NEUROSCIENCE

Developing translational biological psychiatry: Learning from history to build the future

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Abstract

Psychiatric disorders are among the most complex human disorders that, albeit often difficult to diagnose and treat, are widespread in modern society. Biological psychiatry studies biological functions of the central nervous system as mental disorders develop. Today's biological psychiatry is facing multiple conceptual problems that prevent our deeper understanding of disease pathogenesis and delay the invention of new treatments. Thus, providing a historical context to this rapidly developing field may help scientists better understand the existing challenges and their potential solutions. Here, we discuss the main conceptual problems and paradigms of biological psychiatry, including the lack of reproducibility and/or valid theories, through an historical overview of its role in addressing theoretical and clinical questions. We propose a wider use of the translational approach in psychiatry to expand our analyses of psychiatric disorders to other species, and as a tool to create and further develop theories and concepts in this field.

Keywords: biological psychiatry, translational medicine, history of psychiatry, modern psychiatry, conceptual issues in psychiatry.

Introduction

Psychiatric (mental) disorders are the most complex and frequently comorbid human disorders; they are becoming particularly widespread in modern society, but are difficult to properly characterize (Fears et al., 2014; Meyer-Lindenberg and Weinberger, 2006; Nestler and Hyman, 2010; Tsankova, Renthal, Kumar, and Nestler, 2007). Their polygenetic nature complicates genetic studies, which often yield not only disorder-specific genes but also multiple other candidate genes that are associated with other psychiatric disorders, thus showing significant overlaps (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Gaugler et al., 2014; Ikeda et al., 2013; Ivleva et al., 2010; Murphy et al., 2003; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Uddin et al., 2014). Furthermore, the low specificity, lack of personalization and slow pace of innovation in psychiatric practice collectively lead to inadequate treatment of mental diseases (Griebel and Holmes, 2013; McMahon and Insel, 2012).

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Today, depression and other affective spectrum disorders represent the leading causes of human disability (Cryan and Mombereau, 2004; Murray and Lopez, 1997). Despite the high prevalence and harm caused by both depressive and comorbid disorders, they remain poorly understood and are often treatment-resistant and recurrent (Cryan and Mombereau, 2004; Huynh and McIntyre, 2008; Insel and Charney, 2003; Schmidt, Wang, and Meijer, 2011; Wong and Licinio, 2004).

As a field, biological psychiatry studies biological functions of the central nervous system (CNS) and development of mental disorders. In a broad sense, this vibrant field represents a set of changing ideas, approaches and social practices aiming to describe and cure deviant human behavior in terms of neurobiological discourse (D'haenen, den Boer, and Willner, 2002). To better understand the main conceptual problems that biological psychiatry faces today, and to find potential ways of their resolution, it is critical to first consider the historical perspective and main milestones in this field (Fig. 1).

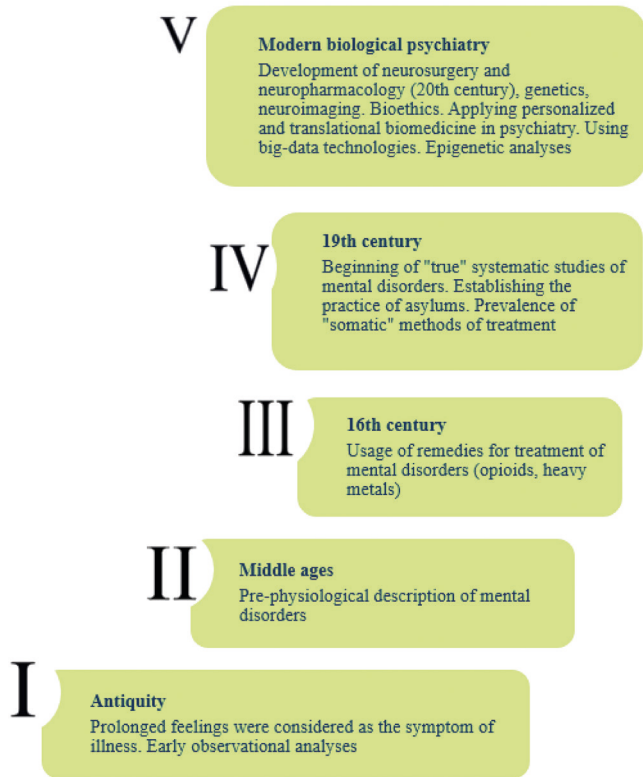

Fig. 1. A brief history of biological psychiatry. It was already mentioned by Hippocrates that most of our feelings, if they are prolonged, should be considered symptoms of illness. Further development of psychiatry was the direct consequence of the growth of medical practice, resulting in pre-physiological hypotheses of mental disorders. Finally, contemporary psychiatry uses a wide variety of treatment methods and modern diagnostic tools.

Milestones in biopsychiatric concepts

The science studying psychiatric disorders — psychiatry — has a much longer history than neurology, which examines disorders with relatively clear and known neural pathology (Wickens, 2014). In fact, many currently recognized psychiatric conditions (e.g., mania, melancholy, and hysteria) were known in the time of Hippocrates (Wickens, 2014), who in his *Aphorisms* noted that most of our feelings, if they are prolonged, should be considered symptoms of illness (Hippocrates, 2004). One of the first preserved notions of clinical depression is the 1500 BC Ebers Papyrus (Scholl, 2002). Notably, the term "melancholy" at that time was broader in meaning than it is now, and included not only low mood, despair and loss of energy, but also fear, aggression, obsessions and even hallucinations, thus incorporating depression, anxiety and psychotic disorders together (Radden, 2003).

