123I-iodobenzovesamicol  SPECT Imaging of Cholinergic Systems in Dementia with Lewy Bodies.

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ABSTRACT

Cholinergic alterations in Dementia with Lewy bodies (DLB) are widely documented in post mortem studies whereas in vivo studies are sparse, particularly at subcortical level. We used $^{123}$I-iodobenzovesamicol, a single Photon Emission Computed Tomography (SPECT) radiotracer of the Vesicular Acetylcholine Transporter (VACHT), to evaluate in vivo in DLB the integrity of the three main cholinergic pathways: the Ch1 (septo-hippocampal), the Ch4 (innominato-cortical) and the Ch5 (ponto-thalamic) cholinergic pathways, as well as the striatal cholinergic interneurons. Secondarily, the involvement of the cholinergic system in cognitive and neuropsychiatric disorders of DLB patients was assessed. **Methods:** Twelve healthy volunteers (age = 72±6.25 years) and 11 DLB patients (age = 76±10.50 years) underwent a dynamic $^{123}$I-iodobenzovesamicol SPECT scan and a magnetic resonance imaging (MRI) scan. MR images were automatically segmented, providing the volumes of several regions of interest (ROIs), including striatum and cholinergic terminals in Ch1 (hippocampus), Ch4 (cortical lobes) and Ch5 (thalamus). For each ROI and each subject, a pharmacokinetic modeling led to the calculation of $^{123}$I-iodobenzovesamicol to VACHT nondisplaceable binding potential (BP$_{ND}$) value. A neuropsychological evaluation of participants was performed, using the MMSE, Grober and Buchske, Isaac Set test, visual Discrimination and Wechsler tests. Cognitive fluctuations and apathy were assessed with the Walker and the Neuropsychiatric Inventory scales respectively. **Results:** Compared to healthy subjects, BP$_{ND}$ values for DLB were significantly decreased in the Ch4 terminal regions of the anterior cingulate, superior and inferior parietal cortices ($P=0.0006, 0.0015, \text{ and } 0.0023$ respectively), in the Ch5 projecting region of thalamus ($P=0.0003$) and in the striatum
All of the neuropsychological test scores were significantly lower in DLB patients than in healthy subjects. Four DLB patients with apathy and 4 DLB patients without apathy were identified. In the anterior cingulate cortex, BPND values were significantly decreased in patients with apathy (p=0.004) and unchanged in patients without apathy compared to healthy subjects. **Conclusion:** Our results confirm the existence of cholinergic alterations in DLB, reaching both cortical and subcortical levels including the Ch5 pathway and the striatum. The alteration of the cholinergic transmission in the anterior cingulate cortex could be closely associated with the development of apathy.

**Key words:** $^{123}$I-iodobenzovesamicol; SPECT; cholinergic pathways; Dementia with Lewy Bodies; apathy
INTRODUCTION

Dementia with Lewy bodies (DLB) is claimed to be the second most common type of neurodegenerative dementia after Alzheimer’s disease (AD) and it represents 15 percents of degenerative dementias (1). Central feature in DLB is a progressive cognitive decline, associated with several criteria including core features of fluctuating cognition, visual hallucinations and spontaneous parkinsonism as well as suggestive features such as sleep disturbances (2). Only two core features or one core and one suggestive feature are sufficient to diagnose a probable DLB, resulting in a large variability of the clinical expression of DLB. Thus, clinical subtypes in DLB may reflect an heterogeneity in neurochemical alteration. Indeed, besides dopaminergic alteration (3), cholinergic systems were shown to be impaired in DLB and the benefit of cholinesterase inhibitor drugs for neuropsychiatric and cognitive symptoms confirms the cholinergic hypothesis in DLB (2). The status of the pre-synaptic cholinergic system in DLB is well documented by post-mortem studies, showing a profound and widespread reduction in choline acetyltransferase activity (4,5). However, in vivo studies are sparse in DLB, showing a decrease of acetylcholine esterase (AChE) activity in cortical regions (6-8) while the integrity of subcortical cholinergic systems remains poorly documented. Indeed, to date, only one Positron Emission Tomography (PET) study explored the cholinergic innervation of thalamus in DLB patients (9) and the integrity of striatal cholinergic interneurons was never assessed, probably because the AChE radiotracers classically used in the PET studies are reported to be ineffective to assess the striatal cholinergic activity (9). $^{123}$I-iodobenzovesamicol is a single Photon Emission Computed Tomography (SPECT) radiotracer binding selectively to a presynaptic cholinergic
marker, the Vesicular Acetylcholine Transporter (VACHT), serving as an in vivo maker of presynaptic cholinergic terminal density. $^{123}$I-iodobenzovesamicol proved to be a successful radiotracer in the evaluation of both cortical and sub-cortical cholinergic status in vivo in various neurological disorders (10-13).

