Schizophrenia Research 115 (2009) 1–7

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The Impact of developmental instability on voxel-based morphometry analyses of neuroanatomical abnormalities in Schizophrenia

Matthew Euler [a], Robert J. Thoma [b,c], Steven W. Gangestad [a], Jose M. Cañive [b,d], Ronald A. Yeo [a,c,*]

[a] Department of Psychology, University of New Mexico, MSC 03 2220 Albuquerque, NM 87131, USA
[b] Department of Psychiatry, University of New Mexico, MSC 03 2220 Albuquerque, NM 87131, USA
[c] Mind Research Network, Pete and Nancy Domenici Hall, 1101 Yale Blvd. NE MSC 11 6040, Albuquerque, NM 87131, USA
[d] New Mexico VA Health Care System, Psychiatry Services, 1501 San Pedro SE, Albuquerque, NM 87108 USA

ARTICLE INFO

Article history:
Received 27 March 2009
Received in revised form 16 August 2009
Accepted 18 August 2009
Available online 22 September 2009

Keywords:
Schizophrenia
Developmental instability
Fluctuating asymmetry
Minor physical anomalies
Voxel based morphometry

ABSTRACT

The etiologic factors underlying schizophrenia have been conceptualized as reflecting two largely genetic components — those unique to schizophrenia and those representing vulnerability to neurodevelopmental deviation in general. The Developmental Instability (DI) approach suggests that the latter can be indexed by minor physical anomalies (MPAs), which assess early prenatal growth abnormalities, and fluctuating anatomic asymmetries (FA), which reflects later deviations. Individuals with schizophrenia ($N = 19$) had elevated scores on both measures as compared to healthy controls ($N = 23$). Further, MPAs and FA were very highly correlated in the sample of individuals with schizophrenia but not in controls. In order to identify neuroanatomic variation linked with the unique factor, we conducted gray matter Voxel Based Morphometry analyses of group membership, with and without treating a composite measure of DI (based on FA, and MPAs) as a covariate. When DI was treated as a covariate, many more gray matter regions were found to statistically differ as a function of diagnosis. These results support the DI approach and suggest that the unique etiologic factors associated with schizophrenia lead to widespread gray matter volume reductions.

1. Introduction

The Developmental Instability (DI) model of individual differences in brain development (Yeo et al. 1999, 2007), based on the evolutionary genetics of normal variation, provides a unique perspective on the origins of neurodevelopmental disorders, including schizophrenia. DI is conceptualized as a vulnerability factor for variation in brain development across both the normal spectrum and neurodevelopmental disorders. We have proposed that two conceptually distinct sets of genetic factors contribute to the etiology of neurodevelopmental disorders: a genetic influence that represents a broad vulnerability for atypical brain development (the DI component), and a set of unique genetic factors that lead to specific neurodevelopmental disorders (e.g., autism, dyslexia, or schizophrenia). The major genetic abnormality underlying the general factor has been suggested to be overall mutation load. New, harmful mutations accumulate at between 1.6 (Eyre-Walker and Keightly, 1999) and 3.0 (Nachman and Crowell, 2000) alleles per generation, and it has been estimated that the total mutation load affecting the human brain is in the range of 500 per individual (Keller and Miller, 2006). Greater mutation load probably leads to relatively lower intellectual functioning (Furlow et al., 1997; Prokosch et al., 2005), accounting for the substantial shared genetic variance between lower intellectual functioning and diverse types of neurodevelopmental disorders (Malaspina et al., 2005; Toulopoulou et al., 2007).

The major impediment to evaluating the importance of mutation load has been the lack of direct measurement. Hence, researchers have relied on imperfect and indirect measures, including minor physical anomalies (MPAs) and fluctuating

* Corresponding author. Department of Psychology, University of New Mexico, Albuquerque, NM 87131, USA. Tel.: +1 505 277 4121; fax: +1 505 277 1394.
E-mail address: ryeo@unm.edu (R.A. Yeo).

0920-9964/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2009.08.014

asymmetries (FA), as described below. However, a recent large-scale study of microdeletions and microduplications with comparative genomic hybridization (Walsh et al., 2008) provided critical and direct support for the hypothesis that greater mutation load contributes to the etiology of schizophrenia. An important implication of this finding is that the specific set of mutations relevant for schizophrenia varies from individual to individual, though lead to the same or very similar neurodevelopmental consequences.

MPAs and FA have been widely used as measures of DI and each occur at an elevated incidence in schizophrenia and other neurodevelopmental disorders (Yeo et al., 2007). MPAs are morphological variants caused by slow or disrupted fetal growth rates. Examples include hypertelorism (wide spaced eyes) and low-set ears, each reflecting slowed growth at a particular point in prenatal development. FAs are deviations from symmetry on bilateral traits (e.g., finger length, ear width) that are symmetric at the population level. They are typically aggregated into composite scores (e.g., Gangestad et al., 2001) that show modest heritability (Johnson et al., 2008). These types of FA measures probably reflect later developmental perturbations than MPAs (Yeo et al., 1997). However, some studies (e.g., Markow and Gottesman, 1989) have constructed FA measures based on dermatoglyphic characteristics, and as such features are determined relatively early in prenatal development, they likely tap similar developmental disruptions as MPAs.

