ORIGINAL RESEARCH

Elevated peripheral blood glutamate levels in major depressive disorder

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Purpose: There is growing evidence that glutamatergic signaling may be involved in major depressive disorder (MDD). In regard to peripheral blood glutamate changes in MDD, inconsistent findings have been reported. The purpose of the present study was to evaluate whether blood glutamate levels differed between MDD patients and control participants.

Materials and methods: We conducted a systematic review and meta-analysis of 12 association studies between blood glutamate levels and MDD in a total of 529 MDD patients and 590 controls. Subsequently, we conducted subgroup analyses and a meta-regression analysis to examine the sources of potential heterogeneity.

Results: A random effects model showed that blood glutamate levels were significantly higher in MDD patients than in controls (standardized mean difference=0.54, 95% CI=0.27–0.82, $p=8.5\times10^{-5}$) with high heterogeneity (I^2=75.0%, $p<0.05$). Subgroup analyses showed elevated glutamate levels in MDD patients compared with controls in plasma, but not serum studies, and in studies using high-performance liquid chromatography but not with mass spectrometry for glutamate assay. A meta-regression analysis showed no effects of age, gender, medication use, sample size, and published year on blood glutamate levels.

Conclusion: Our findings suggest that altered glutamate levels may be implicated in MDD, which provides further evidence of glutamatergic dysfunction in MDD.

Keywords: glutamate, major depressive disorder, blood, association study, meta-analysis

Introduction

Major depressive disorder (MDD) is a common neuropsychiatric disorder with high prevalence.[1] Several pathophysiological mechanisms have been proposed to underlie this disorder, such as altered monoamines, increased inflammation, and abnormalities of the hypothalamic–pituitary–adrenal axis.[2,3]

There is growing evidence that glutamatergic signaling may be involved in the pathophysiology of MDD.[4–6] Dysregulation between the main excitatory glutamatergic and inhibitory gamma-aminobutyric acid-ergic neurotransmission results in cellular damage called "excitotoxicity," and this phenomenon is thought to be the cause of MDD.[7] Glutamate is one of the major excitatory amino acid neurotransmitters. It plays a major role in brain development, affecting neuronal migration, neuronal differentiation, axon genesis, and neuronal survival.[5] Under normal conditions, glutamate has a prominent role in synaptic plasticity, learning, and memory, while it is also known to be a potent neuronal excitotoxin, triggering either rapid or delayed neurotoxicity in pathological conditions.[4] Further, glutamate neurotoxicity results from excessive flux of Ca^2 via ionotropic receptors, and uncontrolled elevation of intracellular Ca^2 leads to a cascade of events that contribute to cell damage and death.[8] Glutamate may also play an important role

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in the treatment of MDD.[9,10] For example, a significant decrease in blood glutamate levels has been observed in MDD after treatment with antidepressants.[11,12] In a recent meta-analysis of 6 randomized, double-blind, and placebo-controlled trials of ketamine, an N-methyl-D-aspartate glutamate receptor antagonist, a rapid antidepressant action of ketamine was observed for MDD during 1 week period.[13] Moreover, a number of studies have shown antidepressant-like effects of glutamatergic agents on behavioral models of MDD.[10]

Recently, we demonstrated elevated plasma glutamate levels in individuals with MDD, using capillary electrophoresis-time-of-flight mass spectrometry.[14] However, with regard to peripheral blood glutamate levels in MDD, inconsistent findings have been reported. Although some clinical studies have shown elevated plasma or serum levels of glutamate in MDD,[11,14–19] others did not observe any differences between MDD patients and control subjects.[12,20–24] Besides, it is still unclear whether peripheral blood glutamate levels can reflect brain glutamate levels, since inconsistent findings of central and peripheral glutamate levels in MDD have been reported. A previous postmortem brain study reported increased levels of glutamate in the frontal cortex of patients with MDD.[25] One previous study demonstrated increased levels of glutamate in the occipital cortex in MDD by using proton magnetic resonance spectroscopy,[26] while a recent meta-analysis of proton magnetic resonance spectroscopy studies showed no change in glutamate levels in the prefrontal cortex in MDD along with decreased levels of glutamate and glutamine combined.[27] Another study demonstrated increased levels of glutamate in the cerebrospinal fluid in depressed patients,[28] whereas other studies have reported decreased levels or no significant differences.[29–31]

In this study, we conducted a systematic review and meta-analysis of association studies to evaluate whether peripheral blood glutamate levels differed between MDD patients and controls.

