Anti-Aβ treatment effects on dominantly inherited AD neuropathology

Preliminary autopsy findings from the DIAN-TU-001 trial of gantenerumab or solanezumab

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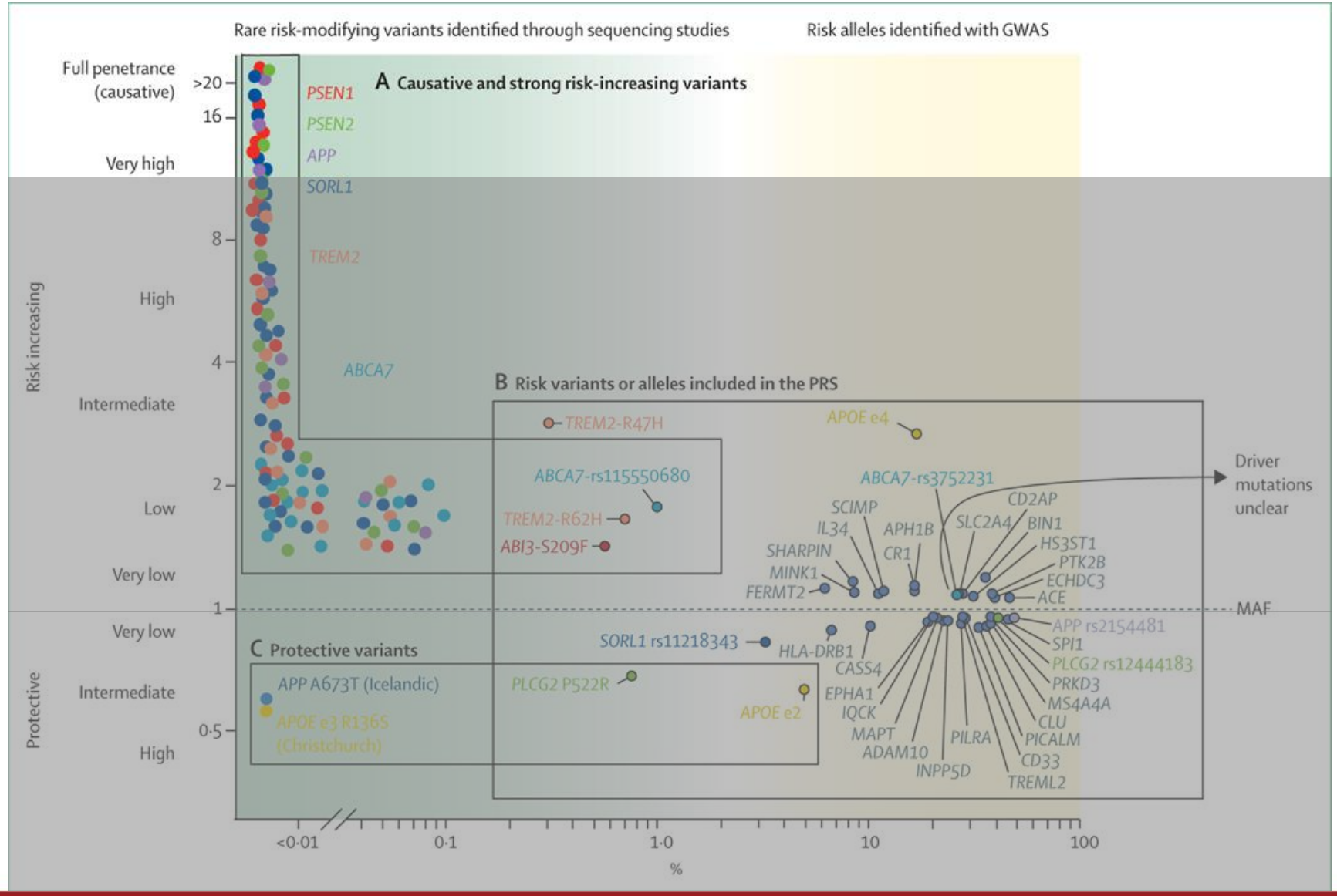
X	No, Nothing to disclose
	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)

Dominantly inherited AD arises from *PSEN1/PSEN2* and *APP* mutations



Scheltens et al. 2021

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

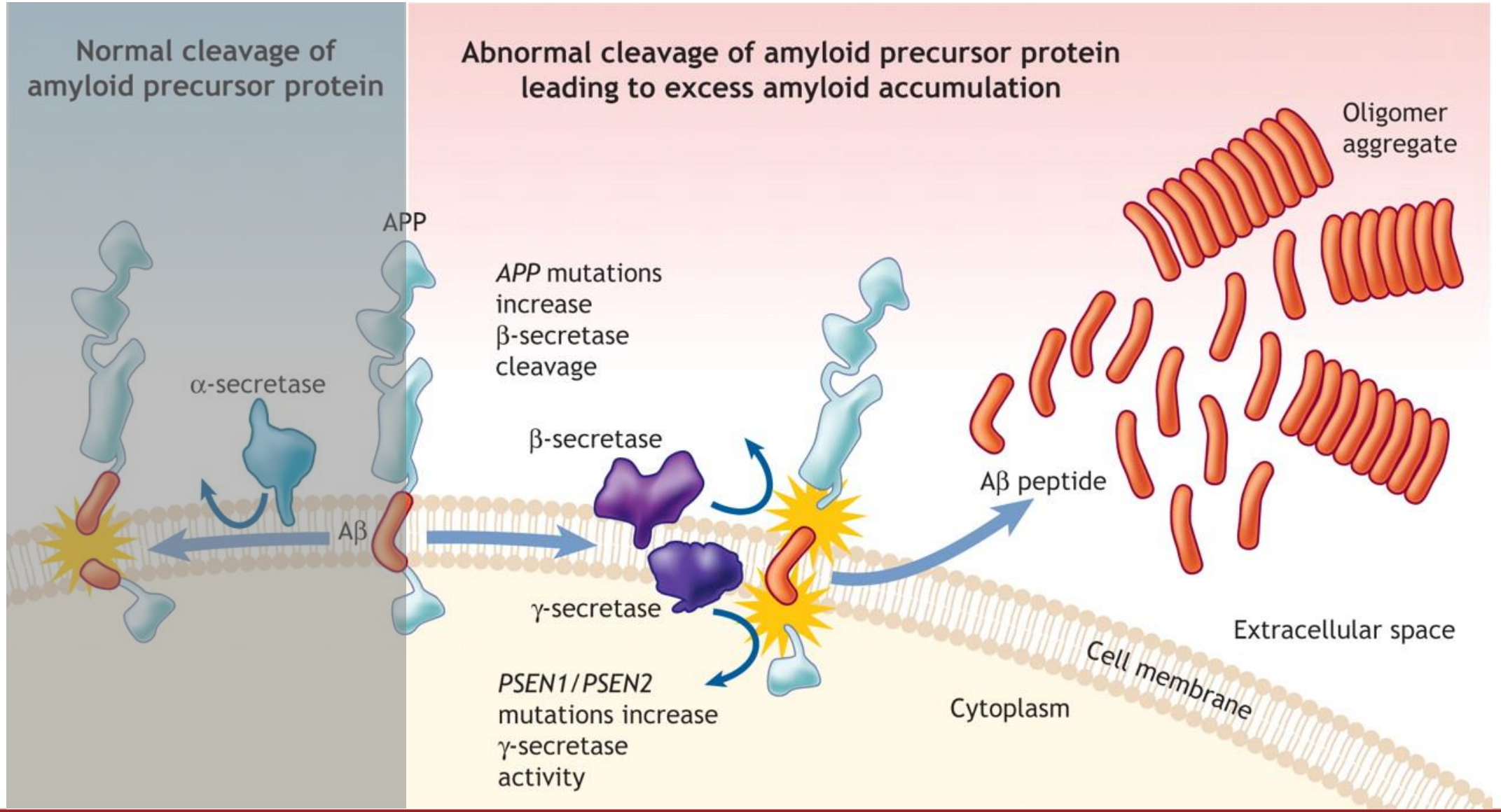
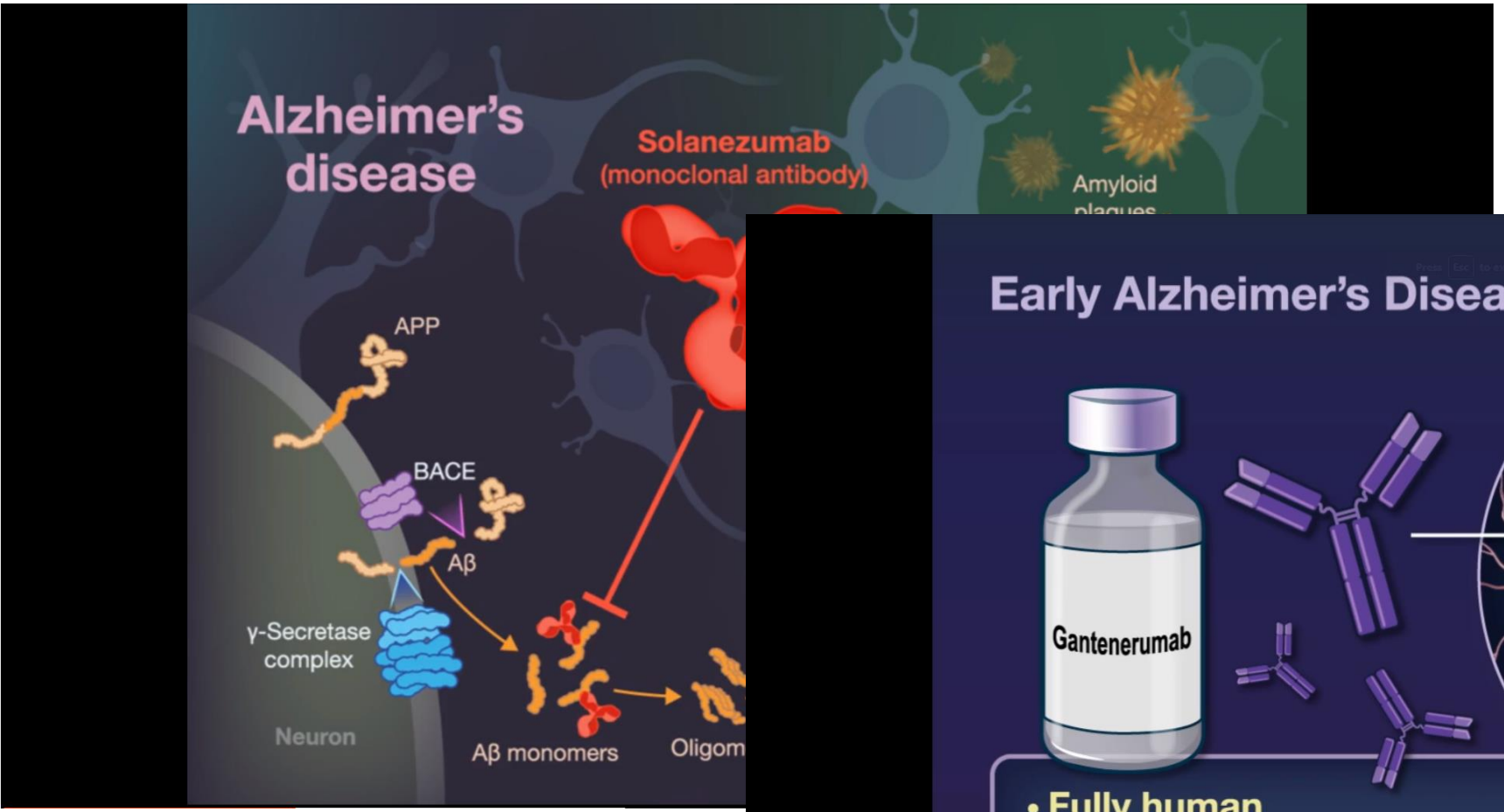
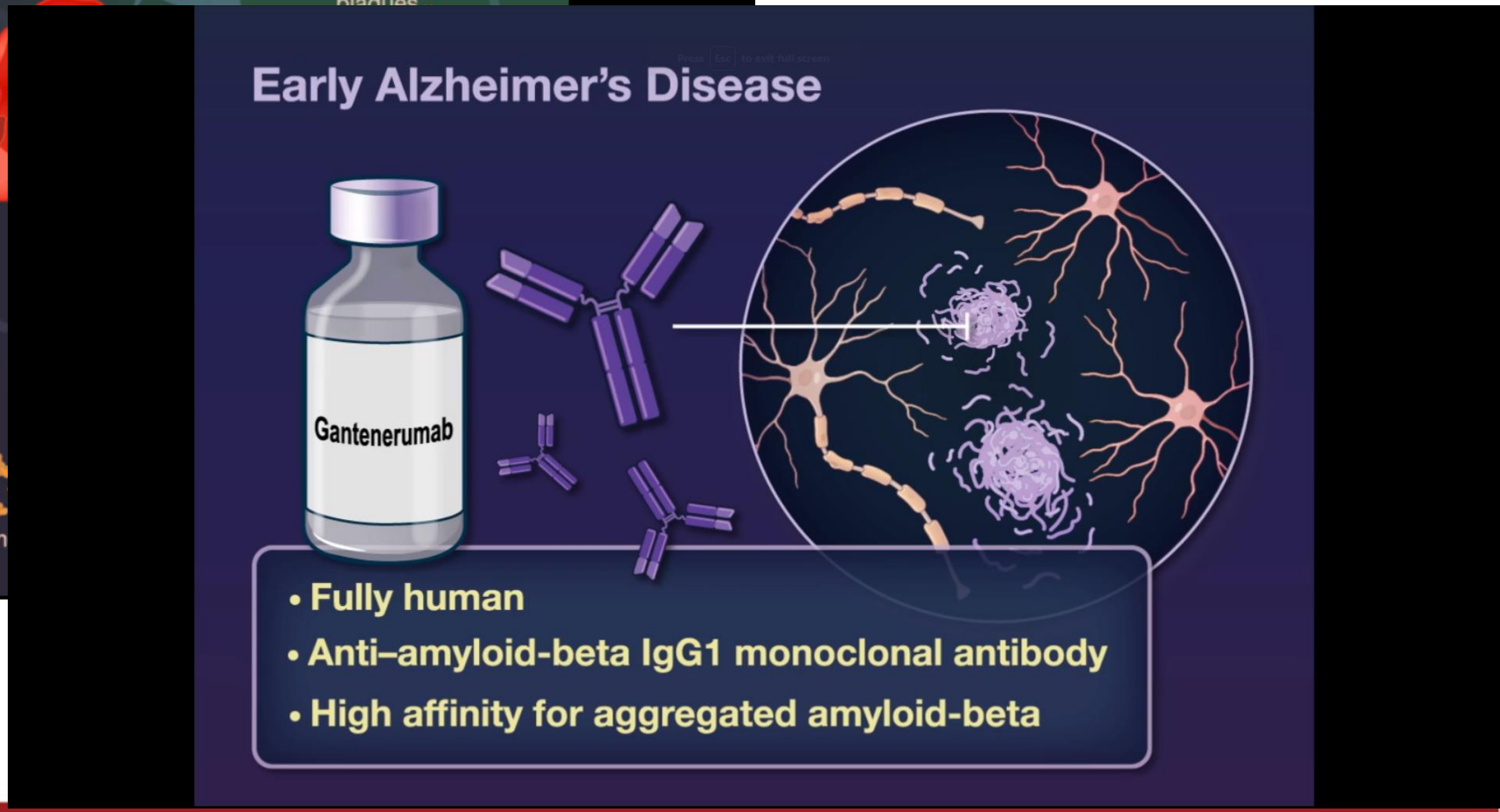


