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The Advents of Hybrid Imaging Modalities: A New Era in Neuroimaging Applications

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Hybrid Imaging modalities have shown great potential in medical imaging and diagnosis. A more comprehensive and targeted view of neurological disorders can be achieved by blending the anatomical and functional perspectives through hybridization. With consistently improving technologies, there have been many developments in fused imaging techniques over the past few decades. This article provides an overview of various bimodal and trimodal hybrid imaging techniques being developed and explored for neuroimaging applications. Recent advancements and potentials are discussed for single photon emission computed tomography-computed tomography (SPECT-CT), positron emission tomography-CT (PET-CT), PET-magnetic resonance imaging (PET-MRI), electroencephalography-functional magnetic resonance imaging (EEG-fMRI), magnetoencephalography-fMRI (MEG-fMRI), EEG-near-infrared spectroscopy (EEG-NIRS), magnetic resonance-PET-EEG (MR-PET-EEG) and MR-PET-CT in the perspective of neuroimaging. A comparison of these hybrid approaches is provided on a single platform to analyze their performance on the basis of several common factors essential for imaging and analyzing neurological disorders and in vivo molecular processes. This article also provides an overview of recently developed advanced imaging technologies that are being hybridized with other imaging modalities and being explored as potential techniques for neuroscience. Novel approaches and clinical applications of hybrid neuroimaging are anticipated with inclusion of new technologies, better sensing capabilities, multimodal probes, and improved hybridization.

1. Introduction

In the past and in recent years, hybrid imaging has attained a much higher position in imaging efficiency and diagnostic accuracy through continuous technological advancements. Hybrid imaging modality system is a combination of two or more imaging modalities engendering a new form of imaging technique. By consolidating the innate advantages of the hybrid imaging, it continues to improve and compete alongside the emergence of newer techniques of medical imaging.

Hybrid imaging has been in the medical scene since 1990s, with the help of amalgamation of either hardware or software images, alike, that allow the congenial combination of functional and anatomical image formation. There are various hybrid imaging modalities present as of now, out of which, positron emission tomography-computed tomography (PET-CT), single photon emission computed tomography-computed tomography (SPECT-CT), PET-magnetic resonance imaging (PET-MRI) are few of the majorly explored approaches for neuroimaging applications.

In the past few decades, many imaging techniques have been introduced, but none of them were precisely productive in revealing the complex anatomy and functionality of the brain simultaneously. With the discovery of modern nuclear imaging techniques, the efficiency has increased, however the limitations weren't annulled. The pioneer of hybrid imaging modalities is SPECT-CT, for which, the basic idea of image fusion was proposed by Kaplan and Swayne in 1989[1] and the modality itself was designed by Blankespoor et al., in 1994.[2]

This trend was followed by Townsend and Nut, as they tried the same method to fuse PET imaging modality and CT image modality independently in 1992.[3] However, the stabilized version was not available till the year 1998. With these systems as pioneers, hybrid imaging modality research in medical field has become a trend. These inventions were followed by various other similar approaches, not only for molecular imaging but also for ultrasound, thermal and various other new techniques.

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The other major group of hybrid imaging modalities is based on the fusion of functional and cognitive neuroimaging techniques such as functional MRI (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) and near-infrared spectroscopy (NIRS) among themselves or with anatomical approaches of imaging.

The need for hybrid imaging in neuroscience is to improve the noise rejection, attenuation correction and provide image fusion for anatomical referencing.[4] Image fusion, also known as functional anatomical mapping (FAM) is very important parameter that should be provided by the hybrid systems. These hybrid systems precisely align the two sets of images and eliminate the inaccuracies caused by breathing movements and other artifacts.

Inventions of imaging modalities have moved forward and now, the newer techniques are collectively known as advanced imaging techniques, which are expected to have high potential and the probability of being used as a hybrid modality. Some of the popular advanced imaging techniques are photoacoustic tomography, thermography, ultrasound imaging, tactile imaging, and functional NIRS (fNIRS). These imaging modalities, when hybridized with other techniques have shown exciting opportunities for expansion of neuroimaging into the unknown domains of brain.

This review article discusses the development and advancements of hybrid modalities for neuroimaging applications and provides an insight on various applications of hybrid imaging modalities in neuroimaging field with comparison of their approaches and capabilities. Further, an overview of the newly developed advanced imaging techniques is provided which are being expected to be explored for hybrid imaging modalities in near future.

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2. Hybrid Imaging Modalities in Action

Neurological disorder related molecular processes in brain are believed to be highly complex and their revelation is not feasible through a single approach of imaging. As discussed in the global burden report by the world health organization about most prevalent diseases, neuropsychiatric disorders that have affected most of the patient population are unipolar depression, and other neurological conditions which thus causes 1/3rd of the adult disability.[5] The exact reason for most of these disorders is still being explored and thus, imaging them at an early stage remains a challenge till now for neuroscientists. The hybrid approach considering anatomical and functional correlation simultaneously is known to have the potentials for providing solutions to these mysterious conditions, and the pace of advancements is looking for new era in neuroimaging applications.

Each imaging modality has its own special area of revelation and sometimes we need information from two or three imaging domains which led to the introduction of hybrid imaging approaches. Some of the most commonly used hybrid imaging systems are PET-CT and SPECT-CT, used for precise anatomical localization and PET-MRI, used for reduced radiation exposure and superior soft tissue contrast. The other explored medicinal imaging approaches are Ultrasound-MRI, PET-SPECT, EEG-fMRI, NIRS-fMRI and NIRS-EEG. They vary according to their approach on imaging the target and process and are used in diagnosis of various neurological diseases and disorders. Various hybrid approaches are discussed in the following sections.

2.1. Acclaimed Hybrid Imaging Techniques

2.1.1. SPECT-CT

SPECT-CT is one of the first hybrid imaging systems to be developed. The basic principle of SPECT-CT imaging system is to estimate the diverse range attenuation map and then consolidate it in the iterative reconstruction of SPECT image. Thus, the advantages of SPECT-CT in neuroimaging is that it gives good CT attenuation correction, anatomical accuracy of image registration, improved region of interest based image analysis and finally image interpretation. Fused pictures enhances imaging understanding in patients with irregular SPECT discoveries and provides data of clinical worth, permitting more precise staging and anticipation, and better administration of the patients.

The perks of combination of SPECT-CT hybrid technique was analyzed by Pfannenberg et al. in the neuroendocrine cancer patients.[6] He proved that SPECT-CT was a lot more accurate as compared to conventional SPECT imaging. On top of that, the results of image fusion also changed treatment options in around 1/4th of the patients. It also provides proper localization and characterization of equivocal lesions, that is, whether they are malignant or benign and have a considerable impact over management of patients as it also suggests the most appropriate therapeutic approach.[7] Chang et al. analyzed pallidoreticular pathway in patients with carbon monoxide intoxication and used SPECT-CT fusion images for semi-quantitative analysis of the ^{99m}Tc-TRODAT-1 signals.[8] The reconstructed ^{99m}Tc-TRODAT-1 SPECT images were fused with CT images using fusion software.

SPECT/CT showed great potential in finding out the location of cancerous cells in thyroid and breast carcinomas but it's usage in finding carcinoma cells in the brain as compared to PET-MRI, was lesser. But that doesn't imply that it wasn't capable enough to provide the physicians with a diagnosis of good quality.[9] Various scientists suggested ways to improve the attenuation correction with accurate co-registration of the CT images. Kathy Willowson et al., had proposed a method to improve and confirm a quantitative technique for SPECT, based on CT. This was done to find out the practicality of this method being imposed on SPECT images of brain tumor with a developing SUV.[10] They concluded that their method is a very feasible method of quantifying the SPECT data. Although SPECT/CT technique has great potential, they have achieved less penetrance into the research and clinical environment in comparison to PET-CT. Some other potentials of SPECT-CT includes the fact that ignoring the ever growing PET-CT installations numbers compared to SPECT-CT, it still stands as the cheaper alternative which has a greater range of compatible radiotracers to choose from and it is easily accessible. Another benefit from using SPECT-CT is its capability to simultaneously image various radiotracers targeted to various biological functions.[11] An useful significance of SPECT-CT is it's possibility to apply absorption and motion correction which is done in order to minimize the amount of artifacts created due to partial absorptions.[12] And, on top of that, simultaneously functioning CT and SPECT would provide a greater edge and attraction to the user with its ability to efficiently provide results. It could be the most commonly chosen modality for detecting tumors of various origins and metastated areas as confirmed by one of the experiments, conducted to assess the advantage of SPECT-CT over SPECT in detecting and accurately locating the neuroendocrine tumors.[13] It concluded that the overall sensitivity, in accordance to the sample and subjects, is 97% in SPECT-CT and 61% in SPECT. Thus it showed that its sensitivity and sensibility is higher than that of SPECT.

2.1.2. PET-CT

PET-CT is recognized as one of the most renowned hybrid approach due to its higher accuracy of imaging.[14] Although the images are acquired sequentially from PET and CT, it gives the most efficient image co-registration and image fusion. PET-CT images are generally acquired in the treatment position and it should be done with proper equipment in order to avoid artifacts caused by movements. PET-CT has been finding applicability in diagnosis of cancerous cells at an early stage, with its highly sensitive detectors. Some of the cancers that have been detected using PET-CT are cervical node metastases, head and neck carcinomas, and even used at times for detection of the cancer's primary origin. Usually tumor cells have much higher metabolic rates compared to normal cells and thus when Flurodeoxyglucose (FDG) is used as glucose tracer, the uptake will be greater in tumor cells than the normal ones. Thus, this property of the tumor cells is used to image it using PET technique. The base concept on which PET works was proposed more than a few decades ago by Otto B Y Warburg and the concept of using FDG as a radionuclide for PET was introduced by Abass Alavi, David Kuhl, and Martin Reivich in 1973.[15]

Compared to CT imaging system that needs the carcinoma cells to be in a large amount in order to detect them, PET-CT using FDG can recognize even a small group of cells. PET-CT with FDG has been proved to give higher accuracy in imaging malignant tumor cells than either of the conventional imaging modalities separately could provide.[16]

It had also been used to detect traumatic brain injury caused by intensification of copper uptake, by Fangyu Peng et al.[17] They performed this experiment on the basis that copper is a necessity for the injured body to recover and it is said to be the second most abundant substance in the brain.[18] Thus, they inferred that the shocked and injured cells would take up more copper for recovery than the normal cell would have. ^{64}Cu of $^{64}CuCl_2$ PET-CT was used as biomarker to locate the traumatized brain cells and study them. Their experiment concluded that when compared to the normal cortex, there is a slowly progressive copper uptake in the injured cortex in both the normal control and sham control. Boss et al. compared PET-CT and PET-MRI fusion images for intracranial masses.[19] They fused low-dose non–contrast-enhanced CT images with ^{11}C-methionine PET image for a better overview of glioblastoma multiforme as shown in **Figure 1**.

