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PERSPECTIVE

Priorities for research on neuromodulatory subcortical systems in Alzheimer's disease: Position paper from the NSS PIA of ISTAART

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[Correction added on February 1, 2023, after first online publication: The first name of the author Christoph Schneider was misspelled and has been corrected now.]

Abstract

The neuromodulatory subcortical system (NSS) nuclei are critical hubs for survival, hedonic tone, and homeostasis. Tau-associated NSS degeneration occurs early in Alzheimer's disease (AD) pathogenesis, long before the emergence of pathognomonic memory dysfunction and cortical lesions. Accumulating evidence supports the role of NSS dysfunction and degeneration in the behavioral and neuropsychiatric manifestations featured early in AD. Experimental studies even suggest that AD-associated NSS degeneration drives brain neuroinflammatory status and contributes to disease progression, including the exacerbation of cortical lesions. Given the important pathophysiologic and etiologic roles that involve the NSS in early AD stages, there is an urgent need to expand our understanding of the mechanisms underlying NSS vulnerability and more precisely detail the clinical progression of NSS changes in AD. Here, the NSS Professional Interest Area of the International Society to Advance Alzheimer's

Research and Treatment highlights knowledge gaps about NSS within AD and provides recommendations for priorities specific to clinical research, biomarker development, modeling, and intervention.

Highlights

- Neuromodulatory nuclei degenerate in early Alzheimer's disease pathological stages.
- Alzheimer's pathophysiology is exacerbated by neuromodulatory nuclei degeneration.
- Neuromodulatory nuclei degeneration drives neuropsychiatric symptoms in dementia.
- Biomarkers of neuromodulatory integrity would be value-creating for dementia care.
- Neuromodulatory nuclei present strategic prospects for disease-modifying therapies.

1 | INTRODUCTION

Despite making up fewer than 1% of neurons in the human brain,[1] the neuromodulatory subcortical system (NSS) nuclei serve as critical hubs for the processes underlying survival, hedonic tone, and homeostasis. Counter to ionotropic fast synaptic transmission, neuromodulation acts through slower, long-lasting signal transduction mechanisms to tune neuronal excitability. The NSS is a phylogenetically conserved network of nuclei located in the brainstem's reticular formation, diencephalon, and basal forebrain. Historically, the neuromodulatory nuclei were considered to encompass only those producing either serotonin (5-HT), dopamine (DA), norepinephrine (NE), or acetylcholine (ACh); however, more contemporary criteria consider whether nuclei produce and release molecules that act on neurons and glia by way of metabotropic receptors. These contemporary criteria expand the NSS to include nuclei that produce histamine, orexin, melanin-concentrating hormone, and dozens of other neuropeptides.[2,3]

NSS nuclei are mostly made up of polygonal, unspecialized neurons with overlapping and symmetrically extending dendritic fields and broad, poorly myelinated axonal outputs enabling neurotransmitter release to extensive projection areas. The shared properties of NSS nuclei make them critical nodes for understanding, diagnosing, and treating neurodegenerative diseases. NSS nuclei are vulnerable to different neurodegenerative diseases and are believed to modulate several psychiatric illnesses. For decades, dysfunction and degeneration (including tau accumulation, decreased transmitter production, synapse loss, and neuron loss) of the NSS have been well documented in Alzheimer's disease (AD), with particular focus on the cholinergic basal forebrain (CBF).[4–12] In fact, the prevailing treatment for AD targets cholinergic system dysfunction.[13] More recent work has provided a full appreciation of the early involvement, severity, and clinical consequences of NSS dysfunction and degeneration in AD, with bodies of literature growing around the locus coeruleus (LC), dorsal raphe nucleus (DRN), hypothalamic nuclei, and others.

In the early 2000s, findings describing the extensive degeneration of lower brainstem nuclei preceding substantia nigra (SN) involvement in Lewy body disease (LBD)[14] challenged early beliefs that Parkinsonism was the earliest manifestation of LBD. Later studies confirmed the association between alpha-synuclein–driven degeneration of caudal brainstem nuclei and early non-motor features of synucleinopathies, such as rapid eye movement (REM) sleep disorder and hyperalgesia.[15]

