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Review Article

Strategical Initiatives in Schizophrenia Research: Beyond the Genetic Paradigm

Denis Larrivee*

Mind and Brain Institute, Loyola University Chicago, USA and Arts and Sciences, University of Navarra Medical School, Spain

***Corresponding Author:** Denis Larrivee, Mind and Brain Institute, Loyola University Chicago, USA and Arts and Sciences, University of Navarra Medical School, Spain.

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Abstract

Despite decades of study - from whole genome studies to risk alleles and copy number variants - the genetic contribution to manifest schizophrenia symptoms remains an enigma. The absence of alignment implicates a tenuous and non-determinative link between genes and their observable effects in psychiatric behavior and a more plastic and subordinate role for genetics in cognition. Gaining increased traction as an explanans for the lack of correlation between gene influence and behavior is a broadly supported thesis that organismal behavior is structured to overcome limitations imposed by strictly deterministic, genetic influences so as to maximize behavioral variation and its control. That is, top down regulation enables and defines organismal behavior and in doing so employs genes and gene products as vehicles to this end. This apparent subordination of genetic influence on behavior favors top down strategical initiatives over genetic studies in schizophrenia research.

***Keywords**: Schizophrenia; Research Domain Criteria; Whole Genome Study; Cognitive Disease; Genetic Architecture; Psychosis*

Introduction

Schizophrenia is among the five leading causes of disability worldwide, affecting both public and personal health at societal and familial levels [1,2]. Its high prevalence and morbidity [3] has motivated schizophrenia research for decades [4]. Despite considerable research effort its pathophysiology nonetheless remains poorly understood. Exacerbating morbidity, schizophrenia's onset is typically in adolescence or early adulthood, and usually lasts a lifetime [5].

Traditionally, schizophrenia has been clinically diagnosed based on a three part grouping of symptom domains, which include psychosis, disorganization of thoughts and behavior, and negative social and volitional symptoms [6]. Of these, psychosis, characterized by delusions and hallucinations, is nearly always present during manifest illness. Patients may additionally suffer from symptoms of one of the remaining two domains, but rarely from all three. Social and cognitive abnormalities overlap widely with other disorders, such as learning and autistic spectrum disorders, raising issues of how these domains are uniquely distinguished in schizophrenia. Both disorders, for example, are associated with a loss of a coherent sense of self, and alterations in self-other distinctions that also characterize other psychiatric disorders. While clinically useful, schizophrenia's behavioral manifestations have proven difficult to bridge to an underlying biology.

Genetic contribution to schizophrenia

Risk alleles and CNVs

Motivating research strategy is the disease's relatively high heritability and its exhibition of a strong and widely replicated familial association [7]. Family history, notably, is a substantive, broadly replicated indicator of risk and the proportion of variance in liability due to added genetic factors is relatively high, approaching 60% [8]. Due to these considerations, there has been significant interest in identifying the genetic factors that increase risk. Propelling interest, moreover, is an increasingly tractable, large scale sequencing capability that has seen dramatic decreases in the costs of whole genome sequencing. Recent efforts have therefore focused on the acquisition of sheer information mass that can be obtained from comprehensive studies of genetic sources, with an overall objective of improving statistical power. Through global consortia like the Psychiatric Genomics Consortium, genomic sequencing has been used to study widely different cultural and geographically distributed populations, expanding the exploratory range so as to incorporate most genetic variation [9].

The genome wide studies, however, have generally confirmed earlier studies of pro-bands that do not situate as Mendelian alleles; that is, as rare alleles having deterministic effects. Additionally, sequencing studies of individuals with very early onset and treatment resistant schizophrenia have failed to discover clear exonic mutations. On the basis of results from standard genetics approaches or global, large scale assays, no Mendelian contributions to schizophrenia therefore appear to exist. Based on multiple studies most genetic risk is instead accounted for by common variants that individually have minimal contribution to phenotype. Single nuclear polymorphisms with 95% confidence intervals, for example, number upwards of 10,000 or more, each contributing a very small risk, but cumulatively accounting for more than 50% of the overall liability. Indeed, the number of risk alleles is likely to extend to thousands of genes. With approximate Bayesian polygenic analysis, posteriorly projected liability rises to nearly 75%. If this is compared with an estimated genetic liability of roughly 60%, then common variants dominate the genetic contribution to liability.

