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Thalamic cholinergic innervation is spared in Alzheimer disease compared to parkinsonian disorders

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ABSTRACT

There are two major sources of cholinergic projections in the brain. The nucleus basalis of Meynert provides the principal cholinergic input of the cortical mantle and the pedunculopontine nucleus–laterodorsal tegmental complex (PPN–LDTC; hereafter referred to as PPN) provides the major cholinergic input to the thalamus. Cortical cholinergic denervation has previously been shown to be part of Alzheimer and parkinsonian dementia but there is less information about subcortical thalamic cholinergic denervation. We investigated thalamic cholinergic afferent integrity by measuring PPN–Thalamic (PPN–Thal) acetylcholinesterase (AChE) activity via PET imaging in Alzheimer (AD), Parkinson disease without dementia (PD), Parkinson disease with dementia (PDD) and dementia with Lewy bodies (DLB). AD ($n=13$; mean age 75.4 ± 5.5), PD ($n=11$; age 71.4 ± 6.4), PDD ($n=6$; age 70.8 ± 4.7), DLB ($n=6$; age 68.0 ± 8.6) and normal controls (NC; $n=14$; age 69.0 ± 7.5) subjects underwent AChE [11C]-methyl-4-piperidinyl propionate (PMP) PET imaging. PPN–Thal PET data were analyzed using the Nagatsuka method. There were no significant differences in mean age between the groups ($F=1.86$, $p=0.134$). Kruskal–Wallis testing demonstrated a significant group effect for PPN–Thal AChE hydrolysis rates ($F=9.62$, $p<0.0001$). Compared to NC, reduced thalamic $k3$ hydrolysis rate was noted in subjects with PDD (−19.8%; AChE $k3$ hydrolysis rates $0.1072\pm0.0143\ \text{min}^{-1}$), DLB (−17.4%; $0.1103\pm0.0112\ \text{min}^{-1}$) and PD (−12.8%; $0.1165\pm0.0114\ \text{min}^{-1}$). Each of these 3 subgroups was statistically different from AD subjects (−0.7%; $0.1326\pm0.0095\ \text{min}^{-1}$) who showed relatively spared thalamic $k3$ hydrolysis rates which were comparable to NC ($0.1336\pm0.0142\ \text{min}^{-1}$). Thalamic cholinergic denervation is present in PD, PDD, and DLB but not in AD. Neurodegenerative involvement of thalamic cholinergic afferent projections may contribute to disease-specific motor and cognitive abnormalities.

1. Introduction

Cortical cholinergic denervation is a well-established pathological hallmark of Alzheimer disease (AD) [7]. The two principle cholinergic projection systems of the brain include the basal forebrain system, in particular the nucleus basalis of Meynert (nBM), which supplies cholinergic projections throughout the cerebral cortex and the pontine projection system, including the pedunculopontine nucleus (PPN) and the lateral dorsal tegmental nucleus (LDTN), both of which provide cholinergic innervation to various subcortical structures including the basal ganglia, thalamus, brainstem and rostral spinal cord [10,20]. While loss of nBM cholinergic neurons is a classic feature of feature of AD [26], less is known about the integrity of the pontine cholinergic projection system and its role in the pathogenesis of AD.

Abbreviations: PPN, pedunculopontine nucleus; LDTC, laterodorsal tegmental complex; PET, positron emission tomography; [11C]PMP, AChE [11C]-methyl-4-piperidinyl propionate; AD, Alzheimer disease; PD, Parkinson disease; PDD, Parkinson disease with dementia; DLB, dementia with Lewy bodies; NC, normal control.

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Table 1
Demographic information.

	AD (n = 13)	PD (n = 11)	PDD (n = 6)	DLB (n = 6)	NC (n = 14)
Age (SD)	75.4 (5.5)	71.4 (6.4)	70.8 (4.7)	68.0 (8.6)	69.0 (7.5)
MMSE (SD)	22.1 (5.0)	27.2 (2.6)	23.8 (2.6)	21.3 (6.7)	29.0 (1.6)
Gender (F/M)	(8/4)	(0/11)	(0/6)	(1/5)	(4/10)

MMSE, Mini-mental State Examination; SD, Standard Deviation; AD, Alzheimer disease; PD, Parkinson disease; PDD, Parkinson disease with dementia; DLB, dementia with Lewy bodies.

Though cortical cholinergic changes are recognized as a universal hallmark of late-stage AD, we have previously reported in vivo imaging findings suggesting that cortical cholinergic deficits in mild to moderate AD are less robust in comparison to those seen in Parkinson disease (PD) with dementia (PDD) of comparable severity of dementia [4]. Interestingly, thalamic cholinergic changes have also been described in PD without dementia and may associate with a propensity for falls and REM sleep behavior disorder [5,15]. As the presence of REM sleep behavior disorder and falls is much more common in PD than in AD, it is possible that clinical phenotypic differences between these neurodegenerative disorders may reflect differences in the integrity of the cholinergic system.

