Review Article

# Associations between brain abnormalities and common genetic variants for schizophrenia: a narrative review of structural and functional neuroimaging findings

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**Abstract:** Schizophrenia is a common psychotic disease worldwide, and several genetic variants have been suggested to influence susceptibility to schizophrenia. However, the exact genetic and neural mechanisms underlying such relationships remain unclear. Neuroimaging endophenotypes have been considered to be desirable for finding genes influencing brain structure and function. Because of its high penetrance of genetic variants and wide applications in clinic practice, neuroimaging could be a great option in schizophrenia study. In this narrative review, we aim to provide a summary of current progress in neuroimaging findings to detect genetic variants that may influence the brain's structure and function, and thus improve understanding of how this interaction affects the onset of schizophrenia. Multiple common genetic variants for schizophrenia including the *ZNF804A*, *DTNBP1*, *DAOA*, *AKT1*, *NTRK3*, and *ERBB4* genes are reviewed. In summary, the current investigations have reported effects of these genetic variants on both structural and functional brain abnormalities (e.g., altered grey matter volumes, white matter integrity and functional connectivity patterns) in schizophrenia within multiple brain regions, especially the frontal, temporal and hippocampal areas. These findings facilitate our understanding of schizophrenia and helping us with early diagnosis, prognosis prediction and medication. However, a deep insight into this field necessitate further investigations and there are a number of challenges to be settled, such as enlarging the sample size; solving the statistical, methodological, and technological limitations; performing not only cross-sectional but also longitudinal observations; focusing on the effect of copy number variants; figuring out the complexity of epistasis and gene-environment interaction; achieving clinical translations; and depict the effect of a polygenic risk score beyond those of single genetic markers.

**Keywords:** Schizophrenia; imaging genetics; endophenotype; neuroimaging; candidate genes

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## Introduction

Schizophrenia is a common psychiatric disease characterized by continuous or relapsing episodes of psychotic symptoms including hallucinations and delusions, from with approximately 1% of the global population suffer (1). It has been proved that schizophrenia is associated with both structural (2) and functional (3) brain abnormalities, which can be revealed by neuroimaging techniques such as functional magnetic resonance imaging (fMRI), structural MRI (sMRI) and diffusion tensor imaging (DTI). Such changes include widespread white matter integrity deficits across multiple tracts with main involvement of the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulum bundle, and corpus callosum; extensive gray matter reductions in frontal, limbic and subcortical regions; as well as functional abnormalities in multiple key circuits particularly involving frontal, temporal, and mesolimbic areas at both task and resting states (4-6).

The diagnosis of schizophrenia is now generally based on clinical symptoms rather than on etiology or neurobiology; however, these symptoms are known to be of great heterogeneity (7). One possible reason is that since schizophrenia is a polygenetic disorder with complex genetic underpinnings, there can be more than one pathway to a given behavior in molecular aspect, and different combinations of susceptibility genes may contribute to any complex behaviors via different molecular pathways (8). It has been demonstrated that both hereditary and environmental factors play roles in the onset of schizophrenia (9), of which heredity accounts for more than 80% (10). Several genetic variants have been suggested to influence susceptibility to schizophrenia, such as the *ZNF804A*, *DTNBP1*, *DAOA* and *AKT1* genes (11). Consequently, although massive legion of genetic association studies has been done, it is hard to get positive outcomes in gene analysis based on such a diagnostic and classification system. In order to solve this problem, more and more scientists start to move away from disease entities to more biologically defined levels, hoping that the penetrance of genes would be more prominent on these levels, that is "endophenotype" or "intermediate phenotype" (12). In specific, endophenotype is a measurable component that is only visible by outside assistance along the pathway between distal genotype and disease. It is associated with candidate genes and is a detectable parameter of the disease (13). It represents the measurements of greater definitude and quantifiability that are expected to involve fewer genes, fewer interacting levels and ultimately single set of neuronal circuit activation or regional alteration (8). An endophenotype should meet the criteria of specificity, self-independence, heritability, familial association, co-segregation and biological and clinical plausibility. In other word, it should have strong association with the disease of interest and genetic variance, great stability over time, and conceptual relationship to the disease. Also, the endophenotype should have higher prevalence among the relatives of ill probands and the ill individuals of certain affected family (14). Therefore, by using endophenotype strategy, psychiatrists could study targeted genes in a more sufficient way.

Combined with genetic analyses, neuroimaging techniques have also been widely used in clinical practice to uncover the effects of different genes on specific brain regions/circuits involved in specific moral, emotional, and cognitive dysfunctions in schizophrenia (15). In fact, the penetrance of some genetic variation has been assumed to be higher at the level of neural phenotypes than at the level of behavioral phenotypes (16), from which neural measures are of greater sensitivity to gene effects than behavioral measures (17). For example, some previous studies have provided evidence that the penetrance of catechol-O-methyltransferase (COMT) genetic variations is high in neuroimaging, with estimated effect sizes of 0.7 to 1.0 and corresponding sample sizes to detect 80% genetic effects of around 80 participants, which are much less than what required for clinical behavioral data (18,19). Considering these advantages as well as great interpretability in neurobiological, biochemical and anatomical aspect, neuroimaging measures has been promoted as one of the most desirable endophenotype adapted to schizophrenia right now. Thus, through quantifying brain structure and function and relating the neural alterations with genetic variants, imaging genetics can make a remarkable advancement in understanding etiology of schizophrenia in the near future (16).

To date, the imaging genetic study of schizophrenia has already attained some progress. However, as a complex genetic disease, schizophrenia has complicated pathogenesis and phenotype, and its imaging genetic research is still at exploration phase. In this review, we aim to provide a summary of current progress to detect genetic variants that may influence the brain's structure (including grey matter/white matter volumes, thickness and integrity) and function (including activation and functional connectivity patterns), and thus improve understanding of how this interaction

 

affects the onset of schizophrenia. Specially, since some genetic variants for schizophrenia such as the *COMT* (20,21) and *NRG1* (22,23) genes have already been repeatedly reviewed in previous reports, here we will focus on some genes that closely relate to schizophrenia but were not much reviewed including the ZNF804A (rs1344706), DTNBP1, DAOA (G72), AKT1, NTRK3 (TRKC), and ERBB4. The review is based on search results from PubMed (www.ncbi.nlm.nih.gov/pubmed/). The searching strategies used for each candidate gene are: "(schizophrenia OR psychosis OR 'schizophrenia spectrum' OR schizoaffective OR delusional) AND (imaging OR neuroimaging OR image OR images OR MRI OR fMRI OR sMRI) AND ('name of each candidate gene')", and all of the reviewed articles are published before November 30$^{th}$, 2020. An overview of related literature papers and main findings are presented in *Table 1*.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1210).

