Exploring Genetic Influences on Cognition: Emerging Strategies for Target Validation and Treatment Optimization

John A. Fossella, Sonia Bishop and B.J. Casey

The Sackler Institute for Developmental Psychobiology, Weill Medical College Cornell University, 1300 York Ave, New York, NY 10021, USA

Abstract: Genomic research has produced an abundance of new candidate targets that remain to be validated as potential treatments for neuropsychiatric disorders. Functional neuroimaging, meanwhile, has provided detailed new insights into the neural circuits involved in emotional and cognitive control. At the growing interface between these independent lines of progress, new efforts are underway to unify our understanding of regional brain function with that of genetic and biochemical influences on behavior. Such a unified understanding of the mechanisms involved in cognitive and emotional control may open up new avenues for therapeutic intervention at the pharmacological and behavioral levels. In line with this, a new initiative sponsored by the National Institutes of Mental Health (NIMH) aims to bridge gaps between clinical diagnostics and the molecular processes that influence susceptibility to psychiatric disorders [1]. A major goal of this initiative is to identify the neural and neurochemical substrates of basic cognitive processes that are disrupted in psychiatric disorders and to examine the influence of genetic factors at the cognitive level. This review describes some well-known findings that are at the forefront of this interface. The progress already made indicates that the goals of the new initiative are well founded and achievable.

Keywords: Genetics; Attention; Cognition; Neuroimaging; Pharmacogenetics; Psychopathology

INTRODUCTION

The neural and neuroendocrine circuits that underlie normal and abnormal behavior are widely distributed throughout the brain and body. The distributed nature of these circuits and their complex modulation of neural function presents obstacles to the development of drug therapies aimed at remediating specific aspects of cognitive or emotional regulation. To further complicate new therapy development, the diagnostic criteria and clinically relevant treatment goals for psychiatric disorders are often vague, heterogeneous and not easily correlated with any specific biochemical marker or measure of neural activity. The integration of cognitive paradigms with neuro-imaging through PET and fMRI has however begun to suggest a number of candidate neural circuits that may be disrupted in disorders such as Schizophrenia [2-4], depression [5,6], obsessive-compulsive disorder [7-10], anxiety disorders [11], attention deficit hyperactivity disorder (ADHD) [12-15] and autism [16]. At the same time, long standing evidence shows that these psychiatric disorders are heavily influenced by genetic factors [17-19]. Despite the large genetic contribution, it has been difficult to identify individual genes that contribute to the risk of illness. This may reflect problems with the current symptom-based measures of disorder. As an alternative to symptom-based diagnostic criteria, a more successful approach may be to perform genetic studies using cognitive and neurophysiological ‘endophenotypes’ [20]. This approach has recently gained momentum and forms the basis of a new initiative sponsored by the NIMH [1]. The initiative aims to identify measures of cognitive and neural function that may serve as endpoints and surrogate outcome measures in clinical trials. These measures must meet three important criteria: i) they must reflect a process disruption of which is central to the given disorder (ii) the process must be thought to have a strong genetic component and (iii) the measures must show good test-retest reliability. The goal of this article is to summarize some of the notable progress associated with this initiative and point out the future potential and limitations of the integration of these methods in basic and clinical research.

To illustrate how cognitive methods can bridge the gap between the clinical setting and molecular biology, consider the case of Schizophrenia. According to DSM IV, for a diagnosis of Schizophrenia to be reached an individual needs to show two or more of the following symptoms:- delusions, hallucinations, disorganised speech, disorganized or catatonic behavior and ‘negative’ symptoms (a reduction or loss in normal functions such as language or goal-directed behavior). It is immediately apparent that this leaves room for a huge degree of heterogeneity amongst patients meeting these diagnostic criteria. Indeed, it hardly seems surprising that genetic markers for ‘Schizophrenia’ per se have not been forthcoming. Furthermore, it raises the question of what we should expect such genetic markers to predict. Do we expect a gene for ‘hallucinations’ or a gene for ‘disorganized behavior’? Surely these vague concepts relate to underlying processes, and it is these processes which are more directly influenced by genetic factors. One candidate process (or arguably class of closely-related processes) is that of ‘attentional control’ or ‘executive processing’.

