Fusion analysis of first episode depression: Where brain shape deformations meet local composition of tissue

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1. Introduction

Our understanding of the brain basis of psychiatric disorders, including Major Depressive Disorder (MDD), has benefited greatly over the past two decades from important advances in Magnetic Resonance Imaging (MRI) technology. Studies of adults with primarily recurrent episodes of MDD have shown significant volumetric differences in temporal (e.g. superior temporal gyrus [STG], hippocampus, amygdala) and frontal (e.g., anterior cingulate cortex [ACC] and orbitofrontal cortex [OFC]) brain regions relative to healthy controls (see Bellani et al., 2010; Bellani et al., 2011; Lorenzetti et al., 2009 for reviews of the neuroanatomy and structural MRI findings associated with MDD). The most consistent finding in these studies is reduced hippocampal volume in adult patients with MDD compared to healthy controls. However, some studies have also failed to find group differences in hippocampal volumes (Hastings et al., 2004; Monkul et al., 2007; Rusch et al., 2001; Vythilingam et al., 2004), and others have even reported larger hippocampal volumes in patients with MDD relative to healthy controls (Frodl et al., 2002; Vakili et al., 2000; Vythilingam et al., 2004).

A large number of approaches have been developed to characterize differences, among individuals and groups, in the neuroanatomical configuration of the human brain. Generally, these approaches are classified...
into those that measure differences in brain shape, and those that measure differences in the local volume (and concentration) of brain tissue after macroscopic differences in shape have been discounted (Ashburner and Friston, 2000). The former approaches analyze the deformation fields required to map individual brains onto some standard reference in order to characterize neuroanatomy. Deformation Based Morphometry (DBM) (Bookstein, 1996) and Tensor Based Morphometry (TBM) (Chung et al., 2001) are widely used approaches that use deformation fields. Shape-analysis methods that are related to DBM/TBM have been widely employed to examine morphometric differences in depression. For example, in MDD, Posener et al. (2003) used high dimensional brain mapping on MRI data to quantitatively characterize the shape and volume of the hippocampus in adults with MDD and healthy controls (mean age = 33 ± 10). They found significant group differences in hippocampal shape, but no evidence for differences in volume. In a more recent study, Zhao et al. (2008) applied SPherical HARMonic (SPHARM) shape analysis to the left and right hippocampi of elderly patients with MDD (age > 60) and healthy controls. Analysis revealed significant shape differences in the mid-body of the left hippocampus between the two groups. Further, patients in a current episode of MDD had lower left hippocampal volumes in comparison to controls, whereas patients in remission (Hawley et al., 2002) from MDD showed no reduction in hippocampal volume. In our previous study (Ramezani et al., 2014), we used multi-object statistical pose and shape analysis, and demonstrated brain morphological differences between adolescents with early-onset MDD and healthy controls.

Approaches that focus on the local composition of brain tissue, such as voxel-based morphometry (VBM), compare tissue images on a voxel-by-voxel basis after the deformation fields have been used to spatially normalize the images. For example, Bell-McGinty et al. (2002) applied VBM using SPM99, and reported smaller gray-matter volume of the right hippocampus, and smaller white-matter volume in the left anterior cingulate and right middle frontal gyrus, in elderly patients with MDD compared to healthy controls. Using VBM in SPMS, Vasic et al. (2008) reported significantly lower left hippocampal volumes in middle-aged patients with MDD in comparison to healthy controls. Similarly, in the same group of middle-aged patients with MDD, Bergouignan et al. (2009) compared VBM using a manual segmentation method and the automated method, and found significant hippocampal volume reductions using both segmentation methods in comparison with healthy controls. Finally, studies focusing on younger age groups, and including relevant covariates (i.e., age, sex, and intracranial volume) have also reported significantly lower hippocampal volumes, particularly in the left hemisphere, in both adolescents with MDD (MacMaster and Kusumakar, 2004) and in patients with early onset MDD and a family history of depression (MacMaster et al., 2008).

In summary, computational neuroanatomical techniques either use the deformation fields themselves to characterize brain structural variation, or use these fields to normalize images that are then entered into an analysis of regionally specific differences in tissue composition. Ideally, a procedure like VBM should be able to automatically identify any structural abnormalities in a single brain image. However, even with many hundreds of subjects in a database, the method may not be powerful enough to detect subtle abnormalities (Ashburner and Friston, 2000). Recently, unified voxel- and tensor-based morphometry (UVTM) that uses locally adaptive combination of TBM and VBM to improve sensitivity is proposed (Khan et al., 2014). UVTM is an extension of the Jacobian modulated VBM (Davatzikos et al., 2001), which gives weights to VBM or TBM analysis based on registration confidence. In modulated VBM, voxel concentration is scaled based on the amount of deformation which was applied in the registration procedure. Although the motivation for multiplying the Jacobian determinant of transformations and the tissue segmentation probabilities is intuitive, it is not clear if the statistically significant regions resulting from VBM and TBM will match, although it is assumed to be. In addition, there has been no quantitative study on determining the optimal weight parameters based on the registration confidence. A more powerful procedure would be to use a voxel-wise multivariate approach. Within a multivariate framework, in addition to images of gray matter concentration, other image features such as white matter concentration, and the deformation fields calculated during the spatial normalization procedure, can also be included (Ashburner and Friston, 2000). Fusion of these multiple images may help in detecting subtle individual differences.

Joint independent components analysis (jICA) (Calhoun et al., 2006a) is a multivariate technique for such “fusion analysis.” It is an extension of independent-components analysis (ICA) that combines information from multiple features, which are a lower-dimensional representation of selected brain structures. jICA, as a group-level analysis technique, uses extracted features from individual subjects’ data and tries to maximize the independence among joint components. jICA and extensions have been successfully applied to combine multimodal functional and structural images to study major depression (Choi et al., 2008), aphasia (Specht et al., 2009) and schizophrenia (Calhoun et al., 2006a; Calhoun et al., 2006b; Sui et al., 2009; Sui et al., 2010; Xu et al., 2009). For example, Choi et al. (2008) combined resting-state functional-connectivity and fractional-anisotropy data within jICA in a dataset of four subjects with MDD and nine healthy control subjects to investigate links between functional connectivity changes and white-matter abnormalities. They reported differences in the strength of connectivity and in the coherence of white-matter tracts among the subgenual anterior cingulate cortex (sACC) and perigenual ACC, anterior midcingulate cortex, caudate, thalamus, medial frontal cortex, amygdala, hippocampus, insula, and lateral temporal lobe.

