A Preliminary Fluorodeoxyglucose Positron Emission Tomography Study in Healthy Adults Reporting Dream-Enactment Behavior

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Study Objectives: To test the hypothesis that healthy adults reporting dream-enactment behavior (DEB+) have reduced cerebral metabolic rate for glucose (CMRgl) in regions preferentially affected in patients with dementia with Lewy bodies (DLB).

Design: Automated brain-mapping algorithms were used to compare regional fluorodeoxyglucose (FDG) positron emission tomography (PET) measurements from previously evaluated DEB cases and controls.

Setting: Tertiary-care academic medical centers.

Participants: Seventeen cognitively normal patients with DEB+ and 17 control subjects (DEB-) who were individually matched for age (59 ± 11 years), education level (16 ± 4 years), sex (67% women), body mass index (26 ± 4.8 kg/m²), first-degree relative with dementia (85%), and proportion of apolipoprotein E (APOE) e4 carriers (13 e4 carriers, 4 noncarriers).

Interventions: FDG-PET.

Measurements and Results: DEB was associated with significantly lower CMRgl in several brain regions known to be preferentially affected in both DLB and Alzheimer disease (parietal, temporal, and posterior cingulate cortices) and in several other regions, including the anterior cingulate cortex (p < .001, uncorrected for multiple comparisons). The DEB-associated CMRgl reductions were significantly greater in the APOE e4 noncarriers than in the carriers.

Conclusions: These preliminary findings suggest that cognitively normal persons with DEB have reduced CMRgl in brain regions known to be metabolically affected by DLB, supporting further study of DEB as a possible risk factor for the development of DLB.

Keywords: Dementia with Lewy bodies, REM sleep behavior disorder, preclinical dementia

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INTRODUCTION

DEMENTIA WITH LEWY BODIES (DLB) IS A SYNUCLEINOPTHY THAT INVOLVES BRAINSTEM CATACHOLAMINERGIC NUCLEI, THE AMYGDALE, ENTORHINAL cortex, and neocortex. The characteristic cognitive profile of DLB includes impaired learning and memory, psychomotor slowing, constructional apraxia, and a more profound visual spatial impairment than in similarly staged patients with Alzheimer disease (AD). The distinction between DLB and AD is not complete, however, because more than three quarters of all patients with DLB have concomitant neuropathologic features of AD. The presence of dementia, DLB is clinically characterized by parkinsonism, visual hallucinations, and rapid eye movement (REM) sleep behavior disorder (RBD). RBD is frequent among patients with DLB, as well as with other synucleinopathies, but very rare or nonexistent among the cerebral amyloidopathies and tauopathies. The estimated prevalence of RBD among patients with DLB is 50%, among patients with Parkinson disease is 58%, and among patients with multiple systems atrophy is 68% to 95%. Among patients initially diagnosed with idiopathic RBD, 65% or more may go on to develop a synucleinopathy.

Dream-enactment behavior (DEB) is the defining clinical feature of RBD. Patients are reported by their bed partners to yell, scream, speak clearly, or move their arms and legs in ways that seem to mimic dream imagery and may fall or otherwise get out of bed as part of their DEB. Injuries can occur to the patient and bed partner as the result of DEB. Symptoms of DEB can be described, and RBD can therefore be suspected, simply on the basis of a proper medical history (although polysomnography adds further sensitivity and specificity by demonstrating REM sleep without muscle atonia). Because of its association with DLB, a history of DEB in a patient with dementia can be helpful in diagnosing DLB.

With the aging of our population, preventing degenerative dementia remains a vital goal. Although effective preventative therapies are lacking, early intervention at a presymptomatic stage of disease with even minimally effective agents may delay the onset and progression of dementia. Apolipoprotein E (APOE) e4 is a major risk factor for AD. Fluorodeoxyglucose (FDG) positron emission tomography (PET) studies of asymptomatic carriers of APOE e4 (and other genes) reveal reduced metabolism (CMRgl) in the same cortical regions that are found to be hypometabolic in patients with AD, thus permitting identification of the earliest possible stages of AD and providing a potential foundation for the design of cost-effective primary prevention trials. Could DEB be used in a similar way to identify the earliest possible stages of DLB?
DLB results in abnormally low measurements of cerebral metabolic rate for glucose (CMRgl) in the same regions of parietal, temporal, and posterior cingulate cortices as in patients with AD (although reductions may be more severe in DLB than in AD) and in an additional region of the occipital cortex. By studying neuropsychiatically healthy adults whose only symptom is DEB, we wanted to explore the possibility that DEB could be predicting the future development of dementia in patients at risk for DLB. In this preliminary study, we used PET data and bed-partner reports of DEB from some of the same cognitively normal subjects in our ongoing study to test the hypothesis that individuals with DEB, when compared with those without DEB, will have lower CMRgl in the same regions as patients with DLB, specifically including bilateral parietal, temporal, occipital, and posterior cingulate cortices.