## Review of current findings

### *ZNF804A (rs1344706)*

As the first common genetic variant associated with schizophrenia identified on a genome-wide level (81), *ZNF804A* rs1344706 was found to play critical role in neurite outgrowth, neural migration, and synapse formation (82). Although not completely consistent, most of the sMRI research shows that ZNF804A risk allele is linked to reduced grey matter volume/thickness for multiple cortical structures in healthy population, but opposite effects in schizophrenia patients. In healthy populations, for example, several imaging genetic studies have revealed that *ZNF804A* risk A allele was linked to reduced gray matter volume of the posterior cingulate, medial orbitofrontal gyrus, and parahippocampal gyrus (24), as well as reduced cortical grey matter thickness of the superior temporal gyrus, anterior and posterior cingulate cortex (26). In schizophrenia patients, oppositely, it was reported that *ZNF804A* risk status was linked to increased cortical volume of the superior temporal gyrus, insula, and hippocampus (25). Yet, one thing worth noticing is that the CC homozygotes often took an intermediary position, which made the potential effect of the risk allele even more complicated. Based on these results, *ZNF804A* risk allele is linked to reduced grey matter volume/thickness in healthy population, but opposite effects in schizophrenia patients. Nevertheless, there are some studies against such a conclusion. For instance, Wei *et al.* (83) found that the risk A allele in *ZNF804A* rs1344706 was associated with thinner cortex, smaller cortical surface areas and lower cortical volumes for multiple cortical structures in unmedicated schizophrenia patients, but opposite effects in healthy controls. Some other researchers reported no significant impact of ZNF804A risk variance on macroscopic brain structures in healthy individuals (84,85) or schizophrenia patients (30).

When it comes to white matter structure, however, the potential effect of ZNF804A is of greater controversy. While it was reported that *ZNF804A* risk allele carriers exhibited greater white matter volume than non-risk allele carriers in both schizophrenia patients and healthy volunteers (27), some other studies found no significant difference in white matter volumes in healthy volunteers (84,85). In some cases, *ZNF804A* risk variant was found to be associated with lower fractional anisotropy (FA) reflecting reduced white matter integrity in corpus callosum and corona radiate (36), as well as brain regions within cortico-limbic circuits of schizophrenia patients (31), and lower FA in the corpus callosum, left forceps minor, and right parietal white matter (35) in healthy controls. Furthermore, several studies reported no significant genotypic effects of ZNF804A on white matter structure in either healthy or schizophrenia patients (26,33,34,86).

The inconsistency in reported effects of ZNF804A risk allele on grey and white matter structures might be attributed to several reasons. Firstly, there are possibly different experimental research methods, magnetic forces, resolutions, and signal-to-noise ratio applied in different studies, leading to inconsistent results and conclusions. Additionally, the too-little sample sizes and variance in ethnicities may account for discrepant findings as well. Importantly, the inconsistency might also result from the epistasis. A recent study in regards to the interaction between *COMT* rs4680 and *ZNF804A* rs1344706 on gray matter volume of the left dorsolateral prefrontal cortex in healthy adults reported that in *COMT* Met-allele carriers, the thymine-guanine (TG) heterozygotes of *ZNF804A* exhibited greater gray matter volume than the other two genotypes, whereas in *COMT* Val/Val homozygotes, the *ZNF804A* TG heterozygotes showed smaller volume than guanine-guanine (GG) homozygotes and comparable volume with thymine-thymine (TT) homozygotes (29). Due to various differences in individual and ethnic genetic

 

**Table 1** Summary of main findings of effects for each genetic variant

| Candidate gene | Reference | Sample | Research method | Main findings of effects of each genetic variant |
|---|---|---|---|---|
| *ZNF804A* (rs1344706) | Lencz *et al.* 2010 (24) | 39 HCs | sMRI | Decreased GM volumes in several regions comprising the default-mode network; increased total WM volume |
| | Donohoe *et al.* 2011 (25) | 38 HCs/70 SZs | sMRI | No effects in HCs; increased hippocampal GM volume in SZs |
| | Voineskos *et al.* 2011 (26) | 62 HCs | sMRI and DTI | Decreased GM thickness in superior temporal gyrus and anterior/posterior cingulate gyrus; no effects on WM integrity |
| | Wassink *et al.* 2012 (27) | 198 HCs/335 SZs | sMRI | Increased total WM volume in HCs; increased total and frontal WM volumes in SZs |
| | Sun *et al.* 2016 (28) | 78 HCs/76 heroin abusers | sMRI | Increased GM volumes in insular, temporal and superior parietal cortices |
| | Xu *et al.* 2018 (29) | 274 HCs | sMRI | Opposite effects on DLPFC GM volume between COMT Met-allele carriers and COMT Val/Val homozygotes |
| | Quidé *et al.* 2018 (30) | 94 HCs/214 SZs | sMRI | No significant effects on GM volume |
| | Kuswanto al. 2012 (31) | 64 HCs/89 SZs | DTI | Decreased WM integrity involving widespread cortico-limbic regions in SZs |
| | Sprooten *et al.* 2012 (32) | 50/83 HCs in two samples | DTI | No significant effects on WM integrity |
| | Wei *et al.* 2013 (33) | 69 HCs/100 SZs | DTI | No significant effects on WM integrity |
| | Fernandes *et al.* 2014 (34) | 250/340 HCs (two samples) | DTI | No significant effects on WM integrity in both samples |
| | Ikuta *et al.* 2014 (35) | 107 HCs | DTI | Decreased WM integrity in corpus callosum, forceps minor, and parietal regions |
| | Mallas *et al.* 2016 (36) | 124 HCs/63 SZs/43 BDs | DTI | Decreased WM integrity across wide brain networks; such effects are significant in the entire sample and the SZ group alone |
| | Esslinger *et al.* 2009 (37) | 115 HCs | Working memory task fMRI | Decreased FC of DLPFC across hemispheres; increased FC between DLPFC and hippocampus |
| | Walter *et al.* 2011 (38) | 109 HCs | Theory-of-mind task fMRI | Decreased FC between DLPFC and posterior temporal cortex; increased FC between temporo-parietal junction and inferior PFC |
| | Esslinger *et al.* 2011 (39) | 111 HCs | Resting-state and emotional task fMRI | Decreased interhemispheric prefrontal FC during both resting and emotional task states |
| | Rasetti *et al.* 2011 (40) | 153 HCs, 78 SZs and 171 SBs | Working memory task fMRI | Decreased DLPFC-hippocampal FC in all groups; decreased FC between DLPFC and the rest of PFC in HCs |
| | Paulus *et al.* 2013 (41) | 94 HCs | Working memory task fMRI | Increased DLPFC-hippocampal FC |
| | Mohnke *et al.* 2014 (42) | 188 HCs | Theory-of-mind task fMRI | Increased frontal-temporo-parietal FC |
| | Zhang *et al.* 2016 (43) | 87 HCs | Resting-state and working memory task fMRI | Increased DLPFC-hippocampal FC during task; decreased hippocampal-posterior cingulate cortex FC during both states |

