

Check for updates

Review Article



Guidelines for the content and format of PET brain data in publications and archives: A consensus paper

Iournal of Cerebral Blood Flow & Metabolism 0(0) 1-10 © The Author(s) 2020 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/0271678X20905433 journals.sagepub.com/home/jcbfm (\$)SAGE

Gitte M Knudsen¹, Melanie Ganz¹, Stefan Appelhoff², Ronald Boellaard³, Guy Bormans⁴, Richard E Carson⁵, Ciprian Catana⁶, Doris Doudet⁷, Antony D Gee⁸, Douglas N Greve⁶, Roger N Gunn⁹, Christer Halldin¹⁰, Peter Herscovitch¹¹, Henry Huang⁵, Sune H Keller¹², Adriaan A Lammertsma³, Rupert Lanzenberger¹³, Jeih-San Liow¹⁴, Talakad G Lohith¹⁵, Mark Lubberink¹⁶, Chul H Lyoo¹⁷, J John Mann¹⁸, Granville J Matheson¹⁰, Thomas E Nichols 19, Martin Nørgaard 0, Todd Ogden 20, Ramin Parsey²¹, Victor W Pike¹⁴, Julie Price⁶, Gaia Rizzo⁹, Pedro Rosa-Neto^{22,23}, Martin Schain²⁰, Peter JH Scott²⁴, Graham Searle⁹, Mark Slifstein²¹, Tetsuya Suhara²⁵, Peter S Talbot²⁶, Adam Thomas²⁷, Mattia Veronese²⁸, Dean F Wong²⁹, Maqsood Yaqub³, Francesca Zanderigo³⁰, Sami Zoghbi¹⁴ and Robert B Innis¹⁴

Corresponding author:

Gitte M Knudsen, Neurobiology Research Unit 6931, Rigshospitalet and Faculty of Health and Medicine, University of Copenhagen, 9 Blegdamsvej, Copenhagen DK-2100, Denmark. Email: gmk@nru.dk

¹Neurobiology Research Unit, Rigshospital and University of Copenhagen, Copenhagen, Denmark

²Center for Adaptive Rationality, Max Planck Institute for Human Development, Berlin, Germany

³Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Amsterdam, The Netherlands

⁴Laboratory for Radiopharmaceutical Research, KU, Leuven, Belgium ⁵Department of Radiology and Biomedical Imaging, Yale University, New Haven, USA

⁶Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital/Harvard Medical School, Department of Radiology, Boston, MA, USA

⁷Department of Medicine/Neurology, Pacific Parkinson Research Center, Vancouver, Canada

⁸Clinical PET Centre, King's College London, London, UK

⁹Invicro and Division of Brain Sciences, Imperial College London, London, UK

¹⁰Center for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm County Council, Stockholm, Sweden;

¹¹Department of Positron Emission Tomography, National Institutes of Health, Bethesda, USA

¹²Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark ¹³Department of Psychiatry and Psychotherapy, Medical University of Vienna, Wien, Austria

¹⁴Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, USA

¹⁵Translational Biomarkers, Merck & Co., West Point, USA ¹⁶Uppsala University, Department of Surgical Sciences/Radiology and Nuclear Medicine, Uppsala University Hospital, Department of Medical Physics, Sweden

¹⁷Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

¹⁸Department of Psychiatry, Molecular Imaging and Neuropathology Division, Columbia University, New York, USA

¹⁹Oxford Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, Nuffield Department of Population Health, University of

²⁰Columbia Mailman School of Public Health, Columbia University, New York, USA

²¹Department of Psychiatry, School of Medicine, Stony Brook University, Stony Brook, NY, USA

²²McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Canada

 $^{^{\}rm 23} Translational$ Neuroimaging Laboratory, McGill Centre for Studies in Aging, Douglas Mental Health University Institute, Montreal, Canada

²⁴Department of Radiology, University of Michigan, Ann Arbor, USA

²⁵Institute for Quantum Life Science, National Institute for Quantum and Radiological Science and Technology, Chiba, Japan

²⁶Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre,

²⁷National Institute of Mental Health, Bethesda, USA

²⁸Centre for Neuroimaging Sciences, King's College London, London, UK

²⁹Department of Radiology, Johns Hopkins Hospital, Baltimore, USA

³⁰Department of Psychiatry, Columbia University, New York, USA

Abstract

It is a growing concern that outcomes of neuroimaging studies often cannot be replicated. To counteract this, the magnetic resonance (MR) neuroimaging community has promoted acquisition standards and created data sharing platforms, based on a consensus on how to organize and share MR neuroimaging data. Here, we take a similar approach to positron emission tomography (PET) data. To facilitate comparison of findings across studies, we first recommend publication standards for tracer characteristics, image acquisition, image preprocessing, and outcome estimation for PET neuroimaging data. The co-authors of this paper, representing more than 25 PET centers worldwide, voted to classify information as mandatory, recommended, or optional. Second, we describe a framework to facilitate data archiving and data sharing within and across centers. Because of the high cost of PET neuroimaging studies, sample sizes tend to be small and relatively few sites worldwide have the required multidisciplinary expertise to properly conduct and analyze PET studies. Data sharing will make it easier to combine datasets from different centers to achieve larger sample sizes and stronger statistical power to test hypotheses. The combining of datasets from different centers may be enhanced by adoption of a common set of best practices in data acquisition and analysis.