Therefore, in order to determine in vivo in DLB if there is a differential cholinergic alteration between cortical and subcortical levels, our objective was to evaluate the integrity of the three main cholinergic pathways – i.e the Ch1 (septo-hippocampal), the Ch4 (innominato-cortical) and the Ch5 (ponto-thalamic) pathways – as well as striatal cholinergic interneurons, in DLB patients comparatively to normal age-matched control subjects. Secondary, a patient subgroup based study aimed at evaluating the involvement of the cholinergic system in cognitive and neuropsychiatric disorders of DLB patients.

**MATERIALS AND METHODS**

**Subjects**

The participants consisted of 23 subjects: 12 healthy volunteers (median age = 72 years; interquartile range = 6.25 years) without neuropsychiatric disorder, included based on a screening interview by an experienced senior neuropsychologist and 11 patients (median age = 76 years; interquartile range = 10.50 years), recruited according to the revised international consensus criteria for the clinical diagnosis of DLB (2). The probable DLB diagnosis was based on at least one core plus one suggestive or 2 core features while one core or suggestive feature was sufficient for a possible DLB diagnosis. For grading the cognitive state of participants, all the subjects were
evaluated with neuropsychological tests including the Mini-Mental State Examination (14), Grober and Buschke test (15), Benton test (16), Visual discrimination test, Isaac Set Test (17) and Wechsler Adult Intelligence Scale (18). Cognitive fluctuations were assessed with the Walker scale (19) while apathy was assessed using the Neuropsychiatric Inventory (NPI) scale (20). For technical reasons, 3 patients were not able to undergo the Walker and NPI examinations and one patient could not undergo the Wechsler test.

The study was initiated after protocol approval by the Institutional Human Ethics Committee (registration number 2009/08) and radioactive drug approval by the National Health Product Safety Agency. After being presented with the basic design of the study and informed that they could withdraw from the investigation at any time, all subjects signed a written informed consent.

Radiochemistry

$^{123}$I-iodobenzovesamicol was prepared by oxidative radioiodination of the respective (-)-5-tributyltin precursor as the (-)-5-position isomer of iodobenzovesamicol (levogyre form) exhibits the greatest affinity and selectivity for the VACHT (21). Synthesis and quality control were achieved as previously described (12). Briefly, after radio-iodination, $^{123}$I-iodobenzovesamicol was purified by high-pressure liquid chromatography and Sep-Pack C18 classic cartridge (Waters) and filtered, leading to 10 ml of sterile solution of $^{123}$I-iodobenzovesamicol. Before injection, the solution was assessed to be pyrogen-free using the Endosafe-PTS portable test system (Charles River Laboratories).
Scanning Protocol

Anatomic MR imaging. For anatomic colocalization with the SPECT data, subjects underwent a 3-dimensional T1-weighted Magnetic resonance (MR) imaging sequence (repetition time/echo time, 7.1/3.5 ms; 8° flip angle; field of view, 256 × 256 mm to cover the whole brain yielding 228 slices [1-mm slice thickness; 1-mm³ isotropic voxel size] using a 1.5-T MR imaging system (Philips, Eindhoven, Holland).