The purpose of the current study was to combine, for the first time, brain shape and regional brain tissue composition using multivariate jICA in order to investigate the brain structural correlates of first-episode MDD. We determined the joint variation of shape and tissue composition in the hippocampal region in a sample of young people suffering from a first episode of MDD in comparison to a sample of young healthy controls. The importance of a young first-episode group is that they have not been subject to the known neurotoxic effects of glucocorticoids resulting from aging and the pathology of chronic depression (Sapolsky, 2000; Schuff et al., 1999). We hypothesize that, whereas conventional univariate analysis may not be sensitive to subtle differences in brain structure in this group, a multivariate technique that jointly analyzes multiple brain characteristics (i.e., shape and tissue composition) may have the requisite sensitivity to capture group differences. Following a group-wise registration using DARTEL (Ashburner, 2007; Bergouignan et al., 2009) to create an average template, we obtained individual gray-matter (GM) and white-matter (WM) tissue maps in the template space, along with the deformation fields required to register the template and the GM and WM maps. Using the jICA technique, we combined these three features, reflecting the tissue composition and shape of the brain in each individual, in order to extract spatially independent joint sources and their corresponding modulation profiles. We hypothesize that the mixing coefficients of the modulation profiles will lead to better discrimination of MDD subjects from the control group compared to the results obtained when brain shape and tissue composition are analyzed separately.

2. Material

2.1. Participants

Eleven young people with MDD (age: 18 ± 0.89, range: 16–21, 2 males, all right-handed) were recruited through referrals from community mental health clinics and through advertisement in a small city in Ontario, Canada. Fourteen healthy control subjects (all 18 years old; all female, all right-handed) were recruited through advertisement. The groups were well matched in age. There were no socioeconomic status (SES) differences between the subjects in the two groups.
(p-value = 0.50). All subjects in the depressed group met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) criteria for a current episode of major depressive disorder based on the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) administered by an advanced doctoral student in clinical psychology. We used the Child and Adolescent version of the Schedule for Affective Disorders and Schizophrenia; K-SADS (Kaufman and Swedner, 2004). The K-SADS is the gold standard for DSM-IV diagnosis in children and adolescents and is the most widely used measure for this purpose in clinical research. Subjects were excluded if they met current or lifetime criteria for bipolar disorder, a psychotic disorder, a developmental disability (e.g., autism spectrum disorder), or a medical disorder that could cause depression (e.g., hypothyroidism). All participants in the MDD group were in their very first episode and were medication-free. This is important because understanding neuroanatomical features that characterize the earliest stages in the course of MDD, not confounded with medication use or recurrent MDD pathology, may provide important clues as to the disorder’s initial etiology. All subjects in the depressed group had moderate to severe levels of symptoms, as defined by a score of 19 or greater on the Beck Depression Inventory (BDI-II (Beck et al., 1996)). The BDI is a 21-item self-report questionnaire that is the most common way to assess the presence and severity of depressive symptoms in adolescent and adult samples. Healthy controls had no current or past history of any psychiatric disorder and all had BDI scores of zero. We chose not to include the Hamilton Depression Rating Scale and to focus exclusively on the BDI as an index of depression severity since there is evidence that the Hamilton possesses a poor psychometric profile (Bagby et al., 2004). This study was cleared by the Health Sciences Research Ethics Board of Queen’s University, and written informed consent was obtained from all participants, and from a parent or guardian for those participants under the age of 18.

2.2. Image acquisition

The MRI data were acquired using a 3.0 Tesla Siemens Trio MRI scanner with a 12-channel head coil in the MRI facility at Queen’s University, Kingston, Canada. A whole-brain 3D MPRA GE T1-weighted anatomical image was acquired for each participant (voxel resolution of 1.0 × 1.0 × 1.0 mm³, flip angle α = 9°, TR = 1760 ms, and TE = 2.6 ms).

3. Methods

In the following two subsections, first the input features to the jICA method, representing tissue composition and deformation of selected brain structures, are described. Then, the multivariate joint independent-components analysis technique, used to fuse multiple features, is briefly reviewed.

3.1. Features

The data type on which we focus in this paper is structural MRI (sMRI). Outcome measures derived from structural images include measures of shape (e.g., deformation) and tissue volume or concentration (e.g., gray or white matter). Below, we describe how we extracted three different features: (1) shape deformation information, and (2) gray- and (3) white-matter concentrations used for voxel-based morphometric (VBM) analysis.

The sMRI data were preprocessed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Briefly, GM, WM, and cerebral spinal fluid (CSF) were segmented using the automated segmentation processes in SPM (Ashburner, 2007; Bergouignan et al., 2009). This resulted in a set of three images in native space, in which each voxel is assigned a probability of being one of the three tissue types. The GM and WM maps were registered using the DARTEL method, which achieves accurate inter-subject registration of images (Ashburner, 2007; Bergouignan et al., 2009). The DARTEL procedure uses the GM and WM maps to create new templates and warps the GM and WM maps of each subject to the DARTEL template. Using DARTEL group-wise registration, the inter-subject registration is more accurate comparing to other SPM tools, therefore less spatial smoothing can be performed. We have used a Gaussian convolution kernel with a Full Width at Half Maximum (FWHM) of 8 mm. To demonstrate the effect of smoothing, we report the results with and without spatial smoothing. The deformation fields (DFs) required for warping the groupwise (DARTEL) template to the GM and WM maps of each subject were also created. These deformation fields show how much the group template structure deviates from each participant’s structure. The absolute value of the deformation field (displacement) for each voxel is used to represent shape morphometry. The warped GM and WM segments along with the deformation fields are input features to the joint analysis method.

To reduce the number of voxels in the analysis, a segmented LPBA40/SPM5 atlas (Shattuck et al., 2008) in MNI space was used to extract the anatomical regions of interest. We selected the hippocampal region since abnormalities in this region have been associated with the pathology of MDD (Bellaniet al., 2010; Bellani et al., 2011; Lorenzetti et al., 2009). To account for small errors in the atlas-to-subject registration, the selected region was dilated using a disk with the radius of 5 voxels, with morphological operators to include adjacent regions in addition to the selected brain structure. Voxels inside the created mask were selected for joint analysis.

3.2. Joint independent-components analysis

We assume that there is a relation between brain tissue type (GM or WM) differences and brain structural deformations. This is not an unreasonable premise: if depression is associated with differences in both the size and shape of brain structures, then differences in the volume and/or concentration of gray and/or white matter might be related to differences in structural deformations in depressed individuals relative to controls. The three features described in the previous section were used as input observations X = {} for jICA in order to combine brain shape deformations and local composition of tissue. jICA can be used to identify any joint set of features S = {} that is anatomically differentiable between depressed subjects and healthy controls, where x_i (i = 1, 2, ..., N) is the vector of stacked features for subject i, and s_i shows the ith joint independent component (source). N is the number of subjects and K is the total dimensionality of stacked vectors. Considering the generative model X = AS, the aim of the jICA method is to find the matrix W = A^{-1} so that the estimation of U = WX is close to S. In this model, A is the matrix of mixing coefficients (also called ICA loading parameters, or the modulation profile), and W is the unmixing matrix. A MATLAB implementation of jICA is provided by the FIT 2.0b software (Calhoun et al., 2006a), available online at http://miolab.mrn.org/software/. A schematic of the jICA approach is shown in Fig. 1.

