PSYCHIATRIA ET NEUROLOGIA JAPONICA

Review Article

Visualization of Neural Circuits and Molecules in Neuropsychiatric Disorders

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Abstract

Biological studies on psychiatric disorders started in the pharmacological field of therapeutic drugs, and once the drug targets were visualized by PET, quantitative data of dopamine D2 receptors in schizophrenia, and serotonin and noradrenaline transporters in depression were reported. However, the measured values of these neurotransmission components largely overlapped with those in normal volunteers, and the diagnostic thresholds were unable to be defined. Relationships with personality traits were found in the diverse distribution of these neurotransmission components in normal volunteers, suggesting that neural transmission can be regulated depending on individual variation, such as personality and behavioral traits, and the values in those with psychiatric disorders are on a continuous spectrum. On the other hand, there have been several reports on specific sets of resting state functional connections in certain psychiatric disorders. However, for the biological confirmation of these connections, manipulation of the circuits in animal models is needed. DREADD is a new technique for manipulating neural circuits in large animals such as monkeys. We developed a PET imaging method to visualize the induced receptor and a new agonist, deschloroclozapine (DCZ). These new tools provide high-signal PET images and rapid response of the induced receptor. To evaluate the functions of neural circuits in the human brain, neurodegenerative disorders can be good models because the affected region can be

visualized by PET using tau imaging. Biological studies of the mechanisms of psychiatric symptoms are important for both mental disorders and neurodegenerative disorders. Multimodal imaging studies together with translational animal research are important for confirmation of neural circuit functions.

Keywords: PET, neurotransmission imaging, functional connectivity, DREADD, tau imaging

Introduction - Perspective of modern mental disorders

The current diagnosis of mental disorders is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association, which is based solely on patient statements and symptoms. However, in spite of repeated revisions of the DSM, our understanding of the true nature of mental disorders has not yet reached the halfway point, and the development of new drugs has not progressed as much as expected and the majority of Western mega-pharmaceutical companies have withdrawn from the mental disorder field. This is largely due to the fact that the biological mechanisms of psychiatric disorders are still poorly understood, and the development of animal models for these disorders has not progressed[16]. Most of the biological research on mental disorders was started from pharmacological studies of antipsychotic and antidepressant drugs the clinical efficacies of which were discovered by chance. For example, the clinical efficacy of chlorpromazine on psychosis was reported in 1952, and the discoveries of current psychopharmacological bases were made in the 1950s and 1960s. On the other hand, Alzheimer's disease was first reported in 1906 and its pathology was reported in 1911. However, for a long time there were no significant discoveries that could lead to its treatment until 1976 when a significant reduction of acetylcholine was reported in postmortem disease brains. Since then many discoveries directly related to the cause of the disease, such as familial Alzheimer gene, were reported from the 1980s onward, with the progress of molecular biology. In this review, I will summarize the research trend in mental disorders from the point of imaging research, and I will discuss research similarities with

neurodegenerative disorders and translational research based on new animal models.

I. Mental disorders from neurotransmission imaging

Many researchers expected to elucidate the pathogenesis of mental disorders by mechanism studies of effective drugs discovered by chance. In particular, the dopamine D2 receptor (D2R), a target molecule of antipsychotic drugs, was visualized in living human brain by positron emission tomography (PET) using [^{11}C]N-methylspirepone in 1983. This method was soon applied to measure D2R in the striatum of schizophrenia patients, and increased density compared with normal subjects was reported in 1986 [23]. This finding seemed to support the hyperdopaminergic hypothesis of schizophrenia. However, the following year, a [^{11}C]raclopride PET study reported no significant difference in D2R in the striatum between schizophrenia and normal subjects[5]. Subsequent PET studies have shown that there is no significant difference in D2R in the striatum, or if there is, it is only a small increase. While most of the early dopamine receptor PET studies focused on the striatum, we focused on extrastriatal dopamine neurotransmission. We measured dopamine D1 receptors, which are abundantly distributed in cortical regions, and found decreased density in the frontal cortex of schizophrenia and negatively correlated with negative symptoms of Brief Psychiatric Rating Scale[13]. Regarding extrastriatal D2R, we found decreased density in the anterior cingulate gyrus and thalamus and negative correlation with positive symptoms using [^{11}C]FLB457[15)22)]. On the other hand, serotonin transporter and noradrenaline transporter, which are target molecules of antidepressants, were both found to be significantly increased in the thalamus of patients with depression[3)9)]. However, the range of density of these receptors and transporters in mental disorders significantly overlapped with those in normal subjects, and there was no clear threshold between them (Fig. 1). Furthermore, the range of density among normal subjects in considerable even among subjects of the same age. Individual differences of neurotransmission components have been shown to present certain biological meanings such as personality. For example, the distribution of serotonin transporter densities was positively correlated with neuroticism[18,19)]. These facts indicate that mental disorders are not groups with distinct abnormal neurotransmission but are rather continuous change from the normal, and even within the normal,

