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Biomarker Development for Brain-Based Disorders: Recent Progress in Psychiatry

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Abstract

Biomarkers are biological measures that are indicative of a specific disorder, its severity or response to treatment. They are widely used in many areas of medicine, but biomarker development for brain-based disorders lags behind. Using examples from the field of psychiatry, this article reviews the concepts of biomarkers, challenges to their development and the recent progress along those lines. In addition to discussing historical biomarker candidates such as cortisol or catecholamine levels, we include progress from recent genetic, epigenetic, proteomic, neuroimaging and EEG studies. Successful identification of biomarkers will advance the field of psychiatry towards the goal of biological tests for diagnosis, symptom management and treatment response.

Introduction

A biomarker is a biological measure that provides information about the state of a normal biologic process, pathogenic process, or pharmacologic response to an intervention [1]. In clinical practice, it must be reliable, reproducible, cost effective, and noninvasive [2,3]. For example, hemoglobin A1c (HbA1c) is measured in peripheral blood, and is widely used to assess glycemic control in patients with diabetes or those at high risk for developing diabetes; it is used both as a clinical diagnostic and for the development of new pharmaceutical treatments. In fact, biomarkers are used widely in a number of fields (Table 1), while others, including brain-based disorders, lag behind.

Neuropsychiatric disorders are a leading cause of disability worldwide [4], though their biological basis generally remain unknown. Diagnosis of psychiatric disorders is based on the presence of characteristic symptoms and is guided by the Diagnostic and Statistical Manual (DSM) or the International Classification of Diseases (ICD). These criteria are periodically revised as more is learned about each disorder. Although this system has been widely used with a high degree of inter-rater reliability, it has achieved this at the expense of validity [5,6]. Notable limitations exist with respect to the diagnostic classification of individuals for research purposes.

Table 1: Examples of biomarkers currently used in clinical practice.

Biomarker	Application
C- Reactive Protein (CRP)	Detect inflammation [119]
Glycosylated Hemoglobin A1c (HbA1c)	Monitor glycemic control [120,121]
Human Epidermal Growth Factor Receptor 2 (HER2)	Select breast cancer treatment [122,123]
Creatine Phosphoskinase (CPK)	Detect muscular injury [124]
Brain Natriuretic Peptide (BNP)	Acute heart failure [125]
Troponin T and I	Myocardiac infarction [126]

For example, symptom assessment can be subjective [7]. Symptoms can overlap, making it difficult to distinguish similar disorders from each other [8,9], and comorbidity is common. Additionally, criteria established for one ethnic or cultural group may not be applicable to others [10].

Independent of diagnosis, the high cost of healthcare and lost productivity weigh heavily on individuals and their governments worldwide [11,12]. Despite the development of a variety of pharmacological treatments, the remission rate for those with psychiatric disorders remains low [13,14]. Because of these reasons, the field would benefit especially from identification and use of biomarkers that can be used to detect the first episode of a disease, chronic illness, symptom severity, treatment response or non-response (Figure 1). There are no biomarkers that are relevant for clinical practice in psychiatry or psychology, but over the past several years, we have seen remarkable progress towards this goal. As the field advances, it is important to review the key criteria a psychiatric biomarker should possess (Table 2).

Central Versus Peripheral Measures

Decades of research support that psychiatric disorders are brain-based, and many argue that the brain is the only place to look for biologically meaningful correlates of brain-based disorders. Studies of postmortem brains provide insight into how those with and without major depressive disorder (MDD) or with and without psychotic symptoms differ on a molecular and functional level [15,16]. Though such studies provide insight into the pathophysiology of MDD, the brain is not generally accessible for molecular testing. Unless the same biological differences are observable in accessible tissues, measures identified in postmortem brains are not practical for biomarker development.

