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Heterogeneity of Brain Structural Variation and the Structural Imaging Endophenotypes in Schizophrenia

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Key Words
Endophenotype · Hippocampus · Intermediate phenotype · Magnetic resonance imaging · Prefrontal cortex · Schizophrenia

Abstract
Schizophrenia is often assumed to comprise a group of biologically distinct disorders, yet it has been difficult to dissect subgroups using biological markers. We review recent brain imaging morphometry studies addressing the issue of heterogeneity within the diagnostic category of schizophrenia. Studies of subgroups of schizophrenia patients have mostly used either symptom structure or clinical course for the delineation of potentially meaningful subgroups. Studies defining subgroups according to outcome, i.e. good versus poor outcome (or 'non-Kraepelinian' vs. 'Kraepelinian', respectively) have shown that while these two subgroups might overlap in the extent (and possibly also strength) of prefrontal deficits, they differ in temporal and occipital areas, where poor-outcome patients show stronger deficits. More recent studies have investigated subgroups of schizophrenia based on factor analysis of psychopathology. They have demonstrated a complex pattern of regional changes, where the typical three subgroups might overlap in prefrontal changes, but show divergence in structural deficits in other areas such as the thalamus, hippocampus, or cerebellum. Altogether, these studies demonstrate that brain structure per se is not a uniform endophenotype, but rather a combination of regional deficits highly heterogeneous in both meeting endophenotype criteria as well as in their distribution within the disease category.

Clinical Heterogeneity and Subtypes of Schizophrenia

Kraepelin's original concept of dementia praecox originates in a synthesis of the previously separately classified disorders of hebephrenia, catatonia, and dementia paranoides. Hence, although the 'Kraepelinian dichotomy' separating schizophrenia from manic-depressive illness provides a delineation of psychotic disorders in two large groups, it also relies on grouping together entities previously conceived of as distinct. Similarly, Eugen Bleuler's conception of the 'group of schizophrenias' acknowledges the clinical (and putatively etiological) heterogeneity of schizophrenia. However, there has been only limited success in delineating different types of schizophrenia on

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clinical grounds, either cross-sectional psychopathology or course of disease. Even though the current classification in DSM-IV (and similarly in ICD-10) defines subtypes of paranoid, disorganized, catatonic, undifferentiated, and residual schizophrenia, it is far from being clear whether these prototypes correspond to distinct biological entities or disease mechanisms.

Biological research on schizophrenia today is mostly directed at unveiling potential biological markers or endophenotypes, or identifying common pathways leading to the disease. As both the phenotype and genotype appear to be complex in nature, the heterogeneity of schizophrenia is one of the main problems in understanding the relation between putative genetic markers and their expression into a clinically identifiable phenotype (e.g. a combination of symptoms, disease course, etc.). Hence, the heterogeneity of biological abnormalities is a core problem in identifying reliable biological markers. It is, therefore, surprising that there are relatively few studies investigating potential subgroups of schizophrenia according to the distribution of a particular biological marker or endophenotype.

In this paper, we aim to provide a selective review on studies using magnetic resonance imaging (MRI) to assess brain structural differences in subgroups of schizophrenia. For the discussion of subgroups, our review focuses selectively on recent morphometry studies that have studied subgroups or 'subsyndromes' using morphometric techniques. For this purpose, we conducted a Medline-based literature search using the phrases schizophreni* and (subtype OR subgroup OR subsyndrome) as well as the phrase 'Kraepelinian'; from the identified papers, we selected those that compared different schizophrenia samples with different phenotypic/clinical characteristics, hence not including those that compared only one putative schizophrenia subtype (e.g. deficit schizophrenia) to controls.

Brain Imaging as a Schizophrenia Endophenotype

Brain structural changes as detected with MRI have been put forward as a putative endophenotype for schizophrenia. In fact, they appear to meet most of the stringent criteria for endophenotypes [1], e.g. being associated with the disorder, heritable (as shown in twin studies), and relatively stable over the course of disease. Also, there are now several meta-analyses, especially on studies employing voxel-based morphometry (VBM). These provide evidence for the regional distribution with increasing spatial resolution, for example by making use of anatomical likelihood estimation techniques [2]. The pattern of brain structural changes in these studies typically involves the medial temporal lobe (the hippocampus, amygdala, and partially also the parahippocampal cortex), the superior temporal cortex (including both the superior temporal gyrus and the transverse temporal gyrus/gyri or Heschl gyrus), as well as the thalamus, medial and lateral parts of the prefrontal cortex, and the insula.