Keywords

Consensus guidelines, data sharing, data structure, open source, positron emission tomography

Received 24 September 2019; Revised 19 November 2019; Accepted 19 November 2019

Background

In recent years, the importance of data sharing has increasingly been recognized by the neuroimaging community as a solution for leveraging optimal and maximally powered research. Reasons to optimize and standardize ways to document and share data include the lack of replication of neuroimaging findings, quality control, and the greater scientific impact of multilateral collaborations. In addition, funding bodies and scientific journals increasingly require that data be shared. Another incentive is the substantial cost needed to acquire neuroimaging data, which also limits sample sizes in individual research grants and across positron emission tomography (PET) sites. Merging data from different sites in a data repository creates larger sample sizes to test hypotheses, allows for comparison across diagnostic groups, and enables hypothesis testing not anticipated in the original studies.

A few important initiatives—for instance, the Human Connectome Project, the 1000 Functional Connectomes Project, the Alzheimer's Disease Neuroimaging Initiative, and the Adolescent Brain Cognitive Development study—have spearheaded neuroimaging data sharing, albeit mainly within the magnetic resonance imaging (MRI) community. As a result, best MRI practices and data analysis and sharing standards are now openly available (e.g. COBIDAS²), and data sharing platforms (e.g. OpenNeuro) are being created. In this context, the Brain Imaging Data Structure (BIDS)³ initiative has

also sought to establish consensus on how to organize and share MRI and functional MRI (fMRI) data obtained in neuroimaging experiments, which should enhance investigators' ability to reproduce experimental results from studies conducted at different sites. BIDS is being developed in an ongoing and inclusive community effort in which many neuroscientists consult to ensure that BIDS covers most common neuroimaging experiments. In addition, BIDS is intuitive and easy to adopt; the specification was intentionally based on simple file formats and folder structures to reflect current lab practices and make it simultaneously accessible to a wide range of scientists coming from different backgrounds, as well as machine-readable. While BIDS was originally based on functional and structural MRI acquisitions, it has now been extended to cover a large range of different modalities (MRI), electroencephalography (EEG), magnetoencephalography (MEG), etc. and several more extensions are under way. 4 In addition, a growing number of software tools (see http://bids-apps.neuroimaging.io/) can accept data organized in the BIDS format.⁵

Despite such efforts, the molecular neuroimaging community encompassing both PET and single photon emission computed tomography has yet to specifically define standards for organizing and sharing such data. In addition, PET acquisition and analysis have some challenges that MRI does not. First, MRI researchers typically use images "as-is" as they come off the scanner, and there is little controversy regarding how those images were reconstructed from k-space; in

contrast, PET images can be reconstructed from raw data in a number of ways. Thus, it becomes necessary to not only accurately report the reconstruction method, but also to save, document, and share the raw data, if a different reconstruction method is to be tested. Second, another difference between PET and MRI is that blood samples are often acquired during PET, and blood analysis results are used concomitantly with PET imaging data to fully quantify outcomes measured for subsequent analyses; therefore, whole blood and plasma data as well must be stored with the PET data, documented, and shared. Finally, PET and MRI use different dynamic modeling techniques. Thus, while the MR community has made strides in data sharing and documentation, these accomplishments are not directly applicable to PET.

In 2016, the NeuroReceptor Mapping conference (NRM2016) in Boston hosted a panel discussion regarding PET data sharing; panelists included Drs Peter Herscovitch, Robert B. Innis, and Gitte M. Knudsen. The audience—comprising roughly 250 PET experts in PET physics, radiochemistry, modeling, pharmacology, and neuroscience—unanimously supported a motion to establish a working group that would propose guidelines for data sharing. The panel subsequently noted that the aims of such a working group would include recommending standards for the content and structure of PET and associated blood data in order to facilitate easier data sharing. The panel also recognized the importance of defining the information that would need to be provided regarding how individual PET datasets were acquired, preprocessed, and modeled to generate outcome measures. As an example, a recent paper reviewed 105 original research articles published by 21 different PET centers that used the radiotracer [11C]DASB to image serotonin transporter binding; the authors noted that quantification was done in a substantially different number of ways, with an associated impact on the outcome variables.⁶ Examples of methodological details that can significantly affect study outcomes include: (1) how PET data are acquired, preprocessed in terms of motion correction, and other procedures like co-registration with structural MRI data to generate time-activity curves for volumes of interest (VOIs); (2) how the reference region is defined; (3) whether an arterial input function is used or the tracer's free fraction in plasma estimated; and (4) which methods are used to estimate outcome measures.⁷

