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ORIGINAL ARTICLE

Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis

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Antidepressants are widely used in clinical practice for the treatment of depression and other mood disorders. Numerous neuroimaging studies have recently examined how antidepressants influence emotional processes. However, both clinical trials and neuroimaging studies have reported inconsistent responses to antidepressants. Moreover, the neuropsychological mechanisms by which antidepressants act to improve depressive features remain underspecified. This systematic meta-analysis summarizes pharmacological neuroimaging studies (before February 2013) and the antidepressant effects on human brain activity underlying emotional processes. Sixty fMRI studies (involving 1569 subjects) applying antidepressants vs control were included in the current quantitative Activation Likelihood Estimation (ALE) meta-analysis. Pooling of results by ALE meta-analyses was stratified for population (mood disorder patients/healthy volunteers), emotional valence (positive/negative emotions) and treatment effects (increased/decreased brain activity). For both patients and healthy volunteers, the medial prefrontal and core limbic parts of the emotional network (for example, anterior cingulate, amygdala and thalamus) were increased in response to positive emotions but decreased to negative emotions by repeated antidepressant administration. Moreover, selective antidepressant effects were uncovered in patients and healthy volunteers, respectively. Antidepressants increased activity in the dorsolateral prefrontal (dlPFC), a key region mediating emotion regulation, during both negative and positive emotions in patients. Repeated antidepressant administration decreased brain responses to positive emotions in the nucleus accumbens, putamen, medial prefrontal and midbrain in healthy volunteers. Antidepressants act to normalize abnormal neural responses in depressed patients by increasing brain activity to positive stimuli and decreasing activity to negative stimuli in the emotional network, and increasing engagement of the regulatory mechanism in dlPFC.

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INTRODUCTION

Depression is a prevalent and debilitating public health problem, affecting more than 16% of adults during their lifetime.[1,2] Antidepressant medication is widely used as the current standard treatment for depression.[3] Antidepressants may improve depressive symptoms by acting on emotional neural systems.[4,5] Numerous neuroimaging studies have recently examined antidepressant effects on emotional processing. However, clinical trials have reported varying therapeutic responses to antidepressant treatment in depressed patients.[6,7] Neuroimaging studies have also reported inconsistent antidepressant effects on activity in emotion-related brain regions.[8,9] To date, the neuropsychological mechanism by which antidepressants act to improve depressive features remains underspecified. For example, it is unclear whether antidepressants alter emotional states by reducing negative emotional neural processes, increasing positive emotional processes or both. Thus, the current study employs meta-analytic techniques to help specify neuropsychological mechanisms underlying antidepressant effects.

Negative emotional bias and anhedonia (inability to obtain pleasure from natural rewards, decreased interest in most activities) are two core features of depression. Depressed patients pay more attention to negative emotions,[10] remember negative affective materials better[11,12] and are more likely to classify ambiguous/neutral faces as negative faces.[13–15] Moreover, depressed patients exhibit an attentional bias away from positive emotions,[16] interpret happy faces as neutral faces, fail to experience pleasure from activities they previously experienced as rewarding[17] and lack reward-motivated behaviors.[18] Consistent with these behavioral findings, functional neuroimaging studies have shown abnormal neural responses to emotional processing in depressive patients[19–24] in brain regions associated with emotion, such as the amygdala, nucleus accumbens (NAcc), insula, anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC).[25–28] A recent meta-analysis revealed that the mood-congruent emotion processing bias was mediated by hyperactivation to negative and hypoactivation to positive stimuli particularly in the amygdala, insula, parahippocampal gyrus, fusiform gyrus and putamen.[22] Anhedonia severity in depressive patients was positively correlated with neural responses to positive pictures in OFC, mPFC, middle temporal and ACC but negatively correlated with activity to positive pictures in NAcc, insula, caudate, putamen and amygdala.[29,30] Depressed patients also show brain volume reductions in the ACC, OFC, hippocampus, putamen, caudate nucleus and prefrontal cortex.[31,32] Thus, negative emotional biases and anhedonia may have their effects in depressed patients through key nodes of the brain's emotional circuitry.

Depression is also associated with deficits in emotion regulation, suggesting a second mechanism by which antidepressant may have its effects on emotional processing. For example,

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depressive symptoms are associated with maladaptive emotion regulation strategies,[33] and depressed patients experience more difficulty in regulating negative emotions.[34] Emotion regulation may be challenging for depressed patients, in part, because of the executive control demands afforded by emotion regulation. Indeed, depressed patients perform poorly on executive control and working memory tasks, especially those engaging the dorsolateral prefrontal (dlPFC), a region key to both emotion regulation and executive control.[21,35–37] Relative to healthy controls, patients show diminished dlPFC activity when instructed to actively downregulate negative emotion. Thus, in addition to altered processing in emotion-related brain regions during emotion generation/experience, depression may alter emotion regulation through less recruitment of emotion regulation neural mechanisms.[38,39]

