

Review

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Review

Imaging-Based Biomarkers in Neurological Diseases- A Critical Review

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Abstract: Imaging-based biomarkers have developed as an effective tool in neurology, providing vital understandings of the structural, functional, and molecular changes associated with neurological disorders. Imaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and computed tomography (CT) have been widely employed to record disease-related alterations in the brain. These techniques provide a wide range of biomarkers, such as functional connectivity patterns, volumetric measurements, molecular imaging agents, and perfusion parameters, enabling the correct identification of neurological disorders. These biomarkers have proven useful in early diagnosis, disease progression tracking, therapy response prediction, and surgical planning. This review emphasizes the various obstacles and limitations that are associated with imaging-based biomarkers. Technical constraints, standardization obstacles, ethical concerns, regulatory challenges, and cost-effectiveness concerns all offer substantial barriers to wider use. It is vital to overcome these challenges if imaging biomarkers are to be successfully integrated into routine clinical practice. Imaging technology advancements like high-resolution imaging, multimodal imaging, and artificial intelligence-based analysis hold immense promise for imaging-based biomarkers in the future. While more study and standardization are needed, their ongoing development and integration into clinical practice have the potential to revolutionize the diagnosis, treatment, and management of neurological disorders, resulting in better patient care and outcomes.

Keywords: PET; MRI; SPECT; CT; depression; epilepsy; atrophy

1. Introduction

Neurological disorders present significant challenges in terms of accurate diagnosis and efficient treatment due to their complexity and heterogeneity. Traditional diagnostic approaches frequently rely on subjective assessments and clinical evaluations, which can lead to limitations in accuracy and reliability. However, the introduction of imaging-based biomarkers has transformed the area of neurology [1]. MRI, PET, SPECT, and CT are the imaging techniques that have distinct benefits in visualising and quantifying structural, functional, and molecular changes in the brain [2–4]. These imaging methods provide useful information regarding tissue integrity, neurochemical changes, and cerebral blood flow, among other things. Researchers and physicians can develop objective and quantitative biomarkers that aid in the diagnosis, prognosis, and monitoring of neurological illnesses by exploiting these imaging properties [5,6].

Imaging-based biomarkers (IBB) are important because they can give a non-invasive and thorough assessment of neurological disorders. These biomarkers allow for early detection, precise

diagnosis, and distinction of disease subtypes. They also offer insights into disease progression, treatment response, and personalized therapeutic interventions [7,8]. Moreover, IBB facilitate the evaluation of novel therapies in clinical trials and contribute to the development of precision medicine approaches in neurology. The integration of IBB in clinical practice has the potential to transform patient care by improving diagnostic accuracy, enabling personalized treatment strategies, and facilitating disease management [9]. Clinicians can use IBB to make informed judgements about the best treatment options for specific patients, ultimately optimising results. Furthermore, IBB can help us better understand the underlying mechanisms and pathophysiology of neurological illnesses. These biomarkers provide crucial insights into disease processes by visualising and quantifying brain alterations, assisting in the identification of novel treatment targets and the development of tailored interventions [10].