These findings in LBD inspired interest in re-examining the chronology of NSS involvement in AD. Independent studies showed that NSS degeneration, including intraneuronal tau aggregation, diminished neuron viability, and cell and synaptic loss, occurs early in AD pathogenesis.[16] At least 15 NSS components, including noradrenergic, serotonergic, cholinergic, and orexinergic nuclei, show abnormal tau neuronal inclusions at Braak stage 0 (i.e., preceding tau pathologic lesions in the entorhinal cortex).[17] Like in LBD, NSS dysfunction and degeneration manifest as non-pathognomonic symptoms in AD. In the case of AD, changes in sleep, vigilance, affect, and appetite precede memory decline and relate to underlying NSS degeneration.[18,19] The relevance of early NSS dysfunction in AD goes beyond just clinical manifestations. Experimental studies show systematic effects of AD-related NSS degeneration resulting in dysregulated neuroinflammation, cortical tau seeding, and exacerbated cortical plaque accumulation.[20–27] The bi-directional relationships between NSS vulnerability and cortical dysfunction and degeneration are underexplored but have important implications for clinical practice and pathogenesis.

The molecular basis of selective vulnerability of NSS nuclei in AD is poorly understood but likely linked to the shared properties of these nuclei. NSS neurons regulate cognition and behavior via long, unmyelinated projections from neurons with relatively high metabolic activity. Additionally, these nuclei require high gene and protein turnover

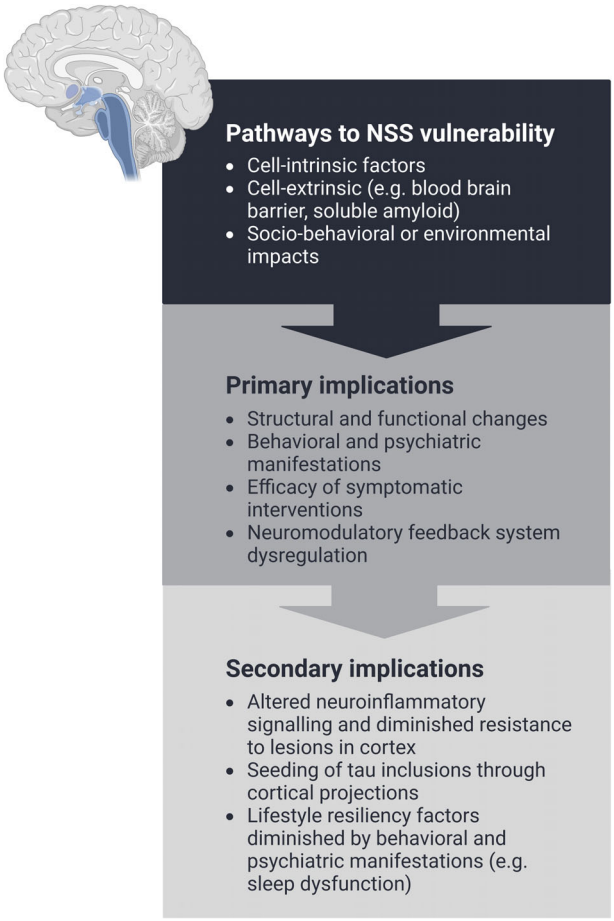

FIGURE 1 The neuromodulatory subcortical system (NSS) professional interest area recommends investment in research on pathways to selective vulnerability in NSS and how dysfunction and degeneration of NSS contribute to pathogenesis and clinical consequences. Myriad disciplines are positioned to generate knowledge within any of these research themes

rates to maintain the cytoskeletal integrity necessary to regulate axonal trafficking/transmission and multi-modal dendritic inputs.[28–32] Finally, the NSS is strategically positioned close to circumventricular organs of the blood–brain barrier, making them uniquely vulnerable to neurovascular contributors to neurodegeneration.[33–35]

The NSS professional interest area (PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART) seeks to congregate a multidisciplinary community of researchers and clinicians with expertise in these highly vulnerable and behaviorally impactful structures. Addressing AD-driven NSS dysfunction and degeneration is a promising strategy to identify, monitor, and modify AD progression from what are currently considered presymptomatic stages. The need for early detection and intervention in AD is widely accepted, but, despite their early involvement, NSS changes in AD remain underrecognized, understudied, and undertreated. The NSS PIA cross-disciplinary efforts seek to improve early detection and intervention in AD by (1) elucidating pathways to selective vulnerability of the NSS in AD and (2) characterizing outcomes and implications of NSS dysfunction and degeneration (Figure 1). In this position paper, professional

