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The Psychiatric Cell Map Initiative: A Convergence Strategy for Schizophrenia?

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Abstract

Despite decades of study on the genetics of schizophrenia - marked by an absence of Mendelian alleles, extraordinary polygenicity and low penetrance of identifiable alleles - there is yet little consensus on how heritability and etiology are linked. Accordingly, new strategies have undertaken to classify intermediate anatomical, biochemical, and physiological domains that may be subject to pathological perturbation on the premise that multiple and diverse perturbations for a given disorder are likely to undergo convergence in the path from genome to clinical phenotype. As a theoretical premise, however, this thesis does not account for aberrations affecting top down regulation, like the inability to attribute self-initiated motor behavior to oneself in schizophrenia patients or to account for voluntary changes in motor circuit dynamics. These findings suggest that study of schizophrenia will be advanced by an improved understanding of top down control over intended behaviors like motor actions rather than bottom up influences on purported common molecular and circuit components..

***Keywords**: Schizophrenia; Psychiatric Cell Map Initiative; Mendelian Alleles*

Introduction

Schizophrenia is among the five leading causes of disability worldwide, affecting both public and personal health at societal and familial levels [1,2]. The disease is known for its relatively high heritability and for exhibiting a strong and widely replicated familial association [3,4]. Yet, despite decades of genetic study there is little consensus on the bridge between heritability and etiological pathology.

A major conclusion of the genetic studies is the polygenic nature of schizophrenia, with risk alleles distributed across the entire genome. Included are many common variants - some estimates place their number in the thousands [5] - with small phenotypic effects, some rare CNVs with moderate penetrance [6] and a few exome variants. In general, the penetrance of these latter is small, nor does there appear to be a direct link to qualitatively distinct symptoms that are observed in clinical settings; hence, while informative regarding the degree of heritable influence, these studies fail to identify specific molecular factors that may substantially influence behavioral symptoms. Accordingly, while it is possible to now assess the relative burden of CNVs and common alleles, to parcel out environmental vs genetic contributions, and to make clinical assessments regarding other family members and their comorbidities [7], the chief theme emerging from the genetic studies is that of little direct effect on clinically recognized symptoms. The range of investigations that have been undertaken over decades of exploration, in fact, from single allele variation to whole genome studies reveal that while genetic influences are clearly at work in cognition [4] - the disease exhibits a demonstrable and statistically significant familial correlation-such influences bear little resemblance to a stepwise biochemical pathway, for which allelic studies and mutational analyses have been traditionally and successfully used for identifying molecular players [8,9].

Bottom up approaches to cognitive disease: The concept of convergence

The research domain criteria: Genetic determinism in circuit failures

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

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] [10].

In contrast to descriptive clinical manifestations, intermediate biological domains are seen as more technically tractable with 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 on pathophysiology that will 'better match research findings and clinical decision making'[3].

The Research Domain Criteria classification rests on three assumptions [11]. First, the RDoC 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 - involved in brain circuit construction - with observed higher order cognitive function. By grounding mental disease in disorders of brain circuits, therefore, such dysfunctions can be diagnostically assessed for incorrect circuit connections, where connectivities can be traced to developmental regimes subject to strict transcriptional oversight and yielding 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, therefore, 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

[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..'

[3]'Enable the identification of targeted treatments …to ensure a better match between research findings and clinical decision making', with specific emphasis on findings from genomics and neuroscience.of pathophysiology..'

be the vehicle through which genetic expression is mediated. In its construction of biomarker classification the research domain initiative thus presupposes a contingency of brain function on this causal order and its contribution to a hetero mixture of clinical symptoms.

The psychiatric cell map initiative: A convergent systems biological approach

This contingency is an explicit feature described in the notion of convergence, a recently proposed theoretical perspective that posits that multiple diverse biological perturbations carrying risk for a given disorder are likely to converge mechanistically in the path from genome to clinical phenotype [12-15]. Endorsed in the Psychiatric Cell Map Initiative, 'the 'converging' pathway is proposed to manifest at many levels, from gene and protein networks within a cell to common patterns of neuronal network dysfunction within the complex, distributed networks of the brain. The National Institute of Mental Health (NIMH), for instance, defines convergent neuroscience as an approach that aims to establish directional bridges across different levels of analysis (e.g. genetic, molecular, cellular, circuit) in order to fully explain emergent phenomena, and ultimately, pathobiology. Higher-level cell-cell interactions, as well as systems-level neural circuitry, especially, is proposed to display behavior that reflects the collective properties of multiple cell types emerging from a 'bottom-up' organization [15]; that is, circuits exhibit manifestations of convergence, in which 'changes in diverse genes, protein networks, cell types, or developmental stages may elicit similar changes in circuit function'. Higher-level cell-cell interactions, as well as systems-level neural circuitry are proposed to represent a promising avenue of convergent investigation, particularly for extending insights gained from a convergent bottom-up approach [16]; that is, circuits represent logical loci for the manifestation of convergence, in which changes in diverse genes, protein networks, cell types, or developmental stages may elicit similar changes in circuit function. By means of hierarchical modular analysis, or other similar approaches, it is proposed to be possible to establish functional relationships leading to testable hypotheses anchoring investigations of higher-order phenotypes [17]; hence, the elimination of key protein entities in lower order networks is expected to impair functional integrity at successive levels of hierarchy, ultimately affecting the behavior of the whole.

