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SHORT REPORT

Contribution of alpha-synuclein pathology to cerebral glucose metabolism in patients with amnestic MCI

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Abstract

INTRODUCTION: The in vivo detection of mixed Alzheimer's disease (AD) and α-synuclein (αSyn) pathology is important for clinical management and prognostic stratification. We investigated the contribution of αSyn pathology, detected by cerebrospinal fluid (CSF) seed amplification assay (αSyn SAA), on [18F]-fluorodeoxyglucose positron emission tomography (FDG PET) pattern in subjects with amnestic mild cognitive impairment (aMCI).

METHODS: We included 562 aMCI participants and 204 cognitively normal controls (CN) with available αSyn SAA and cerebral metabolic rate for glucose utilization (rCMRgl) data.

RESULTS: 24% of aMCI cases were positive (+) for CSF αSyn SAA. Compared to CN, both αSyn+ and negative (–) aMCI participants showed reductions in rCMRgl within AD typical regions. αSyn+ aMCI had lower rCMRgl within AD and dementia with Lewy bodies (DLB) typical regions compared to αSyn– aMCI, even after stratification according to the CSF AT(N) system.

DISCUSSION: αSyn pathology contributes to a distinct FDG PET pattern in aMCI.

KEYWORDS
Alzheimer's disease, biomarker, Lewy body disease, PET

Highlights

- αSyn pathology can be detected in vivo by CSF αSyn SAA.

- We investigated the FDG PET pattern in aMCI patients with CSF αSyn SAA positivity.
- αSyn+ aMCI showed a marked brain hypometabolism in AD and DLB typical regions.

1 | INTRODUCTION

Mild cognitive impairment (MCI) identifies a clinical syndrome characterized by cognitive complaints, objective evidence of impairment in cognitive domains, and preservation of normal functional activities, which does not meet the criteria for dementia.[1,2] Alzheimer's disease (AD) and Lewy body disease (LBD) are among the most common neuropathological substrates[1–6] and MCI subjects may progress to the dementia stage.[1,2,4] In detail, MCI patients with AD pathology most commonly present with episodic memory impairment, known as amnestic MCI (aMCI).[1,2] However, the diagnostic assessment of these patients remains challenging due to the frequent co-occurrence of different pathologies, with 30%–40% of neuropathologically confirmed AD cases having concomitant LBD and with AD pathology reported in more than half of patients with dementia with Lewy bodies (DLB).[7–12] Evidence suggests that amyloid-β, tau, and α-synuclein (αSyn) pathologies may probably exert synergistic effects on each other, contributing to faster cognitive decline, atypical clinical courses, and poorer prognosis.[8,13–16] Therefore, the in vivo identification of MCI due to AD-LBD mixed pathology is important for clinical management and stratification of patients in clinical trials given the possible influence of LBD co-pathology on AD disease-modifying treatment response.

Neuroimaging and cerebrospinal fluid (CSF) biomarkers within the so-called AT(N) system [i.e., amyloid-β deposition (A), tau pathology (T), and neurodegeneration (N)] can identify underlying AD pathology with high accuracy even at preclinical stages.[17,18] Specifically, hypometabolism on [18F]-fluorodeoxyglucose positron emission tomography (FDG PET) in the posterior cingulate and posterior temporoparietal areas indicates ongoing neurodegeneration associated with AD, whereas the occipital hypometabolism is the classic FDG PET pattern in DLB.[5,6,17,19]

While CSF amyloid-β peptides (i.e., Aβ 1-42 and Aβ 1-40) and tau proteins (i.e., pTau and tTau) are well-established biomarkers of AD pathology in clinical routine, CSF misfolded alpha-Syn aggregates (seeds) measured by seed amplification assays (αSyn SAA) have recently gained attention as highly sensitive and specific biomarkers of LBD.[16,20–22] Interestingly, αSyn SAA positivity in AD patients with dementia and MCI mirrors the above-mentioned prevalence observed in neuropathological cohorts.[16,21,22] However, no study to date has investigated the contribution of αSyn pathology detected by means of CSF αSyn SAA to the FDG PET pattern in MCI patients.