In early works, pathology of psychiatric disorders was described as an imbalance of humors associated with relevant temperaments (Wickens, 2014) — the concept of humoralism in early psychiatry. This theory was based on 4 humors (blood, yellow bile, black bile and phlegm), the imbalance and "corruption" of which resulted in diseases and disabilities (Lindemann, 2010; Lloyd, 1983). It is possible that humoralism originated in Ancient Egypt or Mesopotamia (Sudhoff and Garrison, 1926; Van Sertima, 1992), but it was later adopted and developed by Hippocrates (Lloyd, 1983). A four-temperament typology that linked imbalance of humors with temperaments was developed by Galen, who associated each humor with the combination of 2 different qualities (hot/cold and dry/wet), jointly determining the respective temperament (sanguine, choleric, melancholic and phlegmatic) (Boeree, 2014; Kagan, Snidman, Arcus, and Reznick, 1994). This influential concept was widely accepted and used by physicians and researchers, most notably by Avicenna (Lutz, 2002), and it was displaced only with the rise and development of modern theories of CNS pathology and cellular biology.

Before the "true" scientific study of mental disorders began in the late 18th and 19th centuries, their "treatment" was characterized mostly by societal prejudices and punishments, as patients remained highly stigmatized, despite some concern about mental health in times of Greek prosperity and their treatment with different holistic methods (Panksepp, 2004b, 2004c). While some humanistic positions existed in Middle Eastern countries, European countries remained in the Dark Ages for a long time, during which demonization of mental disorders dominated both society and medicine (Andreasen, 2004; Murad and Gordon, 2002; Panksepp, 2004b; Stone, 1997). Indeed, many widely used biological methods of therapy for mental disorders included drubbing, bleeding, starvation and temperature shock; they were based on prejudices rather than scientific rationale, and have since been recognized as ineffective

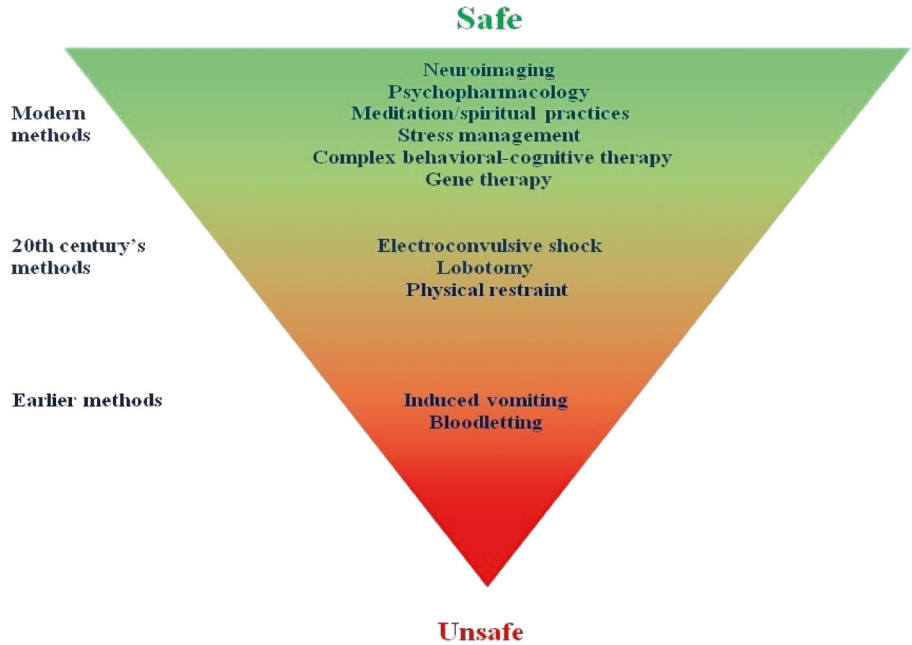

Fig. 2. Evolution of selected commonly used psychiatric treatment methods. The size of each phase displays treatment capacity of methods used at particular time. The color reflects the relative safety of implemented treatments, from safe (green) to unsafe (red).

in modern practice (Panksepp, 2004b) (Fig. 2). Among the relatively effective methods used were placebo-and psychotherapy-like methods that involved witch doctors, shamans and even skull trepanation for so-called "bad spirits extraction" (Panksepp, 2004b). Interestingly, conceptually similar approaches, based on sympathy/social concern and the placebo effect, are currently well known and are used in psychiatric practice with proven therapeutic effects (Harrington, 1999; Mayberg et al., 2002; Moerman, 2002; Panksepp, 2004a; Petrovic, Kalso, Petersson, and Ingvar, 2002; Shapiro and Shapiro, 2000).

Certain views about somatic causes of mental disorders, which are now fundamental in biological psychiatry, could already be found in the 17th century. For example, Thomas Hobbes (1588–1679) suggested that motions of blood, animal spirits, "body parts" and organs caused by phantasms concerning good and evil in the mind may lead to "madness" (Gert, 1996; Hobbes, 1972; Hobbes and Macpherson, 1968). "Madness" was defined as excessive passions, the motion of which "may cause disturbances in different body parts" (Gert, 1996; Hobbes and Macpherson, 1968). Famous iatrochemist and early brain researcher Thomas Willis (1621–1675) also emphasized somatic causes of diseases and noted that brain function disturbances may lead to psychiatric disorders, such as melancholia (Frank, 1980; Willis and Guidott, 1992). Willis also believed such changes to be potentially revealed by anatomical pathology methods like autopsy (Conry, 1978). Around the same time, Robert Burton (1577–1640) published *The Anatomy of Melancholy*, describing melancholic condition in detail, overviewing theories of its causes, expressing his own feelings and suggesting a healthy diet, proper sleep, music, work and social communication as effective treatment methods (Burton, 1931).