Some of the recent developments in PET-CT are that its radiation dose, which receives a major contribution from CT, is reduced. Although, PET and CT being combined together has caused a significant increase in the radiation dose given to the patient.[20–22] This issue was addressed by Tonkopi et al. and they proved that the radiation can be reduced from a whopping 8.1 mSv to 5.5 mSv, without a great deal of difference in the image quality. The overall optimization has decreased the mean effective dose up to 32%.[23]

2.1.3. PET-MRI

PET-MRI idea was developed even before the first successful nuclear medicine hybrid imaging modality was developed. Paul Marsden and Simon Cherry came up with this idea in order to improve small animal scanning.[24] Originally, when the fusion of MRI and PET was developed, there was a definite difference between the images being scanned sequentially and simultaneously.

PET imaging gives deep perception of physiological processes at a low resolution. PET is a wonderful accessory for

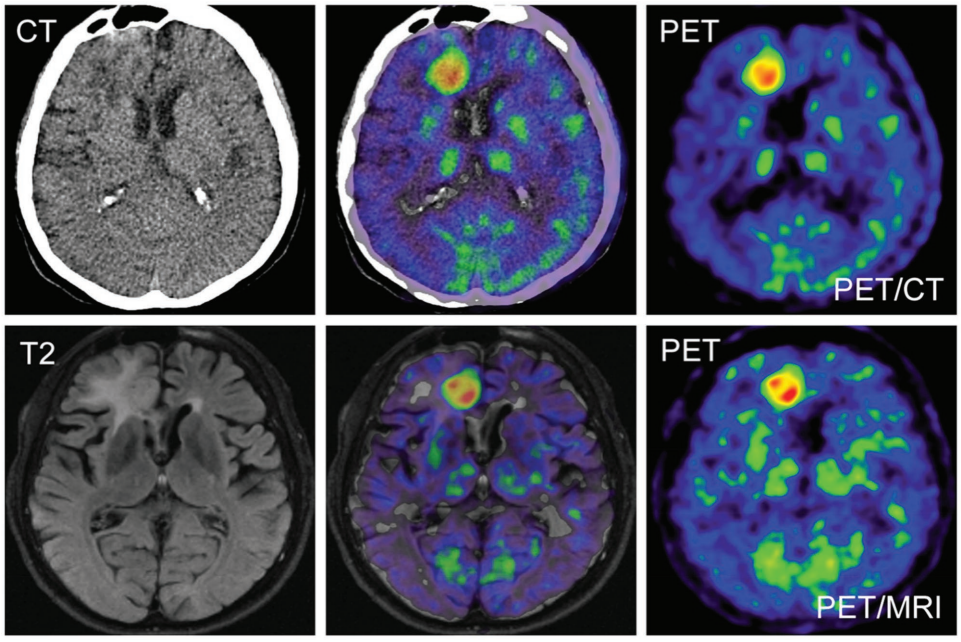

Figure 1. PET/CT and PET/MRI images of 56-y-old patient with glioblastoma multiforme on right side in frontal area close to interhemispheric fissure. (Top) PET/CT data: low-dose non–contrast-enhanced CT scan (left), corresponding fusion image (center), and ^{11}C-methionine PET image (right). (Bottom) PET/MRI data: T2-weighted FLAIR image (left), fusion image (center), and PET image (right). Reproduced with permission.[19] Copyright 2010, Society of Nuclear Medicine and Molecular Imaging.

MRI, with its potential to differentiate tumor from normal cells, and the range of tumor mapping.[25] Sequential scanning of images is said to be much easier since, we can reduce interference to the maximum.[26] But, simultaneously obtaining the images is a better option towards a much promising approach, as when both the scanning are done simultaneously, the images are co-registered intricately in all the planes and also, the overall time taken for scanning can be reduced.

The advantages of PET-MRI include the high sensitivity of the PET, high resolution and great soft tissue contrast of the images from MRI, absence of radiation dose in MRI and low time consumption resulting from the simultaneous scanning.[27] The overall radiation dose is equivalent to that of the discrete MRI and PET imaging systems thus there is no extra ionizing radiation. The reason for this hybridization approach was to combine imaging of soft tissues and the radiotracers present in the body together, thus improving the accuracy of diagnosis.[28] **Figure 2** describes an integrated system for simultaneous PET-MRI hybrid approach.

PET-MRI is majorly used in molecular imaging, neuroimaging and neurological disorder diagnosis to provide better insights.[29] One of the first ever application performed by PET-MRI was scanning for brain tumor. One such frontrunner experiment conducted using PET-MRI was done by Boss et al., where they scanned for head and neck carcinomas using both PET-MRI and PET-CT, thus comparing the results on the basis of image accuracy, time taken, and attenuation correction.[30] His experiment proved the feasibility of PET-MRI in neuro-oncological scanning, but it exhibited absence of indisputable artifacts contributed by the PET insert ring and compared to PET-CT metabolic ratios agreement.[31] Simultaneous PET-MRI for brain tumor imaging with different PET tracers (^{18}F-FDG, ^{18}F-fluoromisonidazole (FMISO), ^{18}F-fluorothymidine (FLT) and ^{18}F-fluoroethyltyrosine (FET)) is shown in **Figure 3**.[32]

One of the many neuropsychiatric disorders detected through imaging is the Parkinson's syndrome.[33] It is done so with the help of dopamine transporters and alpha-synuclein tracers which are a latest development as radiotracers in PET imaging. The developments in the MR technologies also improve the standard of imaging. Some of the new MRI approaches are proton magnetic resonance spectroscopy, iron mapping, diffusion tensor imaging and many more. Jung et al., have tried a PET insert in the PET-MRI imaging system to ease the process of simultaneous scanning.[34] They have concluded that the difference between simultaneous imaging and sequential imaging has very negligible effect on the quality of the image. The result shown a highly efficient and portable PET insert ring for fused imaging system, which can be enhanced with the help of Geiger-mode avalanche photodiode (GAPD) arrays.

Another noteworthy application unique to PET-MRI includes its contribution in the pediatrics department. Compared to other imaging techniques, PET-MRI is deemed as a more suitable neuroimaging technique for pregnant women and children, as it can significantly minimize the amount of radiation exposure and examination time.[35] Another reason why it is considered a boon for pediatric neuro-oncology patients is that PET-MRI is deemed suitable to detect tumors in the central nervous system which are usually solid malignant tumors in children.[36] Combined system is expected to contribute to the betterment of the accuracy and thus help the researchers plan their work accordingly. Some of the specific radiotracers for PET-MRI are ^{18}F-DOPA or ^{11}C-methionine. ^{18}F-FDG can't be used as its uptake by the tumor cells in the brain because the level of uptake is too high that the image comes out with

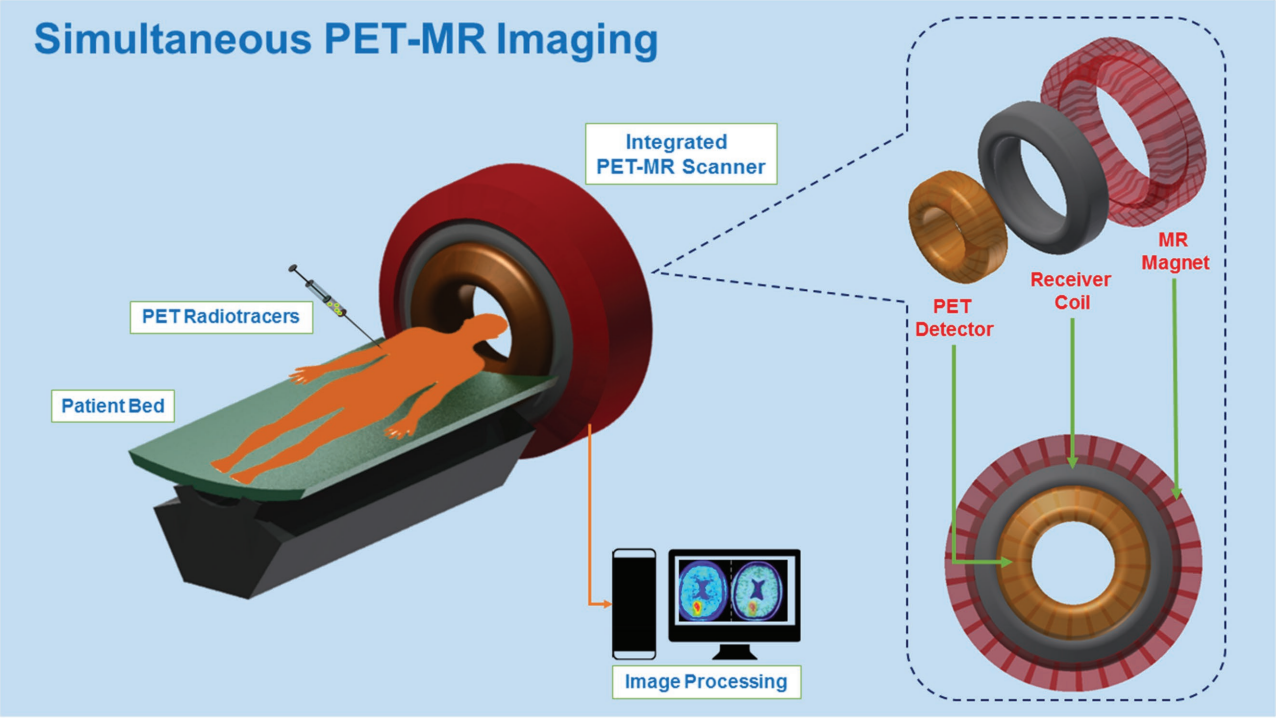

Figure 2. Integrated PET-MRI system design showing isocentric layering of MR receiver coil, PET detector and MR magnet. Patient or subject is provided with radiotracers and functional image of brain is acquired through PET detector together with the anatomical images from MRI.

a poorly differentiated result with poor contrast, which gradually affects the accuracy of the diagnosis. Thus compared to this tracer, the ones mentioned earlier provide a better contrast and thus better accuracy.