Following the endophenotype strategy laid out by Gottesman and Gould [1], one of the major goals of identifying an endophenotype is the ability to delineate a subgroup of patients, which might then be linked to a particular genotype (more) specific to this subgroup than the whole group of patients. The above set of anatomical regions, therefore, might reliably differ between schizophrenia and healthy control subjects, but we do not know whether it might actually be a subset of patients that contributes more to this association than others. If brain imaging markers were useful to 'deconstruct' the biological basis of the disorders, we would not only need a better understanding of the association with different subgroups, but also consider that this association might vary across implicated brain regions [3].

While the delineation of subgroups might be possible using either phenotype or genotype, we will limit ourselves to an overview of studies using the former approach: firstly, those studies linking single symptoms to brain structure; secondly, those using dichotomies such as clinical course/outcome to define subgroups, and thirdly, a few more recent studies using psychopathology ratings to define subgroups of schizophrenia.

Correlations of Symptoms and Brain Structure

A rather large number of morphometry studies have aimed to link specific symptoms of schizophrenia to brain structure, either using correlations (e.g. severity of a symptom correlated with volume) or a dichotomous variable (e.g. hallucinating vs. nonhallucinating patients). In earlier studies, such associations were often performed in an exploratory fashion, and many findings were not replicated in subsequent studies. A few symptoms such as auditory hallucinations and formal thought disorder have more consistently been linked to the superior temporal cortices in several volumetric MRI studies [4]. While a subsequent parcellation study linked anterior parts of the left superior temporal cortex to hallucinations [5], our own studies using deformation-based mor-

phometry and VBM have provided evidence for the regional specificity of a part of Heschl gyrus showing a significant correlation with the current severity of auditory hallucinations in schizophrenia patients [6, 7]. While replicated in a smaller sample [8], a recent VBM study assessing this correlation in a sample of hallucinating patients (the previous studies had included patients irrespective of the presence or history of hallucinations) did not find an association with the left superior temporal cortex [9]. Similarly, studies comparing subgroups of patients based on a history of hallucinations have shown rather divergent findings regarding the superior temporal and prefrontal cortices [10, 11].

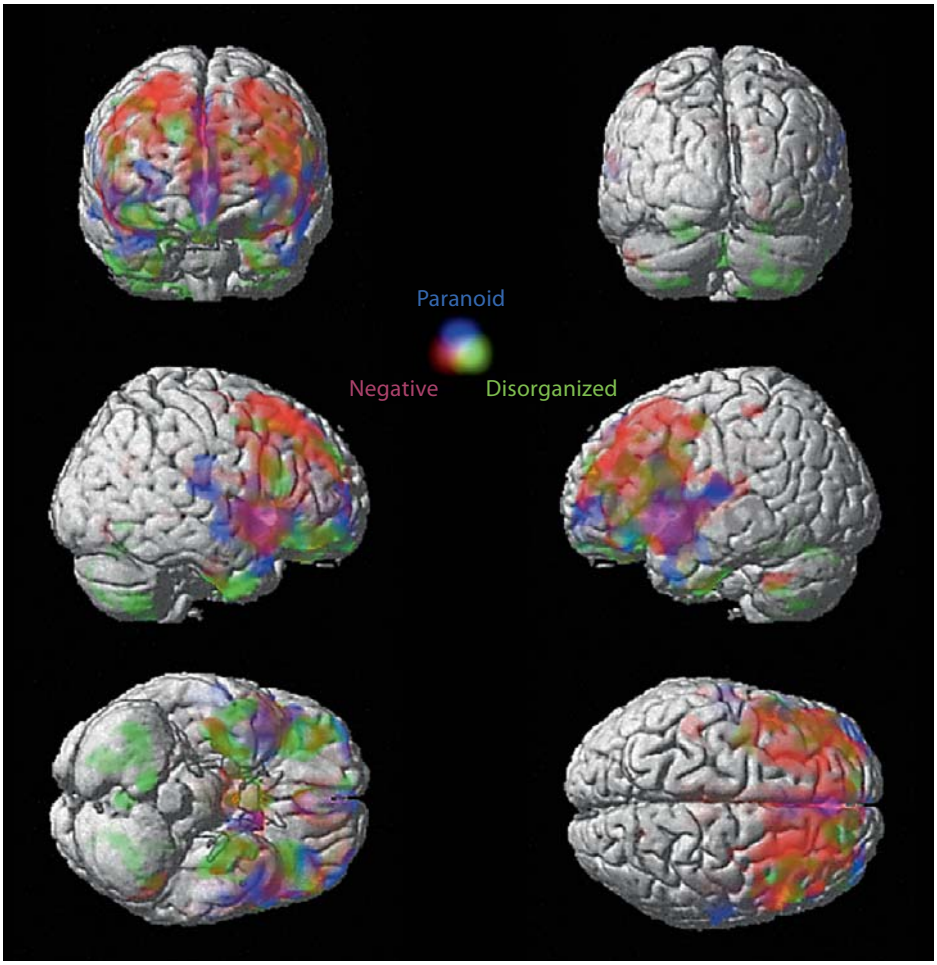
While these studies provide an interesting heuristic approach to certain common pathways in the expression of a phenotype, they also illustrate the limitations of using single symptom correlations to resolve heterogeneity across the schizophrenia population. One challenging problem is that many symptoms are in fact highly correlated to others, especially within the group of positive and negative symptoms, respectively. For example, auditory hallucinations are often highly correlated with the presence or severity of delusional symptoms. Although statistical approaches have included the removal of variance related to other positive symptoms [7], findings will inevitably vary according to the degree of intercorrelation in the sample studied. Also, no brain region appears to show an exclusive correlation to a particular symptom. It appears, therefore, that single symptoms might not be a reliable phenotype marker in providing an additional explanation for the heterogeneity of brain structure in schizophrenia.