Building on these discussions, the panelists established that the long-term goal of the working group would be to facilitate data sharing in the molecular imaging community. A necessary first step in facilitating such sharing would be to establish standards to help scientists interpret future PET neuroimaging

studies as well as appropriately assess the feasibility of accessing such datasets. While variability in study subjects, experimental design, or the PET- and MR-equipment of individual sites is of course inevitable, decisions regarding data acquisition, reconstruction, preprocessing, quantification, and modeling of data, as well as statistical analysis, can also lead to different outcomes and neurobiological interpretations. Thus, the general characteristics one should reasonably request is that the data be accurate, useful, and can reproduce the reported results.

In this context, the panelists decided to confine the guidelines to a set of easily recognizable and achievable goals. As a general rule, the scope included any component that could significantly impact the accuracy and sharing of PET data, such as purity of the radiotracer, blood measurements, camera calibration, image reconstruction, and modeling methods. An overview of the data stream for acquired and derived PET data, including conversion into suitable formats for archiving and/or sharing, is given in Figure 1.

Broadly, the data associated with PET imaging include the following: (1) radiotracers and blood data, (2) acquired (raw) PET data, and (3) reconstructed PET data. Although, in principle, acquired PET data coming directly out of the PET scanner could be shared, we have chosen to adopt a format for PET data sharing comprising a reconstructed 4D PET image file and an additional file that contains meta-data with sufficient information (e.g. frame timing). Reconstructed 4D PET image files were selected because they require the least data processing to share. Derived data are defined as a representation of the output after: (1) image preprocessing, (2) blood processing, (3) kinetic modeling, and (4) statistics.

After the NRM2016 meeting, Drs Knudsen and Innis established specific working groups to represent and discuss each component as well as to define standards for organizing and describing PET datasets. Based on the input of these working groups, this manuscript details the consensus guidelines for reporting PET studies in manuscripts and for data sharing. In addition, we propose and recommend the use of a standardized checklist to be filled in before manuscript submission (Appendix A). We see this work as an important step to understand, interpret, and reproduce published work, but also to facilitate archiving and data sharing.

Study participants

We assume that—consistent with standard practice—any PET neuroimaging manuscript will contain data about the study participants such as age, sex, and race and other clinical information, e.g. healthy control, clinical diagnosis, MMSE score, etc.

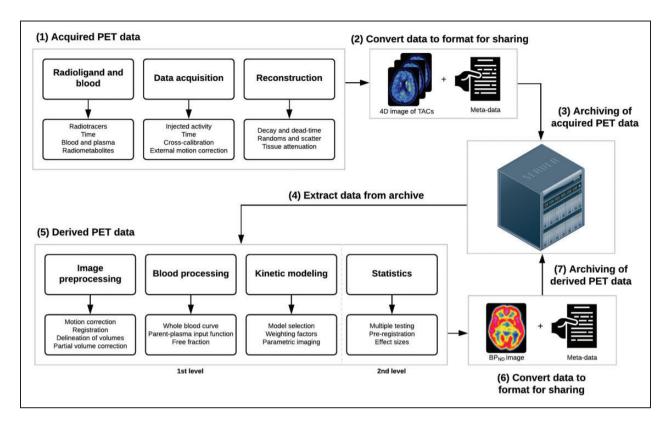


Figure 1. An overview of the data stream for acquired and derived PET data. (1) Together, radiochemistry, blood, PET data acquisition, and reconstruction constitute the acquired data. (2) The acquired data should be converted into a suitable format, and (3) shared and/or stored in an archive. (4) The acquired data may be extracted from an archive, and (5) analyzed at the subject level (first level), applying image preprocessing, blood data processing, and kinetic modeling (or alternative approaches, including graphical) for absolute quantification. Quantified data may be used in a statistical analysis at the group level (second level) that should be accompanied by a correction for multiple testing and reporting of effect sizes. Ideally, approaches for generating acquired and derived data should be pre-registered before carrying out a study, in order to limit researcher degrees of freedom and false-positive results. The preprocessing, blood processing, kinetic modeling, and statistics constitute derived data in the form of binding and/or statistical estimates. (6) The derived data must be converted into a suitable format, and (7) shared and/or stored in an archive. BP_{ND}: non-displaceable binding potential; PET: positron emission tomography; TAC: time-activity curve.

In manuscripts, this information is provided on a group level that does not disclose the identity of study participants.

Acquired PET data

Radiotracers and radiometabolites

Coenen et al.⁸ recently established a consensus nomenclature for radiopharmaceutical chemistry and related areas. The guidelines proposed here adhere to this consensus nomenclature. In the paragraphs that follow, we briefly outline the terminology and parameters deemed essential to PET scan recordings, which can be divided into four sections: (1) radiotracers, (2) time, (3) blood and plasma, and (4) radiometabolites.⁹ It should be noted that (3) and (4) only apply to PET studies where arterial or venous blood samples are acquired.

