Review

ENDOPHENOTYPES IN SCHIZOPHRENIA: A CURRENT REVIEW AND SOME IMPLICATIONS ON THEIR ROLE AS TREATMENT TARGETS

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Summary

Endophenotypes (or intermediate phenotypes) which have become increasingly popular in scientific research in the past decade are heritable abnormalities of the CNS structure and function (including neurocognitive and neurophysiological functions). If compared to established presence of illness, they may be much more closely linked to genetic variations associated with schizophrenia, which may be normally occurring polymoprhisms. Another advantage is their stability over time and the possibility for quantitative laboratory or neuroimaging-based measurement. The identification of endophenotypes that reflect genetic variations may also lead to refinement of diagnosis and better subtyping of the schizophrenic illness. Besides, endophenotypes may be detected in unaffected relatives and patients with subsyndromal or schizophrenia spectrum disorder, for whom specially designed targeted interventions may prove beneficial for overall functioning. Deficits of a number of neurocognitive and neurophysiological measures such as sustained focused attention, verbal declarative memory, working memory, antisaccade visual task performance, prepulse inhibition (PPI), suppression of the P50 auditory evoked potential and some others seem closely related to predisposition to the illness and therefore, may serve as promising endophenotypes. Below is a quick review of some of the most consistent findings in this field. Finally, an example is given of an emerging treatment augmentation strategy that addresses a presumptive endophenotype of schizophrenia associated with a specific genetic locus on chromosome 15, containing the promoter and gene for the α_7 subunit of the nicotinic acetylcholine receptor (α7nAChR).

Key words: genetic variations, subtyping, neuroimaging, neurocognitive and neuropsychological markers, nicotinic receptor

Introduction

Although supported by multiple adoption and family studies, the genetic component in schizophrenia etiology differs from what is found in neuropsychiatric disorders that follow Mendelian modes of genetic transmission, e.g. Huntington disease [1, 2, 3]. Because of that, schizophrenia is considered to be a complex genetic disorder that does not reflect the effect of a single gene alone but involves interactions of multiple genes instead. Most

mental illnesses may be regarded as complex genetic disorders, especially the syndromal psychiatric conditions that are diagnosed on the basis of presence of variable constellations of symptoms. These disorders may result from interactions between several genes, some of which may be normally-occurring polymorphisms, while others are truly different from the unaffected population, environmental influences and epigenetic factors [4]. Given the fact that the human genome contains approximately ten million polymorphic sites, and that interactions between genes (or endophenotypes), as opposed to the effect of a single gene, are responsible for disease liability in most instances, large samples of families and unrelated individuals have to be investigated to determine causal relationships between genes and disease phenotypes [4]. Epigenetic factors include stable covalent modifications of proteins that interact with DNA (e.g. acetylation of histone proteins within the nucleosome) and of DNA itself (e.g. methylation of cytosine residues in promoter regions) that influence transcription. These stable, heritable organic modifications may occur as a result of complex feedback pathways that include exposure to environmental influences [5]. Moreover, the combination of genes that contributes to the emergence of seemingly similar complex genetic disorders may differ among clinically-affected individuals. With technologies available to identify mutant genes and normal polymorphisms and quantify their expression, it may soon be possible to resolve genetically-distinctive disorders within the DSM-IV-TR diagnostic categories. This genetically-determined nosology will be based on different combinations or sets of genes in affected individuals within current categorical diagnostic assignments. The genetically distinctive group of schizophrenias may account for differences in onset, predominant symptom constellation, course, outcome and response to treatment. Given the likely existence of genetically-distinctive disorders, it is remarkable that current pharmacotherapies for schizophrenia are as effective as they are for so many patients, although poor treatment outcomes are often seen, especially with regard to cognitive and negative symptoms.

What Is an Endophenotype?

Endophenotype is a genetic epidemiology term, used to parse behavioral symptoms into more stable phenotypes with a clear genetic connection. In the past decade the term has become increasingly popular in psychiatric genetics where it serves to bridge the gap between high-level symptom presentation and low-level genetic variability, such as single nucleotide polymorphisms [6].

The ideal candidate for an endophenotype is one that can be measured in a quantitative fashion, is distributed continuously in the population, is proximal to the action of the gene (as opposed to the clinical syndrome), reflects a function that, when disturbed, is relevant to the illness, is state independent and artifactually affected by medication, and shows high heritability such that its prevalence among closely-related biological relatives of probands with schizophrenia is higher than the basal rate in the general population [3, 7].

