

Differential atrophy along the longitudinal axis of the hippocampus in Alzheimer's Disease and Suspected Non-Alzheimer's Disease Pathophysiology (SNAP)

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Differential atrophy along the longitudinal axis of the hippocampus in Alzheimer's Disease and Suspected Non-Alzheimer's Disease Pathophysiology (SNAP)

ABSTRACT

Purpose: Cerebrospinal fluid (CSF) biomarkers are increasingly used to support Alzheimer's disease (AD) diagnosis: Alzheimer's Disease continuum (ADc) is defined by abnormal amyloid-beta ($A\beta$), while Suspected Non-AD Pathophysiology (SNAP) refers to normal $A\beta$ with elevated tau. Given the differential properties along the hippocampal longitudinal axis, this study aimed to evaluate antero-posterior subregional hippocampal volume differences among ADc, SNAP, and controls, and their associations with CSF biomarkers and clinical presentation.

Methods: Data from 1242 participants in the Alzheimer's Disease Neuroimaging Initiative were analyzed. Controls (n=234) had normal CSF $A\beta$ (≥ 192 pg/ml), total tau (< 93 pg/ml), and phosphorylated tau (< 23 pg/ml). ADc individuals (n=784) had abnormal $A\beta$, and SNAP (n=224) showed normal $A\beta$ with elevated tau. T1-weighted MRI scans were used to segment the hippocampus into anterior, intermediate, and posterior subregions. Controlling for age, sex, and multiple comparisons, groups were compared using one-way ANOVA, and Pearson correlation coefficients were calculated to assess the relationships between volumetric variables and age, CSF biomarkers, or neuropsychological scores.

Results: ADc individuals showed significantly lower total and subregional hippocampal volumes compared with SNAP and controls ($P < 0.001$). Normalized volumes to total ipsilateral hippocampal volume revealed greater posterior atrophy ($P < 0.001$) and relatively higher anterior volume ($P < 0.01$) in ADc. SNAP and controls showed stronger correlations between hippocampal volumes and age. Several subregional hippocampal volumes correlated with CSF biomarkers, cognitive performance, neuropsychiatric symptoms, and functional impairment.

Conclusion: This study reveals distinct patterns of hippocampal atrophy in ADc and SNAP, enhancing our understanding of their differential pathophysiology and associated clinical features.

27 **Abbreviations:**

28 A β , amyloid- β ; AD, Alzheimer's Disease; ADc, Alzheimer's Disease continuum; ADNI, Alzheimer's Disease
29 Neuroimaging Initiative; AUC, area under curve; CDR, clinical dementia rating; CSF, cerebrospinal fluid;
30 eTIV, estimated total intracranial volume; FAQ, Functional Activities Questionnaire; GDR, geriatric
31 depression scale; MMSE, mini-mental state exam; NPI-Q, Neuropsychiatric Inventory Q; ROC, receiver
32 operating characteristic; Suspected Non-AD Pathophysiology, SNAP; P-Tau, phosphorylated Tau; T-Tau, total
33 Tau.

34 INTRODUCTION

35 Alzheimer's disease (AD) is characterized by the accumulation of amyloid- β (A β) and Tau proteins in the brain,
36 leading to neurodegeneration and cognitive decline [1, 2]. Cerebrospinal fluid (CSF) biomarkers are
37 increasingly used in diagnosing neurodegenerative conditions. Biomarker-based criteria were proposed to
38 classify individuals based on their amyloid, Tau, and/or neurodegeneration/neuronal injury status [3].
39 According to these criteria, indirect evidence of aggregated A β pathology, such as decreased levels in CSF,
40 defines the Alzheimer's disease continuum (ADc). The introduction of these criteria has led to the concept of
41 suspected non-AD pathophysiology (SNAP), which describes individuals with no evidence of A β pathology but
42 with signs of Tau pathology or neurodegeneration, indicated by elevated levels of CSF phosphorylated Tau (P-
43 Tau) or total Tau (T-Tau), respectively. While the revised criteria for AD diagnosis and staging undervalues the
44 clinical significance of SNAP cases, it also highlights that these could correspond to neuropathologically
45 defined primary age-related tauopathy (PART) [4], which is a non-AD condition still understudied, but known
46 to associate with specific clinical and imaging profiles [5, 6].

47 The underlying pathological processes of SNAP remain unclear and need to be distinguished from those of
48 ADc. One of the brain structures affected early on in AD pathogenesis is the hippocampus, which is
49 heterogeneous along its longitudinal axis in terms of gene expression, electrophysiology, connectivity, and
50 function [7, 8]. Furthermore, recent research has shown that the posterior hippocampus is more susceptible to
51 atrophy than the anterior or intermediate portions in clinically defined AD [9].

52 In this study, we used the same algorithm to segment the HPC into those subregions to assess atrophy along the
53 longitudinal axis of the hippocampus in both ADc and SNAP, as defined by CSF A β , P-Tau, and T-Tau levels.
54 We also aimed to determine how these patterns of atrophy could help differentiate between these conditions at
55 an early stage of the ADc. Additionally, we evaluated how various subregional volumetric metrics correlate
56 with clinical presentation and CSF biomarkers.

57 MATERIALS AND METHODS

58 Research design, subjects and variables

59 The data utilized in this study were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI)
60 database (adni.loni.usc.edu), established in 2003 as a public–private partnership led by principal investigator
61 Michael W. Weiner, MD. The primary aim of ADNI has been to investigate whether various metrics, including
62 those derived from magnetic resonance imaging (MRI), are associated with cognitive dysfunction and the onset
63 of AD. This initiative received approval from the institutional ethical committees of all participating
64 institutions, and written informed consent was obtained from all research participants and, when applicable,
65 from collateral informants. The ADNI database encompasses data from over 60 sites across the USA and
66 Canada. Following approval and granted access to the data, we retrieved ADNI data from
67 <https://ida.loni.usc.edu/> across all available cohorts (ADNI-1, ADNI-GO, ADNI-2, and ADNI-3). Individuals
68 were included based on the availability of CSF biomarkers. ADc was defined as CSF A β < 192 pg/ml; SNAP
69 had A β levels $\geq$ 192 pg/ml with T-Tau levels $\geq$ 93 pg/ml or P-Tau levels $\geq$ 23 pg/ml. Sex, age, volumetric T1-
70 weighted MRI acquisition, scores on the Mini-Mental State Exam (MMSE), Clinical Dementia Rating (CDR),
71 Neuropsychiatric Inventory Q (NPI-Q), Geriatric Depression Scale (GDS), and Functional Activities
72 Questionnaire (FAQ) collected closest to the date of lumbar puncture were obtained for analysis.