Radiotracers. Information pertaining to radiotracers should include radiochemical purity, molar or specific activity, formulation, administered radioactivity and mass, and body weight. Specific activity is the measured activity per gram of compound. Molar activity is the measured radioactivity per mole and is measured in Bq/mol or GBq/μmol. In case the molecular weight cannot be determined, or in the context of radionuclide development, the term "specific activity" is used instead of "molar activity." Mode of injection (bolus and injection speed, or bolus-infusion protocol) should also be specified.

Time. Time-related information for PET imaging experiments should include the local time at which scans begin and end, time of radiotracer injection and, if relevant, time of blood sampling following BIDS reporting standards.³ Due to radioactive decay, the measurement time for determining the specific

activity or molar activity must be stated (e.g. "specific activity was 50 GBq/mg' or 'molar activity was 50 GBq/ μ mol' two hours after the end of nuclide production, at the end of synthesis, at time of administration," etc.). If needed for privacy protection reasons, dates can be shifted by a random number of days.

Blood and plasma. Blood and plasma measurements should include the method (if any) used to estimate radiotracer free fraction in plasma (f_P), whole blood and plasma radioactivity, plasma to whole blood radioactivity ratio, and reference time for decay correction. In general, it is assumed that all radioactivity count rates are properly decay-corrected to the time of radiotracer injection. Generally, blood and plasma radioactivity is by default corrected to the first measurement. An additional correction to the time of radiotracer injection is required and thus needs to be stated. That is, if PET acquisition is split into two parts, it is important that the second PET acquisition be decay-corrected to the start of injection.

Radiometabolites. When the fraction of the radioactivity attributable to the parent radiotracer is measured, a description of the analysis method should be included, as should the time-dependent amount of the parent compound and radiolabeled metabolites.

The checklist in Appendix A (Radioligand section) lists recordings of discrete values that relate to radio-chemistry that should be reported when publishing data. Data interpolations, such as those necessary to generate a smooth arterial input function, are discussed in the Derived PET Data section of this paper. For each variable, the appropriate physical units should be reported in accordance with established consensus standards. It should be noted that different laboratories may use different methods to measure discrete values, for example some laboratories measure plasma free fraction with ultracentrifugation while others use equilibrium dialysis. For each relevant measure, we recommend referring to a published reference method.

PET data acquisition

Acquisition of quantitative PET data is only meaningful if activity measurement instruments—for instance, dose calibrators, well counters, and imaging systems (PET/CT and PET/MR)—are identifiable (brand, model) and properly cross-calibrated; this ensures that data collected and analyzed using these instruments are quantitatively consistent. For example, arterial blood sampling requires that blood radioactivity measured with an external coincidence blood sampler or a well counter be quantitatively comparable to brain radioactivity concentrations measured in vivo with the PET scanner.

Quantitative PET results do not only depend on proper cross-calibration of radioactivity measurement devices but also on: (1) PET image acquisition parameters, including external motion correction; (2) reconstruction methods; and (3) other settings such as smoothing (spatial resolution of the images). In addition, the accuracy of correction methods such as normalization, attenuation, and scatter corrections can have a large impact on the quantitative accuracy of PET data.¹⁰

Cross-calibration. Cross-calibration is usually done by PET scanning a phantom, e.g. a uniform cylinder filled with a solution containing a known concentration of radioactivity. This concentration is determined by taking a sample from the phantom's solution to cross-calibrate with well counters. In the case of automated blood sampling, cross-calibration between the scanner and the blood sampling system should also be done. Standard operating procedures have been described in various international standards, such as the NEMA NU 2-2018 standard by the National Electrical Manufacturers Association (www.nema. org), by the American College of Radiology (www. acraccreditation.org), and by the Board of the European Association of Nuclear Medicine (EANM) Research Ltd initiative (http://earl.eanm.org).

The cross-calibration of PET cameras should be limited to defining cross-calibration accuracy specifications that are practically feasible and provide a minimal standard for performing quantitative PET studies. Appendix A lists the parameters for cross-calibrating equipment with minimally required specifications together with the information and data that need to be reported and locally stored.

External motion correction. Subject movement while in the PET scanner leads to blurring of images and potentially incorrect estimates of tracer concentrations. 11 Moreover, as scanner resolutions continue to improve, data become increasingly more sensitive to head motion. In order to correct for subject-specific head motion, external motion correction may be used during PET data acquisition. A number of approaches to motion correction have been proposed, and these operate under the basic assumption that measurements of patient movement during any scan with an external device are accurate. 12 In contrast to MR neuroimaging, where prospective or retrospective motion correction is possible, motion correction in PET can only be done retrospectively because it is applied after the events have been measured. Once the raw PET data have been acquired, one can then choose to either perform an event-based motion correction, where each decay event is adjusted for patient position, or perform post-reconstruction motion correction for given time frames. When external motion correction is carried out, we recommend providing a thorough description of the hardware device and procedure along with a published reference method. In addition, attenuation correction accuracy is degraded by head movement and sometimes subjects need to leave the scanner briefly in the middle of a scan. If a new attenuation map is obtained in the new head position, this needs to be stated.

