



Review

Mapping the depressed brain: A meta-analysis of structural and functional alterations in major depressive disorder

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ABSTRACT

Background: Depression has a lifetime prevalence of up to 20%. Neuroimaging methods have revealed various structural and functional changes that occur in a human brain during a depressive episode. However, we still lack information concerning the extent to which structural and functional changes co-occur in a depressed brain. Furthermore, it is difficult to evaluate from a merely qualitative literature review what regional brain changes in volume and activation are robust across depressed patient samples and consistent across imaging centers. **Methodology and principle findings:** This study is a meta-analysis from 10 selected studies published previously. We applied the statistical anatomical/activation likelihood estimate method (ALE) in a total of 176 depressed patients and 175 controls for the MRI modality and in a total of 102 depressed patients and 94 controls for the PET modality to quantitatively identify those brain regions that show concordant alteration in the midst of a depressive episode across imaging modalities and study sites. We find a convergent change in the limbic-cortical brain circuit in depression compared to controls of both Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) data. The specific changes include lower gray matter volumes in the amygdala, the dorsal frontomedian cortex, and the right paracingulate cortex, as well as increases in glucose metabolism in the right subgenual and pregenual anterior cingulate cortices.

Conclusions/significance: Our current findings represent an important first step towards a more focused approach to neuroimaging unipolar depression. The regions identified could serve as a specific region-of-interest-for-disease template for both individual in vivo imaging studies and postmortem histopathologic exploration.

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1. Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder, defined as a period of at least two weeks of sustained depressed mood and/or anhedonia (Kessler et al., 2005). With a lifetime prevalence for MDD as high as 20% worldwide (Kessler et al., 2005), and treatment resistance contributing significantly to the burden of disease, there is substantial need for a better understanding of the underlying pathophysiology as well as for a better characterization of the structural, and functional neural correlates of depressive symptoms. In the last decade an impressive body of data has been gathered on morphological and functional brain changes characteristic for depression. Above all there is a clear need to link findings derived from different techniques in order to extract the essential comprehensive information to advance the field. To the best of our knowledge, no meta-analysis investigating both change in voxel-based morphometry and alteration in cerebral glucose-metabolism has been conducted for the unipolar depressed brain thus far.

Meta-analyses are essential for reviewing findings from different studies, comparing results in a standardized fashion, and summarizing statistical relations between study characteristics and findings. The anatomical/activation likelihood estimate (ALE) method (Eickhoff et al., 2009; Schroeter et al., 2007; Turkeltaub et al., 2002) goes beyond qualitatively pooling results from diverse neuroimaging studies. This method quantitatively models reported brain coordinates and analyzes the locations on where individual peak coordinates converge in a standard brain space. Concordance between studies is identified by creating statistical probability maps as a measure of likelihood of morphological change/activation on a voxel-wise level across the entire set of studies entering the meta-analysis. Of relevance to the current application, ALE has been previously applied with success in neuropsychiatric populations (Delaveau et al., 2011; Fitzgerald et al., 2008; Schroeter et al., 2007, 2009).

One recent study has used this method to look at functional activation changes in MDD at rest, after treatment, and during emotion-induction (Fitzgerald et al., 2008), and reported only limited overlap between the different designs. A second study has focused on the effect of antidepressant treatment pooling functional studies in depressed patients pre- and post-treatment identifying areas regulated by effective clinical treatment (Delaveau et al., 2011). To characterize the neural correlates of the unmedicated disease we chose a different selection of studies: We compared both Voxel Based Morphometric (VBM) Magnetic Resonance Imaging (MRI) studies investigating structural changes associated with MDD and functional (^{18}F)-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) studies designed to detect differences in glucose-metabolism at rest in depressed versus healthy brain. Both approaches do not involve functional paradigms to elicit

brain activation, which potentially bias imaging results, and we limited our selection to studies that reported brain coordinates from whole-brain analyses.

