100th Annual Meeting

American Association of Neuropathologists

Autopsy findings versus biomarker outcomes in a clinical trial of anti-Aβ therapies in dominantly inherited Alzheimer disease

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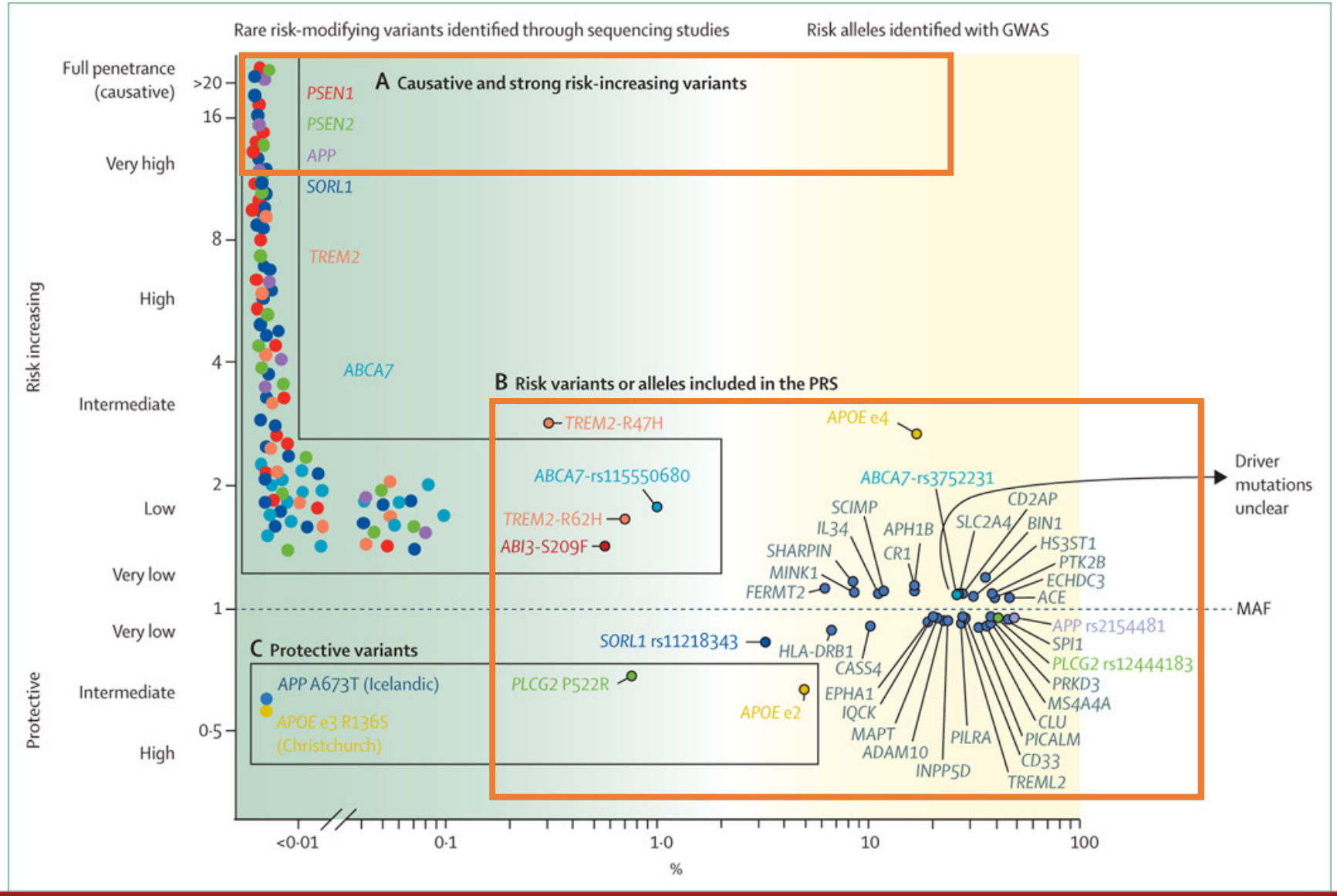
Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

- Learning Objective #1: Describe the longitudinal trends of biomarker and clinical outcomes in clinical trials of anti-Aβ monoclonal antibodies in dominantly inherited Alzheimer disease
- Learning Objective #2: Describe the effects of anti-Aβ monoclonal antibodies on the neuropathology of dominantly inherited Alzheimer disease

Dominantly inherited Alzheimer disease arises from *PSEN1/PSEN2* and *APP* mutations



Scheltens et al. 2021

PSEN1/PSEN2 and *APP* mutations lead to more aggregation-prone forms of Aβ peptide

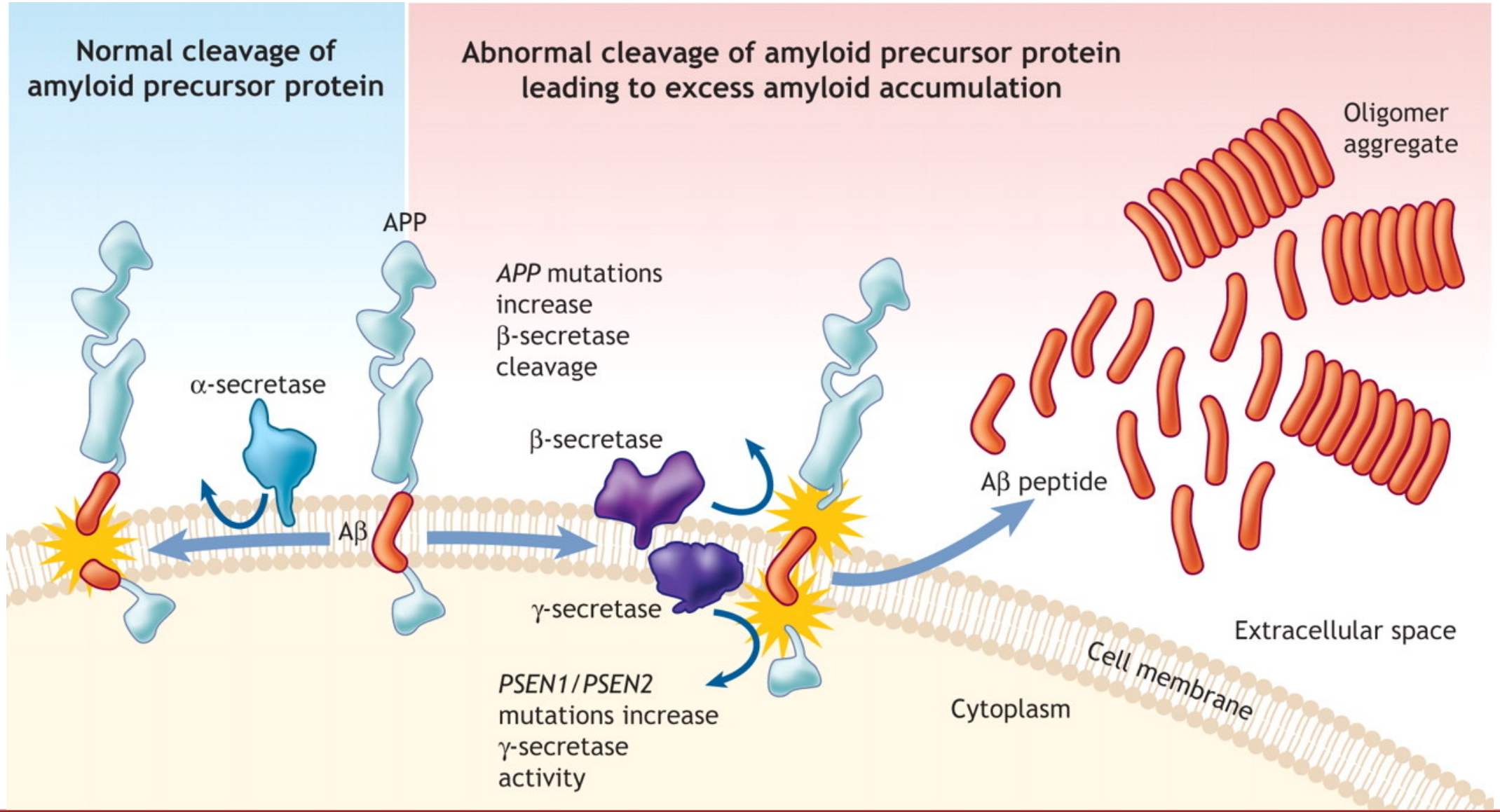
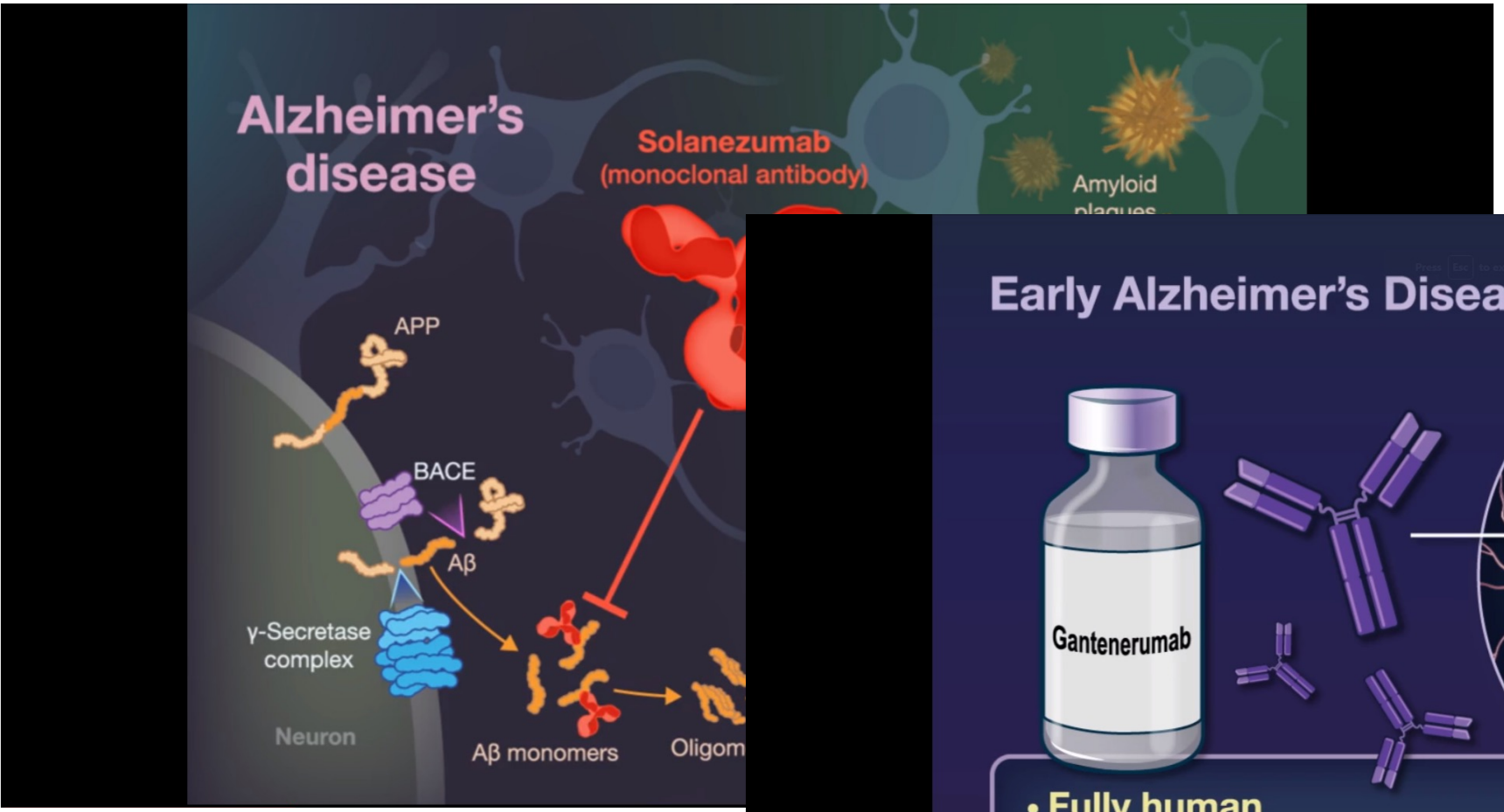
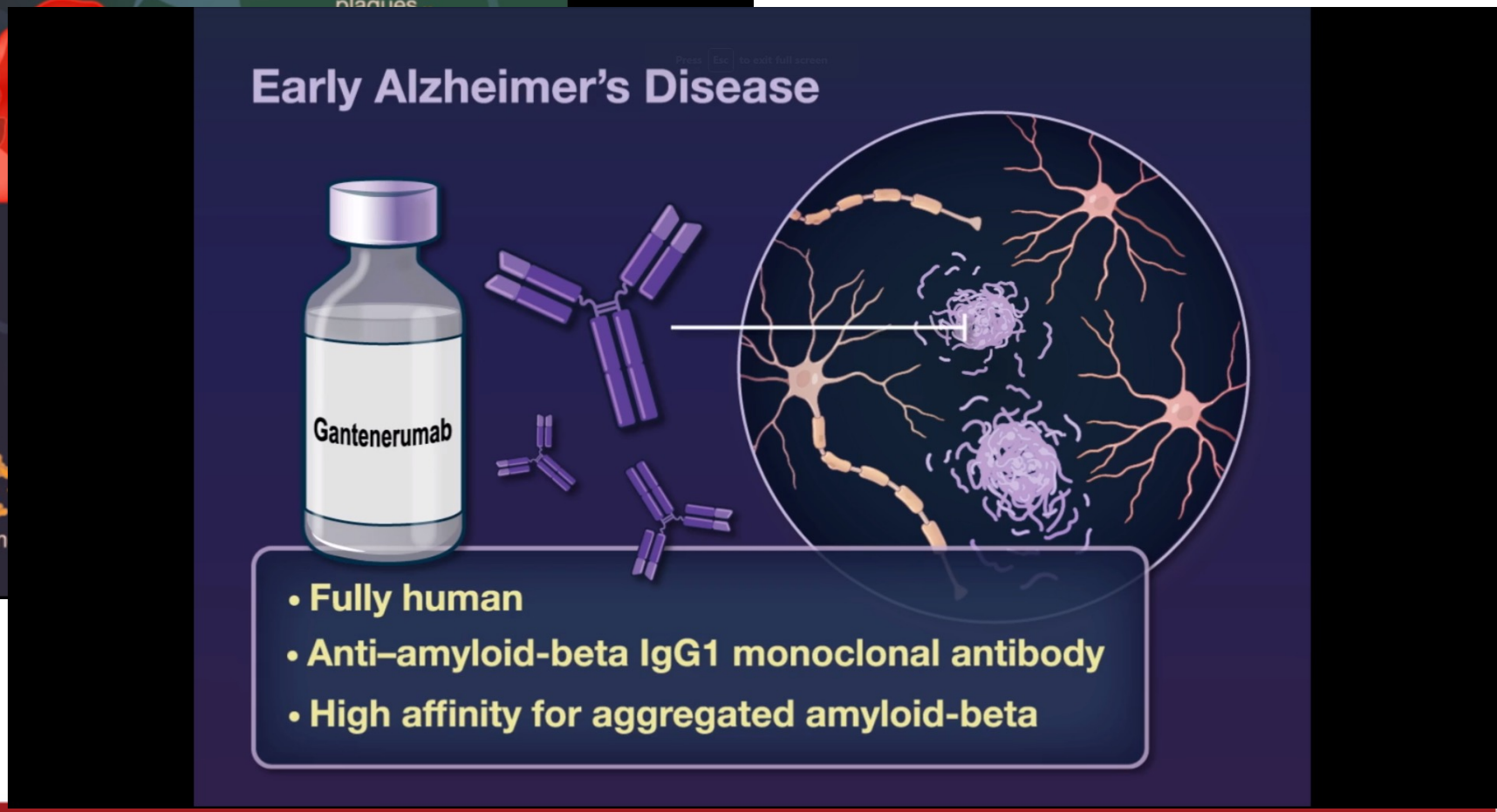


