

SYSTEMATIC REVIEW

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Cortical 5-HT_{2A} receptors in depression and suicide: a systematic review and meta-analysis of in vivo and post-mortem imaging studies

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INTRODUCTION: Major depressive disorder (MDD) is a leading cause of suicide and disability. Better understanding changes to serotonin_{2A} receptors (5-HT_{2A}Rs) in MDD and suicide may help to improve treatments. We systematically reviewed and meta-analysed positron emission tomography (PET), single photon emission computed tomography (SPECT) and post-mortem radioligand binding studies of cortical 5-HT_{2A}Rs in MDD and suicide.

METHODS: Databases were searched from inception to August/September 2024. Binding data were extracted and pooled before random-effects meta-analyses of mean difference (Hedges' g) and variance were undertaken. Simple linear regression was performed to investigate the relationship between receptor binding and depression severity at baseline in PET and SPECT studies. We also assessed study quality and tested for evidence of publication bias.

RESULTS: Data on 556 MDD patients or suicide victims and 526 controls from 31 studies were included. Cortical 5-HT_{2A} binding was significantly lower in living MDD patients, who had not taken antidepressants for between one week and forever, than controls in frontal, prefrontal, cingulate, anterior cingulate and, upon sensitivity analysis, temporal cortex (Hedges' $g = -0.40$ to -0.57). In frontal and cingulate regions, binding effect size correlated with depression severity at baseline. There was study-level evidence of lower regional binding in never-medicated MDD patients than controls which, upon exploratory meta-analysis, reached significance in anterior cingulate cortex. Most PET or SPECT studies were of good or fair quality. The results of most post-mortem analyses were negative and included studies were of variable quality. There was limited evidence of publication bias.

CONCLUSION: In vivo 5-HT_{2A}R binding is reduced in MDD in frontal, cingulate and temporal cortex. This finding is based mainly on studies that used antagonist or inverse agonist radiotracers.

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INTRODUCTION

Major depressive disorder (MDD) is the world's leading cause of suicide [1], an important cause of disability [2] and a major contributor to excess mortality seen in physical health conditions [3]. As few as one-third of MDD patients achieve remission on treatment with current first-line antidepressants [4]; however, better understanding the neurobiology of MDD could help to advance the development of treatment options. Although contested [5], the monoamine hypothesis posits that 5-hydroxytryptamine (5-HT) neurotransmission is reduced in MDD [6, 7]. Of all 5-HT neuroreceptors, the 5-HT_{2A} receptor (5-HT_{2A}R) is the most highly expressed in the cortex [8] and is one of the oldest evolutionarily [9]. 5-HT_{2A}Rs are mostly postsynaptic and are concentrated on the dendrites of glutamatergic pyramidal cells and some GABAergic interneurons in cortical layer V [10, 11].

5-HT_{2A}R density in the living human brain can be quantified with positron emission tomography (PET) and single photon

emission computed tomography (SPECT). PET and SPECT studies report binding potential (BP)—a measure of the binding of a radioligand to a given receptor. As 5-HT_{2A}R ligands compete with synaptic 5-HT, 5-HT_{2A}R BP reflects receptor density, radioligand affinity and endogenous 5-HT levels [12]. BP is calculated by comparing the signal from ligand bound in a brain region of interest with i) free ligand in the plasma (via an arterial input or venous output function) or ii) ligand bound in a brain region with few receptors (a reference region) [12]. An analogous technique uses a reference region approach to determine receptor density in slices or homogenates of post-mortem brain tissue [13].

Studies in humans and animals have shown that 5-HT_{2A}Rs play a central role in neurotransmission, mediating cognitive and neuroendocrine functions [14, 15], and are dysregulated in psychiatric disorders [16, 17]. However, PET, SPECT and post-mortem radioligand binding studies have reached no consensus on 5-HT_{2A}R alterations in MDD, reporting higher, lower or similar

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<ul style="list-style-type: none"> PET or SPECT study of cortical 5-HT_{2A} binding in depression Using a radioligand with satisfactory 5-HT_{2A} affinity and selectivity Mean regional binding values reported, with standard deviation (SD) or standard error of the mean (SEM) For patients: history of MDE or MDD; depressed at time of scanning For controls: no known history of MDE or MDD; not depressed at time of scanning All dates of publication Human subjects of all ages 	<ul style="list-style-type: none"> For patients: history of bipolarity; comorbid psychiatric or neurological illness; significant physical illness; euthymic at time of scanning Controls: any psychiatric, neurological or significant relevant physical illness Non-human subjects Non-English language Review article or inappropriate study design Non-peer-reviewed publication (e.g., conference abstract, letter to editor, preprint) Duplicate hit (in current or previous search)
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Fig. 1 Inclusion and exclusion criteria for PET/SPECT studies of 5-HT_{2A} binding in MDD. MDD major depressive disorder, MDE major depressive episode, PET positron emission tomography, SPECT single photon emission computed tomography.