As a theoretical premise, convergence closely resembles the mechanistic conception that has been advanced by Machamer, Darden, and Craver (MDC) [18,19], among others, to account for neural operation. In the MDC conception all subordinate mechanisms converge in a 'phenomenon', which is the behavior of the mechanism as a whole; that is, all mechanisms are mechanisms of some phenomenon [20,21]. The mechanism of protein synthesis synthesizes protein channels, for example, which function in the permeability changes needed for action potential generation. The boundaries of a mechanism-what it is and what it is not-are thus fixed by reference to the phenomenon that the mechanism underpins. In the convergent notion, underlying genes and gene products and ultimately cell assemblies control cognition, and so behavior itself.

Top down control: Maximizing behavioral responsivity

Superseding genetic determinism: The organism shapes genetic expression

What is ultimately neglected in a conception of convergence, however, is how the determination of the parts, processes, and functions are themselves dictated by the dynamic actions of the individual or organism as a whole. For example, in the case of a 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 dimension beyond that of the succession of internal events leading to functional output. Similar reasoning holds for the generation of an action potential [22,23], oscillatory phenomena, or memory traces. The invoking of design principle is significant for revealing that a global operational form is necessary to explain the origin of different functions, and their associated neural events. In other words, rather than determined primarily from gene properties, efficient causal effects involved in various neural functions emerge from an all encompassing, dynamic 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 process causally responsible for it within the 'global' context of the organized system that makes it possible in the first place [24]. The pacemaker rhythm of the heart,

for example, is not only 'caused' by the activity of the ion channels at the molecular level, but is also dependent on the organizational functioning of the brain, and even the body as a whole. 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 interactions with the environment.

The emergence of various functions is therefore fundamentally related to global influences that induce the alignment of such functions with these two aspects [25,26], evident in an organizational order that governs associations of larger-order dynamic complexes (e.g. seen in organizational motifs and networks [27] and in various organismal behaviors that sustain viability. 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. Such autonomous activity has bearing on how the nervous system is organized and so also how a cognitive disease like schizophrenia can affect its organization to yield clinically relevant symptoms. Indeed, the evolution of top down influences appears to be driven by the 'need' to overcome limitations imposed by a strictly genetic program for regulating the organism's interactions with the world; that is, a drive to organismal autonomy is objectively facilitated by ceding genetic control to progressive improvements in top down oversight.

Regulating genes: Behavioral effects on gene expression and evolution

Accordingly, the relationship between genetic factors and behavior can be expected to be distant and highly non-linear, as the genetic studies of schizophrenia imply. Instead, the need for the organism as a whole to respond flexibly to its surroundings, would predict that global control over behavioral selection modifies genetic expression, rather than be a functional outcome of it, both across time, evolutionarily, and in the course of individual actions. Moreover, its manifestation in a disease of agency like schizophrenia, would predict little influence on individual genes, but significant effects in top down processes associated with autonomous actions. Considerable evidence now supports both of these predictions.

Evolution

Top down, organismal influences are evidenced by effects on evolutionary and adaptive change, among others, that help to explain lacunae in standard evolutionary theory [28,29]. In the Darwinian legacy the environment assumes a dominant force and externalist relation that shapes the sorts of organisms that come to dominate its adaptive space. Organismal variation arises by chance through genetic change that then endows new organisms with features that maximize survival possibility within the existing space. Such a position, however, neglects the active role that organisms are now known to play in modifying the environment to favor their survival. Kant notably ascribed to them a capacity for purposeful action, which meant that self initiated actions determined their adaptive successes. Indeed, to greater or lesser degrees, it can be demonstrated that organisms determine their food sources and types of habitats, and work to modify local environments, e.g. nests, light flux, or temperature selection. The evolutionary significance of self determination through 'niche construction' and environmental conditioning [30,31] thus resides in the realization that the active modification of the environment is itself a force exerting selection pressure on organisms; conversely, the environment can no longer be considered to be the sole force shaping the genetic repertoire. In other words, top down, active influences that govern organismal behavior share with the environment a significant influence in dictating the genes needed not just for survival but for a host of goal oriented actions, which become inscribed in the organism's genetic heritage.