**Table 1** (*continued*)

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| Candidate gene | Reference | Sample | Research method | Main findings of effects of each genetic variant |
|---|---|---|---|---|
| | Zhang *et al.* 2018 (44) | 99 HCs/92 SZs | Resting-state fMRI | Decreased DLPFC-hippocampal FC |
| | Zhao *et al.* 2020 (45) | 101 HCs | Resting-state and memory task fMRI | Decreased training-induced plasticity of DLPFC-hippocampal FC |
| *DTNBP1* | Narr *et al.* 2009 (46) | 42 HCs/62 SZs | sMRI | Decreased whole-brain volume |
| | Dutt *et al.* 2009 (47) | 61 HCs, 128 SZs and 194 SBs | sMRI | No significant effect on hippocampal and lateral ventricular volumes |
| | Donohoe *et al.* 2010 (48) | 38 SZs | sMRI | Decreased GM volumes in dorsolateral prefrontal and occipital cortex |
| | Cerasa *et al.* 2011 (49) | 104 HCs | sMRI | Increased cortical thickness in medial orbitofrontal cortex |
| | Tognin *et al.* 2011 (50) | 52 HCs | sMRI | Decreased GM volume in anterior cingulate gyrus and decreased GM volume in medial frontal area |
| | Trost *et al.* 2013 (51) | 72 HCs | sMRI | Increased GM volumes in hippocampus, anterior middle frontal gyrus and intraparietal cortex |
| | Thirunavukkarasu *et al.* 2014 (52) | 37 HCs; 38 SZs | sMRI | Decreased GM volumes in multiple brain regions |
| | Nickl-Jockschat *et al.* 2012 (53) | 83 HCs | DTI | Decreased WM integrity in temporal lobe and increased WM integrity in widespread regions |
| | Powell *et al.* 2017 (54) | 51 HCs; 24 SZs | DTI | Altered topological properties in WM networks |
| | Mechelli *et al.* 2010 (55) | 61 HCs | Visual matching task fMRI | Increased activation in the lingual, fusiform gyrus and inferior occipital gyri |
| | Thimm *et al.* 2010 (56) | 84 HCs | Memory task fMRI | Increased activation in middle frontal gyrus and cuneus during encoding; increased activation in medial/inferior frontal gyrus and inferior parietal lobule during retrieval |
| | Markov *et al.* 2010 (57) | 57 HCs | Working memory task fMRI | Increased activation in bilateral middle frontal gyrus |
| | Thimm *et al.* 2010 (58) | 80 HCs | Attention task fMRI | Decreased activation in the superior frontal gyrus |
| | Wolf *et al.* 2011 (17) | 56 HCs | Working memory task fMRI | Increased activation in hippocampal, temporal and frontal cortex |
| *DAOA* (G72) | Hartz *et al.* 2010 (59) | 110 SZs | sMRI | Decreased frontal lobe volume |
| | Nickl-Jockschat *et al.* 2015 (60) | 47 HCs | DTI | Increased WM integrity in periinsular region and inferior parietal lobe |
| | Nickl-Jockschat *et al.* 2020 (61) | 49 HCs; 46 SZs | DTI | Decreased WM integrity in corpus callosum and corona radiata |
| | Goldberg *et al.* 2006 (62) | 14 HCs | Episodic memory task fMRI | Increased activation in the hippocampus |

**Table 1** (*continued*)

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| Candidate gene | Reference | Sample | Research method | Main findings of effects of each genetic variant |
|---|---|---|---|---|
| | Hall *et al.* 2008 (63) | 61 HCs | Verbal task fMRI | Decreased activation in hippocampus and parahippocampus |
| | Jansen *et al.* 2009 (64) | 83 HCs | Working memory task fMRI | Decreased activation in the parahippocampal gyrus |
| | Krug *et al.* 2011 (65) | 96 HCs | Verbal task fMRI | Increased activation in middle temporal gyrus and precuneus |
| | Nixon *et al.* 2011 (66) | 82 HCs | Working memory task fMRI | Different effects on prefrontal activation in subjects with different genotypes of COMT |
| | Prata *et al.* 2012 (67) | 40 HCs | Verbal task fMRI | Increased FC of left postcentral and supramarginal gyri with retrosplenial cingulate gyrus |
| | Andrea *et al.* 2012 (68) | 40 SZs | Verbal task fMRI | Increased activation in precuneus |
| | Pauli *et al.* 2013 (69) | 80 HCs | Verbal task fMRI | Increased activation in wide regions including precentral, cingulate, supramarginal gyrus and hippocampus |
| *AKT1* | Tan *et al.* 2008 (70) | 171 HCs | sMRI and working memory task fMRI | Decreased GM volumes in prefrontal and caudate cortex; increased prefrontal activation |
| | Pietiläinen *et al.* 2009 (71) | Two sample consisting of 298 twins | sMRI | Decreased GM density in medial and dorsolateral prefrontal cortex |
| | Tan *et al.* 2012 (72) | 171/96 HCs for sMRI/fMRI | sMRI and memory task MRI | Decreased GM volumes in medial temporal lobe regions; increased activation in hippocampal area |
| | Ohi *et al.* 2013 (73) | 189 HCs; 117 SZs | sMRI | Decreased GM volumes in multiple regions related to attention processes |
| | Blasi *et al.* 2011 (74) | 190 HCs; 66 SZs | Attention task fMRI | Decreased anterior cingulate activity |
| *NTRK3* (TRKC) | Braskie *et al.* 2013 (75) | 392 healthy twins | DTI | Widespread WM integrity can be predicted by a 5-SNP model of NTRK3 |
| | Otnæss *et al.* 2009 (76) | 36 HCs | Encoding task fMRI | Decreased hippocampal activation |
| *ERBB4* | Addington *et al.* 2007 (77) | 165 HCs | sMRI | Increased total GM and WM volumes in childhood, and a steeper rate of subsequent decline in adolescence |
| | Konrad *et al.* 2009 (78) | 59 HCs | DTI | Decreased WM integrity in the temporal lobe including frontotemporal fiber tracts |
| | Zuliani *et al.* 2011 (79) | 36 HCs | DTI | Decreased WM integrity in the anterior limb of internal capsule |
| | Nicodemus *et al.* 2010 (80) | 172 HCs | Working memory task fMRI | Inefficient processing in the dorsolateral prefrontal cortex |

BD, bipolar disorder patient; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; FC, functional connectivity; fMRI, functional magnetic resonance imaging; HC, healthy subject; GM, gray matter; PFC, prefrontal cortex; sMRI, structural magnetic resonance imaging; SZ, schizophrenia patient; WM, white matter.

background, and the interaction with other disparate relevant genetic variants impacting the original modification of the candidate genes, it is plausible that these studies made such different discoveries.

