

A Selected Review of Recent Biological Psychiatric Research in China (translated version)

Y Fu, SH Hu, LCW Lam

Abstract

This review highlights significant biological psychiatric research published by Chinese researchers in recent years. Chinese periodicals with full-text database (Chinese National Knowledge Infrastructure) and English periodicals with PubMed, published from 2003 to 2009 on schizophrenia, depression, bipolar affective disorder, obsessive-compulsive disorder, anxiety disorder and Alzheimer's disease, were reviewed. Articles studying the above-mentioned psychiatric disorders focusing in the area of molecular genetics, neuroendocrine immunology, electrophysiology and psychopharmacology applied to animal models or clinical populations were included. The findings suggest that biological psychiatric research is being developed at a rapid pace and covers a wide perspective from disease mechanisms to clinical interventions.

Key words: *Biological psychiatry; China; Review*

Introduction

Biological methods in neurosciences constitute an important dimension of psychiatric research. They entail molecular genetics, neuro-biochemistry, psychopharmacology, and neuro-immunology and aim to explore the complex aetiology, pathogenesis, treatment, and prognosis of different mental disorders. In the middle of the 20th century, Bennett¹ was among the first to propose the concept of 'Biological Psychiatry' and published his view in the *American Journal of Psychiatry*. The subsequent emergence of the first antipsychotic (chlorpromazine) and the 2 antidepressants (iproniazid and imipramine) prompted formulation of the dopamine hypothesis for schizophrenia and the monoamine hypothesis for depression. These observations laid the theoretical foundation for modern biological psychiatry. In the past decades, research in biological psychiatry has been voluminous. Application of molecular genetics and neuroimaging has greatly facilitated its development and provided a scientific basis for the aetiology of mental illness and its pathological mechanisms. This review examines recent development in biological methods applied to psychiatric research in China.

Dr Yan Fu, Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong, China.

Dr San-hong Hu, Department of Psychiatry, The Third Affiliated Hospital, Sun Yat-sen University, PR China.

Prof Linda CW Lam, Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong, China.

Address for correspondence: *Dr Yan Fu, Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong, China.
Tel: 9471 6152; Email: fuyan_1111@hotmail.com*

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Molecular Genetics

The genetics of mental illness has long been a focus of biological psychiatry research. Classical family studies, adoption and twin studies have confirmed that schizophrenia, bipolar affective disorder, and depression are polygenic in inheritance. However, finding the susceptibility genes responsible for the various minor diseases is difficult. Currently, genome-wide scanning and candidate gene studies are still the most common strategies used. Genome-wide scans make use of DNA genetic markers that cover the entire genome and target the large number of schizophrenic pedigree (often involving siblings); the respective genes often being separated by relatively wide distances (10-20 cM). Through genetic linkage analysis, the disease-related genes are identified at a certain chromosomal region and on that basis, high-density selection of genetic markers (about 10 kb) and sophisticated analyses are used to further narrow down the target area and ultimately identify the susceptibility genes of the particular disease. This strategy entails candidate gene studies, which directly investigate genes hypothesised to be related to a specific disease, by analysis of differences in allele frequencies of such candidate genes and haplotypes in disease and control groups. Genome-wide scanning has the advantage of addressing all the known or unknown biological mechanisms related to the disease, but pinpointing a location is still immensely difficult. The candidate gene approach can directly detail the functioning of certain genes in disease and suggest associated pathogenetic mechanisms. Genome-wide scans use linkage analysis while candidate gene strategies use association studies. The most widely used strategy in China involves the study of associations between candidate genes and clinical cases, while family studies