In the current study we utilized these proxy measures of DI in an attempt to delineate the neural abnormalities associated with the specific genetic influences underlying schizophrenia. Our reasoning is as follows. As has been done in many other studies, Voxel Based Morphometry (VBM) was first used to characterize brain differences between schizophrenia patients and healthy controls (see Honea et al., 2005 for a review). We then treated overall DI, as computed from composite measures of MPAs and FA, and the DI by diagnosis interaction, as covariates. This strategy will remove neuroanatomical variation related to DI in the VBM analyses of group differences, revealing the neuroanatomical impact of the specific and unique etiological influences for schizophrenia. Finally, we examined the replicability in a new sample of two specific findings we have previously cited in support of the DI approach: early neurodevelopmental abnormalities as indexed by MPAs predict individual variation in handedness (Yeo et al., 1997) and later developmental abnormalities as indexed by FA predict individual variation in general intellectual functioning (Furlow et al., 1997).

2. Materials and methods

2.1. Participants

Twenty three healthy control participants (16 male, 7 female) were recruited through ads in the local media, and twenty schizophrenia patients (18 male, 2 female) were recruited from the Albuquerque VA Medical Center and University of New Mexico Mental Health Sciences Center. Participants were adults ranging in age from 22 to 63 (see Table 1); one female (a control) and two male participants (patients) were left-handed. None had a history of head injury, neurological disorder, or unstable medical illness. All participants were screened with the Structured Clinical Interview for DSM-IV Axis-I Disorders, Clinician Version (SCID-CV; First et al., 1996). Three control participants and thirteen schizophrenia patients were smokers. Individuals with a history of alcohol or other substance abuse in the three months preceding the study were excluded, as were individuals who demonstrated any history of either marijuana or cocaine dependence. All patients met predetermined criteria for clinical stability, as they had been treated with the same antipsychotic medications for at least three months and had not had an inpatient stay during the prior year. Control participants were screened via the SCID and Clinical Interview for the presence of DSM-IV Axis-I and Axis-II disorders, and for psychotic disorder in first degree relatives assessed by FH-RDC diagnostic criteria (Li et al., 1997; Fogelson et al., 2004). All patients were taking either atypical ($n=14$; clozapine-3, aripiprazole-1, risperidone-5, quetiapine-3, and olanzapine-2) or conventional ($n=5$; haloperidol-3; perphenizine-1; and fluphenazine-1) antipsychotic medications (One participant was also enrolled in a separate double-blind medication trial at the time of the current study and their specific antipsychotic medication could not be ascertained). As VBM requires identical slice dimensions among the MRIs included in each analysis, three controls were excluded from VBM analyses due to differences in the total number of slices in their MRIs relative to the remainder of the sample. One schizophrenia patient was excluded from all but MPA analyses due to differences in the number of their MRI slices and missing FA and cognitive data.

Table 1
Descriptive statistics and group differences (as determined by independent samples *t*-tests) on age, overall cognitive ability, and developmental instability measures.

	Controls			Schizophrenics				
	Mean	S.D.	*n*	Mean	S.D.	*n*	*t*	*p*
Age	43.30	11.90	23	43.26	10.50	19	.01	ns
Cognition	4.43	4.49	23	-6.84	7.99	19	5.47	.000
DI	-.418	.495	23	.504	1.046	19	3.50	.002
FA	-.320	.080	23	.399	.125	19	2.39	.023
MPA	4.09	2.087	23	8.00	3.866	20	4.04	.000

2.2. Developmental instability measurements

2.2.1. Fluctuating asymmetry

Fluctuating asymmetry measures reflect deviation from perfect symmetry in bilateral features that, across the relevant population, are typically symmetrical. Alternatively, directional asymmetries (DA) occur in features for which a population of organisms shows a consistent structural or functional bias for a particular side of the body. Skeletal FA was assessed by two trained research assistants in all participants using calipers across the feet, ankles, elbows, wrists, and hands. The length and width of each ear and the length of the first four fingers were also measured. Each of these measures was conducted twice (once by each rater) to increase reliability, and the mean of the two measurements was calculated and used as the feature size for calculation of FA. FA for individual traits was calculated by taking the absolute value of the difference between left and right sides, divided by one-half the sum of left plus right sides {individual $FA=|R-L|/[5\times(R+L)]$}. Of the seven body parts measured, only hand width was determined to be directionally asymmetric; it was excluded from the present analyses. FA scores for the ten

Table 2
Regions of decreased gray matter volume in the schizophrenic group as compared to controls in VBM analyses with age and sex treated as nuisance variables.

