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REVIEW ARTICLE

Using big data of genetics, health claims, and brain imaging to challenge the categorical classification in mental illness

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Abstract: Psychiatric disorders in first-degree relatives (FDRs) often differ from the index patient's diagnosis, suggesting that there is genetic contribution to psychiatric disorders in which related cases do not all map to the same diagnosis as the index case. Our aim is to look for psychiatric comorbidities across major mental illnesses using three approaches, genetics, clinical diagnosis, and brain imaging to address common associations and pathology among mental illnesses. Genome-wide association studies from the Psychiatric Genomics Consortium showed single gene polymorphisms are common across 5 major psychiatric disorders, including schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD). Clinically, results of Taiwan's nationwide population studies showed that other major psychiatric disorders were more likely to coaggregate in families with an index case of an individual with a psychiatric disorder, compared to control families. Finally, resting functional connectivity (FC) magnetic resonance imaging (MRI) and whole-brain connectomic analysis of SZ, BD I, BD II, MDD, and healthy controls revealed that the four groups of patients shared similar patterns of abnormal neural substrate in the brain that differed from controls. In conclusion, using big data from genetics, administrative health claims, and brain imaging, we identified concordance, indicating dimensional coherence of genetic heritability, clinical mutual associations, and common neurobiological substrates across major psychiatric disorders. These results will challenge the current diagnostic classification system and possibly move psychiatry beyond descriptive syndromes towards a nosology informed by disease cause.

Keywords: Mental Disorders; Genetic, Heritable; Administrative Claims, Healthcare; Phenotype, Clinical; Common Neural Substrate

1. INTRODUCTION

Psychiatric disorders in first-degree relatives (FDRs) often differ from the index patient's diagnosis, suggesting that there is genetic contribution to psychiatric disorders in which related cases do not all map to the same current diagnostic categories. Clinically, there remains doubt about boundaries between syndromes and the degree to which they signify entirely distinct entities, disorders that have overlapping foundations, or different variants of one underlying disease. Although current psychiatric classification, based on International Classification of Diseases/Diagnostic and Statistical Manual of Mental Disorders categorical diagnoses, is useful, it does not wholly meet clinical needs, leading to new directions in changing psychiatric nosology and therapeutic concepts. For example, transdiagnostic approaches to mental health problems[1] and the "Neuroscience based Nomenclature" (NbN) basis of psychopharmacology[2,3] are current directions for diagnostic challenges.

Big data[4] are described by massive size; processing via filtering, reduction, transfer, and analysis; variation in form from structured (relational database) to unstructured (imaging, video, and audio); and complexity which requires novel computational approaches. This article will use the materials that meet the criteria for big data such as administrative health claims data with "large *n* (number), small *p* (parameters)," whereas brain imaging data meet the definition with "small *n* and large *p*." Big data analyses have the potential to contribute to improving clinical descriptive observation, analysis, and further hypothesis generation and prediction.

This review aims to present studies in genetics, clinical diagnosis by heritability, and brain imaging to document similar patterns and mutual associations among major psychiatric disorders. We ask if a common association and pathology among mental illness are found in these types of big data, then would current diagnosis by categorical classification and therapeutic concept be changed? We used big data from the European Psychiatric Genomics Consortium (PGC group), Taiwan's population-based administrative health claims

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dataset, and more than 500 collected brain images of the patients with major psychiatric disorders and controls.

2. MENTAL MAP AND SHARED MOLECULAR NEUROPATHOLOGY FROM GENETIC ASSOCIATIONS TO PERIPHERAL BIOMARKERS IN MAJOR PSYCHIATRIC DISORDERS

To review genetic variant studies, we searched for keywords of major psychiatric disorders, genetic relationships, and shared molecular neuropathology in major neuroscience literature. We collected four articles from *Nature*, *Science*, *Nature Genetics*, and *Lancet Psychiatry* that investigated shared genetic variants in DNA to transcriptomic specific phenotypes and summarized them as bellows.