Materials and methods
Study selection process for a meta-analysis

Eligible studies were identified in September 2017 with PubMed and Scopus databases, using the keywords ("Major depressive disorder" OR "depression" OR "depressive disorder") AND ("glutamate" OR "glutamic acid") AND ("serum" OR "plasma"). We also conducted an additional manual search of reference lists in the included publications. Studies meeting the following criteria were included for further meta-analysis: 1) studies assessing peripheral blood (serum or plasma) glutamate levels; 2) studies comparing glutamate levels in MDD patients and control subjects; and 3) studies written in English. Three reviewers (Inoshita M, Tomioka Y, and Watanabe SY) selected the articles independently according to the inclusion criteria. The flow chart of the present study's selection is shown in Figure S1.

Data extraction

The following data were extracted from eligible studies: ethnicity, sample size, gender distribution, mean age, mean glutamate concentrations and SD, unit of measure, blood sampling, glutamate assay, medication use, and diagnostic criteria.

Statistical methods

Statistical analyses were performed with the "metafor" package in R (version 3.2.3). A meta-analysis of association studies was performed on standardized mean differences (SMD) using the data of sample size and mean and SD of glutamate concentration.[32,33] When the data were presented as a subgroup, we combined these data into one group and calculated the composite mean using the formula: Composite mean $= \sum_{i=1}^{k}(n(i) \cdot M(i))/N$, where n($i$) was the sample size of ith group, M(i) was the mean of ith group, k was the number of groups, and N was the overall sample size; and composite variance using the formula: Composite variance = (ess+gss)/(N−1), where ess was the overall error sum of squares and gss was the overall group sum of squares. When the data were presented as median and interquartile range, we calculated the mean and SD.[34] When the data were presented with standard error (SE) of the mean, we calculated the SD as $\sqrt{n} \times SE$, where n was the sample size. Heterogeneity across studies was quantified with the I^2 statistic, with 25%, 50%, and 75% indicating small, moderate, and high levels of heterogeneity, respectively.[35] If heterogeneity across studies was found, then an inverse-weight variance random-effects model was applied; otherwise, a fixed-effects model was applied. Publication bias was assessed using a regression test for funnel plot asymmetry.[36] The influence of each selected study on the outcome was assessed using a leave-one-out sensitivity analysis.[37] Subgroup analyses were performed on the basis of blood sampling (plasma or serum), glutamate assay (high-performance liquid chromatography [HPLC] or

mass spectroscopy), medication use, fasting or nonfasting sample, and ethnicity (Asian or non-Asian). Meta-regression analysis was performed to examine the effects of age, gender (% male), medication exposure (% medication-received patients), sample size, and published year.

Results

Meta-analysis

Eleven studies met our inclusion criteria for our meta-analysis[12,14,15–22,24] (Figure S1), and the characteristics of these 11 studies are shown in Table 1. Among the 11 studies, 6 studies reported elevated glutamate levels in MDD,[14,15–19] and the other 5 studies did not find significant differences in glutamate levels between MDD patients and control subjects.[12,20–22,24]

When we conducted a meta-analysis of these 12 association studies between blood glutamate levels and MDD from 11 studies in a total of 529 patients with MDD and 590 control participants, a random effects model showed that blood glutamate levels were significantly higher in patients with MDD than in controls, with high heterogeneity (SMD=0.54, 95% CI=0.27–0.82, $p=8.5\times10^{-5}$, $I^2=75.0\%$, $p<0.05$, Figure 1). A funnel plot analysis indicated no evidence of publication bias in the association studies ($p>0.05$, Figure 2). A leave-one-out sensitivity analysis indicated our result was not driven by any single study ($p<0.05$, Table S1).

