PET is Wonderful 2025
Edinburgh

Containerizing preprocessing tools for clinical PET

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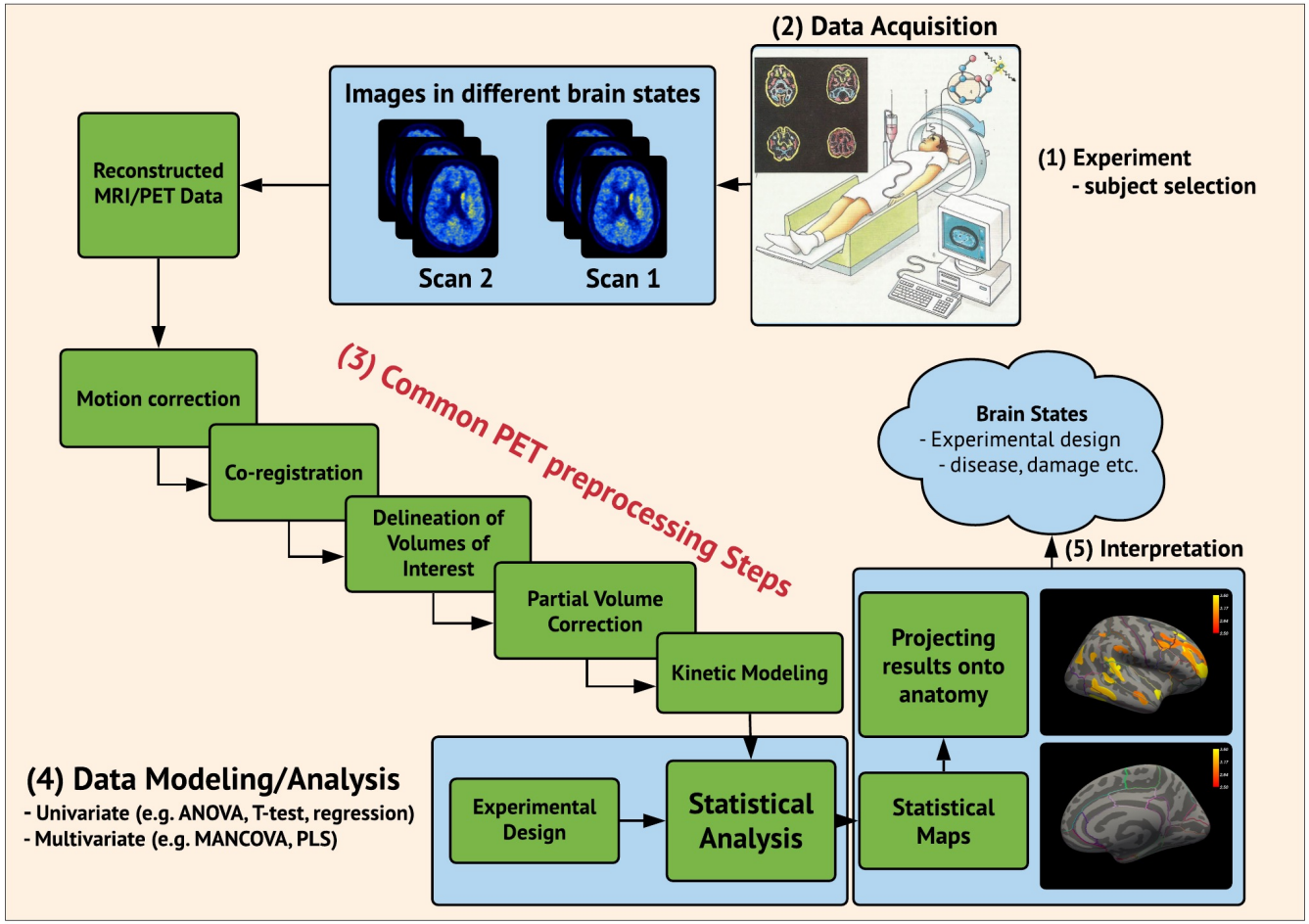
UNIVERSITY OF COPENHAGEN

Agenda

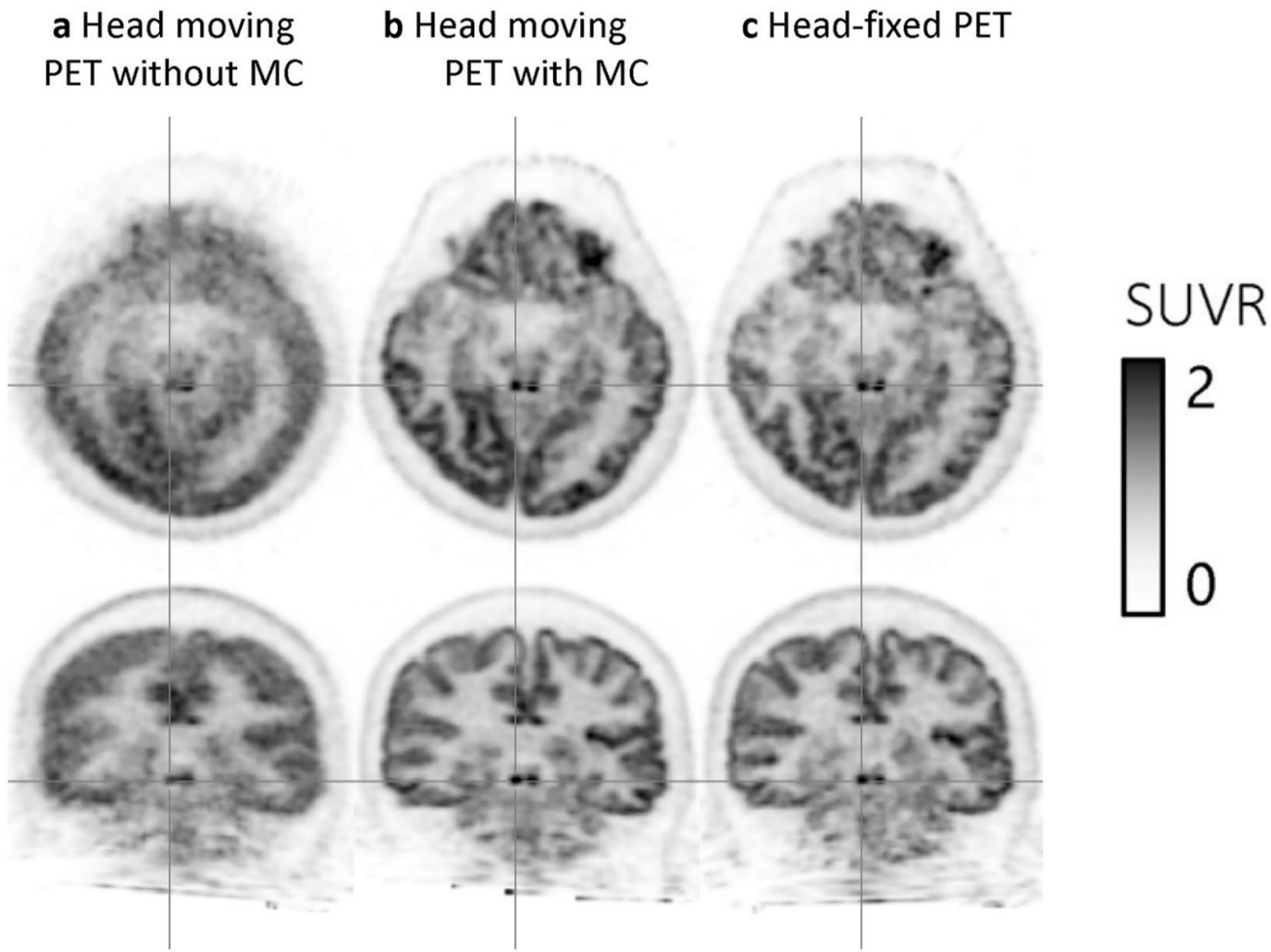
- Background and rationale for doing preprocessing
- Containerizing preprocessing tools to improve reproducibility

Common PET workflow

Norgaard et al. 2019, Neuroimage 199, 466-479.



