Regeneron ISEF 2021: Research Plan

Project Title: NeuroPET-M: A Multimodal PET Scan Platform as a Novel Diagnostic Tool for Neurodegenerative Diseases

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RATIONALE: Neuroimaging is a powerful technique to study i) brain function, ii) mechanisms of brain diseases and iii) to diagnose neurodegenerative diseases.[1-4] In this regard, positron emission tomography (PET) is a powerful imaging technique which enables in vivo examination of brain function and disease diagnosis.[3, 4] PET scans help neurologists to visualize the brain's biochemical levels by injecting a radioactive tracer. Radioactive tracers are essentially molecules that are labelled with a positron emitting isotope[1, 2] that have an affinity toward neurotransmitter sites, specific proteins, and neurochemicals in certain brain regions. A PET scan can project the brain areas where the radioactive tracers can bind, which results in producing an image that presents the location and concentration of the neurotransmitters or proteins of interest.[4-6]

Neurodegenerative diseases can be diagnosed by PET scans of patient's brain region to detect and diagnose diseases.[6, 7] While diagnosing complex brain diseases such as Alzheimer's disease (AD), there are numerous factors involved in the disease pathology such as brain amyloidosis, tau accumulation, neuroreceptor changes, metabolism abnormalities and neuroinflammation.[6, 7] Analysis of PET scan image provides evidence of abnormal biochemistry in the brain. Physicians and Neurologists can use this evidence to predict and diagnose neurodegenerative diseases such as AD for early detection.[6, 7]

Novelty of my research plan: Depending on the disease state, multiple biochemical changes can happen in the brain. PET scans are primarily used to study a single biomarker or neurotransmitter at a time and is one of the most versatile techniques and yet its full potential has not been realized to study and diagnose multiple biomarkers and neurotransmitters in brain.[8-10] *I am proposing a novel software platform called as "NeuroPET-M" which will optimize PET-based neuroimaging by providing a ground-breaking diagnostic tool for neurologists (Figure 1).* In theory, the process would require a set of multiple PET scans for different biomarkers and create an interactive three-dimensional space of the patient's brain, mapping multiple biomarkers and neurotransmitters in the brain. There has been little to no work reported on combining PET scans, and my research project will open up a new chapter in medical diagnostic procedures. Scientifically, it will allow researchers to study and create biomarkers for complex conditions, such as bipolar disorder.[3]

Rather than mapping and analyzing single PET images as a tool to detect a particular biomarker or neurotransmitter of interest, my research will combine multiple PET images to map the locations of multiple biomarkers and or neurotransmitters for more discrete analysis and disease diagnosis. Thus, my project aims to develop a software platform that combines PET scans to produce a multimodal image that maps numerous biomarkers and or neurotransmitter localizations in the patient brain as a novel diagnostic tool.

