1	The Overlap Index as a means of evaluating early tau-PET signal reliability
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33 ABSTRACT

34 In tau positron emission tomography (tau-PET), a reliable method to detect early tau 35 accumulation in the brain is crucial. Noise, artifacts, and off-target uptake impede 36 detection of subtle true positive ligand binding. We hypothesize that identifying voxels 37 with stable activity over time can enhance detection of true positive tau. Methods: 339 38 participants in the clinical spectrum ranging from clinically unimpaired to Alzheimer's 39 Disease Dementia underwent ≥2 serial tau-PET scans with flortaucipir. The "overlap 40 index" (OI) method was proposed to detect spatially identical, voxel-wise standardized 41 uptake value ratio (SUVR) elevation when seen sequentially in serial tau-PET scans. The association of OI with tau accumulation, clinical diagnosis, and cognitive findings 42 43 was evaluated. **Results**: OI showed good dynamic range in the low-SUVR window. 44 Only OI was able to identify subgroups with increasing tau-PET signal in low SUVR 45 meta-ROI groups. OI showed improved association with early clinical disease 46 progression and cognitive scores versus meta-ROI SUVR measures. Conclusion: OI 47 was more sensitive to tau signal elevation and longitudinal change than standard ROI 48 measures, suggesting it is a more sensitive method for detecting early, subtle 49 deposition of neurofibrillary tangles.

50

51 Keywords

52 AV-1451; Flortaucipir; Tau PET; Variability; early detection.

54 INTRODUCTION

Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder 55 56 characterized by abnormal extracellular amyloid- β (A β) plaques and intracellular tau 57 neurofibrillary tangles (NFT)(1). The amyloid cascade hypothesis suggests A β as the 58 primary cause of tau NFT formation and ultimately neuronal loss(2). However, it has 59 also been suggested that the aggregation of pathologic A β and tau might be independent etiologies of AD pathology(3). Studies have found a clear association 60 61 between AD severity and increased tau with positron emission tomography (PET)(4) 62 and that tau-PET is a better predictor of AD dementia (ADD) than amyloid status (1,5). Tau is therefore an attractive target as a biomarker for ADD diagnosis and treatment 63 64 outcome measure.

65

Tau-PET uptake patterns have been associated with Braak NFT staging(6) and ADD 66 67 severity (7,8). Tau-PET signal is associated with aging (4) and with reduced glucose metabolism(7) and can distinguish among clinical phenotypes(7). Longitudinal amyloid 68 69 PET has been studied extensively, tracking participants for over a decade(9). 70 Longitudinal tau-PET studies are in the initial stage of optimization (10-12). Global 71 increases in tau accumulation have been reported, rather than the region-specific 72 sequence that would be expected from the neuropathology literature (4, 10). More 73 longitudinal tau studies are needed to better understand AD pathogenesis. 74

Longitudinal tau-PET reliability is limited by inter-scan variability. The
 standardized-uptake-value-ratio (SUVR) is the most common quantitative measure of

77 radiotracer uptake. SUVR annual change in longitudinal studies has been relatively 78 small compared to group averages(10-12). Annual AV-1451 (Flortaucipir) tau-PET 79 SUVR change in patients with amyloid-positivity and cognitive impairment was around 80 0.05 SUVR(10-12), about 3% of the average cross-sectional SUVR (=1.64) for the 81 group(4). The annual increase was similar to the test-retest variability of AV-1451 with 82 48-hour to 4-week intervals (SUVR changes of up to 0.05)(13). Moreover, for cognitively 83 unimpaired (CU) subjects with amyloid positivity, possibly the earliest stage of AD, the 84 mean annual SUVR change has been estimated at 0.006(10).

85

86 It is therefore important to understand the nature of the variability in serial tau-87 PET scans when neuropathologically-related PET signal changes may be small. 88 Variability is especially problematic in the early stages of tau pathology in which the rate 89 of NFT accumulation is slow and thus difficult to discern relative to the range of random 90 fluctuation noise in tau-PET imaging. To address this problem, we developed a 91 measure of consistency across serial scans called the "overlap index" (OI) based on the 92 hypothesis that random noise/artifacts are unlikely to be repeated over serial scans and 93 voxels with stable signal over time more likely represent true NFT-related binding. We 94 evaluated the ability of OI to measure early, subtle tau-PET signal change, compared to 95 standard region-of-interest (ROI)-based measure, and evaluated for correlation with 96 changes in clinical status.

98 MATERIALS AND METHODS

99 **Participants**

100 Eligible participants (n=339) selected from the Mayo Clinic Study of Aging or the 101 Alzheimer's Disease Research Center had ≥2 serial flortaucipir tau-PET scans with 102 MRI, corresponding to 850 tau-PET scans in total(Supplementary Table1)(10). Studies 103 were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review 104 Boards. Written informed consent was obtained. Enrolled participants are determined to 105 be clinically normal or cognitively impaired by a consensus panel consisting of study 106 coordinators, neuropsychologists, and behavioral neurologists. Methods for defining 107 CU, mild cognitive impairment (MCI), and dementia in both studies conform to 108 standards in the field (14-16). To examine the generalizability of the OI, we also included 109 the longitudinal tau-PET data (n=235, Supplementary Table 2-3) from the Alzheimer's 110 Disease Neuroimaging initiative (ADNI) database (adni.loni.usc.edu).

111

112 **Neuroimaging Methods**

113 Tau-PET imaging was performed with F18-flortaucipir and amyloid-PET with 114 Pittsburgh compound B (PiB) as reported previously (17) (see Supplementary 115 Methods(18-25)). Tau- and amyloid-PET SUVR were normalized to the median uptake 116 in the cerebellar crus. The regional tau-PET SUVRs were calculated by measuring 117 median uptake in each ROI, excluding any voxels segmented as cerebrospinal fluid. A 118 meta-ROI for tau-PET included the amygdala, entorhinal cortex (ERC), fusiform, 119 parahippocampal and inferior temporal and middle temporal gyri(10,24). The tau-PET 120 meta-ROI SUVR was calculated as an average of the median SUVR in each region.

Global cortical amyloid-PET SUVR was computed as a voxel-number weighted average of median uptake across a set of ROIs including the prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate, and precuneus ROIs(24). An SUVR>1.29threshold denoted abnormal tau-PET scans(6). The threshold used to define abnormal PiB-PET was SUVR=1.42(24). Meta-ROI $\triangle SUVR$ was calculated as an annualized difference between the baseline SUVR from the follow-up SUVR.

127

128 **Overlap Index Calculation**

129 OI represents the voxel-wise SUVR elevation consistently present on two serial 130 scans(Fig.1). First, we selected the ROI(or meta-ROI) to be evaluated in the calculation. 131 An intensity threshold (SUVR=1.4) -selected from preliminary experimental 132 tests(Supplementary Fig.1)- was applied to each voxel in the ROI(s). Voxels that 133 survived the intensity threshold were binarized (0/1) as masks (M_b and M_f). Clusters 134 with fewer than 20 contiguous voxels (18-connectivity criterion) were excluded. The 135 spatial overlap between masks (Noverlap) was calculated by counting the number of 136 voxels with an intensity of 1 after multiplying the two masks. OI was calculated by 137 dividing N_{overlap} by the number of voxels where the value is 1 in the M_b (N_b).

