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Review Article

Schizophrenia and Cortical Plasticity: Genetic Effects in Top-Down, Organismal Dysfunction

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Abstract

Schizophrenia displays an extraordinary polygenicity, a feature that remains an enduring biological enigma. Loci identified to date likely comprise only a fraction of the variants that exist, with current findings indicating a likely range of common variants with increased risk for schizophrenia numbering in the thousands. Studies of functional genetic architecture from transcriptional and gene regulatory data, moreover, have provided only tentative insights into neurological dysfunction, while micro anatomical pathology is highly variable. Conversely, schizophrenia is known to affect sensory motor representations and current studies show that schizophrenia impairs higher order and potentially global functions that exert top down influences. Integrating information across sensory systems through cortical mapping, moreover, is known to be a critical step toward building a cohesive bodily representation, which undergoes ongoing plastic refinement through organism-environment interactions. Studies of map plasticity further suggest that hierarchical and global scale regulatory systems oversee representation reorganization. Given that a key developmental feature of constructing a bodily representation is that of transitioning to a top down form of governance driven by sensorial activity, it is likely that the observed genetic effects in schizophrenia are constrained by cellular processes operative within a network system that is driven by sensorimotor influences. Consistent with this, genetic ontologies are correlated with activity dependent, functional reorganization. Significantly, sensorimotor processes are intact in schizophrenia suggesting that lower level circuits and bottom up representational structures are not substantially altered by polygenetic effects. The impairments seen in higher order and potentially global functions suggest that schizophrenia's polygenicity chiefly impacts the modulation of global representational assembly, an effect not manifest at cortical map scales.

Key Words: cortical map plasticity; sensori-motor representations; schizophrenia genetic architecture; peripersonal space

1.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 - more than one in every 100 individuals – morbidity [3,4], reduction in life span of some 20 – 25 years [4], and severity of symptoms has motivated schizophrenia research for decades [5]. Despite considerable research effort its pathophysiology remains poorly understood. Schizophrenia's onset is typically in adolescence or early adulthood, and usually lasts a lifetime, often exacerbated by remissions, functional impairment, and a constellation of residual symptoms [6].

The clinical symptoms leading to a diagnosis of schizophrenia are based on a three part grouping of symptom domains, which include psychosis, disorganization of thoughts and behavior, and negative social and volitional symptoms [5]. Of these, psychosis, which is 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 [7], raising issues of how these domains are uniquely distinguished in schizophrenia. While clinically useful, schizophrenia's behavioral manifestations have proven difficult to bridge to an underlying biology. The disease is known, for example, for its relatively high heritability and for exhibiting a strong and widely replicated familial association [8]. Decades of genetic studies, however, have yet to establish an unequivocal bridge between heritability and etiological pathology. Despite a strong familial association, no mendelian variants have been demonstrated and risk alleles are invariably common and of low penetrance. Genome wide studies have established that copy number variants [9] are risk factors, but these involve many genes, are non-specific for schizophrenia, and display increased risk for multiple psychiatric disorders [6]. For example, the 40 new genetic regions added in recent reports [10,11] are broad and do not conclusively implicate specific genes.

Among schizophrenia's most striking genetic characteristics is an extraordinary polygenicity, a feature that remains an enduring enigma. Loci identified to date are probably a fraction of the variants that exist, with current findings indicating a range of common variants with

potentially increased risk for schizophrenia likely to number in the thousands [6]. Numbers of single nuclear polymorphism (SNPs) with an effect on schizophrenia are estimated at over 12,000 [12]. Collectively these account for well over 50% of the total variance in liability to schizophrenia [13]. Given an estimated heritability around 60% [6], common genetic variation appears to account for the predominant share of heritability in schizophrenia. In line with this, early proposals that schizophrenia risk would include many exonic variants of strong effect have failed to garner substantive evidence [14]. These studies provide strong evidence that the genetic risk for schizophrenia is due to the concerted effects of large numbers of genes that individually exert only small phenotypic influence.