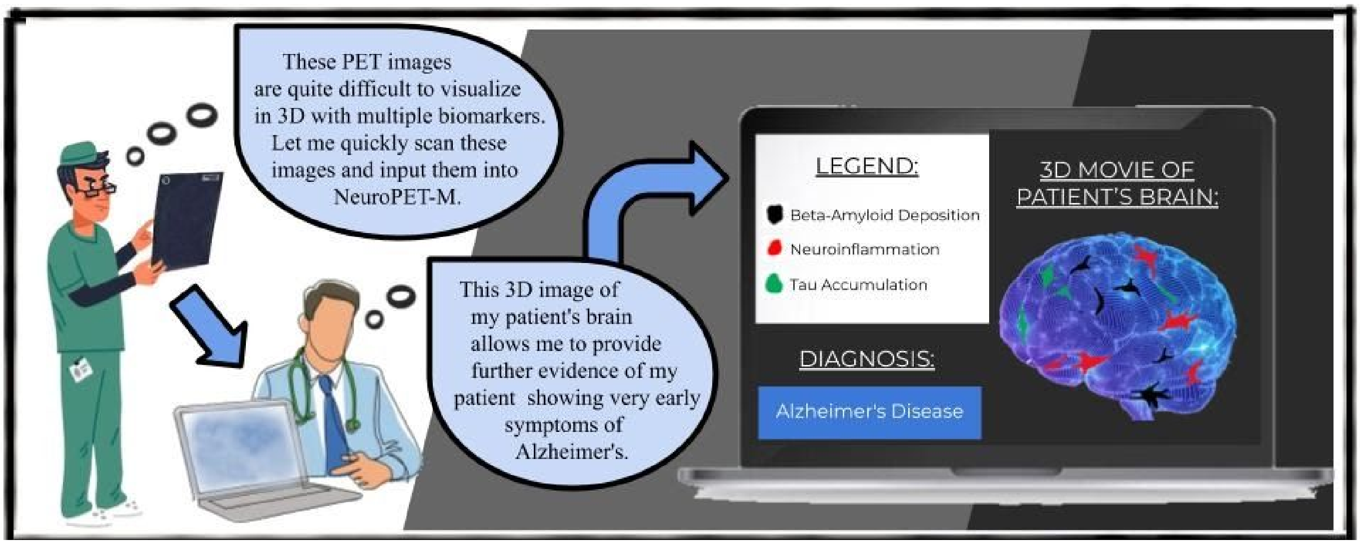

Figure 1: A summary diagram of NeuroPET-M, a novel software platform to diagnose brain diseases.

RESEARCH QUESTIONS:

1. How can we design efficient PET image processing software to advance ease the process of diagnosis?
2. What software design strategy can be used to convert a set of two-dimensional PET into a three-dimensional (3D) space map?
3. What is the most optimized programming language and graphics library that will allow image input and an interactive window output, while also providing computation for images and tensors?
4. What is the current state of research in software development related to translating multiple PET image data into 3D space with multiple biomarkers?
5. How can we differentiate multiple biomarkers and or neurotransmitters in a complex system such as the brain?
6. Is it possible to quantify the output obtained by combining brain PET images to determine the type and location of biomarkers and neurotransmitters involved in disease conditions and what software programming language and design can be used to achieve this?
7. Is there a database of biomarker distribution that relates to disease conditions in the brain? If so, is a self-diagnosing addition to the software possible?

HYPOTHESIS:

1. Combining multiple PET images based on different radiotracers will enable better disease diagnosis and disease detection for brain disorders (Figure 1)
2. Developing novel PET image processing software platforms that can combine multiple scans of patients based on their race, ethnicity, sex and age will serve as a novel tool in disease diagnosis and treatment of brain diseases

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ENGINEERING GOALS:

1. To visualize the location of multiple (more than two) biomarkers in the brain through a software application that takes a set of patients PET images as input and relays a widget consisting of a 3D interactive brain output.
2. To develop a self-diagnosing tool that works by locating abnormalities in biomarkers and cross-referencing to a database to output a possible condition in the patient's brain.

Note: Goals are likely to change as I work on the project

EXPECTED OUTCOMES:

It is anticipated that my research will develop novel software platforms that can be used to study PET images, combine multiple PET images and enable their analysis in disease diagnosis to advance the field of neuroscience. This research will enable development of open access PET image databases that can be used to study the location of multiple neurotransmitters. The results obtained from this work will be disseminated at conferences (eg: Annual Symposium on PET/CT organized by American College of Radiology and Society of Nuclear Medicine and Molecular Imaging, USA).

DESIGN CRITERIA:

1. The proposed software platform will be modularized, object-orientated, lightweight program in terms of time and memory, and user friendly to any end user (eg: physicians or nurses or nuclear medicine technologists).
2. The self-diagnosing tool in the suggested software platform will be correctly diagnosing a patient with a neurodegenerative or neuropsychiatric disease for at least 80% of the test cases.

MATERIALS:

- A workstation with the following recommended specifications:
    - Processor: 3rd Generation Intel® Core™ i7-3520M (3.60 GHz, 4MB L3, 1600MHz FSB), or later generations.
    - Operating System: Windows 8 (64-bit or 32-bit) and higher generations or any Linux distro.
    - Memory: 4GB or higher is acceptable.
    - Storage: 128GB SSD or higher is acceptable.
- A data set of brain PET scan images obtained from healthy volunteers and patient samples available from publicly available resources.
- An internet connection with (at minimum) 25 Mbps for download speed and 5 Mbps for upload.

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PROCEDURE:

A set of brain PET scans of multiple biomarkers from patients and healthy controls available from local hospitals and or through public databases will be acquired. The software application will be designed choosing a set of technologies required to build the application. To satisfy the design criteria for this research and to achieve my engineering goals, programing languages such as Halide (C++ API) and GTK+ will be used to write my software application. It is anticipated that approximately 1-2 months will be required to iterate and draft the first version of the application. The programming inputs used will be a dataset of brain PET scans and the outputs obtained will be a widget that will map a patient's brain into 3D space and localize biomarkers to brain regions. The software application will be subjected to revision and multiple iterations to evaluate its efficiency and accuracy. The real-world test of the software platform will be evaluated by providing this tool to local hospitals which can provide valuable data that will be incorporated to further refine the application. It is anticipated that the first version of this application will be released to a local hospital on a trial basis to obtain feedback on the accuracy and its utility in diagnosing brain biochemistry.