Nevertheless, the role of the nervous system in the function of a healthy individual as well as in the progress of pathological conditions was not actively studied until the 18th century (Wickens, 2014). Around that time, CNS disorders became especially recognized by the rapidly growing medical practice (Wickens, 2014). The existence of clear organic bases for neurological diseases provided neurological methods that were not accessible for psychiatry, and in this way neurological studies built the foundation for further development of psychiatry (Panksepp, 2004b; Wickens, 2014). For example, case history review or autopsy were used by Giovanni-Battista Morgagni (1682–1771) and further applied in neurology by Jean-Martin Charcot (1825–1893), facilitating the relatively fast growth of neurology in the 18–19th centuries (Wickens, 2014). Interestingly, as a result of his postmortem studies of psychiatric patients, Morgagni emphasized the lack of reproducibility of others researchers' results (Bonet, 1700; Morgagni, 1769), also noting that the same diseases may show lesions in different parts of the brain (Morgagni, 1769). However, further development of ideas about the role of the brain in human life continued. For example, Pierre Cabanis (1757–1808) suggested that the brain "excretes" thoughts and this may create complex conscious and mental disorders (Cabanis and Cerise, 1843).

In the meanwhile, studying psychiatric disorders required other approaches, given the lack of pronounced organic lesions and the wide diversity that complicates classification (Wickens, 2014). The 19th century (especially the 1850–1900s) is often called the beginning of true thorough and systematic studies of mental disorders (Panksepp, 2004b). This period started with the works of Benjamin Rush (1745–1813) in the USA, Philippe Pinel (1745–1826) in France and Vincenzo Chiarugi (1759–1820) in Italy, who laid the foundation of "moral treatment" of patients (Panksepp, 2004b). Specifically, they helped establish the practice of asylums for psychiatric patients in small humanistic hospitals, in which therapeutic space was created to recover patients' emotional homeostasis (Panksepp, 2004b). Besides "psychological" treatment, some auxiliary "somatic" methods, such as bloodletting, induced vomiting, diets, physical restraint and electroconvulsive shock, were used, but collectively fell into decline by the 20th century (Panksepp, 2004b).

Etienne-Jean Georget (1795–1828), based on Marie F. X. Bichat's (1771–1802) ideas of vitalism, suggested that mental disorders have an organic nature and introduced the term "technology alibi", which plays a critical role in today's biopsychiatry (Berrios and Marková, 2002; Georget, 1820). The technology alibi is a fundamental assumption of psychiatry that is based on syllogism: the mind is represented in the brain — the mind is tantamount to a set of behaviors — hence, all behaviors are represented in the brain — abnormal behaviors are still behaviors — hence, all behaviors have brain representation — thus, the fact that no brain representation can yet be found for mental disorders must be due to faulty techniques (Berrios and Marková, 2002). In this way, the technology alibi plays a large role in biological psychiatry, providing it freedom to investigate psychiatric diseases as brain diseases without rigorous proof of this claim.

Similarly, Wilhelm Griesinger (1817–1868) viewed all mental diseases as brain diseases, and considered brain lesions as a physiological, not anatomical concept (Berrios and Marková, 2002). However, although Griesinger called mental disorders organic or biological in nature, he did not presume that these disorders must have a reflection in the brain, so his views on physiological lesions were closer to psychological trauma (Porter, 1988). He also noted that official clinical categories would always be arbitrary, whereas "elementary" analytical units (symptoms) are ontologically stable (Berrios, 1996). Theodor Hermann Meynert (1833–1892) described pathological conditions as changes in brain blood supply, and the main causal mechanism — as changes in cellular nutrition caused by these blood supply disruptions and birth defects (Berrios and Marková, 2002; Meynert, 1885). Interestingly, Carl Lange's (1834–1900) theory of emotion was proposed in almost the same period, and is also linked blood circulation, vasoconstriction, perfusion and nutrition to pathological affective conditions (Wassmann, 2010).

A seminal step in the study of psychiatric disorders was made by Emil Kraepelin (1856–1926), often called the father of modern psychiatry (Panksepp, 2004b; Wickens, 2014). Kraepelin first described "dementia praecox", which is now widely known as schizophrenia, and created a dichotomic classification of psychiatric disorders into neuroses and psychoses, which has influenced many others classifications and theories that now are widely used by health organizations (Wickens, 2014). Notably, Kraepelin's classification was largely influenced by Karl Ludwig Kahlbaum (1828–1899) and his protégé Ewald Hecker (1843–1909) (Berrios, 1996; Berrios and Hauser, 1988; Kendler and Engstrom, 2016; Kraepelin, 1905; Kraepelin, 1983), who paid special attention to criticizing the imperfection of 19th-century psychiatric systematics (Kendler and Engstrom, 2016). For example, they noted that this systematics consisted of the symptom complexes, but not the diseases, and recognized that their high heterogeneity complicates understanding of the etiology, the prognosis of course of the diseases and their treatment (Kahlbaum, 1863; Kahlbaum and Berrios, 1996; Kendler and Engstrom, 2016; Kraam, 2004). In response, they suggested a new method of detailed and empirical observations, in which special attention should be paid to broad temporal spectra of disease progression in patients (Kendler and Engstrom, 2016). They identified and described such conditions as hebephrenia, catatonia and cyclic madness (Baethge, Salvatore, and Baldessarini, 2003; Hecker and Kraam, 2009; Kahlbaum, 1973; Kendler and Engstrom, 2016), which were further conceptually developed by Kraepelin (Kendler and Engstrom, 2016).