Image credit: Lianne Friesen and Nicholas Woolridge

Anti-Aβ monoclonal antibodies have been developed to remove Aβ peptides/aggregates





Sperling et al. 2023
Bateman et al. 2023

DIAN-TU AD Secondary Prevention Trial Platform

KNIGHT FAMILY DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit

Solanezumab — *NIA U01 AG042791*

Gantenerumab — *NIA R01 AG046179* — ~200 participants

→ **Gantenerumab Exploratory Open-Label Extension** — *Alz Association, GHR Foundation* — 73 participants

NexGen Atabecestat *Stopped July 2018* — *NIA R01/R56 AG053267*

Cognitive Run-in → **E2814 + Lecanemab** (*2 yr Bio Endpoint*, *4 yr Cog Endpoint*)

→ **Tau NexGen 5th Drug Arm**

→ **Tau NexGen 6th Drug Arm**

→ Biomarker Interims

Population
EYO -10 to +10

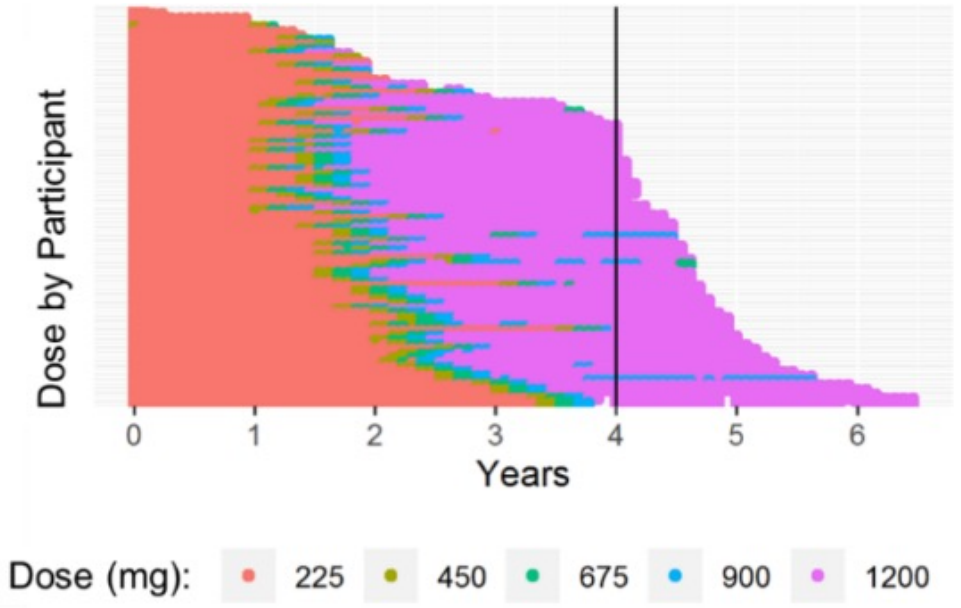
All blinded drug arms have received support from the following groups:
Alzheimer's Association
GHR Foundation
Anonymous Organization

168 participants — *NIA R01 AG053267*

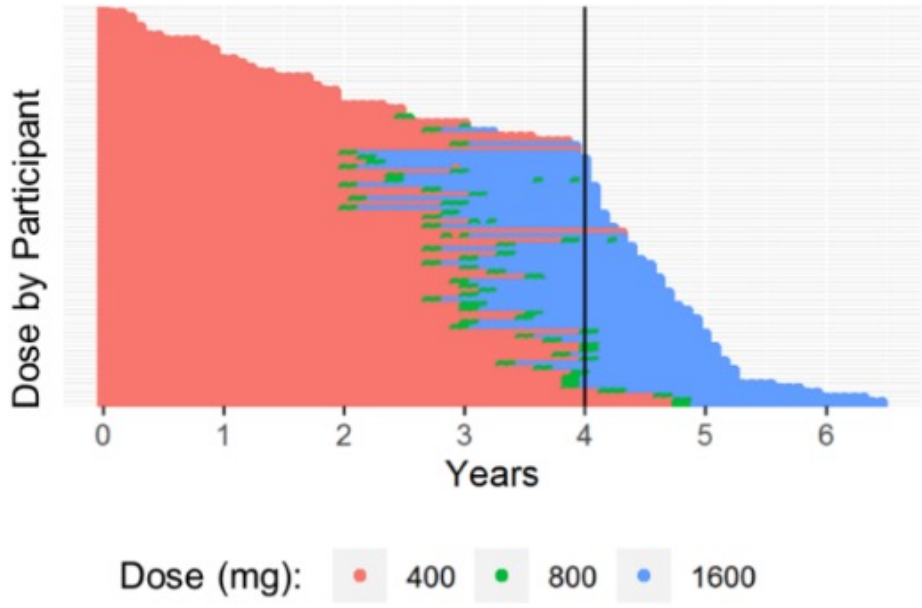
100 participants + 100 participants — ***NIA R01 AG068319 $82M***

Drug doses were increased mid study to improve chances of reaching cognitive endpoint

