

Group-level Regional Cerebral Uptake Quantification in Micro PET-CT

Christopher Leatherday (✉ chris.leatherday@health.wa.gov.au)

Health Technology Management Unit

Virginie Lam

Curtin University

Jan Boucek

Health Technology Management Unit

Liesl Celliers

Harry Perkins Institute of Medical Research

Short communication

Keywords: preclinical, uptake, quantification, PET

Posted Date: August 17th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-56116/v1>

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Abstract

The lack of soft tissue CT contrast is an impediment to accurate quantification of regional cerebral uptake on micro PET-CT. Co-registration to an atlas can aid with quantitative analysis, particularly when MRI is not available.

Methods: A subject CT is cropped to the skull, the brain void is then filled to create a “skull cavity mask”. An MRI mouse brain volumetric template is then co-registered to the skull cavity mask via affine transformation. Each subsequent subject CT is then skull cropped and co-registered to the first, these transformations are then applied to each corresponding PET for group level co-registration.

Results: The method was tested on eight mice with each possible registration permutation; resulting in small variations in regional cerebral PET counts.

Conclusion: We present a semi-automated method that allows for quantification of regional cerebral PET uptake from micro PET-CT images without subject MRI data.

Introduction

Small animal scanners such as CT or PET-CT may provide important anatomical information in preclinical research. However, it usually suffers from a lack of endogenous soft tissue contrast(1) due to design limits. Quantitation of radionuclide uptake in cerebral substructures is crucial in preclinical assessment of imaging agents for neurodegenerative disorders. Co-registration with a subject MRI may be used to identify regional cerebral uptake, however this is subject to scanner availability. The acquisition of high resolution MRI data for volumetric analysis is also time consuming(2). Existing methods for preclinical image registration may also require the use of specialised frames to ensure consistent body positioning(3).

We propose a semi-automated method for group level murine regional cerebral uptake quantification for micro PET-CT scans that utilises freely available software and requires no specialised co-registration hardware.

Methods

Subjects: Eight 12 month old mice were included in the study; (wild type controls (strain C57BL/6J, male), 6 double transgenic Alzheimer’s amyloidosis model (APP/PS1) (3 male)). All animal procedures were approved by the National Health Medical Research Council-accredited Curtin Animal Ethics Committee (approval no. 2016-25). The mice were intravenously administered 20 MBq of the amyloid tracer ¹⁸F-NAV4694 (NAV) before a 30 minute dynamic acquisition on a Sedecal SuperArgus BioPET/CT (4). Following uptake, each animal was anaesthetized with gaseous isoflurane (2%), eyes were protected with Lacri-Lube gel and placed into the PET scanner bed in a supine position and secured with tape. Respiration was monitored throughout the entire scan.

Co-registration: A T1 weighted MRI-based template (AMBMC)(5) was directly co-registered to a subject CT to allow for PET uptake quantification in various brain VOIs (basal ganglia, hippocampus, cerebellum, and cortex, divided into left and right hemispheres to make 8 VOIs in total). To achieve this inter-modality co-registration, a subject CT is first cropped to include only the skull and converted to a binary mask. The skull cavity is then manually filled in slice by slice in the axial plane using ImageJ(6) software, creating a skull cavity mask. The skull cavity mask, having the same approximate overall shape as the brain, is then used as a co-registration target for the T1 template; which is achieved via an affine transformation using FSL(7) software. This subject is termed the Primary Registration Subject (PRS).

Other subjects in the cohort are then co-registered to the PRS, effectively also co-registering them with the AMBMC template. This intra-modality registration is simpler to implement. Other subjects need only to be cropped to the skull and co-registered to the PRS via affine transformation, which is then applied to their corresponding PET. The result is that the T1 template and all other subjects are transformed into the native space of the PRS. The co-registration process is depicted schematically in Figure 1. Figure 2 shows an example of the AMBMC template co-registration process.

The T1 template is directly co-registered to the PRS. For all other subjects, there are two transformations involved (template to PRS and subject to PRS). This could potentially impact transformation accuracy, and therefore PET counts detected in a given VOI. All possible co-registration permutations, with each subject acting in turn as the PRS, were tested for this cohort to determine if the choice of PRS had an effect on co-registration accuracy or detected PET counts.

Results

Impact of Primary Registration Subject Choice on AMBMC Template Co-registration Accuracy: This method has the greatest utility if any single subject CT can be used to create a skull cavity mask and act as the PRS for the AMBMC template.

