Impact of reduced injected dose on the quantification of [^{18}F]RO948 and [^{18}F]Flortaucipir PET for *in vivo* tau pathology

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Background

- Previous research has demonstrated that the injected dose in PET examinations can be reduced without substantial effects on quantitative outcomes
- These reductions can lead to lower radiation burden for subjects, reduced costs for institutions and potential for additional research scans of the same subject
- Here, we investigated the effect of reduced injected doses of [^{18}F]RO948 and [^{18}F]Flortaucipir (FTP) on standardised uptake value ratios (SUVRs) and associated outcomes using a cohort of CN and CN + CI for RO948 and FTP respectively

Method

- Subjects were recruited from the H70 cohort in Sweden for the RO948 data and from the Berkeley Ageing Cohort study for the FTP data (see table for details)
- Images were manipulated to simulate injected doses of 7,5,4,3 and 2 mCi from an original injected dose of 10mCi
- List-mode data were edited to reduce counts and noise in images to accurately represent the simulated injected doses
- Inferior cerebellum-grey was used as a reference region to compute SUVRs in regions-of-interest (ROIs) corresponding to the *in vivo* Braak regions of tau spread
- Differences between true and reduced injected doses (given as a percentage) were calculated in individual regions as:

$$\frac{mean\,[SUVR_{reduced} - SUVR_{true}]}{mean\,[SUVR_{reduced} + SUVR_{true}]}$$

- Mann-Whitney U tests were performed to determine statistical differences between groups

Tracer	RO948	FTP	
Cohort	Gothenburg H70	BACS	UCSF MAC
Diagnosis	CN (32)	CN (52)	MCI/AD (15)
Age (y)	89.4	78.2	69.8
Sex (M/F)	19/13	19/33	8/7
MMSE	28.9	28.7	24.6
Amyloid Status (+/-)	4/14 (14 missing)	23/29	12/3
Scanner	Siemens Biograph mCT flow	Siemens Biograph Truepoint 6	
Scan length	20 minutes (70 minutes p.i.)	20 minutes (80 minutes p.i.)	
Original Injected Dose	10mCi (370MBq)		
Acquisition Type	Dynamic, list-mode		

Table 1: Demographics and acquisition parameters for subject cohorts
CN: cognitive normal, MCI: mild cognitive impairment, AD: Alzheimer's disease, BACS: Berkeley Ageing Cohort Study, UCSF MAC: University California San Francisco memory and ageing centre

Results

- RO948 subjects remained within previously found test-retest (TRT) rates of 6% to injected doses as low as 2mCi[1] (figure 2)
- FTP remains within TRT rates of 3.3% down to 5mCi injected dose but with increased variance[2] (Figure 2)
- At 5mCi, there is highly significant differences between cognitively normal (CN) and cognitively impaired (CI) groups in all Braak regions for FTP (figure 3)
- FTP CN subjects also exhibited significant differences when separated by amyloid status, suggesting early tau accumulation can also be differentiated at lower injected doses (figure 4)

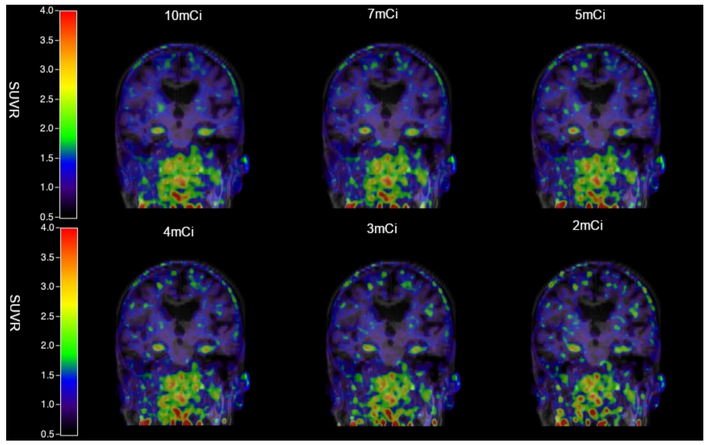

Figure 1 – Focal RO948 retention in a region corresponding to Braak I/II at different simulated injected doses

