Chapter 4:

CSF α-Synuclein Does Not Discriminate Dementia with Lewy Bodies from Alzheimer’s Disease.

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Abstract

In this study, we assessed whether cerebrospinal fluid (CSF) levels of the biomarker α-Synuclein have a diagnostic value in differential diagnosis of dementia with Lewy bodies (DLB) and Alzheimer disease (AD). We also analysed associations between CSF biomarkers and cognitive performance in DLB and in AD. We included 35 patients with DLB patients, 63 AD patients, 18 patients with Parkinson's Disease (PD) and 34 patients with subjective complaints (SC). Neuropsychological performance was measured by means of Mini-Mental Status Examination (MMSE), Visual Association Test (VAT), VAT object-naming, Trail Making Test (TMT), and category fluency. In CSF, levels of α-Synuclein, amyloid β 1-42 (Aβ1-42), total tau-protein (tau) and tau phosphorylated at threonine 181 (p-tau181) were measured. CSF α-Synuclein levels did not differentiate between diagnostic groups (p = 0.16). Higher p-tau181 and higher tau levels differentiated AD from DLB patients (p<0.05). In DLB patients lower Aβ1-42 and higher tau levels were found than in SC and PD patients (p<0.05). In DLB patients, linear regression analyses of CSF biomarkers showed that lower α-Synuclein was related to lower MMSE-scores (β[SE]=6(2) and p<0.05) and fluency (β[SE]= 4(2), p<0.05). Ultimately, CSF α-Synuclein was not a useful diagnostic biomarker to differentiate DLB and/or PD (α-Synucleinopathies) from AD or SC. In DLB patients maybe lower CSF α-Synuclein levels are related to worse cognitive performance.

Introduction

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia after Alzheimer’s disease (AD)1. In pathological studies, DLB accounts for more than 20 % of dementia cases2,3. Clinical hallmarks are cognitive decline accompanied by parkinsonism, visual hallucinations and fluctuating cognitive performance and consciousness4. Unfortunately, diagnostic criteria have modest sensitivity and it can be difficult to differentiate DLB from other forms of dementia, especially AD5. Correct diagnosis is important for adequate clinical management. Next to clinical characteristics, ancillary investigations can aid in making the correct diagnosis6. For DLB, it has been shown that 123 IFP-CIT-SPECT can distinguish this disease from AD with quiet high accuracy in probable cases7. But its value in possible DLB is less clear and SPECT is rather expensive so there is rationale to explore other markers related to the underlying pathology. Analysis of CSF biomarkers is increasingly applied in the diagnostic work-up of neurodegenerative disease. Especially in AD, a typical profile is observed with decreased CSF amyloid β 1-42 (Aβ1-42) and increased total tau protein (tau ) and tau phosphorylated at threonine 181 (p-tau181) when compared to controls8. These CSF biomarkers reflect the main neuropathological features of Alzheimer’s disease, i.e. Aβ and tau depositions. There are no generally accepted biomarkers to distinguish DLB from other types of dementia. Typical neuropathological changes in DLB are the formation of Lewy bodies, consisting of insoluble α-Synuclein and ubiquitin...
depositions and aggregation. These findings are also seen in Parkinson's disease (PD) and multiple system atrophy (MSA), collectively labelled as synucleinopathies. Since α-Synuclein was found in CSF and plasma, several studies suggest that CSF α-Synuclein may serve as a biomarker to differentiate α-Synucleinopathies from other neurodegenerative diseases. Conflicting results have been described, however, since some studies observed reduced levels of CSF α-Synuclein in PD and DLB compared to controls, whereas in other studies no differences between groups were found. Finally, lower levels of CSF α-Synuclein have been reported in AD-patients compared to controls, suggesting it may be a general marker of synapse loss. Our aim was to determine the diagnostic value of CSF α-Synuclein levels to discriminate DLB and PD (α-Synucleinopathies) from AD and controls in a relatively large group of clinically well-characterised patients. In addition, we investigated associations between CSF biomarkers and severity of cognitive impairment in AD and DLB.