Local maxima	Cluster-level *p*	Cluster size	Voxel-level *T*	*X*	*Y*	*Z*
Left middle occipital gyrus	0.270 n.s	221	4.75	-28	-80	14
Left superior temporal gyrus	0.484 n.s	122	4.50	-44	-38	4
Left medial frontal gyrus	0.243 n.s.	240	4.24	-12	62	-18
Right lingual gyrus	0.546 n.s	102	4.17	14	-66	2
Left inferior temporal gyrus	0.258 n.s	229	4.11	-46	-14	-22
Left inferior temporal pole	0.292 n.s	208	3.97	-18	6	-38

remaining measurements were summed to derive a total FA score for each subject. The inter-rater reliability of the FA measurements was assessed by separately computing the ten-trait composite FA measurement from each rater and calculating the two-way mixed intraclass correlation coefficient in SPSS 16.0. The single measure intraclass correlation coefficient of consistency between the two sets of FA measurements was $r(41) = .86$, indicating good inter-rater reliability for the FA measurements. The inter-item correlation (alpha) of these measures averaged together in the feature calculation of FA was .92.

2.2.2. Minor physical anomalies

Minor physical anomalies (MPA) were measured using the Waldrop Scale (Waldrop and Halverson, 1971), which quantifies minor malformations of the head, hair, ears, tongue, palate; and fingers, toes, and hands. Total individual FA and MPA scores were each then converted to *z*-scores and summed to form a composite index of individual developmental instability, as in prior studies (e.g., Yeo et al., 1997).

2.3. Neuropsychological assessment

Each participant received a battery of neuropsychological tests: the Shipley Institute of Living Scale, the Digit Span Forward and Digit Span Backward subtests from the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Auditory Consonant Trigrams, the Logical Memory and Visual Reproduction subtests of the Wechsler Memory Scale—Revised (WMS-R), the Controlled Oral Word Association Test, and Trail Making Tests parts A and B (see Lezak et al., 2004, for all test references). *z*-scores were computed for each test score based on results from the total sample. These were then summed to provide a simple composite measure of general cognitive functioning. Handedness was assessed with the Waterloo Inventory (Steenhuis and Bryden, 1989).

2.4. Image acquisition

For each subject, high-resolution 3D T1-weighted MR images were acquired with a 1.5 T Picker Edge Imager at the Albuquerque VA Functional Neuroimaging Center, using a Field Echo 3D Sagittal sequence (Picker) (TR = 15 ms, TE = 4.4 ms, FOV = 256 mm, flip angle = 25°, matrix 192 × 256, slice thickness = 1.5 mm).