73

74 MRI brain imaging analysis and HPC segmentation

75 Volumetric T1-weighted MRI scans were converted to NIfTI format, downloaded, and subjected to further
76 analysis. Structural data were processed using the standard semiautomatic workflow implemented in FreeSurfer
77 toolkit version 6.0 (<http://surfer.nmr.mgh.harvard.edu/>). This pipeline involves 31 processing steps, including
78 spatial normalization, skull stripping, intensity normalization, gray-white matter tessellation, and segmentation
79 of cortical, subcortical, and white matter regions. This pipeline has been validated against manual
80 segmentations [10] and is considered reliable across sessions, scanner platforms, updates and field strengths
81 [11]. For the purposes of the present study, only left hippocampus, right hippocampus and estimated total
82 intracranial volume (eTIV) were considered. The segmentation of the hippocampus along its longitudinal axis
83 was performed as described by Morais-Ribeiro et al. [9]. Briefly, this segmentation method builds upon an
84 algorithm previously described by Lerma-Usabiaga et al. [12] and is publicly available at

85 <https://github.com/anacoelho/HippocampusAxisAnalysis.git>. Principal component analysis is initially
86 conducted on all points belonging to the hippocampus to derive the longitudinal axis, which is then refined
87 using quadratic Bézier curve. Subsequently, orthogonal planes to the longitudinal axis are defined to perform
88 the sub-segmentation into three hippocampal subdivisions: anterior, intermediate, and posterior. The volume of
89 each subdivision is computed accordingly.

90

91 Statistical analysis

92 Subregional volumes were normalized by either dividing absolute volume by the absolute total hippocampus
93 volume or by eTIV as indicated. Residuals of regression were calculated for volumetric measures and clinical
94 scores, controlling for age and sex, except when analyses over age were performed, in which case adjustment
95 only for sex was conducted in this way. Group comparisons were conducted using one-way ANOVA with
96 adjustment for eTIV, age, and sex, followed by Tukey's multiple comparisons post hoc test – data are presented
97 as box-whisker plots, with the median (center line), 25th to 75th percentiles (box), and minimal and maximal
98 values (whiskers). Pearson correlation coefficients (r) were calculated to analyze the relationship of volume
99 metrics with age, and comparisons between groups were performed using the Jennrich test with adjustment for
100 multiple comparisons using Bonferroni correction – scatterplots with linear regression trend lines and 95%
101 confidence intervals were generated to visualize the correlation data. The discrimination magnitude of the
102 anterior/posterior hippocampal volume ratio between ADc and SNAP in early age was assessed by calculating
103 the area under the curve (AUC) of the receiver operating characteristic (ROC). Correlation analyses (r) between
104 subregional volumetric metrics and either the clinical scores or CSF biomarkers were represented as heat maps,
105 with control for multiple corrections using the Benjamini-Hochberg procedure ($FDR < 5\%$). CSF levels of A β ,
106 P-Tau, T-Tau, and age were compared between groups using one-way ANOVA with Tukey's multiple
107 comparisons post hoc test. Sex distribution between groups was analyzed using the chi-squared test. Outliers
108 were excluded via the ROUT method ($Q\ 0.1\%$). Results were considered significant when $P < 0.05$, except
109 when adjustment for multiple comparisons was conducted (adjusted significance P is indicated in corresponding
110 figures). Tests were two-sided. Stata 16.1 was used for calculating residuals, conducting the Jennrich test,
111 graphing volumetric variations over age, and generating ROCs. Prism 7 (GraphPad) was utilized for outlier
112 identification, one-way ANOVA, Pearson coefficients calculation, graphing box-whisker plots, stacked bar
113 charts, and correlational heat maps.

114 RESULTS

115 A total of 784 individuals classified as ADc (defined by abnormal A β concentration in CSF), 224 SNAP
116 participants (exhibiting normal CSF A β levels but abnormal T-Tau or P-Tau), and 234 controls (displaying
117 normal levels of A β , T-Tau, and P-Tau) were included. As anticipated, ADc individuals exhibited reduced A β
118 levels compared with the other groups, while no differences were observed between controls and SNAP in A β
119 levels. Significant differences were observed among the three groups in both T-Tau and P-Tau levels (Online
120 supplemental data - Fig S1). ADc participants were older compared with SNAP, with no other significant age
121 differences among the groups. There were no differences in sex proportions between the groups (Online
122 supplemental data - Fig S2).

124 Total HPC volume

125 Initially, we compared the volumes of the total HPC among the groups. Controlling for age, sex, and eTIV,
126 ADc participants showed significantly diminished volumes of both right ($P < 0.001$) and left ($P < 0.001$)
127 hippocampus compared with the other groups (Fig 1A, Online supplemental data – Fig S3A). Adjusting for sex
128 and eTIV, a significant age-related decrease in hippocampal volume was observed bilaterally across all three
129 groups. However, on the right, ADc correlation was less pronounced compared with controls ($P = 0.002$) and
130 SNAP ($P < 0.001$); on the left hemisphere, ADc group showed a significantly different correlation compared
131 with SNAP only ($P = 0.006$) (Fig 1B, Online supplemental data - Fig S3B).

133 Volume of subregions along the longitudinal axis of the hippocampus

134 Subsequently, we applied the longitudinal axis segmentation method described by Morais-Ribeiro et al. [9] to
135 divide the hippocampus into three equal subdivisions: anterior, intermediate, and posterior. Controlling for age,
136 sex, and eTIV, ADc participants exhibited decreased volumes in all three subregions compared to the other
137 groups, in both hemispheres ($P < 0.001$; Fig 2A, Online supplemental data - Fig S4A). Furthermore, adjusting
138 for eTIV and sex, a similar pattern of correlation with age was observed for the subregional volumes on both
139 hemispheres, with a decreased influence of age observed in the ADc group compared to controls or SNAP (Fig
140 2B, Online supplemental data - Fig S4B).

141 To investigate differential intrahippocampal changes in these subregional volumes, we normalized the volumes
142 of the anterior, intermediate, and posterior hippocampus to the total ipsilateral hippocampal volume (besides
143 adjustments for age and sex). ADc participants exhibited an increased ratio of anterior hippocampus volume to
144 total hippocampal volume and a decreased ratio of posterior hippocampus volume to total hippocampal volume
145 compared with controls or SNAP, both on the left ($P < 0.001$) and right ($P < 0.01$) hemispheres (Online
146 supplemental data – Fig S5A and C). Notably, ADc showed minimal change in these ratios over time, as
147 opposed to controls or SNAP (exception made for left anterior hippocampus in controls), in which those ratios
148 tend to equalize the ones from ADc in older individuals (Online supplemental data - Fig S5B and D). No
149 differences between groups were found in intermediate hippocampus volume, including over time.