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed literature using PubMed and preprint servers. While the majority of the literature on neuromodulatory subcortical systems in Alzheimer's disease has focused on the locus coeruleus, there is emerging evidence for similar manifestations in other neuromodulatory subcortical structures. We have emphasized this recent literature to draw attention to the relevance of the whole neuromodulatory subcortical system. Such relevant citations are appropriately cited.
2. **Interpretation**: This position paper provides context and recommendations for future research on and funding strategies for neuromodulatory subcortical systems in Alzheimer's disease.
3. **Future directions**: The Neuromodulatory Subcortical Systems (NSS) Professional Interest Area of ISTAART recommends increased funding and focus for research on pathways to selective vulnerability of NSS, biomarkers of NSS integrity, clinical manifestations of NSS degeneration, and symptomatic and disease-modifying treatments for Alzheimer's-type dementia targeting the NSS.

community members specializing in NSS contribute their insights on knowledge gaps within AD and provide recommendations for priorities specific to clinical research, biomarker development, modeling, and interventions focusing on AD-related NSS degeneration. For this position paper, AD tau-mediated NSS degeneration is considered part of AD neuropathological stages even in the absence of amyloid beta (Aβ) cortical plaques.[36,37]

2 | CLINICAL RESEARCH

2.1 | Cohort design

By the time individuals with AD pathology manifest episodic memory loss in typical amnestic AD, NSS atrophy and dysregulation have already reached moderate stages.[17] Thus, cohorts from population-based aging studies are more suitable than clinical dementia cohorts to inform on NSS selective vulnerability because they will capture transition phases when dysfunction and degeneration of NSS nuclei begin. Enriching these cohorts with participants presenting with subjective memory decline[38] and mild behavioral impairment may be required to reach sufficient power to detect changes in NSS. Investigating AD-mediated NSS degeneration requires longitudinal observations and better tools to track granular neuropsychiatric symptoms, subtle cognitive changes, and responses to psychotropic medications. Such cohorts should incorporate existing "amyloid/tau/neurodegeneration (ATN)"-type biomarkers[39] and prioritize enrollment in autopsy studies. Inclusion criteria should prioritize phenotypes such as adult incidence

of unexplained affective symptoms or changes in sleep, vigilance, and appetite.

2.2 | Biomarkers

Neuroimaging has the potential to inform novel perspectives on the dynamic NSS changes in aging and AD and how they might underscore cognitive-behavioral aging trajectories. Recent years have featured a vast improvement in neuroimaging tools to detect the neuromelanin-containing LC and SN in clinical settings in clinically feasible acquisition times.[40–42] Expanding the neuroimager's toolbox to include the detection of other NSS nuclei is a needed but challenging goal because of the size and location of these nuclei. Emerging acquisition sequences and analytical pipelines using deep learning to identify several hypothalamic subregions[43] and the basal forebrain[44,45] based on standard structural neuroimaging are catalyzing this front, but constraints to spatial resolution jeopardize sensitive evaluation of NSS. For example, even the novel pipelines to segment the hypothalamus can only resolve groupings of nuclei as hypothalamic subunits, rather that single subnuclei (e.g., the inferior tubular subunit which includes the infundibular nucleus, ventromedial nucleus, supraoptic nucleus, lateral tubular nucleus, and tuberomammillary nucleus).[43] Expanding adoption of 7T ultra-high-field magnetic resonance imaging and approaches to address noise, such as multi-echo functional sequences[46,47] and multiband imaging,[48,49] may offer solutions. Positron emission tomography ligands specific to NSS and blood oxygenation level–dependent imaging[50] may provide further information about NSS function and integrity.[51,52] Novel neuroimaging methods must leverage effective data sharing and granular *post mortem* validation to improve standardization, reproducibility, and understanding of biological correlations.

Evolving analytical chemistry techniques make evaluating biofluids' neuromodulator and associated metabolite levels more feasible and affordable. Still, it has been challenging to interpret plasma and cerebrospinal fluid (CSF) levels of neuromodulators and their metabolites. CSF neuromodulator levels may have an inverted U-shape in AD because of compensatory overexpression or increased release during the early stages of AD-related NSS changes.[18,53] Moreover, several neuromodulators are produced in the peripheral nervous system. For example, NE detected in saliva and plasma likely reflects peripheral activity rather than LC function. Thus, target detection in CSF likely represents NSS functional integrity best because blood–brain barrier dynamics and peripheral activity influence it less. However, it is not without influence from these variables or analytical differences.