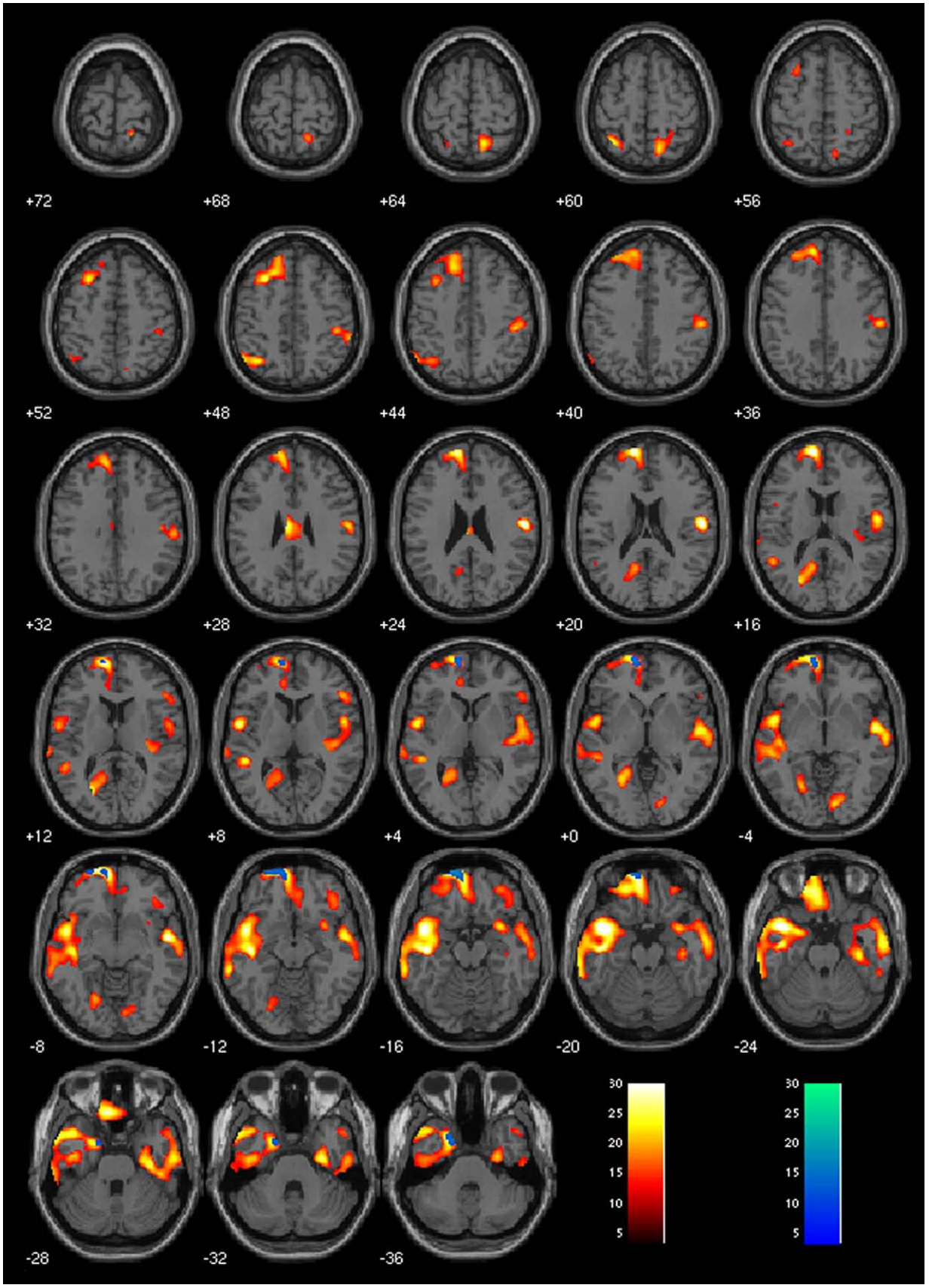
2.5. Voxel based morphometry

Image analysis was performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm) running in Matlab 7.3. MR images were manually aligned to a common space in SPM based on the locations of the anterior and posterior commissures. Study images were spatially normalized, bias corrected, and segmented into gray matter, white matter, and cerebrospinal fluid using the default prior probability maps provided for the unified segmentation routine implemented in SPM5 (Ashburner and Friston, 2005). The modulation step was performed to correct for erroneous volume changes introduced during spatial normalization, though non-modulated segmented gray matter maps were also retained for use in inferential statistics. Total gray matter volumes were obtained from the non-modulated segmented gray matter maps via the 'get totals' matlab script (Ridgway, 2007) available from the author's website (http://www.cs.ucl.ac.uk/staff/G.Ridgway/vbm/). The resulting modulated gray matter probability maps contained 2 × 2 × 2 mm isotropic voxels which were then smoothed with a kernel of 12 mm FWHM.

Statistical analyses for demographic and inferential statistics were performed using SPSS 16.0 for Windows. A maximum

Table 3
Regions of decreased gray matter volume in the schizophrenic group as compared to controls in VBM analyses with DI, the DI × group interaction, and age and sex treated as nuisance variables.

Local maxima	Cluster-level *p*	Cluster size	Voxel-level *T*	*X*	*Y*	*Z*
Left superior frontal gyrus	0.000	5466	6.68	−16	64	−16
Left superior temporal gyrus	0.000	10,851	6.25	−42	6	−22
Right postcentral gyrus	0.000	5730	6.16	56	−12	22
Left cuneus	0.000	1586	5.00	−22	−70	14
Right precuneus	0.018	652	4.94	14	−58	62
Right lingual gyrus	0.022	613	4.64	12	−82	−4
Right inferior frontal gyrus	0.005	920	4.48	52	28	8
Left cingulate gyrus	0.195 n.s.	25,113	4.24	−2	−16	30
Left postcentral gyrus	0.477 n.s.	120	4.13	−34	−36	44
Right Pulvinar Nucleus of Thalamus	0.456 n.s.	126	4.07	12	−32	2
Right middle frontal gyrus	0.283 n.s.	196	4.06	46	28	30
Right middle frontal gyrus	0.154 n.s.	286	3.95	44	10	46


+72
+68
+64
+60
+56
+52
+48
+44
+40
+36
+32
+28
+24
+20
+16
+12
+8
+4
+0
-4
-8
-12
-16
-20
-24
-28
-32
-36
30
25
20
15
10
5
30
25
20
15
10
5