SPECT-CT imaging. SPECT imaging was performed on a SPECT/CT SYMBIA T2 camera (Siemens, Erlangen, Germany) equipped with low-energy thin-section collimators. Participants were orally given 400mg of potassium perchlorate 30 minutes before and 24 h after imaging. After a mean intravenous injection of 227.8 ± 36.8 MBq of ¹²³I-iodobenzovesamicol, the dynamic SPECT images were acquired over 8 h at six different times: 5 frames of 6 min starting at the time of injection, 2 frames of 15 min frames at 2, 3, 5 and 8 h after injection (64 projections with a matrix of 64 X 64 over 360°). Between each of the first 5 acquisitions, the participants were allowed to rest outside of the gantry.

SPECT images were reconstructed on a 64×64 matrix by using a Flash (Siemens) 3-dimensional iterative reconstruction (4 iterations, 8 subsets) and a voxel size of 6.8 × 6.8 × 6.8 mm. Attenuation correction was based on the CT image, and decay correction and normalization for frame duration were also performed. All the frames were rigidly registered together and with the CT image, to ensure the patient's
brain was in the exact same position in all the images during the creation of the dynamic SPECT dataset.

**SPECT Data Processing**

_SPECT Data Registration to MR Images._ For each subject, the participants’ CT and MR images were rigidly coregistered and the transformation parameters were subsequently applied to the SPECT dataset, providing a 4-dimensional dynamic SPECT image registered to the MR image.

Partial Volume Effect Correction of the Dynamic SPECT Dataset. The MR-coregistered SPECT image was corrected for partial volume effect using the Müllër MR based method (22), implemented in PMOD software (version 3.3; PMOD Technologies). For each subject, the MR image was automatically segmented into gray matter, white matter and cerebrospinal fluid probability maps and the partial-volume correction procedure subsequently proceeded, correcting the SPECT data for gray matter spill-out and white matter spill-in.

**Time-Activity Curve Calculation**

For each participant, the MR-registered and partial-volume effect-corrected dynamic SPECT data was used for derivation of regional time-activity curves. For each subject, the MR image was automatically segmented using Freesurfer software (23), providing the volumes and labels of 12 gray matter regions of interest (ROIs), including striatum, thalamus and various cortical structures: prefrontal cortex, motor and premotor
cortices, occipital cortex, superior parietal cortex, inferior parietal cortex, temporal cortex, anterior cingulate cortex, posterior cingulate cortex, hippocampus and cerebellar hemispheres. The PMOD software was used to subsequently apply this gray matter template to each frame of the registered and partial-volume effect-corrected dynamic SPECT data to obtain average decay-corrected regional activities, which were plotted against time to derive regional time-activity curves.

**Quantification of ¹²³I-Iodobenzovesamicol SPECT Data**

The reference method for noninvasive quantification of ¹²³I-iodobenzovesamicol data was used (24), *i.e.* a complete multilinear reference tissue model 2 pharmacokinetic analysis (25), using the cerebellar hemispheres as reference region (26). This method allowed us to calculate ¹²³I-iodobenzovesamicol to VACHT nondisplaceable binding potential (BPND) values for each participant and each ROI. Indeed, the BPND is a parameter whose value is proportional to the density of receptor sites, in this case, VACHT binding sites.

**Statistical Analysis**

Mann-Whitney *U* tests were used to test differences in BPND values in each ROI between healthy subjects and DLB patients, as well as a Kruskal-Wallis one way analysis of variance followed by a Mann-Whitney *U* test to assess differences between healthy subjects and DLB patients subgroups. The results of the present study included corrections for multiple comparisons: with 11 regions examined, a conservative multiple
comparison by using Bonferroni adjustment required a significance level of $P < 0.0045$. Statistical analyses were performed using Statistica software (version 9; Statsoft).