Joint independent components were found using the Infomax algorithm (Bell and Sejnowski, 1995), which is based on minimization of mutual information of components. In this algorithm, the output entropy of a neural network is adaptively maximized with as many outputs as the number of independent components (ICs) to be estimated. In order to use ICA, it is necessary to first specify the number of independent components (ICs) expected. We first attempted to estimate the number of ICs using the Minimum Description Length (MDL) criterion, which is an information-theoretic technique for model order selection (Li et al., 2007). Using the MDL criterion, the number of components in GM and WM was estimated to be 4 and 3, respectively, but because of the heterogeneity in the location and extent of deformations across both groups, this information-theoretic criterion did not converge for the deformation-field dataset. Accordingly, we instead follow the precedent set by Specht et al. (2009) and set the number of ICs equal to 1/3 of...
the total number of subjects: so for 25 subjects here, we specify eight components.1

Separability of the mixing coefficients was used as a criterion for capturing group differences. These low-dimension coefficients reflect how much each subject’s shape deformation and tissue composition are modulated by a joint source. To investigate whether the mixing coefficients truly differ between groups, we used two-sample (unpaired) t-tests. We report mixing coefficients that differ significantly between the two groups (p < 0.05), and for which the corresponding z-score component had more than 10 voxels with values above a threshold of |z| > 2.5 (99.4% cumulative probability). We followed the precedent set by Altena et al. (2010) to select minimum number of voxels within a cluster, and Sui et al. (2013) and Tosun et al. (2012) to select the threshold.

In order to determine whether the fusion analysis is superior (in terms of sensitivity) to analyses based on single features, we compared the result of t-tests on the mixing coefficients from the jICA of GM, WM and DF features to the result of the t-tests on each of the three features separately.

To further investigate the group differences, columns of the mixing coefficient matrix, which reflect the weighting of each joint source in a subject’s GM, WM, and DF, were used as input features to a classification algorithm. A discriminant analysis with a quadratic discriminant function was used to classify the subjects. Performance of the classifier was measured using leave-one-subject-out cross-validation, averaging classification performance across iterations. The joint ICA classification result was compared to classification results obtained with one or two features. The mixing coefficients were used as input features for the classification of depressed and control subjects.

Furthermore, separability of the joint source distributions was quantified by computing a divergence measure between joint histograms. Each of the joint sources was divided into three maps, which correspond to the GM, WM and deformation field features used in the jICA analysis. The map elements (each one representing a specific voxel) were thresholded and sorted in descending order by the voxel value, resulting in a set of voxels representing the greatest differences between groups in each joint source. For each subject, voxels that survived thresholding in all three maps were counted on a three-dimensional joint histogram in a bin defined by the three input feature values (from the input observation matrix X in Fig. 1) at those voxels’ locations (see Calhoun et al., 2006b for more details on computing joint histograms). The group-averaged joint histograms were then calculated by taking the mean of the joint histograms across all the subjects in the group. The difference between the two groups was then assessed using the Renyi divergence formula (Hero et al., 2001). The divergence was also computed for other combinations of features (two or one). The higher the values of the Renyi divergence criterion, the better the discrimination between groups (Calhoun and Adali, 2009). The best combination of features is the one that yields the highest divergence value.

4. Results

We performed VBM analysis on GM and WM images obtained by DARTEL group-wise registration of the maps using the SPM8 toolbox. We used the same explicit mask (described in Subsection 3.1) that we had used for the joint ICA analysis of multiple features. Results show no significant WM, or GM differences using a Family Wise Error (FWE) rate of 0.05 or significance level of 0.001, and cluster size of 10 or more voxels.

We report the statistical difference among joint sources to evaluate the performance of the proposed joint analysis. Two-sample t-test was performed on the mixing coefficients, i.e., the eight columns of matrix A, which correspond to eight independent components, where each column consists of two groups of coefficients (one for each group of participants). One source differed significantly between the two groups (p = 0.004, which passed the Bonferroni correction for multiple comparisons (p < 0.00625)). Fig. 2(a) shows the mixing coefficients (i.e., weights) for this joint source, and its GM, WM and deformation-field components. The weights in the depressed group were significantly higher than in the control group. Fig. 2(b), (c) and (d) depicts the statistical Z maps around the left and right hippocampi (the regions of interest) for this joint source, and Table 1 shows the corresponding stereotaxic coordinates in MNI space. As can be seen in Fig. 2(d) and Table 1, the shape variations appear mostly in the left hemisphere of the brain within the hippocampal region, whereas group differences in the GM and WM concentrations appear in both hemispheres, as shown in Fig. 2(b) and (c). We remind the reader that for each subject, within the jICA framework, the coefficients that modulate the three maps (shape deformations and GM and WM concentrations within each joint source) are the same. In other words, the three maps, which represent the variation of shape deformations, and GM and WM concentrations among subjects, are jointly related. Hence, our results indicate that the statistically significant shape deformations observed within the left hemisphere of the brain in the hippocampal region are related to the statistically significant GM and WM alterations in the hippocampal region in both hemispheres. It is reasonable to infer from these results that local changes in brain tissue composition lead to alterations of shape in distant regions, because the brain is an interconnected organ.

Fig. 1. Schematic of the jICA method. The observation matrix is made by stacking the GM, WM, and DF maps side by side. jICA tries to maximize the independence among maps of joint sources, assuming that they share the same mixing coefficient matrix.

1 We performed subsequent follow-up analyses for 4, 10 and 12 components to further confirm the validity of our model and to test for the stability of the joint independent components. Stability analysis of the results for different numbers of independent components showed replication of findings for 10 and 12 independent components; however, using eight components yielded stronger group differences, and higher z-values. As expected (Ma et al., 2007), under-estimating the number of components (e.g., choosing four as the number of ICs in our case), yielded less reliable results. Results of analyses with 4, 10, and 12 ICs are available from the authors by request.
To determine the sensitivity of the fusion analysis in capturing the group differences, the results of joint analysis of GM + WM + DF, and of separate analysis of each of the GM, WM, and DF were compared. Eight independent-sample t-tests were conducted to compare depressed and non-depressed groups on the columns of the mixing coefficients for joint or separate analysis of features. The modulation profiles differed significantly between the two groups in the fusion analysis of GM + WM + DF features (Table 2). Results show that the combination of shape deformations and local composition of tissue, but neither shape nor local composition of tissue alone, can discriminate between individuals in the two groups. As it can be seen smoothing has not affected the results much.

Table 3 shows the average classification error for jICA (first column), and ICA (last three columns) of GM, WM, and DF, each used as input features in data fusion analysis. Results show that the control and depressed subjects can be classified based on structural MRI data with an error of 32% using the combination of shape deformations and tissue composition (GM + WM + DF). The classification error using shape deformations or tissue composition alone was more than 36%. Considering that the number of subjects is low and the dimensionality of the input MRI dataset is quite high, the results are very promising.