2.2. Other Explored Hybrid Imaging Techniques

Some of the other nuclear medicine imaging modalities recently explored are Ultrasound-MRI, Ultrasound-CT, MRI-CT, PET-SPECT-CT, MRI-Angiography and CT-Angiography.[37] EEG, MEG, fMRI and NIRS make up the popularly used neuroimaging techniques. When fused amongst themselves, based on their common grounds, EEG-fMRI, MEG-fMRI, EEG-NIRS are majorly explored among the group.

2.2.1. EEG-fMRI

Electroencephalography (EEG) is a well-known technique to acquire the electrical nerve impulses from brain activity and the various signals namely, alpha, beta, delta and theta. These signals are differentiated by their wavelength and frequency. When acquired, they help to detect the potential problems associated with the activities and functioning of brain. It is even used to monitor the brain activity of the patients when they are in coma or when they are sedated for brain surgery. The brain waves ranges from 0–100 Hz, where the lowest frequency waves being delta waves and the highest being the gamma waves.[38]

fMRI is a functional neuroimaging technique that identifies the changes connected with the blood flow in the brain.[39] It depends on the BOLD (blood oxygen level dependent) contrast to image the changes and the fact that the blood flow and amount of oxygenation in the brain are connected to the neural activity.

The idea of fusion of EEG with fMRI initially sprouted during the 1990s, but finally demonstrated in 2000.[40,41] EEG is said to be better at locating the neural processes in the brain but regarding detecting sources of the impulses at the deep points of brain, fMRI have proved to be much more efficient than EEG. fMRI is much better at detecting the spatial topography of the neural processes.[42,43] The reason for combining these two modalities is to facilitate the study of electrical activity in regards to its hemodynamic response and also, because fMRI gives excellent spatial resolution, ranging from 0.5 to 2 mm and good temporal resolution.[44]

Simultaneous EEG-fMRI has been used for detecting neurological disorders like epilepsy and also to monitor the mental activity during sleep, coma and other situations. Jean Gotman did an experiment in his laboratory to study the epileptic networks with EEG-fMRI.[45] He concludes that fusing the modalities seems to be an optimistic instrument for studying the discharges of epilepsy because it is not only easy, but also practical, thus, leads the way to a new and better technique for detecting the origin and the after effects of epilepsy. An experimental approach of single-trial EEG-fMRI analysis is described in **Figure 4**.[46]

C. Grova et al. performed an experiment on nine epileptic patients to find a new way to calculate the similitude between

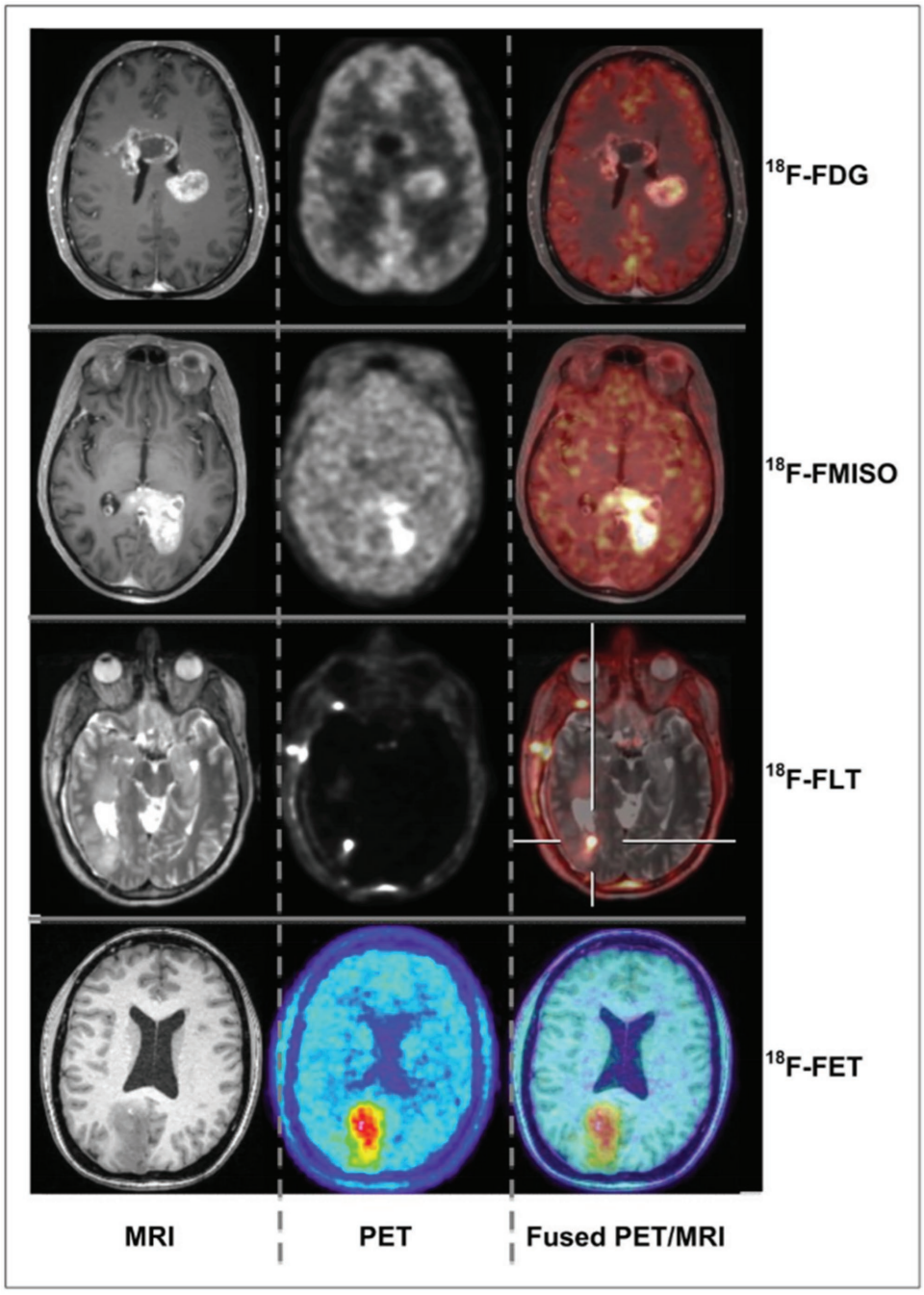

Figure 3. Simultaneous PET/MRI studies in patients with brain tumors. From left to right are shown axial MRI, PET, and fused images for different tracers: ^{18}F-FDG, ^{18}F-fluoromisonidazole (FMISO), ^{18}F-fluorothymidine (FLT) and ^{18}F-fluoroethyltyrosine (FET). Reproduced with permission.[32] Copyright 2012, Society of Nuclear Medicine and Molecular Imaging.

conventional EEG and EEG-fMRI scans.[43] They concluded by proposing a new method that analyses the BOLD responses to the spikes, and this hybrid approach of EEG-fMRI concordance is shown in **Figure 5**.

Some of other common applications of EEG-fMRI in the research currently being conducted in this field include the monitoring of human brain during sleep,[47] study of various senses like auditory sense,[48] optical or visual sense,[49] somatic senses and motor sensors. It provides deeper insight into the eccentric mechanisms and helps in exploring the important role played by sleep in humans. Most clinicians and technicians nowadays rely mostly on the EEG-fMRI reading to determine the normal functioning of the patient's brain. Thomas Deneux used hybrid EEG-fMRI fusion for paradigm-free activity using kalman filtering by estimating the source activity and shown that the fused results are much accurate than individual modality results.[50]

