INITIAL SCANS USING [^{18}F]ACI-12589, A NOVEL PET-TRACER FOR α-SYNUCLEIN

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Disclosures

- Ruben Smith reports no disclosures
- Francesca Capotosti, Tanja Touilloux, Valerie Hliva, Jerome Molette, Efthymia Vokali, Yannis Dimitrakopoulos, Andrea Pfeifer, Marie Kosco-Vilbois and Johannes Streffer are full-time employees of AC Immune SA
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Participant characteristics

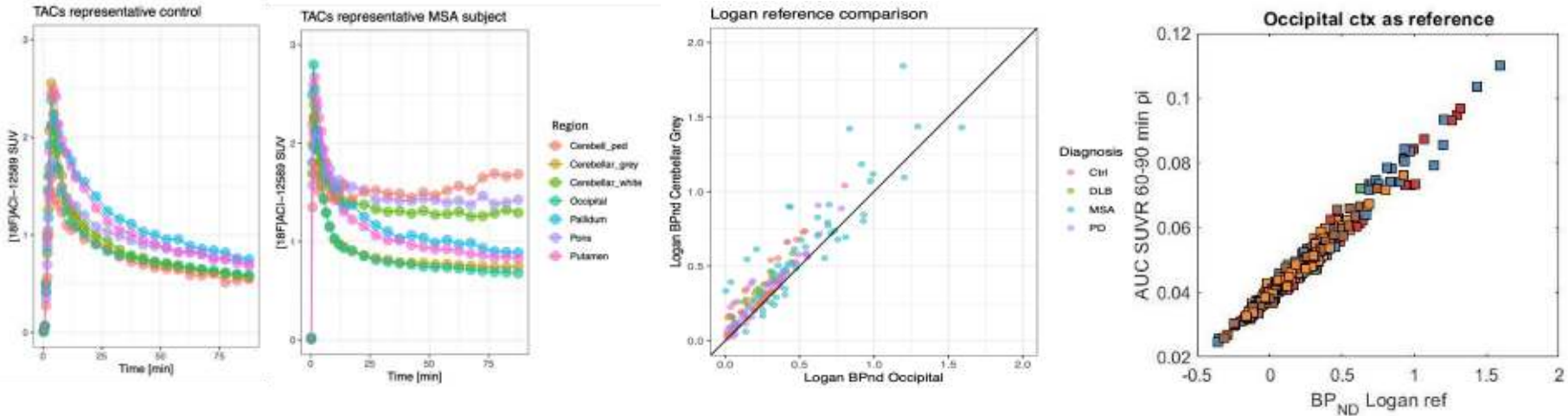
	Control	PD	MSA	DLB	AD	PSP	Ataxias
n (43)	8	8	13	2	5	3	3
Sex (M/F)	5/3	7/1	7/6	2/0	4/1	3/0	2/1
Age (± SD)	63±11	68±6	61±8	81±1	69±4	72±9	54±14
Inj Dose (MBq)	314±39	308±56	297±13	289±1	296±5	298±8	267±67
UMSARS I + II	N/A	N/A	53±23	N/A	N/A	N/A	N/A
UPDRS-III	N/A	65±16	N/A	N/A	N/A	N/A	N/A

AD = Alzheimer's Disease; DLB = Dementia with Lewy Bodies; MSA = Multiple system atrophy;
PD = Parkinson's Disease; PSP = Progressive Supranuclear Palsy.
Ataxias: two participants with Friedrich Ataxia, one with a mutation in the *SAMD9L* gene

[18F]ACI-12589: tracer performance and signal quantification

[^{18}F]ACI-12589 has:

- favorable metabolic stability (60-80% of the parent remaining 90 min post injection)
- fast signal equilibration
- robust signal quantification with similar results obtained with different methods and reference regions (e.g. Cerebellar grey and occipital cortex)
- possibility to use short scan windows (e.g. 60-90 min post-injection)