138
$$Overlap index (OI) = \frac{Noverlap}{Nb}$$

139 Values of 0 indicate no overlap between scans; conversely, values approaching 1

140 indicate consistent elevation of voxels in the follow-up scan.

141

Unlike standard indices that calculate overlap (*e.g.*, Dice coefficient or Jaccard
index), OI is asymmetrically normalized with to the value in only the first scan. Hence,

OI quantifies the extent to which the high-intensity voxels of the first scan are spatially preserved in the second scan. Biologically, the increased topographic extent of tau uptake over time is usually expected. Therefore, we assumed that the index calculated by a standard symmetric measure (*i.e.*, denominator is a union of both scan) could be less sensitive to the detection of early tau where only a small amount of NFT would exist. An overlap size (OS) quantifying a ratio of the overlap area to the size of the total ROI(s), was also defined as following:

151
$$Overlap \ size \ (OS) = \frac{N_{overlap}}{N_{ROI}}$$

NROL is the number of voxels of ROI(s) included for the analysis. The OI and OS werecalculated for each serial scan pair.

154

155 Statistical Analysis

156 To test for significant group differences in OI and SUVR, we ran non-parametric 157 Kruskal-Wallis tests, followed by *post-hoc* Dunn's multiple comparison test. Non-158 parametric tests were applied as they do not require the data to be normally distributed. 159 To address different stages of the typical Alzheimer's continuum, we separated the CU 160 participants using the amyloid positivity: CU individuals with normal amyloid-PET (CUA-, 161 i.e. not in the Alzheimer's continuum) and CU individuals with abnormal amyloid-PET 162 (CUA+, i.e. early in the Alzheimer's continuum). Then, the clinical change seen in 163 participants at the time points of the serial scans were grouped as CUA-toCUA-, CUA-164 toCUA+, CUA+toCUA+ CUtoMCI/AD, MCItoMCI, MCItoAD, and ADtoAD. For more 165 details, please refer to the supplementary data.

167 **RESULTS**

168 Association of OI with SUVR in Single ROI

169 Scatter plots of voxel intensity within 3D space for a specific ROI demonstrate 170 both low and high-OI examples (Fig.2). For low-OI (Fig.2A), inconsistent voxel signal 171 elevation over serial scans can be seen even when median SUVR of the overall region 172 is above the autopsy tau-PET threshold (SUVR=1.29). The median SUVR fluctuated 173 above and below the threshold in these examples. Conversely, high-OI 174 examples(Fig.2B) show consistent high-intensity voxels over serial scans, with voxels 175 clusters gradually enlarging based on visual assessment even when the median SUVR 176 did not numerically increase. Notably, the median SUVRs of Fig.2B was below 177 threshold. More examples for high-OI can be found in Supplementary Fig.2. 178 179 Fig.3 shows the relationship between OI and baseline SUVR for representative 180 ROIs. OI increased exponentially in the low SUVR range and approached 1.0 around 181 SUVR=1.5 (vertical dotted line) for every region. In the SUVR<1.5 range, the SUVR and 182 OI showed a significant linear relationship for all regions (p<0.005). The regional 183 distribution of OI and SUVR for both MCI and AD were calculated by anatomic region, 184 ranked and displayed on a 3D-rendered plot(Supplementary Fig.3A-B), corroborating 185 the statistically significant correlation of regional OI and SUVR (r=0.8489, 186 Supplementary Fig.3C). 187

188 OI Can Characterize Tau Accumulators

189 Meta-ROI also showed a strong linear correlation with baseline SUVR in the low SUVR range (R²=0.3806), reaching values near 1.0 around SUVR=1.5(Fig.4A). Most 190 191 participants (79.65%) had a below-threshold SUVR (<1.5) whereas OI was more evenly 192 distributed (Fig.4A). OI provides a good dynamic range even in this low-SUVR window. 193 This also held true for follow-up scans(Supplementary Fig.4). A relationship between OI 194 and scan interval was tested. High OI values were found even for relatively long scan 195 intervals (>2yrs) in cases where baseline SUVR was high. In contrast, OI was low 196 regardless of the scan interval for low SUVR cases (Supplementary Fig.5). Multivariable 197 linear regression showed that baseline SUVR better explained the OI than the 198 interval(Supplementary table4).

199

200 Next, we investigated an association of meta-ROI OI and \triangle SUVR. If OI is 201 sensitive to tau burden, the metric would show positive correlation with tau 202 accumulation rate, as an increased extent of tau over time is biologically expected (10-203 12). Supplementary Fig.6A shows pairs of meta-SUVR from two sequential scans for 204 each individual subject. Then, the total cohort was separated into low-OI (OI<0.5) and 205 high-OI (OI>0.5) subgroups(Supplementary Fig.6B-C). Importantly, OI discriminates 206 positive tau accumulation (slope>0) from stable tau. Statistically, a significant positive 207 correlation between OI and \triangle SUVR was also demonstrated (R²=0.1603, 208 p<0.0001;Fig.4B). This significance held true for baseline SUVR>1.5(Supplementary Fig.7A; R²=0.1566,p<0.0001). 209

211	Comparison of baseline meta-SUVR value groups (SUVR<1.29,1.29 <suvr<1.5< th=""></suvr<1.5<>
212	and SUVR>1.5) showed increased \triangle SUVR with increased baseline values (p=0.001);
213	however, the comparison between SUVR<1.29 and 1.29 <suvr<1.5 did="" not="" reach<="" td=""></suvr<1.5>
214	significance (Fig.4C;p=0.46). A significant difference in Δ SUVR was detected between
215	low-OI and high-OI groups within the same SUVR range (Fig.4D;p=0.01 and p=0.006
216	for SUVR<1.29 and 1.29 <suvr<1.5, <math="" average="" notably,="" respectively).="" the="">\DeltaSUVR in the</suvr<1.5,>
217	low-OI group was close to zero or even negative (mean=0.002 and -0.048 for
218	SUVR<1.29 and 1.29 <suvr<1.5, a<="" groups="" high-oi="" respectively),="" showed="" td="" whereas=""></suvr<1.5,>
219	positive tendency in Δ SUVR (mean=0.025, 0.019 and 0.041 for SUVR<1.29,
220	1.29 <suvr<1.5 and="" suvr="">1.5, respectively). There was no significant difference</suvr<1.5>
221	among high-OI groups at different SUVR levels. These results imply that the OI can
222	distinguish tau accumulation within meta-SUVR subgroups that cannot be detected by
223	SUVR alone. To test the reliability, we compared the meta-ROI OI from the first and
224	second scans to the second and third scans, when three or more time points were
225	available. The OI of 1-2 and the OI of 2-3 were highly correlated (r=0.8902) meaning OI
226	is consistent over time(Supplementary Fig.7B).