neurotransmission is regulated within a certain range according to individual differences such as personality. In fact, recent molecular genetics and imaging studies have indicated that the concept of mental disorders been shifting toward the view that disorders has should be considered as a continuous spectrum among disorders or between normal[1].

II. Neurodegenerative disorders from abnormal protein imaging

The concept of neurodegenerative disorders has changed from a symptom-based definition to a biomarker-based definition such as genetic abnormalities or accumulated proteins in the brain, such as amyloid, tau, alpha-synuclein, and TDP43 (TAR DNA-binding protein of 43 kDa). In particular, accumulated proteins have recently become visualizable in living human brain. For pathological diagnosis, various stains are used, and such stain compounds can be modified to traverse the blood-brain barrier with less non-specific binding, and by labeling with positron radionuclides, they can be visualized *in vivo* by PET. The imaging of amyloid-ß (Aß), which constitutes senile plaques in Alzheimer's disease, was visualized by [^{11}C]PIB in 2004[7]. Amyloid imaging made it possible to confirm that the accumulation of Aß begins more than a decade before the onset of the disease and is widespread in the brain by the time mild cognitive impairment is clinically observed. Tau protein accumulated in Alzheimer's disease, progressive supranuclear palsy and frontotemporal dementia can be visualized using [^{11}C]PBB3, which we developed in 2013, in addition to several other ligands. In Alzheimer's disease, it accumulates in the medial temporal lobe in the early stages of the disease, and as the clinical symptoms progress, it accumulates widely in the brain[8]. Different from mental disorders, the definite diagnosis of neurodegenerative disorders was based on postmortem pathological studies. The important progression in the diagnosis of neurodegenerative disorders is that a pathological diagnosis has become possible in the living condition using PET with several radio-labelled ligands. This will make the prediction of disease onset and the classification of disease types more objective.

III. Symptoms of mental disorders from functional connectivity and neurotransmission

In contrast to abnormal proteins in neurodegenerative disorders, many proteins involved in neurotransmission are expressed in a normal state, and their amounts overlap greatly between patients and normal controls. This makes them difficult to use as

biomarkers for disease diagnosis. What kind of biological indexes can be used to explain clinical symptoms of mental disorders? Recently, a method of estimating functional connectivity in the brain from resting state brain activity has been used to evaluate neural networks. Although it has been known for a long time that nerves are spontaneously active at rest, such activity was previously regarded as mere noise. However, functional magnetic resonance imaging (fMRI), which can visualize regional cerebral blood flow in the whole brain, has revealed that resting state activity is correlated among brain regions and that this correlation has functional significance. The brain contains a myriad of functional connections, and in recent years, disease-specific combinations of multiple functional connections have been reported in several mental disorders. For example, combinations of 16 functional connectivities have been reported to separate autism spectrum disorder from other mental disorders[20], and combinations of 10 functional connectivities have been reported to separate melancholy depression from other mental disorders[2]. These combinations of functional connectivities have been used to evaluate the differences between normal subjects and patients as well as similarities among mental disorders.

However, it is still unclear whether functional connectivity reflects actual anatomical networks and how it relates to neurotransmission. We are investigating the relationship between functional connectivity and neurotransmission in the brain in healthy subjects by combining resting state brain activity using fMRI and neurotransmission using PET. In addition, we are also investigating behavior and its circuitry background in nonhuman primates. It is well known that depression is associated with lower self-esteem, while self-esteem in healthy individuals is usually biased toward being slightly higher, and this is called superiority illusion. We investigated the brain circuit and the molecular background of superiority illusion using fMRI and PET. The results showed that the higher the superiority illusion, the weaker is the functional connectivity between the anterior cingulate and striatum, and the higher is the dopamine released in the striatum as assessed by PET. This suggests that dopaminergic neurotransmission in the brain is involved in self-evaluation, and that functional connectivity between the frontal lobe and the striatum may have an inhibitory effect on dopaminergic neurotransmission (Fig. 2)[21]. Conversely, a state of low self-esteem

can be thought of as a state with functional connectivity between the frontal lobe and striatum being strengthened, resulting in suppression of dopaminergic neurotransmission. This result indicated that functional connectivity is closely related to the state of neurotransmission, and functional connectivities in depression can be changed by treatment[2]. However, it is not yet known whether neurotransmission is also changed by changing functional connectivity.