METHODS

Study Population

We have been conducting a longitudinal study of cognitively normal Maricopa County residents with 2 copies, 1 copy, and no copies of the APOE e4 allele who undergo biannual brain imaging (FDG-PET and magnetic resonance imaging [MRI]) and neuropsychological testing. Participants were recruited using newspaper advertisements, were 47 to 68 years of age at entry, and reported a first-degree relative with dementia. They understood they would receive no information about their APOE genotype, provided written informed consent, and were studied under guidelines approved by the Mayo Clinic and Banner Good Samaritan Medical Center Institutional Review Boards. APOE genotypes were performed using a polymerase chain reaction-based assay. Each participant scored at least 27 on the Folstein Mini-Mental State Examination (and at least 1 out of 3 on the recall subtest) and scored no greater than 10 on the Hamilton Depression Rating Scale (HAM-D). None had a current psychiatric disorder based on the Structured Psychiatric Interview for Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised. There were no potentially confounding medical or neurologic problems (such as prior stroke, traumatic brain injury, or Parkinsonism). None met the published criteria for age-associated memory impairment, mild cognitive impairment, AD or any other form of dementia or major depressive disorder. The participants also completed a sleep disorders questionnaire developed by the Mayo Clinic Sleep Disorders Center that includes questions regarding DEB:

i. Have you ever been told you make unusual movements such as talking, swinging arms about, acting out dreams, etc. during sleep? If yes, how frequently? What age did they begin? Please describe.

ii. Have you ever caused injury to yourself or others when you were asleep? If yes, how frequently? Please describe.

The questionnaire also asks about other parasomnias such as somnambulism and the estimated duration of symptoms. The instructions for completing this questionnaire explicitly request bed-partner completion or confirmation of the questions. Only individuals endorsing DEB within the preceding 10 years were selected for inclusion. A remote history of somnambulism was not considered exclusionary.

The present study was restricted to persons who endorsed DEB by responding affirmatively to the 2 DEB questions on the sleep questionnaire (DEB+) and persons who denied DEB (all parts of both questions were denied) and other parasomnias who were individually matched to the DEB+ cases by age (within 3 years), education level (within 2 years), sex, and specific APOE genotype. Seventeen individuals who were included in our cohort endorsed DEB, completed neuropsychological testing, and brain-imaging procedures: 13 were APOE e4 carriers, and 4 were e4 noncarriers. The DEB+ and individually matched DEB- groups did not differ in their demographic or clinical characteristics (Table 1). Among those 12 cases endorsing DEB, DEB included yelling and screaming and/or limb movement in all cases (explicit added comment of bed-partner confirmation offered in 8, no additional comment in 4). Of these, 9 specifically indicated DEB occurred within the context of a nightmare (the remaining 3 did not specify). Mean age of onset of DEB was 62.3 (45-74) years, and frequency ranged from daily to annually (daily in 1, weekly in 4, monthly in 7, annually in 1, and not further specified in 4). DEB was accompanied by hitting the bed partner, getting out of bed, or falling out of bed in 4 individuals. Three reported a past history of somnambulism. No details of the DEB were provided in 5 cases (1 APOE e4 noncarrier, 3 APOE e3/4, and 1 APOE e4/4).

