Morphological changes in subregions of hippocampus and amygdala in major depressive disorder patients

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Abstract

Despite many neuroimaging studies in the past years, the neuroanatomical substrates of major depressive disorder (MDD) subcortical structures are still not well understood. Since hippocampus and amygdala are the two vital subcortical structures that most susceptible to MDD, finding the evidence of morphological changes in their subregions may bring some new insights for MDD research. Combining structural magnetic resonance imaging (MRI) with novel morphometry analysis methods, we recruited 25 MDD patients and 28 healthy controls (HC), and investigated their volume and morphological differences in hippocampus and amygdala. Relative to volumetric method, our methods detected more significant global morphological atrophies ($p < 0.05$). More precisely, subiculum and cornu ammonis (CA) 1 subregions of bilateral hippocampus, lateral (LA) and basolateral ventromedial (BLVM) of left amygdala and LA, BLVM, central (CE), amygdalostriatal transition area (ASTR), anterior cortical (ACO) and anterior amygdaloid area (AAA) of right amygdala were demonstrated prone to atrophy. Correlation analyses between each subject's surface eigenvalues and Hamilton Depression Scale (HAMD) were then performed. Correlation results showed that atrophy areas in hippocampus and amygdala have slight tendencies of expanding into other subregions with the development of MDD. Finally, we performed group

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morphometric analysis and drew the atrophy and expansion areas between MDD-Medicated group (only 19 medicated subjects in MDD group were included) and HC group, found some preliminary evidence about subregional morphological resilience of hippocampus and amygdala. These findings revealed new pathophysiologic patterns in the subregions of hippocampus and amygdala, which can help with subsequent smaller-scale MDD research.

Keywords

Hippocampus; Amygdala; Major depressive disorder; Subcortical structures; morphometry

Introduction

Major depressive disorder (MDD) is a widely prevalent (Kessler et al. 2003; Hasin et al. 2005; J. Ferrari et al. 2013), costly (Greenberg and Birnbaum 2005; Wang et al. 2010) and recurrent mental disease (Sullivan et al. 2000), which affecting approximately 350 million people each year (Marcus et al. 2012). Because of the general impairments on cognitive functions (Snyder 2013), MDD patients always meet serious obstructions in social contact, education and occupation (Kessler et al. 2005; Snyder 2013). The causes of MDD are complex, its pathogenesis and profile of effects in the brain are still rudimentary compared with knowledge of other common chronic and potentially fatal multifactorial conditions (Krishnan and Nestler 2008; Nho et al. 2015; Schmaal et al. 2017).

Documented by prior research, hippocampi and amygdalae played a vital role in the regulation of emotional learning (Morris et al. 1998), expression (Adolphs et al. 1994), working memory (Winocur et al. 2006; Saxe et al. 2007) and broad information processing associated with memory (Wood et al. 1999), which were always considered more easily affected in MDD (Sheline et al. 1996; Sheline et al. 1998; Mervaala et al. 2000; C. Lange and E. Irle 2004; Hastings et al. 2004; Videbech and Ravnkilde 2004; Tang et al. 2007; Hamilton et al. 2008; Kronenberg et al. 2009; Van et al. 2009). The study of these two structures may provide a potential seat for a clear description of morphological alterations underlying corresponding neurological dysfunctions. Many prior structural MRI research found that MDD group have reduced volumes of hippocampi (Sheline et al. 1996; Mervaala et al. 2000; C. Lange and E. Irle 2004; Maller et al. 2007), especially on the bilateral sides of tail parts (Maller et al. 2007; Malykhin et al. 2010). Even HC subjects could show a relative smaller volume of left and right hippocampus if their mothers have recurrent episodes of depression (Chen et al. 2010). As for amygdala, volumetric findings in MDD studies are inconsistent (Gunten et al. 2000; Frodl et al. 2002; Frodl et al. 2003; C. Lange and E. Irle 2004; Hastings et al. 2004; Rosso et al. 2005; Kronenberg et al. 2009; Van et al. 2009). Both greater (Frodl et al. 2002; Frodl et al. 2003; C. Lange and E. Irle 2004; Van et al. 2009) and smaller (Sheline et al. 1998; Gunten et al. 2000; Hastings et al. 2004; Rosso et al. 2005; Kronenberg et al. 2009) amygdalae were showed.

To our knowledge, all of the above studies were focusing on volumetric analyses (Sheline et al. 1996; Sheline et al. 1998; Mervaala et al. 2000; C. Lange and E. Irle 2004; Hastings et al. 2004; Tang et al. 2007; Hamilton et al. 2008). Although these previous studies have yielded

many good insights in volumetric changes of MDD group, inconsistent findings (especially for the amygdala) have still not been reasonably addressed. This may due to that volumetric methods usually give a more general description on the whole or partial volume of hippocampus and amygdala, while more subdividable research is still lacking. Recent years, some studies provided evidence that hippocampus and amygdala are anatomically subdividable (Ballmaier et al. 2008; Cavedo et al. 2011; Dudek et al. 2016) — different subregions of hippocampus and amygdala have different inputs from and outputs to different brain regions subserving a number of specific functions. In fact, the internal pathological changes of hippocampus and amygdala during MDD duration are complex and microcosmic —changes of synaptic strength (Linden and Connor 2003; Bannerman et al. 2014), neural circuits (Price and Drevets 2012) and brain-derived neurotrophic factor (Angelucci et al. 2005; Bus et al. 2015) were all be documented. From literature, we found few studies have tried to explore the subregional deformations in hippocampi and amygdalae. Nonetheless, two prior studies, in structure and function, revealed heterogeneous mechanism in different subregions of human hippocampus. Ballmaier et al. (2008) found the regional surface contractions caused by late-onset elderly MDD were occurred in specific subfields rather than the whole left and right hippocampus. Dimsdalezucker et al. (2018) demonstrated CA1 and CA3 subregions of hippocampus differentially support spontaneous retrieval of episodic contexts. These two subregional findings implied that it is advantageous to study the deformations in the scale of subregions in both hippocampi and amygdalae of MDD group.

Several prior studies (C. Lange and E. Irle 2004; Hamilton et al. 2008; Van et al. 2009; Malykhin et al. 2010) pointed out that medicated MDD subjects have increased hippocampal volume compared with unmedicated patients. However, few research have explored whether the recovery effects were also existed in the subregional morphometry of hippocampus and amygdala.

The aim of our study is fourfold. First, by leveraging our novel subcortical morphometry pipeline (Wang et al. 2013a; Lao et al. 2016), we want to validate the hypothesis that the subregional morphometric alterations may more significant and sensitive than the whole volume alterations in hippocampus and amygdala when comparing MDD patients with controls. These subregional alterations can reveal more details about the pathogenesis of MDD and its influence to local brain functions. Second, we try to investigate which of these areas of significance are atrophy areas and which are expansion areas, further determining the morphological change direction of the subregions. Third, we will calculate the correlations between the surface eigenvalues and the scores of Hamilton Depression Scale (see (Bech et al. 1981), HAMD is a measure of the severity of depressive states), attempting to find the potential morphological development tendency of hippocampus and amygdala during MDD duration. Fourth, a MDD subgroup — MDD-Medicated group will be picked to perform the same pipeline with HC group, for exploring the recovery effects in subregional morphometry of hippocampus and amygdala after medicated.

