Effects of p38α kinase inhibitor on basal forebrain volume in Alzheimer's disease

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Disclosures

- *Dr. Alam* is the employee of, and holder of stock in EIP Pharma, Inc, the sponsor of the clinical trial
- *Dr. Prins* is the CEO and co-owner of Brain Research Center
- *Prof. Barkhof* receives grants from EPSRC, EU-JU (IMI), GEHC, ADDI and NIHR Biomedical Research Centre at UCL Hospitals NHS Foundation Trust, as well as personal fees from USC-ATRC, Biogen, Roche, IXICO, Combinostics, Prothena, and Merck; and is the founder and a stockholder of Queen Square Analytics.
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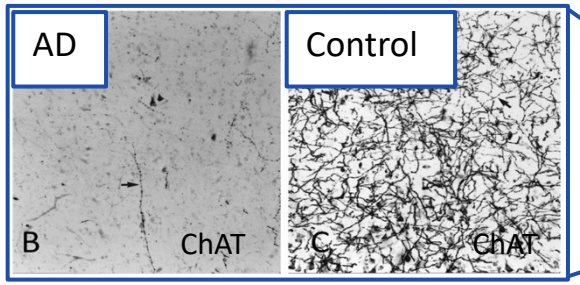
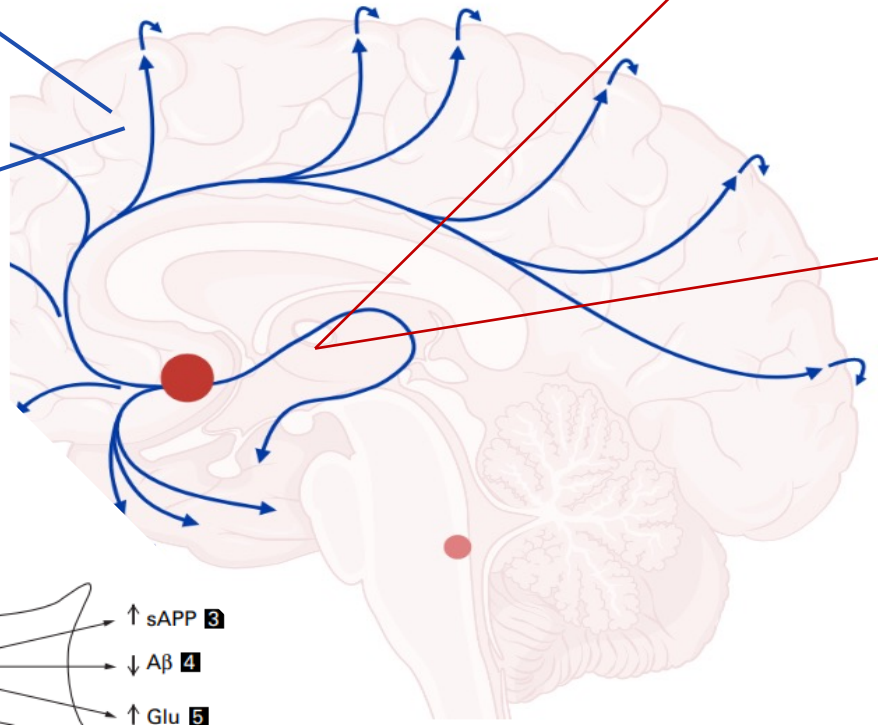
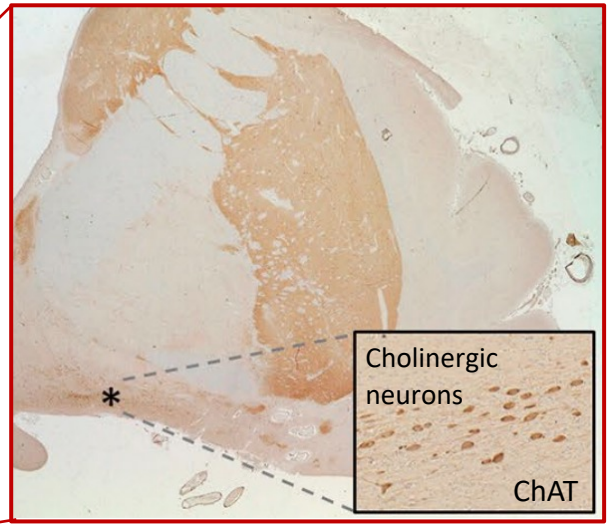
- *Dr. Schoonheim* serves on the editorial board of Neurology and Frontiers in Neurology, receives research support from the Dutch MS Research Foundation, Eurostars-EUREKA, ARSEP, Amsterdam Neuroscience, MAGNIMS and ZonMW and has served as a consultant for or received research support from Atara Biotherapeutics, Biogen, Celgene/Bristol Meyers Squibb, EIP Pharma, Sanofi-Genzyme, MedDay and Merck.

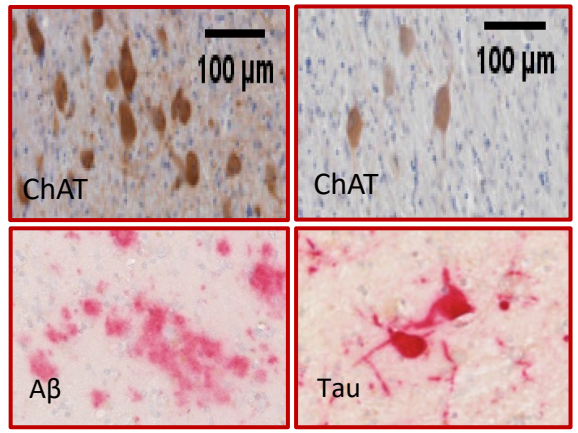
Cholinergic dysfunction in Alzheimer's disease (AD)