150 To consolidate these differential changes along the longitudinal axis of the hippocampus into a single metric,
151 we calculated the ratio of anterior hippocampal volume to posterior hippocampal volume for both hemispheres.
152 This ratio was bilaterally increased in ADc compared with the other groups ($P < 0.001$; Fig 3A, Online
153 supplemental data - Fig S6A), and while SNAP and controls showed progressive increase over time, ADc
154 exhibited minimal changes (Fig 3B, Online supplemental data - Fig S6B). Given that these volumetric
155 differences between groups attenuate over time and the challenge to distinguish neurodegenerative conditions in
156 younger individuals, we sought to evaluate the potential discriminatory ability of this ratio to correctly discern
157 between SNAP and ADc in young individuals (below 60 years old), by calculating the corresponding AUC of
158 ROC curve for right and left hippocampus. We observed minimally satisfactory discrimination between groups,
159 with an estimated AUC of 0.70 for the right side (Fig 3C) and 0.70 0.65 for the left (Online supplemental data -
160 Fig S6C).

161

162 Relationship between subregional metrics and clinical scores

163 Controlling for age and sex, ADc participants demonstrated worse cognition ($P < 0.001$), more neuropsychiatric
164 symptoms ($P < 0.01$), and greater functional impairment ($P < 0.001$) compared with controls or SNAP (Online
165 supplemental data - Fig S7A-E). Correlation heatmaps uncovered significant relationships between these
166 clinical scores and the calculated subregional volumetric measures, with stronger correlations observed in ADc
167 (Fig 4). Notably, more “predictive” variables were detected on the left than the right, for both SNAP and ADc.

168

170 To depict if these subregional volumes correlate with the CSF biomarkers used to define our groups of study
171 (T-Tau, P-Tau and A β), we built correlation heatmaps between those and the same subregional volume
172 variables. Controls showed no significant correlations (Fig 5A), whereas ADc showed multiple significant
173 correlations with levels of T-Tau, P-Tau and A β (Fig 5B). In SNAP, only CSF T-Tau concentration correlated
174 with subregional volumetric measures (Fig 5C).

175 DISCUSSION

176 CSF biomarkers have become integral in aiding the differential diagnosis of neurodegenerative conditions such
177 as ADc, evidenced by A β pathology, and SNAP, characterized by elevated Tau levels in CSF alongside normal
178 A β concentration [3]. Notably, studies focused on the hippocampus have underscored distinct properties along
179 its longitudinal axis [8]. Here, we detail volumetric changes along the hippocampus axis among individuals
180 with these neurodegenerative conditions and controls, alongside exploring their relationship with clinical scores
181 and the CSF biomarkers T-Tau, P-Tau, and A β .

182 The hippocampus plays a pivotal role in learning and memory, and its volume is known to decrease in patients
183 with AD [13]. Our subregional analyses align with recent work by Morais-Ribeiro et al. [9], wherein similar
184 investigations were conducted within an AD group defined by clinical presentation. Both studies underscore the
185 heightened vulnerability of the posterior hippocampus to atrophy (Fig 3, Online supplemental data - Fig S5).
186 Complementing these findings, Wolf et al. employed three-dimensional surface mapping to assess the
187 microstructural integrity of hippocampal subfields, revealing that the association of age with hippocampal
188 microstructural integrity predominantly affects regions situated in the hippocampal body and tail [14].
189 Moreover, our findings indicate that changes in various volumetric subregions exhibit a less pronounced effect
190 of aging in AD compared with controls and SNAP, consistent with decreased volumes observed from early ages
191 in the AD group. We confirm that volumes of the anterior, intermediate, and posterior hippocampus
192 significantly correlate with MMSE scores [9] and expand upon that by demonstrating that these subregional
193 volumes are also associated with CDR score and daily functioning (Fig 4). Interestingly, our analysis reveals a
194 distinct pattern in ADc, wherein volumes of the intermediate and anterior hippocampus are significantly
195 associated with NPI-Q score, which gauges the magnitude of neuropsychiatric symptoms. This finding
196 complements recent research indicating a 42% prevalence of psychosis in AD, which was linked to various
197 histologic and clinical metrics, as well as regional temporal lobe atrophy [15].

198 The ratio of anterior hippocampal volume to posterior hippocampal volume, serving as a consolidated metric
199 capturing both anterior and posterior relative atrophy patterns, not only exhibited significant correlations with
200 global cognition and daily functioning in ADc (Fig 4) but also emerged as a potential neuroimaging biomarker
201 for distinguishing ADc from SNAP at an early stage (Fig 3). Our findings regarding subregional volumes in
202 SNAP are consistent with various studies showing that total hippocampal atrophy and cognitive decline are
203 more pronounced in ADc than in SNAP, with the latter showing no relevant differences compared with controls

204 [16–22]. Expanding on those studies focused on total hippocampal volume assessment, our approach delves
205 into anterior-posterior subregional volumes. Interestingly, while SNAP presents as a relatively benign condition
206 at the cognitive and volumetric levels when compared with controls, we found significant correlations between
207 subregional volumes and T-Tau in SNAP but not in controls, indicative of underlying incipient
208 neurodegeneration in the former. Importantly, early neurodegeneration entails synaptic and neuronal loss, with
209 levels of CSF Tau (rather than A β) being predictive of future cognitive impairments [23].

210 Our analyses revealed various correlations between subregional hippocampal volumes and the levels of
211 biomarkers implicated in the pathophysiology of ADc and SNAP. Significant associations were observed with
212 T-Tau, P-Tau, and A β in ADc, and with T-Tau in SNAP (Fig 5). In ADc, these results are consistent with
213 previous findings regarding total hippocampal volume [24]. Moreover, in AD cases with dementia, postero-
214 medial network regions that coactivate with the posterior hippocampus overlap with areas exhibiting A β and
215 Tau deposition [25]. Since various neurodegenerative disorders involve toxic accumulation of proteins, such as
216 A β and Tau in AD, their regional deposition may explain the anterior–posterior hippocampal atrophy in AD.
217 Interestingly, recent studies of neuropathological and imaging data of AD patients suggest a strong association
218 between antero-medial temporal regions, such as the anterior hippocampus, and the accumulation of transactive
219 response DNA-binding protein 43 (TDP-43) [26], a finding replicated in clinically defined populations
220 exhibiting probable TDP-43 pathology [27]. Furthermore, in AD, iron deposition in the posterior hippocampal
221 CA1 region has been strongly and negatively correlated with memory fidelity [28]. Additionally, other
222 pathologies co-occurring in ADc, such as the presence of Lewy bodies [6] or cerebrovascular changes [29],
223 which are known to differentially affect brain atrophy patterns, can potentially impact the hippocampus along
224 its longitudinal axis and should be taken into account in future studies.