Materials and methods

Participants

Participants in this study included 25 patients diagnosed with MDD and 28 age- and sex-matched healthy controls. The MDD patients were recruited from the Gansu Provincial Hospital, while the HC subjects were recruited through newspaper advertisements. MDD participants were diagnosed by two experienced psychiatrists using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al. 2002). The inclusion criteria for MDD patients were as follows: (1) met the DSM-IV (SCID) for MDD; (2) 19–65 years with the ability to give voluntary informed consent; (3) satisfied criteria for undergoing an MRI scan; and (4) could be managed as outpatients. Of all the MDD patients, six patients were currently medication free, five patients were treated with monotherapy (with one of the lexapro, paroxetine, fluoxetine, deanxit, zoloft and effexor), and 14 patients were treated with combination therapy (with two or more of the lexapro, paroxetine, fluoxetine, deanxit, zoloft and effexor). The HC subjects were enrolled if they had no current or past history of MDD, other major physical or neurological illness, or substance abuse. All HC subjects were interviewed using the Structured Clinical Interview for DSM-IV, non-patient edition. All the MDD and HC subjects were right-handed. HC participants were excluded if they reported a first-degree relative with a mood disorder or for any exclusion criteria of the MRI scanning. Both MDD patients and HC participants have executed the evaluation of 17-item Hamilton Rating Scale for Depression (HAMD-17).

MRI data acquisition

Imaging was performed on a 3.0 T Siemens Trio scanner (Siemens, Erlangen, Germany). The 3D T1-weighted image was acquired covering the whole brain (128 sagittal slices, repetition time (TR) = 2530 ms, echo time (TE) = 3.39 ms, slice thickness/gap = 1.33/0 mm, in-plane resolution = 256×192 mm, inversion time (TI) = 1100 ms, field of view (FOV) = 256×256 mm, flip angle (FA) = 7º). The scans were optimized for the best gray and white matter contrast, both at the cortical and at the subcortical/deep gray level.

Segmentation, reconstruction and registration

All the T1-weighted brain volume MRI scans were automatically segmented using FIRST (available at https://fmrib.ox.ac.uk/fsl/fslwiki/FIRST/), which is an integrated tool developed as a part of the FSL library. These segmented images were spatially normalized to the MNI template space with a 9-parameter (3 translations, 3 rotations and 3 scales) linear transformation using Minctracc algorithm (Collins et al. 1994) for the correction of head tilt and alignment. To equalize image intensities across subjects, registered scans were also histogram-matched. After segmentation for the hippocampus and amygdala for each participant, the results were strictly checked by two independent anatomists to verify their quality.

All the segmentation results of hippocampus and amygdala were then processed through surface conformal slit mapping (Wang et al. 2008). This method allows us to compare and analyze surface data effectively on a simpler parameter domain, which avoids considering the complicated brain surfaces (Wang et al. 2013a). Finally, we aligned surfaces in the

parameter domain with a fluid registration technique to maintain smooth, one-to-one topology (Christensen et al. 2002; Shi et al. 2013). The one-to-one correspondence achieved between vertices allows us to accurately analyze localized information on the surfaces of hippocampus and amygdala.

The whole processing pipeline

Fig. 1 illustrates the whole processing pipeline applied in this paper, which includes the segmentation of subcortical structures, surface reconstruction, surface registration, group difference analysis, the calculation of atrophy and expansion areas and the correlation analysis between surface eigenvalues of MDD subjects and their HAMD scores.

Group differences mapping

To detect group differences in the subdivisions of hippocampus and amygdala, some novel features were used, including:

1. The RD: radial distance, refers to the distance from a medial axis to a vertex on the surface — which represents the thickness of the shape at each vertex to the medial axis (Pizer et al. 1999; Thompson et al. 2004). The iso-parametric curve (see red curves in Fig. 1 d) is perpendicular to the medial axis, on the computed conformal grid (Wang et al. 2011), after which RD value is easily found at each vertex.

2. The TBM: surface tensor-based morphometry (Davatzikos 1996; Thompson et al. 2000; Woods 2003; Chung et al. 2008) examines spatial derivatives (det$J$, where J is the Jacobian matrix of the deformation from the registration) of the deformation maps that register brains to common template. Suppose $\varphi : S_1 \to S_2$ is a map from surface S_1 to surface S_2. The derivative map of φ is the linear map between the tangent spaces $d\varphi : TM(p) \to TM(\varphi(p))$, induced by the map φ, which also defines the Jacobian matrix of φ. In the grid surface, the derivative map $d\varphi$ is approximated by the linear map from one face $[v_1, v_2, v_3]$ to another $[w_1, w_2, w_3]$. First, the surfaces $[v_1, v_2, v_3]$ and $[w_1, w_2, w_3]$ are isometrically embedded onto the Klein disk (Shi et al. 2015), the planar coordinates of the vertices v_i, w_i are denoted by the same symbol v_i, w_i. Then the Jacobian matrix for the derivative map $d\varphi$ can be explicitly computed as (Wang et al. 2009):

$$J = d\phi = [w_3 - w_1, w_2 - w_1][v_3 - v_1, v_2 - v_1]^{-1} \tag{1}$$

Finally, the TBM is defined as $\sqrt{\det(J)}$. TBM is complementary to RD, as the RD primarily measures changes in thickness while the TBM mainly captures changes in local surface area.

3. The MTBM: surface multivariate tensor-based morphometry represented the logged deformation tensors $\left(\log\sqrt{JJ^T}\right)$ (Wang et al. 2013), which was showed in prior studies (Wang et al. 2009; Wang et al. 2013a). Here this feature was used as supplement and reinforcement of TBM results.

4. The RDMTBM: RDMTBM is the combination of radial distance and MTBM, which takes advantage of the vertex-wise changes in thickness and regional surfaces. Here we only made a preliminary exploration of this feature. In future, our team will focus on the classification performance between MDD and HC groups and other applications based on this feature.

Statistics used for the univariate measures were t-tests (for RD/TBM), while the multivariate statistics were computed using the Hotelling's T^2 tests (Hotelling 1992) (for MTBM/RDMTBM). Hotelling's T^2 test is a commonly used multivariate test method, which can be understood as the extension of the t-test and in following papers can find detailed descriptions (Lepore et al. 2008; Wang et al. 2013a; Wang et al. 2013b).

Here we run two permutation tests on the images: a surface vertex-based one that allows us not to assume a normal distribution, and one over the whole structure to correct for multiple comparisons (Nichols and Holmes 2002; Styner et al. 2006).

Given two groups of hippocampus (or amygdala) surfaces, on each surface vertex, we compute a t value with true group labels to represent the difference between the two groups of subjects on this vertex. We then randomly assign the hippocampus (or amygdala) surfaces into two groups with same number of subjects in each group as in the true grouping and re-compute the t value on each surface vertex, which we denote as the t' value. The random group assignment is permuted 10,000 times and results in 10,000 t' values on each vertex. A probability on each surface vertex is computed as the ratio of the number of t' values which are greater than the t value to the number of total permutations. These probability values (p-values) are color coded on an average hippocampus (or amygdala) shape to build the significance p-map (uncorrected, see Fig. 3 and Fig. 4) of the group comparison. Given a pre-defined statistical threshold of $p = 0.05$, the feature in a significance p-map is defined as number of surface vertices with p-values lower than this threshold, which is also regarded as the real effect in the true experiment. The feature is then compared with features that occur by accident in the random groupings. A ratio is computed describing the fraction of the time an effect of similar or greater magnitude to the real effect occurs in the random assignments. This ratio is the chance of the observed pattern occurring by accident and thus provides an overall significance value of the map (corrected for multiple comparisons) (Thompson et al. 2003; Shi et al. 2015).