In the present study, we analyzed FDG PET data in a large cohort of aMCI patients and a group of cognitively normal (CN) participants and investigated the influence of αSyn SAA positivity on the measures of cerebral glucose metabolism in patients with aMCI even after stratification according to the CSF-based AT(N) system.

2 | METHODS

2.1 | Case classification and CSF biomarker analyses

Data used for this study were provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI) and downloaded from the LONI ADNI data repository.[23] As a multicentric and ongoing study ADNI has devoted its focus to characterize participants with MCI and dementia due to AD in high detail via standardized methods by acquisition of multimodal neuroimaging data, fluid biomarkers, and in-depth phenotypical characterizations. Further details regarding inclusion/exclusion criteria and sampling methods can be found on the ADNI website.[23]

For our study, we included data from aMCI participants who had at least one FDG PET scan and CSF biomarker data (αSyn SAA and AD core biomarkers) available. For participants with multiple FDG PET scans and CSF samplings, we used the earliest data. CSF biomarker data were acquired throughout the study time course.

Overall, both cross-sectional standardized FDG PET and CSF αSyn SAA data (i.e., Amprion synuclein seeding assay dataset) were available for $N = 562$ subjects with a diagnosis of aMCI. In addition, we included $N = 204$ CN participants without evidence of αSyn pathology by means of CSF αSyn SAA (αSyn-CN).

For methodological details concerning CSF αSyn SAA, we refer to the corresponding documents within the LONI ADNI data repository, the Amprion website[24] as well as previous publications.[25,26] αSyn SAA was performed by the Amprion Clinical Laboratory (CLIA ID No. 05D2209417; CAP No. 8168002) and detects CSF misfolded αSyn aggregates (seeds).[25,26] A αSyn positive (+) or a αSyn negative (−) result indicates that αSyn aggregates were detected or not, respectively. In detail, in the ADNI data repository, Parkinson's disease or LBD typical Type 1 seeds are labeled as "Detected-1", multiple system atrophy typical seeds are labeled as "Detected-2" ($N = 0$ in our sample of MCI participants), and negative or inconclusive results are labeled "Not Detected" or "Indeterminate". All subjects with indeterminate results were excluded from our analyses.

AD core biomarkers (i.e., "UPENNBIOMK_MASTER_FINAL" dataset) were additionally available for $N = 735$ participants (i.e., $N = 199$ αSyn− CN and $N = 536$ aMCI) and have been measured on the Luminex platform. Cutoff points for CSF Aβ 1-42 (A+) and for pTau positivity (T+) were defined as < 192 pg/mL and > 23 pg/ml, respectively,

as previously established.[27] For additional methodological aspects we refer to the available documentation on the ADNI data repository.

2.2 | Imaging procedures

For our study, we made use of preprocessed, smoothed (i.e., 8 mm FWHM) and global mean intensity normalized PET data, as provided by the ADNI PET Coordinating Center at the University of Michigan. Among others, preprocessing steps aimed to homogenize data by accounting for site differences. Our additional preprocessing with SPM8[28] included deformation into a standard MNI space. All images underwent a visual quality check. With respect to intensity normalization, additional sensitivity analyses were carried out with pons as reference region via proportional scaling (Figure S1).

2.3 | Analyses of imaging and neuropsychiatric data and statistical analysis

Data were analyzed with SPM12.[28] Voxel-wise analyses were conducted using two-sample *t*-tests to examine group-specific differences of the regional cerebral metabolic rate for glucose utilization (i.e., rCMRgl) between αSyn+ aMCI and αSyn− aMCI versus αSyn− CN and αSyn+ aMCI versus αSyn− aMCI. For the latter comparison, we further analyzed subsamples after stratification according to the CSF-based AT(N) system (i.e., subsamples with at least A+ and A+T+). All models included age and sex as covariates of no interest. We performed additional sensitivity analyses with Mini-Mental State Examination (MMSE)[29] and Alzheimer's disease assessment scale–cognitive subscale 13 (ADAS13) scores[30] as additional covariates.