Due to roles in upregulating sympathetic and downregulating parasympathetic activity, the integrity of NSS structures like the LC may also covary with physiological indices such as heart rate variability,[54,55] pupil diameter changes,[56–61] skin conductance, salivary amylase, saccadic and smooth pursuit eye movements, and critical flicker fusion threshold. All of these indices have been explored as functional readouts of NSS changes. Pupillometry has garnered much attention as a tool to evaluate LC integrity and may aid AD clinical stratification,[62–64] but its utility remains unclear. Numerous NSS nuclei, including the cholinergic system, modulate pupil dilation, making it more likely a marker of NSS integrity as a whole than a specific LC marker. Scalp electrophysiologic recordings may also serve as a useful biomarker in AD[65,66] and, as an index of cortical arousal, should be explored as a measure of NSS functional integrity. Systematic neuropathological studies addressing the human NSS along AD progression are critical to inform biomarker development and its integration with clinical studies or diagnostic paradigms.

2.3 | Clinical assessment

An extensive functional neuroanatomic literature and mounting research specific to AD over the past decade have highlighted the tight associations between AD-related NSS dysfunction and neuropsychological manifestations of AD. Individuals with AD pathology can experience a constellation of behavioral and psychiatric symptoms such as apathy, depression, anxiety, irritability, agitation and aggression, delusions, eating disorder, aberrant motor behavior, wandering and sundowning, hallucinations, sleep–wake cycle disorder, disinhibition, elation, and mania.[62,63] Such symptoms negatively affect patients' quality of life and caregiver burden, leading to higher institutionalization rates.[64–66]

Affective symptoms are the most prevalent neuropsychiatric manifestation among people with AD-type dementia.[67] Dysregulation of subcortical regions such as the LC and hypothalamic nuclei are conventionally associated with anxiety.[68,69] While depression has historically been more closely related to the deterioration of the frontal–subcortical–limbic circuit, early AD-related degeneration of the serotonergic DRN has been neglected in clinical and biomarker research and may contribute to depressive mood. Agitation and anxiety are related to AD progression due to impaired emotional regulation networks,[70] and certain neurochemical disturbances, including potential compensatory overactivity of the noradrenergic system.[71]

Diurnal and nocturnal polysomnographic studies in AD patients report sleep fragmentation, diurnal sleepiness with increased napping, and a prominent decrease in slow-wave[72] and an average or modest decline in total sleep and REM sleep time.[73] A combination of early tau-associated dysregulation and degeneration of the noradrenergic, orexinergic, histaminergic, and basal forebrain cholinergic systems, all critical nodes in the ascending arousal network that organizes the sleep–wake cycle, contributes to sleep disturbances in AD.[19,74–82] Sleep disturbances precede memory decline in a significant portion of AD patients. Even during the early stages, these disturbances may also contribute to diminished sleep-dependent brain maintenance, which, in turn, exacerbates the propagation of AD protein hallmarks creating a positive feedback loop.[76,83] Consequently, sleep dysfunction has emerged as a promising modifiable risk factor for delaying or slowing initial AD-related processes before the onset of dementia.

Beyond psychiatric and behavioral manifestations, the NSS critically contributes to higher order cognitive functions such as attention and memory.[84–87] Degeneration of NSS have thus been proposed as significant determinants of cognitive decline.[53,88–90] In line with this,

correlative evidence links dopaminergic[91–93] and noradrenergic[94–96] neuromodulation to cognition.

Currently, psychometric assessment tools for individuals with AD, such as the Neuropsychiatric Inventory (NPI),[97] rely on retrospective subjective ratings by proxy, which are vulnerable to recall bias in quasi-experimental clinical settings. Digital instruments can assess affect, sleep, vigilance, agitation, social behavior, and psychiatric manifestations via objective and immediate measures in ecologically valid (e.g., in-home) settings.[98,99] Furthermore, more sensitive, ecologically valid neuropsychiatric instruments may offer advantages for monitoring the success of disease-modifying therapeutics compared to evaluating cognitive changes alone. Validation of non-intrusive digital sensing systems to capture early cognitive, behavioral, and physiological impairments in preclinical and prodromal AD is ongoing in international multicohort studies.

Observational studies in aging populations should carefully track the numerous psychiatric and behavioral changes associated with dementia in a detailed manner. Cross-disciplinary efforts with groups such as the ISTAART Neuropsychiatric Symptoms, Sleep, and Technology and Dementia PIAs may help to mobilize these efforts. Furthermore, the accumulating evidence of clinical consequences associated with early NSS degeneration in AD pathogenesis begs the question if, despite the lack of specificity for AD, syndromic definitions should be expanded to incorporate non-cognitive symptoms as early manifestations of AD-type neuropathologic lesions.

