For the administrative office:	*Approved*	☐	*date*
	Not approved	☐	*date*

PROJECT FORM

PROJECT TITLE AND ACRONYM

A computational tool for neurodegenerative stratification using PET/MR

PRINCIPAL INVESTIGATOR

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MEMBERS OF THE PNC CENTER

Name	Position*	Department	Role in the project
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Name	Country	Institution	Role in the project
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ETHICS COMMITTEE APPROVAL

Obtained [X] **Submitted** [ ] **To be submitted** [ ]

Data already acquired on an approved ethical committee presented by prof. Cagnin entitled: "Sperimentazione di una rete clinica per la diagnosi differenziale delle demenze a rapida progressione" (codice NRC AOP-0881, CESC 3872/AO/16 approvato il 14/07/2016)

Budget: Post-doc position (Research Grant)	
Cost per year (min 25.000€, max 30.000€):	**27500€**
Total cost:	**55000€**

Date: 27/02/2019

ABSTRACT
(max 200 words)

A “normal” template, to be used as reference, is mandatory in neuroimaging analysis because it allows to infer unknown differences between groups. Moreover, a single subject could be compared to the template to aid qualitative evaluation.
Templates representing average MR metrics and PET activity and several methods for the co-registration of single-subject to templates are available. However, an ideal template should be designed and built for a particular scanner and even for a particular acquisition protocol. In this scenario the acquisition of “normal” cases, the ideal candidate for a template, is a very complex task and frequently leads to a template with few cases. Aim of this project is to build an innovative template derived not from “normal” cases but from clinical cases that will depict the full spectrum of pathology. The aim is twofold:

- create a pipeline for the atlas-based segmentation of combined MR and PET images, in order to extract salient features from each segmented cortical and subcortical area. The Pipeline will be applied to the available dataset of 350 clinical brain PET/MR.
- stratify, area-by-area, the segmented multimodal data, to create a database that could be used to classify new data by means of machine learning techniques.

Description of the research program and expected results
(max 1500 words and max 3 figures)

Nowadays a person affected by a neurodegenerative disease increasingly undergoes a series of brain imaging investigations to detect "in vivo" biomarkers of neurodegeneration as for example brain atrophy (using MRI) or typical patterns of ^{18}F-FDG PET (for example: temporo-parietal hypometabolism in AD or fronto-temporal hypometabolism in FTD) or even pathophysiological hallmarks like beta or tau accumulation (using amyloid/tau tracers). So far, more than 350 non-oncological brain scans have been acquired, using ^{18}F-FDG in the integrated Siemens biograph mMR PET/MR scanner installed at the Nuclear Medicine Unit in Padova. Among these cases the majority are neurodegenerative diseases (including AD, FTD, FTD, DLB, PDD, CBD, MS, PSP, MSA) presenting cognitive deficits that have not been clarified by standard imaging protocols (frequently using MRI) and a minority are uncommon or atypical cases (such as Creutzfeldt–Jakob disease, SLA, autoimmune limbic encephalitis, West Nile encephalitis ecc).

In particular, the PET/MRI Biograph mMR device potentially allows the acquisition of:

- dynamic PET data from which infer information on tracer kinetics;
- several canonical MR sequences, like T1 and T2 weighted, DWI, PWI, DTI, fMRI;
- "special" MR sequences (pulse sequences or EPI navigators) used for movement correction allowing to reach the actual resolution of the scanner that can be used to correct for movement.

A template, to be used as a reference, is mandatory because it allows to compare two populations (for example FTD and FTD-mimickers i.e psychiatric phenocopies) in order to infer unknown differences between groups. Moreover, a single subject could be compared to the template to aid the qualitative evaluation of the nuclear medicine physician or neuroradiologist (as for example for the well-known neurostat or spm methods).
Templates representing average MR [1,2] and PET [3] activity are available and extensively used. They are very useful for the parcellation of cortical and sub-cortical regions in a number of areas. Several methods for the co-registration of single-subject to MR templates are available [4, 5, and 6 for a review], implementing both rigid and elastic transformation approaches.
However, an ideal template should be designed and built for a particular scanner (structural differences among scanners are a strong bias when building a template) and even for a particular acquisition protocol (because also differences in acquisition and reconstruction are a strong bias). In this scenario the acquisition of "normal" cases, the ideal candidate for a template is a very complex task and frequently leads to a template with few cases.

The aim of this project is to build an innovative template derived not from "normal" cases but a template derived from different brain diseases that will depict the full spectrum of neurological disorders. The aim is twofold:

- first, we want to create a pipeline for the atlas-based segmentation of combined MR and PET images, in order to extract salient features from each segmented cortical and subcortical area. Once the pipeline will be set up, we will process the already available dataset of about 350 clinical cases.
- second, we want to stratify, area-by-area, the segmented multimodal data, in order to create a database that could be used to classify new acquired data by means of machine learning techniques.