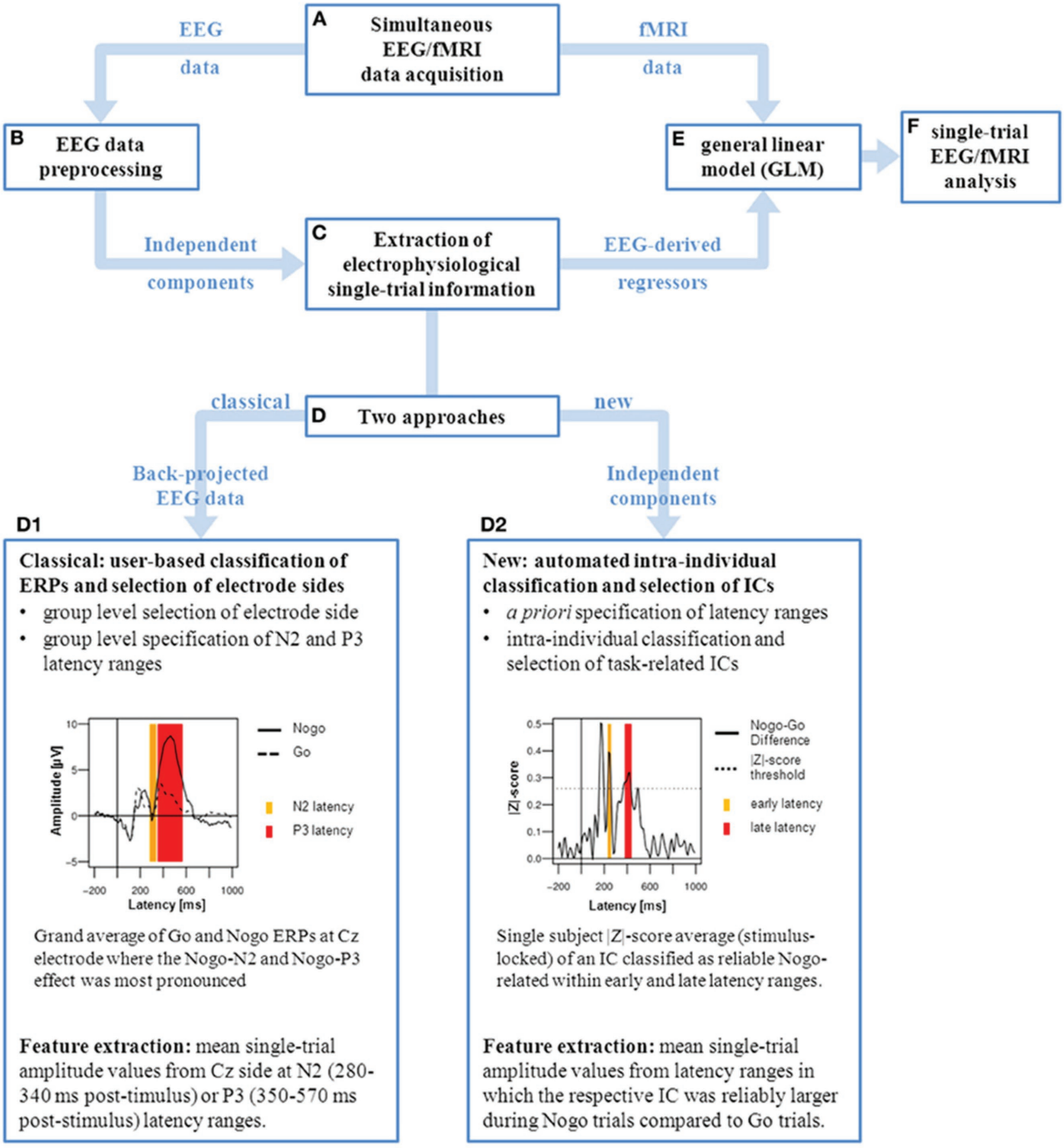

Figure 4. Graphical representation of single-trial EEG/fMRI analysis. After simultaneous EEG/fMRI data acquisition, A) the EEG data is preprocessed and corrected for fMRI artifacts (B) using independent component analysis (ICA). Subsequently the electrophysiological single-trial values can be extracted (C) using different approaches (D). Classically, D1) single-trial amplitude values are extracted from predefined ERP components. This is based on a chosen electrode site where the ERP component of interest (Nogo-N2 and Nogo-P3) is most pronounced in the grand mean average. Followed by the specification of N2 (280–340 ms, yellow) and P3 (350–570 ms, red) latency ranges which cover best the task-related ERP effects on group level at the selected electrode site (Cz). For each participant the mean single-trial values are extracted from these predefined latency ranges. Alternatively (D2), our approach allows to extract single-trial values from independent components (ICs) which are intra-individually classified and selected in an automated procedure. This is based on a priori specification of latency ranges of interest, in this case located prior (early, yellow) and around (late, red) the individual's median response time (RT). ICs are intra-individually classified according their association with the Nogo condition (significantly increased amplitudes in Nogo trials compared to Go trials). For each participant the mean single-trial values are extracted from latency ranges in which the respective IC was reliably larger during Nogo. In both approaches the resulting electrophysiological regressors are included in the general linear model of fMRI data analysis (E) in order to perform the single-trial EEG/fMRI data analysis (F). Reproduced under the terms of the CC-BY 3.0 license.[46] Copyright 2014, The Authors.

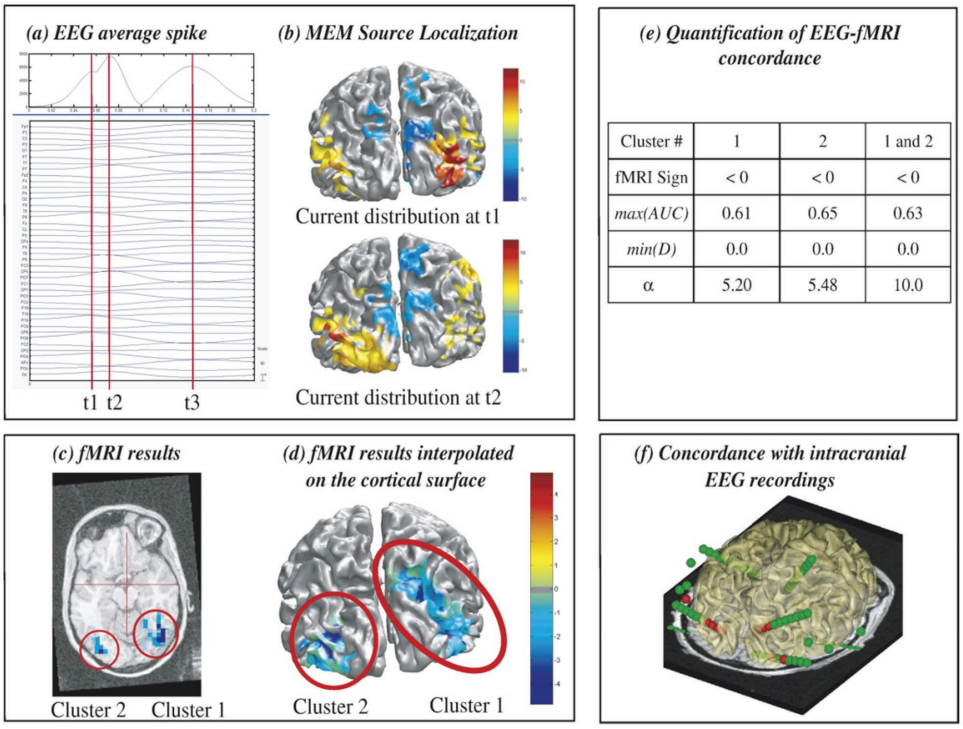

Figure 5. Analysis of patient 3 showing excellent EEG-fMRI concordance. a) Signal and maximum field power of the average spike, local peaks (t_1, t_2, t_3) considered for MEM-concordance are represented using red vertical lines. b) MEM source localization estimated at t_1 and t_2, the positive and the negative parts of $\hat{J}_{MEM}$ being thresholded upon the level of background activity, using Otsu's threshold estimated on $|\hat{J}_{MEM}|$ (Otsu, 1979). c) t-values of the two most significant fMRI clusters obtained with the HRF peaking 5 s after the spike, superimposed on the 3D anatomical MRI. d) Same fMRI clusters after interpolation onto the cortical surface. e) MEM-concordance and fMRI-relevance metrics for cluster 1, cluster 2 and when considering both clusters together. f) 3D representation of the position of the intracranial EEG electrodes with one MRI axial slice and the cortical surface (yellow slightly transparent), active contacts being represented in red. Visual inspection (b,d) and quantitative results (e) showed an excellent EEG-fMRI concordance within right and left occipital regions, and were confirmed by intracranial EEG recordings (f). Adapted with permission.[43] Copyright 2008, Elsevier.

2.2.2. MEG-fMRI

Magnetoencephalography (MEG) is a non-invasive imaging modality especially designed for brain mapping by documenting the magnetic fields induced by electrical currents in the brain. These mild signals are detected using the very sensitive magnetometers. There are two most common types of magnetometers used by MEG, namely, SQUID (Superconducting quantum interference device) and SERF (Spin exchange relaxation free). MEG was first used in 1968 by David Cohen to measure the brain signals.[51] After that, it slowly but steadily developed to the current day MEG modality with good spatial resolution and high temporal resolution. The range of magnetic field recorded by MEG is from femtotesla to picotesla.[52] Compared to other imaging systems used for brain imaging, MEG neither creates any magnetic fields nor does it include any radiation.

MEG has common grounds with MRI in terms of magnetism, and thus is easily combined with MRI for hybrid imaging purposes, that is, to provide a much better structural outlook of the brain, together with cognitive functions.[53] Both the modalities in unison are called as magnetic source imaging. This fused modality works on the basis that areas of brain with stronger BOLD signals or responses have a greater chance of being electrically active over the desired time period. So basically, fMRI collects the information of the brain indirectly through BOLD and MEG collects the information directly, by acquiring the mild brain signals. **Figure 6** briefly summarizes the physiological basis of MEG and fMRI signals and process flow of hybrid MEG-fMRI imaging for brain activity reconstruction.

There are a very few experiments performed using MEG-fMRI. George Northoff et al., have conducted an experiment using MEG-fMRI in order to find out the functional dissociation between the activation of medial and lateral prefrontal cortical spatiotemporal during both positive and negative emotions.[54] They could not find out the role of prefrontal and orbitofrontal cortex activation in positive and negative emotions clearly. But they did conclude saying that negative emotions generated much stronger activation than positive emotions. Cichy et al. explored MEG-fMRI for resolving human object recognition in space and time by relating MEG and fMRI signals as described in **Figure 7**[55] Plis et al. explored fusion of MEG and fMRI for non-linear estimation of neural and BOLD signal changes using their Bayesian sensor fusion model (**Figure 8**).[56] There still a lot of experiments in process for this modality and it have potential applications to be developed.