Subgroup analyses

We conducted subgroup analyses according to blood sampling, glutamate assay, medication use, fasting or nonfasting sample, and ethnicity (Table 2). The pooled SMD from 10 plasma[14,15–22] and 2 serum studies[12,24] was 0.62 (95% CI=0.31–0.93, $p=1.0\times10^{-4}$, $I^2=75.9\%$, $p<0.05$) and 0.16 (95% CI=−0.12–0.45, $p=0.26$, $I^2=0\%$, $p=0.42$), respectively. The pooled SMD from 8 studies using HPLC assay[12,15–17,19–20,22,24] and 4 studies using MS[14,18,19,21] was 0.41 (95% CI=0.22–0.60, $p<1.0\times10^{-4}$, $I^2=28.5\%$, $p=0.22$) and 0.69 (95% CI=−0.069–1.45, $p=0.075$, $I^2=89.7\%$, $p<0.05$), respectively. The pooled SMD from 8 studies using medication-free samples[12,14–16,18,20–22] was 0.59 (95% CI=0.19–1.00, $p=4.0\times10^{-3}$, $I^2=72.9\%$, $p<0.05$). The pooled SMD from 4 studies using fasting samples[16,18,21,22] and 3 studies using nonfasting samples[14,19] was 0.33 (95% CI=0.063–0.59, $p=0.015$, $I^2=0\%$, $p=0.51$) and 0.90 (95% CI=0.031–1.77, $p=0.042$, $I^2=94.1\%$, $p<0.05$), respectively. The pooled SMD from 7 Asian studies[14,17–19,21,24] and 5 non-Asian studies[12,15,16,20,22]

was 0.58 (95% CI=0.14–1.02, $p=0.01$, $I^2=88.6\%$, $p<0.05$) and 0.48 (95% CI=0.21–0.76, $p=6.0\times10^{-4}$, $I^2=0\%$, $p=0.84$), respectively.

Meta-regression analysis

When we conducted a meta-regression analysis to examine the effects of age, gender, medication use, sample size, and published year on the glutamate levels, we found no effects of these variables on blood glutamate levels ($p>0.05$) (Table 3).

Discussion

This is the first systematic review and meta-analysis of association studies between peripheral blood glutamate levels and MDD, and we demonstrated elevated glutamate levels in MDD in the pooled data set (529 patients with MDD and 590 controls). A high level of heterogeneity was observed in this meta-analysis of all studies ($I^2=75.0\%$). To examine the sources of potential heterogeneity, we subsequently conducted subgroup analyses and a meta-regression analysis.
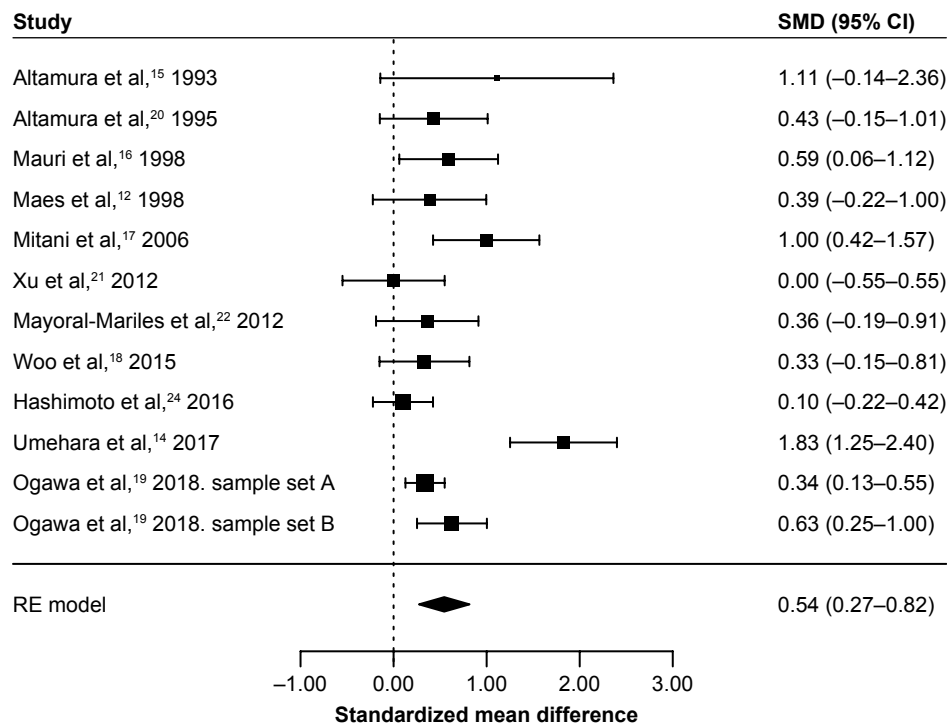
In the subgroup analyses, we classified studies into those that involved the use of glutamate assays (HPLC or mass spectroscopy) and those that involved food consumption (fasting or nonfasting). We also classified studies into groups based on ethnicity (Asian or non-Asian). We revealed significantly elevated glutamate levels in MDD with remarkably reduced levels of heterogeneity when we considered studies that involved only HPLC assays (SMD=0.41 and $I^2=28.5\%$), only fasting samples (SMD=0.33 and $I^2=0\%$), and only non-Asian samples (SMD=0.48 and $I^2=0\%$). These results suggest that the differences of glutamate assay, food consumption, and ethnicity might contribute to the heterogeneity observed in this study. On the other hand, subgroup analysis using studies involving medication-free samples showed significantly elevated glutamate levels in MDD without reduction of heterogeneity level ($I^2=72.9\%$). However, these results from our subgroup analyses must be viewed with caution because of the small sample size.