In terms of functional neuroimaging findings using fMRI, most studies supported that *ZNF804A* risk alleles might bring about adverse effect on the hippocampal-prefrontal cortex functional coupling. The most reproducible result is that *ZNF804A* (rs1344706) contributes to decreased functional coupling between the right dorsolateral prefrontal cortex and the contralateral hippocampal formation both at resting state (44,45,87) and during working memory tasks (41,43,45). Taken together, these findings may highlight the neural impact of the ZNF804A rs1344706 on hippocampal-prefrontal functional connectivity associated with schizophrenia (44). *ZNF804A* risk carriers also exhibited other brain dysfunctions such as higher neural activity in the medial prefrontal cortex and left temporo-parietal cortex than non-risk allele subjects in a dose-dependent way, and also in the left inferior parietal cortex and left inferior frontal cortex during theory of mind task (38).

### *DTNBP1*

*DTNBP1*, also known as dysbindin-1 or dystrobrevin binding protein 1, is now a widely-accepted susceptibility gene of schizophrenia. Many researches have revealed the relationship between *DTNBP1* abnormalities and the incidence of schizophrenia (88) and have indicated its role in the onset of schizophrenia through altering brain development and neurotransmission activity (89). The imaging-genetic change of *DTNBP1* was manifested both in animal and human brains. In dysbindin-1 knockout mice, structural volume deficits were found in the cortical regions, subiculum, dentate gyrus, and striatum, as well as functional differences in dopaminerich brain regions and hippocampus formation (90). In humans, regional structural and functional alterations are equally present under risk variance. Risk allele of the *DTNBP* rs1011313 showed a trend towards reduced grey matter volumes of right parahippocampal gyrus (52) and hippocampal volume (91). However, no association was reported between rs1011313 and lateral ventricular and left or right hippocampal volumes (47). Dysbindin C–A–T haplotype, which is derived from SNPs rs2619539, rs3213207, rs2619538, is known to be associated with an increased risk for schizophrenia (48), as well as neurocognitive impairments in spatial working memory (92) and visual processing (93) in schizophrenia patients. The later neuroimaging studies reported impacts of Dysbindin C–A–T haplotype on brain anatomy: while Donohoe *et al.* (48) reported reduced grey matter volume in left occipital and right dorsolateral prefrontal cortex of the risk-haplotype group in schizophrenia patients, according to Cerasa *et al.* (49), the risk-haplotype group showed higher cortical thickness on medial orbitofrontal cortex than non-risk haplotype individuals among healthy subjects. This inverse association could be explained by the interaction between genotype and diagnosis, though no research was reported to further confirm their correlation. As for SNPs rs101838, the result is more complicated. Risk T variant of rs101838 was found to be associated with reduced FA values in the right perihippocampal region yet elevated FA values in the left prefrontal white matter, left callosal body, the right fornix, the left cerebellum, the right midbrain area, and in proximity of the right superior medial gyrus on healthy subjects (53). Apart from that, the risk allele was also discovered to be significantly linked with higher grey matter volumes bilaterally in frontal cortices and in the basal right thalamus/pulvinar and the left lingual gyrus (51). No evidence of association between *DTNBP* rs1018381 and lateral ventricular or *DTNBP* rs1018381 and hippocampal volumes were found (47). According to Narr *et al.*, the risk variant of *DTNBP1* rs1018381 was also associated with regional thinning in cortices of schizophrenia patients, especially in temporal cortices. While in healthy controls the thickness was found increased in the same areas, exhibiting genotype by diagnosis interactions over broad areas of cortex (46). In another SNPs, rs2619522, the risk alleles showed significant linkage with grey matter volumes increase in prefrontal and parietal cortices and left hippocampus (51).

As for functional modification, stronger activation was seen in *DTNBP1* rs1018381 risk allele carriers when compared with homozygous non-carriers in the healthy population, although no differences were observed in behavioral performance. In a semantic verbal fluency task, stronger activation was observed on the anterior cingulate gyrus and the superior and middle temporal gyrus of the right hemisphere in rs1018381 risk variant carriers (94). In another study under an episodic memory task condition, the rs1018381 risk-allele carriers exhibited elevated neural activity bilaterally in the cuneus and in the left middle frontal gyrus during encoding of the faces, while in the time of the retrieval increased inferior parietal lobule, inferior frontal gyrus, and medial frontal gyrus activation was

 

observed (56). Likewise, risk-allele carriers of rs1018381 also showed significant increase in bilateral middle frontal gyrus activation during the working memory test (57). These results were consistent with previous studies in which changed neural activity did not translate into performance differences under other genetic influence (95,96). Although higher activation is theoretically linked with better task performance, under morbid conditions higher activation of schizophrenia-related regions could represent a greater effort to reach the same behavioral performance as non-carriers, compensating for the genetically compromised deficits. Minor alterations in neurochemical pathways arising from most functional polymorphisms require impact on neural activity in substantial regions within the task-related neural network before they can ultimately bring about significant changes in behavioral performance. These reasons may partly explain that there were no behavioral performance differences observed in above studies. Nevertheless, in several other studies, the risk allele impacts not only in neural activity, but also behavior as well, in which neural inactivation was generally observed during functional tests. Thimm *et al.* (58) found that risk allele carriers of rs1018381 showed impaired performance in the executive control of attention among healthy individuals, whereas decreased neural activity in the left superior frontal gyrus was observed when compared with the non-risk group. In another study, SNP rs1047631, whose G-allele is associated with increased mRNA expression, enhanced regional activation for all emotional conditions in G-allele heterozygotes compared to homozygous A-allele carriers during emotion-specific working memory task, and it significantly affected working memory for happy faces at the behavioral level (17).

As for population of younger generation, there are currently two studies focusing on SNP rs2619538. Each of these studies recruited healthy children, and those who are homozygous for high-risk allele or carriers of risk variant are compared with those homozygous for the low-risk allele. The first study showed high-risk allele carriers associated with reduced grey matter volume in the left anterior cingulate gyrus and reduced white matter volume in the left medial frontal area (50). On the other hand, the second one, which was concerned with altered occipital cortical function during a visual matching task, the risk group exhibited greater activation in the lingual, fusiform gyrus and inferior occipital gyri than non-carriers (55). Both of the studies indicated that effects of the genetic variant in *DTNBP1* are already noticeable in children as young as ten to twelve years old, which are in accordance with the concept that the *DTNBP1* genotype impacts the development of brain, and hence may modulate its vulnerability to schizophrenia.

### *DAOA (G72)*

D-amino acid oxidase activator (*DAOA*), also named as *G72*, can regulate glutamatergic signaling through the N-methyl-D-aspartate receptor pathway, and it is shown to significantly correlate with schizophrenia (97,98). Rs746187 and rs1421292 are the two common SNPs in *DAOA*, which were both found to be associated with greater regional activation in a risk allele-load fashion during verbal fluency task in the healthy population. For rs1421292 greater activation was seen in the right middle temporal gyrus and precuneus (65), while in the case of rs746187, greater activation was found in the areas of precentral, cingulate, postcentral and supramarginal gyrus and hippocampus (67,69). The effect of rs746187 could be further strengthened by its interaction with *DAT*. Additionally, the rs746187 risk allele also showed greater task-dependent functional connectivity of left postcentral and supramarginal gyri with the retrosplenial cingulate gyrus (67). Apart from the healthy population, the same inefficient functional activity was also seen in schizophrenia patients, in which the rs746187 risk allele was related to greater activation in the left precuneus during verbal fluency task (68).