**Materials and methods**

Patients: We selected patients from which CSF was available with probable DLB and PD without dementia from our outpatient memory clinic and movement disorder clinic database. Eighteen PD and 35 DLB patients were retrieved. DLB patients were matched for age and gender with 63 probable AD patients and with 34 controls. The diagnosis was made by consensus in a multidisciplinary team, without knowledge of CSF results. DLB patients were diagnosed according to the consensus criteria of McKeith, PD according to the UK Parkinson's Disease Society Brain Bank (UK-PDSBB) clinical diagnostic criteria and AD patients according to NINCDS-ADRDA criteria. The control group consisted of patients who presented at our memory clinic with subjective complaints (SC), but who had normal clinical investigations and did not have any cognitive deficits. Standardized assessment included medical history, informant-based history, physical and neurological examination, laboratory tests, neuropsychological testing and magnetic resonance imaging (MRI). In PD patients the Hoehn and Yahr scale, a five-point rating system to stage PD (1= mild, 5= severe) was used to reflect severity of symptoms. The Neuropsychiatric inventory (NPI), a 12-item caregiver questionnaire was used to assess behavioural and psychological symptoms of dementia. The local ethical review board approved the study and all patients gave written informed consent.

CSF analysis: CSF was obtained by lumbar puncture between the L3/L4 or L4/L5 intervertebral space, using a 25-gauge needle and collected in polypropylene tubes. Within two hours, CSF samples were centrifuged at 1800 g for 10 minutes at 4 °C. A small amount of CSF was used for routine analysis, including total cells (erythrocytes and leukocytes), total protein, and glucose. Erythrocytes were measured, as these are a known source of α-Synuclein in blood. Excess CSF erythrocytes (e.g. due to traumatic puncture) could therefore potentially confound CSF α-Synuclein-levels. CSF was aliquoted in polypropylene tubes of 0.5 or 1 ml and stored at -80 °C until further
analysis. The technicians performing the analysis did not have access to the clinical data. CSF Aβ1-42, tau and p-tau181 concentrations were determined, using commercially available ELISA’s.

The α-Synuclein assay is based on a previous described procedure. Currently, 4 isoforms of α-Synuclein are known. Isoform α-synuclein-140 comprises the whole transcript of the protein. The other 3 isoforms, α-synuclein-126, α-synuclein-112, and α-synuclein-98 are the results of alternative splicing causing in-frame deletions of exon 3 (amino acids 41-54) and exons 5 (103-130, and respectively both exons 3 and 5). In the current assay, α-synuclein-112 and α-synuclein-98 isoforms are not routinely measured.

A disposable flat-bottom microtiter plate (Nunc Maxisorp F96, Roskilde, Denmark) was coated with 100 μl antibody 211 (0.2 μg/ml in 0.20 M carbonate buffer, pH 9.6) overnight at 4º C. A plate washer (Biotek, Beun de Ronde, Abcoude the Netherlands) was used to wash the plate five times with 250 μl PBS containing 0.05% Tween-20 (PBS washing buffer). All further incubations were performed at 37 ºC, unless stated otherwise, and all measurements were performed in duplicate. 250 μl of blocking buffer (2.5% gelatine in PBS washing buffer) was added and incubated for 2 hr and the plate was subsequently washed five times with PBS washing buffer. Next, 100 μl α-synuclein solution (from 0 to 500 ng/ml diluted in PBS) or CSF (1:2 diluted in PBS) was added to each well and incubated for 2.5 hr. Then, the plate was washed five times with PBS washing buffer, and 100 μl of antibody FL-140, diluted 1:1000 in blocking buffer, was added and incubation was continued for 1.5 hr. Again, the plate was washed five times and 100 μl of the peroxidase labelled goat-anti rabbit antibody (dilution 1:5000 in blocking buffer) were added and incubated for 1 hr. After a final washing step 100 μl of a freshly prepared solution of tetramethyl benzidine (TMB) was applied and incubated for 15 minutes in the dark at room temperature. The reaction was stopped with 50 μl 2N H2SO4 and the absorbance was measured at 450 nm in an ELISA plate reader (Tecan Sunrise, Salzburg, Austria). The lower detection limit of the method was 3.8 ng/ml. The intra-assay coefficient of variation (CV) was 14.9 % at a concentration of 17 ng/ml (n=10) and 5.3% at a concentration of 85 ng/ml (n=10). The intra-assay CV was 11.4 % at a concentration of 88 ng/ml (n=13) and 15% at a concentration of 66 ng/ml (n=16). We excluded 6 outliers (3 AD patients, 2 SC and 1 PD patient) with α-Synuclein levels higher than 100 ng/ml. This exclusion did not alter the outcome of this study (data not shown).

