Review

Autonomic nervous system flexibility for understanding brain aging

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ARTICLE INFO

ABSTRACT

A recent call was made for autonomic nervous system (ANS) measures as digital health markers for early detection of Alzheimer's disease and related dementia (AD/ADRD). Nevertheless, contradictory or inconclusive findings exist. To help advance understanding of ANS' role in dementia, we draw upon aging and dementia-related literature, and propose **a framework that centers on the role of ANS flexibility to guide future work on application of ANS function to differentiating the degree and type of dementia-related brain pathologies.** We first provide a brief review of literature within the past 10 years on ANS and dementia-related brain pathologies. Next, we present an ANS flexibility model, describing how the model can be applied to understand these brain pathologies, as well as differentiate or even be leveraged to modify typical brain aging and dementia. Lastly, we briefly discuss the implication of the model for understanding resilience and vulnerability to dementia-related outcomes.

1. Background

A recent call was made for autonomic nervous system (ANS) measures as digital health markers for early detection of Alzheimer's disease and related dementia (AD/ADRD) (Owens, 2020). Dementia is a multi-dimensional concept comprising one or more cognitive changes that interfere with independence in everyday activities (see DSM-5 criteria). Also, specific types of brain pathology (e.g., amyloid, tau, neurodegeneration, vascular pathology, alpha-synuclein, TDP-43) that extend beyond typical brain aging help further specify the type of dementia. The relationships between ANS measures and various domains of cognition (Forte et al., 2019; Liu et al., 2022) and affective status (e.g., emotional regulation (Zaehringer et al., 2020), negative emotion (Arias et al., 2020), positive emotion (Kok et al., 2013), neuropsychiatric symptoms (Kemp and Quintana, 2013; Liu et al., 2022) across adulthood or in patients with dementia have been well-studied, as has the relationship between ANS and brain throughout the typical aging process (Koenig et al., 2020). However, less is known about the relationship between dementia-related brain pathologies and ANS. The limited research to-date addressing ANS and dementia-related brain pathologies or dementia demonstrates contradictory or inconclusive findings (Allan et al., 2006; Beach et al., 2017; Collins et al., 2012; da Silva et al., 2018;

de de de Vilhena Toledo and Junqueira, 2008; Femminella et al., 2014; Nicolini et al., 2014); further, genetic correlations of ANS with AD/ADRD or brain aging are understudied (Nolte et al., 2017). Hence, ANS markers for early dementia detection, although promising, may be premature since the relationships between ANS function and dementia-related brain pathologies, and their functional implications, remain unclear. In this review paper, we draw upon aging and dementia-related literature from psychophysiology, neuroscience, and cognitive science, and propose **a framework that centers on the role of ANS flexibility – as a fingerprint reflecting individuals' adaptation capacity – to guide future work on the application of ANS function for differentiating the degree and type of dementia-related brain pathologies.** We integrate understanding of ANS flexibility as a marker of integrity of homeostatic processes, as well as a critical signal of an individual's capacity for adaptation to potential harms. Flexible adaptation to physical stressors (e.g., heat or cold stress, pain) or changing environmental demands (e.g., traumatic or threatening events, social/interpersonal interactions, cognitively demanding tasks, etc.) is critical for maintaining a person's everyday function, health span and longevity (Epel and Lithgow, 2014). We suggest here that understanding associations between ANS flexibility and the brain under both conditions will be critical to advancing ANS as a marker of

dementia risk. In proposing this framework, our objective is to help accelerate research and knowledge that can advance ANS indices as digital health markers for AD/ADRD.

2. ANS flexibility

Both normal, homeostatic functioning (e.g., under resting conditions) and an organism's physiological and behavioral responses to a potentially harmful stimulus (i.e., stressor) are tightly regulated by bi-directional, brain and body communication (Schulz and Vögele, 2015). Under both conditions, the ANS plays an integral role in this communication axis. The central nervous system and ANS are tightly and dynamically connected via anatomical, functional, and neurohormonal pathways. Cumulative work suggests the integrity of the central autonomic network (CAN) can top-down regulate ANS flexibility (Beissner et al., 2013; Lin et al., 2017b). According to the neurovisceral integration model (Thayer et al., 2009; Thayer and Lane, 2000), although the ANS is primarily regulated by brain stem and hypothalamus, many cortical networks may contribute significantly to the regulation of ANS, including regulating ANS flexibility. Notably, the characterization of CAN remains as a theory; the exact composition and hierarchy across these networks are largely understudied (Smith et al., 2017). Likewise, afferent signaling from peripheral receptors via ANS pathways to the CNS can bottom-up regulate CNS function. There are several afferent pathways linking ANS function and brain, including gut microbiota's bottom-up neurotransmission (e.g., acetylcholine, Serotonin, Gamma aminobutyric acid) (Łuc et al., 2021), blood pressure-stimulated baroreceptor activity, and via vagus nerve signaling stimulated by peripheral inflammation (Tracey, 2002).

