

Sources of Variability in Brain [18F]FDG Metabolism in Cognitively Unimpaired Individuals

Marco Antônio de Bastiani¹; Giordana Salvi de Souza¹; Guilherme Povala²; Guilherme Schu³; Andrei Bieger¹; Mateus Rozalem Aranha^{4,5}; Artur Martins Coutinho^{5,6}; Wyllians Vendramini Borelli¹; Eduardo Zimmer¹; Laura Willers de Souza^{1,3}

¹ Universidade Federal do Rio Grande do Sul, Brazil; ² University of Pittsburgh, USA; ³ masima: Macunaíma Soluções em Imagens Médicas, Brazil; ⁴ Hospital Sírio-Libanês, Brazil; ⁵ Universidade de São Paulo, Brazil; ⁶ Hospital de la Santa Creu i Sant Pau, Spain

INTRODUCTION

[18F]FDG-PET interpretation relies on comparing an individual's SUVR against normative data from cognitively normal subjects. However, this comparison is sensitive to technical and biological variability. In this study, we quantified the effects of **scanner manufacturer, reference region, age, and sex** on regional [18F]FDG uptake in **449 cognitively unimpaired (CN) adults** from ADNI, to derive covariate-adjusted normative values.

METHODS

Baseline [18F]FDG-PET scans from 449 cognitively unimpaired ADNI participants in three age groups (**Table 1**) were analyzed. Regional SUVR from the DKT atlas (83 regions, four lobes, AD meta-ROI), normalized to three reference regions (pons, whole cerebellum, cortical gray matter), were converted to Z-scores. Per-region linear regression modeled Z-score on age, sex, and scanner manufacturer (Siemens reference; FDR q < 0.05). Generalizability was assessed by 10-fold cross-validation (ΔR^2) and confirmed in amyloid-negative participants (n = 278).

Table 1. Sample demographics and clinical characteristics				
	Age group			p-value
	≤65 years (n = 21)	65–75 years (n = 247)	≥75 years (n = 181)	
Demographic & clinical				
Age	63 (2)	70 (3)	80 (3)	< 0.001
Female sex	10 (48%)	126 (51%)	90 (50%)	0.9
Education (years)	17 (2)	16 (3)	16 (3)	0.5
MMSE	29 (1)	29 (1)	29 (1)	0.8
CDR	0.1 (0.2)	0.04 (0.14)	0.09 (0.27)	0.08
APOE4 carrier	0	6 (2.4%)	5 (2.8%)	0.9
ICV (mm³)	1,518 (188)	1,503 (153)	1,522 (162)	0.5
Amyloid (neg/pos/miss), %	87.0 / 4.3 / 8.7	65.4 / 18.7 / 15.9	55.0 / 25.6 / 19.4	0.017
Race				
White	14 (67%)	227 (92%)	166 (92%)	0.002
Black	1 (4.8%)	15 (6.1%)	10 (5.5%)	
Other races	6 (29%)	5 (2.0%)	5 (2.8%)	
Scanner manufacturer				
GE	5 (24%)	82 (33%)	52 (29%)	0.6
Philips	2 (9.5%)	31 (13%)	29 (16%)	
Siemens	14 (67%)	134 (54%)	100 (55%)	
Image acquisition date				
2005 – 2009	5 (24%)	51 (21%)	51 (28%)	0.2
2010 – 2015	16 (76%)	196 (79%)	130 (72%)	
Values are mean (SD) or n (%). All pairwise comparisons for age were significant (<i>p</i> < 0.001). The ≤65 years group also differed from both older groups for White and Other races (<i>p</i> < 0.001). Amyloid positivity differed across age groups after excluding missing-status participants ($\chi^2(2) = 8.18$, <i>p</i> = 0.017; Cramér's <i>V</i> = 0.15).				
Abbreviations: MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; APOE4, apolipoprotein E ε4 allele; ICV, intracranial volume.				

Table 1. Sample demographics and clinical characteristics. N = 449 cognitively unimpaired ADNI participants, stratified into three age groups (≤65, 65–75, ≥75 years). Values are mean (SD) or n (%). Groups did not differ in sex, education, MMSE, or APOE4 frequency; race and amyloid positivity varied with age. Imaging was predominantly Siemens (55%), then GE (29%) and Philips (16%) (Siemens is the regression reference).

