BRAIN IMAGING WORKING GROUPS SUPPORTED BY JPND

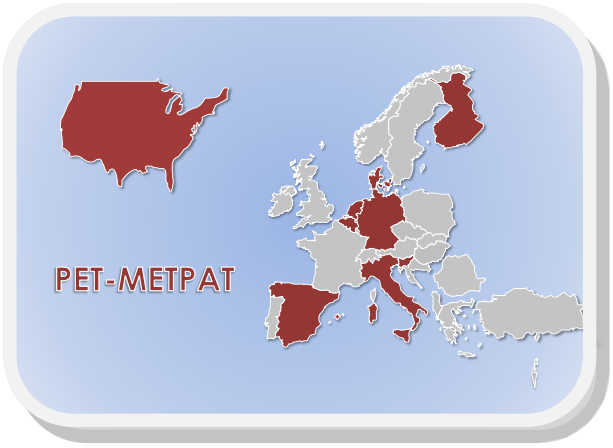
JPND research
EU Joint Programme – Neurodegenerative Disease Research

PETMETPAT

Harmonisation metabolic FDG brain pattern characteristics

This Working Group will investigate how best to perform and process a particular form of brain scan for patients who suffer from a brain disease such as Parkinson's disease or dementia. The scan is called an FDG-PET scan that, using the radiotracer FDG, allows for the measurement of glucose utilisation in the brain. Glucose is the only source of energy for brain tissue: through the breakdown of glucose by oxygen, biological energy carriers like the substance ATP are generated. Much energy is needed by the brain in order to make nervous tissue function possible.

However, the result of an FDG-PET scan performed in one centre is not necessarily the same as one performed in another centre. To be able to compare FDG-PET scans throughout Europe and beyond, it will be necessary to compare results and to agree to how the scan should be performed. If comparisons are made possible, then automated image analysis will be more achievable and data collection for diagnostic and clinical research in larger groups will be possible.



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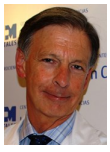

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PETMETPAT Symposium 1: February 17th & 18th – Madrid, ES

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1. SUMMARY

a) Research (to be done):

- Determining the effects of camera, reconstruction algorithms, filtering, and patient protocols on Parkinson's disease-related pattern (PDRP) expression in healthy controls, Parkinson's disease (PD) patients, and a Hoffman 3-D phantom.
- Harmonizing data acquisition and reconstruction in such a way that reliable PDRP scores can be obtained for each patient, independent of the scanning location.
- Investigating the effects of software differences on the PDRP, if any:
    - ScAnVP by Eidelberg & co. (New York) vs. Remco Renken's code (Groningen)
- Investigating the effects of other aspects of data-processing, such as the normalization template:
    - SPM default H_2O vs. FDG template by Daniela Perani's group (Milan)

b) Goals:

- To determine uniform standards of data and image acquisition, reconstruction, and quantification, translated into European standards:
    - Publication with results of research activities
    - Guideline for acquisition and quantification
    - Education
        - Potential conference workshops: SNM/EANM, Human Brain Mapping or Movement Disorder symposia

c) Vision:

- A network of centers (i.e. one "central center" per EU country) which could perform image quantification (SPM and/or SSM PCA) in a standardized manner, using the same software.
- A "benchmark" dataset which is acquired and reconstructed according to the standards determined in the current project. Clinical data for this benchmark dataset must be properly recorded. This benchmark dataset may be used to:
    - Determine which method is best and under which conditions (e.g. SPM versus SSM PCA).
    - Determine if certain changes in the method are helpful (i.e. result in greater diagnostic power).
    - Examples which were discussed include:
        - Excluding controls from the pattern (class-specific pattern)
        - Investigating the effects of 'covariates' (age, gender, ethnicity, education)