228 Meta-ROI OI Relationship to Demographic Data

A pairwise comparison with CUA-toCUA- as the control group demonstrated that OI can detect significant differences from the other subgroups including the smallest degree of clinical change, CUA-toCUA+(Fig.5). Baseline SUVR, baseline SUVR_{pvc}, and Δ SUVR from meta-ROI also showed significant differences from the MCI groups, however no significant difference was seen in comparison with the earlier disease
progression groups such as CUA-toCUA+, CUA+toCUA+ and CUtoMCI/AD.

236	The relationship of cognitive scores with meta-ROI OI and SUVR was also
237	investigated. We found that the meta-ROI OI and meta-SUVR had a significant linear
238	relationship with the cognitive scores(Supplementary Fig.8A-B;linear regression,
239	p<0.005). However, the cognitive scores associated more strongly with OI than the
240	SUVR for the global, language, and visuospatial domain (for OI, R^2 =0.2209, 0.2054 and
241	0.1288 for global, language, and visuospatial domain, respectively and for meta-SUVR,
242	R ² =0.1731, 0.1275 and 0.0667 for global, language and visuospatial domain,
243	respectively). For the memory and attention domain, both showed a similar result (for
244	OI, R ² =0.1859 and 0.1337 for memory and attention domain, respectively and for follow-
245	up meta-SUVR, R ² =0.1810 and 0.1422 for memory and attention domain, respectively)
246	
246 247	To evaluate the generalizability of OI metric, we tested OI in the ADNI dataset.
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247 248 249 250 251	This validated many of the results seen in the Mayo cohort. For meta-ROI, OI reached approached 1.0 around SUVR=1.5(Fig.6A). In addition, meta-ROI OI-based grouping was able to discriminate the positive tau accumulator within the same SUVR range(Fig.6C; p<0.001 for SUVR<1.29 and p=0.02 for 1.29 <suvr<1.5) meta-<="" td="" while=""></suvr<1.5)>
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CUA+toCUA+ and CUtoMCI/AD, respectively;Fig.6D). However, fewer significant
 differences were found in SUVR measurements between groups(Fig.6D).

258

259 **DISCUSSION**

In this study, we proposed OI as a means for early detection of tau-PET bindings by evaluating consistency of serial tau-PET scans and tested the ability of OI to identify subtle, but true positive tau binding in serial scans. Participants with high-OI had a larger serial SUVR change than participants with low-OI, a finding which notably was also seen with participants below the tau cut-off (SUVR<1.29). When compared to ROIbased SUVR measurements, OI alone had a significant association with early disease progression.

267

268 Although SUVR and OI showed a significant linear correlation, OI showed better 269 dynamic range in the low-SUVR window. It may be that the typical ROI-based measures 270 that calculate the median SUVR all voxels are less sensitive to the early development of 271 NFT because the local tau-PET signal can be diluted in the process of obtaining the 272 median of the entire ROI(s)(6). In contrast to the ROI method, OI quantifies the spatial 273 consistency only in those voxels with an elevated tau-PET signal. This characteristic of 274 OI is independent of the size of the tau cluster, thus allowing better characterization of 275 small areas of signal elevation in the low SUVR range in which NFT volume is relatively 276 small. In this respect, OI can better detect early stages of tau pathology than the typical 277 ROI-based measurements. In the high SUVR range, this provides less added value 278 because consistency is high when tau is abundant(Supplementary Fig.9). Because AD

279 is a chronic and progressive disease, early detection before devastating symptoms 280 begin is critically important. Tau-PET is in general a promising biomarker, more closely 281 associated with disease severity than other imaging biomarkers; (26) however, inter-282 scan random variability which does not represent true tau pathology presents a 283 significant hurdle(13,27). A recent autopsy study reported that ROI methods be 284 insufficient to detect subtle tau-PET signals in early tau deposition(6), probably 285 reflecting diminished signal-to-noise when a small volume of true radiotracer binding is 286 present(28). Our results suggest that OI may overcome this limitation and be 287 complementary to typical ROI measures for interpreting the early tau-PET signal.

288

289 OI will likely be also useful in distinguishing true tau accumulation from random 290 variability in longitudinal studies. Our results showed that OI can characterize the 291 participants who will accumulate tau amongst those in the low-SUVR and mid-SUVR 292 groups better than meta-ROI. As described earlier, as an increased extent of NFT over 293 time is biologically expected (10-12), OI which is sensitive to subtle tau burden may 294 better identify subjects with true accumulation that was hidden by ROI SUVR washout 295 or random variability. Clearly, there is a wide standard deviation in the high meta-ROI 296 group with some participants showing negative change. This phenomenon of negative 297 change was also observed in previous longitudinal studies reporting some individuals 298 with high baseline SUVR and negative SUVR changes (10-12). The reasons for these 299 negative SUVR changes are not yet well understood. CSF phosphorylated tau level 300 could decrease in the late AD(29) accounting for the negative change. Noise or partial 301 volume effects due to tau aggregation-driven local atrophy may contribute (30, 31).

Further optimization of OI methods to target the high meta-ROI group is an aim of ourongoing work.

304

305 OI was highest in the inferior, middle, and medial temporal lobes including the ERC, and 306 amygdala, areas of elevated tau PET activity described in the literature(8,32). While 307 nonspecific binding related to AV1451 is not well understood in longitudinal data, a 308 possible limitation is that OI may be vulnerable to suprathreshold off-target binding 309 when it consistently occurs in serial scans. For example, the hippocampal OI may be 310 vulnerable to choroid plexus(Supplementary Fig.10). To minimize this, typical non-311 specific binding areas such as basal ganglia and choroid plexus are excluded from 312 meta-ROI analysis. Four cases of non-specific binding in meninges were observed 313 which only affected the OI measurement when meninges had repeated strong signal in 314 the meta-ROI (Supplementary Fig.11). Future work is needed to characterize the effects 315 of off target binding on the SUVR and OI.

316

The difference between OI and SUVR regarding cognitive findings is marginal. This is not unexpected given that our sample population is mixed and comprised of those without significant cognitive impairment (i.e., CU; ~50% of sample), MCI, or early AD (28% of sample) some of whom have little or no cognitive impairment. Our plans are to expand the OI analysis to larger groups of subjects with cognitive impairment to better define clinically utility.

323

324 The statistical significance between early preclinical groups (i.e., CUA-toCUA- vs. 325 CUA-toCUA+) was only demonstrated in the Mayo cohort. Notably, the mean OI values 326 of CUA-toCUA+ group were not different between the cohorts (p=0.9652, mean 327 OI=0.3573 and 0.3558 for Mayo and ADNI, respectively), but the CUA-toCUA- group showed significantly different mean OI between the cohorts (p<0.001, mean OI=0.1832 328 329 and 0.3125 for Mayo and ADNI, respectively). One possible explanation is the relatively 330 smaller number of samples in the CUA-toCUA- group from ADNI cohort (97 for Mayo 331 vs. 26 for ADNI). However, the reason for high OI values in the early preclinical groups 332 should be investigated with neuropathology studies in the future.