RESULTS

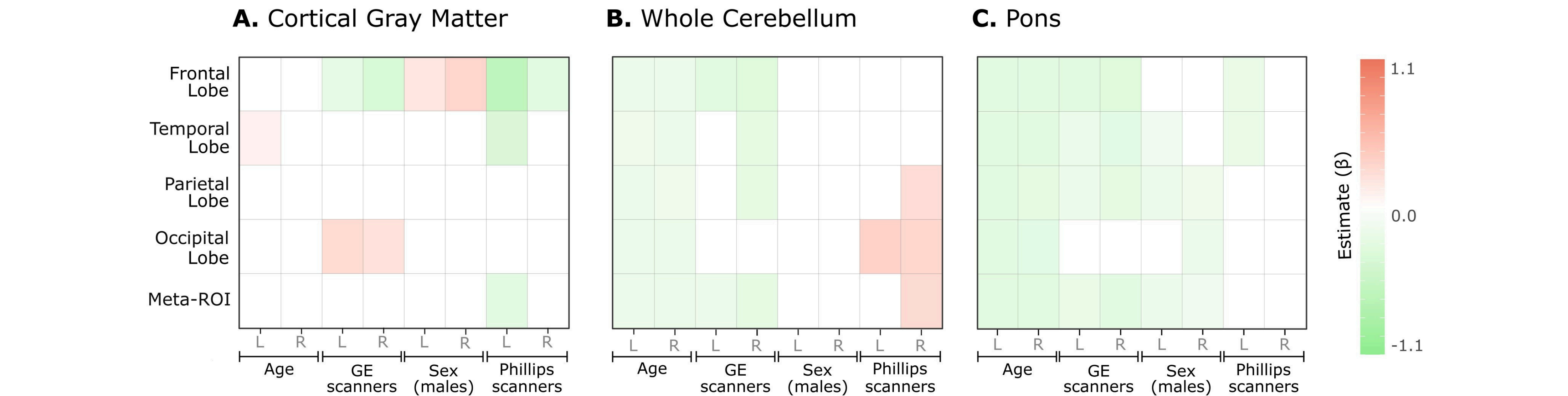


Figure 1. Lobar and AD meta-ROI effects across reference regions. Heatmap of standardized regression coefficients (β) for age, sex, and scanner manufacturer on lobar and AD meta-ROI [18F]FDG Z-scores, stratified by hemisphere (L/R). Only FDR-corrected significant coefficients (p < 0.05) are shown. Cortical gray matter is visibly the emptiest panel (minimal demographic and scanner effects, marking it the most stable reference) while the meta-ROI row stays robust across all three reference regions (adjusted $R^2 \leq 0.03$).