Although neuroimaging findings suggest that abnormal emotion generation/experience and emotion regulation contribute to depression through distinct neural regions, it is unclear how antidepressant treatment changes these neuropsychological mechanisms. For example, different therapeutic responses to antidepressant treatment and inconsistent antidepressant effects on the emotion network have been reported. Moreover, none of the existing reviews or meta-analyses systematically examined antidepressant effects on both positive and negative emotions.[5,40–44] Among the relevant review and meta-analytic articles, only one study[43] conducted coordinate-based quantitative meta-analysis. However, this study was performed only across nine studies and did not consider the valence of emotional processes (that is, combined antidepressant effects on positive and negative emotions). In the current study, Activation Likelihood Estimation (ALE) analysis,[45,46] a coordinate-based whole-brain meta-analytic method to determine anatomical convergence among different neuroimaging studies, was performed separately on fMRI studies examining antidepressant effects on positive and negative emotions. This systematic meta-analysis also aimed to reveal whether antidepressants acted on emotional reactivity, regulation or both. In addition, pharmacological neuroimaging studies were not limited to patients; many neuroimaging studies examined the effects of antidepressants in healthy volunteers as well. Thus, ALE analyses were also conducted separately on studies involving patients with mood disorders and healthy volunteers. This set of analyses revealed, first, common antidepressant effects in healthy volunteers and patients; second, patient- or healthy-specific antidepressant effects; and, finally, whether and how the results observed in healthy volunteers generalized to the patient population.

MATERIALS AND METHODS

Literature searches and selection

A step-wise procedure was used to identify relevant experimental articles focusing on antidepressant effects (mainly selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), which have been the most widely prescribed antidepressants to date) on emotion-related brain activity published before February 2013. First, studies were selected through a standard search in PubMed (http://www.pubmed.gov) and ISI Web of Science (http://apps.isiknowledge.com), with keywords ['selective serotonin reuptake inhibitor' OR 'serotonin–norepinephrine reuptake inhibitor' OR 'SSRIs' OR 'SNRIs' OR 'antidepressant' OR a specific SSRI or SNRI] AND ['fMRI' OR 'magnetic resonance imaging']. Specific SSRIs used as search terms were citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and zimelidine. Specific SNRIs were venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran, sibutramine, bicifadine and bupropion. Next, additional studies were collected by reviewing the reference list of relevant papers in the first step or through the 'related article' function of the PubMed database. Finally, the reference lists of several review articles[5,40–44] were inspected for relevant studies.

The current analysis excluded papers that did not use functional imaging techniques, did not report coordinates in either Montreal Neurological Institute (MNI)[47] or Talairach[48] space, did not involve an emotion-relevant task or did not separate positive and negative emotions. This meta-analysis was limited to regional activation changes (as revealed by task and antidepressant vs control comparisons). Studies focusing on functional connectivity, structural, resting-state or brain–behavior correlations were excluded.

Design of the current study

Studies recruiting patients with mood disorders and/or healthy volunteers were included. A study was considered emotionally relevant if it involved subjects' implicit or explicit experience of positive or negative emotions/affects. Positive emotions can be induced by passive viewing or active judgments on happy faces, pleasant/positive pictures, positive personality/words, erotic/rewarding pictures/videos or monetary gain. Negative emotions can be induced by passive viewing or active judgments on fearful, angry, sad or disgusted faces, unpleasant/negative pictures, negative personality/words or monetary loss.

Antidepressant effects were identified in the contrasts between (1) antidepressant and placebo sessions in within-subject studies; (2) post- and pre-antidepressant sessions in within-subject studies; (3) antidepressant group and placebo/control groups in between-subject studies; (4) group (with or without antidepressant treatment) × Time (post- or pre-treatment) interaction in mix-design studies. Contrasts of 'antidepressant vs control' and 'control vs antidepressant' (control refer to the placebo condition/group, pre-antidepressant baseline or control groups) identified increased or decreased neural responses to emotions by antidepressants.

All articles were individually screened for the presence of MNI or Talairach coordinates, and the contrasts in each article were categorized into four groups based on population and emotional valence: (1) 'healthy-positive emotion' (that is, antidepressant effect on positive emotions in healthy subjects); (2) 'healthy-negative emotion' (antidepressant effect on negative emotions in healthy subjects); (3) 'patient-positive emotion' (antidepressant effect on positive emotions in patients with major depression or anxiety disorder); (4) 'patient-negative emotion' (antidepressant effect on negative emotions in patients). For each of these four conditions, more detailed meta-analyses were conducted separately on studies administrating different classes of antidepressants (that is, SSRIs and SNRIs) and studies employing facial or pictorial stimuli to examine antidepressant effects of different drugs or paradigms. Moreover, to test whether antidepressants affect the abnormalities in emotional reactivity and emotion regulation in a top-down or bottom-up manner, separate meta-analyses were conducted on the studies adopting implicit (for example, gender judgment, passive viewing, location judgment) and explicit (for example, emotion match task, emotion identification/categorization/discrimination, pleasantness rating) emotional processing paradigms.

