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Review

Progress in the application of molecular imaging in psychiatric disorders

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Abstract

Psychiatric disorders have always attracted a lot of attention from researchers due to the difficulties in their diagnoses and treatments. Molecular imaging, as an emerging technology, has played an important role in the researchers of various diseases. In recent years, molecular imaging techniques including magnetic resonance spectroscopy, nuclear medicine imaging, and fluorescence imaging have been widely used in the study of psychiatric disorders. This review will briefly summarize the progression of molecular imaging in psychiatric disorders.

Keywords: molecular imaging; psychiatric disorders; magnetic resonance spectroscopy; fluorescent molecular probe; positron emission computed tomography; single photon emission computed tomography

Introduction

Psychiatric disorders have attracted attention in recent years. Even though they are chronic or disabling health diseases that are not necessarily fatal, psychiatric disorders could still cause major health hazard for humans worldwide (Eaton *et al.*, 2008). Common psychiatric disorders that are not accompanied by obvious pathological changes include schizophrenia, depression disorder, post-traumatic stress disorders (PTSD), bipolar disorder (BD), and obsessive-compulsive disorder (OCD). Relying solely on pathological and physiological indicators, the diagnosis of these kind of psychiatric disorders is very challenging due to their great heterogeneity and potential confusions between the different psychiatric disorders (Meyer *et al.*, 2020). Currently, the diagnosis of psychiatric disorders relies mainly on "mental disorder scales/questionnaires," which are susceptible to subjective bias. Consequently, it is imperative to diagnose and monitor therapeutic the psychiatric disorders by objective indicators.

Molecular imaging is a new imaging research field that emerges from the advanced medical technologies such as magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US), and nuclear medicine imaging. It focuses on using endogenous metabolites or exogenetic probes to monitor physiological and pathological activities within the human body at the molecular level to achieve molecular, cellular, and tissue-specific imaging. In recent years, molecular imaging has shown great power in the diagnosis of psychiatric disorders due to its unique advantages. First, molecular imaging is a non-invasive technique that could reflect physiological processes in the brain at the molecular level, which is usually correlated with changes in clinical behaviors. Second, molecular imaging can detect some cellular and molecular targets, providing a molecular biological basis for subsequent targeted diagnoses and treatments. In addition, as molecular imaging could detect early functional changes in the progression of diseases, it has great value for the early diagnoses and treatments of psychiatric disorders (Hwang *et al.*, 2017).

Currently, commonly used molecular imaging techniques in the diagnoses of psychiatric disorders mainly include magnetic resonance spectroscopy (MRS), nuclear medicine imaging such as positron emission CT (PET/CT) and single photon emission CT (SPECT), all of which could provide crucial information for psychiatric disorder diagnosis at the molecular level.

This review briefly summarizes the findings from the applications of molecular imaging to psychiatric disorders and emphasizes the potential of molecular imaging technique in diagnosis of psychiatric disorders. The summary of molecular markers from three molecular imaging techniques in the psychiatric disorders is shown in Table 1.

Molecular imaging techniques used in the diagnosis of psychiatric disorders

Magnetic resonance spectroscopy (MRS)

MRS is a non-invasive MRI technique that does not rely on radioactive tracers and is free of ionizing radiation. Unlike conventional hydrogen proton MRI, MRS can provide quantitative estimates of the concentration and ratio of metabolites, neurotransmitters, and other chemical substances in different regions of interest in the brain, which are of great clinical value and could be used to evaluate normal and abnormal metabolic conditions

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Table 1: Summary of molecular markers from three molecular imaging techniques in the psychiatric disorders.

Psychiatric disorders	MRS Molecular metabolites	Nuclear medicine imaging Radioligand and receptors	Fluorescent imaging Probes and markers
Schizophrenia	Glu (Merritt *et al.*, 2021) Glx (Nakahara *et al.*, 2022) NAA (Reid *et al.*, 2019) GABA (Kumar *et al.*, 2021) Cho (Chiu *et al.*, 2018) MI (Wang *et al.*, 2020)	[11C]DASB and 5-HTT: (Erritzoe *et al.*, 2003) 99mTc-TRODAT-1 and DAT: (Yang *et al.*, 2022)	H_2S: (Geng *et al.*, 2022)
Depression disorder	Glx (Mirza *et al.*, 2004) GABA: (Simmonite *et al.*, 2023)	[11C]WAY-100635 and 5-HT_{1A}: (Parsey *et al.*, 2010) [11C]GR103545 VT and kappa-opioid receptor (Miller *et al.*, 2018)	Superoxide anion radical (O_2^-): (Ding *et al.*, 2020) ozone (O3): (Li *et al.*, 2019) AChE: (Wang *et al.*, 2019) NE: (Gu *et al.*, 2023) NMDA: (Wang *et al.*, 2020) BDNF: (Li *et al.*, 2019)
PTSD	NAA (Quadrelli *et al.*, 2018) Glu (Sheth *et al.*, 2019) Glx (Yang *et al.*, 2015) GABA (Rosso *et al.*, 2022) Cho (Karl *et al.*, 2010)	[11C]DASB,[11C]GR205171, [11C]AFM, and SERT: (Frick *et al.*, 2016; Murrough *et al.*, 2011) [^{18}F]FPEB and mGluR5: (Holmes *et al.*, 2017)	
BD	NAA (Chabert *et al.*, 2022) Glu (Ino *et al.*, 2023) Glx (Chitty *et al.*, 2013)	[11C]DASB, [123I]ADAM, and SERT: (Cannon *et al.*, 2006; Chou *et al.*, 2016) [11C]WAY-100635 and 5-HT_{1A}: (Sullivan *et al.*, 2009) 99mTc-TRODAT-1 and DAT: (Hsueh *et al.*, 2021) [123I]5IA-85380 and β2$*$-n AChR: (Hannestad *et al.*, 2013)	
OCD	NAA (Chitty *et al.*, 2013)	[11C]MDL 100907 and 5-HT_{2A}: (Simpson *et al.*, 2011) [11C]-SCH23390 and DAT: (Perani *et al.*, 2008)	

in the human brain. By combining the technique with behavioral and cognitive changes, this ultimately provides a reference for assessing brain health.

Specifically, the metabolism and molecular compositions of brain tissues can be characterized by MRS. For example, ^{1}H-MRS can be used to characterize neuronal density and levels of integrity neurochemicals, such as *N*-acetylaspartate (NAA); measuring the ratio of creatine (Cr) to phosphocreatine (PCr) (Cr/PCr) to assess cellular energy levels; and measuring choline (Cho) concentration to calculate the level of cell membrane renewal. In addition, other metabolites could also be detected, such as the major excitatory neurotransmitters including glutamic acid (or glutamate, Glu) and glutamine (Gln) (could be collectively referred to as Glx), which could reflect neuronal activity and excitotoxicity (Lyoo *et al.*, 2002; Yildiz-Yesiloglu *et al.*, 2006).

Nuclear medicine imaging

In the field of molecular imaging, PET and SPECT are commonly used in nuclear medicine. PET and SPECT characterize and measure biological processes *in vivo* by using molecular probes with high specificity and affinity. Molecular probes of PET or SPECT are composed of ligand molecules labeled with radioactive isotopes, in which the ligand molecule could bind to specific target in the body to achieve a high specificity and the radioactive isotopes could release radioactive rays. Molecular probes can be detected by the corresponding scanner, then the localization of the radioactive labeled molecule in the target tissue could be obtained. This provides a non-invasive way to visualize and characterize physiological processes in the body and provides an opportunity to explore them in the entire living brain (Erritzoe *et al.*, 2003; Kim *et al.*, 2013).