The concept of endophenotype (or intermediate phenotype) may facilitate the identification of genetic variations that are associated with schizophrenia and clarify the pathways from genetic variations to alterations of specific neurocognitive and neurophysiological functions and, eventually, the emergence of the clinical syndrome (that is recorded in categorical fashion as present or absent). The deciphering of the genetic architecture of the endophenotypes may also reveal a "network" of genes that must act in concert to produce the endophenotype or clinical syndrome, clarify interactions with environmental influences that lead from endophenotype to illness expression and, perhaps, modifying genetic and environmental influences that prevent an endophenotype from progressing to an overt clinical syndrome [1, 4, 8].

As mentioned above, in the search for disease genes and their causal relation to pathophysiological processes, endophenotypes offer significant advantages in complex diseases characterized by genetic and phenotypic heterogeneity [3]. The statistical likelihood of finding associations between endophenotypes and genetic loci is increased because of their "quantitative" nature and a functional relevance to the disease process itself, as opposed to the categorical presence or absence of schizophrenia. Also, the inclusion of unaffected relatives that manifest the endophenotype in the search for possible associations increases the number of

subjects and the power of investigation respectively [8]. Further, in contrast to the heterogeneity of the clinical syndrome of schizophrenia that occurs even when the disorder is diagnosed using rigorous definitional criteria, sample selection using quantitatively measurable endophenotypes can lead to homogeneity with respect to the presence and severity of the endophenotype [1]. In addition to their heritability, endophenotypes are stable (i.e. they are not state-dependent). Thus, they are detectable in both exacerbated and remitted patients. Their heritability implies that they segregate in biological family members of index patients with schizophrenia, most of whom may be unaffected by the disorder. Moreover, while it is very improbable that the effects of a single abnormal gene or genetic variation on illness will be discernable, there is a greater likelihood that relationships can be found between endophenotypes, reflecting functional neurophysiological and neurocognitive abnormalities, and single genes [1-4, 7, 9, 10-12]. Although certain endophenotypes may be necessary but not sufficient for the manifestation of overt illness in most patients, complex interactions between multiple genetically determined endophenotypes and environmental "second-hit" influences are more likely to result in the clinical disorder [13].

Although endophenotypes represent an appealing target for scientific research, the latter faces multiple challenges. First of all, as the expression of the genetic variations associated with endophenotypes begins early in development, it may be dramatically modified by non-genetic influences [1]. Thus, the theoretically tight correlation between genetic polymorphisms and presumptive quantitative endophenotypes measured in adulthood or at the age of illness recognition may not be found. Also, some phenotypic manifestations of illness may reflect the consequences of adaptive changes and expression of genes that do not represent disease alleles. Furthermore, if the deleterious effect of a disease allele occurs during the development of the brain (so-called "first-hit"), it may not be possible to detect this allele using statistical approaches that seek associations between (endo)phenotype and genotype in large samples. And finally, the interactions between multiple endophenotypes in patients may obscure an association between a single quantitative endophenotype and a specific genetic variation.

When focusing on schizophrenia, some of the endophenotypes may not be closely associated with the disease per se, but rather reflect a disruption along complex circuits involving frontal/temporal cortex and limbic structures that may also be pathologically involved in bipolar disorder patients and their biological relatives. Ideally, elucidation of genetic architecture will lead to a nosology that more accurately reflects pathophysiological differences and suggests pharmacotherapeutic targets more readily, as compared to existing categorical syndromal approaches [14].

Candidate Schizophrenia Endophenotypes

Neuroimaging Markers

Neuroimaging studies of healthy twins have shown very significant heritability of the anatomy of localized middle frontal cortical regions near Brodmann's areas 9 and 46. This means that genetic factors contribute substantially to the development of frontocortical regions implicated in the pathophysiology of schizophrenia [15]. Moreover, associations were found between frontal grey matter differences and test performance across multiple cognitive domains [15]. Thus, brain structures, in addition to neurophysiological and neurocognitive measures, may serve as endophenotypes that are closely linked to schizophrenia susceptibility genes that have functional relevance. (i.e. they influence brain structures which, in turn, underlie cognitive processes). Functional MRI (fMRI) studies showed inefficient prefrontal information processing during performance of a working memory task in unaffected siblings of patients with schizophrenia that resembled the fMRI and information processing deficits seen in patients [16]. These functional imaging data in non-affected siblings support the use of neuroimaging measures as endophenotypes of the disorder. Similar to their affected siblings with schizophrenia, unaffected monozygotic co-twins showed significant callosal displacements, especially an upward bowing of the callosum [15].