are relatively few. This can be attributed to the simplicity and lower costs of the clinical case comparison technique. Candidate genes were mainly related to the dopamine hypothesis, 5-hydroxytryptamine (5-HT) hypothesis, glutamate hypothesis, and neuro-developmental hypothesis. For instance, recent research addressed the relationship of schizophrenia with gene polymorphism of the dopamine D₂ receptor,² disrupted-in-schizophrenia 1 (*DISC1*),³ prostaglandin E receptor 3 (*PTGER3*),⁴ glutamate cysteine ligase modifier,⁵ and 5-HT₆ receptor.⁶ Other research explored the association of tryptophan hydroxylase gene,⁷ synaptogyrin 1 and synapsin II⁸ gene polymorphisms with bipolar affective disorder, as well as the association of gene polymorphism of brain-derived neurotrophic factor (*BDNF*) and glycogen synthase kinase 3 beta⁹ with depression. The most noteworthy is the research team from the Bio-X centre of Shanghai Jiaotong University which systematically investigated several schizophrenia-related genes such as *FXYD6* gene,¹⁰ early growth response gene,¹¹ retinoic acid metabolism enzyme gene,¹² and cytochrome P450 enzyme gene¹³ and achieved important progress in the molecular genomics of schizophrenia and psychopharmacogenetics. Besides, exploration of the association with the mental disease itself, studying the relationship between the genetic markers and the phenotypes of certain quantitative features, such as positive and negative schizophrenic symptoms,¹⁴ aggressive behaviour,¹⁵ ventricular enlargement,¹⁶ and minor physical anomalies,¹⁷ have also attracted growing attention. Important insights can be obtained from such case-controlled association studies, but the big difference in numbers of cases (about 200-700 cases in any single case group) as well as different standards and methods of genotype categorisation make such association studies difficult to replicate and verify. There have been only a few reports on the association of candidate gene polymorphism and transmission disequilibrium in a schizophrenic family. The latest study showed transmission disequilibrium in the gene polymorphism of DNA methyltransferase 3B¹⁸ and *DAOA* gene¹⁹ in the schizophrenia pedigree, but not in *KCNN3*²⁰ and cryptochrome-1²¹ genes. On the other hand, linkage studies of genome-wide scans regarding schizophrenia were primarily targeted at chromosomes 1, 6, 13, and 22. The most comprehensive linkage analysis was conducted by Tang et al²² on the 64 microsatellites of chromosomal regions of a Han family of sufferers from multiple schizophrenia which included 1q21-22, 1q32-44, 5q21-33, 6p24-22, 8p22-21, 10p15-11, 11q23-24, 11p15, 12q23-24, 13q32-34, 22q11-12, 9q34, 16p13, 12q13, 17q25, and 19q13 regions. The results illustrated that the 11q23.2-24.2 region was consecutively implicated with 3 high LOD scores in the course of multipoint nonparametric analysis. Moreover, haplotype analysis was conducted for 6 microsatellite markers of chromosome 11. This revealed that reorganisation operates between the D11s902 and D11s898 region, suggesting that possible disease genes are located at the extremity of D11s902.

In addition, with the completion of the human genome

project and the rapid development of microarray technology, a new research technique known as genome-wide association has become the latest tool in international research efforts. Several researchers have been concerned with genome-wide association study findings in schizophrenia,^{23,24} bipolar affective disorder,^{25,26} depression,^{27,28} Alzheimer's disease,²⁹⁻³¹ and other mental illnesses, but no relevant domestic studies have emerged to date. The only reports that are available dealt with gene chip technology to explore differences in gene expression of peripheral blood leukocytes in schizophrenic patients,³² variations in gene expression of the brain tissues of rats with depression,³³ and the screening out of genes related to desipramine responsiveness.³⁴ The gene chips that were utilised contained the gene numbers of 8464, 5184 and 2048 respectively, and the samples consisted of 6 to 8 cases. No further verification was conducted by real-time fluorescent quantitative polymerase chain reaction tests. It can thus be inferred that although China has attained some success in the research arena of mental illness molecular genetics, there is still a big gap when compared with international standards.