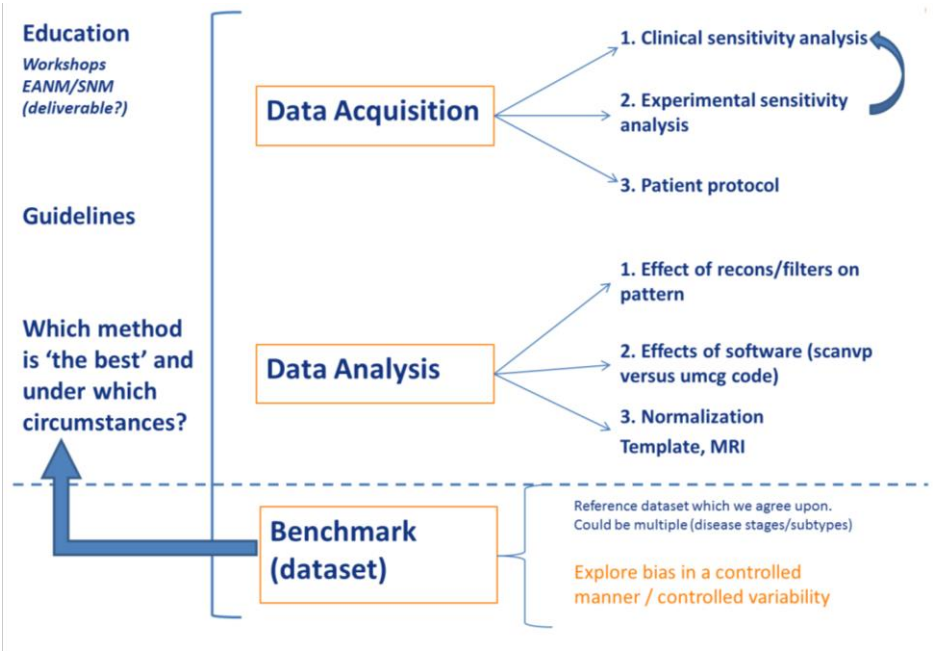
During the current "PETMETPAT" project, it is feasible to investigate both the effects of different systems and reconstruction algorithms on the PDRP score (i.e. "the input data"), and to investigate which factors influence the pattern itself (i.e. "the reference").

The points mentioned under "Vision" reflect the long-term goals and deliverables, for which new funding is needed. However, the results obtained during the JPND project will provide a solid basis, both in terms of knowledge and collaboration.

2. DISCUSSION POINTS AND PLAN

- Goal: Reliable, standardized quantification of FDG PET scans in neurodegeneration
  - SSM PCA (Groningen + Ljubljana) and SPM (Milan).

Several aspects are important to reach this goal, as indicated in the schematic below:



In terms of *Data Acquisition*, there are three categories which should be investigated:

1. Clinical sensitivity analysis
   a. We need to see which centers have access to *raw data* from retrospective scans, and get an idea of the different types of cameras we have. Ideally, there would be 5-10 PD patients and healthy controls for each camera. We would then like to compare several different reconstructions and filters on each camera.
   b. Primary result: What is the range of PDRP scores across various cameras and reconstructions?
2. Experimental sensitivity analysis
   a. 3D Hoffman Phantom studies will be performed at all of the participating centers. The most relevant / optimal reconstructions will be selected for this.
   b. Primary result: Is the range of phantom PDRP scores comparable to that of healthy controls?
   c. The possibility of using a PD "disease" phantom was also discussed (Cologne)
3. How does patient protocol impact PDRP scores?
   a. How does uptake time impact pattern scores? Or reduced frame-time?
      i. For this we would need dynamic scans.
   b. Perhaps from some of the retrospective (or prospective cases) we have available, we can investigate the effects of glucose, BMI, uptake time, etc. on the PDRP scores.
      i. See if there are patients with accidentally very high or very low blood glucose values. Is there a "safe range" for blood glucose levels to ensure proper PDRP score so that in the guideline we can state: "Blood glucose levels must be in between X and Y"?

During the meeting, we decided that every center involved can take part in the phantom studies. This project will be coordinated by Ronald Boellaard. The 3D Hoffmann phantom can be sent around to centers which do not have one, and practical help can be provided to those who are not familiar with these types of phantom studies.

Not every center has raw retrospective data available. Those who are able to provide some data are asked to select 5-10 controls and 5-10 PD patients, reconstructed using different settings which will be suggested by Ronald Boellaard (Groningen). At the end of this document, a survey is provided which each center can fill out.

Based on these surveys, an estimation can be made (i.e. regarding how much data we have, which type of systems, and which kind of reconstructions).

