Supplementary information

Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis

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Supplemental information: 2 figures and 9 tables

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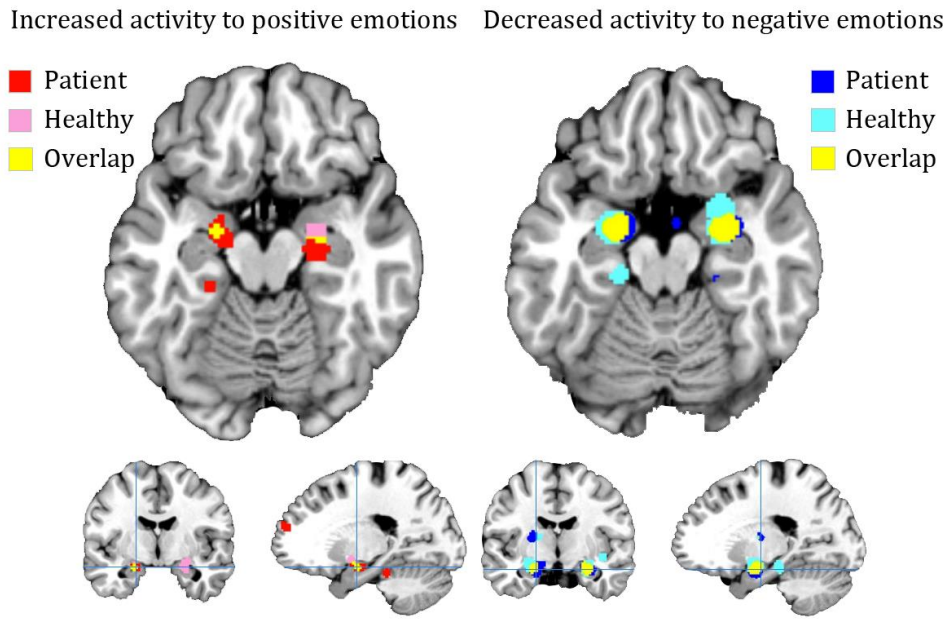

Figure S1. Results of conjunction analysis. In both the "Positive-Increase" and "Negative-Decrease" conditions, the bilateral amygdala activity was overlapping in healthy and patient samples.