Image credit: Lianne Friesen and Nicholas Woolridge

Anti-Aβ monoclonal antibodies have been developed to remove Aβ deposits





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 (Lilly) — NIA U01 AG042791

Gantenerumab (Roche) — NIA R01 AG046179 — ~200 participants

Gantenerumab Exploratory Open-Label Extension

Roche
Alz Association
GHR Foundation
73 participants

NexGen
Janssen
Atabecestat
Stopped July 2018
NIA R01/R56 AG053267

Eisai
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

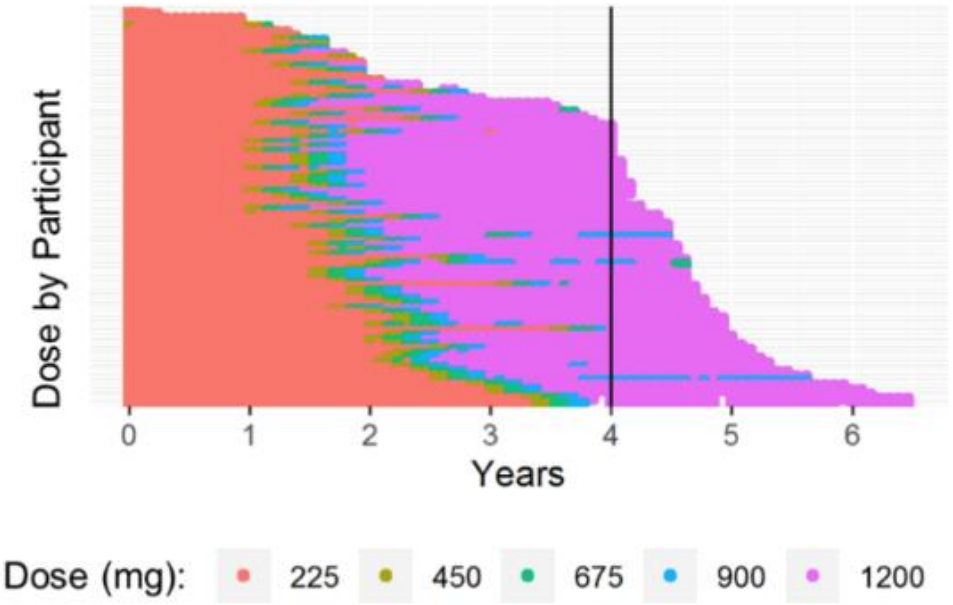
DIAN-TU AD Secondary Prevention Trial Platform