Neuroendocrine Immunology

Since Besedovsky and Sorokin's first hypothesis of a neuroendocrine-immune circuitry in 1977,³⁵ numerous studies have confirmed the relationship of mental illness and regulation disorders of the neuroendocrine-immune system. As the crucial substance for information exchange among the nervous, endocrine and immune systems, cytokines have become the research focus of immunological studies on mental illness both domestically and internationally. For example, a number of researchers have reported significant differences in the levels of serum cytokines such as interleukin (IL)-2, IL-6, IL-8, IL-10, tumour necrosis factor- α between healthy controls and patients experiencing the onset of schizophrenia and depression.³⁶⁻³⁸ Such differences reveal that the occurrence of mental illness may be related to cytokine-mediated immune activation. Both in terms of gene transcription and protein expression, the report by Song et al³⁹ shows that abnormal cytokine levels occur in schizophrenia. Other studies⁴⁰⁻⁴² reported that at 6 to 8 weeks after clozapine treatment of patients with new-onset schizophrenia, levels of certain cytokines (IL-2, IL-6, IL-13 and soluble IL-6 receptor) changed significantly. Both increases and decreases from pretreatment levels have been described; there being no consistent effect. For instance, Li et al⁴⁰ reported that at 6 weeks after clozapine treatment, IL-6 and IL-13 levels were significantly higher than that prior to the treatment. Whereas Guo et al⁴³ indicated that at 4 weeks, 8 weeks and 6 months after starting clozapine treatment, IL-6 levels were significantly reduced, and the rate of change of the level at the end of 8 weeks correlated positively with the extent of symptom reduction. Yao et al⁴⁴ reported that selective serotonin reuptake inhibitor antidepressants can significantly lower IL-2 and IL-6 levels in patients with depression, and correlated negatively with the increase in 5-

hydroxyindoleacetic acid (HIAA) levels. Despite numerous similar reports, most studies registered sample sizes of 25 to 30 cases and 18 to 30 healthy controls, who were generally observed over 4 to 8 weeks, and cytokine levels were primarily determined by enzyme-linked immunology and radioimmunology. Only a few studies went on to explore the mechanism of immune imbalance in mental illness. For example, Qiu et al⁴⁵ found that glucocorticoid receptors may affect the function of fork-head box P3 (Foxp3) and regulatory T cells, directly via the transcription factor Foxp3, or indirectly through IL-10 and transforming growth factor- β . This could reduce the expression of Foxp3 mRNA, resulting in a lowered number of CD4+ CD25+ regulatory T cells, and associated functional deficits and a consequential immune imbalance.

Neuropeptides are another category of neural hormones, neurotransmitters and neuro-modulators of great concern, as they participate extensively in physiological functions (pain perception, sleep, mood, learning, memory) and nervous system differentiation and development. The neuropeptides associated with mental illness include: substance P (SP), neuropeptide Y (NPY), opioid peptides, vasopressin, cholecystokinin, neurotensin, and endothelin. Research in China mainly evaluated the plasma of patients suffering from depression,^{46,47} and animal models with depression, as well as the expression levels of NPY and SP in colonic and pituitary tissues.^{48,49} The inconsistent results obtained to date can be attributed to the variable sensitivity levels of different detection methods, the use of different animal models, and other factors. Studies entailing cerebrospinal fluid sampling have been relatively scanty. Thus, only Hou et al⁵⁰ applied enzyme-linked immunosorbent assay to investigate the cerebrospinal fluid levels of SP, NPY, norepinephrine epinephrine (NE), 5-HT and 5-HIAA in 40 patients with major depressive disorder and 40 controls. Their results showed that both the SP and NE levels in the patients were significantly higher than those in controls, and that NPY expression in patients with recurrent depression was more marked than that at disease onset. This suggests that multiple neuropeptide dysfunctions occur in patients with major depressive disorder. Meanwhile, a small number of studies reported that changes in neuropeptide levels may help to determine drug efficacy. According to a study on 32 patients with depression, Yang et al⁵¹ found that their plasma SP levels decreased significantly 6 weeks after paroxetine treatment, and that there was an obvious positive correlation between changes in plasma SP level and the rate of reduction in the Hamilton Depression Rating Scale (HAM-D) total score. Chen et al⁵² reported that at 8 weeks after undertaking fluoxetine treatment of patients with depression, plasma SP concentrations were significantly lower, and accompanied by an obvious rise in the NPY level as well as lower HAM-D and Hamilton Anxiety Rating Scale scores. These findings indicate that neuropeptides may be involved in the therapeutic mechanism of antidepressant drugs.