Gantenerumab

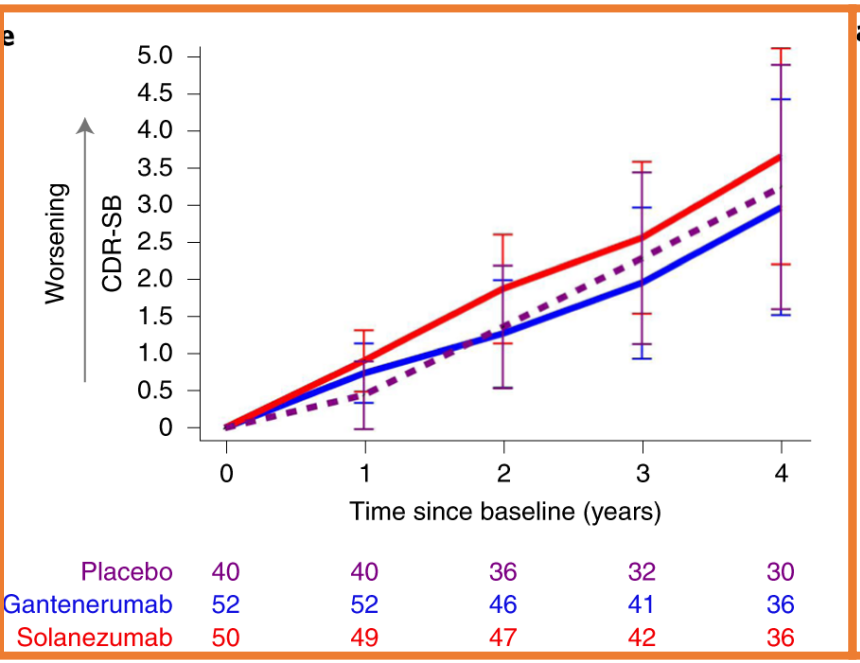


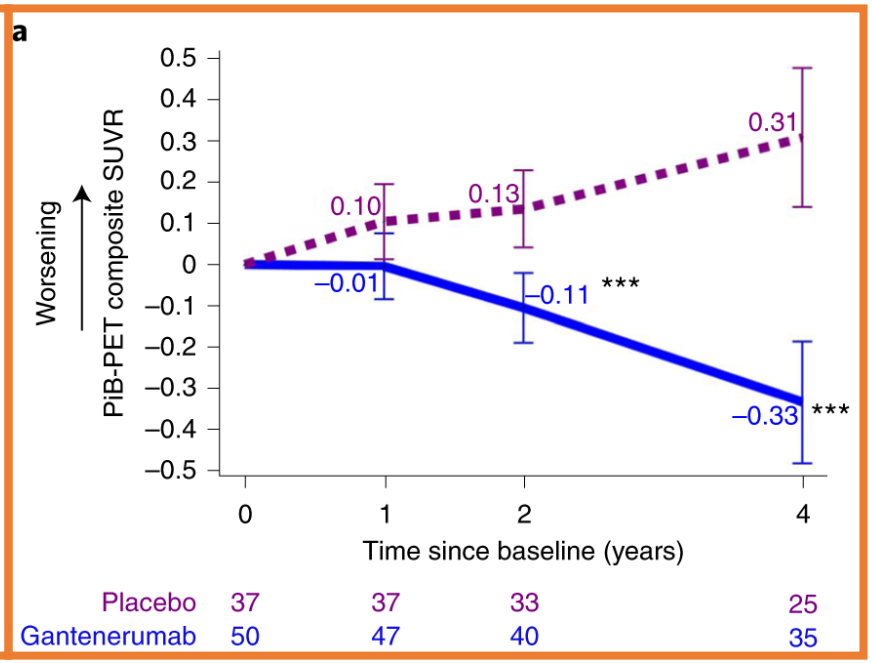
Solanezumab

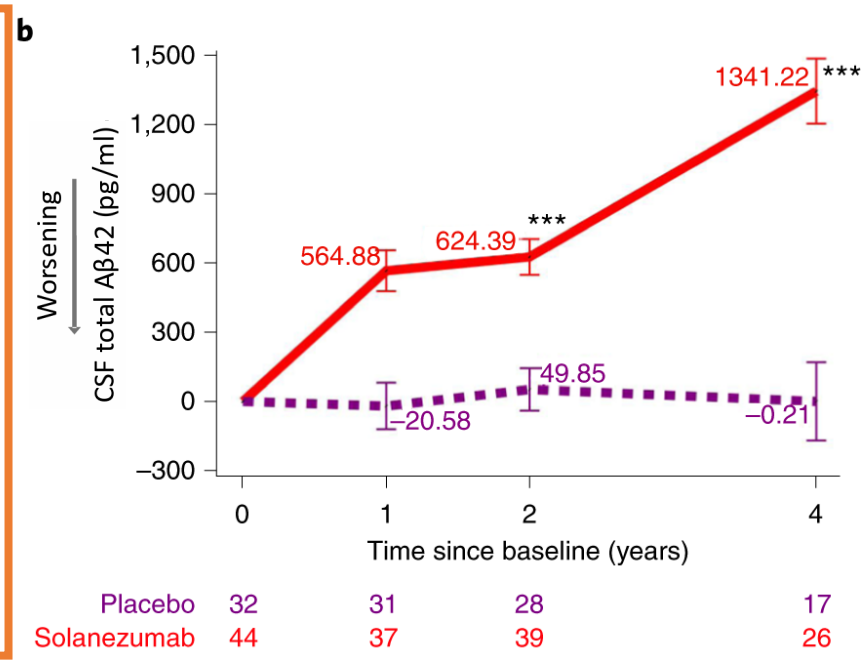


Salloway et al. 2021

Neither drug slowed cognitive decline during the trial, but gantenerumab showed evidence for brain Aβ removal

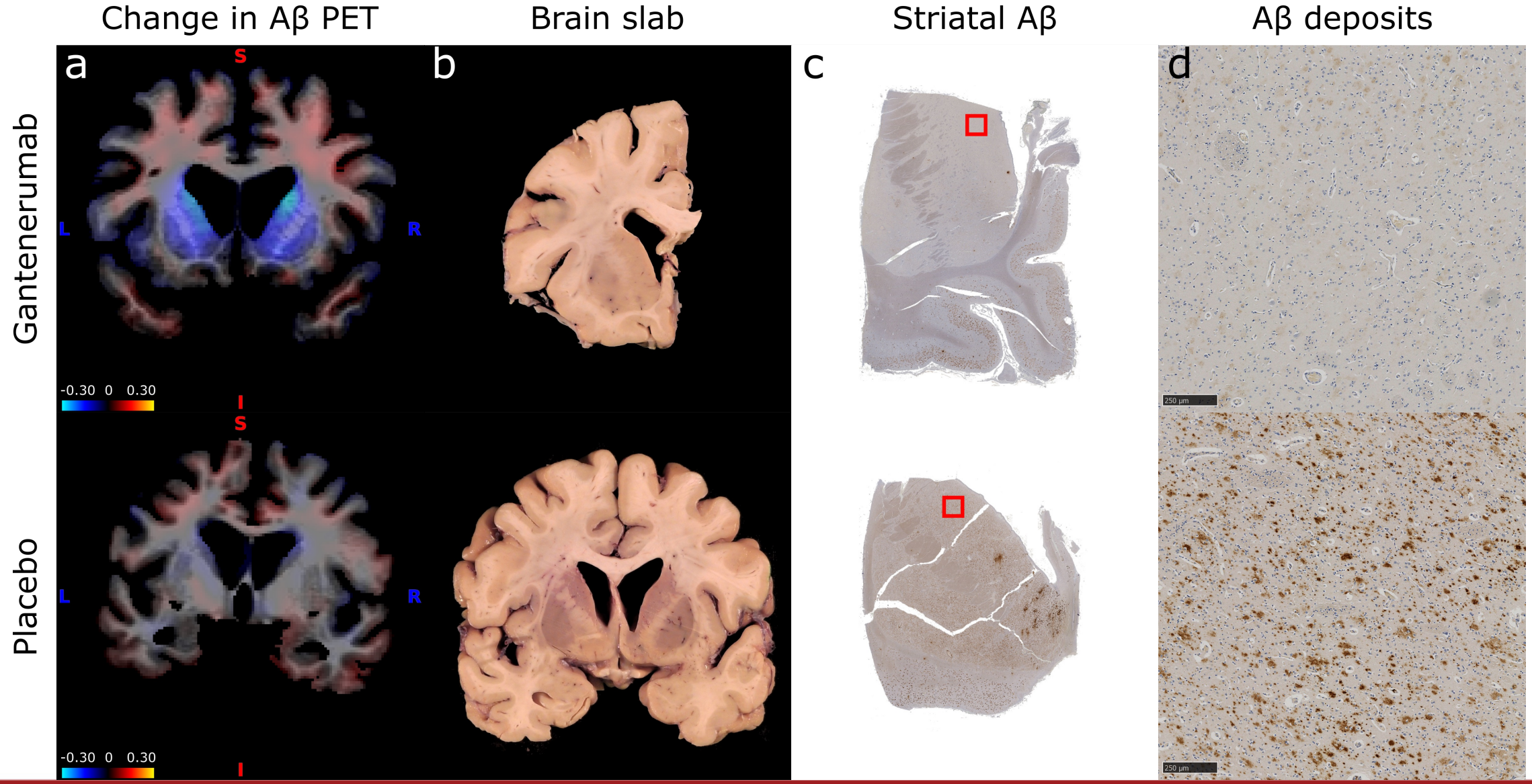






Salloway et al. 2021

Imaging-to-pathology comparison: an illustrative example



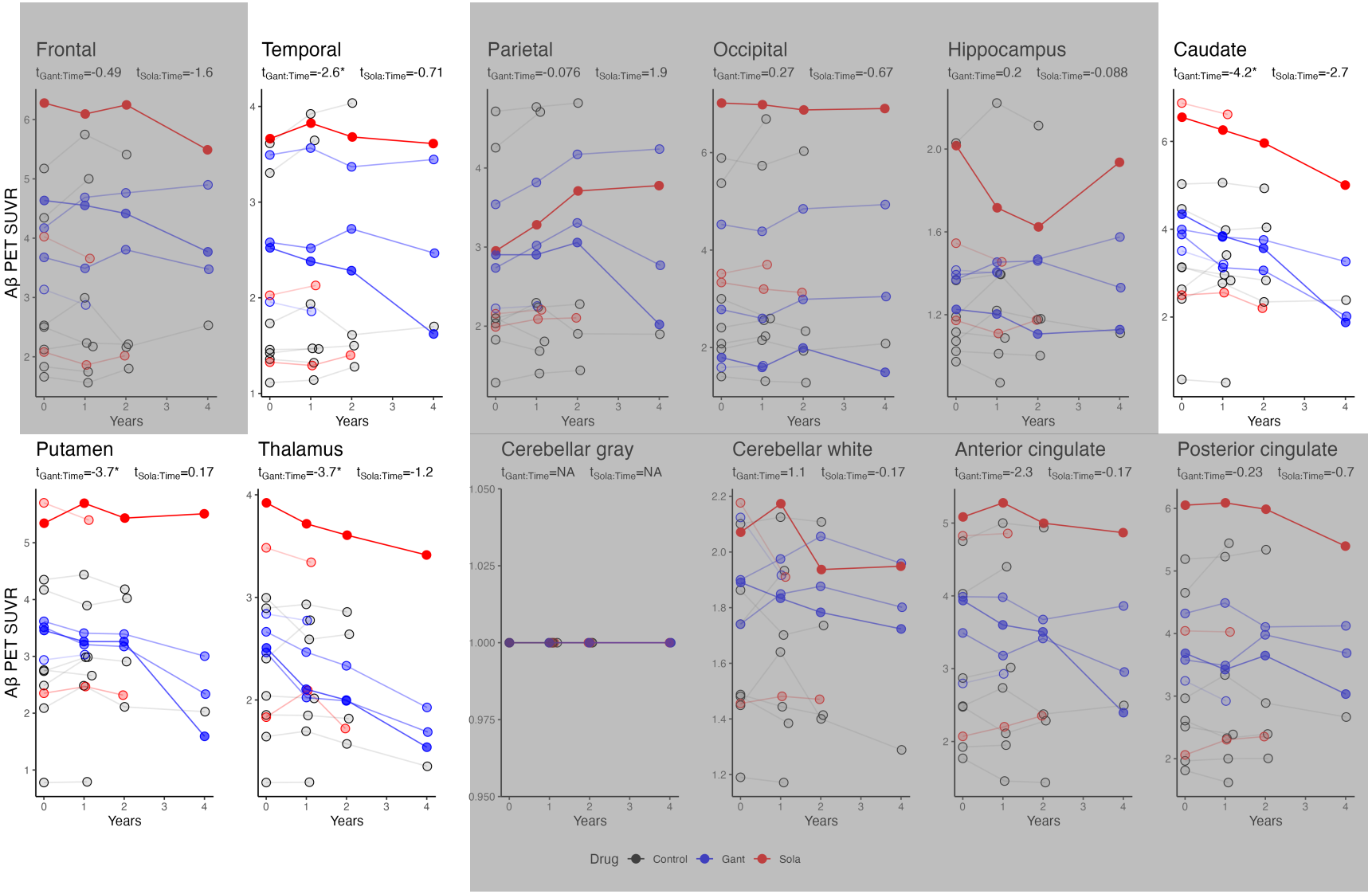
Participant characteristics

	Gantenerumab	Solanezumab	Placebo/No treatment
Total	4	4	12
Female	0	2	5
APOE ε4+	3	0	4 (NA=2)
Family mutation			
PSEN1	3	4	11
APP	1	0	1
CDR® at baseline			
0.5	3	0	5 (NA=2)
1	1	4	3
2	0	0	1
3	0	0	1
Mutation age of onset	49 ± 8	40 ± 9	45 ± 8
Age at baseline	49 ± 7	46 ± 10	46 ± 9
Age at death	54 ± 8	51 ± 10	51 ± 10

Participant postmortem neuropathology

	Gantenerumab	Solanezumab	Placebo/No treatment
Final CDR®			
3	3 (NA=1)	3 (NA=1)	12
Thal phase			
3	1	0	0
5	3	4	12
Braak NFT stage			
V	0	1	0
VI	4	3	12
CERAD NP score			
3	4	4	12
CAA			
1	2	2	3
2	2	0	8
3	0	2	1

Several regions showed longitudinal reductions in Aβ PET SUVR in the gantenerumab arm and in at least one participant in the solanezumab arm



Linear mixed-effects models of the form **SUVR~Drug*Time+(1|Participant)** were used to estimate statistical differences in longitudinal change of Aβ PET between either gantenerumab or solanezumab treatment arms and the control group

$t_{Gant:Time}$ denotes the t-value of the Gant:Time interaction

Asterisks denote p-values<0.05 associated with $t_{Gant:Time}$; no $t_{Sola:Time}$ interaction was significant

