

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Supplement I:

Effects of SSRIs: description of group

After omission of the SSRI using participants, groups were matched on age, gender, scan site, and handedness. Our renewed sample consisted of 207 subjects, i.e. 50 MDD, 48 CDA, 47 ANX, and 62 HC. Table 1 lists all characteristics for the medication free sample. Groups were comparable on all clinical characteristics to the groups that include the SSRI-using participants. Also, no effect of group exists with respect to total grey matter ($F[3,203]=.34$, $p=.80$) and total white matter ($F[3,203]=.18$, $p=.91$). Sample characteristics are listed in Table S1.

Age of onset

Groups were matched on age, edu, gender and handedness. Within diagnostic groups, early onset (EO) did not differ in MADRS and BAI scores. Clinical characteristics are listed in Table S2.

GM images were entered in a one-way ANOVA with group as independent variable and age, gender, GM-totals, and center as covariates.

Recurrence

MDD and CDA were pooled and splitted into a single episode MDD group and a recurrent episode MDD group. Groups (single, recurrent, and HC) were matched on age, gender and handedness.

Groups differed in years of education, MADRS scores and BAI scores (edu: $F[2,204]=14.19$, $p<.001$; MADRS: $F[2,204]=74.8$, $p<.001$; BAI: $F[2;204]=45.11$, $p<.001$). Post hoc tests showed that HC had more years of education and lower scores on MADRS and BAI than single and recurrent MDD.

Clinical characteristics are listed in Table S3. GM images were entered in a one-way ANOVA with group as independent variable and age, gender, GM-totals, and center as covariates.

Supplement II:

Effect of trauma on ACC volumes:

Data regarding the experience of emotional and physical trauma were available (assessed with the Nemesis trauma interview).¹ In our sample of 289 subjects, 55.9 % of MDD, 69.3% of CDA, 57.4% of ANX, and 38.5 % of HC reported to have ever experienced emotional or physical trauma in their lives (ranging from 'once' to 'very often'). To test for the effect of trauma on ACC volumes, we set up ANCOVAs with GM ACC volume as dependent factor, and diagnosis and trauma (yes/no) as independent factor. Age, GM totals, and scan center were entered as covariates. No effect of self-reported trauma was observed on ACC volume ($F[1,277]=.37$, $p=.54$), and no interaction with diagnosis was observed ($F[3,277]=.37$, $p=.26$). The experience of a physical or emotional trauma more than once, occurred in 34 % of MDD, 46% of CDA, 40% of ANX, and 17% of HC before the age of 16. Again, (severe) childhood trauma was not associated with ACC volume when compared to subjects that never experienced trauma ($F[1,215]=1.22$, $p=.27$), and no interaction with diagnosis was observed ($F[3,215]=.84$, $p=.48$).

References:

De Graaf R, Bijl RV, Smit F, Vollebergh WA, Spijker J. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *Am J Psychiatry*. 2002; 159: 620-629.

Supplement table legends

Table S1: Clinical characteristics of the SSRI free sample (N=207)

MDD= Major Depressive Disorder; CDA= Comorbid MDD and anxiety; ANX= anxiety without MDD; HC= healthy controls; c=9 MDD+GAD, 12 MDD+PD, 5 MDD+PD+GAD, 7 MDD+SAD, 7 MDD+SAD+GAD, 5 MDD+PD+SAD, 3 MDD+PD+SAD+GAD; d= 16 PD, 2 PD+GAD, 20 SAD, 7 PD+SAD, 2 PD+SAD+GAD; SSRI = Selective Serotonin Reuptake Inhibitor; T1: baseline measurement; T2: MRI-measurement; MADRS: Montgomery Åsberg Depression Rating Scale; BAI: Beck Anxiety Inventory; IDS: Inventory of depressive symptomatology; FQ: Fear Questionnaire; rem= remitted depressive scores (MADRS: 0-8), mild= mild depressive scores: (MADRS 9-18), mod_sev= moderate to severe depressive scores (MADRS>19); GM= grey matter total volume; WM= white matter total volume.

Table S2: Clinical characteristics of matched early and late depression onset groups vs. HC

MDD= Major Depressive Disorder; CDA= Comorbid MDD and anxiety; HC= healthy controls; EO= early onset MDD (onset of first episode before age of 18); LO= late onset MDD (onset of first episode after age of 18); SSRI= Selective Serotonin Reuptake Inhibitor; MADRS: Montgomery Åsberg Depression Rating Scale; BAI: Beck Anxiety Inventory; GM= grey matter total volume; WM= white matter total volume.

Table S3: Clinical characteristics of matched single episode vs. recurrent episode MDD

MDD= Major Depressive Disorder; CDA= Comorbid MDD and anxiety; HC= healthy controls; SSRI= Selective Serotonin Reuptake Inhibitor; MADRS: Montgomery Åsberg Depression Rating Scale; BAI: Beck Anxiety Inventory; GM= grey matter total volume; WM= white matter total volume.