2. Biomarkers in Neurological Diseases

2.1. Biomarkers for diagnosis

IBB utilize various imaging techniques to visualize and quantify structural, functional, or molecular changes in the brain [11,12]. *Structural imaging techniques*, MRI, provides precise images of the brain's architecture and can identify anomalies linked with neurological disorders [13,14]. Biomarkers obtained from structural imaging include the measurement of brain volume loss or atrophy, which is frequently employed as a biomarker for neurodegenerative conditions such as Alzheimer's disease (AD) or frontotemporal dementia [15]. White matter hyper-intensities seen on MRI scans are indicative of small vessel disease and can assist in diagnosing conditions like vascular dementia [16]. *Functional imaging techniques* capture brain activity and can help to identify patterns associated with the neurological diseases. Functional MRI (fMRI) measures changes in blood flow and oxygenation, can identify aberrant activation patterns in regions of interest, aiding in the diagnosis of conditions such as epilepsy or psychiatric disorders [17,18]. Positron Emission Tomography (PET) imaging with specific radiotracers can detect abnormal protein accumulation, such as amyloid plaques in Alzheimer's disease or dopaminergic dysfunction in Parkinson's disease [19–21]. *Molecular Imaging Biomarkers* techniques utilize radiotracers that bind to specific molecules or receptors in the brain. These biomarkers help diagnose neurological diseases by detecting molecular alterations associated with the condition [22–24]. The use of radiotracers like ^{18}F -florbetapir or ^{11}C -Pittsburgh compound B (PiB) in PET imaging allows for the visualization and quantification of amyloid plaques in Alzheimer's disease [20,25]. PET or SPECT imaging with radiotracers like ^{123}I -FP-CIT or ^{18}F -FDOPA can evaluate dopamine transporter function, aiding in the diagnosis of movement disorders like Parkinson's disease [26–29]. These imaging-based biomarkers provide objective and quantitative measures that assist in the diagnosis of neurological diseases. They complement clinical evaluations, improve diagnostic accuracy, and aid in early detection, allowing for timely intervention and appropriate management of these conditions.

2.2. Biomarkers for disease progression

IBB have proven valuable for assessing disease progression in neurological diseases. Structural imaging biomarkers are frequently employed as a biomarker for neurodegenerative conditions [30,31]. Longitudinal brain volume evaluation can reveal the rate of atrophy, which is valuable for tracking disease development such as AD, Multiple sclerosis (MS), or Huntington's disease (HD) [32–36]. Progressive ventricular enlargement can be seen in neurodegenerative disorders and can be used as a biomarker for disease progression, such as PD or AD [37–41]. *Functional Imaging Biomarkers*, such as fMRI or PET, can offer information regarding changes in brain function that occur as a result of disease improvement. These biomarkers can assist in determining the dynamic nature of neurological conditions. Changes in functional connectivity networks, as measured by fMRI, can signal disease progression in diseases such as AD, PD and MS [42–49]. PET imaging using radiotracers such as fluorodeoxyglucose (FDG) can assess glucose metabolism in the brain, which can indicate disease progression in AD [50–52]. PET and SPECT are molecular imaging modalities that can track the

molecular changes associated with disease progression. These biomarkers enable the detection and quantification of specific molecular targets [53,54]. Tau protein build up, as measured by tau PET imaging, is a biomarker for disease progression in AD and other tauopathies [55,56]. Dopamine transporter availability changes, as measured by PET or SPECT imaging, can indicate disease progression in PD [57,58]. These imaging-based disease progression biomarkers provide important insights into the dynamic changes that occur in neurological disorders throughout time.

2.3. Biomarkers for treatment response

IBB provide objective and quantitative measures of changes in brain structure, function, or molecular profiles following therapeutic interventions. The evaluation of lesion volume on MRI images in conditions such as MS or stroke can show the efficacy of disease-modifying medicines or interventions targeted at minimizing the extent of brain damage [59–61]. Monitoring changes in hippocampus volume during conditions such as AD can act as a biomarker for treatment response and disease progression [62,63]. fMRI and PET scans provide information about changes in brain function and connectivity after treatment, indicating treatment response in disorders such as major depressive disorder (MDD) or schizophrenia [64–66]. Furthermore, these approaches can detect changes in brain activation patterns during specific tasks or cognitive problems, providing information regarding treatment response in disorders such as ADHD or traumatic brain injury [67–71].

These imaging-based biomarkers for treatment response provide valuable insights into the effects of therapeutic interventions on brain structure, function, or molecular profiles. They aid in assessing treatment efficacy, guiding treatment decisions, and optimizing patient management.