We performed post hoc explorations of aMCI subsamples with cross-sectional and longitudinal neuropsychiatric data via Neuropsychiatric Inventory Questionnaire (NPI-Q; i.e., $N = 528$ with baseline data; $N = 461$ with follow-up (FU) data; mean FU 2.73 ± 3.33 years; Kruskal–Wallis $p = 0.93$ for FU - in αSyn+ versus αSyn− $p = 0.93$), analyzing both total scores and the subitem B (NPIB; occurrence of hallucinations).[31]

Statistical significance was determined with the Threshold Free Cluster Enhancement (TFCE) toolbox index,[32] a non-parametric and permutation-based method that does not require the definition of arbitrary thresholds. Results were considered significant at $p < 0.05$ FWE_{TFCE} after 5000 permutations. MRIcron software[33] was used for illustration purposes.

A priori defined regions of interest (ROIs) were created with the WFU pickatlas including the left/right precuneus, cuneus, calcarine gyrus, fusiform gyus, lingual gyrus, superior/middle/inferior occipital gyrus, superior/middle (inferior temporal gyrus.[34] ROIs were considered individually and combined (i.e., DLB ROI). Due to the results obtained in our whole brain analyses, we chose not to include additional small-volume corrected analyses in our imaging analyses, however, ROIs were used for data extraction/illustration.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (e.g., PubMed, Scopus). While α synuclein (αSyn) pathology has been extensively studied in cohorts of patients with cognitive disorders using cerebrospinal fluid (CSF) seed amplification assay (αSyn SAA), no study to date has investigated the influence of CSF αSyn SAA positivity on [18F]-fluorodeoxyglucose positron emission tomography (FDG PET) in amnestic mild cognitive impairment (aMCI).
2. **Interpretation**: aMCI subjects with αSyn pathology had more pronounced hypometabolism in brain regions typically affected in Alzheimer's disease and dementia with Lewy bodies (DLB) compared to aMCI subjects without αSyn pathology. The present results suggest that αSyn pathology contributes to the pattern of cerebral glucose metabolism in aMCI.
3. **Future directions**: The manuscript proposes a framework for the generation of new hypotheses and the conduct of additional studies, which should validate our findings in independent and longitudinal cohorts as well as in presymptomatic participants with αSyn pathology.

Non-imaging analyses were performed with R-Studio (Version 2023.03.1+446). Here, we applied the Kruskal–Wallis test with the post hoc Dunn test for continuous variables. For categorical data, we used the chi-squared test, in case of low frequencies with additional simulations of *p*-values (equivalent to a Fisher's exact test).

3 | RESULTS

Characteristics and descriptive statistics of our study population are highlighted in Table 1. Expectedly, αSyn− CN showed highly significant differences with respect to cognitive performance, ε4 carrier status, and evidence of AD pathology. Within our sample of $N = 562$ aMCI participants, $N = 136$ (24%) had evidence of αSyn pathology. Here, αSyn+ subjects tended to be older than αSyn− subjects but also differed with respect to the results of cognitive test batteries (i.e., via MMSE, ADAS11/13, CDR SB with worse performance in αSyn+ participants). However, these differences were strongly attenuated in AT(N) stratified subsamples only remaining significant for ADAS11/13 (i.e., $p = 0.03$ and $p = 0.014$ respectively). αSyn+ aMCI participants showed a higher prevalence of A+ and A+T+ CSF profiles compared to αSyn− aMCI cases (chi-squared $p = 0.01$ and $p = 0.03$, respectively).

Additional post hoc analyses of MCI subsamples with available neuropsychiatric data via NPI-Q yielded group differences in total scores (i.e., αSyn+ > αSyn− scores, via Kruskal–Wallis: baseline $p = 0.05$; FU: $p = 0.006$). Overall, the presence of hallucinations (NPIB) was rarely

TABLE 1 Sample characteristics and group comparisons.

