Is there an anatomical endophenotype for neurodevelopmental disorders? A review of dual disorder anatomical likelihood estimation (ALE) meta-analyses of grey matter volumes

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The term "neurodevelopmental disorder" broadly encompasses conditions thought to arise early in development and includes schizophrenia, bipolar disorder and autism among others. These conditions share a number of genetic and environmental risk factors postulated to lead to common difficulties in socio-emotional processing, communication and cognitive function. The alternative position is that, while the same traits are affected across these conditions, the nature or direction in which they are modified may be distinct. MRI studies provide a rapidly expanding and rich database which we propose can be used to contribute to this debate. Anatomical likelihood estimation (ALE) is a method of meta-analysis applied to voxel-based MRI studies. We have adapted this method to explore the extent to which schizophrenia and bipolar disorder and schizophrenia and autism share a common brain structural phenotype. We will review this work here and discuss whether there is sufficient other evidence to justify a common framework for further research into the inter-relatedness of such conditions.

autism, schizophrenia, bipolar, grey matter, ALE, meta-analysis

The endophenotype approach to schizophrenia and related disorders considers traits associated with the condition also observable in individuals who do not meet diagnostic criteria. The strategy relies upon assuming a dimensional perspective. It allows the size of samples studied to be greatly expanded as unaffected individuals or relatives who show similar traits to individuals with the illness can be included. In this way the impact of confounds such as medication and illness chronicity are reduced. In this paper we exploit the endophenotype approach in a rather different manner. Symptoms in psychiatry are never pathognomonic. Individuals with similar clusters of symptoms, response to treatment and outcome are categorized into discrete diagnostic groupings, but often the distinctions between diagnostic groups are blurred. This challenge in defining the target condition can be considered to be a disadvantage. However, an alternative is to examine similarities across different conditions from an intermediate or endophenotype perspective and determine whether common causal mechanisms may be at work across diagnostic categories.

1   Voxel-based MRI studies

Schizophrenia, autism and bipolar disorder are increasingly recognized have some common genetic [1,2] and environ-

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mental risk factors [3]. These appear to result in a degree of phenotypic overlap, affecting social and emotional processes, executive function and communication [4–6]. Intermediate between shared risk factors and complex phenotypic expression is brain, thus common developmental pressures driving these conditions would be expected to impact upon a common brain substrate. Brain volume differences between individuals with neurodevelopmental conditions and unaffected participants can be mapped to a brain co-ordinate system using voxel-based morphometry (VBM) methods [7–9]. Compared to manual based tracing techniques, VBM has the advantage of being a largely automated means to explore whole brain. This helps to avoid measurement bias and permits assessment of every volume-element or "voxel" in brain. In contrast, "region-of interest" (ROI) techniques require a priori targets for brain measurement. Moreover, ROI targets largely comprise rather coarse, lobar level structures that can be reliably traced manually. The fine-grained analysis of brain offered by VBM has its own draw backs; it involves multiple image pre-processing routines and challenging statistical approaches which have varied over many years in development. Never-the-less, a sizeable number of VBM studies of disorders such as autism, bipolar disorder and schizophrenia has accumulated, allowing regional brain volume differences across disorders to be registered within a common co-ordinate system or atlas. This repository provides a rich resource to investigate the extent to which neurodevelopmental disorders share an intermediate neuroanatomical phenotype.

2   Anatomical Likelihood Estimation (ALE)

A synthesis of VBM data can be achieved through meta-analysis. There are a number of different options available to extract co-ordinates listed in individual case-control group studies and compute the locations most consistently reported to be affected by a given condition. One such method, anatomical likelihood estimation (ALE), treats the co-ordinates of brain regions with significant group differences reported across multiple studies, as the centre of a 3D Gaussian probability distribution [10,11]. Where multiple studies report co-ordinates in similar location, the probability that a given locus is involved in the target disorder is therefore increased. The result is a probability map summarizing brain regions that have most consistently been implicated in the disorder across the majority of studies. These extend more traditional meta-analyses of manual based ROI approaches that, as mentioned above, are constrained to individual ROIs [12].

