

Amyloid-related longitudinal postsynaptic decline in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is characterized by amyloid- β (A β) plaques, tau neurofibrillary tangles, and synaptic dysfunction. Cellular prion protein mediates A β oligomer neurotoxicity through metabotropic glutamate receptor 5 (mGluR5), leading to synaptic impairment and loss. However, the longitudinal trajectory of mGluR5 and its relationship with amyloid pathology remain poorly understood in vivo. We performed baseline dual-tracer PET imaging in 38 participants and longitudinal [^{18}F] PSS232PET/MR in 23 cognitively impaired patients over a mean follow-up of 14.3 months. Longitudinal analyses revealed widespread reductions in mGluR5 availability among A β -positive individuals, whereas A β -negative participants exhibited more restricted declines. Baseline amyloid pathology predicted accelerated mGluR5 decline in parahippocampus and hippocampus. Higher baseline hippocampal mGluR5 availability was associated with accelerated subsequent cognitive decline, suggesting that preserved or compensatorily elevated mGluR5 may identify individuals at increased risk of future deterioration. These findings indicate that longitudinal mGluR5 decline follows an amyloid-dependent spatiotemporal pattern, with selective medial temporal vulnerability in A β -positive individuals. This study provides in vivo evidence linking amyloid pathology to progressive mGluR5 dysfunction and supports the development of mGluR5-targeted therapeutic strategies for amyloid-positive AD.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by extracellular amyloid- β (A β) plaques, intracellular tau neurofibrillary tangles (NFTs), and progressive synaptic dysfunction culminating in neuronal loss. Among these pathological processes, synaptic injury is increasingly recognized as one of the earliest and most clinically relevant events, showing a stronger association with cognitive impairment than classical neuropathological burden alone. However, the molecular mechanisms underlying progressive synaptic dysfunction in vivo remain incompletely understood, particularly during the preclinical and prodromal stages of AD.

Metabotropic glutamate receptor subtype 5 (mGluR5), a postsynaptic G protein-coupled receptor highly enriched in excitatory synapses, plays a fundamental role in synaptic plasticity, neuronal signaling, learning, and memory. Recent studies have shown that soluble A β oligomers (A β o) and their intermediate assemblies interact with multiple membrane-bound receptors to trigger deleterious signaling events [1]. Cellular prion protein (PrPC) has emerged as a prominent cell-surface receptor with high affinity for A β o. The PrPC-A β o interaction has been implicated in synaptic toxicity, manifesting as impaired long-term potentiation (LTP) and dendritic spine loss [2–4]. Pharmacological blockade of mGluR5 has shown therapeutic efficacy in ameliorating cognitive impairment and preserving synaptic architecture in AD transgenic models[5]. These findings position mGluR5 as a potentially important mediator linking amyloid pathology to downstream neurodegeneration and cognitive deterioration.

Despite growing mechanistic evidence, the in vivo longitudinal characterization of mGluR5 alterations in human AD remains limited, largely due to the lack of suitable positron emission tomography (PET)

radiotracers for repeated clinical assessment. To address this unmet need, specialized radioligands such as [^{18}F]PSS232 (3-(pyridin-2-ylethynyl)cyclohex-2-enone-O-(3-(2-[^{18}F]-fluoro-ethoxy)-propyl) oxime) enable quantitative measurement of mGluR5 availability and provide valuable insights into regional mGluR5 decline in neurodegenerative conditions [6–8]. Postmortem autoradiography and PET studies have demonstrated significant reductions in hippocampal mGluR5 availability in AD brains [9, 10]. Our previous cross-sectional analyses further revealed altered mGluR5 distribution patterns across the AD continuum, supporting the utility of mGluR5 PET as a promising imaging biomarker of synaptic dysfunction [10, 11].

However, whether mGluR5 progressively declines over time during AD evolution, and how such changes are influenced by amyloid burden, remains unclear. Longitudinal assessment is particularly important because cross-sectional measurements may not adequately capture the dynamic synaptic alterations underlying disease progression. Furthermore, whether baseline A β pathology contributes to the subsequent acceleration of mGluR5 loss is unknown; evidence for this relationship would provide in vivo support for the hypothesis that amyloid pathology drives progressive synaptic receptor dysfunction.

In this longitudinal study, we performed serial [^{18}F]PSS232 PET imaging to characterize dynamic mGluR5 trajectories across the AD spectrum. Specifically, we aimed to investigate: 1) whether mGluR5 availability progressively declines over time, reflecting ongoing synaptic receptor loss during AD progression; 2) the influence of amyloid pathology on longitudinal mGluR5 alterations; and 3) the association between longitudinal changes in mGluR5 availability and subsequent cognitive decline. Together, these findings may provide longitudinal in vivo evidence that mGluR5 dysfunction is dynamically linked to AD pathology and cognitive deterioration, further supporting mGluR5 PET as a potential biomarker for monitoring progressive synaptic dysfunction in AD.

Subjects and Methods

Participants

We included 38 participants from the Chinese Preclinical Alzheimer's Disease Study (CPAS), comprising 23 cognitively impaired (CI) patients, including 14 patients with AD dementia and 9 patients with mild cognitive impairment (MCI), and 15 cognitively unimpaired (CU) individuals. Participants were recruited from the memory clinic of Shanghai Jiao Tong University Affiliated Ruijin Hospital and communities in Shanghai. AD dementia was diagnosed according to the 2018 National Institute on Aging -Alzheimer's Association (NIA-AA) criteria for probable AD dementia, and MCI was diagnosed using Jak and Bondi's criteria, as described previously [12–14]. CU individuals showed no impairment in any cognitive domain and no evidence of amyloid pathology on PET scans. Exclusion criteria have been reported in our prior studies [10, 11]. All protocols were approved by the institutional review boards of Fudan University Affiliated Huashan Hospital and Shanghai Jiao Tong University Affiliated Ruijin Hospital. Written informed consent was obtained from all participants or their legally authorized representatives prior to study participation.