In the case of fMRI findings during other tasks such as verbal working memory tasks, in contrast, *DAOA* risk variations were found to positively impact the activation of the hippocampus and parahippocampus in healthy individuals. Hall *et al.* (63) reported significant decrease in hippocampus and parahippocampus activity in both rs3918342 and rs1421292 risk-allele carriers who were also at high familial risk for schizophrenia in an allele-dependent fashion. Goldberg *et al.* (62) found that rs1421292 was associated with altered hippocampal and parahippocampal activation in healthy subjects during episodic memory, with risk allele homozygotes showing decreased activation. No difference in behavioral performance was seen in both the two studies above. Jansen *et al.* (64) found the similar results that risk alleles of the rs3918342 and rs1421292 SNPs were linked to weaker activation and better performance in the right parahippocampal gyrus of healthy people.

Using DTI, it has been showed that variation of DAOA rs2391191 is associated with lower FA, which indicates impaired white matter integrity, in the corpus callosum in first-episode schizophrenia patients (61). However, higher

 

FA values were seen in homozygous risk allele carriers of the rs3918342 and rs1421292 in the right inferior parietal lobe as well as right periinsular region when compared with homozygous wild-type carriers among healthy people (60). These results, though surprising, were in line with a variety of previous studies that risk genetic variation could confer some advantage in the healthy population (53,99). It deserves to be mentioned that genetic variation is of great commonplace among general population, and it only shows low odds ratios in a certain psychiatric disease. Thus, such variation may not necessarily bring about ipsidirectional changes in healthy individuals. Moreover, given that the complex interplay between gene and gene, gene and environmental factors, and so on, its effects on brain structure and function might reasonably lead to favorable alterations (60).

For sMRI, it is worth noting that a significant longitudinal effect of DAOA on volume loss could be seen in haplotype rs3696165A-rs3696167G-rs2391191A-rs77829G homozygotes, which lies in overall frontal lobe, not tissue specific (59). Also, we cannot lose sight of the potential effect of epistasis, where higher activation was found in rs1421292 TT during working memory test in the right dorsolateral prefrontal cortex under COMT Val/Val genetic background, while for COMT Met-carriers rs1421292 TT individuals exhibited lower activation in the same region (66). The epistasis and longitudinal effects are two major concerns when conducting imaging genetic research, but are less considered in current studies. In the latter part of this article, these two concerns will be further elaborated upon.

### *AKT1*

*AKT1* is a serine/threonine kinase involved in numerous signaling cascades concerned with neuron plasticity, growth and differentiation, and implicated in neurodevelopment affecting neuronal morphology and development (100). Thus, *AKT1* was confirmed as a candidate gene for schizophrenia in replications (70,101,102). A previous study revealed that the risk allele of *AKT1* rs1130214 was linked to less gray matter density in the bilateral dorsal prefrontal and medial cortex, as well as in inferior prefrontal cortex in the left hemisphere; moreover, the reduction was more significant in schizophrenia patients, with more affected area in frontal lobe region (71). It was also reported that *AKT1* rs1130233 risk allele resulted in decreased gray matter volumes in the right prefrontal and bilateral caudate cortex, as well as increased prefrontal activation, suggesting increased magnitude of response in the context of working memory task performance (70). The research group then examined the effect of this same SNP during episodic memory tasks in healthy individuals and found risk allele carriers exhibited relatively increased activation on the hippocampal area as well as reduced gray-matter volumes in bilateral medial temporal lobe regions (72). Furthermore, it is worth mentioning that the effect of *AKT1* could be accentuated by interactions of *COMT* or *BDNF* in both studies, which indicated the significance of epistatic effect in genetic variants.

*AKT1* was also shown to be related with attentional control by task-based fMRI or sMRI. The relationship between anterior cingulate activation and increasing load of attentional control, as shown in previous study, is linear, increasing from lower to higher loads (103). However, in healthy *DRD2* rs1076560 *GT/AKT1* rs1130233 A carriers, anterior cingulate activity went down from the intermediate to the higher level of attentional control (74), similar to what was discovered in schizophrenia patients whose cingulate responses were reduced at high attentional control load (104). Additionally, when comparing *DRD2* GT/*AKT1* A carriers with other subjects, intergroup activity differences in cingulate were also distinct at the higher level of attentional load (74). In another case, *AKT1* rs2494732 was also found to correlate with regional volume changes in the anterior cingulate gyrus, the thalamus, and the right inferior parietal lobule, all of which are related to attention processes; in particular, rs2494732 exhibited genotype-diagnosis interaction, in which smaller gray matter volumes were found in patients with risk allele while, in control groups, it was the opposite (73).

### *NTRK3*

*NTRK3*, also known as *TRKC*, encodes the high affinity receptor TrkC for neurotrophin 3'-nucleotidase, both of which are involved in the development of oligodendrocyte and brain myelin as well as the density of the axon and synapse, suggesting that *NTRK3* is a good candidate for schizophrenia (105). Otnaess *et al.* (76) found that the right hippocampus of healthy rs999905 homozygous risk G allele individuals were significantly activated to a greater degree than C allele carriers during encoding of neutral and aversive pictures; in the case of rs4887348 and the rs999905-rs4887348 haplotype combination, similar findings were found, in which the risk genotype

 

exhibited greater hippocampal activation. Nevertheless, the volume of the hippocampus was not correlated to *NTRK3* variants, indicating that the relation between genotype and function might be independent of hippocampal size (76). Braskie *et al.* (75) examined 18 *NTRK3* single-nucleotide polymorphism in 392 pairs of healthy adult twins and their siblings. It was found that the combined effect of *NTRK3* rs1017412, rs2114252, rs16941261, rs3784406, rs7176429 were significantly linked to the mean value of fractional anisotropy across the entire white matter mask, where corticospinal tract, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulum, anterior thalamic radiation, and forceps major and minor exhibited the strongest local effects, suggesting this five-SNP model could be a desirable indicator to predict the integrity of white matter across widespread brain regions. However, when it comes to any single SNPs, neither one of these SNPs had significant link to white matter connectivity, highlighting the importance to study the combined effect of multiple variants in imaging genetics of schizophrenia.