alpha level of $p<.05$ was adopted for statistical tests. VBM statistical analyses were conducted using the multiple regression framework in SPM5. Two primary analyses were conducted; the first examined the relationship between gray matter volume and schizophrenia, and the second examined this relationship when controlling for the effect of DI as well as its interaction with diagnosis of schizophrenia. In the first analysis of gray matter volume in schizophrenia, two contrasts were performed where diagnosis was weighted positively or negatively while age and sex were treated as covariates (i.e. variables of no interest). In the second analysis, age and sex were again treated as covariates as were individual DI composite scores, and the DI composite by diagnosis interaction, while diagnosis of schizophrenia was again weighted positively or negatively. Thus for all analyses, contrasts were defined to test for voxels of increased or decreased gray matter volume associated with diagnosis of schizophrenia, when controlling for variance due to either demographics alone or both demographics and developmental instability. Voxels were considered significant at $p<0.001$ uncorrected for multiple comparisons in the first analysis (schizophrenia effect without controlling DI), and at $p<0.005$ correcting for the false discovery rate (FDR) in the second analysis (schizophrenia effect controlling for DI). In addition, corrected cluster-level p-values (adjusted for non-isotropic smoothness) are reported for both VBM analyses, although analyses emphasized the voxel-wise analysis approach. Specifically, analyses which revealed statistically significant voxels within clusters containing a minimum of 100 contiguous voxels were recorded, and the locations of their maxima were retained. Thus, clusters were thresholded a priori at a minimum of 100 significant contiguous voxels or more. For each cluster containing significant maxima, spatial coordinates were entered into the xjView image viewing program (http://www.alivelearn.net/xjview/) to determine its approximate anatomical locus (Cui et al., 2007).

3. Results

3.1. Developmental instability, diagnosis, and gray matter volume

Descriptive statistics on age, overall cognitive performance, and DI measures are provided in Table 1 along with independent samples t-tests of group differences. As hypothesized, individuals with schizophrenia exhibited greater overall DI, as well as greater FA and MPA scores. The correlations between FA and MPA scores significantly differed across groups ($z=2.38$, $p<.02$), with $r=.74$ ($p<.001$) in the schizophrenia group and $r=.12$ (ns) in controls.

A test of group differences in the estimate of overall gray matter volume using the non-modulated segmented gray matter maps failed to demonstrate significant gray matter volume differences between healthy participants and individuals with schizophrenia (F (1, 39) $=.79$, $p=.37$). Partial correlation analyses controlling for variance due to age and sex demonstrated positive associations between the composite DI measure and non-modulated segmented gray matter volumes in both individuals with schizophrenia ($r=.50$, $p=.041$) and healthy participants ($r=.47$, $p=.047$).

3.2.1. Voxel-based morphometry: diagnosis and gray matter volume

In the first contrast, VBM analyses revealed significant voxels within several clusters of greater than 100 voxels of decreased gray matter volume associated with diagnosis of schizophrenia when controlling for variance due to age and sex (see Table 2 for details on cluster size and locations). In a separate analysis two significant maxima of greater gray matter volume were identified, one in the right middle temporal gyrus (cluster size — 259 voxels), and one in the body of the right caudate nucleus (cluster size — 124 voxels). Neither cluster was statistically significant prior to correcting for multiple comparisons.

3.2.2. Voxel-based morphometry: diagnosis and gray matter volume controlling for DI and DI by diagnosis interaction

Contrasts controlling for the effects of developmental instability on gray matter volume in schizophrenia revealed more regions of decreased gray matter volume than were observed in the analyses described above that did not control for DI. Table 3 lists the approximate anatomical location of each significant maximum within larger clusters. A total of 26,797 voxels of significantly decreased gray matter volume in schizophrenia were observed when controlling for DI, compared to 1122 voxels observed in the prior analysis. No regions of increased gray matter volume in schizophrenia were observed when controlling for variance due to DI and its interaction with schizophrenia diagnosis. Fig. 1 shows the limited extent of regions linked with the diagnosis of schizophrenia when DI and the DI by diagnosis interaction were not treated as covariates; it also shows the much greater extent of group differences when DI and the interaction term were treated as covariates.

3.3. Test of medication effects

While the relatively small sample size prevented a more thorough investigation of the effect of the various antipsychotic medications on gray matter volumes, a test for differences in total gray matter volumes between patients taking conventional versus atypical antipsychotics was not significant ($F(1,19)=1.516$, $p=.250$).

3.4. Neuropsychological measures and DI

To evaluate whether DI findings reported in our previous studies could be replicated here, in the combined sample we examined predictions that (1) better overall cognitive performance would be related to reduced FA (see Prokosch, et al., 2005), and (2) greater MPA scores would predict greater left handedness (see Yeo et al., 1997). Using directed statistical tests (Rice and Gaines, 1994), in which 80% of the critical region was allocated to the tail of the test statistic in the predicted direction, predictions regarding handedness ($r=-.275$,

Fig. 1. Brain regions associated with the diagnosis of schizophrenia as determined by different VBM models, depicted on the SPM5 canonical T1 image. Regions in warm colors are those significant at $p<.005$ (FDR corrected) when DI and the diagnosis x DI interaction were treated as covariates. Regions in blue were significant at $p<.001$ (uncorrected) when these variables were not treated as covariates. Results demonstrate that the neuroanatomic correlates of schizophrenia are much more widespread after taking DI into account as a covariate.

$p<.05$) and general cognitive ability ($r=-.285$, $p<.05$) were confirmed.