3   ALE in schizophrenia

We, and others, have used ALE and modifications based on

ALE to examine brain volume in schizophrenia [13–16]. In general ALE based meta-analysis of the literature in schizophrenia confirms that the disorder is characterized by lower grey matter volumes in frontal, striato-limbic, and temporal lobe regions evident from first presentation prior to drug treatment [17]. In an expanded application of ALE we examined illness "vulnerability" and "progression" in schizophrenia, finding that those with a vulnerability to schizophrenia, through shared genetic risk or because they suffer prodromal symptoms, also have lower grey matter volumes in frontotemporal regions [13]. The latter study indicated that gray matter abnormalities are more extensive in patients at first-episode and even more so in those who suffer chronic illness. This study was limited by the cross-sectional nature of the original studies contained therein. Clearly longitudinal studies are the optimal means to address progression of illness and medication effects directly, but follow-up studies in schizophrenia are extremely challenging (though see [18,19]). The ALE approach therefore serves as a practical substitute, allowing a synthesis of cross-sectional data at different stages of illness and results agree that schizophrenia involves progressive abnormalities within a limbic cortico-striato-thalamic loop system.

4   Dual disorder ALE
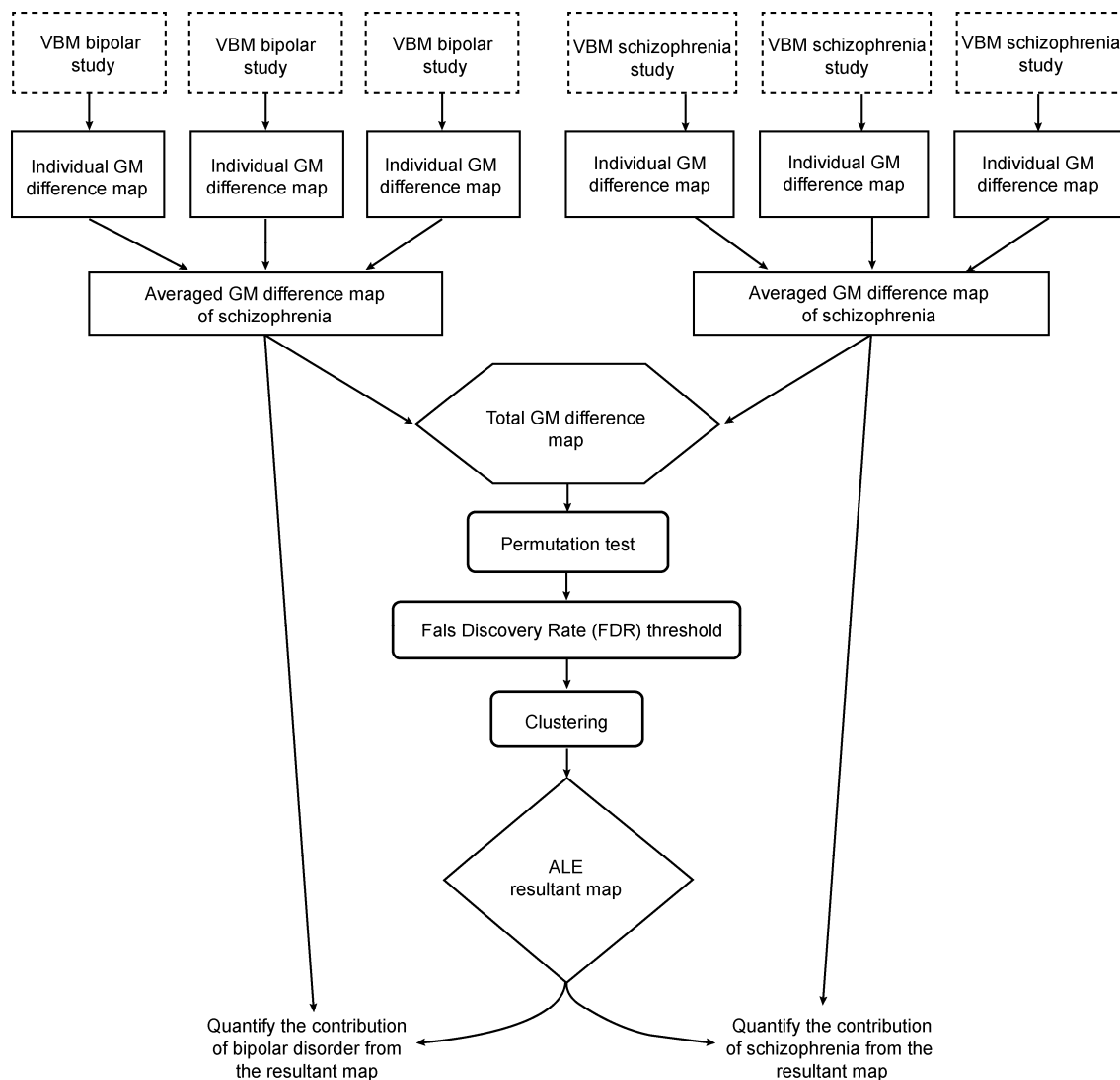
4.1   Schizophrenia and bipolar disorder

There have been fewer VBM studies of bipolar disorder. Never-the-less ALE has proven a useful tool to summarize the literature and examine whether schizophrenia and bipolar disorder act upon the same regions of brain. In order to compare schizophrenia and bipolar disorder effects on brain volume, it is critical to account for multiple confounds of predisposition to illness, chronicity of illness and medication effects. In a preliminary assessment of overlap in brain regions affected by both conditions, Ellison-Wright and Bullmore [20] synthesized data available from a vast number of schizophrenia studies together with data from studies of bipolar disorder. This initial investigation gave a strong indication that these disorders do affect the same brain regions, namely anterior cingulate and insula [20]. A potential limitation to this study was that the heterogeneous collection of schizophrenia studies returned a map of schizophrenia that covered widespread brain regions. Thus the "overlap" could have been, at least partly, a false positive, given the few data points from bipolar studies might have coincided by chance with some part of the extensive schizophrenia map. To address this issue we designed a "dual disorder" ALE study in which VBM studies of bipolar disorder were matched 1:1 to schizophrenia studies on variables such as duration of illness and medication exposure [21]. In addition we modified the ALE kernal to generate a joint map of brain regions affected by schizophrenia and bipolar disorder. This permitted extraction of the percentage contribution

made by studies of schizophrenia or bipolar disorder to the overall result. The pipeline for this modified ALE is shown in Figure 1, taken from our original publication [21].