The calculation of atrophy and expansion areas

After detecting group differences, we performed some analyses to capture the direction of changes in regional group differences that found by radial distance and $\det J$ — to locate which areas are atrophying and which are expanding. Suppose each RD value r at each vertex that we obtained is r^i (i is the vertex id), the significance level given for each vertex is p-value = 0.05, and the N_{MDD} and N_{NC} represented the number of MDD and HC subjects, separately. Then each r^i in each MDD and HC subject can be represented as r^i_{MDD} and r^i_{HC}. Finally, we can list the following expression:

$$\begin{cases} if\left(\left(\dfrac{1}{N_{MDD}}\sum_i^{N_{MDD}} r^i_{MDD} - \dfrac{1}{N_{HC}}\sum_i^{N_{HC}} r^i_{HC}\right) < 0 \&\& p-value < 0.05\right), Surface\ Atrophy \\ if\left(\left(\dfrac{1}{N_{MDD}}\sum_i^{N_{MDD}} r^i_{MDD} - \dfrac{1}{N_{HC}}\sum_i^{N_{HC}} r^i_{HC}\right) > 0 \&\& p-value < 0.05\right), Surface\ Expansion \end{cases} \quad (2)$$

Analogously, we can also generate the following expression for TBM:

$$\begin{cases} if\left(\left(\dfrac{1}{N_{MDD}}\sum_i^{N_{MDD}} \det J^i_{MDD} - \dfrac{1}{N_{HC}}\sum_i^{N_{HC}} \det J^i_{HC}\right) < 0 \&\& p-value < 0.05\right), Surface\ Atrophy \\ if\left(\left(\dfrac{1}{N_{MDD}}\sum_i^{N_{MDD}} \det J^i_{MDD} - \dfrac{1}{N_{HC}}\sum_i^{N_{HC}} \det J^i_{HC}\right) > 0 \&\& p-value < 0.05\right), Surface\ Expansion \end{cases} \quad (3)$$

As we mentioned earlier, the RD measures the thickness changes in the directions that perpendicular to the medial axis, while the $\det J$ indicates the differences in regional surface areas. In both expressions (2) and (3), if the results of the subtractions are smaller than 0, that is, these vertices and parts they represented in MDD group are atrophying relative to HC group, and vice versa for results greater than 0.

The correlation analysis between each MDD subject's surface features (RD/TBM) and their HAMD scores.

The HAMD score level, to some extent, can reflect the severity of depression (Bech et al. 1981; Williams 1988; Williams 2001). Hence, we ranked the HAMD scores for each subject in the MDD group, and calculated its correlations with each subject's eigenvalues in every vertex that detected by RD and $\det J$. The correlation analysis may help to reveal the vulnerable subregions in hippocampus and amygdala, and can predict the trend of deformation during MDD duration. In order to describe the calculation methods of the correlation analysis, we drew the following matrix that represent the whole eigenvalues in MDD group:

$$\begin{pmatrix} v_1^1 & \cdots & v_1^{N_{MDD}} \\ \vdots & \ddots & \vdots \\ v_m^1 & \cdots & v_m^{N_{MDD}} \end{pmatrix} \quad (4)$$

where v refers to each eigenvalue in each vertex (here refers to RD or $\det J$), and m is the total number of vertices for each hippocampus or amygdala. Since each MDD subject has its own HAMD scores, we also list all of their HAMD scores as a matrix as follows:

$$\begin{pmatrix} HAMD_1 \\ HAMD_2 \\ \vdots \\ \vdots \\ HAMD_{N_{MDD}-1} \\ HAMD_{N_{MDD}} \end{pmatrix} \qquad (5)$$

The calculation method is that we continuously extract each row in matrix (4) to perform the Pearson correlation analysis with matrix (5), and according the coefficients (*p*-values and *r*-values) generated in the Pearson correlation analysis to draw these vulnerable parts on the surfaces of the two subcortical structures.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the participants are summarized in Table 1. Significant group differences were only found in HAMD scores ($p < 0.001$), TSD (Time Since Diagnosis) ($p < 0.001$) and right amygdala volumes ($p = 0.048$). Each MDD subject's volume distributions of hippocampus and amygdala along with HAMD scores were showed in Fig. 2

Regional group morphometric differences

Subregions and areas of significant abnormality in the hippocampus and amygdala of MDD group comparing with HC group were showed in Fig. 3 and Fig. 4. The template surfaces for the hippocampus and amygdala (shown in the left parts of Fig. 3 and Fig. 4) were subdivided into multiple distinct subregions according to the guidance of two independent anatomists and some prior studies (Maller et al. 2007; Ballmaier et al. 2008; Cavedo et al. 2011).

With the pathological effects of MDD, the two hippocampus displayed similarity in morphological changes. In terms of RD, the left hippocampus (global $p = 0.0253$) and right hippocampus (global $p = 0.0044$) displays strongly significant clusters that located from the most posterior tail sections (in CA1 and subiculum subregions) to anterior head parts (in subiculum subregion). As for TBM, the two sides of hippocampus (left: global $p = 0.0823$; right: global $p = 0.0283$) show consistent clusters of significance in the tail sections (in CA1 and subiculum subregions), while the right hippocampus displays extra areas of significance on anterior head parts (in subiculum subregion). In conclusion, CA1 and subiculum are two vulnerable subregions in bilateral hippocampus.

Different with hippocampus, the two amygdala show some asymmetry. For left amygdala, no matter in the RD (global $p = 0.1306$) or TBM (global $p = 0.1866$), its areas of significance are mainly included in LA and BLVM subregions. For right amygdala, considering both RD (global $p = 0.0086$) and TBM (global $p = 0.0467$), the significant areas were extensively presented in LA, BLVM, CE, ASTR, ACO and AAA subregions.

Multivariate tests (MTBM/RDMTBM) of hippocampus and amygdala also gave most overlapped clusters of significance that had found in TBM and RD, though their results were more sensitive but a bit noisier. Most of the global *p*-values (except left amygdala) calculated by the four features reached the threshold of 0.05 — which we set here for the statistical significance of each subcortical structure. Obviously, all these features we used here were more sensitive than just considering the overall volumes (Table 1).

Atrophy and expansion areas illustrated

The significant atrophy and expansion regions were captured by combining the group morphometric difference results and the expression (2) and (3). Widespread atrophies (cold colors) and small expansions (warm colors) were marked in "Atrophy" and "Expansion" in Fig. 5. The significant atrophy parts in bilateral hippocampus (Fig. 5) are widely located on anterior head (in subiculum subregion) and posterior tail (in CA1 subregion). The two smaller significant expansion areas (Fig. 5) in left hippocampus are also located on the CA1 subregion. Bilateral amygdalae also showed widespread significant atrophy in LA, BLVM, CE, ASTR, ACO and AAA subregions (Fig. 5). In the TBM of right amygdala, a small significant expansion area were found in CE subregion (Fig. 5 b).

Correlation areas between surface feature values of MDD subjects and their HAMD scores

According to the expression (4) and (5), Fig. 6 was generated. This figure display *r*-values distributions that meet *p*-values less than 0.05 (the threshold we set for each vertex) when performing Pearson correlation analysis between each subject's RD/TBM eigenvalues and their HAMD scores. The correlation results supported these atrophy areas we found before (Fig. 5), although these strong negative correlation areas (r < −0.80, see Fig. 6 a) found here were a little shifted relative to these strong significant atrophy areas (*p* < 0.01, see Fig. 5 a). It is suggested that atrophic subregions of hippocampus have potential but slight tendencies of expanding into CA2–3 subregions, while similar trends in amygdala were seen in medial (ME), accessory basal (AB) and posterior cortical (PCO) subregions. These results revealed new insights to MDD group itself — as the HAMD score increases, these severely atrophy areas in hippocampus and amygdala have a tendency to gradually extend into more subregions (Ballmaier et al. 2008).