2.4 | Neuropathology

Despite the exponential gain of knowledge about AD-related NSS pathology in the past years, many gaps remain. Although more than a dozen NSS nuclei develop AD-tau inclusions preceding changes in the transentorhinal cortex (i.e., before Braak stage I) and others develop AD-type inclusions at very early Braak stages,[16,17,100] systematic neuropathological investigations have mainly focused on the LC, DRN, and CBF.[75,101–104] Moreover, the relationship and timing between the appearance of AD-like neuropathologic inclusions (e.g., hyperphosphorylated tau) and the frank degeneration of NSS nuclei (e.g., loss of axons or cell bodies) have rarely been rigorously characterized.

Existing human brain tissue sampling methods are not presently optimized for collecting NSS nuclei, creating a significant roadblock for NSS research. For instance, the National Institute on Aging–Alzheimer's Association guidelines[105] recommend sampling the basal ganglia at the level of the anterior commissure, pons, and midbrain to collect the basal nucleus of Meynert, LC, and SN, respectively. This scheme is too coarse for capturing the precise anatomical levels, landmarks, and intranuclear gradients of vulnerability. The basal nucleus of Meynert includes several subnuclei[106,107] with varied vulnerability to AD-type neurodegeneration throughout.[108] Similarly, the LC exhibits notable gradients of vulnerability, with the middle rostrocaudal third showing high susceptibility and the caudal third showing relative sparing.[75,109,110]

Furthermore, most brain sampling schemes for age-related neuropathology do not include the hypothalamus, which contains many NSS nuclei showing early vulnerability for AD. Despite its complicated cytoarchitectonics, the main hypothalamic structures of interest can be identified in coronal hypothalamic slides by Nissl staining and immunohistochemistry. The advent of in situ "-omics" and methods enabling RNA sequencing from formalin-fixed, paraffin-embedded brain tissue has expanded the opportunities for molecular studies in individual NSS nuclei and subnuclei, which systematic sampling of the structures can enable.

2.5 | Response analysis

AD's behavioral and psychiatric symptoms begin in the early pathological stages.[19] In many individuals with AD, these symptoms are refractory to treatments by conventional anti-depressant and anxiolytic medications.[111,112] Moreover, these and other psychotropic medications, including sedative drugs, sleep medication, and antipsychotics, often have harmful side effects in AD.[113] This observation is not surprising given the magnitude of degeneration, including frank cell loss, in specific NSS nuclei in AD. In fact, the etiology of these symptoms in AD may widely differ from that in the general population, necessitating research on appropriate disease- or individual-level management of symptoms. Nevertheless, tracking how patients respond to various psychiatric medications, including novel or repurposed agents, in a longitudinal design may facilitate earlier disease detection, subtyping, prognostic stratification, and improved understanding of functional neurobiological AD changes.

3 | MODEL SYSTEMS

A mechanistic understanding of NSS vulnerability in AD and NSS contributions to disease progression remains limited. In vivo research in vertebrate animal models benefits from the phylogenetic conservation of NSS nuclei. For example, the LC has been identified in all Gnathostomata lineages, placing its evolutionary origins to at least 380 million years ago.[114] As such, even aquatic models such as zebrafish[115] offer a platform for research on NSS selective vulnerability.

Unlike their mouse counterparts, rat AD models can develop endogenous hyperphosphorylated tau, even when not carrying a tauopathy transgene.[116] The TgF344-AD rat, which carries a transgene expressing mutant human amyloid precursor protein and presnilin 1,[117] shows tau pathology in the LC before the emergence of forebrain pathology,[116] making it a good option for preclinical studies incorporating subcortical pathologic lesions in AD. Other vulnerable NSS nuclei, such as the serotonergic DRN, histaminergic tuberomammillary nucleus, orexin/hypocretin system, and cholinergic nuclei have yet to be characterized in this model. While the TgF344-AD rat has several advantages for studying NSS, mouse models (e.g., APPsw/PS1, P301S, 3xTg-AD, 5xFAD) are often used due to the available genetic toolkits to manipulate their cell signaling networks. However, while some of these transgenic strains demonstrate pathology within brainstem regions, such as Aβ oligomers and hyperphosphorylated tau in the LC,[26,118–120] they do not recapitulate the temporal disease patterns observed in

humans because the ubiquitous promotors used lead to simultaneous overexpression of Aβ or pathological tau throughout the brain. Also, mouse tau does not contain the full human complement of isoforms and is aggregation-resistant.[64,65] Notably, most AD cases are sporadic, and observations made in models of familial-based systems will not always be generalizable.