The main difference between PET and SPECT is the radioactive isotope used to label the tracer. The most commonly used radioactive isotopes in SPECT are technetium 99m (^{99m}Tc), indium 111 (^{111}In), iodine 123 (^{123}I), thallium 201 (^{201}Tl), etc., which have relatively long half-lives and decay processes that produce a photon. The most commonly used radioactive isotopes in PET are carbon 11 (^{11}C), nitrogen 13 (^{13}N), oxygen 15 (^{15}O), and fluorine 18 (^{18}F), which have shorter half-lives and decay processes that emit a positron. Compared with SPECT, the radioactive isotopes used in PET bind more easily to biological molecules and have better resolution.

Fluorescent imaging

Fluorescent molecular probes are widely used in biological detection. They usually consist of three parts: a recognition group, a fluorescent group, and a linker. The recognition group, also called the receptor, is the part that binds to the analyte, determining

the selectivity and specificity of the probe. The fluorescent group converts the chemical or biological microenvironmental changes caused by the recognition group binding to the analyte into signals that are easily perceptible by humans (color changes) or detectable by instruments (fluorescence), determining the sensitivity of recognition. The linker connects the fluorescent group and the recognition group, allowing the recognition information to be effectively converted into a fluorescent signal (such as changes in fluorescence intensity, spectral shift, fluorescence lifetime, etc.), thereby achieving effective detection of the analyte. The applications of fluorescent molecular probes in psychiatric disorders are the monitoring and tracking the biomarkers of the disease in real-time, which is beneficial for the early diagnosis of the diseases.

Applications of MRS in psychiatric disorders

Application of MRS in schizophrenia

Schizophrenia is a complex neuropsychiatric syndrome with various genetic, neurobiological, and phenotypic features (Kraguljac *et al.*, 2021). It is a severe, episodic, and persistent disease, with the main symptoms during the acute phase being positive symptoms such as delusions, disordered thinking and language, and hallucinations. The subsequent chronic phase is characterized by negative symptoms, such as cognitive deficits and social impairments (Kumar *et al.*, 2020).

Glu, Glx, NAA, gamma-aminobutyric acid (GABA), Cho, and myo-inositol (MI) are commonly used as diagnostic markers in MRS for schizophrenia. Recent studies have focused on changes in Glu and its metabolites in patients with schizophrenia. Multiple studies and meta-analyses have shown that patients with schizophrenia have decreased Glu and Glu metabolite levels in the frontal cortex (especially the medial prefrontal cortex and the anterior cingulate cortex) and increased Glx levels in the basal ganglia compared to healthy controls (Kubota *et al.*, 2020; Kumar *et al.*, 2020; Smucny *et al.*, 2021; Merritt *et al.*, 2021; Nakahara *et al.*, 2022). Figure 1 shows an example plot of the spectral results and the placements of voxels in axial, coronal, and sagittal images from one representative study. However, in patients with treatment-resistant schizophrenia, ultra-treatment-resistant schizophrenia, first-episode schizophrenia, and schizophrenia high-risk patients, the Glx levels significantly increase in dorsal anterior cingulate cortex, posterior cingulate cortex, medial prefrontal cortex and basal ganglia (Chiu *et al.*, 2018; Kim *et al.*, 2018; Chouinard, 2019; Iwata *et al.*, 2019; Romeo *et al.*, 2020; Tarumi *et al.*, 2020; Wang *et al.*, 2020; Nakahara *et al.*, 2022).

Regarding NAA, many studies have shown that schizophrenia patients have lower NAA levels than healthy controls (Brugger *et al.*, 2011; Iwata *et al.*, 2018; Reid *et al.*, 2019; Romeo *et al.*, 2020; Wang *et al.*, 2020). A meta-analysis of 182 studies showed that NAA levels in the frontal, hippocampal, temporal, parietal, and thalamic regions were lower in chronic schizophrenia patients compared to normal controls. In first episode schizophrenia patients, NAA levels in the frontal and thalamic regions were significantly lower than untreated first-episode schizophrenia patients, and NAA concentrations in the frontal region were lower than in healthy controls. NAA levels in the hippocampus of patients with high-risk schizophrenia were significantly reduced. The results therefore indicated that the changes of NAA in schizophrenia appear to not only in the hippocampus, frontal cortex, and thalamus, but also extend to other regions (Whitehurst *et al.*, 2020).

GABA is hard to quantify due to its low concentration in the brain. Few studies have shown that first-episode schizophrenia patients have reduced GABA concentrations when comparing to healthy controls (Chiu *et al.*, 2018; Nakahara *et al.*, 2022). In addition, the level of GABA in the anterior cingulate cortex of ultra-treatment-resistant schizophrenia patients is higher than that in treatment-resistant patients, but it is not correlated with the severity of symptoms (Ueno *et al.*, 2022). A meta-analysis showed that there were no significant differences in GABA levels between patients with schizophrenia and healthy controls in the medial prefrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex. However, in the frontal cortex, the GABA levels were lower in patients with schizophrenia than in healthy controls, and there were significant intergroup differences in GABA levels in the anterior cingulate cortex, which was more pronounced in first-episode schizophrenia patients (Kumar *et al.*, 2021).

Compared to healthy controls, schizophrenia patients have higher concentrations of Cho in the dorsolateral prefrontal cortex and medial temporal lobe (Chiu *et al.*, 2018; Romeo *et al.*, 2020). Individuals at high-risk of schizophrenia show increased MI levels in the medial prefrontal cortex and dorsolateral prefrontal cortex (Romeo *et al.*, 2020; Wang *et al.*, 2020), and first-episode schizophrenia patients show decreased MI levels (Chiu *et al.*, 2018).

Application of MRS in depression

Depression is one of the most common and severe mental disorders, with a lifetime prevalence of 16% in the USA. It can lead to many negative consequences, including health and social problems, with suicide being the most serious, accounting for up to 8% of cases (Lee *et al.*, 2014; Zhang *et al.*, 2016).

In the diagnosis of depression, common metabolites studied in MRS include NAA, Glx, GABA, and Cho. For instance, in patients with depression, the concentration of Glx in the anterior cingulate cortex, amygdala, and hippocampus reduces, and the concentration of GABA in the occipital cortex significantly reduces (Pfleiderer *et al.*, 2003; Mirza *et al.*, 2004). A meta-analysis on NAA has shown no significant difference in NAA levels in the basal ganglia and frontal structures between patients with depression and healthy controls. At the same time, this meta-analysis pointed out that the Cho/Cr value in the basal ganglia was higher in adult depression patients than in normal individuals, and that the results on Cho each of the original studies were inconsistent (Yildiz-Yesiloglu *et al.*, 2006). Overall, research on Glx and GABA may be the most promising, with most studies finding that the levels of Glx and GABA in the brain areas of depression patients are lower than those of healthy controls. However, a recent meta-analysis showed that rostral MFC GABA decreased in depressed patients compared with healthy controls, but the significance of this effect was not present in multiple comparisons after collection (Simmonite *et al.*, 2023).

Application of MRS in PTSD

PTSD refers to a mental disorder characterized by delayed onset and long-term persistence following sudden, threatening, or catastrophic events in life (Rosso *et al.*, 2017). PTSD is defined as an emotional regulation disorder, related to impaired emotional, physiological, and neural responses to threatening and traumatic stimuli (Kaldewaij *et al.*, 2021).