2. Methods

According to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher et al., 2009), we conducted multiple Medline searches to identify all neuroimaging PET and MRI studies of MDD from 2000 to 2009. 529 studies were initially identified. After limiting the results by criteria described below, ten studies were considered eligible to enter the meta-analysis: four FDG-PET studies during rest and six VBM-MRI studies, in a total of 176 depressed patients and 175 controls for the MRI modality and in a total of 102 depressed patients and 94 controls for the PET modality (more detailed information on the included studies can be found in Table 1).

Keywords used in the search were (PET, positron-emission-tomography, OR MRI, Magnetic Resonance Imaging) AND (MDD, major depressive disorder). Additionally, we searched the reference lists of identified articles and reviews. Studies had to fulfill the following criteria: (1) peer-reviewed original research articles, (2) diagnosis according to internationally recognized diagnostic criteria, (3) reported age-matched control group, and (4) results reported as coordinates in a normalized standard stereotactic space (Talairach or Montreal Neurological Institute (MNI) reference system). Studies had to be available in English language, and involve adult human subjects (age limit: 19 years or above). Studies reporting only results pre- and post-antidepressive treatment but no healthy control group, or reporting post-medication effects only were excluded. Region-of-interest studies were excluded to enable a data-driven whole-brain approach for the meta-analysis. The literature search, selection of studies according to the inclusion and exclusion criteria, and compilation of coordinates for the contrasts were performed independently by two investigators.

For the PET studies, a total of 13 peak coordinates were reported for changes in brain metabolism. All PET studies reported medication-free MDD patients and contrasted alteration of glucose metabolism in MDD patients versus control subjects. For the VBM studies, a total of 27 peak coordinates were reported for morphological brain changes. Two VBM studies reported medication-free MDD patients whereas five included patients on antidepressant medication. One study reported findings for remitted depressed patients – all other patient samples were acutely depressed when scanned. The morphological changes reported were consistently volume decreases in patients versus controls, thus medication does not seem to introduce a bias towards the direction of the structural change.

Table 1
Studies included in meta-analysis.

Study	Disorder	Sample size subjects vs controls	Mean age \pm SD	Mean depression score \pm SD	Medication
<i>Voxel Based Morphometric (MRI) studies</i>					
Zou et al., Biol Psych, 2010 (Zou et al., 2010).	Major depressive disorder (MDD), unipolar	23 vs 23	31 \pm 10 vs 37 \pm 13	HDRS ^a : 24 \pm 4	Medication naive
Bergouignan et al., Neuroimage, 2009 (Bergouignan et al., 2009).	Major depressive disorder (MDD), unipolar	21 vs 21	33 \pm 10 vs 28 \pm 6	BDI ^b : 19 \pm 5, MADRS ^c : 29 \pm 7	Antidepressant therapy, no specific information
Frodl et al., Mol Psych, 2008 (Frodl et al., 2008).	Major Depressive Disorder (MDD), unipolar	77 vs 77	43 \pm 12 vs 41 \pm 12	HDRS ^a : 23 \pm 6	16 medication free, others: SSRIs, tricyclic antidepressants and others
Kim et al., Psych Res, 2008 (Kim et al., 2008).	Major Depressive Disorder (MDD), unipolar	22 vs 25	39 \pm 10 vs 35 \pm 11	BDI ^b : 22 \pm 14	10 on psychotropic medication
Yuan et al., Biol Psychiatry, 2008 (Yuan et al., 2008).	Remitted geriatric depression, unipolar	19 vs 16	67 \pm 7 vs 68 \pm 4	HDRS ^a : 3 \pm 2	Medication free for 3 months
Tang et al., Psych Res, 2007 (Tang et al., 2007).	Major Depressive Disorder (MDD), unipolar	14 vs 13	30 \pm 7 vs 30 \pm 7	HDRS ^a \geq 18	Medication naive
<i>Glucose utilization (¹⁸F-FDG-PET) studies</i>					
Saxena et al., Biol Psych, 2001 (Saxena et al., 2001).	Major depressive disorder (MDD), unipolar	27 vs 17	38 \pm 11 vs 33 \pm 12	HDRS ^a : 21 \pm 5	Medication naive or free for >1 year
Kimbrell et al., Biol Psych, 2002 (Kimbrell et al., 2002).	Major depressive disorder (MDD), unipolar	27 vs 17	43 \pm 13 vs 43 \pm 13	HDRS ^a : 17 \pm 8	Medication free for \geq 2 weeks, 1 medication naive.
Brody et al., Arch Gen Psy, 2001 (Brody et al., 2001).	Major depressive disorder (MDD), unipolar	24 vs 16	39 \pm 11 vs 36 \pm 18	HDRS ^a : 19 \pm 5	Medication free for \geq 2 weeks
Kennedy et al., Am J Psychiatry, 2001 (Kennedy et al., 2001).	Major depressive disorder (MDD), unipolar	13 vs 24	37 \pm 9 vs 32 \pm 7	HDRS ^a : 22 \pm 4	Medication free for \geq 4 weeks