Regions in grey are associated with non-significant $t_{Gant:Time}$ interactions

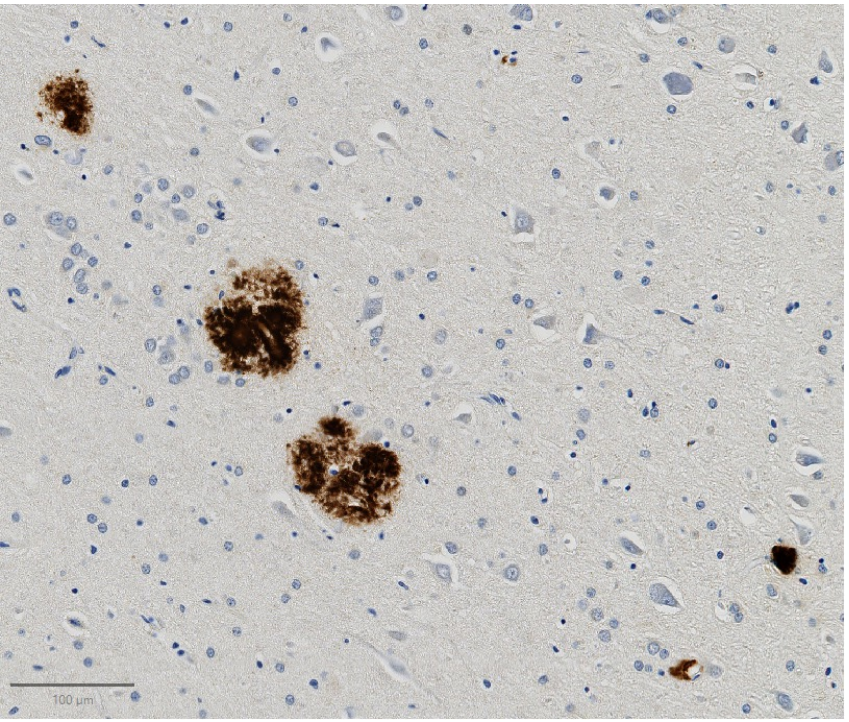
P-values were adjusted by the Benjamini-Hochberg procedure

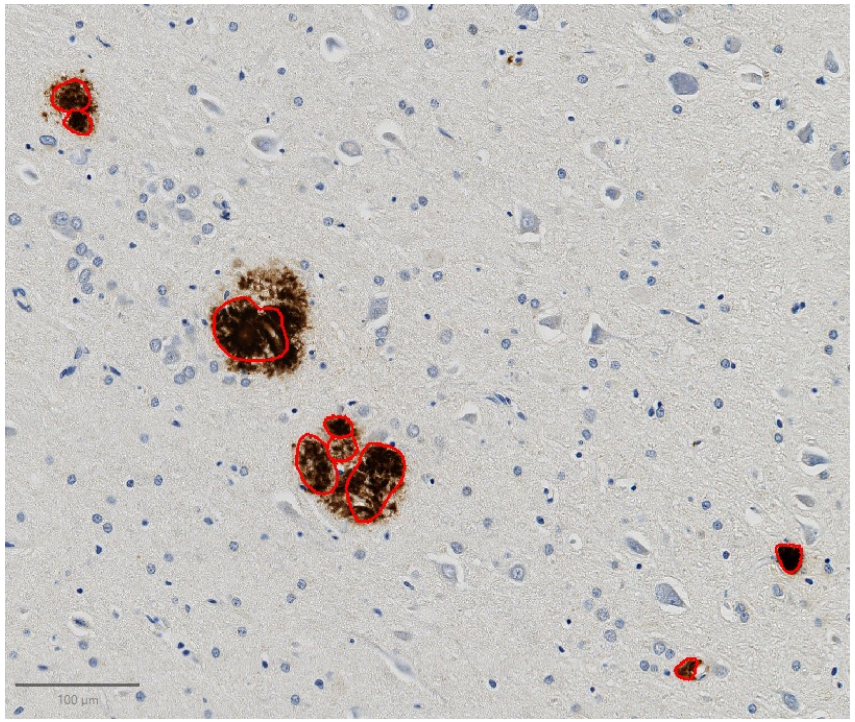
How postmortem neuropathology was quantified:
Aβ (10D5), tau (PHF1), microglia (IBA1), and astrocyte (GFAP) area fractions

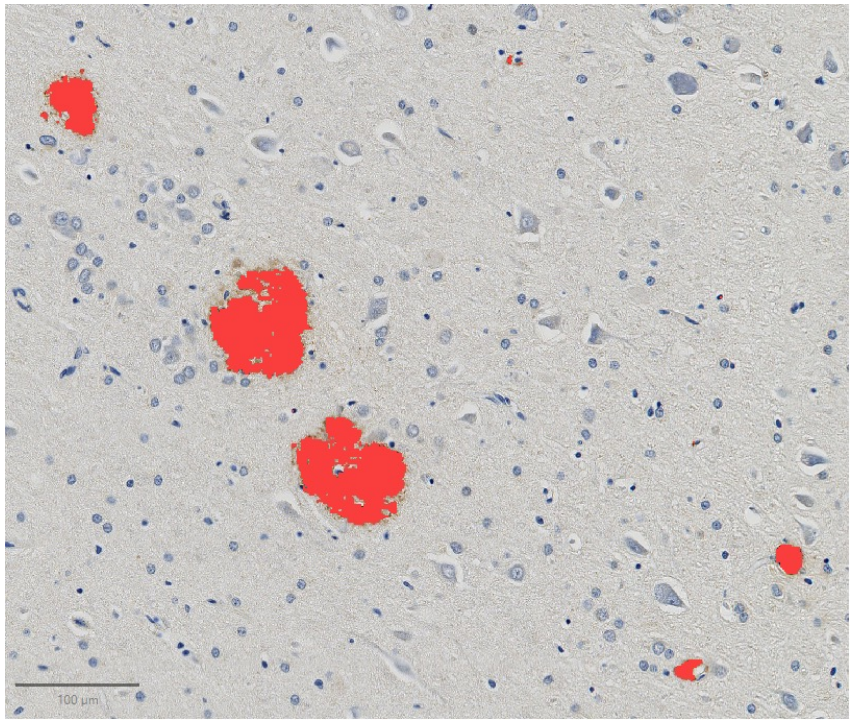
DAB immunohistochemistry
(Antibody for Aβ, 10D5)

StarDist
(Object Detection with Star-convex Shapes)

Pixel classifier
(Thresholder)

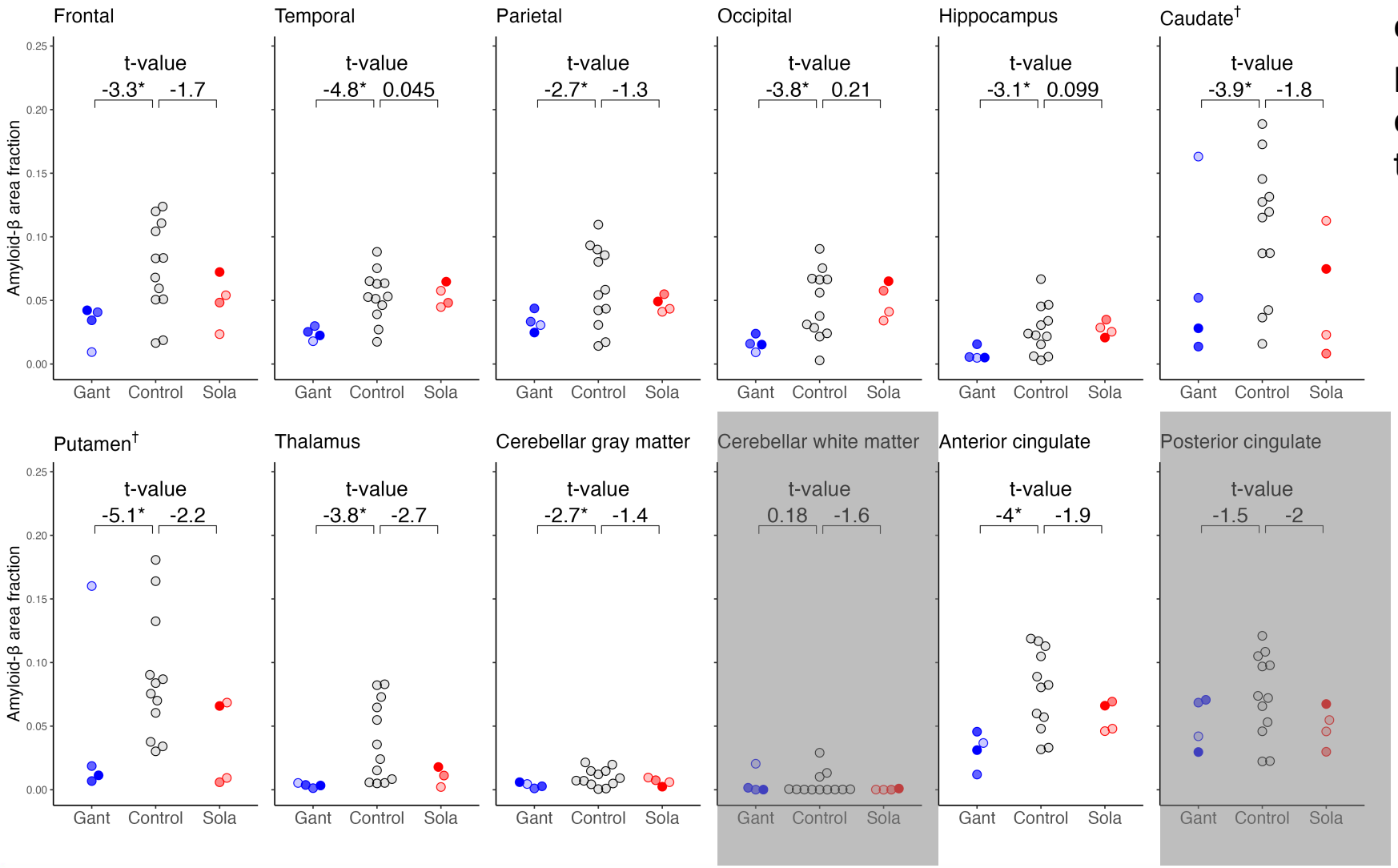






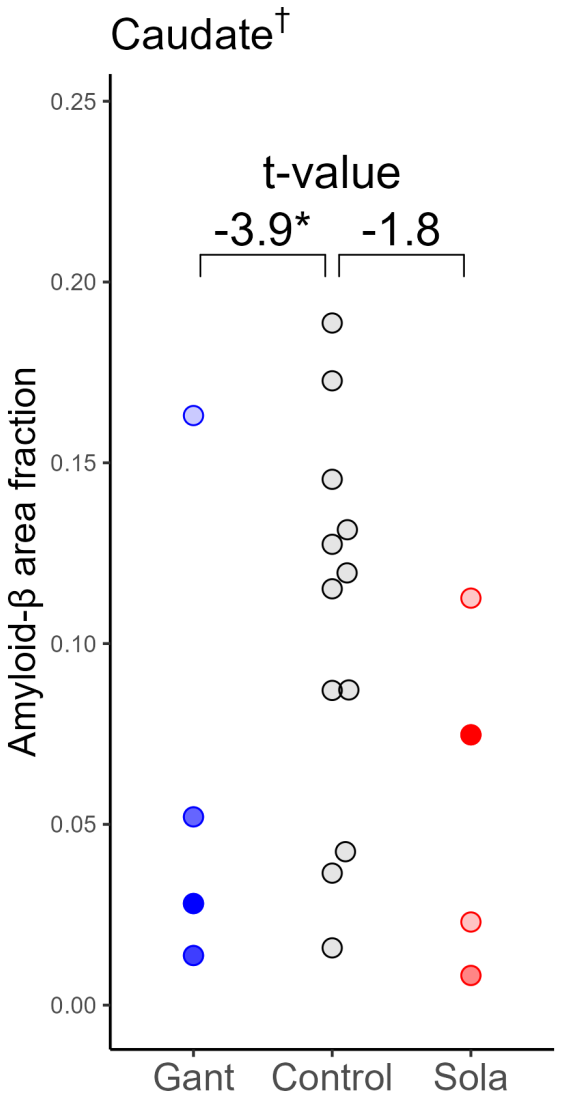
Schmidt et al. 2018
Bankhead et al. 2017