The dice coefficient(8) was used to determine if co-registration accuracy was impacted by the choice of PRS. The gold standard for a given subject was the average dice coefficient for the 8 AMBMC VOIs after affine transformation to that subject's skull cavity mask, and inverse transformation back to the template space; this shows how much overlap is lost due a single registration step and interpolation factors. This was compared to the dice coefficients from a set of indirect forward and inverse transforms for all permutations where another subject in the cohort was used as the PRS. Equation 1 shows the calculation.

$$\text{Dice Coefficient} = \frac{2A}{A+B} \dots \text{(eq 1)}$$

Where A is the number of voxels in a VOI, and B is the number of voxels overlapping between the original VOI and itself after forward and inverse transformation.

The average dice coefficient for a direct registration (where a subject is used as the PRS) was 0.975; the average for all indirect registration permutations was 0.945. Figure 3 demonstrates the distribution of dice coefficients across all registration permutations.

Impact of Primary Registration Subject Choice on Cerebral PET Uptake Assessment: Uptake quantification within each AMBMC VOI for each subject was assessed for all of the registration permutations to determine if the choice of primary registration subject had an impact on the counts measured. Figure 4 shows these results. Table 1 shows the maximum, minimum, and average percentage deviation in PET counts for each VOI.

TABLE 1: Percentage deviation in PET counts between indirect and direct co-registration

VOI	% Deviation Min / Max / Ave
Hippocampus L	0.014 / 2.943 / 0.782
Hippocampus R	0.003 / 1.830 / 0.638
Basal Ganglia L	0.004 / 2.468 / 0.803
Basal Ganglia R	0.001 / 2.796 / 0.889
Cortex L	0.019 / 4.564 / 1.089
Cortex R	0.006 / 3.625 / 0.800
Cerebellum L	0.036 / 2.965 / 0.728
Cerebellum R	0.012 / 3.289 / 0.792

Discussion

Micro-CT provides important structural information for preclinical studies when combined with PET, but its lack of soft tissue contrast can be problematic for the quantification of cerebral PET uptake. By co-registering a murine brain template to a subject PET/CT image, quantification of uptake within cerebral VOIs is possible.

This method shows that quantification of cerebral PET tracer uptake in a large cohort of mice can be achieved by directly co-registering a T1 brain template to a randomly selected PRS, then co-registering each of the other subject CTs to the PRS (therefore also indirectly co-registering each of them to the template). Indirect co-registration does come with a small penalty in registration accuracy as defined by the dice coefficient, with a reduction from an average of 0.975 for direct co-registration to 0.945 for indirect. PET uptake quantification within a given AMBMC cerebral substructure changed by a maximum of 4.56% when compared to direct co-registration, with an average percentage change of 0.82%.

This method does not take into account variations in the size and location of cerebral substructures for a given subject. Previous studies have suggested that this variation amongst healthy mice is only on the order of 5 percent(9); however this is increased in certain substructures of transgenic Alzheimer's models(10). The ability of the method to accurately quantify tracer uptake in individual cerebral substructures could be further assessed by acquiring high resolution volumetric MRI data for each subject in a cohort and manually defining the structures for comparison.

Conclusion

This method allows for PET tracer uptake quantification in cerebral substructures of a large cohort of mice from PET-CT data alone; requiring minimal manual input and computational power, no specialised hardware, and software that is freely available.

Abbreviations

AMBMC: Australian Mouse Brain Mapping Consortium

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

PET: Positron Emission Tomography

PRS: Primary registration subject

VOI: Volume of Interest

Declarations

Ethics approval and consent to participate

All animal procedures were approved by the National Health Medical Research Council-accredited Curtin Animal Ethics Committee (approval no. 2016-25).

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was completed with funding aid from the National Health and Medical Research Council and the Western Australian Department of Health.

Authors' contributions

LC and VL designed the research and helped execute data collection. JB aided with data collection and processing, and research design. CL aided with data collection, performed the final analysis and collation, and authored the manuscript draft. All authors read and approved the final manuscript.

Acknowledgements

NAV was produced with help from Rainer Scharli from the Australian Cancer Research Foundation Cancer Imaging Facility (CIF) and Laurence Morandau from the Radiopharmaceutical Production & Development Laboratory (RAPID). Professor John Mamo and Associate Professor Ryusuke Takechi from the Curtin Health Innovation Research Institute are acknowledged for their contributions towards securing funding and providing mentoring.