333

334 One limitation of this study is the assumption that voxels with artifactual or false-335 positive activity would be less likely to show spatial consistency over-time, an 336 assumption that should be validated with post-mortem neuropathologic data of tau 337 deposition. The SUVR is sensitive to perfusion changes; therefore, interscan 338 comparison may be biased when perfusion differs between the two scans. Despite this 339 limitation, OI performs better for early detection of tau-PET signal and disease 340 progression than the ROI-based SUVR measure. Future investigation with simulation 341 studies will be needed to assess the magnitude of the bias of perfusion on OI. The 342 intensity threshold used in this study was determined observationally. The OI calculation 343 is largely dependent on this threshold level and future work is warranted to determine 344 the optimal threshold among different regions and even at voxel level. Although OI can 345 augment sensitivity to early tau-PET uptake, acquiring two separate PET scans is a 346 disadvantage. Using dynamic scans to derive OI from a single imaging session by

splitting the scan into two segments may address this limitation. Future investigation of
this possible solution is needed, which will require careful optimization given the slow
kinetics of the AV-1451 tracer.

350

351 CONCLUSION

352 By identifying voxels with consistent signal, the OI method could be helpful in 353 measuring early tau-PET signal. This voxel-wise analysis can overcome the limitations 354 of ROI-based measures which had reduced sensitivity to early detection of low levels of 355 tau. The ability of OI to reliably detect true positive binding is likely to have the most 356 impact in the lower SUVR window, reflecting the early stage of neurodegeneration and 357 early tau NFT pathology prior to cognitive decline. Combining the OI method with other 358 methods which minimize inter-scan variability (partial volume correction and optimized 359 reference) may synergistically improve interpretations of longitudinal change in the tau-360 PET signal.

361

362 ACKNOWLEDGMENTS

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365 **DISCLOSURE**

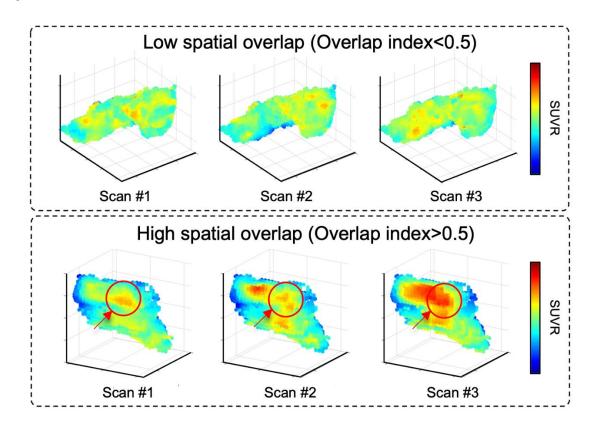
Mr. Senjem has owned stocks and/or options in the following medical-related 366 367 companies: Align Technology, Inovio Biomedical, Johnson & Johnson, Mesa 368 Laboratories, Nvidia, LHC Group, Natus Medical Incorporated, Varex Imaging 369 Corporation, CRISPR Therapeutics, Gilead Sciences, Ionis Pharmaceuticals, and 370 Medtronic. Dr. Gunter reports an abandoned provisional patent for face replacement in 371 MR imaging unrelated to the current publication. Dr. Schwarz has given lectures 372 sponsored by Karolinska Institute unrelated to the current publication. Dr. Knopman 373 served on a data safety monitoring board for the DIAN study, serves on a data safety 374 monitoring board for a Biogen tau therapeutic, and is a site investigator in the Biogen 375 aducanumab trials, an investigator in clinical trials sponsored by Lilly Pharmaceuticals 376 and USC, and a consultant for Samus Therapeutics, Third Rock, Roche and Alzeca 377 Biosciences but receives no personal compensation. Dr. Jack serves on an 378 independent data monitoring board for F. Hoffmann-La Roche, has consulted and 379 spoken for Eisai, and has consulted for Biogen but receives no personal compensation 380 from any commercial entity. Dr. Petersen receives research support from GHR 381 Foundation, has received royalties from Oxford University Press, is a member of a data 382 safety monitoring board for Genentech, and is a consultant for Roche, Merck, Biogen, 383 and Eisai. Dr. Lowe receives research support from GE Healthcare, Siemens Molecular 384 Imaging, and AVID Radiopharmaceuticals, and consults for Bayer Schering, Piramal 385 Life Sciences, Life Molecular Imaging, Eisai, AVID Radiopharmaceuticals, and Merck. 386 No other potential conflicts of interest relevant to this article exist.

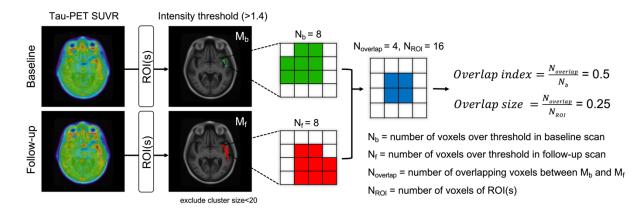
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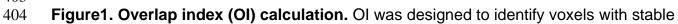
388 KEY POINTS

- 389 **Question**: Is identifying voxels with stable signal over time a more sensitive method for
- 390 detecting early, subtle development of neurofibrillary tangles?
- 391 **Pertinent Findings**: Only OI was able to identify subgroups with increasing tau-PET
- 392 signal in low SUVR meta-ROI groups. OI showed improved association with early
- 393 disease progression and cognitive scores vs. meta-ROI SUVR measures.
- 394 **Implications for Patient Care**: Our findings demonstrate that the proposed method
- 395 could be helpful in detecting tau signal elevation and longitudinal changes than standard
- 396 ROI measures, suggesting it is less vulnerable to random variability and more sensitive
- 397 to early, subtle ligand binding.

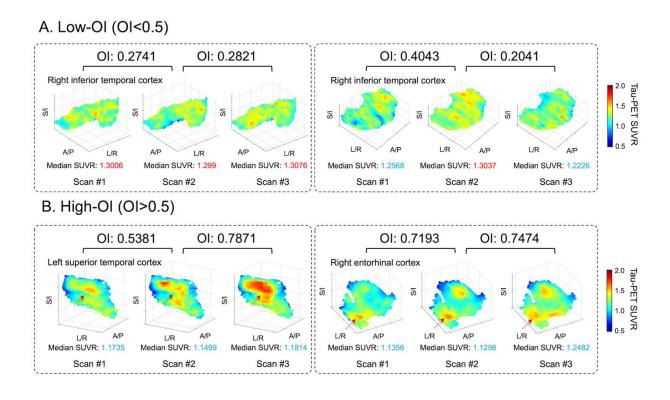
399 Graphical abstract







405 high activity over time using two consecutive tau-PET scans.