RESULTS

Subject Characteristics

In Table 1, the male-female ratio was higher in patients with DLB (7/4) than in controls (3/9). Of a total of 8 DLB patients evaluated with the NPI scale, a subgroup of 4 patients with apathy was identified (NPI score value different from 0) as well as another subgroup of 4 patients without apathy (NPI score value = 0). 8/8 patients evaluated with the Walker examination exhibited a score different from 0 so that the identification of patients subgroups with and without cognitive fluctuations was not possible. In Table 2, DLB patients were age matched with healthy subjects and the MMSE, Grober and Buchske, Isaac Set test, Benton, visual discrimination and Wechsler scores were significantly lower in DLB patients than in healthy subjects ($P = 0.00009, 0.0003, 0.00009, 0.00006, 0.0053$ and $0.00009$ respectively).

Cholinergic Pathways Integrity Assessment

The $BP_{ND}$ results obtained in the Ch1, Ch4 and Ch5 pathways are presented in Table 3. In the Ch1 pathway, no significant differences in $BP_{ND}$ values were observed between patients with DLB and healthy subjects. On the contrary, in the Ch4 pathway, $BP_{ND}$ values for DLB were significantly decreased in the anterior cingulate cortex as well as in the superior and inferior parietal cortices ($P = 0.0006, 0.0015$, and $0.0023$ respectively).
compared to healthy subjects. BP_{ND} values for DLB were significantly decreased in the Ch5 projecting region of thalamus (P=0.0003) and in the striatum (P=0.0042), compared to healthy subjects. In the regions of interest demonstrating an alteration of cholinergic pathways in DLB, a graphic representation of BP_{ND} values obtained for patients with possible (n=2) and probable (n=9) DLB is presented in Figure 1, showing no observable difference between the two groups. For a healthy participant and a representative DLB patient, Figure 2 shows parametric images of simplified BP_{ND}, a parameter reflecting specific / non specific binding (26) calculated in striatum and thalamus from SPECT images obtained at 8 h after injection.

Healthy Subjects and DLB Subgroups Comparison

The statistical comparison of the control group, patients with apathy and patients without apathy in the anterior cingulate cortex and in the inferior parietal cortex is presented in Figure 3. A group effect was found only in the anterior cingulate cortex, with BP_{ND} values being significantly decreased in patients with apathy compared to healthy subjects (p=0.004) and unchanged in patients without apathy.

DISCUSSION

The main result of the present study is that along an impairment of the striatal cholinergic interneurons, the Ch4 (innominato-cortical) and the Ch5 (ponto-thalamic) pathways are altered in DLB, with a relative preservation of the Ch1 (septo-
hippocampal) pathway. In the anterior cingulate cortex, patients with apathy exhibit a significant cholinergic alteration compared to control participants.