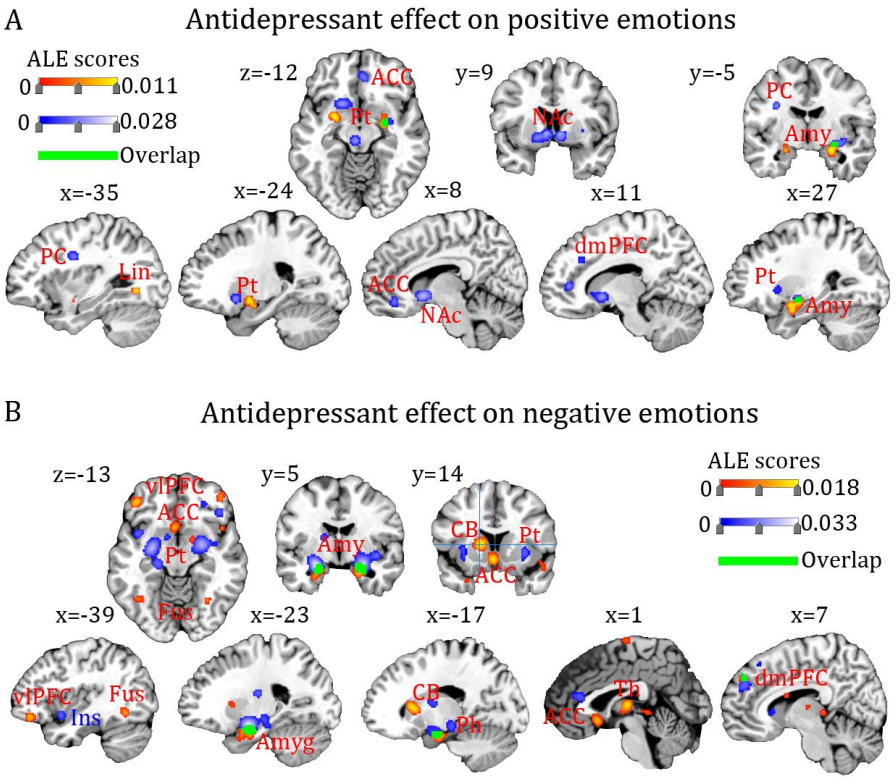

Figure S2. Antidepressant effects in healthy volunteers (collapsing across single and repeated antidepressant administration).

Red: increased activity by antidepressants; blue: decreased activity by antidepressants; green: overlapping brain regions.
vlPFC: ventrolateral prefrontal cortex; Amy: amygdala; Pt:putamen; Th: thalamus; Ins: insula; NAc: nucleus accumbens; CB: caudate body; ACC: anterior cingulate; rACC: rostral anterior cingulate; dmPFC: dorsal medial prefrontal cortex; Ph: parahippocampus; dlPFC: dorsolateral prefrontal cortex; St: superior temporal.

Table S1 Summary of the selected studies in the current meta-analysis.

First Author, year	Positive stimuli	Negative stimuli	Contrast	Subjects	Treatment	Duration
Patient studies						
Kalin, 1997[1]	IAPS	IAPS	T1 vs. T0	MDD (2)	Venlafaxie	14
Davidson, 2003[2]	Victories	Mutilated face	Group x Time	MDD (12) H (5)	Venlafaxie	14
	Victories	Mutilated face	Group x Time	MDD (12) H (5)	Venlafaxie	56
Fu, 2004[3]	-	Sad face morphs	Group x Time	UMD (19)	Fluoxetine	56
Hoehn-Saric, 2004[4]	-	Worry statement	T1 vs. T0	GAD (6)	Citalopram	49
Schaefer, 2006[5]	IAPS	-	Group x Time	MDD (9)	Venlafaxine	153
Fu, 2007[6]	Happy face	-	Group x Time	MDD (19) H(19)	Fluoxetine	56
Anand, 2007[7]	-	IAPS	T1 vs. T0	UMD (12) H(11)	Sertraline	42
Robertson, 2007[8]	-	IAPS	T1 vs. T0	MDD (10)	Bupropion XL	56
Keedwell, 2008[9]	Happy face	Sad face	T1 vs. T0	MDD (11)	Antidepressant	84
Fales, 2009[10]	-	Fearful face		MDD (23)	Escitalopram	56
Benedetti, 2009[11]	Positive word	Negative word	T1 vs. T0	MDD (8)	Venlafaxine	28
Maslowsky, 2010[12]	Happy face	Angry face	T1 vs. T0	GAD (7)	Fluoxetine	56
Cornelius, 2010[13]	-	Fear/angry face	T1 vs. T0	MDD (6)	Fluoxetine	84
López-Sola, 2010[14]	-	Painful	Group x Time	MDD (13)	Duloxetine	7
	-	Painful	Group x Time	MDD (13)	Duloxetine	56
Victor, 2010[15]	Happy face	Sad face	Group x Time	GAD (10)	Sertraline	56
Samson, 2011[16]	-	Sad face	Group x Time	MDD (21)	Mirtazapine/Venlafaxine	28
Anderson, 2011[17]	Happy face	Fear face	T1 vs. T0; Group x Time	RD (14)	Citalopram	Single
		Sad face				

