Transitional Model for SCZ

Subjects: Clinical Neurology

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Translational psychiatry proposes a new psychopathological paradigm in Schizophrenia (SCZ). Firstly an important acquisition is to consider SCZ as a neurodevelopmental disease. SCZ spectrum is a condition in which genes and environment interact in different phases of the development, causing an individual neurobiological vulnerability. Continuous distress may lead to transdiagnostic conditions as emotional dysregulation, SCZ basic symptoms, psychosis. An early and timely diagnosis and treatment is mandatory, too watchful and waiting conservative approach may risk to increase DUP and worsen prognosis and outcome in some cases.In this context translational psychiatry may change psychiatrist clinical approach reconsidering old categories, stimulating a careful analysis of risk factors, and promoting the correct use of new and safer molecules.

Keywords: transitional psychiatry ; schizophrenia ; autism ; ADHD

1. Genetic and Epigenetic in SCZ

The underpinning genetic architecture of SCZ remains unclear. In a seminal genome-wide association study (GWAS) of common variants in 36,989 schizophrenia cases and 113,075 controls, 108 independent loci were found significantly associated with schizophrenia status.While each significantly associated loci was found to confer only a small increase in risk (i.e., median odds ratio (OR) per SNP = 1.08), when the effects of all nominally associated ($p < 0.05$) loci were considered together as a single polygenic risk score (PRS), SCZ PRS was able to explain 18.4% of the variance in case versus control status. Specifically, 40% of the 108 associated loci were located within the sequence boundaries of a single protein coding gene, the remaining associated SNPs were located in non-protein coding regions of the genome, suggesting that many common variants associated with Adult Onset Schizophrenia (AOS) are likely to contribute to disease risk by altering the level of expression of specific proteins, rather than more directly altering protein structure. Implicated genes at associated loci included DRD2, (dopamine D2 receptor), gltatergic signaling and plasticity, (GRIA1, GRIN2A, and SRR); and genes encoding 68 voltage-gated calcium channels, (CAC-NA1C and CACNB2).

A more recent meta-analytic GWAS of common variants in schizophrenia included an additional 5220 schizophrenia cases and 18,823 controls and identified 145 independent loci significantly associated with schizophrenia [1]. Schizophrenia-associated SNPs were enriched for genes that are intolerant to mutation, genes involved in synaptic transmission, and genes that are targets of the fragile X mental retardation protein (FMRP), which is known to regulate the protein-level expression of genes involved in brain development and synaptic plasticity [2]. Together, these seminal studies provided compelling evidence that common risk variants for schizophrenia converge onto neuronal and synaptic gene-sets. SCZ patients have also been found to carry rare and ultra-rare deleterious mutations [3][4]: although the effect size of this overall increased burden is relatively small (OR = 1.07), aggregated at the gene-set lev-el, rare deleterious mutations in schizophrenia patients were found to be enriched for genes that are intolerant to mutation, genes that are expressed specifically in neurons, gene targets of FMRP [5], and genes that are components of synaptic gene-sets, such as the N-methyl-D-aspartate receptor (NMDAR) and activity-regulated cytoskeleton-associated protein (Arc) complexes, all critically involved in modulating synaptic plasticity [3][4][6]. Copy number variants (CNVs) are a particular class of structural variants in which segments of DNA are deleted or duplicated, resulting in genomic imbalances in the normal number of copies of DNA in the region. Large (e.g., >100 kb), rare CNVs (i.e., observed in <1% of the population) have been consistently associated with schizophrenia (e.g., OR = 1.15) [7][8][9]; and have yielded important insights into the genetic etiology schizophrenia, CNV loci associated with schizophrenia, include deletions at the 22q11.2, 2p16.3 (NRXN1), 3q29, 15q11.2, and 15q13.3 loci, duplications at the 16p11.2 and 7q11.23 loci, and deletions or duplications at the 1q21.1 and 7p36.3 (VIPR2) loci [10][11][12].

About 2.5% of patients with SCZ are estimated to carry CNVs at one or more schizophrenia-associated loci [11]. Interestingly, CNVs at many of these specific loci are de novo (not present in parents) and have pleiotropic effects, as they are also associated with broader neurodevelopmental disorders such as ASD and ID [11][13][14][15]. Similarly to common

variants associated with SCZ, as well as other rare and de novo variants, SCZ-associated CNVs disproportionately affect neuronal and synaptic gene-sets [16], including components of the postsynaptic density, and NMDAR and Arc complexes [13], and sets of genes that are involved in excitatory and inhibitory [17].