In addition to investigating the input data (i.e. the data from which the PDRP *score* is determined), we also need to investigate the effects of these metrics on the *pattern itself*. We should determine which pattern can be best used as a reference. For instance, it is possible that results are optimal when reconstruction parameters are such that the resolution of the data matches the resolution of the pattern. Although the effects of reconstruction algorithms on pattern scores has been investigated to some extent (publication by Maja Trošt and results presented during the meeting by Rosalie Kogan), it has not been investigated what happens if we also alter the pattern itself. The groups in Groningen and Ljubljana are experienced users of SSM PCA and will coordinate this part of the project.

Thus, in terms of *Data Analysis,* we suggest the following analyses:

1. Effects of reconstructions and filters on the pattern:
    a. Ljubljana data[1]
    b. Repeat in the Netherlands, others who have 20 controls and 20 PD patients for pattern derivation?
    c. "Cross-over": mix reconstructions of "reference" and "new subjects"
2. Effects of software on PDRP score? (ScAnVP vs. code from Groningen?). The most important thing is to select one approach which is then used by everyone.
3. Which template?
    a. H_2O or FDG-PET: we know the effect on SPM[2]
        i. Systematic: effect on SSM PCA / PDRP scores? Pattern itself?

Finally, we would like to create a *benchmark dataset* to make it easier to compare methods and to see how controlled differences in image quality (noise, resolution, etc.) across a large standardized dataset impacts the robustness of data variability. For instance, it would be valuable to have a dataset of 100 healthy controls. For now, this is beyond the scope of this project.

Results will be recorded in a publication, and subsequently a position paper or guideline will be written (i.e. "Role of FDG Imaging in Parkinson's Disease"). A second deliverable will be education; in the form of workshops during conferences (i.e. at SNM / EANM, Human Brain Mapping or Movement Disorder symposia).

It should be emphasized that the lack of use of FDG-PET in clinical criteria (e.g. for AD, IWG-2 criteria) is mainly based on studies showing poor performance of visual interpretation. This is not based on proper data analysis (i.e. semi-quantitative SPM).[3]

Several issues are likely to be encountered during the project:

1. Ethical and legal aspects related to data sharing
    a. It is proposed that the current group of researchers and centers form a *consortium*. Data shared within the consortium will be used only for the analyses indicated in this document.

2. IT and automatization
    a. We did not yet reach consensus on IT structure and automatization; i.e. how to share data safely.
        i. This could be done via the GLIMPS database; a safe IT-structure was created by the University of Groningen. The UMCG will contact them to see if we can provide a structure within the GLIMPS database for the JPND project. Ideally, we would need a grid system so that data does not cross borders?
        ii. Another option that was mentioned is "CATI," a service platform which provides a central image analysis for a fee.

[1] 'The effect of 18F-FDG-PET image reconstruction algorithms on the expression of characteristic metabolic brain network in Parkinson's disease', Tomse P *et al*, Phys Med 2017
[2] 'A standardized [18F]-FDG template for spatial normalization in statistical parameteric mapping of dementia', Della Rosa *et al*, Neuroinformatics 2014
[3] 'A Cochrane review on brain 18-F-FDG PET in dementia: limitations and future perspectives', S Morbelli *et al*, Eur J Nucl Med Mol Imaging 2015

3. Addition of new centers
    a. During the meeting, it was determined that new centers can only join if they have a significant contribution to make to the project, and if all parties agree. The addition of new centers to the project should be limited, as this adds to the complexity of the group and project.

What kinds of patients?

Diagnosis should be PD, but we cannot be too 'picky'. Decision: collect whatever you have but note down variability!

- For example:
    - Are patients on or off medication at the time of the scan?
        - Which factors influence this? (i.e. at what stage of the disease are patients kept on medication for the scan)?
    - Do patients have hallucinations or not?
    - Are patients demented, mildly cognitively impaired, or not (i.e. MMSE ≥28)?
    - Etc.

For these initial steps, the point is mostly to see the variability in PDRP scores. Meta-data should be as complete as possible (i.e. we should define a list of characteristics that are the minimum after the survey). Careful clinical characterization of patients will come later when we decide on the benchmark dataset.