At the subcortical level, with an impaired Ch5 pathway in the thalamus and altered cholinergic interneurons in the striatum, our results are in accordance with post-mortem studies that have shown a reduction of choline acetyl transferase activity in the thalamus (1) and the striatum (27). The present study confirms and complements previous in vivo PET studies as, to date, a thalamic cholinergic denervation has been found in only one small sample of 6 DLB patients (9). Besides, the critical role of the thalamus in DLB has been recently highlighted in a multimodal MR imaging study suggesting a close relationship between thalamic cholinergic imbalance and fluctuating cognition occurring in DLB (28). At subcortical level, our study could provide a differential diagnosis approach with other dementias such as AD and parkinsonian dementia, who share clinical features with DLB. Indeed, a thalamic cholinergic denervation was found to be present in parkinsonian dementia and DLB but not in AD (9). Thus, the evaluation of thalamic cholinergic innervation in itself does not allow to differentiate DLB from other degenerative dementias and in this regard, an additional assessment of the striatal cholinergic integrity may provide a valuable information. Indeed, until now, the striatal cholinergic innervation remained unexplored in vivo in DLB. Our $^{123}$I-iodobenzovesamicol study completes previous in vivo works by Kuhl et al. who used $^{123}$I-iodobenzovesamicol in AD and parkinsonian patients (13) and who found an unchanged striatal cholinergic status in both AD and parkinson’s patients with and without dementia. As dopamine and acetylcholine strongly interact together in the striatum, a differential alteration of the balance between acetylcholine and dopamine in the striatum may explain the differences observed between Kuhl’s parkinsonian patients
and the DLB patients included in this study. In each of these neurological disorders, a dual molecular imaging approach exploring both neurotransmitters in the striatum would allow to verify this hypothesis. Altogether, our results and Kuhl’s data show that in vivo, a striatal cholinergic alteration is found in DLB but not in AD and parkinsonian dementia, providing evidence that in vivo $^{123}$I-iodobenzovesamicol SPECT imaging might be a valuable tool to differentiate DLB from AD patients and Parkinson disease patients with dementia.

Our findings seem to clarify conflicting results from previous PET studies that assessed the integrity of cortical cholinergic innervation in DLB. Indeed one recent in vivo study showed a variable alteration in cortical AChE activity (29) while 3 others showed a widespread and profound reduction in cortical AChE activity (6-8), especially in the posterior regions of the parieto-occipital cortices. As they demonstrate the existence of a cholinergic damage in the superior and inferior parietal cortices, our results are in good agreement with these findings, excepted in the occipital regions, probably because of differences in tracers used. Indeed, from a physiological point of view, VACHT density is very low in the occipital cortex (24,26) making difficult a patient-vs-control comparison with $^{123}$I-iodobenzovesamicol in this structure. Furthermore, non-cholinergic (i.e. ChAT- or VACHT-negative) but AChE-rich neurons (i.e. chinoceptive neurons) are found in almost all parts of the brain (30), bringing another explanation to the more widespread cortical alterations found in previous PET studies compared to ours. The results of the present study are also congruent with data provided by SPECT perfusion imaging that revealed a perfusion deficit in the inferior parietal cortex of DLB patients, possibly underlying the visuospatial perception deficit met in DLB (31).
Additionally, a spatial congruence of deficit in AChE activity and \(^{18}\text{F}\)-Fluorodeoxyglucose (\(^{18}\text{F}\)-FDG) hypometabolism occurred in parieto-occipital brain regions of patients with DLB (6).

Our results extend prior data by revealing that a cholinergic neuronal loss occurs in the anterior cingulate cortex (ACC) of DLB patients. In this cortical structure, we find that patients with apathy exhibit a significant cholinergic alteration compared to control participants and a trend in lower BP values is observable in apathetic compared to non apathetic patients. The refusal of three individuals to pass the Walker- and NPI-examinations, apart from the fact that it decreases the number of data, could be a selection bias in the sense that refusal could reflect a particular personality profile possibly related to the degree of pathological damage. Although they would need to be confirmed on a larger sample of patients, our findings may provide evidence that alteration of the cholinergic transmission in the ACC could be closely associated with the development of apathy. From a functional point of view, cholinergic neurons of the Nucleus Basalis of Meynert provide the major source of cortical cholinergic innervation through the Ch4 pathway and exhibit a strong positive connectivity with a network of brain regions that orchestrate goal-directed behavior, particularly in the ACC (32). The possible role of acetylcholine in apathy is also documented in animal and pharmacological studies, as the positive effect of cholinergic drugs on apathy has been reported in animal models of apathy (33). In DLB, apathy, hallucinations and sleep disorders are some of the most frequently cited treatment-responsive symptoms after treatment with cholinesterase inhibitor drugs (1,34). Besides, the ACC has extensive projections to the amygdala, ventral striatum and nucleus accumbens and this circuit is
important for goal-directed and motivated behavior (32,35). Other neuroimaging studies, including PET measures of $^{18}$F-FDG metabolism and structural brain changes on MRI, have also supported the role of ACC in apathy (32,36,37).