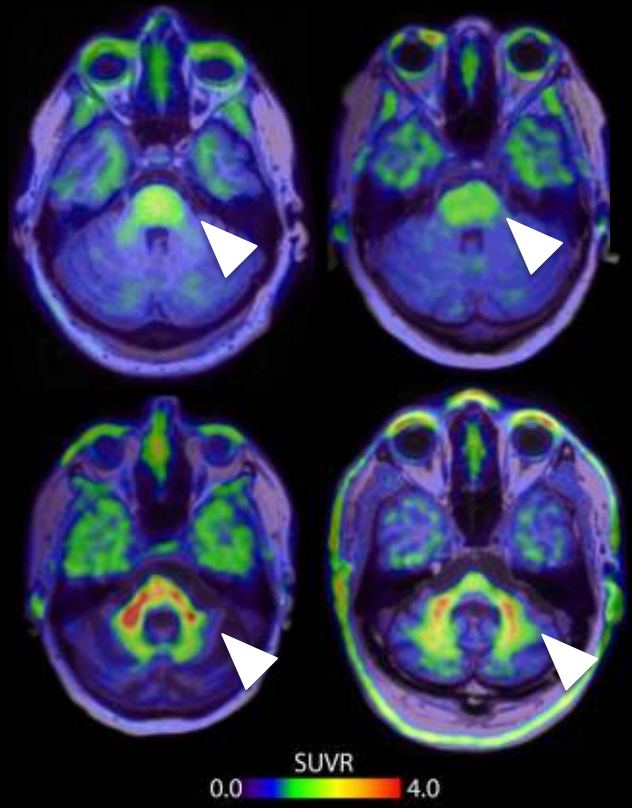
[18F]ACI-12589 uptake in MSA-C

Control,
52 y.o.

Control,
69 y.o.

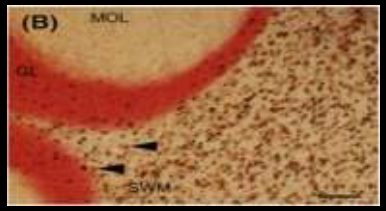
MSA-C,
55 y.o.

MSA-C,
63 y.o.



SUVRs 60-90 min
Occipital cortex as reference region

Clear signal retention in MSA-C cases in cerebellar white matter and peduncles in line with the expected pathological a-syn distribution



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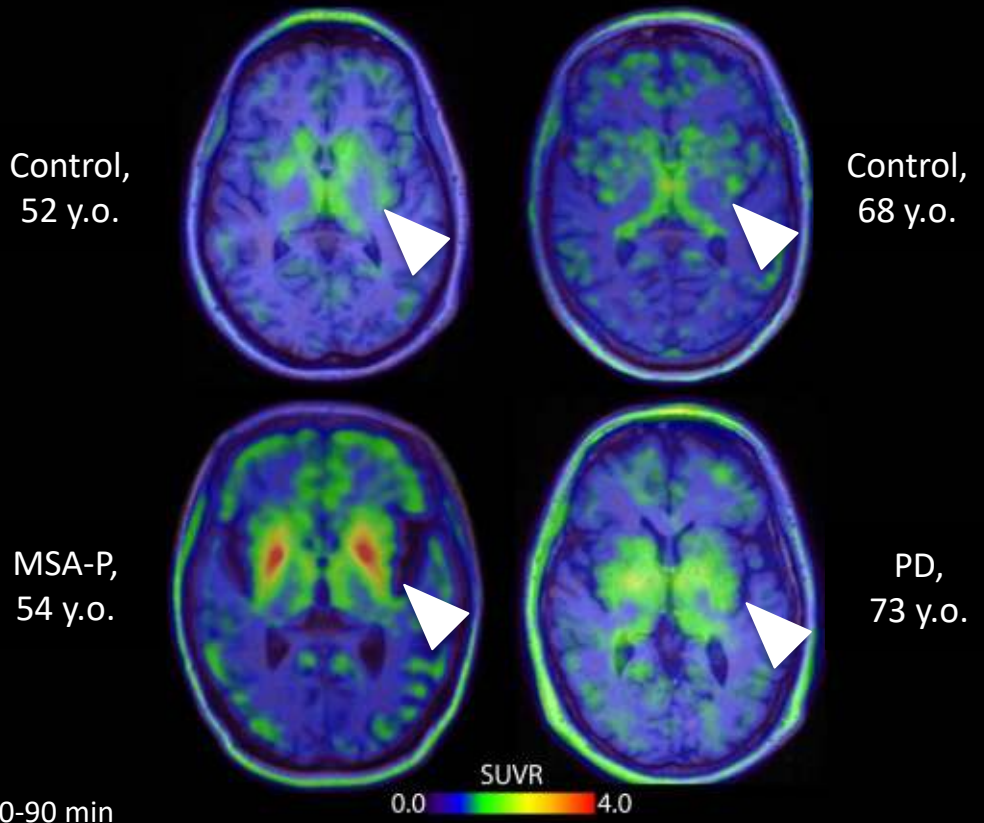
[18F]ACI-12589 uptake in MSA-P