NAA, Glu, Glx, GABA, and Cho are commonly used as biomarkers for diagnosing PTSD with MRS. Regarding NAA, many studies have shown that the levels of NAA and NAA/Cr in the hippocampus and the prefrontal cortex reduced in PTSD patients (Schuff *et al.*, 2001; Mohanakrishnan Menon *et al.*, 2003; Li *et al.*, 2006; Shu

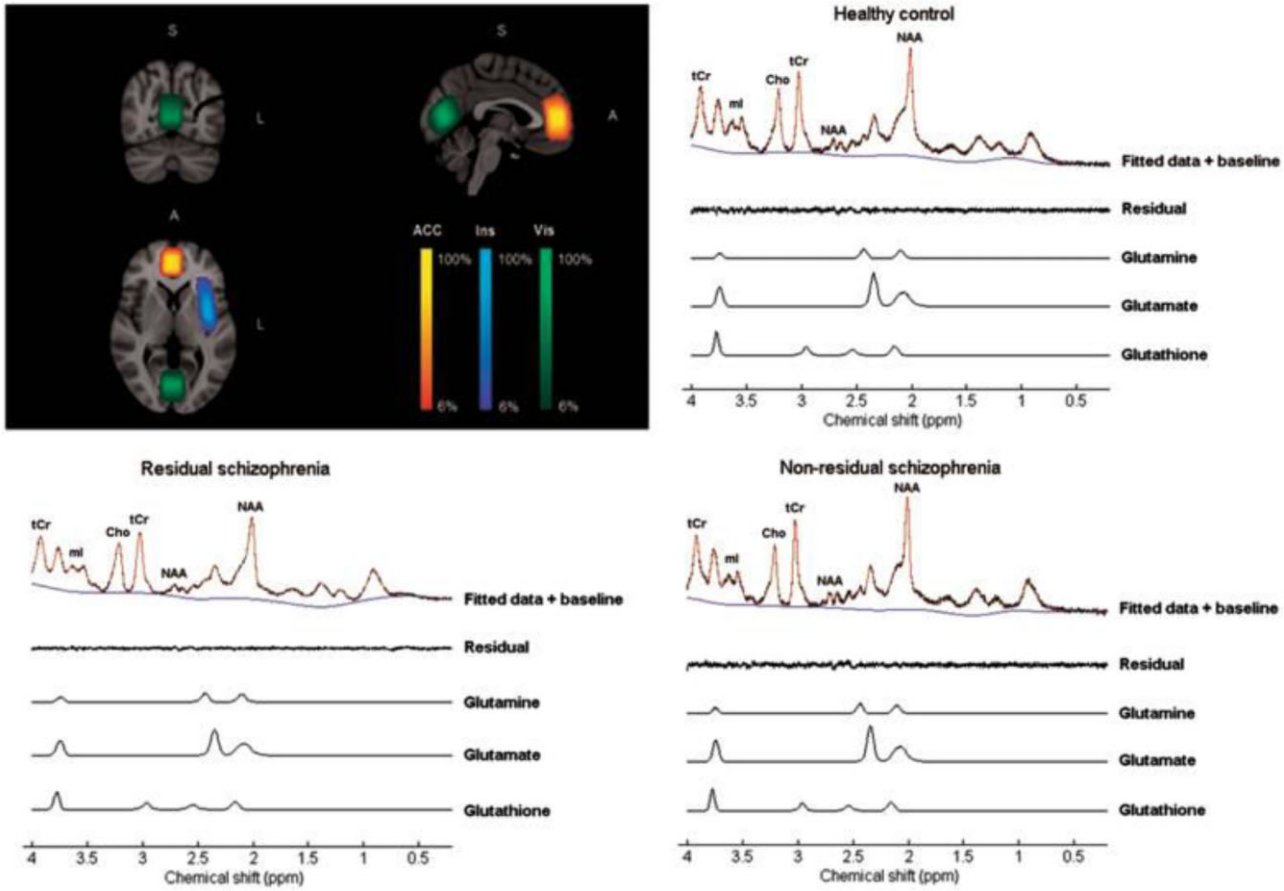

Figure 1: The voxel placements (ACC, anterior cingulate cortex; Ins, left insula; and Vis, visual cortex) on the brain of all patients; Illustrative spectra with baseline and residuals from a voxel located in the ACC of subjects from three groups and corresponding fits for Gln, Glu, and glutathione (Kumar *et al.*, 2020).

et al., 2013, 2008; Meyerhoff *et al.*, 2014; Rosso *et al.*, 2017; Quadrelli *et al.*, 2018; Su *et al.*, 2018; Kaldewaij *et al.*, 2021). Figure 2 shows the placement of voxels in the axial, coronal and sagittal views of the hippocampus during MRS scanning and shows the spectrum result of the single patient. Some studies have also compared the NAA/Cr ratios in the left and right hippocampus and found that the NAA/Cr ratio in the left hippocampus of PTSD patients was significantly smaller than that in the right hippocampus, suggesting that the hippocampal dysfunction in PTSD patients is lateralized. In addition, a meta-analysis has shown that the absolute concentration of NAA decreased in the left hippocampus in PTSD patients compared with healthy controls (Karl *et al.*, 2010). As for other brain regions, PTSD patients have lower NAA/Cr ratios in the basal ganglia (Lim *et al.*, 2003; Karl *et al.*, 2010). The concentration of NAA in the right amygdala was significantly higher in PTSD patients than in trauma-exposed controls, and the concentration of NAA in the left amygdala was higher in older PTSD patients than in trauma-exposed controls (Wang *et al.*, 2019).

Glu and its metabolites have been studied more in recent years and several studies have shown that the concentrations of Glu and its metabolites and their ratios with Cr in the brain are significantly decreased in PTSD patients, with the prefrontal cortex and hippocampus being the most affected regions (Meyerhoff *et al.*, 2014; Yang *et al.*, 2015; Rosso *et al.*, 2017; Sheth *et al.*, 2019). Studies have also shown that the Glx/Cr level in the prefrontal cortex reduce significantly in PTSD patients compared with recovery subjects, and the changes in the Glx/Cr ratio may stem from brain functional impairment in the current stage and recovery in the relief stage (Michels *et al.*, 2014). A study showed that the levels of GABA in the prefrontal cortex and dorsolateral prefrontal cortex increased in PTSD patients, but subsequent studies have shown that the levels of GABA in the brain decreased in PTSD patients, with the medial prefrontal cortex, insula, parietal lobe, temporal lobe, and prefrontal cortex being the most affected areas (Fig. 3) (Meyerhoff *et al.*, 2014; Sheth *et al.*, 2019; Rosso *et al.*, 2022, 2014). Many research results have shown no significant difference in the concentration of Cho or Cho/Cr between PTSD patients and healthy controls, but some studies have shown that the Cho/Cr level is significantly higher in the prefrontal cortex of PTSD patients (Seedat *et al.*, 2005). Additionally, a meta-analysis has shown that the Cho/Cr level was higher in the left hippocampus in PTSD patients compared with healthy controls, with no significant difference in the prefrontal cortex (Karl *et al.*, 2010).

