Schizophrenia is a common severe psychiatric disorder that affects approximately 1% of general population through the life course. Historically, in Kraepelin’s time, schizophrenia was a disease unit conceptualized as dementia praecox; however, since then, the disease concept has changed. Recent MRI studies had shown that the neuropathology of the brain in this disorder was characterized by mild progression before and after the onset of the disease, and that the brain alterations were relatively smaller than assumed. Although genetic factors contribute to the brain alterations in schizophrenia, which are thought to be trait differences, other changes include factors that are common in psychiatric diseases. Furthermore, it has been shown that the brain differences specific to schizophrenia were relatively small compared to other changes, such as those caused by brain development, aging, and gender. In addition, compared to the disease and participant factors, machine and imaging protocol differences could affect MRI signals, which should be addressed in multi-site studies. Recent advances in MRI modalities, such as multi-shell diffusion-weighted imaging, magnetic resonance spectroscopy, and multimodal brain imaging analysis, may be candidates to sharpen the characterization of schizophrenia-specific factors and provide new insights. The Brain/MINDS Beyond Human Brain MRI (BMB-HBM) project has been launched considering the differences and noises irrespective of the disease pathologies and includes the future perspectives of MRI studies for various psychiatric and neurological disorders. The sites use restricted MRI machines and harmonized multi-modal protocols, standardized image preprocessing, and traveling subject harmonization. Data sharing to the public will be planned in FY 2024. In the future, we believe that combining a high-quality human MRI dataset with genetic data, randomized controlled trials, and MRI for non-human primates and animal models will enable us to understand schizophrenia, elucidate its neural bases and therapeutic targets, and provide tools for clinical application at bedside.

**Keywords:** Brain/MINDS beyond human brain MRI project, psychiatry, brain development, traveling subject, multi-modal brain image
Introduction

Schizophrenia is a common severe psychiatric disorder that affects around 1% of the general population through the life course. To date, patients have been diagnosed based on symptomatology, with few tools available to support diagnosis and prognosis. The symptomatology is rather clearly characterized compared to other psychiatric disorders, which comprises verbal hallucination, persecutory delusion, and disturbance of self (positive symptoms); impaired motivation, reduction in spontaneous speech, and social withdrawal (negative symptoms); and cognitive impairment in experimental and social situations (Fig. 1). Recent advances in imaging tools, especially MRI, have elucidated structural brain alterations, particularly those in the prefrontal cortex, temporal cortex, and subcortical regions. Schizophrenia has been considered to be a syndrome, and several neural bases have been suggested, including hyperactivity of the dopaminergic and glutaminergic neural systems. However, there is a need to elucidate the brain mechanisms of schizophrenia and apply them to clinically available biomarkers for differential diagnoses and prediction of the illness course of this disorder.

Considering genetic contribution to brain and disease, brain development and aging through the life course, progressive brain pathology around the onset, and common and disease-specific features of the brain characteristics could provide novel insights into understanding this complex condition in schizophrenia. Technical advances in brain measurement and image analysis, such as multi-shell diffusion-weighted imaging (DWI), proton magnetic resonance spectroscopy (1H-MRS), and harmonizing methods for multi-site datasets can help elucidate pathophysiology and identify neurobiological predictors of schizophrenia in clinical research.

In this article, we review the current evidence on brain characteristics in schizophrenia obtained using MRI studies and their limitations. Next, we would like to introduce the recent topics in clinical neuroimaging studies of schizophrenia. Finally, we would like to discuss future directions in neuroimaging research in psychiatry, including clinical trials using brain imaging to develop potential biomarkers, multi-modal investigations using other neuroimaging and neuro-physiological measures, and bidirectional translational studies between human and non-human primates.