Neuropsychological tests: The neuropsychological test battery was designed to screen the major cognitive functions and included the following tests. Mini-Mental State Examination (MMSE) was used as a measure of global cognitive function. For memory, the Visual Association Test (VAT) was used (range 0-12). VAT object naming was used as a measure for language (0-12). The Trail making Test (TMT) consists of a simple part A and a more complex part B, used to evaluate executive functioning. In TMT the measure of mental speed and the time required for completion is recorded. Category fluency is a test of executive function and language and requires verbal production of as many animals as possible within a time limit of 60 s. Only 8 PD patients underwent
neuropsychological testing; these data were not analyzed. Neuropsychological test results were missing for a number of patients: MMSE 3 cases, VAT 15 cases, VAT object naming 19 cases, TMT-A scores 18 cases, TMT-B scores 36 cases and category fluency 15 cases.

Statistical analysis: For statistical analysis, Statistical Package of the Social Science (SPSS), version 15.0, was used. CSF biomarkers and TMT scores were log-transformed. Group comparisons were performed using chi-squared tests for categorical data and for continuous data we used analysis of variance (ANOVA), corrected for age and sex, with post-hoc Bonferroni tests. Correlations were assessed using bivariate Pearson correlation coefficient. To assess associations between CSF biomarkers and neuropsychological tests in dementia, linear regression analyses were performed. We performed linear regression analyses separately for DLB patients and AD patients. CSF biomarkers were entered as independent variable and neuropsychological test results as dependent variables. In the first model each biomarker was entered separately, with age and sex as covariates. In the second model, CSF biomarkers were entered simultaneously, with age and sex as covariates. Due to colinearity between T-tau and P-tau\textsubscript{181} models contained three biomarkers (i.e. Aβ\textsubscript{1-42}, α-Synuclein, tau or Aβ\textsubscript{1-42}, α-Synuclein, p-tau\textsubscript{181}). Statistical significance was set at p<0.05.

Results

Demographic data, CSF biomarkers concentrations and neuropsychological test results are presented by diagnostic group in table 1. There were group differences in age and the distribution of gender (p<0.05). Post hoc testing showed that DLB patients were older than SC and PD patients. The proportion of males was higher in patients with DLB than SC patients and patients with AD.

In our data the reference range for controls had a median (interquartile range) of 18 ng/ml (14-26 ng/ml). As expected, there were group differences for CSF Aβ\textsubscript{1-42}, tau and p-tau\textsubscript{181} (p<0.05). DLB patients had a profile with decreased Aβ\textsubscript{1-42} and increased tau compared to SC and PD patients. Aβ\textsubscript{1-42} levels were similar, but tau levels were lower in DLB patients compared to AD patients. AD patients had an increased p-tau\textsubscript{181} level compared to DLB patients. SC and PD patients had no differences in biomarker levels.

Neuropsychological test results by diagnostic group are shown in table 1. As expected patients with dementia (DLB and AD) performed worse in all neuropsychological tests, except VAT object naming, which was only reduced in AD. DLB patients were slower on TMT-B than patients with AD.
Table 1 Clinical data, neuropsychological tests and CSF biomarkers by diagnostic group