Reconstruction

Consensus guidelines for PET brain imaging with [18F] FDG were established by the EANM in 2009¹³ and include a guideline for reconstruction. In adherence with this guideline, we recommend that the following parameters be reported when publishing data: (1) the image resolution; (2) the method of reconstruction, including manufacturer-specific algorithms and all algorithm parameters (e.g. 3D-OP-OSEM with 21 subsets and seven iterations, 5 mm uniform PSF, 500 ps TOF, etc.); (3) post-reconstruction filtering (type and size); and (4) the method of attenuation correction. In addition, the methods used to normalize and correct for randoms, scatter, decay, and dead-time should be mentioned if they deviate from the scanner standard. In general, it is assumed that all radioactivity count rates are properly decay-corrected.

The way that PET data are reconstructed has remained relatively unchanged during the last two decades. However, with the introduction of newer technologies (e.g. time-of-flight, PET/MRI), further developments may need to be incorporated. The checklist in Appendix A (section on PET Data Acquisition) lists the recordings of discrete values for data acquisition that should be reported when publishing data.

Derived PET data

No unique or optimal way exists to analyze a PET imaging dataset. Different analytical methods are available, and their applicability depends on many different variables, including the research question, data availability, experimental design, tracer kinetics, and parameters of interest. In this section, we define derived PET data as comprising the following components: (1) preprocessing, (2) blood data processing, (3) kinetic modeling, and (4) statistics, as outlined in Figure 1. A detailed description of how the data have been preprocessed and analyzed should be provided (see Appendix A). In particular, any PET neuro-imaging paper must list preprocessing and analysis

details that would allow an independent research group to replicate the results, if provided with the original data. In addition, we recommend appropriate source control of analytical workflows, including appropriate audit trails, as good practice to improve the ability to replicate independent analyses into the future.

Preprocessing

Figure 2 depicts the multiple preprocessing operations associated with the preprocessing stage for PET data, ranging from quality control, motion correction, registration, smoothing, delineation of VOIs, and partial volume correction. Because the inclusion and choice of each step and its order influence the subsequent quantification procedure, it is important to specify the order of the applied preprocessing operations. which we define here as six preprocessing building blocks (Figure 2). These preprocessing building blocks may be combined interchangeably and used several times during the preprocessing stage. The motion correction procedure should be reported with the reference image used, including information about registration (e.g. interpolation technique, cost function, quality control). When the PET data are registered to either the corresponding MR data or to a template/ atlas, it should also be reported how the data were registered (e.g. affine transformation to MNI152 space, non-linear registration to MNI152 space, or surface-based registration).

In this regard, it should be noted that all of the corresponding MR images need to be corrected for gradient non-linearities in order to correct for spatial distortions and achieve optimal PET-MR registration. If any smoothing and/or resampling is applied to the PET data, the size, type, and shape of the smoothing kernel should be specified and a justification for the chosen size of the kernel should be given.

The technique for delineating VOIs (or brain extraction) should be reported and include the following: (1) information about the space in which the volumes were obtained (PET, MRI, or template/atlas); (2) operational criteria; (3) whether the procedure was manual, automatic, or semi-automatic; (4) whether any thresholding was applied; and (5) if appropriate, a reference to a methods paper. If partial volume correction is applied to the PET data, the assumptions, parameters, and limitations of the technique should be specified, along with a reference to a methods paper. Several papers report the main findings both with and without partial volume correction in order to assess whether the results differed, and we recommend this strategy. In addition, the version number and/or latest update of all software used for preprocessing should be specified.

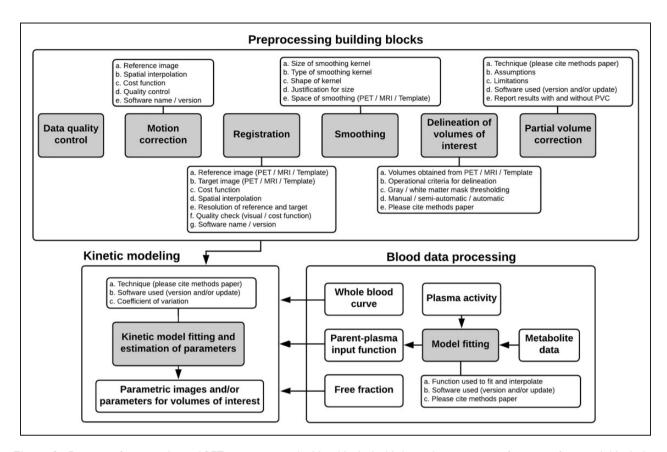


Figure 2. Diagram of commonly used PET preprocessing building blocks highlighting the necessary information from each block that should be reported when publishing and/or sharing data. The output of the preprocessing step can subsequently be combined with blood data processing and kinetic modeling (or alternative approaches) for absolute quantification of the tracer. MRI: magnetic resonance imaging; PET: positron emission tomography; PVC: partial volume correction.

