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State-of-the-art imaging of neuromodulatory subcortical systems in aging and Alzheimer's Disease: challenges and opportunities

Nina Engels-Domínguez[a,b,†], **Elouise A. Koops**[a,†], **Prokopis C. Prokopiou**[a], **Maxime Van Egroo**[a,b], **Christoph Schneider**[a], **Joost M. Riphagen**[a], **Tarun Singhal**[c], **Heidi I.L. Jacobs**[a,b,*]

[a]Gordon Center for Medical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

[b]Faculty of Health, Medicine and Life Sciences, School for Mental Health and Neuroscience, Alzheimer Centre Limburg, Maastricht University, Maastricht, The Netherlands.

[c]Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

Abstract

Primary prevention trials have shifted their focus to the earliest stages of Alzheimer's disease (AD). Autopsy data indicates that the neuromodulatory subcortical systems' (NSS) nuclei are specifically vulnerable to initial tau pathology, indicating that these nuclei hold great promise for early detection of AD in the context of the aging brain. The increasing availability of new imaging methods, ultra-high field scanners, new radioligands, and routine deep brain stimulation implants has led to a growing number of NSS neuroimaging studies on aging and neurodegeneration. Here, we review findings of current state-of-the-art imaging studies assessing the structure, function, and molecular changes of these nuclei during aging and AD. Furthermore, we identify the challenges associated with these imaging methods, important pathophysiologic gaps to fill for the AD NSS neuroimaging field, and provide future directions to improve our assessment, understanding, and clinical use of *in vivo* imaging of the NSS.

Keywords

Neuromodulators; Neuroimaging; Brain aging; Alzheimer's Disease; (Functional) magnetic resonance imaging; Diffusion-weighted imaging; Positron emission tomography; Electrophysiology

[*]To whom correspondence should be addressed: Dr. Heidi Jacobs, PhD, Department of Radiology, Massachusetts General Hospital/ Harvard Medical School, Boston MA 02114, USA, hjacobs@mgh.harvard.edu.

[†]Each of these authors contributed equally

Introduction

Sporadic Alzheimer's Disease (AD) is the most common cause of dementia, affecting over 5 million people in the United States alone and over 30 million people worldwide, with its prevalence expected to further increase (Alzheimer's Association, 2022; Haque and Levey, 2019). AD is characterized by two pathologic hallmarks: amyloid-beta (Aβ) and tau proteinopathies. Despite numerous ongoing research efforts, clinical trials targeting AD have had very limited success in delaying clinical progression of the disease (Cao et al., 2018; Jeremic et al., 2021). The majority of these clinical trials have focused on the clearance of Aβ plaques in individuals with cognitive impairment (Cao et al., 2018). However, it has become increasingly clear that the accumulation and aggregation of Aβ and tau start two to three decades prior to the onset of clinical symptoms (Braak and Del Tredici, 2015; Braak et al., 2011b), marking AD's long preclinical course (Theofilas et al., 2015). The limited clinically relevant advances in therapeutics may reflect that the current window of intervention is suboptimal and consequently, the field's focus has shifted from symptomatic to asymptomatic individuals. To ensure that interventions in these earlier stages are effective and target individuals who are at risk of AD, there is an urgent need for markers predicting early accumulation of AD pathology as well as markers that track subtle clinical progression.

Structural or functional readouts of the neuromodulatory subcortical systems (NSS) may hold promise as a marker of the earliest stages of the disease process (Grinberg et al., 2011). These NSS correspond to the isodendritic core network and consist of a group of nuclei that synthesize monoamines (such as catecholamines and serotonin) and acetylcholine, and have widespread projections to the cortex. As these phylogenetically conserved subcortical nuclei are vulnerable to the earliest AD-related tau depositions even before tau reaches the transentorhinal cortex, this review is restricted to the isodendritic nuclei and the nucleus of the lateral hypothalamus, which has similar transmission characteristics to the isodendritic nuclei (Avery and Krichmar, 2017; Grinberg et al., 2011; Theofilas et al., 2015). The neurotransmitters provided by these nuclei act as neuromodulators, regulating the activity of neuronal and non-neuronal cells, and are essential for higher-order cognitive functioning, which emphasizes the far-reaching consequences of functional or structural alterations in the NSS (Avery and Krichmar, 2017). So far, several NSS nuclei have been identified to accumulate tau pathology prior to cortical involvement (Rüb et al., 2017; Stratmann et al., 2016). These include the noradrenergic locus coeruleus (LC), the serotonergic dorsal raphe nucleus (DRN), the dopaminergic ventral tegmental area (VTA), the orexinergic lateral hypothalamus (LH), and the cholinergic nucleus basalis of Meynert (NbM) (Fig. 1).

The NSS nuclei are among the very earliest regions accumulating pathologic hyperphosphorylated aggregates of tau or pretangles (Moloney et al., 2021). For instance, the number of LC neurons containing hyperphosphorylated tau increases significantly when moving from Braak stage 0 to I (Ehrenberg et al., 2017) and LC volume decreases by ~8% per Braak stage (Theofilas et al., 2017). Yet no significant LC neuronal loss is observed until Braak stage III-IV, which corresponds to the emergence of clinical symptoms (Theofilas et al., 2017). The volumetric changes prior to Braak stage IV likely reflect reductions in dendritic arborization and synaptic inputs, and retraction of LC innervations

to cortical regions, indicating that changes to the functioning and morphology of the LC span the different disease stages of AD. Similar to the LC, the other NSS accumulate hyperphosphorylated tau prior to the transentorhinal cortex (Grinberg et al., 2009; Hampel et al., 2018; Stratmann et al., 2016; Vana et al., 2011), although for the DRN this has been estimated to be at a slightly later time point than the LC (Ehrenberg et al., 2017). These accumulations of pretangle material and the morphological changes in NSS nuclei have been associated with the earliest clinical phenotypes of AD (Ehrenberg et al., 2017; Kelly et al., 2017) and the reported lack of age-correlations during Braak stages 0-I suggest that these changes are likely not merely age-related (Theofilas et al., 2017).

These findings suggest that the NSS undergo significant changes at the very early stages of AD and could serve as indicators of AD-related risk. According to autopsy work, while pathological tau accumulation in the NSS occurs at a very early point in time, amyloid plaques in the brainstem can only be detected at later stages of AD (Braak et al., 2011a; Parvizi et al., 2001). The identification of earlier and less fibrillar forms of amyloid is hampered by the detection limits of our current methods. By identifying the earliest changes *in vivo* in humans, this could create a promising window of opportunity for early interventions. Recent developments in neuroimaging methods have now opened up exciting possibilities to examine these nuclei in greater detail and from multiple perspectives (Betts et al., 2019b; Billot et al., 2020; Priovoulos et al., 2018; Teipel et al., 2005). However, imaging the NSS has its own challenges and these limitations need to be considered when interpreting the data. In this review, we aim to discuss the current state-of-the-art of findings related to *in vivo* neuroimaging of the NSS nuclei to improve the understanding of early AD-related changes. Particular emphasis was placed on structural, functional, diffusion-weighted, positron emission tomography (PET), and electrophysiology imaging. We cover recent contributions and associated challenges, and future perspectives as NSS imaging holds great promise to improve the very early detection of AD, advance differential diagnostics, and aid in the identification of individuals suited for prevention trials.

General challenges in imaging the NSS

Neuroimaging is an excellent non-invasive tool to investigate the brain *in vivo*, facilitating the recording of changes over time in both healthy and disease populations. Advances in neuroimaging have paved the way for research investigating structural, functional, and molecular characteristics of small nuclei. The brainstem nuclei, but also the LH and NbM, are notoriously hard to image due to their small size compared to the spatial resolution of the imaging methods. The small size of these nuclei is particularly challenging in MRI and PET imaging and results in lower spatial resolution of the images, as these methods need larger voxel sizes to obtain a reasonable signal-to-noise ratio (SNR) even at higher MRI (magnetic resonance imaging) field strengths (Fig 2). Moreover, head motion has a profound effect on small structures in the brain, contributing substantially to lower SNR values. Additionally, the proximity of several NSS to non-neuronal tissue can lead to a high variance in the measured signal due to physiological noise, which can be unrelated or confounded with the signal of interest. The physiological noise arises primarily from respiratory and cardiac pulsations in arteries, veins, and cerebrospinal fluid (CSF)- and air-filled cavities, which in turn distort the images. The proximity of the NSS to the CSF in combination with their

small size can result in partial-volume effects when voxels that include multiple tissue types are classified incorrectly in the segmentation process. Furthermore, many studies account for multiple comparisons by utilizing cluster-wise corrections, which are geared towards larger structures, over voxel-wise corrections, which are more suited for the small-sized NSS. Consequently, the size and shape of the NSS are not taken into account, and this can introduce type I errors to the data (Sclocco et al., 2018).

Individual or group comparisons of the measured signal in these NSS warrant the transformation or warping of the images to a common space, either a population-specific template or a standard space image. Existing standard-space templates do not adjust for individual variability in size or location of the NSS, and minor registration errors can result in significant distortions of the anatomy of these nuclei in subsequent processing steps, introducing partial volume effects and biasing the extracted signal of interest; in particular in aging populations and populations with varying degrees of pathology. As the field of neuroimaging is relatively young, there is an urgent need for further validation of the neuroimaging measures in terms of test-retest reliability, registration, and anatomical accuracy.