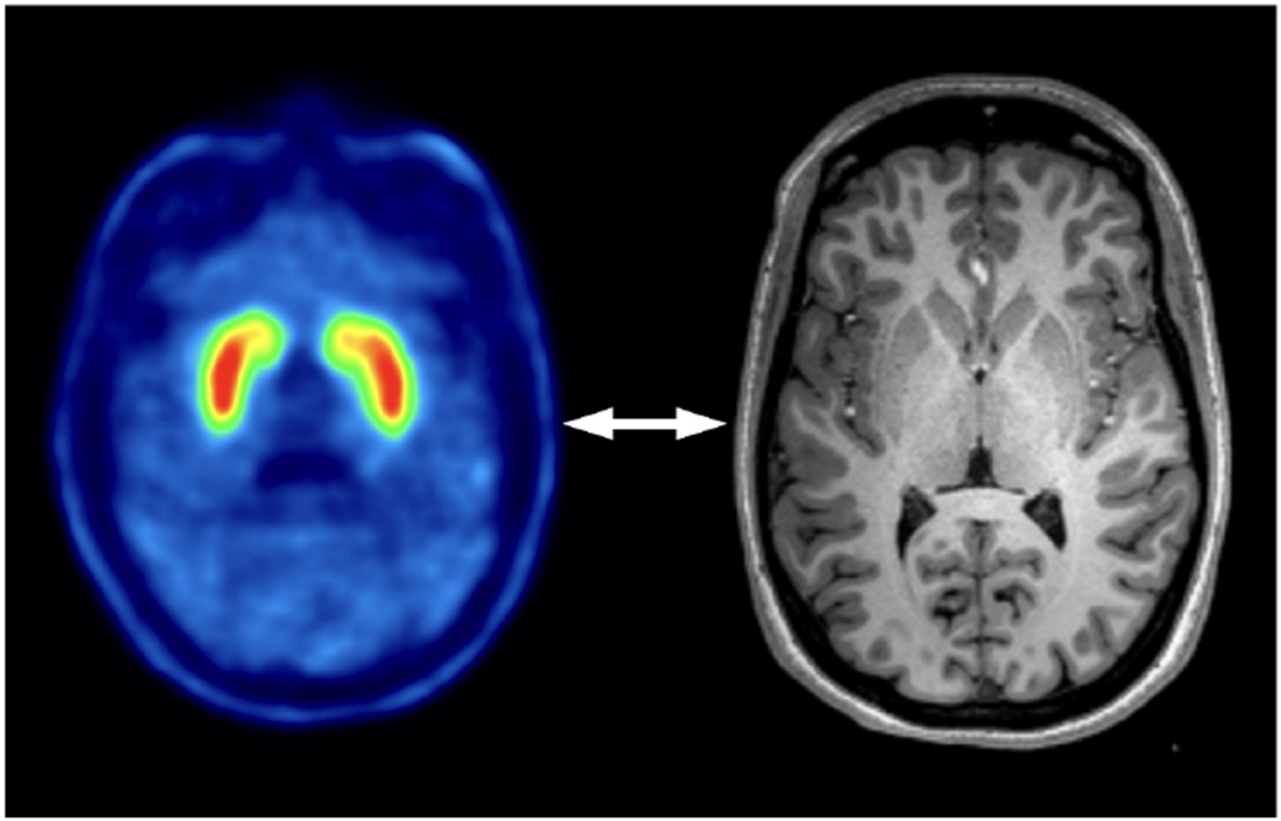
- Head motion renders PET data disturbed or even useless (Green et al. 1994).
- However, in the absence motion, motion correction may underestimate the true underlying signal (Orchard and Atkins 2003).



Iwao, Y., Akamatsu, G., Tashima, H. et al. Brain PET motion correction using 3D face-shape model: the first clinical study. Ann Nucl Med 36, 904–912 (2022).

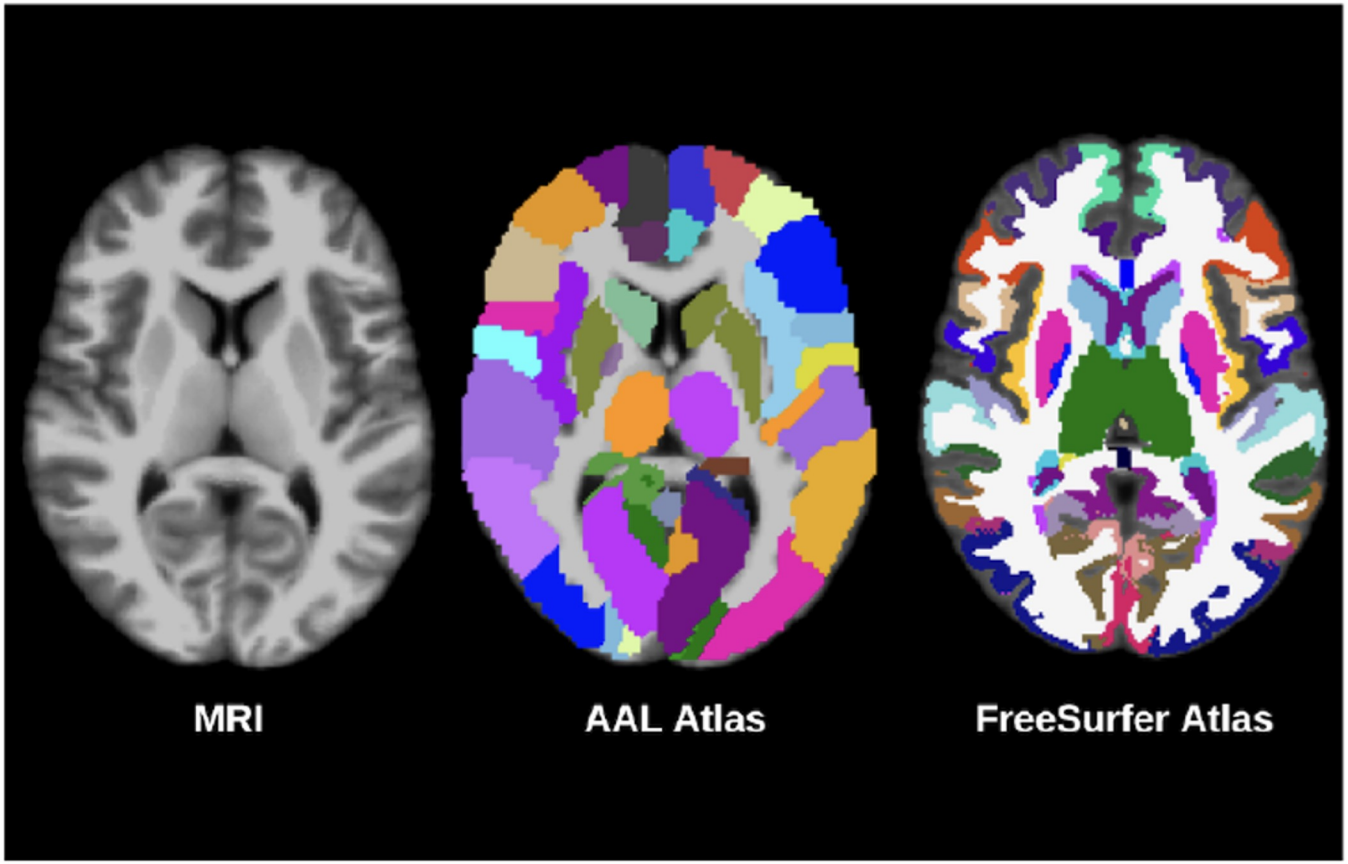
Co-registration

- A precise co-registration is needed, as voxels that move across tissue boundaries are prone to extreme signal changes (Schwarz et al. 2017).
- Resampling with spatial interpolation is carried out because PET and MRI have different resolutions, potentially biasing the signal (Strother 2004).



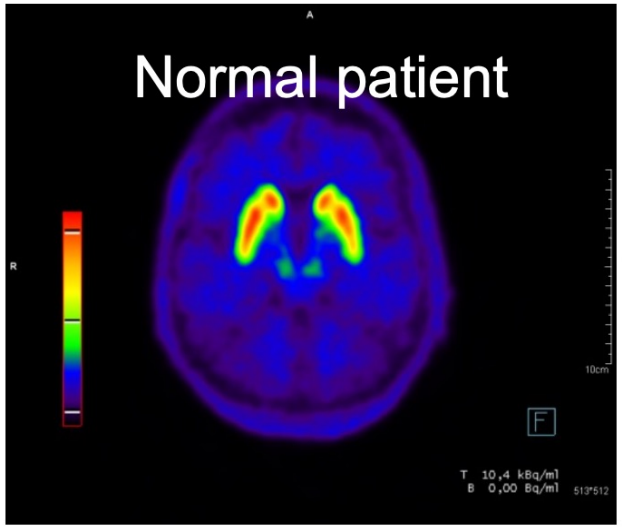
Delineation of volumes of interest

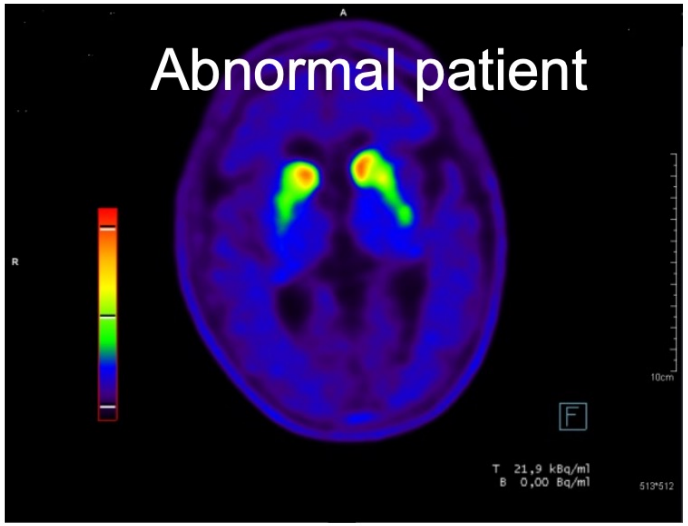
- PET studies are often interested in drawing inferences about specific anatomical brain structures.
- Different definitions of the same region may vary in size, location and delineation technique.