Fig. 3 shows the group-average marginal histograms for for GM, WM, and deformation fields, respectively. As can be seen, the histograms of the normalized intensity values for GM and WM were almost the same for the two groups, whereas the histogram of the absolute deformations showed around 0.3 mm more deformation for subjects with MDD compared to healthy controls.

The sorted maximum Renyi divergence values for different combinations of contrasts are shown in Fig. 4. Higher values indicate better discrimination between the groups. Therefore, as indicated in the figure, combining the deformation fields and tissue composition yielded greater discrimination than utilizing either deformation fields or tissue composition alone.
composition data alone. In particular, combining GM and DF yielded the highest level of discriminatory power in both samples.

5. Discussion

The current study is the first to report that joint analysis of brain shape and tissue composition is sensitive enough to identify subtle, but reliable, differences between young people in a first episode of MDD and healthy controls. However, future work with larger datasets are required to confirm the superiority of the fusion analysis to separate analysis of shape and tissue composition. The identified corresponding sources demonstrate MDD-related links between WM, GM and shape deformation changes in the hippocampus, which were not detectable with univariate voxel-based methods. Assuming that the features share the same mixing coefficient matrix (modulation profile), jICA uses more information to estimate the same number of mixing

Table 2
p-Values of the most significant joint source, obtained from two-sample t-tests performed on the columns of the mixing coefficients generated by jICA (first columns), and ICA (last three columns). First and second rows show the results without and with spatial smoothing of the features. GM: gray matter; WM: white matter; DF: deformation field, each used as input features in data fusion analysis. The p-values displayed in the first column passed a Bonferroni correction for multiple comparison (p < 0.00625).

<table>
<thead>
<tr>
<th>Smoothing</th>
<th>Combination</th>
<th>GM + WM + DF</th>
<th>DF</th>
<th>GM</th>
<th>WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.004</td>
<td>0.069</td>
<td>0.067</td>
<td>0.081</td>
<td></td>
</tr>
<tr>
<td>FWHM: 8 mm</td>
<td>0.005</td>
<td>0.069</td>
<td>0.087</td>
<td>0.036</td>
<td></td>
</tr>
</tbody>
</table>

Table 3
Classification error obtained from discriminant analysis of the mixing coefficients generated by jICA (first column), and ICA (last three columns). GM: gray matter; WM: white matter; DF: deformation field, each used as input features in data fusion analysis.

<table>
<thead>
<tr>
<th>Combination</th>
<th>GM + WM + DF</th>
<th>DF</th>
<th>GM</th>
<th>WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error</td>
<td>32%</td>
<td>36%</td>
<td>36%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Fig. 3. Group-average histogram for the whole dataset on GM (a), WM (b), and deformation field (c). The difference between histograms of the two groups in deformation field was more than GM and WM.
coefficients and may improve source estimations compared to ICA. The observed shape deformations in left hippocampus are related to GM and WM alterations in the hippocampus in both hemispheres (see Fig. 1 and Table 1). These significant shape deformation differences in the left hippocampus are consistent with a previous study of shape (Zhao et al., 2008), and volume differences (Vasic et al., 2008) in late-life MDD; and volume differences in adolescents with MDD (MacMaster and Kusumakar, 2004). Our results provide compelling evidence that shape-deformation differences in the hippocampus between depressed and healthy individuals are present to at least some extent even in the very initial stages of the illness; they do not simply emerge over the recurrent and chronic pathology of the disorder, and they are not simply the result of any potential neurotoxic effects of chronic anti-depressant usage.

Results demonstrate that individuals can be classified relatively accurately (with 68% accuracy) into control and depressed groups using only structural MRI data. This is consistent with previous attempts at the diagnostic classification of MDD using brain structural neuroanatomy (67.6% diagnostic accuracy reported by Costafreda et al., 2009 and 77.8% prognosis accuracy reported by Nouradini et al., 2011 using adult subjects). However, classification results reported using resting-state functional Magnetic Resonance Imaging are higher (94.3% reported by Zeng et al., 2012, 90.6% reported by Ma et al., 2013 and 95% reported by Craddock et al., 2009), suggesting that the analysis of cognitive functional differences may add considerable power to diagnostic classification in MDD.

The group-average histograms for individual features suggest that among individual features, the deformation fields may better discriminate the two groups. However, the combination of GM and deformation fields captured the group differences better than any individual feature alone, or any other combinations of features, as indicated by the values of the Renyi divergence. These results suggest that future studies should use both deformation fields, and regionally specific analyses, such as tissue composition measures, to better understand the brain basis of MDD and capture structural differences between individuals with MDD and healthy controls.

The results reported above should be interpreted in the context of the following limitations. First, this study comprised young women with moderate and severe depression almost exclusively; therefore, generalization to young men in a first episode of MDD, and young men and women with milder levels of depression severity requires further study. Second, we did not assess for the presence of comorbid anxiety disorders or specific subtypes of MDD. Future studies are required to examine variation in brain morphology with differing depression syndromes in order to identify biomarkers of more homogeneous endophenotypes. Third, it will be important in future research to determine whether the present results generalize to children and early adolescents with MDD, as significant corticolimbic plasticity remains throughout childhood and early adolescence (Giedd et al., 2010), which may obscure any potential toxic effects of depression vulnerability. Finally, the participants in this study were volunteers and, thus, may not be entirely representative of the population of young people with depression. Nevertheless, as a community sample, they may be more representative than the subjects of most previous studies, which have relied on treatment-seeking patients in tertiary care centers.

The proposed method based on fusion of brain-tissue composition and shape deformation successfully captured the differences in hippocampal shape and tissue composition between young people in a first episode of depression and healthy control subjects. Specifically, using the jICA method, significant shape deformation differences in the left hippocampus were observed between the depressed and control groups. In contrast, no differences were detected between the two groups when a separate analysis of each feature was conducted. These results suggest that the jICA method may be a more sensitive technique for detecting morphological differences in brain tissue — such sensitivity may be particularly helpful when the sample size is relatively small, or when structural abnormalities are relatively subtle (such as in groups of young people who are very early in their disease course). The current results have important clinical implications. Although prospective studies with individuals at risk for MDD are needed to determine the causal role of these structural differences in MDD, the current results suggest that hippocampal volume loss may be correlated for a particularly severe manifestation of MDD in the first onset.

