Final Report Summary - TRIMAGE (A dedicated trimodality (PET/MR/EEG) imaging tool for schizophrenia)

Executive Summary:
Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. Schizophrenia disorders manifest themselves early in life during very active life periods of education and productive work and can impair functioning through the loss of an acquired capability to earn a livelihood, or the disruption of studies. This causes a high social and economic burden on European societies. In most of the cases, if correctly diagnosed, schizophrenia can be treated, and people who are affected can lead a productive life and be integrated in society. Schizophrenia is usually studied using a translational approach: psychological, social and biological parameters are acquired and analysed together, but the early diagnosis still remains a critical challenge. Currently, there is a strong need for an imaging tool that facilitates the diagnosis of schizophrenia early during development. It is important to stress that precise and early diagnosis cannot be achieved with a single measurement. Additionally, an off-line combination of data acquired separately could be insufficient, because several correlated patient-specific signals may vary over time. As a consequence, the full integration of different diagnostic modalities into a seamless clinical tool is necessary for the application of multiparametric measurements in all schizophrenia patients and especially for prodromic patients.

The main objectives of this project are two-fold: (a) to build and optimise an integrated diagnostic solution including a molecular imaging tool based on simultaneous Positron Emission Tomography (PET), Magnetic Resonance (MR) and Electroencephalography (EEG), and (b) to validate the new tool with possible biomarkers for detecting characteristic patterns in asymptomatic and at-risk patients and for monitoring disease follow-up during drug therapy. The goals of this project follow the scientific and technological developments in both the clinical and technological fields. These developments have been carried out according to three strongly correlated S&T sub-objectives:

- Sub-objective 1 (clinical) - Find new possible biomarkers and define a suitable multimodal paradigm with already available PET, MR, EEG and PET/MR systems that could provide clinical evidence on the feasibility of advanced schizophrenia diagnosis. Specific biomarkers that synergistically define the disease signature are still unavailable and need to be developed.

- Sub-objective 2 (technological) - Design, construction and test of an optimized cost-effective trimodality imaging instrument (brain PET/MR/EEG) for diagnosis, monitoring and follow-up of schizophrenia disorders. This leads to the optimization of well-established imaging modalities and their full integration in a novel dedicated trimodal instrument. In combination with the new set of biomarkers, the brain PET/MR/EEG scanner will represent a complete turn-key solution for the early diagnosis of schizophrenia.

- Sub-objective 3 (clinical/technological) - Validate the trimodal imaging device with regard to the results and the clinical data obtained during the development of the sub-objective 1.

The final product is a trimodal, cost-effective imaging tool consisting of PET/MR/EEG using cutting edge technology with
performance beyond the state of the art, and advanced knowledge about its application for the diagnosis of Schizophrenia. The tool is intended for broad distribution so as to enable effective early diagnosis of schizophrenia and possibly other mental disorders and brain diseases.

Project Context and Objectives:
Schizophrenia affects about 7 per 1000 of the adult population. Several reports demonstrate the economic impact of schizophrenia and the market potential for a device as proposed by TRIMAGE. Schizophrenia is the second most costly disease in terms of the average cost per patient with an average cost being higher than that for cancer and stroke. The earlier the treatment is initiated, the more effective it is. However, a significant number of people with schizophrenia do not receive any medication or are not yet receiving timely, adequate treatment. The WHO estimates that more than 50% of persons with schizophrenia do not receive appropriate care.

Diagnoses of mental disorders are often based on the clinical expertise of the treating physician. This is true also for the treatment: whether the patient responds to a given treatment can currently be assessed only by monitoring the clinical course (2-6 weeks), a long time for the patient and his/her family and for the health system. The trimodality imaging (PET/MR/EEG) device that we have developed in this project aims to give the clinicians an effective tool for the diagnosis and choice of treatment for mental health disorders such as schizophrenia. Early diagnosis of schizophrenia could provide the opportunity to intervene earlier and, thus, to avert the trajectory to psychosis.