In addition to risk alleles, accumulated data from the genome wide studies reveal a number of replicable copy number variants (CNVs) in schizophrenia. Such variants are generated by duplications or deletions of moderately large chromosome segments where the addition or loss of gene copies results in variable gene copy numbers. Copy number variation can thus result in enhanced effects from individual risk alleles. A number of CNVs have been recognized as general risk factors for psychiatric diseases, including schizophrenia and autism. Eight have been consistently linked to psychiatric diseases as a group [10,11], with only two affecting specific genes, neurexin 1, 2p16.3 del and vasoactive intestinal peptide receptor 2 (V1PR2). Neither of these latter genes exhibit Mendelian features.

Interactive gene effects

In the absence of single gene influences interactive effects between genes or gene products constitute probable influences that could account for the familial association observed in the disease. Meta-analyses, for instance, have identified clinical abnormalities that accumulate in unaffected relatives of schizophrenia patients as compared to the general population [12]. suggesting that intermediate effects may relate to underlying variability in combinations of common variants. Variable clusters of accumulated affected genes, notably, have the potential to confer vulnerability to intermediate levels of impairment, where they are expressed as specific phenotypes [13]. Compared to the diagnosis of schizophrenia, with its possibility for affecting multiple brain systems, such endophenotypes offer a more restricted domain for studying the effects of impaired alleles. The use of endophenotypes could thus increase the analytical power of quantitative gene mapping by their simpler mode of transmission and the potential to identify phenotypically unaffected but potentially gene carrying relatives [14]. Cognitive deficits which are variably expressed, therefore, represent promising candidates for relating unique phenotypes to gene clusters.

To date a total of thirteen different candidate endophenotypes have been found, selected for reliability, stability and potentially simple rather than complex genetic transmission and distinguished on the basis of neuropsychological, psychophysiological, and personality criteria. Of these, only five, sensorimotor gating, openness, verbal fluency, early visual perception, and spatial working memory, showed moderate familial correlation, with heritability estimates ranging from 37 to 54% [15]. Two of these, sensorimotor gating and openness, exhibited a simple mode of transmission, with sensorimotor gating displaying the closest correspondence between heritability estimate and variance that could be explained by a Mendelian model. The sensorimotor mechanism, however, appears to be distributed among multiple disorders and to be related to reduced dopaminergic and heightened adrenergic activity in cortico-striato-pallido-thalamic path-

ways [15], suggesting that it may be have an epiphenomenal rather than an etiological relationship to schizophrenia, while the openness characterization is variably manifest.

Genetic implications

From the preceding it is apparent that clinical implications from the genetic studies are few [5]. While the genetic results yield broad themes on an overall genetic architecture, there is little insight into well-differentiated molecular targets. The lack of causal clarity, further, is exacerbated by epidemiological studies, some decades old, that reveal the involvement of both heritable and non-heritable determinants. Important environmental influences with increased risk for schizophrenia, for example, include maternal stress and viral infection of the developing nervous system, urban upbringing, and immigrant trauma.

Fitting the genetic data: Genetic determinism vs top down responsivity

The research domain criteria

The absence of Mendelian alleles, extraordinary polygenicity, and low penetrance of identifiable alleles - hence, a general lack of alignment with schizophrenia's clinical symptoms - has been a stated motivation for the National Institute of Mental Health's initiation of a new classification framework and approach for research in schizophrenia and other mental disorders[1], the Research Domain Criteria.

While relying on a legacy of clinically recognizable, psychopathological determinations the initiative proposes to study and classify intermediate anatomical, biochemical, and physiological domains that are subject to pathological perturbation. Its motivation is rooted in the belief that clinical phenomenology has remained descriptive and largely divorced from a biological underpinning that would enable the identification of more precise etiological markers characterizing the disease state[2] [16].