Kraepelin's main work, *Textbook of Psychiatry*, played a major role in the development of biological psychiatry (Wickens, 2014). In Kraepelin's time, psychiatric disorders were typically diagnosed by the main, most pronounced symptom (e.g., melancholia or madness) which was typically caused by a trauma, such as loss of a friend (Wickens, 2014). Subsequently, Kraepelin made several important observations. For example, comparing the speed of disease progression, he concluded that all diseases can be split into "curable" or "incurable" based on their progression speed (Wickens, 2014). Studying patients with different early clinical representations that later progressed into senile dementia, he found that these conditions can be described as united, called it dementia praecox, and distinguished it in it such subtypes as regular, paranoid, catatonic and hebephrenic (Wickens, 2014). Furthermore, Kraepelin was the first to split psychosis (then viewed as a disjointed cluster of diseases with unclear organic causes) into manic depression and dementia praecox (Wickens, 2014). At the same time,

manic depression itself consisted of all affective spectrum pathologies and was split into externally and internally caused disorders (Davison, 2006). Interestingly, Kraepelin thought that dementia praecox was an incurable disease, in contrast to depression, which is relatively curable and temporal (Wickens, 2014). In contrast, Eugen Bleuler (1857–1939) suggested that dementia praecox could not be an incurable condition since he could see significant improvement in many patients, and argued that this condition is determined through disorganized thinking caused by the split of emotional and intellectual functions (Wickens, 2014). The term "schizophrenia" was chosen for this condition, and its main symptoms were recognized as reduced emotional response, weakened associations, indifference or inability to make choices, and autism (at that time the term was used to describe concentration on a person's own thoughts) (Wickens, 2014). Also, Bleuler noticed that symptoms of schizophrenia can be grouped into positive (e.g., excess activity and thinking) and negative (e.g., reduced or impaired/insufficient activity and thinking) (Wickens, 2014).

Another important opponent of Kraepelin was Carl Wernicke (1848–1905), deservingly considered one of the most important psychiatrists of the 19th century (Lanczik, 1988). One of Wernicke's key findings was the creation of the first CNS model that reflected the connection between different areas of the brain and specific behaviors. This thought was the first of its kind, and highly suitable for direct pathophysiological studies; it was the first example of a model that used a neuropsychological approach for psychiatric disorders (Berrios and Marková, 2002). Interestingly, his model was based on Meynert's ideas that the brain is filled by projections and associative fibers, in which conscious is based (Berrios and Marková, 2002; Wernicke, 1906). Thus, projection lesions lead to neurological diseases, and lesions of the associative system — to psychiatric disorders (Berrios and Marková, 2002; Stein and Ludik, 1998).

In Kraepelin's time, there already were established psychopharmacological practices (Preston, O'Neal, and Talaga, 2010). For example, Kraepelin himself often used opium, morphine, scopolamine and hashish for stimulation, whereas to induce sleep he used chloral hydrate, ether, alcohol, chloroform and bromides (Spiegel, 2003). However, Kraepelin noticed that none of these drugs could treat psychiatric disorders, their use was rather short-term, and some of them could cause addiction (Preston et al., 2010). As other authors reported, the use of these drugs can help to gain control over a patient by sedation, but cannot treat psychotic symptoms *per se* (Preston et al., 2010).

Important, but rather underappreciated, is the contribution to biological psychiatry made by Constantin von Monakow (1853–1930) and Raoul Mourgue (1886–1950) (Berrios and Marková, 2002; von Monakow and Mourgue, 1928), who pointed out that neuropsychiatric phenomena and functions should be viewed as inseparable from the function of time, making an analogy to a process of movement (Berrios and Marková, 2002). According to these views, it may not be correct to associate these processes with specific brain areas in isolation from a change in location of such processes with time (Berrios and Marková, 2002). Indeed, the brain processes information in different areas in complicated patterns, and these diverse parts need to constantly coordinate their functions. Expanding this idea, a psychiatric disorder can be seen as a consequence of time–function disturbance, and should be viewed with the use of the time concept (Berrios and Marková, 2002). Thus, Monakov and Mourge's theory of chronogenic localization was one of the first dynamic models in biological psychiatry.

Adolf Mayer (1866–1950) actively promoted a holistic ("whole self") approach to psychiatric treatment in the late 19th — early 20th centuries (Panksepp, 2004b). For example, he actively used thorough documentation of patients' lives; he also rightly emphasized the importance of both psychological and biological effects that may impact the patient for effective treatment, and the uniqueness of each individual's traits and, consequently, their treatment (Panksepp, 2004b). Mayer's approach was key for pioneers in the field of studying animals' self-regulation, such as Kurt Richter (1894–1988) with his study of appetite, sleep and circadian rhythms (McHugh and Slavney, 1998). Mayer's views about individuality, including his belief that a person's strong and weak sides ought to be taken into account in treatment, have further developed and can be seen today in genetic approaches and personalized medicine in treatment practice (Panksepp, 2004b). In the context of depression, Mayer noted the importance of the interaction of social and biological factors, which mediates individual reactions, and he especially emphasized his preference for the term "depression" rather than "melancholy" (Lewis, 1934).

The second half of the 19th century raised other spectrum ideas that were closely related to psychiatry. For example, Sigmund Freud's (1856–1939) theory of psychoanalysis and psychodynamic approach revolutionized our view of the mind by the popularization of the idea of the unconscious (Panksepp, 2004b). After a slump in interest in Meyer's concept in the 1940s, psychological theories of Viktor Emil Frankl (1905–1997), Albert Ellis (1913–2007), Aaron Beck (born 1921), Freud and others, became influential and widely recognized (Beck, 1979; Blair, 2004; Carhart-Harris et al., 2014; Ellis, 1962; Frankl, 1976; Freud, 1984; Radden, 2003; Seidner, 2009). However, the lack of rigorous scientific argumentation, along with the success of pharmaceutical therapy of psychiatric disorders, led to justified criticism of Freud's theories in the late 20th century. Nevertheless,

these theories continue to be further developed in modern time and have gained improved scientific basis by neuropsychoanalytic methods (Panksepp, 2004b; Solms and Turnbull, 2002).