Brain Imaging

Volumetric T1-weighted MRI and FDG-PET were performed as previously described. Immediately prior to the PET session, MRI was performed on a 1.5 Tesla LX system (General Electric, Milwaukee, WI). T1-weighted sagittal and coronal images of the brain were used to minimize tilt and optimize axial sampling in the PET scanner. A T1-weighted, 3-dimensional, volume spoiled gradient recalled acquisition in the steady state pulse sequence (SPGR, TE = 5 milliseconds, TR = 33 milliseconds, angle = 30°, NEX = 1, FOV = 24 cm, imaging matrix = 256 × 192) was used to acquire 128 contiguous 1.5-mm horizontal brain sections. A double-spin echo sequence (DSE), including T2-weighted and proton density images, was used to acquire 50 contiguous 3.0-mm horizontal slices (TE1 = 20, TE2 = 80, TR = 2500, FOV = 24 cm, imaging matrix = 256 × 192). PET was performed with the 951/31 ECAT scanner (Siemens, Knoxville, TN).

Subject preparation for PET included the insertion of a catheter in the left antecubital vein to permit radiotracer administration and sampling of venous radiotracer activity toward the end of the scan. A 15-minute transmission scan was performed using a source of (68) germanium/ (68) gallium to correct the subsequent

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Table 1—Demographics

<table>
<thead>
<tr>
<th>No.</th>
<th>DEB+</th>
<th>DEB-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.4 ± 7.3</td>
<td>59.2 ± 6.0</td>
<td>.33</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.1 ± 1.7</td>
<td>16.8 ± 2.7</td>
<td>.40</td>
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<tr>
<td>Women, %</td>
<td>52.9</td>
<td>52.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>25.2 ± 2.6</td>
<td>25.3 ± 4.6</td>
<td>.94</td>
</tr>
<tr>
<td>First-degree relative with dementia, %</td>
<td>76.5</td>
<td>94.1</td>
<td>.15</td>
</tr>
<tr>
<td>MMSE score</td>
<td>29.6 ± 0.8</td>
<td>29.6 ± 0.6</td>
<td>.81</td>
</tr>
<tr>
<td>Hamilton Depression Scale score</td>
<td>1.9 ± 1.8</td>
<td>1.9 ± 2.7</td>
<td>.94</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
<td>8.6 ± 4.8</td>
<td>6.5 ± 3.4</td>
<td>.14</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless otherwise indicated. DEB refers to dream-enactment behavior. MMSE, Folstein Mini Mental State Examination.
emission scan for radiation attenuation. Immediately thereafter, a 60-minute emission scan was performed using the intravenous injection of 10 mCi of $^{18}$F-FDG and a dynamic sequence consisting of one 10-second frame, ten 2-second frames, nine 10-second frames, four 30-second frames, a 1-minute frame, a 1.5-minute frame, a 3-minute frame, two 5-minute frames, a 10-minute frame, and a 30-minutes frame. Throughout the emission scan, the subject, who had fasted for at least 4 hours, lay quietly in a darkened room with his or her eyes closed and directed forward. The emission image was reconstructed utilizing a back projection method with measured attenuation correction and a 0.40-cycle per pixel Hanning filter, resulting in a final in-plane resolution of 10.5 mm full width half maximum. The dynamic FDG-PET image series was converted to quantitative measurements of CMRgl (mg per minute/100g) using the image-derived carotid-artery time-activity curve, venous activity samples at the end of the scan to correct for spillover and partial-volume averaging, and the Patlak method. Whole-brain CMRgl was computed in each subject as the average measurement from all intracerebral voxels inferior to a horizontal slice through the falx and superior to a slice through the midthalamus.

The software package SPM99 [43] (Statistical Parametric Mapping 99, Wellcome Department of Imaging Sciences, London, UK) was used to linearly and nonlinearly deform each person’s PET image (in units of PET counts) into the coordinates of a standard brain atlas, digitally approximated by a template created by the Montreal Neurological Institute (MNI template, which is included in the software package); normalize each person’s image for variations in whole-brain measurements using proportionate scaling; smooth the images using a Gaussian kernel with a full width at half maximum of 12 mm; and compute statistical parametric t-score maps. These maps were used to identify brain regions with significantly greater CMRgl reductions in the DEB+ group than in the DEB- controls and then to determine whether the DEB-related CMRgl reductions were significantly greater in the APOE e4 carriers than in the e4 carriers. Statistical maps are projected onto the lateral medial surface of the right hemisphere ($p < .001$, uncorrected for multiple comparisons). The atlas localization and magnitude of maximal CMRgl reductions are shown in Table 3.