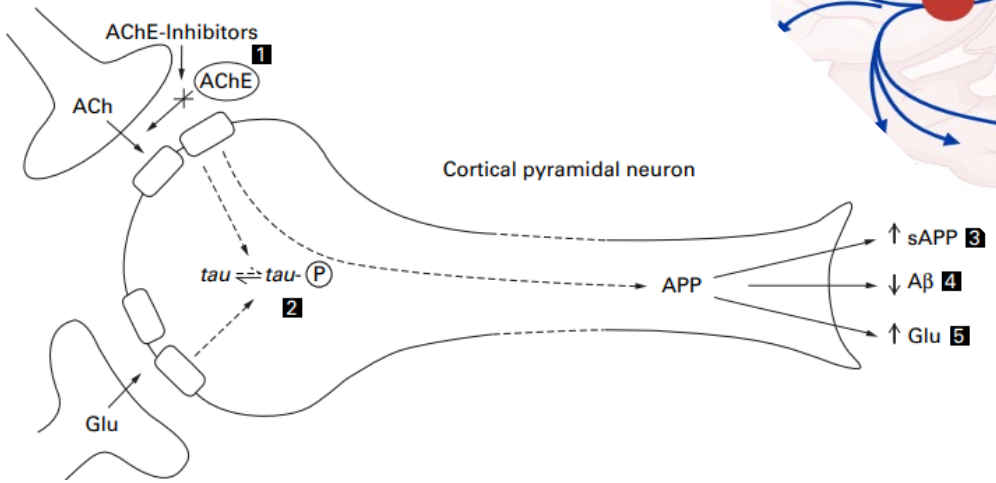
Nucleus basalis of Meynert (NbM)





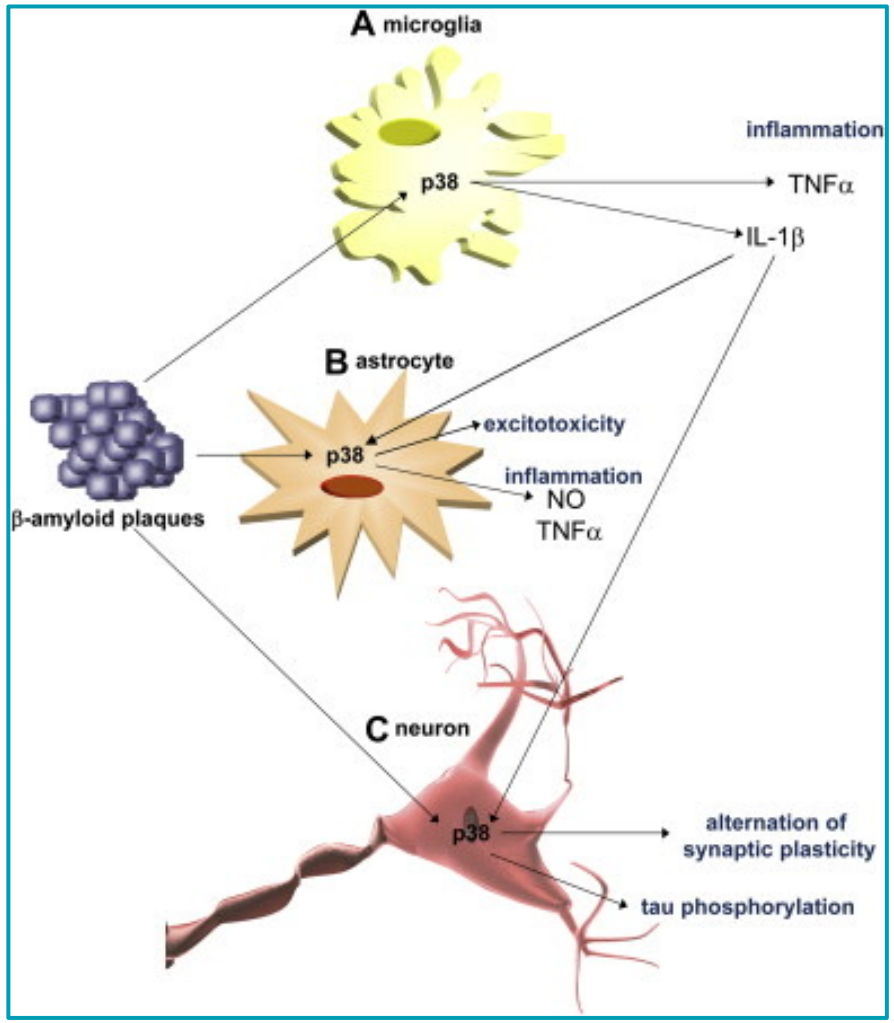


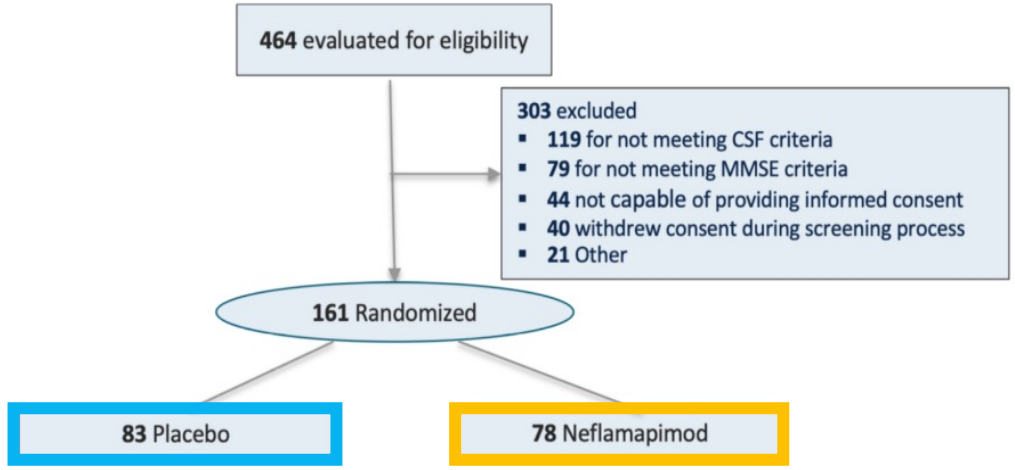


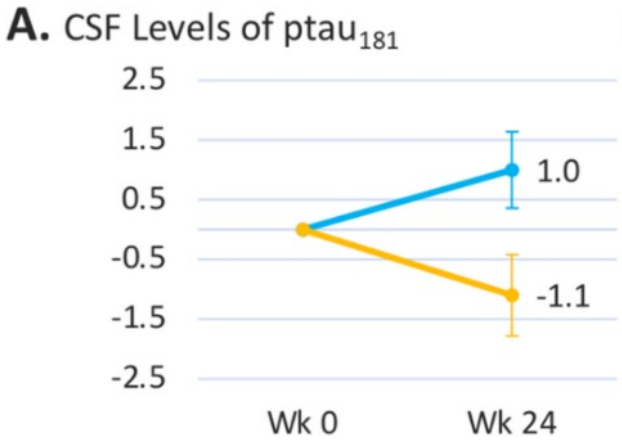


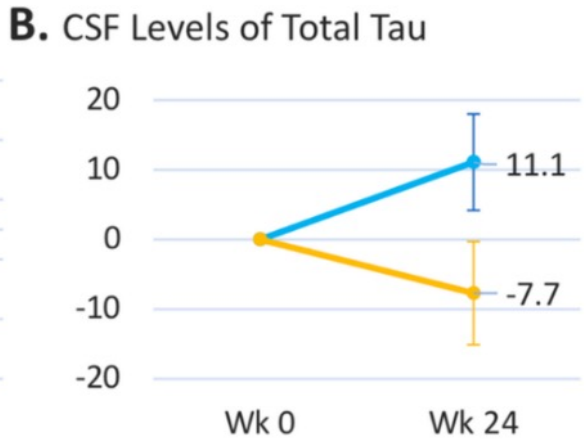
Mesulam et al. , 2013; Ferrari et al., 2018; Liu et al. Acta Neuropathol, 2015; Hampel et al. *Brain*, 2018; Francis et al. *J Neurol Neurosurg Psychiatry*, 1999; Lin et al. *Brain*, 2022