Another important practical limitation of *in vivo* neuroimaging methods is the preclusion of individuals based on surgical interventions or co-morbid illnesses. In MRI, signal distortion can occur due to the forces exerted by the static magnetic field on ferromagnetic materials, and in extreme cases, radio frequency (RF) induced heating and displacement of the implant occur (Espiritu et al., 2021; Jungmann et al., 2017). In PET imaging, interference of certain medical conditions with the uptake of the PET tracer needs to be considered. For instance, in fluordeoxyglucose (FDG)-PET, brain cells can take up high blood sugar levels instead of the injected radioactive glucose (Sprinz et al., 2018). However, diabetes and metal implants (both oral and within the body) are common in the elderly population, and excluding individuals based on age-related comorbidities may result in samples that are less representative of the population.

Imaging the NSS using structural magnetic resonance imaging

A myriad of structural MRI research demonstrated unequivocally that aging and AD are characterized by overlapping as well as distinct patterns of gradual cortical and subcortical gray matter tissue loss. The gray matter changes observed in aging or the early phases of AD most likely reflect a reduction in the dendritic arborization of neurons, while loss of neuronal soma occurs later in the disease (Risacher and Saykin, 2013; Symms et al., 2004). Given that the NSS exhibit a particular vulnerability to tau pathology early in the adult lifespan (Braak and Del Tredici, 2011a, b; Ehrenberg et al., 2017), it remains unknown which and when neurons and neurites in these nuclei are vulnerable or resistant to AD-related pathology. The contrast and spatial resolution of standard T1-weighted imaging are too poor to provide clear boundaries of these nuclei. During the last decade, novel optimized high-resolution MRI sequences and templates were developed that provide a unique opportunity to investigate structural properties of these nuclei.

The cholinergic basal forebrain (or NbM) was one of the first NSS where neuroimaging methods were used to assess its structural properties. A combination of proton density MRI and histological sections of post-mortem brains enabled the localization of the basal forebrain and measurement of its volume (Teipel et al., 2005). By registering the resulting template to study populations, it was demonstrated that basal forebrain volume starts declining from early adulthood on and further aggravates during aging and progression of AD (Grothe et al., 2014). Volume of the basal forebrain was lower in patients with subjective cognitive decline, mild cognitive impairment (MCI), and AD compared to controls (Grothe et al., 2014; Scheef et al., 2019; Teipel et al., 2005; Teipel et al., 2011). Despite substantial multicenter variability, atrophy patterns were similar across studies, showing the most pronounced volume differences between controls and AD patients in the posterior NbM (Kilimann et al., 2014). Individuals progressing from control to amnestic MCI or from MCI to AD exhibited lower basal forebrain volume prior to progression (Brueggen et al., 2015; Kerbler et al., 2015), indicating early involvement of this nucleus in AD's pathogenesis. In both the ADNI and AIBL cohorts, greater Aβ-PET burden was associated with lower posterior basal forebrain volume in Aβ positive controls and lower anterior basal forebrain volume in those with early mild cognitive impairment, but not in those with late mild cognitive impairment (Grothe et al., 2014; Kerbler et al., 2015). When comparing the basal forebrain to the earliest cortical region accumulating tau pathology, the entorhinal cortex, predictive models revealed that atrophy in the basal forebrain preceded atrophy of the entorhinal cortex in the ADNI cohort, which emphasizes the critical role of subcortical changes in initial disease stages (Fernandez-Cabello et al., 2020; Schmitz et al., 2016). These structural changes in the basal forebrain in prodromal AD have been related to declining cognition, and lower basal forebrain volume has been associated with lower memory performance and attentional control in patients with MCI, and worse spatial pattern separation performance in AD (Parizkova et al., 2020). Reductions in basal forebrain volume in preclinical AD individuals were associated with increased microglial inflammation as measured with sTREM2 and C3 expression, and this effect was more pronounced in individuals carrying the APOE-ε4 allele: the strongest and most common genetic risk factor for AD (Schmitz et al., 2020).

Generally, *in vivo* structural information on the LC is obtained with the turbo-spin-echo MRI sequence, either without (Keren et al., 2009; Keren et al., 2015) or with additional magnetization transfer (MT) contrast (Jacobs et al., 2021a; Trujillo et al., 2019), gradient-echo sequences with MT (Chen et al., 2014) and T1-weighted Fast Low Angle Shot (FLASH) sequences at 3T (Betts et al., 2017), or the MT-turbo flash sequence at 7T MRI providing near-isotropic resolution, critical for the rod-shaped nature of the LC (Priovoulos et al., 2018). These sequences generate a hyperintense signal in the LC (and the substantia nigra, not discussed in this review). Since neuromelanin cells in the LC sequester metals, including paramagnetic elements such as iron and copper, it was assumed that the hyperintense MRI signal reflects neuromelanin cell density (Keren et al., 2015). However, more recent MRI modeling and animal imaging studies suggest a more complex biological source is underlying this contrast (Trujillo et al., 2017). Components contributing to this hyperintense signal may include lipids (Priovoulos et al., 2020), water (Watanabe et al., 2019) and tau aggregates (Jacobs et al., 2021a), and the relative contribution of

these components may vary with age, disease or location (Pamphlett et al., 2020). This variation is reflected in the inverted U-shaped relationship between LC intensity (also referred to as integrity) and age across the entire adult lifespan (Jacobs et al., 2021a; Liu et al., 2019; Shibata et al., 2006). However, several other studies were not able to detect a relationship between age and LC integrity (Betts et al., 2017; Maki-Marttunen and Espeseth, 2021; Ye et al., 2021), which may be due to sample size or selection biases towards very healthy individuals, as a negative age-association in older individuals may be explained by the presence of initial AD pathology (Jacobs et al., 2021a). Initial studies with smaller sample sizes demonstrated that LC integrity is lower in AD patients (Betts et al., 2019a; Hou et al., 2021; Olivieri et al., 2019; Takahashi et al., 2015) and MCI patients (Dordevic et al., 2017) relative to healthy older individuals. In the majority of these studies, AD was based on clinical parameters and not on underlying AD pathologic change biomarkers. Olivieri and colleagues (2019) included Aβ pathology in the diagnostic make-up and found no correlation between LC integrity and Aβ. In contrast, Betts and colleagues (2019) reported an unexpected negative correlation between CSF Aβ and LC integrity and no correlation between CSF ptau and LC integrity, though the sample size was modest (n=44) and consisted of a combination of healthy controls, patients with subjective cognitive impairment, MCI, and dementia.

Recently, in well-characterized and larger cohorts of preclinical autosomal dominant and sporadic AD, lower LC integrity has been associated with initial cortical tau and Aβ pathology, starting several years before the preclinical stages of the disease manifest (Dahl et al., 2021; Jacobs et al., 2021a; Jacobs et al., 2022). Lower LC integrity also correlates with cognitive and behavioral changes. In older individuals, lower LC integrity is associated with poor memory for negative emotional events (Hammerer et al., 2018), retrieval of episodic information (Jacobs et al., 2021a), or attentional shifting, specifically in individuals with low cognitive reserve (Clewett et al., 2016). In particular, the rostral part of the LC is susceptible to age-related learning changes (Dahl et al., 2019b). Furthermore, in sporadic preclinical AD lower LC integrity predicted Aβ-related cognitive decline over a time period of 8 years, and at levels below the established Aβ threshold (Jacobs et al., 2021a); neuropsychiatry symptom severity, particularly impulse dyscontrol (Cassidy et al., 2022); daytime sleep-related dysfunction (Elman et al., 2021a); and a higher degree of tau-related nocturnal awakenings (Van Egroo et al., 2021). In prodromal AD, lower LC integrity, especially in the rostral part, has been associated with worse processing speed and episodic memory (Elman et al., 2021a; Olivieri et al., 2019). LC integrity also correlates with imaging markers obtained with other sequences or modalities. In older individuals, lower rostral LC integrity was associated with lower free water diffusion in the cortex and lower global as well as frontoparietal cortical thickness (Bachman et al., 2021; Elman et al., 2021b).

So far, considerably less structural imaging work has been performed on the VTA, raphe nucleus (RN), or the hypothalamic subunits (Billot et al., 2020). In the ADNI cohort, individuals who increased on the clinical dementia rating scale total score from zero to 0.5 exhibited lower T1-weighted VTA signal at baseline compared to those who remained stable at 0, but this did not correlate with any of the CSF biomarkers (Venneri and De Marco, 2020). The authors did not find group differences for the LC, basal forebrain, or

the RN. Other work by the same authors showed a positive relation between VTA volume and both hippocampal volume and memory performance in older individuals (De Marco and Venneri, 2018). These findings suggest that the VTA can be an early marker of incipient memory decline, but more work is needed to determine whether this is specific to AD. In the hypothalamic subunits, lower volume in the anterior hypothalamus in AD patients compared to controls has been reported (Baron et al., 2001), while more recent work using the FreeSurfer parcellation reported large group differences in volume between controls and AD patients in both anterior and posterior subunits (Billot et al., 2020). Recently, a high-resolution hypothalamic atlas has been released, but caution is warranted when deriving conclusions in the context of aging as the template is based on a young population (Neudorfer et al., 2020). The dearth of structural imaging work on the RN, VTA, and hypothalamic subunits underscores the need for dedicated sequences that can identify these small nuclei at the individual level.