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Figures

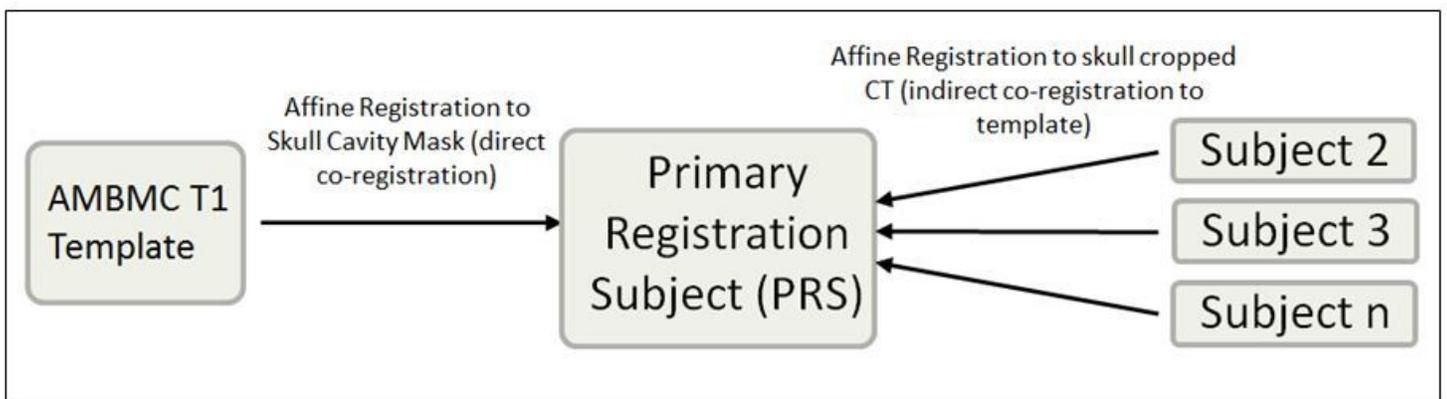


Figure 1

A schematic representation of the co-registration process. The T1 brain template is co-registered directly to the primary registration subject (PRS) skull cavity mask; each other subject CT is skull-cropped and also co-registered to the PRS.

