Can the “connectomic way” provide a link between molecular neurobiology and phenomenological psychopathology? The case of schizophrenia

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Summary
Schizophrenia is a severe and complex mental illness whose aetiology remains unknown. Moreover, changing definitions of the diagnostic criteria of schizophrenia over past decades have not contributed to any substantial progress in terms of deeper pathophysiological understanding of the disease. Nevertheless, to date, significant evidence continues to be accumulated from epidemiologic, genetic and preclinical studies that point to a number of genetic factors that play important roles in the pathophysiology of schizophrenia, especially in terms of disrupted synaptic plasticity molecular processes. Specifically, the most recent approach in human research on schizophrenia is represented by “connectomics” or the study of connectomes, which can be defined as comprehensive maps of connections within an organism’s nervous system. Indeed, it has been suggested that schizophrenic pathophysiology might rely on circuit-based dysfunctions that may represent the consequence, on a network scale, of the impairment in synaptic plasticity and neuronal connections that are increasingly found in preclinical molecular research, and that may stem from de novo and/or inherited disease-variants in target genes as well as from aberrant epigenetic mechanisms. On the other hand, circuit-based dysfunctions may underlie the defects in integration of higher-order cognitive functions that characteristically connote schizophrenia patients, and may account for aberrant self-experience which are typically described in phenomenological approaches to the disease. In this paper, we will critically explore the recent advances on molecular, genetic and neuro-imaging research in schizophrenia. Based on these data, we will emphasise the potential of the connectomic framework as an intermediate step between the biological and the phenomenological levels to capture the complexity of schizophrenia manifestations.

Key words
Basic symptoms • Subjective experience • Schizophrenia • Gene • FMRI • Transcriptome • Epigenetics

Introduction
Despite more than a century of extensive studies and descriptions, the clinical characterisation of schizophrenia remains elusive, almost like the borders of its spectrum conditions. As observed by Tandon et al. 1, “we know enough about the present construct of schizophrenia to recognize that it may be a conglomeration of disparate entities but our current knowledge is insufficient to delineate them”. Indeed, from the original Kraepelinian construct to contemporary DSM-5 formulations, changing definitions of the diagnostic criteria of schizophrenia have not provided any substantial progress – at least in terms of deeper aetiological understanding.
Schizophrenia is syndromically characterised by several, often concomitant symptomatic dimensions, which are typically clustered in major dimensional sets (e.g. positive, negative, cognitive, disorganisation, mood and motor symptom dimensions). These abnormalities are differentially expressed throughout the course of the illness and encompass characteristic distortions of thinking and perception, interpersonal relating, communicational and cognitive impairments, affective flattening and restricted emotional resonance, motor abnormalities, avolition and apathy.

Beyond these descriptive domains, contemporary phenomenologically-inspired psychopathology has enucleated another cluster of phenomena, i.e. disturbances of the basic sense of self, as a core phenotypic marker of schizophrenia spectrum disorders 2 3. This approach 4, which emphasises the psychopathogenic primacy of subtle disorders of self-awareness in the longitudinal development of schizophrenia spectrum conditions, offers an integrative and dynamic view of schizophrenia that coheres with recent trends in neuroscience. Briefly,
Genetics of schizophrenia

Evidence of a genetic contribution to the aetiology of schizophrenia dates back to early studies in twins and adopted offspring. However, in recent years, research on the genetic underpinnings of the disease has faced a profound acceleration due to the combination of large samples of subjects and technological advances. This has allowed the identification of a large set of “risk variants” that are defined as genetic elements that have been associated with an increased risk (i.e. susceptibility) to develop the illness. These risk variants occur across the entire allelic frequency spectrum, and are in many cases also associated with susceptibility for other neuropsychiatric diseases. Moreover, several different types of genetic elements have been found in association with the risk of schizophrenia. Overall, risk alleles may be grouped in: 1) common alleles, which include single nucleotide polymorphisms (SNPs); 2) rare alleles, which include rare copy number variations (CNVs), single nucleotide variants (SNVs), and insertion/deletion mutations (Ins/Del); 3) de novo mutations, which include CNVs, SNVs or Ins/Del that arise from new (de novo) mutations on the DNA sequence.