Neuropsychological assessment

All participants underwent comprehensive neuropsychological assessments at baseline, and CI patients were reassessed at follow-up. All neuropsychological assessments were adapted and validated for the Chinese population [15]. Neuropsychological testing and [^{18}F]PSS232 PET/MR were performed within one month of each other at both baseline and follow-up visits, when applicable. The memory domain was assessed with the 30-minute delayed free recall of the Auditory Verbal Learning Test (AVLT-LDR; 12 items) and AVLT recognition (AVLT-REC; 24 items). The language domain was evaluated using the Animal Fluency Test (AFT; total score) and the Boston Naming Test (BNT; 30 items). Executive function was assessed using the Shape Trails Test (STT) parts A and B, measured as time to completion. Global cognition was evaluated using the Mini-Mental State Examination (MMSE). Six additional tests across three cognitive domains were administered as previously described [11, 16].

PET Image acquisition

All patients underwent baseline [^{18}F]PSS232 PET/MR and [^{18}F]florbetapir amyloid PET/CT. Twenty-three CI patients underwent repeat [^{18}F] PSS232 PET/MR after an average interval of 14.3 months (range, 9.3–28.5 months). [^{18}F]PSS232 PET/MR was performed on a 3T PET/MR scanner (uPMR 790, United Imaging Healthcare). A 30-minute static PET acquisition was initiated 30 minutes after intravenous injection of 185 MBq ($\pm 10\%$) [^{18}F]PSS232. A T1-weighted water-fat imaging (t1_wfi) sequence was acquired for attenuation correction, and a three-dimensional high-resolution T1-weighted MR scan was simultaneously obtained using previously described parameters[22, 25]. [^{18}F]florbetapir PET/CT imaging was performed on a PET/CT scanner (Biograph mCT Flow, Siemens) using previously reported parameters[18]. The 20-minute scans were acquired 50 minutes after intravenous injection of 370 MBq ($\pm 10\%$) [^{18}F]florbetapir [19, 20].

Data preprocessing

Image preprocessing was conducted using Statistical Parametric Mapping 12 (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK; <https://www.fil.ion.ucl.ac.uk/spm>), following previously described procedures[18]. Briefly, PET and T1-weighted MR images were first reoriented, and PET images were coregistered to each participant's T1-weighted MR image. T1-weighted MR images were then segmented into gray matter, white matter, and cerebrospinal fluid, and the resulting deformation fields were used to normalize both structural and coregistered PET images to Montreal Neurological Institute space. Normalized PET images were smoothed with an 8-mm full-width at half-maximum Gaussian kernel.

For [^{18}F]PSS232, standardized uptake value ratios (SUVR) were calculated using the pons as the reference region[11]. Volumes of interest (VOIs) were delineated based on the Desikan-Killiany-Tourville atlas to extract regional PET measurements from the frontal cortex, hippocampus, parahippocampus,

parietal cortex, lateral temporal cortex, medial temporal lobe, occipital cortex, precuneus, and posterior cingulate cortex [21]. [^{18}F]florbetapir PET images were quantified on the Centiloid (CL) scale. Specifically, SUVR values were computed using the standard CL mask images (voi_cxt_2mm.nii and voi_WhICb_2mm.nii) provided by the Global Alzheimer's Association Interactive Network. Centiloid values were subsequently derived from [^{18}F]florbetapir SUVR using our previously established conversion formula[22]. For the primary analyses, amyloid PET positivity was determined by visual read in conjunction with a threshold of 20 CL[23]. Visual assessment of amyloid PET was additionally used for sensitivity analyses. Hippocampal volume was segmented using CAT12 and adjusted for individual intracranial volume, yielding the hippocampal volume ratio (HpVr), calculated as: (hippocampal/intracranial volume) $\times$ 1000.

Statistical analysis

For cross-sectional analyses, normality was assessed using the Kolmogorov-Smirnov test, and homogeneity of variances was evaluated using Levene's test. Continuous variables, including age, years of education, and cognitive scores, were compared between CU and CI groups using independent-samples t-tests. Categorical variables were compared using chi-square tests or Fisher's exact tests, as appropriate. Regional [^{18}F]PSS232 SUVR values were compared across three groups: CU, amyloid-negative cognitively impaired ($\text{A}\beta$ - CI), and amyloid-positive cognitively impaired ($\text{A}\beta$ + CI). Kruskal-Wallis tests were used for overall group comparisons, followed by pairwise post hoc comparisons. For the three planned pairwise comparisons within each brain region, a Bonferroni-adjusted significance threshold of $\alpha = 0.0167$ ($0.05/3$) was applied.

Longitudinal changes in [^{18}F]PSS232 SUVR within CI patients were evaluated using paired t-tests, both in the overall CI group and after stratification by baseline amyloid status. Independent-samples t-tests were used to compare CU participants with CI patients at baseline and follow-up. Because CU participants did not undergo follow-up [^{18}F]PSS232 PET/MR, baseline CU values were used as the reference for both comparisons. Relative SUVR change was computed as (follow-up SUVR - baseline SUVR) / baseline SUVR.

Partial Spearman correlation analyses were used to assess associations between baseline amyloid burden, measured in Centiloids, and relative [^{18}F]PSS232 SUVR change, adjusting for age, sex, education, and the interval between baseline amyloid PET and mGluR5 PET acquisitions. Partial correlation analyses were also performed to evaluate relationships between baseline regional [^{18}F]PSS232 SUVR and both cognitive outcomes at follow-up and rates of cognitive change, with adjustments for age, sex, and education. Relative cognitive change was calculated as (follow-up score - baseline score) / baseline score.

Effect sizes for group comparisons were quantified using Cohen's d for independent-samples t-tests and Cohen's dz for paired-samples t-tests. Regional effect sizes were projected onto cortical and subcortical brain surfaces according to the Desikan-Killiany atlas. All regions were displayed regardless of

statistical significance to provide a comprehensive visualization of effect-size distributions across the brain.

All statistical analyses were performed using MATLAB R2021b; regional effect-size maps were generated in R using the ggseg package[24]. Unless otherwise specified, a two-tailed p-value < 0.05 was considered statistically significant.