<table>
<thead>
<tr>
<th></th>
<th>CON (n=34)</th>
<th>PD (n=18)</th>
<th>DLB (n=35)</th>
<th>AD (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>67 ± 5</td>
<td>67 ± 8</td>
<td>71 ± 8(^{a,b})</td>
<td>69 ± 7</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>16 (44%)</td>
<td>8 (42%)</td>
<td>6 (17%)(^{a,d})</td>
<td>34 (52%)</td>
</tr>
<tr>
<td><strong>α-Synuclein (pg/ml)</strong></td>
<td>18 (14-26)</td>
<td>23 (18-32)</td>
<td>20 (15-27)</td>
<td>16 (13-23)</td>
</tr>
<tr>
<td><strong>Aβ(_{1-42}) (pg/ml)</strong></td>
<td>823 (661-1018)(^{c,d})</td>
<td>875 (719-987)(^{c,d})</td>
<td>479 (386-661)(^{a,b})</td>
<td>484 (387-545)(^{a,b})</td>
</tr>
<tr>
<td><strong>T-tau (pg/ml)</strong></td>
<td>252 (208-354)(^{c,d})</td>
<td>196 (130-268)(^{c,d})</td>
<td>382 (265-574)(^{a,b,d})</td>
<td>613 (416-897)(^{a,b,c})</td>
</tr>
<tr>
<td><strong>P-tau(_{181}) (pg/ml)</strong></td>
<td>48 (38-56)(^{d})</td>
<td>49 (37-60)(^{d})</td>
<td>53 (42-72)(^{d})</td>
<td>82 (63-1143)(^{a,b,c})</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>28 ± 1(^{c,d})</td>
<td>29 ± 1(^{c,d})</td>
<td>21 ± 5(^{a,b})</td>
<td>21 ± 4(^{a,b})</td>
</tr>
<tr>
<td><strong>VAT</strong></td>
<td>12 ± 1(^{c,d})</td>
<td>n.a.</td>
<td>7 ± 4(^{a})</td>
<td>5 ± 4(^{a})</td>
</tr>
<tr>
<td><strong>Naming</strong></td>
<td>12 ± 0(^{d})</td>
<td>n.a.</td>
<td>12 ± 1</td>
<td>11 ± 2(^{a})</td>
</tr>
<tr>
<td><strong>TMT-A</strong></td>
<td>41 ± 13(^{c,d})</td>
<td>n.a.</td>
<td>119 ± 82(^{a})</td>
<td>103 ± 82(^{a})</td>
</tr>
<tr>
<td><strong>TMT-B</strong></td>
<td>100 ± 41(^{c,d})</td>
<td>n.a.</td>
<td>416 ± 190(^{a})</td>
<td>240 ± 124(^{a,c})</td>
</tr>
<tr>
<td><strong>Fluency</strong></td>
<td>24 ± 5(^{c,d})</td>
<td>n.a.</td>
<td>12 ± 5(^{a})</td>
<td>12 ± 5(^{a,b})</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, median (I-Q range), n (%). Differences between groups were assessed with ANOVA, adjusted for age and sex. Biomarkers and TMT are presented as raw data, but statistics were performed using log-transformed data. SC: subjective complaints, PD: Parkinson’s disease, DLB: Dementia with Lewy bodies, AD: Alzheimer’s disease, MMSE: mini-mental state examination, VAT: Visual Association Test, Naming: VAT object naming, TMT: Trail Making Test, Fluency: Category fluency.  

\(^{a}\) p <0.05 compared to SC.  
\(^{b}\) p<0.05 compared to PD.  
\(^{c}\) p<0.05 compared to DLB.  
\(^{d}\) p<0.05 compared to AD. CSF α-Synuclein levels, adjusted for age and sex, were not different among diagnostic groups (p= 0.16, see also figure 1).

Across groups we found no association between CSF α-Synuclein and age, disease duration or CSF storage time. Hoehn and Yahr-scores had a tendency of negative correlation with CSF α-Synuclein levels in PD patients \((r= -0.25, p =0.3)\). NPI-scores for hallucinations had a tendency to be negatively correlated with CSF α-Synuclein levels in DLB \((r= - 0.25, p =0.2)\). We found positive correlations between CSF α-Synuclein levels and CSF total protein and erythrocytes (both \(r = 0.27, p = 0.01\)). When we reanalysed our data, with exclusions of samples with CSF erythrocytes more than 500 erythrocytes per µl (n=18) and CSF protein more than 500 per µl (n=24), there were no essential changes in outcomes. CSF Aβ\(_{1-42}\), tau and p-tau\(_{181}\) were not correlated with age, disease.
duration, CSF total protein, storage time or erythrocytes (data not shown). CSF α-Synuclein levels did not correlate with other biomarkers across groups: Aβ₁₋₄₂ (r= 0.04, p=1.0), tau (r= -0.13, p=0.10) or p-tau₁₈₁ (r= -0.13, p = 0.10).