Various provocative associations have been reported between functional and anatomic neuroimaging abnormalities in schizophrenia and specific genes and genetic loci, including the "valine" polymorphism of the catechol-O-methyltransferase (COMT) gene, leading to the more rapid breakdown of dopamine on

chromosome 22, genes that regulate G-proterin signaling (RGSs) like the "G-protein signaling subtype gene (RGS4)" on chromosome 1q21, and the "disrupted-in-schizophrenia 1 (DISC1) gene" on chromosome 1q421 [15]. Some of them will be briefly summarized below.

The so-called DISC1 (disrupted in schizophrenia), closely related to DISC2, which is also located on chromosome 1 (1q41, 1q42) [17], is a candidate gene of schizophrenia. It is predominantly expressed in the hippocampus (and to some extent in prefrontal cortex), and is thought to be responsible for hippocampus development [18]. It codes a protein with the same name (DISC1) that, in coordination with a wide array of interacting partners, participates in the regulation of cell proliferation, differentiation, migration, neuronal axon and dendrite outgrowth and cell-to-cell adhesion. In schizophrenic patients with certain DISC haplotypes reduction in hippocampus volume was found [19], as well as reduced grey matter density in the prefrontal cortex [20]. Moreover, there were also functional alterations resulting in changes in hippocampus activation (fMRI) in working and declarative memory tasks [21].

Catechol-*o*-methyltransferase (COMT) coded by gene on chromosome 22 (22q11DS) [16], is a key enzyme in dopamine degradation [22]. The velocardiofacial syndrome as a model of a natural genetic disorder on 22q conveys a 25-fold increased risk for schizophrenia [18], and non-psychotic affected subjects also show a strong grey matter loss measured with volumetric MRI, as do patients suffering from childhood onset schizophrenia [23]. The Val108=158Met-allele (Val=Met substitution) leads to a 4-fold increased enzymatic activity in dopamine degradation, thus reducing available dopamine levels and increasing the risk for schizophrenia [24]. Several studies have investigated the association between the COMT Val/Met polymorphism and structural brain schizophrenia-related characteristics. The most consistent finding is a reduced volume of the anterior cingulate gyrus in Val/Val patients relative to either Val/Met (in patients at genetically high risk of developing psychosis) [25], or Met carriers (in chronically ill patients) [26]). Moreover, in those at risk, reduced medial temporal gyrus volumes were found in Val/Val patients as compared to Met carriers [26].

Regulators of G-protein signalling (RGSs), as their name implies, modulate signal transmission after binding different classes of neuro-transmitters to their respective receptors. Postmortem, the expression of "G-protein signaling subtype gene" (RGS4) was found to be downregulated in the brains of schizophrenia patients [27]. Subsequently, several genetic case-control studies showed an association between four RGS4 SNPs and schizophrenia. A meta-analysis [28] suggested an overall significant association, but with multiple differently associated variations across populations, which may account for the inconsistent findings. Regarding brain morphology, a variation at one RGS4 SNO that has previously been associated with psychosis (rs951436) resulted in regionally specific reductions in grey matter (prefrontal cortex, thalamus, and superior temporal gyrus) and white matter prefrontal volume in individuals carrying the A-variant [29].

Neurocognitive and Neurophysiological Markers

Several "candidate" endophenotypes in schizophrenia are associated with neurophysiological and neurocognitive measures, reflecting output of neuronal systems, which may be disrupted as a consequence of disease genes. The list of promising cognitive endophenotypes includes deficits of sustained focused attention, verbal declarative memory, working memory, antisaccade task performance and, perhaps, processing of facial information [3, 7]. The antisaccade task assesses aspects of attention, frontocortical inhibition and working memory. The candidate neurophysiological endophenotypes reflect deficits in information processing that extend from early preattentive processes to higher cortical ones that occur much later (i.e. from as early as 50 ms to later than about 300 ms after stimulus presentation) and fall into two broad categories: measures of inhibitory failure and measures of impaired deviance detection [9]. These fundamental processes regulate the "inflow of information from the environment", inhibiting activation of cortical pathways in response to redundant or irrelevant stimuli, while facilitating this activation in response to novel, or salient stimuli [9]. Prominent candidate endophenotypic measures of inhibitory failure include prepulse inhibition (PPI) of the startle reflex and suppression of the P50 auditory evoked potential. Measures of impaired deviance detection are mismatch negativity and the P300 event-related potential.