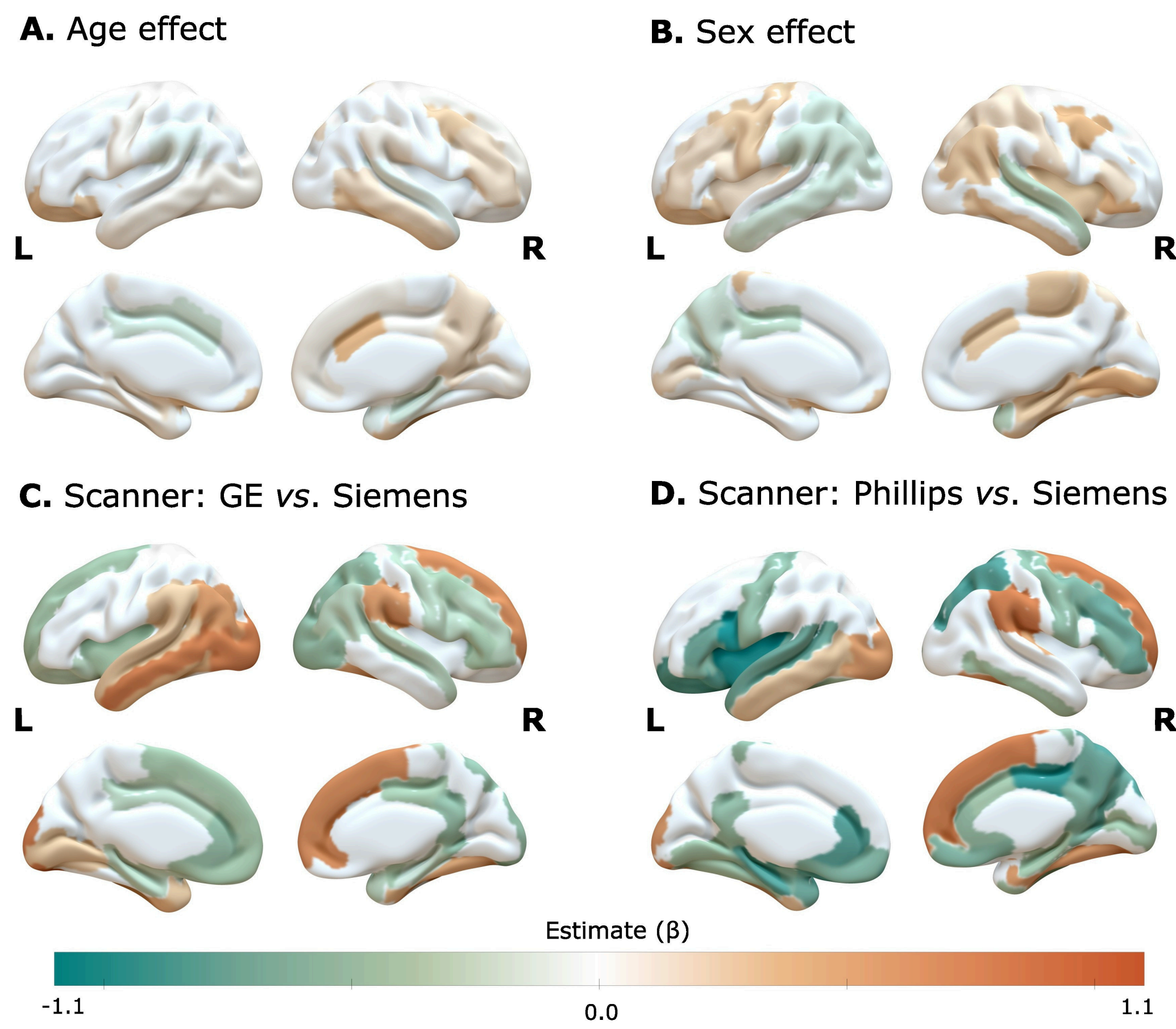


Figure 2. Cortical distribution of age, sex, and scanner effects. Cortical surface representation of standardized regression coefficients (β) using cortical gray matter normalization. Only FDR-corrected significant associations (p < 0.05) are displayed. Scanner manufacturer produces the most widespread effects, with GE and Phillips yielding lower Z-scores than Siemens across frontal and medial-temporal cortex.