Imaging Findings in Subgroups/Subsyndromes of Schizophrenia

Two alternative approaches have been used in a series of recent studies to address the issue of heterogeneity of brain structure in schizophrenia. The first approach is based on using clinical parameters of outcome to classify patients into poor-outcome (also termed 'Kraepelinian' type) or good-outcome ('non-Kraepelinian') groups. This dichotomy takes into account a number of clinical aspects, including longitudinal aspects, and has been used in a series of imaging studies by Mitelman and Buchsbaum [12]. Cross-sectional MRI studies indicate that several brain areas show stronger reductions in poor-outcome versus good-outcome patients, including the thalamus [13] and cingulate [14], while areas like the putamen show stronger progressive volume loss in poor-outcome patients [15]. In a cross-sectional study using atlas-based parcellation, approximating the volume of cortical Brodmann regions, the authors found both good- and poor-outcome patients to overlap in volume reductions of lateral prefrontal areas (BA 45, 44, 46, 47), while differences between these patient subgroups appeared more in the occipital cortices, the superior parietal, and certain medial temporal/parahippocampal regions [16]. While this finding is somewhat surprising, as some areas discriminating the subgroups do not show strong effects of diagnosis per se, it is partially replicated in a recent VBM study where the 'Kraepelinian' subgroup of patients showed stronger grey matter deficits in the basal ganglia and occipital cortices [17].

Taken together, these findings provide evidence that poor outcome is associated with stronger deficits (and possibly also accelerated volume loss over time). However, for the purpose of delineating endophenotypes, there are several limitations. As this dichotomy makes use of clinical variables related to outcome, it might instead be a categorization of a dimensional marker, reflecting overall disease severity. This might bear little relation to biologically valid discriminator markers.

A second approach has been to divide schizophrenia samples into subgroups based on factor analysis of psychopathology ratings. This goes back to some classical studies by Liddle et al. [18], who identified three syndromes of schizophrenia, termed psychomotor poverty, disorganization, and reality distortion, which were related to different patterns of cerebral blood flow. Recently, two large VBM studies have used factor analysis to divide their schizophrenia patient samples into three subgroups with predominantly negative, disorganization, and paranoid symptom profiles [19, 20]. The three-factor solution is an often-replicated delineation of subgroups based on psychopathology, which is also replicated in chronic and old-age populations [21]. Both VBM studies, although differing in several details, showed that there is considerable heterogeneity of spatial distribution and extent of structural deficits across the three schizophrenia subgroups. Our own study showed that the areas of overall disease activity of all subgroups were mostly in the prefrontal areas, while the thalamus, superior temporal cortices, and cerebellum were only affected in one or two subgroups [20] (fig. 1). In an extension of that study, we also assessed whether the three subgroups showed different age-related progression (i.e. an interaction of group by age in a cross-sectional design), demonstrating that the paranoid and to some extent also the negative subgroup



Color version available online

Fig. 1. VBM comparison of schizophrenia subgroups versus healthy controls ($p < 0.01$, FDR-corrected for multiple comparisons; extent threshold $p = 0.05$ [for details and original analyses, see 20]): composite image of group-wise comparisons with negative subgroup (red), disorganized subgroups (green), and hallucinatory subgroup (blue); intermediate colors reflect overlap (superimposed on cortical surface of a single subject T_1 scan). Colors refer to the online version only.

showed a stronger decline in the superior temporal and some smaller lateral prefrontal areas compared to healthy control subjects [22].

The latter studies clearly demonstrate that our understanding of brain structure as a putative endophenotype will have to consider a significant variability of effects both within single areas as well as across the different brain regions.

