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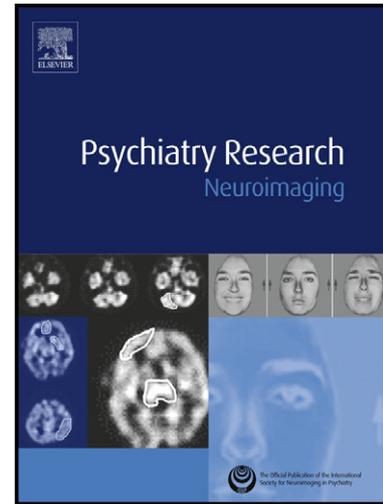
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**Grey-matter texture abnormalities and reduced hippocampal volume are
distinguishing features of schizophrenia**

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Abstract

Neurodevelopmental processes are widely believed to underlie schizophrenia. Analysis of brain texture from conventional magnetic resonance imaging (MRI) can detect disturbance in brain cytoarchitecture. We tested the hypothesis that patients with schizophrenia manifest quantitative differences in brain texture that, alongside discrete volumetric changes, may serve as an endophenotypic biomarker. Texture analysis (TA) of grey matter distribution and voxel-based morphometry (VBM) of regional brain volumes were applied to MRI scans of 27 patients with schizophrenia and 24 controls. Texture parameters (uniformity and entropy) were also used as covariates in VBM analyses to test for correspondence with regional brain volume. Linear discriminant analysis tested if texture and volumetric data predicted diagnostic group membership (schizophrenia or control). We found that uniformity and entropy of grey matter differed significantly between individuals with schizophrenia and controls at the fine spatial scale (filter width below 2 mm). Within the schizophrenia group, these texture parameters correlated with volumes of the left hippocampus, right amygdala and cerebellum. The best predictor of diagnostic group membership was the combination of fine texture heterogeneity and left hippocampal size. This study highlights the presence of distributed grey-matter abnormalities in schizophrenia, and their relation to focal structural abnormality of the hippocampus. The conjunction of these features has potential as a neuroimaging endophenotype of schizophrenia.

Keywords: Classifier, Endophenotype, Magnetic resonance imaging, Neurodevelopment, Psychosis

1. Introduction

The diagnosis of schizophrenia typically signals a lifelong psychotic disorder with pervasive costs to patients, families and society (Gustavsson et al., 2010). The varied and often complex profile of schizophrenia, including the variable expression of positive and negative symptoms, cognitions and behaviours, continues to challenge scientific understanding toward prevention, diagnosis, and therapy. One research goal is the identification of objective biomarkers to indicate the risk, presence and progression of schizophrenia. Consequently, genetic endophenotypes have been sought in affected patients and at-risk families (Gottesman and Gould, 2003), and schizophrenia-related genes have been identified that influence the development of structural and functional microcircuitry within the brain (Harrison and Weinberger, 2005). Genes, while fundamental to vulnerability, are nevertheless difficult to link to the pathoetiological processes that ultimately determine onset of schizophrenia. Hence there is increasing effort to identify proximate imaging endophenotypes of schizophrenia for clinical utility (Meyer-Lindberg and Weinberger, 2006; Rasetti and Weinberger, 2011) which can be combined with other objective markers and traits to give an extended endophenotype for schizophrenia (Prasad and Keshavan, 2008; Keshavan et al., 2011).

In the present study, we tested the hypothesis that grey-matter heterogeneity (quantified from structural magnetic resonance imaging (MRI) of the brain and indicative of subtle distributed differences in cytoarchitectonic organisation) will distinguish the brains of people with and without schizophrenia, thereby representing a putative imaging endophenotype of schizophrenia. This hypothesis about brain texture is motivated by a proof-of-principle study that showed measures of grey-matter heterogeneity distinguished patients with schizophrenia from controls and moreover were sensitive to the patients' genetic status (Ganeshan et al., 2010). Texture analysis (TA) of MR images lies within the domain of

morphological surface measurement and provides a higher order means of assessing differences in cortical complexity (Kassner and Thornhill, 2010). TA enables the quantification of the grey-level pattern on MRI, via pixel inter-relations and spectral properties of the images (Kassner and Thornhill, 2010). Advances in methodological approaches to brain-image analysis, such as automated algorithms and improved image processing (including segmentation procedures), have made TA more accessible and appealing as a research tool for neuropsychiatry (Kassner and Thornhill, 2010). TA has established utility when applied to neuropsychiatric disorders including epilepsy (de Oliveira et al., 2013), multiple sclerosis (Theocharkaris et al., 2009), attention deficit hyperactivity disorder (Chang et al., 2012) and Alzheimer disease (Zhang et al., 2012). Additionally, TA has revealed differences in foetal brains at term reflecting disordered interuterine growth (Sanz-Cortes et al., 2013). Recent studies indicate the potential for grey-matter texture measures to serve as candidate endophenotypes for schizophrenia (Kovalev et al., 2003; Ganeshan et al., 2010) and Asperger syndrome (Radulescu et al., 2013).