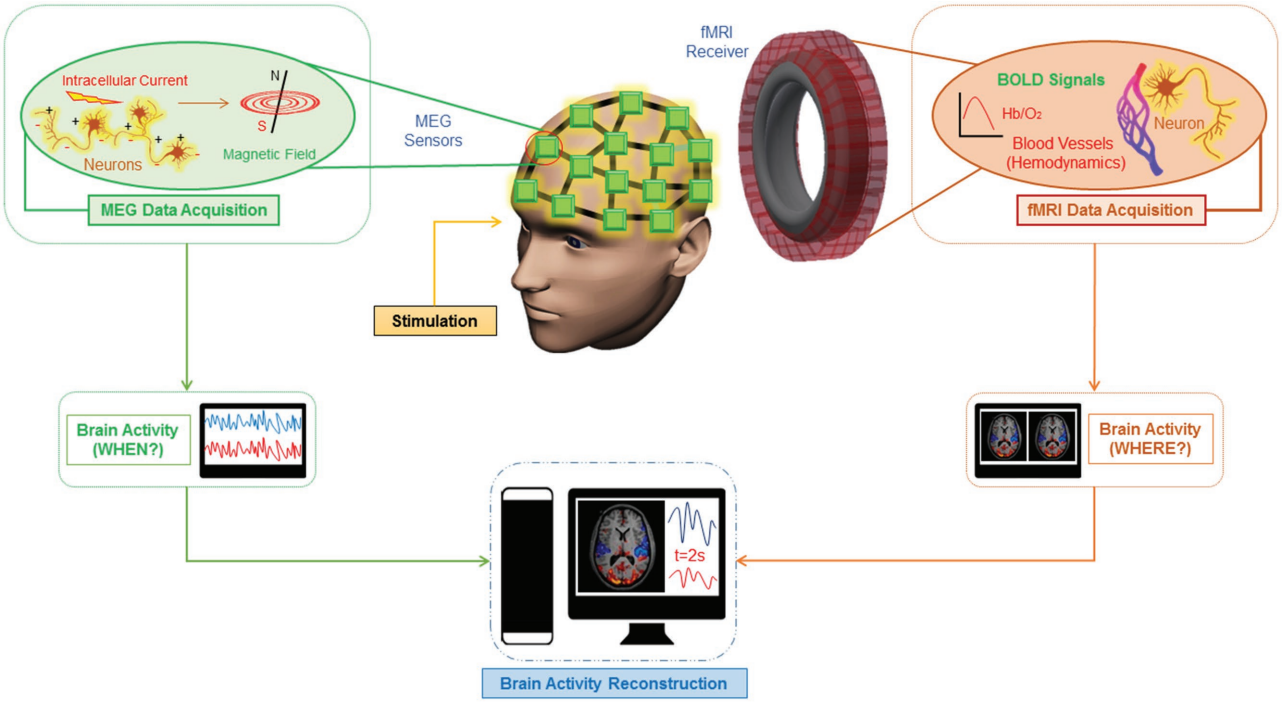

Figure 6. Physiological basis of MEG and fMRI signals and process flow of hybrid MEG-fMRI imaging for brain activity reconstruction. The magnetic field generated by intracellular current is measured by SQUID sensors in MEG and the temporal response is measured. For the similar stimulation, fMRI measures BOLD activity and the hemodynamic responses provides spatial localization. Hybrid data processing provides the details about reconstructed brain activity.

2.2.3. EEG-NIRS

Near Infrared Spectroscopy (NIRS) has been attracting great interest from scientists working on neuroimaging systems, especially from those working on brain computer interface.[57] It is relatively a very new imaging modality and doesn't have a lot of experiments done with it. The reason for NIRS being including in the whole hybrid imaging system circle is its ability to measure the haemodynamic changes in the brain, that to non-invasively.[58] Like fMRI, even NIRS scans can be used to measure and monitor the level of blood oxygenation when a particular task is being done. Unlike EEG, MEG and fMRI, NIRS is an optical imaging system. The primary application of NIRS in neuroscience is to assess the function of brain through the changes in the levels of blood hemoglobin and thus, it might replace fMRI at a few situations but it cannot completely replace fMRI function.[59] It can even be used for pediatrics as there is no ionizing radiation. Three-dimensional NIRS is called Diffuse Optical tomography (DOT) which requires a large separation between the source and the detector to improve the sensitivity and it also requires the longer exposure to the light.

Compared to the other neuroimaging modalities, NIRS can be considered compact and much cheaper. EEG-NIRS system is known to have a great potential in brain-computer interfacing (**Figure 9**). One of the very few experiments performed using EEG-NIRS was conducted by Tadashi Tsubone et al., where they tried to figure out the probabilities of NIRS being used in a mind machine interface (MMI) to activate or deactivate the switch on or switch off control.[60] Yohei Tomita et al., worked to create a simultaneous hybrid imaging system of NIRS and EEG for a brain computer interface (BCI).[61] They did an experiment on thirteen volunteers and compared the results of hybrid and conventional scans, and concluded by proposing a cohesive approach for processing of the signals obtained by dual modality EEG-NIRS interface system. This approach was based on the steady state visual evoked potential of EEG, which enhanced the performance of the imaging system compared to that of EEG MMI. Another experiment conducted by Bonkon Koo et al., was done in order to obtain a self-paced brain interface system depending on motor imagery.[62] On concluding, they mentioned that one of the main problems faced on building this hybrid imaging system was the response time of the BCI depending on NIRS. Fazli et al. shown the enhanced performance of hybrid EEG-NIRS system in a real-time sensory motor rhythm (SMR)-based BCI paradigm and observed improvement in classification accuracy of motor imagery (**Figure 10**).[57]

Vera et al., attempted to detect the changes in the electrocortical activity and haemodynamic activity, when the subject is undergoing bicycle exercise with gradually increasing speed, using fused EEG-NIRS system in two different scenarios, namely, hypoxia and normoxia.[63] They concluded saying that only the brain oxygenation level was affected throughout the exercise and not the cortical activity. Much potential of EEG-NIRS hybrid systems are being explored by researchers and in future, it is supposed to have a great role in neuroimaging.

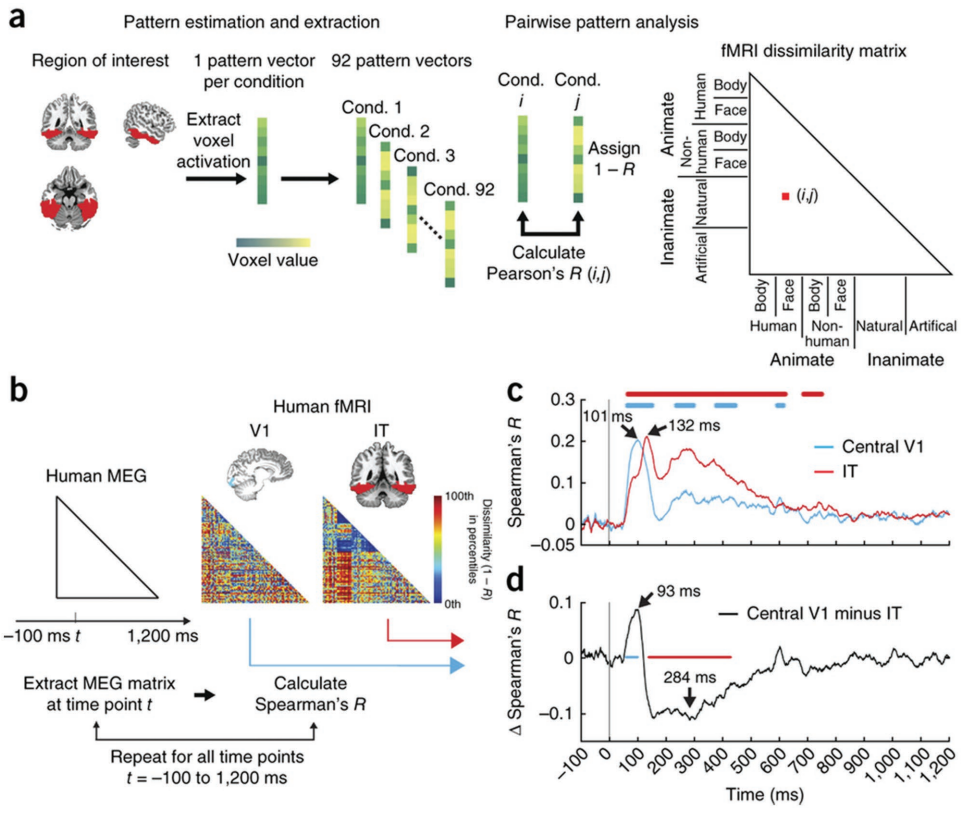

Figure 7. Relating MEG and fMRI signals in V1 and IT. a) fMRI analysis. We selected voxels in two regions of interest: V1 and IT. For each condition (cond.), we extracted voxel activation values, yielding 92 pattern vectors. Then we calculated the pairwise Pearson's correlation (R) for all combinations of experimental conditions (i,j). The dissimilarity measure 1 − R was assigned to a 92 × 92 fMRI dissimilarity matrix indexed by the experimental conditions (i,j). This analysis was conducted independently for each region of interest. b) For each time point t, we correlated (Spearman's rank-order correlation) the MEG decoding matrix to the fMRI dissimilarity matrices of V1 and IT. c) MEG signals correlated with the fMRI dissimilarity matrix of central V1 earlier than with the fMRI dissimilarity matrix of IT. Blue and red asterisks indicate significant time points for V1 and IT. d) Difference between the two curves in c. MEG correlated early more with V1 than with IT, and late more with IT than with V1. Blue and red asterisks in the plots indicate significant time points for positive and negative clusters respectively. Adapted with permission.[55] Copyright 2014, Nature Publishing Group.

2.3. Trimodal Hybrid Imaging Techniques

2.3.1. MR-PET-EEG

MRI and EEG have common grounds in accordance to their temporal and spatial resolution. But still they cannot help in the cases of analysis of resting state or molecular based tasks, as the specialist modality in these areas is PET imaging system. PET or PET-CT dual modality imaging system uses FDG-18F as a radiotracer for the analysis of brain mechanism and this method is universally accepted.[64] Now, even though PET is very good with molecular level analysis, it can't reach high spatial or temporal resolutions. Thus, this provided the scientists and the engineers an idea to combine these three, and they settled on trying for a trimodality imaging system. **Figure 11** shows a comparative overview of MR-PET-EEG trimodality system in comparison to individual and biomodality approach and describes how this approach is provides holistic strength in imaging.[65] The major factor that had kept this fusion at the bay for a long time was the doubt that whether the electronical part of PET would cause disruption to the magnetometers in the EEG part, that is already sensitive enough to pick up the very minute signals of our brain. But, on implementing it, the disturbance was found to be very negligible. Grouiller et al. used MR-PET-EEG to investigate epilepsy patients by successfully recording the trimodality data.[66]

2.3.2. MR-PET-CT

PET-CT hybrid imaging modality was good but it was short of some abilities and still had limitations to be corrected. MRI imaging system had a few abilities that were considered as limitations of PET-CT. Thus, the only way to compensate the limitations of the former was to fuse it with the latter.