225 On the other hand, cognitive deterioration in SNAP subjects appears to be more closely related to neuronal
226 damage rather than A β pathology [30]. In line with the new research framework for AD, SNAP is now
227 conceptually understood to be positive for neurodegeneration, which can be defined based on MRI-detected
228 atrophy, abnormal 18F-FDG PET scans, or elevated CSF Tau levels [3]. Despite our findings that SNAP groups
229 exhibit increased T-Tau levels and corresponding correlations with hippocampal subregional volumes, these
230 volume metrics are not significantly different from controls. This suggests that different neurodegeneration
231 biomarkers track distinct aspects of disease processes, providing similar but not redundant information [31].
232 Furthermore, the underlying pathology of SNAP is heterogeneous. Unlike amyloid pathology, several

233 pathological processes can lead to neurodegeneration, including PART [32, 33], which is the most prevalent
234 pathology that can be observed in people with “pathological” SNAP (that is, with no evidence of amyloid
235 pathology in the presence of Tau pathology) [34, 35]. Additionally, PART typically has a much more limited
236 impact on cognition compared with AD as well, so it may account for at least a subset of individuals with the
237 SNAP biomarker profile [36].

238 Our analyses revealed that left subregional volumetric metrics are particularly predictive of global cognition
239 and daily functioning in both ADc and SNAP (Fig 4), the same side where correlations with T-Tau were found
240 in SNAP (Fig 5). Additionally, we observed differences between ADc and SNAP in their correlations of total
241 (Fig 1, Online supplemental data - Fig S3) and intermediate (Online supplemental data - Fig S3 and S4)
242 hippocampal volumes with age, also on the left side. Altogether, left hippocampal atrophy may better reflect
243 clinical presentation and represent underlying pathophysiology.

244 Some caveats must be considered in interpreting our findings. First, there may be a degree of selection bias
245 inherent in the ADNI cohort's composition and corresponding data collection methods. Second, despite the
246 large sample size, relying on a single database may limit the generalizability of our results. Finally, despite
247 adjusting for well-established potential confounders, as an observational study, there may be other confounding
248 factors that we did not account for.

249 As a future perspective, given that AD mainly declarative memory deficits [37], it is crucial to understand the
250 extent to which subregional atrophy patterns along the longitudinal hippocampal axis impact specific
251 components of this form of long-term memory. For instance, in rodents, dorsal hippocampus lesions impair
252 spatial memory and lesions in ventral hippocampus lead to anxiety-like behavior [8, 38], whereas social
253 memory depends on different subregions along the longitudinal axis [39]. Lastly, SNAP’s etiology remains
254 unclear, with several processes possibly contributing to neurodegeneration. Importantly, while the revised
255 criteria for AD diagnosis and staging acknowledge that SNAP cases could correspond to PART, they do not
256 tackle the biomarker definition and potential clinical significance of SNAP and how it differentiates from AD
257 [4]. Therefore, complementary biomarkers reflecting disease-specific and co-occurring pathologies will be
258 invaluable for improving diagnostic accuracy. These biomarkers may encompass genetic, molecular, imaging,
259 and vascular factors [18].

260

261 **CONCLUSIONS**

262 We demonstrated that ADc displays lower total and subregional hippocampal volumes compared with SNAP or
263 controls, with a particular susceptibility in the posterior hippocampus and less dependency of these volumetric
264 measures on age. Several subregional hippocampal volumes correlate significantly with altered levels of CSF
265 biomarkers in both ADc and SNAP, aligning with the specific pathophysiology involved, and are associated
266 with global cognition, neuropsychiatric features, and functional impairment. The anterior-posterior relative
267 atrophy pattern can contribute to differentiation between ADc and SNAP. Therefore, our work contributes to
268 the growing evidence implicating anterior–posterior gradients in hippocampal disease.

269 **DECLARATIONS**

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274

275 **Competing interests**

276 The corresponding author has been a consultant for Sonae and Guidepoint, has received fees as a speaker from
277 Eisai and conference fees covered from Roche and Lilly. The remaining authors have no disclosures to report.

278

279 **Ethics approval**

280 This study was conducted in accordance with institutional guidelines. Ethics committee approval was not
281 required.

282

283 **Consent to Participate declaration**

284 Participation in ADNI received approval from the institutional ethical committees of all participating
285 institutions, and written informed consent was obtained from all research participants and, when applicable,
286 from collateral informants.

287

288 **Data availability**

289 All data supporting the findings of this case report are contained within the manuscript. Raw data is available
290 upon request to ADNI. Additional data are available from the corresponding author upon reasonable request.

291 REFERENCES

- 292 1. Gordon BA, Blazey T, Benzinger TLS, Head D (2013) Effects of aging and Alzheimer's disease along the
293 longitudinal axis of the hippocampus. *J Alzheimers Dis* 37:41–50. <https://doi.org/10.3233/JAD-130011>
- 294 2. Jack CR, Bennett DA, Blennow K, et al (2016) A/T/N: An unbiased descriptive classification scheme for
295 Alzheimer disease biomarkers. *Neurology* 87:539–547.
296 <https://doi.org/10.1212/WNL.0000000000002923>
- 297 3. Jack CR, Bennett DA, Blennow K, et al (2018) NIA-AA Research Framework: Toward a biological
298 definition of Alzheimer's disease. *Alzheimers Dement* 14:535–562.
299 <https://doi.org/10.1016/J.JALZ.2018.02.018>
- 300 4. Jack CR, Andrews JS, Beach TG, et al (2024) Revised criteria for diagnosis and staging of Alzheimer's
301 disease: Alzheimer's Association Workgroup. *Alzheimer's Dement* 20:5143–5169.
302 <https://doi.org/10.1002/ALZ.13859>,
- 303 5. Quintas-Neves M, Teylan MA, Morais-Ribeiro R, et al (2022) Divergent magnetic resonance imaging
304 atrophy patterns in Alzheimer's disease and primary age-related tauopathy. *Neurobiol Aging* 117:1–11.
305 <https://doi.org/10.1016/j.neurobiolaging.2022.04.013>
- 306 6. Almeida FC, Santos A, Jesus T, et al (2025) Lewy body co-pathology in Alzheimer's disease and primary
307 age-related tauopathy contributes to differential neuropathological, cognitive, and brain atrophy patterns.
308 21:
- 309 7. Poppenk J, Evensmoen HR, Moscovitch M, Nadel L (2013) Long-axis specialization of the human
310 hippocampus. *Trends Cogn Sci* 17:230–240. <https://doi.org/10.1016/J.TICS.2013.03.005>
- 311 8. Strange BA, Witter MP, Lein ES, Moser EI (2014) Functional organization of the hippocampal
312 longitudinal axis. *Nat Rev Neurosci* 15:655–669. <https://doi.org/10.1038/NRN3785>
- 313 9. Morais-Ribeiro R, Almeida FC, Coelho A, et al (2024) Differential atrophy along the longitudinal
314 hippocampal axis in Alzheimer's disease. *Eur J Neurosci* 59:3376–3388.
315 <https://doi.org/10.1111/EJN.16361>