Morphological resilience of MDD subjects after receiving medical treatments

In this part, we analyzed group morphometric differences and drew atrophy and expansion areas between the MDD-Medicated group and HC group, obtained some preliminary evidence about morphological resilience, when comparing with results of group morphometric differences between MDD and HC groups hereinbefore. To simplify, group difference maps between MDD and HC groups are represented as "MDD" (see Fig. 7), while group difference maps between MDD-Medicated and HC groups are represented as "MDD-Medicated" (also see Fig. 7).

There are two aspects that can provide evidence for the morphological resilience of MDD-Medicated group. Firstly, relative to MDD group, MDD-Medicated group has smaller areas of significant group morphometric differences in hippocampus and amygdala when comparing with HC group (see top line of Fig. 7 a~d). Secondly, MDD-Medicated group has

smaller atrophy areas and weaker atrophic effects (see the bottom line of Fig. 7 a~d) in hippocampus and amygdala. These results suggest that hippocampus and amygdala of MDD-Medicated group are closer to HC group in morphometry, which can be understood as morphological resilience after medicated.

Discussion

There are four main discoveries in this paper. Firstly, instead of significant overall volume difference between groups, morphological alterations were more obvious in specific subregions of hippocampus and amygdala in MDD patients (Fig. 3 and Fig. 4). These morphological abnormalities at the level of subdivisions of the hippocampus (reached global significance ($p<0.05$) on both sides) and amygdala (reached global significance ($p<0.05$) on right side) to some extent reminded researchers the pathological changes in subcortical structures may be unreliable or unstable if they were speculated only from the overall volume change directions.

Secondly, although most of the areas of significant group differences were atrophy areas, we found the atrophy and expansion effects in subregions of hippocampus and amygdala exist simultaneously (Fig. 5). Different subregions of hippocampus and amygdala have different degrees of morphometric vulnerability to MDD.

Thirdly, we applied the correlation analysis between surface eigenvalues and HAMD scores, and displayed some potential but slightly morphological development trends along with HAMD scores in hippocampus and amygdala (Fig. 6).

Fourthly, we provided subregional morphometric evidence that medicated MDD patients have stronger morphometric resilience than unmedicated MDD patients (Fig. 7). Our morphometric results of MDD-Medicated group, more subtly, supported prior volume studies about recovery effects brought about by medical treatments (C. Lange and E. Irle 2004; Hamilton et al. 2008; Van et al. 2009; Malykhin et al. 2010).

Prior research and our works

Most of prior research, as we described in earlier, were mainly focusing on using volumetry methods to describe the global volume changes of hippocampus and amygdala. To be specific, Sheline et al. (1996) investigated a sample of ten women with a history of recurrent MDD and found smaller hippocampal volumes than a group of pair-wise matched normal controls. Mervaala et al. (2000) revealed significant hippocampal asymmetry (left smaller than right) in both MDD and control groups, and the present study also showed similar patterns. Using medicated subjects with similar ages to these in our study, C. Lange and E. Irle (2004) found smaller hippocampal volumes in MDD group and revealed the amygdala volume had a tendency to increase first and then continually decrease with prolonged disorder duration. Our MDD-Medicated group, in two aspects, also revealed similar mechanisms: (1) the morphometric atrophy effects in hippocampus of MDD-Medicated group are weaker than that of MDD group but still locally significant; (2) MDD-Medicated group showed weaker atrophy effects and stronger expansion effects in amygdala (Fig. 7 c~d) than MDD group.

To our knowledge, regional structural changes of hippocampus have been documented in a small amount of literatures. Based on manual segmentation, Neumeister et al. (2005) reported decreased hippocampal volume in its whole and more pronounced in the posterior region. Maller et al. (2007) divided hippocampus into head, body, and tail sections, and found local volume reductions in the most posterior region of the tail of the hippocampus in treatment-resistant depressive patients. According to the same subregion (head, body, tail) segmentation method, Malykhin et al. (2010) found significant volume reduction in the hippocampal tail bilaterally, right hippocampal head and right total hippocampus in MDD patients. Their another pivotal finding is that medicated MDD patients showed increased hippocampal body volume compared with both healthy controls and unmedicated patients. Cole et al. (2010) noted the main hippocampal body was relatively intact while deformations were evident particularly in the tail region within the subiculum and CA1 subfield but as well in the CA2–3 subfields. Together, the above two studies further enhanced the persuasiveness that different subregions of hippocampus have different degrees of vulnerability to neuronal damage associated with MDD, as well as the resilience to medication. The findings of smaller expansion areas in the CA1 subregion of left hippocampus in our MDD group also supported their conclusions. More precisely, Posener et al. (2003) indicated specific abnormalities in the subiculum of hippocampus in MDD patients, and Ballmaier et al. (2008) reported extensive morphological abnormalities in the subiculum and CA1 subregions which extended into the CA2–3 subfields in the late-life MDD patients. Our correlation analysis results in hippocampus showed similiar morphological development trends from atrophic subregions (CA1 and subiculum) into CA2–3 subregions.

Only two prior research revealed the morphological changes in the MDD amygdala. Sheline et al. (1998) confirmed that amygdala core nuclei volumes rather than mean total amygdala volumes were decreased in recurrent MDD. Then, the BLVM, CE and ME subregions of MDD amygdala were revealed pronounced in morphometric changes (Joshi et al. 2016). For all we know, our study for the first time mapped the morphological changes in the subregions of MDD amygdala. Our results showed not only morphological differences between different subregions of the same amygdala, but great asymmetry of morphological changes between the left and right amygdala when subjects encountering MDD. As pointed out in a very large sample size MDD research (Schmaal et al. 2016), the total volumes of amygdala in MDD patients have a tendency to decrease with the severity of MDD. Here we only found significant group volumetric differences in right amygdala (table 1). Obviously, when atrophy effects are highly localized, our novel features are likely to detect regional changes in amygdala that volumetric measures may miss.

Vulnerable subregions found in this study and their functions

In primates, the posterior portion of the hippocampus was thought to be more important than anterior areas for encoding of spatial memory and certain forms of nonspatial memory (Moser and Moser 2015), and it was proved mainly involved in memory retrieval in human (Lepage et al. 2015). A study assessed hippocampal function using a virtual-reality spatial memory navigation task and found that depressed patients performed significantly worse than healthy subjects on the spatial memory navigation task (Gould et al. 2007). Therefore,

the atrophy areas found in CA1 subregion in this study provided the structural explanation of impaired spatial memory. The subiculum has been specifically implicated in the retrieval of episodic recollections (Zeineh et al. 2003; Eldridge et al. 2005; Viskontas et al. 2009), and the atrophy of subiculum was showed as the earliest hippocampal anatomical marker of AD (Carlesimo et al. 2015). Memory impairments are associated with hippocampal atrophy in MDD (Golomb et al. 1993; Hickie et al. 2005). In these patterns of memory impairments, deficits in episodic memory are the most commonly reported feature for hippocampus (Tulving and Markowitsch 1998; Smith and Mizumori 2006; Mormino et al. 2009). These deficits usually become more prominent when depression transforms from first episode to recurrent (Fossati et al. 2004). Airaksinen et al. (2007) suggested that low episodic memory performance predated depressive diagnosis and might be considered as a premorbid marker of MDD. Autobiographical memory is usually described as a kind of episodic memory, and a main component of it is the recall of specific event in one's life (Brewer 1986). Many prior research have documented that individuals with MDD have difficulty in recalling specific autobiographical events (Williams and Broadbent 1986; Williams and Scott 1988), especially recalling those positive than negative memories (Lemogne et al. 2006). Together, these atrophy areas found in CA1 and subiculum subregions of hippocampus (Fig. 5) in the present study provided morphological evidence to the underlying causes of impaired spatial memory and episodic memory in MDD patients. Combining with our correlation analysis results (Fig. 6), these extending trends of atrophy areas in MDD group from subiculum and CA1 subregions to others (CA2 and CA3) may predict the latter damages to other hippocampus-dependent subregional functions, such as sociocognitive memory processing (Hitti and Siegelbaum 2014), resistance to cell death (Dudek et al. 2016), fear memory retrieval (Sun et al. 2017) and object mnemonic discrimination (Reagh et al. 2018).