MRI: Magnetic Resonance Imaging; ¹⁸F-FDG-PET: ¹⁸F-fluorodeoxyglucose positron emission tomography.

^a HDRS: Hamilton Depression Score.

^b BDI: Beck Depression Inventory.

^c MADRS: Montgomery and Asberg Depression Rating Scale.

The software GingerALE (<http://brainmap.org/ale/index.html>) was used for the transformation of all reported coordinates into stereotactic standard Talairach and Tournoux space (Talairach and Tournoux, 1988). Coordinates reported in MNI space were converted to Talairach coordinates. The method we used for our meta-analysis is a variation of Activation Likelihood Estimation published originally by Turkeltaub et al. (2002). An improved version of this method was published by Eickhoff et al. (2009). The improvements include the adaptive estimation of the width of the Gaussian for each included experiment and the possibility to perform a random-effects analysis. ALE is frequently referred to as Anatomical Likelihood Estimation when applied to brain volumetric data and comparable in nature to Multilevel Kernel Density Analysis (MKDA) (Wager et al., 2009) and Signed Differential Mapping (SDM) (Radua and Mataix-Cols, 2009).

For each experiment every reported maximum was modeled by a 3-dimensional Gaussian probability distribution centered at the given coordinate. The width of the Gaussian probability distribution was determined individually for each experiment based on empirical estimates of between-subject variability taking into account the number of subjects in each experiment (Eickhoff et al., 2009). For each voxel, ALE was calculated from the union of the Gaussian probability distribu-

tions associated with the different foci. In a random effects analysis, ALE values were combined across experiments and tested against a null hypothesis of random distribution of ALE values (Eickhoff et al., 2009), thereby identifying those regions where empirical ALE values were higher than could be expected by chance. The resulting ALE map was thresholded at $p < 0.05$ (corrected for multiple comparisons by false discovery rate). Statistically significant voxels represent the convergence of the investigated effect across the several studies. We calculated ALE maps separately for FDG-PET and VBM-MRI studies. ALE results were overlaid onto an optimized individual anatomical T1-template (www.brainmap.org/ale/Colin1.1.nii) and cluster centers were anatomically located in Mango (<http://ric.uthscsa.edu/mango>), a neuroimage viewing tool developed by Lancaster and Martinez (Lancaster et al., 2010).

3. Results

As illustrated in Fig. 1 we found significant decreases in morphological volumes within the corticolimbic circuit, a network relevant to MDD, including left amygdala (cluster-size: 744 mm³, center: x: -13.93, y: -2.93, z: -10.99, with a maximum ALE value of 0.0028), left dorsal frontomedian cortex (BA 8, cluster-size; 480 mm³, center: x: -1.01, y: 24.01, z: 47.99,