Volumetric measures have been more widely relied upon in structural neuroimaging studies using MRI (e.g. with voxel-based morphometry, VBM). In schizophrenia, relative reductions in grey-matter volume are reliably reported both for whole brain, and broadly for specific regions. However, there also remains variability across studies in the observed magnitude and distribution of such local volume reductions (Shenton et al., 2001; Shepherd et al., 2012). Some of the most replicated findings suggest grey-matter volume is reduced across large networks, differentially involving frontal, temporal, limbic, thalamic and striatal regions (Fornito et al., 2009; Honea et al., 2005). Regional grey-matter volume is influenced by interacting genetic and environmental factors (Wright et al., 2002; Cannon and Keller, 2006) expressed through cytoarchitectural differences (Hof et al., 2003; Schmitt et al., 2008). However, empirical experience to date suggests that volumetry on its own may be insufficient to generate useful endophenotypes in part because of the regional inconsistency of observed effects.

Cortical surface measures (including cortical thickness, cortical surface area and, indirectly, TA) are now generally regarded as a more proximate index of neurodevelopmental deviations in cytoarchitectural organization (Fischl and Dale, 2000; Mangin et al., 2010) and associated structural connectivity (White and Hilgetag, 2011). In patients with schizophrenia, when compared with healthy controls, prefrontal and temporal cortices show reductions in cortical thickness and surface area, with relative sparing of more posterior regions (Kuperberg et al., 2003; Rimol et al., 2010; Nesvag et al., 2011; Kubota et al., 2011). Cortical surface parameters, like volumetric measures, vary with age and medication history (Wiegand et al., 2004; Nesvag et al., 2011; Kubota et al., 2011). Nevertheless, studies indicate that cortical surface parameters are linked to neurodevelopmental processes that undergo only partial reshaping across the lifespan (Wienberger and McClure, 2002; Mangin et al., 2010). Surface parameters can be viewed as promising endophenotypes (Cannon et al., 2002; Goghari et al., 2007; Goldman et al., 2009; Qiu et al., 2010). Methods for characterizing cortical surface morphology, for example, by folding patterns, continue to emerge. These approaches, including TA, might more closely characterize the hidden architectural structure and subtle influence of antecedent neurodevelopmental events (Mangin et al., 2010)

In the current study, we used TA to quantify grey-matter heterogeneity from MRI brain scans of patients with schizophrenia and healthy controls. We first tested for anticipated differences between the groups. We then tested for relationships between measures of whole brain textural heterogeneity and regional volumes (derived using VBM). Finally, we combined the texture parameters with VBM findings to create composite measures that were tested for their capacity to discriminate individuals with respect to their diagnosis status.

2. Methods

2.1. Participants

We analyzed the T1-weighted structural MRI brain scans of 51 individuals (27 with schizophrenia (SCZ) according to DSM-IV-TR (American Psychiatric Association, 2000), and 24 controls). The majority of the individuals in this sample were males (SCZ: M/F=25/2; controls: M/F=23/1). Exclusion criteria were as follows: (a) antecedents for relevant medical and neurological diseases (i.e., brain trauma, psychoses of metabolic, infectious or vascular origin, epilepsy); (b) DSM-IV-TR criteria for substance abuse or dependence; (c) cognitive disorders (dementia, mental retardation, and learning disorders); and (d) contraindications to MRI scanning. All but two SCZ patients were treated with antipsychotics. The majority of the treated individuals received atypical antipsychotics (21/25). Participants' premorbid IQ was assessed with a measure of crystallized intelligence, the National Adult Reading Test (NART) (Nelson and Willison, 1991). All participants gave written informed consent before enrolment, and the local Research Ethics Committee approved the study in accordance with the ethical standards of the Declaration of Helsinki (1964). The sample examined here was detailed in a previous study (O'Daly et al., 2007).

2.2. Statistical analyses of demographic and global structural data

The initial analysis comprised group comparisons regarding demographic and whole brain volumetric data. Age, IQ, global grey-matter volume, and total intracranial volume entered in analysis of variance (ANOVA) models as dependent variables; diagnostic status was introduced as fixed factor.

2.3. Magnetic resonance imaging (MRI)

All the participants were scanned with a GE Signa 1.5-T system (GE Medical Systems, Milwaukee, WI) at the Maudsley Hospital, London. Axial 3D T1-weighted images were acquired with a fast gradient-echo sequence under the following parameters: slice

thickness=1.5 mm, repetition time (TR) =8.7 ms, echo time (TE) =1.8 ms, matrix size=256 × 192, field of view (FOV) =24 × 18 cm, in-plane resolution=0.94 × 0.94 mm, number of slices=124, flip angle=20°. The total scanning time was close to 8 min.