A large number of common schizophrenia risk alleles have been identified by means of genome-wide association studies (GWAS). GWAS are large, often consortium-based studies where genetic associations are interrogated on a genome-wide basis in very large samples of schizophrenia patients. Through this strategy, it is now possible to detect the association that schizophrenia has with very common alleles that – given their low effect size – would not reach statistical significance in small or even intermediate size samples if considered independently. Indeed, each of these alleles has a weak effect on schizophrenia risk, with a mean odds ratio (OR) <1.2 (i.e. each allele increases the risk of schizophrenia by 1.2 times in subjects carrying the allele compared to non-carrying subjects). However, taken together, these risk alleles are thought to account for approximately 33-50% of genetic liability to develop the disease. GWAS have clarified that schizophrenia may be conceptualised as a disease with a strong polygenic component involving thousands of common alleles, whose coexistence in the subjects causes a cumulative lifetime risk to develop the disease.

Apart from the earliest GWAS, only a few common risk alleles have been found to be associated with schizophrenia; a recent study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) has identified 128 genome-wide significant associations in 108 discrete loci. In this study, genome-wide genotype data were meta-analysed from 49 ancestry-matched, non-overlapping case-control samples including 34,241 cases and 45,604 controls, and from 3 European family-based samples including 1235 parent affected-offspring trios. Among the 108 genetic loci identified, 83 have not been previously implicated in schizophrenia. Despite the fact that 75% of these loci contain protein-coding genes and an additional 8% were within 20 kb from a gene, only in 10 instances was the associated SNP credibly attributable to a known non-synonymous exonic polymorphism, i.e. determining a variation in the protein sequence of the gene’s protein product. The vast majority of polymorphisms appear to exert their effects through the modulation of gene expression, by means of various genetic elements that will be discussed in the next sections. This assumption was partially corroborated by a confirmatory analysis showing that multiple of the credibly causal SNPs identified in the PGC study contained expression quantitative trait loci (eQTL), which are genetic loci that explain a fraction of the genetic variance of a gene expression phenotype. Notably, the PGC study also robustly confirmed the assumption that the polygenic risk score (PRS) can predict case-control status in independent samples. PRS was generated on the basis of the observation that a considerable proportion of phenotypic variation in polygenic diseases can be explained by the ensemble of markers not achieving significance in independent GWAS studies. Therefore, in previous studies, PRS had been constructed from alleles with modest-to-low statistical association with schizophrenia in GWAS studies explaining, however, only a minor part of the liability variance. In the PGC study, PRS explained about 7% of liability variance, suggesting that this needs to be explored more thoroughly. Intriguingly, when individuals in three independent samples from those constituting the PGC mega-analysis were grouped into PRS deciles (i.e. with increasing number of common risk alleles with high-to-moderate statistical association with schizophrenia), the estimated OR of being affected consistently increased in each independent sample with...
a greater number of schizophrenia risk alleles. These results suggest that extensive efforts should be devoted to characterising the highest possible number of common risk alleles ranging from high to moderate association with schizophrenia, and to study their interaction on the genetic, and possibly, molecular level. Interestingly, among the loci significantly associated with schizophrenia were the DRD2 gene, a number of genes (as GRM3) involved in glutamatergic transmission and synaptic plasticity, voltage-gated calcium channels and genes implicated in immune response.

**Epigenetics and transcriptomics of schizophrenia**

Despite the strongest efforts to decrypt the genetic basis of schizophrenia, the great technological advances in molecular genetics suggest that the majority of genetic liability to the disease is generated by variations in post-transcriptional regulatory elements (epigenome) that control the expression of genomic sequences. Despite the fact that all gene expression regulatory events are often included among epigenetics, we will herein separately consider post-translational modifications of DNA and chromatin, often referred to as epigenetics in the strict sense, and RNA-mediated regulatory mechanisms. Epigenetic mechanisms consist of DNA methylation and modifications of histone and/or chromatin structure. DNA methylation occurs via the DNA methyltransferase (DNMTs) enzyme, which contributes to transfer methyl groups to cytosine residues within CpG islands located in the proximity of gene promoter regions. This enzymatic step transforms cytosine in 5-methylcytosine (5-mC), which represses gene transcription. 5-mC may be further transformed into 5-hydroxymethylcytosine (5-hmC) by TET enzymes, which result in DNA demethylation and de-repression of gene transcription.