2012 2014 2016 2018 2020 2022 2024 2026 2028 2030

KNIGHT FAMILY DIAN TU Dominantly Inherited Alzheimer Network Trials Unit

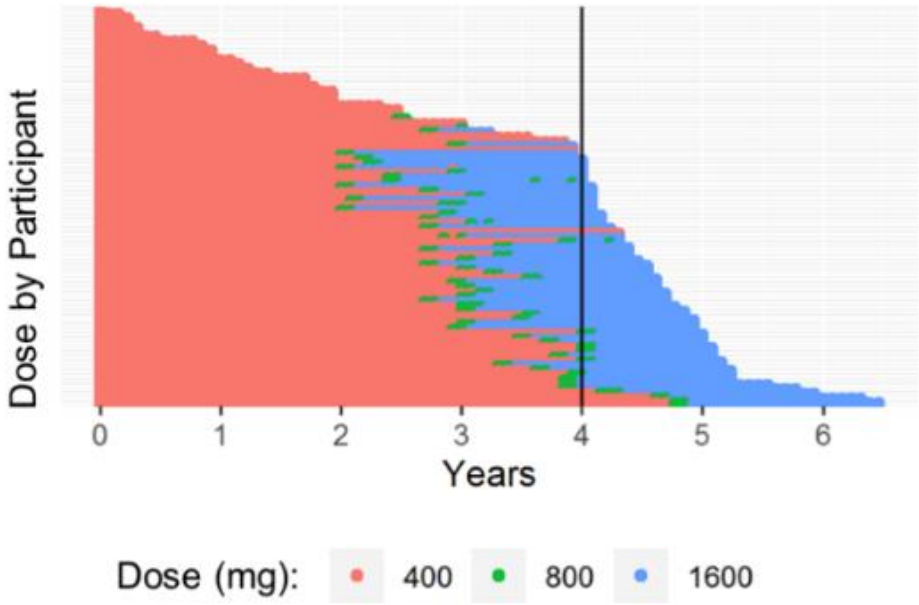
Gantenerumab

Roche



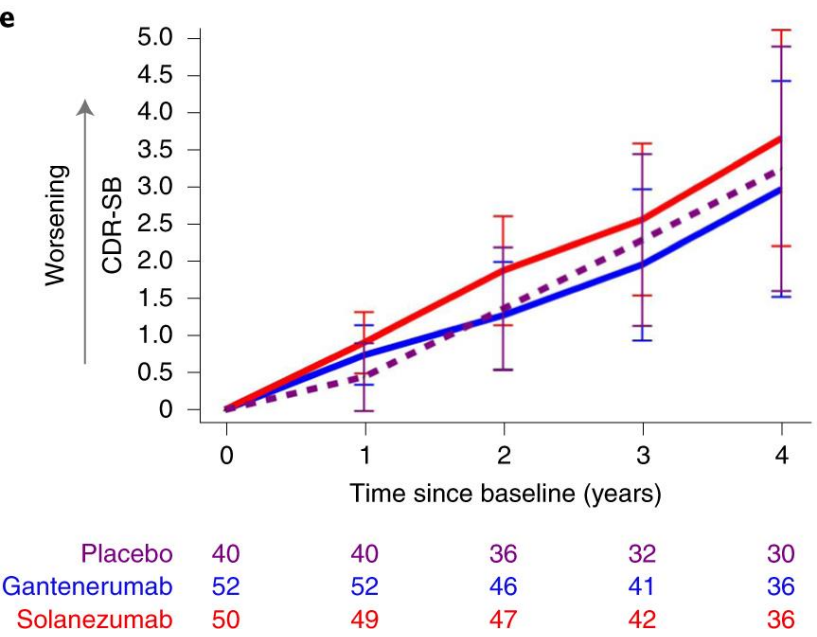
Solanezumab

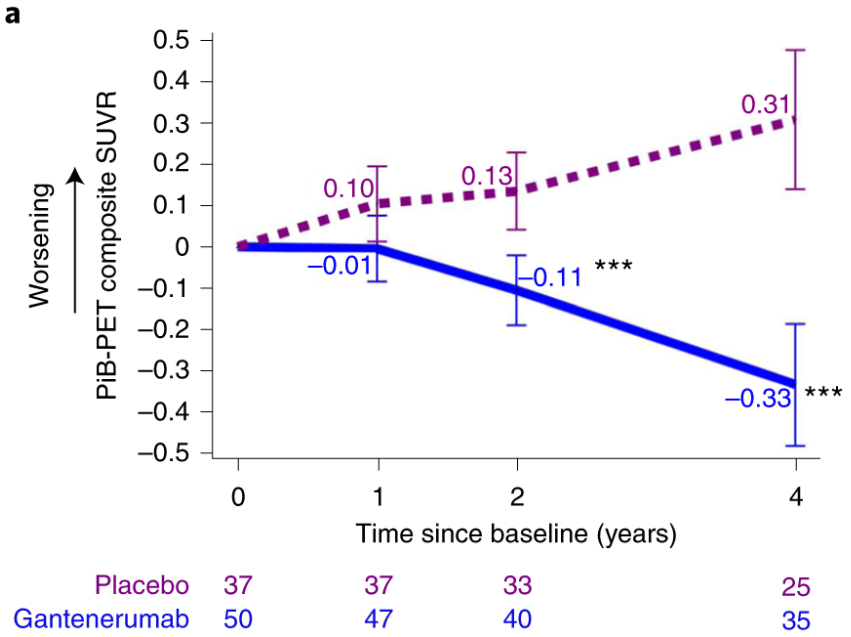
Lilly

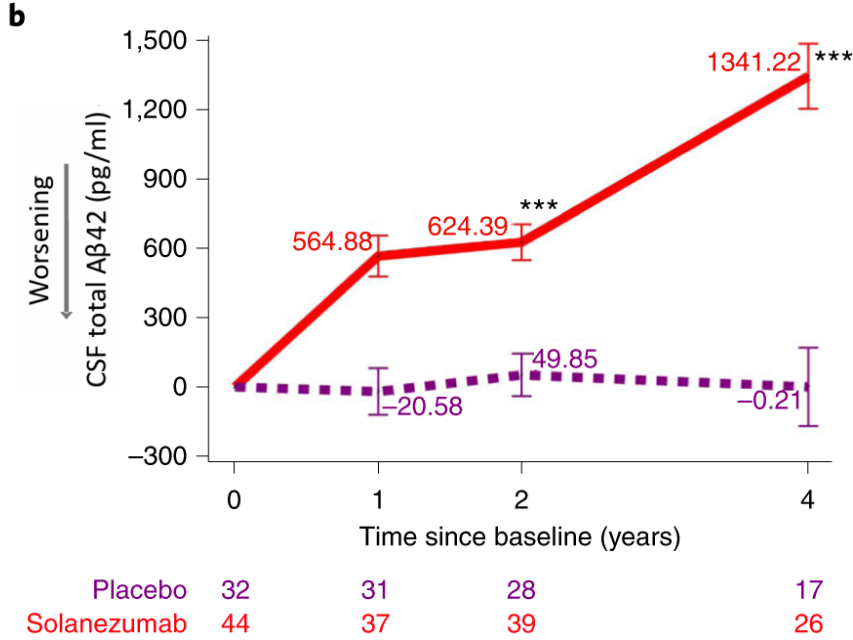


Drug doses were increased mid study

Neither drug slowed cognitive decline during the trial

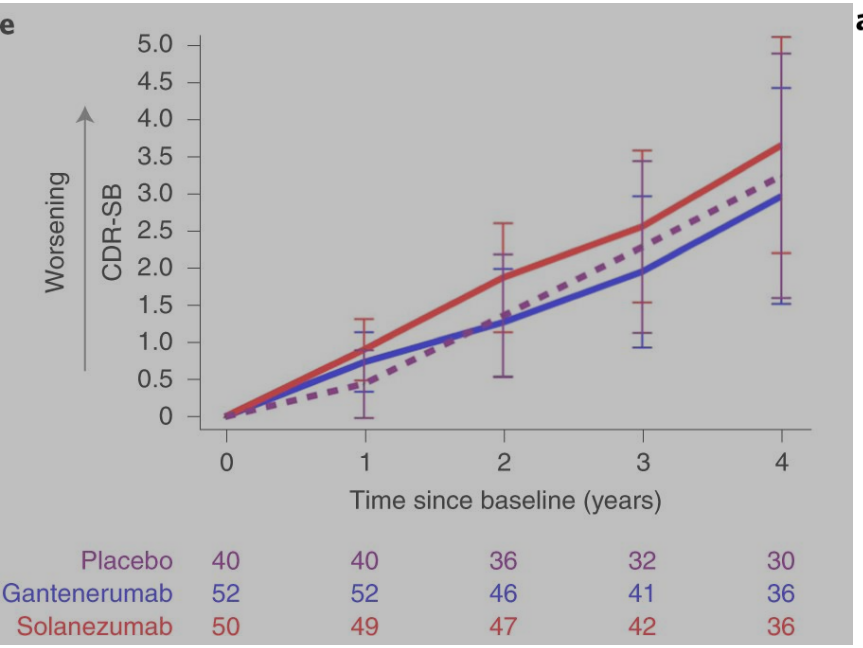


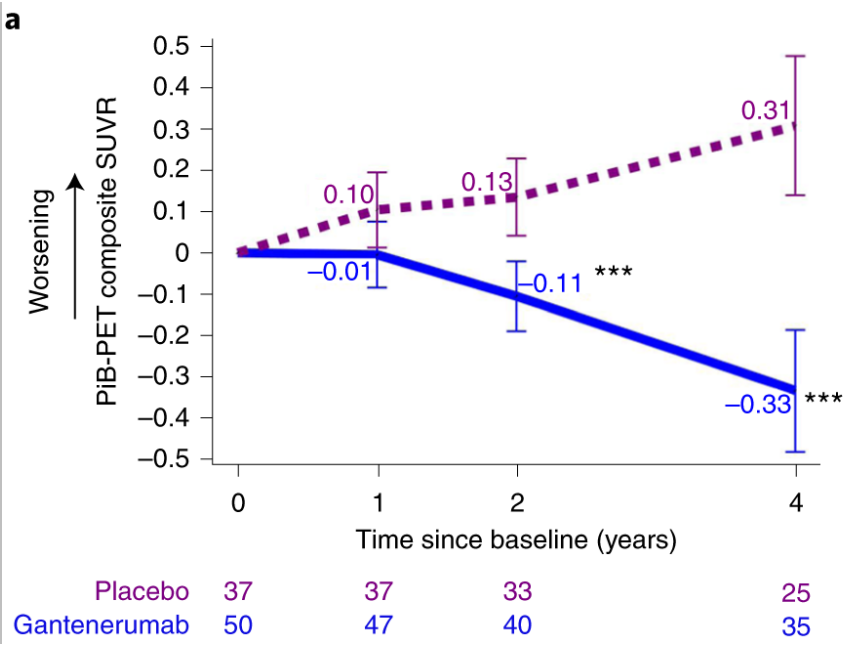


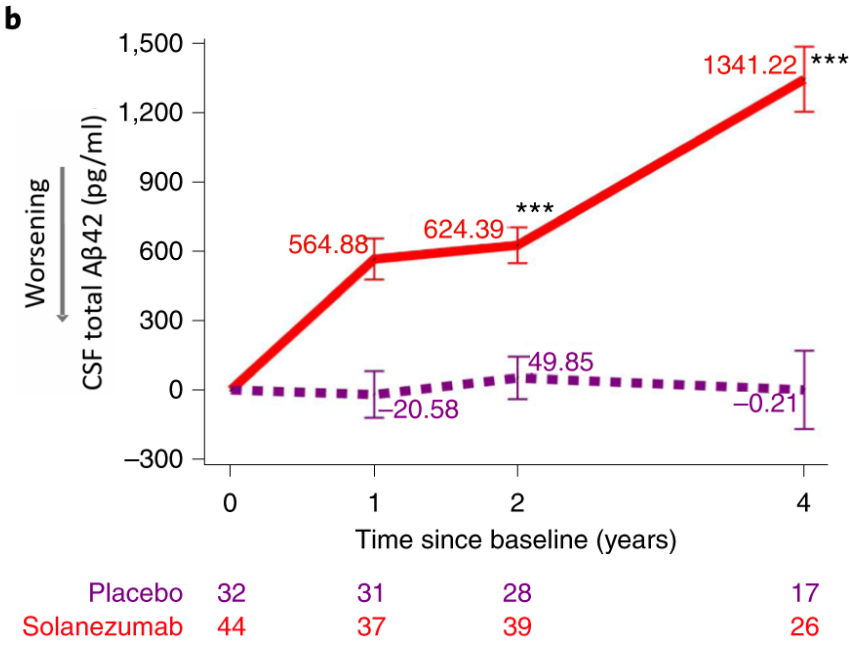


Salloway et al. 2021

But gantenerumab showed evidence for brain Aβ removal

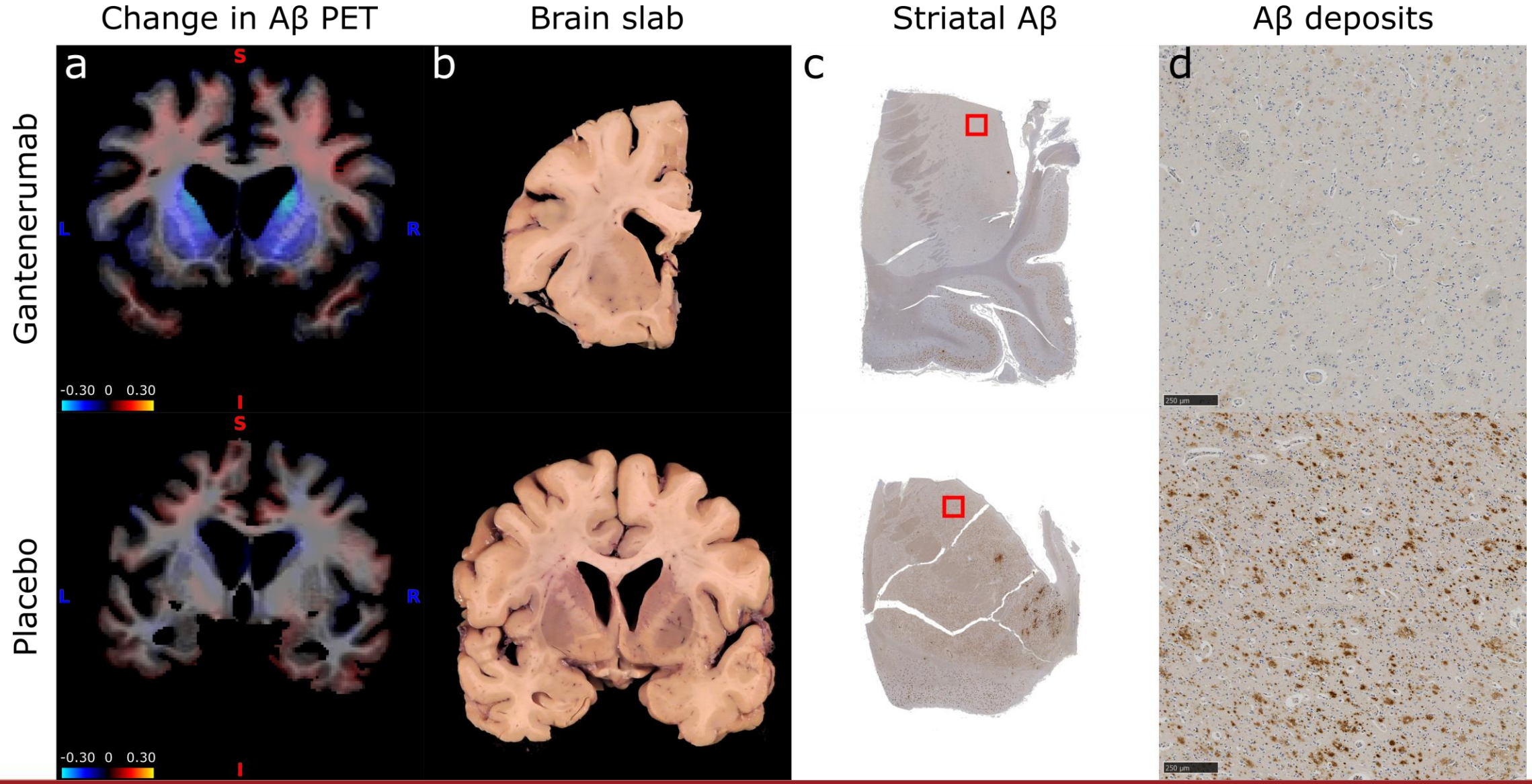