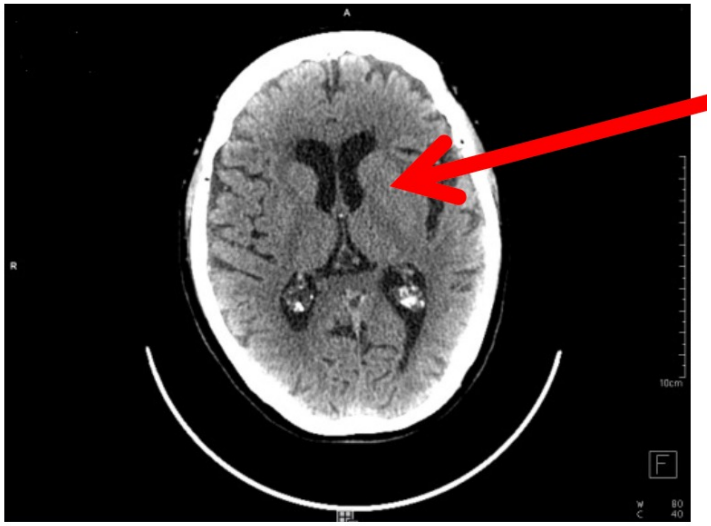


Delineation of volumes of interest

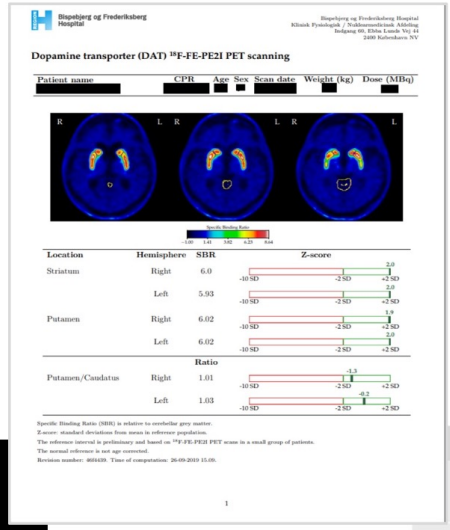
- PE2I visualizes the dopamine transporter in striatum in patients with suspected Parkinson's disease
- Quantitative metrics an important part of the diagnostic workup







Delineation of volumes of interest



Bispebjerg og Frederiksberg Hospital

Bispebjerg og Frederiksberg Hospital
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Indgang 60, Ebba Lunds Vej 44
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Dopamine transporter (DAT) ^{18}F-FE-PE2I PET scanning

Patient name	CPR	Age	Sex	Scan date	Weight (kg)	Dose (MBq)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

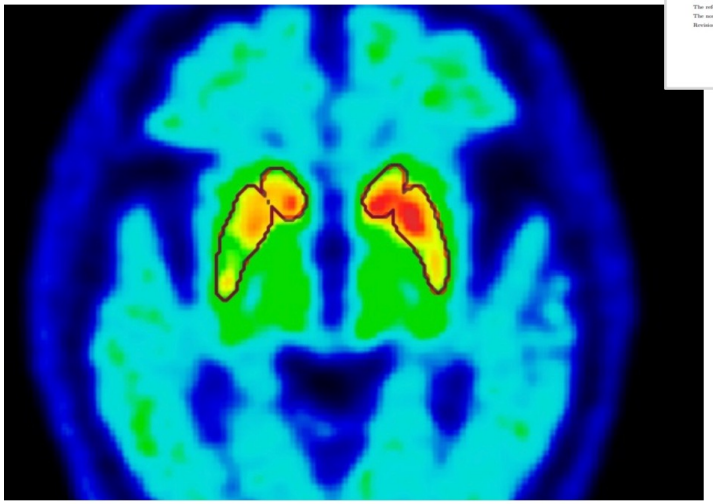
R L R L R L

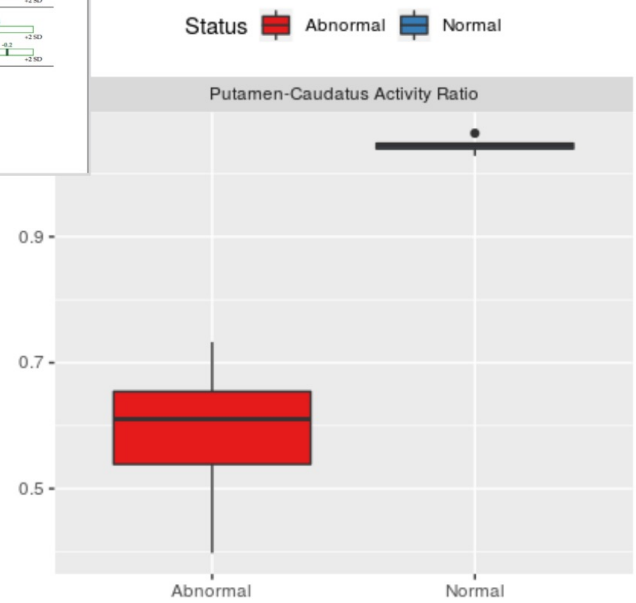
Specific Binding Ratio
-1.00 -1.41 -1.82 -4.23 8.64

Location	Hemisphere	SBR	Z-score
Striatum	Right	6.0	2.0 (-10 SD, -2 SD, +2 SD)
	Left	5.93	2.0 (-10 SD, -2 SD, +2 SD)
Putamen	Right	6.02	1.9 (-10 SD, -2 SD, +2 SD)
	Left	6.02	2.0 (-10 SD, -2 SD, +2 SD)
		Ratio	
Putamen/Caudatus	Right	1.01	-1.3 (-10 SD, -2 SD, +2 SD)
	Left	1.03	-0.2 (-10 SD, -2 SD, +2 SD)

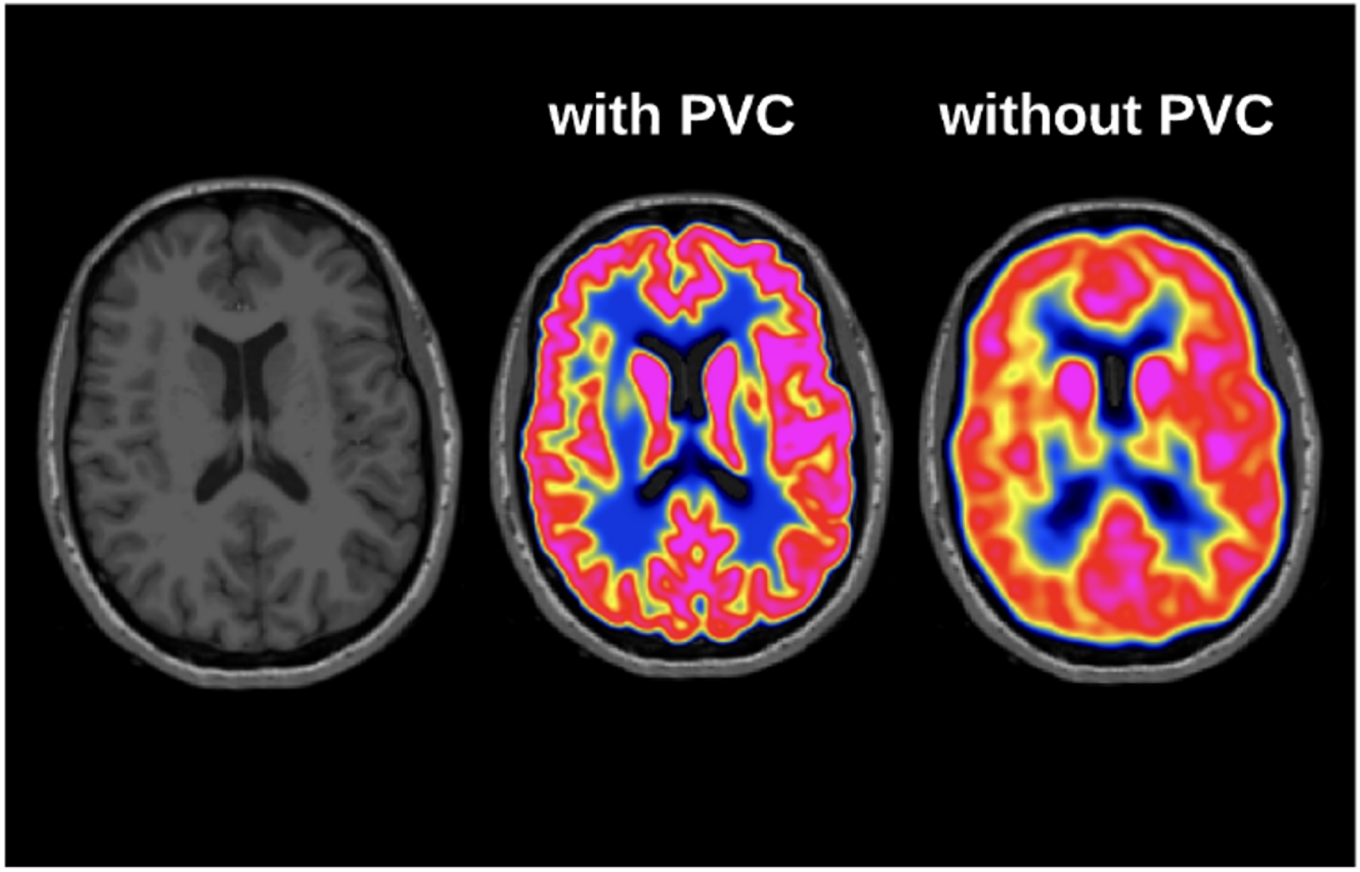
Specific Binding Ratio (SBR) is relative to cerebellar grey matter.
Z-score: standard deviations from mean in reference population.
The reference interval is preliminary and based on ^{18}F-FE-PE2I PET scans in a small group of patients.
The normal reference is not age corrected.
Revision number: 4664439. Time of computation: 26-09-2019 15.09.