2.4. Image pre-processing

The structural images were processed for TA following a previously described protocol (Radulescu et al., 2013). Briefly, the T1 images were re-sliced to a 0.9 × 0.9 × 0.9 mm³ voxel dimension and segmented in six tissue classes (grey matter, white matter, cerebrospinal fluid, bone, soft tissue and air/background) by using the unified segmentation algorithm implemented in SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Grey-matter images resulting from segmentation were normalized to a template (generated from all the participants) using a diffeomorphic registration algorithm (DARTEL) (Ashburner and Friston, 2009) and modulated to preserve the voxel-wise information about the tissue volume, then smoothed with an 8-mm full width half-maximum (FWHM) Gaussian kernel. The 'raw' grey-matter segmented images (re-converted to DICOM format) were used for texture parameters extraction (TA) and the modulated and smoothed grey-matter images were used for VBM.

2.5. Texture analysis (TA)

Heterogeneity within the whole-brain grey-matter images was assessed using published methods (Ganeshan et al., 2010; Radulescu et al., 2013) implemented in TexRAD® (TexRAD Ltd, www.texrad.co.uk, Somerset, UK), a proprietary research software algorithm developed to visualise and quantify textural properties of tissues from medical imaging scans, with texture quantified in terms of statistical and histogram characteristics. In the present study, we extracted grey-matter textural parameters from unfiltered and filtered whole brain volumes: Image filtration consisted of the application to multiple slices of whole brain data of a two-dimensional (2-D) Laplacian of Gaussian (LoG) filter, at three different frequency scales (feature width): fine (filter value=0.5, filter width ≈ 2 mm in diameter), medium (filter value=1.0, filter width ≈ 4 mm in diameter), coarse (filter value=1.5, filter width

≈ 6 mm in diameter). The texture parameter from unfiltered and filtered data captured the average intensity of the grey-level signal within a whole brain image (mean of grey level), the irregularity or complexity of the grey signal (entropy), the distribution of the grey level (uniformity), the average intensity and proportion of the positive grey-level signal pixel values within an image (mean of positive pixels, proportion of positive pixels), variation/dispersion that exists from the mean grey-level intensity (standard deviation), asymmetry of the distribution (skewness) and pointiness or peakedness of the distribution (kurtosis) (Ganeshan et al., 2008). We used a filtration-quantification approach where the initial image filtration highlighted subtle features (at the fine, medium and coarse scales) followed by the use of first order statistical and histogram characteristics. These filtration-quantification-based texture parameters were subsequently entered into statistical analyses to characterise and compare neuroimaging data from patients with schizophrenia and controls (Ganeshan et al., 2008).

2.6. Statistical analyses based on texture parameters

The main statistical analyses of texture parameters were undertaken using the general linear model (ANCOVA) (Fig. 1). We first verified that the data conformed to assumptions for homogeneity of variance (Levene's test) including homogeneity of the correlation slopes (by testing for interaction effect diagnosis × covariates (e.g., grey-matter global volume, age). Texture parameters were then used as dependent variables in models testing for differences between schizophrenia patients and controls. To understand the regional impact of the statistically significant TPs, we further introduced selected texture parameters as covariates in VBM analysis (see below and Fig. 1).

2.7. Voxel-based morphometry (VBM)

Normalized, smoothed grey-matter images were analyzed with SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) using general linear full-factorial models. Diagnosis was the between-subjects factor. We tested for relationships between texture parameters

and regional brain volume by entering them as covariates of interest within the analytic model, testing for both within-group effects of texture parameters on grey-matter regional volumes and interactions with diagnosis. We controlled for effects of age and global grey-matter volume by inclusion as covariates of no interest. Within VBM analyses, we set a high threshold of voxel intensity (0.8) as a masking procedure. Statistical inference was based on voxel-by-voxel t -tests at the whole brain level. We report results that survived a stringent threshold of $p < 0.05$ after correction for voxel-wise multiple comparisons (Family Wise Error; FWE).

Regional grey-matter volumes for each participant were computed from the clusters where texture parameters showed significant within-group or interaction effects. We used these volumetric measures to explore further the relationship between grey-matter texture and volume in schizophrenia patients and controls when controlling for other demographic and neuropsychological characteristics. For example, we anticipated that texture parameters and regional grey-matter volumes would be sensitive to aging, and we verified this hypothesis by regressing age, texture parameters and their interaction on regional grey-matter volumes within each group. Similarly, we tested for related effects of illness duration, adjusted for patient age. We were unable to quantify lifetime exposure to antipsychotic medication, and assumed that this variable is related to illness duration as all participants had been treated with medication.