Results

Demographics and clinical characteristics

Table 1 summarizes the demographic and clinical characteristics of the CU and CI groups. Detailed clinical characteristics at baseline and follow-up are provided in Supplementary Table 1. A total of 38 participants were included: 15 CU individuals and 23 CI patients. Among CI patients, amyloid status was determined by two approaches. Based on Centiloid values, 13 patients (56.5%) were classified as Aβ+ (Centiloid ≥ 20) and 10 patients (43.5%) as Aβ- (Centiloid < 20). By visual assessment, 16 patients (69.6%) were classified as Aβ + and 7 patients (30.4%) as Aβ - .

Table 1
Demographic and Clinical Characteristics of Study Participants

Age, y	CU	CI	p
	69.53 ± 5.17	73.25 ± 6.61	0.021
Gender			0.728
male	4	8	
female	11	15	
APOE			0.01
e4 carrier	4	16	
e4 noncarrier	11	7	
Education	11.37 ± 2.88	11.13 ± 4.08	0.734
MMSE	28.93 ± 1.22	23.43 ± 4.69	<0.001
AVLT_LDR	5.73 ± 2.55	1.39 ± 2.43	<0.001
AVLT_REC	21.87 ± 1.50	16.74 ± 3.71	<0.001
Total_AVLT	77.33 ± 4.27	32.35 ± 14.49	<0.001
AFT	15.53 ± 4.10	11.61 ± 6.26	0.039
BNT	22.00 ± 6.56	20.09 ± 5.00	0.087
STT A	56.80 ± 21.47	98.52 ± 41.54	<0.001
STT B	142.40 ± 52.73	203.74 ± 78.04	0.01
HpVr	4.36 ± 0.48	3.70 ± 0.43	<0.001
Data are presented as mean ± SD unless otherwise specified. Paired samples t-tests were used to compare baseline and follow-up measurements within the CI group. Abbreviations: MMSE , Mini-Mental State Examination; AVLT-LDR , Auditory Verbal Learning Test long delayed free recall; AVLT-REC , Auditory Verbal Learning Test delayed recognition scores (24 items); AFT , animal fluency test; BNT , Boston Naming Test; STT A and B , Shape trials test A and B; HpVr , hippocampal volume ratio; CI , cognitively impaired; CU , cognitively unimpaired; base, baseline; follow, follow-up.			

At baseline, amyloid PET was acquired a mean of 6.5 months prior to [¹⁸F]PSS232 PET, with a range of -0.13 to 23.3 months; negative values indicate that amyloid PET was performed after [¹⁸F]PSS232 PET. All 23 CI patients completed longitudinal [¹⁸F]PSS232 PET/MR imaging, with a mean follow-up duration of 14.3 months (range: 9.3–28.5 months).

Cross-sectional differences in mGluR5 availability

The Kruskal-Wallis test revealed a significant main effect of group in the hippocampus ($p = 0.004$). Post hoc analyses showed that hippocampal [^{18}F]PSS232 SUVR was lower in both the $\text{A}\beta - \text{CI}$ group (1.96 ± 0.21 vs 2.19 ± 0.19 , $p = 0.015$) and $\text{A}\beta + \text{CI}$ group (1.94 ± 0.20 vs 2.19 ± 0.19 , $p = 0.002$) compared with the CU group. No significant differences were observed between $\text{A}\beta - \text{CI}$ and $\text{A}\beta + \text{CI}$ in any region. VOI-based analyses indicated that cross-sectional reductions in mGluR5 availability were most pronounced in medial temporal regions (Fig. 1A-I). These findings were further supported by BrainMap-based visualization, which demonstrated a similar spatial pattern of mGluR5 alterations (Fig. 1J-K).

Longitudinal decreased mGluR5 availability in CI

Consistent with the cross-sectional findings, CI patients exhibited lower hippocampal mGluR5 availability than CU individuals. Longitudinal analyses revealed significant declines in [^{18}F]PSS232 SUVR across multiple brain regions within the CI group, including hippocampus (1.95 ± 0.20 vs 1.79 ± 0.19 , $p < 0.001$), frontal (1.63 ± 0.22 vs 1.46 ± 0.15 , $p < 0.001$), parahippocampus (1.97 ± 0.22 vs 1.84 ± 0.20 , $p = 0.001$), parietal (1.61 ± 0.20 vs 1.45 ± 0.16 , $p < 0.001$), posterior cingulate (1.642 ± 0.220 vs 1.426 ± 0.154 , $p < 0.001$), precuneus (1.60 ± 0.18 vs 1.45 ± 0.16 , $p < 0.001$), and temporal medial lobe (1.87 ± 0.20 vs 1.76 ± 0.18 , $p = 0.003$; Fig. 2A-I, Supplementary Table 2). At follow-up, CI patients also showed significantly lower mGluR5 availability than CU individuals across all examined brain regions.

Stratification by baseline amyloid status revealed distinct patterns of longitudinal mGluR5 decline (Fig. 3). The $\text{A}\beta + \text{CI}$ group showed widespread reductions in mGluR5 availability, with significant declines observed in nearly all regions examined, including the hippocampus ($\Delta\text{SUVR} = -0.184 \pm 0.111$, $p < 0.001$) and parahippocampus ($\Delta\text{SUVR} = -0.163 \pm 0.132$, $p < 0.001$), as well as all other regions except the lateral temporal cortex ($\Delta\text{SUVR} = -0.094 \pm 0.182$, $p = 0.088$). In contrast, the $\text{A}\beta - \text{CI}$ group exhibited a more restricted pattern of decline, reaching statistical significance only in the parietal cortex ($\Delta\text{SUVR} = -0.112 \pm 0.143$, $p = 0.036$), posterior cingulate cortex ($\Delta\text{SUVR} = -0.145 \pm 0.159$, $p = 0.018$), and precuneus ($\Delta\text{SUVR} = -0.089 \pm 0.121$, $p = 0.046$). Notably, the hippocampus and parahippocampus, which showed the most pronounced longitudinal declines in $\text{A}\beta + \text{CI}$ patients, showed no significant decline in the $\text{A}\beta - \text{CI}$ group. Similar patterns were observed when participants were stratified according to visual amyloid assessment (Supplementary Fig. 1). These findings are consistent with the Centiloid-based classification and support the robustness of an amyloid-dependent pattern of longitudinal mGluR5 decline.

