EDITORIAL

Nuclear psychiatric imaging: the trend of precise diagnosis for mental disorders

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Mental disorder is a complex class of diseases characterized by abnormalities in perception, thought, emotion, or behavior activities. According to the 2022 World's Mental Health report [1], nearly one billion people around the world, including millions of children and young people, suffer from a mental health condition. Mental disorders bring a huge burden to society and remained among the top ten leading causes of burden worldwide reported by the Global Burden of Diseases (GBD) 2019 [2]. Both genetics and social environment are influence factors for increasing prevalence of mental disorders. With the development of society and its various impacts, the spectrum of mental disorders is also dynamically changing, and the incidence of anxiety and depression disorders is significantly increased with more than 25% during the first year of COVID-19 pandemic [3].

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So far, no biomarkers have been proved useful and valid enough to change the clinical practice of mental disorders excluding dementia. The diagnosis of mental disorders still relies on the symptomatic judgment by psychiatrists. External descriptive evaluations are mainly used, and underlining biological markers are lacking or difficult to detect in clinical practice. There is still a gap between clinical manifestations and molecular mechanisms. The key to the diagnosis and treatment of mental disorders is understanding the molecular pathological mechanism caused by the genetic, developmental, and environmental factors. Only pathological-based precise classification can achieve precise diagnoses and management of mental disorders. Therefore, we should establish non-invasive and real-time brain detection methods to build the bridge between the neuropathological features and clinical phenotype of mental disorders.

Currently, it is considered that the pathology of mental disorders mainly involves changes of brain structure and dysfunctions of neurotransmitter pathway or neural circuit. It is appealing to apply molecular imaging in mental disorders and drive psychiatry toward a management era. As early in 1882, Italian scientist Angelo Mosso has developed the first technique, known as "human circulation balance," to measure the redistribution of blood in emotional and intellectual activity [4]. In 1918, by injecting filtered air into lateral ventricles, X-ray was used to image ventricular system [5]. Despite the crudity of equipment and methods, these studies represent the earliest exploration of techniques with potential for evaluating mental disorders. Later, a series of imaging modalities have been developed rapidly, by which structural and functional changes of mental disorders can be visualized more sensitively and precisely in vivo. With high-field-strength techniques, as well as advanced scan sequences and analysis methods, the applications of structural and functional MRI have been attracted much attention and widely used to explore the pathological and intervention targets of mental disorders. Many abnormalities have been

reported in different mental disorders; some of them were considered illness-specific [6–8] and provide potential brain-circuit-based intervention targets [9].

Apart from the structural and functional characteristics, another noted trend in this field is the exploration of cellular/molecular alterations. For this aspect, nuclear imaging technology especially positron emission tomography (PET) is undoubtedly one of the most important imaging approaches. Based on the principle of molecular recognition and radionuclide tracing, PET is powerful to identify alterations including but not limited to metabolism, transmitter, receptor, and brain network [10, 11]. PET molecular imaging approaches provide a great opportunity to bring the mental disorders from an era of descriptive classification into a visible and measurable era. To date, a great number of radiotracers have been developed, making PET a potential tool to visualize, characterize, and quantify pathophysiological changes of mental disorders at different stages (especially for the early and ultra-early stage) in a multi-perspective mode [12–14].

Along with the development of molecular tracer technology, the application of PET imaging has been involved in the clinical research of mental disorders by evaluating brain metabolic functions, assessing the expression of neuroreceptors and neurotransmitters, and measuring neuroinflammation. Wherein, brain metabolic functions are associated with activities of neurons and demonstrate specific spatio-temporal patterns. Early in the 1990s, radiotracers $H_2^{15}O$ PET and [18F]-FDG PET were separately used to detect regional cerebral blood flow (rCBF) and regional cerebral glucose metabolism rate (CMRglu) in psychiatric disorders and have yielded some important findings [15]. The alterations of regional brain glucose metabolism are also associated with treatment response in mental disorders. [18F]-FDG PET indicated that reduced glucose metabolism in the right posterior insula was associated with decreased depression scores in major depressive disorder (MDD) patients with regular psychotherapy [16]. For MDD patients with high-frequency repetitive transcranial magnetic stimulation treatment, high [18F]-FDG glucose metabolism of subgenual anterior cingulate cortex (sgACC) was correlated with promised treatment response [17]. Neuroreceptors and neurotransporters changes in neurotransmitter pathways are an important hypothesis in the pathogenesis of mental disorders. PET molecular imaging has the unique advantages to in vivo assess the status of synapses, neuroreceptors, and transporters, such as dopamine, serotonin, and gamma-aminobutyric acid (GABA) systems. [11C]-UCB-J and [18F]-UCB-J have been developed to investigate the synaptic density in human beings [18]. By using [11C]-UCB-J, Sophie et al. revealed that lower synaptic density was correlated with altered networks and symptoms of patients with depression [19]. Various PET radiotracers from dopamine synthesis, release,