Although transgenic rodent models of familial tauopathy exist, their utility for examining NSS vulnerability in AD is limited. While some subcortical systems appear similarly affected in rare, autosomal dominant forms of AD,[121,122] developing new preclinical models of sporadic AD that induce susceptibility to pathologic lesions in NSS is of utmost importance. It is also unclear whether NSS nuclei have the same vulnerability profile in humans and animal models. Emerging mouse models of sporadic AD from consortiums such as Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease should be systematically examined for disease-related phenotypes in NSS nuclei and existing phenotyping schemes.

Due to the small sizes of the NSS nuclei, it remains challenging to analyze their molecular, cellular, and physiological properties in vivo. In vitro models could be particularly useful for defining the effects of AD-type lesions on NSS neurons. Induced pluripotent stem cell (iPSC) and fibroblast-based 2D and organoid differentiation protocols are also being developed to specify noradrenergic, serotonergic, and cholinergic neuron fates.[123–126] Unfortunately, the cells generated from existing protocols represent forebrain neuron populations rather than the isodendritic hindbrain neurons. This limitation is also the case for the SH-SY5Y line,[127,128] which is often used for LC research. Given the selective vulnerability of NSS neurons to neurodegeneration, developing protocols to generate human cells that reflect hindbrain neuron populations is a high priority and would meaningfully complement animal models, biomarker findings, and neuropathology through high-throughput molecular genetic screens, drug screens, electrophysiological recording, or cell signaling assays.

An essential step toward generating valid in vitro differentiation protocols includes investment in research on the developmental origins of NSS nuclei.[129] Understanding of specific developmental origins of NSS beyond recognizing broad categories of transcription factors involved in hindbrain fate is deficient. For example, the LC has been thought to hold a single developmental origin within dorsal rhombomere-1 (r1).[130,131] More recent genetic fate-mapping studies examining the expression of *Fgf8* and *Pax7* have disputed this perception by expanding the developmental origins of the LC to include the isthmus and regions outside of the alar plate of the dorsal neural tube.[131–134]

4 | INTERVENTIONS

As attempts to reverse neurodegeneration are yet to be available, intervention should focus on attempting to reduce or prevent widespread neuronal loss. Targeting NSS function may mitigate neuronal loss and behavioral and psychiatric manifestations of AD. As AD pathology in NSS may be detectable in mid-life well before the typical age by which individuals with cognitive decline seek medical attention,[130,131] interventions during this period are likely to have a stronger impact on late-life brain health than interventions initiated during the cognitive stages of AD.[132,133]

4.1 | Symptomatic therapies

The currently available pharmacological therapies to treat cognitive symptoms in AD-type dementia are based on cholinergic or glutaminergic neurotransmitter deficits, which play roles in distinct cognitive dysfunctions.[135–137] Cholinesterase inhibitors are modestly effective and widely used for mitigating cognitive symptoms associated with degeneration of the basal forebrain.[138]

In addition to cholinesterase inhibitors, existing results from clinical trials suggest that other NSS targeting treatments can be effective in AD. In a phase III trial, the orexin receptor antagonist suvorexant improved sleep in participants with mild to moderate AD.[139] Atomoxetine, a clinically approved NE transporter inhibitor for attention deficit/hyperactivity disorder treatment, showed improving levels of AD biomarkers in participants with mild cognitive impairment due to AD.[140] Other neurotransmitter-based approaches currently under investigation include guanfacine, brexpiprazole, and escitalopram.[141] Still, symptomatic agents targeting cognitive enhancement or neuropsychiatric symptoms currently comprise less than one fifth of all ongoing AD clinical trials.

Neuropsychiatric symptoms like sleep–wake dysfunction are both early symptoms of AD and risk factors for disease progression; thus, whether through appropriate pharmacological or non-pharmacological approaches, improving some neuropsychiatric symptoms may facilitate improved brain maintenance and resistance to AD progression.[76,83]

Not all approaches to neuropsychiatric symptoms are appropriate for AD, though. Neuropsychiatric symptoms are controlled by multiple neurologic and endocrine systems and, thus, a neuropsychiatric disorder can have multiple etiologies. What might cause a neuropsychiatric symptom in the general population may not cause that same symptom in AD. Because of this, therapeutic approaches may differ. For example, sedative medications like benzodiazepines are commonly prescribed for insomnia in the general population but have only a modest effect on mitigating sleep–wake dysfunction in AD and are associated with severe side effects.[142] Whereas comorbid psychiatric conditions often cause insomnia, stress, or poor sleep hygiene in the general population, the dysregulation of the ascending arousal network is a likely etiology for insomnia in AD. The differences in the etiology of neuropsychiatric symptoms in AD versus the general population may affect therapeutic efficacy for commonplace interventions.