ALE analysis

Meta-analysis was based on the ALE method,[45,46] using the revised ALE algorithm[49] in GingerALE 2.3 (www.brainmap.org/ale).[46,49,50] The ALE method has been applied in studies of neuropsychiatric disorders, such as schizophrenia,[51] obsessive-compulsive disorder[52] and depression.[40] GingerALE switched ALE methods from fixed effects to random effects, incorporated variable uncertainty based on the sample size of each study[50] and added the thresholding methods.[46]

The procedure involved the modeling of all reported loci (coordinates of maximum activation) of the selected contrasts as the peaks of a 3D Gaussian probability distribution. Foci in Talairach space were converted to MNI space, and all coordinates reported in this study were in the MNI space. The 3D Gaussian distributions were summed to produce a statistical map that estimated the likelihood of activation for each voxel as determined by all studies in the analysis. The ALE value was computed using permutation testing (5000 permutations) against the null-distribution of random spatial associations of foci across experiments.[50] The current results used a *P*-threshold corrected for multiple comparisons using the false discovery rate fixed to 0.05.[46] All clusters were set to a minimum of 200 mm^3. The threshold ALE result images were visualized using Mango (rii.uthscsa.edu/mango) and overlaid onto an anatomical template (Colin27_T1_seg_MNI.nii, www.brainmap.org/ale). GingerALE also allowed for statistical comparisons between the ALE maps of two distinct sets of foci. Thus, subtraction and conjunction analyses were carried out to reveal statistically significant differences as well as similarities between two data

sets (that is, studies conducted on patients and healthy volunteers). The same threshold was applied to the subtraction and conjunction analyses.

RESULTS

Sixty studies (listed in Supplementary Table S1, including 157 contrasts, 797 foci) were included in the meta-analysis as studies related to antidepressant effects on brain activity underlying emotional processes. Fifty-four contrasts (289 foci) examined antidepressant effects in patients with mood disorders, with 39 contrasts on negative emotions and 15 contrasts on positive emotions. One hundred and three contrasts (508 foci) examined the effects of antidepressant in healthy volunteers, with 63 contrasts on negative emotions and 40 contrasts on positive emotions.

General antidepressant effects

ALE meta-analysis on all selected studies, collapsing across subject groups (patients and healthy) and emotional value (positive and negative emotions), was first conducted to reveal brain regions affected by antidepressants during emotional processes. This analysis was conducted on 157 contrasts (797 foci) and revealed significant activations in the bilateral amygdala, caudate head/NAcc, ACC, caudate body, OFC, thalamus, putamen, dmPFC, parahippocampal gyrus, posterior cingulate (PCC), insula, vlPFC and superior temporal gyrus (see Supplementary Table S2, Figure 1). Moreover, the bilateral amygdala, left NAcc, left putamen and left thalamus were the most statistically robust activations, as these brain regions survived a more stringent threshold of $P < 0.05$ (corrected for multiple comparisons using the Family-wise error rate).

Antidepressant effects in mood disorder patients

Fifteen contrasts compared brain responses to positive emotions between antidepressant and control in mood disorder patients (12 contrasts: antidepressant>control; 3 contrasts: antidepressant < control). The ALE analysis on 12 contrasts (90 foci) revealed that antidepressant treatment increases neural responses to positive emotions in bilateral amygdala, right dlPFC, left hippocampus, vmPFC, ACC, left fusiform, anterior insula and precuneus (Supplementary Table S3, Figure 2a).

Thirty-nine contrasts compared antidepressant and control during negative emotion processing in patients (14 contrasts: antidepressant>control; 25 contrasts: antidepressant < control). The ALE analysis of the 25 contrasts (134 foci) showed that antidepressant treatment in patients was associated with decreased activity to negative emotions in bilateral amygdala, hypothalamus, left putamen, left middle temporal, vmPFC, right poster insula, middle frontal gyrus (MF) (Supplementary Table S3, Figure 2b). Antidepressant treatment (14 contrasts, 55 foci) increased left dlPFC activity (Supplementary Table S3, Figure 2b) during negative emotional processes.

More detailed meta-analyses, separately for studies using different classes of antidepressants and different experimental paradigms, revealed interesting results. Only studies employing SSRI (but not SNRI) administration or facial (but not pictorial) stimuli converged on increased activity in response to positive emotions and decreased activity to negative emotions in bilateral amygdala (see Supplementary Tables S4 and S5 for more details for each condition). Studies employing pictorial stimuli or SNRIs also showed altered activity to positive (increased) and negative (decreased) emotions, but in different emotional brain regions, such as ACC, insula and thalamus. Interestingly, the increased dlPFC activity in response to both positive and negative emotions was mainly mediated by implicit emotional processes, as only studies that employed implicit paradigms revealed convergence on dlPFC activity (Supplementary Table S6).