1



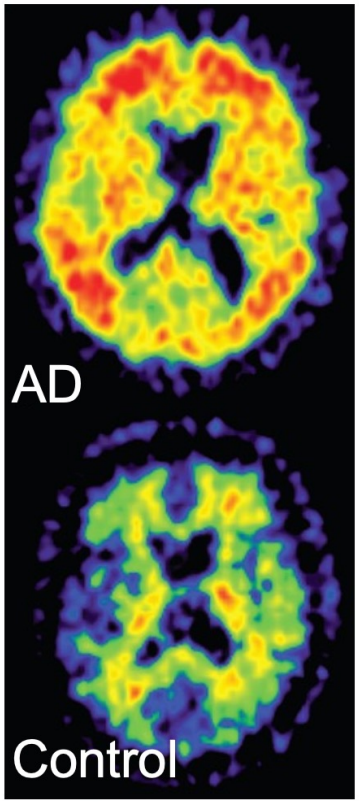


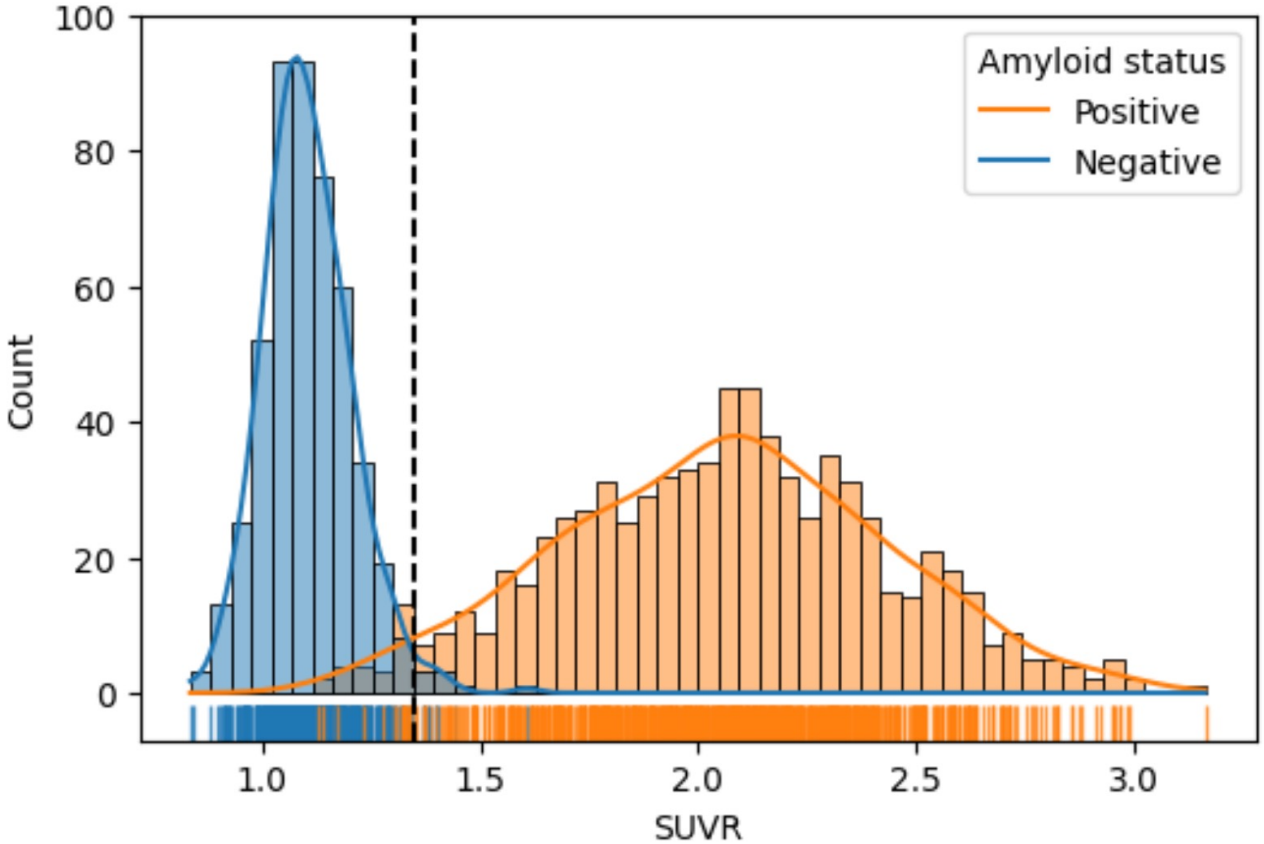
Partial Volume Correction (PVC)



- Prerequisite in cases where brain anatomy may interact with an effect of interest (e.g. age or diagnosis).
- However, it may also cause noise amplification (Rousset 2007), and reflect differences in anatomy and not true radioligand uptake (Greve 2016).

Amyloid status with [11C]PiB





So now we know what preprocessing of PET data is

but we still don’t know how to carry it out

Kinetic evaluation and test–retest reproducibility of [^{11}C]UCB-J, a novel radioligand for positron emission tomography imaging of synaptic vesicle glycoprotein 2A in humans

Journal of Cerebral Blood Flow & Metabolism
2018, Vol. 38(11) 2041–2052
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DOI: 10.1177/0271678X17724947
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Sjoerd J Finnema[1], Nabeel B Nabulsi[1], Joël Mercier[2], Shu-fei Lin[1], Ming-Kai Chen[1], David Matuskey[1], Jean-Dominique Gallezot[1], Shannan Henry[1], Jonas Hannestad[2], Yiyun Huang[1] and Richard E Carson[1,3]

An average PET image (mean of the frames corresponding to 0–10 min) was aligned to each subject's MR image via a rigid registration with mutual information. The individual MR image was normalized to Montreal Neurological Institute space using an affine linear plus nonlinear registration (BioImage Suite 2.5), to extract regions-of-interest (ROIs) from the automated anatomic labeling (AAL) template.[28,29] Regional time–activity curves were obtained by applying the template ROIs to PET space using the inverse of the two image-transformations (i.e. PET-to-MRI and MR-to-template). The following AAL regions were included: amygdala, anterior cingulate cortex, caudate nucleus, cerebellum, frontal cortex, globus pallidus, hippocampus, insular cortex, occipital cortex, parietal cortex, posterior cingulate cortex, putamen, temporal cortex and thalamus. The ROI for the centrum semiovale was based on the AAL region but was eroded by two voxels on all borders to minimize partial volume effects.

Software
MC: ?
Reg: BioImage Suite
Regions: AAL
KinMod: in-house (IH)

%SE less than 25%. Parametric images for the 1T model were created with a basis function method with k_2 limited to the range (0.01–1.0 min^{-1}) and with no post-smoothing. All modeling was performed with in-house programs written within IDL 8.0 (ITT Visual Information Solutions, Boulder, CO, USA).

Kinetics and 28-day test–retest repeatability and reproducibility of [^{11}C]UCB-J PET brain imaging

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Hayel Tuncel[1], Ronald Boellaard[1], Emma M Coomans[1], Erik FJ de Vries[2], Andor WJM Glaudemans[2], Paula Kopschina Feltes[2], David V García[2], Sander CJ Verfaillie[1], Emma E Wolters[1,3], Steven P Sweeney[4], J Michael Ryan[4], Magnus Ivarsson[4], Berkley A Lynch[4], Patrick Schober[5], Philip Scheltens[3], Robert C Schuit[1], Albert D Windhorst[1], Peter P De Deyn[6,7], Bart NM van Berckel[1] and Sandeep SV Golla[1]

Data analysis

Structural 3D T1-weighted MRI images were co-registered to the PET images using Vinci v 2.56 software. The Hammers template,[23] which is incorporated in PVElab,[24] was used to delineate regions of interest (ROIs) on the co-registered MR scan and superimposed onto the dynamic PET scan to obtain regional time-activity curves (TACs). Online arterial blood TACs were calibrated and corrected for plasma to whole blood ratios, radiolabeled metabolites and delay, using the information from manual blood samples. Eventually, individual metabolite-corrected plasma input functions were generated. Various compartmental models[25] were used to fit the regional TACs: single tissue reversible (1T2k) and two-tissue comparing SRTM-derived binding potential (BP_{ND}) with plasma input derived distribution volume ratio (DVR). The white-matter centrum semi-ovale (SO) was manually defined using an in-house built tool and was considered as a reference region. Mean SO VOI size was 5.4 ± 2.5 cc for HCs and 4.0 ± 2.6 cc for AD patients. SUVr using three time intervals (40–60, 50–60 for both groups; and 70–90 min only for HCs) were also evaluated. SUVr values obtained from these time intervals were compared with corresponding plasma input derived DVR values.

Software
MC: no MC
Reg: Vinci
Regions: PVElab / IH
KinMod: in-house

Is there a problem?

Scanning the horizon: towards transparent and reproducible neuroimaging research

Russell A. Poldrack[1], Chris I. Baker[2], Joke Durnez[1,3], Krzysztof J. Gorgolewski[1], Paul M. Matthews[4], Marcus R. Munafò[5,6], Thomas E. Nichols[7], Jean-Baptiste Poline[8], Edward Vul[9] and Tal Yarkoni[10]

Abstract | Functional neuroimaging techniques have transformed our ability to probe the neurobiological basis of behaviour and are increasingly being applied by the wider neuroscience community. However, concerns have recently been raised that the conclusions that are drawn from some human neuroimaging studies are either spurious or not generalizable. Problems such as low statistical power, flexibility in data analysis, software errors and a lack of direct replication apply to many fields, but perhaps particularly to functional MRI. Here, we discuss these problems, outline current and suggested best practices, and describe how we think the field should evolve to produce the most meaningful and reliable answers to neuroscientific questions.

Poldrack et al. 2017, Nature Reviews Neuroscience 18, 115-126.