If any subjects included in the study required a different preprocessing strategy, this should be explicitly stated. Finally, if the preprocessing strategy deviates from published validation studies and/or test–retest studies, the reason for modifying the preprocessing strategies should be provided. For a more comprehensive discussion on preprocessing procedures, we refer the reader to recent articles by Gunn et al.¹⁴ and Nørgaard et al.⁶

Blood data processing

Blood curves should be reported with corresponding time information. In principle, whole blood and plasma time-activity curves should be presented in the same units as the tissue time-activity curves. There are two ways to measure (arterial) blood curves, and these are often combined in PET neuroimaging studies: using a continuous blood sampling system with an external detector, or taking samples manually. For the continuous sampling system, time resolution suffices to measure the peak of the input curve; no interpolation of

time points is required provided the bins selected are short enough. Depending on the sampling catheter length, tracer stickiness, and sampling speed, the delay and dispersion correction may be required and needs to be documented. Manual samples can be used to measure radioactivity, the plasma to whole blood radioactivity ratio, and plasma parent fraction as a function of time. These measures serve to subsequently generate a metabolite-corrected plasma input function to quantify the tissue time-activity curves, as well as to properly correct them for vascular contribution (using the whole blood radioactivity curve). The functions used to fit and interpolate plasma to whole blood ratios and parent fractions should be provided and, if necessary, the resulting metabolite-corrected plasma input curve should be specified (e.g. multi-exponential or Hill function). Any interpolation or fitting of blood data should be specified in enough detail (e.g. with or without any weighting factors) to allow replication of these analyses. For a more comprehensive discussion on blood fitting procedures, we refer the reader to the works of Tonietto et al. 15,16

Kinetic modeling

We recommend that outcome measures be accompanied by variance estimates following model fitting (or alternative model-free approaches), including constraints on the model parameters, weighting schemes, and the definition of the rule (if any) followed to remove outliers. In the case of radiotracers with reversible kinetics, the nomenclature used to refer to the estimated outcome measures should adhere to that laid out in the consensus publication by Innis et al. ¹⁷ The checklist in Appendix A (Data Analysis section) lists the recordings of discrete data analysis values that should be reported when publishing data.

Statistics

As with all studies, appropriate statistical testing is mandatory in PET studies. A challenge specific to this modality is that, because of the high costs associated with PET imaging, such studies are at high risk of being underpowered, thus potentially generating results that cannot be replicated. Power analysis should be conducted a priori to determine the number of subjects required. This calibrates the study to be sufficiently sensitive to detect effects when the true underlying effect size is greater than a specified minimum, given a selected alpha threshold and power level. For some radiotracers, information regarding between- and within-individual variability is available 18 which allows for the power analysis to be conducted more effectively. A strategy to deal with corrections for multiple testing and, preferably, a pre-registration of complete analysis workflows should be done before carrying out a clinical study, a strategy also supported by researchers in the fMRI field.¹⁹

Correction for multiple testing. When considering outcomes from multiple VOIs or a voxel-wise map, appropriate corrections for multiple tests should be conducted. This challenge can be met in several different ways: (1) by having an a priori hypothesis about which VOIs will be affected, appropriately controlling for multiple tests among these VOIs, or using an appropriate global test for the VOIs of these regions, possibly followed by (clearly flagged) exploratory post-hoc analyses; (2) by correcting for multiple tests across all VOIs; or (3) by using a voxel-wise analysis that controls for multiple tests over voxels or clusters. For any of these cases, a multiple-tests method should be validated, should account for dependence among VOIs or voxels, and should control for a standard measure of false positive risk (e.g. familywise error rate or false discovery rate). Of importance, if the data (or a subset thereof) have been previously published in another paper, this should be clarified in the methods section.

Pre-registration. We generally recommend that investigators pre-register complete analysis workflows using the Open Science Framework or AsPredicted. Pre-registration does not constrain the research to a single analysis workflow but, rather, ensures that a workflow has been defined before the analyses are carried out. This limits the researcher's degrees of freedom and reduces the likelihood of reporting results that cannot be replicated.