Parameter	αSyn− CN N = 204	αSyn− aMCI N = 426	αSyn+ aMCI N = 136	Comparison: all groups	Comparison: aMCI groups
AGE	74.4 ± 6.7	72.1 ± 7.7	73.1 ± 7.4	$p = 0.0007$	$p = 0.02$
GENDER (M/F)*	102/102	192/234	48/84	$p = 0.03$	n.s.
ε4 CARRIER (N = 745; y/n)*	51/150	192/219	73/60	$p = 1.973e{-}08$	n.s.
A+ (N = 735; y/n)*	82/117	246/158	97/35	$p = 7.689e{-}09$	$p = 0.01$
A+T+ (N = 735; y/n)*	52/147	217/187	86/46	$p = 1.607e{-}13$	$p = 0.03$
MMSE	29.0 ± 1.3	28.0 ± 1.7	27.4 ± 1.8	$p < 2.2e{-}16$	$p = 0.0003$
ADAS11	6.1 ± 3.3	9.3 ± 4.2	11.1 ± 4.8	$p < 2.2e{-}16$	$p = 0.0002$
ADAS13	9.5 ± 4.8	14.9 ± 6.5	18.0 ± 7.0	$p < 2.2e{-}16$	$p = 1.566e{-}05$
CDR SB	0.06 ± 0.3	1.4 ± 0.9	1.6 ± 0.8	$p < 2.2e{-}16$	$p = 0.02$
CDR GLOBAL	0.01 ± 0.08	0.5 ± 0.03	0.5 ± 0	$p < 2.2e{-}16$	n.s.
Ti (YEARS)	2.96 ± 3.81	1.93 ± 2.64	2.45 ± 2.5	$p = 0.0015$	$p = 0.01$

Note: Data are shown as mean ± SD except for *. Group comparisons were done with Kruskal–Wallis non-parametric ANOVA for numerical and ordinal data and with the Chi-squared test for categorical data (i.e., *).
Abbreviations: ADAS11/13, Alzheimer's disease assessment scale–cognitive subscale (11/13 items); aMCI, amnestic mild cognitive impairment; CDR GLOBAL, Clinical Dementia Rating Global Score; CDR SB, Clinical Dementia Rating Sum of Boxes; CN, cognitively normal; MMSE, Mini-Mental State Examination; N, no; n.s., non-significant; TI, the time interval between PET scan and CSF sampling for αSyn SAA; Y, yes; αSyn, α-synuclein.

reported but occurred more frequently in αSyn+ MCI cases over the course of the study (i.e., hallucinations yes/no, via chi-squared with simulated *p*-values: baseline: αSyn+ 0/128; αSyn− 3/397; $p = 0.56$; FU: αSyn+ 5/112; αSyn− 4/339; $p < 0.05$).

In comparison to αSyn- CN, both αSyn+ and αSyn− aMCI participants showed reductions of rCMRgl within AD typical regions, including the bilateral precuneus, posterior cingulate, heteromodal parietal regions as well as lateral and medial temporal regions (Figure 1). However, in αSyn+ aMCI, these were more extensive and additionally included parts of the occipital cortex (Tables S1 and S2).

Corroborative, comparisons of αSyn+ versus αSyn− aMCI yielded lower rCMRgl in αSyn+ within AD and DLB typical brain regions including the bilateral precuneus, more dorsal aspects of the lateral temporal cortexa as well as parietal and occipital regions (Figure 1 and Table 2). These results remained near to identical in the comparisons αSyn+ A+ aMCI versus αSyn− A+ aMCI and αSyn+ A+T+ aMCI versus αSyn− A+T+ aMCI (Figure 1 and Table 2), and after additional correction for ADAS13 and MMSE scores (Figure S1).

In contrast, relative hypermetabolism was observed in αSyn+ versus αSyn− aMCI, mostly within prefrontal and subcortical structures; however, these differences were largely attenuated in AT(N) stratified subsamples (Table S3).