Baseline amyloid burden predicts rate of mGluR5 decline

Covariate-adjusted Spearman correlation analyses revealed significant associations between baseline Centiloid values and the longitudinal rate of decline in [^{18}F]PSS232 SUVR within medial temporal region after adjustment for age, sex, education, and scan interval. Higher baseline amyloid burden was associated with accelerated mGluR5 loss in the parahippocampus ($r_{\text{cov}} = -0.576$, $p_{\text{cov}} = 0.010$) and hippocampus ($r_{\text{cov}} = -0.579$, $p_{\text{cov}} = 0.009$, Fig. 4). These findings suggest that greater $\text{A}\beta$ pathology at

baseline is associated with accelerated subsequent mGluR5 loss, particularly in medial temporal structures that are highly vulnerable to AD-related neurodegeneration.

Associations between baseline mGluR5 and cognitive outcomes

Partial correlation analyses demonstrated significant associations between baseline regional [^{18}F]PSS232 SUVR and longitudinal cognitive change (Fig. 5, Supplementary Table 3). Higher baseline hippocampal mGluR5 availability was associated with greater decline in AVLT REC ($r_{\text{cov}} = -0.473$, $p_{\text{cov}} = 0.035$), BNT ($r_{\text{cov}} = -0.586$, $p_{\text{cov}} = 0.007$) and AFT ($r_{\text{cov}} = -0.487$, $p_{\text{cov}} = 0.034$). Similar negative associations were observed for the parahippocampus with longitudinal changes in BNT ($r_{\text{cov}} = -0.451$, $p_{\text{cov}} = 0.046$) and AFT ($r_{\text{cov}} = -0.510$, $p_{\text{cov}} = 0.026$).

Analyses examining baseline mGluR5 availability and longitudinal cognitive performance yielded comparable results (Supplementary Fig. 2). Higher baseline [^{18}F]PSS232 SUVR in medial temporal structures was significantly associated with worse follow-up performance in the memory domain. In addition, elevated baseline [^{18}F]PSS232 SUVR in posterior cortex regions was also significantly associated with worse follow-up performance across multiple cognitive domains. We further examined the relationship between baseline [^{18}F]PSS232 SUVR and its longitudinal change (Supplementary Fig. 3). Partial correlation analyses revealed significant associations across most regions, with the strongest effects observed within the same region. These findings indicate that regions with relatively preserved or higher baseline mGluR5 availability experienced greater subsequent reductions over time. This pattern suggests that elevated baseline mGluR5 availability may identify regions undergoing active disease-related change, thereby providing a potential explanation for the observed association between higher baseline mGluR5 levels and greater subsequent cognitive decline.

Discussion

To our knowledge, this is the first longitudinal [^{18}F]PSS232 PET/MR study to characterize the spatial and temporal trajectory of mGluR5 availability in Alzheimer's disease and to examine its relationship with amyloid pathology and cognitive decline. We found that cross-sectional hippocampal mGluR5 reduction in both $\text{A}\beta$ + and $\text{A}\beta$ - CI patients; longitudinally, mGluR5 declines dramatically in amyloid positivity CI patients; Third, greater baseline amyloid burden was associated with accelerated mGluR5 decline in medial temporal regions, and baseline mGluR5 availability was associated with subsequent cognitive deterioration. Collectively, these findings suggest that amyloid pathology may contribute to progressive postsynaptic dysfunction and support mGluR5 as a promising biomarker and potential therapeutic target in AD.

Consistent with previous PET and postmortem evidence of reduced hippocampal mGluR5 in AD[9, 10, 24], we observed significant hippocampal reductions in both $\text{A}\beta$ -positive and $\text{A}\beta$ -negative cognitively

impaired individuals. Notably, hippocampal mGluR5 availability was significantly lower in both A β + and A β – CI groups than in CU participants, with no significant difference between the two A β status groups. These findings suggest a shared synaptic vulnerability in CI that is detectable irrespective of amyloid status. However, longitudinal analyses revealed marked differences according to amyloid status. Over a mean follow-up period of 14.3 months, A β -positive patients exhibited widespread reductions in mGluR5 availability across multiple cortical regions, whereas A β -negative patients demonstrated decline primarily within posterior cortical regions. Given that mGluR5 is widely expressed at the postsynaptic membrane and is often used as a postsynaptic marker[26], these findings suggest that amyloid pathology may accelerate progressive postsynaptic dysfunction during disease progression. This interpretation is further supported by the observation that higher baseline amyloid burden was associated with faster subsequent mGluR5 decline in the hippocampus and parahippocampus, indicating a preferential vulnerability of medial temporal structures to amyloid-related synaptic injury.

A substantial body of experimental evidence indicates that soluble A β species drive synaptic injury through multiple, convergent mechanisms, including dendritic spine loss and synapse elimination[27, 28]. A β disrupts synaptic plasticity by perturbing NMDA and AMPA receptor function, leading to Ca²⁺ dyshomeostasis and impaired plasticity[29, 30]. In parallel, A β -induced Ca²⁺ influx and glial activation reduce glutamate uptake by astrocytes and microglia, further compromising synaptic function[31–34]. A β also engages diverse signaling pathways and molecular targets that impair mitochondrial function and energy metabolism, thereby exacerbating synaptic dysfunction[35–37]. Notably, beyond serving as a postsynaptic marker, mGluR5 may also participate directly in A β mediated neuronal damage as a cell-surface receptor. Renner and colleagues[38] reported that A β 42 binds to mGluR5 and potentiates mGluR5-specific signaling, leading to increased intracellular Ca²⁺, neuronal hyperexcitability, and subsequent synaptic loss. Moreover, a local rise in synaptic intracellular Ca²⁺ may further enhance mGluR5-dependent NMDAR function, amplifying excitotoxic signaling and increasing vulnerability to neuronal death [39].