Data structure for PET and MRI

The prior sections provide guidelines for fully describing and analyzing data in research papers in order to communicate the results and conclusions in the most useful manner. However, if the primary data themselves are to be shared, additional structure and compatibility factors must be addressed. We recommend that the data structure for PET and MRI models the structure introduced by the BIDS initiative (http://bids. neuroimaging.io/). Originally, the BIDS standard³ was designed to guide and outline best practices for storage of raw/unprocessed MRI and fMRI data (in the form of NIfTI images). As noted earlier, the original standard has recently been extended to cover other imaging modalities, such as MEG,20 EEG,21 and intracranial EEG.²² However, in its current form, the BIDS standard does not cover derivatives of the raw data such as preprocessed or otherwise modeled data. Extensions to the specification are being investigated for derived data as well as for additional modalities such as PET. The extensions to BIDS are organized in the form of separate BIDS Extension Proposals (BEPs), which are listed under the "Extending the BIDS specification" section in the original specifications (https://bids-speci fication.readthedocs.io). In this context, it would also be desirable for derived images such as preprocessed data (for instance, after motion correction) to be stored according to the BIDS extension proposal concerning derivatives (BEP023).

As a related goal, Drs Knudsen and Innis propose establishing an archive for PET data based on the recommendations outlined in this paper. Broadly speaking, the purpose of this proposed archive—tentatively known as the OpenNeuroPET Archive—would be to allow researchers to meaningfully share data with each other. The proposed archive, the first one for PET data, would be built around the BIDS standard³ and would also provide support for PET researchers to upload their datasets.

BIDS raw data

We recommend the BIDS extension for PET (BEP009) that includes details of how to store ancillary data such as arterial blood and plasma measurements, as well as metadata relating directly to the images, such as frame times and reconstruction methods. The extension was heavily inspired by the ANC file format used in the MIAKAT software (www.miakat.org). Examples of such PET data are also included on the OpenNeuro Platform (https://openneuro.org/), where PET data are publicly available for download. We recommend that structural MRI data associated with PET experiments be stored according to the original BIDS specification³ and that raw PET data be stored as described in the BIDS PET extension (BEP009). While we have detailed the use of BIDS only to a certain extent, we refer to the main BIDS publication³ with respect to how individual subject meta-data can be stored. The information that an experimenter wants to and is allowed to share can be stored in an external meta file.

BIDS derivatives

BIDS derivatives represent the output from preprocessing, blood data processing, and kinetic modeling (or alternative quantification). The representation should capture the data and metadata in enough detail for any researcher to understand and critically reuse those outputs for subsequent statistical analyses. We recommend that the derived PET data be stored as described in the BIDS PET extension (BEP023).

Data accessibility and privacy matters

It should be noted that we have deliberately avoided discussing standards of privacy (e.g. de-identified versus fully anonymized data), mainly because such details differ between countries and need to be addressed by the individual researchers. Nevertheless, investigators are encouraged to ensure that they obtain the correct participant consent for their study and for future sharing and reanalysis of data by others. Even scan date or absolute time of scan can be regarded as sensitive information,³ and shifting of blood and scan times may be required.

We also refrained from expressing opinions about accessibility, that is about whether data must be made freely available or whether the exchange of data could be constrained, for instance by embargo or co-authorship. Within the guidelines outlined here, we encourage investigators to meet the appropriate regulations for storing and sharing data and merely recommend content and structure guidelines for reading and assessing PET neuroimaging studies.

Moving forward

Although the authors have worked hard to propose these guidelines, we recognize that they are only the first step toward meaningful communication and useful data sharing. As is always the case when creating a set of guidelines a priori, we anticipate that improvements to the guidelines will necessarily follow their "real-world" implementation. For instance, some suggestions will not be useful or feasible, others will need clarification, and many more have yet to be considered. To help the process evolve, we encourage members of diverse communities (e.g. researchers, editors, regulatory bodies, and funding agencies) to send suggestions for improvements to Drs Gitte Knudsen and Robert Innis. In addition, we recommend that these guidelines be reviewed every few years to determine their overall usefulness and to implement revisions. At the time of review and feedback—perhaps during the NRM meeting held every two years—relevant changes that may impact these guidelines can be discussed, including regulations (e.g. data security), policies (e.g. data sharing from journals and funding agencies), and resources (e.g. available archives).

As noted earlier, although guidelines and archives already exist for MRI/fMRI data, they are almost completely missing for the brain PET Furthermore, although the field of MRI/fMRI can provide a useful model for PET, a major difference between the two imaging modalities presents both an opportunity and a challenge. Specifically, MRI/fMRI data are provided in relative terms (e.g. percentage increase over baseline) whereas PET data are provided in absolute Système International units (e.g. nM or kBq/ml). These guidelines allow scientists the opportunity to combine data with the facility afforded by absolute units; nevertheless, the key challenge moving forward is ensuring that each piece of data is accurate and reproducible. This paper is an important first step toward establishing these standardizing guidelines. Furthermore, it also notifies the PET community that Drs Knudsen and Innis seek to establish an archive for PET data based on the recommendations outlined in this paper. The archive, called OpenNeuroPET, will be an extension of OpenNeuro. Like this guidelines paper, the archive will have grass roots input and seek international harmonization. We hope these guidelines—as well as the long-term plans for standardization outlined herein—will facilitate accuracy and reproducibility and broadly help the PET neuroimaging community.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported in part by the Intramural

Research Program (project ZIAMH002852) of the National Institute of Mental Health, NIH.