- 316 10. Fischl B, Salat DH, Busa E, et al (2002) Whole brain segmentation: Automated labeling of
317 neuroanatomical structures in the human brain. *Neuron* 33:341–355. [https://doi.org/10.1016/S0896-](https://doi.org/10.1016/S0896-6273(02)00569-X)
318 6273(02)00569-X
- 319 11. Jovicich J, Czanner S, Han X, et al (2009) MRI-derived measurements of human subcortical, ventricular
320 and intracranial brain volumes: Reliability effects of scan sessions, acquisition sequences, data analyses,
321 scanner upgrade, scanner vendors and field strengths. *Neuroimage* 46:177–192
- 322 12. Lerma-Usabiaga G, Iglesias JE, Insausti R, et al (2016) Automated segmentation of the human
323 hippocampus along its longitudinal axis. *Hum Brain Mapp* 37:3353–3367.
324 <https://doi.org/10.1002/HBM.23245>
- 325 13. Pini L, Pievani M, Bocchetta M, et al (2016) Brain atrophy in Alzheimer’s Disease and aging. *Ageing Res*
326 *Rev* 30:25–48. <https://doi.org/10.1016/J.ARR.2016.01.002>
- 327 14. Wolf D, Fischer FU, de Flores R, et al (2015) Differential associations of age with volume and
328 microstructure of hippocampal subfields in healthy older adults. *Hum Brain Mapp* 36:3819–3831.
329 <https://doi.org/10.1002/HBM.22880>
- 330 15. Almeida FC, Jesus T, Coelho A, et al (2024) Psychosis in Alzheimer’s disease is associated with specific
331 changes in brain MRI volume, cognition and neuropathology. *Neurobiol Aging* 138:10–18.
332 <https://doi.org/10.1016/J.NEUROBIOLAGING.2024.02.013>
- 333 16. Burnham SC, Bourgeat P, Doré V, et al (2016) Clinical and cognitive trajectories in cognitively healthy
334 elderly individuals with suspected non-Alzheimer’s disease pathophysiology (SNAP) or Alzheimer’s
335 disease pathology: a longitudinal study. *Lancet Neurol* 15:1044–1053. [https://doi.org/10.1016/S1474-](https://doi.org/10.1016/S1474-4422(16)30125-9)
336 4422(16)30125-9
- 337 17. Oberstein TJ, Schmidt MA, Florvaag A, et al (2022) Amyloid- β levels and cognitive trajectories in non-
338 demented pTau181-positive subjects without amyloidopathy. *Brain* 145:4032–4041.
339 <https://doi.org/10.1093/BRAIN/AWAC297>
- 340 18. Vos SJB, Delvenne A, Jack CR, et al (2024) The clinical importance of suspected non-Alzheimer disease
341 pathophysiology. *Nat Rev Neurol*. <https://doi.org/10.1038/S41582-024-00962-Y>

- 342 19. Gordon BA, Blazey T, Su Y, et al (2016) Longitudinal β -Amyloid Deposition and Hippocampal Volume
343 in Preclinical Alzheimer Disease and Suspected Non-Alzheimer Disease Pathophysiology. *JAMA Neurol*
344 73:1192–1200. <https://doi.org/10.1001/JAMANEUROL.2016.2642>
- 345 20. Wisse LEM, Butala N, Das SR, et al (2015) Suspected non-AD pathology in mild cognitive impairment.
346 *Neurobiol Aging* 36:3152–3162. <https://doi.org/10.1016/J.NEUROBIOLAGING.2015.08.029>
- 347 21. Wisse LEM, Das SR, Davatzikos C, et al (2018) Defining SNAP by cross-sectional and longitudinal
348 definitions of neurodegeneration. *NeuroImage Clin* 18:407–412.
349 <https://doi.org/10.1016/J.NICL.2018.02.008>
- 350 22. Dani M, Brooks DJ, Edison P (2017) Suspected non-Alzheimer's pathology - Is it non-Alzheimer's or
351 non-amyloid? *Ageing Res Rev* 36:20–31. <https://doi.org/10.1016/J.ARR.2017.02.003>
- 352 23. Babić Leko M, Borovečki F, Dejanović N, et al (2016) Predictive Value of Cerebrospinal Fluid Visinin-
353 Like Protein-1 Levels for Alzheimer's Disease Early Detection and Differential Diagnosis in Patients with
354 Mild Cognitive Impairment. *J Alzheimers Dis* 50:765–778. <https://doi.org/10.3233/JAD-150705>
- 355 24. Byun MS, Kim SE, Park J, et al (2015) Heterogeneity of Regional Brain Atrophy Patterns Associated with
356 Distinct Progression Rates in Alzheimer's Disease. *PLoS One* 10:.
357 <https://doi.org/10.1371/JOURNAL.PONE.0142756>
- 358 25. Dautricourt S, de Flores R, Landeau B, et al (2021) Longitudinal Changes in Hippocampal Network
359 Connectivity in Alzheimer's Disease. 90:391–406
- 360 26. de Flores R, Wisse LEM, Das SR, et al (2020) Contribution of mixed pathology to medial temporal lobe
361 atrophy in Alzheimer's disease. *Alzheimers Dement* 16:843–852. <https://doi.org/10.1002/ALZ.12079>
- 362 27. Lladó A, Tort-Merino A, Sánchez-Valle R, et al (2018) The hippocampal longitudinal axis-relevance for
363 underlying tau and TDP-43 pathology. *Neurobiol Aging* 70:1–9.
364 <https://doi.org/10.1016/J.NEUROBIOLAGING.2018.05.035>
- 365 28. Zhou J, Wearn A, Huck J, et al (2024) Iron Deposition and Distribution Across the Hippocampus Is
366 Associated with Pattern Separation and Pattern Completion in Older Adults at Risk for Alzheimer's
367 Disease. *J Neurosci* 44:e1973232024. <https://doi.org/10.1523/JNEUROSCI.1973-23.2024>