Acknowledgments

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References


Fig. 4. Renyi divergence criteria values for different combination of features on differentiation between histograms. The first six highest value combinations are shown in the figure. The higher the values of the Renyi divergence, the better the discrimination between groups.
Temporal-lobe morphology differs between healthy adolescents and those with early-onset of depression

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1. Introduction

Depression directly affects more than 10% of the population at some point in their lives (World Health Organization, 2004), and is a leading cause of disability, with significant social, health and economic impacts (Olesen et al., 2012). Major Depressive Disorder (MDD) has a typical onset in adolescence and young adulthood, and prevalence rates of MDD by late adolescence equal those in adulthood (Kessler and Walters, 1998). MDD that starts in adolescence is associated with a large number of negative outcomes, including lower educational and occupational attainment, poor physical health, and poor interpersonal functioning (Kandel and Davies, 1986). These outcomes persist into adulthood and predict significant risk for a lifelong pattern of illness (Birmaher et al., 1999). Given the enormous personal and societal costs associated with MDD, studies aimed at uncovering the pathology
of the disorder in its earliest stages are crucial to informing effective prevention and intervention efforts.

Our understanding of the changes in brain neuroanatomy that are associated with MDD have benefited greatly from important advances in Magnetic Resonance Imaging (MRI) technology in the past two decades. Using structural MRI techniques in adult samples, differences in volume and shape have been found between depressed and non-depressed groups in temporal (e.g., superior temporal gyrus (STG), hippocampus, amygdala), frontal (e.g., anterior cingulate cortex (ACC)), and orbitofrontal regions (see Lorenzetti et al., 2009) for a review of the structural MRI findings associated with MDD in adulthood). These studies, conducted in adults, are likely to reflect the pathophysiology of MDD, as well as secondary changes due to longstanding behavioral alteration, and atroge changes (as a result of pharmacologic and other therapies).

To date, a small handful of studies have also investigated pediatric and adolescent-onset MDD and have reported structural differences from healthy controls in similar regions, including the hippocampus (MacMaster and Kusumakar, 2004), amygdala (Rosso et al., 2005), striatum and caudate nucleus (Matsu et al., 2008; Shad, Muddasani, Rao, 2012), superior and middle temporal gyr (Shad, Muddasani, Rao, 2012), and subgenual prefrontal cortex (Botteron et al., 2002). A compelling recent study by (Chen, Hamilton, Gotlib, 2010) even found volumetric differences in the left hippocampus in clinically non-depressed young girls at high risk for depression (due to a maternal depression history), in comparison with girls who did not have a maternal depression history. However, other studies of early-onset depression have failed to find volumetric differences between depressed and healthy control groups in critical brain regions, including the prefrontal cortex (e.g., Nolan et al., 2002), hippocampus (Rosso et al., 2005), and amygdala (MacMaster and Kusumakar, 2004).

One potential reason for the failure to find consistent evidence of morphological differences in critical cortico-limbic circuits in early-onset MDD may be that such differences are subtle. Since the extent of hippocampal volume loss has been found to correlate significantly with the number of depressive episodes (i.e., time spent depressed) in adults with depression (Milne, MacQueen, Hall, 2012; Sheline et al., 1999), differences between depressed and non-depressed groups are likely to be larger in older samples of adults with recurrent depression than in younger individuals in the earliest stages of the illness. Hippocampal volume loss has also been associated with traumatic life events, which can be expected to accumulate with age (e.g., Childress et al., 2013; Vythilingam et al., 2004). More sensitive methods than have been used to date may be required to detect subtle differences in brain morphology associated with depression in its earliest stages, and in its youngest sufferers.

Previous methods used for investigating the morphological differences between individuals with depression and healthy controls can be categorized into three main types: 1) volume analysis; 2) analysis of local composition of tissue; and 3) analysis of shape and volume. The most common approach is hippocampal volume analysis using manual or automated segmentation (Bell-McGinty et al., 2002; Bergouignan et al., 2009; Vasic et al., 2008). In such analyzes the volume of the hippocampal region is measured after isolating it from the rest of the brain. Using this method, several groups have observed smaller hippocampal volumes in adults with MDD (Bremner et al., 2000; Caetano et al., 2004; Frodi et al., 2002; MacQueen et al., 2003; Neumeister et al., 2005; Saylam et al., 2006) whereas other groups have reported no differences or even larger hippocampal volumes (Hastings et al., 2004; Monkul et al., 2007; Ruch et al., 2001; Vythilingam et al., 2004).

Voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Good et al., 2001) which examines voxelwise differences in gray- and white-matter volumes and concentrations throughout the brain, has demonstrated reduced gray matter intensity in the hippocampus of MDD subjects (Bergouignan et al., 2009; Chen et al., 2007; Shah et al., 1998; Vasic et al., 2008). A limitation of VBM is that each individual’s brain data is normalized using non-linear deformation fields to a reference template. Through that process, crucial idiographic information such as the shape of brain structures and their position, orientation and size (pose), both relative to other structures and in absolute terms, is lost (Ashburner and Friston, 2000). This information may be critical for capturing group differences, particularly when such differences are subtle.

Alternatives to VBM approaches include Deformation Based Morphometry (DBM) (Bookstein, 1996) and Tensor Based Morphometry (TBM) (Chung et al., 2001), which are widely used to study the brains of people with schizophrenia, autism, dyslexia and Turner’s syndrome (Frackowiak et al., 2004). Unlike VBM, which analyzes images after the deformation fields have been applied in order to map any individual brain into a standard reference, these approaches take the deformation fields themselves as the dependent variable. Neither of these approaches has yet been attempted to study structural changes in depression. However, shape-analysis methods that are related to DBM/TBM have been employed in two separate studies to examine hippocampal differences in depression. These studies have focused on separate analysis of both shape and volume of the hippocampus using high-dimensional mapping (Posner et al., 2003) or spherical harmonic basis functions (Zhao et al., 2008). These studies with adult and elderly depressed patients reveal significant differences in hippocampal shape, but no volumetric differences. In these analyses, contribution to morphology made by the shape and pose of the hippocampal region and the surrounding regions was largely ignored.

Multi-object analysis enables the simultaneous statistical analysis of multiple brain structures, possibly allowing for the identification of subtle morphological differences across multiple brain regions, between groups. Multi-object methods were originally designed to characterize the shape of a population of geometric entities (Cebralza, Villanueva, Cabeza, 2012; Duta and Sonka, 1998; Lu et al., 2007; Tsai et al., 2003), and have since been applied to the analysis of brain MRI images to discriminate between healthy and clinical populations (e.g., pediatric autism; Gorgowski et al., 2010), but has not yet been employed in the context of major depressive disorder.

In the current study, we report the first use of a multi-object statistical pose and shape model to simultaneously analyze several temporal-lobe structures that have been implicated in MDD. Given that MDD is associated with morphological changes in several brain structures, pose and shape analysis of these brain structures simultaneously may be more sensitive to subtle group differences than is independent analysis of those structures, since simultaneous analysis includes information not just about the pose of brain structures, but about their pose relative to each other. In the current paper we present the method, and then use it to identity temporal-lobe structures of interest and to characterize the relationship between the pose and shape of these structures and the symptomatology of early-onset MDD, when morphological differences between healthy and clinical groups are expected to be mild, and subtle. Use of a young sample at the earliest stage of their depressive illness has important implications for understanding the neurostructural correlates of the etiology of MDD.