Attentional difficulties have been repeatedly linked to Schizophrenia (see [21] for a review). Attentional deficits have been objectively quantified using sensorimotor gating [22], smooth pursuit eye-tracking [23], set-shifting [24],

*Address correspondence to this author at the Sackler Institute for Developmental Psychobiology, Weill Medical College Cornell University, 1300 York Ave, New York, NY 10021, USA; Tel.: +212-746-5830; E-mail: jaf2014@med.cornell.edu

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Target Validation: at the Interface of Genomics and Functional Neuroimaging

A number of lines of research have begun to exploit the advantages of an integrated cognitive, genetic and neuroimaging approach. Positron emission tomography (PET) is a well-established method for measuring specific biochemical processes in the body over time and in 3-dimensions. Individual differences in radioligand binding are often observed. Two genes, the dopamine transporter (DAT) and the dopamine D2 receptor (DRD2) contain genetic polymorphisms that have been associated with psychiatric illness [37-39]. DRD2 and DAT levels also can be probed using specific PET radioligands suitable for quantitative measures of ligand binding. The dopamine transporter carries a polymorphic 4-basepair repeat that varies in length across human populations. The ability of radioligand to bind to the transporter seems to be influenced by the number of repeats. For example, subjects homozygous for the 10-repeat allele showed significantly lower dopamine transporter binding than carriers of the 9-repeat allele [40]. These results may relate to the mechanisms of alcohol addiction since DAT polymorphisms have been associated with the severity of withdrawal [41]. Similarly, PET and genetic studies show that genetic polymorphisms in the DRD2 gene are associated with differences in DRD2 receptor levels [42]. Since these polymorphisms have been found to contribute to the risk of Schizophrenia and alcoholism [39], it is possible that receptor levels are key mediators of disease risk and perhaps valid targets for clinical development and diagnosis. It would be desirable to extend such PET studies to all genes that have been implicated in mental illness, however, it is difficult to obtain safe and selective radioligands that bind to the ever-increasing numbers of candidate targets.

Magnetic resonance imaging (MRI) is a method whose safety, high spatial and good temporal resolution and relative cost make it attractive to the research and clinical communities. Many studies have found differences in brain anatomy and activity for a variety of brain disorders including Schizophrenia [3], depression [6], anxiety disorders [11] and ADHD [14]. MRI-based measures of brain anatomy are of interest since studies in rodents, nonhuman primates and humans have established that genes are major determinants of overall brain size [43-44]. Whole brain volume in monozygotic and dizygotic twin populations show that individual variation in cortical structure is highly heritable (h2 = 0.9) [45-46]. Functional magnetic resonance imaging (fMRI) goes beyond the structural level to quantify activity of brain networks during discrete time intervals. Structural (MRI) and functional (fMRI) approaches can complement the genetic and cognitive endophenotype aims of the new NIMH initiative. In the context of a fMRI study, Egan and colleagues [36] showed that a methionine/valine polymorphism in the catechol-O-methyl transferase gene (COMT) correlated with both performance on a working memory task and associated levels of regional neural activity. Specifically, those subjects with the valine allele showed worse performance and higher levels of brain activation in the prefrontal cortex. The same valine allele also accounts for a portion of the genetic risk towards Schizophrenia. Thus, by assaying a cognitive process thought to be impaired in Schizophrenia, insights linking genetic susceptibility to both functional neural anatomy and psychiatric diagnostic status were possible. Clinical development of compounds selective for the COMT enzyme are underway and it is hoped that ‘cognitive endpoints’ will prove useful in this process [47]. In addition, the relationship between the met/val polymorphism in the COMT gene and PFC activity during working memory performance may take us a step forward to understanding any impact of a COMT-based treatment upon clinical outcome for individuals with Schizophrenia.