Step 1: Preprocessing choices in the PET literature

Review Article

JCBFM

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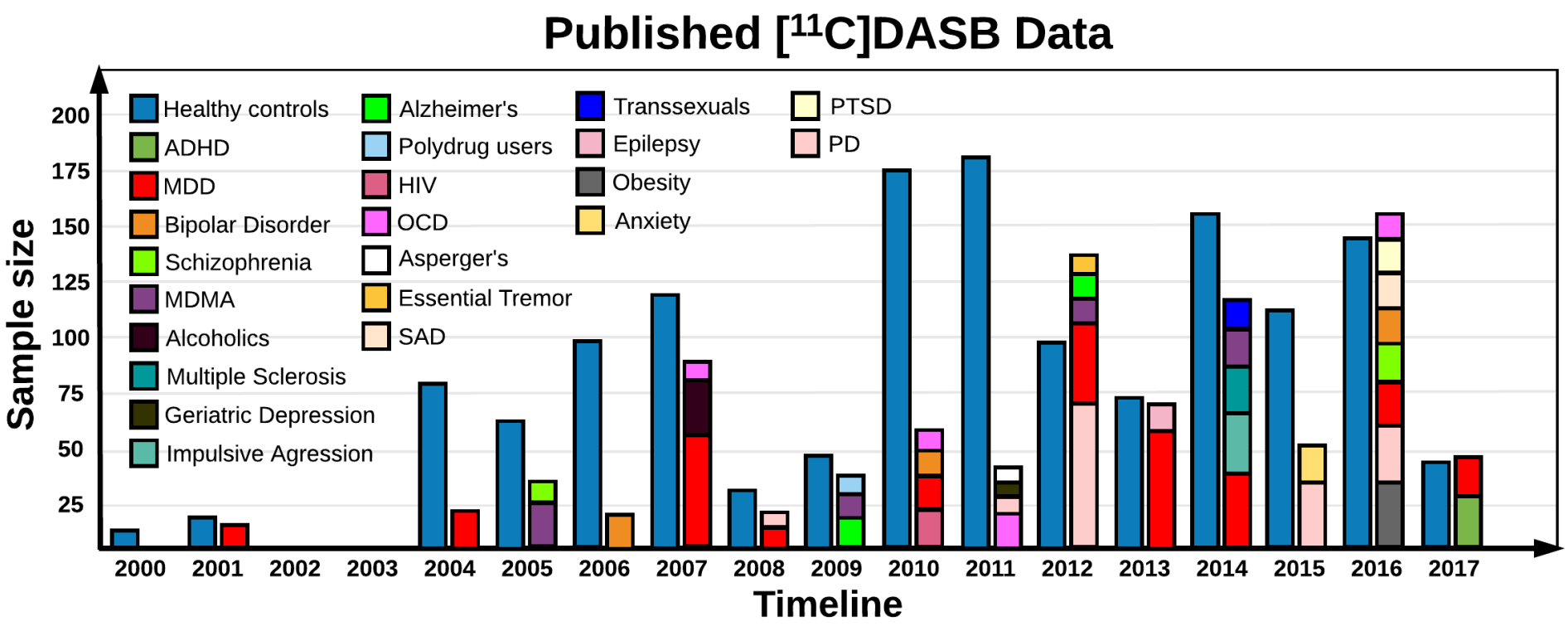
Cerebral serotonin transporter measurements with [^{11}C]DASB: A review on acquisition and preprocessing across 21 PET centres

Martin Nørgaard[1,2], Melanie Ganz[1,3], Claus Svarer[1], Ling Feng[1], Masanori Ichise[4], Rupert Lanzenberger[5], Mark Lubberink[6], Ramin V Parsey[7], Marios Politis[8], Eugenii A Rabiner[9,10], Mark Slifstein[7], Vesna Sossi[11], Tetsuya Suhara[4], Peter S Talbot[12], Federico Turkheimer[13], Stephen C Strother[14] and Gitte M Knudsen[1,2]

Step 1: Preprocessing choices in the PET literature

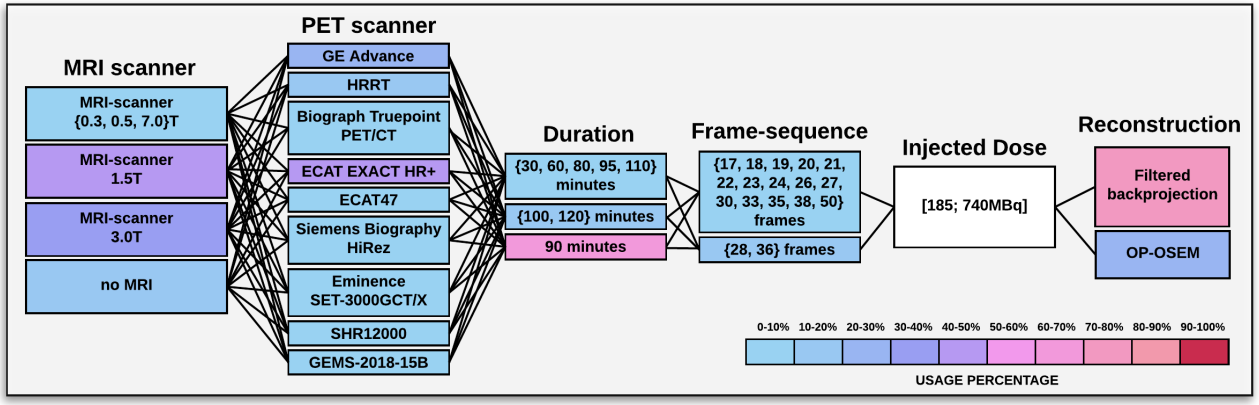


1850 controls acquired over 17 years

Norgaard et al. 2018, JCBFM

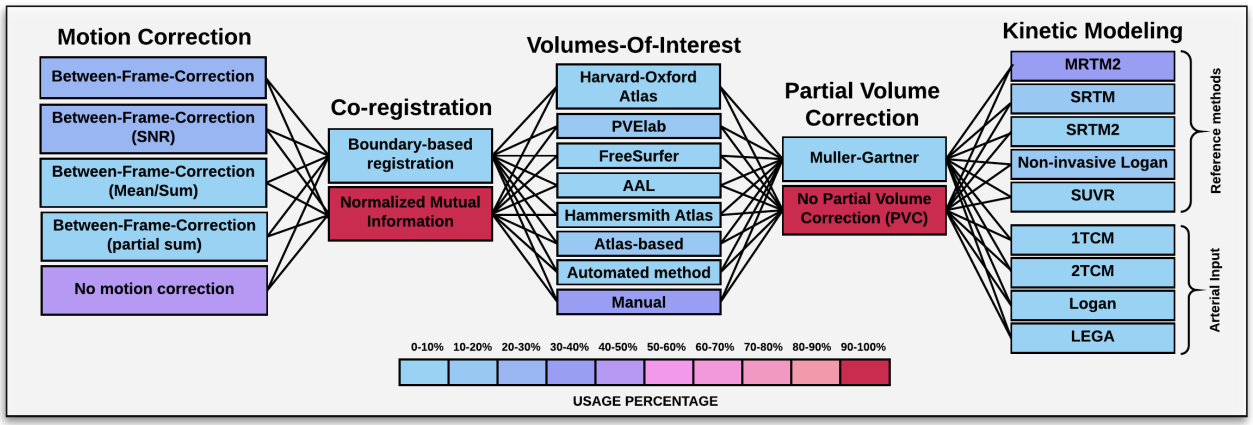
Data acquisition workflow

Norgaard et al. 2018, JCBFM



40% of studies leave out motion correction!

Preprocessing workflow



<u>Combinations in total? 21.150.720 different workflows!</u>

Step 2: Evaluate the variability in within-center data

Original Article

JCBFM
Journal of Cerebral Blood Flow & Metabolism
2020, Vol. 40(9) 1902–1911
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DOI: 10.1177/0271678X19880450
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Different preprocessing strategies lead to different conclusions: A [^{11}C]DASB-PET reproducibility study

Martin Nørgaard[1,2], Melanie Ganz[1,3], Claus Svarer[1], Vibe G Frokjaer[1], Douglas N Greve[4], Stephen C Strother[5] and Gitte M Knudsen[1,2]

Abstract

Positron emission tomography (PET) neuroimaging provides unique possibilities to study biological processes in vivo under basal and interventional conditions. For quantification of PET data, researchers commonly apply different arrays of sequential data analytic methods ("preprocessing pipeline"), but it is often unknown how the choice of preprocessing affects the final outcome. Here, we use an available data set from a double-blind, randomized, placebo-controlled [^{11}C]DASB-PET study as a case to evaluate how the choice of preprocessing affects the outcome of the study. We tested the impact of 384 commonly used preprocessing strategies on a previously reported positive association between the change from baseline in neocortical serotonin transporter binding determined with [^{11}C]DASB-PET, and change in depressive symptoms, following a pharmacological sex hormone manipulation intervention in 30 women. The two