Growing evidence indicates common and rare variants interact to increase risk. Thus, the total burden of common schizophrenia-associated risk alleles that a given individual carries can be summarized by their schizophrenia PRS, which is calculated as their weighted sum of schizophrenia risk-associated SNP alleles at GWAS studies [18]. While SCZ patients have higher PRS than controls, regardless of CNV carrier status, patients who carry risk CNVs that have been previously associated with SCZ have lower PRS compared to patients without risk CNVs [19][20].

There are relatively few genetic studies for Childhood Onset Schizophrenia (COS). Preliminary evidence suggests that in addition to sharing genetic risk factors with Adult-onset Schizophrenia (AOS), the genetic architecture of COS may include greater loading from variants that also confer risk for other neurodevelopmental disorders, such as ASD, ID, and epilepsy: in a study of 130 COS probands and 103 of their healthy siblings, COS probands were found to have significantly higher schizophrenia PRS than their siblings, as well as higher polygenic risk for ASD [21]. Elevated rates of large CNVs have also been found in COS [12], including in CNVs associated with SCZ and other neurodevelopmental disorders. Rates of large, rare CNVs appear to be higher in COS patients compared to controls as well as to patients with AOS; 11.9% of COS probands were estimated to have a neurodevelopmental disease-associated CNV compared to 1.5% of their healthy siblings and 1.4–4.9% of AOS patients [21][22][23]. In particular, a high number of COS probands have been found to carry CNVs at the well-known 22q11.2 locus, which is known to increase risk for multiple psychiatric and developmental disorders, including schizophrenia, ASD, ID and ADHD [21][22][23].

Recently, genome research focused on epigenetic. This mechanism has a role in regulating brain functions, neurogenesis, neurodegeneration, neuronal activity, and cognition. Epigenetic mechanism induces hereditable changing in phenotype, influencing genome functions through modification in DNA, histone, and chromatin structure [24]. The main epigenetic mechanisms consist in DNA methylation, post-translational histone modification, and RNA interference. The totality of these modifications define epigenome, impacting in gene expression program in a temporally and dynamic way [25]. According with neurotransmission hypothesis of SCZ, some authors examined dopaminergic pahtway. They found a hypermethylation in dopamine regulation: DRD1-5 and COMT which encode for dopamine degrading enzymes; DRD4 promoter in peripheral blood. Hypomethylation has been reported for DRD2, DRD4 and DRD6. In the GABAergic pathway, hypermethylation at the pro-moter regions has been found in RELN and GAD1: the most representative genes of the inhibitory neuro-signaling system [26]. Hypermethylation in BDNF I promoter has been also associated to SCZ [27]. Other methylations were detected in genetic loci involved in the regulation of embryonic development such as SOX10 [28] and BAIAP2 [29] in the brain, responsible of dendritic spine density [28]. Epigenetic mechanism act also on immune function with methylation in CTLA4a and OXTR [30]. OXTR encode for the oxytocin receptor which in known to be linked to social cognition deficit in SCZ [31]. Genome methylations has been described in GRIA1: an ionotropic AMPA receptor subunit, important for synaptic plasticity [32][33]. Actually, there are not consensus on the meaning of histone modifications, but some authors investigated H3K9 di-methylation as a putative epigenetic factor underlining SCZ pathogenesis. Micro RNA dysregulation is another epigenetic mechanism probably involved in synaptogenesis that is altered in SCZ [34].

In the epigenome paradigm, age is an important factor because during early developmental phases, the organism is more sensitive to chemical and environmental influences [26]. For these reasons, prenatal and perinatal factors should be particularly considered in clinic for their epigenetic potentiality [27][28]. During pregnancy, maternal infections and maternal immune activation, diet, toxic factors (including alcohol and substance use) has been associated to an increase risk in develop SCZ [29]; asphyxia, maternal and paternal age, low weight at birth are also important information. In addition, in the first years of the life, environmental conditions seem to be associated to SCZ probably for epigenetic influences. In postnatal period, repeated experience of trauma, neglect, substance use (especially cannabis and stimulant use such as cocaine, methamphetamines etc.) are the most important epigenetic risk factor for SCZ [30].