Salloway et al. 2021

Imaging-to-pathology comparison: an illustrative example



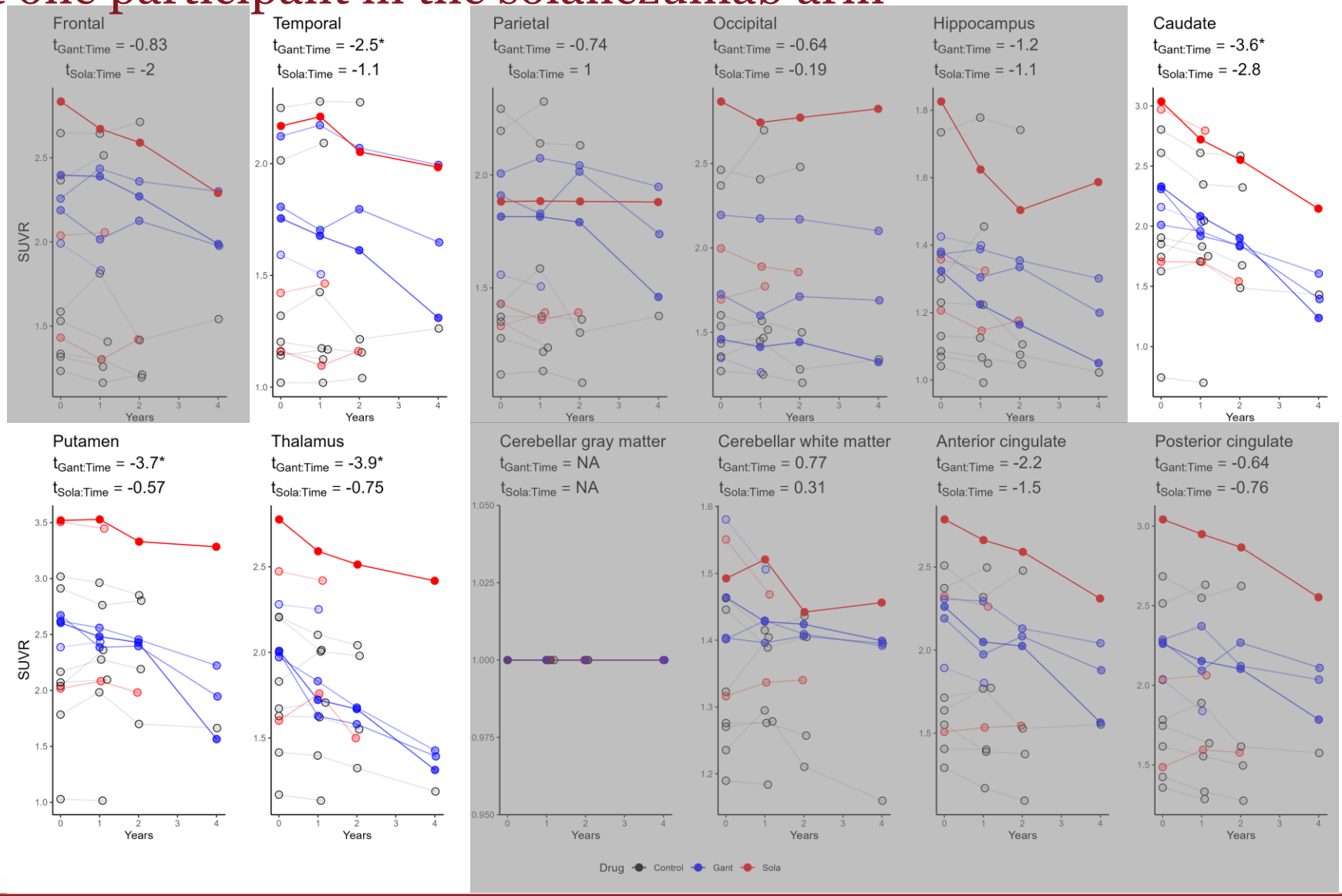
Participant characteristics

	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

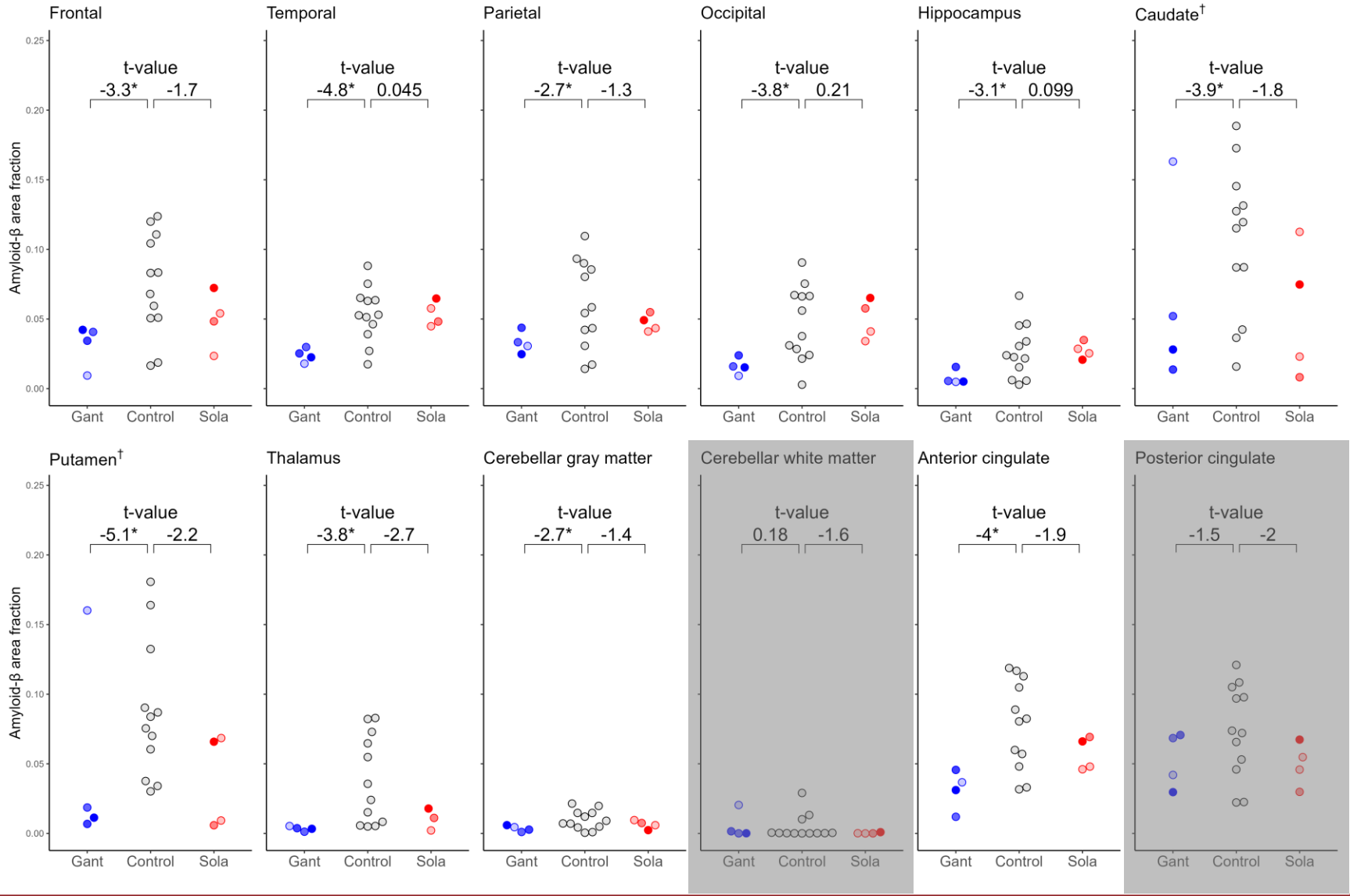
Participant postmortem neuropathology

	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

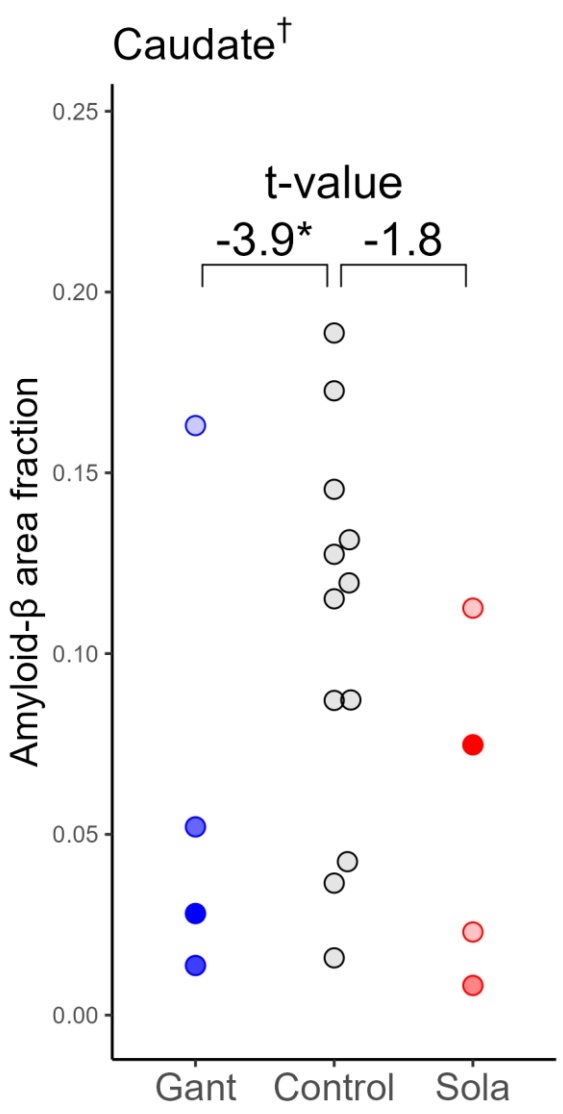
Several regions showed longitudinal decline in Aβ PET SUVR in the gantenerumab arm and in at least one participant in the solanezumab arm

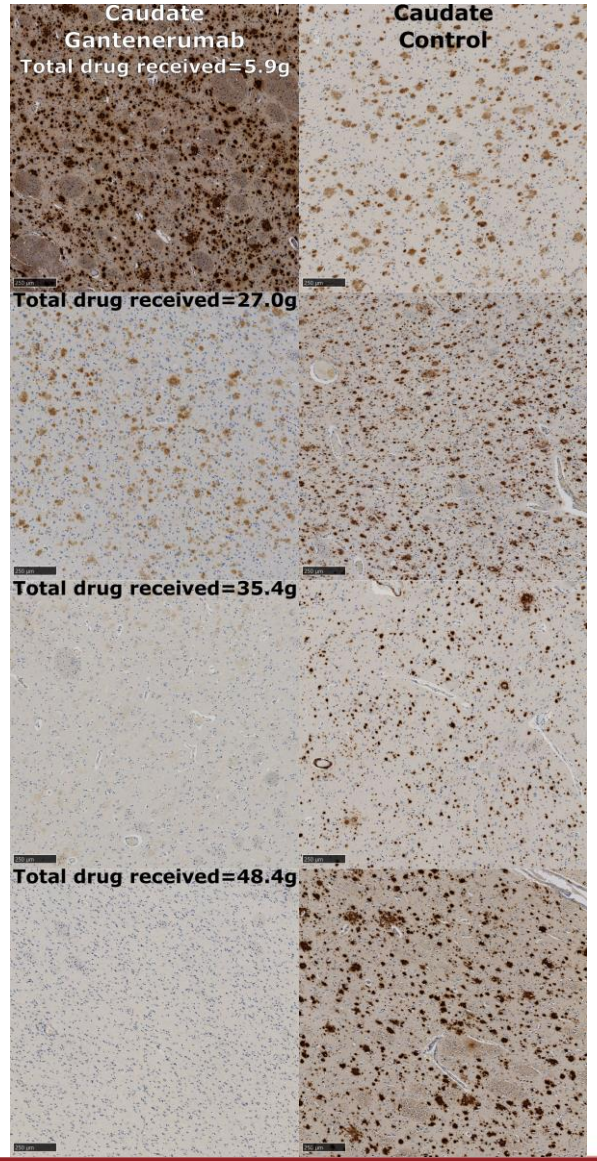


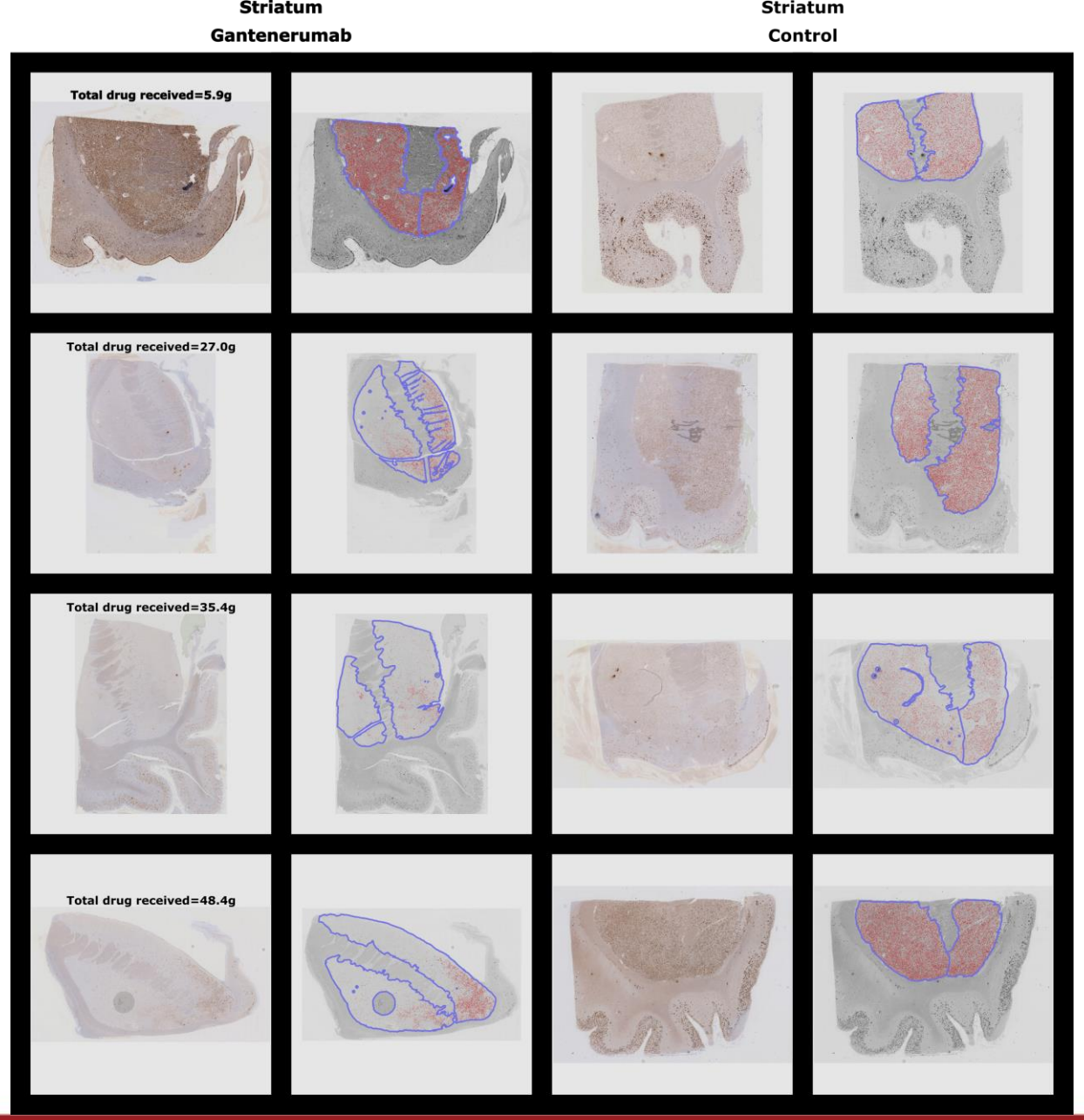
Almost all regions showed reduced Aβ area fraction in the gantenerumab arm (n=4)