The multidisciplinary nature of this project requires the recruitment of a Post doc with a degree in mathematics with experience with both medical imaging and the development of computational approaches regarding PET and MR analysis.

In order to achieve the objectives of this proposal, we are implementing the following procedure, based on 6 tasks.

Task 1: data retrieval

With the support of the Nuclear Medicine Unit staff, the Post doc will retrieve the data from the PACS and will inspect the consistency of the data quality.

Task 2: preliminary preprocessing of data series and possible motion correction

A preprocessing step is necessary to correct possible head movement occurred during the acquisition, between MR sequences and PET data lasting 20-25 minutes. A rigid transformation will be used in this step [5]. The Post doc will visually inspect the result of the task. Moreover, the Post doc will carry on a comparison with the new method proposed in [7] applied to image registration.

Task 3: single-subject MR segmentation

Using Freesurfer software [8, 9], T1 isotropic (1x1 mm) MPRAGE MR images will be segmented. The resulting areas will be labelled using an atlas (as for example the Desikan-Killany) and then topologically mapped to a sphere. Once we have the cortical surface of the subject mapped to the sphere, we finally co-register the subject to the spherical template. Thanks to the preprocessing in Task 2, we have obtained the transformations between the T1 MPRAGE and the other MR series. We can hence create a template-matched, spherical version also for all the other MR series. Below this task workflow is shown.

Task 4: study and development of the mathematical aspects for the elastic MR to PET registration

Regarding the transformation from MR-based segmented areas to PET series, we have to face multiple problems:

- the resolution of PET images is drastically inferior with respect to MR images
- PET images are affected by partial volume effect, especially in atrophic cortical regions.

The idea is to create an additional sphere representing a template for PET data and construct, by resorting to conformal geometry theory [10, 11], the transformation between the points on this sphere and the MR one. On this new template, PET data of each subject will be coregistered. The results will be a set of coregistered, segmented sphere representing the PET activity (see Figure 1). Using again conformal theory geometry [12, 13], it would be possible to flatten the spheres in a more user friendly 2D visualization.

Task 5: creation of the “normalcy” database

Once the PET data have been segmented and co-registered to the template spherical space, we can consider each atlas-based region separately and we can stratify its metabolic activity values in order to obtain, the full spectrum of hypometabolism from the most severe to the near normalcy. This operation will be repeated for all the regions, building a database where the observations are represented by the subjects and the variables (features) are the metabolic activities in the different regions.

Once obtained the database, it will be possible to test it against particular subsets (FTD, ASL, AD, MS) of our cohort that have been validated using long clinical follow up, imaging follow up or CSF biomarkers.

Task 6: classification of a new subject

While implementing the method, new patients with neurodegenerative diseases will be acquired at the Nuclear Medicine Unit, collected and will be employed as test set to assess the predictive capability of our database using machine learning techniques like Random Forest [14], Support Vector Machine [15], and Neural Networks [16].