A recent study compared results from potential biomarkers measured in postmortem brain and those measured in serum [17]. Though not all molecules were comparable between central and peripheral measures, many were, particularly those that were involved in the inflammatory response. In fact, a number of peripheral systems interact with and respond to signals from the central nervous system

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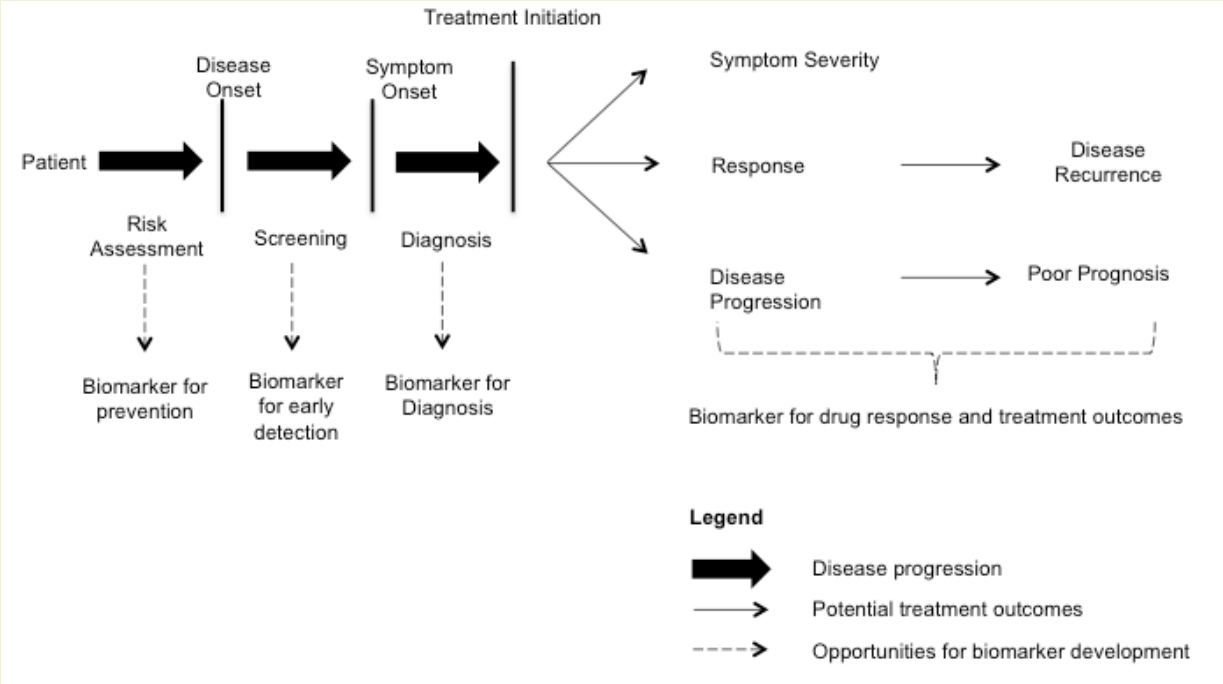

Figure 1: The stages of diagnosis and treatment for psychiatric disorders with areas of focus for biomarker development.

Table 2: Characteristics of a psychiatric biomarker.

• Shoud detect a discrete characeristic related to a disorder, its severity or treatment efficacy
• Should be safe and easy to measure peripherally
• Should have sensitivity >80% for detection and specificity >80% for differentiating from similar traits
• Should be reliable and reproducible to allow standardization between labs
• Should be cost effective to promote use in clinical practice

(CNS) [18,19]. For example, peripheral inflammatory cytokines can access the brain and interact with numerous pathophysiologic domains relevant to psychiatric illness including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and mood-relevant neurocircuitry [20,21]. Researchers with an interest in biomarker development often leverage these relationships by focusing on peripheral tissues that can be readily sampled.

Genetic and Epigenetic Biomarkers

Because of the relatively high heritability of a number of psychiatric disorders [22], genetic or epigenetic studies can provide insight into genes that relate to etiology, disease progression and treatment response. While sequence variants may increase risk for a psychiatric disorder, they will not make effective biomarkers because an individual's genotype is fixed. However, gene expression patterns change over time, and mRNA levels have been associated with psychiatric disorders, symptoms and treatment response. For example, P11 (also known as *S100A10*) is an annexin II light chain protein that belongs to the S100 family [23,24]. Su and colleagues suggested that P11 expression in peripheral blood cells could be used to differentiate post-traumatic stress disorder (PTSD) from other psychiatric conditions including MDD, bipolar disorder (BPD) and schizophrenia (SCZ) [25]. In addition to full-length transcripts, there is also evidence to suggest that splice variants in peripheral blood mononuclear cells (PBMCs) delineate those with SCZ and BPD from each other and from controls [26]. Gene expression patterns are tissue-specific, but the expression patterns between blood and brain are reasonably correlated [27] suggesting that some expression profiles may not only serve as biomarkers but also reflect brain-based differences as well.