The vast number and range of common alleles suggest that genetic risk factors do not target specific tissues and are potentially widely distributed throughout the brain and nervous system. Accordingly, to clarify whether the products of these genes exert their effects on specific targets, recent efforts have focused on the spatiotemporal aspects of genetic expression within the nervous system. Variation in patterns of genetic expression is ongoing throughout the life of the individual, occurring during development [15] and in adulthood in response to environmental factors. In early life, neuronal circuits are structured and connections formed and reformed at different stages of brain development, requiring control over gene products needed for these processes. Throughout life, moreover, the nervous system, and brain especially, is continually shaped by physiological changes and experiences [16]

A system capable of such flexible reorganization, however, harbors the risk of unwanted change, suggesting that studies of gene expression alone may be insufficient to clarify how genetic factors contribute to schizophrenia. For example, faulty practice or excessive demand in the presence of certain predisposing factors may result in unwanted cortical rearrangement and lead to disease [17]. It is manifest that such adaptive changes are subject to regulatory control, which is likely to oversee the spatiotemporal aspects of genetic expression in the brain. Intuitively, the wider the plastic induced changes, the more extensive the regulatory network needed to integrate the changes into brain functioning. Importantly, a key aspect of the regulation of plastic change is the transition from genetic regulation occurring during development, involving patterns of genetic expression conducted by epigenetic mechanisms, to activity dependent regulation that aligns neuronal populations. To date, however, studies of how the expression of risk factors in schizophrenia may affect plastic processes at either of these stages remains indeterminate.

Extensive research in the field of cortical plasticity over the past 30 years, has revealed that the cerebral cortex is a dynamic assembly of highly interconnected and spatially distributed neuronal networks whose morphological and functional connectivity is continuously modified by use-dependent plasticity mechanisms [18]. Salient experience and intensive training lead to widespread organizational changes within the subcortical and cortical representations involved in sensory perception and motor control, thereby promoting new sensorimotor and cognitive skills.

There is compelling evidence that embedded in cortical maps are sensory and motor representations that are use- dependent, dynamically maintained, and involved in plastic changes associated with perceptual and motor learning abilities. Such representations are built through multisensory interactions underpinned by anatomical and functional neural networks. Extant evidence indicates that primary sensory cortical areas do not work in segregation but play a role in early processes of multisensory integration and are mediated by sensorial activity. Integrating information across these sensory systems is known to be a critical step toward building a cohesive representation of the environment and one's body and, as illustrated by numerous illusions, scaffolds subjective experience of the world and self [19].

Significantly, the transfer of function to distributed cortical areas and subcortical structures appears to represent an adaptive strategy for functional compensation [18]. There is a growing consensus that subject-environment interactions, by continuously refining synaptic connectivity and reshaping the anatomical and functional architecture of neural circuits, promote adaptive behavior throughout life. Studies of plastic map reorganization thus suggest that hierarchical and global scale regulatory systems are needed to oversee map reorganization for functional behaviors and that these are built from bodily representations acquired through interaction with the environment. The generation of this or a similar representation as a regulatory device is thus likely to be an essential step in the construction of a robust framework for integrating plastic changes and for executing environmental responses and is likely to include such key features as bodily ownership and/or bodily self consciousness [19]. By contrast, impairments in processes associated with its generation, as may occur in schizophrenia, are likely to result in impaired plastic integration and environmental responses.

Here, we will argue that the effect of polygenicity in schizophrenia is consistent with a disruption in the ability of sensorial activity to generate such a comprehensive framework, i.e., a top down representation regulating cortical plasticity processes, whereas it is inconsistent with activity independent defects occurring during development that are genetically driven.

[2] Genetic and Epigenetic Features of Schizophrenia

While, early etiological hypotheses of schizophrenia posited deterministic exon mutations, these are now regarded as unsupported. Most current evidence indicates that psychiatric disorders, especially schizophrenia, are highly polygenic [14]. Hundreds of different genetic variants are known that potentially influence disease progress. In the case of schizophrenia this situation is significantly amplified, with variant numbers likely involving upwards of thousands. A key empirical finding, moreover, is that genetic risk can be non-specific and overlap across many adult and childhood-onset psychiatric disorders [20]. Included among the common variants are some SNPs mapping to the major histocompatibility complex and early developmental pathways. Significantly, no Mendelian forms of schizophrenia (i.e., rare mutations with deterministic effects) have been identified via standard medical genetics approaches or genomics studies, revealing a distinctly non-Mendelian form of inheritance. This conclusion is bolstered by a sequencing study focusing on individuals with early-onset and treatment-resistant schizophrenia, which identified no clear exonic mutations [21].

The genetic architecture of schizophrenia emerging from these studies is diverse and includes loci across the allelic spectrum [6,14]. These include exonic and non-exonic loci - apparently all common variants of subtle effect - as well as rare and more penetrant copy number variants (CNVs), segments of DNA containing multiple gene doses. A number of CNVs appear to elevate the relative risk for schizophrenia. These usually arise de novo, mainly through non-allelic homologous recombination that may entail duplications, deletions, or both. CNVs contain multiple alleles and are associated with the disruption of a range of developmental programs both within the brain or outside of it, e.g., cardiac, gut, endocrine, and other organs or systems. CNVs generally confer increased risk for multiple psychiatric disorders and typically display highly variable penetrance [22].