Frodl, 2011[18]	-	Angry/sad faces	T1 vs. T0	MDD (11)	Venlafaxine	28
	-	Angry/sad faces	T1 vs. T0	MDD (13)	Mirtazapine	28
Tao, 2012[19]	-	Fearful face	T1 vs. T0; Group x Time	MDD (21)	Fluoxetine	56
Phan, 2012[20]	Happy face	Fear face	Group x Time	GSA (21) H (19)	Sertraline	84
		Angry face				
Wang, 2012[21]	IAPS	IAPS	T1 vs. T0	MDD (18)	Fluoxetine	56
Arnone, 2012[22]	Happy face	Sad face	T1 vs. T0	MDD (30)	Citalopram	56
		Fear face				
Godlewska, 2012[23]	Happy face	Fear face	Between group	MDD (21T, 21P)	Escitalopram	7
Rosenblau, 2012[24]	IAPS	IAPS	Group x Time	MDD (12) H (12)	Escitalopram	56
Stoy, 2012[25]	Monetary Gain	Monetary Loss	Group x Time	MDD (15) H (15)	Escitalopram	42
Ruhé, 2012[26]	Happy face	Angry/fear face	T1 vs. T0	MDD (17)	Paroxetine	42
	Happy face	Angry/fear face	T2 vs. T0	MDD (16)	Paroxetine	84
Healthy volunteer studies						
Takahashi, 2005[27]	-	IAPS	vs. placebo	13	Fluoxetine	Single
Del-Ben, 2005[28]	-	Angry/disgust/fear face	vs. placebo	12	Citalopram	Single
	No loss	Loss	vs. placebo	12	Citalopram	Single
McKie, 2005[29]	-	Negative feeling rating	vs. pre-infusion	12	Citalopram	Single
Harmer, 2006[30]	Happy face	Fear face	vs. placebo	12T12P	Citalopram	7
Völlm, 2006[31]	Reward	Loss	vs. placebo	21T24P	Mirtazapine	7
Norbury, 2007[32]	Happy face	Fear face	vs. placebo	12T12P	Reboxetine	7
Miskowiak, 2007[33]	Positive word	Negative word	vs. placebo	12T12P	Reboxetine	Single

Anderson, 2007[34]	-	Angry	vs. placebo	12	Citalopram	Single
		Disgust				
		Fear face				
Arce, 2008[35]	Happy face	Fear face	vs. placebo	13	Escitalopram	21
		Angry face				
Norbury, 2008[36]	Positive word	Negative word	vs. placebo	12T12P	Reboxetine	7
Bigos, 2008[37]	-	Angry/Fear face	vs. placebo	8	Citalopram	Single
Kukolja, 2008[38]	Happy face	Fear face	vs. placebo	15T16P	Reboxetine	Single
Kumar, 2008[39]	Reward	-	vs. unmedicated	15	Citalopram	3
Murphy, 2009[40]	Happy face	Fear face	vs. placebo	13T13P	Citalopram	Single
Onur, 2009[41]	Happy face	Fear face	vs. placebo	18	Reboxetine	Single
Norbury, 2009[42]	Happy face	Fear face	vs. placebo	16T12P	Citalopram	7-10
Simmons, 2009[43]	IAPS	IAPS	vs. placebo	15	Escitalopram	21
Rawlings, 2010[44]	Happy face	Fear face	vs. placebo	12T16P	Mirtazapine	Single
Windischberger, 2010[45]		Fear/anger/surprise /sad/disgust	vs. placebo	16	Citalopram	10
		Fear/anger/surprise /sad/disgust	vs. placebo	16	Escitalopram	10
McCabe, 2010[46]	Rewarding stimuli	Aversive stimuli	vs. placebo	15T15P	Citalopram	7
	Rewarding stimuli	Aversive stimuli	vs. placebo	15T15P	Reboxetine	7
de Almeida, 2010[47]	Happy (IAPS)	Fear (IAPS)	vs. unmedicated	12	Clomipramine	28
		Anger (IAPS)				
Brühl, 2010[48]	IAPS	IAPS	vs. placebo	16	Citalopram	Single
	IAPS	IAPS	vs. placebo	16	Reboxetine	Single
Brühl, 2011[49]	IAPS	IAPS	vs. placebo	16	Citalopram	Single
	IAPS	IAPS	vs. placebo	16	Reboxetine	Single