In the meta-regression analysis, we found no significant effects of age, gender, medication exposure, sample size, and publication year on blood glutamate levels in MDD patients. However, a significant decrease in blood glutamate levels has been reported in MDD after treatment with antidepressants.[11,12] Besides, a recent study showed significant positive correlations of daily doses of benzodiazepine derivatives and antidepressants with plasma glutamate levels in MDD patients.[19] These studies

Table 1 Characteristics of the included studies

Study	Country	Number of samples (Male, Female)	Mean age (SD)	Mean glutamate concentration (SD)	Unit of measure	Blood sampling	Measureing method	Medication exposure	Fasting information	Diagnosis
Altamura et al,[15] 1993	Italy	MDD: 4 (not available) CTRL: 9 (M7F2)	MDD: not available CTRL: 36.6 (8.3)	MDD: 191.86 (272.90) CTRL: 21.58 (7.61)	nmol/mL	Plasma	HPLC	Medication-free MDD for at least 3 weeks	No information (drawn at 9:00)	DSM-III-R
Altamura et al,[20] 1995	USA	MDD: 25 (M15F10) CTRL: 22 (M13F9)	MDD: 31.6 (9.4) CTRL: 28.7 (8.3)	MDD: 336 (159) CTRL: 265 (165)	Not available	Plasma	HPLC	Medication-free MDD for at least 8 days	No information (drawn at 9:00)	DSM-III-R
Mauri et al,[16] 1998	Italy	MDD: 29 (M15F14) CTRL: 28 (M16F12)	MDD: 47.4 (10.9) CTRL: 42.5 (14.2)	MDD: 86.05 (147.84) CTRL: 21.97 (23.54)	nmol/mL	Plasma	HPLC	Medication-free MDD for at least 4 weeks	Fasting blood	DSM-IV
Maes et al,[12] 1998	Belgium	MDD: 35 (M17F18) CTRL: 15 (M10F5)	MDD: 50.7 (14.4) CTRL: 47.5 (15.0)	MDD: 155.66 (57.51) CTRL: 134 (49)	µmol/L	Serum	HPLC	MDD with a washout period of 10 days	No information (drawn at 7:45)	DSM-III-R
Mitani et al,[17] 2006	Japan	MDD: 23 (M11F12) CTRL: 31 (M17F14)	MDD: 38.0 (11.3) CTRL: 41.5 (10.3)	MDD: 94.0 (48.1) CTRL: 59.6 (17.7)	nmol/mL	Plasma	HPLC	6 medication-free MDD and 17 medicated MDD	No information	DSM-IV
Xu et al,[21] 2012	China	MDD: 26 (M7F19) CTRL: 25 (M9F16)	MDD: 32.4 (8.9) CTRL: 32.1 (8.2)	MDD: 51.72 (33.67) CTRL: 51.72 (33.67)	µmol/L	Plasma	MS-based method	First-onset treatment-naïve MDD	Fasting blood	DSM-IV
Mayoral-Mariles et al,[22] 2012	Mexico	MDD: 18 (M0F18) CTRL: 45 (M0F45)	MDD: not available for 18 MDD CTRL: not available for 45 CTRL	MDD: 44.1 (14.0) CTRL: 39.3 (12.75)	µM/L	Plasma	HPLC	Medication-free MDD	Fasting blood	Beck Depression Inventory
Woo et al,[18] 2015	Korea	MDD: 68 (M16F52) CTRL: 22 (M4F18)	MDD: 65.3 (7.0) CTRL: 68.9 (6.3)	MDD: 58.53 (28.63) CTRL: 49.5 (21.0)	µmol/L	Plasma	LC-MS/MS	Medication-free MDD	Fasting blood	DSM-IV
Hashimoto et al,[24] 2016	Japan	MDD: 70 (M33F37) CTRL: 78 (M31F47)	MDD: 40.2 (9.9) CTRL: 37.2 (9.8)	MDD: 4.78 (2.24) CTRL: 4.57 (2.03)	µM	Serum	HPLC	Among 70 MDD, 66 were medicated with antidepressants	No information	DSM-IV
Umehara et al,[14] 2017	Japan	MDD: 33 (M10F23) CTRL: 33 (M10F23)	MDD: 47.1 (13.2) CTRL: 46.5 (10.1)	MDD: 0.061 (0.030) CTRL: 0.021 (0.0061)	Relative concentration	Plasma	CE-TOFMS	Medication-free MDD	Not fasting blood (drawn in the morning)	DSM-IV
Ogawa et al,[19] 2018. sample set A	Japan	MDD: 147 (M74F73) CTRL: 217 (M100F117)	MDD: 42.1 (12.1) CTRL: 41.2 (13.9)	MDD: 44.53 (24.53) CTRL: 37.27 (19.04)	µM	Plasma	HPLC	Most MDD patients were medicated	Not fasting blood	DSM-IV
Ogawa et al,[19] 2018. sample set B	Japan	MDD: 51 (M27F24) CTRL: 65 (M20F45)	MDD: 44.2 (13.4) CTRL: 43.4 (13.4)	MDD: 44.55 (18.74) CTRL: 34.52 (13.23)	µM	Plasma	LC/MS	Most MDD patients were medicated	Not fasting blood	DSM-IV