Recent genome-wide association studies (GWAS) from the PGC cross-disorder group showed that single nucleotide polymorphism (SNP) may be common across five major psychiatric disorders, that is, schizophrenia (SZ), bipolar disorder (BD), major depressive disorder (MDD), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD).[5] They found that the genetic correlation of common SNPs was high between SZ and BD (0.68 + 0.04, SE), moderate between SZ and MDD (0.43 + 0.06, SE), BD and MDD (0.47 + 0.06, SE), and ADHD and MDD (0.32 + 0.07, SE). The lowest correlation was between SZ and autism (0.16 + 0.06, SE). Specific SNPs were associated with a range of psychiatric disorders, particularly calcium channel activity genes which have pleiotropic effects on psychopathology.[6] There were 4 GWAS significant SNPs: rs2535629, rs11191454, rs1024582, and rs2799573 that showed the same positive direction of effects in five major psychiatric disorders (95% CI, 0-0.25). For example, rs1024582 near the *CACNA1C* gene on chromosome 12 has high association with both SZ and BD, suggesting that the relationship between these two disorders is highly correlated. Other SNPs had similar findings, which suggest close associations among the five major psychiatric disorders.

Gandal et al[7] raised the question of how genetic variants interact with environmental and epigenetic factors in the brain to impart risk for clinically distinct disorders. They compared gene-expression microarray results of the cerebral cortex between 700 patients with five major psychiatric disorders and matched controls with inflammatory bowel disorder. Using brain transcriptomes to determine disease-related signatures shared across major psychiatric disorder, results showed the rank order of transcriptome by microarray for all disease pairs was highest in SZ-BD and were gradually lower in ASD-SZ, ASD-BD, SZ-MDD, and BD-MDD (all $p < 0.001$-0.05). In addition, comparison of differential gene-expression signatures revealed a significant overlap among ASD, SZ, BD, and BD and MDD (all Spearman $p \geq 0.023$, $p < 0.05$). Comparison of the regression slopes among significantly associated disease pairs between ASD, BD, and MDD with SZ separately indicated a gradient of transcriptome severity higher from ASD pairs followed by SZ and BD pairs, then lowest in SZ and MDD pairs. Furthermore, in the proteome level, Liu et al[8] had conducted proteome-wide association studies (PWAS) on four common psychiatric disorders by integrating large-scale GWASs and two independent human brain proteomes from the dorsal prefrontal cortex of Banner dataset (n = 152) and Religious Orders Study and Rush Memory and Aging Project (ROSMAP) dataset (n = 376). They identified 61 proteome-wide significant (PWS) genes whose cis-protein abundance in the human brain was associated with the risk of four common psychiatric disorders, which included 46 genes for SZ, 12 genes for BD, 5 genes for depression, and 2 genes for ADHD. They also identified 18 overlapping genes at both proteome-wide and transcriptome-wide levels showing significant associations with psychiatric disorders, strongly suggesting that genetic risk variants likely confer risk of psychiatric disorders by regulating messenger ribonucleic acid (mRNA) expression and protein abundance of these genes. These results provided new insights into the genetic component of protein abundance in psychiatric disorders and prioritizing promising targets for further mechanistic investigation and development of new therapeutics.

Recently, Marshall[9] generated a mental map using similar genetic variants that underlie several psychiatric disorders. In one study of 200 000 people,[10] SZ was significantly correlated with most of the other disorders. In contrast, some disorders such as post-traumatic stress disorder (PTSD) showed only weak correlations with other mental illnesses. The strongest association was found between SZ and BD and MDD with anxiety disorders. This implies that the way clinicians have partitioned mental disorders into categorical classification may not fit clinical care. Instead, one prominent model with a multidimensional approach[8] for individual patients with mental disorders has been proposed. Whether genetic risk for psychiatric disorders is reflected clinically was unclear. Therefore, we asked if overlap of clinical phenotypes exists in families among five major psychiatric disorders, corresponding to the genetic findings.