Despite the current broad based knowledge of the genetic architecture of schizophrenia, understanding how it contributes to etiology also requires much knowledge of the functional genomic architecture—i.e., the relation between implicated loci and regulatory processes that influence gene expression and affect biological processes. This understanding is at an earlier stage.

Most genetic variation that contributes to common psychiatric disorders is not in protein-coding regions, which is likely to be the case for

schizophrenia also, implicating regulatory sites that can affect biochemical pathways. To locate such regulatory sites requires 'annotation' of non-coding regions [23]. This is complicated by the variety of mechanisms and variable genetic distances from potential sites, requiring a variety of methodological approaches [24]. Such approaches can include, for example, gene expression surveys, open chromatin, eQTLs, chromatin QTLs, methylation QTLs, histone marks, and regulatory chromatin interactions, which are carried out initially for bulk tissues or sorted types of cells but increasingly employed at the single-cell level.

A majority of non-coding regions have regulatory functions that are shared across tissues, although a remaining, substantive portion appears to be cell specific [26], which may be important for the brain with its higher and longer developmental trajectory compared to other tissues.

To date, variants of roughly 50 genes encoding different chromatin regulators, have been tentatively linked to various neurodevelopmental syndromes [27]. While chromatin defects in the brain were traditionally considered static lesions of early development that occurred in the context of rare genetic syndromes, more recent studies show that mutations and maladaptations of the epigenetic machinery cover a much wider continuum. These include transcriptional human brain networks that span development or brain regions or more generalized protein-protein interaction networks (PPIs) [28] and are correlated with molecular pathways, developmental epochs, or brain circuits based on enrichment of genetic variation. In one study master regulator candidates identified in schizophrenia were correlated with functional enrichments of the dorsolateral prefrontal cortex. Here, SZ showed enrichment of processes related to the cytoskeleton and neuronal structure, with some effect on ion transport and homeostasis. Despite such results, in other cases of clear genetic heterogeneity such as that of ASD and SCZ, risk in both diseases was seen to converge on shared molecular pathways [29], challenging the notion that intracellular and molecular processes can be directly mapped to neural and brain functioning.

Currently, thus, genome wide studies have yielded comprehensive and detailed portraits of the genetic architecture of schizophrenia, whereas knowledge of the functional genomic architecture - how these loci interact in the nucleus (often across large distances), how gene and isoform expression are coordinated for many genes, and how these affect networks – is incomplete, with expression details of brain regions, cell types, and developmental stages, i.e., where and when functional architectures are operative, not fully determined. Nonetheless, while application of functional genomic approaches to define regulatory regions and target genes has yielded some tentative clues as to the developmental and cell type architecture of psychiatric disorders, transcriptional roles in cell populations and neuronal organization is likely to be highly constrained by network and circuit structures.

[3] Sensory-motor Representations Embedded in Topographic Cortical Maps Undergo Plastic Changes

Even with the availability of knowledge of genetic architecture, development, and gene expression, the etiopathology of schizophrenia is unlikely to be fully accounted for by developmental events overseen by genetic regulation. Neurons, notably, do not function in isolation and their activity depends on the dynamical interplay between their intrinsic properties, inputs from other neurons, and interaction with the environment. In principle, developmental events alone cannot accommodate this dynamic interplay, since these rely on bottom up genetic programming rather than on top down functions carried out by large populations of neurons. Psychiatric and behavioral pathologies are thus likely to be chiefly affected by how interaction with the environment shapes the nervous system.

Indeed, etiopathologies of psychiatric diseases are likely to arise at the intersection of the transition from developmental and genetic control to top down regulation, given the fundamental role of sensori-motor activity in shaping the nervous system. Numerous studies show that the interaction with the environment modifies the nervous system through plastic change [18]. Topographical representations of sensory information, particularly, are emerging as a fundamental, modifiable, organizational patterns for perceptual processing across the sensory cortex in many mammalian species [30,31]. These organized topographies within sensory pathways function to compare and combine information carried by various specialized neuronal populations. For example, to enhance the brain's ability to discriminate among different stimuli, sensory neurons that respond to similar features are frequently organized into distinct clusters or columns, which is likely to increase the efficiency of such local processes as lateral inhibition and gain control.

All modalities studied to date have been found to contain maps that align sensory features of the environment with orderly representations within the cortex. Somatosensory areas containing topographic maps of the body surface are a major feature of parietal cortex. In primates, the parietal cortex contains four somatosensory areas, each with its own map, while rodents have at least three. Within each map, intracortical circuits process tactile information, mediate spatial integration, and support active sensation. Somatosensory maps are plastic throughout life in response to altered use or injury. In humans, the most extensively studied cortical map is the representation of visual space.