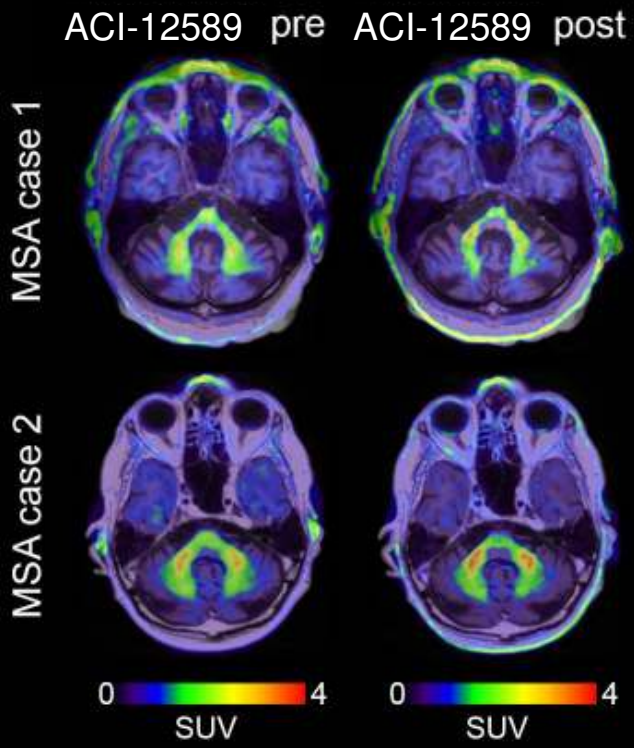


Strongest retention in basal ganglia of MSA-P cases

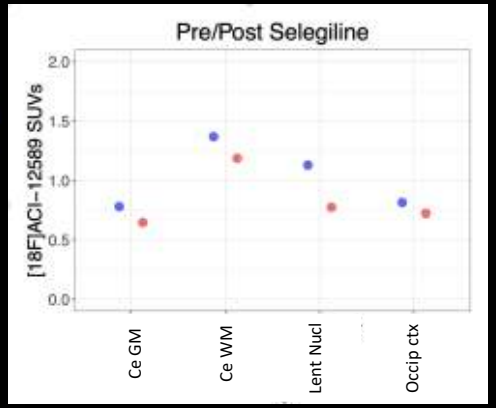
Retention observed in certain PD cases and to a lower extent in some controls

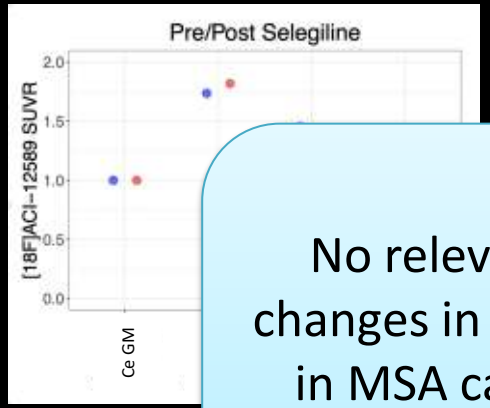
SUVRs 60-90 min
Occipital cortex as reference region

[18F]ACI-12589 signal in MSA is not due to MAO-B



Selegiline treatment (10mg)
6 days, mean values (n=6)