The search for diagnostic biomarkers has been a leading endeavor in biological psychiatry. Pinto et al[11] systematically investigate the most studied peripheral biomarkers for major psychiatric disorders by reviewing the experimental design features of articles and on the basis of available meta-analytical evidence to investigate variation in their levels across different diagnoses. Of the six molecules most commonly studied as plasmatic markers of SZ, MDD, or BD, five (brain-derived neurotrophic factor [BDNF], tumor necrosis factor [TNF]-alpha, interleukin [IL]-6, C-reactive protein, and cortisol) were generally the same across diagnoses. Meta-analyses showed variation in the levels of these molecules to be robust across studies, but variation patterns were similar among disorders, suggesting that there are real biological commonalities, which reflects transdiagnostic systemic consequences of psychiatric illness.

3. OVERLAP OF CLINICAL PHENOTYPES USING TAIWAN NATIONAL HEALTH INSURANCE RESEARCH DATABASE

Psychiatric disorders are highly heritable and have substantial psychiatric comorbidity. Previous studies in this aspect focused more on mutual associations of mood disorders. Heritability of major mental illness using genetic epidemiological studies[5–7] were reported before. Data related to family transmission of major psychiatric disorders in population-based studies were rare, particularly for all major mental disorders. Here, we review publications[12–16] related to coaggregation of major psychiatric disorders in individuals and their first-degree relatives (FDRs) from nationwide population-based studies in Taiwan. These studies demonstrated that risks in FDRs for the index disorder and other comorbid psychiatric disorders were higher than in matched controls. RR for psychiatric disorders in FDRs of individuals with each of major mental disorders are summarized in Table 1 and Fig. 1.

The Taiwan National Health Insurance (NHI) program was established in 1995, providing compulsive health insurance covering 99.6% of 23 million residents in Taiwan. The NHI Research Database (NHIRD) provides comprehensive de-identified information on demographics, which include family relationships, and claim data on outpatient and inpatient care, medical diagnoses, prescriptions, and procedures. From January 1, 2001 to December 31, 2011, individuals with the same major psychiatric diagnosis (using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) criteria for diagnosis) twice were identified as index psychiatric cases. The FDR

Table 1

Summary of relative risk of comorbidity in FDRs of patients with major psychiatric disorders

	Adjusted relative risk (95% CI)				
	SZ	BD	MDD	ASD	ADHD
FDR of SZ[12]	6.4 (6.2-6.6)	3.3 (3.2-3.4)	2.0 (2.0-2.1)	2.7 (2.4-3.0)	1.8 (1.7-1.9)
FDR of BD[13]	2.6 (2.6-2.7)	6.1 (6.0-6.3)	2.9 (2.8-3.0)	2.1 (1.9-2.3)	2.2 (2.1-2.3)
FDR of MDD[a]	0.9 (0.9-0.9)	1.9 (1.8-1.9)	2.0 (1.9-2.0)	3.9 (3.7-4.1)	6.8 (6.7-7.0)
FDR of ASD[16]	3.1 (2.7-3.4)	2.2 (2.0-2.5)	1.9 (1.8-2.0)	17.5 (15.5-19.7)	3.9 (3.7-4.2)
FDR of ADHD[17]	1.7 (1.6-1.8)	2.2 (2.1-2.3)	2.1 (2.0-2.1)	4.1 (3.9-4.4)	6.9 (6.7-7.0)