Gene expression patterns cannot be detected in all tissues, but many epigenetic modifications can. Epigenetic marks, such as histone modifications, DNA methylation and miRNA, help to regulate gene expression [28-30]. High-throughput technologies have made epigenetic marks easier to assay, and numerous studies have described associations with psychiatric diagnoses, symptoms or treatments [31-34]. This promising area of research has been providing insight into biological mechanisms through which gene expression varies in response to the environment [35]. For example, exposure to antiepileptic medications can promote widespread changes in DNA methylation as well as other epigenetic modifications [36-39]. In addition to medication exposure, preclinical research using animal models and clinical research with human subjects [40-42] supports the hypothesis that exposure to early life stressors may result in DNA methylation changes in the glucocorticoid receptor (*NR3C1*), a hormone-activated factor that mediates many of the downstream effects of the stress hormone cortisol. These studies are helping to elucidate how environmental factors modify gene regulation to increase risk for some psychiatric disorders [43].

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Protein Biomarkers

Dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis is a hallmark of multiple psychiatric illnesses. As stress levels vary so too do the levels of cortisol, which can be assessed in saliva, urine, blood or hair. Changes in serum cortisol level have been reported in MDD as well as many other disorders [44,45]. Cortisol levels decrease in patients with schizophrenia [46]. They also decrease following treatment with an antipsychotic medication [47], and discontinuation of that antipsychotic increases cortisol levels again [48]. Some studies report an inverse relationship between PTSD severity and cortisol levels, while other report no difference [49] or even higher levels [50]. This may be because cortisol also associates with trauma exposure [51,52], a risk factor for depression and other psychiatric disorders [53], making it difficult to distinguish the molecular correlates of an experience that increases risk for a disorder from the disorder itself.

Driven by discrepancies in the literature and reports that catecholamine levels also differentiate PTSD from controls, Young and Breslau reported that urinary catecholamines, but not cortisol, levels distinguish those with PTSD from trauma exposed individuals without PTSD or non-exposed subjects [54]. Previous studies have used urinary analysis of catecholamine neurotransmitters (norepinephrine and dopamine) to delineate those with and without depression [55,56] as well as those that respond to treatment [57,58]. Despite being easy to assay and consistent with our present understanding of psychopathology, the measurement of cortisol and catecholamines is not particularly useful in discriminating between disordered and healthy individuals, and thus these measures are not likely to be informative biomarkers.

It is difficult, if not impossible, for a single molecule to discriminate between all potential diagnoses, symptoms and treatment responses across the broad range of human psychopathology. Indeed biomarkers for SCZ have been consistently implicated in a variety of psychiatric disorders as well; the common link is that all of these putative biomarkers have an inflammatory or immune activation component [59,60]. Because of this, investigators have begun to focus on identifying a profile of multiple biological markers to increase predictive capabilities. A recent study compared serum from controls to patients with SCZ, MDD, euthymic BPD and Asperger's Syndrome [61]. Examination of 51 analytes [62] distinguished the serum from the majority SCZs from those with other psychiatric disorders or controls. This study suggests that profiles of multiple biomarkers may be more successful than examination of a single molecule.