The visual cortex contains multiple regions in which neurons are organized with respect to the neural arrangement of the retina, [32], which serves as a map of visual space known as a visual field map (VFM). Recent studies have also revealed cortical field maps (CFMs) in the human auditory cortex and partial CFM topographies for olfaction and gustation (taste). Together, these findings suggest that CFMs serve as building blocks of sensory processing [33,34].

Plastic changes in maps

Cortical and subcortical somatotopic representations in the adult mammalian cortex are not static neuroanatomical and functional entities and remain malleable beyond critical periods of post-natal development. They are also substantially reorganized after peripheral nerve lesion, amputation, or spinal cord injury [18,35].

Significantly, cortical representations of sensory surfaces that reorganize after partial peripheral deactivations come to be activated by inputs from skin regions near the deactivated zone. In humans with forelimb amputations, sensations referred to the missing hand during stimulation of the remaining arm have been taken as evidence of cortical reorganization. These more extensive adjustments are too large to be explained by the potentiation of any known connections existing in normal animals, implicating additional mechanisms. For example, these data provide evidence that one of the mechanisms subserving large scale reorganization in the cortex is a relay of topographic changes that occur subcortically.

Building on these findings, in vivo imaging studies reveal that dendritic rearrangement provide the connectivity changes that could act as the substrate of adult cortical plasticity [18]. These studies have shown that while a number of dentritic spines remain stable over several weeks, subsets of spines exhibit sprouting and retraction associated with synapse formation and elimination after sensory deprivation. Such studies suggest that sensory representations in the adult brain are dynamically maintained and that cortical plasticity is a multifaceted property involved in recovery of function and perceptual learning.

Collectively, these findings support the notion that subject–environment interactions continuously refine synaptic connectivity throughout life, reshaping the architecture of neural circuits and remodeling sensory representa- tions embedded in topographic maps [36].

[4] Regulating the Plasticity of Cortical Maps

Perceptual representations are built from cortical maps through multisensory interactions that are underpinned by dense anatomical and functional neural networks [18,42]. It is therefore reasonable to conclude that control over changes in these representations will engage plasticity mechanisms associated with the constituent cortical maps. This engagement is likely to feature several properties, including multisensory integration, a homeostatic and global framework, and top down oversight.

Multisensory integration

There is compelling evidence that primary sensory cortical areas do not work in segregation but play a role in early processes of multisensory integration [37]. The medial superior temporal complex, for instance, was initially classified as part of the visual system, but has since been found to contain multisensory integrative mechanisms. [38]. Consistent with this, unilateral vestibular loss produces a well-known vestibular syndrome in humans and animals that includes posturo-locomotor, oculomotor, and cognitive disorders whose expression gradually decreases over time [39]. To compensate for the loss of vestibular inputs, the central nervous system initiates multimodal sensory substitution and synaptic reweighting [40] that mainly take place within the vestibular nuclei and other subcortical and cortical structures [41]. Additionally, distinct sets of neurons display characteristics consistent with the integration of multiple senses. Recordings from certain cat neurons display non-linear effects in summed neural gain, for example.

Global representations and plasticity regulation

Functionally, multisensory integration serves the purpose of enabling organism–environment interactions. Hence, the integration of sensory input must be framed by representations of the perceiver that behaves and interacts with environmental events. Critically, the perceiver is linked to his physical body, which is always present in every experience. Bodily representation can therefore be expected to constitute a framework within which multisensory integration is globally organized. Indeed, current evidence is consistent with the notion that any experience of the external world ought to rely on a multisensory bodily representation of the entity to be subject of the experience [42]. Motion perception, for example, which arises from multisensory inputs, needs to be considered in such a global sensory framework, within which neuronal populations process and integrate multiple information sources relevant to organismal behavior [43].

One candidate that has been posited to serve in this role is the peripersonal space (PPS) [42]. Studies of the PPS reveal that it is the domain immediately adjacent to and surrounding an organism's body and hence acts as an immediate interface between the body and environment. It is encoded by multisensory neurons within a fronto- parietal network that possesses somatosensory receptive fields. It has been suggested that the PPS constitutes an interface for body–environment interactions in which potential contacts with external stimuli are detected and initiate reactionary (defensive or approaching) behaviors. This space has been documented around different body parts, including the hands, face, and trunk, and is posited to operate as a stochastic body representation, i.e., a representation making statistical inferences about prospective events.