408 Figure 2. Examples for low-OI and high-OI. Three consecutive 3D scatter plots are 409 displayed in each box for four different examples, representing the tau-PET SUVR of each voxel in each scan from an individual subject. (A) shows low-OI and (B) shows 410 411 high-OI cases. Below each rendering, the median SUVR represents a median value for 412 all voxels in each region. The colorbar indicates the intensity of each voxel. Font color of median SUVR is red when >1.29 and blue when <1.29. Red arrows in B indicate the 413 414 regions showing spatial consistency. Various anatomic regions are plotted and labeled 415 in each panel.

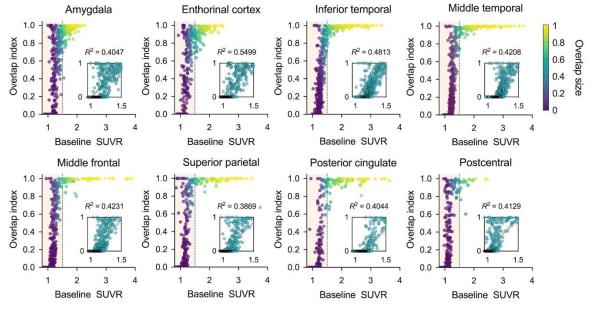
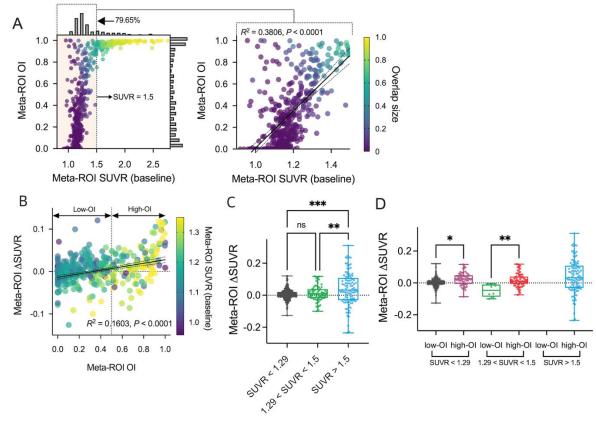


Figure 3. Relationship between OI and baseline SUVR in single ROI. Bilateral ROIs

419 were included in the calculations. A small panel inside the figure illustrates an enlarged

420 view of the lower SUVR range (from 0.9 to 1.5).



422 423 Figure 4. Relationship between meta-ROI OI and meta-ROI SUVR. (A) A scatterplot 424 (left) of baseline SUVR and OI for meta-ROI. Histograms are displayed along SUVR 425 and OI axis, respectively. The low SUVR range (<1.5) was magnified in a separate 426 scatterplot (right) with linear regression (solid black line) and 95% confidence band 427 (dotted black lines). (B) Scatterplot of meta-ROI OI and \triangle SUVR with regression. (C) Comparison of ∆SUVR between SUVR based subgroups. (D) The SUVR based 428 429 subgroups in C were further separated into low-OI and high-OI categories. *p<0.05, 430 **p<0.05, ***p<0.005, *post-hoc* Dunn's tests.

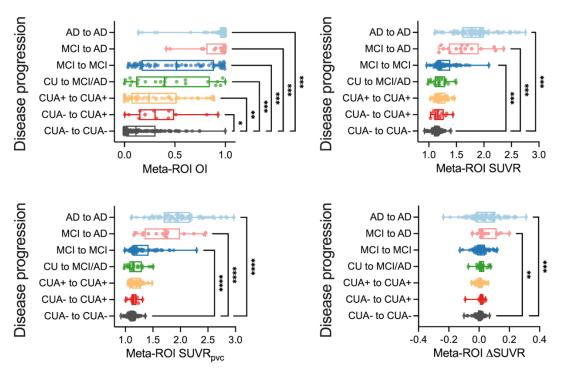
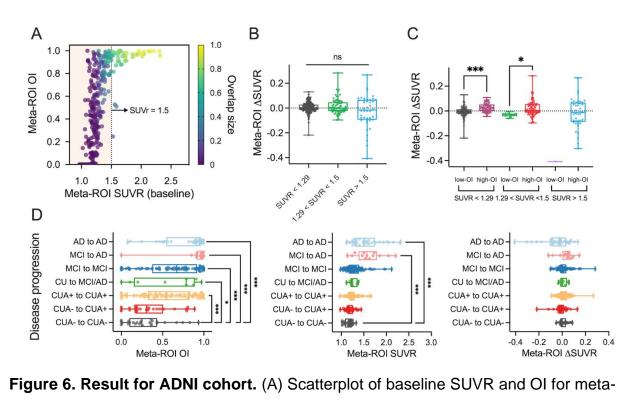




Figure 5. Association of overlap index with disease progression. (A) Tau-PET

- 434 variables in different clinical groups. OI, baseline SUVR, baseline SUVR_{pvc}, and Δ SUVR
- 435 from meta-ROI of CUA-toCUA- were compared with those of other groups. *p<0.05,
- 436 **p<0.05, ***p<0.005, *post-hoc* Dunn's tests.



438 439

440 ROI. (B) Comparison of \triangle SUVR between SUVR based subgroups. (C) The SUVR

- 441 based subgroups in B were further separated into low-OI and high-OI categories. (D)
- 442 OI, baseline SUVR, and Δ SUVR from meta-ROI of CUA-toCUA- were compared with
- those of other groups. *p<0.05, **p<0.05, ***p<0.005, *post hoc* Dunn's tests.

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1 Supplemental Data

2 Neuroimaging methods

3 T1-weighted MRI was acquired using 3T scanners manufactured by General 4 Electric (GE) and Siemens using a 3D Sagittal Magnetization-Prepared Rapid 5 Acquisition Gradient Recalled Echo (MPRAGE) sequence (number of scans=544 and 6 306 for GE and Siemens, respectively). During the analysis, two scans were excluded 7 because MRI data was unusable due to motion. Tau-PET and amyloid PET scans were 8 acquired using the PET/CT scanner by GE and Siemens operating in 3D mode (number 9 of scans=817 and 33, for GE and Siemens, respectively for tau-PET; number of 10 scans=782 and 31, for GE and Siemens, respectively for amyloid-PET). To harmonize 11 the inter-scan difference, for PET scanners, different filters were applied to each during 12 reconstruction in order to harmonize resolution according to the method of Joshi et al 13 (1). For MRI scanners, we have previously shown that the effects on PET quantification 14 are negligible (2). A CT scan was obtained for attenuation correction. For tau-PET, an 15 intravenous bolus injection of ~370 MBq (range 333-407 MBq) F18-flortaucipir was administered, and PET/CT imaging was performed with a 20-minute PET acquisition of 16 17 four 5-min dynamic frames, 80-100 minutes after injection. Amyloid PET imaging was 18 performed using Pittsburgh compound B (PiB) and consisted of four 5-min dynamic 19 frames, 40–60 min after injection of 628 MBq (range 385–723 MBq) of 11C-PiB. The 20 mean and standard deviation of specific activity for the entire period that the images 21 were acquired was 2.58 (± 0.32) Ci/µmol and 3.44 (± 0.78) Ci/µmol for PiB and AV1451, 22 respectively. An iterative reconstruction algorithm was applied. Emission data were 23 reconstructed into a 256×256 matrix with a 30-cm field of view (in-plane pixel size = 1.0

24 mm). Standard corrections for attenuation, scatter, random coincidences and decay
25 were applied as well as a 5 mm Gaussian post-reconstruction filter. The images from
26 the four dynamic frames were averaged to create a single static image.