Regarding treatment-induced changes in neurotransmission, we found that dopaminergic neurotransmission in the anterior cingulate was altered in depressed patients after electroconvulsive therapy (Fig. 3)[14]. Altered dopaminergic neurotransmission in the anterior cingulate was also observed in a monkey model of depression with hypothyroid, which we developed as a lower motivation model of depression. Although the regions were consistent, the direction of change was opposite. While D2R measured by [^{11}C]FLB457 decreased in the anterior cingulate after electroconvulsive therapy in patients with depression, binding was increased in the monkey model of depression. These changes can be explained by the downregulation of D2R after dopamine release increased by electroconvulsive therapy, and upregulation of D2R with decreased dopamine release in the monkey model of depression in the same region.

In order to elucidate the biological background of changes in neurotransmission and functional connectivity in disease and therapy, it is essential to simultaneously manipulate circuits and measure neurotransmission in model animals. However, local disruption experiments could not be applied by repeatedly blocking or reversing function. Recently, optogenic or chemogenic techniques have been used to turn on/off specific circuits. However, in large animals such as monkeys, the brain is too large for optogenetics to work well. In the monkey brain, expressed mutant acetylcholine receptors in specific neurons and drugs such as CNO (clozapine N-oxide) can be used to control the neural circuits as chemogenetics DREADD (designer receptors exclusively activated by designer drugs). Since circuit manipulation techniques in animals have the potential to clarify the circuits and neurotransmission function associated with specific behaviors, it is important to clarify the neural circuits and neurotransmission function involved in the specific symptoms that constitute the mental disorders. This method may be very important for reconstructing mental disorders from

their components when ideal animal models of mental disorders are still lacking. The induction of artificial genes into the target region by viral vectors is important for the manipulation of circuits in animals. In rodents it is not a big obstacle to confirm the expression of artificial genes in removed brain because the number of rodents can be increased. However, in monkeys, it is not practical to remove the brain for each experiment. If the expression of an artificial gene can be confirmed *in vivo*, the question of whether the circuit was irrelevant or the induction of the artificial gene simply did not work can be answered immediately when there is no change in the target behavior. For this purpose, we developed the visualization method of artificial receptors by DREADD using PET, and we succeeded in quantifying the expression of artificial receptors in the targeted region *in vivo*. This method enabled us to monitor the expression level of the artificial receptors and to easily make another induction decision when the expression level was not sufficient. In addition, since the artificial receptors are expressed throughout the induced nerve, it is possible to identify the nerve's route and projection site[11]. Currently, CNO is mainly used as a drug to control the on/off of nerve activity in DREADD. However, some problems have been reported with CNO, such as its low permeability to the brain and the fact that it becomes metabolized to clozapine in some animal species. We attempted to develop a new drug for DREADD that would solve these problems, and succeeded in developing a compound called DCZ (deschloroclozapine). It took about 90 minutes for CNO to reach its peak concentration in the brain after intravenous injection, making it difficult for rapid changes in behavior like optogenics with on/off of light. DCZ, on the other hand, is rapidly distributed in the brain after intravenous injection, making rapid changes in behavior easy. In addition, DCZ has high affinity for artificial receptors and is 100 times more potent than CNO. Therefore, [^{11}C]DCZ labeled PET ligand can visualize artificial receptors with high sensitivity (Fig. 4)[12].

Although replicating changes in functional connectivity and neurotransmission in disease is difficult in living humans, it is hoped that this new method of generating symptom-based animal models will help to clarify the circuitry and neurotransmission underlying specific symptoms of mental disorders.

