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Endophenotypes in schizophrenia: A selective review

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ABSTRACT

Background: Given the wealth of data in the literature on schizophrenia endophenotypes, it is useful to have one source to reference their frequency data. We reviewed the literature on disease-liability associated variants in structural and functional magnetic resonance images (MRI), sensory processing measures, neuromotor abilities, neuropsychological measures, and physical characteristics in schizophrenia patients (SCZ), their first-degree relatives (REL), and healthy controls (HC). The purpose of this review was to provide a summary of the existing data on the most extensively published endophenotypes for schizophrenia.
Methods: We searched PubMed and MedLine for all studies on schizophrenia endophenotypes comparing SCZ to HC and/or REL to HC groups. Percent abnormal values, generally defined as >2 SD from the mean (in the direction of abnormality) and/or associated effect sizes (Cohen's *d*) were calculated for each study.
Results: Combined, the articles reported an average 39.4% (SD = 20.7%; range = 2.2–100%) of abnormal values in SCZ, 28.1% (SD = 16.6%; range = 1.6–67.0%) abnormal values in REL, and 10.2% (SD = 6.7%; range = 0.0–34.6%) in HC groups.
Conclusions: These findings are reviewed in the context of emerging hypotheses on schizophrenia endophenotypes, as well as a discussion of clustering trends among the various intermediate phenotypes. In addition, programs for future research are discussed, as instantiated in a few recent large-scale studies on multiple endophenotypes across patients, relatives, and healthy controls.
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1. Introduction

Schizophrenia is an inherited, likely complex genetic disorder that "runs in families" and the single best predictor for developing the illness is having an affected first-degree relative (Waddington et al., 2007). However, most affected individuals lack a family history, leaving open the question of how risk is acquired in such cases. Therefore, it is important, while studying prevalence rates for endophenotypes in patients and first-degree relatives, to also be aware of prevalence rates within the general population.

Because the pathophysiology of schizophrenia remains unknown, there are presently no laboratory tests or biological markers (biomarkers) related to the central etiopathology of the illness. *Biomarkers* are objectively measured characteristics that are "indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Atkinson, 2001)." They are disease-specific indicators of the presence or severity of the biological process directly linked to the clinical manifestations and outcome of a particular disorder (Ritsner, 2009). For example, hemoglobin A1c (HbA1c or glycosylated hemoglobin) is a minor component of hemoglobin which binds glucose and whose levels are proportional to average recent blood glucose concentrations. HbA1c is thus a useful indicator of adequacy of blood glucose control in patients with type II diabetes, as well as being related to the pathophysiology of this disorder of carbohydrate metabolism and in detecting an

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important disease feature, i.e. pathologically elevated blood glucose.

In contrast, *Endophenotypes*, or "intermediate phenotypes," are best considered as quantifiable biological variations or deficits that are types of stable trait markers or indicators of presumed inherited vulnerability or liability to a disease (Ritsner, 2009). Because the pathophysiology of schizophrenia remains obscure, and thus biomarkers are lacking, genetic research into the disorder has generally focused on the clinical phenomenology of this complex and likely multi-determined, multi-path, inherited disorder as the relevant phenotype. Endophenotypes are associated with the illness, state-independent, co-segregate within families and are found in some unaffected relatives of individuals with the disorder (because they represent vulnerability for the disorder, not the disorder itself), although at a higher prevalence than in the general population (Gottesman & Gould, 2005). They are not visible to the naked eye and are assessed by experimental, laboratory-based methods rather than by clinical observation. Because schizophrenia is likely to fall into the category of common, multi-genetic disorders (analogous to hypertension or type II diabetes; Pearlson and Folley, 2008a,b) endophenotype strategies are increasingly employed by researchers, based on the presumption that endophenotypes have more straightforward inheritance patterns and are coded for by smaller numbers of genes than are complex, heterogeneous phenomenological entities such as Diagnostic and Statistical Manual-IV-TR (DSM-IV-TR; American Psychiatric Association, 2000) diagnostic categories. Seen in this light, the endophenotype is "intermediate" between a clinical entity and the associated disease vulnerability genes. The hope is that by employing endophenotypes, the search for the etiopathology, including genetic determinants, of schizophrenia is made more straightforward (Chan and Gottesman, 2008; Pearlson and Folley, 2008a,b).