synaptic dopamine level to $D_{2/3}$ receptors, and dopamine transporter availability were used in mental disorders. Differences in mean and variability of dopaminergic indices were found in patients with schizophrenia [20]. [18F]-DOPA indicated that dopamine dysregulation in striatal was associated with pathology of schizophrenia [21]. Besides, Anne et al. revealed that striatal decarboxylation rate at baseline measured by [18F]-DOPA could predict psychotic symptoms and treatment response in antipsychotic-naïve schizophrenia [22]. Similarly, 5-HT receptor and transporter studies were carried out in various mental disorders using different PET radiotracers, and different patterns of 5-HT receptor and transporter dysfunction were found in neuropsychiatric disorders [23]. GABA receptor-induced signaling was also involved in the pathophysiology of mental disorders. [11C]-Ro154513 revealed GABA-A receptor expressed less in the hippocampus of patients with schizophrenia [24]. These PET radiotracers provide tools to investigate in-depth alterations of mental disorders. More recently, the role of neuroinflammation is considered important in mental disorders. It is exciting that several PET radiotracers such as [11C]-PK11195, [18F]-DPA-714, and [11C]-PBR28 were available to determine neuroinflammation in mental disorders. Studies from four different centers revealed that 18-kDa translocator protein (TSPO) binding in the anterior cingulate cortex and prefrontal cortex was increased by 15–67% and 25–35%, respectively [25]. Increased TSPO in untreated patients with MDD was associated with effective treatment response of celecoxib [26]. In addition, PET imaging has also been used in the development of psychotropic drugs for a long time, for example, titrating the therapeutic dose of psychotropic drugs by receptor or transporter occupancy [27], exploring the mechanism of action of unclear chemical substances by detecting their different receptor bindings [28], and predicting the treatment response. In general, PET molecular imaging could reveal the molecular alterations of mental disorders from different perspectives, followed by guiding precise diagnosis and management in mental disorders.