We also found that baseline mGluR5 was associated with cognitive declines. Notably, the strong association between higher baseline mGluR5 availability and faster subsequent cognitive decline may suggest that, at an early disease stage, mGluR5 helps identify individuals at higher risk of imminent deterioration. One potential pathophysiological explanation is that elevated baseline mGluR5 reflects compensatory upregulation or pathological hyperactivation. mGluR5 may initially increase or be maintained to support synaptic function, but this compensation may eventually fail and accelerate neuronal dysfunction. This interpretation aligns with our longitudinal observation that regions with higher baseline mGluR5 availability exhibited more rapid subsequent decline. Finally, accumulating preclinical evidence indicates that mGluR5 is not only a postsynaptic marker but also a potentially modifiable node in A β -related synaptic pathology. Specifically, mGluR5 antagonists have been reported to reduce or prevent the synaptotoxic effects of A β [40], whereas silent allosteric modulators may restore synaptic integrity in certain model systems[41]. Although the translational relevance remains to be established, these data are consistent with a dynamic role of mGluR5 in AD pathophysiology.

Several limitations warrant consideration. Firstly, the interval time between baseline A β PET and mGluR5 PET was relatively long (mean ~ 6 months). However, because A β deposition is typically slow and protracted, this delay is unlikely to have substantially altered global amyloid burden[42]. Secondly, the longitudinal interval for mGluR5 imaging was relatively short; only one-year interval was designed in this study. Finally, the sample size was modest, which may have limited statistical power to detect cognitive changes and to fully characterize long-term trajectories.

In this longitudinal [^{18}F] PSS232 PET/MR study, we demonstrate that progressive reductions in mGluR5 availability represent a prominent feature of cognitive impairment and are strongly influenced by amyloid pathology. A β -positive patients exhibited widespread longitudinal mGluR5 decline, whereas A β -negative patients showed a more restricted pattern of change. Greater baseline amyloid burden was associated with accelerated mGluR5 loss in medial temporal regions, and baseline mGluR5 availability predicted subsequent cognitive deterioration. Together, these findings provide in vivo evidence supporting an amyloid-associated acceleration of postsynaptic dysfunction and highlight mGluR5 as both a sensitive biomarker of synaptic integrity and a promising therapeutic target in Alzheimer's disease.

Abbreviations

MMSE

Mini-Mental State Examination

STT A and B

Shape trials test A and B

AVLT-LDR

Auditory Verbal learning Test long time delayed free-recall

AVLT-REC

Auditory Verbal Learning Test recognition scores (24 items)

BNT

Boston Naming Test

AFT

Animal Fluency Test.

Declarations

Conflict of Interest

The authors report no competing financial interests in relation to the work described.

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Figures

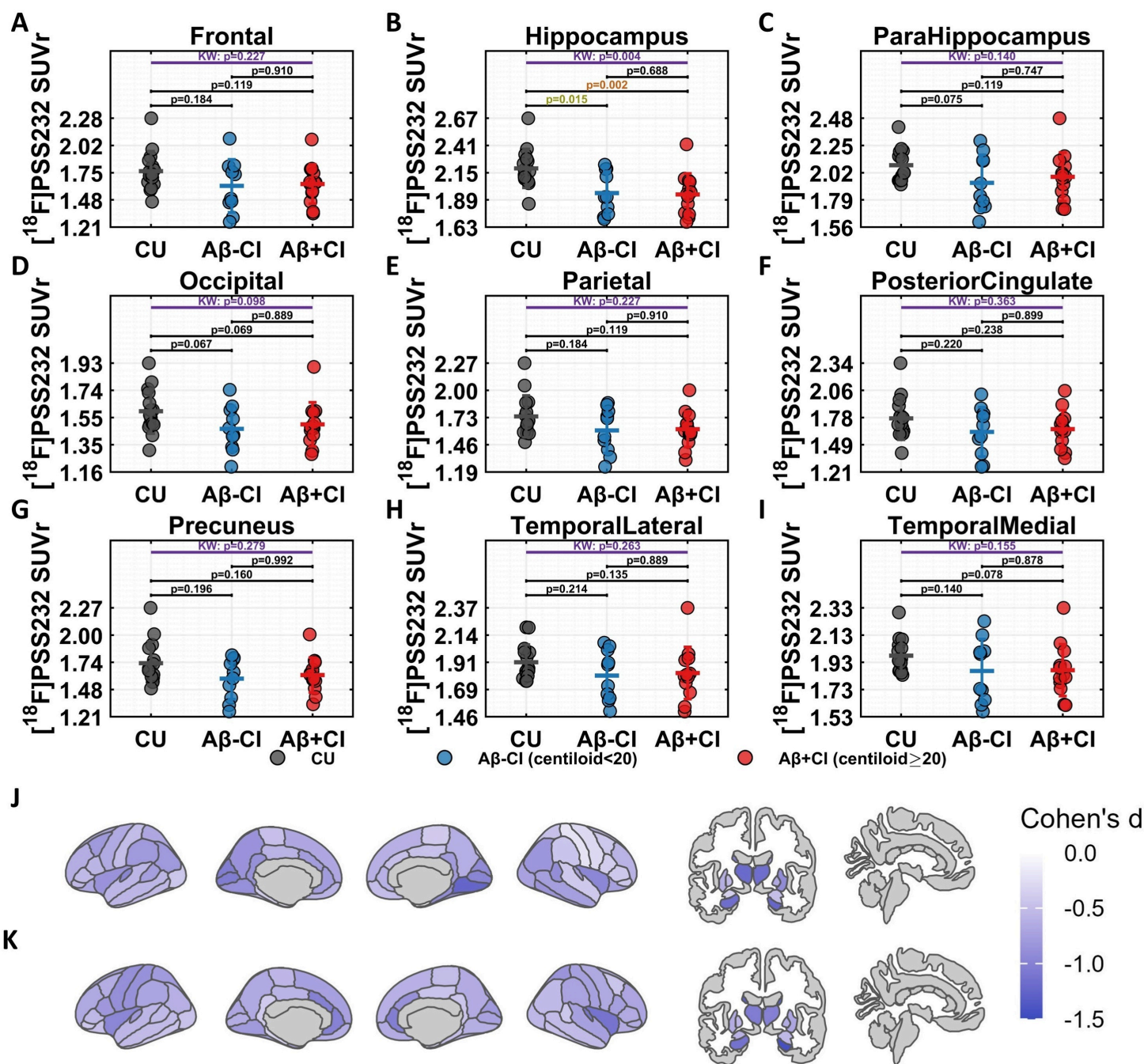


Figure 1

Comparison of mGluR5 availability by cognitive and amyloid β status.