IV. Common symptoms between neurodegenerative and mental disorders

In order to understand the

mechanism of symptoms expressed in mental disorders, it is a classical and also new approach to analyze the mechanism of symptom expression in neurodegenerative diseases, where the causes of the disorders are more clearly understood. In the past, localized brain functions were studied in damaged brains, but now it is possible to evaluate brain functions using various imaging techniques. Accumulated tau protein in the brain correlates well with brain dysfunction in neurodegenerative disorders (Fig. 5), suggesting the possibility of elucidating the symptom-related circuit through reginal tau deposition and various psychiatric symptoms that appear in neurodegenerative diseases. For example, by analysis of tau accumulation and apathy in Alzheimer's disease, we found tau accumulation in the orbitofrontal cortex and decreased white matter integrity in the uncinate fasciculus forming a cortico-limbic network associated with apathy. This finding confirmed the importance of these neural circuits in the development of clinical symptom apathy [6]. In order to confirm the function of these circuits more directly, behavioral change of animals by on/off of the circuit using DREADD can be used.

As s disease related to tau, chronic traumatic encephalopathy (CTE) has recently drawn attention with its prominent psychiatric symptoms. Especially in the United States, a famous professional wrestler who committed suicide after suffering from memory impairment and depression, and a former American football player who committed suicide after suffering from memory impairment, depression, and alcoholism were reported, and their postmortem examinations revealed neurofibrillary changes in a wide range of brain regions. There is also a condition called post-traumatic psychosis in which psychiatric symptoms such as hallucinations and delusions, and higher brain dysfunction such as memory impairment and executive dysfunction also occur 4 to 6 years after head injury, and the response to antipsychotic medication is considered to be low. We investigated clinical symptoms and brain tau accumulation by PET with [^{11}C]PBB3 in patients with repetitive mild head injury due to contact sports like boxing, and in patients with chronic head injury for an average of 21 years after traffic accidents. The results showed tau accumulation in superficial white matter at the border with gray matter in the group with symptoms of delayed brain injury (Fig. 6), and psychotic symptoms such as hallucinations and delusions tended to become more severe as the accumulation increased[17].

Initially, we expected to find a characteristic pattern of tau accumulation in head trauma patients with psychotic symptoms, which would lead to the identification of brain circuits involved in psychotic symptoms. However, as a result, we were only able to find a relationship between the amount of tau accumulation in the superficial white matter and the severity of the symptoms. In the future, by using [^{18}F]PM-PBB3, which is more sensitive to tau accumulation, we expect to detect more subtle tau accumulations in the early stages of the disease and to detect brain circuits related to early symptoms. Variety of psychiatric symptoms such as depression were also observed in more common neurodegenerative disorders such as dementia with Lewy bodies and Parkinson's disease. When PET ligands for α-synuclein, which we are currently being developed, become available for clinical use, we may be able to identify the brain circuitry associated with the early symptoms of these disorders.

Conclusion

Psychiatry is a field of medicine in which there are as yet no clear biomarkers for the diagnosis of disorders, and we are still using operational diagnostic criteria based on a combination of clinical syndromes. The U.S. National Institutes of Health (NIH) has proposed the Research Domain Criteria (RDoC), which is based on the view that the current classification of psychiatric disorders will eventually have to be reclassified according to biological information. In fact, there have been attempts to classify depression into several biotypes based on differences in functional connectivity using fMRI. However, the RDoC approach, which aims to integrate various biological information, has yet to redefine real mental disorders. On the other hand, once the organic cause has been identified, disorders classified as mental disorders will no longer be mental disorders. For example, anti-NMDA receptor encephalitis, which was clinically difficult to differentiate from schizophrenia, was identified as an autoimmune disease, and since then, research on the pathogenesis of the disease was performed from an immunological perspective. In addition, tau PET revealed that some patients with geriatric mental disorders showed only tau accumulation without amyloid accumulation[10]. Such patients with tau lesions may be classified as tauopathies, like CTE. However, even if the etiology is identified, the mechanism of the symptom formation is still unclear. The current treatments for mental disorders are still symptomatic therapies, and even if several etiologies are identified

in the future, it will still be important to elucidate the mechanism of symptom formation in both mental and neurodegenerative disorders. For this purpose, this will require not only analysis of the responsible circuits and molecules related to the symptoms of the disorders in clinical studies, but also verification of the circuit functions using animals. Such basic clinical bidirectional approach will be essential for the future research of neuropsychiatric disorders (Fig. 7).

Note: This is a review article based on an educational lecture given at the 115th Annual Meeting of the Japanese Society of Psychiatry and Neurology.

There are no conflicts of interest to be disclosed in relation to this paper.