Together, dynamic neurophysiological (i.e., afferent and efferent) processes involving the parasympathetic (PNS) and sympathetic (SNS) branches of ANS are activated in efforts to maintain homeostasis and to achieve homeostatic adaptation in the face of threats. The SNS has long been recognized as the predominant support for energy mobilization in response to environmental demands, such as the 'fight or flight' response to threat, while PNS or vagal tone provides a "brake" to regulate SNS' response (Thayer et al., 2009). A recent meta-analysis concludes that in response to different types of internal and external stimuli (e.g., cognitive, social, emotional, physical), SNS activates and PNS withdraws to a roughly equal extent (Brindle et al., 2014). Whether and how age affects SNS (Brindle et al., 2014) or PNS (De Meersman, 1993) response remains to be precisely understood. Whether and how *brain* aging impacts SNS and PNS function is poorly understood, but is of growing interest (Lin et al., 2017b; Lin et al., 2020; Santos et al., 2017). We suggest that findings elaborating on these pathways hold promise for understanding dementia-related brain pathologies and autonomic function. In addition to exteroceptive stimulation of ANS activity, ANS participates in and is regulated by interoceptive signaling under so-called resting or "off-task" conditions. Measures of ANS activity during rest/off-task have been associated with cognitive function and affective states(Friedman, 2007; Thayer et al., 2012; Thayer et al., 2009), and, more recently, pathological brain aging (Lin et al., 2017b).

In the following sections, we will first provide a brief review of literature within the past 10 years on ANS and dementia-related brain pathologies. Next, we will present an ANS flexibility model, describing how the model can be applied to understand these brain pathologies, as well as differentiate or even be leveraged to modify typical aging and dementia. Lastly, we will briefly discuss the implication of the model for understanding resilience and vulnerability to dementia-related outcomes.

3. Existing literature and problems on ANS flexibility and brain aging

The relationship between ANS and brain aging, or dementia risk, has been studied in various ways, given the complexity of defining and operationalizing brain aging. First, from studies of brain biochemistry, shared signaling pathways linking ANS and dementia or dementia pathologies have been identified. Two relatively conclusive, while inter-related mechanisms are: (1) acetylcholine deficits, and (2) vascular and cardiac pathologies. Acetylcholine is an important neurotransmitter for presynaptic and postsynaptic communication, particularly along PNS regulatory pathways. Thus, deficits in neurotransmissions seen in many dementia pathologies (e.g., beta-amyloid affects acetylcholine) plus advanced brain atrophy may worsen the negative influence of dementia pathologies on ANS flexibility; Further, SNS and PNS control of cardiac activity is affected by acetylcholine deficits. Cumulative heart neuronal network research suggests that cardiac nervous system impairment damages ANS and central nervous system concurrently. Beta-amyloid also acts on cardiac tissue (a.k.a., cardiac amyloidosis), in addition to cerebral areas (Elia and Fossati, 2023). The literature has examined the role of acetylcholinesterase inhibitors (Lista et al., 2023) or cardiac treatments (e.g., highly blood-brain barrier permeable beta-blockers (Beaman et al., 2023)) in slowing the progress of AD while modulating ANS function. However, these therapies may not act to modify beta-amyloid generation or clearance given the role of beta-amyloid as a cause for acetylcholine deficits or selected cardiac dysfunctions. In addition, emerging work discussed the potential role of locus coeruleus-noradrenaline system in linking abnormal tau and SNS (Behl et al., 2022), which is worth further investigation. Of note, declined functions in the locus coeruleus-noradrenaline system (Lee et al., 2018), acetylcholine synthesis (Gibson et al., 1981) or cardiac nervous system or vasculature (Häggqvist et al., 1999) are seen in typical aging processes. Further investigation is needed to specify the role of these signaling pathways in linking dementia pathologies and ANS.

Second, some brain imaging research has focused on CAN's role for brain aging and ANS. For example, while cortical thickness of ventro-medial prefrontal cortex (PFC) was found to explain the relationship between a decline in ANS flexibility, as indexed by heart rate variability (HRV), and increase in age (Koenig et al., 2020), age itself does not seem to affect the relationship between brain function and ANS (Tsvetanov et al., 2015).

Third, recent systematic review and meta-analysis underscore the increased attention to understanding whether impaired ANS function is a risk factor for clinical phenotypes of dementia. All-cause dementia cases have worse autonomic dysfunction than controls (Allan et al., 2007; Weinstein et al., 2021). Persons living with Parkinson's disease dementia and dementia with Lewy bodies had worse autonomic dysfunction compared to those with AD and vascular AD mixed dementia (Allan et al., 2007; Kim et al., 2018); however, findings are inconsistent regarding the role of PNS in differentiating AD or MCI vs. healthy control (Cheng et al., 2020; Collins et al., 2012; da Silva et al., 2018; Lin et al., 2017b; Meel-van den Abeelen et al., 2013), while SNS is understudied (Mellingsaeter et al., 2015; Zulli et al., 2005).

Finally, emerging studies have examined the relationship between ANS and brain pathologies related to dementia; however, findings are too premature to draw a conclusion on the relationship between dementia pathologies and ANS flexibility (Table 1).