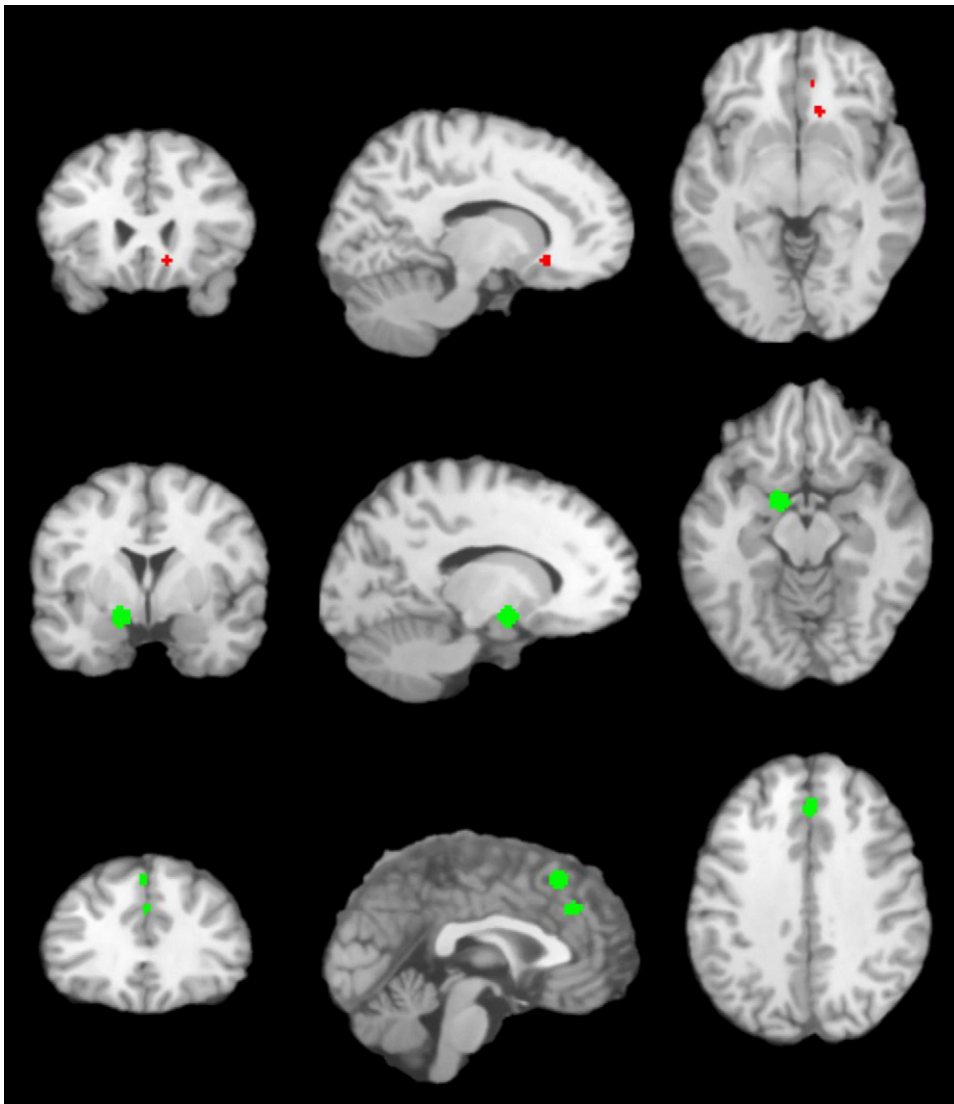


Fig. 1. Patterns of regional decreases in gray matter volume (green) and regional increases in glucose metabolism (red) in depressed patients at rest, rendered onto a single subject brain (images are neurological). Fig. 1, top panel, illustrates the following cluster for the analyzed PET foci in red: (1) an 80 mm³ cluster in the right subgenual anterior cingulate cortex (sACC; center: x: 11.82, y: 20.53, z: -4) with a maximum ALE value of 0.0013, and (2) an 80 mm³ cluster in the right pregenual anterior cingulate cortex (center: x: 8.18, y: 35.47, z: -4) with a maximum ALE value of 0.0013. Middle and bottom panels of Fig. 1 illustrate the following clusters for the analyzed VBM foci in green: (1) an 744 mm³ cluster in the left amygdala (center: x: -13.93, y: -2.93, z: -10.99) with a maximum ALE value of 0.0028, (2) a 480 mm³ cluster in the left dorsal frontomedian cortex (center: x: -1.01, y: 24.01, z: 47.99) with a maximum ALE value of 0.0025, and (3) a cluster of 360 mm³ in the right paracingulate cortex (center: x: 1.45, y: 32.17, z: 32.53) with a maximum ALE value of 0.0018.

with a maximum ALE value of 0.0025), and right paracingulate cortex (BA 9, BA 32; cluster size: 360 mm³, center: x: 1.45, y: 32.17, z: 32.53, with a maximum ALE value of 0.0018). No brain regions were identified which showed gray matter increases in MDD.