Patients vs healthy

Next, the effects of antidepressant in healthy volunteers and patients with mood disorders were compared. Most studies on patients adopted repeated treatment (chronic/subchronic antidepressant treatment, that is, antidepressant administration for a few days or weeks). Only one study on patients adopted

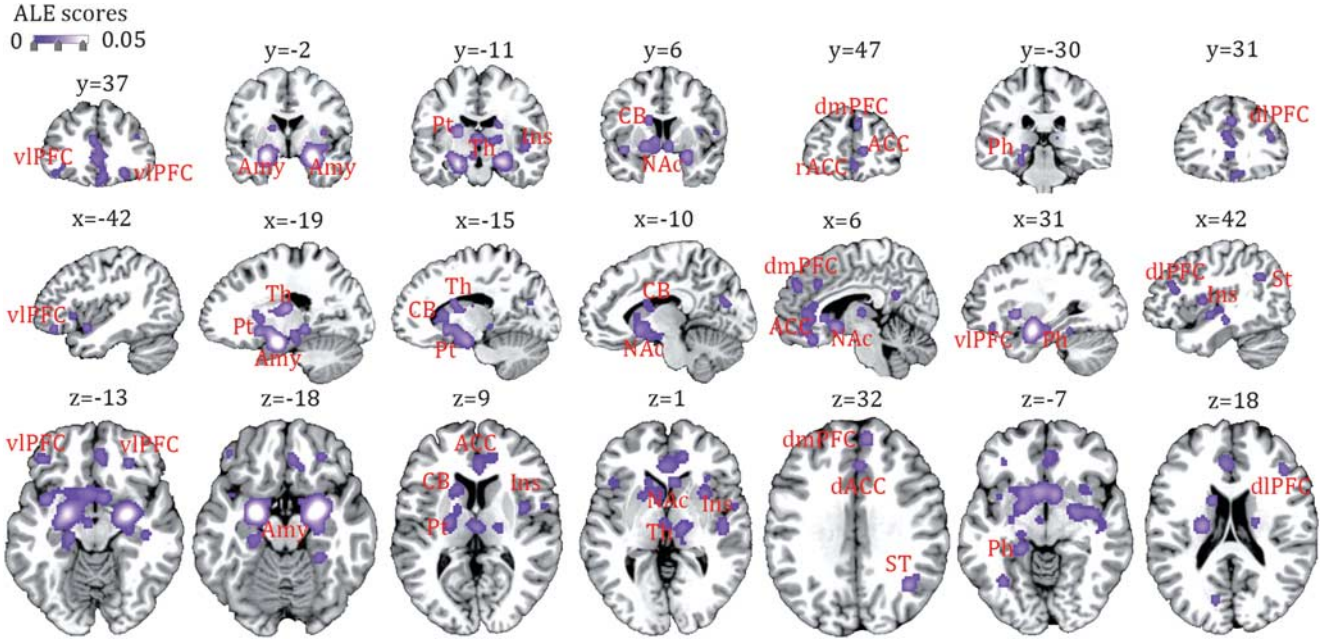

Figure 1. Brain regions showing general antidepressant effects of all the selected studies. ACC, anterior cingulate; Amy, amygdala; CB, caudate body; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsal medial prefrontal cortex; Ins, insula; NAcc, nucleus accumbens; Ph, parahippocampus; Pt, putamen; rACC, rostral anterior cingulate; St, superior temporal; Th: thalamus; vlPFC: ventrolateral prefrontal cortex.

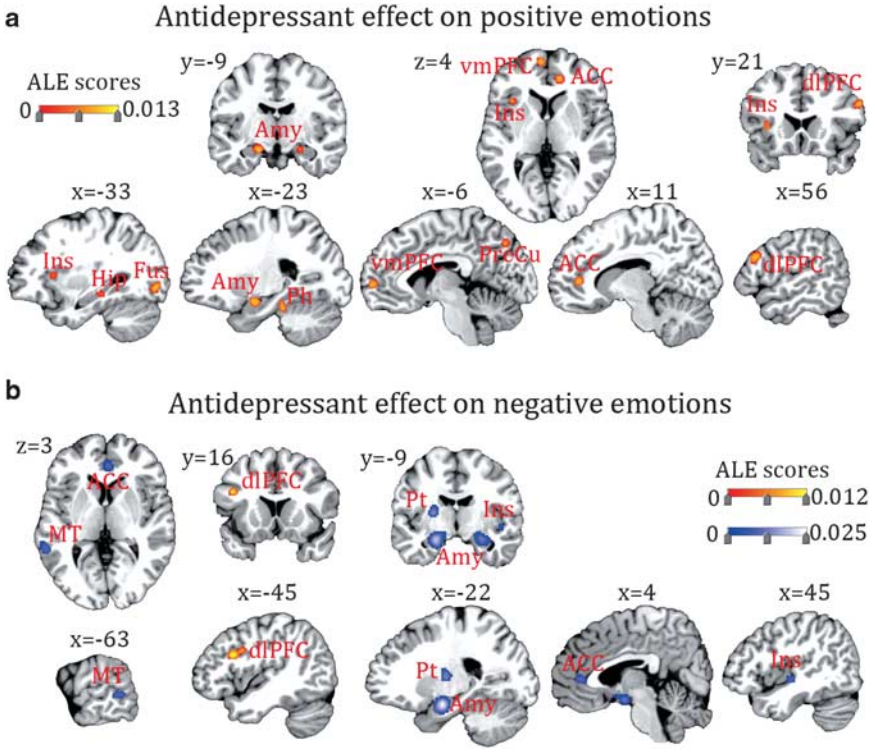

Figure 2. Antidepressant effects in mood disorder patients. Red, increased activity by antidepressants; blue, decreased activity by antidepressants.

single/acute administration of antidepressant. Thus, only studies using repeated antidepressant administration were included in this section for comparison.