p38α inhibitor neflamapimod (NFMD) reduces CSF tau in AD



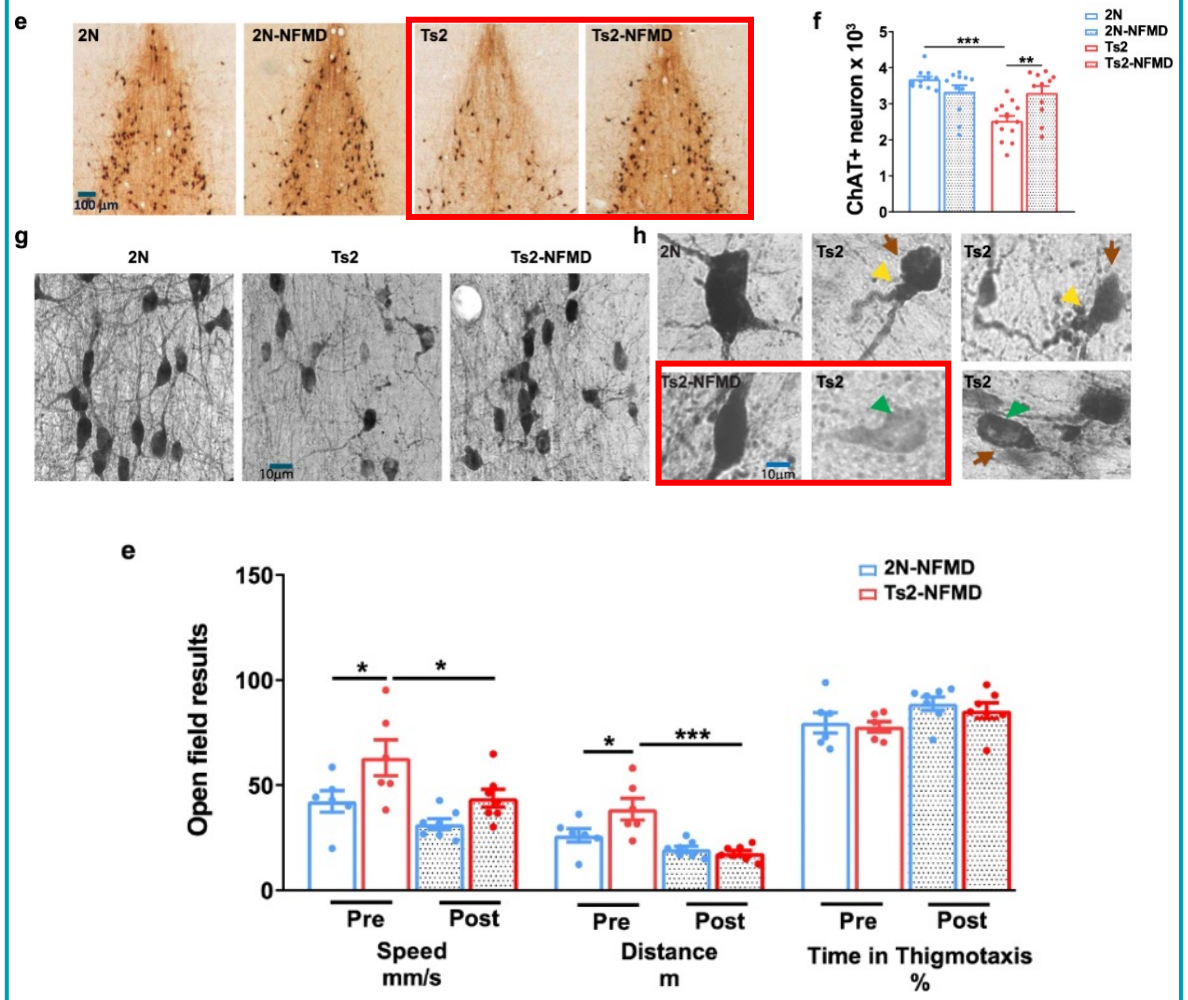






Munoz and Ammit, Neuropharmacology, 2010; Prins et al, Alz Res Ther, 2021, 27:106; Alam, J of Alzheimer's, 2015

NFMD restores cholinergic neurons in preclinical mouse model



NFMD improves cognition and function in a clinical trial in dementia with Lewy body

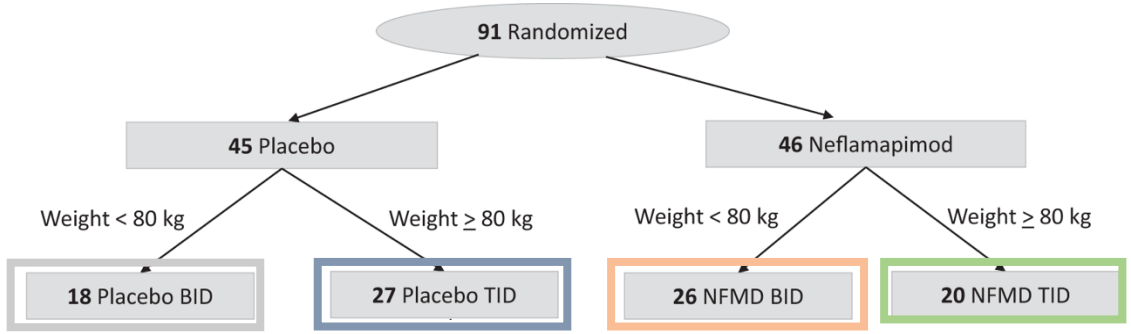


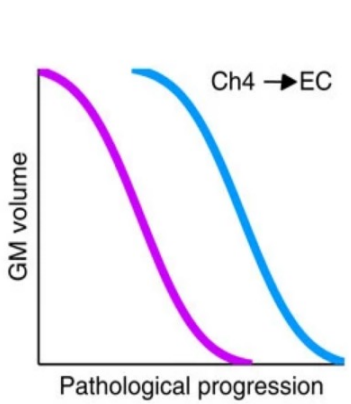
Table 2 | Efficacy outcome measures in the clinical study