In our dual disorder ALE analysis we found that schizophrenia and bipolar studies made an almost equal contribution to the final result, with both conditions leading to lower grey matter in prefrontal cortex, thalamus, left caudate, left medial temporal lobe, and right insula in patients relative to controls [8]. In general any brain region implicated in bipolar disorder was also implicated in schizophrenia. However, the brain was more extensively affected by schizophrenia—patients with schizophrenia had a bilateral pattern of lower grey matter volumes while bipolar disorder predominantly affected the right hemispheric. Patients with schizophrenia, but not bipolar disorder, had consistently lower grey matter volumes in the left amygdala and insula.

These results support the stance that bipolar disorder and schizophrenia are on the same spectrum with substantial shared neuroanatomical phenotype. They fit with evidence for shared cognitive difficulties in each disorder which carry similar prognostic value [22]. The less extensive brain involvement in bipolar disorder is also consistent with classical evidence for its more benign course leading some to speculate that mood symptoms in the psychosis-spectrum are a protective response which may herald a better prognosis [23]. However, perhaps the strongest evidence supporting a shared aetiology of these disorders comes from genetics. Schizophrenia and bipolar disorder have common susceptibility genes such as COMT and neuregulin 1 [24,25]. COMT is contained on chromosome 22q11 along with multiple other genes implicated in behavioural disorders including schizophrenia [26] and bipolar disorder [27]. More generally, in a study of more than 2 million families in Sweden, relatives of probands with one or other diagnosis were at substantial increased risk for either disorder [28]. The authors subsequently concluded that the genetic basis

Figure 1 Flow chart of dual disorder ALE quantification.

of schizophrenia and bipolar disorder is partly shared. Taken together with evidence of a common neuroanatomical phenotype in schizophrenia and bipolar disorder, we agree with van Os and Kapur's proposal that what is inherited in psychosis, and related brain maturation disorders, is not a specific condition but altered brain development [29].

4.2 Schizophrenia and autism spectrum disorders

The genetic and environmental influences modulating brain development in schizophrenia and bipolar disorder appear to be at work in other disorders affecting brain maturation. There is long-standing evidence for increased incidence of mood disorders and schizophrenia in the families of individuals with autism spectrum, especially those with Asperger's syndrome [30–35]. Examples of genes implicated in both schizophrenia and autism spectrum include those encoding synaptic proteins such as contactin-associated protein-2 (CNTNAP2) and Neurexin-1 (NRXN1) [1,2].

However, the link between schizophrenia and autism is not straightforward. Crespi and Badcock [36] have proposed that schizophrenia and autism are "diametric opposites". They contend that autism and schizophrenia are associated with reciprocal changes in gene regulatory pathways; in autism there is a functional gain which leads to brain overgrowth and impoverished theory of mind; in schizophrenia there is down regulation causing brain under-growth and over attribution of intent [36]. Supporting his hypothesis, Crespi and colleagues [37] have summarized evidence from studies of copy number variants (CNVs) in each disorder and observe them to be associated with reciprocal variants at four loci where deletions predispose to one condition and duplications predispose to the other. Even so, the authors acknowledge that a number of specific gene markers for schizophrenia and autism are just the same and they cannot fully exclude out a partial genetic overlap in these conditions [37].