Challenges pertaining to structural imaging of the NSS and potential solutions

The majority of the structural imaging work on NSS has focused on the LC, and this has highlighted the need to validate the underlying biological substrates that contribute to the variability in MRI signals when imaging the small nuclei of the NSS. The test-retest reliability of TSE sequences that are used to image the LC were moderate, with Dice coefficients between 0.65 and 0.74 and inter-rater reliability between 0.54 and 0.64 (Tona et al., 2017). Inadequate reproduction of findings can have far-reaching implications that hamper the disentanglement of measurement error from actual meaningful change over time. Additionally, registration and anatomical accuracy of NSS imaging are in similar need of validation. The identification of the LC on MRI images is often based on intensity values extracted from normalized images and this segmentation is performed in native space or after warping the images to a template or a standard space image. These warps can introduce partial volume effects, distort the anatomy, and bias the exact size of the structure. This warrants caution when providing anatomical localization or inferring volumetric measures from MRI scans, particularly since post-mortem data has shown that neuroimaging methods tend to underestimate the length of the LC, as the caudal part is anatomically much more diffuse. Furthermore, templates derived from dedicated LC sequences acquired within a study sample should be distinguished from templates that are based on other imaging domains with insufficient resolution and contrast to provide accurate anatomical information. Creating sample-specific templates derived from dedicated sequences has the advantage that it is less dependent on the operator, and previous work indicated good correlations with manual identification of the LC (Giorgi et al., 2022; Maki-Marttunen and Espeseth, 2021). Another method employed to improve the SNR and consequently the registration is the upsampling of images (Betts et al., 2017; Dahl et al., 2019a), but even the preferred sinc approach can introduce minor blurring and interpolation effects, particularly in small regions as the NSS nuclei. This could result in false positives when aiming to detect associations between voxel intensities and other variables of interest. Therefore, visual inspection of image registration is required to ensure that the warping of the template to each individual image is accurate. The use of existing templates as a tool to identify the LC or other NSS via other imaging modalities not providing sufficient anatomical detail facilitates comparison and standardization across studies. However, caution is warranted

because minor registration issues can result in significant changes to these tiny structures, and templates do not account for individual variability in size or location of these regions (Fig. 3). For example, the LC position can differ by at least 2–3mm within the axial plane of the brainstem from one individual to another (Keren et al., 2009). This variability was also reported by a recent study comparing various published templates (Dahl et al., 2021). Even with the ongoing improvements in spatial resolution of neuroimaging methods, validation against post-mortem data, the ultimate ground truth, is needed to confirm the accuracy of localization and volumetric measurements of the LC obtained with MRI.

Imaging the NSS using functional magnetic resonance imaging

Blood-oxygenation-level-dependent functional MRI (BOLD-fMRI) is a valuable imaging technique to investigate the function of the NSS *in vivo*. Recent advances in ultra-high field MRI have facilitated the measurement of functional changes in small structures with considerably higher spatiotemporal resolution than most other neuroimaging techniques (Filippi et al., 2019; Sclocco et al., 2018; Singh et al., 2022), providing unique information relevant to the development of accurate functional biomarkers of AD pathology and cognitive decline (Schumacher et al., 2019; Wang et al., 2021).

The BOLD-fMRI signal depends on the hemodynamic response, making it an indirect measure of neuronal activity (Buxton et al., 2004). In addition to detecting derivatives of neuronal activation, BOLD-fMRI has been extensively used to quantify functional connectivity (FC): the degree of temporal co-variation in the BOLD-fMRI signal between spatially distributed brain regions (Varangis et al., 2021). In the context of AD, BOLD-fMRI has frequently been used to evaluate AD-related disruption in FC between NSS and other brain regions and to investigate the potential of these functional changes to improve early diagnostics of AD.

Resting-state (rs) FC analyses of the basal forebrain in healthy individuals have revealed two distinct anatomical subdivisions with different connectivity profiles: the anterior-medial subdivision, which is characterized by connectivity with the ventromedial prefrontal and retrosplenial/posterior cingulate cortices, and the posterior-lateral subdivision, which is characterized by connectivity with the insula and the dorsal attention network (Fritz et al., 2019). These distinct functional subdivisions of the basal forebrain have been reproduced in clinical populations (Chiesa et al., 2019; Herdick et al., 2020; Li et al., 2017). Even though initial studies reported a decrease in the strength of these basal forebrain FC networks in MCI patients compared to healthy individuals (Li et al., 2017), a more recent investigation including a larger sample spanning all diagnostic groups of the AD spectrum failed to reproduce these results (Herdick et al., 2020). In the latter study, the results obtained with rsFC contrasted with the basal forebrain volume decline and structural connectivity changes across diagnostic groups, and the neuropathologic studies suggesting cholinergic depletion in AD (Bohnen et al., 2018).

RsFC analysis of the LC, in young and healthy individuals, revealed strong FC with the entire neocortex, hippocampus, amygdala, thalamus, pallidum, and many brainstem nuclei (Singh et al., 2022; Zhang et al., 2016). With aging, the LC demonstrated similar

connectivity patterns with most of these regions. However, areas such as the lingual and parahippocampal gyri showed diverse connectivity patterns that varied across different age ranges. For example, negative correlations with age were reported for the FC between the LC and the lingual and parahippocampal gyri in a group of young adults between 18 and 49 years of age (Zhang et al., 2016). In contrast, positive correlations were reported for these regions in individuals between 65 and 80 years of age (Jacobs et al., 2015). Curvilinear associations between LC FC and age in a large set of brain regions were reported by a study focusing on the adult lifespan (Jacobs et al., 2018b). The authors speculated that early age-related increases in LC FC might reflect brain maturation, whereas late-life increases might reflect aberrant neuronal firing related to AD pathology.

Whereas FC generally reflects the co-variation of signals in distinct brain areas, whole-brain global connectivity reflects the correlation of time series of gray matter voxels with every other gray matter voxel in the brain. Asymptomatic individuals at risk for familial AD demonstrated lower resting-state whole-brain global connectivity of the LC (Del Cerro et al., 2020b). In line with this finding, lower global task-related modulation of LC FC during the execution of an attention task has been reported in patients with late-life major depressive disorder (Del Cerro et al., 2020a), and in those at increased risk for AD (Byers and Yaffe, 2011). However, these task-related LC FC alterations were not observed in individuals with amnestic MCI, which is reminiscent of the variation in reported results comparing cholinergic basal forebrain FC across diagnostic groups (Herdick et al., 2020). In cognitively healthy older individuals, group baseline fMRI and Aβ-PET imaging with longitudinal cognitive measurements were combined and the results indicated that lower novelty-related LC activity and lower FC between the LC, the amygdala, and the hippocampus are associated with steeper Aβ-related cognitive decline (Prokopiou et al., 2022). These latter findings suggest that before cognitive decline becomes apparent, changes to the LC's functional properties are associated with markers of AD pathology (Kelberman and Weinshenker, 2022).

RsFC analysis of the VTA in young and healthy individuals revealed significant FC with other brainstem nuclei, including the raphe, laterodorsal tegmental, and periaqueductal gray nuclei (Singh et al., 2022), and with the hippocampus, amygdala, and regions within the prefrontal and cingulate cortices (Kahn and Shohamy, 2013; Murty et al., 2014; Tomasi and Volkow, 2014). From early to middle adulthood, a decrease in connectivity between the VTA and the somatomotor cortex was related to an age-related decline in dopaminergic signaling (Manza et al., 2015). Lower FC of the VTA with the left hippocampus was associated with less hippocampal volume and worse memory performance in a cohort comprised of healthy individuals and AD patients, but this result was not replicated within each diagnostic group, possibly due to lower statistical power (De Marco and Venneri, 2018).

In young and healthy individuals, rsFC analysis of the RN showed significant FC with the substantia nigra, caudate, putamen, and the LC (Singh et al., 2022). In the context of AD, Zhou et al. (2010) reported lower rsFC between the DRN and the default mode network in AD patients. Serotonin projections from the DRN play a critical role in supporting neurogenesis and proper functioning in the hippocampus (Alenina and Klempin, 2015), a key region implicated in learning and memory, suggesting that dysfunction of the serotonin

system might be associated with AD-related cognitive and memory decline (Leal and Yassa, 2013). In support of this, lower FC between the CA2, CA3, and subiculum hippocampal subfields has been associated with decreased serotonin transporter density in patients with MCI compared to healthy controls (Barrett et al., 2017).

The LH has been reported to have significant connectivity with arousal-related brainstem nuclei, such as the RN and the LC, as well as the striatum, thalamus, orbitofrontal cortex, middle and posterior cingulum, and temporal brain regions (Kullmann et al., 2014; Kullmann and Veit, 2021; Singh et al., 2022). In AD patients with versus without depression, lower rsFC between the LH and the middle temporal and superior temporal gyri has been reported (Liu et al., 2018), indicating that abnormal FC between the hypothalamus and the temporal lobe may reflect the pathophysiology of AD-related depression.

Challenges pertaining to functional imaging of the NSS and potential solutions

So far, FC studies investigating AD-related changes have not resulted in consistent reports on disease stage specific alterations. Nonlinear age effects, as suggested for the LC (Jacobs et al., 2018b), together with varying FC analysis methods and sample sizes are likely contributing to the inconsistency in reported findings. BOLD-fMRI has limited sensitivity compared to structural and diffusion MRI, which partly stems from the proximity of the brainstem to CSF-rich regions as well as the impact of physiological processes (e.g., cardiac pulsation and respiration) on the NSS BOLD-fMRI signal (Brooks et al., 2013). Dissociating the contribution of these non-neuronal contributions to the BOLD-fMRI signal is complicated due to its inherent dependency on blood circulation dynamics and vascular anatomy (Bernier et al., 2018; Bright and Murphy, 2015). Therefore, recording and modeling the contribution of physiology data may improve the sensitivity of the BOLD-fMRI signal in NSS regions (Brooks et al., 2013; Jacobs et al., 2020). Modeling individual- and region-specific hemodynamic response functions showed substantial improvement in signal extraction from the tiny subcortical structures (Lewis et al., 2018; Prokopiou et al., 2022). Furthermore, increases in SNR can be achieved with optimized brainstem-weighted registration techniques (Prokopiou et al., 2022), and using dedicated structural imaging sequences to accurately localize the NSS (Turker et al., 2021). Such dedicated MT-weighted structural sequences are already in use for imaging of the LC (Priovoulos et al., 2018; Trujillo et al., 2019). In general, the sensitivity of the BOLD-fMRI signal to detect pathological changes in the NSS can be significantly improved using multi-echo fMRI, albeit thereby limiting the enhancement of spatial resolution (Markello et al., 2018), and ultra-high-field fMRI (Jacobs et al., 2020; Sclocco et al., 2018; Singh et al., 2022).