Thus far, the inconclusive findings between ANS function and the behavioral phenotype or pathology of dementia may be due to the complexities seen in brain structure and function in relation to typical aging (e.g., neural dedifferentiation (Koen and Rugg, 2019), posterior to anterior shifting (Davis et al., 2008)), dementia pathologies, interoceptive regulation, and supporting cognitive tasks or affective status. Carefully delineating relationships between ANS function and central nervous system, and evaluating the cause and consequence, are needed to shed light on links between ANS function and dementia.

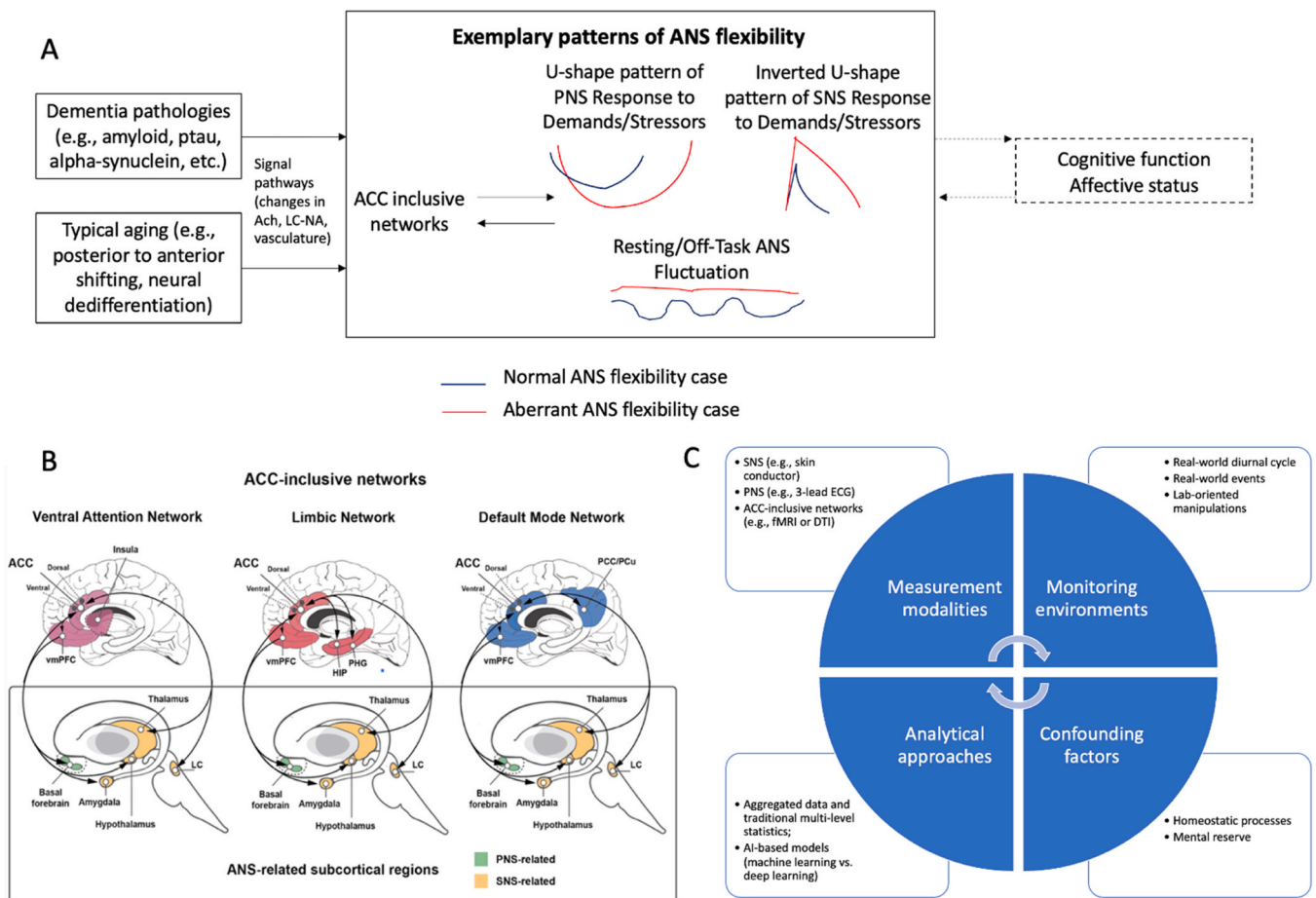## 4. An ANS flexibility model for understanding brain aging

We here propose **a developing ANS flexibility model for understanding brain aging** (Fig. 1), underscoring attention to the

Table 1
ANS and dementia-related brain pathologies.