Replications of such multi-tiered genetic and imaging studies are poised to expand as the focus of interest in fMRI studies, population genetic association studies and clinical treatment studies increasingly start to overlap. For example, genetic polymorphisms in the serotonin transporter gene that have been associated with emotional dimensions of psychopathology such as anxiety [48], have also been the focus of fMRI studies [49]. Similarly, polymorphisms in the BDNF gene have been examined in clinically diagnosed Schizophrenia [50], with performance on cognitive tasks involving episodic memory and with hippocampal activation assessed via fMRI during a working memory task [51].

Electroencephalographic (EEG) and event related potential (ERP) measurements have also long been used to probe psychological, cognitive and neurophysiological processes in studies of mental illness and genetics. The extensive literature, temporal specificity, ease and low cost make this approach ideal for validation strategies that exploit cognitive endophenotypes. Although fewer single gene association studies have been reported than for MRI-based studies, the basis for EEG and ERP endophenotypic assays is well substantiated. For example, in alcoholism, a reduction in the P300 amplitude in patients and in first degree relatives has been studied [52]. Additional family and twin studies show that individual differences in the P300 are at least moderately heritable [53,54]. Another ERP
component, the P50, has been used to study early sensory processing of paired stimuli in Schizophrenia [22]. Impairment in the P50 is a reliable marker for Schizophrenia and has been shown to be heritable [31]. Polymorphisms in the alpha 7-nicotinic cholinergic receptor were shown to contribute to the susceptibility of the disorder and a reduction in the P50 response [55].

**Treatment Optimization: at the Interface of Pharmacology, Functional Neuroimaging and Genomics**

Integrating knowledge from molecular, functional anatomic and clinical levels may not only provide insight into the mechanisms of psychopathology, but also yield information that can be used to optimize treatment outcome. Experience with pharmacological therapies shows that there is tremendous variation in how individual patients respond to medication. Schizophrenia, for example, is one of the most well-studied brain disorders and there is an extensive literature on its pharmacologic treatment. One of the difficulties in the pharmacologic treatment of Schizophrenia is the consistent finding that approximately 20% of patients do not respond to initial therapy, an additional 30% do not sustain a response to therapy and some 20% of patients experience adverse side effects that prevent further treatment [56]. While there are many possible reasons for this finding, including diagnostic and environmental heterogeneity, one possible reason for the individual differences in the response to medication may be genetic differences among patients. Pharmacogenetic studies seek to identify specific types of genetic variation influencing the response that individual patients have to a particular medication. Many processes such as drug absorption, distribution and metabolism are known to influence drug response and genes that correspond to these processes such as receptors, transporters and metabolic enzyme have been explored in candidate gene studies. Surprisingly, the predisposition to respond or not respond can be accounted for by variation in relatively few genes. So-called ‘extensive metabolizers’ and ‘poor metabolizers’ of at least 40 drugs can be distinguished by polymorphisms in the cytochrome P450 enzyme CYP2D6 [57-58]. Other P450 genes such as CYP2C19, CYP2C9, CYP2E1 and CYP2A6 as well as the glutathione S-transferase genes GSTM1 and GSTT1 and N-acetyltransferase gene NAT2 have been shown to influence the metabolism of various medications. Variations in CYP2D6, for example, influence the toxicity of tricyclic antidepressants [59] and the breakdown of haloperidol [60]. The molecular genetic influences on metabolism are supported by twin and family investigations of the heritability of medication response [61-63]. As an example, consider that only 30-60% of patients who are resistant to typical antipsychotics show a response to clozapine. Genetic polymorphisms in the serotonin system may mediate clozapine response [64]. PET studies have shown that polymorphisms in the dopamine D1 receptor (DRD1) gene influence baseline metabolic activity in the dorsolateral frontal cortex in response to clozapine treatment [65, 66]. These polymorphisms showed significant associations with changes in attention and working memory; two cognitive functions that are disrupted in Schizophrenia [56] and which are thought to, at least in part, be dependent upon prefrontal cortical function. Taken together, these findings are tantalisingly suggestive about how genetic factors, impairments in cognitive mechanisms and altered neurochemical modulation of the prefrontal cortex may tie together to explain at least one part of the puzzle that Schizophrenia provides. They also indicate how functional neuroimaging and genomics may be used in conjunction to advance our understanding and treatment of psychiatric disorders.