27

28 The static tau-PET image volumes of each participant were rigidly co-registered 29 to the corresponding T1-weighted MRI using 6-degree-of-freedom registration 30 ("spm_coreq") in SPM5. The automated anatomic labeling (AAL) atlas (3) was 31 normalized to the custom template (4) using the unified segmentation method in SPM5 32 giving a set of labels corresponding to the custom template space. SPM5 unified 33 segmentation (5) with a custom elderly template generated from 200 AD and 200 34 controls and tissue priors (4) was used to segment the MRI into GM, WM, CSF, and to 35 warp the atlas labels from template space to subject space. Within each subject, SPM5 co-registration was performed on the longitudinal series of MRI images to align to the 36 37 mean across all images, thus forming a new mean image, and repeated until 38 convergence (6). SUVR images were normalized to the uptake in the cerebellar crus 39 (7). For each timepoint, the tau-PET images were resampled into the space of the mean 40 MPRAGE. The regional SUVRs were calculated by measuring median uptake in each 41 ROI, excluding any voxels segmented as cerebrospinal fluid. A meta-ROI for tau-PET 42 included the amygdala, entorhinal cortex (ERC), fusiform, parahippocampal and inferior 43 temporal and middle temporal gyri (8,9). The tau-PET meta-ROI SUVR was calculated as an average of the median SUVR in each region. We did not use a voxel-number 44 45 weighted average for the meta-ROI SUVR calculation because the weighted average 46 might penalize small ROI values such as for the entorhinal cortex or amygdala,

47 anatomic regions of known early NFT accumulation. Global cortical amyloid PET SUVR 48 was computed as a voxel-number weighted average of median SUVR in each meta-ROI 49 region including the prefrontal, orbitofrontal, parietal, temporal, anterior and posterior 50 cingulate, and precuneus ROIs (9). The threshold used to define abnormal PiB PET 51 was SUVR=1.42 (9). All analysis was performed using non-partial volume corrected 52 (PVC) PET images. For comparison with non-PVC images, tau-PET with PVC was 53 evaluated. For the PVC, each PET image voxel was divided by the value in the tissue 54 mask to generate a PVC image (10) and an unsmoothed binary MRI grey matter mask 55 applied to yield a grey matter sharpened PET image.

56

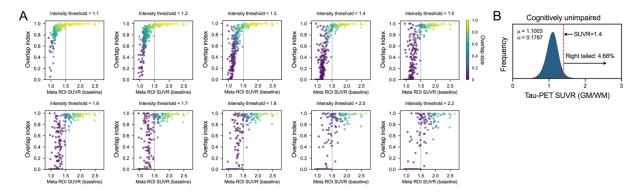
57 Statistical tests

58 The association of regional OI and regional SUVR from the total cohort was 59 assessed with Pearson's correlation to evaluate the topographical relationship of the 60 two measurements. An association of OI with SUVR in the lower SUVR range (<1.5) 61 was tested using linear regression. Meta-ROI \triangle SUVR for each individual was calculated 62 by subtracting the baseline SUVR from the follow-up SUVR and dividing by the time 63 difference in years. To investigate the association of OI with meta-ROI Δ SUVR, the total 64 cohort was separated into three sub-groups (SUVR<1.29, 1.29<SUVR<1.5 and 65 SUVR>1.5) of baseline meta-ROI SUVR, further separated into low-OI (OI<0.5) and high-OI (OI>0.5) group based on meta-ROI OI value. The difference of meta-ROI 66 67 △SUVR between groups was tested by *post-hoc* Dunn's multiple comparison test after 68 non-parametric Kruskal-Wallis tests. To address different stages of the typical 69 Alzheimer's continuum, we separated the CU participants using the amyloid positivity: 70 CU individuals with normal amyloid PET (CUA-, i.e. not in the Alzheimer's continuum)

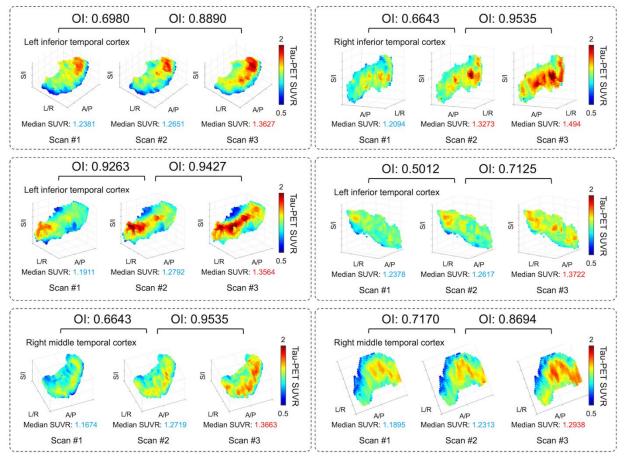
71 and CU individuals with abnormal amyloid PET (CUA+, i.e. early in the Alzheimer's 72 continuum). Then, the clinical change seen in participants at the time points of the serial scans were grouped as CUA-toCUA-, CUA-toCUA+, CUA+toCUA+ CUtoMCI/AD, 73 74 MCItoMCI, MCItoAD, and ADtoAD. Subjects for which clinical diagnosis was not 75 available were excluded from the diagnostic group analysis. The associations with 76 diagnostic change groups were assessed by *post-hoc* Dunn's multiple comparison test 77 after non-parametric Kruskal-Wallis tests. Analysis was performed using Matlab (version 78 9.4) and GraphPad Prism (version 9.0.0).