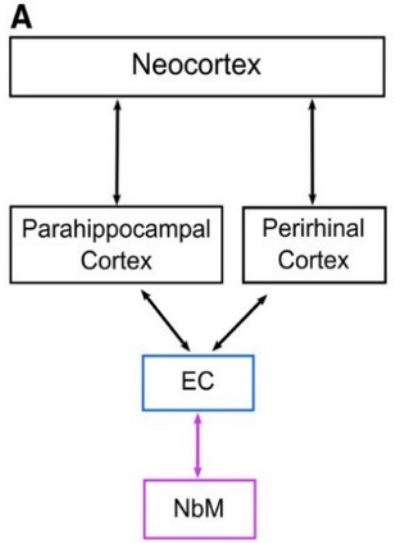
Outcome measure	All Neflamapimod (NFMD; includes 40 mg BID and 40 mg TID participants) vs. All Placebo						
	Number of particpants		Mean baseline values		Change from baseline		
	NFMD	Placebo	NFMD	Placebo	Drug-Placebo Difference On-Study (95% CI)	*p*-value	Cohen's d Effect Size for Improvement - *d*
NTB* Composite	39	37	0.04	0.05	0.04 (−0.11, 0.19)	>0.2	0.10
Attention Composite	39	36	0.04	−0.02	0.14 (−0.06, 0.35)	0.17	0.18
Clinical Dementia Rating Sum of Boxes (CDR-SB)	41	42	4.9	5.1	−0.45 (−0.83, −0.06)	0.023	0.31
International Shopping List Test (ISLT)	42	42	14.3	13.6	−0.17 (−1.61, 0.87)	>0.2	−0.02
Timed Up and Go (TUG)	39	38	12.7	13.5	−1.4 (−2.7, −0.1)	0.044	0.22

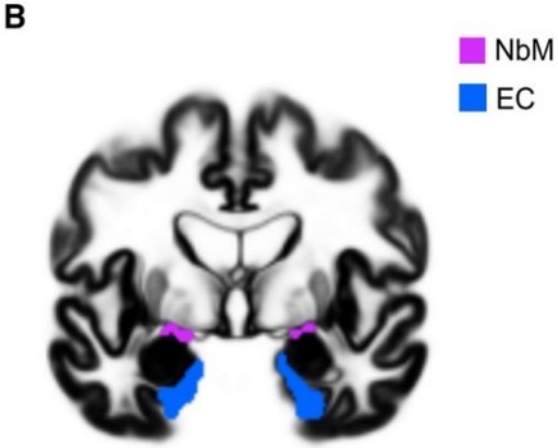
Jiang et al, Nature Communications, 2022

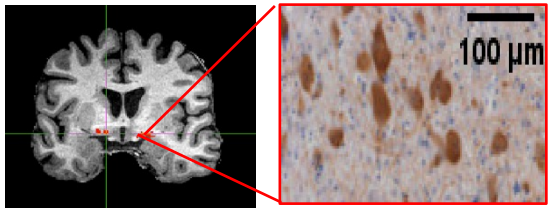
MRI-measured NbM integrity are potential biomarker for AD progression and treatment effect

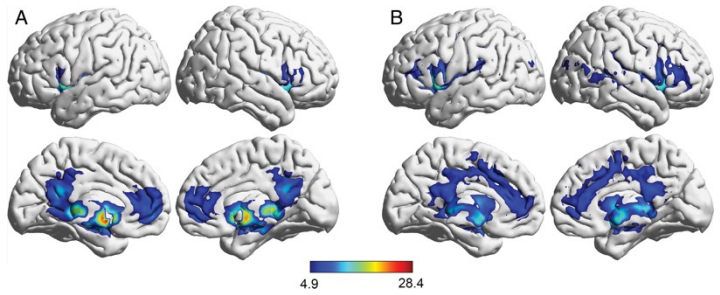
- NbM structural alteration is an upstream event for AD progression in the brain
- Microstructural alteration in the NbM is a proxy of cholinergic loss.
- Functional changes in NbM connectivity correlates with memory function in preclinical AD.





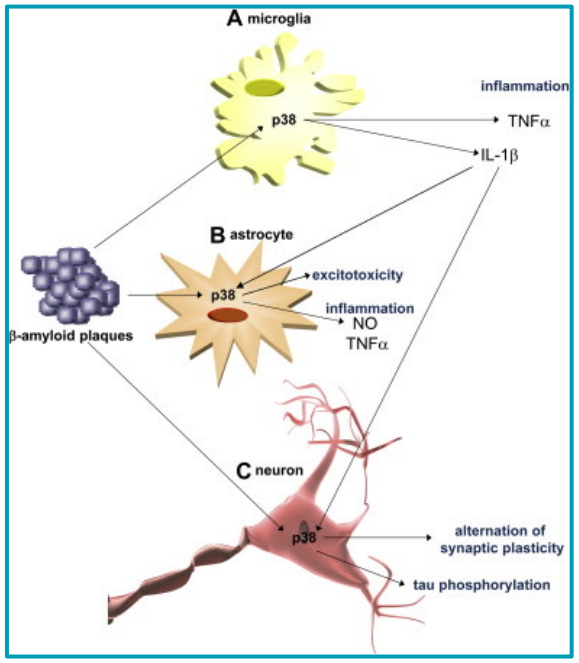


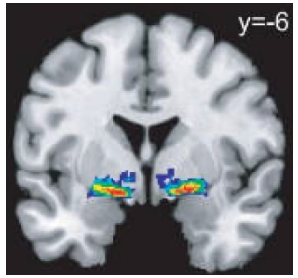


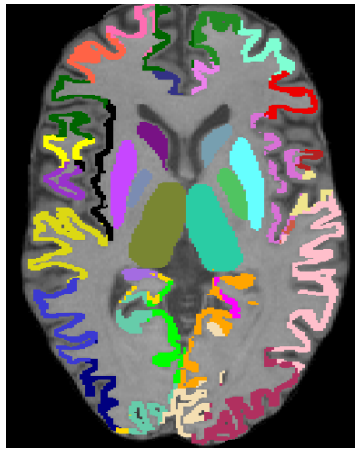


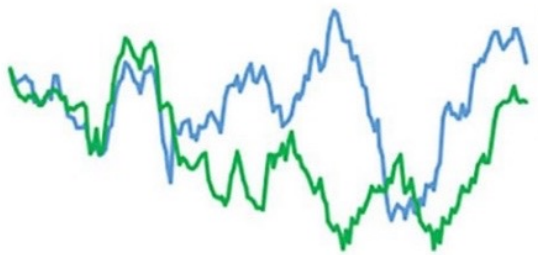
Fernández-Cabello et al. *Brain*, 2020; Teipel et al. *J of Alzheimers*, 2022; Lin et al. *Brain*, 2022; Chiesa et al.Radiology, 2018; Zheng et al. 2022