Abler, 2011[50]	Erotic video	-	vs. placebo	18	Paroxetine	7
	Erotic video	-	vs. placebo	18	Bupropion	7
Kukolja, 2011[51]	-	IAPS	vs. placebo	11T15P	Reboxetine	7
Tendolkar, 2011[52]	Positive picture	Negative picture	vs. placebo	18	Duloxetine	14
van Marle, 2011[53]	-	Fear/anger	vs. placebo	19	Duloxetine	14
Anderson, 2011[17]	Happy face	Fear face	vs. placebo	12	Citalopram	Single
	-	Sad face	vs. placebo	12	Citalopram	Single
Ossewaarde, 2011[54]	Monetary reward	-	vs. placebo	19	Duloxetine	14
Culbertson, 2011[55]	Rewarding video	-	vs. placebo	14T16P	Bupropion XL	56
Marutanin, 2011[56]	Monetary reward	-	vs. placebo	16	Paroxetine	Single
Papadatou-Pastou, 2012[57]	Positive word	Negative word	vs. placebo	12T12P	Reboxetine	Single
Grady, 2012[58]	-	Fear	vs. placebo	20	Citalopram	Single
		Anger				
Di Simplicio, 2012[59]	Positive word	Negative word	vs. placebo	19T15P	Citalopram	7
Macoveanu, 2013[60]	Win	Loss	vs. placebo	22	Citalopram	Single

: Treatment decreased the activation; : Treatment increased the activation; : Treatment did not influence the activation.
For the “subjects” column:
MDD: major depression disorder; UMD: unipolar major depression; RD: remitted depressed patient; H: healthy volunteers; T: antidepressant treatment; P: placebo.
IAPS: pictorial stimuli from the International Affective Picture System

Table S2 Brain regions showing general antidepressant effects across all selected studies

Brain regions	Hemi.	BA	Weighted Center			MNI coordinates			Volume (mm^3)
			x	y	z	x	y	z	
FDR, qN< 0.05; Volume> 200 mm^3									
Amygdala	L		-15.94	3.01	-12.18	-22	-6	-20	15776
NAc	L					-6	14	-6	
NAc	R					6	10	-8	
Putamen	L					-18	12	-8	
Caudate Body	L					-16	16	6	
Midbrain	L					-6	-12	-12	
Amygdala	R		27.05	-4.81	-16.49	26	-4	-18	10240
Insula	R					46	-16	0	
Anterior Cingulate	R	32	3.05	38.13	0.76	12	44	4	6000
Anterior Cingulate	L	24				-2	36	0	
Anterior Cingulate	L	32				-4	34	20	
Medial Frontal	R	11				14	28	-18	
Thalamus	R		8.21	-14.58	6.93	0	-14	6	2704
Thalamus	R					14	-14	4	
Thalamus	R					14	-28	4	
Thalamus	L		-20.75	-8.87	14.44	-22	-14	14	2664
Caudate Body	L					-14	4	18	
Parahippocampal	L	27	-21.86	-28.86	-11.54	-20	-34	-6	1920
Parahippocampal	L	28				-22	-22	-12	
Parahippocampal	L	35				-24	-28	-18	
Putamen	R		31.19	15.12	-1.92	30	14	-2	912
dmPFC	R	6	7.8	50.76	34.52	8	50	34	912
Superior Temporal	R	39	37.92	-56.21	30.8	38	-56	30	688
vlPFC	L	47	-41.4	40	-13.19	-44	40	-14	520
Cingulate Gyrus	L	32	1.83	29.56	34.92	2	30	36	520
vlPFC	R	47	27.38	37.52	-14.68	28	38	-14	440
Cuneus	L	18	-10.52	-72	21.09	-12	-74	18	432
Precuneus	L	31				-10	-70	22	
Precentral Gyrus	R	44	55.92	2.94	4.84	56	2	4	352
Posterior Cingulate	R	30	7.27	-49.22	23.98	8	-50	24	320
vlPFC	L	45	-45.5	22.33	-1.94	-46	22	-2	288
Hippocampus	R		40.73	-20.94	-12.64	40	-22	-12	224