Brain pathology	Study	ANS measure	Results
Abeta1–42	Yu et al.(Yu and Li, 2021)	Autonomic dysfunction by SCOPA-AUT	Level of Abeta1–42 in CSF was oppositely, weakly related to gastrointestinal dysfunction in persons living with PDD (r = −0.1).
	Santos et al.(Santos et al., 2017)	HF-HRV at rest and reactivity to cognitive stress task	No change between rest and reactivity to task in older adults with abeta+ ; however, reactivity was higher in abeta+ than abeta-
p-tau181	Yu et al.(Yu and Li, 2021)	Autonomic dysfunction by SCOPA-AUT	p-tau181 concentration was higher in those with urinary dysfunction in persons living with PDD (r = 0.10) and healthy controls (r = 0.20).
AD-associated neurodegeneration	Lin et al.(Lin et al., 2017b)	HF-HRV at rest and reactivity to cognitive stress tasks	Higher HF-HRV at rest, but not reactivity, was related to worse neurodegeneration.
Alpha-synuclein	Pablo-Fernandez et al. (De Pablo-Fernandez et al., 2017)	Autonomic dysfunction	No relation between alpha-synuclein and autonomic dysfunction in PDD.
	Gibbons et al.(Gibbons et al., 2016)	Autonomic dysfunction	Alpha-synuclein was higher in those with autonomic failure across PDD and healthy control.
	Yu et al.(Yu and Li, 2021)	Autonomic dysfunction by SCOPA-AUT	Alpha-synuclein was related to more thermoregulatory dysfunction in SWEDD patients (r = 0.27).
Vascular pathology	Nicolini et al.(Nicolini et al., 2020)	HRV to Ewing's tests	LF and LF/HF to postural changes were related to cerebrovascular burden in naMCI
TDP-43	N/A		

NOTE: Pubmed search include specific type of brain pathology + ANS related terms ("autonomic nervous system", autonomic, "heart rate", "heart rate variability") up to December 2020.
AD = Alzheimer's disease; HF = high frequency; HRV = heart rate variability; LF = low frequency; PDD = Parkinson's disease dementia; SWEDD = scan without evidence of dopaminergic deficit; TDP-43 = TAR DNA-binding protein 43;

Fig. 1. An ANS flexibility model for understanding brain aging. A. Examples of normal (expected) versus aberrant patterns of ANS responding reflect distinct trajectories of brain aging; B. Parallel loops between ACC-inclusive cortical networks and ANS-related subcortical regions (conceptual); C. Operational aspects for the model – measurement modalities, monitoring environments, analytical approaches. Abbreviations: ACC=anterior cingulate cortex; ANS = autonomic nervous system; vmPFC=ventromedial prefrontal cortex; PCC=posterior cingulate cortex; PCu=precuneus; HIP=hippocampus; PHG=parahippocampal gyrus; LC=locus coeruleus; PNS=parasympathetic nervous system; SNS=sympathetic nervous system.

relationship between expected and aberrant patterns of ANS flexibility and various brain changes, including pathological and normal brain aging, in older adults at risk for or with dementia. Determined by dementia-related pathologies combined with typical brain aging, and their impact on selective brain regions essential to regulating ANS function, ANS patterns would be distinguished by unique neural signatures, or fingerprints. Also emphasized is attention to ANS patterns during rest/off-task as well as in response to environmental demands or stressors. Such fingerprints would be useful to reflect the influence from certain types and degrees of dementia pathology, and to differentiate typical aging from dementia. We also consider the roles of previously discussed signaling and vascular pathways (e.g., changes in the locus coeruleus-noradrenaline system, acetylcholine synthesis, or cardiac nervous system or vasculature) in the model. Both dementia pathologies and typical aging processes bring changes in these signaling pathways. Evaluating the amount or type of changes in the signaling pathways may help validate the accuracy of the ANS-based fingerprints in reflecting certain dementia pathologies or differentiating between pathological and typical aging. Fig. 1A presents examples of normal (expected) versus aberrant patterns of ANS responding that we suggest reflect distinct trajectories of brain aging.

4.1. Resting/off-task ANS fluctuation

Dynamic ANS fluctuations at rest are essential for functional health. ANS participates in and is affected by interoceptive signaling, which is reflected in fluctuation of ANS at both short term and over 24-hour circadian rhythm monitoring. For example, evidence suggests a circadian rhythm of SNS outflow (Biaggioni, 2008), which can be seen via assessment of rhythmic neurotransmitter output along sympathetic neural pathways. Respiratory sinus arrhythmia (RSA) is an example of ongoing, dynamic influence of ANS on heart activity: Regulated by the PNS, RSA reflects a coupling of the respiration pattern with heart rate, wherein inhalation is coupled with an increase in heart rate, and exhalation with a decrease in heart rate. The cost for maintaining dynamic fluctuation of ANS activity may be higher in those with more burden of disease, as compensatory processes that mitigate effects of neurodegeneration on ANS regulation in early-stage dementia, such as early stage AD, may weaken with disease progression (Lin et al., 2017b). Thus far, less is known about normal or abnormal interoceptive signaling that may affect resting/off-task ANS fluctuations or circadian rhythms, and how various dementia pathologies play a role in interoceptive signaling. Systematic examination of this signaling and associated ANS patterns could be further addressed through advanced time-series dynamic analytical techniques (see Section 5).