Some antidepressant effects were common in healthy and patient samples, for example, antidepressants (relative to placebo) decreased activity to negative emotions (Negative—Decrease) but increased activity to positive emotions (Positive—Increase) in the similar emotional neural network. Moreover, no brain region showed significant difference in antidepressant effects on negative (decrease) and positive (increase) conditions between healthy and patient samples. For patients, antidepressant treatment increased neural responses to positive emotions in bilateral amygdala, right dlPFC, left fusiform, ACC, vmPFC, precuneus and anterior insula, but decreased activity to negative emotions in the bilateral amygdala, left putamen, ACC, left middle temporal, right posterior insula and MF (Supplementary Table S7). For healthy volunteers, antidepressants increased the bilateral amygdala, left putamen and right parahippocampal activity to positive emotions (Table 1), but decreased activity in response to negative emotions in the bilateral amygdala, right putamen, ACC, left parahippocampal gyrus, thalamus and dlPFC (Table 2). Conjunction analysis further showed that, in both conditions (Positive—Increase and Negative—Decrease), the bilateral amygdala was statistically overlapping in healthy individuals and patients (Supplementary Figure S1 and Supplementary Table S8).

Selective antidepressant effects were also uncovered in patients and healthy volunteers. Increased left dlPFC activity (−44/18/26; −46/8/30, BA9) to negative emotion was only found in patients (13 contrasts, 53 foci). Among the studies conducted on healthy volunteers, only four contrasts (six foci) reported increased activity in response to negative emotions, and no convergence was revealed. This suggested that the increased dlPFC activity during negative emotion might be specific to patients. However, decreased activity in the bilateral NAcc, left putamen, dmPFC and ACC to positive emotions occurred only in studies examining antidepressant effects in healthy volunteers (Figure 3 and Table 1). Only 3 contrasts (10 foci) on positive emotional processing among patient studies reported decreased activity, and no convergent activation was observed. Direct comparison was not conducted because of the small number ($n = 3$ or 4) of contrasts in one of the populations. Interestingly, the healthy selective decreased activity to positive emotions in the NAcc, putamen, midbrain, mPFC and ACC was only found in studies administrating SSRIs (but not SNRIs, Supplementary Table S4) or studies using pictorial stimuli (but not faces, Supplementary Table S5).

Single vs repeated antidepressant effects in healthy volunteers

Half of the studies examining antidepressant effects in healthy volunteers employed single administration, and the other half employed repeated administration of antidepressants (Supplementary Table S1, also see Supplementary Figure S2 for the antidepressant effects in healthy volunteers collapsing across single and repeated administration). To further explore the antidepressant effects on emotional processes in healthy volunteers, separate meta-analyses were conducted on studies using single or repeated antidepressant administration.

As shown in the above section, repeated antidepressant administration increased activity in the bilateral amygdala, left putamen and right parahippocampal activity and decreased activity in the bilateral NAcc, left putamen, dmPFC, ACC in response to positive emotions (Figure 3 and Table 1). However, 17 contrasts, examining acute antidepressant effect on positive emotions (8 contrasts: antidepressant>control; 9 contrasts: antidepressant < control, Table 1), did not show any convergent activation. For negative emotions, no increase-effect was associated with repeated antidepressant administration. Rather, it converges on decreased activity in the bilateral amygdala, right

Table 1. Antidepressant effects on positive emotions in healthy volunteers

Brain regions	*Hemi.*	*BA*	*Weighted center*			*MNI coordinates*			*Volume (mm^3)*
			x	*y*	*z*	*x*	*y*	*z*	
Repeated antidepressant administration on positive emotions									
Antidepressant>control (based on 10 contrasts, 31 foci)									
Amygdala	R		24.45	−5.68	−16.72	24	−8	−14	576
Parahippocampal	R					26	0	−24	
Putamen	L		−22	−2.35	−13.21	−22	0	−10	200
Amygdala	L					−22	−6	−18	
Antidepressant < control (based on 13 contrasts, 73 foci)									
NAcc	L		−6.81	12.54	−6.63	−8	12	−4	3776
Putamen	L					−16	14	−8	
NAcc	R					8	12	−6	
NAcc	R					10	22	−2	
dmPFC	R	6	15.11	31.79	31.52	14	32	32	520
Cingulate gyrus	R	32				16	24	36	
Anterior cingulate	L	24	−12.13	32.29	−5.21	−4	34	0	504
Midbrain	L		−4	−24	−14	−4	−24	−14	456
vmPFC	R	32	12.8	44.96	4.91	12	44	6	416