In contrast to descriptive clinical manifestations, intermediate biological domains are here seen as more amenable to the techniques used to measure physical features of the nervous system and so are considered informatively more reliable than symptomatic clinical characterization. Accordingly, it seeks to establish a framework for research [16] on pathophysiology that will better 'match research findings with clinical decision making'.

The RDoC classification rests on three assumptions. First, the framework conceptualizes mental illnesses as brain disorders. In contrast to neurological disorders with identifiable lesions, the RDoC posits that mental disorders can be addressed as disorders of brain circuits. Second, RDoC classification assumes that the dysfunction in neural circuits can be identified with the tools of clinical neuroscience, e.g. electrophysiology, functional neuroimaging, and the new methods for quantifying connections *in vivo;* that is, brain disorders are constituted by objective physical changes leading to circuit disarray that can be detected by such tools. Third, the RDoC framework assumes that data from genetics and clinical neuroscience will yield biosignatures that will augment clinical symptoms and signs used for clinical management; that is, by bridging the gap from lower level genetic origins upwards to neuroscientific substrata.

From these stated assumptions it is evident that the research domain initiative presupposes a tight coupling between lower level genetic, molecular and cellular features associated with brain circuit construction that can be observed in higher order cognitive functions. By grounding mental disease in disorders of brain circuits, therefore, such dysfunctions can be diagnostically assessed for incorrect circuit connections, where the connections can be traced to developmental regimes subject to strict transcriptional oversight and yielding

[1]'Diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics'.

[2]'History shows that predictable problems arise with early, descriptive diagnostic systems designed without an accurate understanding of pathophysiology'.

relatively fixed network operations. Brain circuits are thus understood to be generated from genetic coding, which then maps directly onto behaviors; defective coding, by this reasoning, induces psychiatric symptoms via the routing of defective gene products through dysfunctional circuitry.

In the explicit circuit-based sense that the initiative endorses, functional consequences emerge from computational architectures that upwardly and linearly process behaviorally relevant output. Hence, the genetic architecture is regarded as the source of intermediate and even global level domains; that is, higher order behavior, up to and including the 'organism as a whole' is understood to be the vehicle through which genetic expression is mediated. In its construction of biomarker classification the research domain initiative thus presumes the reflection of this causal order and its contribution to a hetero mixture of clinical symptoms.

Following the logic of this premise, much study has been devoted to identifying genetic factors underpinning schizophrenia's clinical manifestations, including a number of genome wide investigations seeking to detect rare mutations, as noted. The lack of alignment between these, the genetic studies, and clinical pathophysiology, however, has rendered this premise uncertain. Indeed, findings from these studies remain largely non-specific with regard to how genetic influences bear on clinical phenomena, suggesting that the populating of higher order cognitive phenomena from lower level transcriptional and gene product activity is likely to be very indirect. Extant findings indicate, in fact, that genetic influences are a necessary but not a primary determinant of mental behavior, findings that are reminiscent of the inability to use genome sequencing studies taken from the human genome project to make etiological inferences [17] or to establish correlations between gene number and organismal complexity, dubbed the N value paradox. These observations suggest that organizational capacities for complex behavior - traced ultimately to nervous system operation - are largely independent of gene number, genome size, and even gene type.

