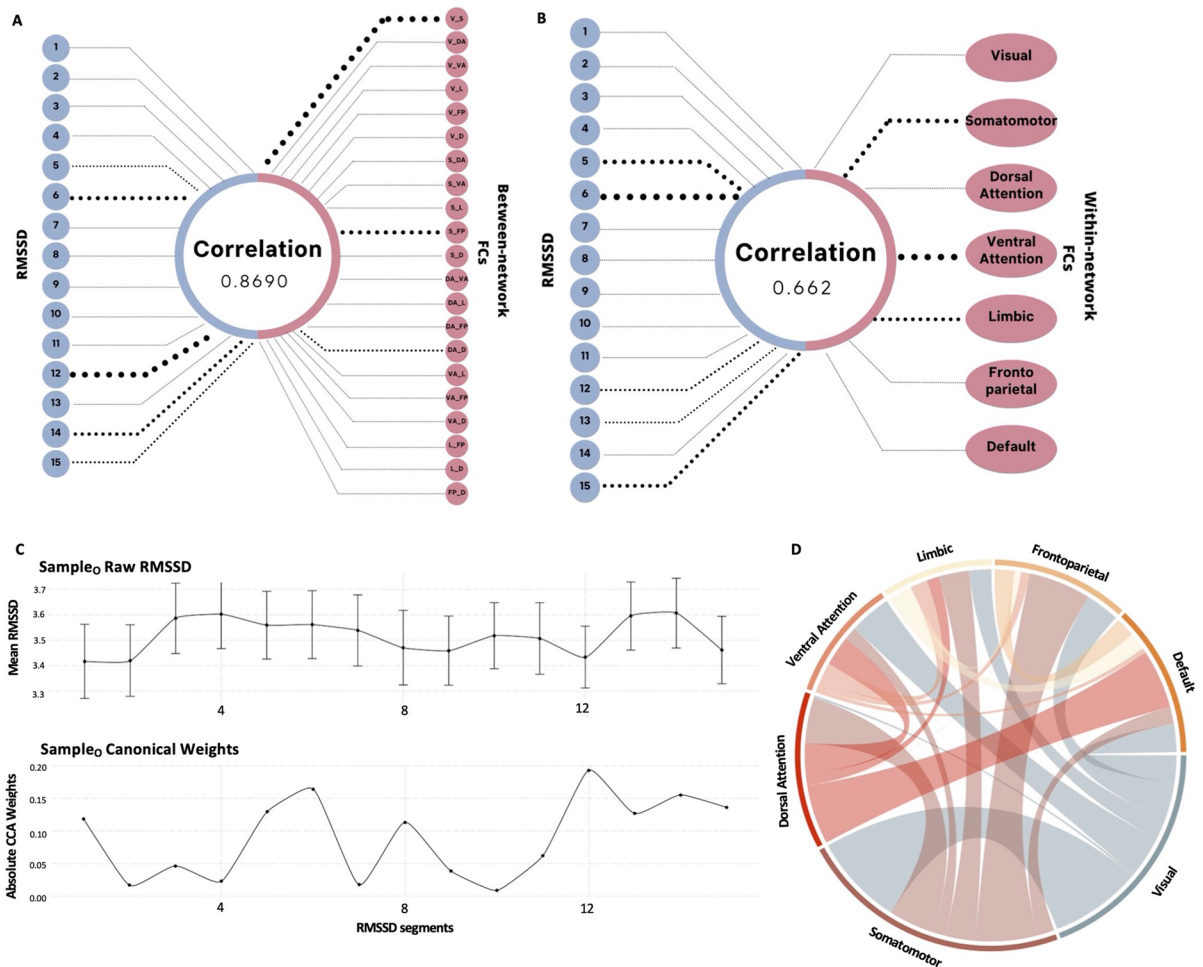
Fig. 2 CCA results of RMSSD and brain network FC measures from $Sample_O$. **A** Canonical correlation structure of RMSSD segments and between-network FCs for CC1-RMSSD-betweenFC-var_O. **B** Canonical correlation structure of RMSSD and within-network FCs for CC1-RMSSD-withinFC-var_O. **C** Raw values (Mean ±1SE), *upper* for $Sample_O$ RMSSD segments, and absolute CCA weights/canonical vector for $Sample_O$ RMSSD segment contributions to CC1-RMSSD-betweenFC-var_O, *bottom*. **D** Absolute CCA weights/canonical vectors for between-network FCs (the colors are arbitrary) contributions to CC1-RMSSD-betweenFC-var_O. Note. In A and B, the top 3 FC and top 5 RMSSD values in terms of contribution are shown with dotted lines, and the width of the line in **A**, **B**, and **D** represents the contribution of that particular connection or segment to CC1-RMSSD-betweenFC-var_O or CC1-RMSSD-withinFC-var_O. ln RMSSD, natural log-transformed root mean square of successive differences. V, visual; S, somatomotor; DA, dorsal attention; VA, ventral attention; L, limbic; FP, frontoparietal; D, default.