Abbreviations: BA, Brodmann's area; dmPFC, dorsal medial prefrontal cortex; Hemi. hemisphere; L, left; MNI, Montreal Neurological Institute; NAcc, nucleus accumbens; R, right; vmPFC, ventral medial prefrontal cortex. Note: single-antidepressant administration did not have significant effects on positive emotions in healthy volunteers. The *x-y-z* coordinates are the MNI coordinates for the weighted center-of-mass and peak locations of each cluster. Quantitative estimates of the between-subject and between-template variability were empirically determined in order to more explicitly model the spatial uncertainty associated with each coordinate (a correction that also includes a weighting of each study by the number of included subjects').[42]

putamen, ACC, left parahippocampal gyrus, thalamus and left dlPFC (Table 2). However, single-antidepressant administration showed a discrepant effect on negative emotions; a similar neural network was found to be both increased and decreased by single-antidepressant administration. Some studies (22 contrasts, Table 2) converged on decreased activity in the bilateral amygdala, right hippocampus, right parahippocampal gyrus, dmPFC, thalamus and right vlPFC. However, other studies (17 contrasts, Table 2) revealed convergence on increased activity in the bilateral amygdala, right parahippocampal gyrus, temporal pole, caudate body, ACC, thalamus, vlPFC, left fusiform, dmPFC and middle temporal. These results suggested that single-antidepressant administration both increased and decreased activity in multiple brain regions (overlapping and nonoverlapping) during negative emotion processing in healthy volunteers. Subtraction and conjunction analyses were then carried out to examine statistically significant differences and similarities between these two data sets (that is, the 'antidepressant>control' and 'antidepressant < control' contrasts). The bilateral amygdala (left: −22/−7/−22; right: 21/−6/−18) and dmPFC (8/50/34, BA6) were both increased and decreased by single-antidepressant administration. Moreover, the subtraction analysis did not show any significant activation selectively increased or decreased by antidepressants.

DISCUSSION

Neuropsychological mechanism underlying antidepressant effects

The current meta-analysis has shown converging evidence that antidepressant medication in patients with mood disorders affects emotional circuitry (including the bilateral amygdala, ACC, insula, putamen, mPFC and hypothalamus), by decreasing its activity to negative emotions and increasing its activity to positive emotions. Antidepressants also influence brain regions thought to have a key role in emotional regulation, such as dlPFC, by enhancing dlPFC activity during positive and negative emotions. Depressed patients exhibit a mood-congruent processing bias in this emotional network, specifically hyperactivity to negative emotions and hypoactivity to positive emotions in the amygdala, insula, ACC, parahippocampal gyrus and putamen.[22,53,54] Such mood-congruent bias in the emotional network has been believed to cause negative emotional bias and is implicated in the pathogenesis of depression.[19,54,55] Abnormal activation in the emotional network co-occurs with decreased activation in the prefrontal area. The emotional network is sensitive to voluntary regulation, mediated by prefrontal cortex, especially the dlPFC.[38,39,56] Hypoactivity in the prefrontal area has been suggested to underlie deficits in emotion regulation in depressed patients.[21,35–37] Combined with the current findings, antidepressants act to normalize the abnormal neural responses in depressed patients through reduction of mood-congruent biases by increasing activity to positive emotions and decreasing activity to negative emotions in the amygdala, insula and ACC, and increasing regulatory responses in dlPFC. Thus, through these neuropsychological processes, antidepressants may act to improve depressed patients' abnormalities in emotional reactivity and deficits in emotional regulation, so as to reduce negative emotional bias and anhedonia.

Emotional processes are mediated by a complex network consisting of multiple brain regions. A systematic, quantitative meta-analysis[28] of 162 neuroimaging studies of emotion classified the activated brain regions into distributed functional groups. For example, the 'medial PFC group', including ACC and PFC, is associated with emotion generation and regulation. The 'lateral paralimbic group', consisting of the NAcc, putamen, anterior insula and posterior OFC, has a key role in motivational drive and reward learning. The 'core limbic group', consisting of the amygdala, thalamus and hypothalamus, may serve as an integrative emotional center, responsible for emotional reactivity and emotional salience encoding. The 'medial posterior group' (that is, V1 and PCC) is likely to have a role in visual processing and attention to emotional stimuli. The current findings suggest that, for patients, some emotion functional groups (for example, medial PFC and the core limbic groups) are sensitive to antidepressant medication, whereas other functional groups (for example, the lateral paralimbic and the medial posterior groups) may be less sensitive. It would be beneficial for future research to directly address how antidepressant medication affects different symptoms, such as

Table 2. Single and repeated antidepressant effects on negative emotions in healthy volunteers