The sub-objective 1) of the TRIMAGE project was addressed by conducting pilot studies on schizophrenic patients and healthy volunteers by using PET/MR scanners available to the collaboration. It was conducted by psychiatric teams and neurologists assisted by imaging experts in MR and PET and EEG. The recruitment of patients and healthy volunteers required for defining a suitable paradigm to be validated on the trimodal imaging PET/MR/EEG device started in 2015 at TUM and in late 2016 at Jülich, after the approval of the respective Ethics Committee and Radiation Protection Committee of both institutions. The experimental procedure at TUM was based on the 3T mMR tomograph and the tracer used was [18F]-Dopa; 51 subjects have been scanned (27 patients and 24 controls). The experimental procedure at Jülich was performed on the available Siemens MR-BrainPET unit equipped with a MR compatible EEG. The mismatch negativity (MMN) paradigm has been identified as a good marker and the used tracer was [11C]-ABP68: 16 patients and 29 healthy controls have been examined. The preliminary results of the pilot study both in Munich and Jülich have been published in the journal European Psychiatry (A. Del Guerra et al., 2018, vol. 50, 7-20) and are very promising.

The sub-objective 2) concerned the construction of the simultaneous TRIMAGE PET/MR/EEG scanner. The PET system is based on LYSO pixelated scintillators, SiPM photodetectors, TRIROC ASIC and fully digital electronics. The PET is a full ring composed by 18 rectangular sectors on a cylindrical geometry, with an inner radius of 157.2 mm and an axial length of 165 mm. Each sector is made of 3 square detectors, axially juxtaposed of size 52.8 mm, each one hosted in an RF shielded cassette. The Monte Carlo simulation gives a sensitivity of the scanner of about 7% at the centre of the FOV and a spatial resolution of about 2 mm (FWHM), i.e. well beyond the PET performance of the available 3T PET/MR whole body systems. MR compatibility has been studied theoretically and by simulation and its assessment has been done on the relevant parts of the system. The results obtained with a point-like radioactive source on two completely assembled detectors in coincidence give an energy resolution of about 20% (FWHM) and a coincidence time resolution of about 600 ps (FHWM). The entire PET tomograph has been fully assembled and tested at Pisa University.

In March 2017 the superconducting 1.5 T magnet (liquid helium free) of the MRI system was delivered by the manufacturer (SSI, USA) to RS2D, and the installation started. The gradient coils were also delivered, and they work to specs both as strength and uniformity region (250 mm DSV on X, Y, Z axis). The inner diameter of the gradient coil is 580 mm and the DSV is 300 mm. The necessary specific electronic/hardware components of the MRI system were developed. The RF coil was manufactured by Affinity imaging and can be used as a transmit/receive birdcage coil or as a transmit birdcage and 8 receive array. The development of the necessary MRI sequences (including MPRAGE, and EPI) has been implemented on a preclinical PET/MR system and then transferred to the TRIMAGE MR scanner. MR attenuation correction for PET was developed based on external attenuation maps given from specific subjects. The 1.5T-720 mm cryogen-free magnet now works to specifications. The EEG compatibility with MR and PET for simultaneous operation has been extensively tested on the available 3TMR Brain PET scanner at Julich and also on Trimage MR magnet, being this a new technology magnet operating with a cryocooler compressor to reach superconductive temperature.
At the end of the project all the three instruments have proved to work to specs. To complete the assembly of the trimodal instrument, it was necessary to find a proper location to be dedicated to its use. Although in the original proposal Jülich had been selected for hosting the scanner, during the execution of the project the original destination was not usable anymore and it was decided to move the installation to the Pisa University Hospital.