(RMSSD-betweenFC-var_O and RMSSD-withinFC-var_O). A detailed behavior of the raw RMSSD at each segment is presented in Fig. 2C, along with the absolute value of CCA weights. The network contributing most to the withinFC CCA weights in canonical covariate 1 (CC1) is the ventral attention network, and the betweenFC CC1 weights are highest in for connections between the somatomotor and visual networks, followed by somatomotor-frontoparietal and dorsal attention-default mode network FC (see Fig. 2D). Note that we are considering the absolute value to determine the contribution of the segment or brain network; nevertheless, we use the original weight for calculating the canonical variable of each feature.
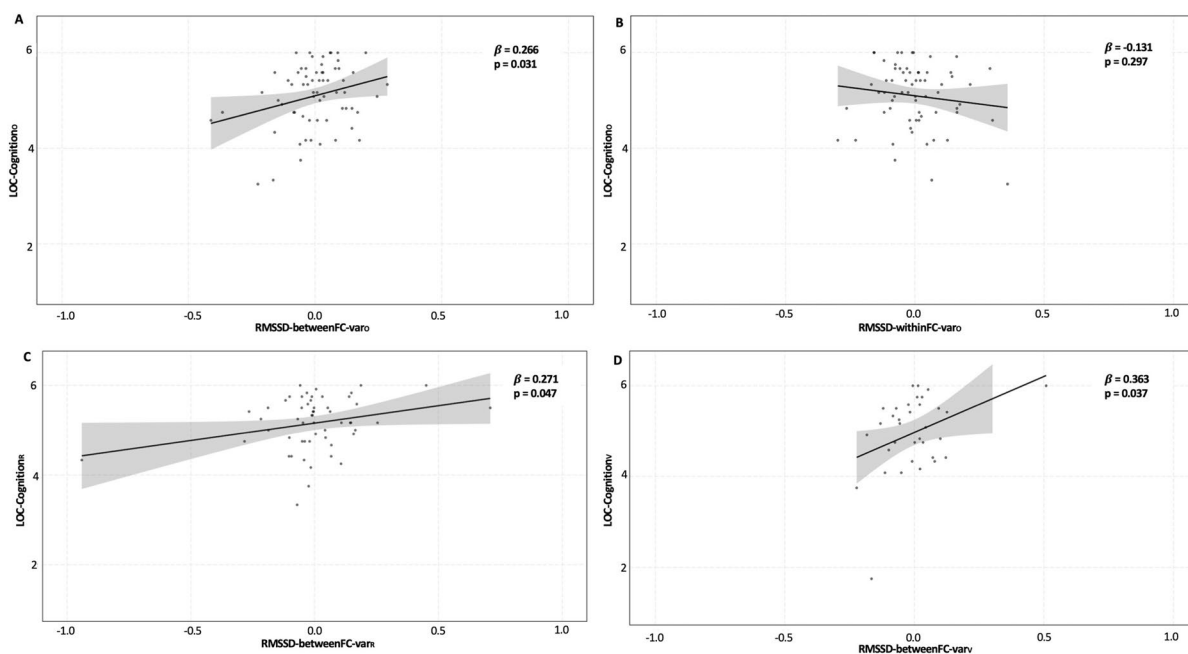
Linear regression

To assess the relationship between the potential autonomic flexibility biomarkers and participants' internal LOC-Cognition, we performed linear regression analyses. RMSSD-betweenFC-var$_O$ ($\beta = 0.266$, SE $= 0.971$, CI $= [0.190, 4.073]$, $p = 0.031$, Fig. 3A), but not RMSSD-witihnFC-var$_O$ ($\beta = -0.131$, SE $= 0.999$, CI $= [-3.046, 0.946]$, $p = 0.297$, Fig. 3B), was significantly associated with the extent to which a participant believed they were in control of their own cognition. For comparison, we also performed linear regression analyses to test for the relationship between the canonical variables and external LOC and found no significant relationships for either RMSSD-betweenFC-var$_O$ ($\beta = 0.095$, SE $= 1.003$, CI $= [-1.237, 2.772]$, $p = 0.447$) or RMSSD-withinFC-var$_O$ ($\beta = -0.004$, SE $= 1.008$, CI $= [-2.047$,