Much evidence indicates that this bodily representation is distributed across the brain, presumably through nerve networks, which have a central focus in the parietal cortex. A recent study reveals that five different medio-laterally oriented pillar domains span the extent of the parieto-frontal network, the posterior parietal, anterior parietal, cingulate, frontal, and prefrontal cortex. Different information processing streams encode, for example, fast hand reaching and its control, complex visuomotor action spaces, hand grasping, action/intention recognition, oculomotor intention and visual attention, as well as behavioral goals and strategies, and reward and decision value outcome.

These appear to be embedded within a larger eye–hand coordination network, from which they can be selectively set in motion by task demands. [44]

Plastic changes occurring in this system are also distributed widely across the nervous system. Studies of the separation of the spinal cord from the brain and their connection through experimentally accessible tracts, notably, have made it possible to show that motor learning depends on plasticity in both structures, which interact to produce a new behaviour [45]. For example, examination of the neural substrates of H-reflex conditioning during functional recovery after peripheral denervation and motor sequence learning shows that all have both cranial and spinal components, suggesting that the substrates of other motor behaviors are similarly distributed.

Top Down regulation of representational plasticity

The presence of bodily representations is strong evidence for the existence of a corresponding global regulatory system of representational plasticity. Extant evidence from numerous sources supports the notion that it is overseen by top down control.

Recent evidence shows, for example, that visual and motor plasticity share common neural mechanisms suggesting their interaction [46]. This is confirmed by findings showing that when visual and motor plasticity are elicited at the same time in adult humans, visual plasticity is impaired, while motor plasticity is spared. Simultaneous activation of working memory and visual plasticity also leads to impairment in visual plasticity. These unilateral interactions between visual, working memory, and motor plasticity demonstrate a clear link between these three forms of plasticity. Hence, local neuroplasticity in separate systems is likely to be regulated globally, to preserve overall homeostasis in the brain.

In cases of reward stimuli, modulation of top down inhibitory input is known to adjust stimulus representations [47]. For instance, recent experimental findings suggest that inhibitory circuits exert top down influences to regulate learning and are themselves highly modulated by diverse long-range inputs such as reward signals. Interneuron circuits can store information about rewarded stimuli to yield long-term changes in excitatory connectivity in the absence of further reward. In these circuits stimulus-tuned somatostatin-positive interneurons develop strong connections to parvalbumin-positive interneurons during reward, selectively disinhibiting pyramidal layer neurons henceforth. This triggers excitatory plasticity, resulting in enhanced stimulus representation.

In other cases, it is known that learning enhances top down modulation of representations by higher brain areas, while suppressing bottom up sensory inputs [48]. One study of the effect of associative learning on circuit mechanisms thought to underly representations monitored long term changes in the activity of L2/3 excitatory neurons in the visual cortex in conjunction with the activity of L4 neurons, a bottom up source, and retrosplenial cortex neurons, a top down source. During learning, L4 responses gradually weakened, while RSC inputs became stronger. Moreover, the temporal response of L2/3 assumed a ramp-up response with learning, coinciding with a similar change in RSC inputs. These changes coincided with reduced the activity of somatostatin-expressing inhibitory neurons (SOM-INs) in V1 limiting suppressive effects of this activity. When disrupted by RSC inactivation or SOM-IN activation the learning induced changes were reversed. The results thus demonstrate a plastic shift in excitation properties that is directly related to the top down modulation caused by learning.

Several studies have shown that top down modulation involves corticofugal projections, which are ubiquitous across mammalian sensory systems and enable the neocortex to control ascending sensory representations in a predictive or feedback manner. In the case of the mouse auditory cortex the inferior colliculus (IC) is a major descending auditory pathway that controls IC neuron selectivity, plasticity, and

auditory perceptual learning. In one study IC neurons integrated inputs from multiple corticofugal axons, generating reliable, tonic depolarizations even during prolonged presynaptic activity. Additionally, activating ascending and descending pathways at latencies expected to occur in vivo caused an NMDA receptor-dependent, supralinear excitatory postsynaptic potential summation, indicating that descending signals could nonlinearly amplify IC neurons' immediate acoustic responses. These results showed that heterosynaptic cooperativity could influence the auditory cortico-collicular pathway's role in plasticity and perceptual learning.

[5] Activity Dependent Generation of Sensory and Motor Representations

Currently, most evidence indicates that genetically programmed, developmental events transition to top down regulatory oversight and that this transition is mediated by sensorial activity. Sensorial activity continues to modulate cortical maps throughout life and constitutes a primary vehicle for shaping global representations. Much of this evidence has been obtained from studies of cortical map plasticity, suggesting that the refining of sensorimotor representations is a critical element needed to oversee interactions with the world.