(A-I) VOI-based cross-sectional comparison of mGluR5 availability across different brain regions. The plots highlight that mGluR5 availability is significantly lower in the hippocampus in both A β -CI and A β +CI groups compared with the CU group. Grey circles represent CU participants, blue circles represent A β -CI participants (Centiloid < 20), and red circles represent A β +CI participants (Centiloid $\geq$ 20). (J, K) Brain maps showing Cohen's d effect sizes from independent-samples t-tests (CU vs A β -CI, CU vs. A β +CI). Color scale: blue = negative effect size. Cortical and subcortical parcellations follow the Desikan–Killiany and atlases. Grey regions were not included in the analysis. **Abbreviations:** CI, cognitively impaired; CU,

cognitively unimpaired; **ANOVA**, Analysis of Variance; **SUVr**, Standardized Uptake Value Ratio; **VOI**, Volume of Interest.

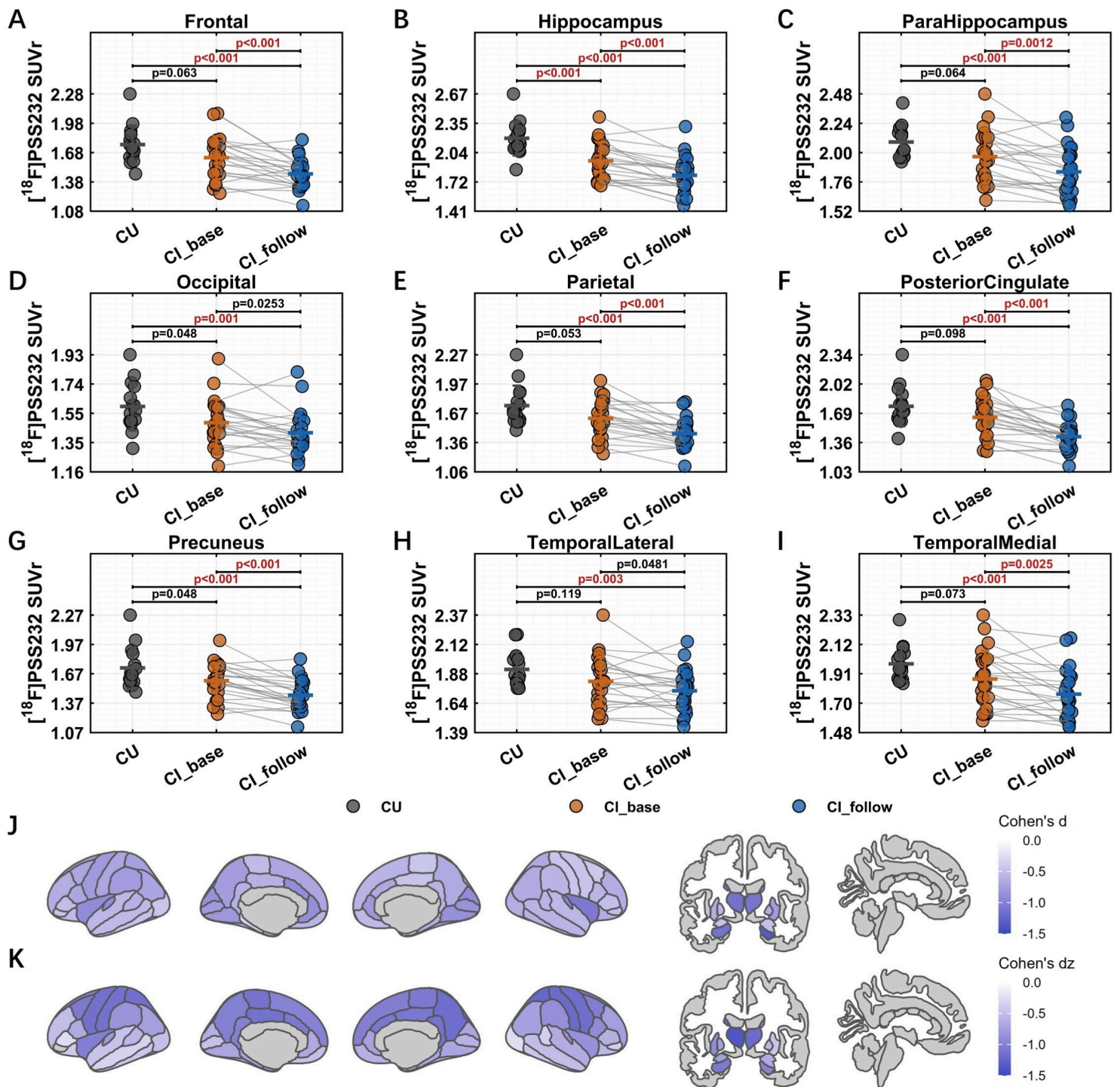


Figure 2

Longitudinal changes in mGluR5 availability.

(A-I) VOI-based comparison of mGluR5 availability across different brain regions. Lines track longitudinal measurements from individual CI subjects across visits. Black circles represent CU subjects,

orange circles represent CI patients at baseline, and blue circles represent the same CI patients at the follow-up visit. **(J)** Brain maps of Cohen's d effect sizes from independent-samples t -tests (CU vs. CI at baseline). **(K)** Brain maps of Cohen's d_z effect sizes from paired-samples t -tests (baseline vs. follow-up in CI). Color scale: blue = negative effect size. Cortical and subcortical parcellations follow the Desikan–Killiany and atlases. Grey regions were not included in the analysis. **Abbreviations:** **CI**, Cognitively Impaired; **CU**, Cognitively Unimpaired; **SUVr**, Standardized Uptake Value ratio.