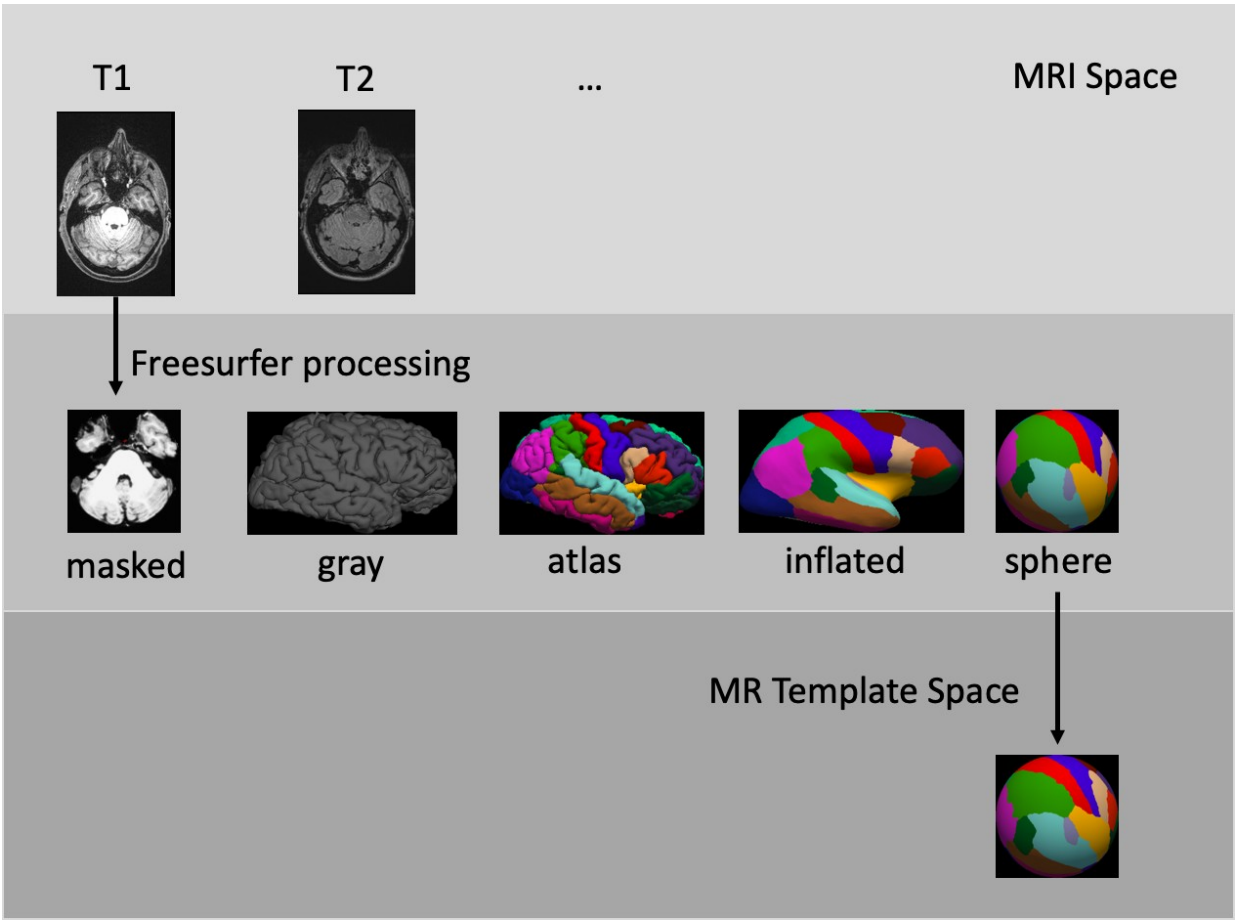


Figure 1. Flow chart showing the MR images segmentation steps.