Some of the most dramatic instances of sensorial modulation of cortical maps have been obtained in the visual system. In early development, responsiveness to visual input in the binocular visual cortex is nearly fully attenuated by monocular deprivation (MD) [49] Termed ocular dominance plasticity (ODP), attenuation occurs early in development and anatomically corresponds with an absence of 'ocular dominance columns' that form in the presence of normal visual input. The development of such patterned eye-specific connections depends on action potentials in the optic nerve fibers, which occurs even before the retina receives visual input [50]. With attenuation during this critical period, there is expansion of cortical maps associated with the unoccluded eye into the receptive field of the contralateral eye. Changes in inhibitory circuitry are a major contributing mechanism during the critical period, triggering the initiation of plasticity in the V1 region of the cortex. [50]. In the visual cortex, the development of inhibitory GABA circuitry precedes CP onset, with inhibitory inputs to excitatory neurons strengthening in L4 and L2/3 following opening of the eye

In adults, sensory input continues to modulate plastic processes that shape cortical mapping. Following peripheral damage to a sensory modality, for example, multimodal integration can induce sensory substitution in the deprived cortical zones and enhance a compensatory plasticity in the spared areas. The capacity for tactile perception to substitute, in part, for loss of vision is well established [52]. Neuroimaging studies, for example, give evidence that the occipital visual cortex can be recruited by tactile tasks in blind subjects. In one study use of positron emission tomography (PET) showed that blind subjects activate primary and secondary visual cortical areas during tactile discrimination tasks, unlike normal subjects who exhibited deactivation in these areas [53]. In monkeys, stimulation of digit tips, but not whole digits specifically increases the extent of the corresponding representational zones within layer IV of area 3b in SI and sharpens the sizes of constituent neurons' receptive fields [54].

Expansion and refinement of such topographic representations involve large-scale receptive field shifts on skin surfaces, implying an orderly redistribution of effective inputs within the reorganized cortical network [55], while simultaneously occurring at the expense of adjacent proprioceptive maps. Experience-dependent remodeling of receptive fields and topographic organization of the auditory cortex have also been observed in behaviorally trained animals [56]. For instance, monkeys trained on auditory frequency discrimination exhibited sharper receptive fields and enlarged regions of the primary auditory cortex (A1) responding to the trained frequency [55].

Activity induced sensorial modification also functions to shape not just existing representations but also the memory based recollection of such representations. Stimulus selective response plasticity, for example, is a form of activity dependent plasticity that displays a lasting latent modification of the visual cortex (V1), which occurs when responding to novel visual stimuli [57]. The SRP is highly selective for a variety of stimulus features, such as orientation, frequency, and contrast and its manifestation is seen only after initial recording intervals and many hours of sleep. Mechanistically, the SRP requires not only canonical Hebbian synaptic plasticity within V1, but also the opposing engagement of two subclasses of cortical inhibitory neurons: the parvalbumin- and somatostatin- expressing GABAergic interneurons. These latter evoke pronounced shifts in the power of cortical oscillations from high frequency (gamma) to low frequency (alpha/beta).

Supporting activity dependent, cortical map changes are a host of subcellular plasticity mechanisms. While Hebbian plasticity is perhaps best known, occurring when an action potential closely aligns with a previously depolarized membrane, continued activation of synaptic junctions can lead to over-potentiation. This possibility led to the discovery of another form of plasticity that can overcome overpotentiation. In this form of plasticity neurons have evolved the ability to regulate all the synapses on a neuron in unison in an orchestrated fashion, a process termed scaling. Scaling serves to coordinately regulate the entire neuronal complement of synaptic receptors such that the entire population of synapses is scaled up or down, thereby keeping the total transmitter gated conductance within a stable range that does not exceed the homeostatic capacity of the neuron.

Collectively, these and other mechanisms, such as back-propagating action potentials, time dependent coincidence occurrence and modulation of membrane biophysical properties [58], and synaptic non-neuronal partnering - e.g., astrocytic modulation of information flow that is critically dependent on and contributory to localized activity [59] - support a large array of activity dependent processes enabling neuronally driven, cortical map modulation.

[6] Aligning Schizophrenia's Genetic and Epigenetic Findings With Representational Plasticity in Top Down and Developmental Models

Given its potential for phenotypic and behavioral variability, representational plasticity affords a prospective neurological substrate to which the clinical manifestations of schizophrenia can be mapped [14]. Using this substrate thus enables consideration of how closely aligned genetic and epigenetic factors are to modulating sensorial representations in schizophrenia. Much current evidence suggests an indirect influence at the level of the global control over plasticity mediated through neuronal and glial populations that give rise to behavior.