Imaging the NSS using diffusion-weighted imaging

Experimental animal and human *in vivo* studies have provided support for the hypothesis that pathological tau propagates through neuroanatomical connections and spreads via synaptic connectivity (Ahmed et al., 2014; Arnsten et al., 2021; Jacobs et al., 2018a; Khan et al., 2014), resulting in the characteristic topographical pattern of tau progression in AD (Braak et al., 2011b). The trans-entorhinal cortex (TEC) is the first cortical site to harbor hyperphosphorylated tau and neurofibrillary tangles, corresponding to Braak stage I (Braak

et al., 2011b; Sanchez et al., 2021). Furthermore, the TEC receives dense projections from several neuromodulatory nuclei, including the LC, DRN, and NbM (Harley et al., 2021). The structural connections between the TEC and these nuclei are therefore of particular interest to investigate the associations between AD pathophysiological progression and the integrity of fiber bundle tracts. *In vivo* measurement of the axonal fiber bundles that form the structural connections between proximal and distal areas in the human brain is achieved with diffusion-weighted imaging (DWI).

DWI is a magnetic resonance-based technique measuring the restriction of microscopic Brownian motion of water molecules in the brain, based on their displacement within each voxel after applying diffusion gradients. In the axonal fiber bundles, both axonal membranes and myelin sheaths highly restrict the movements of water molecules, causing them to primarily diffuse in parallel with the longitudinal axis of a given fascicle. In turn, the modeling and quantification of such diffusion along axonal bundles yield useful metrics related to axonal density, membrane integrity, and orientation among specific pathways which are often affected by neurodegenerative disorders. Accordingly, one major application of DWI in the context of aging and AD has been the assessment of structural connectivity between brain regions, and most often between cortical areas. In the brainstem, fibers are densely packed and many different pathways run in close proximity, facilitating information transfer between the spinal cord, the cerebellum, and the cortex to support a broad range of physiological and cognitive functions (Zhang et al., 2020). However, this intricate environment poses important challenges to the use of DWI, and studies using DWI to investigate the NSS in the context of aging and AD are relatively scarce.

In a study on individuals across AD stages, the integrity of the LC-TEC structural connections, measured with radial diffusivity (RD), decreased proportionally to disease severity (Sun et al., 2020). RD is a voxel-wise measure of transverse diffusion perpendicular to the principal direction of axonal fiber bundles indicated by the axial diffusivity (AD) in a voxel. The relative length of the principal diffusion direction compared to the transverse diffusion is captured by the fractional anisotropy (FA) metric, which gives a summary indication of the directionality of the diffusion profile within a voxel. In the late mild cognitive impairment (LMCI) group, higher RD values were observed compared to a control group of cognitively unimpaired amyloid-negative participants. In particular, these associations were localized in the laterally bending part of the LC-TEC pathway, past the inferior part of the thalamus. In the AD group, the highest RD values of the LC-TEC pathway were observed, and these changes extended more towards the LC compared to the LMCI group. The authors concluded that the earliest stages of the disease may be related to degradation of the fiber tracts that are in proximity to the TEC, whereas changes closer to the LC could only be detected in more advanced disease stages.

Pathological tau may propagate from the LC to the NbM in the basal forebrain, before reaching the TEC (Braak et al., 2011b; Jethwa et al., 2019; Tiernan et al., 2018). In individuals with early mild cognitive impairment (EMCI) and AD patients, higher free water (FW) diffusivity, reflecting an increase in the volume fraction of extracellular space and thus indicating neurodegenerative processes, was reported among the LC-TEC tract and the NbM compared to cognitively unimpaired participants (Chu et al., 2022; Ofori

et al., 2015; Pasternak et al., 2009). After controlling for amyloid status, differences in FW-corrected FA were reported for the NbM and the septum of the forebrain. In the EMCI group, these changes were restricted to the anterior medial portion of the LC-TEC tract, whereas in AD higher FW values were reported throughout the LC-TEC pathway, including the dorsomedial portion of the tract extending from the LC to the basal forebrain. Moreover, higher FW values in the LC-TEC tract and the NbM were associated with lower performance on a series of global cognitive measures (MoCA, MMSE, and LASSI-L). Neurofilament light chain, a cytoplasmic protein that is increased in CSF or blood plasma when neuro-axonal damage or neurodegeneration is present, was positively associated with FW in the LC-TEC tract, the NbM, and the horizontal limb of the diagonal band of the basal forebrain. These results align with the findings reported in the previous study where AD-related alterations to the LC-TEC tract were observed (Chu et al., 2022; Sun et al., 2020).

In another study among 33 cognitively unimpaired older individuals, the LC-TEC pathway was reconstructed with geometric-optics based entropy spectrum pathways, and the proposed metric of equilibrium probability within these pathways showed a negative association with CSF tau (Solders et al., 2021). This indicates that LC-TEC pathway reconstructions with higher probabilities of less anatomical constraints were paired with higher CSF values of p-tau, which was mirrored by the significant negative associations between average LC-TEC FA values and CSF p-tau and total tau, reflecting that elevated tau levels are associated with degradation of the LC-TEC pathway.

Altogether, these DWI studies suggest an association between the disease stage and the degradation of the fiber tracts connecting the LC to the TEC, such that the degradation of the LC-TEC pathway is increasingly more apparent as neuropathological tau accumulates and spreads throughout the brain.

In addition to characterizing the projections originating from the neuromodulatory nuclei, DWI-related contrasts have been used to delineate some of these neuronal populations (Bianciardi et al., 2015; Singh et al., 2021), but also to investigate diffusivity within their boundaries as a proxy measure of their microstructural integrity. Two studies investigating fractional anisotropy (FA) in the LC reported higher FA values in older individuals compared to their younger counterparts (Langley et al., 2020; Porat et al., 2022), whereas lower FA values were observed in the ascending noradrenergic tract of older individuals (Porat et al., 2022). Accordingly, another study showed a decrease in RD and mean diffusivity (MD) values in the LC of older adults, which was further related to memory performance (Langley et al., 2022). These findings may relate to the diffuse projections of the LC, resulting in the fiber bundle tracts that run within the gray matter of the LC to branch out and have highly diffuse orientations. Another caveat is that the majority of these highly branched LC projections are either unmyelinated or thinly myelinated.

Challenges pertaining to diffusion-weighted imaging of the NSS and potential solutions

Similar to brainstem fMRI, technical limitations are inherent to the use of DWI to investigate brainstem neuromodulatory nuclei and their projections in aging and AD. First, an important challenge is that both respiratory and cardiac pulsations can significantly

distort brainstem images, such that particular attention should be devoted to the proper preprocessing of DWI images. Second, the inherent poor resolution of diffusion sequences (typically around $2mm^3$ isotropic) significantly hinders the investigation of DWI metrics within the boundaries of smaller brainstem nuclei, such as the LC. Consequently, these factors have restricted the models that can be used to analyze brainstem diffusion images. Recently, advances in diffusion signal modeling based on biophysical approaches have proposed novel quantitative metrics that aim to significantly refine the DWI-based characterization of tissue microstructure. Among them, the neurite orientation dispersion and density imaging (NODDI) model has attracted particular attention in clinical research (Kamiya et al., 2020; Zhang et al., 2012). By considering the diffusion signal within each voxel and distinguishing between the intra-cellular, extra-cellular, and free water compartments, the NODDI model provides microstructural indices related to the density of neurites and their orientation dispersion in the underlying tissue (Zhang et al., 2012). Combined with the use of dedicated connectome or ≥ 7T MR scanners, the application of these advanced microstructural diffusion models in the context of AD should improve our understanding of the complex and intricate anatomy of fiber bundles in the brainstem area and within the neuromodulatory nuclei of interest, and provide crucial information on how these are affected throughout the disease process (Chu et al., 2022; Lin et al., 2022; Qin et al., 2013).

Imaging the NSS using positron emission tomography

PET imaging has played a major role in advancing our understanding of the trajectory of AD pathology and it has developed into a prominent diagnostic tool. Radiotracers binding to transporters, receptors, and enzymes enable *in vivo* visualization and quantification of AD pathology and the accompanying characteristic functional metabolic brain changes, such as the accumulation of Aβ plaques, neurofibrillary tau tangles, neuroinflammation, changes in synaptic density and glucose metabolism, as well as neurotransmitter receptor density, synthesis and transport (Bao et al., 2021; Nordberg et al., 2010). In particular, Aβ-PET (Barthel et al., 2011; Curtis et al., 2015; Klunk et al., 2004; Lister-James et al., 2011) and tau-PET (Xia et al., 2013) have revolutionized the understanding of AD pathophysiology. Despite the small anatomical structure of the NSS, their high tracer binding affinity due to high concentrations of molecular targets enables their visualization and quantification using specific PET radioligands and high-resolution PET scanners.