FDRs of individuals with SZ had relative risk of 6.4 for SZ, 3.3 for BD, 2.0 for MDD, 2.7 for ASD, and 1.8 for ADHD, compared to FDRs of control individuals, indicating increased comorbid major psychiatric disorders in the FDRs of individuals with SZ. Model 1 analysis: similar results with a bit smaller effect of RR in SZ (5.49; 95% CI, 5.29-5.70) and other comorbid conditions. Model 2: after removal of the identified SZ cases of the patients' FDR, the rest of the FDRs still had greater RRs higher than the controls for BD (2.69; 95% CI, 2.54-2.85), MDD (1.82. 95% CI, 1.76-1.88), ASD (2.24; 95% CI, 1.99-2.52), and ADHD (1.72; 95% CI, 1.62-1.82), strongly suggesting comorbidities other than the index illness among five major mental disorders. Dose-dependent relationship: individuals with more than one FDR with SZ had 20-fold higher risk (RR, 20.75; 95% CI, 18.9-22.8) and individuals with one FDR with SZ had 4-fold higher risk (RR, 4.75; 95% CI, 4.63-4.86) compared to individuals with no FDR with SZ. Similar findings with >=2 vs 1 FDR were observed in BD (RR, 9.3; 95% CI, 7.77-11.10 for >1 FDR; RR, 3.2; 95% CI, 3.11-3.35 for 1 FDR), MDD (RR, 4.0; 95% CI, 3.42-4.70 for >1 FDR; RR, 2.1; 95% CI, 2.00-2.10 for 1 FDR), ASD (RR, 7.0; 95% CI, 4.69-10.3 for >1 FDR; RR, 2.5; 95% CI, 2.32-2.74 for 1 FDR), and ADHD (2.5; 95% CI, 1.82-3.29 for >1 FDR; RR, 1.6; 95% CI, 1.54-1.69 for 1 FDR) (all $p < 0.001$). ADHD = attention deficit hyperactive disorder; ASD = autistic spectrum disorder; BD = bipolar disorder; FDRs = first-degree relatives; MDD = major depressive disorder; RR = relative risk; SZ = schizophrenia.
[a]Unpublished data.

of these index subjects (parents, children, siblings, and twins) could be traced through relationships in the dataset. Among the total population of beneficiaries (N = 23258175), patients with psychiatric disorders (n = 431887) and their FDRs were identified, resulting in 1017430 pairs (Fig. 2). The proportion of person times calculated for these FDR pairs were as follows: children 40%, siblings 23%, parents 22%, spouse 15%, and twins (n = 1712, 0.016%). Then, four controls were matched by age, gender, and type of relative to each case, resulting in 4069720 control pairs. RRs and 95% CIs were calculated to determine the risks of the five major psychiatric disorders between FDR groups of the index patient subjects vs control subjects. The RRs for type of family relationships were obtained by the prevalence of each disorder divided by the prevalence in the control group. Further, to study dose-dependent effects of more than one FDR in the same family with a psychiatric disorder on increasing the risks, relationships were also assessed between the risks of major psychiatric disorders and number (0, 1 vs ≥2) of FDRs with the specific disorder. Sensitivity analyses were also performed in model 1 by repeating the same psychiatric diagnosis equal or above three times for diagnostic validity and stability and model 2 by adjusting age, gender, urbanization, and income level and excluding the index cases.

The first result (Table 1) revealed that FDRs of individuals with SZ had RR of 6.4 for SZ and with smaller odds of BD, MDD, ASD, and ADHD, relative to FDRs in the controls, indicating increased comorbid major psychiatric disorders in the FDRs of individuals with SZ. Sensitivity test in Model 1 and Model 2 analysis revealed similar results with a little bit smaller effect of odds in SZ and other comorbid conditions (footnote of Table 1), strongly suggesting comorbidities other than the index illness among five major mental disorders.[12] There was also a dose-dependent relationship; individuals with more than one FDR with SZ had 20-fold higher risk and individuals with one FDR with SZ had 4-fold higher risk compared to individuals with no FDR with SZ. Similar findings were also observed in BD, MDD, ASD, and ADHD (details in footnote of Table 1)

Although no separate diagnosis for BD type I (BD I) and BD type II (BD II) in ICD-9 CM, we categorized BD I as cases hospitalized with diagnosis of bipolar manic or mixed. In analysis of individuals with BD (n = 184598), one-third was categorized in the BD I group, whereas two-thirds were in the BD II group. FDRs of BD had 6.1 times greater risk (95% CI, 6.0-6.3) of BD than FDRs of controls (Table 1). Among kinship relationships in the BD group, risk of BD in FDR was highest in twins (RR,