Aim: Assess the effects of NFMD on the NbM in early AD using structural and functional MRI



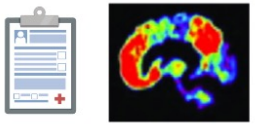






Study design

Study population
(n = 15)



Enrollment

ANNALS of Clinical and Translational Neurology
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RESEARCH ARTICLE

An exploratory clinical study of p38α kinase inhibition in Alzheimer's disease

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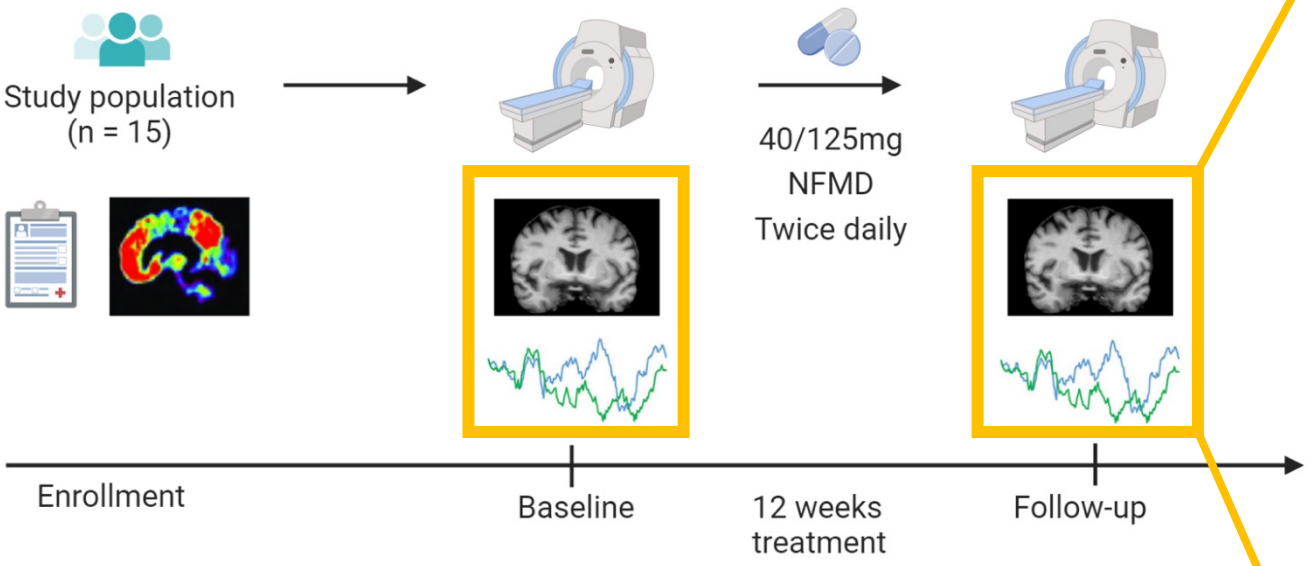
Inclusion criteria

- Double-blind dose-controlled
- Male or female, age 60–85 years with MCI due to AD or mild AD
- Elevated ^{11}C-PiB PET amyloid plaque load
- MMSE between 20-28

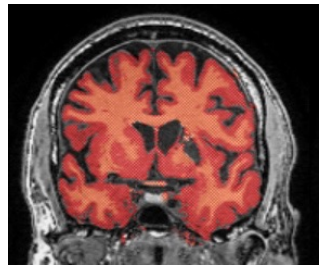
Study design



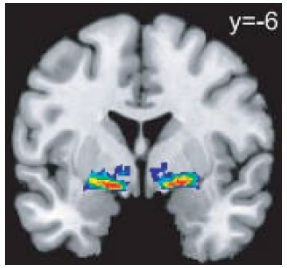
Patients	
Clinical characteristics	
N	15
Gender M/F (%M)	9/6 (60%)
Age median (years)	66,5
Range	(63-85)
MMSE median	23
Range	20-28

3D T1 MRI

- Global brain volume (sienax)
- NbM volume (NbM probabilistic atlas and FSL registration)

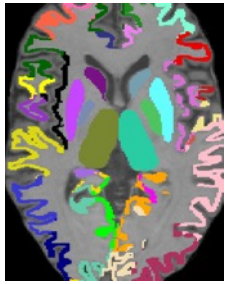


SIENAX



Kilimann et al., 2014

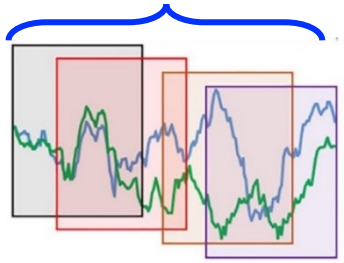
Resting-state functional MRI

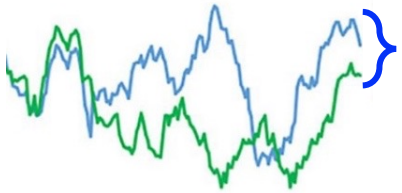


NbM

- Default-mode
- Frontoparietal
- Attention
- Visual
- Sensorimotor
- Limbic
- Deep grey matter