NAc: nucleus accumbens; dmPFC: dorsal medial prefrontal cortex; vlPFC: ventrolateral prefrontal cortex

Table S3 Antidepressant effects in mood disorder patients

Brain regions	Hemi.	BA	Weighted Center			MNI coordinates			Volume (mm^3)
			x	y	z	x	y	z	
Antidepressant effects on positive emotions									
Antidepressant > Control (based on 12 contrasts, 90 foci)									
Amygdala	L		-20.78	-4.87	-16.83	-22	-4	-16	744
dlPFC	R	9	55.95	24.38	25.56	56	24	26	600
Amygdala	R		23	-14	-18	22	-14	-18	496
Hippocampus	L		-27.25	-29.89	-17.02	-30	-28	-14	472
vmPFC	R	10	19.14	57.12	-8.42	20	58	-8	376
Anterior Cingulate	R	32	12.28	43.3	4.86	12	44	4	360
Fusiform Gyrus	L	19	-32.13	-82.63	-6.29	-32	-82	-6	320
vmPFC	L	10	-7.33	61.4	2.44	-8	62	2	296
Precuneus	L	7	-1	-70.58	39.9	-2	-72	42	232
Insula	L	13	-36.01	20.31	5.59	-36	20	6	224
Antidepressant < Control (based on 3 contrasts, 10 foci): insufficient studies									
Antidepressant effect on negative emotions									
Antidepressant > Control (based on 14 contrasts, 55 foci)									
dlPFC	L	9	-44.56	16.37	25.64	-44	18	26	608
						-46	8	30	
Antidepressant < Control (based on 25 contrasts, 134 foci)									
Amygdala	L		-19.3	-3.63	-17.87	-22	-6	-20	3888
Amygdala	R		28.55	-3.31	-20.39	30	-4	-20	2656
Hypothalamus	R	25	5.13	-0.64	-15.45	6	-2	-16	616
Putamen	L		-23.56	-8.82	9.99	-24	-10	10	576
Middle Temporal	L	21	-62.22	-41.39	2.41	-62	-42	2	456
Anterior Cingulate	R	24	1.66	42.22	4.54	2	42	4	392
Insula	R	13	46	-13	-6	46	-12	-6	240
Middle Frontal	L	10	-32.42	49.31	17.54	-32	50	18	232

dlPFC: dorsolateral prefrontal cortex
vmPFC: ventral medial prefrontal cortex

Table S4 SSRIs and SNRIs effects in mood disorder patients and healthy volunteers

Conditions	SNRI	SSRI
	Patients	
Positive Increase	dlPFC, fusiform, ACC, mPFC, insula, dmPFC, precentral	Amygdala (bi.)
Positive Decrease	none	none
Negative Increase	none	dlPFC
Negative Decrease	Hypothalamus, insula, cerebellum, MT	Amygdala (bi.), ACC, putamen, middle frontal
	Healthy volunteers (Repeated administration)	
Positive Increase	none	none
Positive Decrease	ACC	NAc, Midbrain, ACC, vmPFC
Negative Increase	none	none
Negative Decrease	Amygdala (r), putamen, ACC, mPFC, insula	Amygdala (bi.), putamen, Parahippocampal, insula
	Healthy volunteers (Single administration)	
Positive Increase	none	none
Positive Decrease	none	none
Negative Increase	Thalamus, caudate body, dmPFC	Amygdala (bi.), ACC, thalamus, caudate body, vlPFC, middle temporal, dmPFC,
Negative Decrease	none	Amygdala (bi.), dmPFC, vlPFC, fusiform

dlPFC: dorsolateral prefrontal cortex; ACC: anterior cingulate cortext; dmPFC: dorsal medial prefrontal cortex; MT: middle temporal cortex; (bi.): bilateral; (r): right hemisphere; vmPFC: ventral medial prefrontal cortex; NAc: nucleus accumbens; vlPFC: ventral lateral prefrontal cortex.