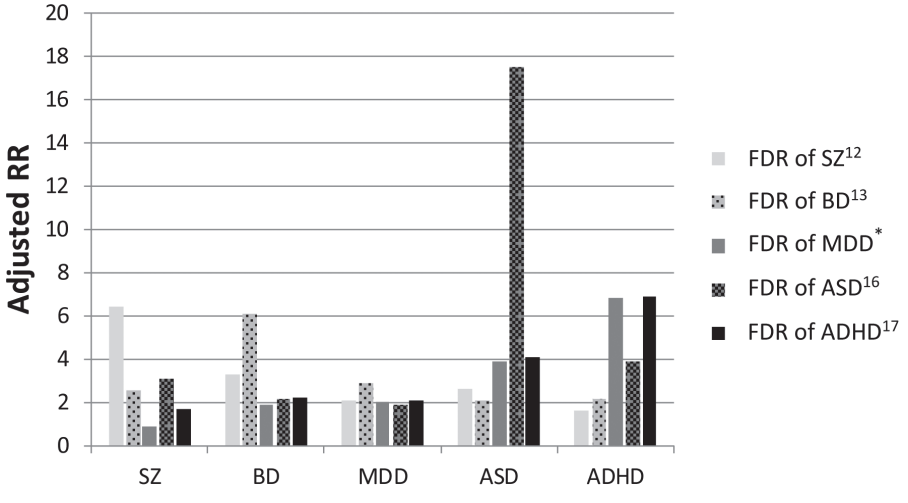

Fig. 1 Illustration for adjusted greater risks to develop illnesses in first-degree relatives (FDRs) of patients with major psychiatric disorders vs matched controls. ADHD = attention deficit hyperactive disorder; ASD = autistic spectrum disorder; BD = bipolar disorder; MDD = major depressive disorder; RR = relative risk; SZ = schizophrenia. *Unpublished data.