4.2. U-shape PNS pattern

In response to environmental (exteroceptive) demands or challenges, the redistribution of resources supporting regulation of the ANS by CAN can be observed via assessment of HRV change (Thayer et al., 2012). An initial decrease or suppression of the PNS response occurs, reflected in reduced HRV, which signals the re-allocation of neural resources to support acute response to the stimuli, and diminished capacity to sustain signaling to the hypothalamus that supports PNS cardiac control. The subsequent increase or rebound phase represents the return of neural resources in regulating the PNS when individuals have adapted to the stimuli or stimuli are no longer challenging enough to require additional neural resources. This entire process—suppression and then rebound of the PNS—in response to a challenge reflects an individual's capacity for adaptation to environmental changes or demands (Lin et al., 2016; McDermott et al., 2019; Thayer et al., 2009). This U-shape pattern of PNS response to external stimuli also supports the idea of positive neuroplasticity, in which the positive brain changes are driven by environmental demand exceeding available neural resources (similar to the suppression phase of PNS response to demands or stressors); such

positive changes would be diminished when the demand-neural resource mismatch reduces (similar to the rebounding phase of PNS) (Chen et al., 2020; Lin et al., 2017a; Lovden et al., 2011). Individuals with more capable brain resources may have less suppression and faster rebound. Further, when older adults can relocate brain resources, as seen in the typical aging-associated neural dedifferentiation or posterior-to-anterior shifting, compensatory processes may afford intact PNS responding. However, among those with dementia pathologies that affect the brain's functional compensation, PNS activation during the first phase would show greater decline in order to leverage enough resources to respond to the stimuli, and/ or a longer time to rebound during the second phase.

4.3. Inverted U-Shape SNS pattern

In response to environmental demands or stressors that initiate homeostatic adjustments, a typical SNS response pattern would reflect increased SNS activation, with declines once adaptation is achieved or the stimuli is no longer present. Aberrant SNS patterns (associated with poor health risks) may include exacerbated SNS responding (Cacioppo et al., 1998), and/or prolonged SNS activation when recovery is expected (Panaite et al., 2015), or blunted responses to stimuli (Wade et al., 2020). While aging is associated with an overall chronic overactivity of SNS (Esler et al., 2001; Rowe and Troen, 1980), laboratory evidence suggests attenuated SNS activity in response to demanding tasks in older compared to younger adults (Uchino et al., 2010). As indicated in Table 1, fewer studies have focused on the role of dementia pathologies specifically on the SNS, as the majority of studies to-date have addressed indicators of autonomic dysfunction more broadly.

4.4. Anterior cingulate cortex (ACC)-inclusive networks

ANS flexibility manifests by enhancing transmission of specific neurotransmitters (acetylcholine, noradrenaline, and others) (Groves and Brown, 2005). Several key cortical (i.e., ACC and insula) and subcortical regions support the central regulation of ANS flexibility (Beissner et al., 2013; Lin et al., 2017b), forming several essential cortical (i.e., salience network, limbic network, and default mode network) and subcortical (i.e., Noradrenaline system for SNS and Acetylcholine system for PNS) subnetworks within the larger CAN. These regions and related networks also link to dementia pathologies (see our summary in Table 2). How resilient or vulnerable these key regions are to typical or pathological brain aging may determine the degree of ANS flexibility. For example, a shift from medial PFC, including ACC, to lateral PFC in the typical aging process would lead to lesser ANS responsivity to emotional stimuli, or more effort required to respond accurately to cognitive stimuli (Grossman et al., 2002; Reuter-Lorenz and Park, 2014). Neurodegeneration leads to compensational hyperactivation of ACC, which in turn is related to higher levels of interoceptive and exteroceptive regulation of ANS (Lin et al., 2017b). These regions might also switch their involvement with networks during the change of status (e.g., off- to on-task) or type of stimuli (e.g., physical vs. cognitive). For example, when a person first encounters a cognitively challenging task, massive neural communication would be activated to adjust to the task. With effective learning, such adaptations can reorganize the neural communications (Chen et al., 2020; Lin et al., 2017a). Also, the timeframe for adaptation can vary across individuals. Given ACC-inclusive networks in supporting interoceptive and exteroceptive regulation as well as their relationships with typical and pathological aging, these brain regions' circuitry involvement during interoceptive and exteroceptive regulation should be considered as a third component of the proposed ANS flexibility model. We here emphasize several parallel loops of ACC-inclusive cortical networks (Fig. 1B), and SNS and PNS-related subcortical regions that may explain the neural linkage between ANS flexibility and dementia pathologies.

Table 2
Essential brain regions underlying ANS flexibility.