2.4. Predictive biomarkers

Predictive biomarkers derived from imaging techniques in neurological diseases are valuable tools for identifying patients who are more likely to respond to specific treatments or have a higher risk of disease progression. Combining imaging data with genetic information can help identify predictive biomarkers [72,73]. Certain genetic variants may influence treatment response or disease progression. For example, in multiple sclerosis, specific genetic markers, when combined with imaging biomarkers like lesion load or brain volume, can help predict the likelihood of disease progression or response to disease-modifying therapies [19,74]. Identifying specific imaging patterns or signatures that are associated with treatment response or disease progression can serve as predictive biomarkers. By identifying predictive biomarkers, clinicians can better stratify patients, optimize treatment selection, and personalize therapeutic interventions.

2.5. Prognostic biomarkers

Prognostic biomarkers provide insights into the likely disease course, progression, or outcomes for individual patients. MRI, provide valuable biomarkers for assessing disease prognosis. Measurement of brain volume loss or atrophy over time can serve as a prognostic biomarker in AD, PD or MS [75–79]. Greater rates of brain atrophy often indicate a more severe disease course or worse outcomes. In conditions like MS, the volume and distribution of brain lesions assessed through MRI can provide prognostic information. Higher lesion load often correlates with more aggressive disease progression or disability accumulation. Functional imaging techniques, such as fMRI or PET, offer insights into brain function and connectivity that can serve as prognostic biomarkers [80–85]. Alterations in functional connectivity networks assessed by fMRI can provide prognostic information in AD, stroke, or traumatic brain injury [86,87]. PET imaging can assess metabolic activity in the brain, providing prognostic information in conditions like brain tumors or epilepsy. Higher metabolic activity in certain regions may indicate more aggressive tumor behavior or seizure recurrence [88–90]. Molecular imaging techniques, including PET or SPECT, can offer prognostic biomarkers by assessing molecular targets associated with disease progression or treatment response.

3. Application of Imaging Biomarkers (IB) in Specific Neurological Diseases

IB play a crucial role in the evaluation and management of various neurological disorders. They provide valuable insights into the structural, functional, and molecular changes that occur in the brain, aiding in early diagnosis, differential diagnosis, disease staging, and monitoring of treatment response (Table 1).

Table 1. Outlining imaging-based biomarkers in specific neurological disorders.

Neurological Disorders	Imaging-based Biomarkers
Alzheimer's disease	Amyloid PET imaging, Tau PET imaging, Hippocampal volume, Cortical thickness, Functional connectivity disruption, FDG-PET hypometabolism
Parkinson's disease	DaTscan SPECT imaging, Dopamine transporter imaging, Substantia nigra hyperechogenicity, Diffusion tensor imaging (DTI) alterations, Functional connectivity changes
Depression	Prefrontal cortex alterations, Hippocampal volume reduction, Amygdala hyperactivity, Default mode network dysfunction, Serotonin transporter imaging
Epilepsy	Hippocampal sclerosis on MRI, Cortical dysplasia on MRI, Epileptic network characterization using functional connectivity, PET/SPECT imaging for seizure focus localization
Multiple Sclerosis	Corticospinal tract degeneration on DTI, Whole-brain atrophy, Motor cortex hyperexcitability on fMRI, Hypometabolism on FDG-PET, Functional connectivity alterations
Stroke	Infarct volume and location on MRI, Perfusion imaging for assessment of ischemic penumbra, Collateral circulation evaluation, Functional connectivity changes, Vascular imaging (CTA/MRA) for stenosis/occlusion detection