Brain regions	*Hemi.*	*BA*	*Weighted Center*			*MNI coordinates*			*Volume (mm^3)*
			x	*y*	*z*	*x*	*y*	*z*	
Single-antidepressant administration on negative emotions									
Antidepressant>control (based on 22 contrasts, 179 foci)									
Amygdala	R		20.47	−0.8	−21.73	24	−2	−22	2752
Parahippocampal	R	28				18	−10	−16	
Amygdala	L		−22.62	−3.19	−26.19	−20	−8	−22	2032
Temporal pole	L	38				−30	10	−32	
Caudate body	L		−15.23	15.79	6.5	−14	16	6	1504
Anterior cingulate	L	25	−2.45	16.06	−8.36	−2	16	−10	976
Thalamus (medial dorsal nucleus)	L		0.26	−13.2	4.76	2	−14	6	872
vlPFC	L	47	−42.13	39.96	−15	−42	40	−14	672
Thalamus	R		10.41	−30.06	3.02	14	−28	4	584
Fusiform gyrus	L	37	−37.69	−59.05	−9.63	−38	−60	−10	392
dmPFC	R	6	16.25	6.44	66.16	16	6	66	352
Middle temporal	R	21	54	3	−31.22	54	4	−32	304
vlPFC	R	10	44.6	45.16	−11.86	44	44	−12	256
dmPFC	L	6	−1.93	−14.3	71.92	−2	−14	72	256
Cingulate gyrus	R	24	10.97	8.75	19.23	10	8	20	208
dmPFC	R	8	7.85	51.52	34.84	8	52	36	208
Antidepressant < Control (based on 17 contrasts, 86 foci)									
Amygdala	R		23.5	−6.24	−14.81	20	−8	−16	1840
Hippocampus	R					28	−14	−20	
Parahippocampal	R	28				24	−18	−26	
Amygdala	L		−24.32	−8.95	−18.79	−24	−8	−20	1560
dmPFC	R	6	8.41	51.28	32.07	8	50	32	528
dmPFC	R	8				10	52	40	
Thalamus	L		−23.63	−15.59	15.7	−24	−16	16	416
vlPFC	R	47	43.58	29.16	−15	44	28	−14	400
dmPFC	R	6	11.47	36.06	51.38	12	36	52	272
dmPFC	R	8				8	34	50	
Repeated antidepressant administration on negative emotions									
Antidepressant < control (based on 20 contrasts, 83 foci)									
Amygdala	R		25.8	−2.01	−18.39	26	−4	−18	2208
Amygdala	L		−24.21	−3.9	−15.85	−24	−4	−16	1784
Putamen	R		31.27	21.46	−2.48	30	14	−2	1768
Anterior cingulate	L	24	0.06	34.38	15.29	0	34	16	688
Cingulate gyrus	L	32				−2	32	22	
Parahippocampal	L	35	−19.84	−25.19	−16.53	−20	−24	−16	368
Thalamus	L		−15.75	−4.18	11.03	−16	−4	12	336
dlPFC	L	46	−48.51	35.17	16.83	−48	36	16	296

Abbreviations: BA, Brodmann's area; dmPFC, dorsal medial prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; Hemi., hemisphere; L, left; MNI, Montreal Neurological Institute; R, right; vlPFC, ventrolateral prefrontal cortex.

depressive mood, decreased motivation, through its effects on distinct emotion functional groups.

The antidepressant effects on emotional reactivity and emotion regulation suggest two possibilities for a primary mechanism: (1) enhanced/restored ability for 'top-down' emotion regulation, which in turn leads to altered emotional reactivity; (2) 'bottom-up' alteration in emotional reactivity, which leads to dlPFC increases. Evidence from the current analysis and previous research may lend support for the 'bottom-up' mechanism. First, previous research suggested that antidepressants may target limbic regions directly, rather than through prefrontal regulation.[38] Second, the current meta-analysis focused on the second-generation antidepressants (that is, SSRIs and SNRIs). SSRIs and SNRIs are believed to block the reuptake and to potentiate neurotransmission of serotonin and noradrenaline, which are implicated in emotional processing.[4,41,57] Third, if antidepressants act to enhance 'top-down' regulation, we would expect this regulatory effect in healthy subjects as well, as altered emotional reactivity was observed in both samples. However, increased dlPFC activity caused by antidepressants was identified only in studies recruiting patients, but not in healthy volunteers studies. Fourth, the antidepressant effect of increased dlPFC activity in patients was only observed in studies employing implicit paradigms (bottom-up processing), whereas decreased amygdala responses to negative emotions were observed in studies using either implicit or explicit (top-down processing) paradigms. If antidepressants enhance or restore the ability for 'top-down' emotion regulation, we would expect similar or even greater increases of dlPFC activity in explicit studies. Although the above evidence suggests that antidepressants may act more directly to normalize emotional reactivity in the emotional network, which in turn leads to prefrontal disinhibition, direct evidence is lacking and needs to be clarified in future research by applying dynamic causal modeling analysis or transcranial direct current stimulation manipulations.

The results reported here have important implications in the treatment of depression. Cognitive behavioral therapy is another efficacious treatment for depression.[58,59] Although both treatments affect emotion-related and prefrontal circuits to a similar end state of normalized emotional network and prefrontal activity, the mechanism by which each treatment acts may differ. Although it has been proposed that cognitive behavioral therapy targets prefrontal function as it focuses on increasing inhibitory

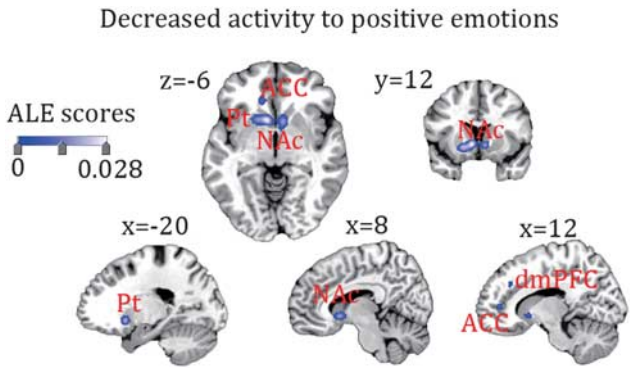

Figure 3. Decreased neural responses to positive emotions by repeated antidepressant administration in healthy volunteers. ALE, Activation Likelihood Estimation.

executive control,[36] the current findings raise the possibility that antidepressants may act more directly on the emotional network. Taken together, a combination of an early antidepressant medication and follow-up cognitive behavioral therapy may therefore result in a better therapeutic effect, a possibility that needs to be directly addressed in future research.