MR-PET-CT is one of the very few hybrid imaging systems that consists of three modalities. It has both advantages and limitations but the scale drops more towards the former than the latter for now.[67] One of the major problems faced in designing this hybrid modality is to figure out the technique to run both the PET-CT and MRI simultaneously within a single set time frame. But the difference in the time taken by PET-CT and MRI to complete a scan stands in the way. And one of the major advantages of this trimodality is

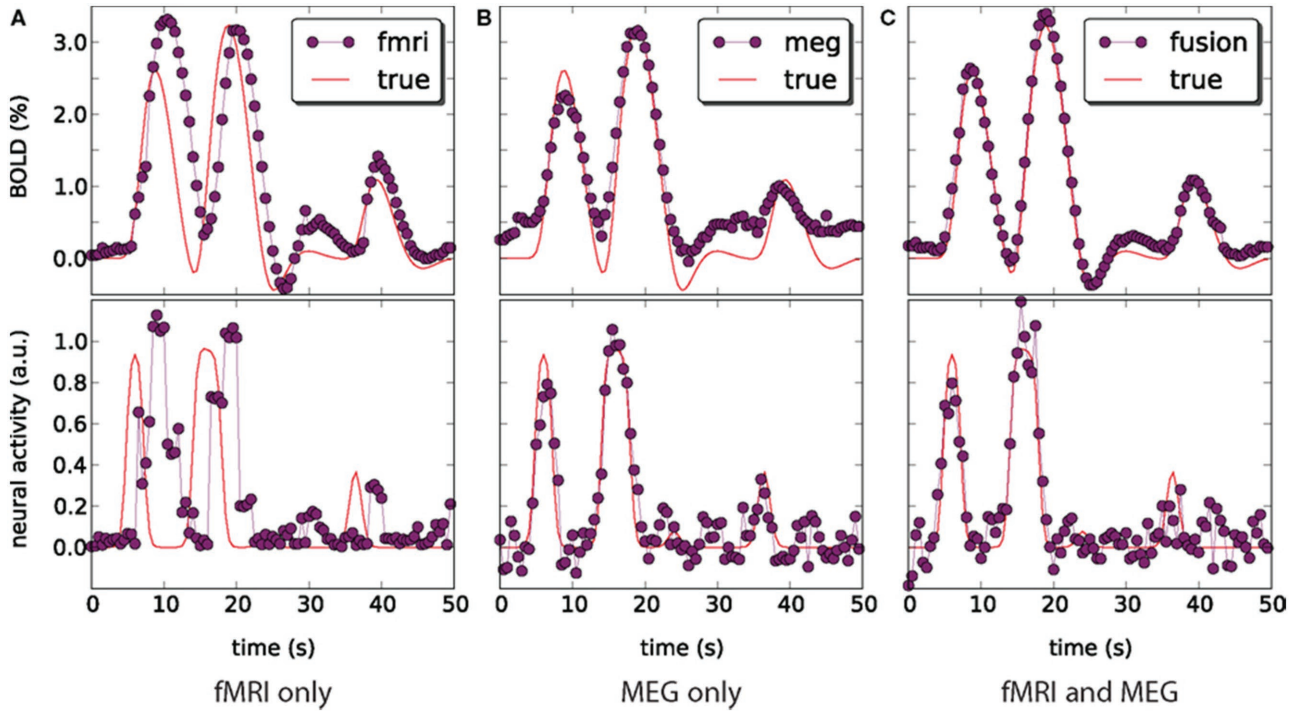

Figure 8. BOLD (top) and neural activity (bottom) signal plots. Each plot displays the ground truth signal (lines) plotted with the corresponding signal estimate produced by our Bayesian sensor fusion model (circles). When the estimated curve falls close to the true curve, the model is performing well. A) Estimation using only fMRI signal data; B) estimation from only the MEG signal; C) the result of fusing both channels of data into a single estimate. We see that the fusion approach matches both the BOLD response and the neural activity more closely than do either of the single-channel estimates. Specifically, the fusion estimate tracks the BOLD response better than MEG and resolves a temporal ambiguity in the fMRI-only estimate. The temporal ambiguity corresponds to the hemodynamic delay, which is present as a parameter in our model. In (A,C) we have deliberately set the delay parameter to 0 to demonstrate that the fusion approach can use the MEG channel to resolve the hemodynamic delay without relying on a manually set parameter. Reproduced with permission.[56] Copyright 2010, The Authors.

that it allows possibility for the use of a normal CT based correction for the attenuation of PET scan images. Coming to its application in the real field, it can be used in cancer cell scanning of both whole body and brain. This fused system can be considered multifunctional as it can provide information on the status of primary and the surrounding tumors and also contributes in the detection of lymph node metastases.[68]

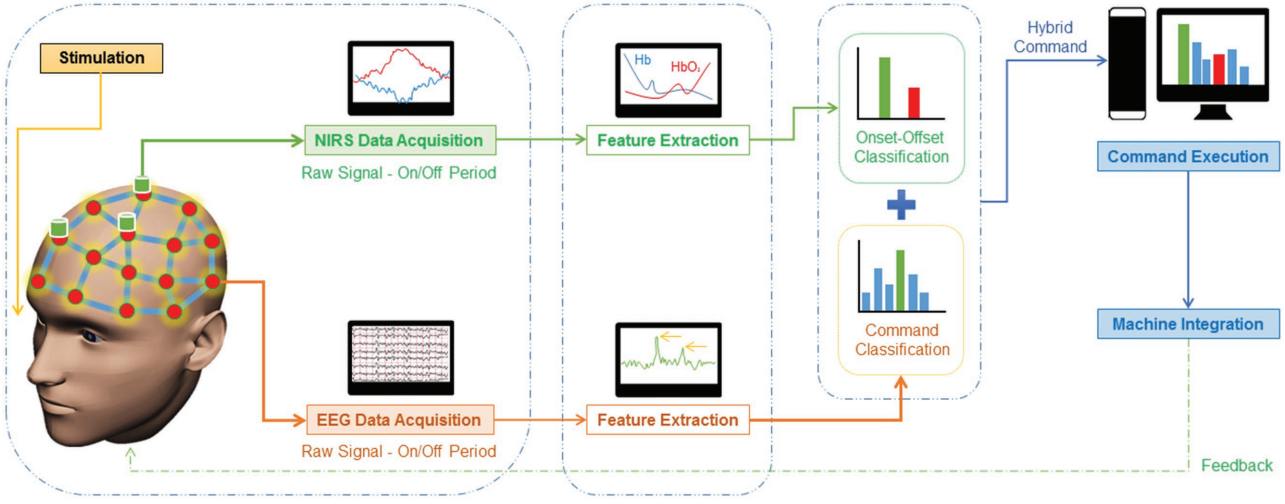

Figure 9. Principles of brain computer interfacing using EEG and NIRS simultaneously. The NIRS and EEG data are simultaneously acquired in response to a stimulation given to the subject. NIRS data extracted features are used to provide Onset-Offset Classification and EEG provides command classifications which are further combined as hybrid execution command and integrated with machine.

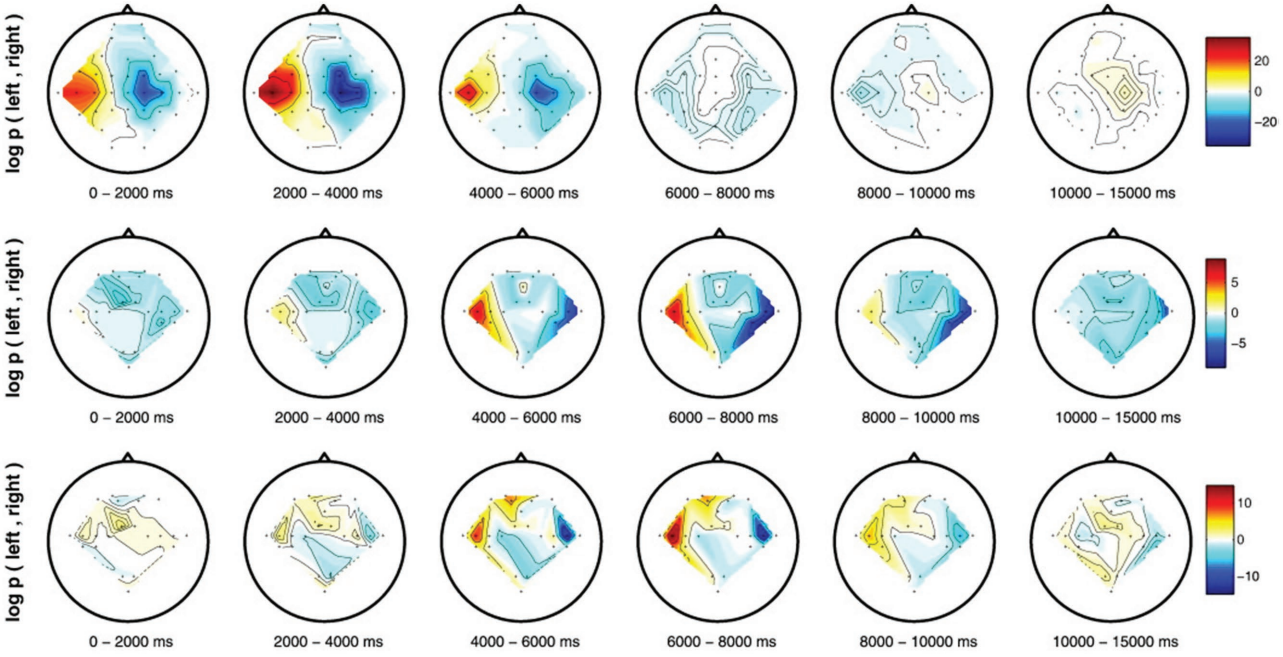

Figure 10. Scalp evolution of grand-average log p values for motor imagery in EEG and NIRS over all subjects (top: EEG, middle: [HbO], bottom: [HbR]). Red color denotes higher values of the left class, while blue colors indicate higher values within the right class. Note that the width of the color-scale on the right indicates the level of significance. Adapted with permission.[57] Copyright 2012, Elsevier.