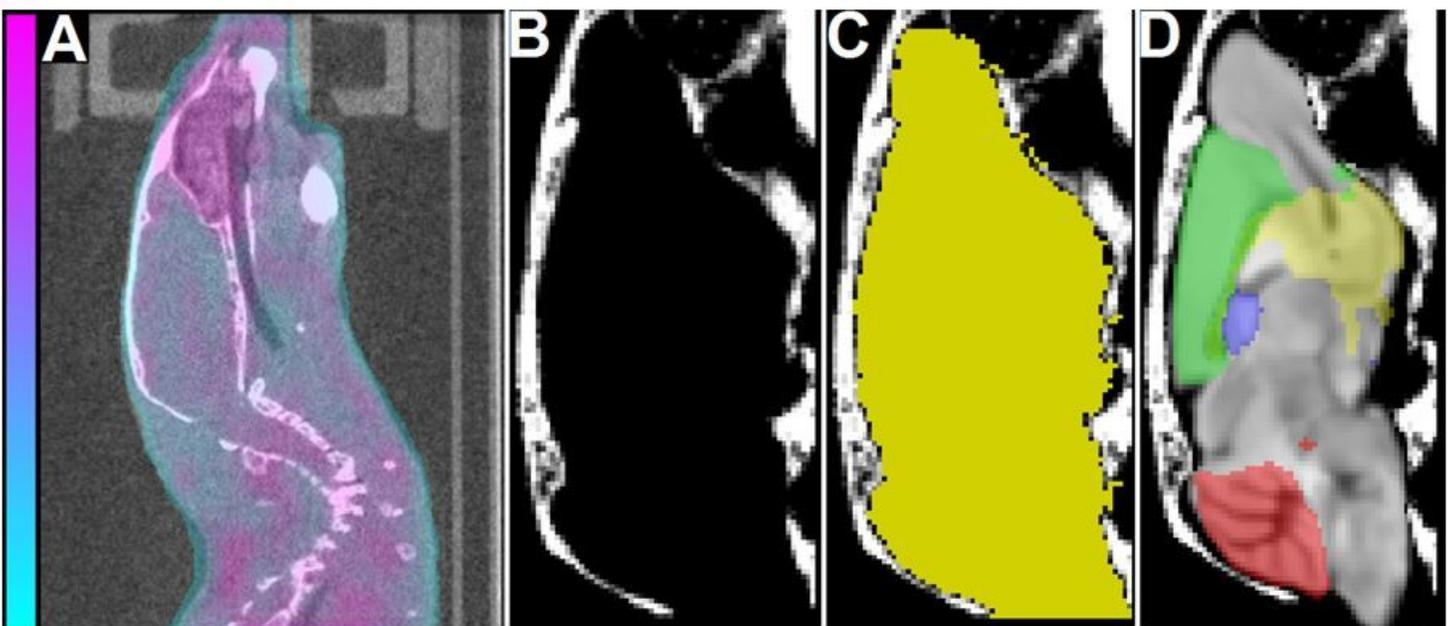


Figure 2

(A) A sagittal slice of a subject PET-CT image. (B) The subject CT after skull cropping. (C) Skull cavity mask shown in yellow inside the subject CT. (D) The AMBMC T1 template after co-registration to the skull cavity mask, overlaid on the subject skull cropped CT. Cerebellum (red), cortex (green), hippocampus (blue), and basal ganglia (yellow) VOIs are highlighted.

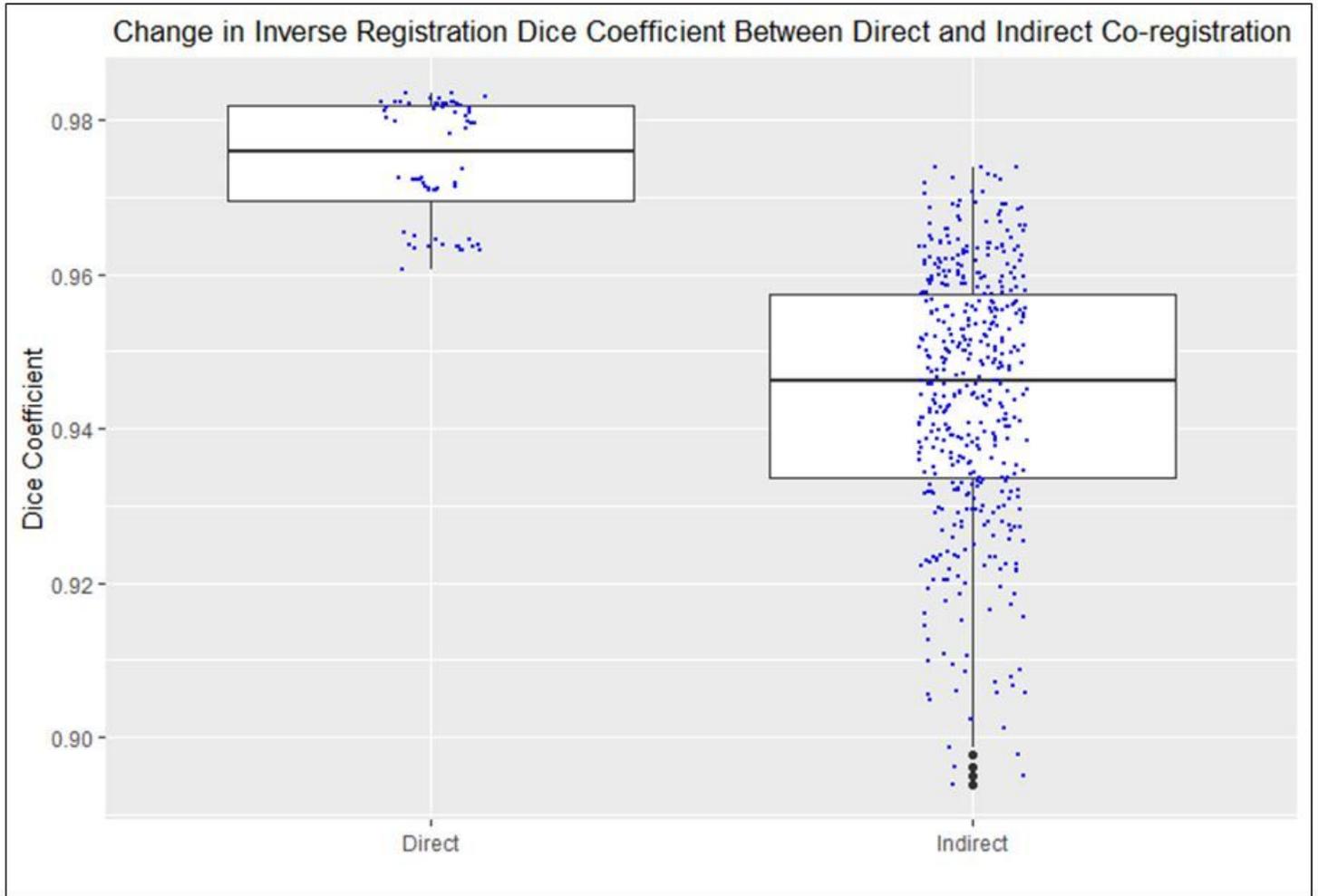


Figure 3

Dice coefficients for each AMBMC VOI after applying forward and inverse transformations for direct and indirect co-registration to each subject.