2. Materials and methods

2.1. Participants

Nineteen depressed subjects (age: 18.1 ± 1.1, 3 males, all right-handed) who met the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders; American Psychiatric Association, 2000) criteria for a current episode of MDD were recruited through referrals from community mental health clinics. Twenty-six healthy participants (age: 17.96 ± 0.2, 1 male, all right-handed) who met the DSM-IV-TR criteria for a current episode of MDD were recruited through referrals from community mental health clinics.
that could cause depression (e.g., hypothyroidism). All participants were medication-free prior to the study. This study was cleared by the Queen’s University Health Sciences Research Ethics Board, and written informed consent was obtained from all participants and by a parent or guardian for participants under 18 years. All participants were compensated $10 for their time and were given a picture of their brain to keep.

2.2. Clinical examination

All participants in the depressed group were diagnosed based on a structured diagnostic interview administered by an advanced doctoral student in clinical psychology (the Child and Adolescent version of the Schedule for Affective Disorders and Schizophrenia; K-SADS; Kaufman and Schweder, 2004). The K-SADS is the gold standard for deriving DSM-IV diagnoses in children and adolescents and is the most widely used measure for this purpose in clinical research. This clinician interview was administered by graduate-level students in clinical psychology who were trained and supervised by a registered clinical psychologist with over 20 years of expertise in the assessment and diagnosis of depression in adolescence. Participants were scored in the mild to severe depression range, as defined by a Beck Depression Inventory (BDI-II; Beck et al., 1996) score. The BDI is a 21-item measure designed to assess the presence and severity of depression symptoms, and is the most commonly used depression measure in adolescent and adult samples (Cusin et al., 2010). The BDI was administered by trained graduate or senior undergraduate-level students who went over the measure with each participant to
ensure that they understood the questions. We chose not to include the Hamilton Depression Rating Scale and to focus exclusively on the BDI as an index of depression severity for the primary reason that there is evidence that the Hamilton possesses a poor psychometric profile (Bagby et al., 2004).

The MRI data were acquired using a 3.0 Tesla Siemens Trio MRI scanner with a 12-channel head coil in the MRI facility at Queen’s University, Kingston, Canada. A whole-brain 3D MPGRAGE T1-weighted anatomical image was acquired for each participant (voxel resolution of 1.0 × 1.0 × 1.0 mm$^3$; flip angle $\alpha = 9^\circ$, TR = 1760 ms, and TE = 2.6 ms). The subjects filled out the BDI immediately after being in the scanner.

2.3. Multi-object statistical analysis

Pose and shape analysis of multiple brain structures, shown schematically in Fig. 1, involves three steps: a) preprocessing the MRI data to extract surface points on brain structures of interest; b) finding the pose and shape variations among these brain structures; and c) Principal Component Analysis (PCA) on pose and shape variations in the subject population.

2.3.1. Preprocessing

The structural MRI data of the subjects were preprocessed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Briefly, Grey Matter (GM), White Matter (WM) and Cerebral Spinal Fluid (CSF) were segmented using the automated segmentation processes in SPM. This resulted in a set of three maps for GM, WM and CSF in native space for each subject, in which each voxel was assigned a probability of being one of the three tissue types.

The LONI Probabilistic Brain Atlas (LPBA40/SPM5) (Shattuck et al., 2008) in MNI space was used to extract the left and right hippocampus, parahippocampal gyrus, putamen, and superior, inferior and middle temporal gyri from the brain of each participant (shown in Fig. 2); these are structures that have been shown to be associated with MDD in adulthood (Lorenzetti et al., 2009). The LONI atlas is constructed using the MRI data of 40 healthy volunteers, and 56 structures were labeled manually. We used the maximum-probability values at each voxel to segment the regions of interest in the atlas. To accomplish segmentations in each of the participants, we used the DARTEL algorithm to register the LONI atlas to each participant’s structural MRI, and extracted surface points, $V = \{v_{ni}\}_{n=1}^{N}\_{i=1}\ldots L$, indexing the coordinates of the surface voxels on each of the selected brain structures (Ashburner, 2007)$^3$. Here, $v_{ni}$ consists of all surface points of the $i$th structure of subject $n$, $L = 12$ is the number of structures (six in each hemisphere), and $N = 45$ is the number of subjects in the training set. For each subject, the surface boundary of each brain structure was used to compute the volume of that structure. Structure volumes were compared between the MDD and control groups.

2.3.2. Pose and shape analysis

Since all surface points are extracted using the atlas in MNI space, the correspondences among the surface points (between homologous points in different subjects) were known. We used those correspondences to compute the linear (rigid plus scaling) deformation required to warp each structure in each participant to the mean shape of each structure calculated across participants, using the generalized Procrustes analysis (Dryden and Mardia, 1998). Pose variations were calculated using translation, rotation, and scaling values of these deformation fields. Each transformation for a voxel, $\mathbf{x}$, is defined as $T(\mathbf{x}) = sR\mathbf{x} + \mathbf{d}$, where R is a rotation matrix, $\mathbf{d}$ is a translation vector, and s is a scale factor. These transformations form a Lie group, which is a Riemannian manifold so conventional statistical analysis in Euclidean space is not applicable. However, a logarithmic transform was used to put the members of the Lie group into linear tangent space, appropriate for conventional statistical analysis. The logarithm of the transformation is defined as:

$$\log(T) = \left[ \begin{array}{ccc} l & -r_z & r_x \ \\ r_z & l & -r_y \ \\ -r_y & r_z & l \ \\ 0 & 0 & 1 \end{array} \right]$$

where $l = \log(s)$, and $(r_x, r_y, r_z)$ is the rotation axis with angle $\theta = \sqrt{r_x^2 + r_y^2 + r_z^2}$. Thus, each transformation, $T_{n,b}$ which represents the transformation from the $b$th structure in the mean shape to the corresponding structure in the nth instance, was expressed as a vector with seven variables: $(r_{nx}, r_{ny}, r_{nz}, l, x, y, z)^T$.

For the purpose of statistical analysis, each transformation was normalized using the mean transformation for each structure, $M_b$, and mapped to the tangent space: $u_{n,b} = log(M_{b}^{-1}T_{n,b})$ (Bossa and Olmos, 2006; Pennec, 2006)$^2$. The transformation vectors were concatenated for each individual to form a 7L×1 vector: $u_b = [u_{b,1}^T \ldots u_{b,L}^T]^T$ and the matrix of all transformations for all individuals was created: $U^p = [u_1^T \ldots u_{N}^T]^T$.