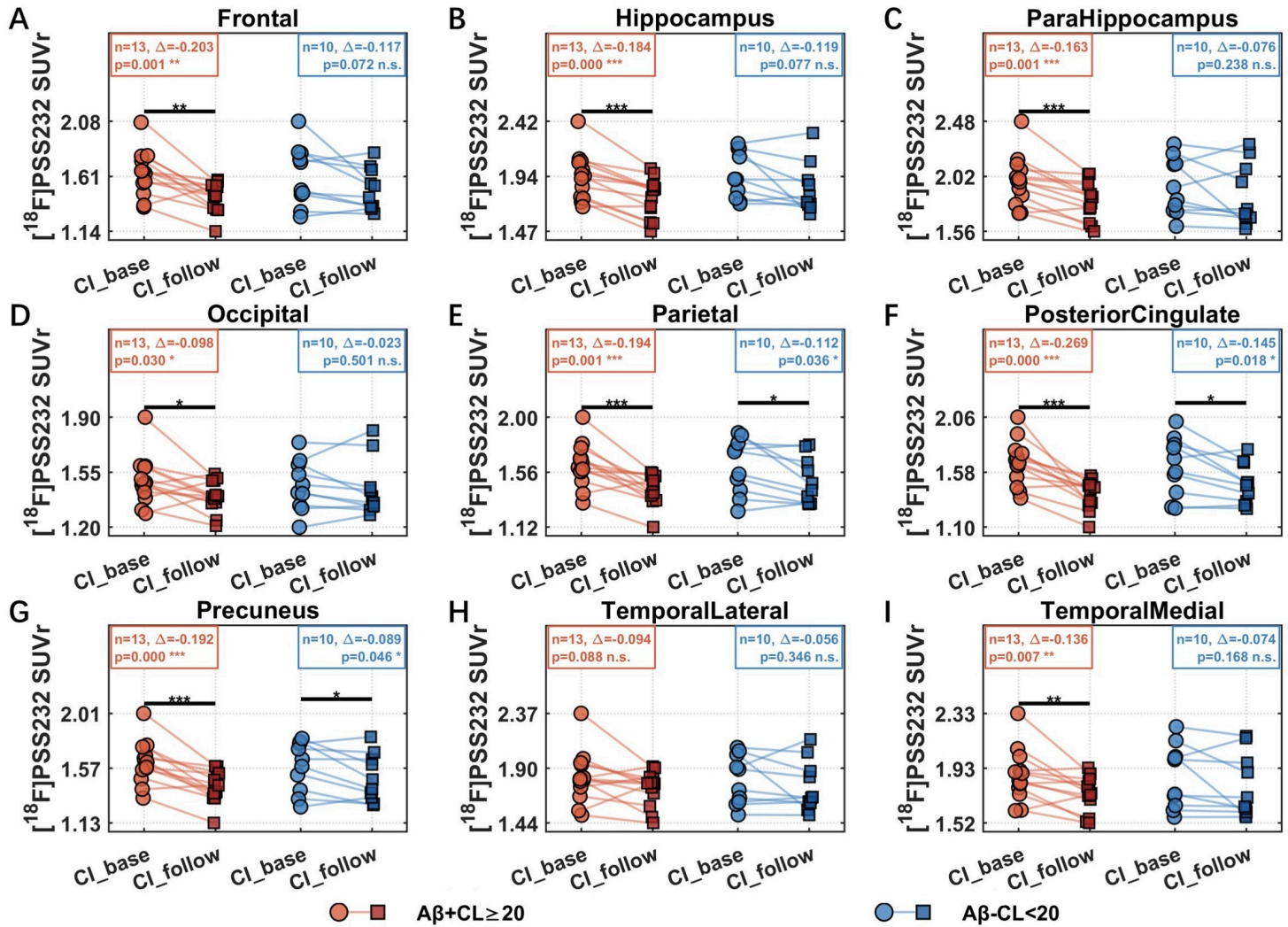


Figure 3

Longitudinal mGluR5 decline is greater in amyloid-positive cognitively impaired patients.

VOI-based plots showing longitudinal changes in mGluR5 availability across nine brain regions in CI patients. Participants were stratified by baseline Aβ status into Aβ+ group (Centiloid ≥ 20; red) and Aβ- group (Centiloid < 20; blue). For each participant, circles denote baseline, squares denote follow-up, and a connecting line tracks the individual change over time. The results from paired t -tests demonstrate a significant and widespread longitudinal decline in mGluR5 availability in the Aβ-positive group.

Abbreviations: **Aβ**, Amyloid-beta; **CI**, Cognitively Impaired; **CL**, Centiloid; **SUVr**, Standardized Uptake Value ratio.

