Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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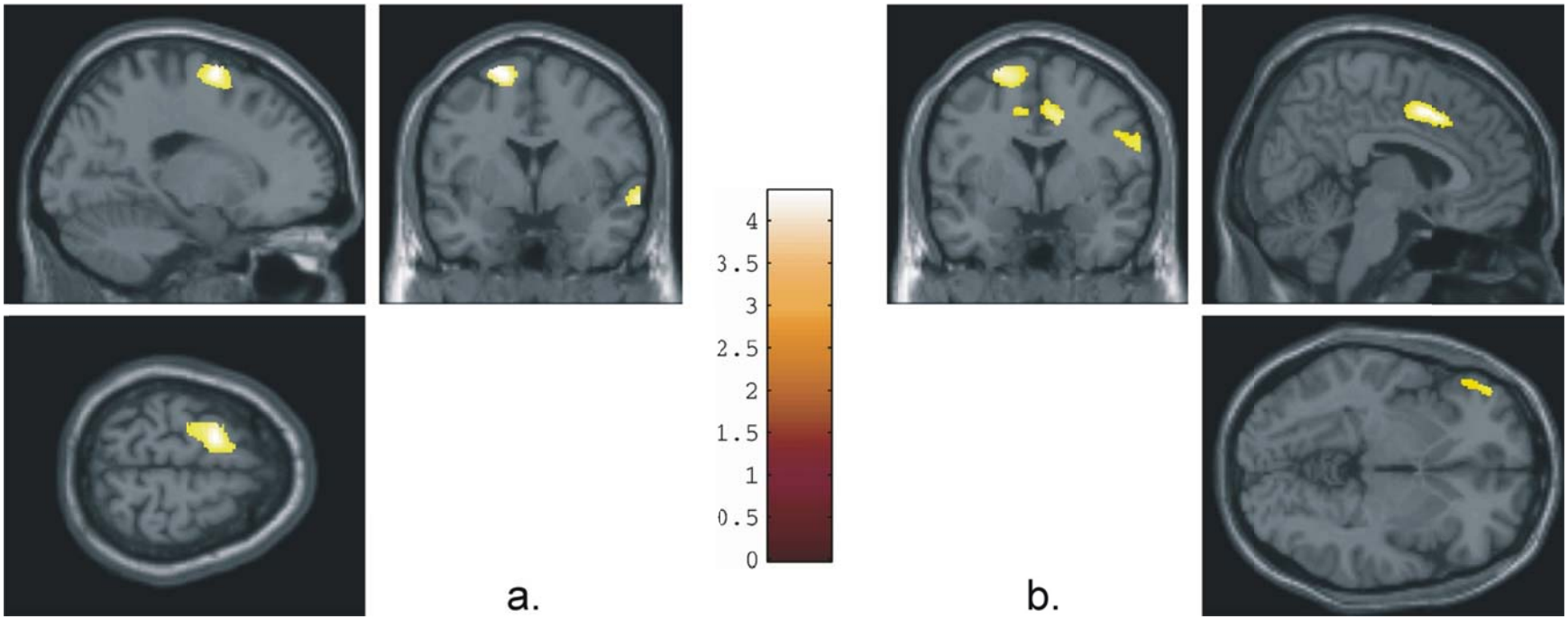

Fig. S1: VBM results of second-level between-group analyses covaried for age and sex, $p < 0.005$ (uncorrected at the voxel level, $p < 0.05$ corrected for spatial extent). (**A**) Brain regions with decreased grey matter volume in medicated and unmedicated patients with MDD ($n = 43$) compared to healthy controls ($n = 29$). The colour bar indicates t values. Patients had less grey matter volume than controls in the right superior temporal cortex (x=65, y=1, z=–7, Z=3.50, k=368) and in the left superior frontal/middle frontal gyrus (x=–17, y=1, z=67, Z=3.75;k=873). (**B**) Brain regions with decreased grey matter volume in medicated patients with MDD ($n = 29$) compared to healthy controls ($n = 29$). The colour bar indicates t values. The following brain regions exhibited lower grey matter volume in patients compared to controls: bilateral cingulate gyrus (left: x=–14, y=–7, z=46, Z=3.22; right: x=7, y=8, z=43, Z=4.00, k=1475), left superior frontal and left precentral gyrus (x=–23, y=0, z=68, Z=3.73 and x=–25, y=–15, z=69, Z=2.94, k=1276), right precentral gyrus (x=62, y=2, z=25, Z=3.16, k=297), right middle temporal gyrus (x=43, y=–62, z=14, Z=3.13, k=198) and left middle frontal gyrus (x=–48, y=46, z=–3, Z=3.27, k=142).

Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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Table S1: Brain areas showing brain perfusion changes at rest in medicated patients with MDD (*n*=29) compared to controls (n=29)*

	SPM analysis						BPM analysis					
Comparison	Region	*x*	*y*	*z*	*Z*	No. of voxels	Region	*x*	*y*	*z*	*Z*	No. of voxels
Controls > patients	Left parahippocampal gyrus	–10	–50	0	4.28	3832	Right parahippocampal gyrus	14	–50	–2	4.25	3750
	Cuneus	10	–92	10	4.02		Cuneus	10	-90	10	4.10	
	Right parahippocampal gyrus	12	–48	0	3.98		Left parahippocampal gyrus	–22	–28	–12	3.40	
	Left anterior cingulate	–10	28	–6	3.44	188	Left anterior cingulate	–8	28	–6	3.43	207
Patients > controls	Right inferior parietal lobule	34	–62	44	4.19	2838	Right inferior parietal lobule	54	–34	34	4.29	2739
	Right superior temporal gyrus	54	–46	8	3.54		Right superior temporal gyrus	54	-46	8	4.22	
	Right superior frontal gyrus	18	56	10	3.76	3920	Right superior frontal gyrus	20	22	44	3.81	3797
	Right medial frontal gyrus	10	38	38	3.70		Right medial frontal gyrus	18	42	20	3.72	
	Right middle frontal gyrus	36	16	48	3.67		Right medial frontal gyrus	4	26	46	3.72	
	Right middle frontal gyrus	36	50	8	3.58		Right superior frontal gyrus	18	56	10	3.71	
	Left medial frontal gyrus	–8	18	52	3.42		Right middle frontal gyrus	34	16	50	3.52	
	Right superior frontal gyrus	28	32	38	3.32		Right inferior frontal gyrus	38	4	30	3.02	
	Right lentiform nucleus	30	–10	6	4.24	771	Right lentiform nucleus	28	–20	6	4.15	833
	Right caudate	16	8	12	3.03		Right caudate	16	8	12	3.03	
							Left middle frontal gyrus	–36	–4	54	3.53	213

BPM = Biological Parametric Mapping; MDD = major depressive disorder; SPM = Statistical Parametric Mapping.

*Results of second- level *t* test (standard SPM8 analysis) and analysis of covariance (BPM analysis), $p < 0.005$ uncorrected at the voxel level, $p < 0.05$ corrected for spatial extent.

Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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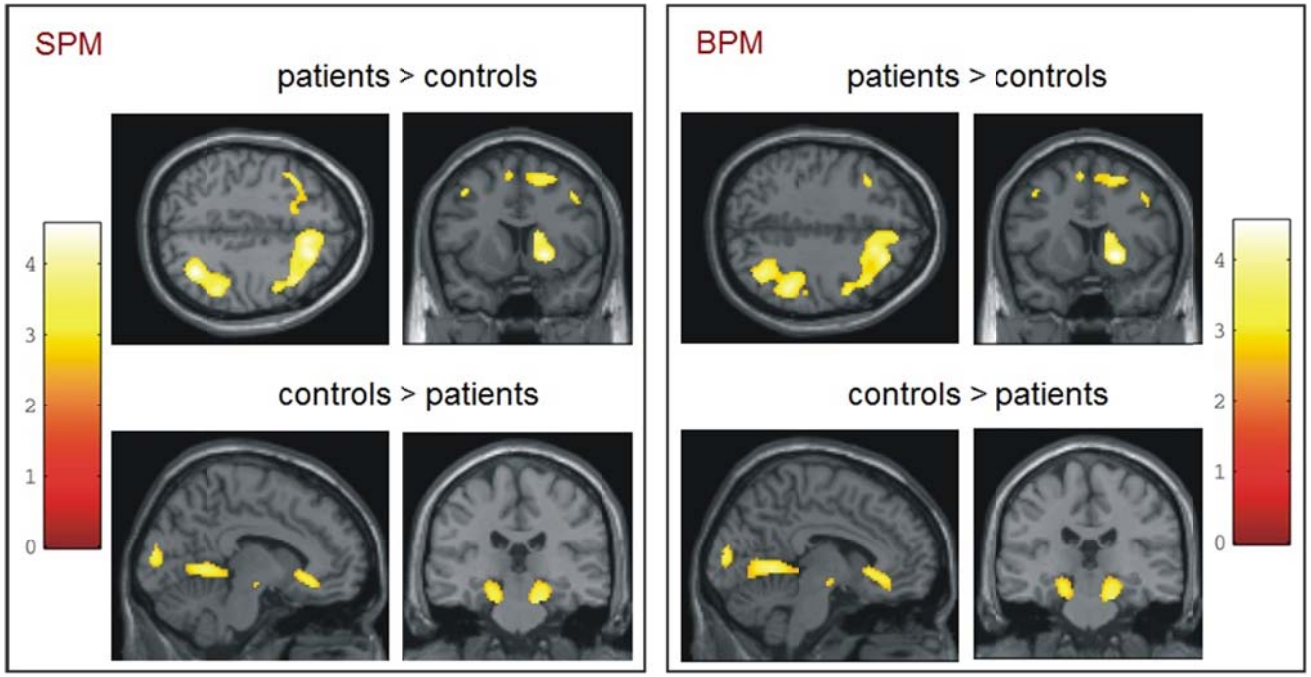

Fig. S2: Regions with abnormal regional cerebral blood flow (rCBF) in medicated and unmedicated patients with MDD (n = 43) compared to healthy controls (n = 29). For purposes of visual comparison, results of the standard SPM8 analysis uncorrected for brain volume change (left) together with results of the BPM analysis (i.e., rCBF data with individual voxel-wise brain volume as covariate; right). Results of the second level between-group analysis, p <0.005 (uncorrected at the voxel level, p <0.05 corrected for spatial extent). The colour bar indicates t values.

Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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Table S2: Demographics and clinical scores for controls and patients with MDD (medicated sample)

	Group; mean ± SD*		
Characteristic	Controls (n = 29)	Patients (n= 29)	*p* value
Age, yr	34.5 ± 10.7	38.9 ± 9.5	0.10
Education, yr	14.9 ± 2.6	13.1 ± 2.3	0.009
Sex, male:female	11:18	15:14	—
Duration of illness, yr	—	7.4 ± 7.2	—
No. of episodes	—	3.4 ± 2.1	—
BDI score	1.5 ± 2.4	27.7 ± 8.4	< 0.001
HAMD score	0.9 ± 1.7	20.1 ± 5.3	< 0.001

BDI: Beck Depression Inventory; HAMD: Hamilton Rating Scale for Depression.
*Unless otherwise indicated.

Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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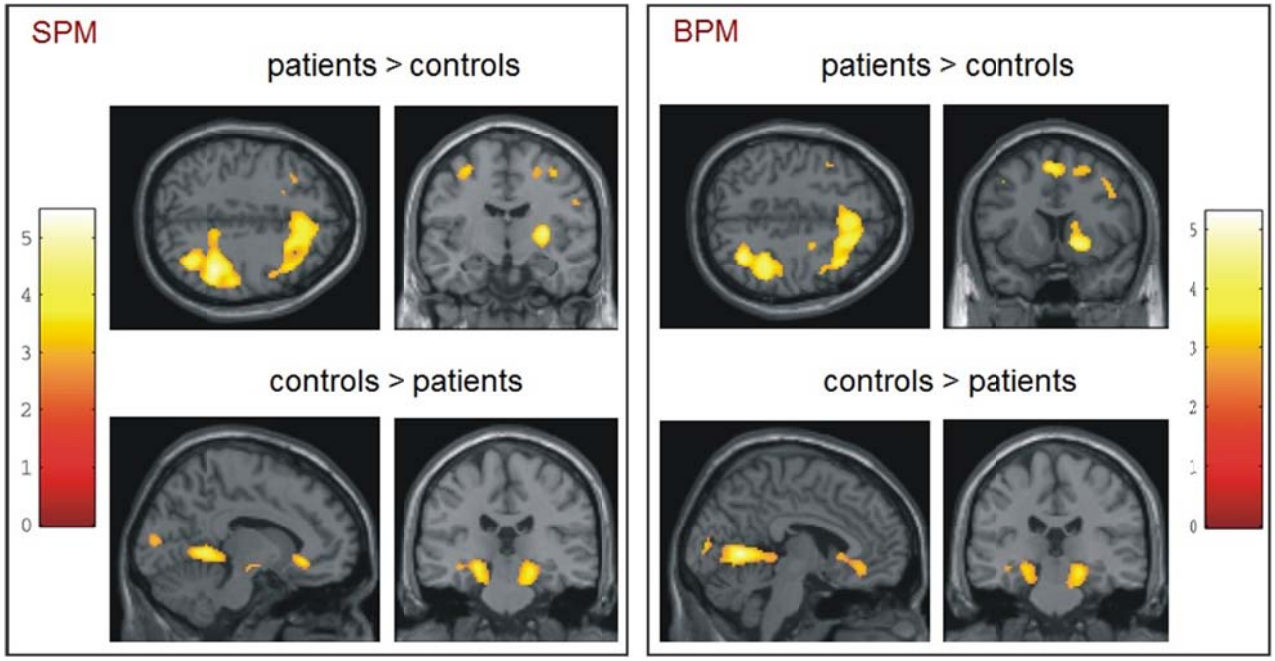

Fig. S3: Regions with abnormal regional cerebral blood flow (rCBF) in medicated patients with MDD ($n = 29$) compared to healthy controls ($n = 29$). For purposes of visual comparison, results of the standard SPM8 analysis uncorrected for brain volume change (left) together with results of the BPM analysis (i.e., rCBF data with individual voxel-wise brain volume as covariate; right). Results of the second-level between-group analysis, $p < 0.005$ (uncorrected at the voxel level, $p < 0.05$ corrected for spatial extent). The colour bar indicates t values.

Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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Table S3: Pharmacological treatment of medicated patients with MDD (*n* = 29)

Medication	Dose, mg/d	No. of patients
Escitalopram, monotherapy	10–20	5
Escitalopram + agomelatine	20, 25	1
Citalopram, monotherapy	20–40	2
Citalopram + pregabalin	40, 75	1
Venlafaxine, monotherapy	75	1
Venlafaxine + mirtazapine	37.5–375, 15–60	3
Duloxetine, monotherapy	60	1
Duloxetine + olanzapine	60, 7.5	1
Duloxetine + agomelatine	30, 25	1
Duloxetine + mirtazapine	90, 45	1
Mirtazapine, monotherapy	15–30	2
Bupropione, monotherapy	300	1
Fluoxetine, monotherapy	20	1
Fluoxetine + agomelatine	30, 50	1
Fluoxetine + lithium	80, 900	1
Paroxetine + mirtazapine	20, 15	1
Sertraline, montotherapy	50	1
Setraline + pregabalin	200, 600	1
Sertraline + bupropione + trimipramine	200, 150, 50	1
Sertraline + mirtazapine	50, 15	1
Tranylcypromine, monotherapy	60	1

Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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Table S4: Brain areas showing brain perfusion changes at rest in unmedicated and medicated patients with MDD (*n* = 43) compared to controls (*n* = 29)*