1.980], $p = 0.973$). Given the significant relationship between RMSSD-betweenFC-var$_O$ and internal LOC-Cognition$_O$, we performed follow-up analyses to test the reliability and validity of RMSSD-betweenFC-vec$_O$ by applying it to RMSSD data from replication and validation samples.

Reliability

We applied RMSSD-betweenFC-vec$_O$ to RMSSD data collected during the same auditory working memory task post-intervention to generate a canonical variable: RMSSD-betweenFC-var$_R$, and performed the same linear regression as above with internal LOC-Cognition$_R$, controlling for intervention effects. We found that, similarly to that in Sample$_O$, RMSSD-betweenFC-var$_R$ had a significant association with LOC-Cognition$_R$ ($\beta = 0.271$, SE $= 0.971$, CI $= [0.033$,

Fig. 3 Relationship between RMSSD canonical variables and participants' belief in their own control of their own intellectual abilities. **A** Linear regression analysis showed that RMSSD-betweenFC-var$_O$ was significantly related to internal LOC-Cognition in the original sample, when HRV data was collected during an ACT (auditory working memory) task. **B** Linear regression analysis showed that RMSSD-withinFC-var$_O$ was not significantly related to internal LOC-Cognition in the original sample, when HRV data was collected during an ACT (auditory working memory) task. **C** Linear regression analy-

sis on the replication sample, which was the post-intervention data of the original sample, controlling for intervention effects, identified the same significant association between RMSSD-betweenFC-var$_R$ and internal LOC-Cognition. **D** Linear regression analysis in the validation sample, consisting both healthy older adults and individuals with aMCI (controlling for MoCA score), identified the same significant association between RMSSD-betweenFC-var$_V$ and internal LOC-Cognition, when HRV data was collected during an n-back (visual working memory) task

2.630], $p = 0.047$), suggesting this relationship is reliable over a 1 month period (see Fig. 3C).

Validity

To additionally test the validity of RMSSD-betweenFC-vec$_O$, we used RMSSD data from another project collected while participants completed a similar working memory task while having HRV data collected, as well as completing the same measure of internal LOC-Cognition. The working memory task in the replication sample was a visual task, while the original sample used an auditory working memory task. We also used HRV data collected during the Stroop task (measuring inhibition), allowing us to assess the generalizability of RMSSD-betweenFC-vec$_O$. To control for the fact that this sample included both healthy older adults and individuals with aMCI, we also included MoCA score as a covariate in these regressions. We found that RMSSD-betweenFC-var$_V$ generated using visual working memory RMSSD data ($\beta = 0.36$, SE $= 0.136$, CI $= [0.023, 0.574]$, $p = 0.037$, Fig. 3D), but not RMSSD-betweenFC-var$_V$ generated using Stroop task RMSSD data ($\beta = 0.08$, SE $= 1.486$, CI $= [-0.354, 0.657]$, $p = 0.685$), was significantly associated with LOC-Cognition$_V$. This demonstrates the validity of our original finding, and suggests that RMSSD-betweenFC-vec$_O$ generalizes across working memory tasks using different sensory modalities, but not to RMSSD data collected during executive function tasks more broadly.

Discussion

Using CCA, we identified a canonical variable reflecting autonomic regulation, using both neural and peripheral physiological signals. The RMSSD canonical variable generated using CCA constrained by between-network FC (RMSSD-betweenFC-var$_O$) was significantly associated with older adults' belief that they were in control of their intellectual abilities (internal LOC-Cognition). No similar relationships were found using a similar RMSSD canonical variable that was constrained by within-network FC or when associating either canonical variable with external LOC-Cognition. A replication analysis suggested that the RMSSD canonical vector generated by CCA with RMSSD and between-network FC data