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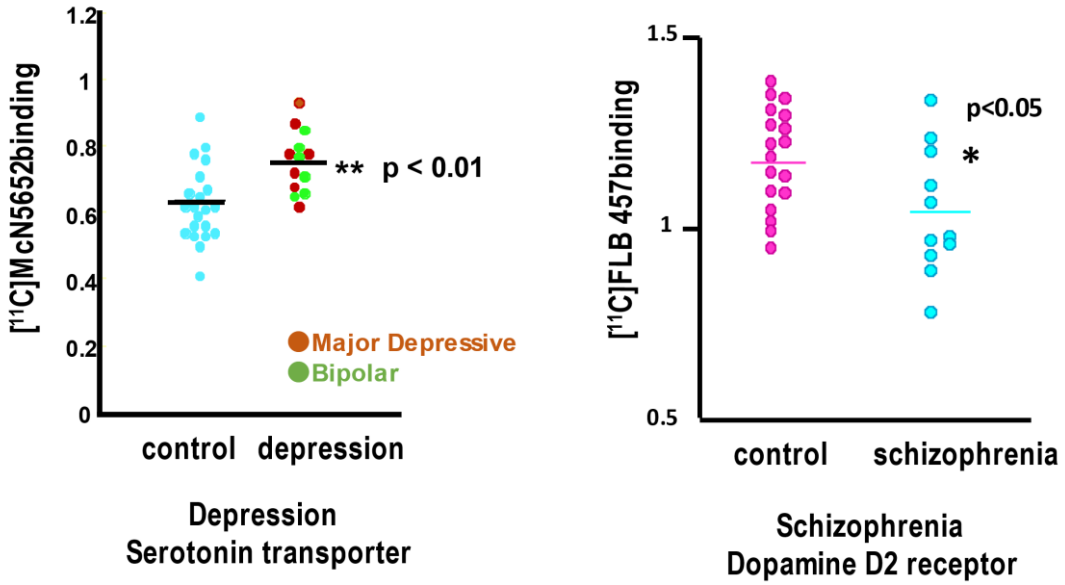

Fig 1. Target molecules of therapeutic drugs in mental disorders.
The serotonin transporter in drug-free depression measured by PET was significantly increased in the thalamus, and dopamine D2 receptor density in the anterior cingulate in untreated schizophrenia was significantly decreased (modified from refs. 3 and 15). However, there was a large variation in density in healthy subjects and a large overlap with the patient group (modified from refs. 3 and 15).