Brain MRI Findings in Schizophrenia through the Life Course

Progressive brain pathology around the onset of schizophrenia

As shown in the meta-analyses of MRI findings at various stages of schizophrenia, both first-episode and chronic patients have gray matter reduction predominantly in the frontal and temporo-limbic regions compared with healthy controls, and its extent is assumed to be more extensive in the chronic stages (Fig. 1M and 1N). A series of longitudinal MRI studies on schizophrenia have shown that the brains of patients with first-episode, but not those of chronic patients, exhibited progressive gray matter reduction in the prefrontal and frontal and insula cortices, superior temporal gyrus, and fusiform gyrus, which was associated with the development of positive symptoms and cognitive impairments in a region-specific manner, but could be alleviated by the administration of antipsychotic medication. These active brain changes might reflect excessive dopamine neurotransmission in the peri-Sylvian regions that could cause clinical symptoms. In earlier clinical stages, both cross-sectional and longitudinal neuroimaging findings in individuals with high-risk status for psychosis have suggested that brain changes observed in those with psychotic disorders preceded the onset of florid psychotic symptoms, while the patients further exhibited progressive gray matter reduction in the prefrontal, temporal, and insular regions during the transition period. These findings support the pathological model of schizophrenia that the patients have neurodevelopmental abnormalities but also exhibit active gray matter loss mainly in the frontal and temporo-limbic regions in the initial years around the onset, which may underlie the first manifestation of positive symptoms. Further research is needed on other morphological characteristics (e.g., gyriﬁcation and sulcus pattern) and subcortical structures in the various clinical stages of schizophrenia.

Age-related decline or dementia praecox?

As proposed by Kraepelin, historically, schizophrenia had been conceptually defined as dementia praecox that refers to a chronic and progressively deteriorating psychotic illness with early onset (i.e., late adolescence or early adulthood). While the current evidence supports the notion that schizophrenia arises from an early neurodevelopmental disturbance, the patients likely have a high prevalence of Alzheimer disease in later stages and may have common neurodegenerative markers with those having dementia (e.g., cerebrospinal fluid markers of brain amyloidosis and high frequency of Lewy bodies and argyrophilic grains in autopsy cases) (Fig. 1K). These findings and progressive brain tissue loss in schizophrenia may partly support the concept of Kraepelin’s dementia praecox. However, the clinical course of schizophrenia is not consistent with a neurodegenerative model because a substantial number of patients maintain symptomatic remission and do not necessarily show persistent progression in cognitive and functional deficits throughout the illness stages (Fig. 1D–F, I–J; also see the following section “Schizophrenia is a syndrome and not solely a result of one brain pathology”). Furthermore, in sharp contrast to active gray matter loss during the first-episode,
brain changes in cortical thickness\textsuperscript{65} and activity\textsuperscript{66} in chronic stages of schizophrenia are comparable to those observed in age-matched healthy controls (Fig. 1N). Thus, schizophrenia appears to be a neurodevelopmental disorder with limited progressive brain pathology occurring during the evolution and early phases of psychosis, while the patients may exhibit age-related brain changes thereafter. Clinical and biological findings in schizophrenia suggestive of neurodegeneration could be partly explained by normal age-related brain changes\textsuperscript{67} and/or brain changes secondary to neurodevelopmental or medication effect.\textsuperscript{68}

**Genetic factors and brain pathology in schizophrenia**

In schizophrenia, subcortical brain volumes, such as hippocampus and putamen, and cortical structures (cortical area, thickness, and volume) are moderately to highly heritable ($h^2 \approx 0.20$–$0.80$) with a complex polygenic architecture (Fig. 1G and 1K).\textsuperscript{11,12,21} Brain volumes, particularly in the frontal, temporal, and limbic regions, were linearly differed among schizophrenia patients, while these were unaffected in first-degree relatives of their patients and healthy subjects.\textsuperscript{13} Large-scale genome-wide association studies (GWASs, $n \approx 13000$–$82000$) for these traits have been performed using the Psychiatric Genomics Consortium (PGC)\textsuperscript{14} and the Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA) consortium,\textsuperscript{15,16} the Cohorts of Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, and the UK Biobank.\textsuperscript{17} Each GWAS has identified several genetic loci associated with the risk of schizophrenia, subcortical brain volumes, and cortical structures.\textsuperscript{14–17} Since alterations in the subcortical volumes and cortical structures may be useful intermediate phenotypes to understand genetic mechanisms implicated in the pathophysiology of schizophrenia, there could be genetic correlations of schizophrenia with the subcortical volumes and the cortical structures.