During this period, there were still multiple manipulations that are now considered radical, such as metrazole- or insulin-induced seizures, electroconvulsive therapy and lobotomy (Panksepp, 2004b; Valenstein, 1974). Widespread use of psychosurgery helped to effectively stabilize agitated psychotic patients, but it was done at a high human cost, since lobotomized patients often became unenergetic, passive and "emotionally dead" (Preston et al., 2010). Electroconvulsive treatment, on the other hand, could have a good effect on some patients (Preston et al., 2010). However, its use was far from perfect and often led to strong side effects. Furthermore, it was widespread and prescribed inappropriately, often ignoring the lack of positive response in some groups of patients (Preston et al., 2010). However, the most affected patients continued to be kept in overcrowded hospitals and "treated" with such crude methods as isolation and restraint, due to the absence of other, more effective therapies (Preston et al., 2010).

The next period in biological psychiatry, which is often called psychopharmacological, started with the discovery of highly efficient chlorpromazine by Jean Delay (1907–1987) and Pierre Deniker (1917–1998), and lithium drugs by John Cade (1912–1980) in the late 1940s — early 1950s (Cade, 2000; López-Muñoz et al., 2005; Panksepp, 2004b). These findings led to an avalanche of psychopharmacological discoveries. For example, Paul Janssen (1926–2003), based on the knowledge that chlorpromazine-like drugs cause their effects primarily through the dopaminergic system, created haloperidol and risperidone — the ancestors of today's atypical antipsychotics (Panksepp, 2004b).

Around the same time, the first drugs with antidepressant activity were discovered, as Delay and Max Lurie tested an antitubercular drug, isoniazid (which also caused a stimulating effect in patients), and found improvement in depressed patients after treatment with the drug (Ayd and Healy, 1996; Healy, 2001; Selikoff and Robitzek, 1952). The effect of iproniazid was discovered in the same way (López-Munoz, Alamo, Juckel, and Assion, 2007; Robitzek, Selikoff, Mamlok, and Tendlau, 1953). The antidepressant effect of these two drugs is related to their inhibition of monoamine oxidase A (MAO-A) (López-Munoz et al., 2007). Additionally, Roland Khun (1912–2005) presented the first tricyclic antidepressant, imipramine, following an attempt to improve chlorpromazine action (Kuhn, 1958). As a result of translational research of the 1960s, benzodiazepines — anxiolytic drugs that cause sedative and antiagressive effects, such as chlordiazepoxide — were also introduced (Panksepp, 2004b). In the USSR, Svyatoslav Lapin and Grigory Oxenkrug put forth the serotonergic theory of depression (Lapin and Oxenkrug, 1969), which subsequently led to the discovery of selective serotonin reuptake inhibitors (SSRIs) — currently, the most prescribed (Coupland et al., 2015) and one of the most efficient antidepressant medications today (Cuijpers, van Straten, van Oppen, and Andersson, 2008).

Clinical success of psychopharmacological drugs and the development of neurochemical synaptic transmission theory dramatically accelerated the description of the main neurochemical brain systems and the growth of preclinical psychopharmacology (Charney, Buxbaum, Sklar, and Nestler, 2013; D'haenen et al., 2002; Panksepp, 2004b; Preston et al., 2010). Consequently, powerful behavioral analysis and psychoactive drug screening methods were created. In such studies, animals were essentially used as "biological computers" in which drugs with potential psychoactive effect were placed, and behavioral reactions were collected as output information reflecting the effect of the drug. However, excessive focus on such methods led to a relatively slow pace of psychobehavioral systems' analyses (Panksepp, 2004b), thus necessitating further development of methodology and theories in this field.

With the advent of genetics, the focus of biological psychiatry began to shift to identifying family patterns in psychiatric disorders. As these studies shed light on a high genetic load of some psychiatric disorders, finding the genetic component of other diseases proved to be complicated (Preston et al., 2010). Recent advantages in biotechnology have made it possible to systematically test single nucleotide polymorphisms or large copy number variants by genome-wide association studies (GWAS) (Wray et al., 2014). Today, various copy number variants are found for shizophrenia, autism, bipolar and major depressive disorders (Lee and Avramopoulos, 2014). Other approaches that are relatively effective and widely used in translational psychiatry include disease-specific differential gene expression studies. Unfortunately, both approaches consistently reveal significant overlaps and shared molecular pathways across psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics, 2013; Gandal et al., 2018). Furthermore, although some disorders show high heritability, for the vast majority of cases, their genetic etiology remains unclear, meriting further scrutiny (Lee and Avramopoulos, 2014).

While psychiatric genetics countinues to grow with improvements in experimental and analytical methods, the field of psychiatric epigenetics has also begun to gain momentum (Lee and Avramopoulos, 2014). Epigenetics refers to processes that alter gene expression without changes in DNA sequence, primarily through DNA methylation and changes in histone structure (Roach, Bronner, and Oreffo, 2011). Multiple studies have shown