Moving beyond this approach, other investigators advocate the use of proteomic approaches to more comprehensively assess how proteins interact temporally and spatially in a particular disease state [16,63,64]. Because expression products can be extensively modified after translation, proteomic approaches provide insight beyond those offered by genetic or epigenetic measures. In a recent study, a shotgun proteomic experiment compared post-mortem tissue from 24 MDD patients and 12 controls [16]. A large number of proteins were identified that differed between the two groups, many of which had been implicated in other psychiatric disorders. In addition, the proteomic signature successfully differentiated MDD patients with and without psychotic symptoms. Proteomic approaches are applicable to all bodily fluids typically explored in biomarker studies and do so in an unbiased manner that may reveal novel markers [65]. However, to realize its potential to biomarker research, predictive differences detected in the brain must also be observable and predictive in peripheral tissues. Future studies in this area are likely to be highly promising.

Neuroimaging & Electroencephalography Biomarkers

Not all potential biomarkers require sampling of fluid or tissues. Magnetic Resonance Imaging (MRI), diffusion tensor imaging (DTI) and positron emission tomography (PET) provide a remarkable ability to detail the morphological and functional characteristics of the brain without being invasive. For example, a recent meta-analysis of neuroimaging studies identified a number of brain regions whose properties reflect clinically relevant outcomes in depressed subjects and may be appropriate biomarkers [66]. Higher activity levels in the anterior cingulate cortex (ACC) has been observed in patients with MDD and those that are more likely to respond to antidepressants [67,68]; the meta-analysis confirmed that higher baseline activity of the ACC is predictive of clinical improvement [66]. The subgenual ACC is a target for deep brain stimulation, a technique used to treat MDD patients who are resistant to other therapies [69,70].

Similarly, higher baseline activation of the insula predicts poor clinical response in patients with MDD [66]. A study examining brain glucose metabolism with PET scans reported that subjects with lower glucose metabolism in the insula were more likely to respond to cognitive behavioral therapy while those with higher glucose metabolism in the insula were more likely to respond to ecitalopram [71]. While replication of this finding is necessary, it could dramatically reduce the time to identify an effective treatment. Neuroimaging studies have substantial potential to produced informative biomarkers for psychiatric disorders, but many studies have small samples sizes and limited power to detect between group differences. For this reason, meta-analyses will be essential as neuroimaging biomarkers move forward. Neuroimaging is promising, but its predictive value is currently limited. It is also quite expensive, limiting the likelihood that it will be adopted for widespread clinical use [72].

Electroencephalography (EEG) measures brain electrical activity via electrodes placed on the head. Oscillation frequencies associate with brain function and are classified by range: <4 Hz (delta), 4-8 Hz (theta), 8-12 Hz (alpha) and 12-30 Hz (beta). EEG is non-invasive, easy to administer, well tolerated, widely available and much less expensive. However, it has lower spatial resolution compared to neuroimaging methods. Despite this, EEG has widely been used in the diagnosis of epileptic seizures, and is being used to identify potential biomarkers of antidepressant response [73]. For example, studies suggest that baseline theta activity associates with treatment response in patients with MDD [74,75]. Treatment response may also associate with hyperactivity of the theta band in the anterior cingulate cortex [76,77], the region of the brain that associated with antidepressant response in neuroimaging studies [67,68]. The observed increased theta in the ACC may reflect increased metabolism in the ACC in response to effective treatment [78]. An increase in alpha wave activity has also been reported in depressed patients who are not on medication [75,79], and those who respond to SSRI treatment have detectable differences in alpha wave characteristics when compared to non-responders [80-82]. These observations support the idea that EEG measures may be informative for tracking treatment response. However, studies with limited power and uncertainty of findings in the light of comorbidity complicate the interpretation of these studies [83-85].

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A Candidate Biomarker: BDNF

The literature is full of association studies linking psychiatric disorders to varying environmental exposures, genetic or molecular factors and physiological measurements or traits. However, few of these achieve the level of confidence and reproducibility required to investigate it as a biomarker. One example of a gene that has been evaluated as a potential biomarker is Brain-derived neurotrophic factor (BDNF), a small, basic protein with approximately 50% homology to other known neutrophins [86,87]. As a class, neutrophins have been implicated in the development and survival of sympathetic neurons and neural crest-derived sensory neurons [86,88]. BDNF supports existing neurons and promotes growth and differentiation of new ones [89,90]. It also supports in synaptic plasticity, which is involved for learning and memory [91]. Of relevance to its use as a biomarker, BDNF is expressed in the central and peripheral nervous systems at similar levels [92,93].