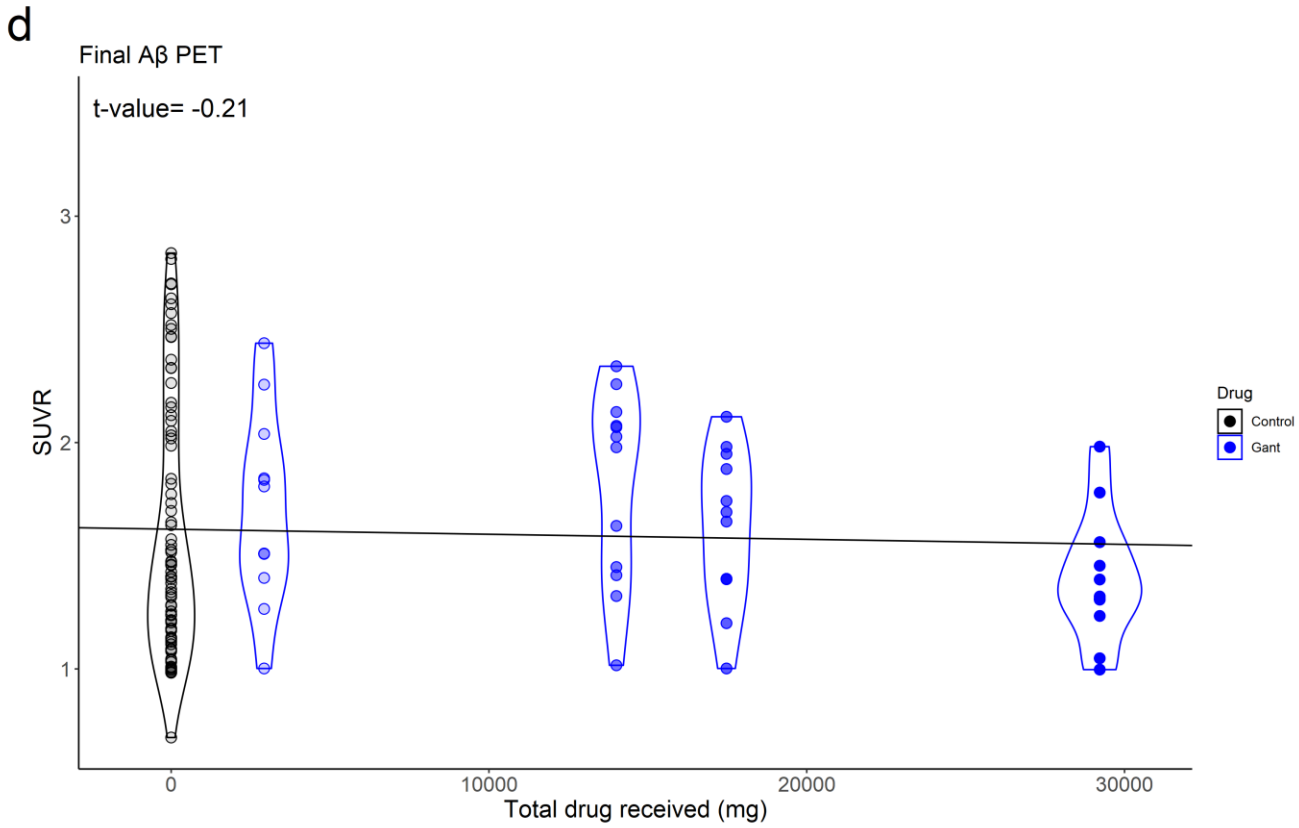
Some regions have a striking dose-dependent treatment effect

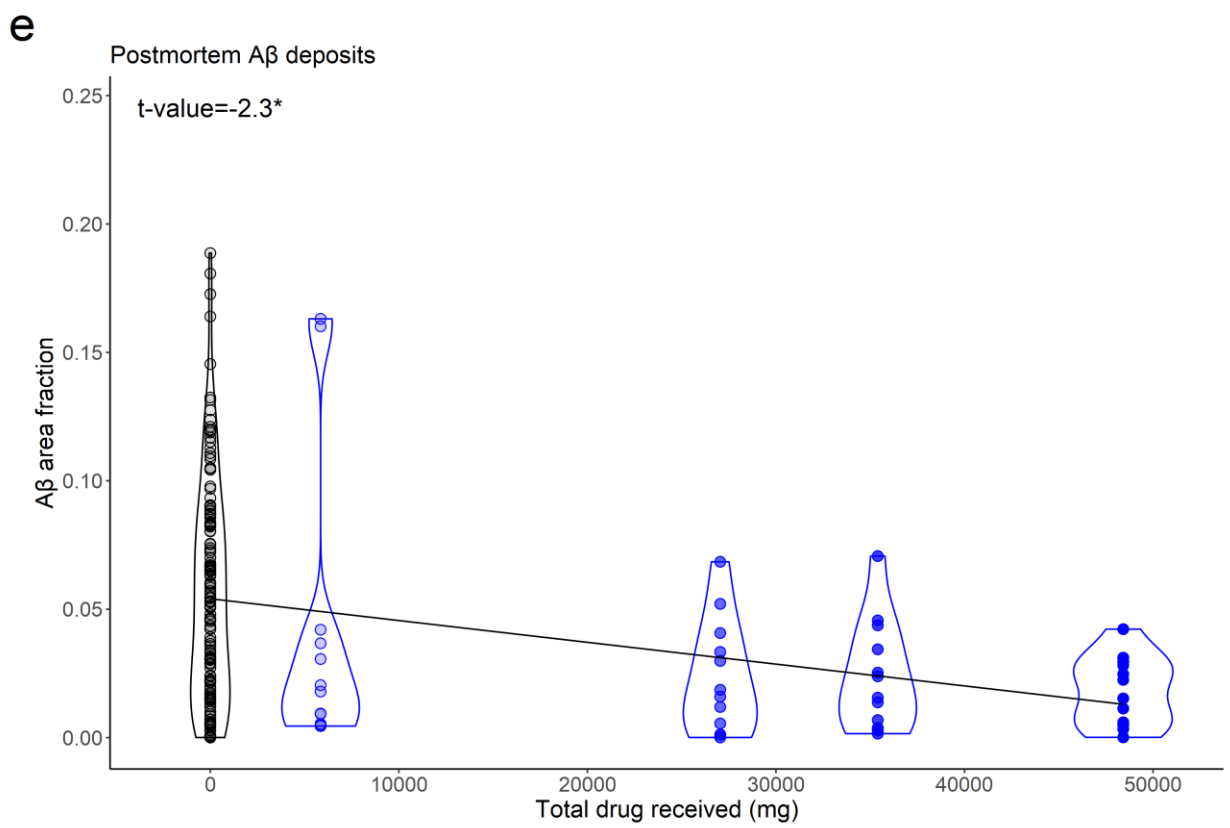




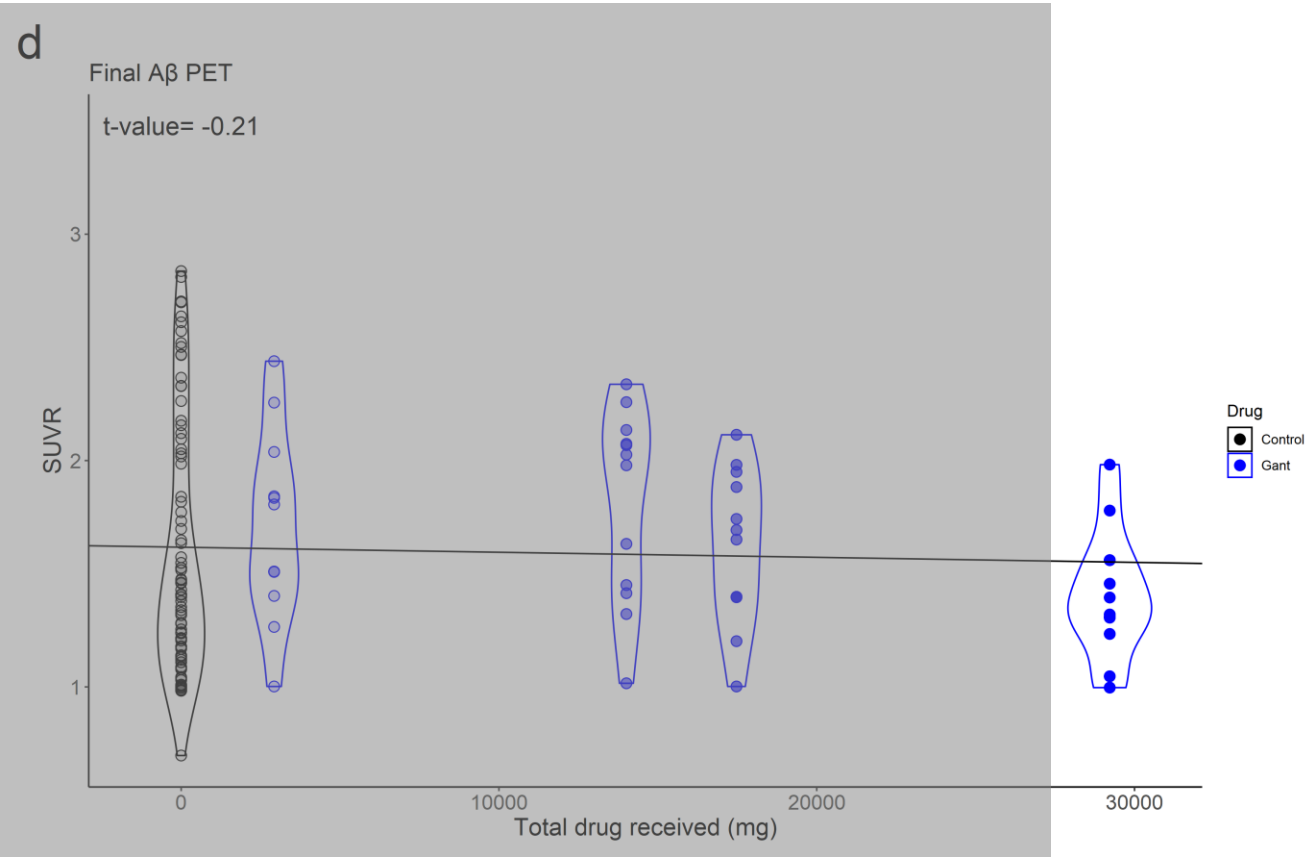

Striatum
Gantenerumab
Striatum
Control
Total drug received=5.9g
Total drug received=27.0g
Total drug received=35.4g
Total drug received=48.4g