4. Discussion

Our overall measure of DI, as well as FA and MPA scores individually, was significantly greater in schizophrenia patients than controls. While many studies have now demonstrated similar results for MPAs, far fewer reports are available for FA (Yeo et al., 2007). To the best of our knowledge, no study has examined both types of DI measures in the same sample of schizophrenia patients. Interestingly, FA and MPA scores were highly correlated in the schizophrenia group and unrelated in controls. As MPA scores are likely to reflect early prenatal variability in development, while FA measures capture later prenatal as well as postnatal developmental variability (Yeo et al., 1997), this observation has implications for the nature of neurodevelopmental abnormalities in schizophrenia. In the presence of the specific genetic factor leading to schizophrenia, the tendency to have early deviation in brain development predicts the tendency to have later deviations. In controls, lacking the specific schizophrenia genetic factor, early and later developmental deviations are independent. That is, later developmental events are buffered from variability in earlier development. Thus, the specific schizophrenia factor may be construed as initiating a "cascade" of abnormal growth and development. In contrast, no such cascade is evident behaviorally or anatomically in two other prominent disorders linked with DI, ADHD and dyslexia, suggesting qualitatively distinct specific genetic factors.

Kelly et al. (2005) reported that *greater* CSF volumes were associated with *fewer* MPAs in a sample of schizophrenics. This suggests that ventricular enlargement, perhaps the single most prominent brain abnormality in schizophrenia, is linked with the specific etiologic component, rather than DI. If so, other neurodevelopmental disorders linked with DI, such as dyslexia or ADHD, should not have enlarged ventricles, as they do not have the specific schizophrenogenic etiology. Though the literature on ventricular anatomy in these two disorders is surprisingly sparse, both ADHD (Filipek et al., 1997) and dyslexia (Pennington et al., 1999) appear to be characterized by normal ventricle size.

The nature and significance of progressive neuroanatomical changes during adolescence and adulthood in schizophrenia has been hotly debated (see DeLisi, 2008 for a recent review). Some theorists have consistently emphasized early neurodevelopmental abnormalities (e.g., Weinberger, 1987), while others have drawn attention to possible progressive decreases in gray matter volumes and progressive increases in ventricle volumes (e.g., Lieberman, 1999). To a certain extent, the current results may help bridge this conceptual gap, linking an increased probability of early abnormalities (e.g., in neural proliferation and migration leading to atypical laterality) with an increased probability of those occurring later in life (e.g., in pruning and dendritic arborization leading to enlarged ventricles).

Our VBM analyses suggest that the full extent of the schizophrenia specific effect on brain abnormality has been masked by the effects of comorbid DI. The extent of gray matter reduction in schizophrenia is much greater when DI and its interaction with diagnosis are statistically controlled. In healthy controls, DI is associated with modest, but widespread gray matter increases (Euler et al., 2008), especially in right frontal regions. Fig. 1 reveals the magnitude of the DI effect on gray matter in schizophrenia. Far more frontal and anterior temporal gray matter reductions are noted when DI is treated as a covariate. The impact of the schizophrenia specific etiologic factor is apparently quite widespread in the current sample. Increases in gray matter cortical thickness have been reported for both predominantly genetic (e.g., autism; Hardan et al., 2006) and predominantly environmental (e.g., fetal alcohol syndrome; Sowell et al., 2007) neurodevelopmental disorders. Further, a recent report indicates that early life stress leads to *greater* prefrontal cortical volume in rhesus monkeys (Spinelli et al., 2009), perhaps due to reduced gray matter pruning or greater glial development.

These widespread gray matter effects are consistent with expectations, as current VBM analyses did not control for group differences in overall gray matter volumes- a procedure appropriate for hypotheses involving relative or localized rather than absolute volumetric differences (Mechelli et al., 2005). Thus, while differences revealed when controlling for DI were not attributable to differences in *total* brain size (as assessed by correlation analyses), they nonetheless reflect more global group differences in gray matter volumes, rather than precisely delineated regional effects. Hence, the current results are perhaps best interpreted as suggesting a global effect of DI to increase gray matter volumes in schizophrenia, though additional research is needed to address this issue. It is unlikely that the current results are due to medication effects, as the current sample of schizophrenia patients comprised a mixed group of individuals taking typical and atypical antipsychotic medications. Moreover, antipsychotic medications have been shown to particularly affect basal ganglia volumes (Lang et al., 2001, Scherk and Falkai, 2006).

As an example of the possible impact of our results, consider the recent study by Liu et al. (2009) utilizing parallel independent components analysis to identify single nucleotide polymorphisms that (1) distinguished patients from controls, and (2) were correlated with fMRI activations distinguishing the groups. The analysis revealed that relevant genetic variation predicted an fMRI component consisting largely of parietal activations. As DI is partly heritable (Johnson et al., 2008) and has voxel-wise gray matter volume correlates in normals (Euler et al., 2008), one might expect that had Liu et al. covaried DI their results might be quite different. Most obviously, one might anticipate more widespread fMRI activations linked with a more specific subset of genetic variations.