### *ERBB4*

Serving as the receptor for NRG1 protein, *ERBB4* is crucial in neural development, involved in myelination of neuroglia, signal transmission, and response to stimulation (106), and is supposed to strongly correlate with schizophrenia. The post-mortem of brain tissue in schizophrenia patients had also demonstrated the elevation in expression of *ERRB4* (107). The risk G-allele carriers of rs4673628 was found to be significantly associated with lower FA in healthy people within both the left and right anterior limb of the internal capsule (79), whose association with schizophrenia has already been shown in several studies (108,109), with subjects bearing the risk allele showing reduced FA. It was also reported that in healthy individuals, people homozygous for rs839523 risk allele showed lower FA in the temporal lobe white matter, including frontotemporal fiber tracts which were present in white matter abnormalities in schizophrenia as well (110), while no significant regional brain volume differences were demonstrated in brain areas (78). When it came to regional activation however, patients with *NGR1* rs10503929 risk allele showed no significant dorsolateral prefrontal cortex inefficiency when compared with non-carriers. Nevertheless, the combined interaction with *ERBB4* rs1026882 risk alleles could exhibit deficient efficiency in dorsolateral prefrontal cortex, and the effects could be further magnified with the interaction by *AKT1* risk alleles (80).

*ERBB4* variation also presents longitudinal impact on children. In a recent study, regions, including those altered in schizophrenia patients, present an inverted-U shape across the children's growth in both their area and volume, exhibiting the pruning of the gray matter structures as the brain matures after around age 10 (111). The researchers found that subjects of *ERBB4*-rs7598440 risk genotype have subclinical cortical changes in these schizophrenia-related regions, where TT-risk genotype showed a more pronounced age-related growth and steeper decline (77). Moreover, combined with family history, the homozygous risk T children with no family history had subtle cortical changes across the age span, primarily in the superior parietal cortex and left temporal lobe, as compared to the non-risk individuals Furthermore, homozygous risk T children with family history had more pronounced age-related changes compared to the non-risk genotype subjects, mainly located in the frontal lobes (111).

### *Other susceptibility genes*

*GAD* encodes glutamate decarboxylase, the key enzyme in GABA synthesis which plays a critical role in GABAergic system and regulates the migration of neuron in the cortex. For these reasons, it is considered to be a candidate gene for schizophrenia. *GAD1* variations were found to be associated with increased rate of frontal gray matter loss in children and adolescents with childhood-onset schizophrenia (112). In a working memory task-based fMRI study, risk allele of SNP rs7557793 was found linked to abnormal greater activation in prefrontal area, exhibiting inefficient activation of right dorsal prefrontal cortex in normal subjects; this was also known as a physiologic phenotype associated with schizophrenia in unrelated healthy individuals (113). In another research of SNP rs3749034, cortical gray matter thickness reduction was found in risk G-allele homozygotes in an area corresponding to the left parahippocampal gyrus, where the average thickness reduction in this cluster region of G-allele homozygotes was 7.54% as against A carriers, suggesting the impact of *GAD1* on pathogenesis of schizophrenia (114).

*GRM3*, which regulates glutamate neurotransmission and synaptic plasticity, was found to be linked to schizophrenia-related intermediate phenotypes such as abnormal cortical activation and impaired cognition (115), and it was confirmed to be linked to schizophrenia in a recent large-scale genome-wide association study (116). Significant

 

correlation was found between *GRM3* rs7808623 and FA values in a component containing tracts from the cortico-cerebellar-thalamic-cortical circuit of patients but not in controls (117). Excluding that, it was reported that during verbal fluency task the prefrontal hemodynamic response was linked to *GRM3* rs274622, especially in schizophrenia subjects of whom C-allele carriers were found to be associated with significantly smaller prefrontal activation than homozygous T allele patients (118).

*CHRM* encodes cholinergic muscarinic receptors, and it is implicated in the pathophysiology of schizophrenia (119). In a recent report comparing the first-episode treatment-naive patients with healthy controls, *CHRM3* was found to play a role in abnormal thalamo-orbital frontal cortex functional connectivity in these schizophrenia patients (120). Moreover, another report indicated that individuals who were C-allele homozygotes at rs2067477 had reduced gray matter volume in the right precentral gyrus compared to those A-allele carriers among schizophrenia or schizoaffective disorder patients (121).

*NRG3*, or neuregulin 3, is critical to embryonic cerebral cortex development through the regulation of proliferation, differentiation, and migration of neural progenitor cell (122), and it is generally considered as a susceptibility locus for schizophrenia. *NRG3* was also revealed to exhibit a genotype by group interaction during working memory, in which rs10748842 risk allele homozygotes were observed to link to greater activation on right ventrolateral prefrontal cortex in schizophrenia patients while this allele association found to be reversed in healthy individuals (123).

Omitting these susceptibility genes mentioned above, there are still some other relevant genes under intensive study right now which may impact the imaging phenotype of individuals, though their exact effects on schizophrenia and underlying neural mechanisms need further investigation. *NOS1* encodes nitric oxide synthase, which can catalyze the biochemical reaction that generates nitric oxide. Because of the vasodilation effect of nitric oxide, any variation affecting *NOS1* expression will be very likely to influence the regulatory mechanism of blood flow through the cortical microvasculature, ultimately impacting the degree of regional brain activation. This hypothesis is consistent with hypofunction found in prefrontal cortex and superior parietal lobe in *NOS1* rs6490121 risk carriers, whose inefficiency may contribute to cognitive dysfunction in schizophrenia (124). Apart from that, *DLG1*, *THBS4*, and *FADS1* are considered as the potential susceptibility genes for schizophrenia as well. It has been pointed out in a systematic literature research that chances are good that *DLG1*, *THBS4*, *FADS1*, and *NOS1* are closely related to schizophrenia, which may bring about a deconstruction of neural connectivity, leading to the morbid brain modification (125). Further investigation is required to confirm the correlation of these potential genes as well as their impact on imaging phenotype of schizophrenia.

## Prospects and challenges

As mentioned above, imaging genetics is one of the most exciting and cutting-edge methods to study schizophrenia. Neuroimaging has the higher level of penetrance in common genetic variants, and the effect size of genetic variation is magnified at the level of brain structure and function. Hence imaging genetics is enabled to use a considerably smaller number of subjects than clinical phenotypes, helping us better understand the role of genetic polymorphisms on schizophrenia. However, a deep insight into this field necessitates further investigations and more challenges to be settled. Here, prospects and challenges for imaging genetics in schizophrenia will be discussed.