Some limitations merit consideration in this study. First, the low number of investigated patients did not allow us to significantly discriminate apathetic from non-apathetic patients in the anterior cingulate cortex with $^{123}$I-iodobenzovesamicol. Secondly, in the regions of interest presenting an alteration of cholinergic pathways in DLB, no difference in BP$_{ND}$ values was observed between patients with possible and probable DLB, suggesting that the cholinergic system is similarly affected in all patients, irrespective of the course of the disease. However, in other brain areas where no significant cholinergic alteration was found, we cannot exclude that the presence of two patients with possible DLB could mask cholinergic deficits. Finally, although a fully automated and quantitative method was used, the low resolution of SPECT imaging can represent a limitation to studying thin gray matter areas such as the cortical structures. In this regard, $^{18}$F-fluoroethoxybenzovesamicol (38) could be a very useful PET radioligand to explore cholinergic integrity in larger groups of DLB patients.

CONCLUSION

Altogether, our in vivo results support a general cholinergic neuronal loss in DLB, reaching both cortical and subcortical levels, with the exception of the Ch1 pathway. In the striatum of patients, our results confirm previous post-mortem studies and show for
the first time in vivo the alteration of cholinergic interneurons in DLB. By juxtaposing our results with those of Kuhl et al. (13), ¹²³I-iodobenzovesamicol appear to be a valuable tool to differentiate DLB from both AD and parkinsonian dementia. As the reciprocal balance of dopamine and acetylcholine is well known in the striatum and given the parallel alteration of the dopaminergic systems in this pathology, it would be interesting to explore more thoroughly and subsequently in vivo in DLB patients both cholinergic and dopaminergic neurotransmission, for a better understanding of the relationship between these two neurotransmitters in this pathology.

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BIBLIOGRAPHY


FIGURE LEGENDS

FIGURE 1.

Graphic representation of \( BP_{ND} \) values obtained for patients with possible (n=2) and probable (n=9) DLB in the regions of interest showing an alteration of cholinergic pathways in DLB.
FIGURE 2.

Representative simplified $BP_{ND}$ parametric images of a healthy participant and patient with DLB, acquired at 8 h after injection (transverse view). Simplified $BP_{ND}$ calculation, i.e. specific / non specific binding in striatum and thalamus, has been extracted from SPECT images by calculating (region of interest activity concentration (i.e. total binding) — reference region activity concentration (i.e. non specific binding) / reference region activity concentration) and is presented overlaid with the MR image of each subject. Solid white arrows label the striatum and dotted white arrows label the thalamus. For patient with DLB, specific / non specific binding is visually lower in striatum and thalamus than for healthy participant.
FIGURE 3.

BPND values calculated in the anterior cingulate cortex and in the inferior parietal cortex for healthy subjects and apathetic and non-apathetic patients. *$P = 0.004$ versus healthy subjects. **$P = 0.0008$ versus healthy subjects.
TABLE 1

Patient demographics, Walker and NPI scores.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Type</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Walker Score / 22</th>
<th>NPI Apathy Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Possible DLB</td>
<td>68</td>
<td>F</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Possible DLB</td>
<td>81</td>
<td>M</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Probable DLB</td>
<td>78</td>
<td>F</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>Probable DLB</td>
<td>70</td>
<td>M</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Probable DLB</td>
<td>76</td>
<td>M</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Probable DLB</td>
<td>65</td>
<td>M</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Probable DLB</td>
<td>70</td>
<td>M</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Probable DLB</td>
<td>61</td>
<td>M</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Probable DLB</td>
<td>81</td>
<td>F</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>Possible DLB</td>
<td>76</td>
<td>F</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Probable DLB</td>
<td>81</td>
<td>M</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

NPI = Neuropsychiatric Inventory.
**TABLE 2**

Statistical comparison of age and neuropsychological performances.