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been recognised as constituting a neuro-

endocrine pathogenetic mechanism of depression. Among the local studies on this subject, the discovery that certain Chinese herbal medicinal ingredients influence HPA axis function in animal models with depression is particularly noteworthy, as are the effects they have on monoamine neurotransmitters. For instance, Hu et al⁵³ placed rat models raised in solitude with depression, in conditions of chronic and unpredictable mild stress. They found that pepper alkali demonstrated an ample antidepressant effect and counteracted corticotropin-releasing hormone (CRH) release and increased levels of adrenocorticotrophic hormone (ACTH) caused by chronic stress. Zhang et al⁵⁴ reported that Guanyu capsule can induce behavioural correction in rats suffering from depression and damage to their olfactory bulbs, and that 1.2, 0.6 and 0.3 g/kg of the capsule conspicuously reduced plasma ACTH and cortisol (CORT) levels in their animal model. Zhang⁵⁵ introduced improvements to the Koizumi method and built up rat models of post-stroke depression. By means of electron microscopy, they found that Shugan Jiannao Tiaoyu tablets (SJTT) can significantly reduce damage to hippocampal neurones by chronic stress. They also reported that high doses of SJTT and fluoxetine can curb the expression of hypothalamic CRH mRNA (possibly as part of the antidepressant mechanism) in the rat models. Through an in-depth investigation into the mechanism and functioning of traditional Chinese medicine, botanical natural medicines may have growing importance in the treatment of mental illness.

Electrophysiology

Since Berger first applied conventional electroencephalography (EEG) in 1929, EEG physiology has been extensively promoted and applied in psychiatric medicine. Conventional EEG is by far the most common and practical neuroelectrophysiological technique, and is used in almost 95% of psychiatric hospitals in China. Sleep EEG (SEEG) has also become an important research tool for studying mental illness. Numerous studies have looked into SEEG changes in schizophrenia, depression, obsessive-compulsive disorder, and Alzheimer's disease.⁵⁶⁻⁶⁰ For instance, a comparative analysis by Ou et al⁶¹ showed that compared with obsessive-compulsive disorder and anxiety patients, those with depression have reduced sleep duration, and amounts and intensity of rapid eye movement sleep, but there were no statistically significant differences between the 2 groups. In addition to spontaneous potentials, evoked potentials have become electrophysiological research tools. They include visual-evoked potentials (VEPs), auditory-evoked potentials (AEPs) and event-related potentials (ERPs), all of which are contingent negative variation, P300 and N400 potentials, as well as mismatched negativity. Being the most vital endogenous component of ERPs, internationally as well as domestically P300 potentials have become the most scrutinised of neuroelectrophysiological indicators. Consistently, patients with schizophrenia, depression or senile dementia exhibit lower P300 amplitudes