Higher prevalence of impaired PPI has been determined in unaffected siblings of

schizophrenia probands, as compared to control subjects. Thus, PPI of the (acoustic) startle response is an attractive candidate phenotype.

Mismatch Negativity (MMN) is the electrophysiological response, beginning as early as 50 ms and peaking as late as 200 ms after stimulus presentation, to an "oddball" auditory stimulus that abruptly interrupts a sequence of repetitive standard sounds. The "oddball" or deviant stimulus can be distinguished from the standard repetitive one by changes in duration, pitch or loudness. The evoked MMN response is a preattentive and highly stable characteristic over time that reflects some automatic "sensorimemory" process. This response is elicited in sleeping infants and even in brain-injured and comatose patients. Schizophrenia patients show deficits in deviance detection, as reflected in a reduced response to an "oddball" auditory stimulus that may be correlated with functional disability. In contrast to the early preattentive response to an "oddball" stimulus in the MMN paradigm, the P300 event-related potential reflects a variety of higher order cognitive processes, including "directed attention, the contextual updating of working memory, and the attribution of salience to a deviant stimulus." [9]. Schizophrenia patients have been reported to show reduced amplitude and prolonged latency of the evoked P300 response to an oddball stimulus, reduced amplitude being the more robust and reliable abnormal response. Correlations have been reported between P300 abnormalities and measures of decreased volume in left superior temporal gyrus and frontal lobe in schizophrenia. The possibility of linkage of P300 abnormalities to the region on chromosome 6 containing the dysbindin gene, a candidate gene in schizophrenia, was shown in a collaborative study on the genetics of alcoholism, and the DISC1 gene in a family pedigree that included schizophrenia patients and unaffected family members with a balanced translocation of the long arm of chromosome 1 and the short arm of chromosome 11 [9]. In any event, MMN and the P300 abnormality are promising neurophysiological endophenotypes that may reflect genetic variations occurring among patients with schizophrenia and closely related, unaffected biological family members.

P50 Suppression Deficit: an Endophenotype in Schizophrenia, which May Be Used as a Treatment Target

Ordinarily, the amplitude of the P50 waveform evoked in response to the second of an identical pair of auditory stimuli presented 500 ms apart is reduced, as compared with the amplitude of the response evoked by the first stimulus of the pair. The amplitudes of the two evoked potentials are averaged over multiple trials. When examining the T/C or P50 suppression ratio in longitudinal studies or clinical trials, a decrease in the amplitude of the second evoked potential, as opposed to increased amplitude of the first, is interpreted as better evidence of improved sensory gating [12].

Using the "P50 Suppression" paradigm, a sensory gating abnormality has been demonstrated in a large population of patients with schizophrenia and their closely related biological relatives, many of the latter being unaffected with the illness [12, 30]. Moreover, the sensory gating deficit, reflected in an abnormality of P50 suppression that segregates within families of probands with schizophrenia appears to be inherited in an autosomal dominant fashion [12, 30]. The failure to suppress P50 after repeated exposure to identical stimuli in clinically unaffected, closely-related biological relatives suggests that this endophenotype may be a "necessary but not sufficient" condition for overt expression of at least some presentations of schizophrenia. Sensory gating is not an example of learning, rather it is a preattentional, pre-conscious neurophysiological process that allows the individual to "ignore" repetitive stimuli in the environment; this facilitates the direction of attentional resources toward novel and less predictable stimuli.

The integrity of the CA3 and CA4 region of the hippocampus and cholinergic projection pathways into this region is necessary for normal suppression of the evoked P50 response to the second of a pair of identical auditory stimuli presented 500 ms apart. Importantly, the density of nACh receptors (nAChRs) in the hippocampus, containing the α_7-subunit appear to contribute prominently to normal suppression of the P50 response. An inverse relation between density of hippocampal α_7 nAChRs and magnitude of suppression of the homologous P20-N40 complex in rodents has been reported

among inbred mouse strains [31].