Common environmental risk factors are also associated with autism and schizophrenia, particularly prenatal exposures such as maternal inflammation and vitamin D deficiency [38–48]. We therefore hypothesized that this array of shared aetiological pressures acting in autism and schizophrenia might lead to common neuroanatomical features. To test this we used our dual-disorder ALE approach to synthesize VBM studies of autism and schizophrenia and quantify the extent to which studies implicated similar brain regions in these conditions. The results from an autism-schizophrenia ALE revealed that, compared to typically developing control groups, both conditions resulted in lower grey matter volumes in posterior cingulate, right parahippocampal gyrus, putamen and insula and left thalamus, implicating limbic cortical-striato-thalamic circuitry in evolution of these conditions [49]. Lower grey matter volume in left putamen was only evident in autism, whereas lower grey matter in left amygdala and left insula were associated with

schizophrenia only.

Our autism-schizophrenia ALE combined studies of either classical autism, high functioning autism or Asperger's syndrome into a single autism spectrum group. However, it should be acknowledged that autism is not a single disorder but a spectrum with wide phenotypic expression [50]. Indeed we have previously suggested that, on the spectrum of complex neurodevelopmental disorders, which includes autism, schizophrenia and Asperger's syndrome, our results indicate changes to brain anatomy in Asperger's syndrome may be closer to schizophrenia [21]. This is not a new idea — many years ago Wolff described children with a diagnosis of schizoid personality disorder as phenotypically akin to the eponymous syndrome described by Asperger [51]. Most interestingly these children went on to develop schizophrenia spectrum disorders in adulthood. More recent investigations have revealed increased dopamine activity in the caudate in Asperger's syndrome [52], reminiscent of schizophrenia [53] as well as high paranoia scores [54] and "negative" symptoms in autism spectrum which respond to the anti-psychotic risperidone [55]. In addition to overlapping anatomical and genetic anomalies in basal ganglia loop systems in autism-schizophrenia spectrum conditions, the physiological functioning of this circuitry has been shown to be altered. Specifically sensorimotor gating impairment has been reported across schizophrenia, schizotypal personality disorder, relatives of patients with schizophrenia, high functioning autism and Asperger's syndrome [9,56–59]. These disorders have been described as a "family of sensorimotor gating disorders" [60] and our results point to a common neuroanatomical basis for this endophenotype. These numerous contact points in aetiology and phenotypic expression of the neurodevelopmental disorders are unlikely to be explained by simple co-morbidity. We propose that they reflect a diagnostic overlap and encourage a broader examination of endophenotypes across these disorder categories.

5 Limitations

A limitation to our discussion of neuroanatomical phenotypes, is difficulty directly comparing the 2 dual-disorder ALE studies. This is because in each analysis reviewed, the VBM studies included were matched according to somewhat different criteria. For example the bipolar disorder/schizophrenia ALE matched studies on illness duration and medication history and included studies of patients in receipt of psychotropic medication. In contrast, the autism/schizophrenia ALE matched mainly treatment naïve patient studies. The impact of medication on morphology of cortico-striatal circuits is a critical issue in these studies. Anti-psychotic drugs appear to act to increase basal ganglia size [18,61]. This may represent a "normalising" effect, since prior to treatment first episode patients with schizo-

phrenia tend to have smaller basal ganglia sizes [7,18,61]. However anti-psychotic drugs may also act to lower regional grey matter volumes in cortex, but the exact pattern and mechanism behind this observation is far from clear [18]. Mood stabilizing medications used to treat bipolar disorder are also considered to have a neuroprotective effect. The mood stabilizer lithium has been reported to cause grey cortical volume increase after only 4 weeks [62]. Other mood stabilizers such as sodium valproate and carbamazepine are thought to have neuroprotective effects through their interaction with cell plasticity regulators such as brain-derived neurotrophic factor (BDNF), bcl-2, and mitogen-activated protein kinases [63]. Thus, in evaluating endophenotypes of neurdevelopmental disorders, it is crucial to consider the impact of drug treatment on expression of the phenotype.

6   Conclusion

In summary we believe that deeper exploration of endophenotypes across diagnostic boundaries holds promise. Potentially a better understanding of common causal mechanisms will improve efforts to prevent or alleviate the difficulties faced by individuals with a wide range of neurodevelopmental conditions. However, it is important not to lose sight of the unique features which are specific to diagnoses within the spectrum so that in time intervention strategies can be better targeted towards the individual.

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