Antidepressant effect in healthy volunteers and patients

Common and specific antidepressant effects were uncovered in healthy volunteers and patients. Meta-analyses of studies on antidepressant effects both in healthy volunteers and in patients converged on decreased activity to negative stimuli and increased activity to positive stimuli in the emotional network consisting of the bilateral amygdala, putamen, ACC, insula, left MF, especially the bilateral amygdala, which was statistically overlapping in healthy and patient populations. The similar alteration of emotional reactivity in healthy volunteers and patients suggests that the antidepressant effect on emotional reaction in healthy volunteers generalizes to depressed patients.

However, this conclusion about generalization should be treated with caution in that patient- and healthy-specific effects were also revealed. The antidepressant effect of increased dlPFC activity to negative and positive emotions was only observed in depressed patients, whereas the decreased activity to positive emotions in the reward/motivation-related regions (for example, NAcc, putamen, OFC and mPFC)[28,60,61] was only observed in healthy volunteers. There are three potential explanations for the differential antidepressant effects between patients and healthy volunteers. First, it is possible that different neuropsychological/psychopharmacological mechanisms underlie antidepressant effects in healthy and patient populations. Second, the differential antidepressant effects may arise from differences between patients and healthy volunteers at baseline, as depressed patients showed abnormal decreases of neural activity in dlPFC and the reward system.[30,62] Thus, the lack of antidepressant-mediated decreases in activity to positive stimuli in the reward circuitry in patients may be due to the lack of reward-related activity to positive stimuli in patients at the baseline. The lack of antidepressant-mediated increases in emotional regulation in dlPFC in healthy volunteers may be because, relative to patients, healthy volunteers are already better at regulating emotions at the baseline. Finally, differences in treatment duration/dosage, emotional stimuli (see Supplementary Table S5) or experimental paradigms (see Supplementary Table S6) may also contribute to the differences in antidepressant effects between patients and healthy volunteers. In an effort to account for the potential confound of dosage regimens, the current meta-analysis compared patients and healthy volunteers only in those studies adopting repeated treatment, although treatment duration is still much shorter in healthy volunteers (3–56 days, mean = 13.56 days, mode = 7 days) than in patients (7–153 days, mean = 53.44 days, mode = 56 days).

Single vs repeated antidepressant effects

Half of the studies (17 studies, 56 contrasts) examining antidepressant effects in healthy volunteers employed single administration, whereas the other half (18 studies, 47 contrasts) employed repeated administration. Separate analyses were conducted to reveal antidepressant effects of single and repeated administration. The convergent antidepressant effects on positive emotions mainly arise from the repeated treatment, as only studies using repeated administration show significant and consistent antidepressant effects, whereas single administration of antidepressant did not reveal significant, consistent effect on positive emotions. Moreover, discrepant effects of single-antidepressant administration were found in negative emotion processing. Single-antidepressant administration was associated with both increased and decreased neural responses in the emotional network. Such differing effects are not driven by a single study. Both the increased and decreased activity in the emotional network showed statistically significant anatomical convergence among different studies. In addition, increased reactivity to negative emotions in the emotional network was only observed in single administration. One possible explanation for less consistent results of single-antidepressant administration may be partly caused by higher (relative to repeated administration) and various doses used in single-antidepressant administration studies. Supplementary Table S9 showed that, within a same specific drug, single administration studies used equal or higher doses than repeated administration studies. Moreover, repeated studies administrated the same dosage within each specific drug. However, different single-administration studies (even within the studies administrating the same drug) used different dosages and different ways of administration (that is, oral or intravenous administration). Previous studies have shown that single administration of antidepressants may induce anxiety, which may be explained by the specific increased negative emotional responses in the amygdala revealed by the current meta-analysis. Alternatively, the differential single-antidepressant effects may be mediated by other factors, such as age, sex, disease condition or one's genetic makeup.[63–65] For example, our recent study[66] suggested that a serotonin-related genetic polymorphism (that is, serotonin transporter promoter polymorphism, 5-HTTLPR) modulated the single-SSRI effect on brain activity in response to emotional faces. We showed that single-SSRI administration increased amygdala and insular activity in the long/long genotype but tended to decrease amygdala and insular activity in the short/short genotype group of 5-HTTLPR. Future research should further explore factors that influence acute antidepressant effects and examine the relationship between short-term and long-term antidepressant effects on brain activity.

In summary, antidepressant medication normalizes mood-congruent processing biases in the emotional network and abnormally disengaged prefrontal control, which is implicated in depression. Common alterations in the emotional network caused by antidepressants are observed in both patient and healthy populations, namely that emotional network reactivity is increased in response to positive emotions and decreased to negative emotions by antidepressants. The current meta-analysis reveals multiple antidepressant-mediated brain regions, which can be utilized in new depression treatment, such as providing neural targets for neurofeedback training and transcranial magnetic stimulation treatment for depression.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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