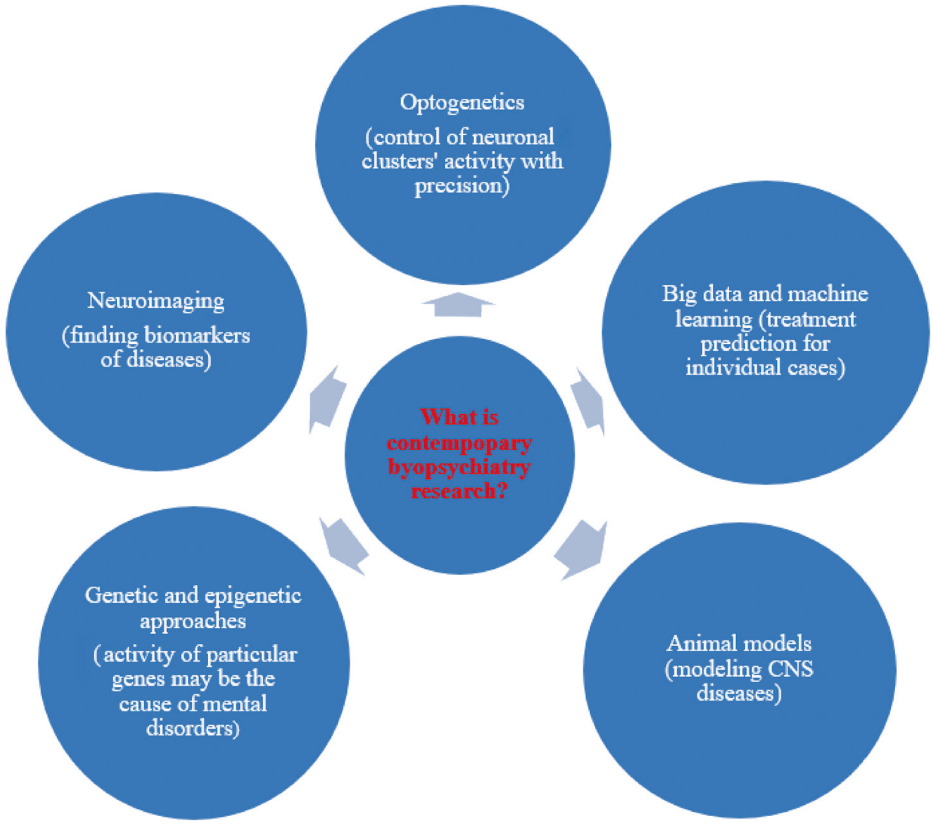

Fig. 3. The diversity of common methods used in contemporary research in biological psychiatry research, and their potential implementation.

the role of epigenetics mechanisms in different aspects of psychiatrc disorders (Peedicayil, Grayson, and Avramopoulos, 2014; Yasui, Peedicayil, and Grayson, 2016), although it remains unclear how exactly epigenetic factors contribute to the pathophysiology of specific mental disorders (Kato, 2009).

In parallel, the first international classifications of mental disorders were created, thereby continuing Kraepelin's work (APA, 1960) and putting forth novel disorder constructs and theories. For example, depression pathogenesis theories developed then primarily viewed the disorder as a neurochemical imbalance (Schildkraut, 1965), and were based on robust antidepressant effects that continue to play an important role in today's scientific discussions and antidepressant development.

Finally, modern biological psychiatry is a skyrocketing field powerfully enriched by many new effective methods and tools (Fig. 3). For instance, neuroimaging has emerged as a valuable tool that allows researchers to investigate brain structures and activity of humans and animals *in vivo* (Linden, 2012; Misgeld and Kerschensteiner, 2006). These techniques include computerized tomography (CT) and magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon emission computerized tomography (SPECT), near-infrared spectroscopy (NIRS), magnetoencephalography (MEG) and electroencephalography (EEG)/event-related potentials (ERP) (Linden and Fallgatter, 2009). Developing early neuromorphological works of Ramon y Cajal (1852–1934) (Finger, 2000) and Alois Alzheimer (1864–1915) (Berrios, 1990), modern neuroimaging studies in psychiatry picked up in 1976 with the finding of enlarged cerebral ventricles in schizophrenics (Johnstone, Crow, Frith, Husband, and Kreel, 1976). Neuroimaging can potentially be used to find biomarkers of disease, prognosis or treatment; investigate biological pathways; and help redefine diagnostic boundaries and monitor new therapies (Linden, 2012). Unfortunately, although some imaging and electrophysiological phenotypes are associated with mental disorders, none of them are currently valid as a diagnostic marker (Linden, 2012). Nevertheless, these techniques create a productive basis for brain functional mapping and connectomics studies. These connectome-based approaches present new opportunities in studies of psychiatric diseases, and the identified disrupted networks may potentially represent valuable biomarkers of psychiatric disorders such as depression (Gong and He, 2015).

Another extremely effective recent research tool in biological psychiatry is optogenetics — a method which enables precise control of the activity of neuronal clus-

ters and has become an effective tool in both neural circuits and behavioral studies (Chen, Zeng, and Hu, 2012; Francis, Chaudhury, and Lobo, 2014; Hegemann and Sigrist, 2013; Yizhar, Fenno, Davidson, Mogri, and Deisseroth, 2011; Zeng and Madisen, 2012). Optogenetic methods have now enabled acquisition of insights into a broad range of questions in behavior, physiology and pathology, spanning domains of sensation, cognition, and action (Deisseroth, 2015). Comprehensively discussed recently (Deisseroth, 2015), these methods continue to contribute to modern biological psychiatry.

Complementary and alternative medicine (CAM) in psychiatry is an integrative approach combining different treatment techniques that concentrate on lifestyle changes, relatively low-invasive natural drugs and traditional medicine practices. These techniques include such treatments as exercise, sleep, nutrition, stress management, light therapy, St. John's Wort (SJW), S-adenosylmethionine (SAMe), yoga, meditation, acupuncture and a variety of spiritual practices (Muskin, 2008; Vora, Aloysi, and Zhuk, 2017). Use of these techniques is especially promising in the treatment of depression, and inclusion of integrative approach treatments based on management and light treatment is highly recommended in both treatment-resistant and recurrent cases (Vora et al., 2017). SJW and SAMe are among the few well studied CAM drugs and may be considered as treatment medication for some patients (Vora et al., 2017).