**Figure 1** log CSF α-Synuclein levels (pg/ml) by diagnostic group

Subsequently, we assessed associations between CSF biomarker levels and performance on neuropsychological tests in DLB and AD, using linear regression analyses (table 2). Adjusted for age and gender, MMSE-score was related to lower levels of CSF α-Synuclein (see also figure 2) and higher levels of tau and p-tau₁₈₁ in DLB patients. Furthermore, impaired performance on the VAT was related to higher levels of tau and impaired object naming was related with lower Aβ₁₋₄₂ levels. When we entered all biomarkers simultaneously in the second model, relationships with tau disappeared. Additionally, lower α-Synuclein was now also related to worse category fluency. In AD patients we observed a different picture. Worse performance on the VAT was related to higher levels
**Figure 2** Scatter plot of CSF α-Synuclein by MMSE in DLB

**A:**

Scatterplot of the distribution of log transformed CSF α-Synuclein levels (pg/ml) and MMSE in patients with DLB. The X-axis shows the MMSE scores and the Y-axis the CSF α-Synuclein levels. The MMSE and CSF α-Synuclein levels have a positive association in the DLB group, as shown by linear regression analysis with age and gender as covariates (β=6.2, p<0.05).

**B:**

Scatterplot of the distribution of log transformed CSF α-Synuclein levels (pg/ml) and MMSE in patients with AD. The MMSE and CSF α-Synuclein levels have no association in the AD group, as shown by linear regression analysis with age and gender as covariates (β=-1.1, p=0.35).
Table 2 Linear regression: biomarkers and neuropsychological performance DLB - AD

<table>
<thead>
<tr>
<th></th>
<th>DLB</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (SE)</td>
<td>α-Synuclein</td>
</tr>
<tr>
<td>MMSE 1</td>
<td>6 (2)*</td>
<td>4 (3)</td>
</tr>
<tr>
<td>2</td>
<td>5 (2)*</td>
<td>1 (3)</td>
</tr>
<tr>
<td>VAT 1</td>
<td>-1 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>2</td>
<td>-1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Naming 1</td>
<td>0 (0)</td>
<td>1 (0)*</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>1 (1)*</td>
</tr>
<tr>
<td>TMT-A 1</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TMT-B 1</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fluency 1</td>
<td>3 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>2</td>
<td>4 (2)*</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

Numbers represent regression coefficients (standard error) from linear regression analysis. Model 1: each separate biomarker level was entered separately in a model together with age and sex. Model 2: biomarker levels (α-Synuclein, Aβ42 and tau) were entered into one model with age and gender. Due to collinearity with T-tau, p-tau<sub>181</sub> levels were entered into one model with α-Synuclein, Aβ<sub>1-42</sub> and age and gender. DLB: Dementia with Lewy bodies, AD: Alzheimer’s Disease, MMSE: mini mental state Examination, VAT: Visual Association Test, Naming: VAT object naming, TMT: Trail Making Test, Fluency: Category Fluency
**Discussion**