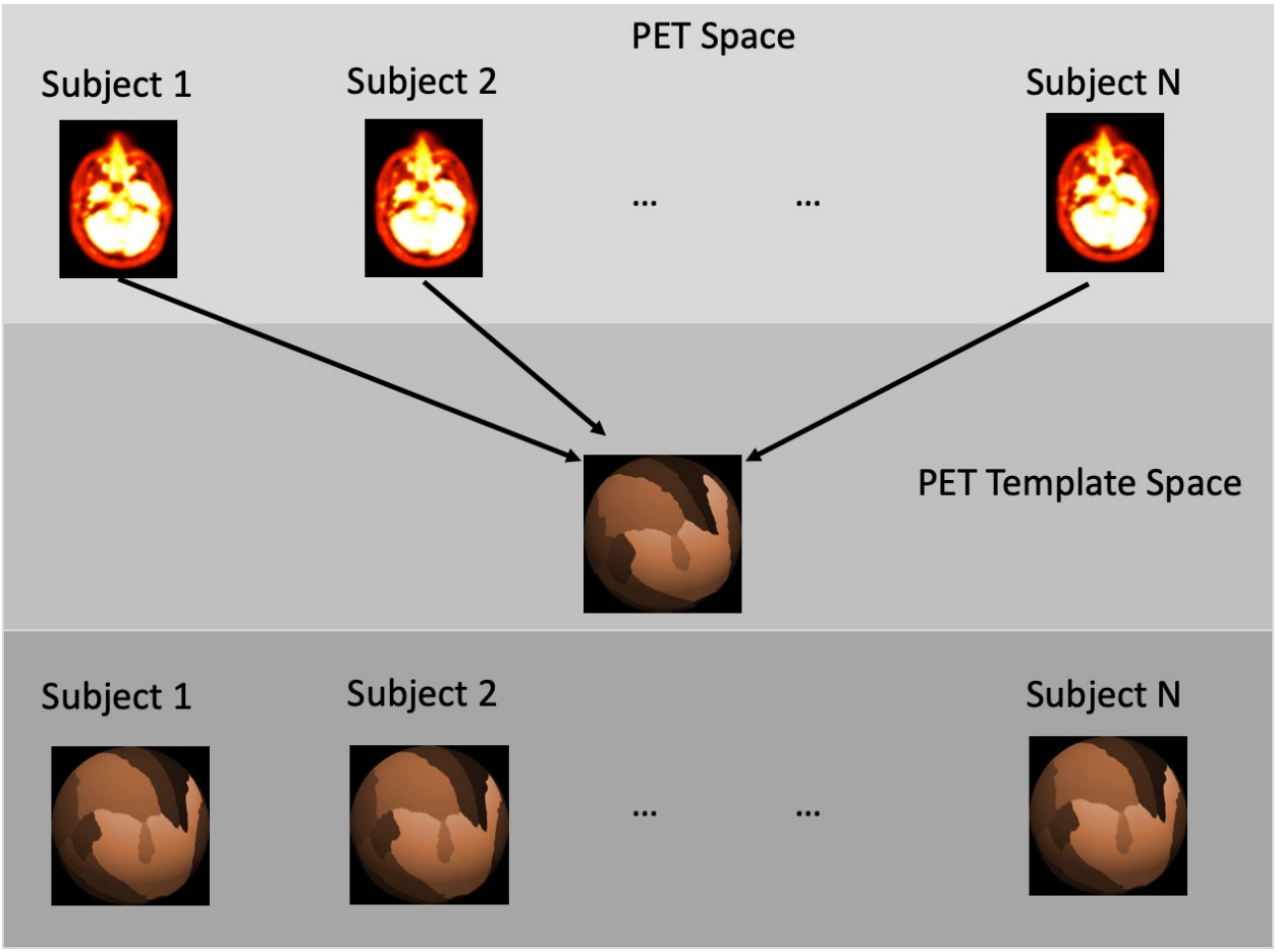


Figure 1. From single subject PET to spherical, template-coregistered PET data

This project fits well with the PNC research platforms because:

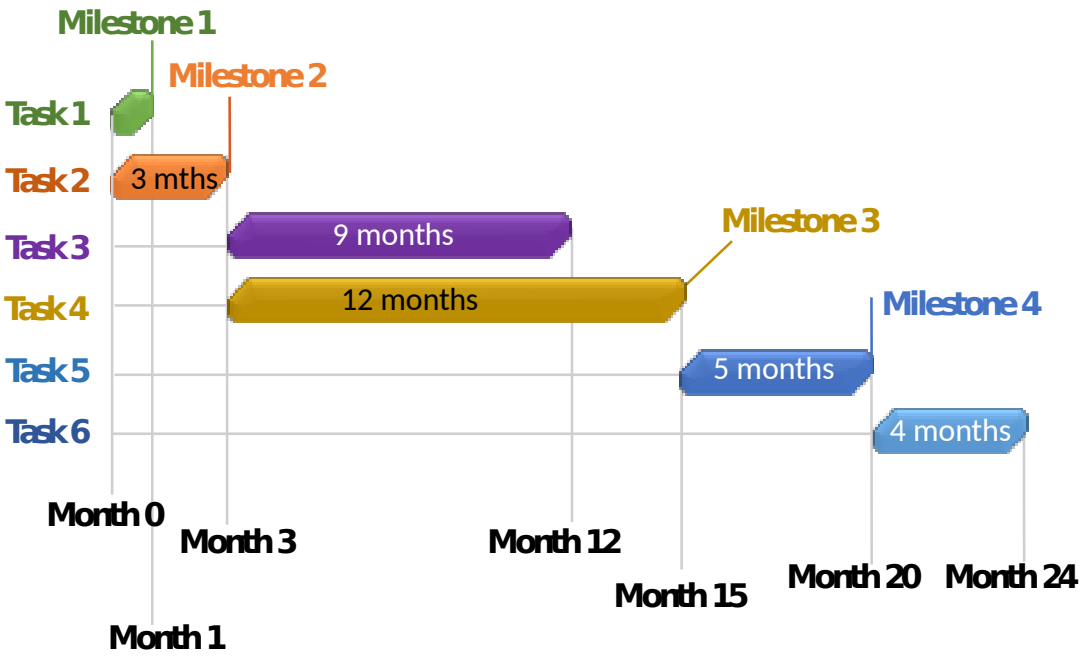
- it deals with Multimodal Neuroimaging and Analysis Methods and Computational Neuroscience;
- the data that will be used have already been acquired using the PET/MRI Biograph mMR 3T at Nuclear Medicine unit;
- the multidisciplinary nature of this proposal makes necessary the involvement of researchers from different areas;
- It allows to build a method that, if successful, could have a potential commercial interest;
- It allows PET/MR multicentric collaborations in order to both collect a higher number of patients and grants application.

Project milestones and timeline
(max 500 words)

This project, organized in 6 tasks, has the following timeline:

	Start (month)	End (month)	Duration (months)
Task 1	1	1	1
Task 2	1	3	3
Task 3	3	12	9
Task 4	3	15	12
Task 5	15	20	5
Task 6	20	24	4

Milestone 1 (month 1): The collection of the data is essential for the continuation of the project.
Milestone 2 (month 3): The preprocessing and quality check of the data has to be concluded successfully in order to proceed to the next task
Milestone 3 (month 15): The development and implementation of the new coregistration method is needed to analyze the data and build the database.
Milestone 4 (month 20): The construction and validation of the database is essential for the final task of classification of new patients.



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