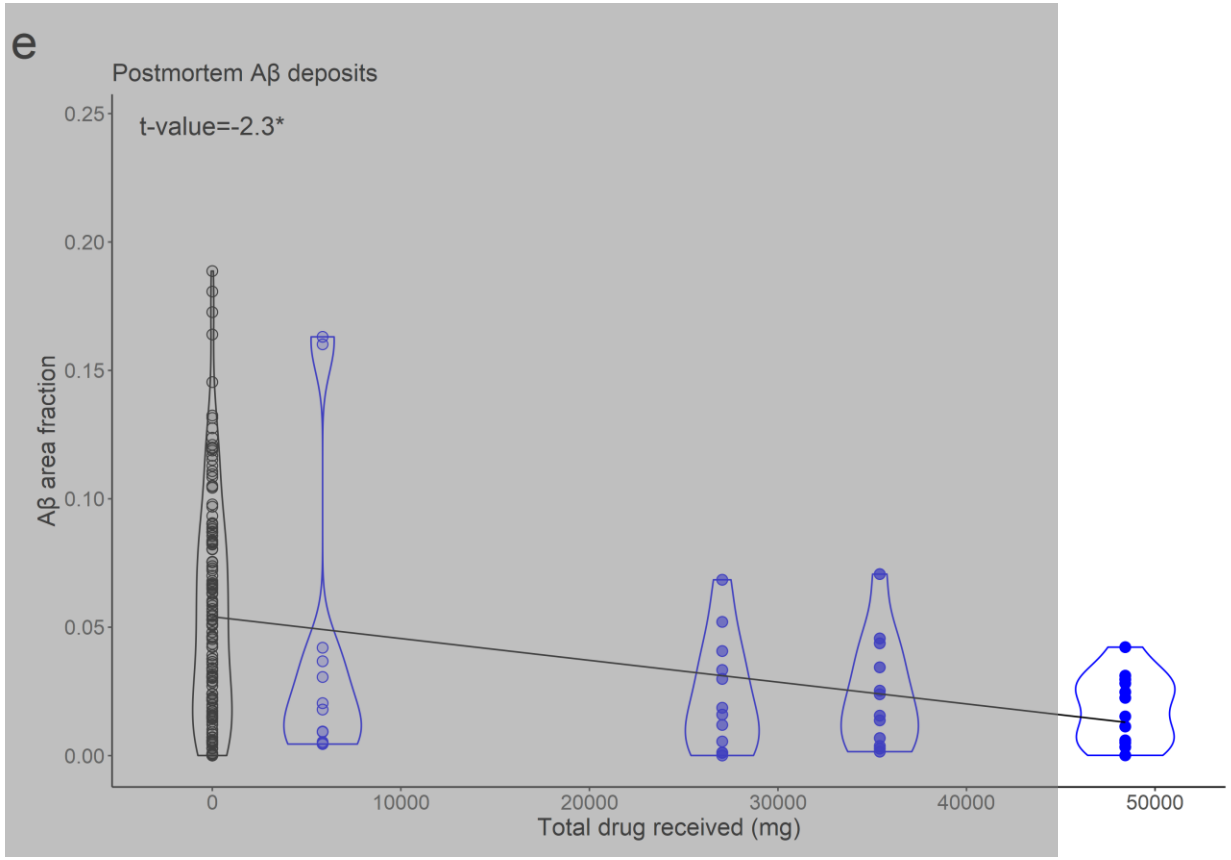
Overall, there is a dose-dependent treatment effect at postmortem assessment



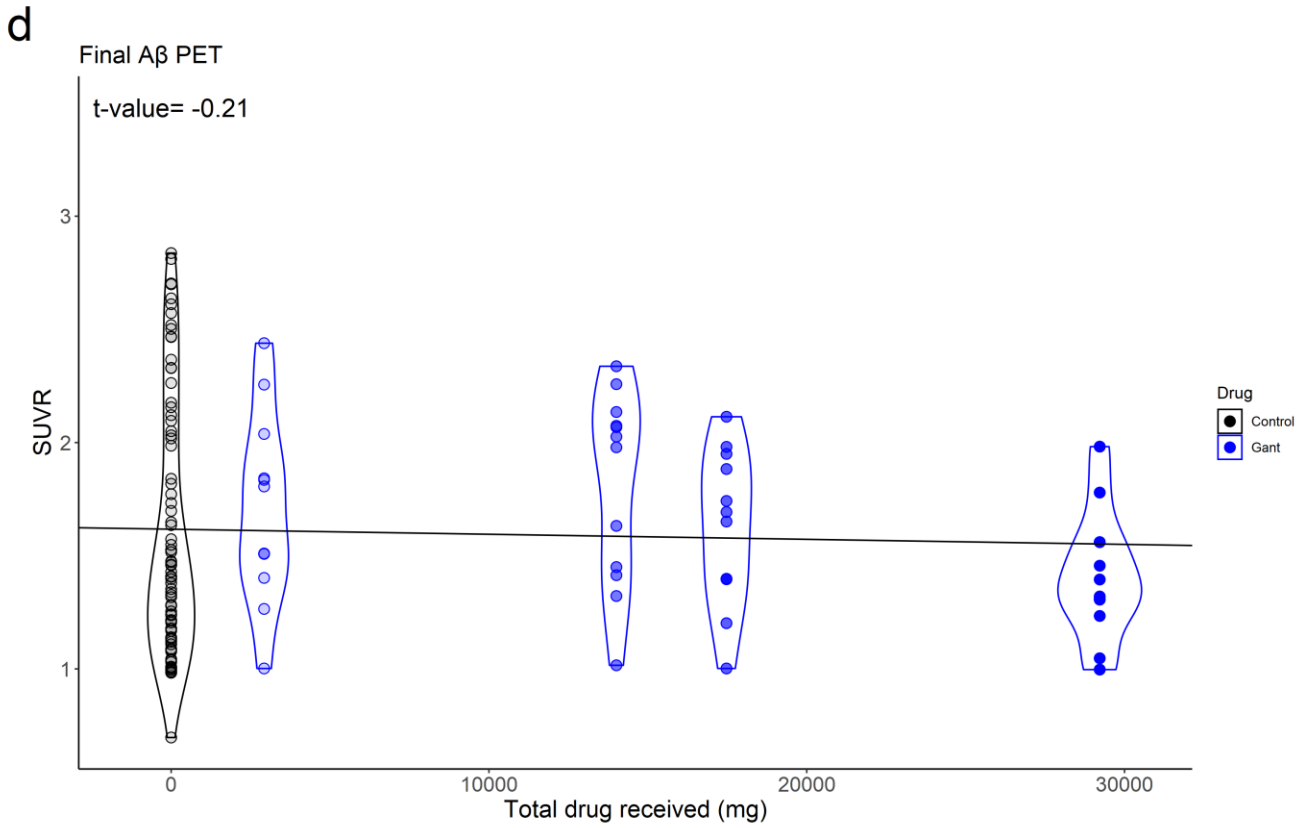


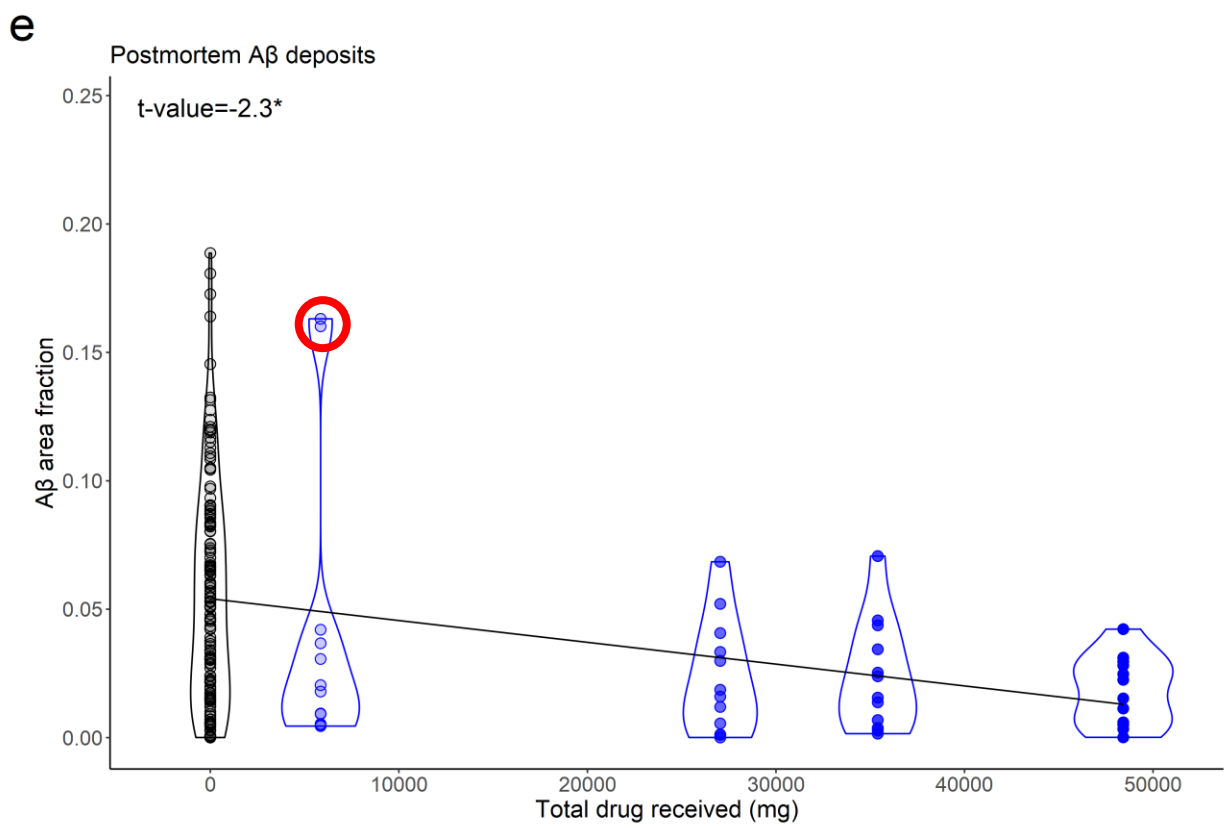
This effect is not seen at final Aβ PET due to the lower cumulative drug dose received