We demonstrated a weak shared genetic etiology between the risk for schizophrenia and the hippocampus volume ($r_g = -0.18$) from large-scale GWASs using linkage disequilibrium score regression (LDSC) analysis.\textsuperscript{18} In addition, in a Japanese population ($R^2 = 0.032$), although based on a small sample size, we indicated that higher polygenic risk scores for schizophrenia were associated with smaller left superior temporal gyrus volumes,\textsuperscript{20} which was one of the specific cortical alterations for brain pathophysiology in schizophrenia.\textsuperscript{19} In contrast, recent large-scale studies reported weaker genetic overlap between schizophrenia and cortical structures (cortical area, thickness, and volume) ($r_g < -0.20$), e.g., superior temporal cortical area ($r_g = 0.15$) and insula volume ($r_g = -0.17$).\textsuperscript{16,17} These findings suggest the shared genetic etiology of schizophrenia with subcortical volumes and cortical structures, although these correlations are relatively small.
Developing psychosis and adolescent brain

Although brain volume and functional alteration around the onset of psychosis have been well investigated in clinical neuroimaging studies, when these alterations are established and spread in those who will later have the onset still remains unknown (Fig. 1L and 1M). Especially, adolescent development has been monitored since the brain regions and the corresponding cognitive functions that are developed during adolescence are similar to those which get altered in schizophrenia, and the onset of schizophrenia and the emergence of attenuated positive symptoms are more prominent during adolescence and early adulthood (Fig. 1A–C). Therefore, prospective cohort neuroimaging studies targeting general population, or familial and/or sub-clinical risk population, are needed. 23,24

In cohort studies, two main concerns should be considered for elucidating schizophrenia-related neural basis: brain development in adolescence (Fig. 1L) and the assessment of subthreshold symptoms (Fig. 1A–C). Although physical development is prominent during adolescence, brain development seen in MRI seems complex. The intracranial volume increases according to physical development, but the cortical thickness, surface area, and subcortical volumes show little difference or reduction during adolescence (Fig. 1L). 25,26 Therefore, most of the structural characteristics decrease relatively according to adolescent development. This means that previous clinical findings must be interpreted cautiously, because most studies found volume reduction in clinical groups. 4–7 Future longitudinal studies will elucidate whether these brain alterations are in line with the brain pathology of schizophrenia and/or normal adolescent development in cohort studies.

The other concern is the continuity of subthreshold symptoms between cohort and clinical studies. Since cohort studies generally enroll thousands of participants from the general population, the surveys assess their symptoms using self-reported questionnaires. One limitation of subjective symptom severity is a response bias which may reduce the validity and reliability to clinical syndromes. 69 Additionally, in assessing psychological symptoms of children and adolescents, reliability of responses from the participants and/or their parents should be considered, based on their understandings of questionnaires and the relationship between children and their parents during adolescence. 69

Psychotic experiences (PEs) 69,70–72 assessed using a self-report questionnaire may demonstrate the continuity between cohort and clinical investigations (Fig. 1A). However, a systematic review did not show a significant difference in later onset of psychosis between adolescents with and without simple PE. 72 The review suggests that continuity, frequency, distress, and multiple positive responses of the PEs (Fig. 1B) may predict later onset of psychosis, and neuropyschological findings showed similar characteristics between population-based severe PE participants and people with clinically determined high-risk status (Fig. 1C). 70 Therefore, severe PEs would be a link between cohort and clinical studies in neuroimaging.

Recent Advances in Brain MRI Studies on Schizophrenia

Multi-shell diffusion weighted image

Since most of the structural alterations in schizophrenia have been found using T1-weighted images, DWI provides morphological information in another perspective by calculating simple tensor images and more complex algorithm images. 73–75 DWI with multi-shells (i.e., multiple b-values) provides even more detailed structural information with neuroanatomical accuracy, taking advantages of different diffusivity degrees of water in tissue structures. For example, diffusion kurtosis image derived from multi-shell DWI provides better contrasts for white matter regions, where the fiber bundles are crossed, as well as gray matter, than diffusion tensor images derived from single-shell DWI. 34–36,76 Novel tools, neurite orientation dispersion and density imaging (NODDI) 77 can estimate neurites structures, and many fiber orientation distribution algorithms derived from multi-shells 34–36 can improve false-positive and true-negative fiber tracking. The meso- and micro-level information, including the structure of neurite and fiber bundles, may provide new insights into brain volume alterations because patients with schizophrenia do not show huge macro-level brain atrophy, but rather meso-level alteration. Furthermore, since postmortem studies in schizophrenia only showed synaptic loss in the cortex, 78 the details of brain volume change according to the disease, as well as brain development and aging, still remain unknown. 79