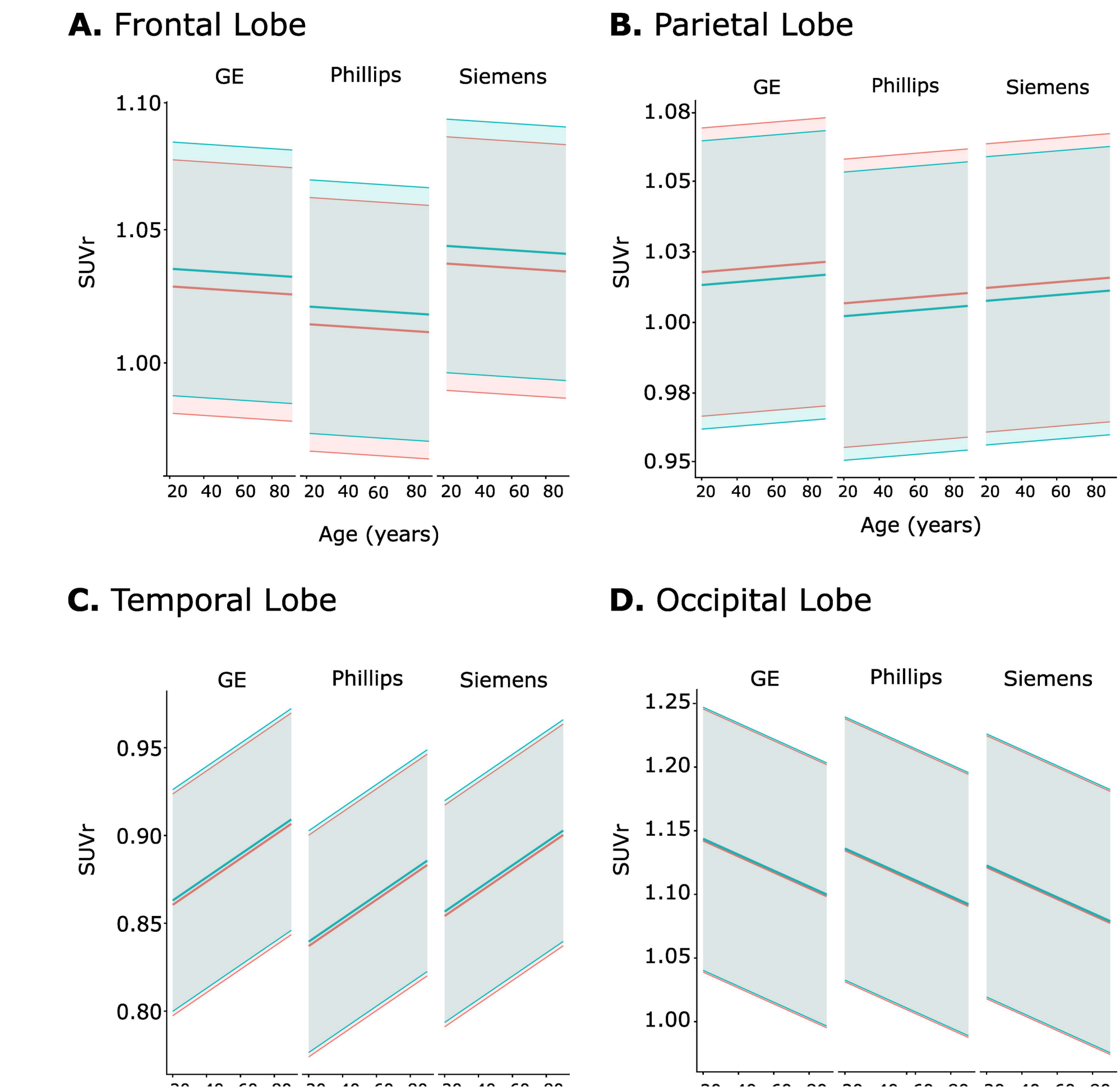
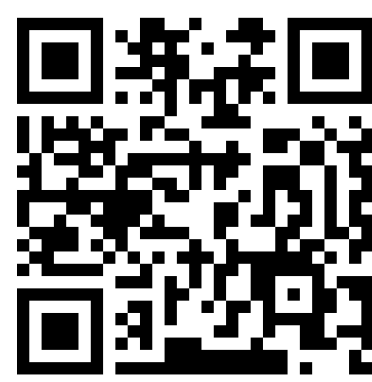


Figure 3. Normative [18F]FDG SUVR distributions. SUVR across age, stratified by scanner manufacturer and sex, using cortical gray matter normalization. Lines represent mean SUVR for each age–manufacturer stratum; shaded areas represent 95% confidence intervals. The frontal lobe shows the widest manufacturer spread, illustrating the scanner sensitivity, persistent even in amyloid-negative participants, that motivates these covariate-adjusted normative references.

TAKE HOME-MESSAGE

Scanner manufacturer and age dominate variance in brain [18F]FDG quantification, exceeding sex. Cortical gray matter normalization minimizes confounders and the AD meta-ROI is highly robust, underscoring the need for harmonization and careful reference-region selection in normative modeling.



SCAN ME

masima
precision medicine
for brain diseases

contato@masima.com.br