The LC is the earliest site that accumulates detectable phosphorylated tau in AD (Braak et al., 2011b), preceding widespread neurodegeneration. Thus far, PET imaging of pathologic tau in the LC has not been achieved due to constraints related to the high off-target binding of the currently available tau radiotracers to neuromelanin (Aguero et al., 2019; Lee et al., 2018; Lowe et al., 2016; Marquié et al., 2015). Nevertheless, the LC is known to be the primary seat of noradrenergic neurons in the brain, and PET ligands targeting the norepinephrine transporter (NET) have been used to visualize and quantify the LC NET concentration in health and disease (Ding et al., 2006). For example, prior PET studies using [C-11]methylreboxetine (also known as [C-11]MeNer) have demonstrated an upregulation of NET in the LC in cocaine abuse patients (Ding et al., 2010) and a decreased NET concentration in Parkinson's disease patients with REM sleep behavioral disturbances

(Sommerauer et al., 2018). In individuals with AD, a post-mortem autoradiography study demonstrated a decreased NET density in the LC using an F-18 labeled methylreboxetine analogue ([F-18]FMeNER-D2) (Gulyas et al., 2010), but to the best of our knowledge, an *in vivo* study using a NET PET ligand has not been reported in the AD population.

While the LC is the primary source of noradrenaline release in the brain, it also sends dopaminergic axons to the dorsal hippocampus (Kempadoo et al., 2016). Therefore, one approach to infer the catecholamine synthesis of the LC is the use of [^{18}F]Fluoro-m-tyrosine ([^{18}F]FMT) PET imaging; this radiotracer binds to the enzyme AADC (aromatic amino acid decarboxylase) in monoamine synthesizing pathways. [^{18}F]FMT signal is observed in dopamine synthesizing pathways and in regions synthesizing serotonin and noradrenaline as well (Brown et al., 1999; Ciampa et al., 2022; Kempadoo et al., 2016). Higher LC synthesis of [^{18}F]FMT has been associated with lower rates of pathological tau accumulation in the temporal cortex, measured with [^{18}F]Flortaucipir PET, in individuals with substantial Aβ burden, as quantified with [^{11}C]Pittsburgh compound B PET (Ciampa et al., 2022). The detrimental effect of tau on memory was absent in those with a higher synthesis of [^{18}F]FMT in the LC, indicating a protective effect of NE (Ciampa et al., 2022). In later stages of AD, it has been proposed that neurodegeneration and local hypometabolism are present within cortical and subcortical areas, which can be measured as a reduction in FDG-PET signal (La Joie et al., 2012). Recently, the absence of significant group differences in LC FDG-PET signal were reported in a study comparing individuals with AD and controls (Liu et al., 2021). However, as LC metabolism may not decline in a linear manner over the course of AD, an average FDG-PET value based on individuals in varying stages of the disease may not capture disease-stage specific changes in LC metabolism (Jacobs et al., 2021b; Weinshenker, 2018). Similarly, FDG-PET has been used to investigate glucose synthesis in other NSS. In the VTA, a reduction in FDG-PET signal has been related to apathy, a behavioral symptom often reported in AD (Schroeter et al., 2011). In the NbM, a reduction in FDG-PET signal in the left NbM was reported by two studies (Herholz et al., 2004; Nicolas et al., 2020). At an early stage in the AD disease process, higher uptake values were reported in those with MCI compared to the control group, and this effect was modulated by educational level suggesting that in those with a higher educational level, a compensatory upregulation of cholinergic activity occurs (Nicolas et al., 2020). Overall, these findings suggest that a decline in glucose synthesis is related to later stages of AD, and this association may not be linear in NSS with potential increases in glucose synthesis in the early stages of AD.

In the RN, decreases in transporter and receptor densities in cortical pre-and post-synaptic serotonergic projection areas have been reported in AD patients as assessed with 5-HTT ([^{11}C]DASB; (Ouchi et al., 2009; Smith et al., 2021)), 5-HT$_{1A}$ ([F-18]MPPF; (Kepe et al., 2006; Lanctot et al., 2007; Truchot et al., 2008)) and 5-HT$_{2A}$ ([^{18}F]altanserin; (Blin et al., 1993; Hasselbalch et al., 2008; Marner et al., 2012; Meltzer et al., 1999)) binding tracers (Merlet et al., 2004). In mild AD, neocortical loss of 5-HT$_{2A}$ receptors (Marner et al., 2012) may precede a reduction in 5-HT$_{1A}$ receptors in the RN, as well as decreasing receptor densities in meso- and neocortical postsynaptic serotonergic projection areas, which occur in later disease stages (Kepe et al., 2006). At the early stages of the AD continuum, the reduction in 5-HTT and 5-HT$_{2A}$ but not in 5-HT$_{1A}$ binding suggests a loss of RN projecting

serotonergic axons to meso- and neocortical regions while the serotonergic cell bodies in the RN itself are still preserved (Marner et al., 2012).

Cholinergic activity related to the NbM can be measured with PET ligands targeting vesicular acetylcholine transporter (VAChT), acetylcholinesterase enzyme (AChE), α7-nicotinic acetylcholine receptor (α7 nAChR), α4ß2-nicotinic acetylcholine receptor (α4ß2 nAChR), and muscarinic acetylcholine receptor (mAChR) (for a review, see: Tiepolt et al. (2022)). Multiple PET studies showed cholinergic system abnormalities in AD patients in the basal forebrain and cerebral cortex (Tiepolt et al., 2022). Using [F-18]FEOBV-PET, a marker for VAChT, a reduction in VAChT concentration in widespread cortical regions was identified in AD, which correlated with worsening of disease (Aghourian et al., 2017). Further, using (−)-[F-18]Flubatine, a marker for α4ß2 nAChR, AD patients' executive function and episodic memory were associated with reduced α4ß2 nAChR availability in cortical regions, and in the same study, a decreased basal forebrain α4ß2 nAChR availability correlated with memory scores (Sabri et al., 2018). In addition, reduced α4ß2 nAChR availability in the basal forebrain was associated with lower frontal assessment battery scores in AD patients (Okada et al., 2013). Similarly, an α7 nAChR marker ([C-11]MeQAA) has shown an association between α7 nAChR availability in NbM and cognition deficits in individuals with AD (Nakaizumi et al., 2018). An interesting study combining [C-11]-N-methyl-4-piperidyl acetate (MP4A)-PET (a marker for AChE) with functional MRI demonstrated significantly reduced cortical AChE activity in AD patients as compared to healthy controls, particularly in the lateral temporal lobe (Richter et al., 2018). Further, it was demonstrated that cholinergic integrity in the hippocampus predicted a favorable response to treatment with an AChE inhibitor (rivastigmine), as determined by clinical assessment and fMRI (Richter et al., 2018; Tiepolt et al., 2022). In an older study using [C-11]MP4A, reduced AChE was seen in the amygdala and cerebral cortex but relatively preserved and even increased AChE activity and glucose metabolism were reported for the right NbM in mild to moderate AD (Herholz et al., 2004). This preservation or increase in NbM metabolism as determined with FDG-PET may be accompanied by significant reductions in cortical acetylcholinesterase and may reflect a compensatory phenomenon (Aghourian et al., 2021; Herholz et al., 2004; Richter et al., 2022). These reports underscore the importance of understanding the temporal and mechanistic relationship between the early degeneration of cortical cholinergic axon terminals, which has been hypothesized to reflect cortical Aβ toxicity (Thal et al., 2002), and degeneration of the cholinergic cell bodies in the NbM itself.

Challenges pertaining to PET-based imaging of the NSS and potential solutions

NSS structures are anatomically complex and small in size relative to the spatial resolution of PET, which is limited by physical factors including positron range, annihilation non-collinearity, as well as detector size, inter crystal scatter, and crystal penetration (Brzezinski et al., 2014). To facilitate the accurate detection of tiny brainstem nuclei, the use of high-resolution anatomical imaging of brainstem nuclei using dedicated MR sequences, accurate PET/MRI co-registration algorithms, and point-spread function models are needed (Baete et al., 2004; Jacobs and Cherry, 2001; Mehranian et al., 2017; Song et al., 2020; Song et al., 2019; Sudarshan et al., 2021; Zhu and Zhu, 2019). Furthermore, future studies are

required to better understand associations between the capacity of tracer uptake to various monoaminergic pathways (e.g., [^{18}F]FMT), AD-related pathology and clinical symptoms. Additionally, the development of high-field combined MRI/PET systems will help improve our understanding of the NSS. Despite these challenges, the high relative concentration of neurotransmitter receptors and transporters in the NSS leads to a high contrast to noise ratio for various PET radioligands, which facilitates the assessment of molecular changes in NSS in AD.

Imaging the NSS using electrophysiology recordings

Unlike other *in vivo* imaging methods in humans, electrophysiology is a direct measure of neuronal electric activity, and consequently has outstanding temporal sensitivity. A wide variety of invasive and non-invasive electrophysiological recording methods are popular in scientific settings (for reviews, see Frank et al. (2019); He et al. (2011)). In particular, the magnetoencephalogram (MEG) and the electroencephalogram (EEG) have been used extensively to identify general neurophysiological hallmarks of AD (Yener et al., 2022). Unfortunately, little is known about the pathological electrophysiological changes in the human NSS in the context of AD, primarily due to the evident challenge of acquiring electrophysiological data from the human midbrain and brainstem. That is why current research investigating direct recordings of the NSS is limited to deep brain stimulation (DBS) electrodes. However, implantation of DBS electrodes is not without risks, and this procedure is not applied without proven medical effectiveness. Consequently, animal models of AD are often used to directly investigate disease-related alterations in NSS neuronal activity. In humans, studies investigating subcortical DBS in the NbM (Kuhn et al., 2015) and the fornix (Fontaine et al., 2013; Laxton et al., 2010; Leoutsakos et al., 2018) in the context of AD reported no consistent improvements in cognitive scores (Jakobs et al., 2020). Lacking access to direct electrical recordings in the human NSS, often proxy signals like cortical oscillations or event-related potentials (ERPs) that can be recorded with EEG or MEG are investigated through targeted de/activation of specific NSS via tasks, stimulation, or pharmacological intervention (Babiloni et al., 2020; Muthukumaraswamy, 2014; Schumacher et al., 2020). Unfortunately, such studies come with the caveat that these patterns are always subject to other influences as well, e.g., sleep, stress, comorbidities, and medication (Banis et al., 2014; Borghini et al., 2014; Muthukumaraswamy and Liley, 2018; Uhlhaas and Singer, 2010).