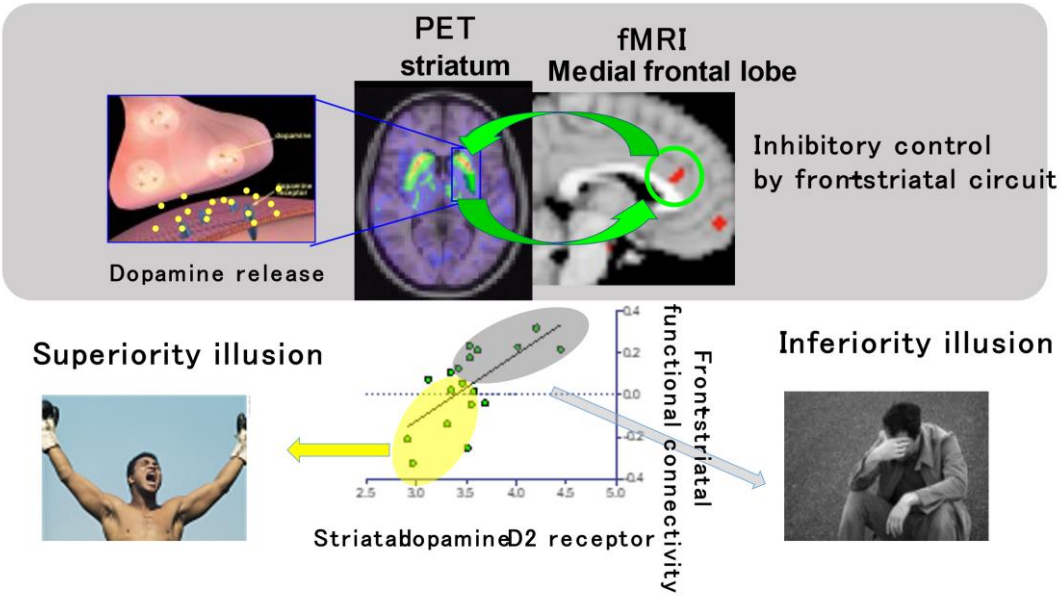

Fig. 2. Molecular and circuit basis of the superiority illusion

The degree of superiority illusion was assessed in healthy subjects with functional connections between the striatum and the medial frontal lobe by fMRI, and dopaminergic neurotransmission by PET using [^{11}C]raclopride. Since [^{11}C]raclopride binding, a ligand for dopamine D2 receptors, has been reported to be negatively correlated with endogenous dopamine synthesis, we hypothesized that individuals with low [^{11}C]raclopride binding should have high endogenous dopamine synthesis. Functional connectivity and striatal dopamine D2 receptor binding varied greatly among subjects, subjects with weak functional connectivity had low [^{11}C]raclopride binding, and these subjects had high superiority illusion. This indicates that weak inhibition of the frontal lobe to the striatum enhances dopaminergic neurotransmission and enhances the superiority illusion.

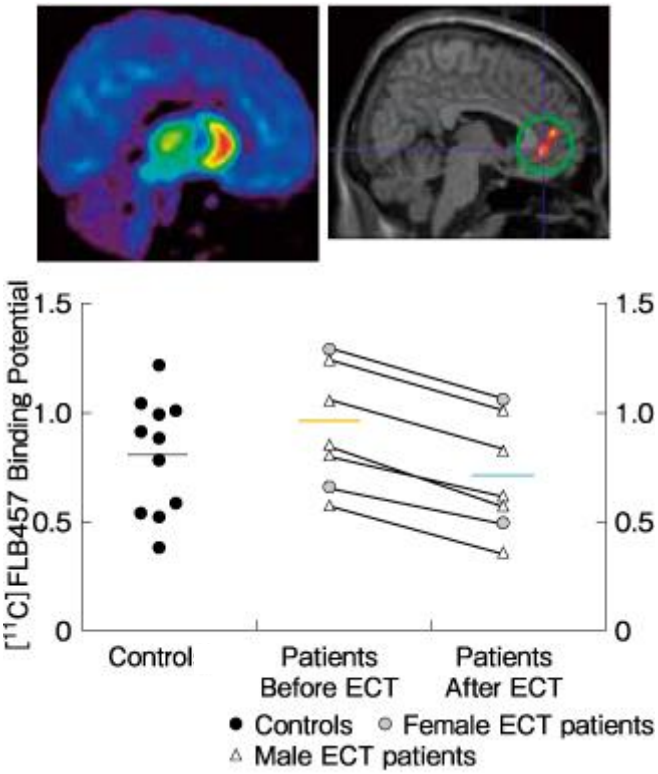

Fig. 3. Dopamine D2 receptors before and after electroconvulsive therapy in patients with depression

D2R in the brain was measured by PET using [11C]FLB457 before and after electroconvulsive therapy in patients with depression. After treatment, D2R in the anterior cingulate was decreased. This suggests that electroconvulsive therapy increased the release of dopamine in the anterior cingulate, resulting in the downregulation of D2R in the same region.
Upper left: D2R distribution in sagittal section measured by [11C]FLB457.
Top right: D2R-reduced region.
(Adopted from Reference 14)

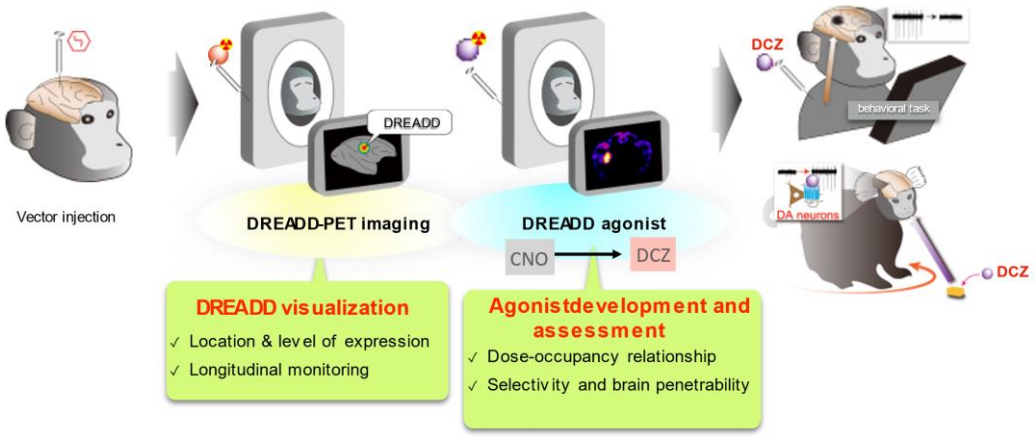

Fig. 4. PET visualization and functional manipulation of artificial receptors expressed in monkey brain.