From a data analysis standpoint, the use of big data grants unparalleled opportunities to investigate different scientific problems. Today, numerous modern technologies, including mobile technologies, social media and internet, can be used to quickly collect and analyze big data from a large number of patients. These practices have already proved to be effective (Swendsen and Salamon, 2012), although they raise various practical and ethical questions, ranging from psychiatrist–patient personal boundaries violation and the ethics of high-scale medical data monitoring (Andlauer, Lydall, Nawka, and Guloksuz, 2015). As these challenges complicate the use of modern technologies by some psychiatrists (Andlauer et al., 2015), digital healthcare data being collected at an incredible speed, at a rate of about 50% per year (Monteith, Glenn, Geddes, and Bauer, 2015). Thus, there is hope that the growing use of big data in psychiatry will provide opportunities for exploration, descriptive observation, hypothesis generation, and prediction for clinical, research and business issues (Monteith et al., 2015). Indeed, there have already been some promising findings in the following areas: suicide, substance abuse, bipolar disorder, safety of antipsychotic medications, depression management and screening, association of head injuries with psychiatric disorders, the use of natural language processing to identify treatment-resistant depression and the risk of autism (Castro et al., 2015; Grether, Anderson, Croen, Smith, and Windham, 2009; Huybrechts et al., 2012; Kessler et al., 2015; Orlovska et al., 2014; Perlis et al., 2012; Valuck et al., 2012; Wu et al., 2013). Another interesting potential use of big data in psychiatry is finding behavioral traits that were previously difficult or impossible to detect (Monteith et al., 2015).

A good combination of big data with machine learning approaches can also help achieve some goals of personalized medicine, since it should provide high quality treatment prediction for individual cases (Gillan and Whelan, 2017). Personalized medicine, as a concept, was developed a long time ago, first introduced by Hippocrates and not undergone many changes since (Abrahams and Silver, 2010). However, what has changed is the rapid growth of sophisticated methods, theories and an overall understanding of how we should apply these theories to treat individual diseases. Thus, modern personalized medicine is concentrating on finding ways to successfully and most effectively treat each patient based on the knowledge of internal and external factors suggested to be involved in pathogenesis (Emmert-Streib, 2013). Personalized psychiatry looks especially promising since psychiatric patients tend to exhibit significant inter-individual variability in their responses to psychoactive drugs (Costa e Silva, 2013). Unfortunately, the field is still mostly in the information-gathering stage, and a deeper understanding of biomarkers, genes and environmental factors is therefore needed to develop truly personalized psychiatric approaches (Ozomaro, Wahlestedt, and Nemeroff, 2013).

The modern term "holistic psychiatry" is usually described as the "whole self" approach, including mind and body concepts (Wallace, 2008), an increased humanistic aspect in treatment of psychiatric diseases (Linnett, 2006), a systemic (organizational/integrative) view on human behavior (Angyal, 1948) and questioning of our understanding self and identity in a psychiatric context (Crossley, 2012). All of these holistic categories represent the whole-person care approach that is highly desired yet remains hard to reach for biological psychiatry. It is also worth noting that the role of other physiological systems in psychiatric disorders, such as the endocrine, gastrointestinal, immune, and other systems, is beginning to receive increased attention (Ma et al., 2017).

Sex and gender differences are also experiencing resurged interest in current psychiatric practice. Although physicians have been trying to understand the biological differences between men and women for centuries, they continue to face challenges in the context of sex-specific psychiatric diseases. Furthermore, our previous views on such differences were quite sexist and highly based on cultural understanding of gender roles in the past. For instance, maleness has traditionally been seen as superior to femaleness, and some psychiatric diagno-