3.1. AD and other dementias

The use of IB into the clinical practise has changed the way AD and other dementias are assessed and managed. Amyloid PET imaging with radiotracers like ¹⁸F-florbetapir (FTP) or PiB allows for the visualization and quantification of amyloid plaques in the brain. These biomarkers help in the early and accurate diagnosis of AD, as the presence of amyloid plaques is a hallmark of the disease [91–94]. Amyloid PET imaging can differentiate AD from other forms of dementia and aid in patient stratification for clinical trials [95–97]. Tau PET imaging, using FTP, allows for the detection and quantification of tau pathology in the brain. Tau pathology, including neurofibrillary tangles, is closely associated with disease progression in AD and other tauopathies [95,98–100]. Structural MRI is widely used in AD and other dementias to evaluate brain atrophy which differentiate between normal aging and pathological changes associated with neurodegenerative diseases [101,102]. Structural MRI biomarkers, such as hippocampal volume or whole-brain volume, can aid in the early detection and tracking of disease progression [103–105]. In AD and other dementias, fMRI can reveal alterations in functional connectivity patterns, such as disruptions in the default mode network [106,107]. These biomarkers aid in the understanding of disease mechanisms, assessing disease severity, and predicting cognitive decline.

3.2. Parkinson’s disease

Imaging techniques such as PET or SPECT with radiotracers targeting dopamine transporters, such as ¹²³I-FP-CIT or ¹⁸F-FDOPA, can assess the integrity and availability of dopaminergic neurons in the brain [108]. Dopamine transporter imaging also helps in monitoring disease progression and evaluating the response to dopaminergic therapies. fMRI or PET, provide insights into changes in brain function and connectivity in PD include resting-sate functional connectivity, task-based activation, structural imaging etc [109–113]. Altered functional connectivity patterns, such as disruptions in the default mode network or corticostriatal networks, have been observed in PD. fMRI or PET during specific motor tasks can assess changes in brain activation patterns. They provide information about the effects of PD on motor circuitry and help evaluate the response to therapeutic

interventions, such as deep brain stimulation [114–116]. High-resolution MRI or specific imaging sequences, such as susceptibility-weighted imaging (SWI), can visualize and measure the substantia nigra. These imaging biomarkers aid in the detection of substantia nigra degeneration, a characteristic feature of PD [117–119]. MRI-based volumetric analysis can evaluate changes in specific brain regions, such as the basal ganglia or cortical areas. These biomarkers can help in disease staging and monitoring disease progression [120]. PET or SPECT, can provide insights into molecular changes associated with PD [121]. Radiotracers targeting alpha-synuclein aggregates, a pathological hallmark of PD, are under development [122,123]. These biomarkers may help in the early diagnosis and monitoring of disease progression. An illustration with respect to imaging biomarkers used in AD and PD are depicted in Figure 1.

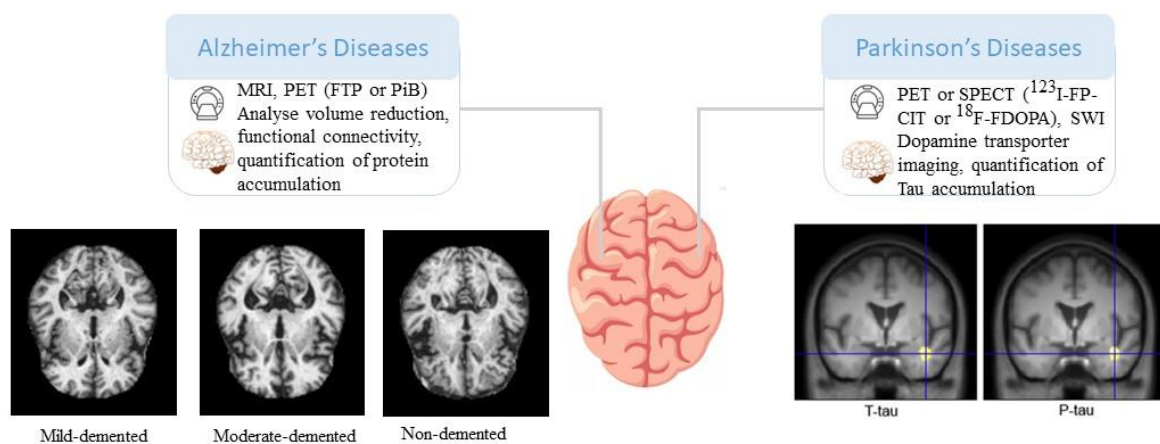


Figure 1. Images showing changes in brain during AD and PD adopted from [124,125].