Finally, we used a stepwise linear discriminant analysis to test the hypothesis that a combination of grey-matter texture and regional volumes would usefully predict a diagnosis of schizophrenia. Before this analysis, we computed regression scores (one per participant) for multi-collinear predictors (fine filter texture parameters) using data reduction by principal component analysis. Subsequently, over three-quarters of the entire participant image data were selected randomly to generate the discriminant model, while the remaining data were used for validation. The stepwise linear discriminant analysis tests for, and retains in the

model, only the variables with the greatest discriminative value (using F -values by default, minimum F to enter=3.84, maximum F to remove=2.71). A cross-validation procedure (leave-one-out) was used in generative sample, for model creation, and the model was further validated in the remaining 30% of the sample. For all statistical analyses conducted outside the imaging space, we used SPSS 20.0 software (IBM® SPSS® Statistics 20.0).

3. Results

The group of patients with schizophrenia and control participants (Table 1) did not significantly differ with respect to age ($F_{(1,49)}=0.17$, $p=0.682$), IQ ($F_{(1,49)}=2.9$, $p=0.095$), global grey-matter volume ($F_{(1,49)}=1.39$, $p=0.243$), or total intracranial volume ($F_{(1,49)}=1.01$, $p=0.319$).

3.1. Texture parameters

There were significant between-groups differences in measures of grey-matter texture at the fine spatial scale (but not at other spatial scales). Specifically, the grey-matter of patients with schizophrenia was less uniform (more heterogeneous) than that of the controls, as indicated by higher values for entropy ($F(1,49)=8.23$, $p=0.006$, effect size $\eta^2=0.146$) and mean positive pixels ($F(1,49)=4.07$, $p=0.049$, effect size $\eta^2=0.078$). Conversely, the controls had higher values of uniformity ($F(1,49)=9.92$, $p=0.003$, effect size $\eta^2=0.171$) compared with the schizophrenia group (Fig. 2). Parameters at other spatial frequency scales did not discriminate between the patient and control groups at threshold significance.

3.1. Voxel-based morphometry

We tested for regions where local grey-matter volume correlated with the fine texture parameters (extracted from whole brain data) identified above (fine entropy, mean positive pixels and uniformity). Effects were observed in brain structures already implicated in schizophrenia: Entropy was inversely correlated with the grey-matter volume of the right

amygdala (MNI: 26 -3 17; cluster size=158 voxels, Z score=3.58; Fig. 3). Mean of positive pixels inversely correlated with a region of left cerebellum (MNI: -29 -68 -19, $K=224$, Z score=3.47; Fig. 3). Uniformity showed a positive correlation with grey-matter volume of left hippocampus (MNI: -24 -15 -18, $K=105$, Z score=3.56; Fig. 3). These TA correlations were significant in the schizophrenia group only, but not in controls (Fig. 3, correlation plots). Moreover, the examined texture parameters had no effect on any other grey-matter regional volumes in the control group.

3.3. Texture parameters, age and illness-duration effects on regional volumes

In controls, neither the age, nor the fine filtered uniformity nor the age-by-uniformity interaction predicted the volume of the identified left hippocampal cluster. In the schizophrenia group, however, age marginally predicted the volume in the left hippocampal cluster (partial correlation coefficient=0.347, $p=0.048$); uniformity, as noted above, did predict the volume of the left hippocampal cluster, explaining the greatest proportion of the variance (partial correlation coefficient=0.428, $p=0.017$). When the interaction term, uniformity \times age was introduced in the model, the age effect became statistically non-significant and only the uniformity effect remained significant. In addition, the interaction effect was not significant. Age marginally predicted the volume of the left hippocampal cluster (partial correlation coefficient=0.347, $p=0.048$, as did age-adjusted illness duration (partial correlation=0.358, $p=0.039$).

3.4. Stepwise linear discriminant analysis

Texture parameters at the fine spatial scale were correlated, as was expected (Pearson coefficient >0.8). We therefore used principal component analysis to derive composite measures for each individual of the three discriminatory texture parameters. High correlations were also observed between left hippocampus and right amygdala volumes, but these measures were not combined together. We applied stepwise linear discrimination analysis, a conservative approach that removes redundant variables from the model, to

identify which specific region could add to grey-matter texture to predict diagnostic group membership. This approach identified the combination of left hippocampal grey-matter volume and fine texture score as best classifying schizophrenia patients and controls (canonical correlation=0.489, Wilks' Lambda=0.761, $p=0.006$). The classification accuracy for the group from which the model was derived was 70%; the cross-validation accuracy within these selected cases was 65%, and the classification accuracy in the remaining validation sample (independent group) was 72.7% (Table 2).