Application of MRS in BD

BD is a major affective disorder characterized by severe emotional fluctuations (manic or depressive episodes) and a tendency toward remission and recurrence. NAA, Glu, and Glx are commonly used biomarkers for diagnosing BD with MRS. Regarding NAA, multiple studies have shown that the levels of NAA and NAA/Cr ratio in multiple brain regions in BD patients are lower than those in healthy controls, such as the prefrontal cortex, hippocampus, anterior cingulate cortex, and left basal ganglia (Fig. 4)

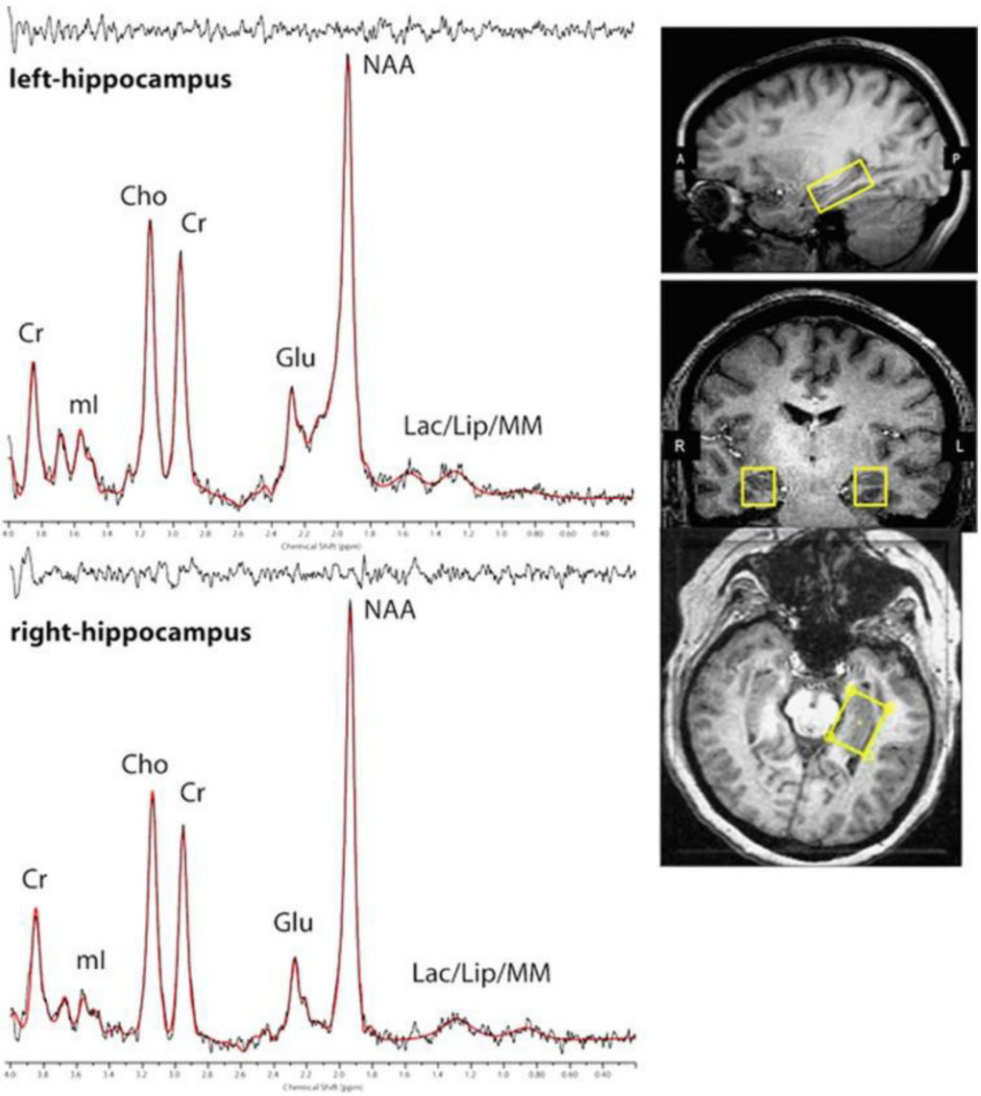

Figure 2: The placement of voxels in the axial, coronal, and sagittal views of the hippocampus and MRS spectral fitting of hippocampus position of a single patient (Kaldewaij *et al.*, 2021).

(Zhong *et al.*, 2018; Lai *et al.*, 2019; Tannous *et al.*, 2021; Chabert *et al.*, 2022; Gupta *et al.*, 2022). In addition, a study of 92 patients with bipolar affective disorder during depressive episodes (50 with suicidal tendencies, 42 without suicidal tendencies) found that the NAA/Cr ratio in the right lentiform nucleus of BD patients without suicidal tendencies was higher than that of BD patients with suicidal tendencies and the healthy control group, indicating the NAA/Cr ratio of the right lentiform nucleus could distinguish whether BD patients had suicidal tendencies. The NAA/Cr ratio in the left prefrontal cortex of the two BD groups (with or without suicidal tendencies) was significantly lower than that of the HC, and the NAA/Cr ratio in the left thalamus was significantly higher than that of the HC, indicating abnormal NAA metabolism in BD patients with or without suicidal tendencies (Zhong *et al.*, 2018). Regarding Glu and its metabolites, the current consensus is that the levels of Glu, Glx, and Gln in the prefrontal cortex of BD patients generally increase (Soeiro-de-Souza *et al.*, 2018; Scotti-Muzzi *et al.*, 2021; Melloni *et al.*, 2022; Ino *et al.*, 2023), and the level of Glx varies depending on the patient's mood, with a more significant increase observed during depressive episodes (Gigante *et al.*, 2012; Chitty *et al.*, 2013).

Application of MRS in OCD

OCD is a type of anxiety disorder characterized by persistent and repetitive obsessions and compulsions. NAA is a commonly used biomarker for diagnosing OCD with MRS. Since Elbert *et al.* first conducted MRS studies on OCD patients and found significantly decreased relative NAA levels in the right striatum of OCD patients (Ebert *et al.*, 1997), subsequent studies have also confirmed the decline of NAA levels in the brains of OCD patients, including but not limited to the prefrontal cortex and anterior cingulate cortex, and the degree of NAA levels decrease is related to the severity of the disorder (Tükel *et al.*, 2014; Weber *et al.*, 2014; Moon *et al.*, 2018).

Applications of nuclear medicine in psychiatric disorders

Applications of nuclear medicine in schizophrenia

For serotonin system, post-mortem radioligand studies on schizophrenia patients have shown that, compared with control