3.3. Neuropsychiatric disorders

Imaging biomarkers have important applications in the evaluation and management of neuropsychiatric disorders. These biomarkers enhance our understanding of the underlying neural mechanisms and help guide personalized treatment approaches.

3.3.1. Major Depressive Disorder (MDD):

Resting-state functional connectivity assessed by fMRI can reveal alterations in functional networks, such as the default mode network or the limbic system, in individuals with MDD. These biomarkers help in understanding the neurobiology of depression and predicting treatment response. Structural MRI biomarkers, such as hippocampal volume, have been associated with MDD. Reduced hippocampal volume may indicate increased vulnerability to depression or treatment resistance [126–129].

3.3.2. Schizophrenia:

Structural imaging techniques can detect alterations in brain structure, such as decreased gray matter volume in specific regions like the prefrontal cortex or hippocampus. These biomarkers aid in the diagnosis and staging of schizophrenia [130,131]. Resting-state fMRI can reveal disrupted functional connectivity networks, such as the default mode network or the salience network, in individuals with schizophrenia [132,133]. These biomarkers help in understanding the underlying neural circuitry abnormalities and predicting clinical outcomes.

3.3.3. Bipolar Disorder:

Diffusion Tensor Imaging (DTI) can assess white matter integrity and identify alterations in fiber tracts in individuals with bipolar disorder. White matter connection disruptions may be used as

indicators for disease diagnosis and development [134–136]. In patients with bipolar disorder, task-based fMRI can reveal aberrant activation patterns during cognitive activities, emotional processing, or reward processing [137–139]. These biomarkers help researchers understand the brain underpinnings of symptoms and predict treatment response.

3.3.4. Obsessive-Compulsive Disorder (OCD):

Individuals with OCD exhibit altered functional connection patterns, such as enhanced connectivity between the orbitofrontal cortex and the basal ganglia. These biomarkers aid in the knowledge of the brain circuits involved in the pathophysiology of OCD [140–142]. MRI-based measurements of cortical thickness can identify regional abnormalities in individuals with OCD, particularly in regions associated with cortico-striato-thalamo-cortical circuits [143–145].

3.4. Epilepsy

MRI, a structural imaging technique play a crucial role in the evaluation of epilepsy, helps in identifying the underlying structural abnormalities that can cause seizures. High-resolution structural MRI allows for the detection of focal cortical dysplasia, hippocampal sclerosis, brain tumors, vascular malformations, and other structural lesions associated with epilepsy. These biomarkers aid in the localization and characterization of the epileptogenic zone [146–148]. Quantitative analysis of brain regions, such as the hippocampus or amygdala, can help identify abnormalities related to mesial temporal lobe epilepsy (MTLE) [149,150]. Functional imaging techniques provide insights into brain function and connectivity in epilepsy. They help in localizing the epileptogenic zone and understanding the network abnormalities associated with seizures [151,152]. Simultaneous electroencephalography (EEG) and fMRI recordings allow for the identification of blood oxygen level-dependent (BOLD) signal changes associated with epileptic activity. These biomarkers aid in localizing the epileptogenic zone and mapping the functional connectivity network associated with seizures [153–155]. Resting-state fMRI can reveal changes in functional connectivity networks such as the default mode network or the salience network. These indicators can help with surgical planning by providing insight into the functional abnormalities associated with epilepsy [156,157]. PET, can provide biomarkers related to specific molecular targets in epilepsy. PET imaging with FDG can assess regional glucose metabolism in the brain. Hypometabolism in specific regions, such as the temporal lobe, may indicate the epileptogenic focus or the extent of the epileptic network [152,158]. PET imaging with radiotracers targeting specific neurotransmitter receptors, such as the GABA-A receptor or the serotonin transporter, can provide insights into neurotransmitter abnormalities in epilepsy [159].