4. Discussion

4.1. Interpretation

The current study brings further evidence in support of distributed cytoarchitectonic abnormalities in schizophrenia manifest through measures of grey-matter heterogeneity at a fine spatial scale across brain, and quantifiable from standard structural MRI brain scans. Moreover, we argue for a testable and useable imaging endophenotype of schizophrenia, derived from the simple combination of a measure of fine grey-matter homogeneity and hippocampal volume. The classification accuracy of this pairing of tangible (i.e., with face-validity) features is compelling when compared with black-box or related classification approaches involving many more components (e.g., Yoon et al., 2006; Kawasaki et al., 2006). For example, an alternative approach to classification using a support vector machine, applied to the same dataset, reached an equivalent classification accuracy (70.6%) when the left hippocampus was included alongside five other textural and volumetric features (authors' unpublished observations). In using the more straightforward linear discriminant analytic (LDA) approach, we also overcame risks of overfitting data from this relatively small sample.

Neuropathological studies of people with schizophrenia indicate the presence of cytoarchitectural abnormalities within cortical grey matter and particularly in hippocampus, typically reduced hippocampal volume (Tammimga et al., 2010). However, such findings are not always replicated (particularly if controls are family members) (Gothelf et al., 2000). Disarray of pyramidal neurons at the boundary of CA1-CA2 and disordered laminar architecture of the entorhinal cortex, i.e., misplaced and aberrantly clustered neurons, have also been reported in schizophrenia (Weinberger, 1999, Harrison, 2004). These findings too are controversial, due to variable replication. More consistent is the finding of reduced size of hippocampal neuronal cell bodies (Weinberger, 1999, Harrison, 2004). Nevertheless, a stronger proposition is that microscopic abnormalities are present at dendritic and synaptic levels within the hippocampal formation (Harrison, 2004). Interestingly, these microstructural differences are accompanied by reduced molecular markers of neurogenesis (e.g., Reif et al., 2007). Involvement of white matter (myelin) and oligodendrocytes in schizophrenia has been reported in the dorsolateral prefrontal cortex (Uranova et al., 2004), superior frontal gyrus (Hof et al., 2003) and visual cortex (Matthews et al., 2012), consistent with distributed neurodevelopmental perturbation (supported also by an absence of histopathological indicators of neurodegeneration and gliosis (Harrison, 2004)). The observed depletion of prefrontal oligodendrocytes has been linked to quantitative neuroimaging abnormalities in white matter in schizophrenia brains (Hof et al., 2003). Importantly, more recent post-mortem stereological studies also demonstrate marked oligodendrocyte depletion within the posterior hippocampus (Schmitt et al., 2009), providing further evidence of the central role of the hippocampus to the pathophysiology of schizophrenia reinforced by our *in vivo* observations.

The observed differences in fine textural parameters between schizophrenia patients and controls confirm and extend the findings of a previous smaller study of an independent dataset (Ganeshan et al., 2010). The additional discovery in schizophrenia of the association between whole-brain fine texture abnormalities and the size of medial temporal lobe regions has pathoetiological implications: Abnormalities in grey-matter texture may represent the

consequence of neurodevelopmental processes including disturbed neural migration and differentiation (Radulescu et al., 2013). Regional correlation between whole brain texture abnormalities may thus reveal the historical focus and origin of (now distributed) perturbations in neural micro-circuitry underlying the progression of schizophrenia. The observed link between fine grey-matter abnormalities and hippocampal volume suggests abnormality within a discrete neurocognitive system. In this study, the fact that this combination also predicts diagnosis of schizophrenia implicates a unitary aetiological pathway. However, our result is based on a schizophrenia group that included patients with a history of hallucinations (O'Daly et al., 2007). This is relevant since recent neuroimaging studies, quantifying the volume and shape of hippocampal subfields, report inverse correlations between the presence of positive symptoms (i.e., hallucinations) and hippocampal CA2-3 volume (Kuhn et al., 2012), and between the severity of positive symptoms and deformation of the posterior CA1 (Zierhut et al., 2013). Hippocampal CA regions are encompassed within our volumetric findings. This is certainly not the first time that the link between neurodevelopmental insult to hippocampus and the pathoetiology of schizophrenia has been made (Arnold and Trojanowski, 1996; Weinberger, 1999; Harrison, 2004). Our findings nevertheless contextualise focal hippocampal involvement within distributed cortical abnormalities. We also observed a weaker association between fine grey-matter texture and cerebellar volume in schizophrenic patients. Association between grey-matter heterogeneity and cerebellar volume has been observed in autism too (Radulescu et al., 2013) and therefore may be indexing a parallel neural system for which an aberrant neurodevelopmental trajectory is shared between schizophrenia and autism. Speculatively, the expression of social cognitive deficits and abnormal mental coordination (i.e., 'cognitive dysmetria'; Andreasen and Pierson 2008) in both these two disorders may arise from a common genetic basis (Psychiatric Genomics Consortium, 2013). Our findings in this study also broadly converge with those of an earlier study, which used different MRI textural features to differentiate the scans of patients with schizophrenia from those of controls

(Kovalev et al., 2003). The latter study ascribed textural differences in part to sulcal widening of inferior brain regions, including the medial temporal lobe.