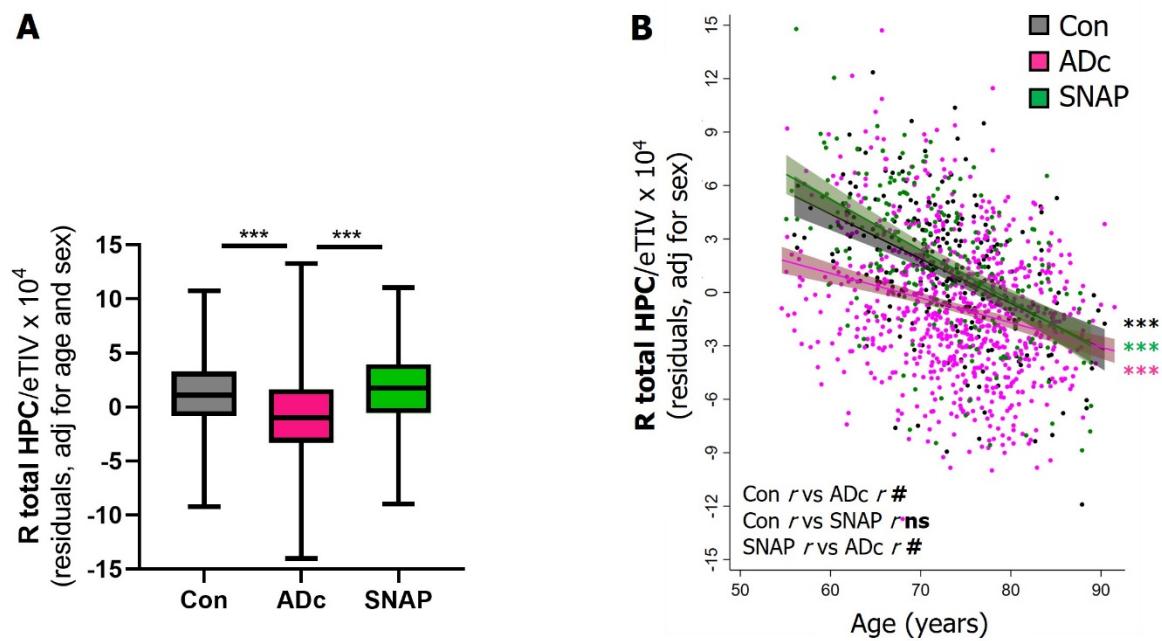
- 368 29. Quintas-Neves M, Almeida FC, Gauthreaux K, et al (2024) Fazekas scale magnetic resonance imaging
369 assessment in Alzheimer's disease and primary age-related tauopathy. *Neuroradiology* 66:.
370 <https://doi.org/10.1007/S00234-024-03464-2>
- 371 30. Weiner MW, Veitch DP, Aisen PS, et al (2017) Recent publications from the Alzheimer's Disease
372 Neuroimaging Initiative: Reviewing progress toward improved AD clinical trials. *Alzheimers Dement*
373 13:e1–e85. <https://doi.org/10.1016/J.JALZ.2016.11.007>
- 374 31. Jack CR, Wiste HJ, Weigand SD, et al (2015) Different definitions of neurodegeneration produce similar
375 amyloid/neurodegeneration biomarker group findings. *Brain* 138:3747–3759.
376 <https://doi.org/10.1093/BRAIN/AWV283>
- 377 32. Villeneuve S (2016) Cause of Suspected Non-Alzheimer Disease Pathophysiology: If Not Tau Pathology,
378 Then What? *JAMA Neurol* 73:1177–1179. <https://doi.org/10.1001/JAMANEUROL.2016.2842>
- 379 33. Wisse LEM, de Flores R, Xie L, et al (2021) Pathological drivers of neurodegeneration in suspected non-
380 Alzheimer's disease pathophysiology. *Alzheimers Res Ther* 13:.. [https://doi.org/10.1186/S13195-021-](https://doi.org/10.1186/S13195-021-00835-2)
381 [00835-2](https://doi.org/10.1186/S13195-021-00835-2)
- 382 34. Lowe VJ, Lundt ES, Albertson SM, et al (2019) Neuroimaging correlates with neuropathologic schemes
383 in neurodegenerative disease. *Alzheimers Dement* 15:927–939.
384 <https://doi.org/10.1016/J.JALZ.2019.03.016>
- 385 35. Crary JF, Trojanowski JQ, Schneider JA, et al (2014) Primary age-related tauopathy (PART): a common
386 pathology associated with human aging. *Acta Neuropathol* 128:755–766. [https://doi.org/10.1007/S00401-](https://doi.org/10.1007/S00401-014-1349-0)
387 [014-1349-0](https://doi.org/10.1007/S00401-014-1349-0)
- 388 36. Lowe VJ, Peller PJ, Weigand SD, et al (2013) Application of the National Institute on Aging-Alzheimer's
389 Association AD criteria to ADNI. *Neurology* 80:2130–2137.
390 <https://doi.org/10.1212/WNL.0B013E318295D6CF>
- 391 37. Knopman DS, Amieva H, Petersen RC, et al (2021) Alzheimer disease. *Nat Rev Dis Prim* 7:.
392 <https://doi.org/10.1038/S41572-021-00269-Y>
- 393 38. Moser MB, Moser EI (1998) Distributed encoding and retrieval of spatial memory in the hippocampus. *J*

394 Neurosci 18:7535–7542. <https://doi.org/10.1523/JNEUROSCI.18-18-07535.1998>

395 39. Meira T, Leroy F, Buss EW, et al (2018) A hippocampal circuit linking dorsal CA2 to ventral CA1 critical

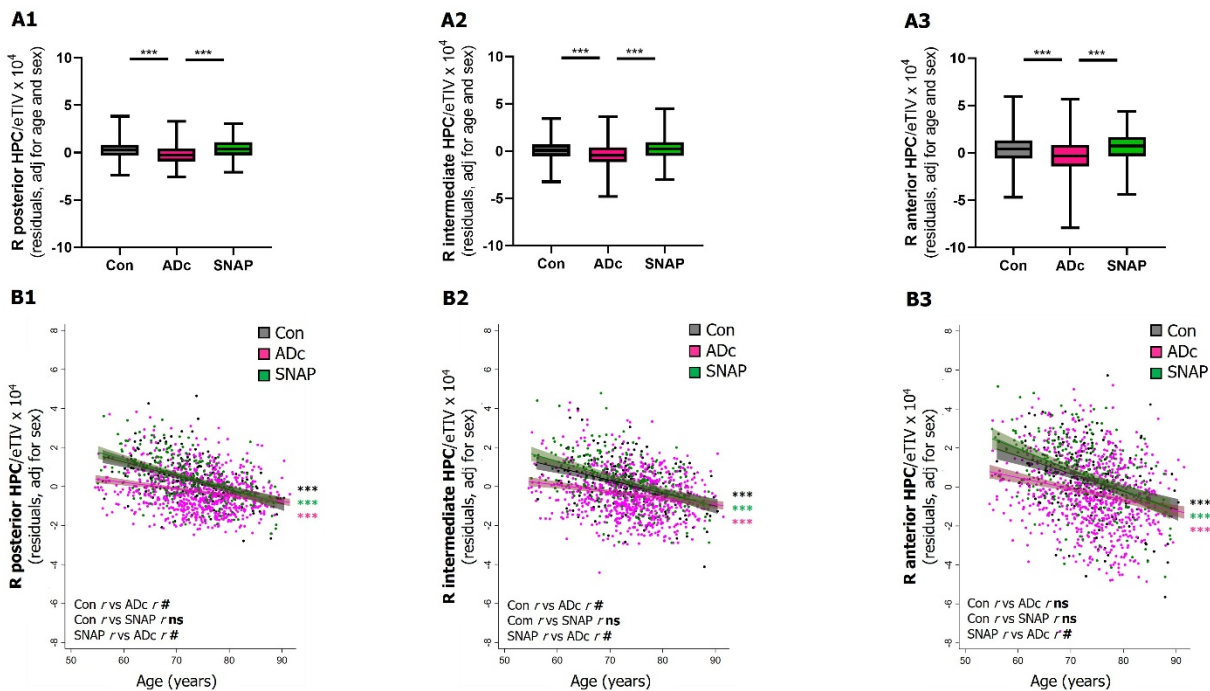
396 for social memory dynamics. Nat Commun 9:. <https://doi.org/10.1038/S41467-018-06501-W>