The organism as a strategical framework for schizophrenia

Gaining increased traction as explanans for the lack of correlation between gene influence and behavior is a thesis supported by a growing body of evidence which indicates that the gene repertoire is itself relatively plastic [18], subject to modulation by factors extrinsic or at least relatively independent of regulation by the genes themselves [19], and the product of top down influences that have become inscribed in its informational archives [20]. That is, within the organism there exist capacities that enable organismal operation to supercede genetic influence so as to flexibly interact with the external world [21]. This thesis posits that the fundamental biological unit is the organism, and not the gene, and that organismal behavior is structured to overcome limitations imposed by a strictly deterministic genetic influence so as to maximize behavioral variation and its control [22]. According to this reading, autonomous, globally integrated behavior is crucial to organismal viability and acts to enlist or constrain the influences of individual gene products; that is, top down regulation enables and defines organismal behavior and in doing so employs genes and gene products as vehicles to this end. A notable mechanistic process often proposed to move beyond strictly genetic influences, for instance, is epigenetics. Hence, an organismal view would predict that the link from gene to circuit - and circuit to cognition - is increasingly tenuous with the upward progression toward the neural regulation of behavior.

The emergence of various functions is therefore fundamentally related to global influences that induce the alignment of such functions with these two aspects [23], evident in an organizational order that governs associations of larger-order dynamic complexes (e.g. seen in organizational motifs and networks and in various organismal behaviors that sustain viability). The chief influences affecting organization and performance, therefore, are situated by the organisms' capacity 'to autonomously structure the circumstances of its survival' [22]. The observations of massive numbers of affected alleles in schizophrenia are certainly consistent with this conclusion. This is to say that cognitive operations governing behaviors can be expected to selectively modulate many subordinate processes that are required by distinctive behaviors and so variably enlist the participation of numerous alleles.

What is ultimately neglected in genetic strategies, therefore, is the determination of the parts, processes, and functions dictated by the dynamic actions of the organism as a whole. For example, in the case of the flagellar motor, the motor's performance must also conform to an organizational design principle to be functional, which is to say that the explanation for the motor's function must include a dimen-

sion beyond that of the succession of internal events leading to functional output. This latter explanation, often termed the "why" or antecedent question of Hempel and Oppenheim [24] is significant for revealing that efficient causal interactions require the design principle as an a priori condition for their realization; hence, answers to the 'how' question reveal only efficient causal interactions enabled by the presence of an organizational form, and not the organizational principle dictating the function. The invoking of design principle is thus significant for revealing that a global cause is necessary to explain the origin of different functions. In other words, rather than determined primarily from gene properties, efficient causal effects involved in various neural functions emerge from an all encompassing organization that is critical for determining which genes are needed for operation. To understand any cellular or organismic phenomenon, therefore, it is necessary to situate the 'local' molecular and 'neural' process causally responsible for it within the 'global' context of the organismal and nervous system that makes it possible in the first place [17]. Viewed from this organismal perspective the parts and processes of the organism are also necessarily framed by the organism's overriding existential objective, which is pursued in its dynamic interaction with the environment.

Implications

Consistent with this line of inference, prior to 2008 all claims of causal genetic factors have failed the test of time [15], with no definitive claims emerging since. These difficulties point rather, to strategical directions that are less conditioned by the identification of specific molecular species and instead involve broader functional entities incorporating multiple components that are not rigidly or exclusively interdependent. The massive number of affected alleles and the generally enigmatic character of manifest clinical symptoms and endophenotypes - reflective of most cognitive diseases; e.g. more than 13 different, major hypotheses have been advanced to date to explain AD etiopathology - pose significant uncertainties for the selection of research strategies, which have as their ultimate objective 'cure of the cause' rather than partial and symptomatic therapeutic intervention. Indeed, the 'Return of the Organism in the 21st century' may offer the requisite explanatory vehicle for cognition and cognitive disease that 20th century DNA and genes established for subcellular biochemistry and metabolic dysfunction.

Conclusion

Together, these findings suggest that standard genetic strategies aimed at isolating causal inferences from among clinically significant alleles are unlikely to prove fruitful for deciphering etiology in the short term, and likely to become an arduous pursuit for the foreseeable future. The studies, rather, implicate a diffuse effect, exerted globally, involving large numbers of molecular functions in affected neurons and circuits; that is, an effect likely to be mediated at systemic and even organismal levels of neuronal function. Hence, the apparent subordination of genetic influence to behavior favors top down strategical initiatives over genetic studies in schizophrenia research.

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