density to controls [18, 19]. Such mixed findings might reflect that many subjects were taking antidepressants shortly before imaging, as 5-HT_{2A}R density is sensitive to alterations in synaptic 5-HT levels (and because 5-HT_{1A}R agonism by antidepressants may regulate 5-HT_{2A}R density directly) [20]. Additionally, some antidepressants, several neuroleptics with antidepressant properties [21] and all classical psychedelics target the 5-HT_{2A}R. Psychedelics have shown promise in the treatment of depression [22, 23], where 5-HT_{2A}R occupancy correlates with the intensity and mysticism of a psychedelic experience [24, 25], which may in turn predict the magnitude of antidepressant effects [26]. Meanwhile, the commonest cause of MDD patient death in many post-mortem studies—suicide—may also confound the relationship seen between depression and 5-HT_{2A}R density.

We have systematically reviewed PET and SPECT studies of cortical 5-HT_{2A}R binding in MDD. Two earlier reviews [27, 28] summarised differences in regional 5-HT_{2A}R binding between MDD patients and healthy controls by comparing the medians and interquartile ranges of binding values from PET and SPECT studies. Our review extends this work by presenting the first meta-analysis of the PET and SPECT literature, and includes new case-control and within-subjects studies to attempt to separate illness from medication effects. We performed meta-analyses of the group variability of 5-HT_{2A}R binding, which can help to interpret the results of meta-analyses of mean difference, especially if these are negative [29]. We also present the first systematic review and meta-analysis of post-mortem radioligand binding studies of cortical 5-HT_{2A}R binding in MDD and suicide.

METHODS

Registration and reporting

This review was registered with PROSPERO ([CRD42019137947](#)) in June 2019. Since registration, we decided to recruit additional reviewers to screen studies and extract data; to include studies with groups unmatched for gender; to include studies with groups unmatched for age, provided age was included as a covariate in analyses; and to systematically assess study quality. We follow the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement when reporting this work [30].

Study selection

We systematically searched PubMed, EMBASE, PsycINFO and Web of Science databases from inception. We searched for all PET or SPECT studies of 5-HT_{2A}R density in MDD on 8th February 2024 and updated these searches on 30th August 2024. We searched for all post-mortem radioligand binding studies of 5-HT_{2A}R density in MDD and suicide on 6th September 2024. See Supplementary Figures 1 and 2 for the full search strategy for each database.

The titles of all identified studies, with or without abstracts, were manually screened by the lead author and one co-author (APN for PET and SPECT studies; GT for post-mortem studies), who then reviewed

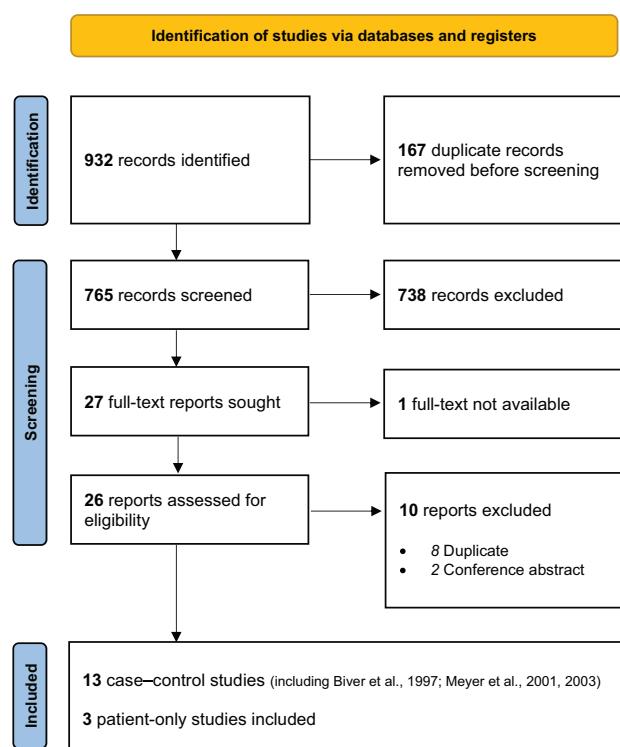


Fig. 2 PRISMA flow-chart for finding, screening, excluding and including PET and SPECT studies of 5-HT_{2A} binding in MDD.

the full-text version of all potentially eligible studies. Any disagreements were resolved by discussion. See Figs. 1 and 2 for the inclusion and exclusion criteria and PRISMA flowchart for PET and SPECT studies. See Supplementary Figures 3–5 for the inclusion and exclusion criteria and PRISMA flowcharts for post-mortem studies. PET and SPECT searches also identified within-patient studies that looked at relationships between 5-HT_{2A}R binding, antidepressant treatment and clinical outcome.