(RMSSD-betweenFC-vec$_O$) could be used to generate a canonical variable (RMSSD-betweenFC-var$_R$) that showed the same relationship using RMSSD data collected during the same auditory working memory task 6 weeks later. Validation of RMSSD-betweenFC-vec$_O$ in a second dataset suggested that the relationship between canonical variables generated using this vector and internal LOC-Cognition generalizes to RMSSD data collected during working memory tasks presented in a different format (visual stimuli), but not tasks measuring inhibition (Stroop task). Overall, these findings suggest that this marker of autonomic regulation relates to internal LOC-Cognition in older adults at risk for dementia and may provide a potential means of intervening in internal LOC-Cognition to improve resilience and adherence to interventions in this at-risk population. Previous studies have generally focused on identifying autonomic markers that may be important in dementia using mean HRV (F. [17] or specific dynamic patterns of HRV (Q. [5]. By using a data-driven approach that maximized the association between HRV time series and brain networks, we hoped to find a marker of adaptation capacity that reflects integrated peripheral and neural signals underlying autonomic regulation and is sensitive to processes seen in brain aging. Replicating and validating the relationship between this marker and a behavioral trait reflecting resilience provide confidence that this approach has identified a meaningful marker of adaptation capacity that may implicate future therapeutics development for slowing/preventing dementia. Particularly, interventions aimed at modifying adaptation capacity may benefit from the ability to use this marker as a validated measure to assess whether autonomic regulation is being adjusted in a meaningful way. One example is research that aims to modulate adaptation capacity during cognitive training (F. V. [18] to put participants in the optimal state to show broad cognitive improvements that may rely on autonomic regulation during training (Quanjing [5]).

These findings have several additional implications. Firstly, the finding of constraining the HRV data using between-network, but not within-network, FC suggests that identifying specific neural signals reflecting autonomic function is a critical aspect of understanding adaptation capacity and how it relates to internal LOC-Cognition. CCA weights were characterized by high influence from connections between

the somatomotor network and visual, frontoparietal, and dorsal attention networks, as well as by connections between the dorsal attention and default mode network. Previous work has often highlighted cingulate, insular, and subcortical regions as critical elements of the central regulation of ANS [37]. Our results suggest that connections between sensory regions may have been overlooked, in line with recent work highlighting the hierarchical involvement of the whole brain in processing ANS signals [38]. Tight coupling between autonomic and sensorimotor functions is a critical aspect of adaptive behavior, and our results add to the literature suggesting a critical relationship between sensorimotor brain regions and the ANS [23, 35]. This is particularly important in individuals at risk for dementia because sensory regions are affected later by dementia pathology [2, 3] and may therefore be more easily modifiable by interventions aimed at causing brain plasticity to slow or prevent cognitive decline. Additionally, the involvement of connections between the dorsal attention and default mode networks is also of note. These connections are known to be critical for dynamic changes between internal and external states [41] and are also known to change during aging and dementia [9]. Our findings suggest that these task-related dynamics may also relate to autonomic regulation. The findings that between-network connections were more functionally relevant are also in line with findings showing that these connections are essential for explaining individual differences in behavior (van den [42]. Why these connections are more strongly related to the patterns of autonomic regulation seen in the working memory HRV data is a question for future research,however, the neurovisceral integration model [38] suggests that communication between different levels of neural hierarchies (at which these different networks exist: Margulies et al. [24] is critical for autonomic regulation, allowing for both bottom-up and top-down communication between brain and peripheral signals. These between-network connections may be more involved in this type of hierarchical integration of signals during autonomic regulation.

The finding that these results generalize across working memory tasks is also particularly interesting. We used a sliding window approach to generate time series of HRV data in response to cognitive stress to build on previous work suggesting that these conditions are essential for identifying signals reflecting adaptation capacity [5]. The results further support this approach and suggest that HRV responses at specific time points to cognitive stress seem to be particularly important for identifying markers of adaptation capacity that relate to resilience. Our findings go further to suggest that markers of adaptation capacity identified using different cognitive stressors may reflect measures of resilience to different extents. The results of this study do not imply that autonomic responses during, for example, the Stroop task do not contain important information about adaptation capacity and resilience. However, they do suggest that markers of adaptation capacity developed during specific cognitive stressors contain unique information and cannot necessarily be assumed to produce the same autonomic responses: the canonical vector generated during working memory could not be applied to HRV data during the Stroop task to produce a canonical variable that similarly reflected internal LOC-Cognition. It is less clear from this study exactly what this unique information is, except that it occurs more at specific time points and that the specific temporal pattern is unique to working memory tasks. Given that the important time points are relatively early on (5 and 6) and late into task performance (12–15) and appear to occur in runs, they may reflect a person encountering a challenge in the task and adapting to it or a response to increased boredom/fatigue. We do not know from these findings whether these responses do not occur in the Stroop task, if they occur differently, or at different time points, given we are validating a specific biomarker developed in the working memory task and did not conduct an exploratory CCA in the Stroop task. However, it is interesting that they do appear to occur in the same timeframe in a different working memory task, suggesting they may reflect a general response to this type of task. It is also unknown if this pattern appears at rest or during recovery, but given the lack of generalization to the Stroop task and the specific temporal nature of the response, we believe it seems unlikely.