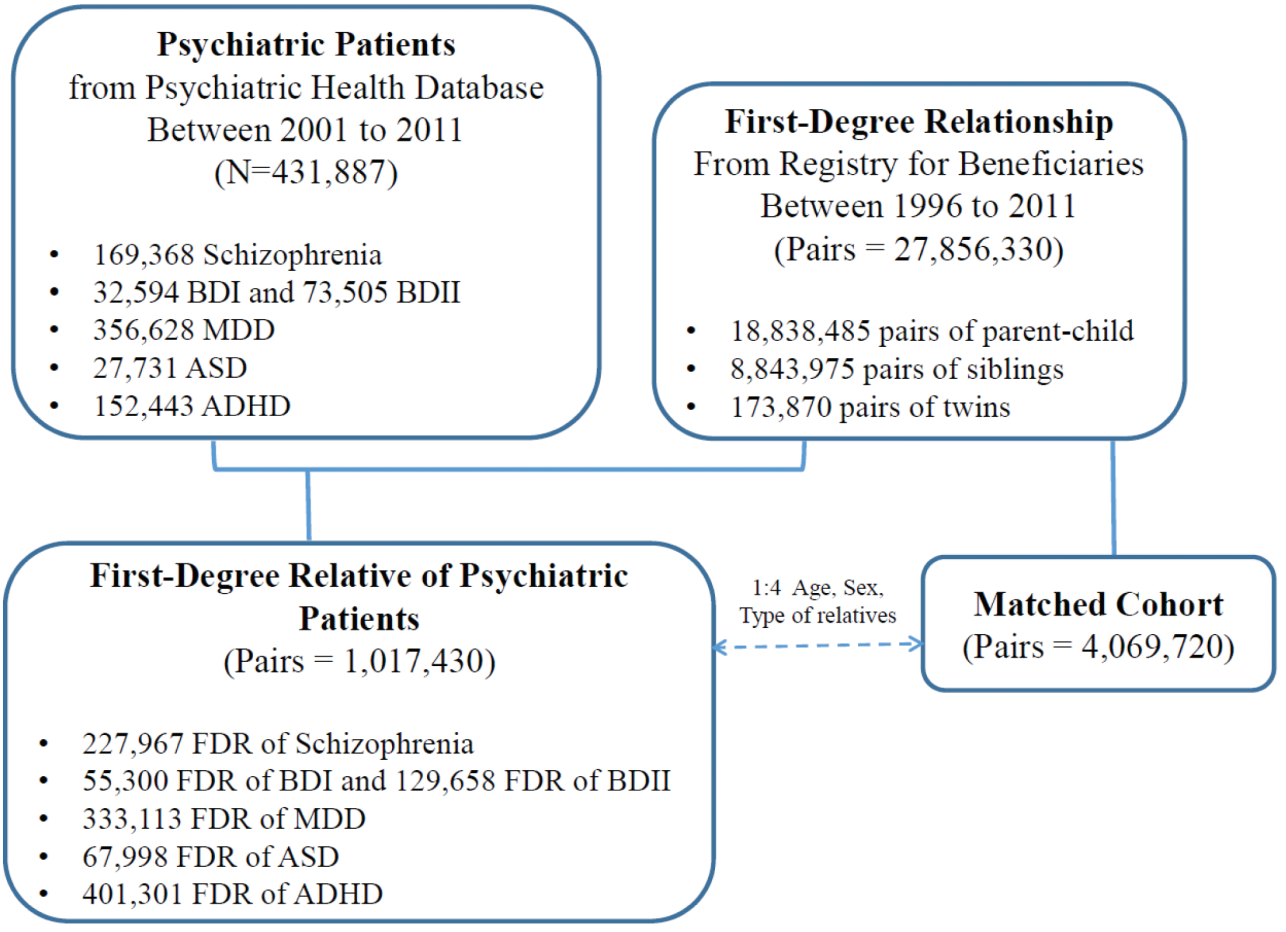

Fig. 2 Flow chart for selection of patient—first-degree relatives (FDRs) pairs and matched controls. ADHD = attention deficit hyperactive disorder; ASD = autistic spectrum disorder; BD = bipolar disorder; MDD = major depressive disorder.

41.9; 95% CI, 32.8-53.5) compared to other kinship subgroups, when all of them used control as a reference (RR, 1).[13] The FDRs of BD twins also had 16.9-fold greater risk (95% CI, 12.6-22.8) to develop SZ. Table 2 shows that FDRs of individuals with BD I had more than two times higher risk of developing BD I than developing BD II ($p < 0.001$). In contrast, FDRs of BD II did not differ in their risks in developing BD I and BD II (p = non-significant [ns]),[14] indicating stronger heritability in BD I than BD II. A dose-dependent relationship for more than 1 FDRs of the individual with BD vs only one FDR suffered from mental disorders had greater risk (29.1 [95% CI, 25.87-32.7] vs 6.1 [95% CI, 5.92-6.29], respectively; $p < 0.001$), higher than none found in the FDRs. Similar findings were observed in SZ (8.78 vs 2.59), MDD (7.71 vs 2.88), ASD (7.31 vs 2.04), and ADHD (3.47 vs 2.22)[13] (all $p < 0.001$).

Regarding obsessive-compulsive disorder, FDRs of individuals with obsessive–compulsive disorder (OCD) were more likely to have a major psychiatric disorder, compared to FDRs of the total population (RR, 8.1; 95% CI, 7.68-8.57);[15] relative risks were higher for all disorders SZ, BD, MDD, ASD, and ADHD (RR, 2.0; 95% CI, 1.86-2.09), (RR, 2.9; 95% CI, 2.69-3.04), (RR, 2.7; 95% CI, 2.58-2.76), (2.4; 95% CI, 2.10-2.71), and (RR, 2.2; 95% CI,2.07-2.32), respectively. A dose-dependent relationship was found between the number of OCD FDR and the risk of each major psychiatric disorder. For example, compared to individuals with no FDR with OCD, individuals with more than 2 FDRs with OCD have a 32.5-fold higher risk for OCD, 8.2-fold higher risk for BD, 6.1–fold higher risk for MDD, and 5.9-fold higher risk for ASD (all $p \leq 0.001$).