In amygdala, the LA subregion is a crucial site of neural changes that occur during fear conditioning (Ledoux et al. 1990; Rodrigues et al. 2004). The BL subregion mainly involved in unconscious processing modulated activity (Etkin et al. 2004), while the VM subregion might be pivotal for controlling the predatory behavior (Fonberg 1981). The ACO subregion mainly involves in generating innate odour-driven behaviors (Root et al. 2014) and the AAA subregion initiates defensive and aggressive responses elicited by olfactory (Cádiz-Moretti et al. 2017). Besides, the ASTR subregion is engaged in distinct forebrain circuits (Shammah-Lagnado et al. 1999), while the CE subregion is required for fear acquisition, whereas conditioned fear responses are driven by output neurons in the ME subregion (Ciocchi et al. 2010). Previous research revealed that even higher familial risk in MDD seems to be associated with smaller amygdala volumes (K et al. 2012). Observed by Dannlowski et al. (2007), the hyperactivity in right amygdala could be a determinant for a more severe depression course. Combining the above two studies and our asymmetrical results in amygdala morphometry (Fig. 4 and Fig. 5), it is suggested the functional hyperactivity in the right amygdala may be a potential compensation mechanism for its volume decrease. A prior research observed the significant activity in right amygdala in the negative-word/self-reference condition and in left amygdala in positive-word/self-reference condition (Yoshimura et al. 2009). Abercrombie et al. (1998) revealed that metabolic rate in the right amygdala was positively correlated with negative affect of MDD patients. As a result, the biased morphological changes found in MDD amygdala in this study structurally revealed

the typical emotional feature of MDD patients — positive emotion diminishes while negative emotion elevates (Silk et al. 2003; Liverant et al. 2008; Heller et al. 2009). Additionally, Phelps et al. (2001) and Zald (2003) have suggested that the right amygdala responds to unanticipated or unconscious processing of emotional stimuli. The hyperactivity of unconscious rapid path to the right amygdala in MDD patients sometimes may lead to perception of threats when none exist (Ahmari 2015). Correlation analysis results (Fig. 6) showed that the strong atrophy subregions of amygdala have slightly tendencies of expanding into ME, AB and PCO subregions, these may indicate further pathological alterations induced by MDD.

Limitations

There are several limitations in this study. First, the group size may be further improved, larger sample size may provide stronger statistical effects. Second, our study is cross-sectional. Longitudinal and follow-up subjects are needed in further study to determine the possible causative mechanisms in subregions, such as apoptosis and decreased neurogenesis (Lucassen et al. 2006), which may be driven by hypercortisolemia or diminished neurotrophin levels (Czéh and Lucassen 2007). Third, we did not collect genetic data and ignored these environmental factors that caused MDD. A prior research identified some gene-based associations to the presence of depressive symptoms in older adults (Nho et al. 2015). Some other studies (Caspi et al. 2003; Lesch 2004; Uher 2008; Schnittker 2010) found the gene-environment interactions play a crucial role in understanding why stressful experiences lead to MDD in some people but not in others. For example, the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on MDD (Caspi et al. 2003).

Conclusion

Although some limitations exist, we found the subiculum and CA1 subregions of bilateral hippocampus, the LA and BLVM subregions of left amygdala and the LA, BLVM, CE, ASTR, ACO and AAA subregions of right amygdala were more vulnerable than other subregions in MDD patients. Our correlation analysis results supported the vulnerability of these atrophy subregions and revealed some potential morphological development trends in MDD hippocampus and amygdala. Comparing results between MDD-Medicated group and MDD group, we provided some preliminary evidence that medicated MDD patients have stronger morphological resilience in hippocampus and amygdala. Our research can serve as a cohesive force which gradually convert volumetric research of MDD subcortical structures into subregional studies.

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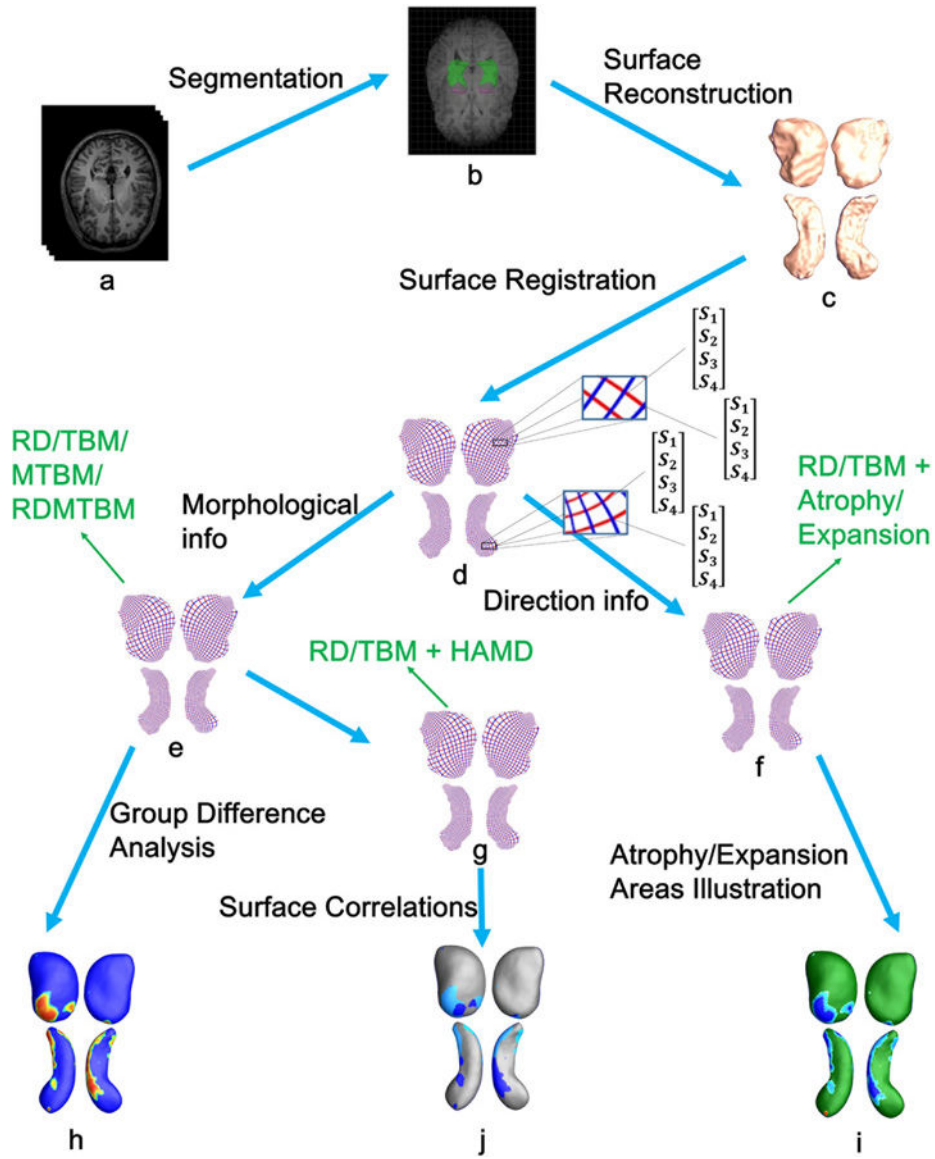
Fig. 1.