In vivo [^{11}C]-methyl-4-piperidinyl propionate (PMP) positron emission tomography (PET) imaging assessment of acetylcholinesterase (AChE) activity in the human brain is a reliable marker for cholinergic terminal integrity [24] and also allows the differential assessment of cortical and subcortical (PPN–Thal) cholinergic systems in vivo. We performed [^{11}C]-PMP PET imaging in subjects with AD and various alpha-synuclein-related disorders (PD, PDD, and dementia with Lewy bodies – DLB) to assess the possible differential role of the pontine cholinergic projection system in these neurodegenerative diseases. We hypothesized that thalamic cholinergic denervation is present in these parkinsonian disorders but not in AD.

2. Methods

2.1. Subjects

This study involved 50 subjects: 13 with AD, 11 with PD, 6 with PDD, 6 with DLB, and 14 normal controls (NC). Results of the cortical AChE data from these subjects have been published previously [4]. There were no significant differences in mean (SD) age among the groups (Table 1): those with AD, 75.4 (5.5) years; those with PD, 71.4 (6.4) years; those with PDD, 70.8 (4.7) years; those with DLB, 68.0 (8.6) and NCs, 69.0 (7.5) years; $F = 1.86$, $p = 0.134$).

Mini-mental State Examination (MMSE) scores (mean [SD]) were decreased in the groups with dementia with those with AD being 22.1 (5.0); those with PD, 27.2 (2.6); those with PDD, 23.8 (2.6); those with DLB 21.3 (6.7); and NCs, 29.0 (1.6); ($F = 8.15$, $p < 0.001$) but the scores were not significantly different between the AD group and PDD/DLB-affected groups ($t = -0.25$, $p = 0.80$). MMSE scores were not significantly different between those who had PDD and those who had DLB (mean [SD], 23.8 [2.6] and 21.3 [6.6], respectively; $t = 0.86$, $p = 0.41$). Gender distribution was different among groups: AD (8 women, 4 men); PD (0 women, 11 men); PDD (0 women, 6 men); DLB (1 woman, 5 men); NC (4 women, 10 men). The overrepresentation of males in our cohort may reflect both the increased prevalence of Parkinson disease amongst men [3] as well as the relatively male-predominant gender demographics of subjects recruited from the Veteran Affairs Healthcare system. However, previous AChE PET studies in NC did not find AChE-activity gender differences in either cortical or thalamic regions of interest [16].

AD subjects were diagnosed using the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) criteria [2,18]. PDD was diagnosed in patients having a history of idiopathic PD with incident dementia. DLB was clinically diagnosed following the Consortium on dementia with Lewy bodies' criteria [17]. No subjects were taking anticholinergic or cholinesterase inhibitor drugs. Subjects with PD, PDD, and DLB were taking a variable combination of carbidopa-levodopa, selegiline hydrochloride, or dopamine agonists. Dopaminergic medications were withheld for at least 12–18 h (overnight withdrawal) prior to PET imaging the next morning. All NC subjects had a normal neurological examination at the time of the study. This study was approved by the institutional review board and informed consent was obtained for all subjects.

2.2. AChE PET and magnetic resonance imaging

The [^{11}C]PMP radioligand is an acetylcholine analogue that serves as a selective substrate for AChE hydrolysis [11]. The hydrolyzed radioligand becomes trapped as a hydrophilic product locally in the brain following the AChE biodistribution. The [^{11}C]PMP was prepared using a previously described method [25]. Dynamic PET scanning was performed for 80 min following a bolus intravenous injection of 15 mCi (555 MBq) of [^{11}C]PMP. Sequential emission scans were obtained in 3-dimensional imaging mode using an emission computed axial tomograph (ECAT HR+; CTI PET Systems, Knoxville, Tenn), which acquires 63 transaxial slices (slice thickness, 2.4 mm with an in-plane resolution of 4.1 mm). A thermoplastic mask was made for each subject to minimize head movement. The PET emission data were corrected for attenuation, scatter, and radioactive decay.

A volumetric spoiled-echo gradient recall MRI was collected for each subject using a 1.5-T scanner (Signa; GE Medical Systems, Milwaukee, WI). The MRI data were cropped in preparation for alignment with the PET data using AnalyzeAVW software (Biomedical Imaging Resource; Mayo Foundation, Rochester, MN).

2.3. Data analysis

All dynamic PET image frames were spatially co-registered within subjects with a rigid-body transformation to reduce the

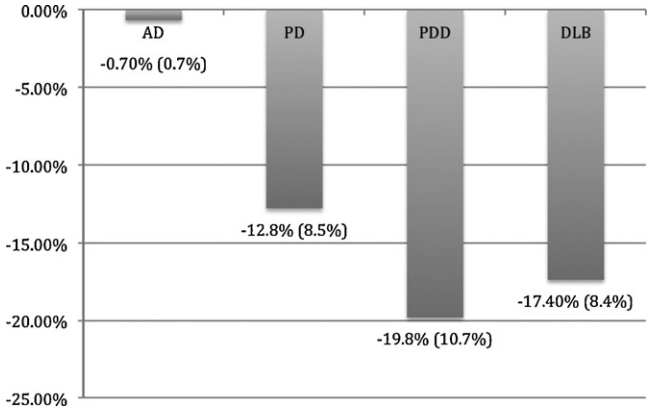

Fig. 1. Relative (% difference) subcortical cholinergic denervation in Alzheimer disease and alpha-synucleinopathies compared to healthy controls.