Overall our data show whole brain indices of fine texture reflecting cytoarchitectural organization are linked to hippocampal volume. These data suggest that distributed networks interacting with the hippocampus are compromised in schizophrenia. Additional research methods to quantify local neural integrity and white matter cortical connections (e.g., high field MR spectroscopy of the hippocampus and diffusion tensor imaging) are warranted to characterize causality in the relationship between hippocampal neural integrity and grey-matter microstructural organisation. Our focus on grey-matter TA was motivated by evidence from neuropathology and neuroimaging suggesting that this tissue compartment is most likely to encompass micro-structural anomalies in schizophrenia (e.g., Harrison, 2004). Moreover, this focus also allowed us to explore directly relationships with grey-matter volumetric measures from the same individuals, allowing us to equate the two measures. In both cases, the accuracy and precision of grey/white matter segmentation is important. Nevertheless, it remains likely that abnormalities in myelination contribute to microstructural (hence textural) differences within grey matter across the brain (Matthews et al., 2012). As noted, additional neuroimaging approaches (e.g., diffusion-weighted imaging) may be better suited to address neurodevelopmental abnormalities in white-matter structure. However, these techniques have yet to enter conventional neuroimaging assessment of psychiatric patients.

Within this study, we tested for effects of age, not least because age-related changes in grey-matter volume are reported across VBM studies (Groelsch et al., 2010; Lemaitre et al., 2012). Overall, in controls, our findings mirror those of a larger dataset of a normal aging population, which described relative sparing of medial temporal lobe with respect to volume (and cortical surface parameters) (Lemaitre et al., 2012). The weak effect of age observed in the schizophrenia patients is more difficult to interpret, not least because of the potential confound of medication in this relatively small sample. Further studies will be necessary to

clarify the relationship between regional volumes, texture parameters and age in schizophrenia. One interesting question is what exactly is the relationship between MRI-derived fine grey-matter textural parameters and brain architecture? Insight comes from post mortem studies reporting correspondence between high-resolution MRI and histological sections from the same individuals, stained for grey matter (cytoarchitecture) and white matter (myeloarchitecture) (Osechinskiy and Kruggel, 2009; Annese, 2012). Of note, myeloarchitecture dominates cytoarchitecture in terms of relative influence on structural MR signal variability in humans (Eikhoff et al., 2005). These studies suggest that texture parameters might be linked to the organization of subjacent myeloarchitecture and cytoarchitecture. Differences in fine texture possibly reflect microstructural disorganization in schizophrenia that originates in differences in structural connectivity. Axonal tension forces determine cortical shape and morphology (cortical folding) at the time of synapse formation (Van Essen, 1997; Hilgetag and Barbas, 2006). Since cortical folding is under genetic control (Rogers et al., 2010), sensitive indices of morphology including texture parameters may usefully serve as endophenotypes encapsulating local structural connectivity abnormalities in schizophrenia. Our data, while indirect, suggest that parameters of grey-matter texture, in conjunction with associated hippocampal volumetric measures, offer accessible, understandable, and testable imaging endophenotypes in schizophrenia.

4.2. Limitations

This study is informative only in the context of gender quasi-homogeneity. Consequently, the results may not extend to the female population, especially since gender differences in schizophrenia have been widely demonstrated (Hafner, 2003). Arguably, a potential limitation is the fact that the group of schizophrenia patients comprised participants with a history of hallucinations (O'Daly et al., 2007). While the presence of hallucinations is representative of a typical clinical sample in schizophrenia, yet it is possible that correlations between grey-matter texture and regional volumes were specifically mediated by microstructural re-arrangements specific to perceptual aberrations. Our findings provide a proof-of-principle case for further

investigation into the use of brain-texture analyses to enrich inferences gained from conventional structural neuroimaging. These proposed studies will benefit from a prospective approach in larger patient populations powered to quantify influences including gender, medication and medical histories on textural and volumetric features

We used a very stringent mask of voxel intensity for volumetric comparisons and correlation with the texture parameters. While this reliably minimized the risk of false-positives, we cannot exclude the possibility of an increased false-negative rate, previously associated with masking in VBM (Ridgway et al., 2009). Even if we were to conclusively demonstrate texture parameters as a robust endophenotype, we acknowledge the potential non-genetic and environmental influences on these measures (i.e., age, medication, history of substance abuse). Also, further clarification of the relationship between grey-matter heterogeneity and hippocampal morphology might be achieved by applying more sophisticated computational methods for the parcellation and morphological characterization of MRI brain scans (Zierhut et al., 2013).