4.2 | Disease-modifying interventions

Based on neuropathological, biomarker, and clinical evidence of early NSS dysfunction in AD, protecting the NSS from

neurodegenerative changes may improve AD outcomes through several pathways. NSS nuclei project widely throughout the brain as central nodes of nervous-system–wide modulatory activity. Experimental studies suggest that NSS activity is neuroprotective against cortical AD pathology via neurotransmitters' cell signaling and endocrine properties. For example, β-adrenoreceptor–mediated engagement of the cAMP receptor element-binding protein pathway by NE leads to upregulation of canonical brain-derived neurotrophic factor and nerve growth factor production loops.[143] Maintaining LC–NE integrity may help stabilize such pathways, slowing cortical neurodegeneration. In animal models, LC dysfunction exacerbates Aβ plaque burden in the cortex,[22–25] potentially via microglia function.[144] The vast projections of the NSS may additionally facilitate disease spread into the cortex, with preclinical evidence indicating the capacity of subcortical tau to seed forebrain pathology.[20,21]

4.3 | Cerebrovascular health

Cerebrovasculature is extensively innervated by subcortical noradrenergic, dopaminergic, serotoninergic, and cholinergic neurons.[145–150] Several human *post mortem* and *ante mortem* biomarker studies have established associations between NSS degeneration and markers for cerebral amyloid angiopathy, blood–brain barrier breakdown, and neurovascular integrity.[151–153] In line with this, in vivo studies have shown that experimental lesioning of noradrenergic[154,155] and cholinergic[156,157] systems leads to deleterious changes in cerebrovascular structure and function.[156]

The NSS nuclei are uniquely exposed to the brain's extensive vascular system. The LC, SN, and several hypothalamic nuclei have some of the densest capillary beds in the brain,[33–35] raising questions about possible vascular contributions to their vulnerability. Furthermore, NSS nuclei uniquely interface structurally with the cerebrovascular system.[158] For instance, tanycytes, a specialized type of glia cell, are found within circumventricular organs at the third and fourth ventricles near hypothalamic and brainstem NSS nuclei, including the LC.[159–161] Tanycytes serve as a tri-directional interface among CSF, blood, and these nuclei for hormone and neurotropic factor detection and release. Despite their functional importance, research on tanycytes has been limited by methodological constraints since their discovery in the 1950s.[162] Recent development with single cell -omics technology is well positioned to revive research on tanycytes, fill in critical gaps about NSS neurovascular unit physiology, and uncover factors influencing vulnerability of the NSS.

There are critical knowledge gaps in the reciprocal interactions between NSS integrity and cerebrovascular health and the mechanisms by which the NSS regulates vascular tone, perfusion, permeability, and neurovascular coupling; moderate or mediate risk factors for cerebrovascular disease; and contribute to the development of cerebrovascular lesions during the early course of AD.[163] Research programs addressing these underexplored areas in human clinical series will be of critical importance for understanding the impact of NSS degeneration on postsynaptic cerebrovascular cell dysregulation and how this relates to NSS-mediated neuronal and glial dysfunction, AD neuropathology, and alterations in functional connectivity. In model systems, work incorporating new technologies to stimulate or inhibit various afferent and efferent NSS inputs, next-generation single-cell transcriptomics, and small animal neuroimaging approaches may offer exciting new possibilities to home in on the precise mechanisms underlying NSS-associated phenomena in the cerebrovascular system within and outside of the context of AD.

4.4 | Non-pharmacological interventions

The non-pharmacologic interventions under evaluation for AD span from "electroceuticals" (i.e., transcutaneous vagal nerve stimulation [tVNS]), gene and stem-cell therapy, cognitive training, mindfulness, and relaxation, to diet and exercise.[164–171] While many of these interventions do not target the NSS in isolation, they do modulate NSS due to the fundamental neuromodulatory tone with which they engage.

Transcutaneous vagal nerve stimulation is being explored to improve memory function.[167,172–175] In principle, the delivery of electrical pulses to the cymba concha in the outer ear engages the innervating vagus nerve. Signals travel via synaptic endings at the nucleus tractus solitarius to several regions, including the LC. Due to the LC's widespread projections to the neocortex, allocortex, and other NSS, tVNS may enable improved noradrenergic tone in AD.[176] Non-invasive stimulation of the greater occipital nerve—mediated by NSS activation—has improved memory function in studies of healthy young humans and animal models.