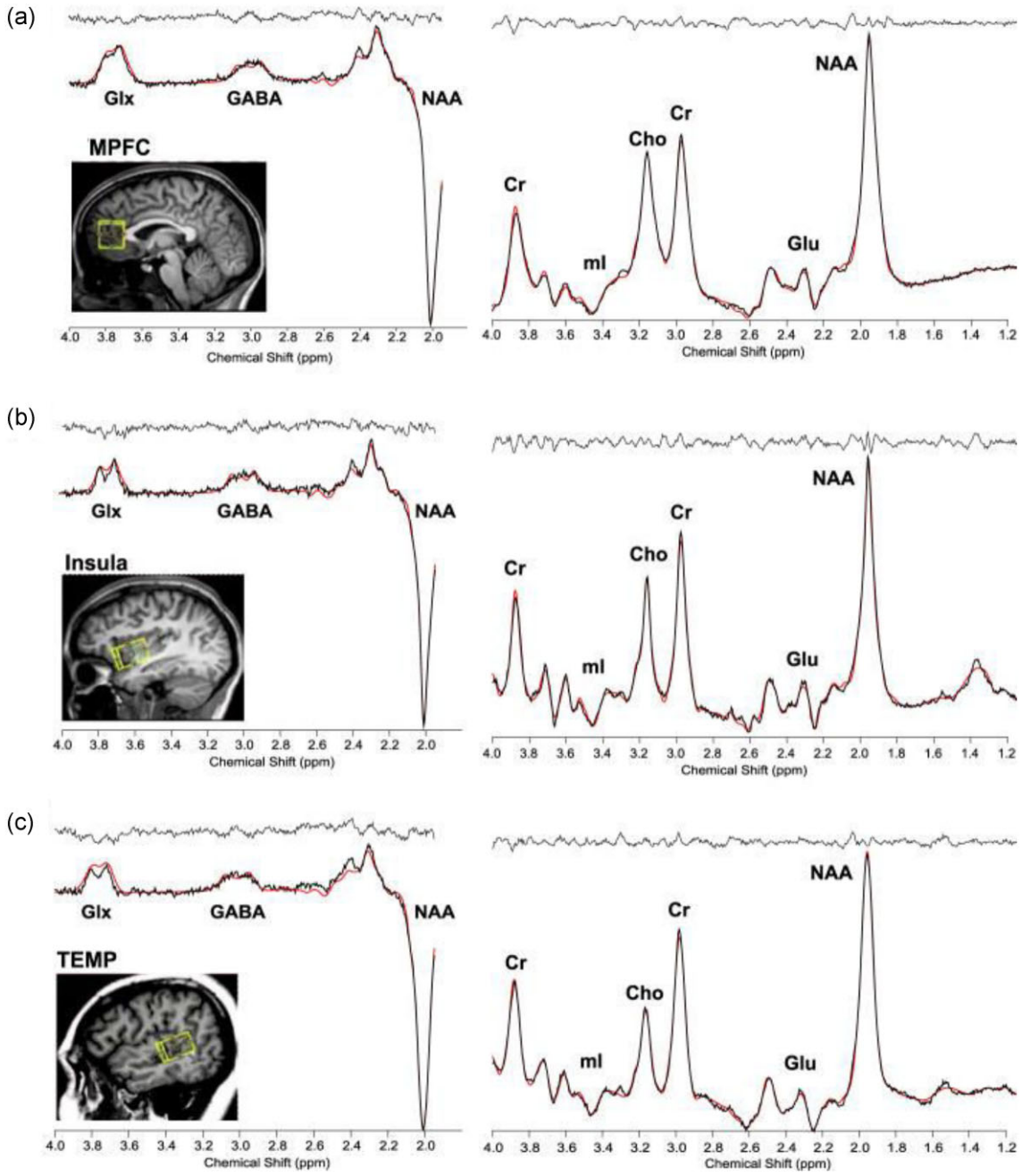

Figure 3: GABA^{+} data were fitted using MEGAPRESS and T_1-weighted structural images to show the location of voxels in the: (A) medial prefrontal cortex, (B) right anterior insula, and (C) right temporal cortex (Rosso *et al.*, 2022).

groups, the level of 5-hydroxytryptamine transporter (5-HTT) in the striatum increased 60–100%, while the level of 5-HTT in the cortical area decreased 50–75% (Joyce *et al.*, 1993). However, a PET study of 10 schizophrenia patients using [^{11}C]DASB showed no difference in 5-HTT compared with healthy controls in the midbrain, thalamus, dorsal caudate, dorsal putamen, ventral striatum, amygdala, entorhinal cortex, hippocampus, parahippocampal gyrus, and the anterior cingulate cortex (Frankle *et al.*, 2005). Another study investigating the hypothalamic 5-HTT found no difference between schizophrenia patients and control individuals, but there was a negative correlation between the level of hypothalamic 5-HTT and the severity of symptom in the schizophrenia group (Kim *et al.*, 2015).

In terms of the dopamine system, two SPECT studies using 99mTc-TRODAT-1 as radioligand have both indicated a reduced availability of dopamine receptors (DAT) in schizophrenia patients compared with healthy controls (Chang *et al.*, 2020; Yang *et al.*, 2022). In addition, a meta-analysis has shown that, compared with major depressive disorder patients, schizophrenia patients had increased dopamine availability in the striatal-hypothalamic-cortical pathway, while the dopamine availability in the midbrain-cortical pathway decreased (Nikolaus *et al.*, 2019).

Application of nuclear medicine in depression

For serotonin system, studies have found the low affinity of two radioligands, [^{11}C] McNeil 5652 and [^{11}C] DASB, in various brain

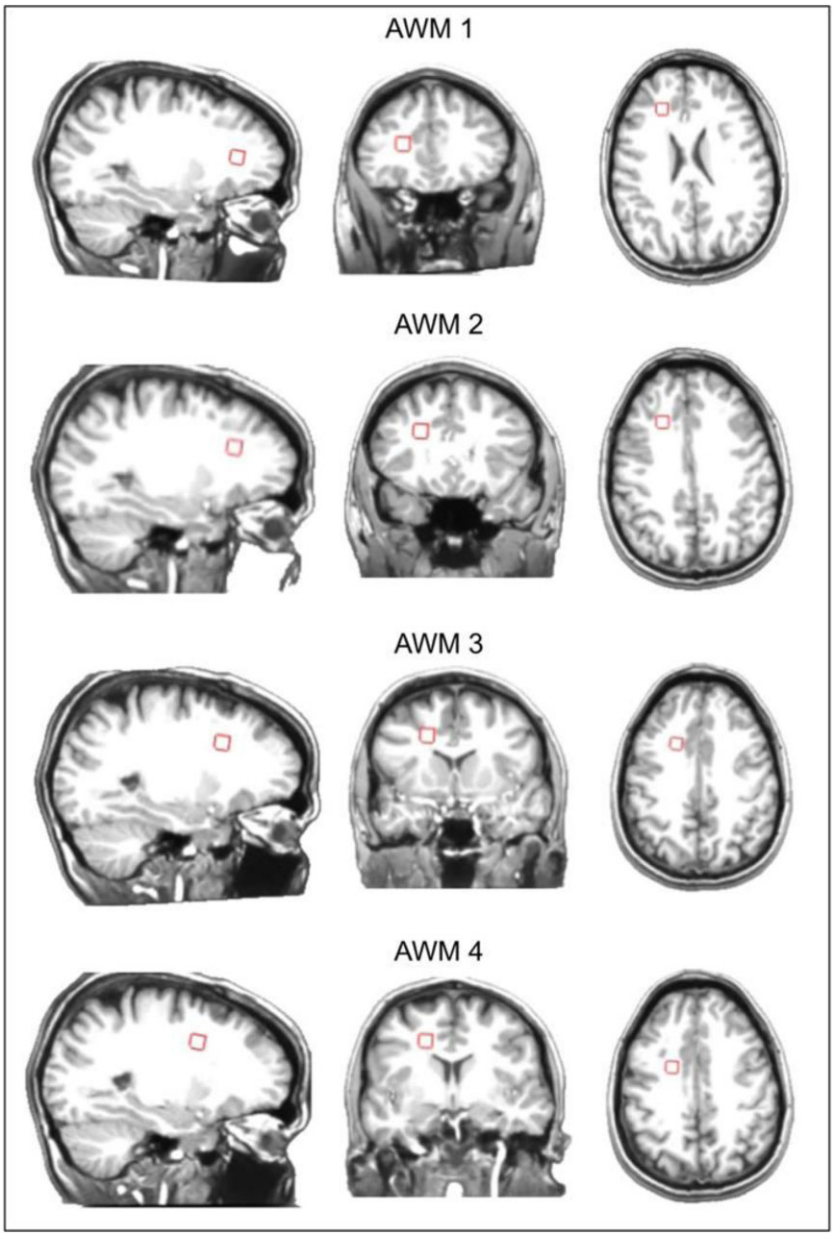

Figure 4: Voxel position: quantifying metabolite levels in the four voxels in the former white matter, showing sagittal, coronal, and cross-sectional views of each voxel (Tannous *et al.*, 2021). AWM denotes prewhite matter.