1) Expression of artificial receptors locally in the monkey brain using viral vectors. 2) Visualization of artificial receptors (hM4D) by PET. Improvement of the DREADD agonist from CNO to DCZ. If the position of the artificial receptor is misplaced or the amount of expression is low, these methods make it possible by administering the viral vector again. (3) DCZ is administered to the monkeys to control neural activity via the artificial receptors.

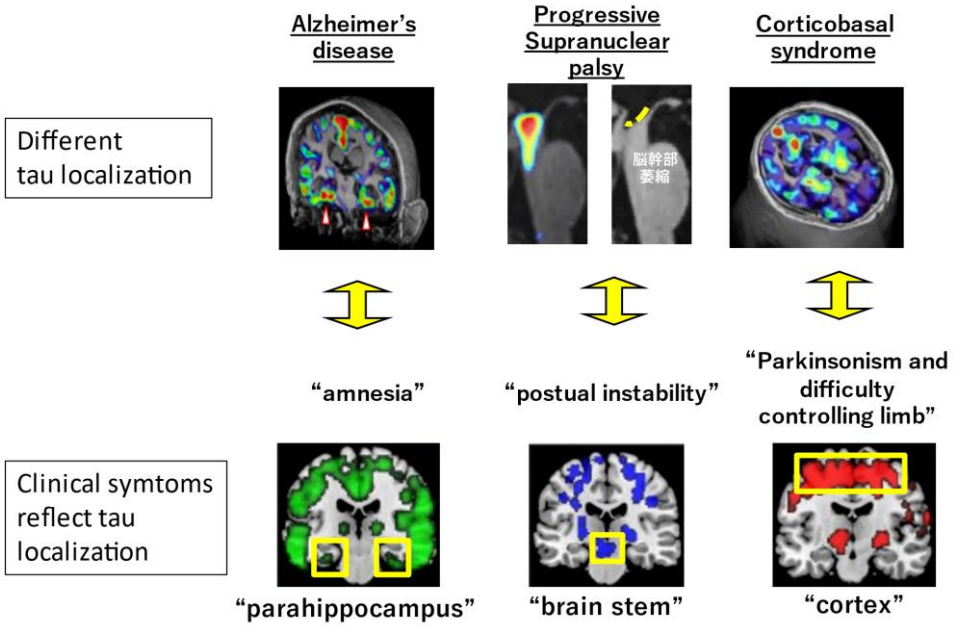

Fig. 5. Accumulation of tau protein and clinical symptoms
The accumulation region of [^{11}C]PBB3 reflects the tau protein accumulation. Each disorder shows a characteristic accumulation pattern, and clinical symptoms correspond to tau accumulation regions.