There are two significant limitations that impact interpretation of the current results. First, our sample sizes are quite small. One consequence may be that our VBM results without covarying DI (see Table 1) reveal less abnormality than that seen in VBM studies utilizing larger samples (e.g., Meda et al., 2008). For this reason, we have not attempted to carefully delineate the additional brain regions associated with diagnosis when DI was controlled, beyond merely noting the prevalence of additional temporal lobe abnormalities. Rather, we consider the differing VBM results more as a "proof of principle," demonstrating the possible beneficial effects of systematically including DI in both neuroanatomical and genetic investigations of schizophrenia. Second, the DI measures utilized, though

standard in the field, are not optimally sensitive to the underlying construct of interest. Based on a detailed psychometric analysis (Gangestad et al., 2001), we have demonstrated that composite FA measures correlate only .5 or so with the latent construct of DI. Hence, the obtained effect sizes may substantially underestimate the true magnitude of the relationship between DI and diagnosis.

Role of funding source

Research grants from NIH, NIAAA, and the Veterans Administration provided support for recruitment and personnel costs.

Contributors

Drs. Thoma and Canive collected the study data. Mr. Euler conducted Voxel Based Morphometry analyses, and conducted the statistical analyses with Dr. Yeo. Dr. Yeo prepared the first draft of the manuscript. All authors participated in the conception of the study, interpretation and discussion of the results, and subsequent drafts and review of the manuscript.

Conflict of interest

There are no conflicts of interest.

Acknowledgement

The authors would like to thank Vince Calhoun, Andrew Mayer, and Matthew Shane for technical assistance. This research was supported by National Institutes on Alcohol Abuse and Alcoholism grants 1K23AA016544-01 and 1R21AA017313-01 to Dr. Thoma and by National Institute of Mental Health MH-65304 and VA CSR&D IIR-04-212-3 grant to Dr. Cañive.