Observational studies have shown that lifestyle-related risk factors, like alcohol consumption, smoking, diabetes, hypertension, cerebrovascular disease, stress, anxiety, depression, and sleep–wake dysfunction are statistical contributors to the emergence and severity of AD-type dementia.[168,169,177,178] NSS integrity is tightly linked to many of these risk factors, including sleep–wake dysfunction,[179–182] stress,[183–185] depression,[186,187] drug abuse,[188,189] eating disorder,[190] and diabetes.[191,192] Therefore, it is reasonable to expect that positive lifestyle changes may galvanize NSS resilience to AD. To answer these questions, studies need to incorporate better tools to measure NSS function and lifestyle factors, particularly regarding socio-economic status. The impact of lifestyle adaptations at the individual level is unknown and challenging to measure. While doctors should motivate their patients to improve their lifestyles, it is also important to not instill false hopes in the effectiveness of the individual case when necessary. Thus, while a healthy lifestyle certainly decreases the risk for AD dementia on average,[178] the field should more deeply explore such interventions on a physiologic level, focusing on NSS, to predict individual benefits over time.

5 | CONCLUSION

Interest in the role of NSS vulnerability in AD etiology and pathogenesis is nascent. While only several of the many nuclei affected in

TABLE 1 Domain-specific recommendations from the ISTAART Neuromodulatory Subcortical Systems PIA

Research domain	Recommendations
Clinical manifestations	• Develop and deploy more sensitive, granular neuropsychiatric instruments in longitudinally followed cohorts to better evaluate clinical manifestations of NSS degeneration, especially for earlier AD stages. • Follow representative population-based cohorts longitudinally with serial neuropsychiatric and cognitive instruments, biomarkers (including AD biomarkers), and neuropathologic endpoints to capture age-related changes and the full range of AD neuropathologic changes versus other neuropathologic entities. • Revise AD syndromic definitions to include neuropsychiatric manifestations as supportive clinical features indicative of NSS degeneration and incorporate such symptoms as endpoints in clinical trials.
Neuropathology and biomarkers	• Integrate AD-specific and NSS-specific biomarkers and neuropathologic endpoints in population-based cohorts to enable clinicopathological study of NSS degeneration. • Revise autopsy guidelines to more systematically sample NSS structures in neuropathologic evaluation and biobanking. • Harmonize brainstem neuropathologic work with cell and molecular biologic approaches to investigate mechanisms underlying selective vulnerability. • Develop a staging scheme for NSS degeneration to understand the order by which structures are affected, including all NSS structures. • Systematically evaluate *ante mortem* biomarkers of NSS structure integrity against gold-standard *post mortem* anatomical and neuropathological observations. • Assess all biomarker-based risk stratification frameworks in clinically and demographically diverse populations. • Develop and harmonize in vivo imaging tools and EEG for evaluation of NSS structural and functional integrity.
Pathophysiology	• Describe and select animal models carefully, considering how each incorporates effectors of degeneration and exhibits temporal involvement patterns in NSS nuclei. • Guide the development of animal, organoid, and cell models with discovery-based "omics" in human *post mortem* tissue to understand the strengths and limitations of experimental systems. • Pursue a better understanding of pathways underlying NSS development to establish iPSC differentiation protocols into NSS-type neurons.
Interventions	• Granularly document psychotropic medication use in well-characterized cohorts to enable biologically informed, hypothesis-driven response analyses. • Develop guidelines for treating neuropsychiatric symptoms in AD versus the general population informed by possibly unique etiologies. • Identify the mechanisms underlying how non-pharmacological interventions mitigate neurodegenerative disease risk.

Abbreviations: AD, Alzheimer's disease; EEG, electroencephalogram; iPSC, induced pluripotent stem cells; ISTAART, International Society to Advance Alzheimer's Research and Treatment; NSS, neuromodulatory subcortical system; PIA, professional interest area.

early AD stages have been investigated, the appreciation for their roles has enabled novel perspectives on neurodegenerative motifs and clinical paradigms. Notably, the study of NSS vulnerability has required the integration of numerous disciplines from throughout the AD field (Table 1). We propose that additional investment in multidisciplinary approaches to understanding NSS selective vulnerability and consequences of NSS dysfunction and degeneration will accelerate the establishment of better diagnostic frameworks, identification of potent therapeutic targets, and understanding of core effectors of age-related brain diseases. A comprehensive understanding of NSS degeneration requires studies on central themes in cell biology, systems neuroscience, bioinformatics, physiology, neuropathology, neuropsychology, medical physics, analytical chemistry, epidemiology, and public health. The NSS PIA will continue to congregate research teams united by a focus on NSS degeneration in AD, train new investigators, and serve as a forum for developing research strategies to bridge translational gaps and deliver better outcomes for patients and families.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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