Magnetic resonance spectroscopy

The glutamatergic hypothesis is one of the mechanisms by which the pathophysiology of schizophrenia is explained. 10 Owing to the development of 1H-MRS, we can non-invasively measure glutamatergic neurometabolite levels in the brain of humans in vivo. A recent meta-analysis was conducted by Merritt et al. to examine glutamatergic neurometabolite levels, as measured by 1H-MRS, in patients with schizophrenia. 37 The authors reported that there were elevations in levels of glutamate (Glu) and glutamate + glutamine (Glx) in the basal ganglia and Glx levels in the medial temporal lobe within that patient population, suggesting that schizophrenia may be associated with the elevations in the levels of glutamatergic neurometabolites across several brain regions. 57 However, it is noteworthy that these findings considered participants with stages of illness that included the high-risk state, first-episode psychosis, and chronic schizophrenia. The authors also conducted subgroup analyses and found increased medial frontal Glx in high-risk individuals, elevated basal ganglia Glx levels in patients with first-episode psychosis, and increased frontal white matter and medial temporal Glx levels in patients with chronic schizophrenia. These findings suggest that glutamatergic dysfunction may be implicated for the pathophysiology of schizophrenia, warranting future research for the development of novel glutamatergic modulators for schizophrenia.
Multi-modal brain image analysis
As described above, different MRI sequences provide different types of brain information: multi-shell DWI provides assumable structural information of axon and neuropils, and MRS provides metabolism levels of neurotransmitters (Fig. 2). Integrating different types of information by scanning multiple MR contrasts would contribute to elucidation of schizophrenia pathogenesis as well as develop better treatment intervention. The Human Connectome Project (HCP) acquired multiple imaging modalities, as well as demographic and behavioral data in healthy individuals. It succeeded in capturing both general and specific features of structural and functional connectives among individuals, as well as creating image preprocessing pipelines for integrating different MR modality data, which provided additional information such as T1-weighted (T1w)/T2-weighted (T2w) ratio myeline map. In addition, using multiple MR contrasts provides better estimate to locate brain surface (T2w) ratio myeline map. In addition, using multiple MR contrasts provides better estimate to locate brain surface and boundaries among brain regions, including its subfields in individual data. For example, Broadman area 55b contributes to language function and its boundary from the frontal eye field and premotor eye field is considerably different among individuals. A multi-modal segmentation using T1-weighted FreeSurfer (https://surfer.nmr.mgh.harvard.edu) Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA) preprocessing, T1w/T2w ratio myelin map, and functional MRI during a language task can successfully differentiate the region 55b from other regions individually.

MRI scans for the target identification in brain stimulation studies
In recent years, there have been an increasing number of attempts to perform MRI measurements before and after the intervention in clinical trials to develop MRI-derived indices as biomarkers for predicting treatment response. MRI is particularly important in repetitive transcranial magnetic stimulation (rTMS), which is exactly the same approach used in the neuroradiology field to precisely identify the target site for gamma knife therapy in brain tumors.

Indeed, over the past quarter century, numerous clinical trials using rTMS have been conducted on patients with depression to investigate its clinical effectiveness worldwide, and, currently, rTMS therapy has emerged as a non-invasive promising strategy for depression, especially in the context of treatment-resistant depression. When patients undergo rTMS, clinical MRI is not only performed as a screening test to exclude organic diseases in the brain but also it is increasingly performed prior to the start of rTMS treatment for the purpose of implementing MRI-guided high-precision neuronavigation to determine the stimulation site in more sophisticated ways. On the other hand, although rTMS has been shown to be useful in depression, the neurobiological mechanisms associated with antidepressant effects have not yet been fully elucidated. Thus, there has been a great amount of research in academia on the use of multimodnal high-quality MRI measurements to elucidate the therapeutic mechanisms of rTMS and to identify predictors of response based on MRI findings prior to treatment initiation.