In schizophrenia, an over-representation of hypermethylated promoter regions has been found, determining a downregulation of several schizophrenia-related genes. BDNF, reelin (RELN) and COMT are among genes whose expression has been reported to be downregulated as a consequence of hypermethylation. On the other hand, recent studies have demonstrated that TET1 and 5-hmC DNA modifications are increased in the cortex of schizophrenia patients. Overall, it appears that the methylation state in schizophrenia patients may be altered, either in the sense of a hyper- or a hypomethylation on target genes. Notably, the methylation state by epigenetic mechanisms is also strongly affected by pre- and post-natal environmental factors, implicating that the level of gene expression is a dynamic phenomenon, with multiple regulatory steps that are variably modulated. For instance, reduced maternal care may alter both genome-wide and target gene methylation, and thereby their levels of expression, leading to enduring changes that modify adult behaviour and neurobiology.

The regulation of DNA expression is also mediated by non-coding parts of the genome. It has been estimated that, although at least 80% of the genome is actually transcribed, only a minor part (less than 2%) is constituted of protein-coding genes, with the remaining part is composed of non-protein coding elements. Altogether these elements constitute the so-called transcriptome, which is the object of the most advanced research. Non-coding RNA has evolved with organism complexity, leading to an extremely sophisticated regulatory system in humans, which has been considered to have allowed the emergence of cellular complexity and higher-order cognitive processes, and is considered to underlie the tremendous complexity of the primate brain. The most important non-coding RNAs belong to two major families: small RNAs (sRNA; less than 200 bp) and long non-coding RNAs (lncRNA; >200 bp). The former include: 1) small nucleolar RNA (snoRNA); 2) small interfering RNA (siRNA); 3) piwi-interacting RNA (piRNA); 4) microRNAs (miRNA), which are the most recent genomic elements to evolve, and repress gene expression by binding to transcribed RNA sequences with imperfect complementarity. This strongly increases the range of target sequences that can be regulated by miRNAs, whose primary function is to interfere with protein expression and to promote transcript degradation. MiRNAs have been implicated in fine-tuning of neuronal plasticity and have been considered to contribute to a supposed disruption of PSD-mediated synaptic plasticity in schizophrenia. Reduction of miRNA expression, as in the case of the Dicer mutant (i.e. a transgenic mouse line lacking Dicer, the enzyme responsible for the maturation of piRNA and miRNA), is associated with enhanced learning and memory. Indeed, reduced miRNA expression allows the translation at dendritic spines of mRNA encoding synaptic proteins that regulate synaptic functions. On the other hand, however, a group of miRNAs, including miR-132 and miR-134, has been found to be increased by synaptic activity and may concur in enhancing synaptic strength, by promoting the expression of CREB or BDNF, which ultimately leads to dendritic spine formation and maturation. These observations suggest that the type and direction of regulatory steps provided by sRNAs are extremely complex, and represent a tool by which evolution has obtained a remarkable scaling of human genome complexity.

Transcriptome analysis has recently gained interest as a technique to evaluate the whole part of the genome that is transcribed in schizophrenia patients. Distinctive
transcriptome alterations of PFC pyramidal neurons have been found in schizophrenia patients compared to both schizoaffective patients and non-affected controls. Recently, transcriptome analysis of the human genome has reached incredible power, approaching the single base resolution by means of next-generation RNA-sequencing, thereby providing an extensive depiction of the developmental regulation of human cortex transcription across the life span. This methodological approach promises to uncover the genome elements that could be differentially regulated in schizophrenia, and that could pre-date its neurodevelopmental course.

Molecular biology and molecular imaging studies

Molecular biology studies offer the opportunity to understand the molecular underpinnings of putative dysfunctions in schizophrenia and to relate them to distinct behavioural phenotypes relevant to the disease. In general, molecular studies (also often referred to as preclinical studies) are carried out in two systems: in vitro, i.e. in cultured cells, and in vivo, i.e. in animal models of the disease. Despite the great informative power of these studies, inference on the pathophysiological basis of schizophrenia, as well as for other psychiatric diseases, should be made cautiously given the intrinsic reductionism of transposing molecular alterations and behavioural phenotypes from animals to human beings. Notwithstanding these limitations, preclinical studies are essential to investigate putative pathophysiological models and to advance knowledge on the neurobiological functions of candidate genes or genomic elements.