Comparison	Region	*x*	*y*	*z*	*Z*	no. of voxels
Controls > patients	Right cuneus	14	–92	8	4.09	232
	Right parahippocampal gyrus	26	–24	–20	3.54	349
	Left parahippocampal gyrus	–24	–30	–20	3.13	145
	Left superior temporal gyrus	–38	8	–18	3.19	167
	Left anterior cingulate	–6	20	-4	2.90	45†
Patients > controls	Right superior parietal lobule	32	–64	44	3.46	381
	Right inferior parietal lobule	40	–54	50	3.46	
	Right middle frontal gyrus	24	32	42	4.04	509
	Right medial frontal gyrus	10	26	44	3.40	
	Right superior frontal gyrus	8	30	50	3.43	
	Left superior frontal gyrus	–12	18	50	3.90	389
	Left middle frontal gyrus	–20	22	50	3.35	
	Right lentiform nucleus	28	–6	10	3.38	262

*Results of second between-group analyses covaried for medication status, uncorrected height threshold $p < 0.005$.

†Indicates that this region did not survive a cluster-corrected threshold of $p < 0.05$.

Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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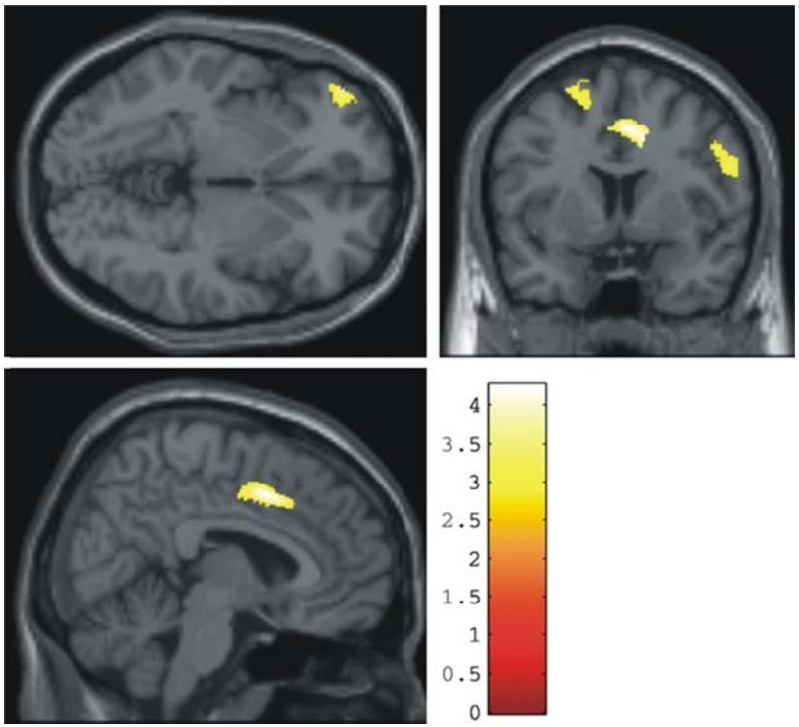

Fig. S4: Brain regions with decreased grey matter volume in medicated patients with MDD ($n = 29$) compared to healthy controls ($n = 29$). Results of the second-level between-group analysis, $p < 0.005$ (uncorrected at the voxel level, $p < 0.05$ corrected for spatial extent). The colour bar indicates t values.

Appendix 1 to Vasic N, Wolf N, Grön G, et al. Baseline brain perfusion and brain structure in major depression: a multimodal magnetic response imaging study. *J Psychiatry Neurosci* 2015.

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Table S5: Brain areas showing grey matter volume differences between controls and medicated patients with MDD (n=29)*

Region	*x*	*y*	*z*	*Z*	no. of voxels
Right cingulate gyrus	7	6	44	3.82	1211
Left cingulate gyrus	–12	22	39	3.29	
Right inferior temporal gyrus	55	–48	–19	3.35	582
Left middle frontal gyrus	–46	47	–3	3.28	196
Right precentral gyrus	64	–5	20	3.16	604
Right inferior frontal gyrus	56	3	25	3.14	
Left middle frontal gyrus	–23	2	68	3.06	375
Left superior frontal gyrus	–15	10	54	2.94	

*Results of the second level *t* test, $p < 0.005$ uncorrected at the voxel level, $p < 0.05$ corrected for spatial extent.