80 Supplementary Figures

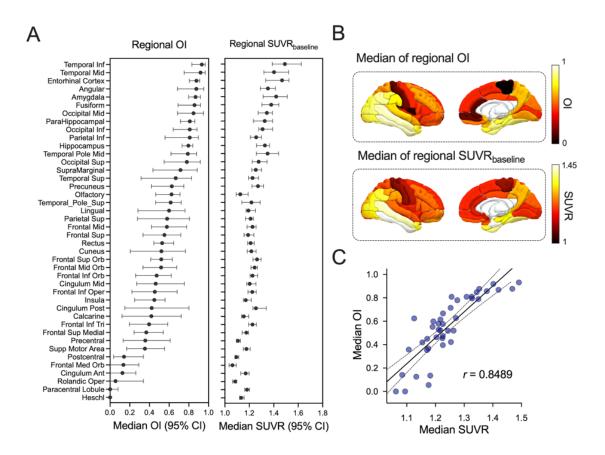




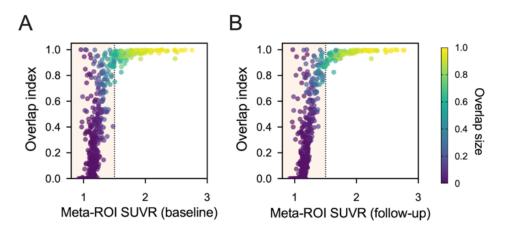
83 Supplementary Figure 1. Intensity threshold comparison. (A) In order to determine 84 the intensity threshold, experimental tests were performed for various threshold levels 85 (from 1.1 to 2.2). We found that OI was easily saturated if the OI threshold was low because too many voxels were included in the mask. In contrast, if a more stringent 86 threshold was applied, fewer voxels survived and the OI calculation became unstable. 87 88 For these higher intensity thresholds, identifying abnormal regions is not typically a 89 diagnostic dilemma and standard ROI analysis is sufficient. The threshold level used for 90 the main analysis (SUVR=1.4) was determined observationally. (B) A histogram of 91 voxel-wise SUVR values for all the gray and white matter in the brain over a cognitively 92 unimpaired group was derived. The arbitrarily determined threshold (SUVR=1.4) 93 corresponds to a right-tailed 4.68% (1.67xSD) meaning that the voxels with SUVR >1.4 94 are fairly rare in the brain of CU participants, serving as a reasonable threshold for the 95 purposes of OI calculation.



- 98 Supplementary Figure 2. Examples of high-OI cases. Three consecutive 3D scatter
- 99 plots in each dotted box represent tau-PET SUVR of each voxel in each scan from an
- 100 individual subject with high OI (>0.5) and low median SUVR at the first scan (<1.29).



104 Supplementary Figure 3. Topographical pattern of overlap index. (A) For each 105 specific brain region, the median of regional OI and regional SUVR from CI cohort was 106 displayed with 95% confidence intervals. The brain regions were sorted high to low in 107 the median of regional OI. Bilateral hemispheres were used together for OI and SUVR 108 calculation. (B) Median of regional OI and SUVR illustrated in 3D rendering plot. (C) 109 The scatter plot illustrates an association between median SUVR and median OI. r 110 indicates the Pearson's correlation coefficient. The black solid line and dotted lines represent a regression line and its 95% confidence band, respectively. 111 112



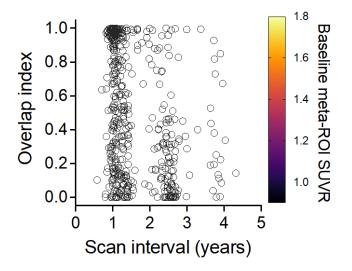
114 Supplementary Figure 4. Association of OI with baseline and follow-up SUVR. (A)

115 The scatterplot illustrates the association between baseline SUVR and OI for meta-ROI.

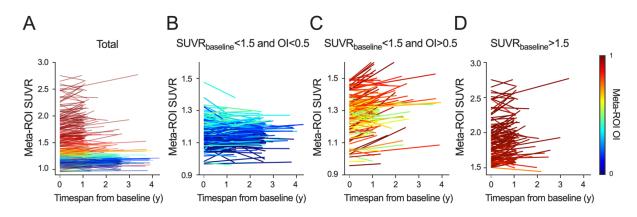
116 The dot's color indicates the overlap size. (B) The scatterplot illustrates the association

between follow-up SUVR and OI from meta-ROI. The dot's color indicates the overlap

118 size.



121 Supplementary Figure 5. Association of OI with inter-scan interval.



124 **Supplementary Figure 6.** (A) Spaghetti plot of SUVR trajectory from baseline to next

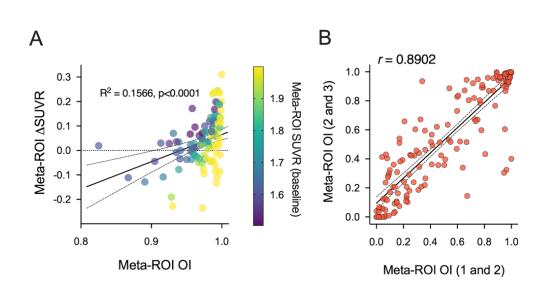
125 follow-up showing meta-ROI SUVR for all individuals. The line color was coded by each

126 individual OI. (B) Spaghetti plot of SUVR trajectory showing meta-ROI SUVR for

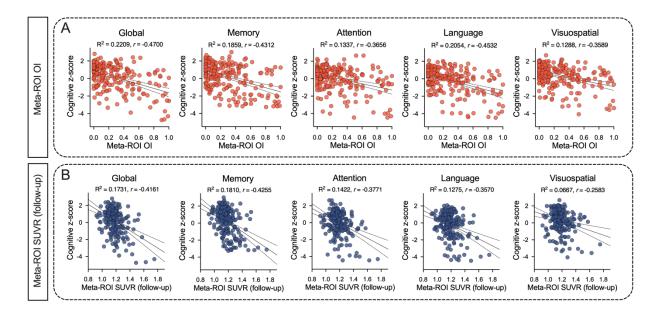
127 SUVR<1.5 and OI<0.5. (C) Spaghetti plot of SUVR trajectory showing meta-ROI SUVR

128 for SUVR<1.5 and OI>0.5. (D) Spaghetti plot of SUVR trajectory showing meta-ROI

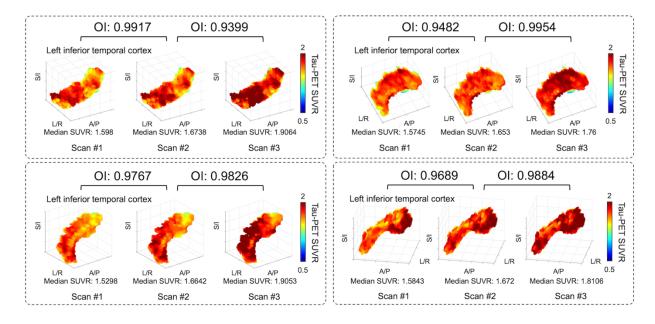
- 129 SUVR for SUVR>1.5.
- 130



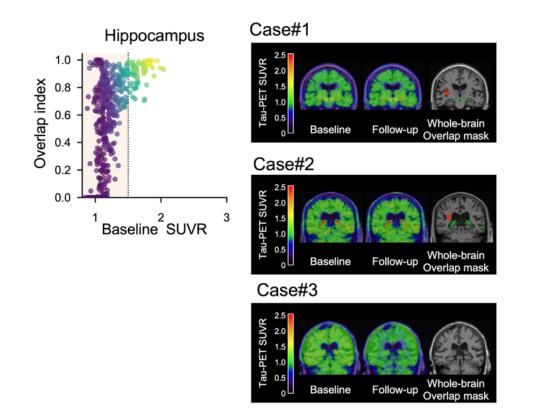
Supplementary Figure 7. (A) Association between meta-ROI OI and meta-ROI ∆SUVR
where baseline SUVR>1.5. The black solid line and dotted lines represent a regression
line and its 95% confidence band, respectively. (B) Consistency of the OI metric. The
meta-ROI OI from the first and second scans and that from the second and third scans
in the cohort who had three or more time points were compared. r indicates the
Pearson's correlation coefficient.