For simplicity, only the surfaces of left amygdala and hippocampus are used for illustration. In the pipeline, letters **a—j** represent: **a** T1-MR images; **b** subcortical structure segmentation; **c** reconstruction of 3D surface models; **d** one-to-one correspondence obtained from surface registration; **e** surface morphological information acquisition; **f** combine RD/TBM values with atrophy/expansion areas calculated by expression (2) and (3); **g** combine RD/TBM values with HAMD scores; **h** group difference analysis; **i** the atrophy and expansion areas of MDD group versus HC group; **j** the correlation analysis between each MDD subject's surface eigenvalues (RD/TBM) and their HAMD scores.
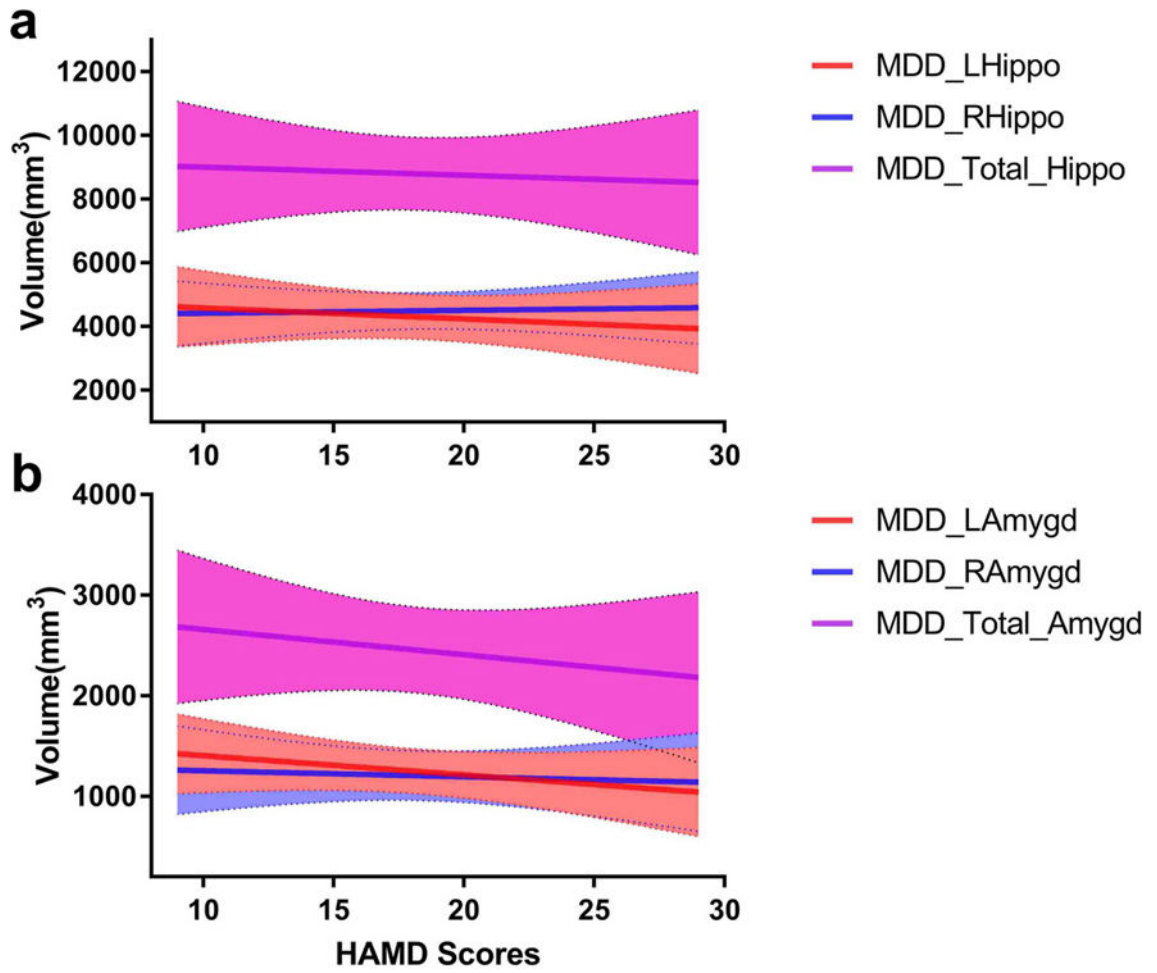
Fig. 2.
a Left, right and total hippocampal volume distributions along with HAMD scores in the MDD group. **b** Volume distributions of left, right and total amygdala along with HAMD scores in MDD group.
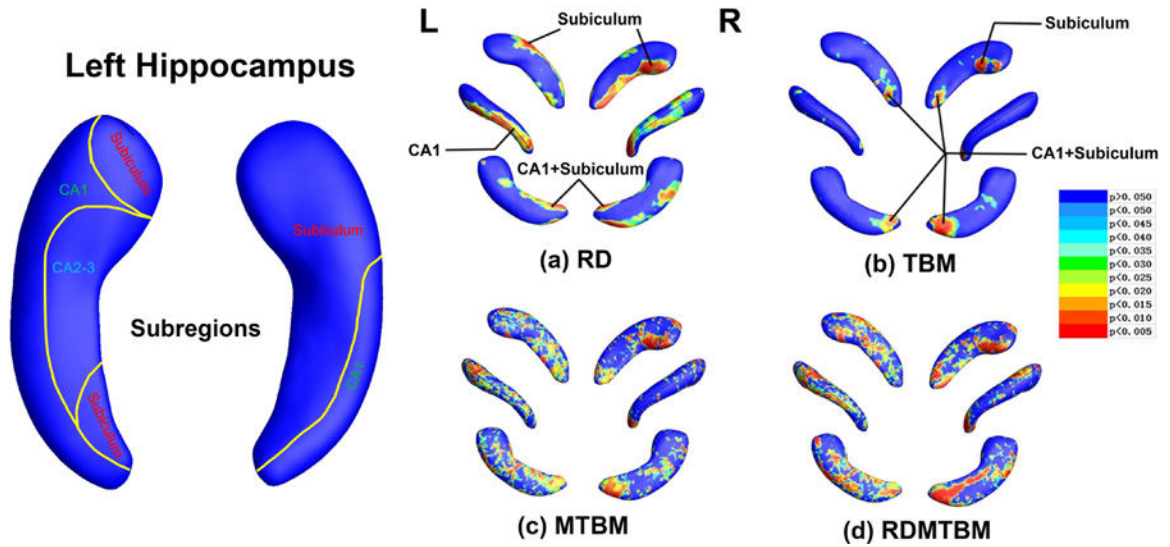
Fig. 3.