Kruskal–Wallis with post hoc Dunn test of extracted ROI data showed lower rCMRgl in αSyn+ aMCI versus both αSyn− aMCI and αSyn− CN for the combined DLB ROI but not in αSyn− aMCI versus αSyn− CN. Similar observations were made for some but not all of our individual ROIs (Figure 2 and Table S4).

Sensitivity analyses taking into account the time interval (TI) between PET scan and CSF sampling (e.g., samples used for αSyn SAA) showed almost identical results for the comparison αSyn+ versus αSyn− aMCI (Supplementary Materials and Figure S1).

4 | DISCUSSION

In the present study, we showed that CSF αSyn SAA positivity occurred in 24% of aMCI patients and contributes to a distinct FDG PET hypometabolism pattern in this population. Furthermore, the FDG PET pattern was strongly preserved even in αSyn+ aMCI cases with CSF-based evidence of concurrent AD pathology, and after additional correction for cognitive test performance.

Taken together, our data should be interpreted in the context of the mixed AD-LBD pathology, in which it is difficult to identify the main driving pathological event (AD or LBD), rather it is easier to consider the notion of a neuropathological spectrum.[16,35] In our cohort of aMCI subjects the prevalence of αSyn SAA positivity was in accordance with that reported by *Bellomo et al.*[22] Accordingly, we found a high prevalence of Aβ and tau pathology in αSyn SAA-positive subjects which well reflects the frequent co-occurrence of the three pathologies.[7,9–12,16,20] Of note, αSyn SAA-positive MCI cases performed worse on global cognitive tests and were more likely to develop neuropsychiatric manifestations at FU, a finding consistent with previous studies.[16,20,22]

Most interestingly, we have described here, for the first time, the contribution of αSyn pathology on FDG PET pattern in aMCI, with involvement of typical AD regions as well as posterior brain areas, which are typically reported in MCI with Lewy bodies (MCI-LB) and DLB.[5,6,17,19,34,36–38] On one hand, given that AD is the most common neuropathological substrate of aMCI[1,3–5] we suggest that the vast majority of our patients most likely have aMCI due to AD with LBD co-pathology. The lack of core and supportive clinical features (i.e., hallucinations) and proposed biomarkers for MCI-LB in most of our cases supports this hypothesis.[5,6] On another issue, the preservation of the same FDG PET pattern in αSyn+ A+ cases, independent of T status, indicates a strong spatial association between Aβ burden and αSyn