To the best of our knowledge, no studies have been published on direct recordings of oscillatory or spiking activity in the human NbM through implanted DBS electrodes in individuals in AD. Patients with MCI displayed a drop in the theta frequency during an oddball task as well as the absence of the beta band component (Lee et al., 2019). In studies using non-invasive electrophysiological methods, the larger group sizes and the inclusion of a healthy control group are mitigating the much lower spatial specificity, and different proxies have been used to establish AD-related changes to the cholinergic system. The EEG-ACh index, derived from pharmacological ACh blocking (Johannsson et al., 2015; Snaedal et al., 2010), shows strong correlations with cortical atrophy across MCI and AD patients (Petrova et al., 2020). Furthermore, NbM volume loss and increased MD along the lateral NbM tract correlated with a slowing of the global alpha peak (Rea et al., 2021; Schumacher

et al., 2020). Overall, oddball tasks have revealed disease-specific shifts in low oscillatory EEG components in MCI compared to age-matched healthy individuals (Rosenblum et al., 2022), and oddball-evoked ERP latencies have shown to increase with central cholinergic blocking (Pekkonen et al., 2005) and to decrease under cholinergic therapy (Onofrj et al., 2003; Thomas et al., 2001) and NbM DBS for AD (Dürschmid et al., 2020).

Akin to the NbM, no direct recordings of the VTA have been reported in humans. However, DBS implantation in the neighboring substantia nigra (SN) showed phase-locking of SN firing with prefrontal theta power (Kamiński et al., 2018). Rodent studies have emphasized the functional importance of the VTA/SN theta frequency activity (Shi, 2005; van der Velden et al., 2020), its strong temporal link with prefrontal cortical activity (Mishra et al., 2021), and showed a reduction in theta rhythm firing in dopaminergic VTA neurons in models of familial AD (Vorobyov et al., 2019). As a result, prefrontal theta power appears to be a good candidate for a noninvasive electrophysiological proxy of VTA activity.

Currently, there are no studies reporting on DBS electrodes in the human RN or the LH in the context of AD. Interestingly, even though the dopaminergic system is strongly implicated in attention, oddball ERPs remain largely unaffected by SSRIs, tryptophan depletion or genetic polymorphisms (d'Ardhuy et al., 1999; Enge et al., 2011; Fischer et al., 2015).

LC neurons have two distinct patterns of population firing, phasic and tonic, creating a functional balance across time to allow task engagement and disengagement (Aston-Jones and Cohen, 2005). There are no studies investigating changes in LC firing patterns in humans *in vivo* (Feinstein et al., 1989). In animals, LC phasic bursts were found connected to slow oscillations in the hippocampus and prefrontal cortex, which in turn modulated the power of cortical theta and gamma rhythms (Durán et al., 2021; Eschenko et al., 2012; Neves et al., 2018; Sara and Hervé-Minvielle, 1995; Totah et al., 2018; Xiang et al., 2022). Injection of preformed synthetic tau fibrils into the mouse LC led to a decrease in alpha peak frequency in the hippocampus and lowered phase-amplitude coupling between hippocampal theta and prefrontal gamma oscillations, indicating that cortical proxies of LC activity can indeed display AD-related changes in the LC (Ahnaou et al., 2019). In humans, norepinephrine release during an attention task (as inferred from pupil size) was associated with cortical alpha and beta band desynchronization events (Dahl et al., 2020). Further, frontal midline beta/theta ratio as well as task-evoked potential changes were recently linked to noradrenergic activity, albeit without the direct measurement of LC activity (Burger et al., 2020; Melnychuk et al., 2021). Specifically, the P3b ERP in oddball tasks has been associated with cognition and showed a decrease in amplitude in MCI and AD (Ashford et al., 2011; Porcaro et al., 2019; Porcaro et al., 2022), but other systems besides the noradrenergic system contribute to the P300 response (Brown et al., 2015). In intervention settings, transcutaneous peripheral nerve stimulation methods, including the vagus nerve and occipital nerve, which are assumed to increase LC activity (Sclocco et al., 2020), resulted in decreased occipital alpha power and increased theta-gamma phase-amplitude coupling as well as increases in the P3b amplitude (Lewine et al., 2019; Sharon et al., 2021; Vanneste et al., 2020) and improved memory function in older individuals (Jacobs et al., 2015).

Challenges pertaining to electrophysiological recordings of the NSS and potential solutions

Technical limitations that apply to electrophysiological recordings to investigate the NSS are primarily related to their size and location. First, the NSS lie far from the surface of the head, hindering the ease with which their electrical activity can be picked up with sensors at or around the head surface. Second, the small size of the NSS translates to their limited contribution to the electrical signals that are captured farther away. These factors limit the utility of non-invasive electrophysiology measures to investigate the NSS directly. Invasive electrophysiology measures evade these challenges, but these come with additional ethical considerations due to the risks attached to brain surgery. Thus, further exploration of the connection between non-invasive electrophysiological signals and the NSS will help our understanding of electrophysiological changes in the human NSS in the context of cognition and AD.

Discussion

AD is characterized by a long and gradually progressive asymptomatic phase characterized by a multitude of silent neuropathologic, morphologic and functional brain changes. As a result, the focus in the AD field has shifted towards earlier intervention with the aim of slowing down and ultimately stopping AD before irreversible damage has occurred (Sperling et al., 2020). Autopsy studies have identified the NSS nuclei as the first regions accumulating tau pathology, highlighting the presence of AD-related pathology well before cortical pathology or clinical symptoms are evident (Braak and Del Tredici, 2011a, b; Braak et al., 2011b). Therefore, reliable *in vivo* measurements of changes in these systems are critical for the early detection of AD, and in turn, will improve the identification of individuals who are more likely to benefit from prevention trials.

The NSS nuclei are notoriously difficult to image *in vivo* due to their size, location, and susceptibility to artifacts. However, the development of new methods taking advantage of ultra-high-field imaging to provide better spatial and temporal resolution together with new radioactive isotopes providing insight into molecular and neurotransmitter changes, have revolutionized the *in vivo* study of the human NSS in the context of neurodegenerative diseases. This progress is evident from the doubling of the number of publications on neuroimaging of the NSS in AD during the last decade. The aim of this review was to discuss the current state of knowledge on neuroimaging these systems *in vivo* in AD using currently available methods and identify methodological as well as pathophysiological gaps in the literature.

This non-exhaustive review of the literature showed that research investigating the NSS has primarily focused on the LC-norepinephrine and the NbM-cholinergic systems (Table 1). The latter system because of the availability of post-mortem validated templates and the former because of the structural MRI-sequences allowing the identification of the nuclei at the individual level. These studies have consistently shown that morphological changes in these nuclei start early in adulthood and accelerate during aging and AD, consistent with autopsy data. Diffusion data suggest that the extent of white matter degradation of the fiber bundles connecting the LC or NbM with the entorhinal cortex is related to disease

progression. Lower structural integrity (volume or intensity) of these nuclei was associated with the earliest accumulations of cortical tau pathology, suggesting that changes in these NSS precede pathology in the cortex. In support of this hypothesis is the observation that lower catecholamine synthesis in the LC, as measured with PET, was associated with greater cortical tau accumulation. Interestingly, both the LC and the NbM nuclei seem to have a specific regional vulnerability to tau pathology. Within the LC, the rostral-dorsal part is more vulnerable to AD-related changes, while the posterior NbM exhibited the earliest volumetric changes, indicating that certain clusters or neuronal ensembles may be more vulnerable to tau. The exact physiologic properties contributing to the vulnerability of these neuronal ensembles remain unclear. Recent animal literature demonstrating that tonic activity is associated with cognitive decline suggest that neurons exhibiting different firing patterns may have a different neurochemical makeup (Noei et al., 2022; Totah et al., 2019). Probing firing patterns with neuroimaging is challenging given its temporal resolution, though recent computational modeling work was able to link phasic LC activity to specific LC-related network dynamics (Munn et al., 2021). Another way to probe phasic activity is through the P300 wave, which is characterized by a lower amplitude in MCI and AD patients compared to clinically normal adults. Cortical EEG measurements such as P300 and P3b combined with saliva alpha-amylase (Ventura-Bort et al., 2018) and data from non-human primate research suggest P3a is more governed by dopamine while P3b seems to be related to the LC norepinephrine system (Polich, 2007), indicating that EEG-measurements can be a promising non-invasive, affordable, and widely available tool to assess the function of these NSS and possibly their interrelationships.

So far, the dopaminergic VTA, the orexinergic lateral hypothalamus, and the serotonergic DRN have received much less attention in AD. There is an urgent need for imaging methods that enable the anatomic identification of these nuclei at the individual level to facilitate the study of structural and functional changes in these nuclei. Investigating the NSS nuclei at the individual level is critical for our understanding of interindividual variability and factors that determine progression of versus resilience against AD-related processes. Even though the current spatial resolution of PET is limited given the small size of these nuclei, several tracers allow examination of these neurotransmitter systems *in vivo*. These tracers revealed that cell bodies in these nuclei remain intact early in the disease course, at which time cortical axonal terminals and projections are degenerating. However, there are currently only a small number of PET imaging studies that report on the NSS, whereas these studies are pivotal to further our understanding of the neurochemical changes within the chronological framework of NSS changes in AD. Similarly, functional MRI studies reported a loss of connectivity between the VTA or DRN and cortical regions in older individuals and patient populations. Whether regions that show strong functional connectivity to the NSS exhibit similar levels of tau pathology accumulation has yet to be investigated. As our field is developing new methods to image different properties of these nuclei, we have the opportunity to answer important pathophysiologic questions to understand why these systems are selectively vulnerable in the early stages of the disease; what the functional consequences are of degeneration of projections; when projections start to degenerate and how they impact NSS neurons, cortical neurons or networks; and finally, whether supporting the NSS nuclei can prevent the retraction of their projections. Such insights can benefit

our understanding of AD, improve early detection and even provide novel opportunities for interventions.