2. A Transitional Model for SCZ

The re-conceptualization of SCZ as neurodevelopmental disorders with fetal origin [35], and the importance of gene x environment interaction significantly before the onset of clinical symptoms [36] should have implications not only in terms of nosological categorization and clinical management, but also in terms of organization of the systems of care, particularly in the transition from adolescent to adulthood.

In most of European countries, medical care for children and adolescent with psychiatric disorders is independent and splitted from that for adults. To this different organization correspond specific training (either as independent curriculum or as sub-specialty of adult psychiatry training), and specific Scientific Societies affiliation. The construct of developmental

psychopathology (so far a relatively unusual construct for adult psychiatrists) may be the cultural basis to overcome this split, and its negative consequences in patients management [37][38]. Both the lack of timely interventions as well as inappropriate intervention (i.e., obesity induced by long term use of SGA) may lead to severe impairment later in life. In the last two decades a five-fold increase in the use of antipsychotic medication in adolescents, and 9-fold increase in children (compared to the 2-time increase in adults), usually prescribed for non-psychotic disorders [39], indicate the different evolving attitude of psychiatrists in the use of medications, with poor integration between child/adolescent and adult psychiatrists. These new attitudes are supporting innovative approach for a neuroscience based nomenclature in the classification of drugs [40]. The increased knowledge that “antipsychotic” medication should be used to modulate salience of both external stimuli and internal feeling [41], rather than just managing psychotic symptoms, may be considered an important contribution of child & adolescent psychiatrists to the systems of care for mental disorders.

The difficult communication between mental health services in the transition of patients from adolescence to the adulthood is also based on the poor expertise of adult psychiatrists in neurodevelopmental psychiatric disorders, mainly ASD, ADHD and ID (i.e., adult psychiatry ignores important anamnestic elements), patients are not adequately supported in adult service, with not always justified change of diagnosis and treatment.

Another crucial issue is the management of adolescent patients at risk for psychosis. As mentioned in a previous section of the paper, only 30% of young people seeking help for psychotic-like symptoms may considered at high risk of psychosis, and only less than 20% of these high risk subjects eventually develop clear psychotic symptoms, but about 70% of them may result functionally impaired on global functioning often developing depression, anxiety, substance abuse, bipolar disorder or persisting attenuated psychotic symptoms [42]. A recent study including 2330 youth to early intervention services were assessed longitudinally, 4.3% (n = 100) met criteria for new-onset full-threshold Bipolar Disorder (FT BD) and 2.2% (n = 51) met criteria for a new-onset FT PD. The emergence of FT BD was associated with older age, lower social and occupational functioning, mania-like experiences (MLE), suicide attempts, reduced incidence of physical illness, childhood-onset depression, and childhood-onset anxiety. The emergence of a PD was associated with older age, male sex, psychosis-like experiences (PLE), suicide attempts, stimulant use, and childhood-onset depression [43].

Considering that many risk factors may be similar to symptoms of neurodevelopmental psychiatric disorders, transition processes should include both high risk people as well as subject with neurodevelopmental psychiatric disorders with different levels of severity.

Two main models of transition between child/adolescent and adult services may be considered: using a “transition team” that operates independently from both services to bridge the gap, or the use of shared care official protocols interlocking child/adolescent and adult services facilitating a gradual transfer of care. The independent transition service model has been implemented in early intervention in psychosis, but with inconsistent effects [44][45]. The main feebleness of this model is the introduction of additional and unnecessary splits within the system. The interlocking model may work when it is flexible to the needs of young adults rather than focused specifically on chronological age.

According to the interlocking model transition should be planned by the services of first referral. During transition, child/adolescent and adult services, both at community level and at a second-or third-level hospital, should consider meeting and shared full information, considering evidence-based, up-to-date recommendations about the diagnosis and management of psychiatric disorders at different developmental stages as part of their continuing professional development. Appropriate adult services should include primary care, adult community mental health teams and access to dedicated services for specific disorders.

Transition protocols should be available to all clinical teams and should include psychoeducational material that provides high quality, comprehensive, and appropriately written information for both young people and their parents/caregivers. This material should include information about how management of their own symptoms and problems, and access advice and support. Information should also be developed in a media format that is readily accessed by young people, e.g., use of phone applications and internet sites.

Full information about adult psychiatric and general psychiatry services should be made available to the young person and their family. Full information about the previous young person care should be available to the adult teams, including a detailed clinical transition report. Collaboration with educational and/or occupational agencies is usually also needed.

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