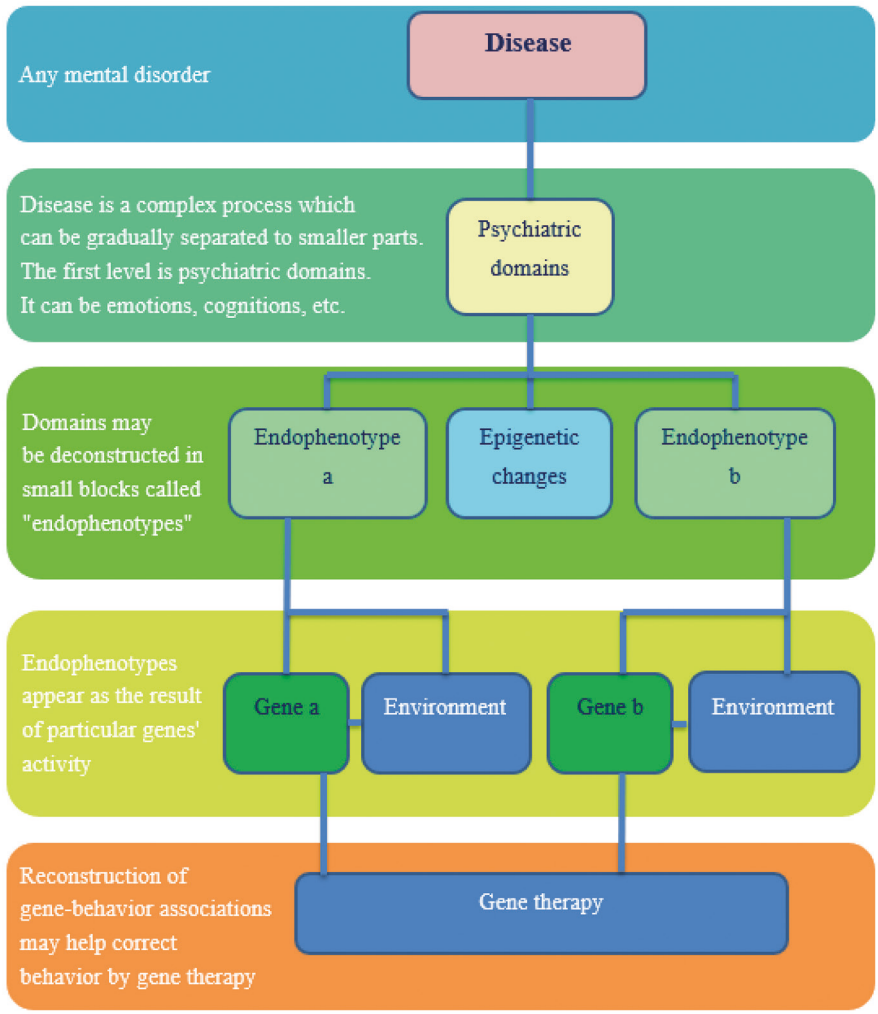

Fig. 4. Endophenotype- and domain-based therapy strategies in biological psychiatry. Human brain diseases may be deconstructed into smaller units — major psychiatric domains (e.g., affect, cognition, activity) — which can be further deconstructed into endophenotypes. As genes' activity modulates behavioral patterns, their interaction leads to a particular endophenotype which results in specific behavioral patterns. Thus, correction of a particular gene's activity may help correct endophenotypes and, eventually, cure the disease that contains this aberrant endophenotype.

ses (e.g., hysteria and borderline personality disorder) were "reserved" for females (Nissim-Sabat, 2013). For today's gender psychiatry, the main challenge is to untangle social and cultural factors from biological (Hirshbein, 2010). Understanding the sex impact on psychiatric disease predisposition and progression may help to increase effectiveness of treatment and make it more personalized.

Discussion

In conclusion, the need for new methods of treatment necessitates further development of current CNS pathogenesis theories of brain disorders which could explain how exactly psychiatric disorders emerge, how psychological and biological processes develop, and how these disorders relate to treatments. Especially promising here is the approach of translational biopsychiatry, which provides a unique, evolution-based vision of psychiatric diseases. However, there are major problems which biopsychiatry is facing. For example, the field needs novel sensitive biomarkers of psychiatric disorders, especially for its early/presymptomatic progression (Panksepp, 2004b). Another problem, already discussed here, is the need for new classification systems of psychiatric disorders. Many established disease classifications have been justly criticized for a long time for low accuracy, diagnostic heterogeneity, high comorbidity, troubled use and blurred categories (Aragona, 2009b; Baca-Garcia et al., 2007; Kendell and Jablensky, 2003; Pincus, Zarin, and First, 1998). Thus, a new taxonomical system may require a radical rethinking of psychiatric disorders, probably in terms of neurobiological discourse (Aragona, 2009a; Tadafumi Kato, 2011).

Works dedicated to this problem began to appear in the 1970s. For example, Irving Gottesman (1930–2016)

coined the term "endophenotype" (Fig. 4) and aimed to reconstruct gene–behavior associations by deconstructing complex disorder systems into small blocks (Gottesman and Gould, 2003; Gould and Gottesman, 2006). Endophenotypes are objective, biological or behavioral signs of disorders which exist in an organism regardless of the presence or absence of the disorder, and can be found in a patient's relatives that were not affected by the disease in higher levels than the average population level (Cannon and Keller, 2006; LaPorte et al., 2010). In the last decades, the concept of endophenotype has become widely accepted and is one of the most influential in biological psychiatry (Braff, 2015; Cannon and Keller, 2006; Flint and Munafo, 2014; Glahn et al., 2012; Glahn et al., 2014; Hasler, Drevets, Gould, Gottesman, and Manji, 2006). However, even this concept alone could not solve the problems of the spectrum nature of psychiatric diseases and cross-linking of genetic determinates, molecular pathways, and symptoms (Kalueff, Ren-Patterson, LaPorte, and Murphy, 2008; Kalueff and Stewart, 2015).

One of the recent outcomes of the endophenotype concept was the cross-species trait genetics approach (Kas, Fernandes, Schalkwyk, and Collier, 2007). This approach is based on the idea that behaviors should be conserved in genetic variance across species due to their involvement in common survival mechanisms that allow adaptation to an ever-changing environment. This concept suggests that genotype–phenotype relationships exist between animals and humans in terms of traits (Kas et al., 2007).

Another important concept was developed by the US National Institute of Mental Health (NIMH) as a Research Domain Criteria (RDoC) project (https://www.nimh.nih.gov/research-priorities/rdoc/ (Cuthbert and Insel, 2010; Insel et al., 2010)) to facilitate the translation of modern molecular biology, neuroscience and behavioral approaches in an attempt to better explain the physiology of mental disorders (Ceusters, Jensen, and Diehl, 2017). The concept has created a matrix in which "constructs" (representing aspects of behavior) are related to "elements"/"units of analysis" (representing primarily biomarkers). Constructs are further combined into psychiatric domains; currently 5 psychiatric domains are described: Negative or Positive Valence Systems, Cognitive Systems, Social Processes, Arousal and Regulatory Systems, and an additional 6th Motor Systems Domain is currently under debate (Garvey and Cuthbert, 2017). Currently, this trans-diagnostic approach is actively collecting data for further investigations. Such trans-diagnostic, cross-domain/cross-disorder approaches in psychiatry are receiving increasing attention and are markedly improving our understand of comorbidity, cross-disorder biomarkers and pathologies (Harvey, 2004).

Conclusion

From the brief historical perspective provided here, one can see that the current problems of biological psychiatry are still the same as they were at its start. Today, like centuries ago, the field still faces the lack of reproducibility; problems with systematization, proper terms and understanding of psychiatric disorders core domains; as well as the lack of humanistic approaches. The field, though rapidly progressing, still lacks connection between psychology and psychiatry, between biology and psychology, between data and valid theories. The lack of disorder progress trajectory-based approaches and the technology alibi still serve as crutches for psychiatric theoretical constructs. To address such problems, a wider use of translational approaches in psychiatry is urgently needed, representing a unique tool to study evolutional conservative traits of disorders pathogenesis. If successful, such an expansion of views on psychiatric disorders may provide a powerful base for new theories and could help create fundamentally new concepts of consciousness and mind across a wide spectrum of organisms.

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