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399

400 **Fig. 1** Comparison of total right hippocampus volume between groups. Controlling for age, sex and eTIV, ADc
401 show significantly diminished volumes of the right hippocampus (HPC) compared to controls and SNAP (A).
402 Adjusting for sex and eTIV, the three groups show a significant decrease of the right HPC volume with age (B)
403 - ADc correlation is significantly different from the other groups. # $P < 0.01(6)$; *** $P < 0.001$; ns, non-
404 significant; R, right



405

406 **Fig. 2** Subregional right hippocampal volumes normalized to eTIV comparisons between groups. On the right
 407 hemisphere, ADc displays reduced volume of posterior (A1), intermediate (A2) and anterior hippocampus
 408 (HPC) (A3). The three groups have a significant decrease of the right posterior (B1), intermediate (B2) and
 409 anterior HPC volume (B3). ADc correlation with age is significantly different from the remaining groups in
 410 posterior HPC and in intermediate; in anterior HPC, it is different from SNAP. # $P < 0.025$; *** $P < 0.001$; ns,
 411 non-significant; R, right

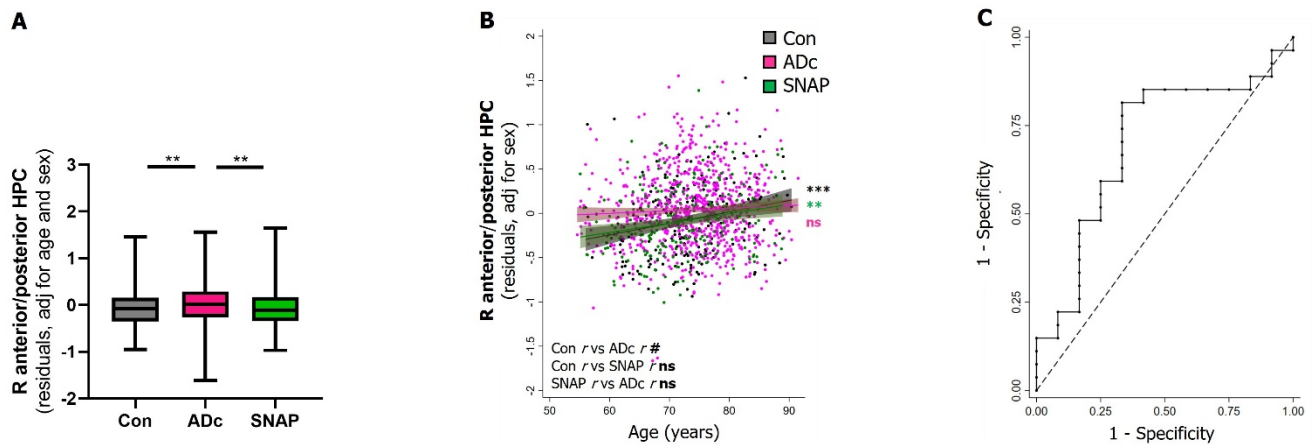
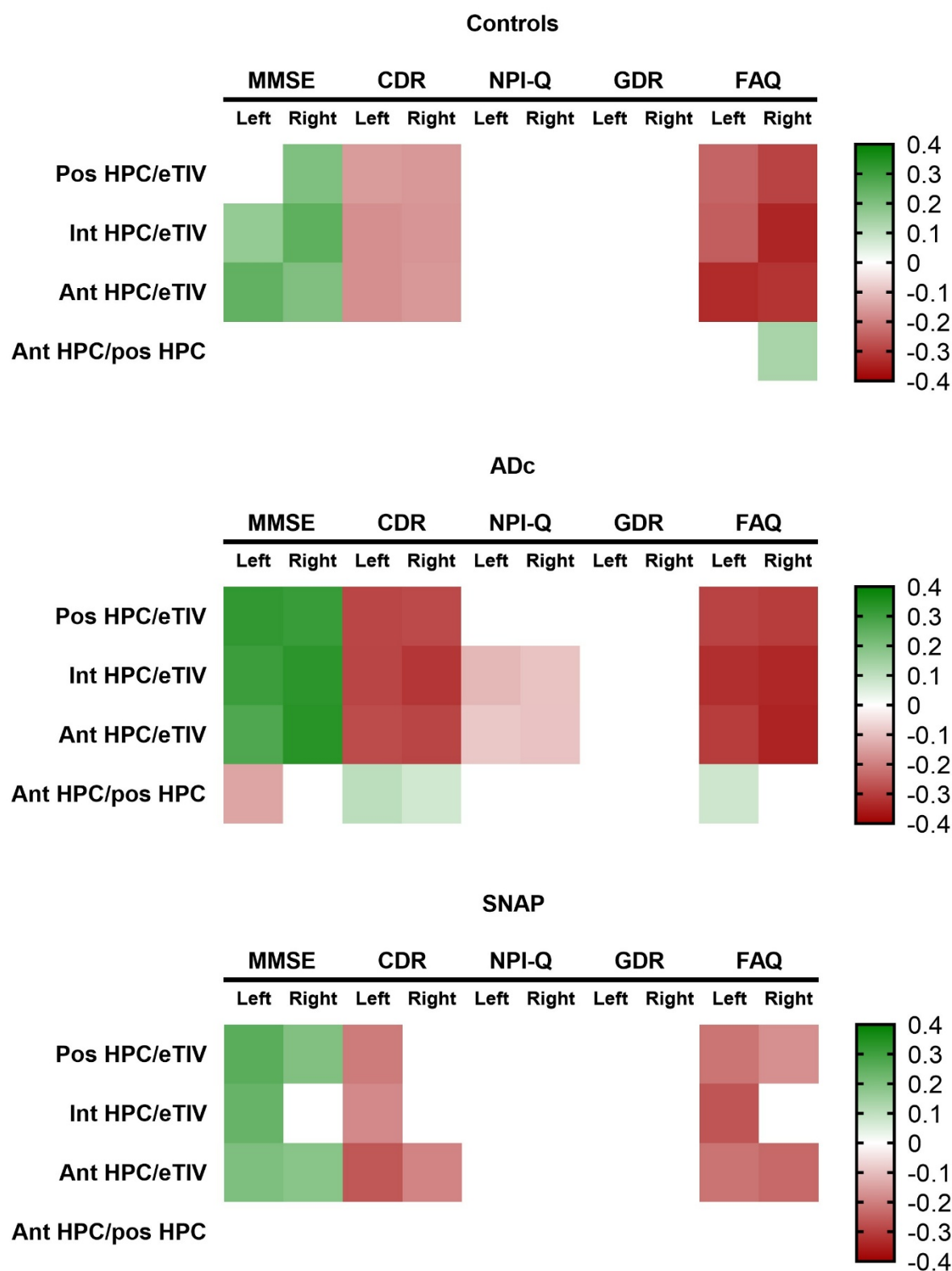