Essential brain regions	Involved brain network	Link to dementia pathologies	Ref
Basal forebrain (including NAcc and Pallidum)	Acetylcholine system, PNS related subcortical regions	Tauopathy, and amyloidosis both cause destruction of acetylcholine system; acetylcholine is important for memory.	(Geula et al., 2021; Hampel et al., 2018; Schmitz et al., 2016)
Amygdala, Locus Coeruleus, Hypothalamus, Thalamus	Noradrenaline system, SNS related subcortical regions	Amyloidosis, TDP-43, and tauopathy occur early; Noradrenaline can stimulate pathology, but also important for clearance and reserve.	(Ahmed et al., 2018; Cykowski et al., 2014; Giorgi et al., 2021; Mather, 2012, 2021; Satoh and Iijima, 2019; Vogt et al., 1990)
Insula	Interoception related region; involved in ventral attention network	Left insula atrophy occurs across all types of dementia, Plasticity protects memory against AD pathology (indexed by amyloid/ptau ratio).	(Beissner et al., 2013; Fathy et al., 2020; Jacot-Descombes et al., 2020; Kitamura et al., 2020; Thayer et al., 2012)
ACC	Exteroception related region; involved in salience network, limbic network, and default mode network.	Amyloid affects this region early.	(Beissner et al., 2013; Eisenbarth et al., 2016; Grothe and Teipel, 2016; Lin et al., 2017b; Rub et al., 2016; Santos et al., 2017; Szili-Torok et al., 2001; Thayer et al., 2012)

NOTE: ACC = anterior cingulate cortex; PNS = parasympathetic nervous system; SNS = sympathetic nervous system; TDP-43 = TAR DNA-binding protein 43; AD = Alzheimer's disease.

Table 3
Possible relationships between the ANS flexibility model and dementia pathologies.

Aging pathologies	Exteroceptive ANS pattern		Interoceptive ANS fluctuation	Strength of ACC-inclusive networks	
	Cognitive stimuli	Valence/arousal stimuli		Cognitive stimuli	Valence/arousal stimuli
Typical aging	normal	normal	abnormal	A N- ACC↓; insula -	A N↓; ACC↑; insula -
Amyloid	abnormal	abnormal	abnormal	A N↑; ACC ↓; insula ↓	A N↑; ACC ↓; insula ↓
p-tau181	abnormal	abnormal	abnormal	A N↑; ACC ↓; insula ↓	A N↑; ACC ↓; insula ↓
Neurodegeneration	abnormal	abnormal	abnormal	A N↑; ACC ↑; insula ↓	A N↑; ACC ↑; insula ↓
Alpha-synuclein	abnormal	abnormal	abnormal	A N↑; ACC ↑; insula ↓	A N↑; ACC ↑; insula ↓
Vascular pathology	abnormal	abnormal	abnormal	A N-; ACC -; insula ↓	A N-; ACC -; insula ↓
TDP-43	abnormal	abnormal	abnormal	A N↑; ACC ↓; insula ↓	A N↑; ACC ↓; insula ↓

A = Acetylcholine system; N = Noradrenaline system; ACC = anterior cingulate cortex

5. Methodological directions to consider in the ANS flexibility model

Table 3 summarizes the possible changes of components of ANS flexibility during the typical and pathological aging process. However, to formally test the validity of the ANS flexibility model of brain aging in differentiating typical vs. pathological aging, or the type of dementia pathologies, we need to address the gaps in the measurement, analysis, and confounders of ANS function overall as well as their application to specific components of the ANS flexibility model.

5.1. Measurement of ANS flexibility: Considerations

In humans, ANS function has been measured in both self-report, blood biochemistry, and peripheral measures of physiology. Self-report measures primarily assess ANS symptoms (e.g., numbness,

digestive pattern, anxiety, burning, dry mouth, irritability, hunger, nervousness, sexual patterns, trembling). Blood-derived norepinephrine and epinephrine provide markers of SNS activation. Non-invasive, peripheral measures include electrocardiography, photoplethysmogram, galvanic skin response, accelerometer, thermometer, strain gage, thermal actuator, ballistocardiography, etc. Among them, the gold standard physiological measures are those underpinned solely (or predominantly) by PNS or SNS activity (see reviews by (Groat et al., 2019; Kourtis et al., 2019)). For example, measures of heart rate variability (HRV), derived from the electrocardiography signal, are commonly used to identify PNS activation and vagal tone. These include frequency-domain indices from spectral analysis, such as high frequency (HF-HRV, usually 0.15–0.40 Hz), or time-domain indices such as the square root of the mean squared differences of successive NN intervals (RMSSD). SNS activities can be captured reliably via the galvanic skin response, or via sympathetic baroreflex sensitivity from Doppler ultrasound. While an

in-depth critical analysis of the gold standard measures of PNS and SNS activity is beyond the scope of this review, we suggest that multiple measures used in combination will afford a more integrated understanding of the patterns of ANS activation that may contribute to and be affected by brain aging/pathologies (see next section regarding novel analytics). We also emphasize (and in our own work, prioritize) peripheral markers of PNS and SNS activity due to their non-invasiveness, cost-effectiveness, and, importantly, the ability to assess neural activity (via fMRI) concurrently with SNS and PNS-instigated physiological functions and changes. Finally, existing technologies for peripheral measurement of SNS and PNS afford opportunities for ecologically valid assessment of ANS function (also discussed in the next section).