Abbreviations: MDD, major depressive disorder; CTRL, control; HPLC, high-performance liquid chromatography; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; LC-MS/MS, liquid chromatography–tandem mass spectrometry; CE-TOFMS, capillary electrophoresis-time-of-flight mass spectrometry.

Study		SMD (95% CI)
Altamura et al,[15] 1993		1.11 (−0.14–2.36)
Altamura et al,[20] 1995		0.43 (−0.15–1.01)
Mauri et al,[16] 1998		0.59 (0.06–1.12)
Maes et al,[12] 1998		0.39 (−0.22–1.00)
Mitani et al,[17] 2006		1.00 (0.42–1.57)
Xu et al,[21] 2012		0.00 (−0.55–0.55)
Mayoral-Mariles et al,[22] 2012		0.36 (−0.19–0.91)
Woo et al,[18] 2015		0.33 (−0.15–0.81)
Hashimoto et al,[24] 2016		0.10 (−0.22–0.42)
Umehara et al,[14] 2017		1.83 (1.25–2.40)
Ogawa et al,[19] 2018. sample set A		0.34 (0.13–0.55)
Ogawa et al,[19] 2018. sample set B		0.63 (0.25–1.00)
RE model		0.54 (0.27–0.82)

−1.00   0.00   1.00   2.00   3.00
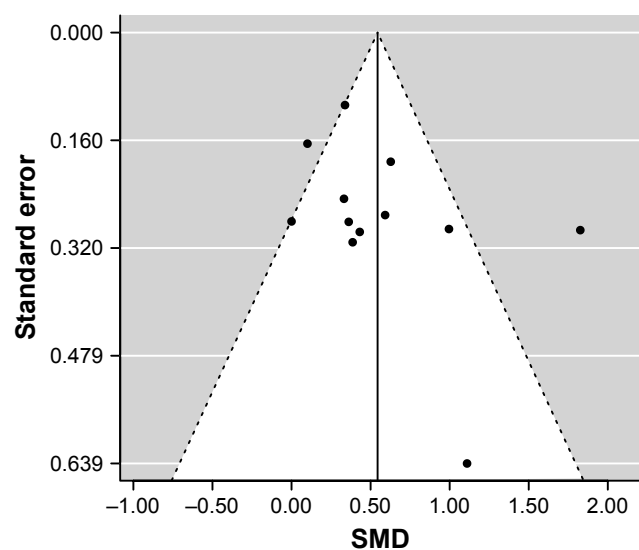**Standardized mean difference**

Figure 1 RE meta-analysis of association studies between peripheral blood glutamate levels and MDD.
Abbreviations: RE, random effect; MDD, major depressive disorder; SMD, standardized mean difference.

suggest that medications, such as antidepressants and benzodiazepines, may affect blood glutamate levels in MDD patients. In this meta-regression analysis of medication exposure, the sample size was small (only two studies[17,24] out of ten used medicated MDD samples), and we were unable to analyze the effect of medication in detail due to insufficient information on drugs used in these included

Figure 2 Publication bias assessed with funnel plot.
Abbreviation: SMD, standardized mean difference.

studies. Further studies assessing the effects of medication on blood glutamate levels according to types and dosages of antidepressants will be needed.