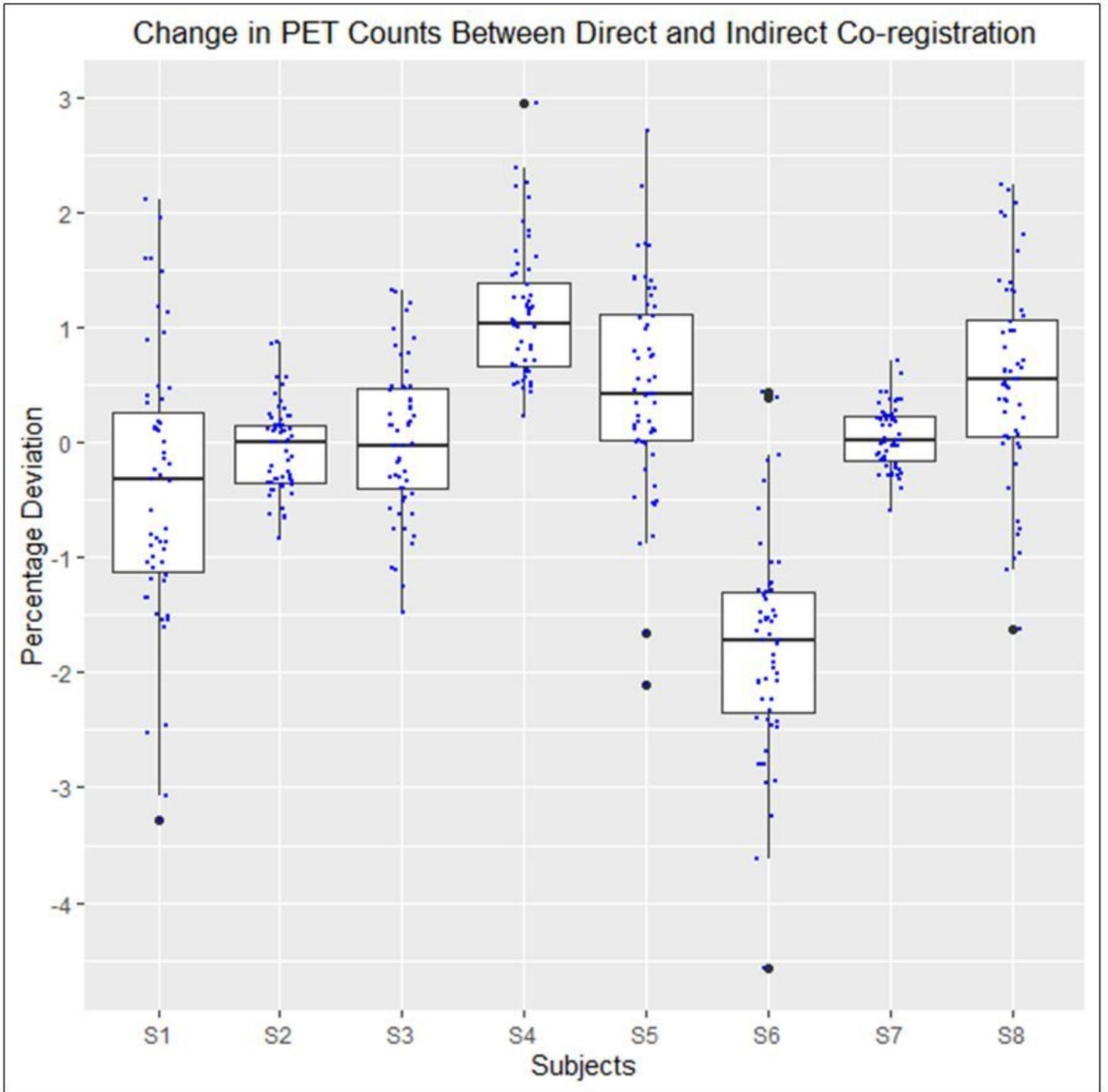


Figure 4

Average percentage deviation in PET counts detected in each VOI for each subject between direct and indirect co-registration.