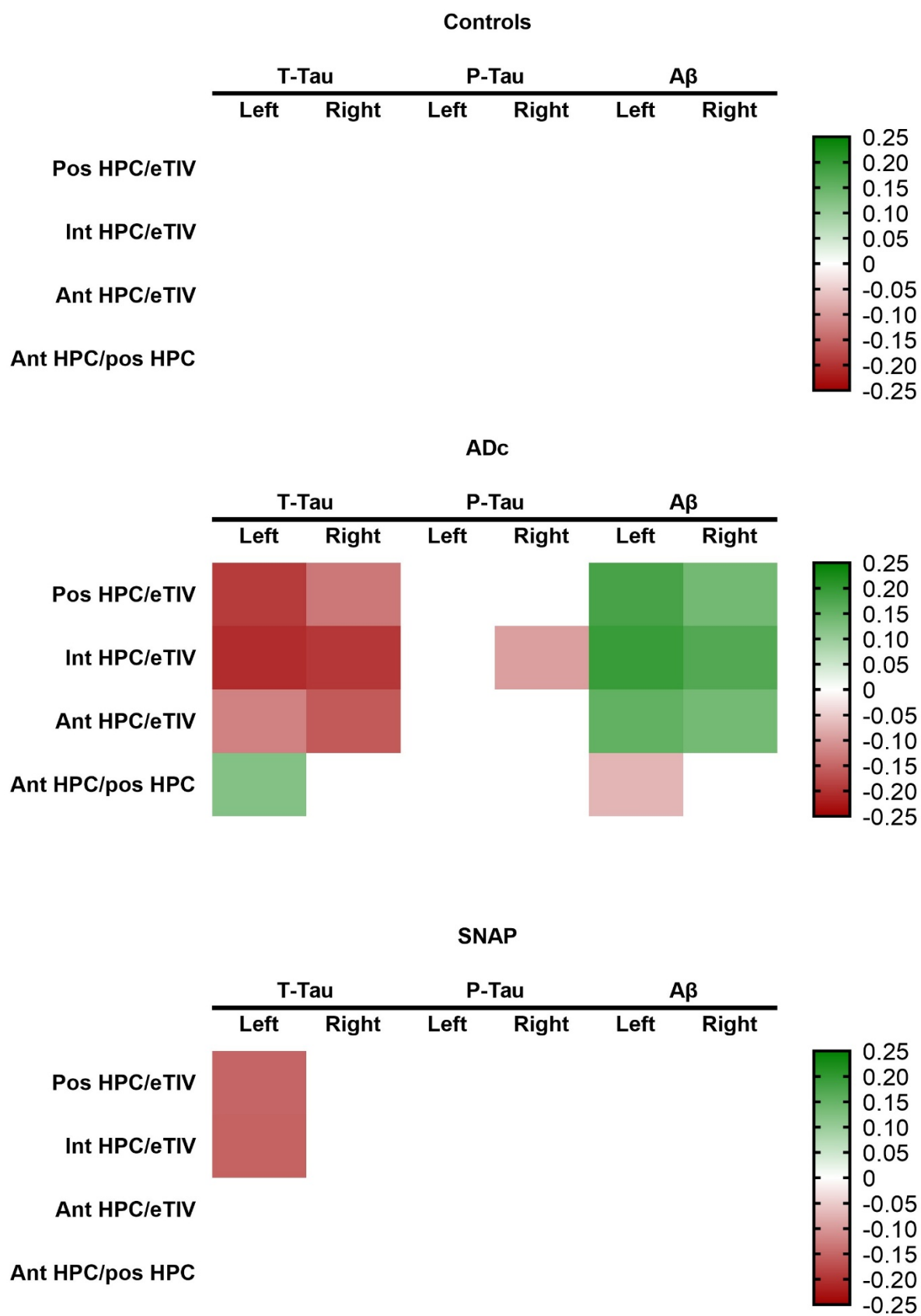
Fig. 3 Anterior/posterior right hippocampal volume ratio compared between groups. On the right hippocampus (HPC), ADc also display increased anterior/posterior HPC volume ration compared to the other groups (A). Over age and controlling for sex, there is significant increase of this ratio in controls and SNAP, with no significant change in ADc (B) – that variation is significantly different between controls and ADc. AUC of ROC for the right ratio to distinguish ADc from SNAP is estimated at 0.70 (C). # $P < 0.01(6)$; ** $P < 0.01$; *** $P < 0.001$; ns, non-significant; R, right



419

420 **Fig. 4** Correlation analyses between hippocampal subregional volumetric measures and various clinical scores.
 421 In all of these analyses, adjustment for age and sex was performed. Only significant results are colored, after
 422 correction for multiple comparisons with Benjamini-Hochberg method (FDR < 5%). Color and brightness

423 indicate magnitude of Pearson coefficient r according to the color code displayed. Controls, ADc and SNAP
424 show various significant correlations between hippocampal (HPC) subregional metrics and mini-mental state
425 exam score, clinical dementia rating and functional activities questionnaire score; no significant correlations
426 were found with geriatric depression scale; ADc is the only group in which there are significant correlations
427 with neuropsychiatric inventory Q score. Refer to Online supplemental data - Tables S1, S2 and S3 for detailed
428 Pearson coefficients, corresponding P values and adjusted alpha level that indicates statistical significance.
429 MMSE, Mini-Mental State Exam, CDR, Clinical Dementia Rating; NPI-Q, Neuropsychiatric Inventory Q;
430 GDR, Geriatric Depression Scale; FAQ, Functional Activities Questionnaire



432 **Fig. 5** Heat map of correlation analyses (r) between hippocampal subregional volumetric measures and CSF
433 levels of T-Tau, P-Tau and A β , for controls (A), ADc (B) and SNAP (C). Adjustment for age and Benjamini-
434 Hochberg method (FDR < 5%) was used to control for multiple comparisons. Only significant results are
435 colored, according to the color code displayed. Refer to Online supplemental data - Tables S4, S5 and S6 for
436 detailed Pearson coefficients, corresponding P values and adjusted alpha level that indicates statistical
437 significance

Supplementary Files

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