Our study has several limitations. First, the sample size was relatively small. Second, there was high heterogeneity among the studies in this meta-analysis. Larger studies with detailed information on participants, such as severity of symptoms, existence of psychosis, types of antidepressants and doses, and metabolic parameters, will be needed to validate our findings and reveal hidden factors that could explain the heterogeneity. Finally, it is still unclear whether peripheral blood glutamate levels can reflect brain levels of glutamate in MDD. Shulman et al[38] examined the relation between plasma and medial prefrontal cortical glutamate levels in healthy male volunteers, and they found no correlation between them. However, they measured glutamate levels in the limited brain region, and they assessed glutamate levels of healthy subjects, not patients with MDD. Further studies will be needed to examine this relationship between them.

Conclusion

We conducted a systematic review and meta-analysis of association studies between peripheral blood glutamate levels and MDD, and we demonstrated elevated blood glutamate levels

Table 2 Results of subgroup analyses analysis of association studies between peripheral blood glutamate levels and MDD

Variables	Number of association studies	Subgroup analysis				Heterogeneity	
		SMD	95% CI lower	95% CI upper	p-value	I² (%)	Q (p-value)
Blood sampling							
Plasma	10	0.62	0.31	0.93	0.0001	75.9	2.9×10⁻⁴
Serum	2	0.16	−0.12	0.45	0.26	0	0.42
Glutamate assay							
HPLC	8	0.41	0.22	0.60	<0.0001	28.5	0.22
MS	4	0.69	−0.069	1.45	0.075	89.7	<1.0×10⁻⁴
Medication							
Medication free	8	0.59	0.19	1.00	0.004	72.9	6.8×10⁻⁴
Food consumption							
Fasting	4	0.33	0.063	0.59	0.015	0	0.51
Not fasting	3	0.90	0.031	1.77	0.042	94.1	<1.0×10⁻⁴
Ethnicity							
Asian	7	0.58	0.14	1.02	0.01	88.6	<1.0×10⁻⁴
Non-Asian	5	0.48	0.21	0.76	0.0006	0	0.84

Abbreviations: MDD, major depressive disorder; SMD, standardized mean difference; HPLC, high-performance liquid chromatography; MS, mass spectroscopy.

Table 3 Result of a meta-regression analysis in patients with MDD and controls

Moderator	Number of association studies	Meta-regression analysis				Heterogeneity	
		Slope	95% CI lower	95% CI upper	p-value	I² (%)	Q (p-value)
Age (mean year)	10	0.0078	−0.027	0.042	0.66	82.3	<1.0×10⁻⁴
Gender (% male)	11	0.0006	−0.018	0.019	0.95	79.7	<1.0×10⁻⁴
Medication exposure (% medication-received patients)	10	−0.0018	−0.012	0.0083	0.73	74.8	1.2×10⁻⁴
Sample size	12	−0.0012	−0.0041	0.0017	0.42	72.2	2.4×10⁻⁴
Published year	12	−0.0018	−0.035	0.032	0.92	77.3	<1.0×10⁻⁴

Abbreviation: MDD, major depressive disorder.

in MDD. Our findings suggest that changes in glutamate levels may be implicated in MDD and provide further support for the glutamatergic dysfunction hypothesis of MDD.