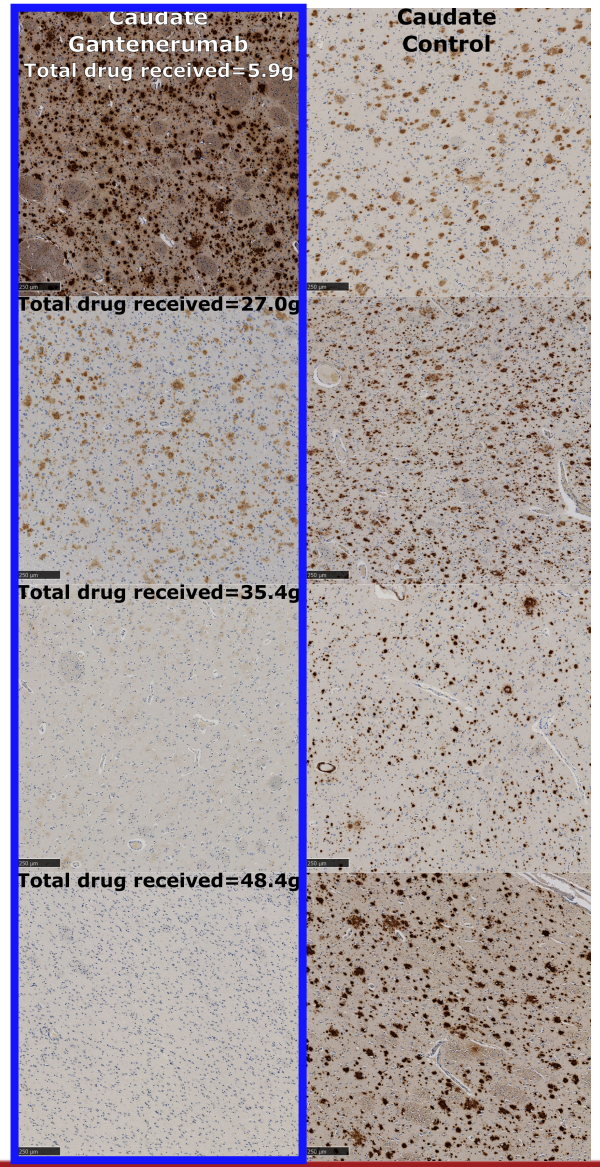
Almost all regions showed reduced Aβ area fraction in the gantenerumab arm (n=4)

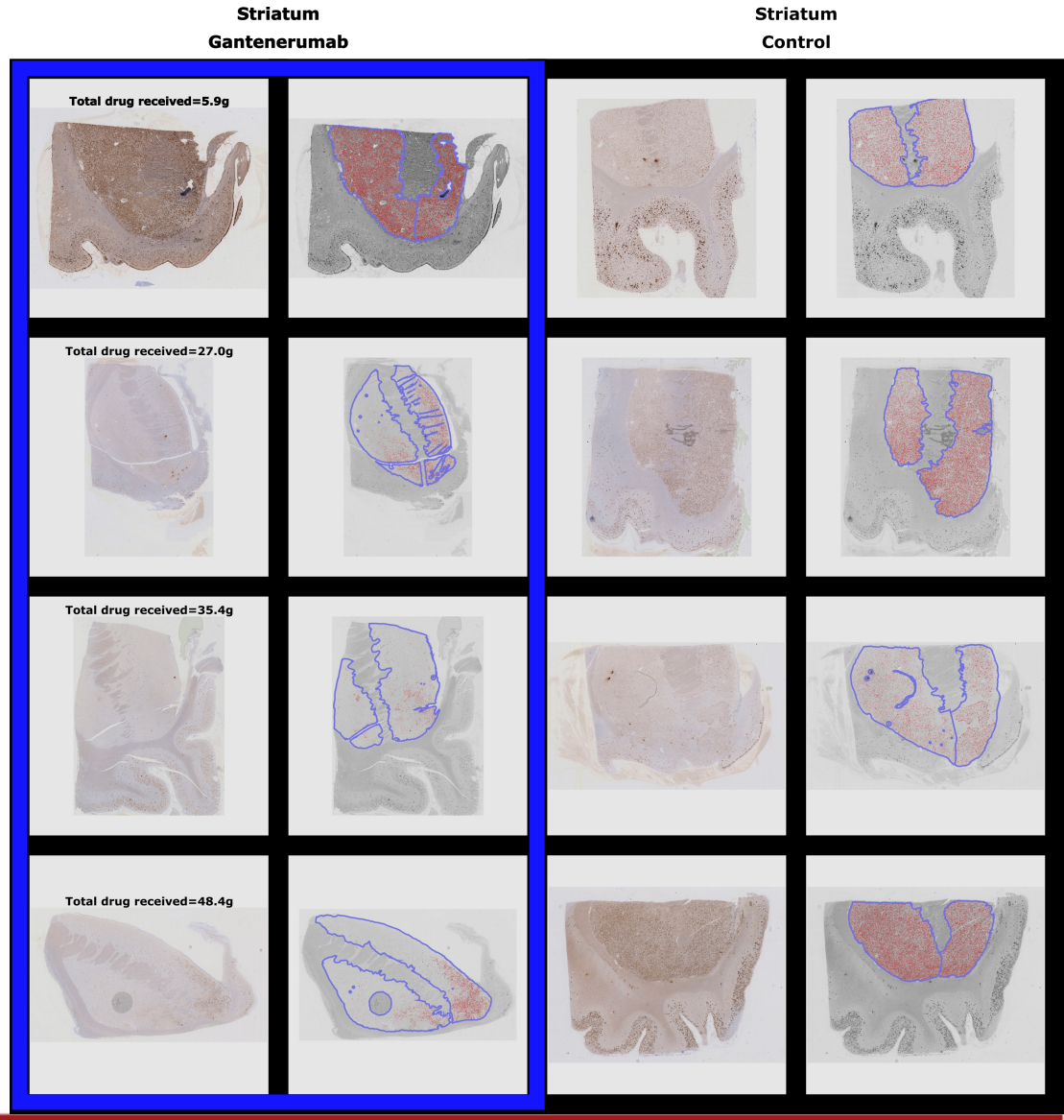


Welch two sample t-tests were used to estimate statistical differences in postmortem neuropathology between either gantenerumab or solanezumab treatment arms and the control group

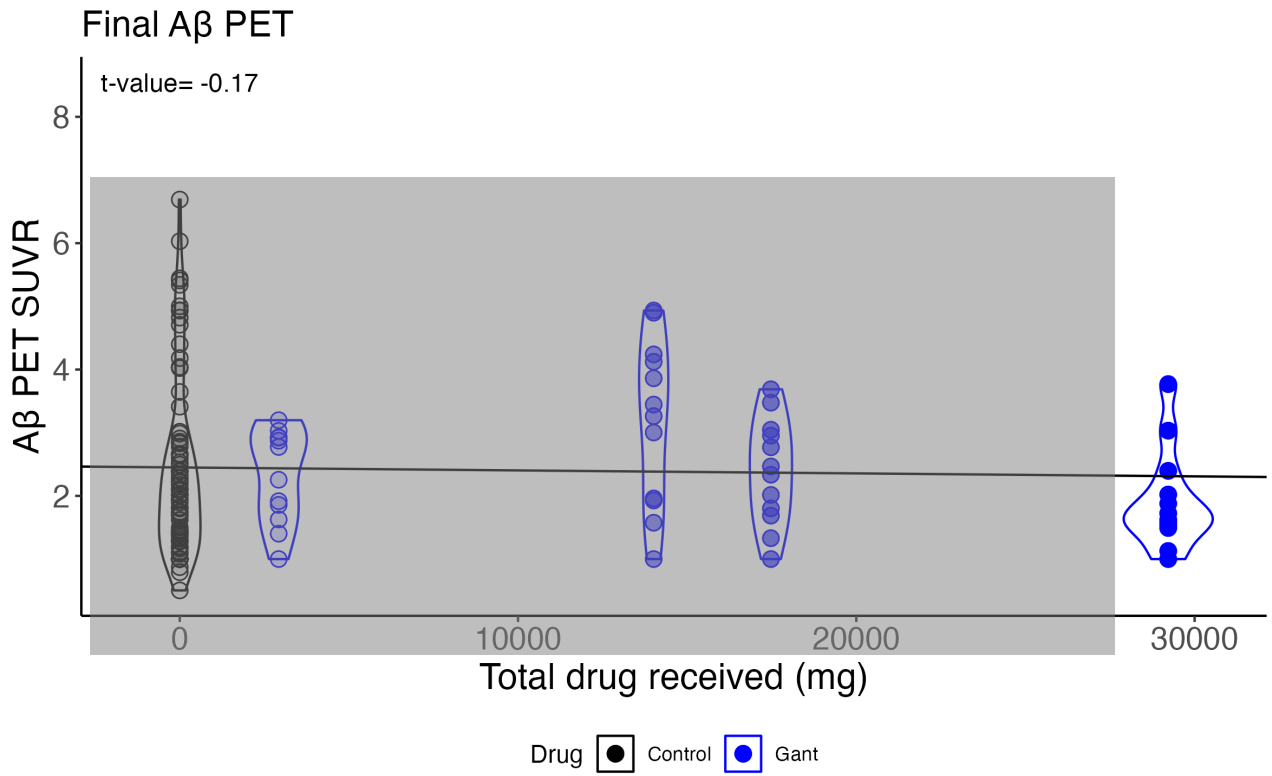
Some regions have a dose-dependent treatment effect