### Statistical Analysis

The possibility of Type 1 error is an important consideration with the large number of statistical tests used in voxel-based analyses. We used a significance threshold of $p < .001$ (uncorrected for multiple comparisons) over brain regions with hypothesized CMRgl reductions in the DEB+ cases than in the DEB- controls and then to determine whether the DEB-related CMRgl reductions were significantly greater in the APOE e4 carriers or noncarriers (interaction). The interaction between DEB and APOE was examined under the framework of the general linear model implemented in the statistical parametric mapping computer package.

### Table 2—Results of Neuropsychology Testing

<table>
<thead>
<tr>
<th>Tests of Frontal or Executive Function</th>
<th>DEB+</th>
<th>DEB-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Oral Word Association</td>
<td>45.6 ± 10.8</td>
<td>46.9 ± 13.1</td>
<td>.76</td>
</tr>
<tr>
<td>Test</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wisconsin Cart Sorting Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categories</td>
<td>4.6 ± 1.9</td>
<td>5.4 ± 1.3</td>
<td>.19</td>
</tr>
<tr>
<td>Total Errors</td>
<td>32.2 ± 23.0</td>
<td>29.9 ± 18.0</td>
<td>.75</td>
</tr>
<tr>
<td>Perseverative Errors</td>
<td>15.9 ± 13.6</td>
<td>15.2 ± 9.3</td>
<td>.87</td>
</tr>
<tr>
<td>WAIS-R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Symbol Substitution</td>
<td>12.6 ± 2.5</td>
<td>12.9 ± 2.3</td>
<td>.72</td>
</tr>
<tr>
<td>Digit Span</td>
<td>12.0 ± 2.4</td>
<td>12.0 ± 2.6</td>
<td>.99</td>
</tr>
<tr>
<td>Mental Arithmetic</td>
<td>12.2 ± 2.1</td>
<td>12.1 ± 2.4</td>
<td>.82</td>
</tr>
<tr>
<td>Paced Auditory Serial Attention Task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 second</td>
<td>46.9 ± 12.6</td>
<td>51.4 ± 6.6</td>
<td>.21</td>
</tr>
<tr>
<td>2 second</td>
<td>33.3 ± 12.7</td>
<td>38.1 ± 8.7</td>
<td>.22</td>
</tr>
<tr>
<td>Visualspatial Tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex Figure Test Copy</td>
<td>35.3 ± 1.0</td>
<td>34.2 ± 2.2</td>
<td>.07</td>
</tr>
<tr>
<td>WAIS-R Block Design</td>
<td>12.5 ± 1.9</td>
<td>12.8 ± 3.1</td>
<td>.79</td>
</tr>
<tr>
<td>Facial Recognition Test</td>
<td>46.3 ± 3.1</td>
<td>46.1 ± 4.0</td>
<td>.85</td>
</tr>
<tr>
<td>Judgment of Line Orientation Test</td>
<td>25.5 ± 3.0</td>
<td>25.5 ± 3.6</td>
<td>.99</td>
</tr>
<tr>
<td>Verbal Memory Tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory Verbal Learning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Learning</td>
<td>47.9 ± 7.5</td>
<td>45.6 ± 11.1</td>
<td>.49</td>
</tr>
<tr>
<td>Long-Term Recall</td>
<td>9.4 ± 3.1</td>
<td>9.1 ± 3.4</td>
<td>.80</td>
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<tr>
<td>Selective Reminding Test-free recall</td>
<td>88.1 ± 9.1</td>
<td>89.8 ± 8.7</td>
<td>.57</td>
</tr>
<tr>
<td>Visual Memory Tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex Figure Test Recall</td>
<td>19.0 ± 5.0</td>
<td>19.4 ± 5.8</td>
<td>.80</td>
</tr>
<tr>
<td>Benton Visual Retention Test, no. correct</td>
<td>7.0 ± 1.4</td>
<td>7.1 ± 2.3</td>
<td>.93</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. DEB refers to dream-enactment behavior.
provide an effective balance between reducing both Type 1 error and the risk of missing important and empirically relevant results.34

RESULTS

The DEB+ and DEB- groups did not differ in their age, education background, sex, body mass index, family history of a first-degree relative with dementia, Folstein Mini Mental State Examination score, Hamilton Depression Scale score, or Epworth Sleepiness Scale score (Table 1). Furthermore, they did not differ on any neuropsychological test score (Table 2).