Although new mutations, deletions, or copy number variants may account for some cases (Walsh et al., 2008), other affected individuals are believed to acquire their liability for the disorder through inheritance of several common single nucleotide polymorphism (SNP) based variants, likely acting multiplicatively (Gangestad and Yeo, 2006). At a genetic level, collections of smaller numbers of SNPs may manifest as endophenotypic abnormalities (Campbell et al., 2006).

Population geneticists often assume the Hardy–Weinberg equilibrium (Hardy, 1908) when predicting genetic outcomes in subsequent populations, stating that genes and their phenotypes remain constant barring changes. However, changes including mutations (particularly caused by duplications), selection, migration, and other consequences of population and individual mating choices can cause disorders to be introduced and propagated by these forces, disrupting the Hardy–Weinberg equilibrium. Complex inherited disorders are examples of such disequilibrium including schizophrenia (Sullivan et al., 2003), bipolar disorder (Smoller and Finn, 2003), multiple sclerosis (Oksenberg and Barcellos, 2005), and type II diabetes (Permutt et al., 2005), which affect multiple loci and have been related to population drift. Thus, through multiplicative and additive models, these relatively prevalent disorders can persist in the population. This complicates the known inheritance of these disorders, but it also makes it possible to observe these multiple loci pooling in certain individuals, which are likely to be more affected by the clinical phenotypes.

It is thus likely not uncommon for healthy individuals in the general population to possess one or a few schizophrenia-associated endophenotypes, although actual prevalence rates are poorly documented. Theoretically, these endophenotypes could be neutral or even beneficial singly, if not combined with other intermediate phenotypes (Keller and Miller, 2006, Pearlson and Folley, 2008a,b). Like the hypothesized "thrifty genes" associated with type II diabetes, they may confer selective advantage under particular circumstances (Neel, 1962). These multiple genetic loci (polygenes) of small relative effect are likely additive or epistatic (interactive) with regard to cumulative schizophrenia risk; only in combination are they deleterious and likely then often in conjunction with environmental events.

There is a wealth of data in the literature on disease-related endophenotypes in schizophrenia patients (SCZ) and their first-degree relatives (REL), yet very few reviews of prevalence rates within all three categories [SCZ, REL, and healthy controls (HC)], despite the theoretical importance of such information. Heinrichs (2001) provides a thorough review of endophenotypes, but concentrates mainly on SCZ and REL, with little data on HC. Recent articles, such as the "Just the Facts" series in this journal (Tandon et al., 2008a,b; Keshavan et al. 2008), have brought to light the importance of evaluating endophenotypes for schizophrenia in order to assess research progress in this area thus far. As a prelude to further study of the co-occurrence of multiple schizophrenia biomarkers in a large, representative community sample, including all three categories, we surveyed the existing literature on the most widely published endophenotypes (Heinrichs, 2001) in order to continue our examination of the prevalence of endophenotypic abnormalities in the general population (Pearlson and Folley, 2008a,b). Articles that compared SCZ to HC or REL to HC (or both) within six different groups of endophenotypes (structural and functional brain abnormalities, sensory processing measures, neuromotor abnormalities, neuropsychological measures, physiologic abnormalities and minor physical anomalies) were included in this review. A conservative definition of abnormality was utilized in this review based on a model of statistical infrequency. As such, depending on available data, percent of abnormal findings, generally defined as greater than two standard deviations (SD) from the mean (in the direction of abnormality) and/or effect sizes (Cohen's *d*; Cohen, 1988) were extracted from each article. Under our summaries of each endophenotype, the total number of articles reviewed is reported; however, not all articles reviewed reported data on SCZ, REL, and HC samples. The number of articles reported within tables for each endophenotype reflect the number of articles that report unique data contributing to the calculations of each summary statistic, which may be different that the overall total within each endophenotype.

The purpose of this review was to assess the frequency of these established endophenotypes in all three categories, in order to provide a source of reference, as well as a beginning point for discussion on prevalence rates within SCZ, REL, *and* HC.

2. Structural and functional brain abnormalities

2.1. Ventricular volume

A Medline search was completed with the search terms of "schizophrenia" combined with "ventricular volume or lateral