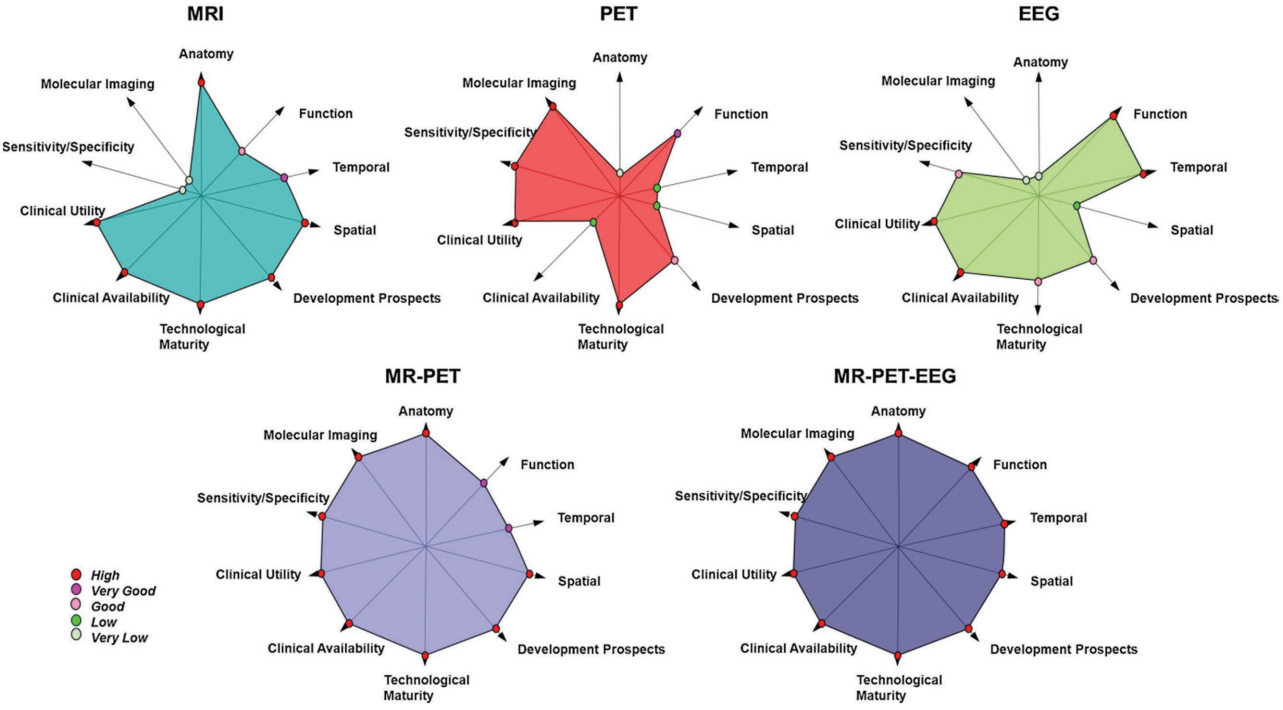

Figure 11. Fingerprint diagrams giving an overview of the strengths of MRI, PET, and hybrid MR–PET, and hybrid MR–PET–EEG. Starting at the origin, the further one traverses along a given axis, the better that particular attribute is fulfilled. MRI can provide exquisite spatial resolution and the technology is widely available. However, MRI is not strong in the area of molecular imaging and its specificity is also somewhat limited. PET on the other hand, has poorer spatial and temporal resolution than MRI but it is extremely specific—an attribute conferred upon it by the choice of radiolabelled tracer—and is also very sensitive. Both MRI and PET have a poor temporal resolution regarding mapping of brain function, for example. In a hybrid scanner capable of simultaneous measurement of all three dataset, all the chosen attributes are fulfilled in entirety. Reproduced with permission.[65] Copyright 2012, Elsevier.

2.4. Advanced Hybrid Imaging Techniques

Advanced imaging modalities are invented in the past five years and have already been used as hybrid imaging modality or have a great probability of being fused with another imaging modality that has commonalities. Those advanced imaging systems that are already incorporated for hybrid modalities are PET-Cerenkov light imaging modality,[69] Fluorescence – X-Ray Computed Tomography (FMT-XCT),[70] Fluorescence – Diffuse Optical- Computed Tomography (FT/DOT/XCT),[71] Fluorescence Molecular Imaging- Computed Tomography (FMT-CT),[72] Photoacoustic Imaging,[73] Thermoacoustic Tomography,[74] Elastography,[75] Magnetic Resonance Elastography,[76] Event-Related Optical Signal (EROS),[77] Diffusion Tensor Imaging (DTI)[78] and Thermoencephaloscopy (TES).[79]

Photo-acoustic imaging, a combination of ultrasound with optical imaging contrast, is a well explored recent technique which has shown a great potential in imaging animal or human organs with high spatial resolution and wide contrast range. It integrates lavish optical contrasts with a high ultrasonic spatial resolution in deep laying tissues.[80] This technique is becoming very eminent in imaging field as it rules out the limitations of other conventional imaging techniques to an extent. Researchers have also explored resting-state functional connectivity (RSFC) approach of neuroimaging with a mouse brain using functional connectivity photoacoustic tomography (fcPAT) system as shown in **Figure 12**[81]

Cerenkov-light imaging is a newly developed technique which uses an optical camera to detect visible photons from high-speed electrons. When fused with PET, the hybrid PET/Cerenkov-light imaging successfully demonstrated fused images from simultaneously acquired images, and reduced the limitations of Cerenkov-light imaging alone.[69] Other discussed advanced systems are still in preclinical research experimentations and are supposed to impact neuroimaging field with great potentials in near future.

3. Hybrid Modalities: A Comparative Overview

The capabilities and applicability of different individual modalities are governed by its anatomical, functional and cognitive approach of imaging. Together, when these modalities are hybridized, the complimentary outcome provides great potential and it is a field of active discussion for comparing them on common grounds. By considering various factors including sensitivity, spatial resolution, temporal resolution, accuracy, financial inclusion and radiation dose, the discussed modalities were compared on a common platform. The comparative analysis in the form of radar diagram is shown in **Figure 13** in two different groups, one among SPECT-CT, PET-CT and PET-MRI, and the other among EEG-fMRI, MEG-fMRI and EEG-NIRS, splitting on the basis of similarity of the procedures and the principle.

4. Limitations and Future Speculations

Hybrid imaging modalities are very proficient but the ever growing need for better and customized imaging specifications is driving the demand for new hybridization approaches. The various limitations of currently available modalities and the flaws in their integration are counted among the biggest challenges. An overview of advantages, limitations and applications of hybrid various neuroimaging approaches is presented in **Table 1**.

PET-CT as mentioned earlier is an amazing invention but its major defects are that it is acquired sequentially rather than simultaneously, increasing the time period for which the patient has to refrain from making big or sudden movements.[82] Thus, it increases the chances of artefacts created in the scanned image. Major limitation of SPECT-CT is that it takes a long time to scan, thus giving way to motion artefacts.[83] It also has low spatial resolution and a very crucial handling that requires tough training for the technician. Another pitfall that would not affect the image, but rather the patient, that attracted the attention was the increase in dose of radiation during scanning. In case of PET-MRI, there were a few sacrifices done by the engineers in order to stuff the PET detector ring onto the MRI scanner modality. In order to do that, they had to compromise on the performance of the MRI scanner as the narrow bore system was replaced with wide bore system that left a few centimeters for the detector to squeeze in. As far as mutual interference is concerned, the effect of PET detector ring is negligible on MRI than that of MRI scanner on PET imaging. There is a considerable change in the count rate of PET due to heating caused by switching magnetic field gradients in MRI scanner. In spite of the fact that there is no obvious alteration in the PET image but the overall performance is affected.[84,85]

During EEG-fMRI registration, as the biological basis of EEG and fMRI imaging is different, it makes the results interpretation more difficult.[86] Also, as an inherent limitation, the sensitivity of fMRI is limited by the temporal resolution of the BOLD signal and the spatial resolution in EEG is limited as the electrode is located at a distance of about 1 cm from the cortex. Together, these issues are hurdles in this hybrid approach of imaging. With purely magnetic source imaging like MEG-fMRI, although they use same platform for signals, the hybrid acquisition is limited by the interference of signal and the feasibility of fusing the instruments. Beside this, the inherent limitations of involved modalities, sensitivity and resolution plays an important role in limiting its applicability for neuroimaging.

EEG and NIRS are well known to be hybridized for cognitive neuroimaging as they are sensitive to different cascades of events linked to the same neural activities, and they have complementary spatial and temporal resolution. But, configuring the device simultaneously and electrode placement is a major issue.[87] Beside this, the signals are need to be acquired and processed in same time frame which is sometime limited by precision and signal processing algorithms. Trimodality systems and advanced imaging systems are still in nascent phase and thus the feasibility for clinical studies are being explored by researchers.

Although every hybrid imaging modalities have their own limitations and downfalls, the range of these limitations continues to reduce with new inventions in individual modalities and also with the approaches of hybridization. The ongoing advancements is anticipating rapid clinical