In conclusion, our study highlights the presence of abnormal fine brain texture in schizophrenia and shows this to be an accessible imaging signature that is potentially useful for creating an in vivo schizophrenia endophenotype, represented by a combination of cortical surface-based measurements (textural parameters) and regional grey-matter volumes, especially within the medial temporal lobe.

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in the implementation of this textural analysis software in oncology-related applications. ER, NM, SSS, HDC have no conflict of interest to declare in relation to the study.

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Figure legends:

Fig. 1. Methodological flow chart showing the principal analyses after grey-matter texture parameters extraction. *Abbreviations:* DVs=dependent variables; GLM=general linear model; TPs=textural parameters; GM=grey-matter; VBM=voxel based morphometry; SCZ=schizophrenia.

Fig. 2: Box plots (means and confidence intervals) of the fine textural parameters significantly different between patients with schizophrenia and controls.

Fig. 3:

Top panels: Effects of fine spatial scale texture parameters on grey-matter regional volumes. Statistical Parametric Maps are overlaid on an MRIcron (Rorden and Brett, 2000) template. Colour bars: T scores from the VBM analysis; x, y, z : MNI coordinates; R^2 =coefficient of multiple correlation/ explained variance.

Bottom panels: Plots of correlation between fine texture parameters and grey-matter regional volumes in schizophrenia and controls.

Table 1: Demographic and structural data			
	Schizophrenia (<i>n</i> =27)	Control group (<i>n</i> =24)	Total (<i>n</i> =51)
	Mean ± SD ^c	Mean ± SD ^c	Mean ± SD ^c
Age	31.11±9.33 (min=18; max=48)	32.17±8.9 (min=19; max=57)	31.61±9.04 (min=18; max=57)
IQ ^d	107.19±7.59 (min=94; max=124)	110.54±6.33 (min=94; max=123)	108.76±7.16 (min=94; max=124)
Grey matter	0.71±0.05 (min=0.6; max=0.79)	0.73±0.07 (min=0.6; max=0.87)	0.72±0.06 (min=0.6; max=0.87)
Total intracranial volume ^e	1.54±0.1 (min=1.3; max=1.72)	1.58±0.14 (min=1.26; max=1.87)	1.56±0.12 (min=1.26; max=1.87)
Duration of illness	6.07±6.03 (min=1; max=23)	-	-

^a Schizophrenia; ^b control group; ^c SD=standard deviation; ^d intelligence quotient; ^e in litres.

Table 2: Classification results^a						
Diagnosis			Predicted group membership			Total
			Control	Schizophrenia		
Cases Selected (~70%)	Original	Count	Control	15	5	20
			Schizophrenia	7	13	20
		%	Control	75.0	25.0	100.0
			Schizophrenia	35.0	65.0	100.0
	Cross-validated	Count	Control	13	7	20
			Schizophrenia	7	13	20
		%	Control	65.0	35.0	100.0
			Schizophrenia	35.0	65.0	100.0
Cases not selected	Original	Count	Control	3	1	4
			Schizophrenia	2	5	7
		%	Control	75.0	25.0	100.0
			Schizophrenia	28.6	71.4	100.0