Pharmacological, receptor binding and genetic data converge to implicate diminished expression and impaired signal transduction by the α7nAChR as an important pathogenetic mechanism of the disorder [32, 33]. Postmortem studies of brains of patients with schizophrenia revealed decreased expression of the α7nAChR (e.g. frontal cortex, hippocampus and thalamus). Genetic studies have also shown evidence of "linkages" between impaired P50 sensory gating abnormalities, the locus on chromosome 15q13-14 that contains the gene for the α7nAChR (CHRNA7), abnormal promoter variants of CHRNA7 and schizophrenia [34]. The existence of disturbances of nAChR-mediated neurotransmission should not be surprising having in mind the approximately three-fold to four-fold higher prevalence of cigarette smoking among schizophrenia patients, as compared with the general population.

From a descriptive perspective, P50 gating deficits and "hippocampal" pathology may be reflected in disturbances of focused attention, sensory flooding and disturbance of associations that are commonly manifested in this disorder. There has been much speculation about the relationship of the P50 abnormality to descriptive phenomena of schizophrenia (e.g. sensory flooding), as well as positive, negative and cognitive symptoms. Also, although the "generator" of the P50 response is not known with certainty (or even if there is only one generator), evidence consistent with a (primary) hippocampal location suggests that the P50 abnormality could be involved in the disturbance of associations (i.e. inability to gate "loose" or contextually-inappropriate associations and, thereby, prevent their emergence into consciousness). In addition to the hippocampus, other potential sites of this generator include Heschl's gyrus superior temporal gyrus, prefrontal cortex and rhinal cortex [35]. Nonetheless, a recent review of this area referenced some work reporting possible correlations between P50 abnormalities and measures of attention, cognitive processing speed, a visual implicit memory task, forward digit span that may be related to working memory, and a semantic priming task in patients with schizophrenia [35]. However, P50 abnormalities were shown prior to overt illness in a study of persons at high genetic risk and those manifesting prodromal symptoms. Thus, the P50 endophenotype segregates with, and is demonstrable before, the earliest manifestations of clinical disorder, supporting its potentially important role in pathophysiology and as a treatment target.

Nonetheless, in spite of all the limitations, the promising data on impaired P50 suppression and diminished expression of the α7nAChR in schizophrenia has led to the identification of the α7nAChR as a pharmacotherapeutic target in this disorder [13]. Unfortunately, few α7nAChR agonists can be safely selected, and nAChRs have been proved to rapidly desensitize upon exposure to agonist.

Choline, the precursor of acetylcholine, has been shown to mimic the latter at the α7nAChR. Furthermore, local generation of choline in areas surrounding α7nAChR may be an important regulator of α7nAChR -mediated neurotransmission. Importantly, choline is a naturally-occurring metabolite which lacks many potential toxic or medical adverse side effects that may be associated with synthetic analogues. However, earlier studies of choline administration to patients with schizophrenia, usually administered in the context of treating neuroleptic-associated tardive dyskinesia, proved to have no significant beneficial clinical effect [13]. This lack of effect of choline may have been due to the rapid desensitization kinetics of the α7nAChR.

One possible strategy to overcome these challenges is to combine CDP-choline, a dietary source of exogenous choline with good brain blood flow penetrability, and galantamine, a positive allosteric modulator of nAChRs in addition to its action as an inhibitor of acetylcholinesterase. This combination is used with the hope that the agonist effect of choline would be potentiated by galantamine's ability to improve the efficiency of coupling between choline's binding to the receptor and channel opening, while also preserving the receptor in a sensitive state [13, 36, 37]. In a preclinical mouse model of schizophrenia, galantamine was shown to modulate the effect of CDP-choline on mouse popping behavior (i.e. irregular episodes of intense jumping behavior) elicited by a noncompetitive NMDA receptor antagonist binding to the same hydrophobic channel domain as phencyclidine (PCP) [37].

Deutsch et al. (2008) in an open label 12 week pilot study combined CDP-choline, titrated up to 2 g per day and galantamine up to 24 mg per day, both in divided doses, as an adjuvant therapy to the stable antipsychotic medication regimens of

six patients with schizophrenia with residual symptoms [37]. All the patients tolerated the combination and completed the trial with transient GI disturbance being the most commonly seen side effect. Three of the patients responded with significant reductions of clinical global severity scores, and both total and subscale scores on the Positive and Negative Symptom Scale (PANSS). Symptoms across several domains of psychopathology improved in at least some of the patients, including hallucinations, social withdrawal, flattened affect and poor personal hygiene [37]. Encouraged by the promising findings of the pilot investigation, these authors are currently running a double-blind placebo-controlled study of the adjuvant therapeutic efficacy of the same combination. Besides treatment efficacy and safety, the ability of the combination to improve the P50 deficit is also being measured [38].