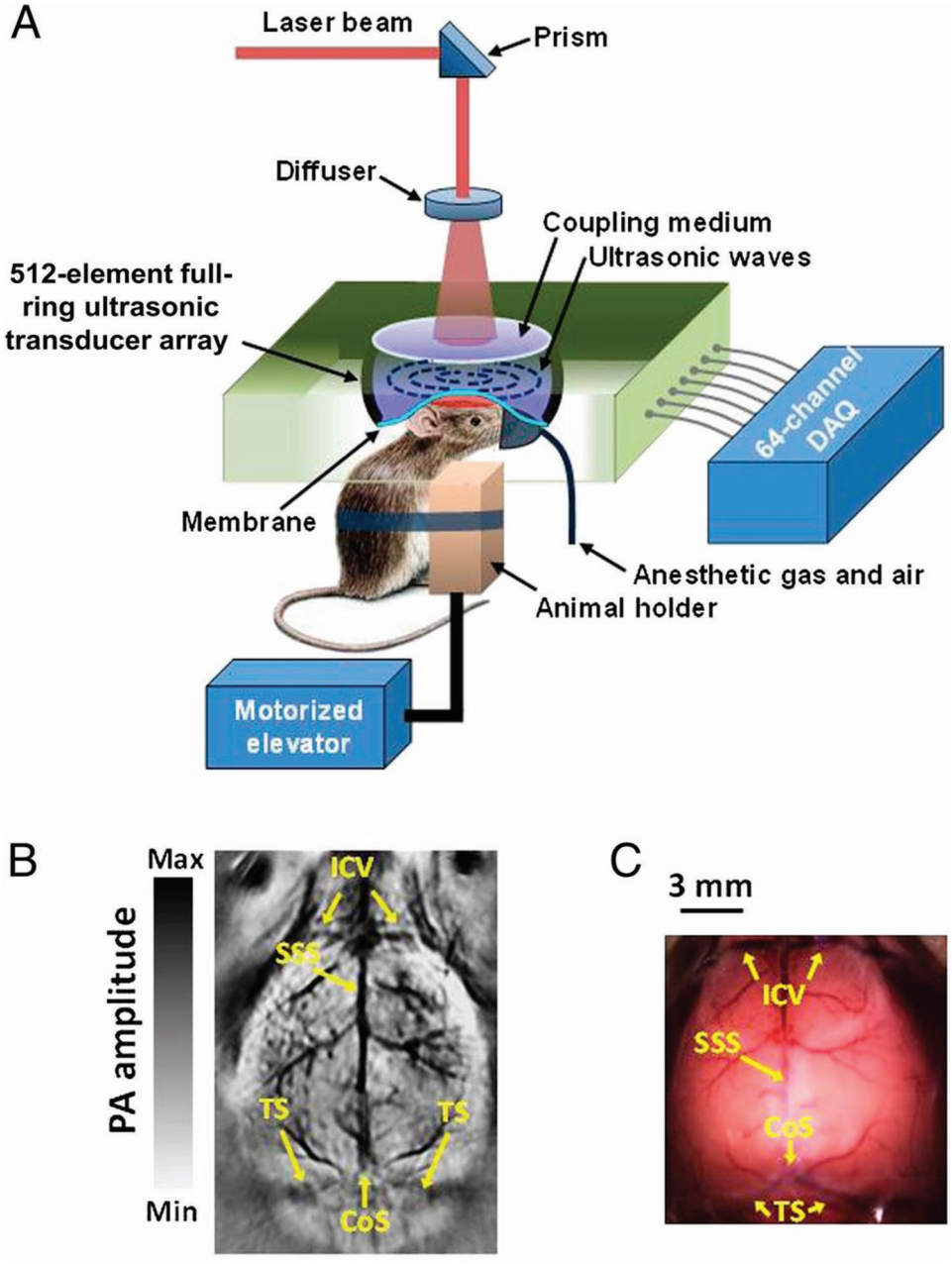

Figure 12. fcPAT. A) Schematic of the fcPAT system. B) Cerebral vasculature of a mouse brain imaged by fcPAT. C) Photograph of the cortical vasculature corresponding to (B) with scalp removed. CoS, confluence of sinuses; ICV, inferior cerebral vein; SSS, superior sagittal sinus; TS, transverse sinus. Adapted with permission.[81] Copyright 2013, Proceedings of the National Academy of Sciences.

adoption of these hybrid systems for various neuroimaging applications. Apart from nuclear imaging methods, in near future, non-invasive and zero radiation exposure techniques like optical imaging, DTI, fcPAT, TES and other emerging advanced modalities will be explored for huge strides in clinical practices.

Beside this, recent advancements in multimodal probe development is paving path for better equipped hybrid imaging approach. Functionalized nanoparticles are explored by researchers which can enhance the diagnostic/ theranostic capabilities by acting as contrast agents as well as for targeted drug delivery. These probes are known to have great potential for hybrid neuroimaging as they have the ability to act for multimodalities for various clinical applications including tumor and neurodegenerative disorders.[88,89] With ongoing researches and technical advancements, the holistic developments in multimodal approaches will be marked by inclusion of new technologies, better sensing capabilities and other ways of bringing hybrid neuroimaging modalities in clinical applications.

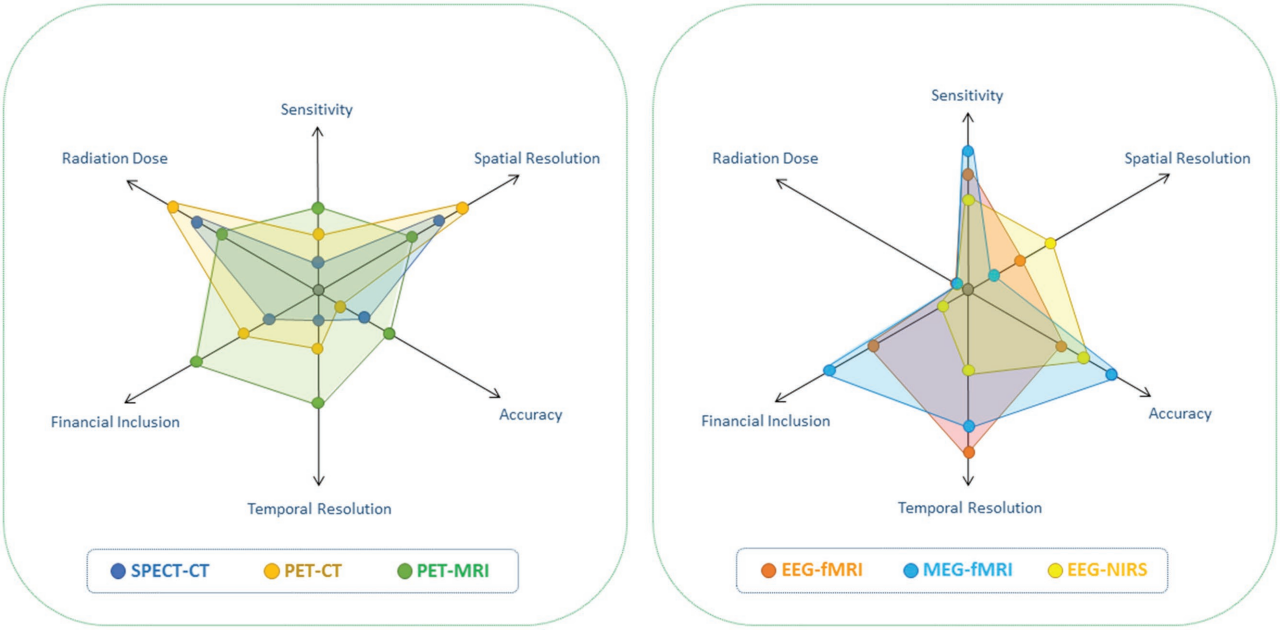

Figure 13. A comparative overview of hybrid imaging modalities for neuroimaging applications on various factors. Group 1 systems include modalities for hybrid anatomical and functional neuroimaging (SPECT-CT, PET-CT and PET-MRI) and Group 2 systems include modalities for hybrid functional and cognitive neuroimaging (EEG-fMRI, MEG-fMRI and EEG-NIRS).

5. Conclusion

The ever-growing need for new and better medical imaging equipment is driven by vibrant research approaches and exploration of mysteries of neuroscience, including neurological disorders. Hybrid imaging modalities have provided a complementary approach to overcome the limitations of individual modalities, thus paving the path for a much more accurate diagnosis in a short time frame and decreased harmful effects. The multimodality systems are providing a customized way of looking at a specific problem and thus diagnosing it in an accurate fashion. With new inventions in advanced platforms

Table 1. An overview of advantages, limitations, and applications of hybrid various neuroimaging approaches.

Hybrid System	Signal Acquisition	Advantages	Limitations	Neuroimaging Applications
SPECT-CT	Sequential Acquisition: Metabolic activity (SPECT) and hard tissue presence(CT)	Precise image fusion, improved attenuation correction and better localization	Long scan time causes motion artefacts, low resolution, and higher radiation dose in comparison to individual modality.	Neuroendocrine tumour spotting and residue detection.
PET-CT	Sequential Acquisition: Metabolic activity (PET) and hard tissue presence(CT)	Better localization, better accuracy, low noise contribution and shorter scan time	CT causes beam hardening artefacts, high cost and higher radiation dose in comparison to individual modality.	Cancer diagnosis and staging, dementia and epilepsy diagnosis.
PET-MRI	Simultaneous Acquisition: Metabolic activity (PET) and soft tissue presence(MRI)	High resolution with spatial and temporal correlation, high sensitivity, excellent soft tissue contrast range, low scan time and no ionizing radiation.	Considerable change in count rate of PET due to heating caused by changing magnetic field in the scanner, sacrifice of narrow bore system for simultaneous PET-MRI and high cost.	Brain tumour detection, imaging neurodegenerative disorders, stroke detection, epilepsy diagnosis and brain activation studies.
EEG-fMRI	Simultaneous Acquisition: Electric neural activity (EEG) and BOLD signal (fMRI)	Complimentarily enhanced spatial (fMRI) and temporal (EEG) resolution, accurate detection of neural processes and facilitates study of electrical activity of nerves correlated with haemodynamic response.	High frequency limitation is due to removal of gradient artefact and low frequency limitations due to interference of EEG signal with other artefacts.	Detection of neurological disorders, majorly epilepsy, monitoring of brain signals during sleep, coma and active states.
MEG-fMRI	Sequential Acquisition: Magnetic neural activity (MEG) and BOLD signals (fMRI)	Better spatial resolution, good acquisition of very mild magnetic neuro-signals along with bold signal.	Feasibility of fusion, signal interference, very expensive and not portable.	Cognitive, neuropsychological and behavioural studies, neural activity imaging.
EEG-NIRS	Simultaneous Acquisition: Electric neural activity (EEG) and haemoglobin concentration change (NIRS)	Non-invasive, no radiation dose, haemodynamic change measurement along with neural activity mapping, compact and easy integration, low equipment cost.	Artefact prone and low spatial resolution.	Neural activity imaging, locating intercranial bleedings, cognitive studies and Brain-computer interfacing.

of non-invasive imaging, the field of neuroscience is moving towards a better way of peeping inside the brain for anatomical, functional, and cognitive perspectives and their interrelations. With these hybrid instrumentations, the image processing and algorithm development for brain activity reconstructions are simultaneously growing to support the approaches and present the data in a much simplified and specific manner. Together, in a holistic way of advancement, it can be concluded that hybrid imaging approaches have great potential in diagnosing neurological disorders and mysteries.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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