Based on the reviewed findings, we put forward the hypothesis that regional brain structural changes could be considered as separate putative endophenotypes, each linked to a specific form of schizophrenia. Pursuing such a strategy could ultimately allow for the delineating of subtypes of schizophrenia based on a biological marker with stable endophenotype properties. For use as a biological marker, additional studies would be useful to indicate a biological subtype of the disease based on a detected brain structural pattern (i.e. a combination of regional deficits). This would also have implications for the increasing number of imaging studies in prodromal schizophrenia and the early detection of the disease, which would depend on a genetically mediated marker (or pattern) that is relatively stable to changes of clinical state and/or medication. An example of the model is given in figure 2.

Conclusions

Brain structural alterations are among the most promising endophenotypes for schizophrenia. However, an overview of recent studies exploring the heterogeneity of brain structural patterns in subgroups of schizophrenia clearly emphasizes the fact that different subgroups of patients show different degrees and extent of structural deficits, and that some regional effects might only be evident in a subset of patients. The anatomical set of regions derived from meta-analyses is, therefore, a suitable indica-

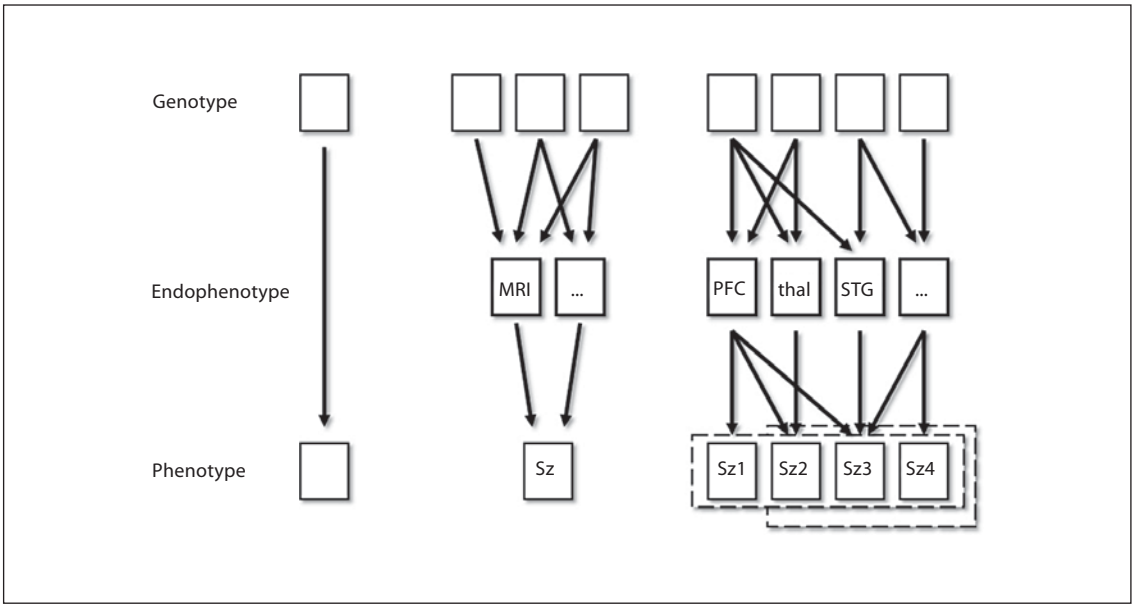


Fig. 2. Brain-imaging endophenotypes and biologically distinct subgroups in schizophrenia. The diagram illustrates the problem of identifying endophenotypes in brain imaging. While a simple genotype-phenotype relation (left side model) has been refuted for schizophrenia, many approaches rely on the identification of multiple endophenotypes for schizophrenia (middle model). However, taking into account that there might be different subgroups of schizophrenia (right side model; subgroups delineated as Sz1–4), each of these subgroups might have a different (and possibly specific) relation to a particular imaging endophenotype, e.g. a particular brain structure such as the prefrontal cortex (PFC), the thalamus (thal), or the superior temporal gyrus (STG). Each of these imaging endophenotypes, however, might also differentially be influenced by the genotype, e.g. specific risk genes. The dotted lines (right side model) indicate potential different boundaries of diagnostic classification systems, which might include different biologically related subgroups into disease entities like 'schizophrenia'.

tor of the general pattern of brain structural alteration in schizophrenia, but not a useful schizophrenia endophenotype per se. Rather, specific brain regions or a combination thereof (i.e. anatomical patterns) might show suitable endophenotype characteristics that would allow the 'deconstruction' of biologically meaningful subtypes of the disease. Finally, such viable intermediate phenotypes might then be linked to a specific genotype, which might provide a clearer link between genetic variation and phenotypes [23].

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