### *Sample size*

Although some genetic variants such as COMT have been suggested to be of greater sensitivity (19), some other variations may have smaller effect size and larger sample sizes are needed to detect the effects (126). Sample size is thus a significant problem for many contemporary imaging genetic studies. Expanding the scale and scope of existing studies can provide deeper insight into imaging genetics of schizophrenia, since current researches lack the sophistication and power to model complicated interactions while effectively controlling for other important modulatory factors (127). However, acquiring large number of subjects is a huge task with great expense and long duration. Fortunately, the emergence of large collaborative projects brings us new hope. Several large-scale collaborative consortiums have been established to overcome the problem of sample size as well as enrich the database, including the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium (128), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (129), and the IMAGEN study (130). The large sample size achieved through international collaboration and new methods will likely overcome the difficulty in detecting a true signal of a small

 

effect size and help to elucidate the complicated interplay especially within genetic variants and with environmental factors. In addition, the collection of large datasets now means that quantitative trait locus based approaches are now possible, where genome-wide association with DTI-based phenotypes can be examined (131). However, the challenges of privacy arise as more data becomes available, in which sociological, ethical, and legal aspects of cases will possibly preclude or prohibit such open sharing. Since images and sequence data are considerably high-dimensional and highly identifiable, it must be sure that data sharing structure, data privacy-preserving, and data mining technologies meet the necessary privacy requirements. Politically, appropriate data sharing standards and practices must be established within and across research consortia. Technologically, federated data sharing systems with greater security, additional fault-tolerance, and more sophisticated role management must be constructed. Statistically, techniques must be advanced, extending from meta-analyses to the interpretation of statistics computed from data sampled under heterogenous protocols (132). Only in this way will researchers be able to more effectively collaborate and learn from larger populations in the future.

### *Statistical, methodological and technical advancements*

Excluding large sample size, data analysis and processing need to keep abreast as well. Examining each of these data points in a hypothesis-free manner will result in an extraordinary number of tests, which requires exorbitant corrections in multiple tests, and result in millions of hypotheses, excessive computation costs and an inordinate amount of data to analyze. Luckily, with the development of statistical innovation, new methods and technologies for data reduction with appropriate statistical thresholds can facilitate the work, such as polygenic analysis, parallel ICA performed in the Jamadar studies, and new analytical methods to collapse and/or integrate a variety of data types into relevant risk models as well as a random field theory (12,133). For instance, Chen *et al.* (134) proved that pICA-R could possibly be a multivariate approach of great promise for application in imaging genomics to find reliable genetic risk factors under a scenario of relatively small effect size and high dimensionality. Hu *et al.* (135) demonstrated that Sparse Multi-Canonical Correlation Analysis could be a powerful tool for combining genetic, epigenetic and neuroimaging datasets to explore different level of biomarkers for the correlation and interaction between these diverse factors.

As for methodology and technology, the promise of imaging-genetics research will also benefit from key advances in both aspects. The methodological advancement refers to the integration of a multimodal approach, which will be able to enhance its efforts to elucidate the relationships between genes and altered neural phenotype, such as the combined connectivity assessment by magnetoencephalography and fMRI, multimodal network-based statistic, and novel dynamic fMRI analyses (136-138). Furthermore, modern imaging genetics should go beyond modalities of just genetic variants and imaging, integrating other variables tightly connected with imaging genetics. Also, we need to figure out an appropriate way to integrate these data systematically with embedded biological hierarchy, and incorporate multiple levels of biological variables into broader imaging genetics (139). In technological advancement, acceleration in techniques will not only allow for the detection of metabolites and neurotransmitters of neural system *in vivo* (e.g., NMR, SPECT, and $H^1$MRS), but also functionally facilitate the chances to understand the role of a risk locus at even more microscopic level, i.e., a molecular level. These innovations will be very likely to transform the current recognition of neural phenotype, extending to a more microscopic and detailed level, potentially with higher penetrance, and thus provide better chance to understand the imaging genetics of schizophrenia.

### *Longitudinal observation*

The need to carry on large-scale prospective studies starting from childhood is another important consideration. Most existing studies available are cross-sectional and have focused on adults, but lack of longitudinal observations, especially on children or adolescents, since almost all psychopathologies which come out in adulthood have their signs of warning in childhood (140). Longitudinal observations will help to consider time-dependent effect of genetic variants. Also, consideration of developmental trajectories is useful to determine any developmental shifts in neuroimaging and neurogenetic pathways, which may contribute to predictive utility in identifying schizophrenia risks as a function of various stressors (134). Thus, researchers can appropriately utilize imaging-genetics to work out issues relevant to disease risk in childhood and adolescence, as well as disease heterogeneity in adulthood (131). Generally, the appearance of neural

 

aberrations was prior to the onset of schizophrenia in children. Although not all the children will finally develop into schizophrenia, if we can detect these abnormal neural changes prior to the development of schizophrenia through longitudinal neuroimaging observation, and combined with genetic identification, we may hopefully have the early chance to predict as well as stratify kids at high risk through imaging genetic biomarkers of risk patterns. Also, clinical outcomes are very likely to be optimized if we can normalize brain development during the period when the brains are still highly plastic. Furthermore, continued imaging genetic research at the interface of genes and brain holds great promise for further explicating the neurobiological mechanisms behind schizophrenia, like how the risk of schizophrenia emerges in the context of environmental adversity (141), which in turn, may facilitate the development of therapeutic interventions tailored to individual neurobiologies. Another necessity to conduct studies from childhood is that endogenous shifts, say hormone fluctuations during puberty, can influence gene expression, and the development of cortices will generally keep on until adulthood (140). Consequently, what we found from present imaging genetic studies on adult populations is likely inapplicable to those of younger populations. As a result, it is necessary to examine the associations between genetic polymorphisms and alterations in brain function and morphology across development.

### *Copy number variants (CNVs)*

Copy number variants (CNVs) are defined as the gain or loss of a segment of DNA greater than one kilobase. So far, very few studies focused on the effect of copy number variation on brain-based phenotypes, even though a relationship between CNVs with schizophrenia has been identified in many studies (142). Convergent evidence has shown that such CNVs are of more commonplace among schizophrenia patients than in general population. Compared with frequent genetic variants, such as SNPs, the disease risk of some CNVs is much higher, which can correspond to several times increase (21,142). Meyer-Lindenberg (143) indicated that the importance of the sizeable amount of variation in CNVs will be recognized by the future imaging genetics. However, despite the promise of CNVs, given that the low incidence of individual CNVs, it is still of great difficulty to conduct relevant research on imaging genetic aspect. Up until now, a few explorations have been made. Global CNVs burden was found to exert no major effects on brain volume neither in schizophrenia subjects nor in healthy individuals (144), but regional CNVs at 22q13.31 were discovered to be associated with decreased gray matter concentration in the peri-limbic cortex (145). Although multi-site collaboration can be a potential source of data, it is necessary to work out policies to control for different equipment or experiments, as well as different local populations or environments. Also, these data should meet computational feasibility and mathematical validity (139). Additionally, how to effectively dwindle the expense of the project with such great sample size is another problem needed to be addressed. Future advancements should strive to a sophisticated condition before we can better understand its function in imaging genetics of schizophrenia.