Removing outliers does not change the dose-dependent effect





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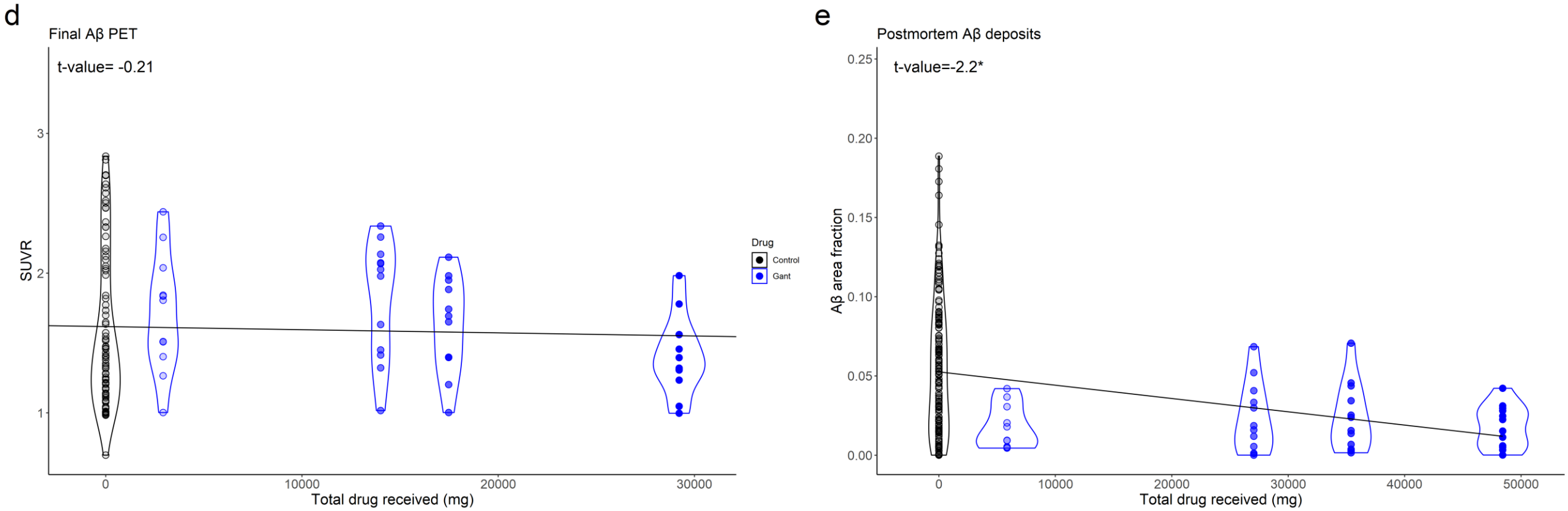
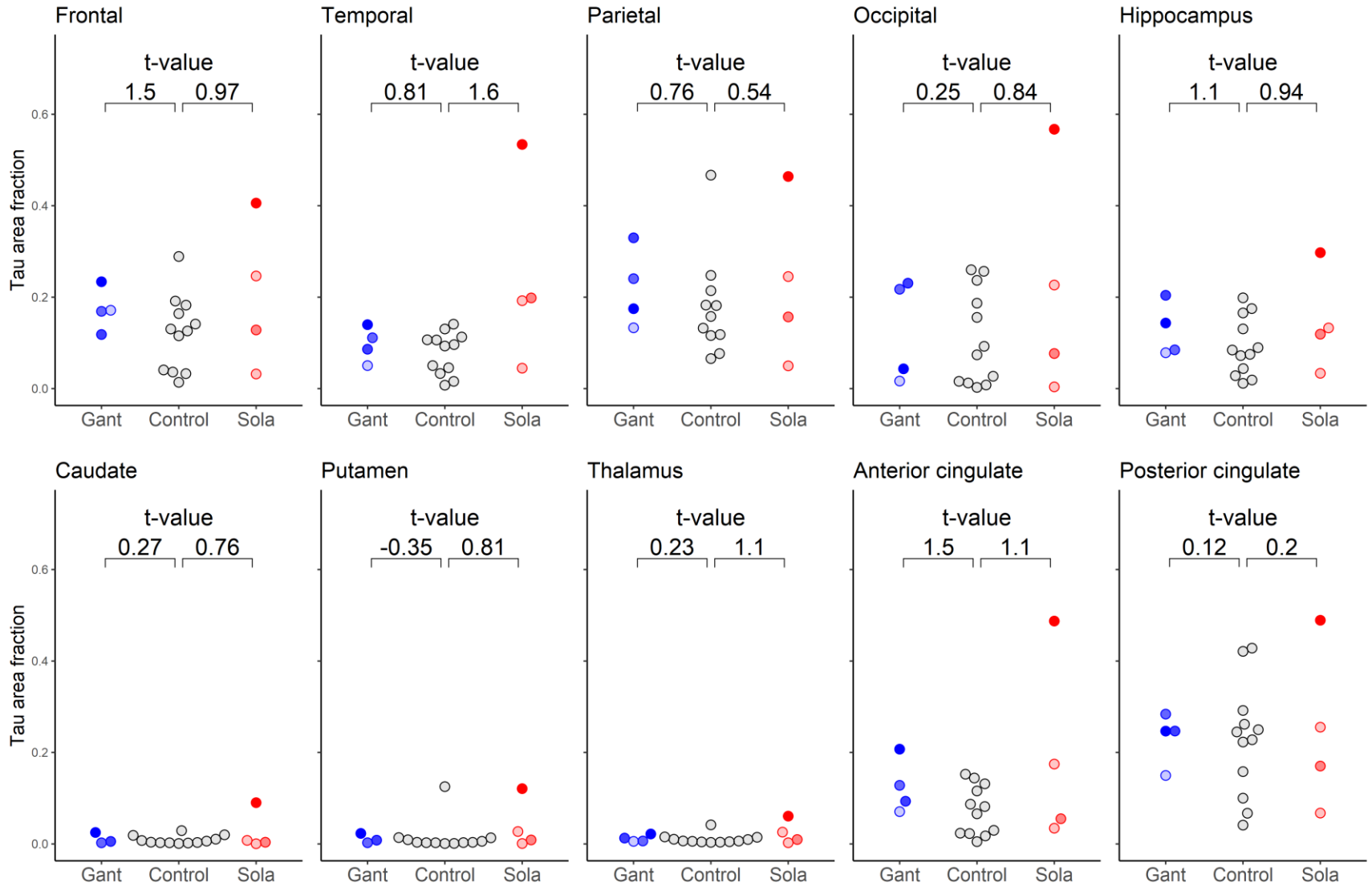
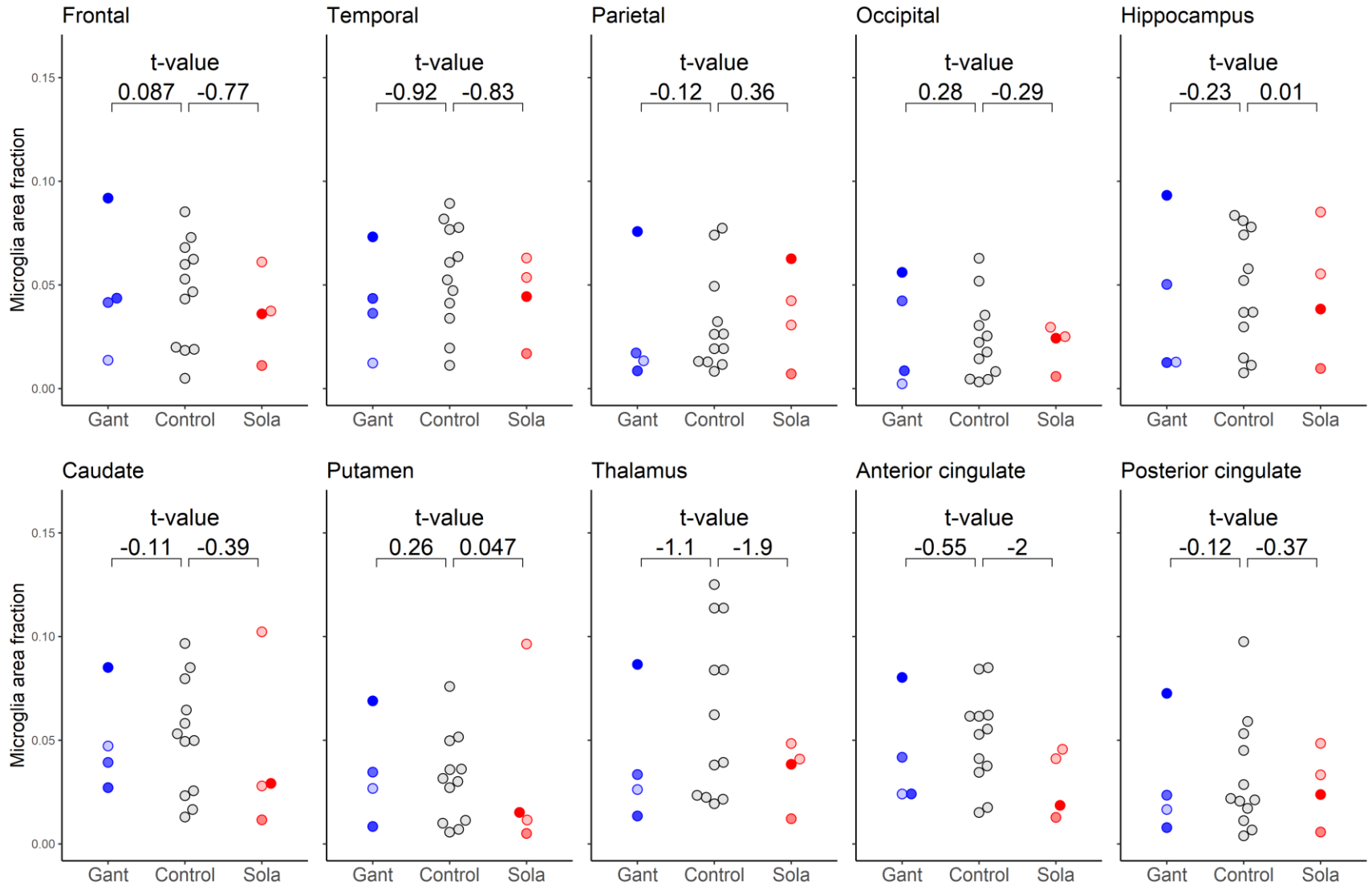


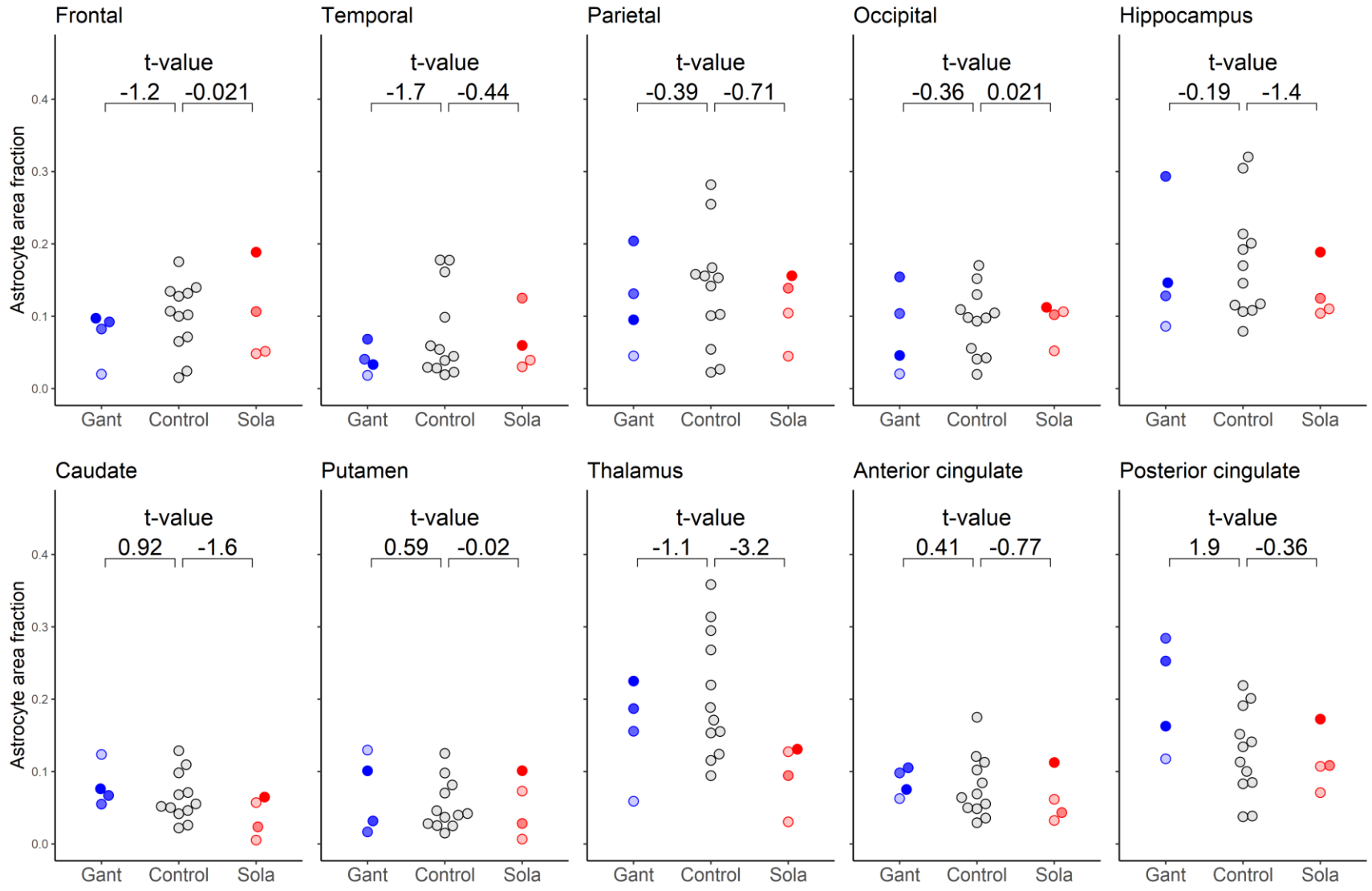
Postmortem tau neuropathology shows no significant difference across groups



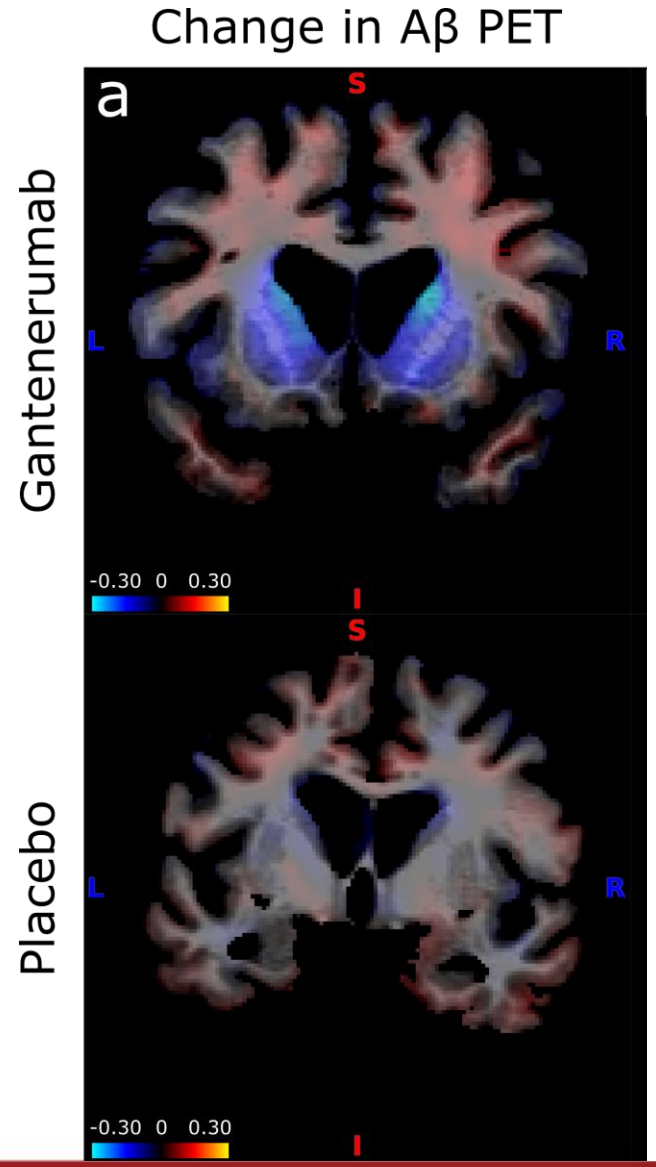
Postmortem microglia neuropathology shows no significant difference across groups