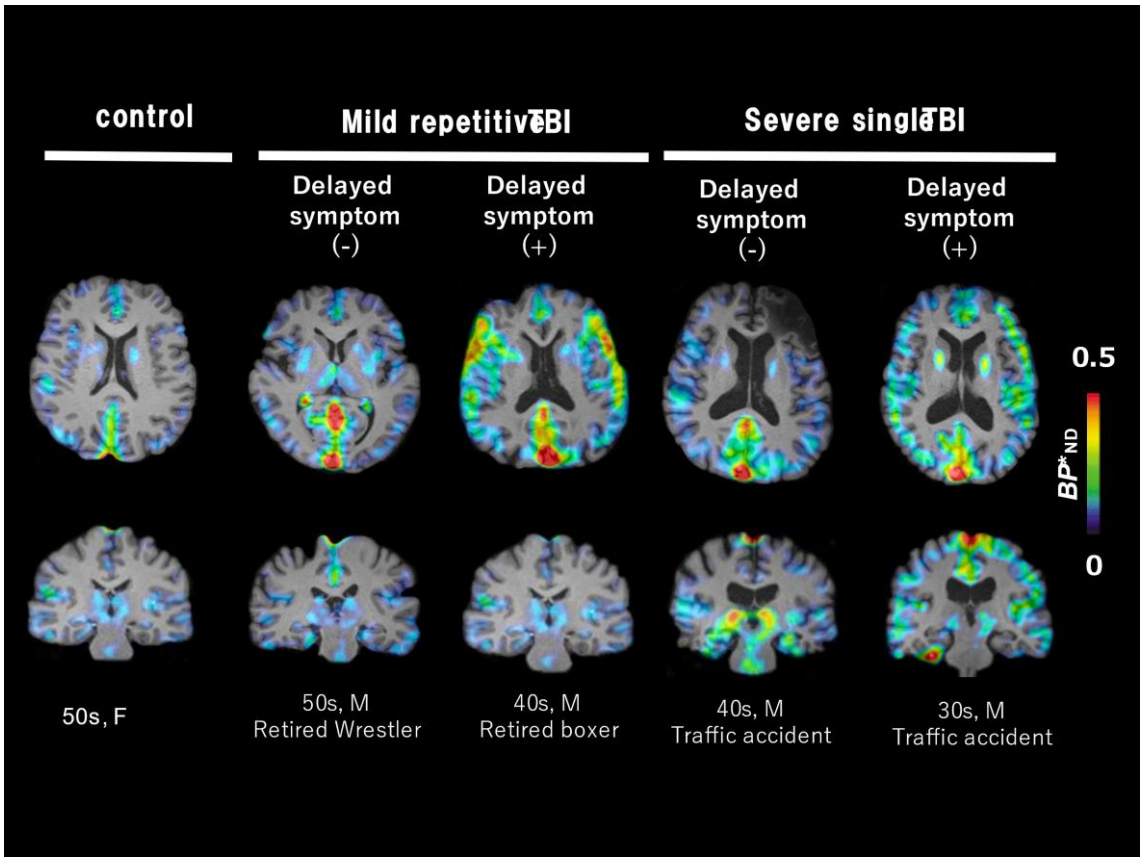

Fig. 6. PET tau imaging of head injury

PET images with [^{11}C]PBB3 of head injury patients. Tau protein accumulated in large areas of the head injury patient brains.

TBI: traumatic brain injury

(Modified from reference 17)

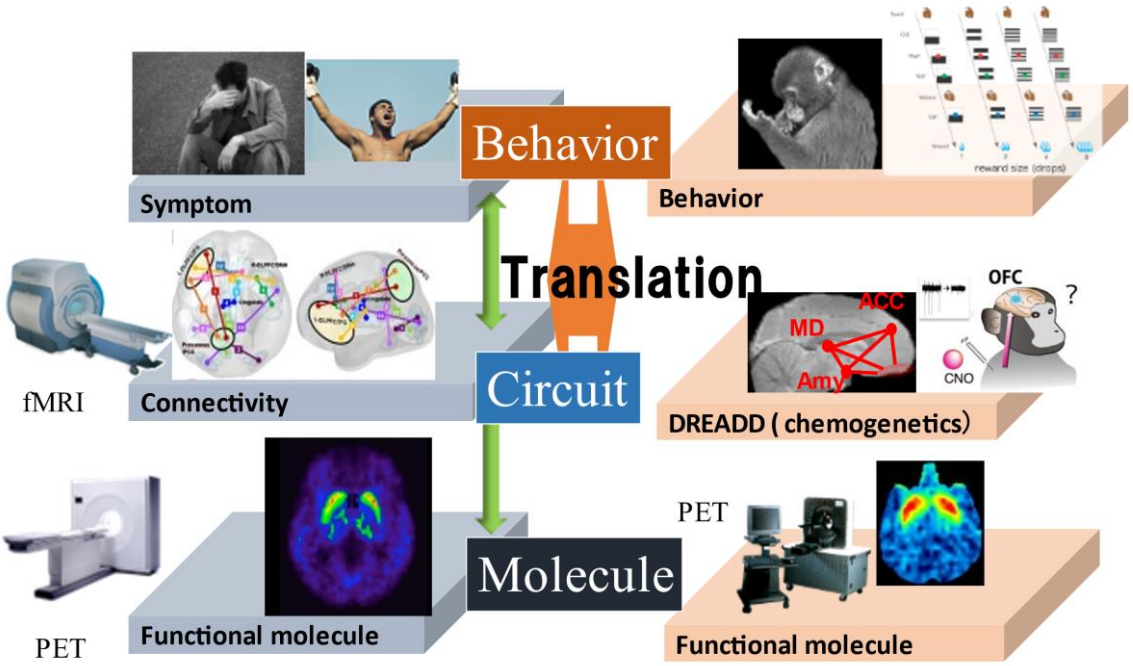

Fig. 7. Basic clinical bidirectional approach of functional molecules and circuits in neuropsychiatric disorders