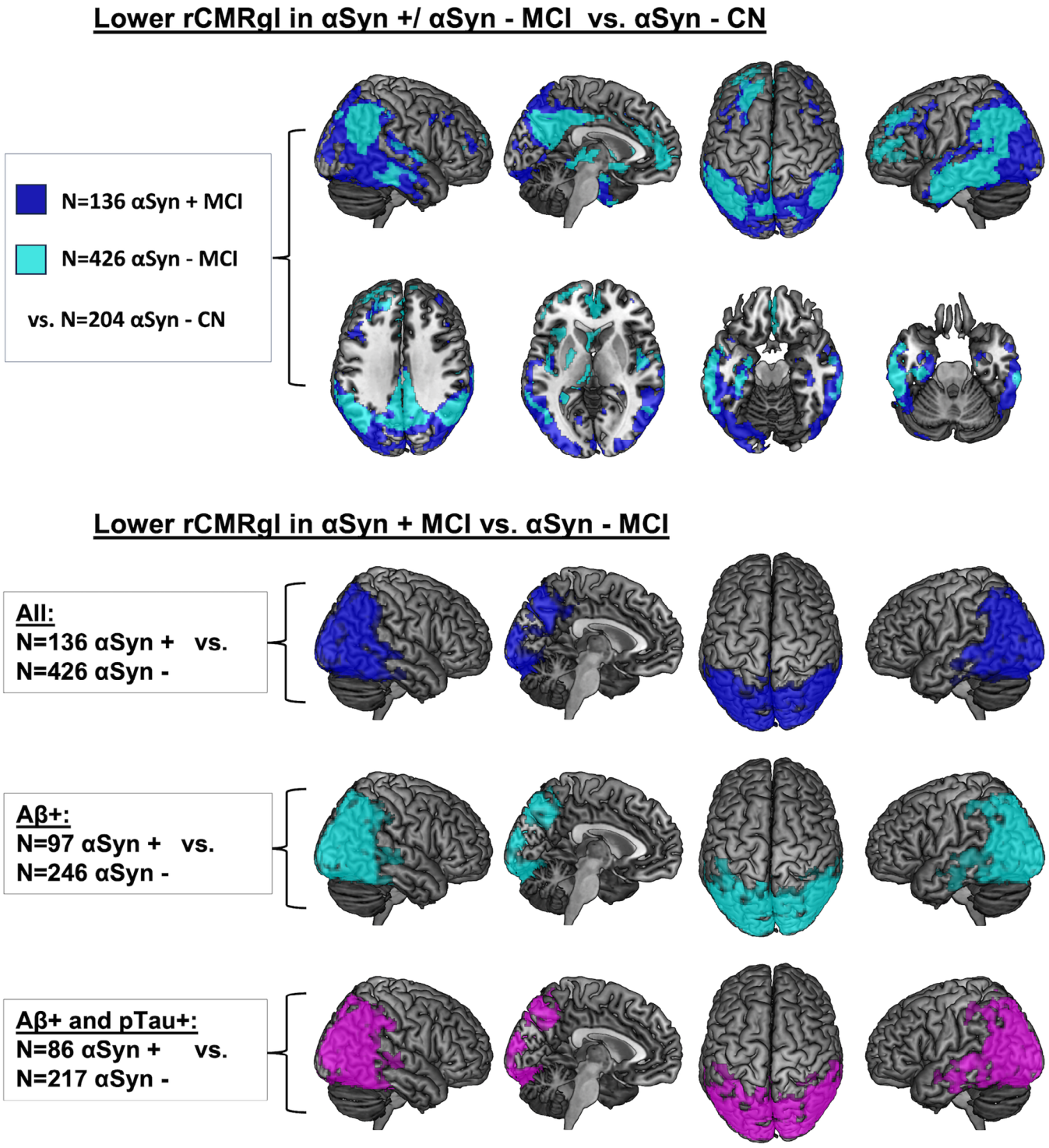

FIGURE 1 rCMRgl differences in the diagnostic groups. Reductions of the rCMRgl in αSyn+ and αSyn− aMCI participants in comparison to αSyn− CN participants (top two rows) and in αSyn+ aMCI participants in comparison to αSyn− aMCI participants with respective subsamples after stratification according to the CSF-based AT(N) system [amyloid-β positivity (A+) and pTau positivity (T+)] [i.e., top row: no stratification, entire sample; middle row: evidence of at least amyloid-β positivity (A+); bottom row: evidence of both amyloid-β and pTau positivity (A+T+)]. All results are illustrated at $p < 0.05$ FWE_{TFCE} whole-brain correction with a search depth of 16 voxels. aMCI, amnestic mild cognitive impairment; CN, cognitively normal; CSF, cerebrospinal fluid; rCMRgl, regional cerebral metabolic rate of glucose; αSyn+, α-synuclein positive; αSyn -, α-synuclein negative; αSyn, α-synuclein.

TABLE 2 Lower cerebral glucose metabolism in αSyn+ versus αSyn− aMCI participants.