Shape variations are computed as the residual deformation required to map the mean shape of each structure to the corresponding structure for each subject, after the linear transformation for pose has been applied. Subsequently, similar to the pose variation extraction method

Fig. 2. Segmented structures in both hemispheres of the brain which are used for multi-object statistical analysis. Surface points of putamen (blue), hippocampus (green), parahippocampal gyrus (red), and ITG (cyan); MTG (yellow), and STG (magenta) in both hemispheres of the brain are shown in (a) anterior to posterior view, and (b) posterior to anterior view. Structures in left hemisphere of the brain are shown in (c).
Our objectives were to 1) identify pose and shape features that would differentiate the two groups; and 2) investigate the relationship between these features and the clinical index of depression (i.e., BDI scores).

To achieve the first objective, we first use a random-forest classification (Breiman, 2001) approach to sort the selected principal components. Random forests are a learning method for classification that use multiple decision trees for training. The decision tree splits the weights related to the considered principal components to maximize diversity among the subjects (Coppersmith, Hong, Hosking, 1999). As a result, a tree with nodes and leaves is constructed, where its top node shows the weights with maximum separability. We perform unpaired two-sample t-tests (assuming unequal variance in the two groups) only on the top-node weights for pose and shape, i.e. one component for pose and one component for shape. As this study was designed to be hypothesis-generating and sensitive to morphological differences in brain structures between adolescent depressed individuals and control participants, a significance level of \( p < 0.05 \), uncorrected for multiple comparisons, was used (Haynes et al., 2012; Rothman, 1990).

In order to visualize the significant pose component, associated with the top node weights, the norms of the three pose parameters (three translation, three rotation, and one scale variables) were computed. Subsequently, the mean of each parameter was removed and the result was divided by the standard deviation of the parameter. For the shape, the mean of the significant shape principal component associated with the top node weights was removed and the result was normalized to the component’s standard deviation. The higher the absolute value of the normalized pose or shape component, the more the contribution of that member of the principal component to capture the differences between the two groups.

To achieve the second objective, we calculate Spearman correlation coefficients between the Beck Depression Inventory score and the top-node pose and shape weights.

## 3. Results

### 3.1. Behavioral results

The groups were matched for age (\( p = 0.52 \)). There were no socio-economic status (SES) differences between the subjects in the two groups (\( p = 0.93 \)). The BDI differed significantly between the two groups (\( p < 0.001 \)). Fig. 3 shows the boxplot of the BDI for the two groups.

### 3.2. Volume analysis

We first assessed the volume differences between the MDD and control groups for each structure. Unpaired two-sample t-tests (assuming unequal variance in the two groups) with a significance level of \( p < 0.05 \), uncorrected for multiple comparisons, was used to detect volume differences between the two groups. The volume of both the left parahippocampal gyrus and the left superior temporal gyrus was significantly greater (\( p = 0.019 \) and \( p = 0.034 \) respectively) in the depressed than the control group.

### 3.3. Pose and shape analysis

The goal of our multi-object analysis was to investigate the pose and shape differences in brain structures between the participants with MDD and healthy controls. The first four principal components of pose capture two standard deviations (95%) of the variation in pose, and the first eight components of shape capture one standard deviation (68%) of the variation in shape. The random-forest classification trees for pose and shape were built on these components. Statistical analyses using unpaired two-sample t-tests were performed on the top component for each tree.
The two groups differed significantly \((p = 0.031\) with corresponding statistical power of 0.77 \((Ellis, 2010)\) for the pose component, and \(p = 0.042\) with corresponding statistical power of 0.89 for the shape component). Table 1 shows the normalized pose parameters across different brain structures for the most significant pose component. The translation component differed significantly between the two groups in the left putamen, left and right hippocampus, and left ITG. Rotation also differed between the groups in the left putamen, right hippocampus, and left and right ITG, and scale differed between groups in the left and right putamina. Fig. 4 shows the normalized shape component across different structures in the brain. As can be seen in the figure, many regions of all the structures examined show variations of the shape that are more than 1.96 (two standard deviations away from the mean), in both hemispheres.

To investigate the relation between the pose and shape weights that were significantly different between the two groups and BDI scores, Spearman correlation coefficients were calculated between the pose and shape values and BDI. The significant pose component correlated significantly with BDI (Spearman correlation: 0.38, \(p = 0.0086\), slope: \(-0.039\), intercept: 0.39), but the significant shape component did not (Spearman correlation: 0.15, \(p = 0.298\), slope: \(-0.89\), intercept: 8.8). Fig. 5 shows the distributions of the pose scores (a) and shape scores (b) across BDI. The four male subjects are identified with a circle.

4. Discussion

We conducted a statistical analysis of pose and shape information from several brain regions in order to examine whether the brains of individuals with early-onset MDD differ from those of healthy controls. Indeed, despite a rather small number of participants, we were able to observe statistically reliable differences in the medial temporal lobe regions, and we also determined that some features captured by the pose and shape analysis correlated with depressive symptomatology as measured by the Beck Depression Inventory. The sensitivity of this method may be related to its ability to capture differences in the spatial relationships among structures, not simply differences within an individual structure. A concern about the results is that we did not make any formal adjustments to correct for multiple comparisons, which potentially introduced a risk of false-positive results. Therefore, the p-values should be interpreted with caution \((Devonshire et al., 2012)\). As such, future studies with larger samples are needed to further validate these results.

We observed volume differences, with a significance level of \(p < 0.05\), uncorrected for multiple comparisons, in the left parahippocampal gyrus and the left superior temporal gyrus (STG) structures between the depressed group and the control group. The STG volume and GM density differences between the MDD and control subjects were previously shown by Vyithilingam et al. \((2004)\) and Shah et al. \((2002)\). The individuals studied by these authors had been diagnosed with MDD at least 2 years earlier — so a later stage of the illness than the clinical group in the current study. Our results indicate that differences in STG are present right from the earliest stages of the disease.

The most significant component of the pose, highlighted in Table 1, showed that the left and right putamina, the left and right hippocampi, and the left and right inferior temporal gyri were more affected by MDD. The scale parameter of the right putamen is the only parameter that showed at least two standard deviations of variation. The translation mostly affected the left inferior temporal gyrus, and the rotation mostly affected the left putamen.

Shape analysis revealed that all examined structures, including the putamen, hippocampus, parahippocampal gyrus, and superior, middle and inferior temporal gyri, differed between the two groups, suggesting that multiobject shape analysis is a sensitive tool for the

Fig. 4. Shape principal component that was significantly different between the two groups. The component is normalized by removing the mean and divided to its standard deviation. Inferior and superior views of the (a, b) left putamen, (c, d) right putamen, (e, f) left hippocampus, (g, h) right hippocampus, (l, j) left parahippocampal gyrus, (k, l) right parahippocampal gyrus, (m, n) left superior temporal gyrus, (q, r) right superior temporal gyrus, (s, t) left middle temporal gyrus, (u, v) left inferior temporal gyrus, and (w, x) right inferior temporal gyrus. The color smoothly varies from black through red, orange, yellow and white, to show the minimum through maximum difference values. Left side of the pictures shows the left side of the brain, right shows right side, top is the anterior and bottom is the posterior.