References

Ashburner, J., Friston, K., 2005. Unified segmentation. Neuroimage 26, 839–851.
Cui, X., Jeter, C.B., Yang, D., Montague, P.R., Eagleman, D.M., 2007. Vividness of mental imagery: individual variability can be measured objectively. Vision Res. 47 (4), 474–478.
DeLisi, L.E., 2008. The concept of progressive brain change in schizophrenia: implications for understanding schizophrenia. Schiz. Bull. 34, 312–321.
Euler, M.J., Thoma, R.J., Parks, L.K., Gangestad, S.W., Yeo, R.A., 2008. Fluctuating asymmetry and individual variation in regional gray and white matter volumes: a voxel based morphometry study. Evol. Psychol. 65, 628–636.
Eyre-Walker, A., Keightly, P.D., 1999. High genomic deleterious mutation rates in hominids. Nature 397, 344–346.
Filipek, P.A., Semrud-Clikeman, M., Steingard, R.J., Renshaw, P.F., Kennedy, D.N., Biederman, J., 1997. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurol. 48, 589–601.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1996. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Clinician Version. American Psychiatric Press, Washington, DC.
Fogelson, D.L., Nuechterlein, K.H., Asarnow, R.F., Payne, D.L., Subotnik, K.L., 2004. Validity of the family history method for diagnosing schizophrenia, schizophrenia-related psychoses, and schizophrenia-spectrum personality disorders in first-degree relatives of schizophrenia probands. Schizophr Res. 68 (2-3), 309–317 Jun 1.
Furlow, B., Armijo-Prewitt, T., Gangestad, S.W., Thornhill, R., 1997. Fluctuating asymmetry and psychometric intelligence. Proc. Royal Soc. London: B 264, 823–829.
Gangestad, S.W., Bennett, K.L., Thornhill, R.J., 2001. A latent variable model of developmental instability in relation to men's sexual behavior. Proc. Royal Society of London: B 268, 1677–1684.
Hardan, A.Y., Muddsani, S., Vemulapalli, M., Keshavan, M., Minshew, N.J., 2006. An MRI study of increased cortical thickness in autism. Am. J. Psychiat. 163, 1290–1292.
Honea, R., Crow, T.J., Passingham, D., Mackay, C.E., 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am. J. Psychiat. 162, 2233–2245.
Johnson, W., Gangestad, S.W., Segal, N.L., Bouchard, T.J., 2008. Heritability of fluctuating asymmetry in a human twin sample: the effect of aggregation. Am. J. Human Biol. 6, 651–658.
Keller, M.C., Miller, G.F., 2006. Resolving the paradox of common harmful, heritable mental disorders: which genetic models work best? Behavioral Brain Sci. 29, 385–404.
Kelly, B.D., McNeil, T.F., Lane, A., Henricksson, K.M., Kinsella, A., Agartz, I., 2005. Is craniofacial dysmorphology correlated with structural brain anomalies in schizophrenia? Schizophr Res. 80, 349–355.
Lang, D.J., Kopala, L.C., Vandorpe, R.A., Rui, Q., Smith, G.N., Goghari, V.M., Honer, W.G., 2001. An MRI study of basal ganglia volumes in first-episode schizophrenia patients treated with risperidone. Am. J. Psychiat. 158, 625–631.
Lezak, M.D., Howieson, D.B., Loring, D.W., 2004. Neuropsychological assessment, 4th Ed. Oxford Press, New York.
Li, G., Silverman, J.M., Smith, C.J., Zaccario, M.L., Wentzel-Bell, C., Siever, L.J., Mohs, R.C., David, K.L., 1997. Validity of the family history method for identifying schizophrenia-related disorders. Psychiat. Res. 70, 39–48.
Lieberman, J.A., 1999. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biol. Psychiat. 46, 729–739.
Liu, J., Pearlson, G., Windemuth, A., Ruano, G., Perrone-Bizzozero, N.I., Calhoun, V., 2009. Combining fMRI and SNP data to investigate connections between brain function and genetics using parallel ICA. Hum. Brain Mapping 30, 241–255.
Malaspina, D., Reichenberg, A., Fennig, S., Davidson, M., Harlap, S., Wolitzky, R., Rabinowitz, J., Susser, E., Knobler, H.Y., 2005. Paternal age and intelligence: implications for age-related genomic changes in male germ cells. Psychiatr. Genetics 15 (2), 117–125.
Markow, T.A., Gottesman, I.I., 1989. Fluctuating dermatoglyphic asymmetry in psychotic twins. Psychiat. Res. 19, 37–43.
Mechelli, A., Price, C.J., Friston, K.J., Ashburner, J., 2005. Voxel-based morphometry of the human brain: methods and applications. Curr. Med. Imaging Rev. 1, 105–113.
Meda, S.A., Guiliani, N.R., Calhoun, V.D., Jagannathan, K., Schretlen, D.J., Pulver, A., Cascella, N., Keshavan, M., Kates, W., Buchanan, R., Sharma, T., Pearlson, G.D., 2008. Large scale ($N=400$) investigation of gray matter differences in schizophrenia using optimized voxel-based morphometry. Schizophr. Res. 101, 95–105.
Nachman, M.W., Crowell, S.L., 2000. Estimate of the mutation rate per nucleotide in humans. Genetics 156, 297–304.
Pennington, B.F., Filipek, P.A., Lefly, D., Churchwell, J., Kennedy, D.N., Simon, J.H., Filley, C.M., Galaburda, A., Alarcon, M., DeFries, J.C., 1999. Brain morphology in reading disabled twins. Neurol. 53 (4), 723–729.
Prokosch, M., Yeo, R.A., Miller, G., 2005. Intelligence tests with higher g-loadings show higher correlations with body symmetry: evidence for a general fitness factor mediated by developmental stability. Intelligence 33, 203–213.
Rice, W., Gaines, S., 1994. Heads I win, tails you lose. Trends Ecol. Evol. 9 (6), 235–237.
Ridgway, G. 2007. get_totals.m. [Computer software]. Retrieved October 8, 2008, from http://www.cs.ucl.ac.uk/staff/G.Ridgway/vbm/.
Scherk, H., Falkai, P., 2006. Effects of antipsychotics on brain structure. Curr. Opin. Psychiatr. 19, 145–150.
Sowell, E.R., Mattson, S.N., Kan, E., Thompson, P.M., Toga, A.W., 2007. Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. Cereb. Cortex 18, 136–144.
Spinelli, S., Chefer, S., Suomi, S.J., Higley, J.D., Barr, C.S., Stein, E., 2009. Early stress induces long-term morphologic changes in the primate brain. Arch. Gen. Psychiat. 66, 658–665.
Steenhuis, R.E., Bryden, M.P., 1989. Different dimensions of hand preference that relate to skilled and unskilled activities. Cortex 25, 289–304.
Toulopoulou, T., Picchioni, M., Rijsdijk, F., Hua-Hall, M., Ettinger, U., Sham, P., Murray, R., 2007. Substantial genetic overlap between neurocognition and schizophrenia. Arch. Gen. Psychiatry 64 (12), 1348–1355.
Waldrop, M.F., Halverson, C.F., 1971. Minor physical anomalies and hyperactive behavior in children. Brunner/Mazel, New York.
Walsh, T., McClellan, J.M., McCarthy, S.E., et al., 2008. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 320, 539–543.
Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiat. 44, 660–669.
Yeo, R.A., Gangestad, S.W., Edgar, C., Thoma, R.J., 1999. The evolutionary genetic underpinnings of schizophrenia: the developmental instability model. Schizophr. Res. 39, 197–206.
Yeo, R.A., Gangestad, S.W., Thoma, R.J., Shaw, P., Repa, K., 1997. Developmental instability and cerebral lateralization. Neuropsychology 11, 552–561.
Yeo, R.A., Gangestad, S.G., Thoma, R.J., 2007. Developmental instability and individual variation in brain development: implications for the etiology of neurodevelopmental disorders. Curr. Dir. in Psychol. Sci. 15, 245–249.