Data collection

Mean (sub)regional binding values and standard deviations (SDs) were extracted for patient and control groups. We did not pre-specify regions for analysis; rather, all available cortical binding data were extracted. Binding data extraction was completed independently by the lead author and one co-author (APN for PET and SPECT studies; GT for post-mortem studies), who resolved any discrepancies by discussion. Additional information, such as demographic, medication and imaging details, was extracted by the lead author.

Where studies presented data for medicated and unmedicated subgroups of patients, these data were extracted and recorded

separately. Where multiple studies reported binding values from the same subjects, only data from the larger study were included. Data that were only presented graphically were extracted using WebPlotDigitizer (<https://automeris.io/WebPlotDigitizer/>)—a semi-automated data extraction tool with high intercoder reliability and validity [31]. We contacted study authors whenever data could not be retrieved from the text or graphs. Binding data were ultimately not retrieved for three eligible PET or SPECT studies [32–34] and one eligible post-mortem study [35].

Meta-analysis and meta-regression

(Sub)regional means and SDs were pooled. We pooled lateralised data from the left and right hemispheres. Then, if a study did not provide an overall binding value for a given region, subregional data were combined as per Supplementary Figure 6. Pooled means were calculated by taking the arithmetic mean of included means. Pooled SDs were calculated using the following formula for combining SDs of paired samples (see [36]):

$$\sigma_x = \sqrt{\frac{1}{4}\sigma_a^2 + \frac{1}{4}\sigma_b^2 + \frac{1}{2}\rho\sigma_a\sigma_b}$$

Where σ_x is the pooled SD; σ_a and σ_b are the standard deviations of the paired samples a and b ; and ρ is the coefficient of the correlation between samples a and b , estimated to be 0.8. When we needed to pool three or more SDs, we pooled σ_a and σ_b to give σ_c then entered σ_c into the equation with σ_c , and so on.

Meta-analyses of standardised mean difference were undertaken. We employed Hedges' g , which is considered superior to other measures when sample sizes are small or uneven [37]. We used an inverse-variance random effects model due to moderate-to-high heterogeneity between some studies, as determined by the I^2 statistic. We analysed *in vivo* MDD, post-mortem MDD and post-mortem suicide studies separately. A forest plot was constructed for each region for which there were case-control data available from at least three studies. We preferentially included unmedicated patient data (although most post-mortem analyses included medicated, unmedicated and mixed cohorts). If a study presented both medicated and unmedicated patient data, an additional regional forest plot was constructed containing medicated patient data. Exploratory forest plots were constructed for regions for which there were case-control data available from at least two studies in never-medicated MDD cohorts. Forest plots were also constructed to compare regional binding before and after antidepressant treatment in the same patients, wherever there were within-subjects data available from at least three studies. Finally, for post-mortem suicide studies only, we used forest plots to examine any effect of suicide method. If a study separately presented data from violent and non-violent suicides, two regional forest plots were constructed (one containing violent suicide data; one containing non-violent suicide data). If at least three studies presented both violent and non-violent suicide data for the same region, another forest plot was constructed, directly comparing violent with non-violent suicides. The Benjamini-Hochberg procedure can be used to adjust p values to correct for multiple comparisons. We applied this correction wherever the same binding data could have been included in two or more meta-analyses of mean difference.

We also meta-analysed group differences in the variability of 5-HT_{2A}R binding, by calculating the variance ratio (VR) and coefficient of variation ratio (CVR). In accordance with published methods (see [29]), we first calculated the natural logarithm of VR and CVR—lnVR and lnCVR—which were later backtransformed to give VR and CVR. Both ratios compare within-group variance of an outcome, where VR or CVR > 1 indicates that there is greater outcome variability within the patient than control group. The larger the mean value of a biological variable, the greater the variance tends to be [38], to which VR is vulnerable but CVR is not; this is known as mean scaling [29]. We applied the

Benjamini-Hochberg procedure wherever the same data could have been included in two or more meta-analyses of variance.