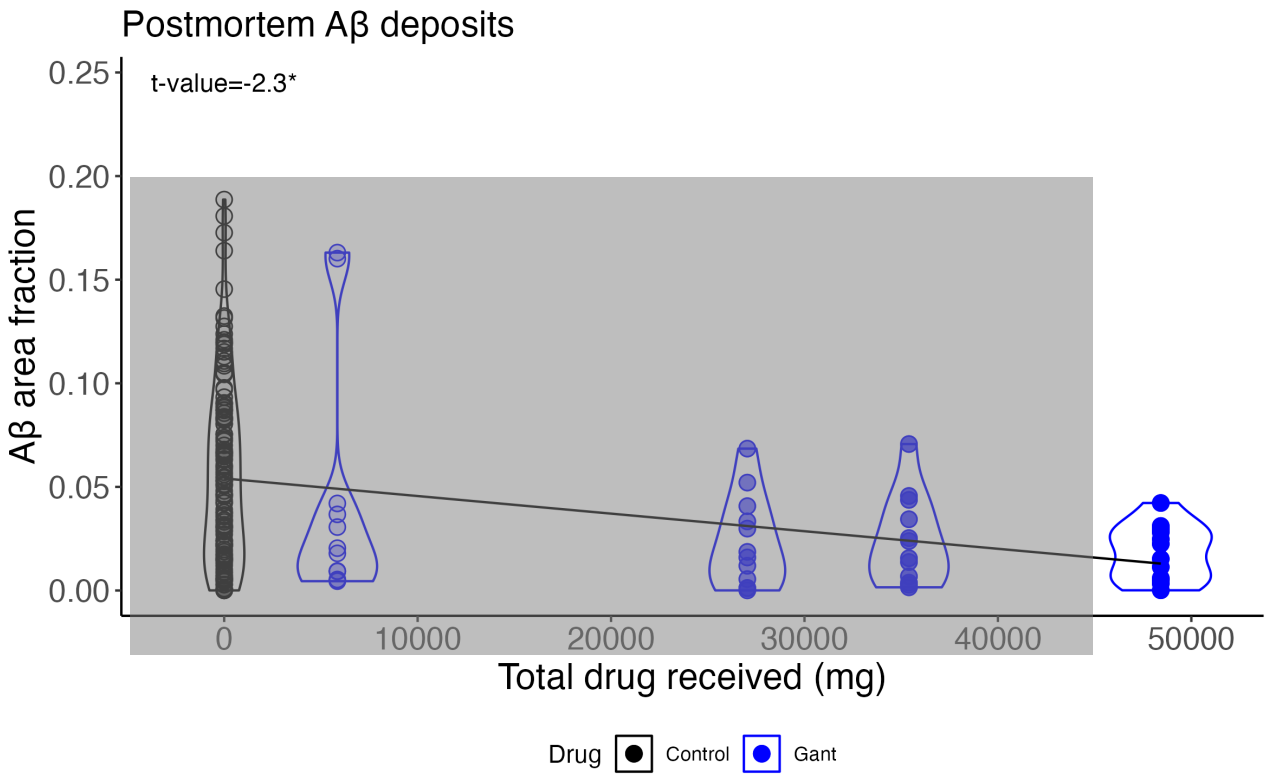




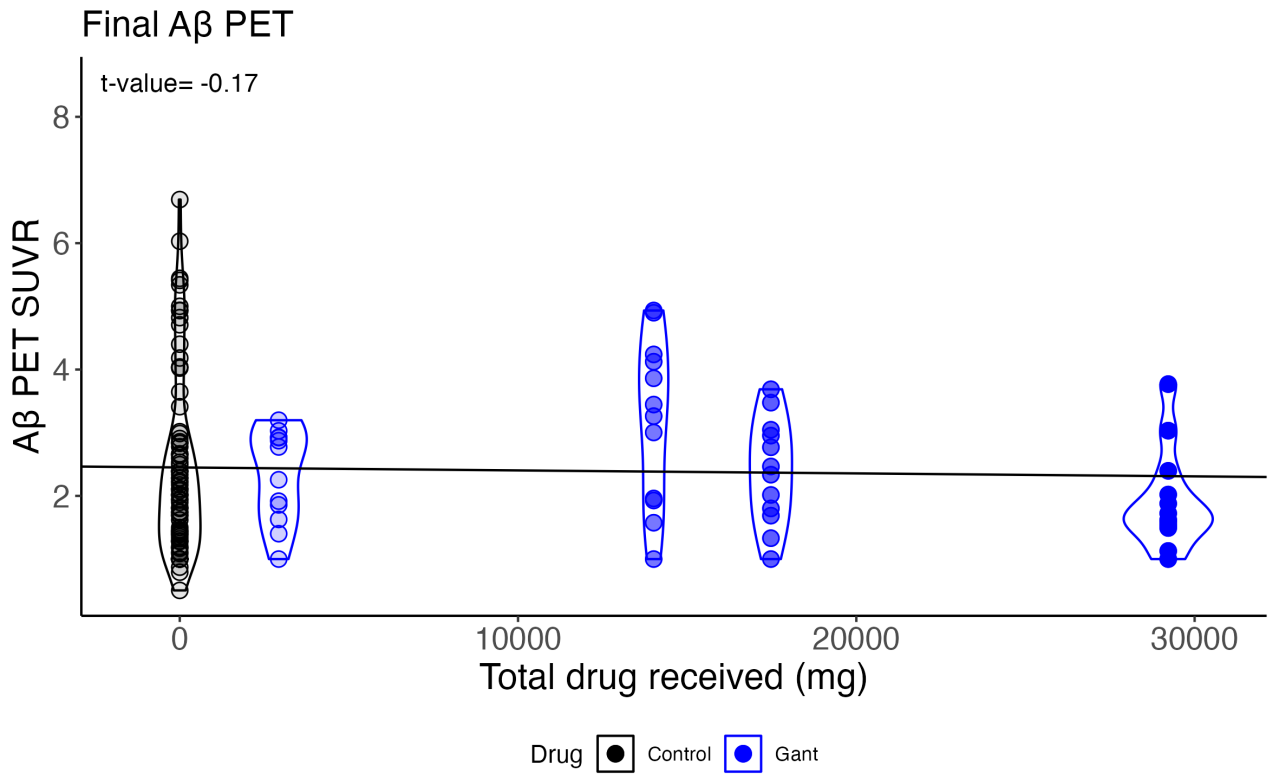


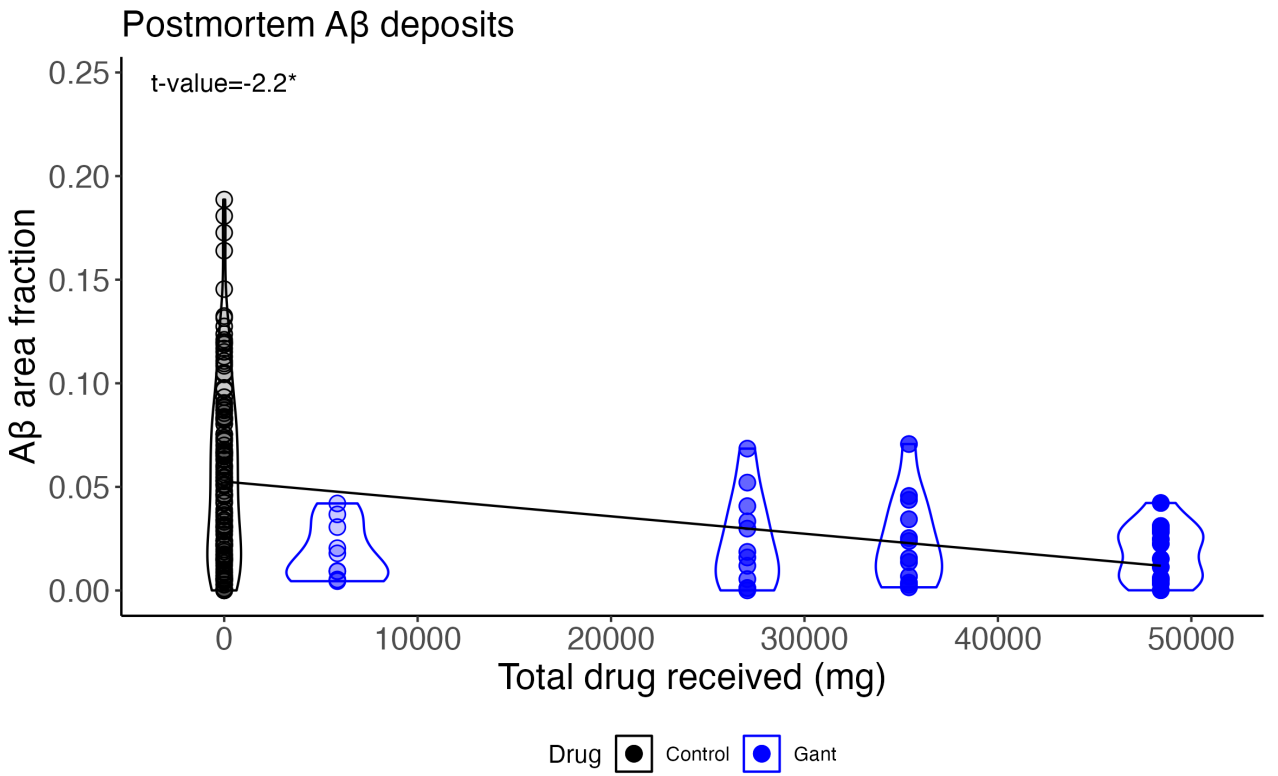
Overall, there is a dose-dependent treatment effect at postmortem assessment, but this effect is not seen at final Aβ PET due to the lower cumulative drug dose received