Changes in BDNF expression or function have been implicated in numerous psychiatric disorders [94-96]. Serum levels of BDNF are lower in subjects with MDD than in healthy controls, but they increase following treatment with an antidepressant [97-100]. DNA methylation of the *BDNF* promoter in peripheral blood delineates MDD cases from controls without any history of psychopathology [34], and methylation of this region has been proposed as a biomarker for depression [15]. Similarly, BDNF has also been proposed as a biomarker for schizophrenia [97-100]. Serum BDNF levels are lower in schizophrenics and also correlate with both positive and negative symptoms [101]. However, BDNF cannot be considered specific biomarker if it predicts both disorders.

Because of the overlap in core symptoms between psychiatric disorders, many biomarker studies focus on symptoms that change with disease status. Indeed this strategy may be more practical for measuring the progression of an illness or for guiding treatment response. BDNF expression and function may simply represent an underlying symptom or intermediate phenotype common to both MDD and schizophrenia. BDNF responds to stress and changes in brain function [102]. Its levels are tightly correlated with the activity of multiple neurotransmitter systems and may be a final common pathway for some psychotropic medications [100,103]. Thus, while BDNF is promising as a biomarker, further studies will be necessary to define its specific utility.

Future Directions

Psychiatric disorders are very complex and their causes are multifactorial [104-106]. Psychiatric diagnoses are inherently made on clinical grounds based on the presence of a particular group of signs and symptoms that result in distress and/or functional impairment. For biomarkers to become a realizable goal, the field must move beyond its current reliance on diagnosis. One way to do this is to identify endophenotypes, originally defined as an internal phenotype discovered by biochemical test or microbiological test [107]. In contrast to other potential traits of interest, endophenotypes should also be heritable and co-segregate with a disorder [108]. This approach has been useful in providing trait markers of psychiatric and other medicals disorders; however, the underlying etiology of endophenotypes may still be heterogeneous [109].

Identification of discrete behavioral or functional characteristics may result in more rigorous study design and greater reproducibility, both for basic and clinical research. The Research Domain Criteria (RDoC) project represents a substantial effort towards accomplishing that goal. RDoC is a concerted effort to classify psychopathology based on distinct observable behavior or neurobiological measures, even if these basic dimensions are common across multiple traditionally defined diagnoses. Efforts such as the RDoC initiative will reduce the heterogeneity in classifying subjects for basic and clinical research, potentially leading to more precise and replicable studies.

In addtion to alternate systems of classification, new technological approaches are being leveraged for biomarker studies. For example, magnetoencephalography (MEG) can provide dynamic information on brain activity, but this approach has not been utilized as extensively as EEG or neuroimaging. MEG signals have been used to successfully categorize subjects with different neurological, psychiatric and medical illensses including multiple sclerosis, Alzheimer's disease, schizophrenia, chronic alcoholism, Sjogren's syndrome and facial pain. In this study, each illness could be distinguished from each other and from healthy controls with a high degree of confidence [110]. Since that initial study, this approach has been applied to autism [111-113], Alzheimer's disease [114], as well as migraine and other pain syndromes [115,116]. However, it has been only sparsely applied to studies of psychiatric disorders and treatment response [117,118]. As MEG and other noninvasive technologies are developed and adopted, we are likely to learn more about how healthy brain activity is altered in the context of psychiatric illness.

Conclusions

The need for biomarkers in the field of psychiatry is clear, but progress towards their development has been limited. With the recent advances in high-throughput biological assays and neuroimaging techniques, it seems that the field is on the forefront of a breakthrough that will translate research findings into reliable clinical tests. In all likelihood, development of a panel of biomarkers or a strategy that combines neuroimaging and peripheral measures may be more productive than reliance on a single measure or technique. Clinically informative biomarkers will likely also be limited in scope to a highly specific group of patients or type of treatment. As the field of psychiatry achieves a greater understanding of the molecular or functional signatures of an individual's diagnosis, relapse, treatment and recovery, access to mental health screening and services will become more widely available.

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