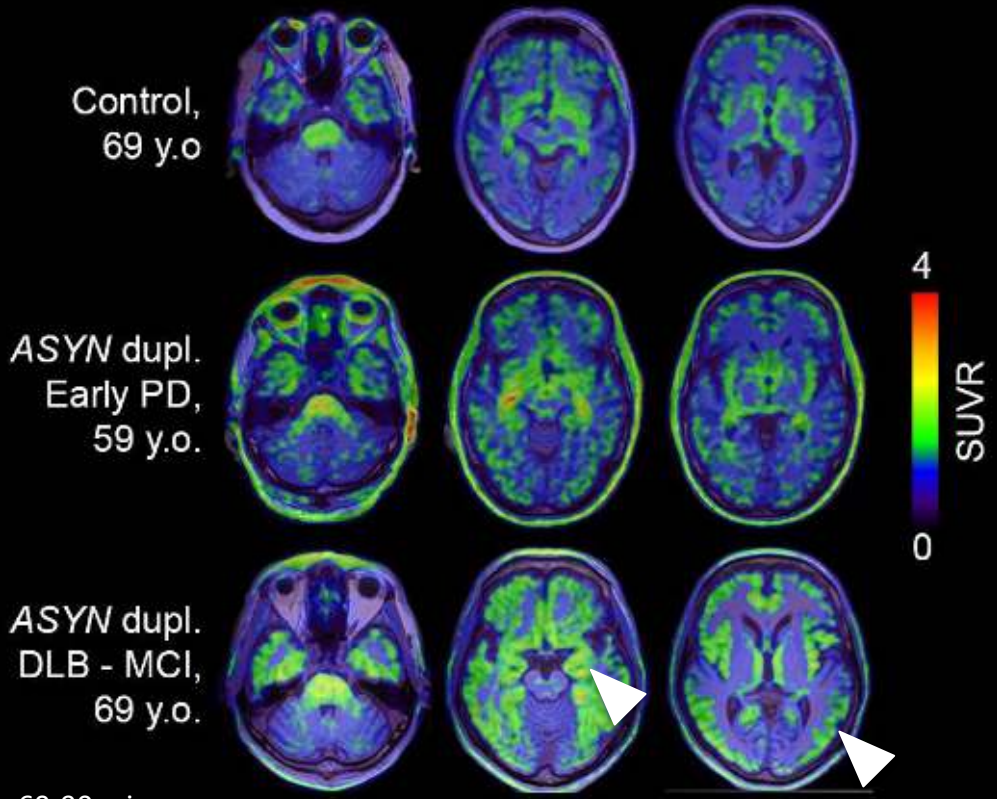




No relevant changes in signal in MSA cases after complete MAO-B blocking with Selegiline

Ce GM = Cerebellar grey matter; Ce WM = Cerebellar white matter; Lent Nucl = Lentiform nucleus; Occip ctx = Occipital cortex; SUV = Standardized Uptake Value; MAO-B = monoamineoxidase-B

[18F]ACI-12589 uptake in genetic PD cases



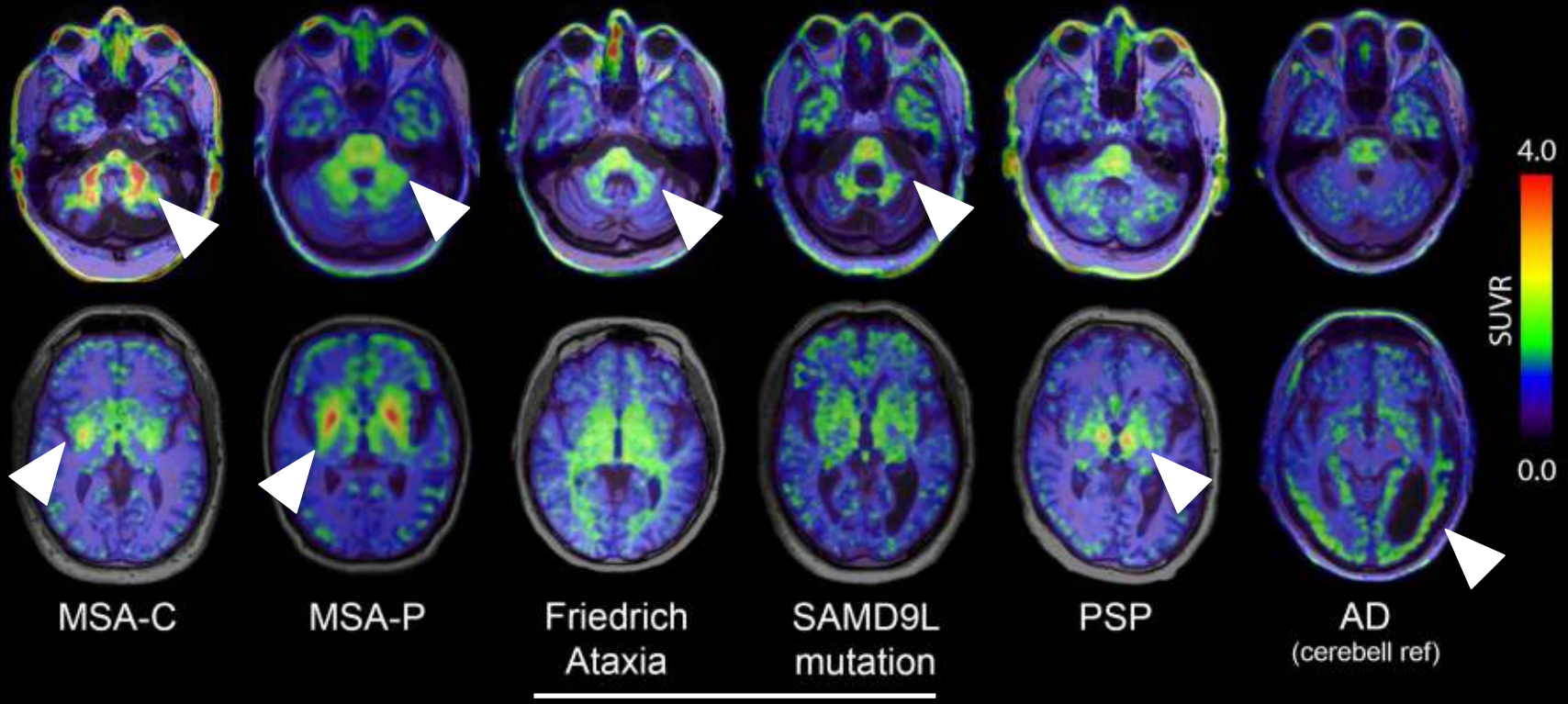
SUVRs 60-90 min
Cerebellar grey matter as reference region