Furthermore, in recent years, the therapeutic potential of TMS for schizophrenia has also been investigated in academic centers. Although a number of clinical trials indicated moderate therapeutic effect for this disorder, its clinical efficacy remains controversial yet. Moreover, the neurobiological mechanisms of action remain unclear. Thus, MRI measurements are often combined with rTMS clinical trials in patients to investigate the therapeutic mechanisms by which rTMS acts. In this context, TMS-related functional neuroimaging, especially functional MRI, is often performed in patients with schizophrenia to examine the brain functional changes following rTMS treatment.

Open neuroscience in clinical neuroimaging studies
Since the volume of brain images from one participant and the sample size in neuroimaging studies have dramatically increased during recent years, there is a need to provide access to the data for researchers publicly to utilize them. Moreover, most brain imaging software packages have been developed using public funds and are freely available; sharing analytic programs have also been a common practice to utilize and validate the developed analytic techniques via GitHub (https://github.com), GitHub, San Francisco, CA, USA) and other online resources. Several websites are available for open neuroscience where researchers can upload and download MRI data freely to promote neuroimaging studies (e.g., International Neuroimaging Data-Sharing Initiative [INDI]. http://icon1000.projects.nitrc.org; OpenNeuro [https://openneuro.org]; Open fMRI [https://www.openfmi.org/dataset/ds000224]). Data from several, recent large projects, such as HCP, UK BioBank, and the Adolescent Brain Cognitive Development (ABCD) project, are intended for open access. Open access has also been requested for clinical MRI data, and several datasets are publicly available for schizophrenia imaging, such as the Decoded Neurofeedback (DecNet) Project (https://briefreport.org/caneconmedit) and the Brain/MINDS DATA PORTAL (https://www.brainminds.riken.jp). The Human Connectome Studies Related to Human Disease projects (https://www.humanconnectome.org/disease-studies) are further expanding from the original HCP, and open access to the clinical data has been planned for researchers.

The Brain/MINDS Beyond Human Brain MRI project (BMB-HBM, FY2018–FY2023) is a national project in Japan, which aims to establish clinically relevant imaging biomarkers. Data collection in psychiatric and neurological disorders across the lifespan has also been scheduled initially...
at 13 sites where measurement machines and multi-modal scan procedures have been fixed beforehand (Fig. 2). The imaging, demographic, clinical information, and harmonizing database will be made publicly available by the end of the project, FY2024.

**Existing Limitations and Future Directions of Brain MRI Studies on Schizophrenia**

**Schizophrenia is a syndrome and not solely a result of one brain pathology**

Schizophrenia includes heterogeneous disorders with regard to divergent clinical course of symptoms, cognitive dysfunction, and treatment response, and in turn the underlying biological mechanisms (Fig. 1E, 1J, and 1O). Currently, the primary treatment for schizophrenia involves dopamine receptor antagonism by antipsychotics. The clinical effects of antipsychotics have provided the basis for the dopamine hypothesis of schizophrenia, which posits that aberrant dopaminergic function is implicated in schizophrenia pathophysiology. However, approximately 20% to 35% of patients with schizophrenia do not respond to first-line antipsychotics and are thus considered to have treatment-resistant schizophrenia (TRS). Clozapine is the most effective antipsychotic for TRS. In contrast to other antipsychotics, clozapine has lower affinity for dopamine D2 receptors. Moreover, previous studies that used positron emission topography demonstrated lower dopamine synthesis capacity in the striatum of patients with TRS compared with that in patients who had treatment-responsive schizophrenia. Taken together, these findings suggest that the pathophysiology of TRS might not be associated with increased striatal dopamine levels. On the contrary, employing 1H-MRS, our group conducted two independent studies noting that glutamatergic neurometabolite levels in the anterior cingulate cortex were increased in patients with TRS and in those with clozapine-resistant schizophrenia in comparison with healthy controls. These findings suggest that dopaminergic dysfunction and glutamatergic dysfunction may contribute to the heterogeneity of schizophrenia. Since there were no replicated neuroimaging findings of TRS, further research is needed to examine glutamatergic dysfunction in patients with TRS in order to elucidate the heterogeneity of schizophrenia.