Hippocampus statistical *p* maps: overall *p*-values are $p = 0.0253$ and $p = 0.0044$ for left and right hippocampus RD (**a**), $p = 0.0823$ and $p = 0.0283$ for left and right hippocampus TBM (**b**), $p = 0.0093$ and $p = 0.0147$ for left and right hippocampus MTBM (**c**), $p = 0.0080$ and $p = 0.0067$ for left and right hippocampus RDMTBM (**d**). **L**, left; **R**, right.
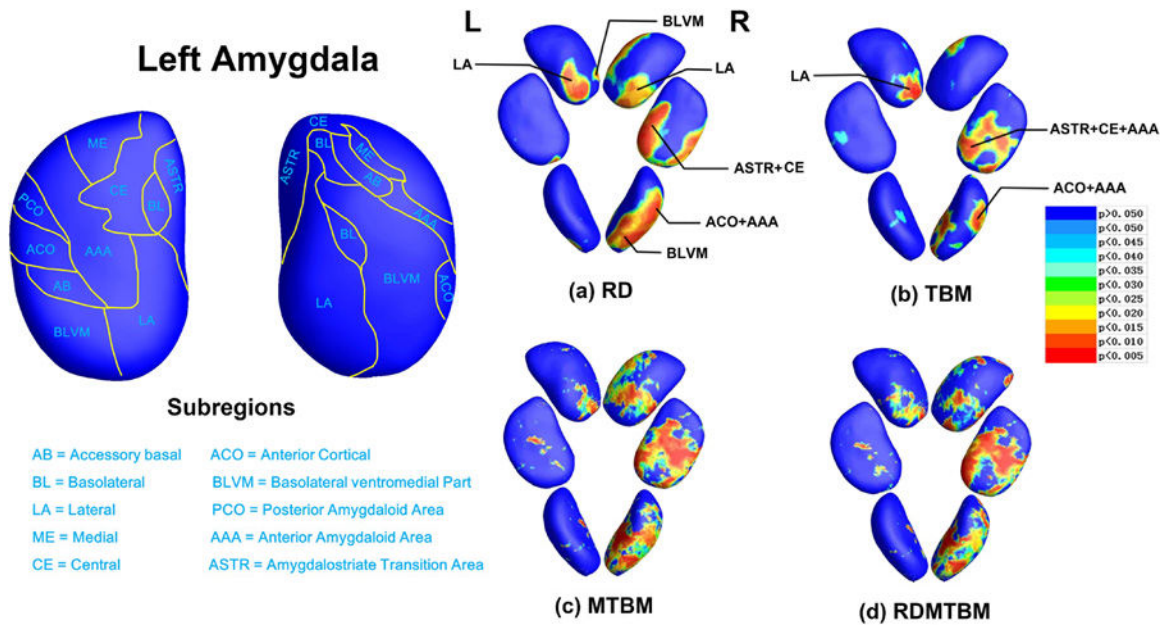
Fig. 4.

Amygdala statistical *p* maps: overall *p*-values are *p* = 0.1306 and *p* = 0.0086 for left and right amygdala RD (**a**), *p* = 0.1866 and *p* = 0.0467 for left and right amygdala TBM (**b**), *p* = 0.1552 and *p* = 0.0147 for left and right amygdala MTBM (**c**), *p* = 0.1241 and *p* = 0.0094 for left and right amygdala RDMTBM (**d**). **L**, left; **R**, right.
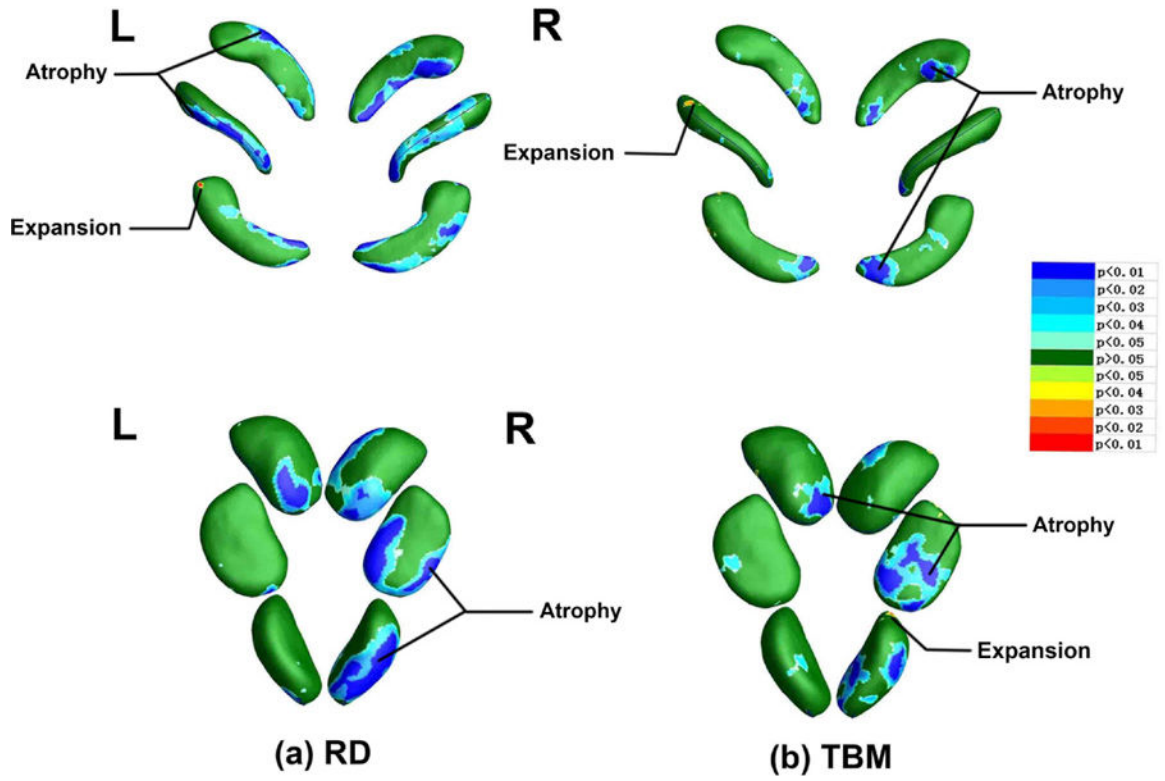
Fig. 5.
a Atrophy and expansion areas of hippocampus and amygdala in radial distance. **b** Atrophy and expansion areas of hippocampus and amygdala in det*J*. The cold colors represent atrophy areas, while warm colors represent expansion areas.
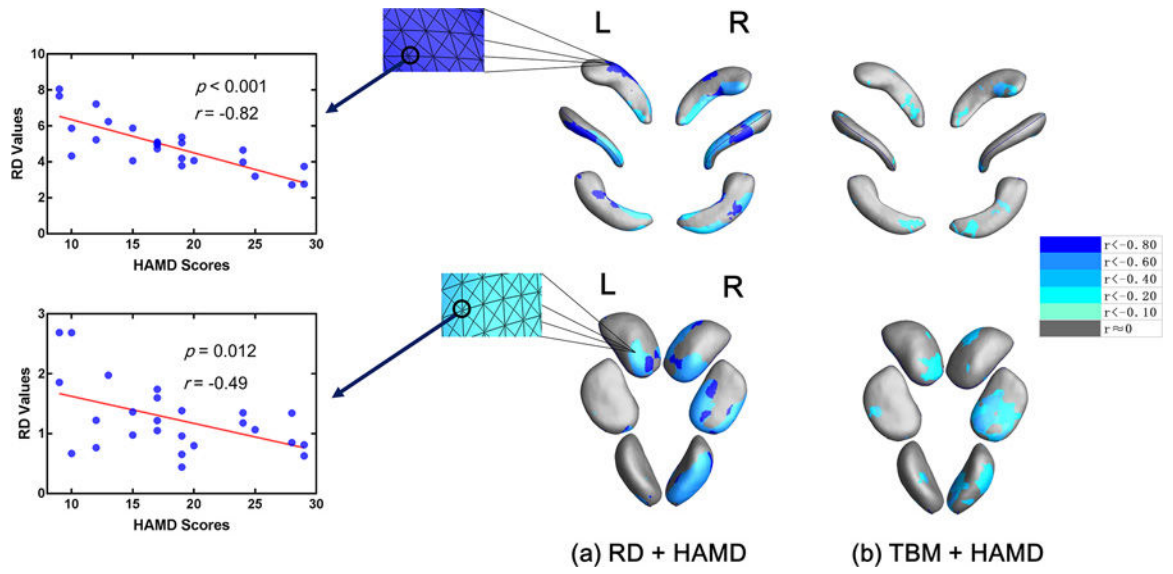
Fig. 6.