Negative studies are less likely to be published than positive studies, especially if they have smaller sample sizes. This publication bias was assessed using Egger's test [39] and by visual inspection of funnel plots. The risk of bias of case-control studies was assessed using the Newcastle-Ottawa Scale ([40]; see also [41]), which involved rating the selection, comparability and exposure of cases and controls. For comparability, we considered whether studies matched or adjusted for age and gender. If ascertainment of exposure was by clinical interview, investigators need not have been blinded to case or control status for a study to score highly if other processes were robust (e.g., structured interview, independent assessment by two clinicians).

Finally, for patient groups in case-control *in vivo* studies, we completed meta-regressions to investigate relationships between study-level regional binding effect sizes and depression severity (mean baseline Hamilton Depression Rating Scale (HDRS) score). Data from studies using the 17- or 21-item version of the HDRS were included, as both versions should provide the same mathematical total for the same patient [42]. Simple linear regression using Pearson's coefficient was performed for regions in which a significant difference in mean group binding was found by meta-analysis. We applied the Benjamini-Hochberg procedure wherever the same binding data could have been included in two or more meta-regressions.

All analyses were performed using the metafor package [43] within RStudio (v4.4.1, cran.r-project.org). Results were considered statistically significant if $p < 0.05$.

RESULTS

Our main analyses included data on 188 MDD patients and 170 controls from ten case-control PET and SPECT studies [44–53], and 349 MDD patients or suicide victims and 356 controls from 19 post-mortem studies [54–72]. Two post-mortem studies were excluded [73, 74] because their data were included in a larger study [69]. Additional within-subjects data on 19 MDD patients were included from two patient-only PET or SPECT studies [75, 76]. See Table 1 and Supplementary Tables 1 and 2 for a summary of study-level results alongside other extracted information.

PET and SPECT studies

MDD patients versus controls

Meta-analysis of group differences in mean binding. Two studies presented separate data for medicated and unmedicated patients; however, only unmedicated patient data could be included in analyses (all medicated patients in Messa et al. [44] were euthymic; repeated measures data from Attar-Lévy et al. [45] were included in within-patient analyses). 5-HT_{2A}R binding was significantly lower in unmedicated MDD patients than controls in frontal (Hedges' $g = -0.40$, 95% CI = [-0.75, -0.05], $p_{uncorrected} = 0.026$, $p_{corrected} = 0.039$; heterogeneity $I^2 = 55\%$, $p = 0.02$; number of studies, $N = 9$), prefrontal ($g = -0.41$ [-0.69, -0.13], $p_{uncorrected} = 0.004$, $p_{corrected} = 0.012$; $I^2 = 0\%$, $p = 0.46$; $N = 5$), cingulate ($g = -0.57$ [-0.87, -0.27], $p_{uncorrected} = 0.0002$, $p_{corrected} = 0.0006$; $I^2 = 0\%$, $p = 0.44$; $N = 4$) and anterior cingulate ($g = -0.57$ [-0.92, -0.22], $p_{uncorrected} = 0.001$, $p_{corrected} = 0.002$; $I^2 = 0\%$, $p = 0.41$; $N = 4$) cortex. There were no significant differences in temporal ($g = -0.31$ [-0.72, 0.09], $p_{uncorrected} = 0.13$, $p_{corrected} = 0.18$; $I^2 = 56\%$, $p = 0.03$; $N = 7$), occipital ($g = -0.17$ [-0.52, 0.19], $p_{uncorrected} = 0.36$, $p_{corrected} = 0.36$; $I^2 = 38\%$, $p = 0.16$; $N = 6$) or parietal ($g = 0.22$ [-0.40, 0.85], $p = 0.49$; $I^2 = 72\%$, $p < 0.01$; $N = 5$) cortex. See Figs. 3 and 4 for seven of these forest plots.

Of the studies meta-analysed, seven used 5-HT_{2A}R antagonists (2-[123I]ketanserin, [18F]setoperone, [18F]fluoroethylspiperone (FESP), [123I]5-I-R91150), two used an inverse agonist ([18F]altanserin) and one used an agonist ([11C]CIMBI-36) as their radioligand. We

Table 1. PET/SPECT studies: MDD versus controls.