**Clinical and brain characteristics are shared with schizophrenia and other psychiatric disorders**

Since most of the clinical studies in neuroimaging have been conducted in case–control fashion, the extent to which the findings are schizophrenia-specific or rather reflect common psychiatric features still needs to be investigated. In genetic and neuropsychological studies, as well as in neuroimaging studies, disease-specific difference from healthy controls includes common features in psychiatric disorders. Nevertheless, several studies showed the possibility of...
differentiation between psychiatric disorders using brain images.30–32 Recently, machine learning algorithms could be used as a better tool for differentiating between the diseases,33,110 which could also be applicable to earlier clinical stages of schizophrenia.110

As described earlier, schizophrenia is thought to consist of various subtypes. Recent machine learning studies also try to differentiate among different subtypes of schizophrenia.8 To be able to visualize the differences among schizophrenia- and subtype-specific brain characteristics, larger sample size (i.e., at least 200) recruited from various methods (e.g., multi-site studies) may be needed. However, to combine those with the large MRI datasets from multi-sites, the differences derived from machine and protocol differences, and individual variance should be considered (see the following two sections in detail).

**Smaller disease-specific brain characteristics compared to machine- and protocol-derived differences**

In multi-site MRI studies, site differences in scanner and/or image-acquisition protocols negatively impact the reliability and reproducibility of image analyses, resulting in measurement bias (Fig. 3).80 In the initial multi-site MRI study, Jack et al. standardized imaging protocols across sites to reduce the effects of different imaging protocols on the MRI quality.111 Moreover, previous studies have attempted to correct the biases using image preprocessing methods for treating raw MRI data.112–115

The aforementioned attempts were made to standardize imaging protocols and image preprocessing, but the measurement bias could not be eliminated completely.116 Fortin et al. have effectively harmonized fractional anisotropy and mean diffusivity data from diffusion tensor imaging using ComBat42 and estimated the cortical thickness42 to improve the statistical and machine learning classification power. As a more effective method of harmonization, Yamashita et al. extended general linear model (GLM) harmonization using a traveling subject (TS) dataset,44 which can differentiate machine and protocol-derived difference from sampling variability, including sociodemographic factors and disease-related factors, and can diminish only machine and protocol-derived difference (Fig. 3).

Harmonization is a promising method for reducing bias and improving reproducibility of multi-site datasets using a statistical approach41,42,44 and has become an essential process not only for schizophrenia data analysis but also for all imaging multi-site studies. Since patients with schizophrenia have smaller hippocampus (Cohen’s d = −0.46) than healthy control,9 if the measurement bias exceeds this effect size, the disease cannot be identified. BMB-HBM project also planned to measure TS for 13 sites. As of 2020, over 600 sessions from 75 participants were measured and preliminary findings showed that harmonized protocol, preprocessing pipeline, and TS harmonization work are promising (Fig. 2).41

### Non-disease-related individual differences are the source of highest variability in brain MRI characteristics

The TS approach can also differentiate among the factors of variation in brain imaging variables in which the signals in resting state during functional connectivity contribute to individual variance, and then measure the bias and disease-specific factors.44 Individual variance in neuroimaging characteristics is thought to consist of age and gender, and then handedness, IQ, socioeconomic status, and other environmental factors.31,32,80 Unlike genetic studies, brain characteristics considering these sociodemographic characteristics could reveal disease-associated factors more accurately.32,80

Previous studies often used linear models to consider the variables; however, these variables are complex and hierarchical.31 For example, men have greater brain volumes compared to women, and smaller brain volumes in patients with schizophrenia suggest severe symptoms and poorer clinical outcomes. However, men with schizophrenia are more likely to have severe symptoms and poorer clinical outcomes compared to women with schizophrenia. Another example regarding medication is that antipsychotics medication is thought to decrease brain volume and function, but the patients with severe forms of condition are prescribed more medication doses.

### Translating human brain MRI research into non-human primates

The findings from *in vitro* and animal model studies have been generally applied to human studies or clinical trials, the so-called forward translational approach; however, this approach has been applied to few psychiatric disorders. Instead, a biological candidate from clinical studies is often investigated to provide further basic neuroscience investigation (reverse translational approach). Bi-directional translational approaches would be crucial for elucidating the pathogenesis of neuropsychiatric disorders, since the neural information provided by human brain images is limited in terms of spatial and temporal resolution. On the other hand, cognitive and behavioral phenotypes, as well as social forms, are different between human beings and non-human animals, especially rodents.