To summarize, FDRs of individuals with SZ had 6.4-fold higher risk than controls to develop SZ[12]; FDRs of individuals with BD had 6.1-fold higher risk than controls to develop BD[13]; FDRs of individuals with MDD had 2.0-fold higher risk than controls to develop MDD (unpublished data); FDRs of individuals with ASD had 17.5-fold higher risk than controls to develop ASD[16]; and FDRs of individuals with ADHD had 6.9-fold higher risk than controls to develop ADHD.[17] Overlap of clinical phenotypes among the FDRs of five major psychiatric disorders (Table 1) suggests that the FDRs including parents, children, siblings, and twins of patients with a psychiatric disorder have

Table 2

Comparison of relative risk to develop BD I and II disorders in the FDRs of BD disorders[14]

FDRs of BD	RR of BD I	RR of BD II	*p*
FDR of BD I	14.02	6.39	<0.001
FDR of BD II	5.07	5.88	ns
FDR of matched controls	1.00	1.00	

FDRs of individuals with BD I had more than two times higher risk of developing BD I than developing BD II (14.0 vs 6.4; 95% CI, 11.3-15.1 vs 6.1-6.8, respectively) ($p < 0.001$). In contrast, FDRs of BD II did not differ in their risks in developing BD I and BD II (RR, 5.9 vs 5.1) (95% CI, 5.5-7.0) (p = ns).

BD I = bipolar disorder type I; BD II = bipolar disorder type II; FDRs = first-degree relatives; ns = non-significant; RR = relative risk.

not only the highest increased risk for the index disorder but also has higher prevalence of other mental illnesses. The results also indicated that the disorder with most genetic heritability is ASD, whereas the least is MDD.

4. BRAIN IMAGING ANALYSIS TO IDENTIFY A COMMON NEURAL SUBSTRATE AND ILLNESS-SPECIFIC FUNCTIONAL DYSCONNECTIVITY ACROSS MAJOR PSYCHIATRIC DISORDERS

Since major psychiatric disorders like SZ and BD are highly heritable, brain imaging studies were investigated in their non-psychotic FDR to search for biomarkers for the genetic liability. In early 2000s, several studies, using magnetic resonance imaging (MRI)[18,19] functional MRI[20] found that unaffected SZ siblings relative to healthy controls had structural brain abnormalities such as smaller cortical gray matter with larger third ventricle volume and reduction of amygdalohippocampal complex as well as abnormal activity across cortical and subcortical areas, indicating unexpressed genetic liability in schizophrenia. In addition, one study[21] had evidenced morphometric brain abnormalities of anterior-limbic neural substrate were associated with the unaffected FDR in the family of BD, which may be a potential candidate as a morphological endophenotype of BD. The Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA)[22] Bipolar Working group used a large-scale sample size with comparable number of BD patients and healthy controls to investigate cortical abnormality differences and found that BD patients, relative to controls, had thinner cortical gray matter in the frontal, temporal, and parietal regions. And longer duration of illness was also associated with reduced cortical thickness, suggesting that the brain pathophysiology in BD being not only related to heritability but also environmental factors. Nevertheless, few neuroimaging studies have been conducted across phenotypically related diagnosis like SZ, BD, and MDD to look for common neural substrates in the brain among major psychiatric disorders.