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Supplement tables

Table S1: Clinical characteristics of the SSRI free sample (N=207)

		MDD	CDA c	ANX d	HC
N		50	48	47	62
gender	male/female; N	20/30	12/36	13/34	23/39
scan site	amc/lumc/umcg; N	12/20/18	16/21/11	14/15/18	26/25/11
handedness	left/right; N	6/44	4/44	3/44	5/57
History of SSRI use	1/2/3/4 *; N	7/3/4/36	5/7/5/31	3/7/3/34	
age	in years; mean ± sd	36.22 ± 10.02	36.58 ± 10.9	35.11 ± 9.85	39.89 ± 9.46
education	in years; mean ± sd	12.56 ± 2.45	12.04 ± 3.4	13.23 ± 3.27	14.34 ± 2.85
MADRS	total score; mean ± sd	12.56 ± 9.78	20.17 ± 9.58	10.87 ± 8.76	1 ± 1.78
	range	0-39	2-43	0-35	0-7
	severity class: rem/mild/mod_sev; N	19/18/13	6/17/25	-	-
IDS T1	total score; mean ± sd	27.54 ± 10.17	32.65 ± 10.61	22.51 ± 11.91	5.03 ± 3.52
IDS T2	total score; mean ± sd	20.58 ± 15.43	28.56 ± 11.15	19 ± 10.83	3.59 ± 3.64
	range	1 - 57	5 - 55	4 - 49	0 - 17
BAI T1	total score; mean ± sd	11.62 ± 9.38	17.90 ± 9.09	15.26 ± 9.73	1.84 ± 3.14
BAI T2	total score; mean ± sd	8.78 ± 8.59	17.94 ± 9.22	15.30 ± 10.28	1.84 ± 3.14
	range	0 - 50	1 - 46	0 - 42	0 - 10
FQ	total score; mean ± sd	20.58 ± 15.43	24.65 ± 21.47	29.98 ± 23.82	7.62 ± 8.10
	range	0 - 79	0 - 78	0 - 84	0 - 29
onset MDD	age in years; mean ± sd	25.26 ± 9.49	22.36 ± 11.72	-	-
onset ANX	age in years; mean ± sd	-	17.5 ± 10.54	15.38 ± 11.49	-
recurrence MDD	single/recurrent episode; N	21/29	21/27	-	-
ANX	diagnosis in lifetime; N	14	-	-	0
	diagnosis in past year; N	6	-	-	-
MDD	diagnosis in lifetime; N	-	-	25	0
	diagnosis in past year; N	-	-	1	-
GM	ml; mean ± sd	735.07 ± 57.90	725.2 ± 73.7	738.44 ± 79.77	728.69 ± 75.26
WM	ml; mean ± sd	495.04 ± 60.85	489.65 ± 60.18	489.70 ± 67.78	486.55 ± 59.83

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Table S2: Clinical characteristics of matched early and late depression onset groups vs. HC

		MDD		CDA		HC
		EO	LO	EO	LO	
N		23	38	32	40	48
gender	male/female; N	8/15	12/26	8/24	14/26	17/31
scan site	amc/lumc/umcg; N	4/8/11	12/16/10	10/11/11	16/14/10	19/22/7
handedness	left/right; N	1/22	5/33	2/30	3/37	5/43
SSRI use	current yes/no; N	7/16	7/31	14/18	21/19	0/48
age	in years: mean ± sd	34 ± 10.5	37 ± 8.1	32.4 ± 9.9	37 ± 9.6	37.7 ± 8.9
education	in years: mean ± sd	13 ± 2.9	12.3 ± 2.6	12.3 ± 2.6	12.6 ± 3.1	13.7 ± 2.2
MADRS	total score: mean ± sd	14.4 ± 9.4	13.2 ± 9.4	19.7 ± 8.8	19.1 ± 9.7	.8 ± 1.6
BAI	total score: mean ± sd	9.2 ± 7.2	8.9 ± 9.1	20.3 ± 8.7	16.3 ± 9.1	1.9 ± 2.6
onset MDD	age in years: mean ± sd	15.17 ± 2.55	30.13 ± 7.32	13.22 ± 3.52	28.18 ± 7.37	-
GM	in ml: mean ± sd	742.2 ± 65.8	724.7 ± 68.8	746.5 ± 69.3	732.9 ± 78.9	738.4 ± 75.4
WM	in ml: mean ± sd	467.1 ± 62.2	491.1 ± 62.6	485.6 ± 59.6	509.5 ± 71.1	486.4 ± 58.8

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Table S3: Clinical characteristics of matched single episode vs. recurrent episode MDD

		MDD + CDA		HC
		single	recurrent	
N		68	85	58
gender	male/female; N	27/41	24/61	21/37
scan site	amc/lumc/umcg; N	19/35/14	26/26/33	17/26/22
handedness	left/right; N	5/63	7/78	5/53
diagn	MDD/CDA; N	29/39	36/49	-
SSRI	current use yes/no; N	26/42	30/55	-
age	in years; mean ± sd	37.37 ± 10.13	37.51 ± 9.60	38.9 ± 8.96
education	in years; mean ± sd	13.08 ± 3.12	12.45 ± 3.11	14.59 ± 2.6
MADRS	total score: mean ± sd	10.31 ± 11.11	16.14 ± 10.1	.98 ± 1.83
BAI	total score: mean ± sd	9.37 ± 10.4	13.2 ± 9.2	1.96 ± 2.46
GM	ml; mean ± sd	732.34 ± 77.97	727.94 ± 63.91	730.83 ± 75.06
WM	ml; mean ± sd	492.33 ± 65.12	491.09 ± 61.52	486.67 ± 60.76