^a Linear discriminant analysis

Figure 1

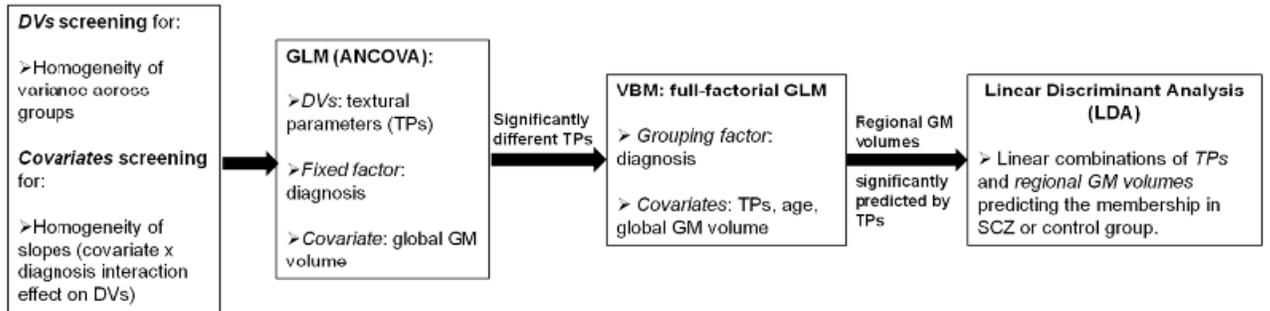


Figure 2

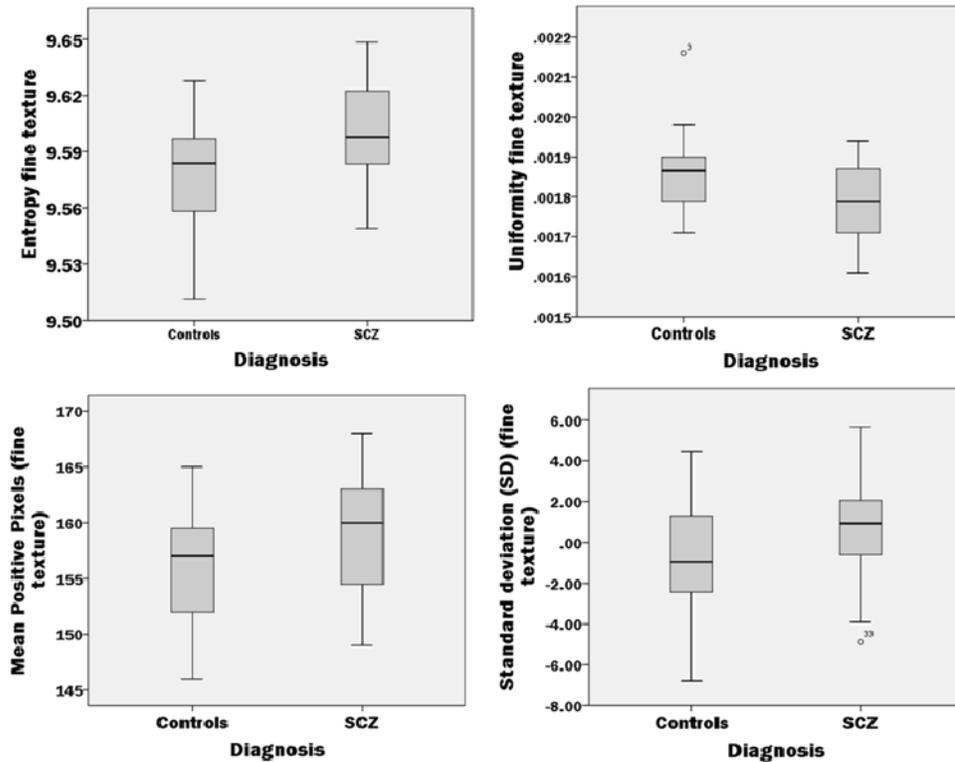
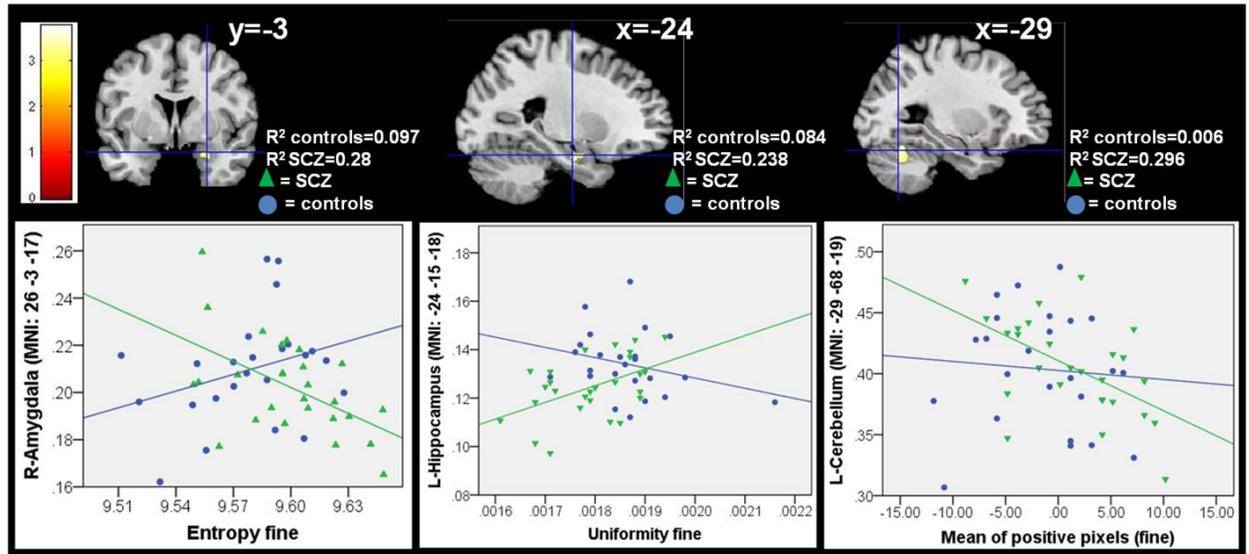


Figure 3:



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Highlights

- Abnormal gray matter texture is observed in brain scans schizophrenic patients
- Brain texture measures are sensitive to microstructural abnormalities
- Fine textural heterogeneity predicts medial temporal lobe volumes in schizophrenia
- Brain texture with hippocampal size can be used to classify scans by diagnosis
- Our findings suggest an imaging endophenotype for schizophrenia

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