regions of depressed patients (Reivich *et al.*, 2004; Oquendo *et al.*, 2007; Reimold *et al.*, 2008). For the serotonin 1A receptor (5-HT1A), one study using [^{11}C] WAY-100635 found decreased binding potential of the radioligand to 5-HT1A in depressed patients compared to healthy controls (Parsey *et al.*, 2010). A meta-analysis of 5-HTT found decreased the transporter was in the midbrain and amygdala for patients with severe depression, and as the age of the study population increased, striatal 5-HTT decreased more markedly. There was a significant correlation between the severity of depression and decreased amygdala 5-HTT (Gryglewski *et al.*, 2014). For the dopamine system, an SPECT study using [123I]-FP-CIT as a radioligand found significantly reduced binding of [123I]-FP-CIT to the bilateral striatum, tail nucleus, and shell nucleus in depressed patients with and without anhedonia. However, DAT availability has no significant changes in patients with prominent anhedonia after treatment (Camardese *et al.*, 2014). A measurement of kappa-opioid receptor density using [^{11}C] GR103545 VT as a radiotracer found no significant differences between severe depressed patients and healthy controls, and was not related to childhood adversity or life stress (Miller *et al.*, 2018). In addition, some studies have found a decreased affinity of radioligands for serotonin 2 receptors (5-HT2), dopamine synthesis, dopamine D1 receptors, histamine H1 receptors in depressed patients (Kano *et al.*, 2004; Mintun *et al.*, 2004; Bragulat *et al.*, 2007; Cannon *et al.*, 2009). In studies of type A monoamine oxidase, depressed patients had higher binding of radioligands compared with healthy controls (Meyer *et al.*, 2006).

Application of nuclear medicine in PTSD

A multi-tracer PET study used highly selective radiotracers [^{11}C] DASB and [^{11}C] GR205171 to assess the availability of serotonin

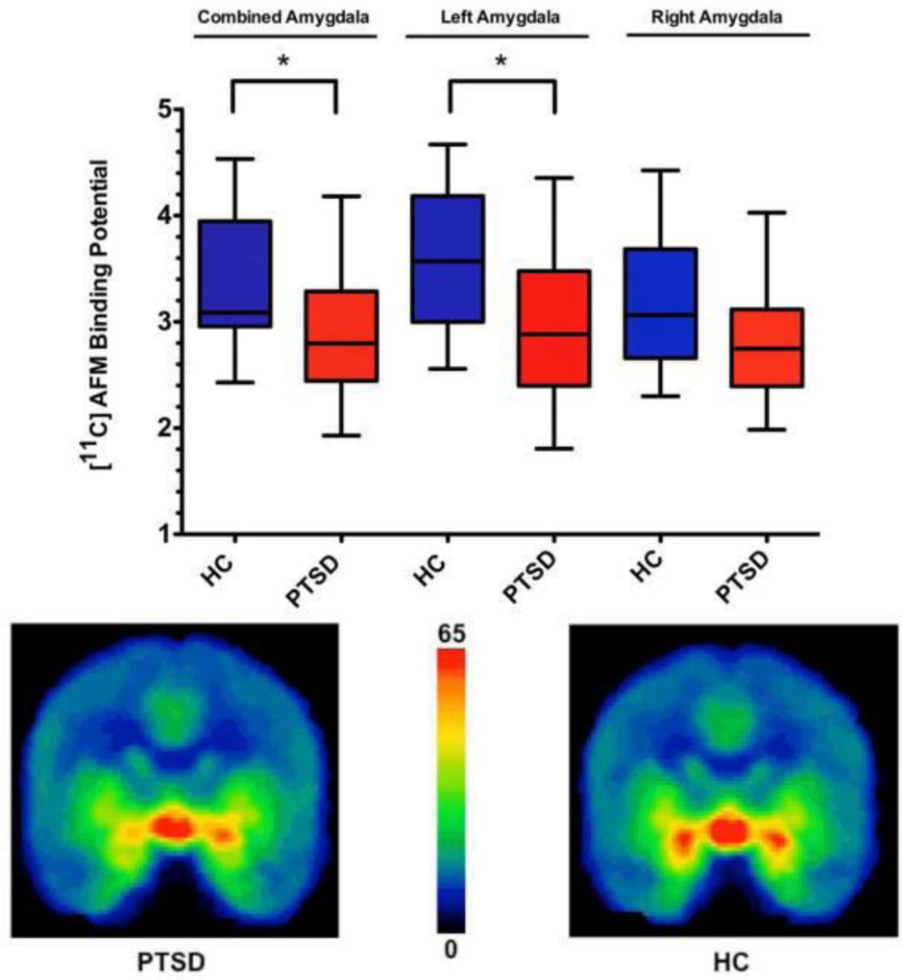

Figure 5: Reduced amygdala [^{11}C] AFM BPND in PTSD patients compared to healthy participants (Murrough *et al.*, 2011).

transporters (SERT) and neurokinin-1 receptors in the central anterior cingulate cortex and posterior cingulate cortex, respectively. In the serotonin system, PTSD patients showed significantly increased SERT availability in the central anterior cingulate cortex and decreased SERT availability in the amygdala, and increased availability of neurokinin-1 receptors in the amygdala (Frick *et al.*, 2016). Another study using [^{11}C] AFM as a radioligand found decreased SERT availability in the amygdala of PTSD patients (Fig. 5) (Murrough *et al.*, 2011).

In terms of the glutamatergic system, another study used [18F] FPEB to quantify the availability of metabotropic Glu receptor 5 (mGluR5) in PTSD individuals by binding to its negative allosteric modulatory site. The study found significantly elevated mGluR5 availability in the prefrontal cortex (including the dorsolateral prefrontal cortex, orbitofrontal cortex, and ventromedial prefrontal cortex), parietal cortex, and occipital cortex of PTSD patients compared to healthy controls (Holmes *et al.*, 2017).

Application of nuclear medicine in BD

For serotonergic system, a PET study using [^{11}C] DASB as a radioligand showed that, compared to the control group, patients with BD had a significantly higher binding rate of radioligands to SERT in the insula, prefrontal cortex, thalamus, caudate, and posterior cingulate cortex, and a significantly lower binding rate in the brainstem at the level of the pons (Cannon *et al.*, 2006). Another PET study using [^{11}C] WAY-100635 as a radioligand found that compared to healthy controls, patients with BD had an increased binding of radioligands to 5-HT1A (Sullivan *et al.*, 2009). In a PET study using [C]- (R) -PK11195, patients with BD had focal activation of glial cells in the right hippocampus, but this trend was not significant in the left hippocampus compared to healthy controls (Haarman *et al.*, 2014). Two SPECT studies using [^{123}I] ADAM as the radioligand both found a significant decrease in SERT availability in the midbrain and caudate nucleus of patients with BD, and the authors of both studies believed that the SERT availability was associated with certain cytokines, which may further explain the role of SERT and cytokines in the pathophysiology of BD (Hsu *et al.*, 2014; Chou *et al.*, 2016).