DATA ANALYSIS:

The 2D-PET scan data of multiple biomarker locations in the brain will be combined to obtain 3D brain PET scan images using the proposed software interface.

In practice, brain PET scan outputs generated from the computer software are displayed either as a horizontal or vertical slice across the brain. Location of biomarkers or neurotransmitters or brain regions are mapped based on the radioactivity observed. A color coding scheme is used to interpret the intensity of radioactivity. For example, black color indicates no radioactivity whereas grey indicates intermediate levels of activity and white representing highest radioactivity. Other color codes that can be used include rainbow colors with red representing the highest level of radioactivity and blue or violet or black representing low levels of activity. The image data mining of brain PET scans will be conducted by measuring the location of the biomarker and the gradient of colour at that location. This will also be quantified to correlate with concentration levels of the biomarkers and or neurotransmitters by comparing with healthy PET image data. This information will be used by mapping the localizations of each biomarker into 3D space.. This information will be used to cross-reference with the known database of diseases and provide an output from the self-diagnosis tool that is relevant toward the PET scans provided. Effort will be put in place to combine multiple 3D PET image frames to obtain animated movies of 3D-PET scan.

RISK AND SAFETY:

The entire research will be conducted from my home using my laptop. Known PET images will be obtained from online resources. Due to the Covid-19 situation, my meetings with my mentor Dr. Nekkar Rao will be organized via a virtual platform. Therefore, I do not anticipate any potential risks and safety precautions to follow for this project.

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TIMELINE:

Approximately 4-months will be used to complete this proposal. The first month will be used to conduct a thorough literature review related to the project and another three months will be used to design, develop and optimize software platforms and to document the results obtained.

BIBLIOGRAPHY:

1) Fumita, M and Innis, R. B. In vivo molecular imaging: Ligand development and research applications (Chapter 31). In *Neuropsychopharmacology*: The Fifth Generation of Progress. Edited by Kenneth L. Davis, Dennis Charney, Joseph T. Coyle, and Charles Nemeroff. American College of Neuropsychopharmacology (2002).
2) Tai, Y. F., Piccini, P. Applications of positron emission tomography (PET) in neurology. *J. Neurol. Neurosurg. Psychiatry* 75, 669-676 (2004).
3) Shen, L. H., Tseng, Y. C., Liao, M. H., Fu, Y. K. The role of molecular imaging in the diagnosis and management of neuropsychiatric disorders. *J. Biomed. Biotechnol*. 2011, 439397 (2011).
4) Positron emission tomography molecular imaging for drug development. *Br. J. Clin. Pharmacol.* 73, 175-186 (2011).
5) Niyonambaza, S. D., Kumar, P., Xing, P., Mathault, J., Koninck, P. D., Boisselier, E., Boukadoum, M., Miled, A. A review of neurotransmitters sensing methods for neuro-engineering research. *App. Sci*. 9, 4719 (2019).
6) Schilling, L. P., Zimmer, E. R., Shin, M, Leuzy, A., Pascoal, T. A., Benedet, A. L., Borelli W. V., Palmini, A., Gauthier, S., Rosa-Neto, P. Imaging Alzheimer's disease pathophysiology with PET. *Dement. Neuropsychol*. 10, 79-90 (2016).
7) Chandra, A., Valkimadi, P. E., Pagano, Cousins, O., Dervenoulas, G., Politis, M. Application of amyloid, tau, and neuroinflammation PET imaging to Alzheimer's disease and mild cognitive impairment. *Hum. Brain. Mapp*. 40, 5424-5442 (2019).
8) Krzemien, W., Gajos, A., Kacprzak, K., Rakoczy, K., Korcyl, G. J-PET Framework: Software platform for PET tomography data reconstruction and analysis. *SoftwareX* 11, 100487 (2020).
9) Roberto de la Prieta (February 8th 2012). Free Software for PET Imaging, Positron Emission Tomography*, Current Clinical and Research Aspects*, Chia-Hung Hsieh, IntechOpen, DOI: 10.5772/31882. Available from: https://www.intechopen.com/books/positron-emission-tomography-current-clinical-and-research-aspects/free-software-for-pet-imaging
10) Vaquero, J. J., and Kinahan, P. Positron Emission Tomography: Current challenges and opportunities for technological advances in clinical and preclinical imaging systems. *Annu. Rev. Biomed. Eng*. 17, 385-414 (2015).