Spinal cord, operant conditioning

In line with findings on autonomous actions affecting evolutionary patterns are observations from modern experimental paradigms illustrating top down induction of new motor behaviors. These paradigms reveal, among other characteristics, 'voluntary' or operant

initiated conditioning, plasticity in shaping behavior, multi-realizability (overlapping or multi-use functional modules), and distributed control mechanisms over brain and spinal cord. In Operant conditioning the strength of a behavior is modified voluntarily through an associative learning process. Responses to stimuli are under the control of the organism and are operants as, for example, in the case of a child who may face a choice between opening a box and petting a puppy. Operant conditioning modifies behavior based on its consequences, with studies revealing that simple spinal reflex behaviors in humans, monkeys, rats, and even mice can be gradually changed through learning and practice [32]. The change in motor behaviors involves a hierarchy of spinal and supraspinal plasticity [33]; hence, with the operant method, CNS plasticity is broadly targeted by top down control, that is, by the organism, rather than being non-specifically induced.

Cumulatively, these paradigms reveal that the neuronal components of motor behaviors are not rigidly or exclusively interdependent and that the induction of such elements is quasi or even largely independent of unique genes, protein clusters, or, at systemic levels, of individual circuit elements, being instead dictated by apparently intentional control.

Schizophrenia: Distinct changes in global behavior are paired with diffuse genetic effects

Consistent with effects on top down control, impairments in global brain activity have become evident in schizophrenia [34]. The inability of first rank schizophrenia patients to monitor their own actions, for instance, led Frith to propose that the etiological basis for schizophrenia's clinical symptoms lay in a defective central monitoring system that normally functioned to attribute self generated events or even thoughts, to the individual [35]. Dysfunctional monitoring, according to this model, resulted in an inability to correctly attribute the origin of self made actions to oneself, revealed in clinical symptoms of psychosis; symptoms, for example, like acoustic-verbal hallucinations, thought insertion or withdrawal, or delusions of alien control (the so-called "First rank symptoms" [34] that refer to feelings or experiences of losing control of oneself and/or being controlled or influenced by other agents.

Similarly in motor movements, when shown moving hands of uncertain origin, schizophrenia patients were consistently worse than healthy subjects in judging whether the movement they saw was theirs or not. Additionally, the degree of uncertainty was directly related to the severity of the disease. Those with first rank symptoms were worse than those without [36]. In the experiment [37] described the rate of attribution errors in patients with first rank symptoms went up to 80%, as opposed to 50% in patients without such symptoms and 30% in healthy subjects. These symptoms clearly correspond to what can be categorised as attribution errors. Taken together, these results reveal an etiological origin coincident with global control over event execution.

Conclusion

There is now evidence from such diverse sources as evolutionary findings, voluntary effects on brain plasticity, and system perturbations of motor behavior indicating that top down regulation is fundamental to central nervous system function, a strong argument that systemic and top down influences supersede regulation imposed by the genetic order, even while the latter maintains an essential role in determining its operations. This evidence implicates the presence of a distinctly different cognitive architecture from that of the bottom-up, mechanist model proposed in convergence theory. Accordingly, it has bearing on the sorts of studies that may improve traction in investigations of schizophrenia, with its argument for a prioritization of higher order function over that of information based, lower level molecular and cellular operations. Given the systemic integration of an organism, lesions of higher-order neural functions appear linked to dysfunctional global brain activity, with risk alleles contributing non-specifically to cognition. For schizophrenia, these higher order functions can be expected to be subordinated to existential priorities and the integration of the organism as a whole; that is, those functions involved in autonomous pursuits requiring self-recognition and self-directedness are those likely to be disrupted by the disease.

Bibliography

1. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva, Switzerland: WHO Press (2008).

2. Jablensky A. "Epidemiology of schizophrenia: the global burden of disease and disability". *European Archives of Psychiatry and Clinical Neuroscience* 250.6 (2000): 274-285.

3. Cardno AG and Gottesman II. "Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics". *American Journal of Medical Genetics* 97.1 (2000): 12-17.

4. Giusti-Rodriguez P and Sullivan PF. "The genomics of schizophrenia: update and implications". *Journal of Clinical Investigation* 123.11 (2013): 4557-4563.

5. Durbin RM., *et al*. "A map of human genome variation from population scale sequencing". *Nature* 467.7319 (2010): 1061-1073.

6. Malhotra D., *et al*. "High Frequencies of de novo CNVs in bipolar disorder and schizophrenia". *Neuron* 72.6 (2011): 951-963.