### *Confronting complexity: epistasis and G×E*

Complexity of epistasis and gene-by-environment interactions is another challenge future imaging genetic studies have to confront (143). Epistasis can be understood as the genetic effect modified by gene-gene interaction, but it is non-additive. Although genetic studies have linked many genetic variants with schizophrenia, each variant is only associated with a small effect (116,146). Therefore, epistasis is assumed as a plausible account for the missing heritability found in multiple common complex traits in biological sense. For example, *DAOA* and *COMT* risk genes were found to exert multiplicative influence on dorsolateral prefrontal cortex, where significant activation might be explained by the interplay between genes (80). Hibar *et al.* (147) found that significant interaction terms of SNP-SNP pairs explained additional 1.9% variance in brain volume than the total amount of variance brought about by the additive SNP terms; allowing for the fact that quite a few SNPs explain less than 2% of the variance of complicated phenotype respectively, an extra 1.9% of the variance was significant and would be omitted if only considered main effects in models. Furthermore, the original genetic effect on brain-based phenotypes could also be greatly altered, even reversed, by other genetic variants, such as *ZNF804A* as we previously discussed (29), which was found to exert disparate impact on the brain phenotype under different COMT genotype. The interactions between genes and their combined interactive effects, though generally not considered in the past, has gradually receive more attention in current imaging genetic studies. However, the attempts to search SNP-SNP interactions on genome wide are rarely made due to the complexity of statistical

 

tests (147). Another study indicated the application of SNP-set methods to conduct genome wide association study, in which multiple SNPs with mild marginal effects, epistatic effects, nonlinear SNP-effects that can be easily missed by single SNP methods could be identified through this approach (148). Future studies focused on this uncharted territory will definitely further our understanding of the interactions within genome.

The significance of gene-environment interaction in schizophrenia has been indicated in many of human and animal model studies as well; environmental exposure such as maternal infection during pregnancy, prenatal maternal nutritional deficiency, obstetrical complications, urbanicity and season of birth have already been demonstrated and associated in schizophrenia (149). Future imaging genetic studies will have to take environmental factors into account, since the exposure to one or more of these factors interacting with determinate genetic background can impact the expression of hereditary factors, modulating neuronal migration, myelination and neurotransmission, all of which affect brain maturation and neuroendocrine responses and alter phenotype on brain circuitry, morphology, and function (116,150). Also, different genotypes have disparate sensitivity to certain environmental factor. For example, Met homozygotes in *COMT* Val158Met were more liable to reduced efficiency in processing reward outcome under high levels of childhood adversity exposure as against Val carriers (151). Likewise, significant genotype-by-cannabis use interaction effects could be observed in the context of specific *CNR1* genotype, in which heavy cannabis use contributed to conferring white matter abnormalities (152). Neuroimaging is believed to be the best approach to study gene-environment interaction, because it may provide "unbiased evidence for differential sensitivity to environmental exposures" (153). Illness phenotypes under investigation is likely to influence assessment of the environmental exposure, bringing about risk of bias. Therefore, replacing the outcome under investigation by neuroimaging, could serve as an alternative to reduce the bias. Furthermore, neuroimaging can also help us to understand the genetic effect with environment in a sensitive way, and further contribute to the understanding of underlying mechanism. Fathoming these interactions in a deeper sense will help us effectively prevent high-risk population from detrimental factors, circumventing the potential harms from adverse circumstances. Even though high-risk individuals have been exposed to the unfavorable factors, these theories will potentially help to reduce or even eliminate the adverse impact on the mental system. In the future, researchers should also recognize the importance of parallel human and animal research in imaging genetic-environmental study. On one hand, animal experiments can provide promising molecular biological targets for human neuroimaging gene-environment studies, such that researchers can concentrate on genes of interest and neuroimaging manifestation of the correlative brain circuits in human brains. On the other hand, experimental animals will provide an effective and practical system to impose different environmental factors on relatively genetically homologous entities which could not be realized in human beings. Besides, animal models can help to uncover the underlying molecular mechanisms of these neuroimaging gene-environment observations in human researches (154). These dynamic exchanges across human researches and animal models may hopefully bring more comprehensive and insightful information on neuroimaging gene-environment interactions, and they may elucidate the potential biological mechanisms underlying its etiology and pathophysiology of psychopathology. Finally, it needs to be emphasized that most published gene-environment researches have been focused on risk factors so far, relatively neglecting the importance as well as the contribution of protective factors. Thus identification of environment enrichment ameliorating or even rescuing genetically produced abnormalities could be a new emerging field of research waiting to be uncovered in the future (149).

### *Clinical translation*

At this stage, because of the relatively low consistency of results, the main aim of imaging genetics in schizophrenia is still help understanding the neural function of genetic loci, and far from serving as a diagnostic or screening tool in clinical practice (155). Nevertheless, the potentials of clinical translation of imaging genetics in schizophrenia have been explored. For example, recent findings have suggested that imaging-genetic data from carefully characterized patient samples could be used to aid in prognosis (156). In addition, with the advent of big data, the chances are extremely good that these imaging genetic information will be a steady flow of data put into practice. Particularly, the use of machine learning will fulfill data-driven automatic feature learning and enable us to model highly complex data patterns (157). However, it is still premature to integrate machine learning into clinical healthcare. On the one hand, it is hard to guarantee the quality of all data to prevent bias (158); on

 

the other hand, algorithms are likely to overfit predictions to spurious correlations in the data, or multiple collinear, correlated predictors might generate unstable estimates. Thus, models must be tested on truly independent validation data sets, from different periods or populations that played no part in the development of model (159).

As for treatment innovation, it is critical to move towards greater customization. Future imaging genetic studies have to get through the development of frameworks in schizophrenia for determining when and for whom certain treatments will work. Longitudinal imaging genetic observation could help to identify the time-dependent effect of genetic variants and the developmental aberrations of different stages, instructing the appropriate timing of different interventions. Identifying more homogenous subgroups of individuals within the same genetic and neuroimaging phenotype and environmental exposure, and targeting specifically at these special population, are essential to individualized therapy (160). In addition, therapeutic responses could be evaluated by early changes in circuit structure or function and brain morphology by neuroimaging, which provide possible access to evaluate the curative effect of certain medical intervention.

### *Single genetic markers to polygenic risk score*

While most work we discussed so far is mainly concentrated on the single genetic effect of certain genes, a worth-noticing approach to assess genetic risks for schizophrenia to compute a "polygenic risk score (PRS)" for each individual, which has been used in this field for a number of years (161,162). By this way, each individual can be simply proxied by a single schizophrenia PRS index, facilitating the evaluation of neurobiological phenotypes related to genetic variations at individual levels (163). Combining PRS and neuroimaging, potential relationships between the variations in schizophrenia PRS and individual differences in brain functions/structures have been recently highlighted (163,164). However, further studies are warranted since studies on such relationships are still limited and contradictory (165).

## Conclusion

In summary, combining genetic and neuroimaging techniques, the imaging genetics is currently a desirable approach to investigate schizophrenia. The current investigations have made some progress on relationships between brain abnormalities and common genetic variants for schizophrenia, facilitating our understanding of schizophrenia and helping us with early diagnosis, prognosis prediction and medication. However, there are still challenges like inadequate database, complexity of epistasis and gene-by-environment interactions, as well as methodological, statistical and technological incapacity that are not fully addressed. Future progress may further facilitate our insight into this psychiatric disease and improve our current schizophrenia healthcare mode.

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