Increased retention in disease-relevant brain regions in genetic PD cases

Signal increased in a late symptomatic case

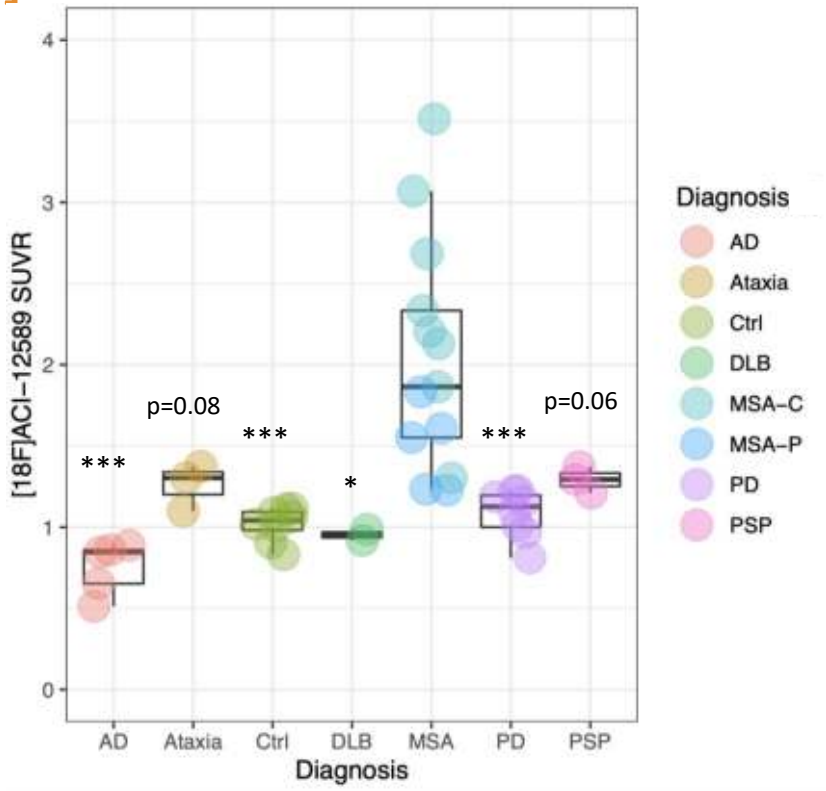
These data compatible with specificity of the signal for pathological α-syn

[18F]ACI-12589 in other neurodegenerative disorders



SUVRs 60-90 min
Occipital cortex used as reference region, except in the AD case where cerebellar cortex was used.
PSP and AD cases were negative in a CSF alpha-synuclein RT-QuIC assay (performed on CSF collected ~2-3 years prior to scans)