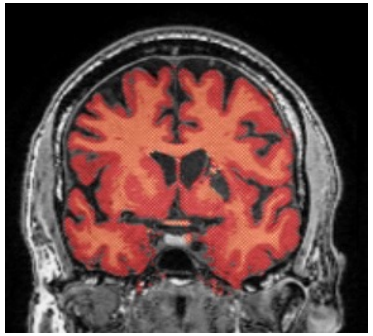
Dynamic: coefficient of variation

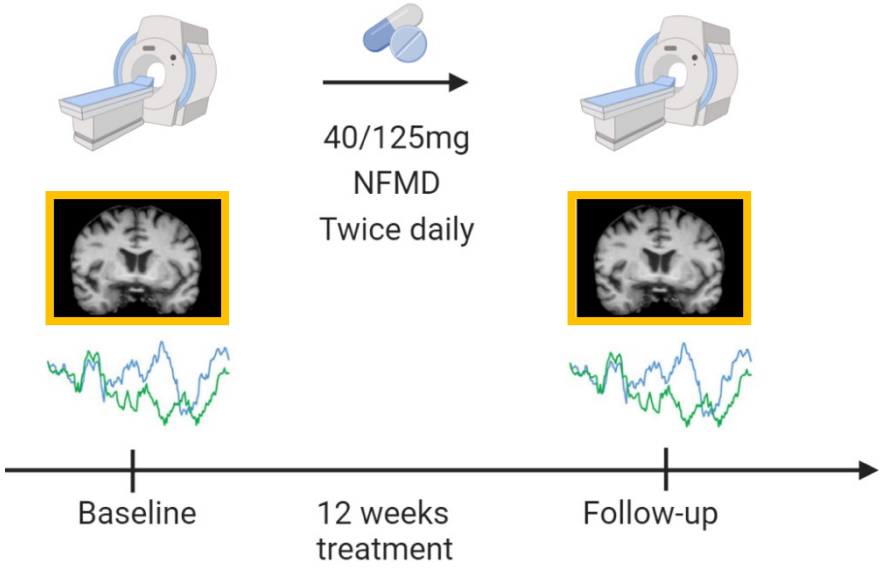


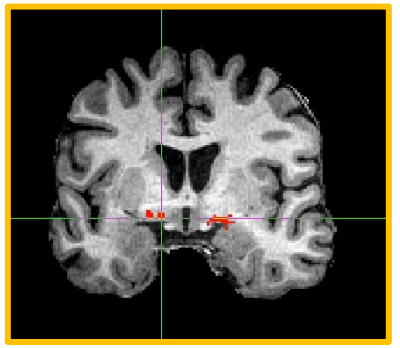


Static: correlation

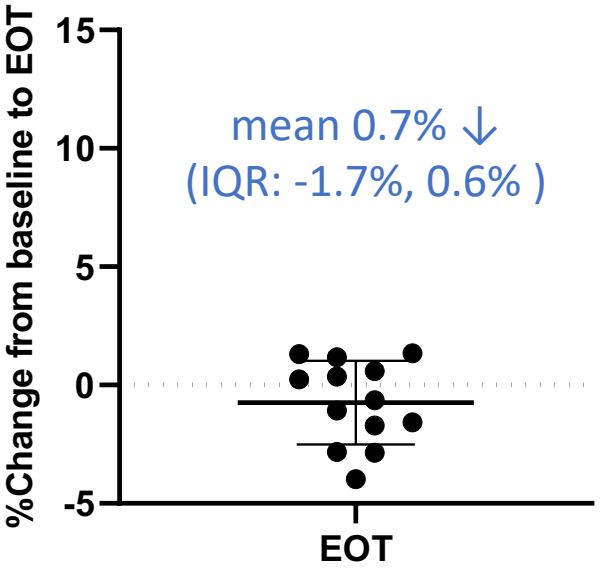
Increased NbM volume at follow-up







%Change in brain volume



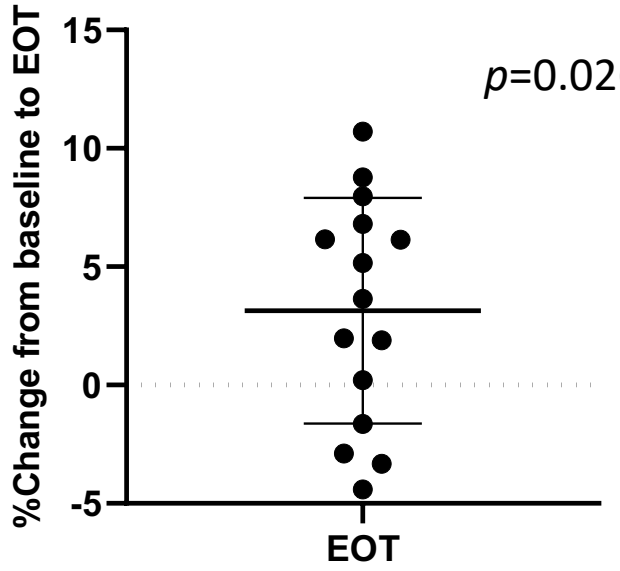
mean 0.7% ↓
(IQR: -1.7%, 0.6%)

NbM volume
469 (SD=47) mm^3

NbM volume
483 (SD=49) mm^3

mean 3,1% ↑
(IQR: -0,7, +6.5%)