We hypothesized that a common neurobiological substrate might underlie mental illness. Brain imaging data were analyzed to investigate if these major psychiatric disorders shared similar neural substrate pathology. Two approaches of brain imaging were performed using functional connectivity (FC) MRI. First, the study examined thalamocortical FC[23]; second, we identified all common neural substrates with connectomic abnormalities in the whole brain among individuals with 4 major psychiatric disorders and healthy controls.[24] In the studies, participants included SZ (n = 100), BD I (n = 100), BD II (n = 88-100), MDD (n = 100), and healthy controls (HCs) (n = 100-150). The first study[23] used the thalamus to derive FC maps for each subject and then compared each patient group with HCs. Conjuctional analysis was performed to identify thalamocortical abnormalities among the four major psychiatric disorders. The results showed that the four patient groups shared a similar pattern of thalamocortical dysconnectivity characterized by decreases in thalamic cortical FC with dorsal anterior cingulate cortex (ACC), prefrontal cortex (PFC), and inferior parietal cortex and by increases in FC with postcentral, precentral gyrus, superior temporal and lateral occipital cortex. Further network analysis demonstrated that the frontal-parietal regions showing hypo-connectivity belonged to the salience network. The second study[24] aimed to identify common neural substrates using the whole-brain connectomic analysis across the four major psychiatric disorders. Multivariate distance matrix regression (MDMR) method was used to identify structures where the overall pattern of FC was different between each patient groups and the HC group. Conjuctional analysis was the final step to illustrate common neural regions with FC abnormalities across the four major psychiatric disorders. The results revealed that the psychiatric disorders shared a similar pattern of connectomic dysconnectivities including thalamus, postcentral gyrus, and association cortices in the frontal and parietal regions. The number of voxels with connectomic abnormalities was also found to exhibit a gradient from highest in SZ (1269) followed by in BD I (1004), BD II (779), and MDD (199), indicating greater pathology of neural substrates in the brain for schizophrenia and bipolar disorder. These common neurobiological substrates were also similar to previous studies by using vowel-based morphometry or resting state/task stimulating FcMRI through meta-analysis.[25,26] These imaging findings in the brain identify a concordance with genetic and clinical overlap across psychiatric disorders. Furthermore, using functional MRI imaging data from large samples of SZ, BD, and MDD, two recent articles identified common alterations in modular architectures in the brain with more widespread in patients with SZ than BD and MDD[27]and transdiagnostic dysconnectivities within somatomotor and salience networks and between subcortical-limbic and subcortical-dorsal attention networks,[28] suggesting that prominent psychiatric disorders share common impairments. Moreover, they also found executive control network to be illness-specifically disconnected from prefrontal-limbic pallidal circuit in MDD, prefronto-striato-parietal circuit in BD, and default mode network in SZ, suggesting unique dysconnectivity profiles that hypothetically mediate the more distinctive features of the disorder-specific psychopathology.

In conclusion, since large-scale genetic association studies in mental health disorders have not yet been conducted in Taiwan, we searched for relevant published articles and found that genetic associations and shared molecular neuropathology varied among major psychiatric disorders. Next, by using big data in the Taiwan NHIRD, the studies demonstrated that FDRs of individuals with major psychiatric disorders had higher prevalence not only of the index disorder but also higher comorbidity across other psychiatric disorders compared to the matched cohort controls. This overlap of clinical diagnosis corresponds with the findings of shared molecular neuropathology, confirming high heritability in major mental illnesses. Finally, a common neural substrate with either thalamocortical or whole-brain connectomic dysconnectivities for four major mental disorders was demonstrated as evidence of similar brain activity and neuroanatomy. Therefore, these imaging results in the brain complementarily support the evidence from genetic and clinical studies.

Given the multidimensional complexity of psychiatric nosology, categorization of psychiatric disorders for research, communication, and clinical decision-making is still required. This current review harnesses big data to strongly suggest that the categorical classification of mental health disorders over the past century does not meet the needs of clinical practice in the future. Most psychiatrists are hopeful that, in the long run, replacing this framework with one that is grounded in biology will lead to new drug and treatment.[9] To move from categories to a multidimensional approach for psychiatric diagnosis and therapeutic concept, the system of NbN was initiated by Zohar et al[2] in 2014 to replace the current indication-based nomenclature from classifying psychotropic drugs by their pharmacological profile and to provide updated and more useful framework to better inform pharmacological decisions. This pharmacologically driven nomenclature that embeds contemporary neuroscience understanding of the mechanisms of drug action will help clinicians with the next pharmacological step, decrease stigma, and enhance adherence by a naming system that lays out a rationale for selecting a specific psychotropic.[3] "What are the roots of mental illness?" Michael Marshall[9] said, is a fundamental question in which researchers are beginning to untangle the common biology that links supposedly distinct psychiatric conditions.

Our future work needs more big data approaches using advanced AI and machine learning techniques to assist in establishing new models for psychiatric diagnosis and for targeting therapy.

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