[18F]ACI-12589 retention in middle cerebellar peduncles



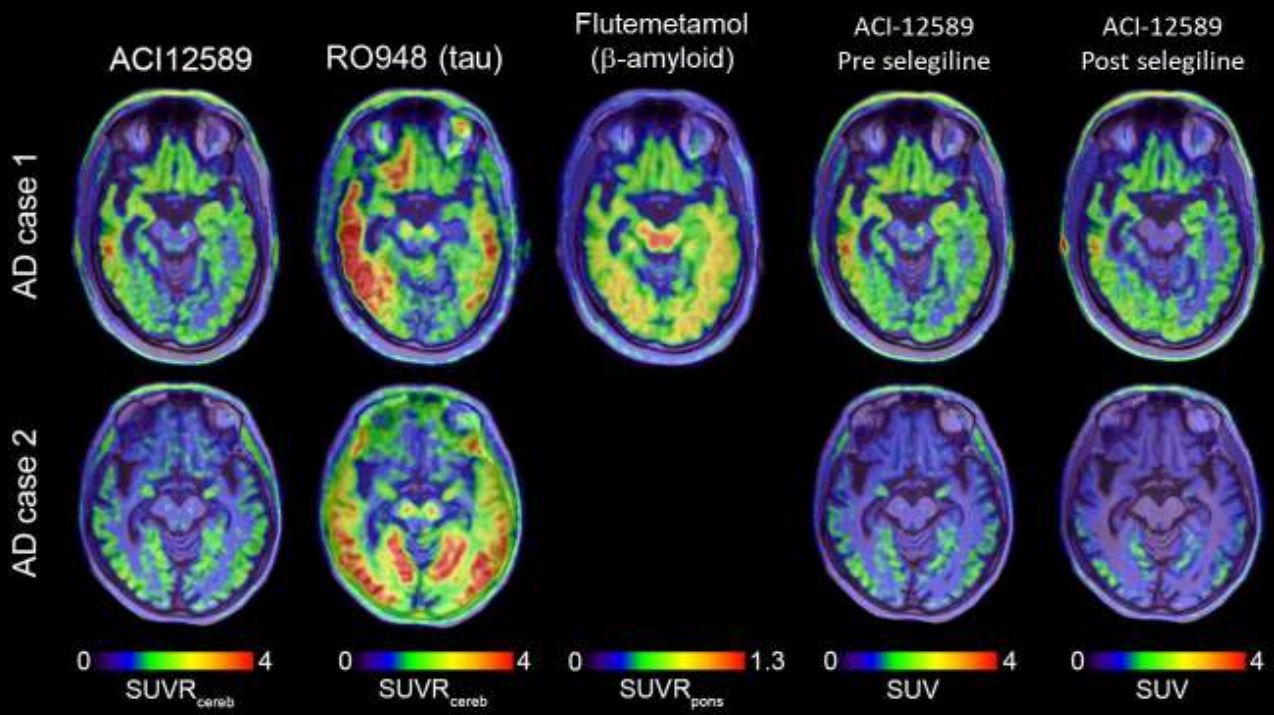
For MSA, signal retention in cerebellar peduncles is higher as compared to other neurodegenerative diseases and controls

Similar results were obtained in the cerebellar white matter

Occipital cortex used as reference region

Ataxia = two cases with Fredreich Ataxia and one with a SAMD9L mutation; Ctrl = Control; DLB = Dementia with Lewy Bodies; MSA-C = Multiple system atrophy – cerebellar phenotype; MSA-P = Multiple system atrophy – parkinsonian phenotype; PD = Parkinson's Disease; PSP = Progressive Supranuclear Palsy; SUVR = Standardized Uptake Value Ratio. Mann-Whitney U-tests ** $p<0.01$; * $p<0.05$. Statistical comparisons to MSA shown.

[18F]ACI-12589 uptake in AD cases



ACI-12589 retention in AD varies across different cases

The ACI-12589 retention overlaps to some degree with areas of high Tau PET signal but not to β-amyloid

No changes post MAO-B inhibition

AD cases were negative in a CSF alpha-synuclein RT-QuIC assay. CSF collected ~2-3 years prior to scans.

Conclusions

- [18F]ACI-12589 shows a rapid brain uptake and fast signal equilibrium allowing robust signal quantification within short imaging windows
- Strong binding was observed in disease-affected brain areas in MSA cases
- Similarly, retention was seen in genetic PD cases carrying an *ASYN* gene duplication
- Signal retention was also observed in some other neurodegenerative diseases, such as AD, PSP and hereditary ataxias
  - further investigations are needed to assess whether this is due to α-syn co-pathology and/or off-target binding
- In MSA, [18F] ACI-12589 retention is significantly higher in cerebellar peduncles and cerebellar white matter in comparison to other neurodegenerative diseases
- This suggests that [18F]ACI-12589 retention can be used to support an MSA diagnosis

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