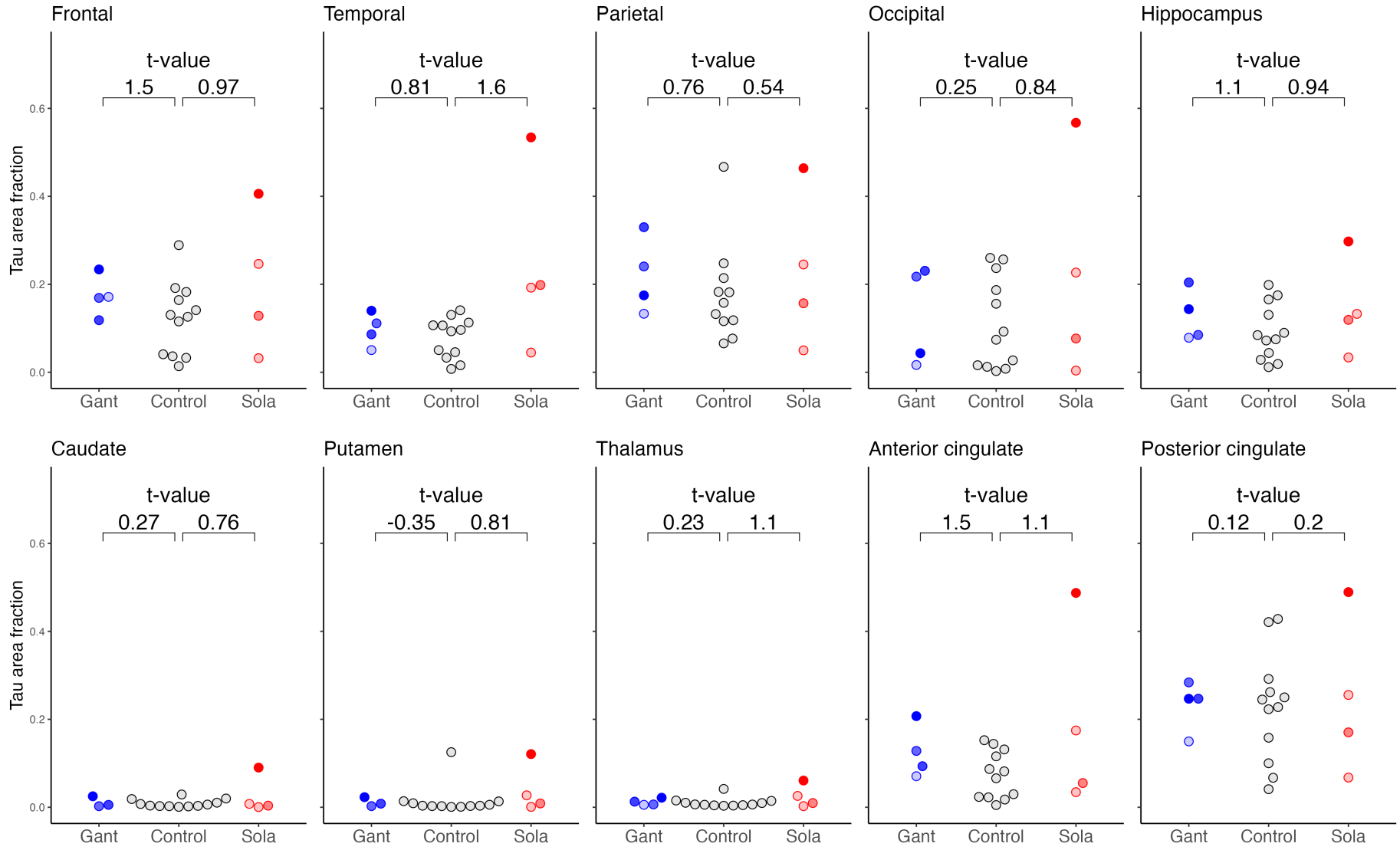


Removing outliers does not change the dose-dependent effect

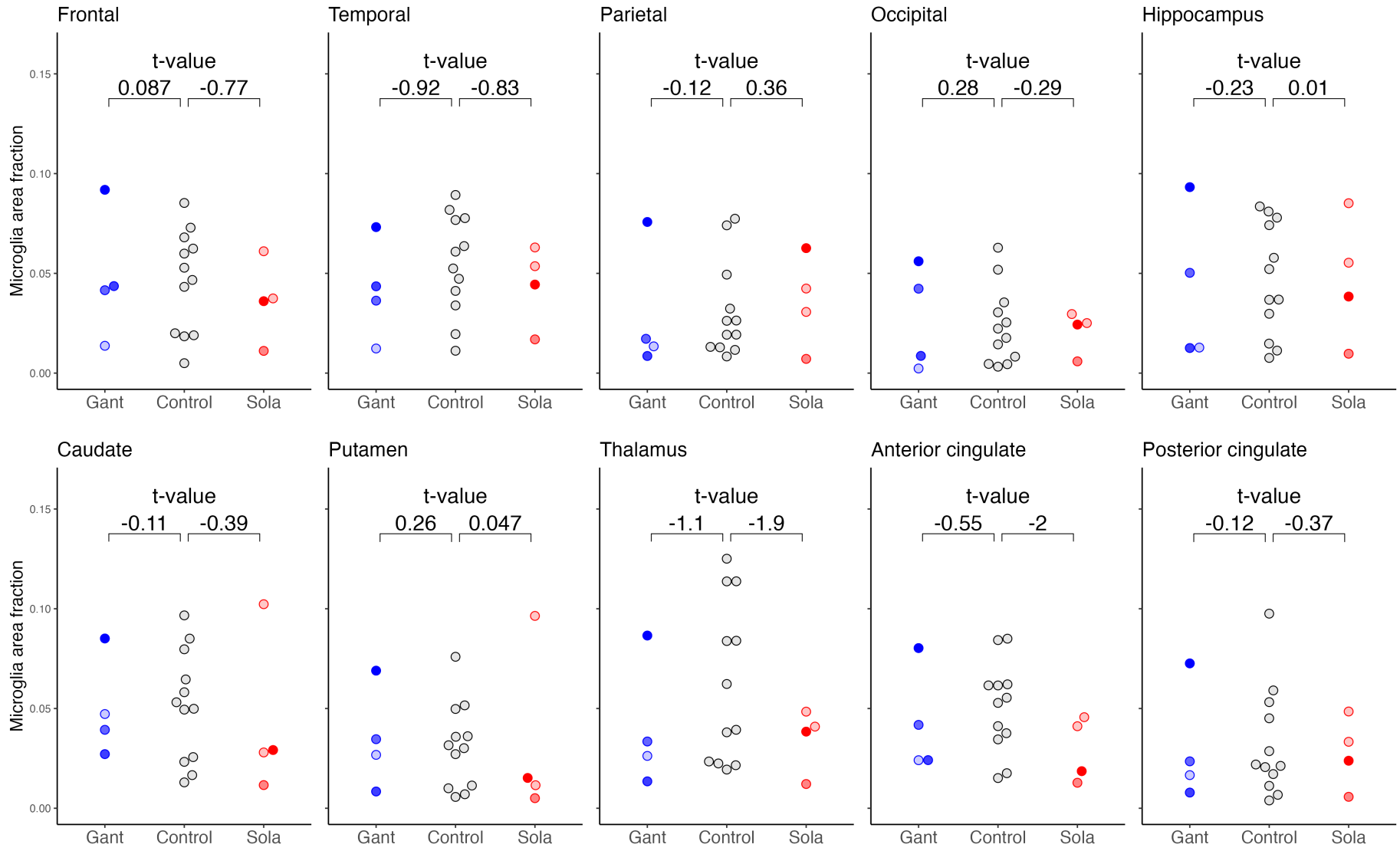




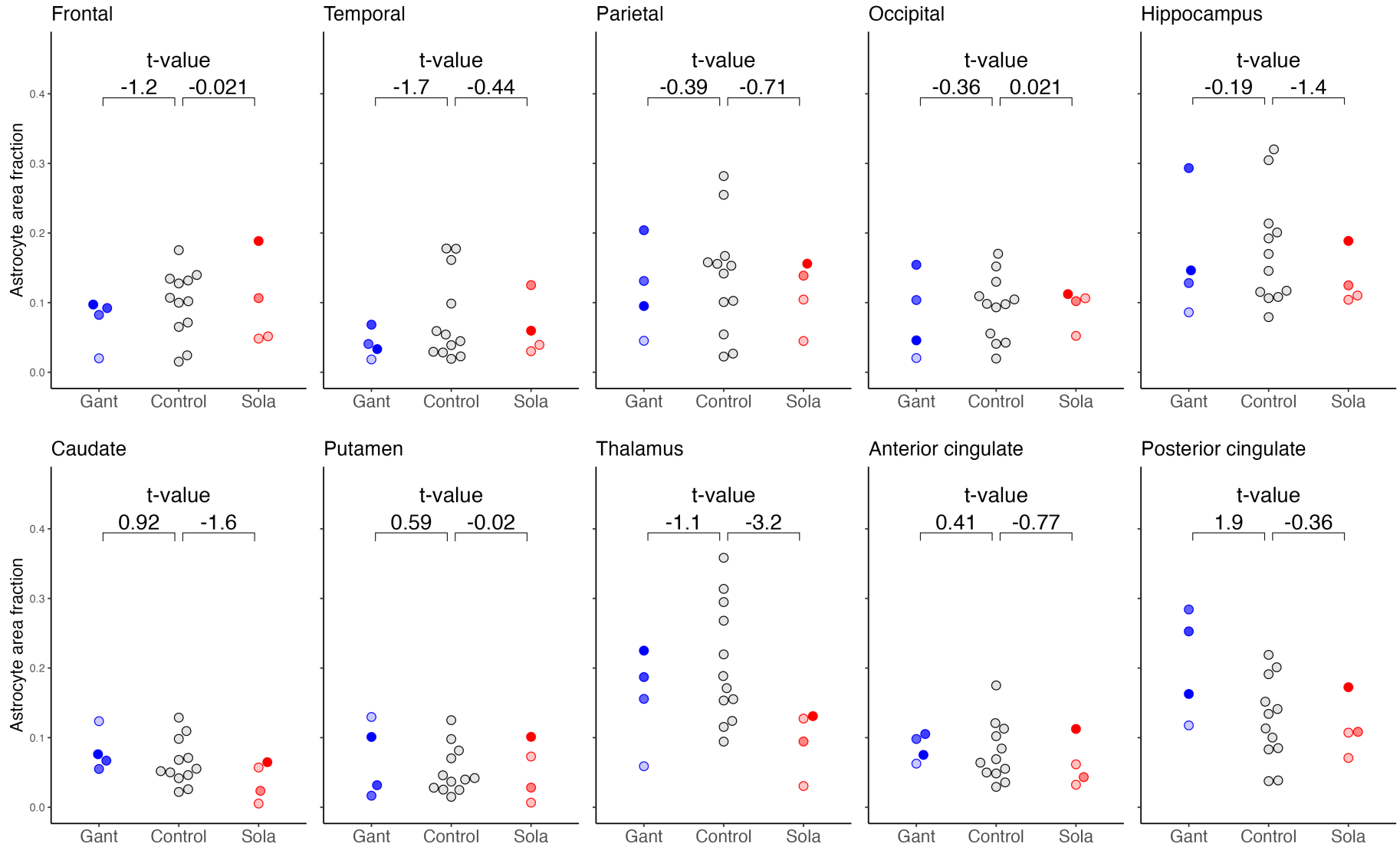
Postmortem tau neuropathology shows no significant difference across groups



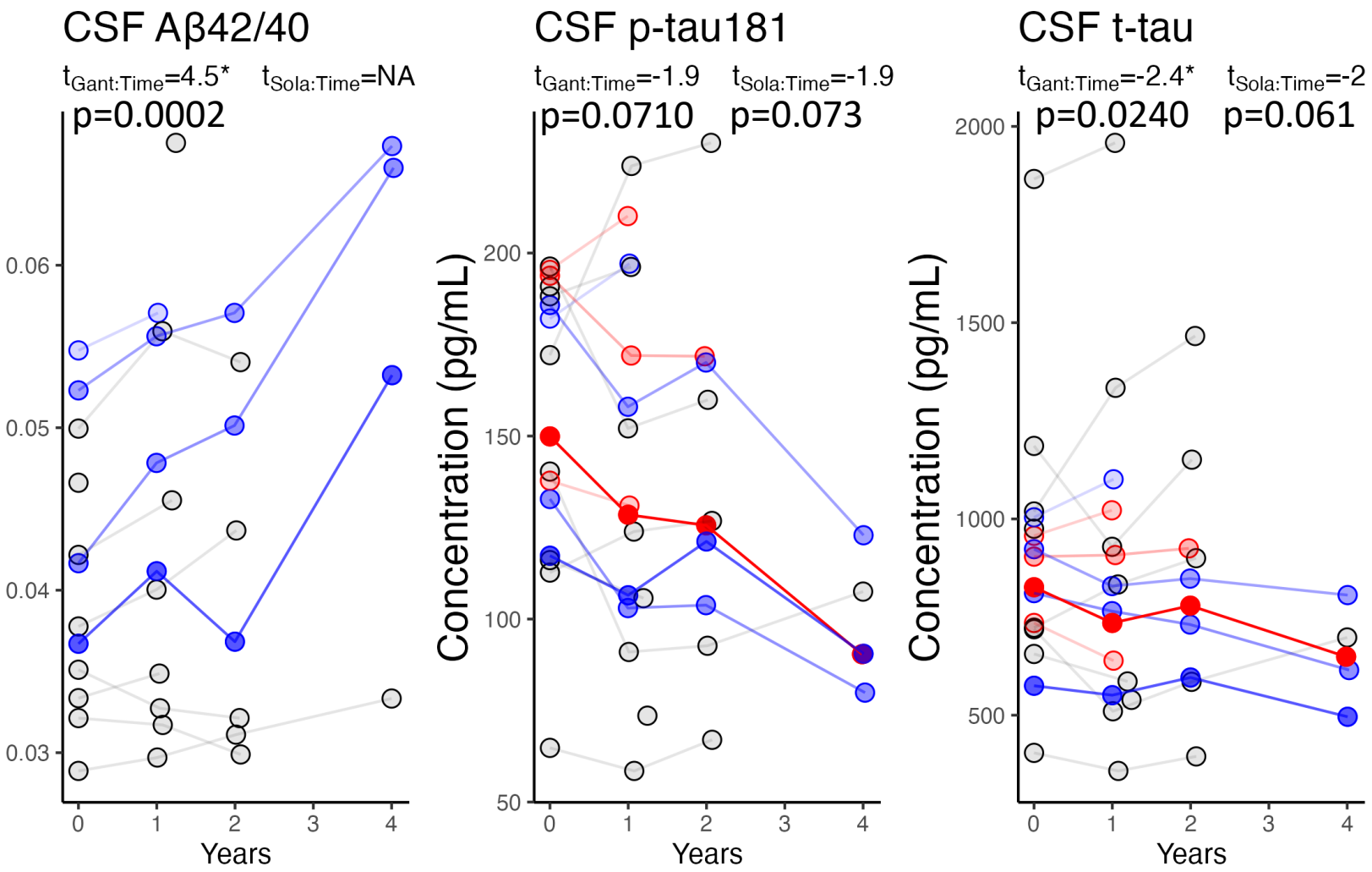
Postmortem microglia neuropathology shows no significant difference across groups



Postmortem astrocyte neuropathology shows no significant difference across groups



CSF Aβ42/40 increased, CSF t-tau decreased significantly in gantenerumab vs controls



Linear mixed-effects models of the form **CSF~Drug*Time+(1|Participant)** were used to estimate statistical differences in longitudinal change of CSF biomarkers between either gantenerumab or solanezumab treatment arms and the control group