- 144 Supplementary Figure 8. Association of overlap index with cognitive scores. Four
- 145 cognitive domains (memory, attention, language and visuospatial) and global scores
- 146 (average of all domains) were tested. Only participants who had cognitive scores were
- 147 included in this analysis (Supplementary Table1). (A) Relationship between meta-ROI
- 148 OI and cognitive scores. The black solid line and dotted lines represent a regression line
- and its 95% confidence interval, respectively. r shows Pearson's correlation coefficient.
- 150 (B) Relationship between meta-ROI Δ SUVR and cognitive scores. The black solid line
- and dotted lines represent a regression line and its 95% confidence interval,
- 152 respectively. r shows Pearson's correlation coefficient.
- 153



- 155 Supplementary Figure 9. Examples of high SUVR cases. Three consecutive 3D
- 156 scatter plots in each dotted box represent the tau-PET SUVR of each voxel in each
- 157 scan from an individual subject. OI becomes saturated (close to 1) in the high SUVR
- 158 range because serial scans with abundant tau signals tend to be consistent.
- 159



- 161 **Supplementary Figure 10. Choroid plexus bindings.** High OI was frequently
- 162 observed in the lower baseline SUVR range in hippocampus. The coronal slices show
- 163 the baseline tau-PET, follow-up tau-PET, and their overlap mask between high-intensity
- voxels (SUVR>1.4) for three representative cases. The red arrows indicate the choroid
- 165 plexus overlap between baseline and follow-up scans.
- 166

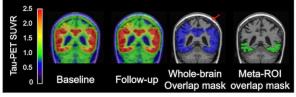
Case#1

Baseline clinical diagnosis: CU Meta-ROI SUVR – baseline: 1.2046, follow-up: 1.0286 Meta-ROI OI: 0



Case#3

Baseline clinical diagnosis: AD Meta-ROI SUVR – baseline: 1.7420, follow-up: 1.8856 Meta-ROI OI: 0.9843



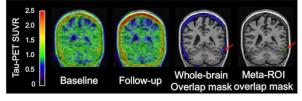
Case#2

Baseline clinical diagnosis: MCI Meta-ROI SUVR – baseline: 1.2847, follow-up: 1.2663 Meta-ROI OI: 0.5179



Case#4

Baseline clinical diagnosis: FTD Meta-ROI SUVR – baseline: 1.0579, follow-up: 1.0208 Meta-ROI OI: 0.8018



- 168 Supplementary Figure 11. Meninges binding. The coronal slices show the baseline
- 169 tau-PET, follow-up tau-PET, overlap mask of whole brain and overlap mask within the
- 170 meta-ROI for four representative cases. The red arrows indicate the meninges overlap
- 171 between baseline and follow-up scans.
- 172

173	Supplementary	Table 1	. Participant	demographics.
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Baseline Characteristics	Summary
Number of participants (total)	339
Total tau-PET scans, n (%)	
2	189 (55.75)
3	129 (38.05)
>4	21 (6.19)
Time between consecutive scan, years*	
Median (IQR)	1.24 (1.04, 2.32)
Min, max	0.58, 4.32
Age at baseline PET, years	
Median (IQR)	68 (62, 76)
Min, max	33 95
Education, years {1}	
Mean (SD)	15.39 (2.66)
Male sex, n (%)	195 (57.52%)
PiB SUVR at baseline {16}	
Median (IQR)	1.72 (1.34 2.14)
Min, max	1.16 3.38
Diagnosis at baseline, n (%) {1}	
Cognitively Unimpaired	172 (50.74)
Mild Cognitive Impairment	62 (18.29)
Alzheimer's Dementia	47 (13.86)
Lewy Body Dementia	9 (2.65)
REM sleep Behavior Disorder	7 (2.06)
Frontotemporal Dementia	9 (2.65)
Posterior Cortical Atrophy	8 (2.36)
Logopenic Progressive Aphasia	2 (0.59)
Progressive Supranuclear Palsy	1 (0.29)
Progressive Fluent Aphasia/semantic aphasia	4 (1.18)
Progressive associative agnosia/prosopagnosia	1 (0.29)
Unknown	17 (5.01)
APOE ε4 carrier, n (%) {3}	128 (38.10)
Short Test of Mental Status score at baseline, median (IQR) {15}	35 (31 37)
Cognitive z scores at baseline, median (IQR)	
Global {174}	0.6906 (-0.3220 1.1513)
Memory {159}	0.6084 (-0.4529 1.3066)
Attention {165}	0.3680 (-0.4391 0.9368)
Language {159}	0.3230 (-0.4653 0.8395)
Visuospatial {170}	0.5789 (-0.0615 1.2111)

^{*} Based on all scans for all individuals.

175 {} Brackets in the characteristics column indicate the number of participants missing this

176 particular variable.

Baseline Characteristics	Summary
Number of participants (total)	235
Total tau-PET scans, n (%)	
2	158 (67.23)
3	67 (28.51)
>4	10 (4.26)
Time between consecutive scan, years*	
Median (IQR)	1.03 (0.98, 1.25)
Min, max	0.58, 2.92
Age at baseline PET, years	
Median (IQR)	74 (69, 79)
Min, max	56 90
Education, years	
Mean (SD)	16.32 (2.51)
Male sex, n (%)	112 (47.66%)
AV45 SUVR at baseline {75}	
Median (IQR)	1.17 (1.03 1.36)
Min, max	0.81 1.72
Diagnosis at baseline, n (%) {1}	
Cognitively Unimpaired	127 (54.04)
Mild Cognitive Impairment	78 (33.19)
Alzheimer's Dementia	30 (12.77)
APOE ε4 carrier, n (%) {6}	128 (48.47)

177 Supplementary Table 2. ADNI participant demographics.

178

179 * Based on all scans for all individuals.

180 {} Brackets in the characteristics column indicate the number of participants missing this

181 particular variable.

Supplementary Table 3. Image IDs for ADNI cohort.

MRI_ImageID											
1573620	11084935	1655397	11142379	1990073	11325694	1758062	11316836	1640943	11039209	11185266	I1004681
1906797	11266356	1910675	11184047	11153132	11019265	11068952	11006005	1801187	11222562	11325980	I1182315
I1050345	1695035	1655561	1895057	11086094	11188738	11047958	11190195	1955110	1766317	11012942	1996464
1687384	1916119	1920960	11142367	11253141	11326332	11229050	11325533	11116518	1992457	11320847	I1169375
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	1946089	11232727	1858115	11145242	11206710	11178741	11191368	11232729	1761087	11017333	11333863	

Supplementary Table 4. Multivariate regression analysis. Each independent variable was standardized (i.e., centering and scaling) for the analysis.

Variables	Coefficient (95% Confidence interval)	P value	
Scan interval	-0.04512 (-0.06856 to -0.02168)	0.0002	
Baseline SUVR	0.2506 (0.2271 to 0.2740)	<0.0001	
Intercept	0.4881 (0.4657 to 0.5105)	<0.0001	

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