Additionally, we observed increases in glucose metabolism in MDD in the right subgenual and pregenual anterior cingulate cortices (cluster sizes: 80 mm³: sACC, BA 25, center: x: 11.82, y: 20.53, z: -4, with a maximum ALE value of 0.0013 and BA32, center: x: 8.18, y: 35.47, z: -4, with a maximum ALE value of 0.0013) as can be viewed in Table 2.

4. Discussion

In summary, our results identify regions within the limbic-cortical circuit that in MDD are consistently affected by decreases in gray matter volume and changes in glucose metabolism during rest. The consistent decrease in amygdala volume we observe is in line with evidence from specific region-of-interest analysis of the amygdala in unmedicated MDD-patients (Hamilton et al., 2008) and complemented by findings in postmortem brains of patients who had suffered from unipolar depression (Altschuler et al., 2010; Bowley et al.,

Table 2

Overview of ALE (anatomical likelihood estimate) analysis in human depressed versus healthy brains: Voxel Based Morphometric (VBM) Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) studies in MDD (major depressive disorder) during rest.

Region	Hemisphere	BA (Brodmann area)	Volume (mm ³)	Weighted center (x, y, z) ^a			Max ALE value
<i>Areas of decreased volume in patients</i>							
Dorsal frontomedian cortex	L	8	480	−1.01	24.01	47.99	0.0025
Paracingulate cortex	R	9, 32	360	1.45	32.17	32.53	0.0018
Amygdala	L		744	−13.93	−2.93	−10.99	0.0028
<i>Areas of increased metabolism in patients</i>							
Pregenuar anterior cingulate cortex	R	32	80	8.18	35.47	−4	0.0013
Subgenual anterior cingulate cortex	R	25	80	11.82	20.53	−4	0.0013

^a Coordinates in Talairach Atlas space.

2002). Additional evidence for specific morphometric changes in the frontal cortex can be derived from histopathological studies (Rajkowska et al., 1999), revealing abnormal cytoarchitecture in frontal cortical regions in subjects with MDD. Such neuroplastic changes could cause a potential dysregulation in the fronto-limbic circuit supporting the histopathologically generated hypothesis of disease-specific glial pathology in depression (Schroeter et al., 2008, 2010).

The overall in-vivo human data investigating amygdala-morphology in unipolar depression has yielded conflicting results thus far. The data from studies on acutely depressed patients versus healthy controls show both increased (Frodl et al., 2002, 2003; Lange and Irlle, 2004; van Eijndhoven et al., 2009; Weniger et al., 2006), and reduced (Frodl et al., 2008; Hastings et al., 2004; Tang et al., 2007) amygdala volumes. A hypothesis that could potentially consolidate these heterogeneous findings builds upon data that shows amygdala volumetric enlargements in a sample of first episode versus recurrent MDD patients (Frodl et al., 2002) and takes into account the trend for chronic depression or multiple depressive episodes to be associated with gray matter loss of the amygdala (Hamilton et al., 2008; Lorenzetti et al., 2009; Sheline et al., 1998) thereby supporting the concept that volumetric alterations of the amygdala in unipolar MDD could be interpreted as state related.

A second interesting result from our analysis is the glucose-hypermetabolism found in the sACC of unmedicated depressed patients at rest. This brain region has mainly been associated with sadness (Vogt, 2005), and has been implicated in MDD previously (Drevets et al., 1992) but with somewhat inconsistent observations: While most reports describe a correlation of symptom severity with increased glucose utilization in the sACC (Bench et al., 1993; Drevets et al., 1999; Mayberg et al., 1997; Osuch et al., 2000), there is some evidence describing an inverse relationship of functional glucose hypometabolism in the sACC with depression scores, reviewed by Price and Drevets (2010). One possible way to consolidate those differences would be to understand the increase in glucose-metabolism in this brain region as an initial compensatory mechanism that occurs during the beginning of the disease and in an unmedicated state. This concept is supported by studies that report increases in perfusion in this region when inducing sadness in healthy controls (Liotti et al., 2002). Tryptophan depletion in patients with remitted depression has also been shown to result in increased metabolism in the sACC (Neumeister et al., 2004), interestingly in this data set the abnormalities in glucose metabolism were independent of recurrence of mood-symptoms. The authors suggest that this finding points toward a trait abnormality in the