Conclusion

Endophenotypes are heritable abnormalities of the CNS structure and function (including neurocognitive and neurophysiological functions) that may be more closely "linked" to genetic variations associated with schizophrenia as compared to the definite presence of illness. The endophenotypes usually represent quantitative laboratory-based measures that are normally distributed within the population. The presence of endophenotypes in unaffected biological relatives supports the view that they may not be "sufficient" for manifestation of overt illness, but the functions that they reflect may, nonetheless, be involved in the pathophysiology of the disorder. Endophenotypes may be a method for subtyping the illness that has a biological basis, as opposed to a descriptive one, as well as resolving members of the "group" of schizophrenias from each other. Very importantly, a genetically determined disruption of a function may be an ideal and manageable target for a strategically-designed intervention. The efficacy of the endophenotypically-targeted intervention could be measured in a quantitative and objective way, avoiding many of the pitfalls associated with subjective rating instruments that require staff training and practice to achieve reliability and avoid "definitional drift" between raters.

Positive preliminary results support a novel pharmacological strategy to target the presumed basis of the P50 sensory gating deficit in schizophrenia (i.e. deficient expression of the α7nAChR in the brains of patients with schizophrenia). The intervention is an adjuvant one and involves adding a combination of the selective α7nAChR agonist CDP-choline (a dietary source of choline) and the positive allosteric modulator of nAChRs galantamine to the usual antipsychotic medications. It is hoped that galantamine will improve the efficiency of coupling between the binding of choline and channel opening while preserving the receptor in a sensitive, as opposed to refractory, state that would avoid the further exacerbation of the α7nAChR deficiency that exists in schizophrenia, and is associated with prolonged exposure to an agonist. The strategy is promising and serves as a paradigm for developing targeted endophenotypic interventions for treatment of schizophrenia.

References

1. Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. Schizophr Bull. 2007;33(1):21-32.
2. Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. Annu Rev Clin Psychol. 2006;2:267-90.
3. Thaker GK. Schizophrenia endophenotypes as treatment targets. Expert Opin Ther Targets. 2007;11(9):1189-206.
4. Schork NJ, Greenwood TA, Braff DL. Statistical genetics concepts and approaches in schizophrenia and erlated neuropsychiatric research. Schizophr Bull. 2007;33(1):95-104.
5. Deutsch SI, Rosse RB, Mastropaolo J, Long KD, Gaskins BL. Epigenetic therapeutic strategies of neuropsychiatricdisorders: ready for prime time? Clin Neuropharmacol. 2008;31(2):104-19.
6. Gottesman I, Gould T. The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. Am J Psychiatry. 2003;160(4):636-45.
7. Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, et al. The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. Schizophr Bull. 2007;33(1):49-68.
8. Braff DL. Introduction: the use of endophenotypes