7. Parnas J., *et al*. "Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers. Results from the Copenhagen High-Risk Study". *Archives of General Psychiatry* 50.9 (1993): 707-714.

8. Pak W. "Why Drosophila to study phototransduction?" *Neurogenetics* 24.2 (2010): 55-66.

9. Aso Y and Rubin GM. "Dopaminergic neurons write and update memories with cell-type-specific rules". *eLife Sciences* 5 (2016): 156.

10. Insel TR. "Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders". *American Jour- nal of Psychiatry* 167.7 (2010): 748-751.

11. Insel TR. "The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry". *American Journal of Psychiatry* 171.4 (2014): 395-397.

12. Geschwind D and State MW. "Gene hunting in autism spectrum disorder: on the path to precision medicine". *Lancet Neurology* 14.11 (2015): 1109-1120.

13. Sestan N and State MW. "Lost in translation: traversing the complex path from genomics to therapeutics in autism spectrum disorder". *Neuron* 100 (2018): 406-424.

14. Willsey J and State MW. "Autism spectrum disorders: from genes to neurobiology". *Current Opinions Neurobiology* 30 (2015): 92-99.

15. Cantor RM., *et al*. "ASD restrictive and repetitive behaviors associated at 17q21.33: genes prioritized by expression in fetal brains". *Molecular Psychiatry* 23 (2018): 993-1000.

16. Nelson NB and Valakh V. "Excitatory and inhibitory imbalance and circuit homeostasis in autism spectrum disorders". *Neuron* 87.4 (2015): 684-698.

17. Willsey J., *et al*. "The psychiatric cell map initiative: a convergent systems biological approach to illuminating key molecular pathways in neuropsychiatric disorders". *Cell* 174 (2018): 505-520.

18. Machamer P., *et al*. "Thinking about mechanisms". *Philosophy of Science* 67 (2001): 1-25.

19. Kalkman D. "Unifying biology under the search for mechanisms". *Biology and Philosophy* 30 (2015): 447-458.

20. Craver C and Tabery J. "Mechanisms in Science". *The Stanford Encyclopedia of Philosophy* (Summer (2019).

21. Glennan SS. "Mechanisms and the nature of causation". *Erkenntnis* 44.1 (1996): 49-71.

22. Hempel CG and Oppenheim P. "Studies in the logic of explanation". *Philosophy of Science* 55 (1948): 135-175.

23. Braillard PA. "Systems biology and the mechanistic framework". *History and Philosophy of the Life Sciences* 32 (2010): 43-62.

24. Nicholson DJ. "The return of the organism as a fundamental explanatory concept in biology". *Philosophy Compass* 9.5 (2014): 347-359.

25. Walsh DM. "Organisms as natural purposes: The contemporary evolutionary perspective". *Studies in History and Philosophy of Biological and Biomedical Sciences* 37.4 (2006): 771-791.

26. Ruiz-Mirazo K and Moreno A. "Autonomy in evolution: from minimal to complex life". *Synthese* 185 (2012): 21-52.

27. Diez I and Sepulcre J. "Neurogenetic profiles delineate large-scale connectivity dynamics of the human brain". *Nature Communications* 9 (2018): 3876.

28. Kirschner MW and Gerhart JC. "The Plausibility of Life: Resolving Darwin's Dilemma". New Haven: Yale University Press (2005).

29. Müller GB and Newman SA. "Origination of Organismal Form: Beyond the Gene in Developmental and Evolutionary Biology". Cambridge: MIT Press (2003).

30. Odling-Smee J., *et al.* "Niche Construction: The Neglected Process in Evolution". Princeton: Princeton University Press (2003).

31. Lewontin RC. "Organism and environment" In Learning, Development and Culture. H. C. Plotkin (ed.). New York: Wiley Press (1982): 151-172.

32. Wolpaw JR. "The negociated equilibrium model of spinal cord function". *Journal of Physiology* 596 (2018): 3469-3491.

33. Chen XY and Wolpaw JR. "Ablation of cerebellar nuclei prevents H-reflex down conditioning in rats". *Learning and Memory* 12 (2005): 248-254.

34. Jeannerod M. "The sense of agency and its disturbances in schizophrenia: a reappraisal". *Experimental Brain Research* 192 (2009): 527-532.

35. Frith C., *et al*. "Explaining the symptoms of schizophrenia: abnormalities in the awareness of action". *Brain Research Review* 31 (1992): 357-363.

36. Franck N., *et al*. "Defective recognition of one's own actions in schizophrenia patients". *American Journal of Psychiatry* 158 (2001): 454-459.

37. Daprati, E., *et al*. "Looking for the agent: an investigation into consciousness of action and self consciousness in schizophrenic patients". *Cognition* 65 (1997):71-86.

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