Understanding the full implications of normative brain aging and dementia pathology on ANS flexibility, and the clinical and functional significance of these factors, requires attention to the environmental context within which ANS is being measured. This is particularly the case for understanding ANS responsivity to exteroceptive stimuli or stressors. There is a tradeoff in internal vs. ecological with lab vs. field measures, such as ecological momentary assessment. Lab measures provide well-controlled simulation of challenges to capture ANS flexibility linked to the challenge in real-time (see example from our recent study of ANS flexibility responding to different formats of working memory tasks (Peralta-Malváez et al., 2023)); however, the tasks may or may not reflect real-world challenges. The ecological/moment-to-moment measure of ANS can provide continuous data collection across a day or multiple days, reflecting an individual's responsivity to real-world challenges; however, this approach often requires data aggregation (e.g., averaging measures across time), which can preclude coupling of momentary meaningful events (typically reported via digital surveys) with acute, concomitant ANS change.

How to capture sensitively useful data reflecting real-world challenges and ANS flexibility is an important question. A 24-hour measure of ANS function is common, with findings inconsistent regarding the relationship between PNS, or SNS, and brain/cognitive aging. This may be due in part to oversimplified data analysis strategies. Contemporary advanced data analytics may prove highly useful for discerning the role of brain pathologies in ANS flexibility.

5.2. Novel nonlinear analytical approaches for understanding ANS flexibility and brain pathologies of dementia

Conventional analysis is typically driven by averaging ANS data across fixed time windows, which may miss important dynamic changes. Dynamic analysis will more appropriately capture ANS flexibility by continuously and simultaneously analyzing multiple paths of neural communications within a functional magnetic resonance imaging (fMRI) run (for those essential brain regions), as well as ANS measures at rest or of on-task reactivity.

For example, our recent experiment linked segments of RMSSD in response to cognitively challenging tasks and resting fMRI based brain networks using a canonical correlational analysis (Peralta-Malváez et al., 2023). Separately, artificial intelligence (AI) oriented approaches related to dynamic time-series analyses of high-dimension data like fMRI have been presented extensively in the literature (e.g.,(Manning et al., 2018)). There are two types of dynamic analyses for ANS measures: deep learning vs. machine learning. Deep learning driven models, such as deep neural network, have reached a high predictive rate for selected diseases (e.g., resting electrocardiography for predicting arrhythmia) (Hannun et al., 2019b). The same approach can be applied to predict various types of brain pathologies. The only problem is the black-box nature of revealed features, many of which can be mathematically appropriate but physiologically unclear. These features together may reflect a reliable biomarker, but be difficult to give any mechanistic interpretation, or become therapeutic targets. Alternatively, we have been using a different machine learning approach called Shapelet analysis to analyze temporal dynamics of HF-HRV data during cognitive training sessions (Chen et al., 2020). Compared to nonlinear methods such as approximate entropy that are heavily dependent on the recording length, the Shapelet method can capture temporally ordered features at both local and global scales, allowing for more flexible and robust detection of subtle, dynamic changes in data. The analysis feeds back the exact shape of an ANS measure that is most predictive of the outcomes. Leveraging such novel analytics may prove invaluable for identifying more subtle but clinically meaningful implications of normal and abnormal brain aging for ANS flexibility.

Some additional points worth mentioning or reemphasizing here when adopting these novel analytical approaches: first, simultaneously monitoring multiple features from SNS and PNS (e.g., combining portal skin conductor and 3-lead ECG in the real-world and/or in response to acute stressors), as opposed to our described work focusing on indices of PNS activity, may strengthen the utility of these AI models. Second, AI models, particularly for developing new diagnostic biomarkers, may require large amounts of data. For example, a recent paper using deep neural network to detect and classify clinically significant arrhythmia using portal ECG included data from over 53,000 patients (Hannun et al., 2019a). Whether it is feasible to consider ANS indices alone as biomarkers differentiating types of dementia/dementia pathologies, or typical and pathological brain aging, is unknown. A clear mechanistic understanding of ANS, ACC-inclusive networks, and brain aging should regardless be the first step. Finally, ensuring explainability of AI models for digital measures is crucial to fulfill their intended purposes (see our discussion on explainability in (Turnbull et al., 2022)).

5.3. Additional contributors to ANS function

Several contributing factors to ANS flexibility should be considered in research on the role of brain aging and pathologies in ANS flexibility: (1) Homeostatic processes: overall cardiac function, sleep-related processes, body position (sit vs. stand), motion, and breathing pace can all influence ANS flexibility (Ishaque et al., 2021; Tobaldini et al., 2013). Evidence suggests there may be valuable insights gained by assessing the role of dementia pathologies in ANS responses during homeostasis-related state. For example, in older adults with MCI, a preclinical stage of AD/ADRD, PNS activity is lower during non-rapid eye movement sleep, but not during wake or rapid eye movement sleep, compared to those with subjective cognitive impairment (Kong et al., 2020); (2) Mental reserve: both premorbid cognitive and emotional capacities can influence an older person's ANS flexibility (e. g.,(Heffner et al., 2021)).

In summary, to validate the ANS flexibility model, e.g., for differentiating types of brain pathologies, dementia, or typical and abnormal aging, we need to select the right combination of items from the four operational aspects for the model – measurement modalities, monitoring environments, analytical approaches and confounding factors (see Fig. 1C) based on specific research questions, targeted sample, study design, and budget.