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Author contribution
Shusuke Numata designed the study. Tetsuro Ohmori and Shusuke Numata managed the research. Masatoshi Inoshita, Yukiko Tomioka, and Shin-ya Watanabe collected the data. Makoto Kinoshita, Masahito Nakataki, Atsushi Tajima, and Hidehiro Umehara undertook the statistical analysis. Masatoshi Inoshita, Masahito Nakataki, and Shusuke Numata wrote the draft. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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Supplementary materials
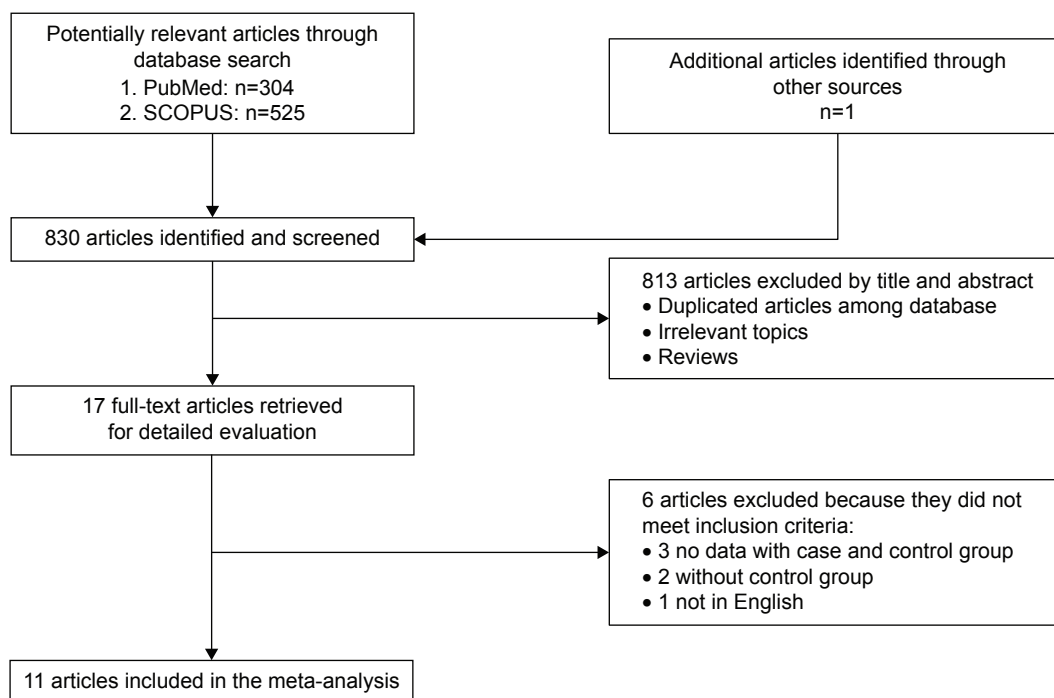
Figure S1 Flow chart of the study selection process.

Table S1 Result of leave-one-out sensitivity analysis

Omitting study	SMD	95% CI lower	95% CI upper	*p*-value	*I*² (%)	Q (*p*-value)
Altamura et al,[1] 1993	0.52	0.25	0.80	2.2×10^{-4}	76.9	1.2×10^{-4}
Altamura et al,[2] 1995	0.56	0.26	0.85	2.4×10^{-4}	78.1	$< 1.0 \times 10^{-4}$
Mauri et al,[3] 1998	0.54	0.24	0.84	3.7×10^{-4}	78.0	$< 1.0 \times 10^{-4}$
Maes et al,[4] 1998	0.56	0.26	0.86	2.1×10^{-4}	78.0	$< 1.0 \times 10^{-4}$
Mitani et al,[5] 2006	0.51	0.22	0.79	4.5×10^{-4}	75.4	3.3×10^{-4}
Xu et al,[6] 2012	0.59	0.31	0.87	$< 1.0 \times 10^{-4}$	75.0	2.1×10^{-4}
Mayoral-Mariles et al,[7] 2012	0.56	0.27	0.86	2.0×10^{-4}	77.8	$< 1.0 \times 10^{-4}$
Woo et al,[8] 2015	0.57	0.27	0.87	1.9×10^{-4}	77.5	$< 1.0 \times 10^{-4}$
Hashimoto et al,[9] 2016	0.60	0.31	0.88	$< 1.0 \times 10^{-4}$	72.7	5.5×10^{-4}
Umehara et al,[10] 2017	0.40	0.24	0.55	$< 1.0 \times 10^{-4}$	22.3	0.22
Ogawa et al,[11] 2018. sample set A	0.57	0.27	0.88	2.2×10^{-4}	72.8	1.4×10^{-4}
Ogawa et al,[11] 2018. sample set B	0.54	0.24	0.84	4.9×10^{-4}	77.0	1.1×10^{-4}

Abbreviation: SMD, standardized mean difference.

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