To minimize such a gap between human subjects and animal models, a Japanese national brain project, Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS),117 has developed non-human primate, common marmoset (*Callithrix jacchus*), as an animal model.118,119 Compared to other non-human primates, common marmosets develops in the environments which are more similar to those of humans, which may result in their development being comparable to that of human.118,119 and evolution to understand why schizophrenia develops.120 Indeed,
unlike chimpanzees and macaque monkeys, both parents participate raring their offspring, colonized by family unit. Most of the neuropsychiatric diseases are said to have originated from some aberrant neural developmental processes. Taking advantages of its short generational interval, common marmoset is also suitable to study developmental processes. In addition, neuropsychiatric phenotypes are rarely observed in other non-human animals in natural condition, suggesting that humans must have got it through the evolutional process. Thus, comparing and investigating the differences from non-human animals would provide the insights into why only humans develop neuropsychiatric disorders.

Narrowing macro-findings (MRI data) from human studies into micro-studies (cytoarchitectonic, molecular, or genetic data) with animals would efficiently lead to the answers of current hypotheses on neuropsychiatric pathogenesis. Recent advances of neural observation and manipulations, such as calcium imaging, optogenetics, and the designer receptors exclusively activated by designer drugs (DREADD) available in animal models, allowed to observe the trajectory of the alteration in the developmental course. Thus, bi-directional translational approach using both human and animal data with multi-modality would extend further investigations on neuropsychiatric fields.

**Interpretation to other brain measurements:**

**EEG and MEG research in schizophrenia**

Due to their non-invasiveness and excellent temporal resolution in the millisecond range, neurophysiological approaches, such as electroencephalography (EEG) and magnetoencephalography (MEG), have revealed novel insights into sensory and cognitive abnormalities in patients with schizophrenia. Among the several EEG/MEG indices, mismatch negativity (MMN) and gamma-band oscillation including auditory steady-state response (ASSR) are currently attracting attention as highly reproducible biomarkers in schizophrenia.

**Fig. 3** TS harmonization of the brain images from multi-clinical sites. When considering the data harmonization, the biases from different recruitment methods (sampling bias, i.e., Site a–c) and scanners and protocols (measurement bias, i.e., Machine x–z) should be eliminated. An MRI research is generally conducted for a specific condition (e.g., schizophrenia) using a machine in a site, given that the multi-site data as the aggregation of the case–control studies (i.e., X_{a,x}, X_{b,y}, and X_{c,z}) are unable to differentiate between sampling and measurement biases. TS data are supposed to include only measurement biases, and sampling bias from each site can be estimated. TS, traveling subject.
information processing which may reflect altered predictive coding in schizophrenia.\textsuperscript{126–128} The amplitude of MMN (especially duration MMN) is reduced in chronic schizophrenia, first-episode schizophrenia, and even at the clinical high-risk state.\textsuperscript{125,129} Mechanistically, this reduced MMN amplitude may reflect N-methyl-D-aspartate receptor (NMDAR) dysfunction in patients with schizophrenia since NMDAR antagonists reduce the MMN amplitude.\textsuperscript{129–131} Thus, MMN has the potential to be a useful therapeutic biomarker for detecting disrupted NMDAR-mediated neurotransmission in schizophrenia.