pathogenesis of MDD that can be unmasked by tryptophan depletion. sACC-hypermetabolism has also been discussed as a potential predictor of treatment response as there is substantial evidence showing the increase in glucose utilization in this region to be reversible with response to antidepressants (Mayberg et al., 1997, 2000).

As glucose metabolism pattern in the sACC is also affected according to medication, and response to treatment, a more heterogeneous pattern in glucose-utilization depending upon the progression of the disease is expected to contribute to the challenge of consolidating these findings from different study designs. Thus, more studies addressing this question in a homogenous population of unipolar depressed patients in a longitudinal design are warranted.

The peak in regional metabolism in the sACC is particularly interesting to discuss in light of the revealed morphometric findings in the amygdala: using advanced gray matter parcellation methods based on tractography (Anwander et al., 2007; Johansen-Berg et al., 2004) anatomical connectivity between the sACC and the amygdala has previously been investigated in the human brain in vivo (Johansen-Berg et al., 2008). The authors found anatomical connections between the sACC and the amygdala (Johansen-Berg et al., 2008), results that are complemented by the clusters identified in our quantitative meta-analysis, as well as in a path-modeling meta-analysis (Seminowicz et al., 2004). One plausible explanation integrating findings from both imaging modalities suggests that a decrease in gray matter volume in the amygdala is compensated by an increased glucose-metabolism in the sACC. This modulation might be viewed as the brain's adaptive compensatory reaction at the beginning of a depressive episode; which, when continued for a prolonged period, could induce neuroplastic changes in amygdala-volume. To adequately explore these assumptions, standardized and well-controlled longitudinal studies applying both FDG-PET and VBM-MRI in MDD patients are needed.

Several limitations need to be considered in the interpretation of these results. Firstly, only a small number of studies have examined brain activation using FDG-PET at rest or changes in gray matter volume using MRI voxel-based morphometry in homogenous patient samples and performed analysis on a whole-brain level reporting coordinates in standard space. While it would be preferable to include a larger number of studies, we believe that it is important to apply consistent criteria for the inclusion of studies in such a quantitative review to obtain truly disease-specific results that capture the essential neural correlate characteristics for

the phenotype of a depressive episode. We acknowledge the pilot character of our data-set and view this study as a first step towards a systematic quantification of the brain changes in the midst of a depressive episode.

Partial volume effects (PVE) could confound the findings of increased activity in brain regions that are smaller than two times the full-width-half-maximum (FWHM) of the PET camera used for the glucose-utilization studies (Rousset et al., 1998). The sACC is such a small brain region and PVE could cause spill-over effects. However, PVE would rather be expected to result in underestimating glucose-metabolism in the ACC (Drevets et al., 2008). Additionally, studies exploring the effects of successful antidepressive treatment including pharmacologic intervention (Mayberg et al., 2000), psychotherapy (Goldapple et al., 2004), deep brain stimulation (DBS) (Mayberg et al., 2005), and electroconvulsive therapy (ECT) (Nobler et al., 2001) have demonstrated the increase in brain metabolism in this region to be reversible. These results argue for an actual increase in glucose metabolism in this region in an unmedicated state of the disease.

In conclusion, our data involving a large cohort of a homogenous unipolar depressed patient population provide a compelling first quantitative framework for a dysfunctional sACC-amygdala circuit that has been discussed in the pathophysiology of MDD. Future studies are warranted that are carefully designed to provide more functional and structural data at rest and in an unmedicated state to maximize the benefit from the novel statistical ALE method to generate a region-of-interest-for-disease template for unipolar depression.

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Conflict of interest

None.

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