Regarding dopamine neurotransmitter imaging, a SPECT study using 99mTc-TRODAT-1 as a radioligand found that, compared to healthy adults, patients with BD had significantly higher levels of striatal DAT availability (Hsueh *et al.*, 2021). In the cholinergic system, a SPECT study using [^{123}I] 5IA-85380 as a radioligand found that in all evaluated brain regions (frontal lobe, parietal lobe, temporal lobe, prefrontal cortex, hippocampus, amygdala, thalamus, and caudate), the $\beta 2*$-n AChR availability of patients with BD in a depressive state was significantly lower than that of patients with normal mood and healthy adults (Hannestad *et al.*, 2013).

Applications of nuclear medicine in obsessive disorders

For the serotonergic system, a [^{11}C] DASB-PET study showed that, compared to patients with late-onset OCD, patients with early-onset OCD had significantly increased SERT availability in the striatum during long-term treatment with escitalopram (Lee *et al.*, 2018). In addition, another [^{11}C] DASB-PET study found that the SERT binding was reduced in the insula cortex of OCD patients, although the reduced binding was also observed in the orbitofrontal cortex compared to the control group (Matsumoto *et al.*, 2010). However, caution should be exercised in interpreting this finding due to the very low levels of 5-HTT binding in this region. The availability of 5-HT2A receptors was significantly reduced in the anterior cingulate, dorsal lateral, and medial prefrontal cortex, as well as in the parietal and temporal association cortices of OCD patients (Perani *et al.*, 2008). Additionally, there was a significant correlation between the availability of the serotonin 2A (5-HT2A) receptor in the orbitofrontal and dorsal lateral prefrontal cortex and the severity of clinical symptoms. However, a [^{11}C] MDL 100907-PET study comparing 5-HT2A availability in the brains of OCD patients and healthy controls did not find any significant differences in the orbitofrontal cortex or other regions of interest. Despite this, there was a significant correlation between [^{11}C] MDL 100907 binding and age of onset in the orbitofrontal cortex, with a higher binding rate associated with earlier onset age (Simpson *et al.*, 2011).

In terms of dopaminergic system, a PET study using [^{11}C]-SCH23390 found a decrease in the binding potential of [^{11}C]-SCH23390 to D1 receptors in the bilateral prefrontal cortex and striatum of drug-naive OCD patients compared to controls. In OCD patients, a decrease in dopamine D1 receptor binding in the bilateral prefrontal cortex was also positively correlated with greater symptom severity (Olver *et al.*, 2010, 2009). Conversely, no significant correlation was observed in the striatum. In the entire striatum, especially in the ventral aspects, radioligand uptake related to dopamine D2 receptors was also significantly reduced, possibly reflecting endogenous dopaminergic hyperactivity (Perani *et al.*, 2008).

Applications of fluorescent molecular probes in psychiatric disorders

The application of fluorescent molecular probes in psychiatric disorders mainly focused on schizophrenia and depression. There was no study that met our review requirements regarding the application of fluorescent probes on PTSD, BD, and obsessive disorders. In addition, at present, the application of fluorescent molecular probes in schizophrenia and depression is still under a preclinical and experimental phase, without main human applications.

Application of fluorescent molecular probes in schizophrenia

Excessive production of hydrogen sulfide in the brain is considered one of the pathological and physiological bases of schizophrenia. Zhuo Wang *et al.* designed and synthesized a series of SiR-B near-infrared fluorescent probes with different substituents, among which Mindo-SiR showed a good ability of blood–brain barrier penetrating and a good reactivity to H_2S *in vitro* and *in vivo*. This study used the Mindo-SiR fluorescent probe for the first time to image the changes in endogenous and exogenous hydrogen sulfide (H_2S) in the brain of a mouse model of schizophrenia, successfully demonstrating that the level of endogenous H_2S was abnormally high in the brain of schizophrenic mice (Geng *et al.*, 2022).

Application of fluorescent molecular probes in depression

The superoxide anion radical (O_2^-) is a product of the single electron reduction of oxygen molecules. As the first type of reactive oxygen species produced in peroxisomes, it plays a crucial role in the pathological mechanism of brain diseases (Xiao *et al.*, 2020). Tang's group successfully constructed a dual-photon probe TCP capable of a real-time and specific detection of O_2^- by combining the fluorescent caffeic acid molecule structure with the Ser-Lys-Leu peptide targeting peroxisomes through a Gln amide fragment. Cerebral fluorescence imaging of mice with depressive phenotype using TCP and a hydrogen peroxide (H_2O_2) probe BN under 800 nm dual-photon laser irradiation showed that the excess O_2^- and H_2O_2 induced inactivation of catalase and a decrease in tryptophan hydroxylase-2 content, which could result in the dysfunction of the serotonin system in the mouse brain and eventually lead to depression (Ding *et al.*, 2020).

Similarly, ozone (O_3) as an important type of reactive oxygen species also plays a critical role in depression. Tang's group designed and synthesized a near-infrared fluorescent probe ACy7 for detecting O_3 in the brains of live small animals. O_3 underwent a specific ring-closing reaction at the end double bond of the probe's vinyl group (Fig. 6), resulting in an expanded conjugated system of the "front" of heptamethine cyanine emitting near-infrared fluorescence and making the probe highly specific, sensitive, and capable of a deep tissue penetration. Researchers used ACy7 for visualizing and analyzing O_3 within cells and found that O_3 levels increased significantly in phaeochromocytoma cells (PC12 cells) under Glu stimulation compared to normal cells. In addition, imaging analysis of mouse brain revealed a significant increase in O_3 in depressed mice compared to normal mice. This study also found that the excessive O_3 in the brain of depressed mouse led to an excess production of the pro-inflammatory cytokine IL8, which could induce the depression phenotype (Li *et al.*, 2019).

As a neurotransmitter, acetylcholine plays a regulatory role in brain neural transmission, while acetylcholinesterase (AChE), as its corresponding hydrolytic enzyme, indirectly affects the efficiency of neural transmission. Tang's group designed and synthesized a fluorescent probe MCYN that connects an AChE recognition fragment, dimethylaminoformyl, and has dual-photon imaging effects. Under 800 nm dual-photon excitation light, MCYN could detect the reduction of AChE activity caused by the AChE inhibitor neostigmine in PC12 cells and the increase of AChE levels in a mouse model of depression. Furthermore, the researchers treated PC12 cells stimulated by Glu and Glu/caffeic acid ethyl ester with the O_2^- dual-photon fluorescent probe and probe MCYN. They found that the excessive activation of AChE induced by oxidative stress may lead to depression-related behaviors in mice (Wang *et al.*, 2019).