Table S5 Antidepressant effects on facial and pictorial stimuli in mood disorder patients and healthy volunteers

Conditions	Facial stimuli[1]	Pictorial stimuli
Patients		
Positive Increase	Amygdala (bi.)	dmPFC, insula, precentral, thalamus
Positive Decrease	none	none
Negative Increase	dlPFC	none
Negative Decrease	Amygdala (bi.), putamen	ACC, vlPFC, middle frontal, vmPFC, Amygdala (r)
Healthy volunteers (Repeated administration)		
Positive Increase	none	none
Positive Decrease	none	ACC, dmPFC, putamen, midbrain, vmPFC, NAc
Negative Increase	none	none
Negative Decrease	Amygdala (bi.), thalamus, parahippocampal	ACC, insula, dlPFC
Healthy volunteers (Single administration)		
Positive Increase	none	none
Positive Decrease	none	none
Negative Increase	Amygdala (bi.), fusiform	Thalamus, caudate body, dmPFC
Negative Decrease	Amygdala (bi.), vlPFC	none

dlPFC: dorsolateral prefrontal cortex; ACC: anterior cingulate cortext; dmPFC: dorsal medial prefrontal cortex; (bi.): bilateral; (r): right hemisphere; vmPFC: ventral medial prefrontal cortex; NAc: nucleus accumbens; vlPFC: ventral lateral prefrontal cortex.

[1]Note: Almost all the studies used facial stimuli (for patients and repeated administration healthy subject studies) also used SSRIs administration (only one study used SNRIs administration and one study employ mixed SSRI/SNRI administration). Thus it is difficult to conclude whether these effects merely arise from SSRIs administration or also selective for facial stimuli, which could be an interesting topic for future empirical studies to test.

Table S6 Antidepressant effects on implicit and explicit emotional processes in mood disorder patients and healthy volunteers

Conditions	Explicit emotional processing	Implicit emotional processing
	Patients	
Positive Increase	none	Amygdala (r), fusiform, insula, precuneus, dmPFC, **dlPFC**
Positive Decrease	none	none
Negative Increase	none	**dlPFC**
Negative Decrease	Amygdala (bi.), Hpothalamus, middle frontal, insula, vlPFC	Amygdala (bi.), insula, vmPFC, dmPFC
	Healthy volunteers (Repeated administration)	
Positive Increase	Amygdala (r)	none
Positive Decrease	NAc, putamen, ACC	dmPFC, midbrain, ACC, vmPFC, NAcc
Negative Increase	Parahippocampal	none
Negative Decrease	Putamen, Amygdala (bi.), insula, Parahippocampal, ACC, thalamus, dlPFC	Amygdala (r)
	Healthy volunteers (Single administration)	
Positive Increase	none	none
Positive Decrease	none	none
Negative Increase	Amygdala (bi.), caudate body, vlPFC, ACC, thalamus, dmPFC, superior/middle temporal	Thalamus, fusiform, dmPFC, vlPFC
Negative Decrease	Precentral	Amygdala (bi.), fusiform, thalamus, vlPFC, dmPFC

dlPFC: dorsolateral prefrontal cortex; ACC: anterior cingulate cortext; dmPFC: dorsal medial prefrontal cortex; (bi.): bilateral; (r): right hemisphere; vmPFC: ventral medial prefrontal cortex; NAc: nucleus accumbens; vlPFC: ventral lateral prefrontal cortex.