An animal model of a disease should provide face, predictive, and construct validity. In schizophrenia, no animal model exists that can ensure complete validity in each of these domains, while the majority offer optimal validity in one or two domains, but not in the other(s), and researchers are used to choosing the animal model on the basis of their experimental aims. Animal models offer different paradigms to study the molecular underpinnings of schizophrenia. Transgenic mice are experimental animals engineered to express rare mutations with variable penetrance, as when studying the neurobiological effects of these genetic variants (which may lie both in protein-coding or non-coding genome) and their behavioral correlates. A myriad of transgenic mice models have been developed to study different molecular lesions that have been suggested to be present in schizophrenia, and many imply genetic alterations that directly or indirectly impair the neurobiology of glutamatergic neurotransmission and PSD-mediated synaptic plasticity. Transgenic mice lacking the excitatory synaptic signaling scaffold IRSp53 showed impaired social communication and increased NMDA receptor activity in the hippocampus. De novo mutations in the Shank3 gene found in a family with mental retardation and schizophrenia were expressed in a mouse line and showed aberrant glutamatergic synaptic plasticity. Ddo(-/-) transgenic mice are an animal model of increased D-aspartate, which appears to have a protective effect against phencyclidine-mediated NMDA receptor hypofunction and decreased hippocampal expression of NMDA receptor subunits 2A and 2B.

Another intriguing preclinical approach is the technique of gene expression molecular imaging that in some sense may combine, on the preclinical level, transcriptome analysis and functional neuroimaging. The technique allows a precise topographical description of the regions where specific genes of interest are expressed either in basal conditions or after a range of neurochemical, genetic, or behavioural manipulations, thereby providing a brain map of transcriptionally active areas. These studies have investigated expression levels of candidate genes for schizophrenia, whose neurobiological action is pivotal for PSD-mediated synaptic plasticity, such as Homer1a or GSK-3. Expression rates of Homer1a have been found to be modulated by different antipsychotics along distinct and antipsychotic-selective temporal and topographical patterns. Moreover, expression maps of this gene are profoundly affected in animal models of the disease, such as after ketamine administration or in phencyclidine-treated ddo(-/-) mutant mice. Molecular imaging of gene expression has also been used to provide maps of functional connectivity changes among brain regions in distinct animal paradigms, such as chronic haloperidol administration, representing a preclinical correlate, with a high translational potential, of connectomics in humans.

Structural and functional neuroimaging

Research on schizophrenia determinants in the living patient has dramatically improved up to the evolution of fine neuroimaging techniques, such as computer tomography (CT) and magnetic resonance imaging (MRI).
Can the “connectomic way” provide a link between molecular neurobiology and phenomenological psychopathology?

These techniques were first, and are still, used to investigate structural abnormalities in brains of schizophrenia patients at different stages of disease, even in the prodromal stage, or in at-high-risk individuals, and in different ages. This approach had the merit of bringing attention to the disease-relevant brain areas and to progression of the disease along clinical stages.

Structural studies have allowed demonstration of a global reduction of brain volume in schizophrenia patients. A recent systematic meta-review of structural brain alterations in schizophrenia revealed evidence of abnormalities in several brain regions. The most replicated findings involved grey matter reductions of the anterior cingulate cortex, medial and inferior PFC, temporal lobe, hippocampus, amygdala, thalamus and insula. Other brain regions have also shown alterations; however, these alterations were more likely due to disease progression or medication effects. A recent advance in structural neuroimaging has been the advent of diffusion tensor imaging (DTI), which traces white matter tracts. The combination of MRI and DTI has been crucial to pool together data on structural abnormalities of grey matter and the anatomical connections among abnormal areas in schizophrenia patients, paving the way to the subsequent “connectomic” step of neuroimaging. Indeed, a recent meta-analysis of DTI findings in schizophrenia has identified two white matter tracts with significant reductions: one connecting the PFC, anterior cingulate cortex and thalamus; and another one connecting the PFC, hippocampus/amygdala and insula. Although it may be that disturbed connections in schizophrenia are not limited to the above-mentioned tracts, these studies have the great value of promoting a shift from a classical structural view to a more complex one, where relevance is given to how brain regions interconnect with each other, which may represent, on a neuronal circuit level, the mirroring of molecular alterations in synaptic plasticity and connections between neurons.