6. Applications of the ANS flexibility model of brain aging

We here suggest two potential applications of the ANS flexibility model of brain aging, upon appropriate validations, as a novel biological resilience index in old age and for the understanding of emotion and cognitive regulation.

Resilience refers to the neurobiological capacity to adapt and maintain normal functional capacity in the face of environmental or physical adversity, such as dementia pathologies (Russo et al., 2012). This contrasts with concept of *resistance,* which denotes in the context of AD or brain aging an absence of brain pathology or physiological aging indicators despite present risks (e.g., APOE4-positive, family history of dementia, or chronological age, respectively) (Arenaza-Urquijo and Vemuri, 2018; Stern et al., 2018; Whitson et al., 2015). Importantly, incidence of diseases or chronic health conditions is often unavoidable

in aging, but resilience against adverse health events may prolong normal function. Therefore, the ability to adapt or cope with these adversities may be a more meaningful predictor of functional independence than a disease-free status (Borras et al., 2020; Hildon et al., 2010). Resilience is known to be a homeostatic process involving the ANS as well as the central nervous system, and brain networks identified as important for resilience are also known to be involved in ANS regulation; identifying homeostatic mechanisms involving the ANS may help clarify how specific brain networks can confer resilience while being vulnerable to brain pathologies. Given the inconclusive findings regarding neuropathological effects on ANS (Allan et al., 2006; Beach et al., 2017; Collins et al., 2012; da Silva et al., 2018; de de de Vilhena Toledo and Junqueira, 2008; Femminella et al., 2014; Issac et al., 2017; Nicolini et al., 2014), further research is required. Further, in typical aging process, the integrity of ACC-inclusive cortical networks may directly relate to cognitive function.

Several theories argue the importance of ANS flexibility for cognitive and emotional regulation (Forte et al., 2019; Kemp et al., 2017; Mulcahy et al., 2019; Porges, 2001; Thayer and Lane, 2000). The proposed ANS flexibility model may provide linkage between selected types of brain aging and functional health. For example, ANS flexibility may protect cognitive function or affective status against the negative influence of brain aging. ANS flexibility may also help identify older adults who may benefit from interventions to promote wellbeing and everyday function. ANS flexibility itself may be the therapeutic target, the change of which may help slow down brain aging. Mechanisms underlying the improvement include modifying the central efficiency of ANS flexibility, stimulating activity of the baroreflex, or regulating the dopamine and cholinergic transmission. There are several categories of interventions that can explicitly improve ANS flexibility, including cognitive training, physical exercise, music, non-invasive brain stimulation and biofeedback intervention (Dedoncker et al., 2016; Goessl et al., 2017; Lin et al., 2020; Makovac et al., 2017; Martin et al., 2017; Mojtabavi et al., 2020). For example, our recent cognitive training enhanced the strength of ACC-seeded cortical networks (e.g., ventral attention/salience network), as well as the flexibility of interoceptive and exteroceptive ANS function in older adults with MCI; these improvements were interrelated and related to improvement in attention and processing speed (Lin et al., 2020). We are now testing whether targeting ANS directly through HRV biofeedback intervention can strengthen the impact of cognitive training on cortical networks and the cognitive functions they support (Lin et al., 2021).

7. Implication for interoception science

Recently, NIH initiated a call for revitalizing interoception science (Chen et al., 2021). We suggest the current framework is ideal for advancing understanding of interoception – how individuals sense and regulate bodily states. The relationship between ANS function and brain has drawn a lot of attention due to the cumulative evidence elaborating the ANS' key role in top-down and bottom-up interoceptive signaling, including in response to exteroceptive stimuli (Thayer et al., 2012). Emerging studies suggest the genetic/heritable effects on ANS function are stronger for interoceptive compared to exteroceptive regulation (De Geus et al., 2007; Neijts et al., 2015; Wang et al., 2009). Thus, the signaling pathways through which interoceptive and exteroceptive stimuli exert effects on ANS and its flexible responding may differ. Of note, interoception deficits can distinguish neurodegenerative syndromes (Marshall et al., 2017). In all, clarifying the contribution of brain and ANS aging and dementia-related brain pathologies to interoception may reveal key pathways to cognitive and neuropsychiatric symptoms in dementia.

8. Conclusion

The growing promise of ANS measures as digital health markers of AD/ADRD necessitates further refinement of our understanding of the role of brain aging and dementia-related pathologies in ANS regulation and function. The heterogeneity of dementia pathologies and their likely distinct implications for PNS and SNS regulation and interoceptive signaling present challenges to forwarding ANS based digital markers as biomarkers or therapeutic targets for dementia at this time. This also suggests, however, a research opportunity. Our proposed framework of ANS flexibility, integrating understanding of brain aging and pathologies, ANS regulation, and adaptation, may be well suited to guide research directions in ANS-related digital health markers of AD/ADRD.

Declaration of Competing Interest

Authors (F.V.L., & K.H.) claim no conflict of interest or biomedical financial interest.

Data Availability

No data was used for the research described in the article.

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