All the steps have been completed to identify the proper site for the scanner: the site must respect the proper radioprotection (Lead shielded rooms, hot area and cold area, etc.) and MR regulations (Faraday cage etc.). A suitable site was found at the Pisa University Hospital, and now it is already being prepared to host the TRIMAGE system. In order to make the validation pilot study of the TRIMAGE scanner, it was necessary to obtain all the authorizations from the Radiation Protection Authority, from the local Ethics Committee and from the ministry of Health for the use of the scanner as a Medical device. All the documentation to receive each authorization have been delivered already. When all the authorizations will be received, the scanner will be ready to validate the possible biomarkers for Schizophrenia on patients and to be more in general an asset for other clinical investigations of brain disease.

The final product of the TRIMAGE project, i.e. the PET/MR/EGG brain scanner will have a strong technological impact, not limited to the field of schizophrenia and brain disorders. More innovations will result from side tasks of the project. Some of the expected outcomes, which will have a technological impact, are:

i. Progress in SiPM fabrication and readout,
ii. New methods for improved DoI information and sensitivity optimization in PET,
iii. Improved algorithms for PET/MR attenuation correction and image quantification,
iv. Design, integration and performance evaluation of a PET/MR compatible insert,
v. Realistic GATE simulations using computational brain phantoms,
vi. Identification of possible Schizophrenia biomarkers, through a multimodal approach,
vii. Realization of a targeted clinical study using the recently introduced PET/MR scanners.

During the 5 years of the project, a project logo, a brochure set and other project identity resources were delivered. The TRIMAGE website is online and is being maintained with the latest updates coming from the consortium. The number of TRIMAGE publications is substantial. As of today, the publication list accounts for 21 peer reviewed scientific articles on the most impacting journals in the field, 24 conference presentations and 3 other presentations.

The TRIMAGE project is set in an emerging area of multimodal brain imaging applications, where new kinds of expertise are being introduced. In order to reinforce the future generation of scientists for continuing development in these specialised emerging fields, TRIMAGE partners participated in the following actions:

i. Training of young scientists via lectures at universities, and education of young researchers during practical training sessions as well as seminars.
ii. Practical skills have been developed by supervising diplomas and doctoral theses. Where appropriate, exchanges have been organised for PhD/Post doc students between TRIMAGE partners.
iii. Organization of scientific schools and workshops.

A series of 5 workshops on PET/MR has been co-organized yearly from 2014 to 2018. Papers from these workshops have been published on special issues of international peer-reviewed journals. Five training schools on PET/MR have been organized: the first one in Athens in May 2014, the second one in Jülich in March 2016, the third one in Lisbon in May 2017, and the fourth one in Isola d’Elba in May 2018. A workshop dedicated to “Schizophrenia and other mental disorders” was organized in June 2017 in Pisa.

In parallel to more general external communication, TRIMAGE has included education within medical programs to help open up a new generation of clinicians to its technology at national and European levels, in particular with psychiatrists, clinicians and doctors. Partners participated in topical workshops and seminars aimed at stressing the interdisciplinary character of biomedicine with particular reference to the emerging area of multimodal imaging and personalised therapeutic treatments.
via biomarkers identification.

In summary, the TRIMAGE Project has been a fully interdisciplinary project in the field of neurological imaging. Its achievement of the planned objectives has already ensured a scientific and clinical follow-up for the use of the new technology TRIMAGE scanner for brain imaging. The translational capability of its finding will be the aim of future research.

Project Results:
The TRIMAGE project has been a truly interdisciplinary project with neurologists and psychiatrists collaborating with engineers, physicists and SME’s to contribute new findings to the field of imaging in schizophrenia and other mental disorders. The science and technology results have been achieved in the clinical investigations for the search of possible new biomarkers for schizophrenia and in the innovative PET/MR/EEG brain scanner, which was completely designed, built and tested within the TRIMAGE consortium. The major outcomes are described in the following sections.

For the complete details of the main S&T results/foregrounds please see attachment s-t-results.pdf.

Potential Impact:
For the complete description of the potential impact see attachment potential-impact.pdf.

List of Websites:
site: www.trimage.eu
email: trimage_po@unipi.it

other information available in the attachment other-information.pdf

Related information

| Documents and Publications | final1-s-t-results.pdf |

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