Step 2: Evaluate the variability in within-center data

Archival Report

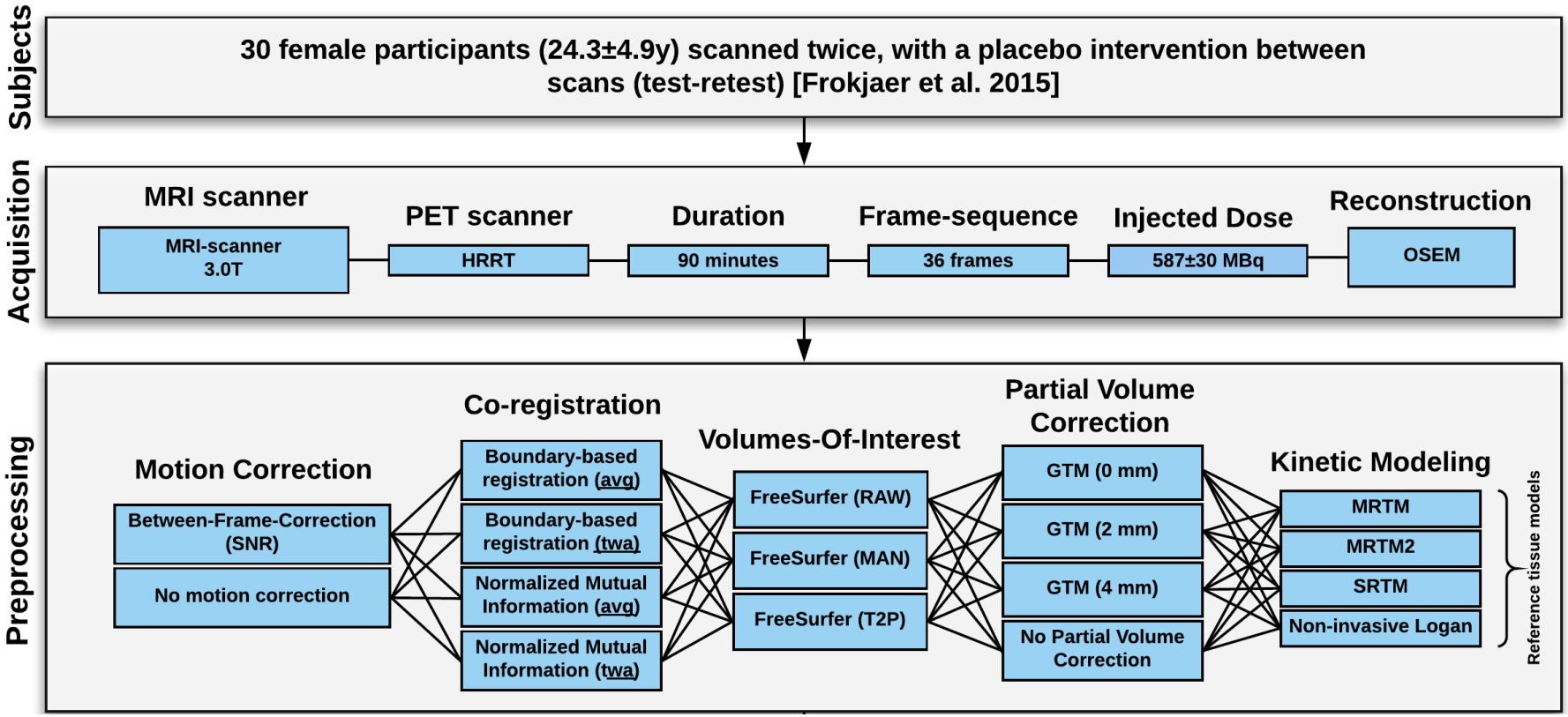
Biological Psychiatry

Role of Serotonin Transporter Changes in Depressive Responses to Sex-Steroid Hormone Manipulation: A Positron Emission Tomography Study

Vibe Gedsoe Frokjaer, Anja Pinborg, Klaus Kähler Holst, Agnete Overgaard, Susanne Henningsson, Maria Heede, Elisabeth Clare Larsen, Peter Steen Jensen, Mikael Agn, Anna Pors Nielsen, Dea Siggaard Stenbæk, Sophie da Cunha-Bang, Szabolcs Lehel, Hartwig Roman Siebner, Jens Damsgaard Mikkelsen, Claus Svarer, and Gitte Moos Knudsen

Impact factor: 9.6; current citations 157

Step 2: Evaluate the variability in within-center data



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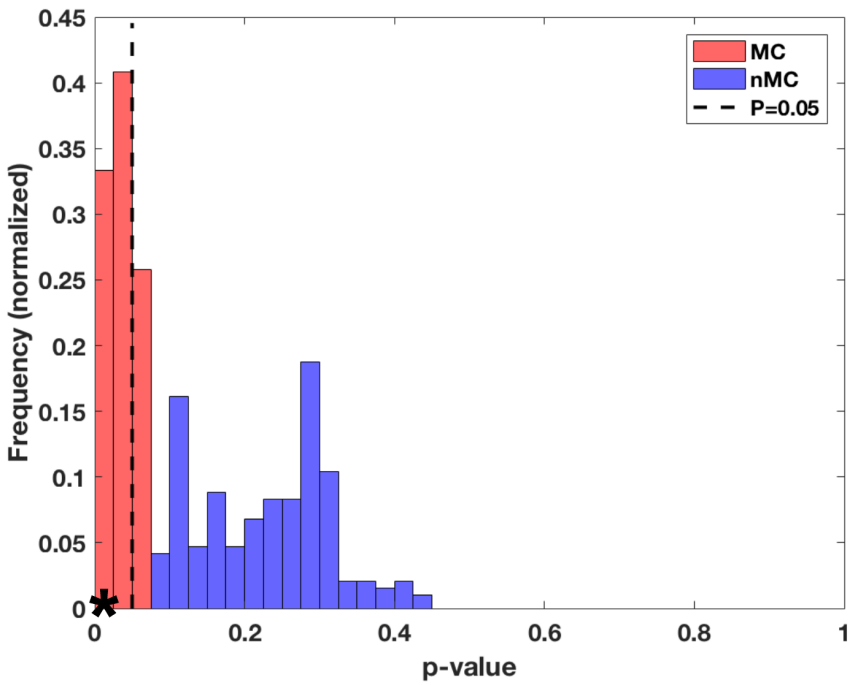

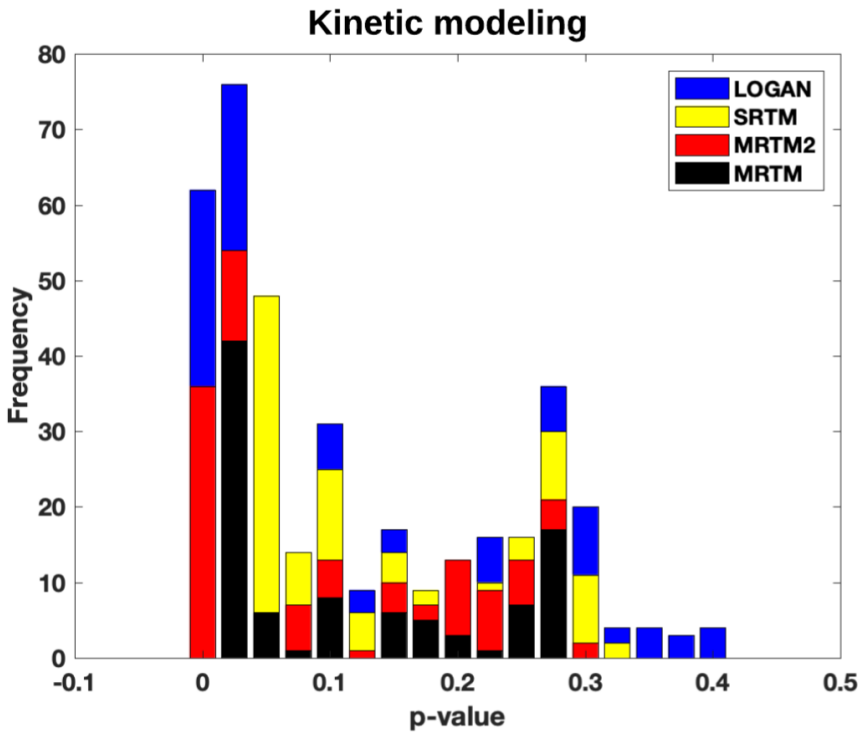

Histogram of p-values obtained across 384 preprocessing strategies examining the association between change in neocortical BP_{ND} and in Hamilton score from baseline following a pharmacological intervention.

36% of pipelines (re)produce a significant result

Norgaard et al. 2019, JCBFM

The NRM grand challenge 2018

Veronese et al. 2021, JCBFM

Original Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
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DOI: 10.1177/0271678X211015101
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SAGE

Reproducibility of findings in modern PET neuroimaging: insight from the NRM2018 grand challenge

Mattia Veronese[1,*], Gaia Rizzo[2,*], Martin Belzunce[3], Julia Schubert[1], Graham Searle[2], Alex Whittington[2], Ayla Mansur[2,4], Joel Dunn[3,5], Andrew Reader[3] and Roger N Gunn[2,4]; and the Grand Challenge Participants[#]

Abstract

The reproducibility of findings is a compelling methodological problem that the neuroimaging community is facing these days. The lack of standardized pipelines for image processing, quantification and statistics plays a major role in the variability and interpretation of results, even when the same data are analysed. This problem is well-known in MRI studies, where the indisputable value of the method has been complicated by a number of studies that produce discrepant results. However, any research domain with complex data and flexible analytical procedures can experience a similar lack of reproducibility. In this paper we investigate this issue for brain PET imaging. During the 2018 NeuroReceptor Mapping conference, the brain PET community was challenged with a computational contest involving a simulated neurotransmitter release experiment. Fourteen international teams analysed the same imaging dataset, for which the ground-truth was known. Despite a plurality of methods, the solutions were consistent across participants, although not identical. These results should create awareness that the increased sharing of PET data alone will only be one component of enhancing confidence in neuroimaging results and that it will be important to complement this with full details of the analysis pipelines and procedures that have been used to quantify data.

So preprocessing of your data matters

what to do about it?

Software for PET analysis pipelines (many more exist!)

SOFTWARE for analyzing PET (and MR) data

SOFTWARE	Motion correction	Registration	Smoothing	Delineation of Volumes of Interest	Partial Volume Correction (PVC)	Pharmacokinetic Modeling	**Open source**
AIR	x	x					x
FreeSurfer	x	x	x	x	x	x	x
FSL	x	x	x	x			x
SPM*	x	x	X	x			
PMOD	x	x	x	x	x	x	
MIAKAT*	x	x	x	x	x	x	
PVElab*		x		x	x		
APPIAN		x		x	x	x	x
Kinfitr						x	x
PETPVC					x		x

*Runs via MATLAB, and is therefore not open source.