Table S7 Repeated antidepressant effects in mood disorder patients (Only including studies employing repeated antidepressant administration)

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 11 contrasts, 89 foci)									
Amygdala	R		23	-14	-18	22	-14	-18	560
dlPFC	R	9	57.63	22.68	27.15	58	22	28	464
Fusiform Gyrus	L	19	-32.04	-82.66	-6.34	-32	-82	-6	448
Anterior Cingulate	R	32	12.27	43.03	5.17	12	44	6	432
Amygdala	L		-19.84	-7.47	-17.63	-20	-8	-18	416
vmPFC	L	10	-7.37	61.58	2.31	-8	62	2	344
Precuneus	L	7	-0.71	-70.54	39.76	-2	-72	42	320
Insula	L	13	-36.33	20.5	5.7	-36	20	6	312
dlPFC	L	10	-23.19	59.05	18.72	-24	58	18	240
dmPFC	L	8	-8.17	32.5	43.72	-8	32	44	200
Antidepressant < Control (based on 3 contrasts, 10 foci): insufficient studies									
Repeated antidepressant administration on negative emotions									
Antidepressant > Control (based on 13 contrasts, 53 foci)									
dlPFC	L	9	-44.56	16.37	25.64	-44	18	26	608
Antidepressant < Control (based on 23 contrasts, 131 foci)									
Amygdala	L		-18.8	-2.92	-17.36	-20	-6	-18	3544
Amygdala	R		27.56	-3.76	-20.03	28	-4	-20	2288
Putamen	L		-24.16	-9.12	10.55	-24	-10	10	672
Hypothalamus	R		5.1	-0.62	-15.44	6	-2	-16	624
Anterior Cingulate	R	25				6	8	-12	
Middle Temporal	L	21	-62.16	-41.37	2.43	-62	-42	2	464
Anterior Cingulate	L	24	1.66	42.22	4.54	2	42	4	392
Insula	R	13	46	-13	-6	46	-12	-6	240
Middle Frontal	L	10	-32.42	49.31	17.54	-32	50	18	232

dlPFC: dorsolateral prefrontal cortex
vmPFC: ventral medial prefrontal cortex
dmPFC: dorsal medial prefrontal cortex

Table S8 Conjunction analysis on studies on healthy volunteers and mood disorder patients (Only including studies employing repeated antidepressant administration)

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 (healthy: 10 contrasts, 31 foci; patient: 11 contrasts, 89 foci)									
Amygdala	R		24	-10	-16	24	-10	-16	8
Amygdala	L		-22	-5.73	-17.72	-22	-6	-18	64
Repeated antidepressant administration on negative emotions									
Antidepressant < Control (healthy: 20 contrasts, 83 foci; patient: 23 contrasts, 131 foci)									
Amygdala	R		26.03	-4.12	-18.48	26	-4	-18	1376
Amygdala	L		-22.52	-3.87	-17.8	-22	-4	-18	992

Table S9 SSRIs and SNRIs dosage in mood disorder patients and healthy volunteers

Drugs	Healthy (Repeated)		Healthy (Single)		Patients	
	Dosage	Num.	Dosage	Num.	Dosage	Num.
Duloxetine	60 mg	3	-	0	60-120	1
Reboxetine	4 mg	4	**4 mg**	**4**	-	0
			8 mg	**2**		
Venlafaxine	-	0	-	0	18.75-112.5 mg	2
					37.5-225 mg	1
					225 mg	1
Citalopram	20 mg	6	**20 mg**	**3**	10-40 mg	1
			40 mg	**2**	20-40 mg	1
			50 mg	**1**	7.5 mg (in.)	1
			7.5 mg (in.)	**4**		
Escitalopram	5-10 mg	3	-	0	10 mg	1
					10-20 mg	1
					10-30 mg	2
Fluoxetine	-	0	50 mg	1	20 mg	2
					5-40 mg	2
					20-60 mg	1
Mirtozapine	-	0	**15 mg**	**1**	30-45 mg	2
			30 mg	**1**		
Paroxetine	20 mg	1	20 mg	1	20 mg	1
Bupropion	150 mg	1	150 mg	1	60-120 mg	1
					100 mg	1
Sertraline	-	0	-	0	50-100 mg	1
					50-200 mg	1

Num. = number of studies
in. = intravenously administrated antidepressants, and other studies used oral antidepressant administration.

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