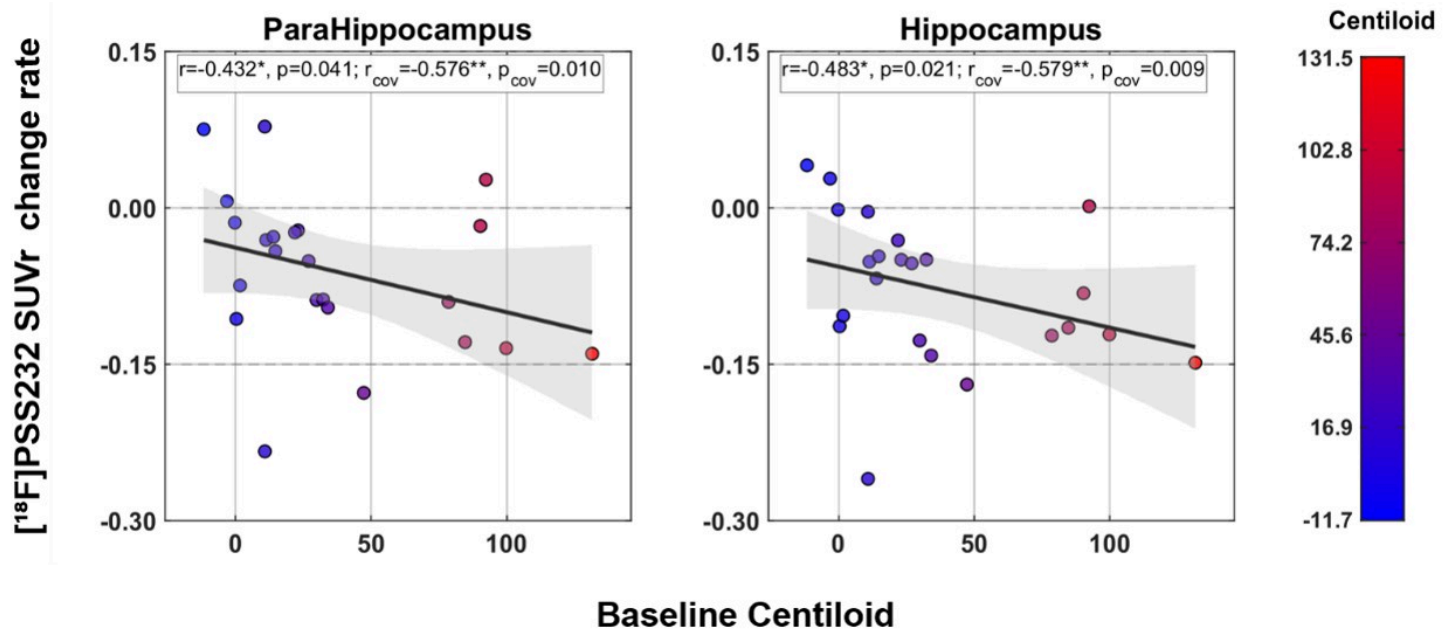


Figure 4

Baseline amyloid burden predicts the change rate of longitudinal mGluR5 decline.

Scatter plots illustrate the relationship between baseline amyloid burden (Centiloid) and the longitudinal rate of change in [¹⁸F] PSS232 SUVR in the parahippocampus and hippocampus. Solid lines depict the linear regression fit, with shaded areas representing 95% confidence intervals. Partial correlations adjusted for age, sex, education, and scan interval (r_{cov} , p_{cov}) are presented. * $p < 0.05$, ** $p < 0.01$.

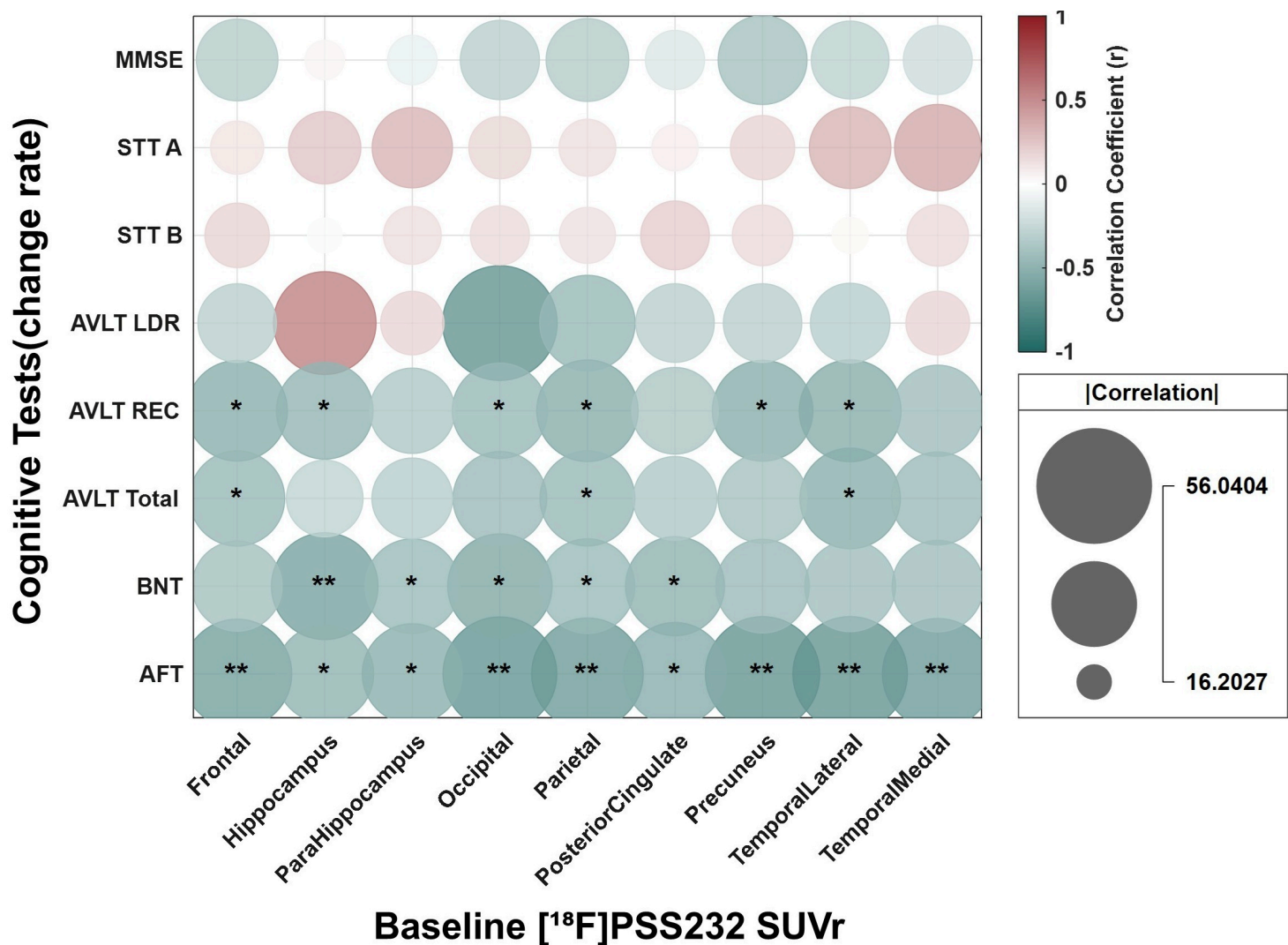


Figure 5

Partial correlation analysis between baseline [¹⁸F] PSS232 SUVR and the rate of cognitive change.

The partial correlations (adjusted for age, sex, and education) between baseline [¹⁸F] PSS232 SUVR and longitudinal rate of change in cognitions. Each bubble represents a correlation coefficient, with bubble size proportional to the absolute correlation strength and color indicating the direction and magnitude of the relationship. Bubble Size = $|r| \times 50 + 10$. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

Abbreviations: **MMSE**, Mini-Mental State Examination; **STT A and B**, Shape trials test A and B; **AVLT-LDR**, Auditory Verbal learning Test long time delayed free-recall; **AVLT-REC**, Auditory Verbal Learning Test recognition scores (24 items); **BNT**, Boston Naming Test; **AFT**, Animal Fluency Test.

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