We found no differences in levels of α-Synuclein in CSF between DLB, PD, AD and SC. However, lower CSF α-Synuclein levels were related to worse cognitive performance in DLB patients. Our findings suggest that CSF α-Synuclein is not a useful biomarker to distinguish DLB and/or PD from AD and SC. A possible explanation could be that CSF α-Synuclein does not reflect the disease process in α-Synucleinopathies. The pathological hallmark of this group of diseases is the Lewy body, an intracytoplasmic inclusion body that contains aggregates of insoluble α-Synuclein. It has not been elucidated yet what the exact relationship is between intracellular α-Synuclein aggregates and extracellular α-Synuclein levels. CSF levels of α-Synuclein represent the pool of extracellular α-Synuclein secreted by neurons, but it is not known if the concentration changes in pathological situations as it does for Aβ. Another potential confounding factor is overlap in histopathology in neurodegenerative diseases. Neuropathologic studies reported the presence of α-Synuclein pathology in brains of AD patients in around 60% of cases\(^{28}\). A decrease of CSF α-Synuclein levels in AD patients compared to healthy subjects has been described\(^{15}\). α-Synuclein pathology has also been found in brain tissue of 10-37% of aged healthy subjects although the load seems to be much higher in PD/DLB\(^{3,29}\). This mixed pathology could explain why the levels of α-Synuclein could not discriminate between DLB/PD and AD. In this study, DLB patients had decreased CSF Aβ1 -42 and increased tau compared to PD and SC patients. Tau levels in DLB were less elevated than in AD patients. This has been described by others and is in line with histopathological findings\(^{30,31}\). Most DLB patients have sufficient amyloid plaques to meet the pathological criteria of AD, although patients display severe diffuse tangle pathology to reach Braak stages V or VI\(^{32}\). P-tau181 levels were solely elevated in AD, underscoring the results of previous studies that this marker can be used to discriminate between AD and DLB\(^{33}\). Our results are in agreement with recent studies in which CSF α-Synuclein concentrations did not differ between α-Synucleinopathies and healthy controls\(^{13,14,15}\). In contrast, two earlier studies described lower levels of α-Synuclein in CSF of PD and DLB patients compared to controls and AD patients\(^{11,12}\). An explanation for these discrepant results could be the use of different antibodies, possibly binding to different parts of the α-Synuclein protein. Also these discrepancies could be partly due to the application of different assays. The assay of Tokuda *et al.* required protein-enriched CSF and the assay of Mollenhauer *et al.* required elongated incubation (48 h at 4º C) of unconcentrated CSF. To our knowledge, this is the first study that investigate the relation between neuropsychological data other than the MMSE and CSF α-Synuclein levels. Lower CSF α-synuclein levels were related to worse cognitive performance (MMSE, category fluency) in DLB patients in the present study. This is in agreement with a recent finding by Ballard et al., who found a positive correlation between the CSF α-Synuclein and MMSE in 12 DLB-patients\(^{34}\). Ohrfelt et al. found results of lower CSF α-Synuclein related to worse MMSE in AD patients\(^{15}\). Although MMSE-scores were comparable between DLB and AD patients we could not replicate this finding. If CSF α-
Synuclein is related to neuronal pathological aggregation of α-Synuclein, the observed correlation between CSF α-Synuclein levels and MMSE in DLB patients possibly reflects disease severity. When biomarkers were assessed separately in DLB, associations between cognitive performance and lower Aβ1-42 and higher tau were found. This suggests a synergistic effect of AD-pathology in DLB. In AD patients, tau was related to worse memory performance. This is comparable with previous studies, which suggested that higher CSF tau reflects the intensity of the disease process in AD. This study contributes to the still sparse literature on CSF α-Synuclein and shows that this protein is not a reliable diagnostic biomarker, at least when using an immunosorbent assay designed by van Geel et al. Further investigation is needed to determine technical aspects of the assays and the specific species and isoforms of CSF α-Synuclein that might be detected. Several studies support the idea that soluble oligomers of CSF α-Synuclein are the pathogenic components that drive neurodegeneration and neuronal cell death. Future studies focus on the detection of these soluble α-Synuclein oligomers and a novel specific ELISA method has recently been described. DLB is a clinically heterogeneous disease and involves several neuropathological processes. In view of the current suboptimal diagnostic accuracy, a biomarker that would provide early and correct diagnosis would be an asset. It has to be further clarified how mixed pathology is reflected in the CSF and how this influences the diagnostic ability of CSF biomarkers. The tendency of CSF α-Synuclein to be related with cognitive performance in DLB and AD needs additional investigation, as to how this associates with underlying neurodegenerative processes.

References