%Change in NbM volume

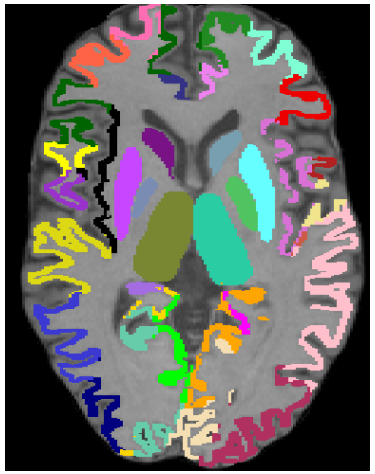


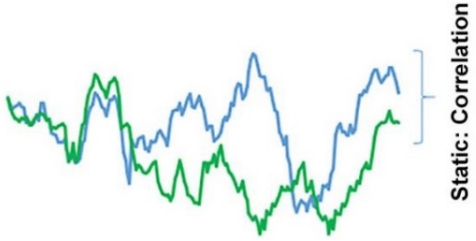
p=0.026

8/15 participants >3% increase

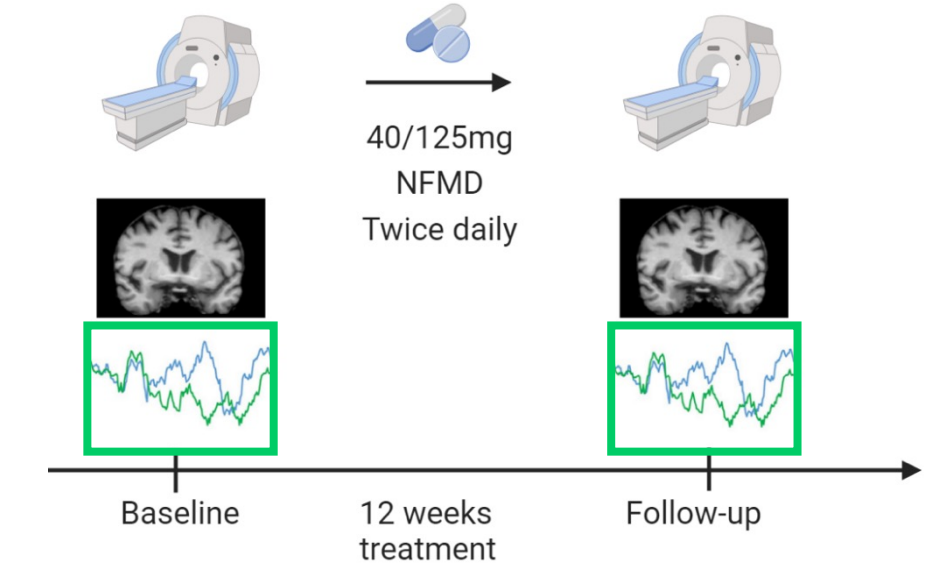
EOT=end of treatment

Increased dynamic connectivity between NbM-deep grey matter (DGM)





No change in static connectivity



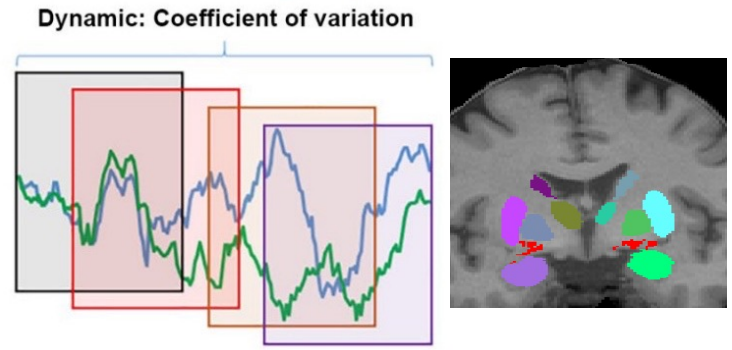
0,83
(SD=0,13)

0,90
(SD=0,12)

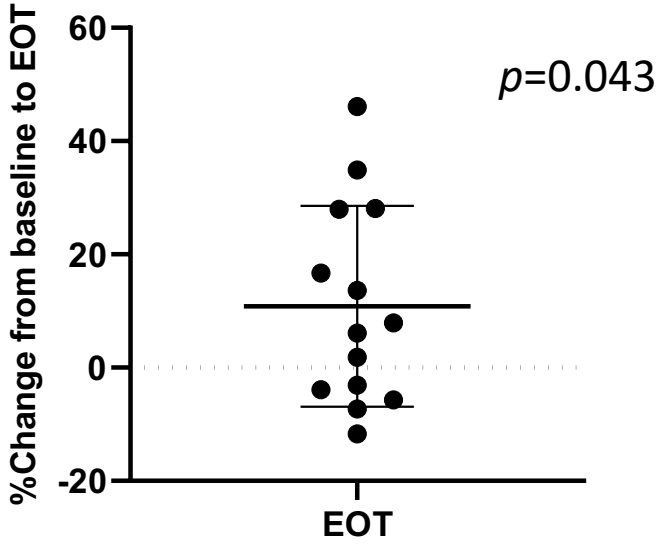
mean 11% ↑
(IQR: -3.7, +25,2%)

6/13 participants >10% increase

NbM-DGM dynamic connectivity



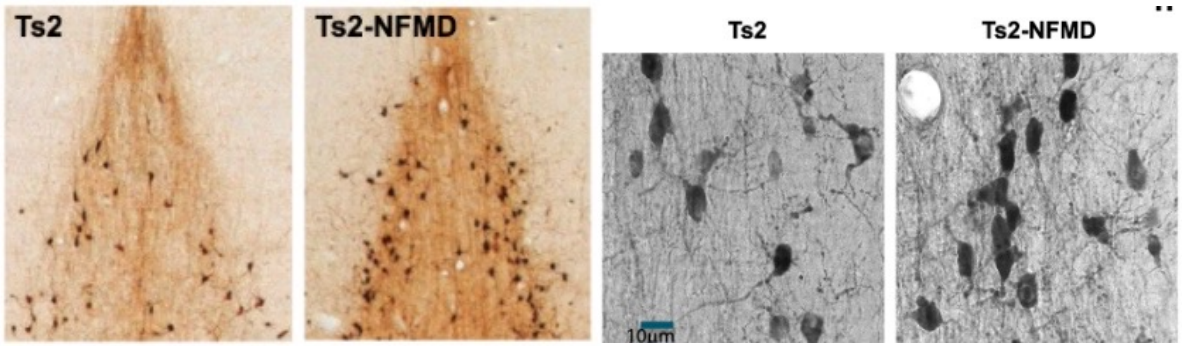
%Change in dynamic connectivity



EOT=end of treatment

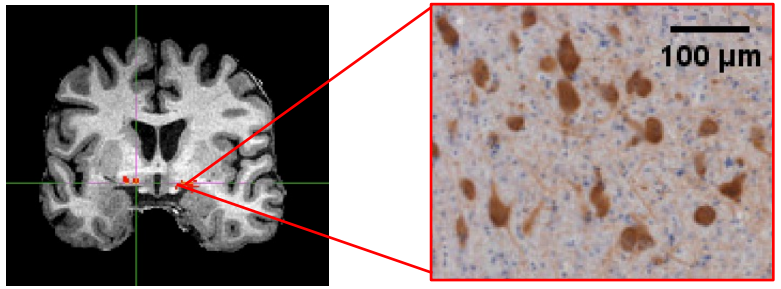
Discussion

Increased NbM volume and NbM-DGM connectivity in early AD patients treated with NFMD