REFERENCES

AIR: http://air.bmap.ucla.edu/AIR5/index.html
FreeSurfer: https://surfer.nmr.mgh.harvard.edu/
FSL: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki
SPM: https://www.fil.ion.ucl.ac.uk/spm/
PMOD: https://www.pmod.com/web/
MIAKAT: http://www.miakat.org/MIAKAT2/index.html
PVElab: https://xtra.nru.dk/pveout/
APPIAN: https://github.com/APPIAN-PET/APPIAN
Kinfitr: https://github.com/mathesong/kinfitr
PETPVC: https://github.com/UCL/PETPVC

But why are we using specific tools over other tools?

- Domain knowledge - often we use the tools we are familiar with
- Availability – ”everything I need is available in PMOD”
- Code language – e.g. python vs. Matlab vs. R vs. C++
- Resources – operating systems (e.g. windows vs. Linux)
- Infrastructure - local computers vs. servers
- Easy - there is a ”cost” involved in switching practices

Publish your computer code: it is good enough

Freely provided working code — whatever its quality — improves programming and enables others to engage with your research, says **Nick Barnes**.

14 OCTOBER 2010 | VOL 467 | NATURE | 753

If your code is not good enough to share, then why is it good enough to publish the results that rely upon it?

Containerizing preprocessing tools to improve reproducibility

- What are containers and why researchers care?
- Docker

What are containers?

Why do we care?

A container is a unit of software that packages code with its required dependencies in order to run in an isolated, controlled environment. This allows you to run an application in a way that is predictable, repeatable, and without the uncertainty of inconsistent code execution across diverse development and production environments. A container will always start up and run code the same way, regardless of what machine it exists on.

https://www.digitalocean.com/community/conceptual-articles/introduction-to-containers

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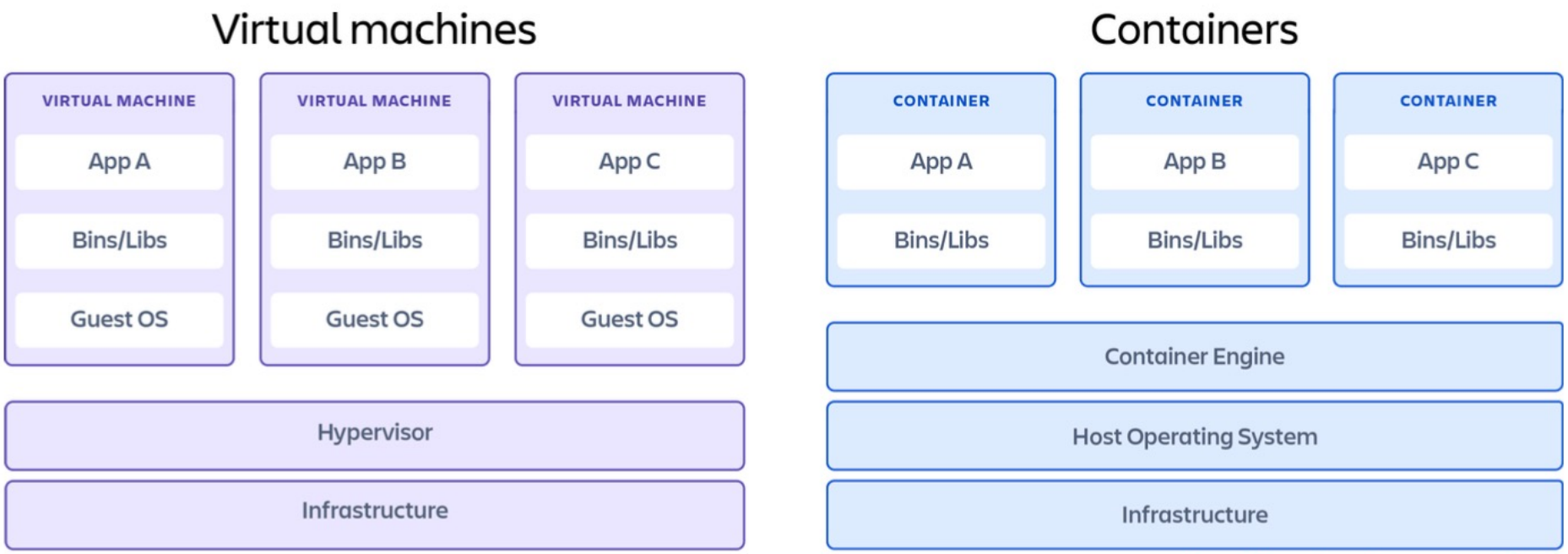
https://www.digitalocean.com/community/conceptual-articles/introduction-to-containers

Isn't this the same as virtual machines?



From the Atlassian documentation

First contact with docker

Container Images

Images are software bundles

- when executed become containers

Images are made of layers

- each layer encapsulates a set of filesystem changes
- layers are akin to software deployment steps

Layers are **unmutable**

- except for a R/W layer that is added on top by the container runtime

Layers are described in the `Dockerfile`

- The `Dockerfile` establishes the instructions to create an image
- The `Dockerfile` is some sort of recipe

Building an image: docker/whalesay

1 The `Dockerfile`

```
# Containers are generally bootstrapped from an existing OS image
# Alpine Linux is a Linux distribution very small and simple
# It's special in that it is not based on the GNU Core Utilities
FROM alpine

# Our container will need perl
RUN apk add --no-cache perl

# Copy the original 'cowsay' program into one layer
COPY cowsay /usr/local/bin/cowsay

# Ensure permissions
RUN chmod a+rx /usr/local/bin/cowsay

# Copy the replacement of the cow asciiart with a whale
COPY docker.cow /usr/local/share/cows/default.cow

# Instruct the runtime to execute the new program
ENTRYPOINT ["/usr/local/bin/cowsay"]
```

Building an image: docker/whalesay

2 The `cowsay` script

Because it is a very long perl script, we just download it:

```
$ curl https://raw.githubusercontent.com/docker/whalesay/master/cowsay -o cowsay
```

Building an image: docker/whalesay

3 The replacement for the cow (`docker.cow`)

```
##
## Docker Cow
##
$the_cow = <<EOC;
    $thoughts
     $thoughts
      $thoughts
EOC
$the_cow .= <<'EOC';
                    ##         .
              ## ## ##        ==
           ## ## ## ## ##    ===
       /""""""""""""""""\___/ ===
      {                       /  ===-
       \______ O           __/
         \    \         __/
          \____\_______/

EOC
```

Building an image: docker/whalesay

4 Build it

```
$ docker build -t oesteban/whalesay .
```

Docker images and the *Docker Hub*

Images can be distributed through **registries**.

- *Docker*'s official registry is called *Docker Hub*
- Thanks to *Docker Hub* we could fetch and execute the `hello-world` image
- Website: hub.docker.com

- PETPrep_hmc

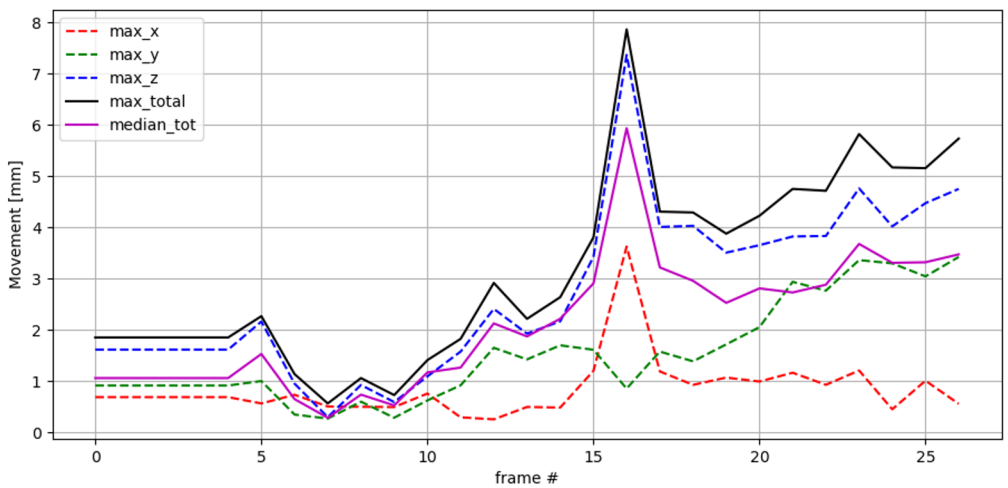
```
docker pull martinnoergaard/petprep_hmc:latest
```