to deconstruct and understand the genetic architecture, neurobiology, and guide future treatments of the group of schizophrenias. Schizophr Bull. 2007;33(1):19-20.
9. Michael S, Ritsner BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. Schizophr Bull. 2007;33(1):69-94.
10. Benes FM. Searching for unique endophenotypes for schizophrenia and bipolar disorder within neural circuits and their molecular regulatory mechanisms. Schizophr Bull. 2007;33(4):932-6.
11. Joyce EM, Roiser JP. Cognitive heterogeneity in schizophrenia. Curr Opin Psychiatry. 2007;20:268-72.
12. Adler LE, Olincy A, Waldo M, Harris JG, Griffith J, Stevens K, et al. Schizophrenia, sensory gating, and nicotinic receptors. Schizophr Bull. 1998;24:189-202.
13. Deutsch SI, Rosse RB, Schwartz BL, Weizman A, Chilton M, Arnold DS, et al. Therapeutic implications of a selective α_7 nicotinic receptor abnormality in schizophrenia. Isr J Psychiatry. 2005;42(1):33-44.
14. Berrettini WH. Genetics of psychiatric disease. Annu Rev Med. 2000;51:465-79.
15. Bearden CE, van Erp TGM, Thompson PM, Thompson PM, Toga AW, Cannon TD, et al. Cortical mapping of genotype-phenotype relationships in schizophrenia. Hum Brain Mapp. 2007;28:519-32.
16. Callicott JH, Egan MF, Mattay VS, Bertolino A, Bone AD, Verchinksi B, et al. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. Am J Psychiatry. 2003;160:709-19.
17. Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, et al. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: schizophrenia. Am J Hum Genet. 2003;73(1):34-48
18. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry. 2005;10(5):434-49.
19. Seidman LJ, Faraone SV, Goldstein JM, Kremen WS, Horton NJ, Makris N, et al. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. Arch Gen Psychiatry. 2002; 59:839-49.
20. Cannon TD, Hennah W, van Erp TG, Thompson PM, Lonnqvist J, Huttunen M, et al. Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. Arch Gen Psychiatry. 2005;62(11):1205-13.
21. Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR, et al. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. Proc Natl Acad Sci USA. 2005;102(24):8627-32.
22. Akil M, Kolachana BS, Rothmond DA, Hyde TM, Weinberger DR, Kleinman JE. et al. Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. J Neurosci. 2003;23(6):2008-13.
23. Eliez S, Schmitt JE, White CD, Reiss AL. Children and adolescents with velocardiofacial syndrome: a volumetric MRI study. Am J Psychiatry. 2000;157(3):409-15.
24. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA. 2001;98(12):6917-22.
25. McIntosh AM, Baig BJ, Hall J, Job D, Whalley HC, Lymer GK, et al. Relationship of catechol-O-methyltransferase variants to brain structure and function in a population at high risk of psychosis. Biol Psychiatry. 2007;61(10):1127-34.
26. Ohnishi T, Hashimoto R, Mori T, Nemoto K, Moriguchi Y, Iida H, et al. The association between the Val158Met polymorphism of the catechol-O-methyl transferase gene and morphological abnormalities of the brain in chronic chizophrenia. Brain 2006; 129 (2):399-410.
27. Mirnics K, Levitt P, Lewis DA. Critical appraisal of DNA microarrays in psychiatric genomics. Biol Psychiatry. 2006;60(2):163-76.
28. Talkowski ME, Seltman H, Bassett AS, Brzustowicz LM, Chen X, Chowdari KV, et al. Evaluation of a susceptibility gene for schizophrenia: genotype based meta-analysis of RGS4 polymorphisms from thirteen independent samples. Biol Psychiatry. 2006;60(2):152-62.
29. Buckholtz JW, Meyer-Lindenberg A, Honea RA, Straub RE, Pezawas L, Egan MF, et al. Allelic variation in RGS4 impacts functional and structural connectivity in the human brain. J Neurosci. 2007; 27(7):1584-93.
30. Leonard S, Adams C, Breese CR, Adler LE, Bickford P, Byerley W, et al. Nicotine receptor function in schizophrenia. Schizophr Bull. 1996;22(3):421-45.
31. Stevens KE, Freedman R, Collins AC, Hall M, Leonard S, Marks MJ, et al. Genetic correlation of hippocampal auditory evoked response and α-bungarotoxin binding in inbred mouse strains. Neuropsychopharmacology. 1996;15(2):152-62.
32. Adler LE, Hoffer LD, Griffi th J, Waldo MC, Freedman R. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. Biol Psychiatry. 1992;32(7):607-16.
33. Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J

Psychiatry. 1993; 150: 1856-1861.
34. Leonard S, Freedman R. Genetics of chromosome 15q13-q14 in schizophrenia. Biol Psychiatry. 2006; 60: 115-122.
35. Potter D, Summerfelt A, Gold J, Buchanan RW. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. Schizophr Bull. 2006; 32(4):692-700.
36. Deutsch SI, Rosse RB, Schwartz BL, et al. Effects of CDP-choline and the combination of CDP-choline and galantamine differ in an animal model of schizophrenia: Development of a selective α_7 nicotinic acetylcholine receptor agonist strategy. Eur Neuropsychopharmacol. 2008;18:147-151.
37. Deutsch SI, Schwartz BL, Schooler NR, et al. First administration of cytidine diphosphocholine and galantamine in schizophrenia: a sustained alpha7 nicotinic agonist strategy. Clin Neuropharmacol. 2008;31(1):34-39.
38. Deutsch SI, Schwartz BL, Rosse RB, et al. Schizophrenia endophenotypes as treatment targets. In: The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes, Volume 1. Ristner M (editor). Springer 2009; 113-122.