Current disease models and diagnostic criteria position the presence of Aβ deposition as a requirement for AD neuropathologic change (Jack et al., 2018). These models do not yet include early changes in the NSS, reflecting the current debate on whether these early tau depositions in the NSS are age-related or may convey information on AD-risk. Autopsy data and the reviewed studies indicate that the NSS nuclei are affected at an earlier timepoint in the disease process, and the structural and functional changes in the NSS correlate with cognitive decline and disease progression as well as the initial accumulation of AD pathology (Rüb et al., 2000; Rüb et al., 2017; Stratmann et al., 2016). It is important to note that even though by age 50, almost every case at autopsy exhibits tau pathology in the NSS nuclei, not everyone will ultimately develop AD. There is a need to identify factors or properties relating to the NSS that contribute to AD risk. These observations highlight that the AD field needs to move to earlier asymptomatic stages of the disease to gain breakthroughs in the treatment of AD. Correspondingly, these observations emphasize the urgent need to determine the exact sequence of NSS-related changes in the temporal evolution of the pathophysiologic cascade of AD biomarkers, and the value of these NSS changes as biomarkers for early detection and monitoring disease progression or selecting individuals for clinical trials. Multidisciplinary collaboration where neuropathologists, neuroimagers, biofluid researchers, neuropsychologists, and clinicians join forces is necessary to improve the state-of-the-art methods; to understand the evolution of neurobehavioral, cognitive, and pathologic changes by establishing longitudinal cohorts starting from midlife or even earlier on; and to assess new interventions targeting the NSS (Future Directions box).

In concert, related fields can provide insights into critical tools to enlarge the current arsenal available to examine the NSS. For the noradrenergic system, the NET transporter ligand MeNER has been used to give an indication of NET-binding in Parkinson's Disease (Nahimi et al., 2018; Sommerauer et al., 2018). This tracer would enable the investigation of the cortical correlates of NE-neurochemical changes in AD *in vivo*, and clarify how these changes relate temporally and spatially to other functional, structural and metabolic changes, as well as to overall amyloid, tau deposition, and neuroinflammation. Already, post-mortem work in AD has demonstrated a correlation between NET transporter density and the cortical Braak stages (Gulyas et al., 2010). Additionally, a recent biomarker-driven, phase II trial of atomoxetine (a NET inhibitor) in individuals with MCI due to AD demonstrated improved metabolic activity in medial temporal lobe circuits, significant reductions in CSF total Tau and pTau181, and improvements in synaptic, metabolic and neuroinflammation markers following treatment with atomoxetine (Levey et al., 2021), revealing that modulating the NSS can be of great therapeutic relevance for AD.

Early pathological changes in subcortical regions have the potential to alter cell firing patterns (Ahnaou et al., 2019), and the ensuing breakdown of physiological networks could be a central driver of AD progression. At present, DBS electrode placement in subcortical regions facilitating *in vivo* electrophysiology recordings in humans is not practiced for AD. While DBS provides a unique possibility of directly recording field potentials, it is limited

by the scarcity of implants that are applied to research and resulting measurements can be confounded by the indication warranting the DBS placement. Nevertheless, implanted electrodes with novel wireless transmitters can record data during daily life, unencumbered by a test setup and situation. Both invasive and non-invasive electrophysiological recordings related to subcortical structures can provide us with specific early functional biomarkers in preclinical AD, prior to our ability to detect structural changes. Overall, longitudinal observations of subcortical structures over the course of AD progression would advance our understanding of pathological changes in NSS activity and this may lead to the development and monitoring of interventions targeting specific physiological functions.

The exploration of neuroscientific and clinical AD-related hypotheses will be facilitated by improving, developing, harmonizing, and integrating multimodal neuroimaging methods with biofluid data, as well as cognitive and neuropsychiatric metrics; but it also necessitates the delineation of the healthy NSS. This work warrants the consideration that AD is often examined in the context of the aging brain, and it can be difficult to separate the effects of aging from those of AD. Interestingly, some of these NSS nuclei are known to be highly resilient against the accumulation of tau. The comprehensive study of the NSS across the lifespan will allow us to assess the temporal order of detrimental or compensatory changes in the NSS compared to modifications that remain within the normative range. Ultimately, this will allow us to map protective as well as risk factors to provide insight into the unanswered question why some individuals progress to AD and other do not (Szot et al., 2006).

Summarizing, recent developments in neuroimaging methods have revived the focus on the NSS in AD as the next frontier for early detection and intervention of AD. This review demonstrated that imaging the NSS *in vivo* in great detail is feasible and provides important directions to understand the role of the NSS in the earliest pathophysiology and symptomatology of AD. Future research investigating the functional properties of NSS in relation to AD would greatly benefit from large-scale studies, including large clinical cohorts, to overcome statistical power limitations.

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Highlights

- Structural and functional alterations of NSS predict AD-related phenotypes.
- Multimodal examination of NSS provides complementary information on AD pathogenesis.
- Post-mortem validation is crucial for accurate *in vivo* localization of NSS in humans.
- *In vivo* NSS measurements are essential for early detection and treatment of AD.

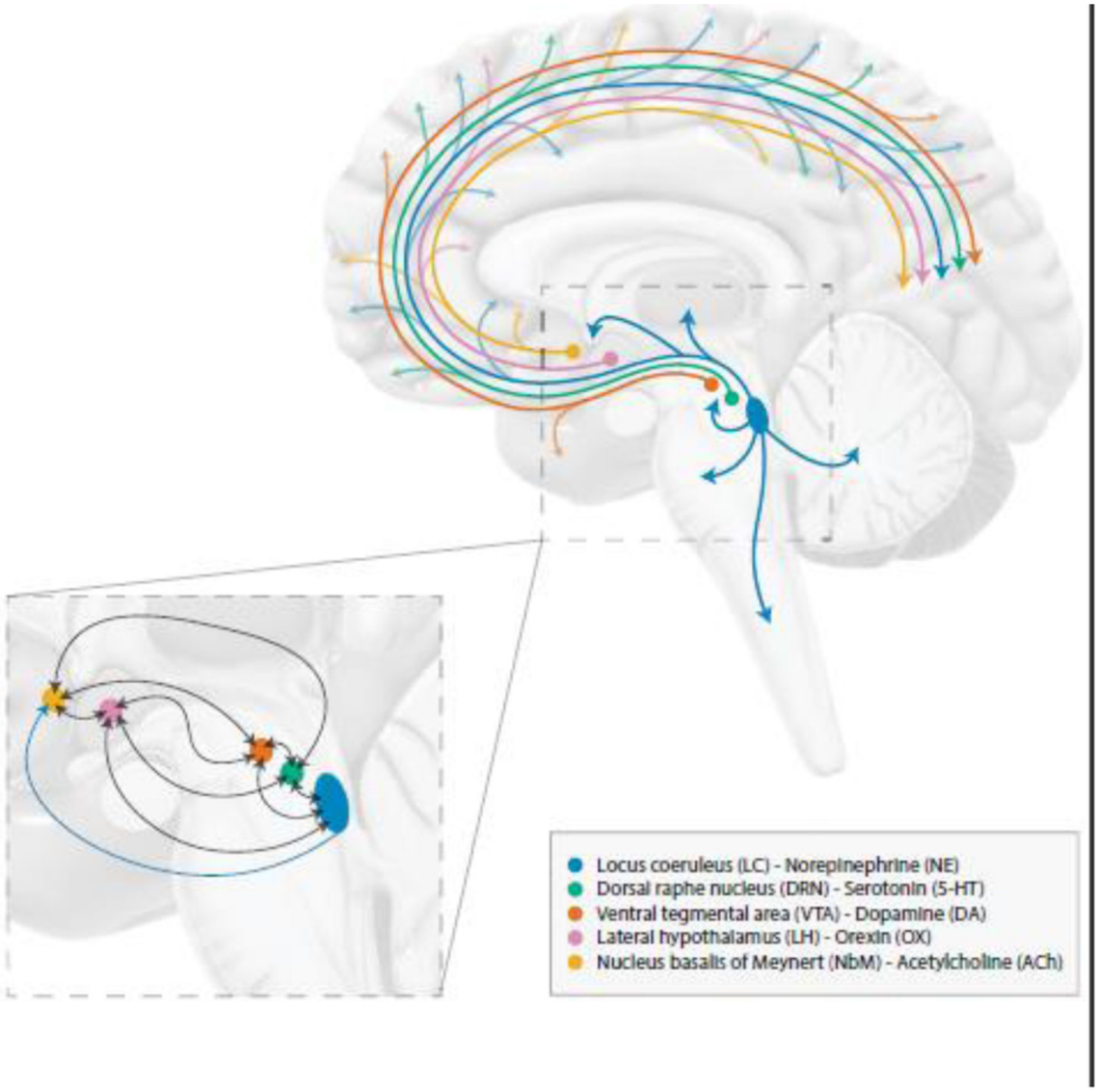

Figure 1. Location of the NSS and their most important projections and interactions.