Imaging results are summarized in Table 3. In comparison with the DEB- group, the DEB+ group had significantly lower CMRgl in a right medial parietal/posterior cingulate region (one of several areas known to be preferentially affected in patients with DLB as well as in patients with AD) (Talairach coordinates X[16], Y[-30], Z[48], p = .00031) (Figure 1a). Conversely, there were no reductions in CMRglu in the DEB- group relative to the DEB+ group. We next examined each of the 2 APOE groups separately. In comparison with the APOE e4 noncarrier/DEB- group, the APOE e4 noncarrier/DEB+ group had significantly lower CMRgl in bilateral medial parietal/posterior cingulate and right lateral parietal regions known to be preferentially affected in patients with DLB (Figure 1b, Table 3). In comparison with the APOE e4 carrier/DEB- group, the APOE e4 carrier/DEB+ group did not have significantly lower CMRgl in any hypothesized region, perhaps because regional CMRgl in the AD-related regions also known to be preferentially affected by DLB was already reduced in both APOE e4 carrier groups.

Our posthoc analysis of the interaction between DEB and APOE e4 status indicated that DEB-related CMRgl reductions in the APOE e4 noncarriers were significantly greater than those in the APOE e4 carriers in bilateral medial parietal/posterior cingulate, left parietotemporal, right parietal, and right temporal regions known to be preferentially affected by DLB, as well as in patients with AD (Figure 1c, Table 3).

In exploratory analyses of regions not known to be preferentially affected in FDG PET studies of DLB, the aggregate DEB+ group (p = .00054) and APOE e4 noncarrier/DEB+ subgroup (p = .000067) each had significantly lower CMRgl than their DEB- counterparts in the left rostral anterior cingulate cortex. The APOE e4 carrier/DEB+ group had greater CMRgl reductions than the APOE e4 carrier/DEB- group in bilateral medial frontal regions (p < .001, uncorrected for multiple comparisons). DEB-related CMRgl reductions in the rostral anterior cingulate region, left hippocampus, and left midbrain were significantly greater in the e4 noncarriers than in the e4 carriers (Figure 1c, p < .001, uncorrected for multiple comparisons).

DISCUSSION

This study provides preliminary evidence of functional brain alterations in cognitively normal persons reporting DEB, a condition frequently found in patients with DLB. In comparison with normal control subjects, persons reporting DEB had significantly lower CMRgl in some brain regions previously found in FDG-PET studies to be preferentially affected by DLB. The interaction between DEB and APOE shows that the DEB effects are much more pronounced in the e4 noncarriers than in the carriers. One possible explanation for this is that e4 has a known robust impact on cortical metabolism34,26-29 and may, therefore, be camouflaging the DEB effect. That is, when the e4 carriers are subtracted from one another, the e4 effect as well as the overlapping DEB effect may be subtracted out. Overall, our findings, though preliminary, support the possibility that DEB is identifying a population at risk for DLB.

If confirmed, these findings also raise the possibility of using PET to detect and track the brain changes preferentially affected in normal persons with DEB, determine the extent to which DEB and the brain changes with which they are associated predict the subsequent onset of DLB, and provide a promising biologic surrogate for the evaluation of prevention therapies facilitating the investigation of the ability of a putative treatment to retard progression of these brain changes without having to study thousands of clinical-trial participants or wait many years for symptomatic onset of DLB. In many respects, these DEB-related brain changes and their implications for the early detection, tracking, and prevention of DLB are similar to our previously reported APOE e4-related brain changes and their implications for the early detection, tracking, and prevention of AD.26-29