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>DLB patients</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>age</strong></td>
<td>72 (6.25)</td>
<td>76 (10.50)</td>
<td>0.3376</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>29.50 (1.25)</td>
<td>21 (6.50)</td>
<td>0.00009*</td>
</tr>
<tr>
<td><strong>Grober and Buchske</strong></td>
<td>47.5 (2.25)</td>
<td>32 (9)</td>
<td>0.0003*</td>
</tr>
<tr>
<td><strong>Isaac Set Test</strong></td>
<td>76.50 (14.50)</td>
<td>33 (14.50)</td>
<td>0.00009*</td>
</tr>
<tr>
<td><strong>Benton</strong></td>
<td>14 (1.75)</td>
<td>9 (5)</td>
<td>0.00006*</td>
</tr>
<tr>
<td><strong>Visual discrimination</strong></td>
<td>10 (0)</td>
<td>9 (5.5)</td>
<td>0.0053*</td>
</tr>
<tr>
<td><strong>Wechsler codes</strong></td>
<td>43.50 (18.50)</td>
<td>10.50 (13.25)</td>
<td>0.00009*</td>
</tr>
</tbody>
</table>

Data are median with interquartile range in parentheses. *Significantly reduced versus healthy subjects (Mann-Whitney, \( P<0.05 \)). MMSE = Mini-Mental State Examination.
### TABLE 3

BPND values in each ROI.

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Healthy subjects (n=12)</th>
<th>DLB patients (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ch1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.15 (0.04)</td>
<td>0.10 (0.08)</td>
<td>0.2954</td>
</tr>
<tr>
<td>Ch4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate cortex (BA 24, 32)</td>
<td>0.17 (0.09)</td>
<td>0.07 (0.10)</td>
<td>0.0006*</td>
</tr>
<tr>
<td>Posterior cingulate cortex (BA 23)</td>
<td>0.15 (0.07)</td>
<td>0.06 (0.14)</td>
<td>0.0074</td>
</tr>
<tr>
<td>Prefrontal cortex (BA 11, 12, 9, 44, 45, 46, 47)</td>
<td>0.19 (0.08)</td>
<td>0.17 (0.13)</td>
<td>0.8777</td>
</tr>
<tr>
<td>Motor and pre-motor cortices (BA 4, 6, 8)</td>
<td>0.14 (0.07)</td>
<td>0.10 (0.11)</td>
<td>0.0110</td>
</tr>
<tr>
<td>Occipital cortex (BA 18)</td>
<td>0.05 (0.09)</td>
<td>0.02 (0.06)</td>
<td>0.1962</td>
</tr>
<tr>
<td>Superior parietal cortex (BA 1, 2, 3, 5, 7)</td>
<td>0.09 (0.04)</td>
<td>0.02 (0.05)</td>
<td>0.0015*</td>
</tr>
<tr>
<td>Inferior parietal cortex (BA 39, 40, 43)</td>
<td>0.17 (0.06)</td>
<td>0.07 (0.12)</td>
<td>0.0023*</td>
</tr>
<tr>
<td>Temporal cortex (BA 20, 21, 22, 41, 42)</td>
<td>0.08 (0.07)</td>
<td>0.05 (0.06)</td>
<td>0.0150</td>
</tr>
<tr>
<td>Ch5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.45 (0.09)</td>
<td>0.14 (0.13)</td>
<td>0.0003*</td>
</tr>
<tr>
<td>striatum</td>
<td>2.59 (0.80)</td>
<td>1.43 (0.85)</td>
<td>0.0042*</td>
</tr>
</tbody>
</table>

Data are median, with interquartile range in parentheses. *Significantly reduced BPND versus that of healthy subjects (Mann-Whitney, P<0.0045).
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