3.5. Multiple sclerosis

Structural imaging techniques, such as MRI, play a crucial role in the diagnosis, monitoring, and prognosis of multiple sclerosis. The quantification of T2 hyperintense lesions on MRI scans provides a biomarker of disease burden and dissemination in space, aiding in the diagnosis and monitoring of MS progression. The detection and quantification of contrast-enhancing lesions on post-contrast MRI scans indicate acute inflammation and blood-brain barrier disruption. These biomarkers help in identifying disease activity and monitoring treatment response [160–163]. Longitudinal assessment of brain volume loss or atrophy provides a biomarker of neurodegeneration and disease progression in MS. It correlates with physical disability and cognitive impairment [164]. Diffusion Tensor Imaging (DTI) measures the diffusion of water molecules in the brain's white matter, providing insights into the integrity of fiber tracts [165]. DTI-based biomarkers in multiple sclerosis includes Fractional Anisotropy (FA) and Mean Diffusivity (MD). Reduced FA values indicate axonal damage and demyelination in white matter tracts. Decreased FA in specific regions, such as the corpus callosum or corticospinal tracts, correlates with physical disability and disease progression [166,167]. Increased MD values reflect tissue damage and inflammation. Elevated MD is associated with active lesions and predicts disability progression in MS [168]. Functional imaging techniques, such as fMRI,

provide insights into brain activity and functional connectivity in multiple sclerosis, include Resting-State Functional Connectivity for altered functional connectivity patterns, such as disruptions in the default mode network or sensorimotor networks have been observed in MS [169].

PET imaging techniques offer molecular imaging biomarkers in multiple sclerosis. PET imaging with radiotracers targeting microglial activation, such as PK11195 or TSPO, can visualize neuroinflammation in MS. Increased uptake of these radiotracers is associated with disease activity and severity. Emerging PET radiotracers targeting myelin, such as ¹¹C-PIB or ¹⁸F-GE180, hold promise for assessing myelin integrity and repair in MS [170,171].

3.6. Stroke

Computed Tomography (CT) Imaging is widely used for the initial assessment of stroke patients due to its availability and speed. Non-contrast CT scans can rapidly detect acute ischemic changes and differentiate between ischemic and hemorrhagic strokes. They provide information about the location and extent of early ischemic changes [172–174]. CT Angiography (CTA) is a technique for visualising blood arteries in the brain and determining occlusions or stenosis. It aids in the identification of the underlying aetiology of a stroke, such as atherosclerosis, arterial dissection, or embolism. MRI imaging techniques provide precise information on the structure of the brain and can distinguish between different stroke subtypes [175,176]. Diffusion-Weighted Imaging (DWI) can detect acute ischemic lesions within minutes of stroke onset. It provides valuable information about the affected brain tissue and helps determine the viability of the tissue at risk (Okorie et al., 2015). Perfusion-Weighted Imaging (PWI) assesses cerebral blood flow and can help to identify areas of hypoperfusion or ischemia. It aids in estimating the extent of the penumbra, which is potentially salvageable tissue, and guides decisions regarding reperfusion therapies [177,178]. Magnetic Resonance Angiography (MRA) provides detailed images of blood vessels and helps in visualizing the site and extent of vessel occlusion or stenosis. It aids in determining the appropriate treatment approach, such as endovascular intervention or anticoagulation [179–181]. Perfusion imaging techniques, including CT or MRI-based perfusion imaging, provide quantitative measures of cerebral blood flow and help assess tissue viability. They aid in determining the extent of the ischemic penumbra, which guides decisions regarding reperfusion therapies [182–185]. These imaging biomarkers by providing objective measures of brain damage and vascular abnormalities, imaging biomarkers enhance clinical decision-making, optimize patient care, and improve long-term outcomes in stroke patients (Table 2).