Fig. 5. Pose (a) and shape (b) scores that generated the significant difference between the MDD subjects and controls across the beck Depression Inventory Index (BDI). Pose scores are significantly correlated to the BDI (Spearman correlation: 0.38, \(p = 0.0086\), slope: \(-0.039\), intercept: 0.39). Shape scores are not significantly correlated to the BDI (Spearman correlation: 0.15, \(p = 0.298\), slope: \(-0.89\), intercept: 8.8). A circle has been drawn around the data of male subjects.
examination of morphological differences in clinical samples. Moreover, within the most significant component of the shape, we identified regions that were at least two standard deviations away from the mean of that component, highlighting regions that were more affected by MDD.

Importantly, depressive symptomatology, as indexed by BDI scores, correlated with the pose of the structures (Fig. 5(a)). While the volume increase in the fusiform gyrus, cuneus and precuneus has been previously shown to have an association with the BDI increase in MDD (Kroes et al., 2011), we are the first to show that pose variations of multiple structures are also affected by MDD, and correlate significantly with BDI.

The significant brain structural abnormalities seen here in early-onset depression are consistent with those observed in previous work (MacMaster et al., 2008; MacMaster and Kusumakar, 2004; MacMaster et al., 2014). However, MacMaster et al. only investigated volumetric differences between brain structures, after isolating each structure from the rest of the brain. Here, we have investigated the morphometric differences using simultaneous pose and shape analysis of multiple structures. As a result, we can capture differences due to the relationship among structures, and also differentiate between pose and shape morphometric differences.

The neural mechanisms underlying the observed morphometric differences in MDD have received empirical attention. Depression is associated with chronic dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis with the resulting chronic release of cortisol and other neurotoxic stress hormones (Burke et al., 2005). Glucocorticoid neurotoxicity has preferential effects on hippocampal neurogenesis (e.g., De Vry et al., 2012; Sapolsky, 2000). Indeed, in both preclinical and human clinical studies chronic stress and depression are associated with long-term changes in the hippocampus in the expression of genes involved in synaptic plasticity, such as brain-derived neurotrophic factor (BDNF; e.g., Law et al., 2009; Mondelli et al., 2011). Our results extend the state of the literature by suggesting that through the use of sensitive pose and shape analyses, the structural differences in MDD can be observed at the very initial stages of the illness, suggesting that they do not just emerge over the recurrent and chronic pathology of the disorder. In addition, as all of our depressed participants were medication naïve, the structural differences are not due to any potential neurotoxic effects of chronic anti-depressant usage. As such, they may emerge as a result of premorbid epigenetic vulnerabilities. For example, hippocampal volume differences have been shown in individuals with particular polymorphisms of genes known to impart risk for depression, but only in the context of environmental adversity, such as a history of childhood trauma (e.g., Teicher, Anderson, Polcari, 2012), or maternal depression (e.g., Chen, Hamilton, Gotlib, 2010). Future prospective, longitudinal studies that follow children at risk of depression as a result of these vulnerabilities through to the onset of syndromal MDD are required to clarify the precise etiological and pathological mechanisms underlying the relation of hippocampal volume loss to MDD.

A concern about the method is the possible dependence on the quality of the segmentation. In this work, the segmentation comes from an atlas and the registration of the atlas to the brains of the individual participants. A potential alternative is to manually segment the structures in individual brains prior to a group-wise registration. In future studies, we can also use polyaffine transformations in a logarithmic domain (Arsigny et al., 2009; Commowick et al., 2008), instead of similarity transformations for registration of multiple structures. An affine transformation would further encompass anisotropic scaling and shearing.

The current study investigated morphological variation in the pose and the shape of the hippocampus and surrounding structures in early-onset MDD compared to control participants. Although a large number of previous studies have shown differences between MDD subjects and controls (Bergouignan et al., 2009; Bremer et al., 2000; Caetano et al., 2004; Chen et al., 2007; Frodl et al., 2002; Neumeister et al., 2005; Saylam et al., 2006; Shah et al., 1998; Vasic et al., 2008), ours is the first, to our knowledge, to simultaneously analyze multiple structures, and to separate pose and shape in morphological analysis. The value of the presented method is that it identifies structures of interest and characterizes types of differences (i.e., pose and shape) that can then be fed back into models/theories on etiology. In other words, what is more relevant than finding group differences is pinpointing the effect of underlying mechanisms that lead to MDD on brain structures and their interrelationships. Future studies should consider differences between MDD and control groups in other brain structures of relevance to MDD, and should also investigate whether the present results generalize to adults with recurrent MDD, as well as younger children with MDD. In addition, although current results (Fig. 5(a) and (b)) did not reveal any differences in the structures we examined between male and female individuals with MDD, we had very few young men in our study. Further studies with young men are needed to ensure that the results observed here generalize across sexes.

Recently, a few studies have focused on the White Matter (WM) integrity using Diffusion Tensor Imaging (DTI), to assess the structural connectivity of the network between healthy controls and MDD subjects. Korgaonkar et al. (2014) showed structural connectomic alterations between nodes of the default mode network and the fronto-thalamo-caudate regions in 95 MDD outpatients comparing to 102 matched control subjects. However, Choi et al. (2014) found no significant differences in WM integrity disruption between 134 medication-free MDD patients and 54 healthy controls. Future studies may use multivariate approaches to include analysis of geometric changes (pose and shape), tissue concentrations (WM and GM) and structural connectome (DTI).

In summary, using multi-object statistical pose and shape analysis, we demonstrated brain morphological differences between adolescents and young adults with early-onset MDD and healthy control subjects. Relative pose information and shape information of multiple structures in brain, which are usually disregarded, were shown to be important in capturing the group differences. Within this framework, the shape formations were analyzed separately from rigid transformations and scale (i.e., the pose information). Therefore, we could identify the type of morphological differences (pose and shape). Within the simultaneous analysis of multiple structures the relative differences among structures were captured. The differences were more pronounced in the moderate and severely depressed participants. Moreover, morphological features (pose) significantly correlate with depressive symptoms across both normal and depressed participants.

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Appendix A

Fig. 6 shows the distribution of the volume of each structure for the depressed and control groups.
Fig. 6. Distribution of the volume of each structure between the two groups, (a) left putamen, (b) right putamen, (c) left hippocampus, (d) right hippocampus, (e) left parahippocampal gyrus, (f) right parahippocampal gyrus, (g) left inferior temporal gyrus, (h) right inferior temporal gyrus, (i) left middle temporal gyrus, (j) right middle temporal gyrus, (k) left superior temporal gyrus, and (l) right superior temporal gyrus. The central red mark is the median, the edges of the blue box are the 25th and 75th percentiles, and the whiskers show the extreme values of the volumes.

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