Dockerfile

```
# Use the official Python base image for x86_64
FROM --platform=linux/x86_64 python:3.9

# Download QEMU for cross-compilation
ADD https://github.com/multiarch/qemu-user-static/releases/download/v6.1.0-8/qemu-x86_64-static /usr/bin/qemu-x86_64-static
RUN chmod +x /usr/bin/qemu-x86_64-static

# Install required dependencies for FSL and Freesurfer
RUN apt-get update && apt-get install -y --no-install-recommends \
    build-essential \
    curl \
    ca-certificates \
    git \
    tcsh \
    xfonts-base \
    gfortran \
    libjpeg62 \
    libtiff5-dev \
    libpng-dev \
    unzip \
    libxext6 \
    libx11-6 \
    libxmu6 \
    libglib2.0-0 \
    libxft2 \
    libxrender1 \
    libxt6

# Install FSL
ENV FSLDIR="/opt/fsl" \
    FSLOUTPUTTYPE=NIFTI_GZ \
    PATH="/opt/fsl/bin:$PATH"

RUN curl -sL https://fsl.fmrib.ox.ac.uk/fsldownloads/fslinstaller.py -o fslinstaller.py && python3 fslinstaller.py -d /opt/fsl -o && echo ". /opt/fsl/etc/fslconf/fsl.sh"
>> ~/.bashrc

# Install Freesurfer
ENV FREESURFER_HOME="/opt/freesurfer" \
    PATH="/opt/freesurfer/bin:$PATH" \
    SUBJECTS_DIR="/data/output"

RUN curl -sL https://surfer.nmr.mgh.harvard.edu/pub/dist/freesurfer/7.4.1/freesurfer-linux-centos7_x86_64-7.4.1.tar.gz | tar xzC /opt && \
    echo ". /opt/freesurfer/SetUpFreeSurfer.sh" >> ~/.bashrc

ENV PATH="/usr/local/bin:$PATH"

# Install BIDS application and its dependencies
RUN pip3 install numpy nibabel pybids bids-validator

# Clone and install petprep_hmc from GitHub
RUN rm -rf /opt/petprep_hmc && git clone https://github.com/mnoergaard/petprep_hmc.git /opt/petprep_hmc
RUN pip3 install --no-cache-dir -e /opt/petprep_hmc

# BIDS App entry point
ENTRYPOINT ["python3", "/opt/petprep_hmc/run.py"]
CMD ["--help"]
```

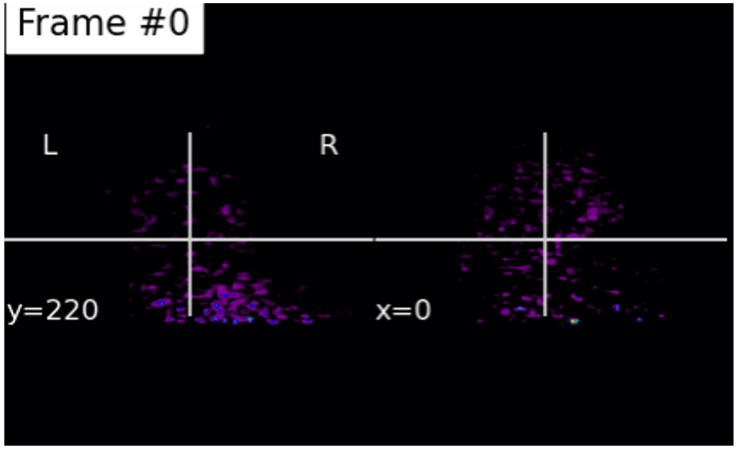
PETPrep Robust Head Motion Correction

```
docker run -it --rm \
      -v /path/to/bids_input:/data/input \
      -v /path/to/bids_output:/data/output \
      -v /path/to/freesurfer_license:/opt/freesurfer/license.txt \
      martinnoergaard/petprep_hmc:latest \
      --bids_dir /data/input \
      --output_dir /data/output \
```

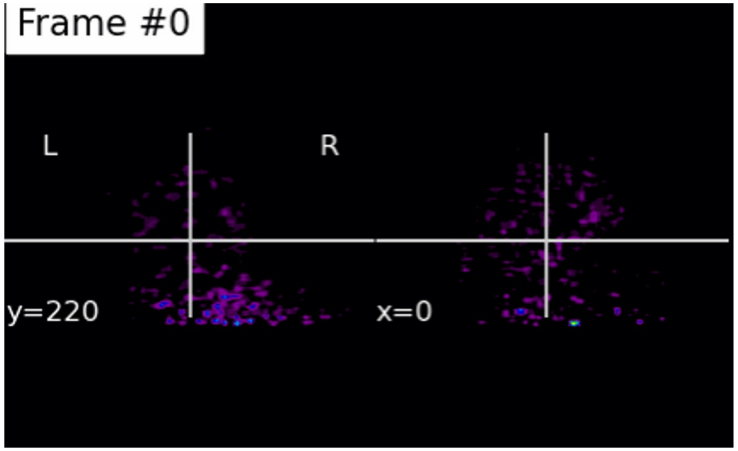


https://github.com/mnoergaard/petprep_hmc

Without motion correction

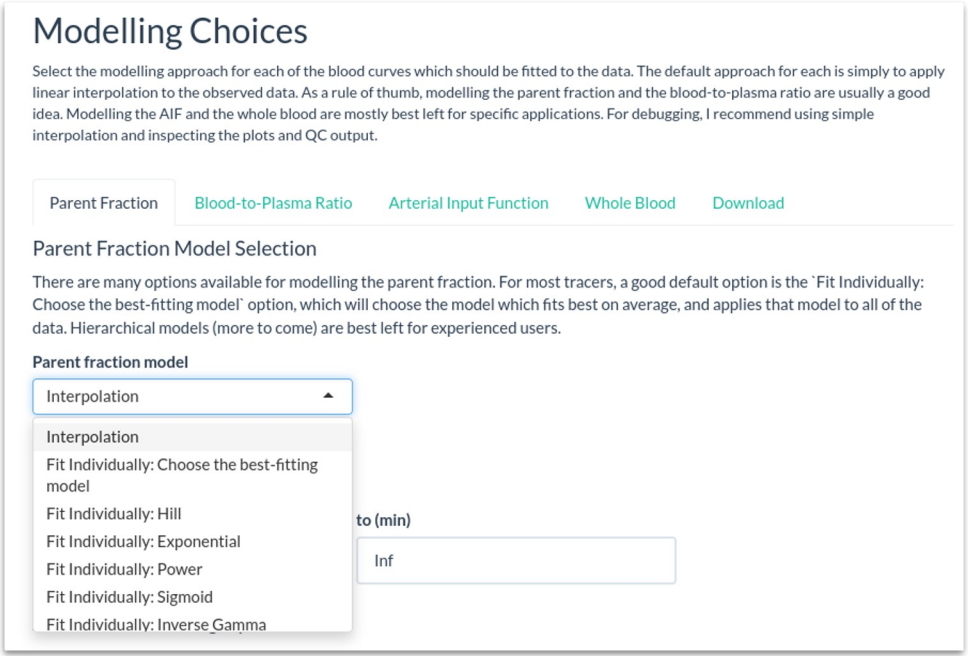


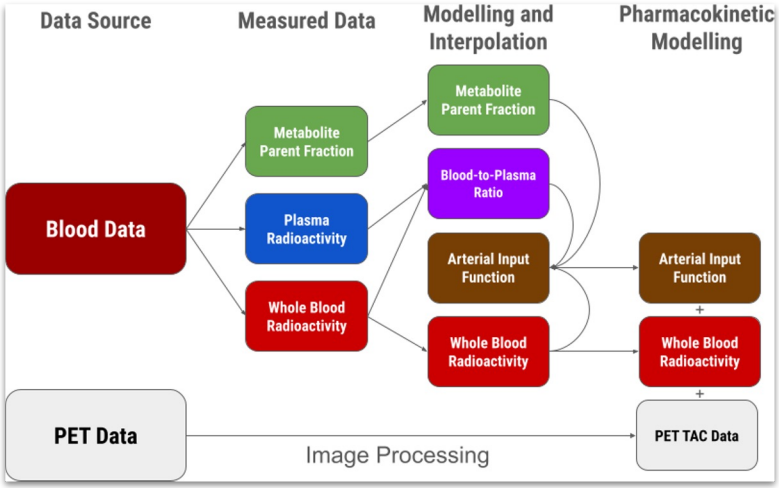
With motion correction

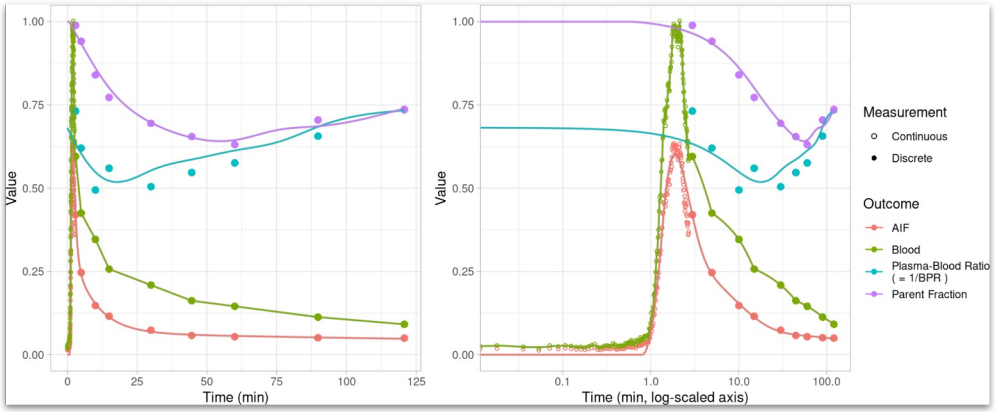


bloodstream for Blood Modelling

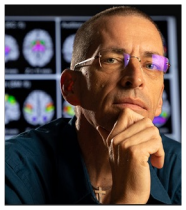
```
docker run -v /path/:/data/ bloodstream

docker run -v /path/:/data/ bloodstream config.json
```



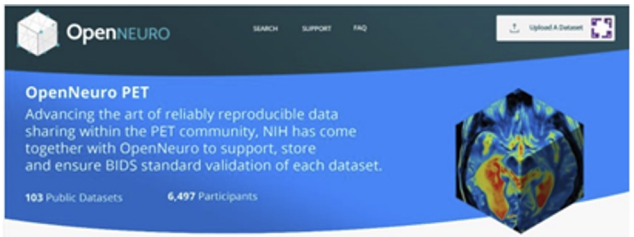




Thank you for your attention



Georgia State University



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