Table 2. summarizing the imaging techniques commonly used in the assessment of stroke and their respective roles.

Imaging Technique	Role
Non-contrast CT	Rapidly detects acute ischemic changes and differentiates between ischemic and hemorrhagic strokes. Provides information about the location and extent of early ischemic changes.
CT Angiography (CTA)	Visualizes blood vessels in the brain and identifies occlusions or stenosis. Helps determine the underlying cause of stroke.
MRI	Provides detailed information about brain structure and differentiates between stroke subtypes
Diffusion-Weighted Imaging	Detects acute ischemic lesions within minutes of stroke onset. Provides information about affected brain tissue and helps determine tissue viability.
Perfusion-Weighted Imaging	Assesses cerebral blood flow and identifies areas of hypoperfusion or ischemia. Aids in estimating the extent of the penumbra
Magnetic Resonance Angiography (MRA)	Provides detailed images of blood vessels. Helps visualize vessel occlusion or stenosis and determine treatment approach.
Perfusion Imaging (CT or MRI)	Provides quantitative measures of cerebral blood flow. Assists in assessing tissue viability and determining the extent of the ischemic penumbra.

4. Challenges and Limitations

4.1. Technical limitations

While IBB have shown great promise in the treatment of neurological disorders, they also face certain technical limitations and challenges. Spatial resolution affects accurate detection of small-scale changes or lesions, with fMRI having lower resolution than histopathology. Temporal resolution can be slow, making it difficult to capture quick changes in brain activity. Signal-to-Noise Ratio (SNR) impacts data quality and reliability, with low SNR reducing sensitivity. Image artifacts, patient movement, and limited contrast agents contribute to lower SNR. Expertise is required for interpreting imaging biomarkers. Developing reliable algorithms for data analysis and extracting meaningful biomarkers is complex. Validation against gold-standard measures or clinical outcomes is necessary to establish reliability and clinical utility.

4.2. Standardization and reproducibility

Standardization and reproducibility pose challenges IBB due to protocol variations, acquisition parameters, data analysis methods, and software tools. Consensus on standardized imaging protocols is lacking, resulting in variability in image quality and biomarker measurements. Diverse analysis methods and software tools contribute to inconsistencies in measurements. Multicentre studies face additional challenges from equipment variations, requiring calibration and harmonization efforts. Longitudinal studies rely on consistent protocols and reliable follow-up imaging. Maintaining consistent acquisition parameters and minimizing platform or software changes are crucial for longitudinal biomarker comparability and reproducibility.

5. Future Directions and Potential Impact

Advancements in imaging technology, including multimodal imaging, molecular imaging, AI integration, and real-time imaging, will provide comprehensive insights into neurological disorders. This will enhance diagnosis, treatment decision-making, and targeted therapies. Furthermore, integrating imaging biomarkers into clinical practice holds promise for neurological disorder treatment. They enhance diagnostic accuracy, guide personalized treatment, monitor disease progression, aid surgical planning, and enable prognostic predictions. Integration facilitates early and accurate diagnosis, tailored interventions, and timely treatment adjustments. Imaging technology in telemedicine expands access to specialized care.

6. Conclusions

IBB have shown promise in neurological disorder treatment, aiding in diagnosis, treatment selection, monitoring, and prognostication. Technical limits, standardisation concerns, ethics, legislation, and cost-effectiveness are among the challenges. Imaging technology advancements such as high-resolution, multimodal, molecular imaging, AI, and real-time imaging will improve accuracy and sensitivity. Integration with personalized medicine and precision imaging will enhance outcomes. Standardizing protocols, analysis, and addressing ethical/regulatory aspects will facilitate clinical integration. The future of IBB in neurological disorder treatment is promising but requires concerted efforts for widespread implementation.

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