NSS modulate a wide range of cognitive functions and behaviors, as illustrated by their widespread projections to (sub)cortical structures. Blue: the noradrenergic LC, green: the serotonergic DRN, orange: the dopaminergic VTA, pink: the orexinergic LH, yellow: the cholinergic NbM. For simplification purposes, visualization has been limited to main projections and interactions between the NSS. Abbreviations: DRN, dorsal raphe nucleus; LC, locus coeruleus; LH, lateral hypothalamus; NbM, nucleus basalis of Meynert; NSS, neuromodulatory subcortical systems; VTA, ventral tegmental area.

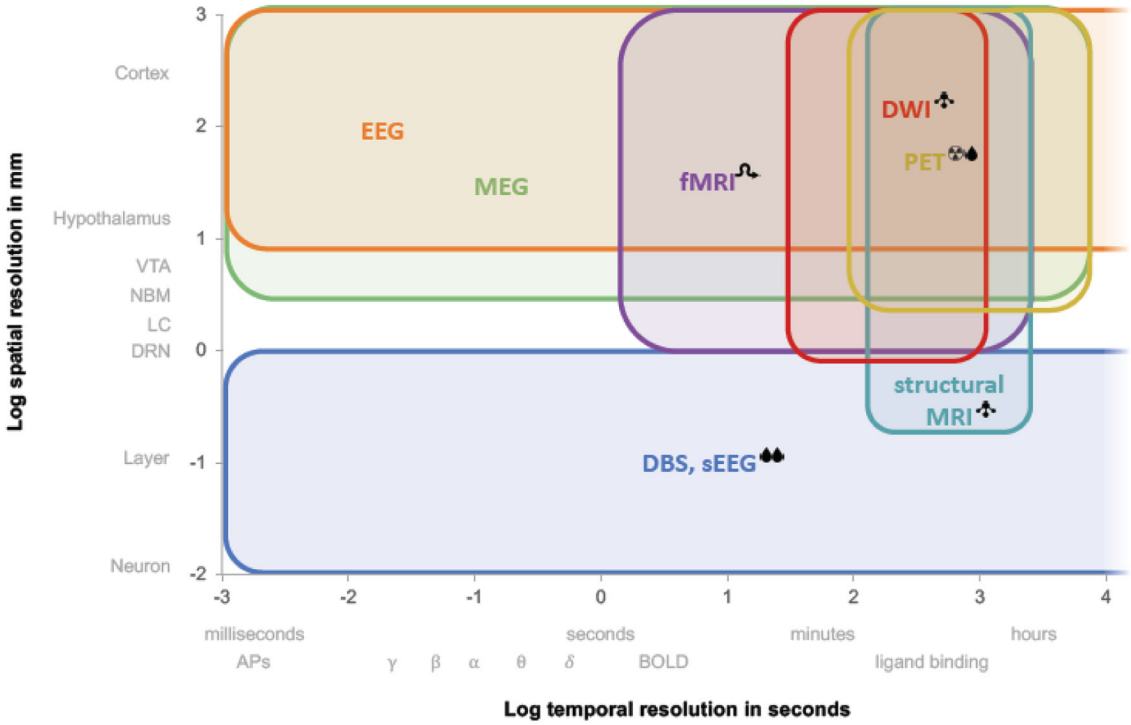

Figure 2. Imaging method comparison pertaining to NSS imaging.

Current neuroimaging tools differ greatly in spatial and temporal resolution, as well as in their invasiveness and the type of measurements taken. Legend: , invasive; , radioactive; , structural only; , indirect measure of neuronal activity; $\delta\ \theta\ \alpha\ \beta\ \gamma$, EEG bands. Abbreviations: APs, action potentials; BOLD, blood oxygen dependent level; DBS, deep brain stimulation; DWI, diffusion-weighted imaging; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; sEEG, stereoencephalography.

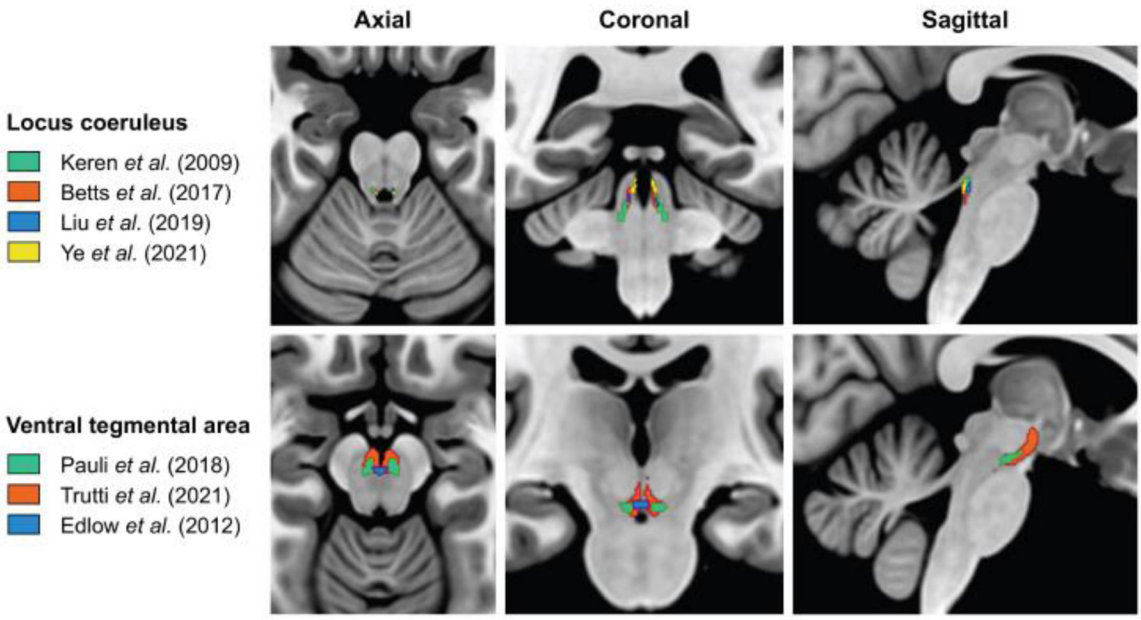

Figure 3. Multiplanar visualization of the spatial discrepancies among several published atlases of the LC and the VTA.

Differences in the data acquisition approach (e.g., in vivo vs. post-mortem, 3T vs. 7T), in the characteristics of the investigated population (e.g., lifespan vs. specific age range; healthy controls vs. patients), and/or in the image processing methods (e.g., registration/normalization pipeline) may lead to significant discrepancies in the location and spatial coverage of a generated atlas for a given NSS. Top: LC atlases retrieved from Keren et al. (2009) (green), Betts et al. (2017) (orange), Liu et al. (2019) (blue), and Ye et al. (2021) (yellow). Bottom: VTA atlases retrieved from Pauli et al. (2018) (green), Trutti et al. (2021) (orange), and Edlow et al. (2012) (blue). All atlases are superimposed on the MNI152 template in MRIcroGL software (https://www.nitrc.org/projects/mricrogl). Abbreviations: LC, locus coeruleus; VTA, ventral tegmental area.

Table 1.

Reported findings of studies included in this review.

	LC	RN	VTA	LH	NbM
Structural MRI					
Asymptomatic	↓ **Intensity** with greater age, in the context of AD pathology (Jacobs et al., 2021) ↔ No age-relationship (Betts et al., 2017; Maki-Marttunen and Espeseth, 2021; Ye et al., 2021) ↓ **Intensity** associated with initial tau and aβ (Dahl et al., 2021; Jacobs et al., 2021; Jacobs et al., 2022) ↓ **Intensity** associated with poor memory (Dahl et al., 2019; Hammerer et al., 2018; Jacobs et al., 2021), attention (Clewett et al., 2016) ↓ **Intensity** associated with nocturnal awakening (Van Egroo et al., 2021) ↓ **Intensity** correlated with lower cortical FW (Elman et al., 2021b) and lower cortical thickness (Bachman et al., 2021)		↓ **T1-signal** in those progression to CDR=0.5 (Venneri and De Marco, 2020) ↓ **Volume** associated with lower hippocampal volume and worse memory (De Marco and Venneri, 2018)		↓ Posterior **volume** associated with greater aβ-PET (Grothe et al., 2014; Kerbler et al., 2015) ↓ **Volume** precedes entorhinal atrophy (Fernandez-Cabello et al., 2020; Schmitz et al., 2016) ↓ **Volume** associated with higher microglial activation in APOE-E4 (Schmitz et al., 2020)
MCI/Prodromal AD	↓ **Intensity** in CDR=0.5/1 or MCI compared to controls (Cassidy et al., 2022; Dordevic et al., 2017; Elman et al., 2021a; Jacobs et al., 2021; Takahashi et al., 2015) ↓ **Intensity** associated with neuropsychiatry (Cassidy et al., 2022), sleep-related dysfunction (Elman et al., 2021a) ↓ **Intensity** (rostral) associated with worse processing speed, memory (Elman et al., 2021a; Olivieri et al., 2019)				↓ **Volume** compared to controls (Grothe et al., 2014; Kerbler et al., 2015; Teipel et al., 2011) & MCI progressing to AD (Brueggen et al., 2015) ↓ **Volume** associated with lower memory, attention (Parizkova et al., 2020)
AD	↓ **Intensity** observed in AD patients, as compared to healthy controls (Betts et al., 2019; Hou et al., 2021; Olivieri et al., 2019; Takahashi et al., 2015).			↓ **Volume** compared to controls (Baron et al., 2001; Billot et al., 2020)	↓ **Volume** compared to controls, predominantly posterior (Kerbler et al., 2015; Kilimann et al., 2014; Teipel et al., 2005; Teipel et al., 2011) ↓ **Volume** associated with lower pattern