Although nuclear molecular imaging has made great progress, given that mental disorders are clinically heterogeneous and neuropathology inconsistent, wider and deeper research of pathological features of mental disorders are needed. Herein, we propose the concept of nuclear psychiatric imaging which expects to achieve a true transformation from traditional manifestation-based diagnosis to transpathology-based diagnosis in mental disorders (Fig. 1). To overcome these challenges, the application of PET imaging in mental disorders needs to be expanded from the following three aspects: First, explore more specific molecular targets of mental disorders and develop more specific nuclear medicine molecular tracers. For example, neuroinflammation is a multifaceted physiological and pathophysiological
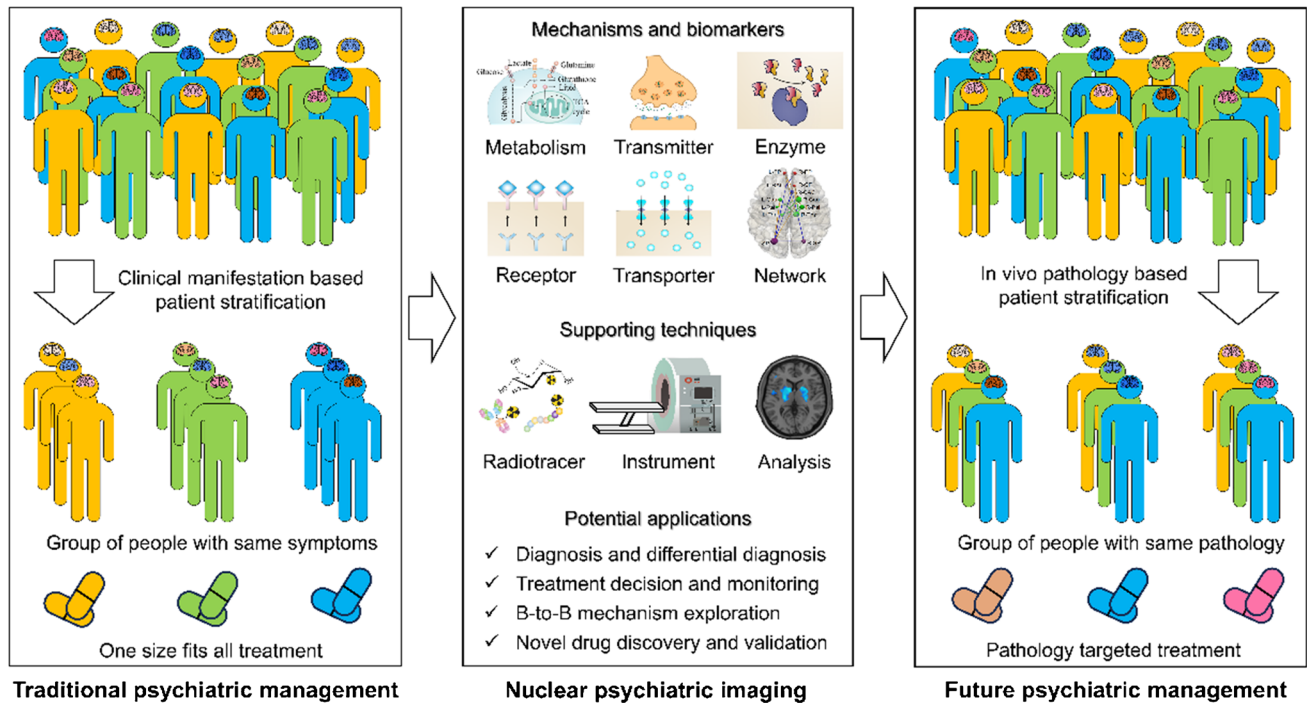
Fig. 1 Nuclear psychiatric imaging drives a pathology-based psychiatric management. As yet, psychiatric patients were mostly diagnosed and grouped according to clinical manifestations, with regulating monoamine neurotransmitter system being the mainstream strategies for treatment. Nuclear psychiatric imaging has the great potential to explore mechanisms and biomarkers based on various characteristics of mental disorders. With advanced radiotracers, imaging instruments, and analysis methods, nuclear psychiatric imaging would facilitate the diagnosis and differential diagnosis, treatment decision and monitoring, bench-to-bed mechanism exploration and translation, novel drug discovery and validation. In the future clinical practice, psychiatric patients would be diagnosed and grouped according to the in vivo pathology, and the treatment would be pathology targeted

response to brain injury and mental disorders [25]. Development of radiotracers for TSPO and other inflammatory targets for PET imaging of neuroinflammation is at a particularly promising stage. The endocannabinoid system (ECS) has received increasing attention due to its involvement in many different functional processes in the brain, including the regulation of emotion, motivation, and cognition [29, 30]. Development of PET radiotracers for ECS targets (e.g., receptors, ligands, synthesizing, and degrading enzymes) is also a promising research field that will lay the foundation for future research of diseases and the drugs related to the ECS. Second, optimizing, developing, and integrating novel imaging approaches. Utilizing single- or even multi-tracer PET fusion with computed tomography (CT), MRI, magnetic resonance spectroscopy (MRS), or electroencephalogram (EEG) can offer enhanced benefits and compensate for the disadvantages of each imaging system compared to using a single modality [31]. Third, exploration of new analytical methods. Algorithms and artificial intelligence (AI) will facilitate the reconstruction of images, capturing subtle changes and analyzing information. With AI-based image reconstruction or enhancement methods, scanning times can be reduced while maintaining or improving quantification

accuracy and enabling attenuation corrections. AI-based big data analytics can also be used to select the most promising leads to design appropriate treatments for the target of a disease [32, 33].

In summary, mental disorders remain a major challenge facing the health system worldwide, due to the insufficient knowledge on the pathogenetic mechanisms as well as lack of biomarkers. The past few decades have witnessed great progress in the field of medical imaging, especially for the MRI and PET. Because of the unique advantage of molecular recognition and ultra-high sensitivity, applications of nuclear molecular imaging have gained much attention in mental disorders. To date, a roster of imaging approaches and analysis methods have been established to assess various characteristics of mental disorders in vivo, including metabolism, neurotransmitter, enzyme, receptor, transporter, and brain network. The nuclear psychiatric imaging has the great potential to promote the development of scientific research and clinical practice for mental disorders. In this regard, a close collaboration is required between researchers and clinicians in nuclear medicine and psychiatry, with the common goal of improving the management of patients with mental disorders.

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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