For one thing, activity dependent plasticity engages transcription in all cell classes, from neurons and their glial partners to non-neuronal cells including endothelia [60] implicating a role for systemic cellular events. Receptive fields of cortical maps are not hard-wired but continually adjust to ongoing changes in incoming sensory information. This experience dependent plasticity continually shapes cortical map representations. When rat whiskers are removed, for example, neural activity for the spared whiskers is potentiated in neighboring cortical columns, resulting in spared whisker representation expanding into adjacent cortical columns of the deprived whisker fields [61]. Moreover, glial cell morphology and activity can be modulated in an experience dependent manner [62]. For example, astrocytic coverage of synapses changes dynamically in response to neuronal activity [59] directly influencing synaptic transmission. Astrocytes are also known to exert long term and long distance modulatory effects on synaptic activity.

Transcriptional studies reveal that over time transcription is dynamically correlated with recent experience. A common way to interpret large-scale molecular datasets is through the use of gene ontology (GO) features, which can comprise cell components, molecular functions, or processes that genes contribute to. In one study, the majority of transcriptional

regulation after exposure to an enriched environment (EEE) can be linked to general cellular processes (Figure 3A), although the direction of the transcriptional regulation, i.e. up- vs down-regulation, depends on the sensory history; immediately after EEE the vast majority of differentially expressed transcripts are up- regulated (170 upregulated, 31 downregulated), whereas in the 4h group downregulated genes are more prevalent (29 upregulated, 98 downregulated) [63].

Collectively, these studies show that changes in genetic expression are linked to plastic changes that depend on the level of the cellular organization.

This is consistent with the notion that the concerted operation of neuron groups lies at the basis of functions performed by the nervous system and interfaces with the environment to generate increasingly refined behaviors. Accordingly, the effect of these genes lies in their impact on the functional organization of cellular clusters, such as resting state networks or cortical maps; that is, at a systemic and organizational level. Given schizophrenia's breadth of polygenicity, the very modest influence of individual genes, and their cumulative heritability, these genetic factors are unlikely to exert significant influence on specific mechanisms primarily operative at subcellular or low level cellular circuits [14]; that is, they do not selectively target microanatomical or physiological structures, but collectively influence the behavior of larger neuronal and glial populations.

Consistent with this, sensorimotor processes such as action identification, are intact in individuals with schizophrenia, suggesting that lower level circuits and bottom up representational structures are not substantially affected by the disease [64]. By contrast, a wide variety of studies show that schizophrenia impairs higher order and potentially global functions that exert top down influences, including self attribution of motor activities and impaired mirror neuron activity [64-66]. Given that top down influences in animal models are known to modulate the overall plasticity of cortical and subcortical maps, one distinct possibility is that schizophrenia impairs the ability to regulate global plasticity.

It is known, especially, that bodily representation is substantially affected [42], suggesting an impairment in the integration of multisensory inputs at a global level. Infants perseverating toward an object at a site of previous reaching rather than where last seen hidden, as in the A not B test, is regarded as a failure of one of a class of executive control tasks [67]. This failure to move toward a goal where last seen has been interpreted as due to an insufficiency in mechanisms needed to situate the motor plan [68], which are associated with representing the self as the whole body. In like manner, the representation of the body used to configure the spatial domain that distinguishes self from other in social settings is distorted in schizophrenia [42].

Significant impairments are also seen in recognition of the self as the source of one's actions. Motor actions undertaken on behalf of the self, particularly, are an increasingly well understood paradigm for self initiated behavior. There is a general consensus, for instance, that anticipatory internal models function to control and correct externally executed actions that have been identified as self initiated. Significantly, individuals suffering first rank symptoms of schizophrenia are unable to consciously attribute self initiated actions to themselves [64,69] suggesting that the relationship between the planning and execution of motor actions and their source is impaired.

On the basis of this relationship Frith notably proposed the existence of a comparator model that functioned to identify self made actions and that induced false attributions of alien control when impaired [70]. The model proposed by Frith, however, ascribed authorship after actions were undertaken, suggesting that self authorship was unnecessary for their execution. In an elegant series of experiments Fourneret and Jeannerod [64] challenged this hypothesis by exploiting differences in conscious and habitual awareness to assess whether schizophrenia patients were impaired under both conditions or only when new or novel actions were performed. To conduct the experiment they made use of phenomenal features known to characterize the motor simulation mechanism. These features emerged in the cybernetic arrangement of the mechanism, which utilized sensorial feedback from the sense of sight and that of kinesthesis for the execution of actions. While information from the two senses is normally congruent it was possible to experimentally manipulate the sense of sight so that what was seen by the subject was a 'false' visual image. Manipulating the sense of sight in this way yielded a sensorial conflict between the two sets of sensory signals at the time of the motor action. Critically, actions based on this sensorial conflict remained automatic when the conflict was of only modest size. Under these experimental circumstances, normal subjects were able to automatically negociate the experimental paradigm despite remaining unaware of the discrepancy. When schizophrenia subjects performed the same paradigm they were also capable of negociating the discrepancy between the visual and kinesthetic cues; that is, under the same circumstances schizophrenia patients automatically undertook compensatory actions similar to those of normal subjects, indicating that their comparator function was intact, hence the impairment did not lie at a low order, sensorimotor level.