An important question we are unable to answer in this study is the extent to which the state of participants during fMRI data collection would alter this biomarker. Although participants were cognitively challenged during HRV data collection, they were at rest for fMRI data collection. Resting-state data is the most commonly used fMRI modality when assessing trait relationships with behavior, as we have done

in this study. Some research suggests that trait FC is robust to task-related changes, reflecting a "finger-print" [11] of the person that changes little during tasks [13] and is governed by similar principles to task-related activity [26]. Alternatively, some studies suggest that FC measures obtained from task-based data may be better able to predict behavioral traits [10], suggesting important changes in response to task demands. Answering this question is also not straight-forward methodologically,there is disagreement in the field over how to generate FC from task-based data: should task-related signals be regressed out to gen-erate true baseline FC (e.g., Gratton et al. [13] or do task-related changes reflect traits in a similar way to how we have conceptualized HRV responses to cog-nitive demands in this study? Should you analyze task-related changes specifically using a Psychophysi-ological Interaction (PPI) analysis [30] or collapse across the entire time series to generate FC data [12]? Although beyond the scope of the current study, these are important questions for future research,given that the state of participants during HRV data collection is critical for the identification of this biomarker, it may also be true that the state of participants during fMRI data collection is equally important. However, it is important to note that using resting-state fMRI data to constrain the CCA produced significant findings, suggesting this specific biomarker has value, whether or not it can be improved upon by using task-based fMRI data.

There are some limitations associated with this study. To create a common correlated space between the functional networks (Y) and HRV (X), we use CCA. CCA builds a simple linear model in X space and one in Y space to create a joint correlated space. The linear models generate positive and neg-ative weights. For interpretability, we only focused on the magnitude of the weights when attempting to understand which connections were contribut-ing most strongly to the canonical vector. We have avoided interpreting the direction due to some of the controversies over how to explain negative FC and its physiological meaning [4]. Future studies may choose to use non-negative CCA [36]; instead, how-ever, we chose to use regular CCA to try and maxi-mize the correlation between HRV and FC data. In addition, for simplicity, we only used RMSSD measures from the HRV time series and Yeo and Krienen's [46] cortical networks for resting-state

FC. More advanced data-driven extraction of whole brain (including subcortical regions) FC and raw HRV signals (using time series signal processing or a more advanced deep learning approach) could potentially reveal additional shared signals reflect-ing adaptation capacity. Additionally, although we aimed to replicate and validate our findings, all samples used were relatively small and demographi-cally homogenous. Larger samples will be needed to understand the true generalizability and effect sizes related to the RMSSD-betweenFC-vec$_O$ bio-marker. In general, our sample size is on the smaller side for CCA analyses, although critically we reduced the dimensions of the brain and HRV data prior to CCA to ensure the number of variables did not exceed the number of samples [27]. Importantly, we replicated and validated our results in an inde-pendent sample, suggesting that the sample size was sufficient to identify meaningful signal in the data. It is a challenge to collect large datasets in this criti-cal at-risk population, particularly due to the noisy HRV data seen in older adults at risk for dementia that often leads to considerable data loss (as seen in our study). CCA in small samples can lead to noisy estimates, which is why it is particularly important in these studies to validate using out-of-sample predictions, as in this study. Finally, all our analy-ses were cross-sectional in nature. To understand whether there are any causal relationships between internal LOC-Cognition and RMSSD-betweenFC-vec$_O$, future studies will need to use designs with an experimental manipulation or longitudinal data as individuals progress into dementia and potentially shift to a more external LOC-Cognition. These studies will be essential if RMSSD-betweenFC-vec$_O$ is to help identify any means of intervening to improve/maintain internal LOC-Cognition in older adults at risk for dementia.

Data and code availability Data and code used for this pro-ject can be accessed at https://github.com/CogTLab/CCA_LOC.

Declarations

Conflict of interest The authors declare no competing inter-ests.

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