$t_{Gant:Time}$ denotes the t-value of the Gant:Time interaction

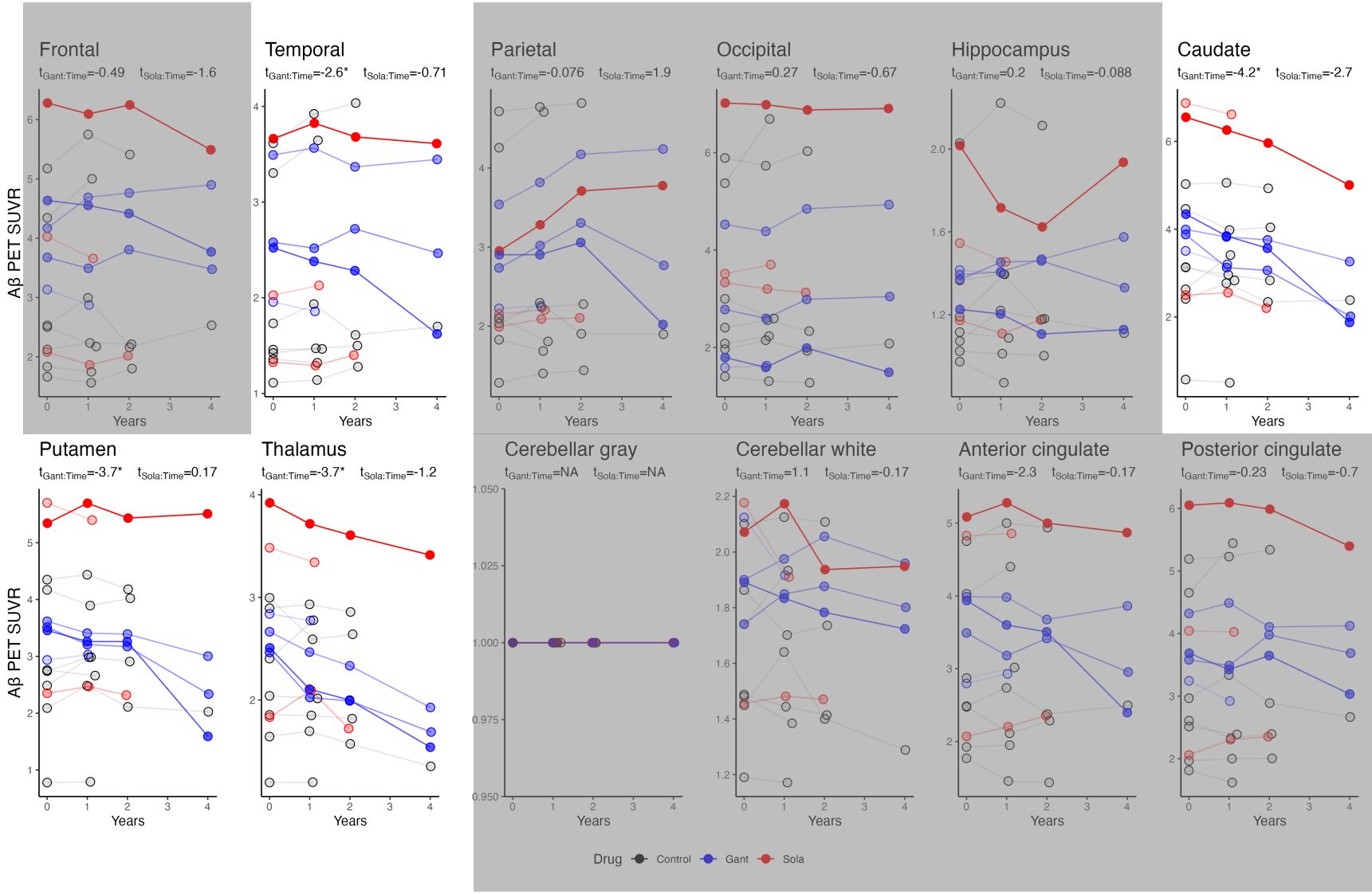
Asterisks denote p-values<0.05 associated with $t_{Gant:Time}$; no $t_{Sola:Time}$ interaction was significant

No solanezumab arm participants had CSF Aβ42/40

Five control group participants did not have longitudinal CSF measurements

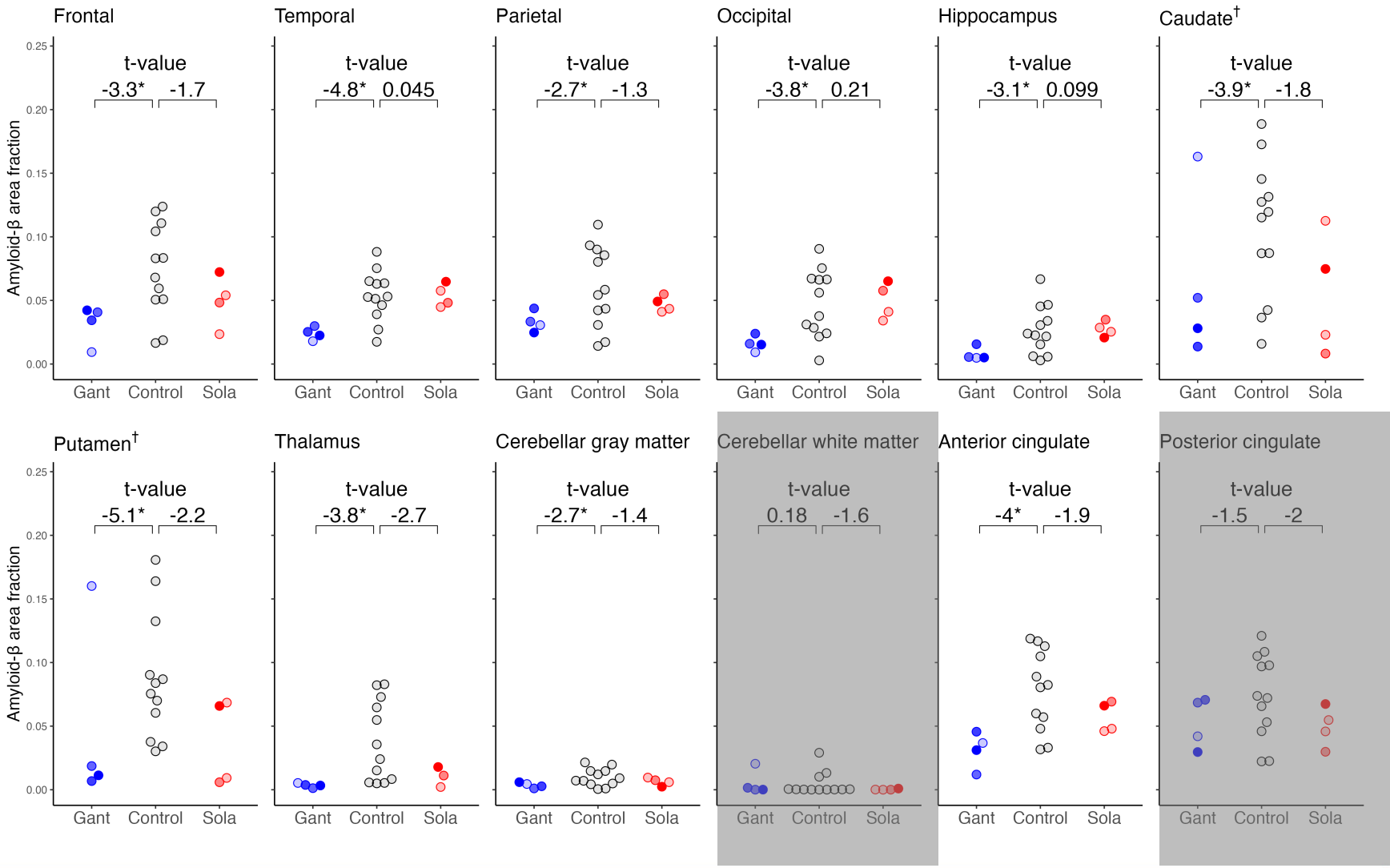
Summary

- Aβ PET SUVR shows longitudinal decline in the gantenerumab arm



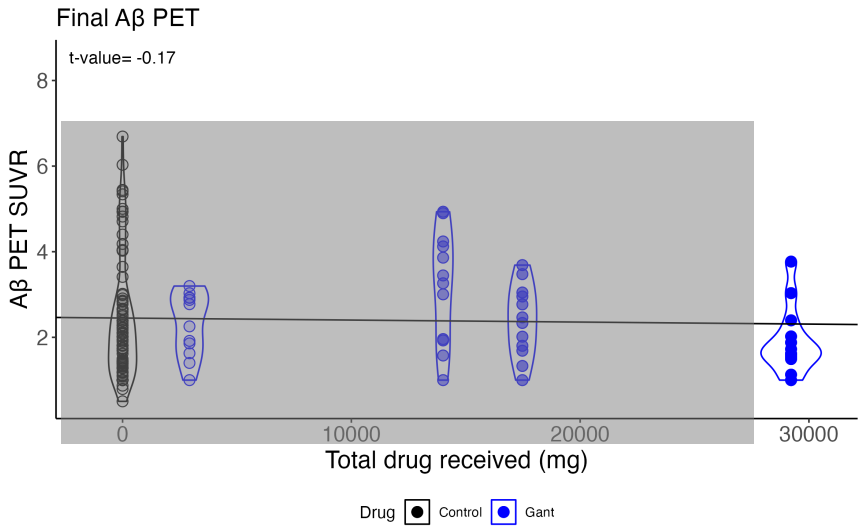
Summary

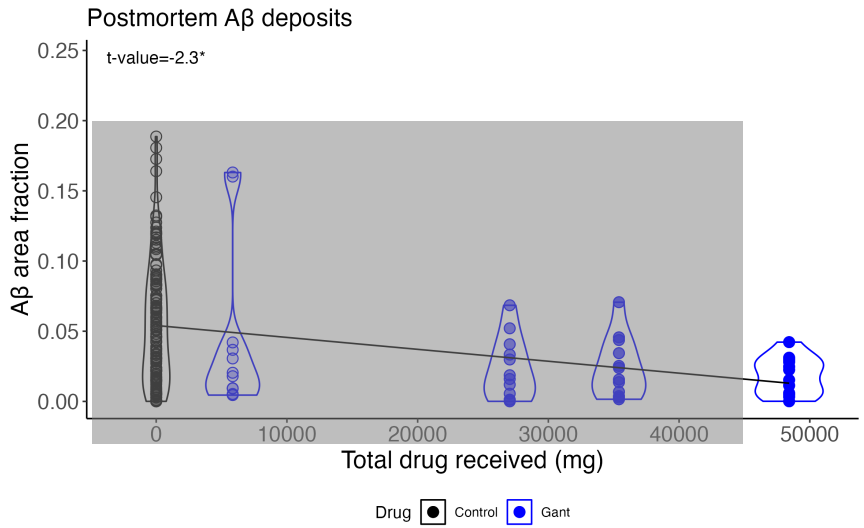
- Aβ PET SUVR shows longitudinal decline in the gantenerumab arm
- Aβ area fraction is significantly lower in the gantenerumab arm (n=4)



Summary

- Aβ PET SUVR shows longitudinal decline in the gantenerumab arm
- Aβ area fraction is significantly lower in the gantenerumab arm (n=4)
- Dose-dependent treatment effects may cause differences in autopsy findings versus biomarker outcomes if participants continue to receive treatment after the final biomarker visit





Summary

- This study provides the best neuropathologic evidence to date of Aβ reduction in a trial of anti-Aβ monoclonal antibodies
- Future trials may optimize this effect with higher doses, more effective anti-Aβ therapeutics, earlier intervention, and/or combined treatments

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David Clifford, Associate and Medical Director | Jorge Llibre-Guerra, Assistant Medical Director

S. Alexander, E. Andrews, N. Angeloff, J. Bartzel, J. Beatty, J. Bur, D. Burgdorf, T. Carril, R. Carrow, E. Cook, K. Ferguson, A. Fuqua, E. Gruebbeling, E. Hart, R. Hawley, D. Heller, M. Jany, M. Jorke, B. King, N. Landers, J. Mallmann, T. Mayhew, K. McCann, I. Meshulam, D. Morrison, J. Murphy, M. Nies, M. Qassem, L. Sawicki, J. Schillizzi, W. Simpson, A. Stiebel, A. Stueve, S. Sweeney, E. Ziegemeier

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Biomarker – L Ibanez
Biostatistics – C Xiong
Cognition – J Hassenstab
Genetics – C Cruchaga/AM Goate
Imaging – T Benzinger/B Gordon
Neuropathology – R Perrin

DIAN Expanded Registry
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Japan: Niigata University (Ikeuchi), Tokyo University (Niimi/Ikeuchi)

South Korea: Asan Medical Center (Lee)

Spain: Hospital Clinic of Barcelona (Sanchez-Valle)

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