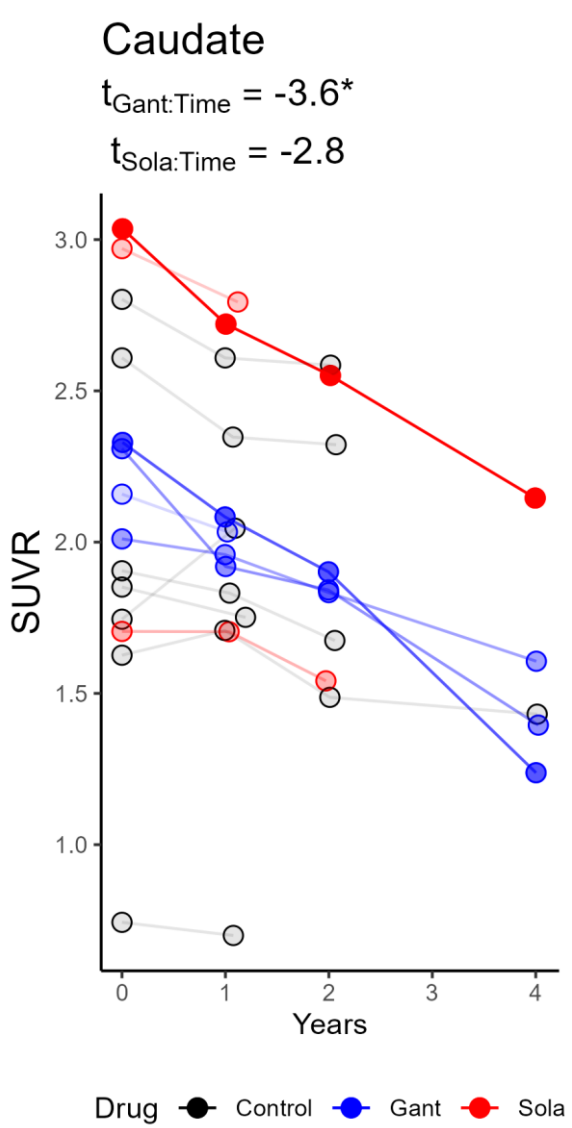


Postmortem astrocyte neuropathology shows no significant difference across groups

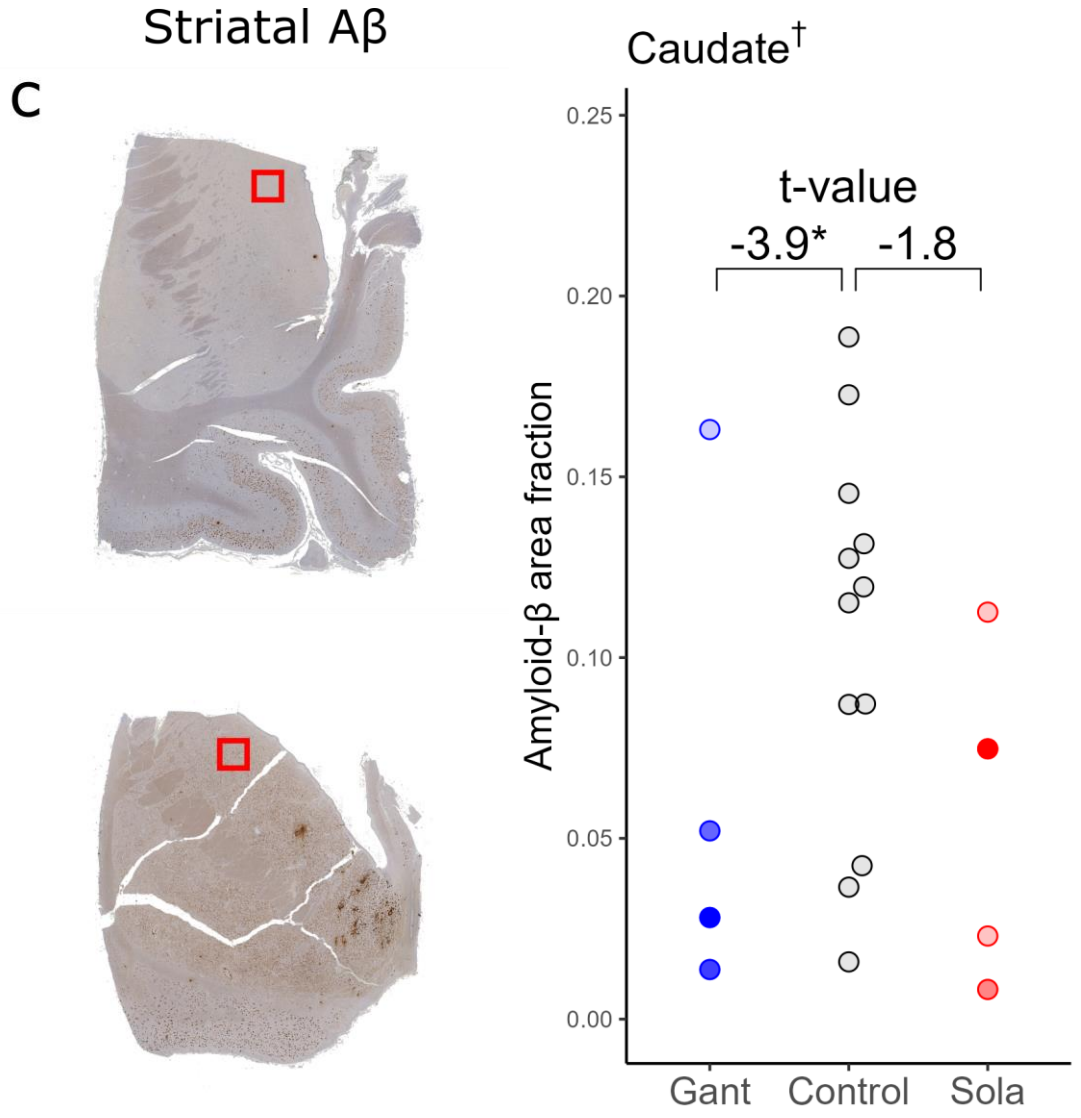


Key results: Aβ PET shows longitudinal decline in the gantenerumab arm

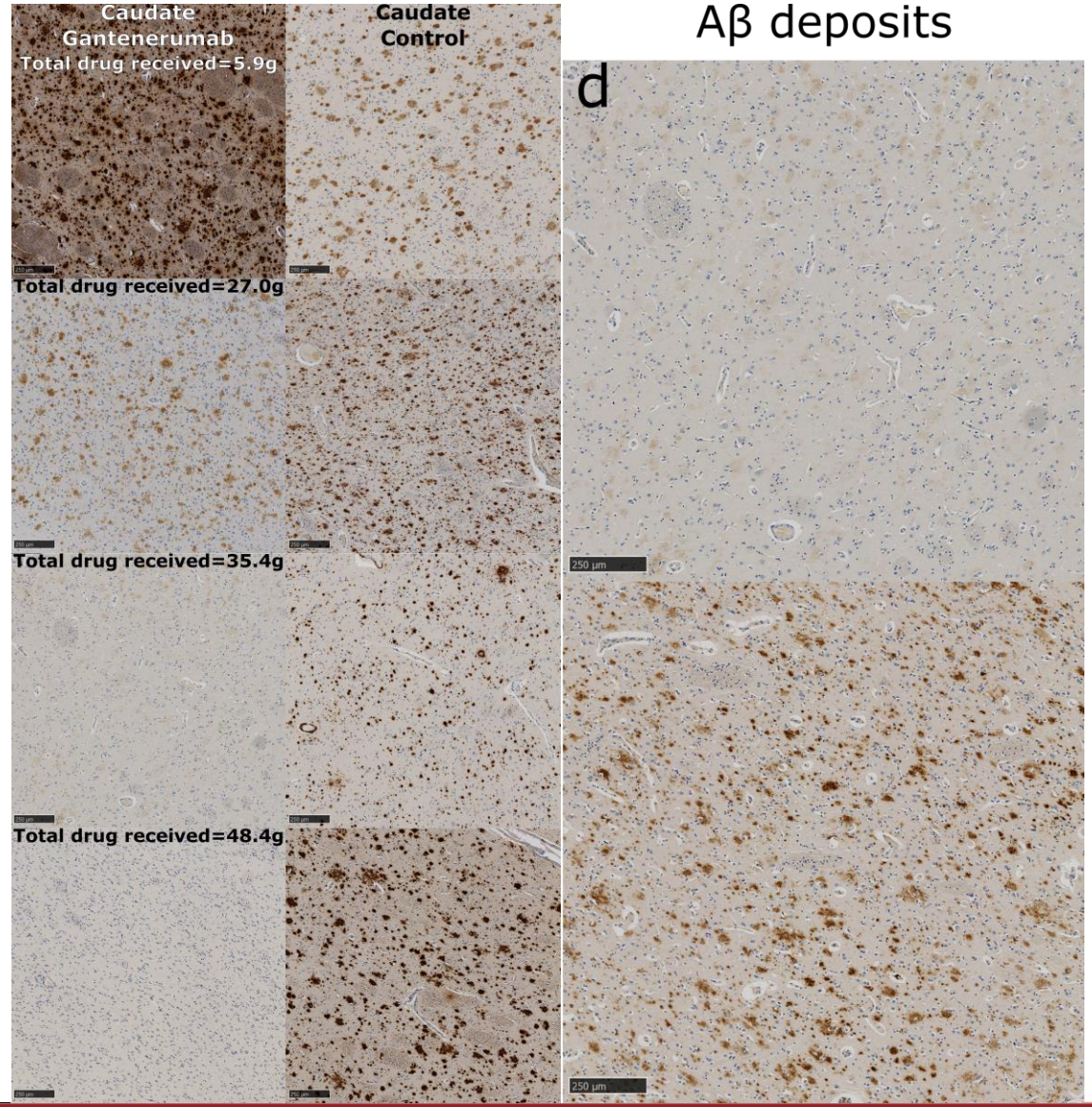




Key results: Aβ area fraction is significantly lower in the gantenerumab arm (n=4)



Key results: some regions have striking dose-dependent treatment effects



Acknowledgements

- We gratefully acknowledge the outstanding commitment of the participants, family members, and caregivers whose participation was critical to the success of the DIAN-Obs and DIAN-TU trial.
- We thank the DIAN-Obs and DIAN-TU study teams for their exceptional dedication and amazing accomplishments which ensured the success of the trial.
- We appreciate the robust intellectual collaboration between the DIAN-TU investigators, patients and family members, Roche/Genentech, and Eli Lilly & Co., the DIAN-TU Pharma Consortium, the NIH, and regulatory representatives who were critical in making this study possible.
- We thank the Alzheimer's Association, GHR Foundation, Anonymous Organization, industry partners (Avid Radiopharmaceuticals [a wholly owned subsidiary of Eli Lilly & Co.], Signet, Cogstate), and regulatory representatives for their support.

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Knight ADRC T32 (5T32AG058518-04)
PET/MR in ADRD T32 (1T32AG066592-01A1)

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- The study was conducted in accordance with the Declaration of Helsinki (version 7) and the International Conference on Harmonization and Good Clinical Practice guidelines. Protocols for the study have received prior approval by the local Institutional Review Board (IRB) or Ethics Committee of each DIAN site and by the Washington University IRB for the Knight ADRC. The clinical trial registration number is NCT01760005.

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- Washington University holds patents for one of the treatments (solanezumab), previously tested in the DIAN clinical trials. If solanezumab is approved as a treatment for Alzheimer’s disease or Dominantly Inherited Alzheimer’s Disease, Washington University will receive part of the net sales of solanezumab from Eli Lilly, which has licensed the patents related to solanezumab from Washington University.