Brain region	Equivk	p(FWE_{TFCE})	TFCE	MNI_{xyz}
Lower rCMRgl in αSyn+ aMCI versus αSyn− aMCI (whole sample)				
Left precuneus	**30023**	**0.000**	**1839.11**	**−36−78 38**
Left angular gyrus		0.000	1718.32	−46−76 30
Left middle temporal gyrus		0.000	1702.37	−48−72 12
Lower rCMRgl in αSyn+ aMCI versus αSyn− aMCI (all at least A+)				
Left middle occipital gyrus	**27894**	**0.000**	**1695.67**	**−28−82 22**
Left precuneus		**0.000**	**1689.37**	**−34−78 36**
Left middle temporal gyrus		0.000	1615.20	−48−74 26
Right inferior parietal lobule	**2**	**0.046**	**263.17**	**48−42 56**
Right posterior cingulate	**4**	**0.046**	**262.58**	**8−52 4**
Lower rCMRgl in αSyn + aMCI versus αSyn− aMCI (all A+T+)				
Left middle occipital gyrus	**23570**	**0.001**	**1238.71**	**−28−82 22**
Left precuneus		0.001	1235.36	−34−78 36
Left middle temporal gyrus		0.001	1202.13	−48−74 24

Note: Results are listed at $p < 0.05$ FWE_{TFCE} whole-brain corrected with corresponding cluster size equivalent (equivk), TFCE scores, and MNI coordinates. Bold data indicate primary peaks, and non-bold data indicate secondary peaks within a cluster.
Abbreviations: aMCI, amnestic mild cognitive impairment; TFCE, threshold free cluster enhancement; αSyn+, α-synuclein positive; αSyn−, α-synuclein negative; αSyn, α-synuclein.

load in the cerebral cortex possibly due to the cross-seeding ability of misfolded protein aggregates.[39–41]

However, we cannot exclude that at least some of our patients may have a primary MCI-LB with AD co-pathology. Indeed, aMCI may also represent a clinical presentation of LB-MCI (especially if multidomain).[5,42,43] In addition, although our results should be interpreted cautiously because of the small sample size, we found a higher prevalence of hallucinations at FU in αSyn SAA-positive MCI participants. Accordingly, in the study by *Rossi et al*., 38% of MCI-LB cases had an aMCI profile, and 44% of αSyn SAA-positive MCI due to AD patients developed at FU a core or supporting clinical feature of DLB (i.e., hallucinations).[20] Similarly, in the study by *Quadalti et al*., αSyn SAA positivity was associated with a higher prevalence of hallucinations, and only 9% and 16% of αSyn SAA-positive A+T+ cases met the diagnostic criteria for DLB/PD at baseline and FU, respectively.[16]

All these data highlight the difficulty of early clinical diagnosis of mixed AD-LBD pathology, as well as of the clinical and pathological separation of the two entities and underline the urgent need for accurate in vivo biomarkers. Here, a main advantage of FDG PET over amyloid imaging and CSF biomarkers relies in its high performance in predicting short-term conversion to dementia in MCI subjects.[19,38] Nevertheless, we suggest that both AD and LBD pathologies play a substantial and independent role in influencing the clinical phenotype and brain metabolic profile of aMCI patients. Thus, the clinical, biomarker, and pathological signature of AD-LBD may possibly represent a unique entity, rather than a combination of features observed in pure LBD and AD cases.[35]

This has important clinical implications. Indeed, with the emergence of new disease-modifying therapies for AD,[44,45] the presence of mixed AD-LBD pathology should be necessarily taken into account in clinical trials, as LBD pathology may be responsible for independent disease progression despite the removal of Aβ pathology.[16] In this regard, a possible cause of therapeutic trial failures in neurodegenerative dementias could be attributed to imperfect patient recruitment due to shared pathologies.[46,47]

The major strength of our study relies on the large cohort of patients and their detailed characterization, including CSF biomarkers and FDG PET data. In addition, we used an αSyn SAA, that has been well-validated and shown to have a very high sensitivity and specificity for αSyn pathology.[22,25,26] A limitation of our study is that the CSF samples were collected at different times compared with the FDG PET data, but this should not have significantly affected our results as i) additional sensitivity analyses confirmed our main findings and ii) the development of proteinopathies and the corresponding biomarker changes generally occur very slowly and since the preclinical stages.[17,22] In addition, the CSF biomarker cutoffs adopted for the ADNI cohort are lower than those currently used in other studies. In addition, other more detailed clinical data (e.g., subtle motor signs) were not sufficiently available for the present study and require future analysis as well as the investigation of FDG PET pattern in presymptomatic αSyn SAA-positive cases.