Structural neuroimaging, however, has the important limitation of being static, and thus does not provide a link between aberrant brain functioning and psychotic symptoms. This gap has been partially overcome by the advent of functional MRI (fMRI), which measures activity in target brain areas while the patient is actively carrying out specific behavioural tasks. One of the earliest and most reliable findings from fMRI studies has been the observation of PFC hypofunction during different executive functions, mostly working memory, although a more recent conceptualisation of experimental data points to an inefficient engagement of the PFC during executive functions in schizophrenia patients. Intriguingly, decreased activation of the dorsolateral PFC during cognitive and emotive processing is one of the most significant findings in a meta-analysis of fMRI studies in at-risk individuals, and has been recently replicated in another sample of at-risk subjects.

A series of elegant studies has linked the expression of discrete allelic variants in candidate schizophrenia genes to brain activity during behavioural tasks, a research field known as imaging genomics. Indeed, in healthy individuals, greater PFC activity during working memory processes has been associated with functional SNPs that reduce the expression of dopamine D2 and serotonin 2A receptors (D2R and 5-HT2AR, respectively). The COMT genotype predicted differential parahippocampal and hippocampal activity during memory encoding in schizophrenia patients compared to controls. In schizophrenia patients, the rs6314 non-synonymous variant of the 5-HT2AR gene was significantly associated with inefficient activation of the PFC during a working memory task, impaired working memory and attentional control, and poor response to olanzapine. Although functional alterations in schizophrenia have been found in several other brain regions associated with aberrant behavioural tasks, the emerging concept is that functional abnormalities may derive from aberrant neural circuitry connection, a research field named connectomics.

Connectomics and psychopathology of schizophrenia

The connectome can be defined as the complete map of the brain’s neural elements and their structural interactions that allow the complex integration and segregation of relevant information. Connectomics has taken advantage of the development of resting state MRI (rsMRI), which explores the extent of connections between brain areas at rest. Indeed, decreased connectivity between the PFC and the thalamus under resting conditions have been described by rsMRI, which supports prior evidence of a direct correlation between reduced activation in the left dorsolateral PFC, rostral/dorsal anterior cingulate cortex and left thalamus during cognitive tasks.

Connectomics, which represents the most recent advance in human research on schizophrenia, is revealing all its promising potential, as it is putting a spin on the conceptual pathophysiological framework of schizophrenia. Indeed, schizophrenia is increasingly considered as a network-based disease, where dysfunctions in multiple candidate circuit networks concur to generate the complex and heterogeneous clinical phenotype. Although a comprehensive connectome of the human brain remains a far distant scientific goal, one of the key advantages of such an approach lies in its revitalisation of the hierarchical system approach. Complex systems and network science are the methodological vectors that allow the
convergence of contemporary technological advances in neuroscience, capturing network connectivity across multiple spatial scales and accounting for individual variability and structural plasticity. One of the challenges of such an approach is, however, to clarify how alterations of the connectome, while shaping brain dynamics, also support the multiple phenotypic manifestations of schizophrenia.

Traditional operational psychopathology of schizophrenia emphasizes the prominence of major symptom clusters: positive symptoms (e.g. delusions and hallucinations), negative symptoms (e.g. abulia, emotional-expressive flattening, passive/apathetic social withdrawal and an overall “disorder of relating”), and disorganisation (e.g. formal thought disorder, conceptual disorganisation, poor attention). Contextual to this triad, organisation (e.g. formal thought disorder, conceptual disorganisation, poor attention). Contextual to this triad, organisation (e.g. formal thought disorder, conceptual disorganisation, poor attention). Contextual to this triad, organisation (e.g. formal thought disorder, conceptual disorganisation, poor attention). Contextual to this triad, organisation (e.g. formal thought disorder, conceptual disorganisation, poor attention). Contextual to this triad, organisation (e.g. formal thought disorder, conceptual disorganisation, poor attention). Contextual to this triad, organisation (e.g. formal thought disorder, conceptual disorganisation, poor attention). Contextual to this triad, organisation (e.g. formal thought disorder, conceptual disorganisation, poor attention).