Turning briefly to the issue of adverse side effects, a good example of the potential role of functional genomics here is provided by research into tardive dyskinesia. This is an involuntary movement disorder of the face and body, that occurs in approximately 30% of patients treated with antipsychotic medications. Pharmacogenetic analysis of the DRD3 gene which encodes a dopamine receptor expressed abundantly motor control regions including the basal ganglia and ventral putamen, show that a serine to glycine substitution at amino acid 9 contributes to the overall risk of tardive dyskinesia [67-69]. The risk is further compounded by polymorphisms in the metabolic CYP1A2 gene. Patients who carried the high risk alleles at both DRD3 and CYP1A2 showed the highest levels of tardive dyskinesia while those with the low risk alleles showed the lowest levels of tardive dyskinesia. These findings on adverse effects were further augmented by FDG-PET studies that found that patients with the high risk alleles of DRD3 showed elevated levels of glucose metabolism. Together, these studies have delineated a sub-group of patients for whom antipsychotic medication may be contraindicated.

Just as pharmacogenetics has opened up new avenues for treatment optimization, many groups have explored the possibility that neuroimaging might provide information to optimize treatment response. Differences in brain structure and function between healthy controls and patients have been documented in disorders such as Schizophrenia [2, 4, 51] depression [6], ADHD [70] and anxiety [11,71]. Subsequent studies have examined whether these structural and functional differences are normalized in response to pharmacologic treatment. For example, in Schizophrenia, there are many findings of structural abnormalities such as reduced grey matter, reduced thalamus volume and increased ventricle size, as well as functional abnormalities such as low blood flow in the frontal cortex [34]. Investigations of whether any of these abnormalities can be reversed or partially reversed after treatment with antipsychotic medication consistently find an increase in blood flow in the basal ganglia [72-75]. The basal ganglia shows a structural response to treatment that is dependent on the class of antipsychotic medication given. Treatment with typical antipsychotics such as haloperidol (DRD2 antagonist) may increase the volume of the caudate nucleus while atypical antipsychotics such as clozapine (mixed DRD2, 5HT2A antagonist) show either no change or a reversal of the previous volume increase [4,76]. In addition, the atypical medication risperidone did not affect blood flow in the basal ganglia, while the typical medication led to increased blood flow in the basal ganglia [77]. These structural and functional differences may be related to differences in improvement in positive and negative symptoms and cognitive impairments [78,79] thus providing a basis for the optimization of treatment using neuroimaging. Ideally, these studies need to be
complemented by additional work integrating psychopharmacological techniques with fMRI studies using cognitive paradigms focusing on different aspects of attentional control/executive function. Through integration of genetic analysis, psychopharmacological studies, and both structural and functional neuroimaging techniques, together with careful specification of outcome endpoints in terms of symptom subsets and/or specific cognitive functions, we can hope to make greater progress in both understanding and treating such heterogeneous diagnostic entities as Schizophrenia.

There is also a high degree of heterogeneity within groups of individuals meeting diagnostic criteria for ADHD. This condition provides a second example of the attempt to improve treatment with the aid of genetics and neuro-imaging studies. Structural MRI studies on ADHD consistently show reduced caudate nucleus volumes [12,13,70]. In addition, performance on cognitive tasks designed to measure inhibitory control and activate the frontal cortex and basal ganglia have shown that caudate volume can be an accurate predictor of performance [25,80]. Furthermore, this structural MRI phenotype also predicts response to treatment. Filipek et al., [81] found that subjects with smaller and more symmetrical caudate nuclei showed a more favorable response to treatment with stimulant medication. The Multimodality Treatment of ADHD (MTA) project [82] carries out cognitive, genetic, structural and functional imaging work in various treatment groups in an effort to better understand the underlying mechanisms of ADHD and to develop improved methods for treatment optimization. Swanson et al., [83] has suggested that at least two treatment groups exist in ADHD, one characterized by genetic abnormalities and the other characterized by brain structure abnormalities that might respond differentially to behavioral vs. medication therapy. The development of additional projects along these lines targeted at other psychiatric illnesses may well lead to similar advances in our understanding of Depression, Generalised Anxiety and other vitally important, common, and debilitating but yet remarkably poorly understood conditions.