Norepinephrine (NE), as an important neurotransmitter, is closely related to depression. Caixia Yin *et al.* have designed a red fluorescent probe for a specific detection of NE, using a "protection-deprotection" strategy: the cyanine dye with longer emission wavelength was modified with water-soluble sulfonic acid and connected to a leaving group thiol carbonic ester for protection; the unique β-hydroxyethylamine part of NE could trigger nucleophilic substitution and an intramolecular nucleophilic reaction to remove the protecting group, release the fluorescent

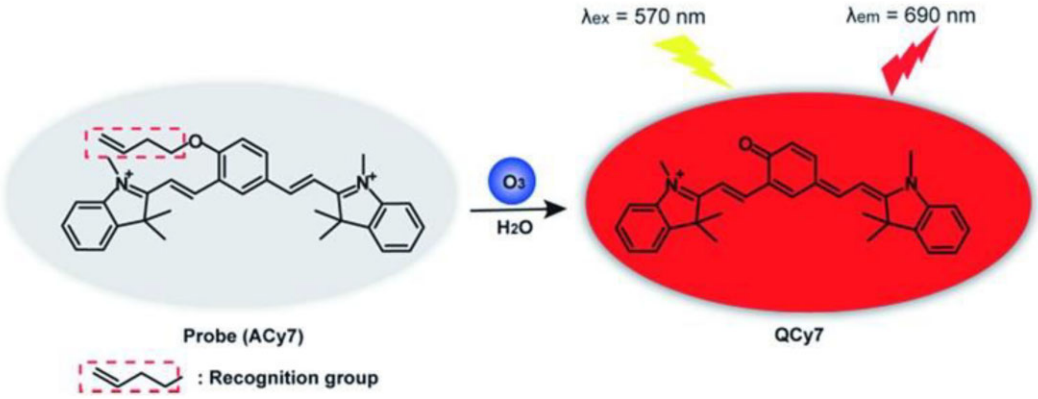

Figure 6: Reaction of near infrared fluorescent probe ACy7 with O_3. [104]

group, and thus achieve specific detection of NE. The authors also used this probe to achieve the imaging of NE neurotransmission under potassium ion stimulation, and for the first time, the real-time fluorescent imaging of NE levels in the rat brain after antidepressant stimulation (Zhou *et al.*, 2020). Pengli Gu *et al.* have developed a new tryptamine-based red fluorescent probe LNE for the real-time tracking of NE, which could be significantly increased by triggering the deprotection of the thio-carbonyl ester ligand by nucleophilic substitution of NE. LNE showed significant NE selectivity and sensitivity *in vitro* compared to other analytes. In addition, LNE responded quickly (<10 minutes), and the fluorescence signal changed positively with NE concentration, enabling tracking of NE changes *in vivo*. Importantly, the probe has been successfully used for real-time visual and imaging of NE in live cells and animals with depression-like behavior (Gu *et al.*, 2023).

The occurrence of depression is closely related to the overactivation of *N*-methyl-D-aspartate receptors (NMDARs) in the brain, and the activity of NMDARs is also closely related to Zn^{2+} and H. Tang's research team designed a dual-color fluorescent probe to simultaneously monitor the levels of Zn^{2+} and H in the brains of depressed mice. When encountering Zn^{2+}, the probe emitted bright blue fluorescence at 460 nm, and the red fluorescence at 680 nm weakened with the addition of H. Using the blue/red dual-fluorescence signal of dual-color fluorescent probe, the researchers observed that the levels of Zn^{2+} and H in PC12 cells increased synchronously under oxidative stress conditions, and *in vivo* imaging revealed for the first time that Zn^{2+} and H in the brains of mice with depressive-like behavior decreased simultaneously. Further results suggested that NMDARs might be the cause of synchronous fluctuations of Zn^{2+} and H in depression (Wang *et al.*, 2020).

The "neurotrophic hypothesis" suggests that human depression is related to the reduced expression and function of brain-derived neurotrophic factor (BDNF), and these changes are closely related to the polarity of cells' Golgi apparatus. Tang's research team designed and synthesized a polarity-sensitive near-infrared fluorescent probe, Golgi-targetable fluorescent probe (Golgi-P), for detecting the polarity of the Golgi apparatus in small animal brain *in vivo*. The probe consisted of *meso*-tetraphenylporphyrin and benzoyl difluoroboron as supplying and withdrawing electron groups, respectively, forming a highly conjugated skeleton sensitive to the polarity of cells' Golgi apparatus; the nitrogen atom side chain of meso-tetraphenylporphyrin was connected to L-cysteine, achieving precise localization of the Golgi apparatus. Using Golgi-P, the polarity changes of the Golgi apparatus in PC12 cells under Glu stimulation were successfully located and imaged. Meanwhile, through *in vivo* imaging, the researchers first achieved the polarity detections in the brains of normal mice and depressed mice, and revealed that the changes in the polarity of Golgi apparatus were closely related to the level of neurotrophic factors (Li *et al.*, 2019).

Discussion

Owing to the ability to provide information to explain the causal and pathophysiological mechanisms of mental disorders, molecular imaging technology has become one of the important tools for studying these major psychiatric disorders. Molecular imaging technology can provide important clues for explaining the development process of diseases and proposing treatment methods by studying the characteristics of molecular compositions of the brain tissues. In molecular imaging technology, MRS is widely used to explore metabolic processes of molecules, PET and SPECT technology can non-invasively monitor the activity of macromolecules such as proteins and neurotransmitters, and fluorescent molecular probes can target organs with specific features and be activated by specific pathogenic biomarkers. With the continuous development and improvement of imaging technology, we are able to explore the molecular-level mechanisms of psychiatric disorders more deeply, providing inspiration and insights for seeking safer and more effective treatments, and improving the accuracy of clinical diagnoses.

When studying psychiatric disorders, technologies such as MRS, PET, and SPECT enable us to probe the chemical and biological changes in patients' bodies. These changes are usually associated with the concentration of specific substances, such as neurotransmitters, metabolites, proteins, etc. Through this method, researchers can explore how these substances play a key role in different types of psychiatric disorders, which can help us better understand the physiological processes of these diseases. In addition, these technologies can also help doctors to make patient-specific treatment plans. Molecular imaging can be used to monitor changes in the concentration of certain substances in the same brain region during treatment, as well as the relationship between these changes and clinical manifestations, to evaluate the effectiveness of drug therapy. This personalized assessment approach can make treatments more effective and better achieve treatment goals. In summary, the use of these imaging technologies is improving our understanding of psychiatric disorders and bringing more effective methods for the treatment of them.

Although imaging technologies including MRS, PET, SPECT, and fluorescent imaging are widely used in medical studies, they still have some limitations that need to be addressed in future. On one hand, the study subjects for these technologies are relatively small, and the number of repetitions is limited, which may lead to markedly different results. On the other hand, these technologies usually only characterize a single metabolite, neurotransmitter, or other biological molecules by a single examination, and it is challenging to map the changes of a single chemical substance to the overall disease, thus they may only provide a limited information on the disease. Therefore, it may not provide comprehensive information for the overall diagnosis and treatment of the disease. In conclusion, even though these imaging technologies provide valuable information for research and treatment in the medical field, we still need to further research and explore other imaging techniques to understand the mechanisms of different diseases more comprehensively and accurately. The existing research discoveries of molecular imaging techniques in psychiatric disorders have great value. In addition, multiparametric methods have been used to evaluate demyelinating (like multiple sclerosis) diseases in clinical settings. Similarly, if molecular imaging techniques are combined with other advanced imaging technologies such as functional MRI, high-precision structural MRI, and deep learning, it may provide a more comprehensive characterization of the pathology of psychiatric disorders (Lai *et al.*, 2019; Mustafi *et al.*, 2019; Gatto *et al.*, 2021; Kotoula *et al.*, 2023).

Author contributions

Jia Tan (Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing), Guangying Zhang (Data curation, Formal analysis, Methodology, Project administration, Resources, Writing – original draft), Jiaqi Hao (Data curation, Investigation, Resources, Writing – review & editing), Huawei Cai (Project administration, Validation, Visualization), Dingping Wu (Project administration, Resources, Software, Supervision), Zhuoxiao Su (Data curation, Resources, Writing – review & editing), Beibei Liu (Methodology, Project administration), and Min Wu (Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Visualization, Writing – review & editing)

Conflicts of interest

There are no conflicts to declare.

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