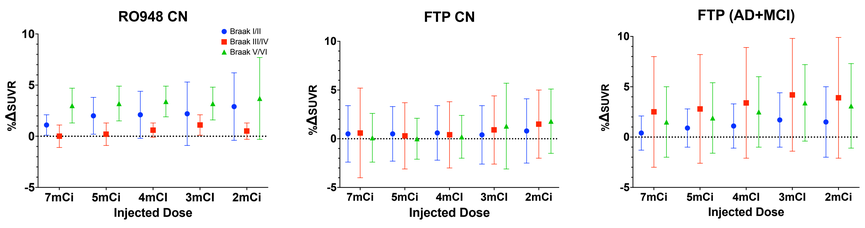

Figure 2 – Percentage change in SUVR compared to original injected dose for each simulated injected dose of RO948 and FTP in relevant ROIs

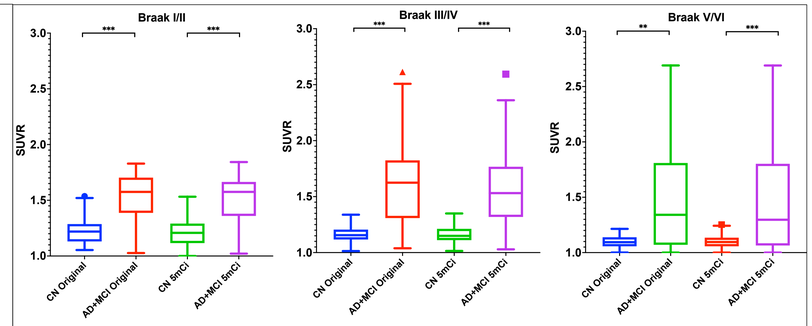

*Figure 3 – Comparisons of FTP CN and CI subjects for Braak regions at original injected dose and at 5mCi simulated injected dose (*** = p < 0.001, ** = p < 0.01)*

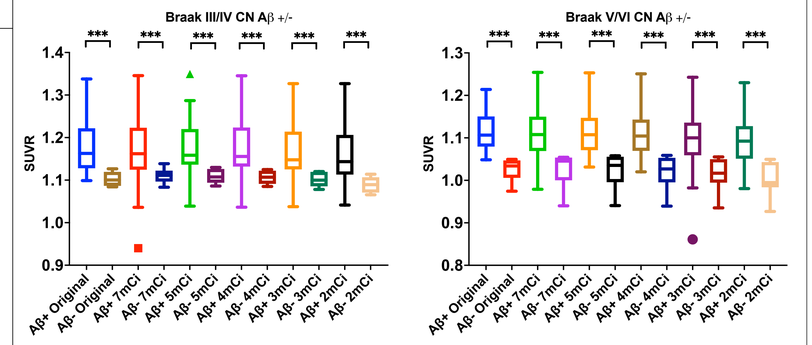

*Figure 4 – Comparisons of FTP amyloid positive and negative subjects at each injected dose level for Braak regions III/IV and V/VI (*** = p < 0.001)*

Conclusion

- A conservative reduction to 5mCi injected dose for FTP still generates robust SUVRs across demographics measured
- Within a CN cohort RO948 can be lowered to at least 5mCi injected dose also, however a cohort of CI subjects needs to be included to verify similar results
- Implications for reduced injected doses include:
  - Reduced dose to patients
  - Potential for more scans of same subject in research scans before reaching dose limit
  - Reduced costs to institutions and/or more scans from same tracer batch
- Ongoing work aims to include CI group for RO948, assess dose reduction in [^{18}F] GTP1, assess the limit of clinical utility and assess effects on longitudinal analysis

Summary

Flortaucipir and RO948 scans remain clinically useful with carefully selected reductions in injected dose

(1) Wong DF, Comley RA, Kuwabara H, Rosenberg PB, Resnick SM, Ostrowitzki S, et al. Characterization of 3 Novel Tau Radiopharmaceuticals, 11C-RO-963, 11C-RO-643, and 18F-RO-948, in Healthy Controls and in Alzheimer Subjects. J Nucl Med. 2018 Dec;59(12):1869–76.
(2) Devous MD, Joshi AD, Navitsky M, Southekal S, Pontecorvo MJ, Shen H, et al. Test–Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F 18. J Nucl Med. 2018 Jun 1;59(6):937–43.