When the conflict was sufficiently large, normal subjects became consciously aware of the disparity and intentionally discounted the 'false' visual input, thereafter attending only to the somatotopic and kinesthetic input to correct their movements, a correction they consciously attributed to themselves. Those with schizophrenia, on the other hand, were significantly impaired in making similar adjustments; hence, the experiments linked the impairment not only to a loss in self recognition, as proposed in the Frith model, but to an impaired agential ability, that is to a global capacity for self regulation, which challenged that thesis. Consistent with these findings other studies have shown that schizophrenia patients are impaired in goal seeking also [71].

By contrast, extant data from animal models suggest that schizophrenia is unlikely to substantially affect early developmental processes, when the initial stages of network and map formation are occurring. During this period synapse organization arises from fate mapping programs and the interaction of activity independent cues that begin to position potential synaptic partners in apposition to each other. Subventricular zones, particularly, contain primitive maps of the cortex that direct neurons to approximate destinations, where synaptogenesis commences with dendritic and axonal proliferation. In this initial phase, synaptic density greatly exceeds the density at maturation suggesting the presence of only rough maps. In fact, this 'circuit scaffolding' is substantially refined by synaptic activity, which 'prunes' away excess synapses and generates organized maps and networks [72].

During these early stages, proto maps are built from smaller units, with limited regulatory oversight. Here, activity- dependent plasticity rules organize synapses into spatial clusters according to the correlated activity they experience [73]. The onset of plasticity during critical periods also requires the introduction of inhibitory circuit elements, including fast-spiking, GABAergic, parvalbumin and interneurons, which begins to initiate and extend map regulation regionally [74]. This is evidenced by the acceleration of critical period onset when stimulating inhibitory circuit maturation, e.g., premature, pharmacological activation of GABAA receptors with benzodiazepines, and by failed maturation of inhibitory neurons via deletion of Gad65, an enzyme needed for production of GABA, which prevents onset of the critical period [75].

Intracortical inhibition also controls the spatial selectivity of cortical neurons through the segregation of converging synaptic inputs into smaller field sets. Receptive-field enlargement of somatosensory neurons, for instance, occurs when GABA-mediated local inhibition is antagonized by an intracortical micro-iontophoretic injection of bicuculline methiodine [76]. GABA levels are regulated in a use-dependent manner, implicating their functional relevance to field refinement. At an organizational level this implies both the sharpening of receptive fields and the remodeling of boundaries between map territories. Consistent

with this, intracortical inhibition following deafferentation is hypothesized to regulate map plasticity by enabling or disabling subsequent activity-dependent strengthening of excitatory connections [77].

Mechanistically, integration of smaller units has been proposed to require the synchronization of neural signals within distributed networks, thus requiring the initial formation of smaller units. In this regard, it is relevant to mention a study exploring the influence of somatosensory inputs on the activity of A1 neurons using laminar current source density and multiunit recordings. The findings from this study show that somatosensory inputs elicited by median nerve stimulation amplify the neuronal responses evoked by auditory inputs during a high-excitability phase of ongoing local neuronal oscillations and suppress those occurring during a low-excitability phase within the supra- granular layers [78]. Further analysis indicated that this effect was mainly due to a somatosensory-induced phase resetting of auditory oscillations to an optimal excitability phase, which enhanced the ensemble response of temporally coherent auditory inputs. Of relevance, it is known that sensory information in visual and posterior parietal areas is stored for reduced lengths of time in SZ compared to normal subjects [79]

Conclusion

To date massive amounts of data have been accumulated on the genetic architecture of schizophrenia, yet the contribution from genetic risk factors and gene function assays remains inconclusive. Behaviorally and neurologically, schizophrenia presents with more distinctive manifestations, including representational and behavioral impairments. Current evidence indicates that representational encodings involve large cellular populations, are modifiable by sensory dependent activity, built from smaller idiosyncratic entities, and coordinated by global top down regulation. The inherent possibility of harm from malconstructed activation patterns implicates global oversight of representational constructs likely to have gone awry in schizophrenia. Strategical initiatives for genetic and epigenetic investigation may thus be best situated within a framework of cortical plasticity regulation.

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