FUTURE PERSPECTIVES

The confluence of information relating behavior with functional anatomy, physiology and molecular biology has contributed to a more comprehensive understanding of the pathogenesis of brain disorders. Many factors bode well for future progress in treatment development. Firstly, pharmacogenetics has already been used to optimize treatment regimens for chemotherapy [84], peptic ulcer treatment [85], hypertension [86], asthma [87] and antiretroviral therapy for HIV [88] and should be easily adapted to psychopharmacology. Secondly, the NIMH has recognized that cognitive neuroscience can be used to fill knowledge gaps between drug mechanisms and clinical outcome. By incorporating cognitive measures as surrogate endpoints in clinical trials, it is hoped that the so-called ‘translational bottleneck’ can be bridged. The ‘brain imaging initiative’, a $100 million effort sponsored by the National Institute for Drug Abuse (NIDA) aims to collect both brain imaging and genetic data on thousands of human subjects over the next ten years and will provide more extensive evaluation of this principle [89].

Still many regulatory and economic challenges, beyond the scope of this review, remain. The vast economic resources expended in meeting regulatory standards for safety and efficacy pose a barrier to the widespread implementation of more advanced cognitive and genomic approaches. The large sample sizes needed for genetic studies and the accompanying investment in genotyping and neuroimaging technology will be costly. The increased specificity of medicines that are custom tailored by genotype and brain structure/activity will fragment patient markets and conflict with the current ‘one size fits all’ or ‘blockbuster’ drug development model. Even if small, genetically defined clinical trials gain FDA approval, it is not clear whether the cost of development, though cheaper, will be offset by sales to a smaller, anatomically and genetically defined patient populations. These worries however, may be overstated. The Orphan Drug Act, passed by Congress in 1983 offers many financial incentives for medication development for diseases that affect less than 200,000 people [90]. Incentives for treatments that affect small, genetically fragmented populations have been proposed [91]. The most successful example of a personalized medicine is Herceptin™ a treatment designed against a specific form of breast cancer. This treatment was designed based on the finding that about 25% of breast cancer patients overexpress HER-2, a cell surface marker involved in tumor growth [92]. Genetech Inc. first developed a diagnostic test to determine that HER-2 status among patients and then carried out clinical trial among women preselected for their HER-2 status. These studies, carried out from 1994 -1996 demonstrated the clinical efficacy of the treatment in a population of patients [92]. Much like the current NIMH initiative hopes to ensure, FDA approval of Herceptin™ was based on newly approved surrogate endpoints related to tumor shrinkage that set a more specific threshold of efficacy. Currently, annual sales of Herceptin™ have vastly surpassed initial expectations and validated the ‘genetically-based’ personalized medicine strategy. The development of this compound was supported by personalized diagnostic tests and continues to be developed through the use of functional imaging studies [93].

In summary, genomic research has produced an abundance of new target molecules for the treatment of brain disorders in parallel with functional neuroimaging studies providing insights into neural circuits involved in behavior. With this progress, new efforts are underway to unify the understanding of functional brain anatomy with physiological, cellular and molecular processes that influence behavior. In this way, cognitive neuroscience is being viewed as an important intermediate step between bridging cellular neurophysiology and clinical psychiatry. This review has described some well-known findings that bridge this gap based on cognitive neuroscience, functional neuroimaging and genomics.

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