and extended latency⁶²⁻⁶⁴, while the P300 amplitude of patients with depression increased significantly and latency shortened after drug treatment,⁶⁵ no such changes ensued after treatment of schizophrenia.⁶⁶ However, there was no agreement as to whether ERP P300 values reflect acquired versus genetic traits. Shi et al⁶⁷ discovered that neuregulin 1 (Arg38Gln) gene polymorphism is associated with P300 latency, while Wang et al⁶⁸ reported that parents of patients with new-onset schizophrenia showed no major difference in P300 amplitude and latency compared with the controls. This indicates that no particular familial aggregation is involved in P300 potential variation, and that changes in such potentials are unrelated to catechol-o-methyl transferase gene polymorphism. Therefore, it cannot be substantiated that P300 potential changes are genetic markers of schizophrenia. At present, other features of brain-evoked potentials are being studied in combination with brain electrophysiology. These involve: clinical scales, psychological testing, and functional imaging. Together, they allow comprehensive probing into the features of mental illness. In China too, there have been research studies incorporating clinical assessment with ERP studies. Using a modified version of the Modified Overt Aggression Scale, Barratt Impulsiveness Scale 11, and the Buss Durkee Hostility Inventory, Li et al⁶⁹ identified extended ERP P300 latency and lower amplitudes in male patients exhibiting aggressive behaviour than the non-aggressive controls. Liu et al⁶² also found that compared with patients with positive schizophrenia, the negative patients showed significantly lower VEP, AEP and somatosensory-evoked potential amplitudes, as well as longer AEP latency. Meanwhile, the cognitive impairment factor was negatively correlated with P300 amplitude, but only at the locations of Fz and T3. This suggests that the P300 amplitude reduction in frontal and temporal lobes of schizophrenic patients reflects a certain degree of cognitive impairment. A small body of research has attempted to integrate psychological testing and functional imaging. For instance, Peng et al⁷⁰ applied and combined P300 potentials with the Chinese version of the newly promoted MATRICS Consensus Cognitive Battery (MCCB). They found that the P300 latencies and amplitude variations at the Fz, Cz and Pz points were associated with the MCCB test results in frontal, parietal and occipital lobes, which seemed to validate a link between neurophysiological and neuropsychological aspects of brain cognitive functions.

Psychopharmacology

Among the various treatments in mental illness, psychotropic medication is the most important and effective. Progress in psychopharmacology has provided a scientific basis for guiding the invention of new drugs and revealing the aetiology of mental illness. At present, psychopharmacology research mainly focuses on pharmacokinetics and pharmacodynamics. Using high-performance liquid chromatography, research is continuing in the pharmacokinetics of psychotropic drugs

like quetiapine, olanzapine, venlafaxine, and paroxetine.⁷¹⁻⁷⁴ Additional studies have tried to explore the correlation between the activity of drug-metabolising enzymes and drug disposition,⁷⁵ plasma concentration, efficacy, and side-effects.⁷⁶ Such work has resulted in reference value for monitoring drug safety and efficacy in clinical practice. On the other hand, pharmacogenetics provided a novel method of dissecting inter-individual differences in medication responses (including toxicity) from the perspective of molecular genetics. For instance, several candidate genes such as those for CYP450,^{77,78} *BDNF*,⁷⁹ 5-HT₇ receptor⁸⁰ and the dopamine D₂ receptor⁸¹ were associated with psychotropic drug responses, while others yielded positive associations with side-effects like tardive dyskinesia⁸²⁻⁸⁴ and weight gain.⁸⁵⁻⁸⁷ Although some confounding factors, such as what is vaguely defined as 'drug response' and 'the treatment effects of earlier psychoactive drugs' may affect the accuracy and certainty of results, pharmacogenetic studies are still promoted as a means of implementing gene-directed individual therapy. Meanwhile, it is recognised that future trends in psychopharmacogenetics will entail investigation of a number of genetic markers, exploration of interactions between susceptible genes in core families and siblings, as well as definitions of drug response as remission and preventive recovery in the long term.

Conclusion

In summary, this article reviewed biological psychiatric research in areas of molecular genetics, neuroendocrine immunology, neuroelectrophysiology, and psychopharmacology in China. Whether through the use of animal models or patients, molecular genetics, neural biochemistry, electrophysiology and pharmacology, research periodicals indicate that extensive investigations are proceeding into the pathogenesis of a variety of mental disorders viewed from different perspectives. Despite the achievements to date, there have been no revolutionary postulations regarding the biological nature of mental illness. Nevertheless, there have been significant contributions towards a more systematic and comprehensive understanding of the pathogenesis of mental illness, all of which bodes well for the future.

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