However, over and above canonical symptom domains, decades of empirical, phenomenological research in schizophrenia has revealed the topicality of anomalous subjective experiences. These are subtle, not-yet psychotic experiential distortions, which can be supra-organised and thematised into overt symptoms (such as positive, negative and disorganised ones). Anomalous subjective experiences incorporate two major, partly overlapping constructs: basic symptoms (BS) and self-disorder. The concept of BS was proposed by Gerd Huber to indicate the early, immediate experiential manifestations stemming from the putative neurobiological substrate of schizophrenia vulnerability. BS were extensively catalogued in the Bonn Scale for the Assessment of Basic Symptoms (BSABS), and the concept of BS proved particularly important for early diagnosis, therapy, prevention and rehabilitation. Indeed, patients experience and communicate the BS as deficiencies with complaint quality and are able to cope with, adapt and compensate for them as long as the cognitive-affective complexity of the experiential field does not give rise to the emergence of productive-psychotic symptoms. Recently, a set of at-risk BS, denoting pre-psychotic prodromal states, has been operationalised in the context of new assessment tools derived from the BSABS (i.e. Schizophrenia Proneness Instrument – adult and child/youth version – SPIA/CY). The two at-risk criteria, i.e. the at-risk criterion Cognitive-Perceptive Basic Symptoms (COPER) and the high-risk criterion Cognitive Disturbances (COGDIS), indeed, identify help-seeking subjects early on and before the threshold of transition into productive-psychotic symptoms.

Strictly related to BS, Parnas and Sass’ Self-Disorder (SD) notion specifically focuses on certain anomalous subjective experiences indicative of a pervasive perturbation of the very sense of being a self, endowed with a unique, stable and embodied first person perspective. Indeed, according to Sass and Parnas, schizophrenia involves subtle, enduring changes of “the experiential sense of being a vital and self-coinciding subject of experience or first person perspective on the world”. SD includes an array of fleeting, yet irreducible feelings of estrangement and perplexity, distortions of the stream of consciousness and fluidity of the basic sense of identity, as well as transformations in bodily experience. A detailed anthology of SD is presented in the Examination of Anomalous Self-Experience (EASE), a newly developed instrument that was specifically designed to support the psychopathological exploration of SD.

Although neither BS nor SD are incorporated in the current diagnostic criteria, they recur in the narratives of subjects vulnerable to schizophrenia, and have been captured by phenomenological psychopathology with expressions such as “loss of the natural evidence” (Blankenburg), “loss of the vital contact with reality” (Minkowski) or “inconsistency of natural experience” (Binswanger). Overall, the empirical literature on BS and SD reveals anomalous subjective experiences that:

- aggregate selectively among schizophrenia patients compared to other mental illnesses and, among psychosis, discriminate schizophrenia from affective psychosis or other psychotic disorders;
- predict subsequent development of schizophrenia spectrum disorders;
- index pre-psychotic clinical high-risk populations, as well as genetically high risk ones;
- follow a gradient distribution in unaffected first degree relatives and correlate with their subclinical schizotypal traits.

Overall, stratified empirical research shows that anomalous subjective experiences (BS and SD) delineate important phenotypes of the schizophrenia spectrum disorders, extending the potential for vulnerability characterisation to the “silent” (i.e. subclinical) side of the spectrum (including putatively schizotypic individuals).

Conclusions

Although a connection between the more recent advances in schizophrenia neurobiology and psychopathology appears hazardous, nonetheless, a speculative theoretical framework may be warranted. Circuit-based dysfunctions may represent the consequence, on a network scale, of the impairment in synaptic plasticity and neuronal connections that are increasingly found in preclinical molecular research, and may stem from de novo and/or inherited disease-variants in target genes as well as from aberrant...
epigenetic mechanisms. On the other hand, circuit-based dysfunctions may underlie the defects in the integration of higher-order cognitive functions that characteristically connote schizophrenia patients, and that may account for aberrant self-experience, which are typically described in phenomenological approaches to the disease.

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