3.TASKS PER CENTER

The tasks for each center are indicated below. These will be further specified after we receive a filled-out survey from each center. After we have received all surveys, we can determine if we have, for instance, enough data for the clinical sensitivity analysis.

Center	**Tasks**
HM Hospitales de Madrid, Madrid, ES	• Phantom study, don't have a Hoffman phantom (should be sent to them) • Few retrospective cases, some prospective. Are going to start a new research project and will save the raw data for those scans so that they can be used for JPND.
UMCG, Groningen, NL	• Phantom study • Coordination and centralized analysis of phantom studies (Ronald + Rosalie) • Coordination and centralized analysis of scans with different reconstructions (clinical sensitivity analysis) • Harmonization of "data analysis" part together with Ljubljana • Analysis of dynamic data ○ Effect of uptake time / frame duration on PDRP score
AMC, Amsterdam, NL	• Phantom study, provide aid in phantom studies to other centers • Organization of education & workshops • Jan Booij will inform if the VU has retrospective raw data of PD and controls (not available from AMC).
UHC, Cologne, DE	• Phantom study • Would like to implement SSM PCA code • Will ask ASAP participants if they have data to contribute • May have some prospective data ○ Are in contact with Munich, may be able to obtain data from the SPM paper by Granert *et al*. (HC, PD, AD, PDD, DLB, MCI)

KCLJ + IJS, Ljubljana, SI	• Phantom study. Hoffmann phantom should be sent from Groningen to Ljubljana as this center does not own a Hoffman. • Harmonization of 'data analysis' part together with Groningen (also see below)
HSR, Milan, IT	• Phantom study • Can provide prospective data (not retrospective as there is no raw data)
CHR Namur, Namur, BE	• Phantom study, will get help for this from Dutch centers (Groningen or Amsterdam). • Will try to collect 5 prospective (PD?) cases with raw data.
UW-Madison Advisory group, Wisconsin, US	• Phantom study
AUH, Arhus, DK	• Are asked to fill out survey as well and indicate any possible "focus points" or other roles they wish to fulfill.
TYKS, Turku, FI	• Are asked to fill out survey as well and indicate any possible "focus points" or other roles they wish to fulfill.

Coordinators per project:

Data acquisition	Phantom studies – Ronald Boellaard (Groningen) Clinical data – Nico Leenders / Rosalie Kogan (Sanne Meles) Patient protocol – Ronald Boellaard / Nico Leenders / Rosalie Kogan
Data analysis	Groningen + Ljubljana
Education & Guidelines	Jan Booij (Amsterdam), Daniela Perani (Milan)

Focus points per center: During the meeting, it became clear that some centers have their own specific interests and focus points which could benefit the JPND project. These are outlined below.

Center	**Focus**
HM Hospitales de Madrid, Madrid, ES	PET-MRI • Pattern scores in PET-MRI? Some patients also have a CT. Effect of MRI or CT attenuation correction on pattern score? • Atrophy, partial volume correction
UMCG, Groningen, NL	Groningen & Ljubljana are expert users of SSM PCA and will coordinate / analyze PDRP pattern scores. UMCG will focus specifically on the analysis of phantom data (Ronald Boellaard). Together, these centers will decide on which software and which reference pattern is used throughout the project. Aid other centers who wish to apply the SSM PCA method. Provide code that can be used easily.
KCLJ + IJS, Ljubljana, SI	
HSR, Milan, IT	Which method is best under which circumstances? i.e. SPM for differential diagnosis and SSM PCA for disease progression and sensitivity for subtle brain changes in prodromal stages? Wish to disseminate SPM method to academic centers.

4. TIMELINE

We would like all comments on this document and surveys to be submitted to *r.v.kogan@umcg.nl* / *k.l.leenders@umcg.nl* by **Wednesday, March 1st, 2017**.

Hoffman 3-D phantom should be completed before **Friday, May 5th, 2017***
**Ronald Boellaard + Rosalie Kogan will make instructional video for how to use Hoffman 3-D phantom, and Ronald will specify type of reconstructions.*

A further schedule of tasks will be sent out once we have received completed surveys from all of the centers and assessed the next steps.