Oscillations in the gamma-band (30–100 Hz) generated in the neocortex by interactions among neurons in local circuits are used as another reliable neurophysiological biomarker in schizophrenia.\textsuperscript{122} Gamma-band oscillation deficit has been studied extensively in schizophrenia using evoked activity paradigms, especially in ASSR task which is highly reproducible.\textsuperscript{132,133} Many studies have demonstrated a decreased evoked power and phase synchronization of 40-Hz ASSR (elicited by 40-Hz steady click sounds) in both the early and chronic phases of schizophrenia.\textsuperscript{134–136} In addition to decreased stimulus-locked 40-Hz ASSR oscillations, recent reports showed increased (non-phase-locked) spontaneous gamma-band oscillation (induced power) during click-sound stimulation in schizophrenia,\textsuperscript{136} along with the primary auditory cortex volume deficits.\textsuperscript{133} Progressive reduction in auditory evoked gamma-band oscillation is also seen over time in first-episode, but not in clinical high risk, suggesting that evoked gamma-band oscillation may index the abnormal progressive neural synchronization phenomenon that occurs after the onset of the illness. Biologically, the mutual balance between excitation and inhibition within the neural network is critical for generating gamma-band oscillation.\textsuperscript{137} Normal neuronal information processes rely on an appropriate excitability and inhibitory (E/I)-balance, while failure to maintain this mutual balance is hypothesized to cause deficits in gamma-band oscillations in schizophrenia.\textsuperscript{136,138,139} Moreover, our previous discovery of increased spontaneous broadband gamma power in schizophrenia\textsuperscript{136} resembled the increased spontaneous broadband gamma power that is often reported in animal models of schizophrenia based on E/I-imbalance due to NMDAR hypofunction.\textsuperscript{140,141} Hence, spontaneous gamma-band oscillation has a huge potential as a translatable neurophysiological biomarker in schizophrenia.

Simultaneous EEG-functional MRI (fMRI) recording has also attracted attention because the combination of EEG and fMRI allows the integration of fine spatial and accurate temporal resolution.\textsuperscript{142} In EEG/MEG studies, regardless of whether it is a spontaneous activity or an induced activity such as MMN or ASSR, modeling the neural generators of scalp EEG/MEG data is the method of choice since MEG/EEG source modeling is an inverse problem. In this regard, assuming that EEG and fMRI recordings reflect the same brain activity state, simultaneous EEG-fMRI acquisitions may ensure and identify the neural generators of scalp EEG/MEG data which would lead to evaluate precise neural connectivity dynamics. Especially, simultaneous EEG-fMRI recording will enable the evaluation of functional neural networks involving subcortical regions, such as the thalamus. Although there are many challenges, including the strong EEG artefacts generated by MR gradient currents, these modalities are highly complementary and their integration may help to detect detailed abnormal neuronal phenomena in schizophrenia, which require high temporal and spatial resolution (Fig. 2).\textsuperscript{143,144}

**Discussion**

This review summarized brain alteration of schizophrenia in MRI studies, which identified schizophrenia as a brain disorder, and the illness course was characterized by progressive brain pathology around the onset of disease, but not dementia praecox. However, we have little knowledge on genetic contribution and its relationship with brain alternation from large sample size genome studies. To elucidate this, we need to understand the developing and aging course of the human brain, and then compare it with the corresponding trajectory of schizophrenia brain characteristics, since the size effect from schizophrenia is smaller than that from age, sex, etc. We should also consider schizophrenia as a syndrome which is composed of multiple brain pathologies and subtypes, including various prognoses and common characteristics with other psychiatric disorders. To observe those on brain MRI scans, we need to use a larger sample size dataset from various recruitment methods and backgrounds, considering machine and protocol differences.

In the image acquisition and analysis aspects, recent advances in brain MRI studies could provide different aspects and greater SNR, which could see more robust findings in schizophrenia studies. Multi-shell diffusion-weighted image, MRS, and multi-modal brain image analysis would be promising candidates.

The BMB-HBM project\textsuperscript{41} was launched considering these limitations and includes the future perspectives of MRI studies, such as multi-site recruitment targeting various psychiatric and neurological disorders, restricted machines and harmonized multi-modal protocols, standardized preprocessing, and TS measurement. A strategy for data sharing to the public has already been discussed and is planned in FY 2024. In the future, combining MRI with genetic data will be needed for elucidating how schizophrenia risk genes contribute to brain pathology in this condition,\textsuperscript{12,15–17,21} by testing whether schizophrenia-related genetic loci would be associated with the alteration in meso- and micro-structures and cortical myelination. Moreover, harmonizing MRI protocols for non-human primates were developed,\textsuperscript{145} which may be easier to interpret.
than those protocols in human studies on development and aging. These projects may provide better understandings of schizophrenia, its neural bases and therapeutic targets, and clinical application tools at bedside.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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