Acknowledgements

The authors thank Ioline Henter (NIMH) for expert editorial assistance in the preparation of this manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID iDs

Antony D Gee https://orcid.org/0000-0001-8389-9012
Thomas E Nichols https://orcid.org/0000-0002-4516-5103
Martin Nørgaard https://orcid.org/0000-0003-2131-5688

Supplemental material

Supplemental material for this article is available online.

References

- Poldrack RA and Gorgolewski KJ. Making big data open: data sharing in neuroimaging. *Nat Neurosci* 2014; 17: 1510–1517.
- 2. Nichols TE, Das S, Eickhoff SB, et al. Best practices in data analysis and sharing in neuroimaging using MRI. *Nat Neurosci* 2017; 20: 299–303.
- Gorgolewski KJ, Auer T, Calhoun VD, et al. The brain imaging data structure, a format for organizing and describing outputs of neuroimaging experiments. Sci Data 2016; 3: 160044.
- 4. Contributing to and extending the BIDS specification, https://bids-specification.readthedocs.io/en/latest/06-exten sions.html#bids-extension-proposals (2018, accessed 1 November 2019).
- Gorgolewski KJ, Alfaro-Almagro F, Auer T, et al. BIDS apps: improving ease of use, accessibility, and reproducibility of neuroimaging data analysis methods. *PLoS Comput Biol* 2017; 13: 1–16.
- Nørgaard M, Ganz M, Svarer C, et al. Cerebral serotonin transporter measurements with [¹¹C]DASB: a review on acquisition and preprocessing across 21 PET centres. *J Cereb Blood Flow Metab* 2019; 39: 210–222.
- Nørgaard M, Ganz M, Svarer C, et al. Optimization of preprocessing strategies in positron emission tomography (PET) neuroimaging: a [¹¹C]DASB PET study. Neuroimage 2019; 199: 466–479.
- 8. Coenen HH, Gee AD, Adam M, et al. Consensus nomenclature rules for radiopharmaceutical chemistry – setting the record straight. *Nucl Med Biol* 2017; 55: v–xi.
- 9. Moein MM, Nakao R, Amini N, et al. Sample preparation techniques for radiometabolite analysis of positron

- emission tomography radioligands; trends, progress, limitations and future prospects. *TrAC Trends Anal Chem* 2019; 110: 1–7.
- van den Heuvel OA, Boellaard R, Veltman DJ, et al. Attenuation correction of PET activation studies in the presence of task-related motion. *Neuroimage* 2003; 19: 1501–1509.
- 11. Carson RE, Barker WC, Liow JS, et al. Design of a motion-compensation OSEM list-mode algorithm for resolution-recovery reconstruction for the HRRT. In: *IEEE nuclear science symposium*, Portland, OR, 2003.
- Rahmin A, Rousset OG and Zaidi H. Strategies for motion tracking and correction in PET. PET Clinics 2007; 2: 251–266.
- Varrone A, Asenbaum S, Vander Borght T, et al. EANM procedure guidelines for PET brain imaging using [18F] FDG, version 2. Eur J Nucl Med Mol Imaging 2009; 36: 2103–2110.
- Gunn RN, Slifstein M, Searle GE, et al. Quantitative imaging of protein targets in the human brain with PET. Phys Med Biol 2015; 60: R363–R411.
- Tonietto M, Rizzo G, Veronese, et al. Plasma radiometabolite correction in dynamic PET studies: insights on the available modeling approaches. *J Cereb Blood Flow Metab* 2016; 36: 326–339.
- Tonietto M, Rizzo G, Veronese M, et al. Modelling arterial input functions in positron emission tomography dynamic studies. In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Milan, Italy, 2015, pp. 2247– 2250. IEEE.
- Innis RB, Cunningham VJ, Delforge J, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* 2007; 27: 1533–1539.
- 18. Haugbøl S, Pinborg LH, Arfan HM, et al. Reproducibility of 5-HT2A receptor measurements and sample size estimations with [18F]altanserin PET using a bolus/infusion approach. Eur J Nucl Med Mol Imaging 2007; 34: 910–915.
- 19. Poldrack RA, Baker CI, Durnez J, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nat Rev Neurosci* 2017; 18: 115–126.
- 20. Niso G, Gorgolewski KJ, Bock E, et al. MEG-BIDS, the brain imaging data structure extended to magnetoencephalography. *Sci Data* 2018; 5: 180110.
- 21. Pernet CR, Appelhoff S, Gorgolewski KJ, et al. EEG-BIDS, an extension to the brain imaging data structure for electroencephalography. *Sci Data* 2019; 6: 103.
- 22. Holdgraf C, Appelhoff S, Bickel S, et al. iEEG-BIDS, extending the brain imaging data structure specification to human intracranial electrophysiology. *Sci Data* 2019; 6: 102.