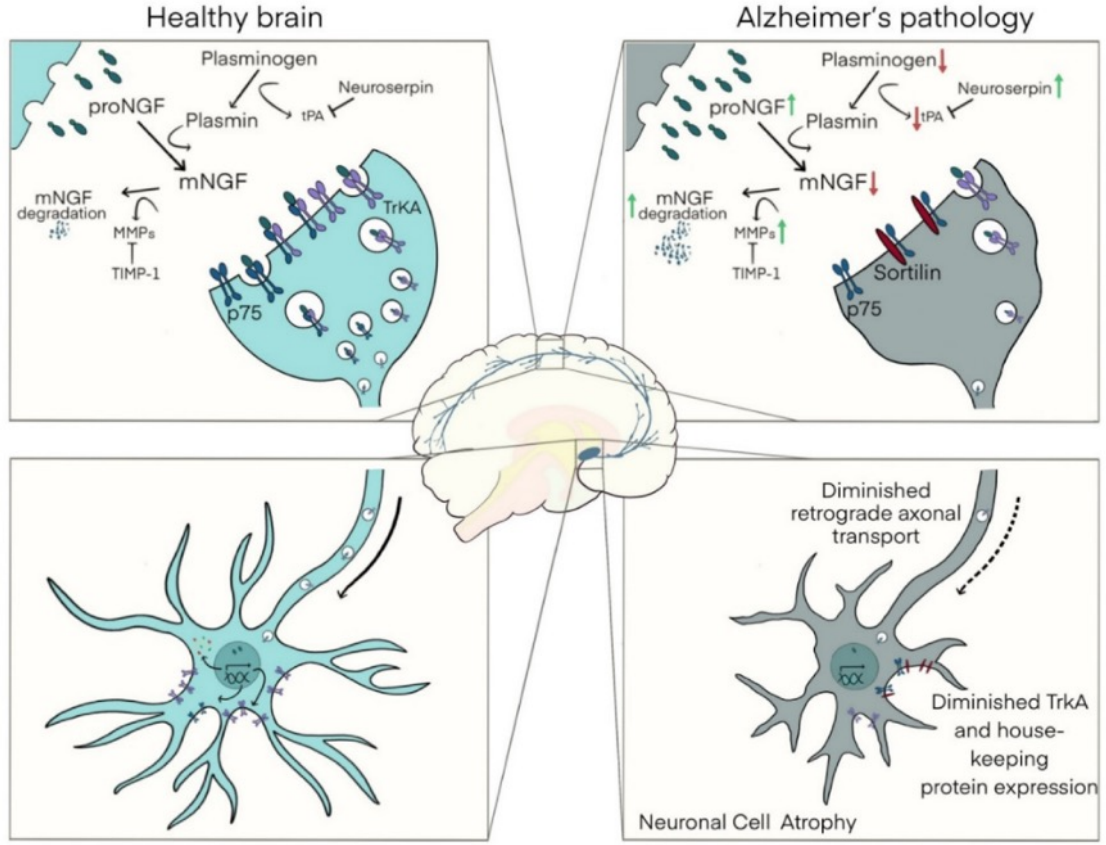


(Jiang et al., 2022)

- NbM volume reduces 0.5%-1% annually in untreated AD, and is correlated with cholinergic neuronal loss.

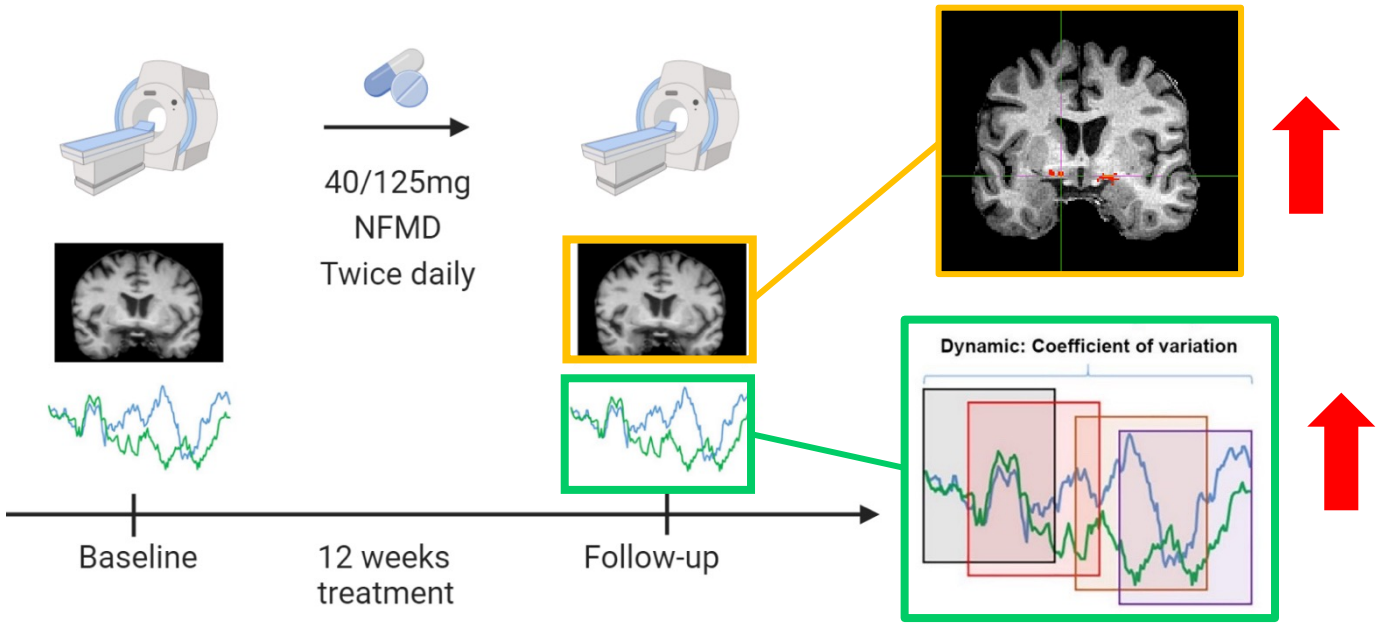


- In AD, cholinergic neurons shrink, are depleted of phenotypic markers, and/or persist in an atrophic state



Mufson et al. *Expert Rev Neurotherpeutics*, 2006; Schmitz et al. *Nat Comm,* 2016*;* Lin et al. *Brain*, 2022; Chiesa et al.Radiology, 2018; Carmo et al. Cells, 2022; Fernández-Cabello et al. *Brain*, 2020

Conclusions



- Neflamapimod treatment is associated with increasing NbM volume and NbM-DGM dynamic connectivity, suggesting p38α kinase inhibition has a positive impact on the cholinergic degenerative process in AD.
- Functional and structural MRI assessments of the NbM may be potential biomarkers for therapeutic effects.
- Further evaluation of the potential effect of neflamapimod on the NbM in *placebo-controlled clinical trials* in AD and correlation with *clinical outcomes* is warranted.

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anatomy & neurosciences

Alzheimer Center Amsterdam
Amsterdam UMC

Patients in clinical trials

Trend of correlation between NbM volume and NbM-DGM dynamic connectivity at follow-up