Although our study has several potentially important implications, it also has significant limitations. First, our subjects lacked polysomnographic confirmation of RBD. In the absence of objective confirmation, it is possible that some of our patients reporting DEB did not have RBD. However, in a Mayo Clinic study completed in 2002 comparing responses on the sleep questionnaire to polysomnographic confirmation of RBD, Boeve et al found that bed-partner responses yielded a sensitivity of 92% and a specificity of 100% for the diagnosis of RBD.45 Further, Eisensehr reported that the diagnosis of RBD can often be suspected on the basis of clinical symptoms and polysomnographic documentation.
of a sleep history, with a specificity greater than 90% even though greater sensitivity was added by polysomnography. Finally, any DEB-related misclassifications would have been expected to reduce rather than enhance our ability to detect DEB-related group differences. Despite these caveats, confirmation in persons with polysomnographically confirmed RBD is needed. Second, our sample sizes were small, particularly regarding APOE e4 noncarriers, whom we have shown had a much stronger DEB effect than the e4 carriers. Although small sample sizes are more likely to cause false negative findings (Type II errors) than to cause false positive findings (Type I errors), our findings need to be independently confirmed and extended to larger samples. We believe the reason for our e4 enrichment in this study reflects the e4-enriched cohort from which these subjects were drawn, although we cannot exclude the possibility that there may be an association between APOE e4 and DEB. Further study of this question is needed. Third, our preliminary findings used a significance threshold of p < .001, uncorrected for multiple comparisons. Although this threshold is commonly used in brain-mapping studies and has been shown by our group and others to help optimize the trade-off between Type I and Type II errors, additional studies are needed to replicate our findings in independent samples—preferably using larger numbers of e4 noncarriers and correction for the number of comparisons in the postulated DLB-related brain regions—to help further address the possibility of Type I errors.

Brain-imaging studies of patients with DEB are comparatively few and, to date, have centered on the dopaminergic system. Albin et al found reduced striatal dopamine terminals in a cohort of 6 patients with RBD using C-11 dihydrotetrabenazine PET. Gilman et al also found reduced striatal dopaminergic terminals in patients with multiple system atrophy and RBD. Hilker et al using 6-fluorodopa ¹⁸FD-PET in patients with early-stage PD and RBD found an inverse correlation between mesopontine ¹⁸FD uptake and REM-sleep duration. Shirakawa et al found reduced frontal and pontine blood flow using single photon emission computed tomography in 20 patients with RBD. In our study, we identified reduced FDG metabolism in brain regions known to be affected by DLB, including parietal, temporal, and posterior cingulate/medial parietal cortices, as well as areas less-consistently reported, including the anterior cingulate, medial frontal cortex, midbrain, and hippocampus. Why such reductions exist, even in symptomatic patients, is far from clear. In tauopathy-related dementia syndromes, such as frontotemporal dementia, metabolic reductions tend to parallel structural reductions and clinical deficits so that FDG-PET studies show reduced frontotemporal metabolism in the same regions that MRI studies show atrophy and that neuropsychological studies show cognitive deficits referable to executive (and other) skills. AD does not behave in this way. Maximal deficits on imaging studies, even in presymptomatic and early cases, reflect complex heteromodal association areas and not medial temporal or basal forebrain regions (areas where the earliest pathologic changes have been shown to occur). An alternative theory is that the hypometabolic areas in AD reflect a dysfunctional "default-mode network," the activity of which is correlated with hippocampal function. Even if the hippocampus itself is not found to be severely hypometabolic, the network with which it is associated therefore is hypometabolic. Given the neuropsychologic overlap between AD and DLB, and consequent overlap in functional hypometabolism, this theory may be relevant for DLB as well. Further, other networks involving dopaminergic and other subcortical systems may be affected in DLB and may help to explain additional areas of dysfunction in DLB.

Is there a risk factor for synucleinopathy-related dementia and DLB? APOE e4 is a major genetic risk factor for AD, and PET scans of asymptomatic carriers of the e4 allele show reduced cortical metabolism in the same brain regions as are found in patients known to be affected by AD. Despite known genetic associations with α-synuclein, parkin, and tau, no common polymorphism analogous to APOE has been identified for Parkinson-related dementia syndromes. Nonetheless, with the recently discovered association between RBD and synucleinopathies, particularly DLB, there exists a significant opportunity to identify individuals with DEB who are at risk for DLB. RBD is not uniquely associated with DLB but also occurs in patients with Parkinson disease and multiple system atrophy. Still, existing evidence suggests that DLB is prominently represented among the synucleinopathies that cause RBD and may be the most frequent synucleinopathy associated with RBD. Just as not every patient with APOE e4 will develop AD, not every patient with RBD will develop DLB, but the correlation between RBD and DLB among the synucleinopathies is strong.

Based on these preliminary findings of reduced cortical metabolism in neuropsychiatically healthy adults with DEB, further study of patients (particularly APOE e4 noncarriers) with polysomnographically proven RBD and longitudinal followup are warranted to determine the degree to which these findings may predict conversion to a symptomatic synucleinopathy, particularly DLB.

ACKNOWLEDGMENTS

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