a Correlation areas of hippocampus and amygdala in radial distance. **b** Correlation areas of hippocampus and amygdala in det*J*. Negative correlation enhanced when colors changing from grey to blue.
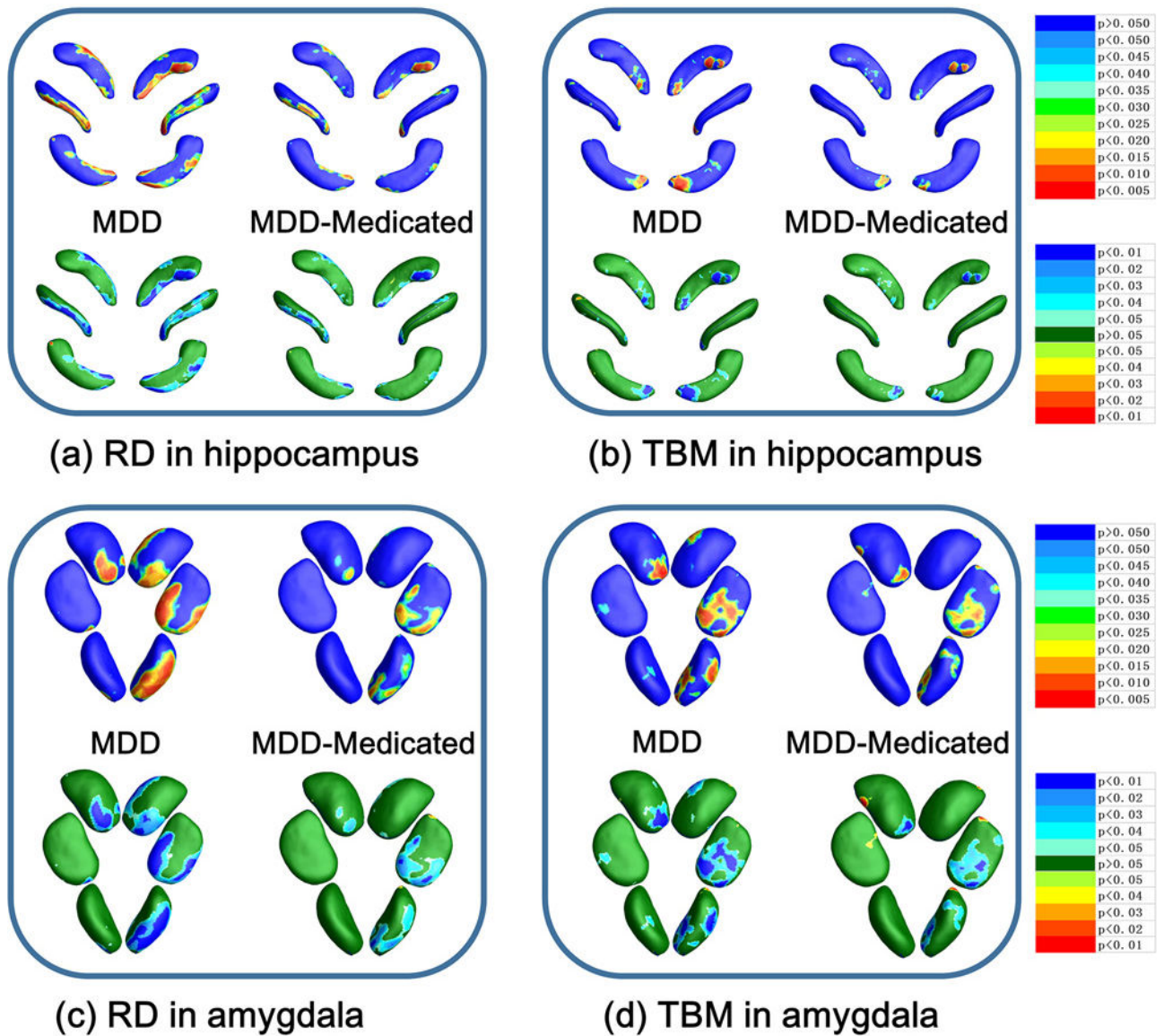
Fig. 7.

a RD results of MDD group vs. MDD-Medicated group in hippocampus. **b** TBM results of MDD group vs. MDD-Medicated group in hippocampus. **c** RD results of MDD group vs. MDD-Medicated group in amygdala. **d** TBM results of MDD group vs. MDD-Medicated group in amygdala. Hippocampus statistical p maps in MDD-Medicated group: overall p-values are $p = 0.0533$ and $p = 0.0616$ for left and right hippocampus RD (**a**), $p = 0.1787$ and $p = 0.1751$ for left and right hippocampus TBM (**b**). Amygdala statistical p maps in MDD-Medicated group: overall p-values are $p = 0.6572$ and $p = 0.0535$ for left and right amygdala RD (**c**), $p = 0.3033$ and $p = 0.0384$ for left and right amygdala TBM (**d**).

Table 1

Demographic and clinical data of participants

Variables	MDD ($N = 25$)		MDD-Medicated ($N = 19$)		HC ($N = 28$)		MDD vs. HC	MDD-Medicated vs. HC
	Mean	(SD)	Mean	(SD)	Mean	(SD)	$P*$	$P*$
Ages(years)	36.6	12.8	36.2	12.8	34.3	12.4	NS	NS
Sex	15 (60%) men		12 (63.2%) men		15 (53.6%) men		NS#	NS#
HAMD	18.2	6.4	18.1	6.3	0.8	1.4	<0.001	<0.001
TSD(years)	6.4	6.0	7.2	6.5	0	0	<0.001	<0.001
THV(mm^3)	8798.2	2710.5	8998.4	2704.3	9863.1	1743.8	NS	NS
LHV(mm^3)	4303.5	1687.2	4280.8	1472.4	4701.4	991.6	NS	NS
RHV(mm)	4494.7	1351.2	4717.6	1337.3	5161.7	926.6	NS	NS
TAV(mm)	2453.3	1023.1	2702.4	1006.9	2916.1	702.8	NS	NS
LAV(mm)	1247.7	540.7	1388.5	530.9	1405.3	349.9	NS	NS
RAV(mm)	1205.6	583.9	1313.9	589.1	1510.7	511.3	0.048	NS

SD Standard Deviation, *NS* Not Significant, *TSD* Time Since Diagnosis, *THV* Total Hippocampus Volume, *LHV* Left Hippocampus Volume, *RHV* Right Hippocampus Volume, *TAV* Total Amygdala Volume, *LAV* Left Amygdala Volume, *RAV* Right Amygdala Volume

P^* Student's *t*-test for independent samples

$NS^\#$ χ^2 test