In conclusion, we have shown that aMCI subjects with αSyn pathology have a distinct FDG PET pattern with a diffuse brain hypometabolism in regions typically affected in AD and DLB. Given the epidemiological relevance of both diseases, a deeper characterization of the AD-LBD phenotype may improve early diagnostic assessment with less risk of misdiagnosis and recruitment of heterogeneous candidates in clinical trials as well as treatment indication with new disease-modifying drugs.

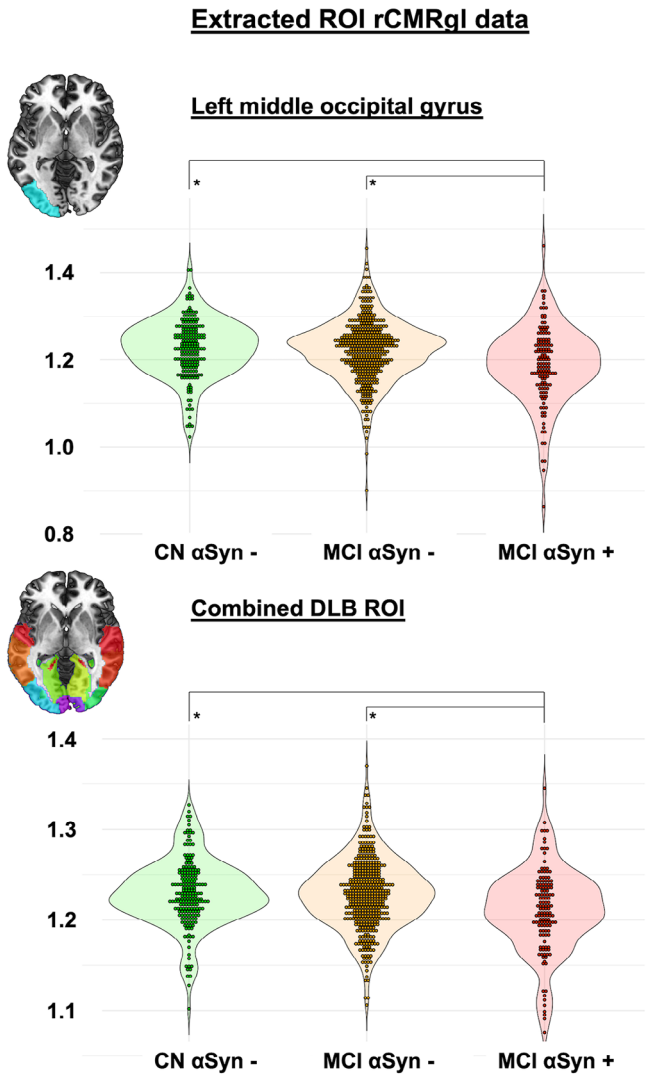

FIGURE 2 Violin plots of extracted rCMRgl data within exemplary ROIs. * indicates $p \leq 0.0001$ via non-parametric Kruskal–Wallis test (all αSyn− CN > αSyn− aMCI > αSyn+ aMCI; corrected for multiple comparisons). aMCI, amnestic mild cognitive impairment; rCMRgl, regional cerebral metabolic rate of glucose; αSyn +, α-synuclein positive; αSyn, α-synuclein.

AUTHOR CONTRIBUTIONS

Conception and design of the study: Samir Abu-Rumeileh and Christopher M. Weise. *Acquisition and analysis of data*: Samir Abu-Rumeileh, Garegin Arajyan, Eric M. Reiman, Markus Otto, Christopher M. Weise. *Drafting of the manuscript*: Samir Abu-Rumeileh and Christopher M. Weise.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All participants gave informed consent through their local IRBs prior to study participation. Within the ADNI protocol, all procedures involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments (for details see www.adni.loni.usc.edu). Data are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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