Study	Sample	Diagnosis	Mean HDRS at baseline (SD)	Mean age (SD)	Age matched?	Gender (M:F)	Medication status	Imaging modality	Binding in MDD relative to controls	Any correlation between binding and medication status, depression severity or suicidality?
D'haenens et al. [47]	19 drug-free MDD	DSM-III-R for major depression	22.63 (5.37)	44.9 (14.3)	Yes	6:13	Not reported	No psychotropics for at least 1 wk; 10 patients were AD-free for at least 3 wk	SPECT 2-[123I]bilirubin; Antagonist; 1.1 nM in human cortex [107]; Test-retest data not found	↑ in bilateral PC; (↓) in superior FC, anterior FC and posterior TC; ND in CS, inferior FC and anterior TC
	10 controls	Not reported	—	35.8 (10.8)	—	5:5	—	—	—	None found – ND in binding values between subjects off ADs for less than 1–3 wk versus more than 3 wk
Biver et al. [32]	8 drug-free unipolar MDD	DSM-III-R for MDE or MDD	32.8 (7.3)	48.1 (9.7)	Not reported (included as covariate in analyses)	2:6	Not reported (covariate in analyses)	No psychotropics for at least 10 days; No ADs for at least 3 wk; Never received ADs or ECT	PET [18F]litanseerin; Inverse agonist 0.36 nM in human cortex [91]; Acceptable test-retest data [108]	↓ in Rt posterolateral OFC and Lt anterior insular cx; (↓) in Lt posterolateral OFC and Lt anterior insular cx
	22 controls	No major psychiatric disorder, neurological disease or drug misuse; No family history of major psychiatric disorder	—	38.3 (12.0)	—	12:10	—	Not reported	—	None found
Attar-Levy et al. [45]	7 AD-free MDD	DSM-III for MDE without psychotic symptoms	54 (6)	40 (11)	Yes	3:4	Authors declined to match by pairs (prior study showed no effect of sex on setoperone binding)	6 patients were taking BZDs; No ADs for at least 2 wk (6 patients were AD-free for 1 yr) "None used medication"	PET [18F]setoperone; Antagonist; 0.7 nM in rat brain [109]; Acceptable test-retest data [110]	↓ in FC; (↓) in TC and PC; (↑) in OC
	7 controls	No mental or physical disease; All had normal MRI or CT head scan	—	38 (10)	—	4:3	—	—	—	None found
Meyer et al. [48]	14 drug-free unipolar MDD	DSM-IV for MDE secondary to MDD; No psychotic symptoms, bipolarity, other axis I disorder or alcohol or drug abuse; No suicide attempt during past 5 yr	22.5 (3.7)	32.3 (6.4)	Yes	12:2	No – more females in MDD group ($p = 0.01$) but no significant effect of age in study	PET [18F]setoperone; Antagonist; 0.7 nM in rat brain [109]; Acceptable test-retest data [110]	(↓) in PFC	None found – ND in binding values between subjects with and without a history of suicide attempt
	19 controls	Screened using SCI for DSM-III-R	—	31.8 (6.9)	—	8:11	—	—	—	—
Yatham et al. [49]	20 drug-free MDD	DSM-IV for major depression; No other axis I or II diagnosis	27.1 (5.5)	40.1 (9.5)	Yes	9:11	Yes	No psychotropics for at least 2 wk	PET [18F]setoperone; Antagonist; 0.7 nM in rat	↓ in FC, TC, PC and OC
										None found – no correlation between binding values

Table 1. continued

Study	Sample	Diagnosis	Mean HDRS at baseline (SD)	Mean age (SD)	Age matched?	Gender (M:F)	Gender matched?	Medication status	Imaging modality	Binding in MDD relative to controls	Any correlation between binding and medication status, depression severity or suicidality?
Meyer et al. [33]	20 controls	No alcohol or substance abuse within past 6 mo No history of psychiatric illness, as per SCI for DSM-III-R No first-degree relative with mood disorder or schizophrenia	DSM-IV for MDE secondary to MDD; No psychotic or bipolar symptoms and no other axis I diagnosis; No history of alcohol or drug abuse	21.8 (3.8)	30.8 (6.1)	Yes	12:7	Yes	PET	[¹⁸ F]Biperazine; Antagonist; 0.7 nM in rat brain [109]; Acceptable test-retest data [110];	ND in MFG, lateral OFC, PHG, posteromedial TC and rostral ACC
Messa et al. [44]	19 AD-naïve unipolar MDD	Screened using SCI for DSM-IV-R	—	31.8 (6.9)	31:11	—	—	No psychotropics for at least 3 mo; No AIDs for at least 6 mo	PET	[¹⁸ F]FESP; Antagonist; Not clear; Test-retest data not found	Not reported
Meyer et al. [34]	19 controls	DSM-IV for single or recurrent MDE; No other axis I diagnosis; No alcohol or drug abuse during the past 6 mo	—	38.8 (range 21–52)	7:12	Yes	11:9	—	PET	[¹⁸ F]FESP; Antagonist; Not clear; Test-retest data not found	Not reported
Meyer et al. [34]	20 controls	No history of psychiatric or neurological disease; No first-degree relative with mood disorder	DSM-IV for MDE secondary to MDD; No bipolar disorder or other axis I disorder; No psychotic symptoms; No history of alcohol or drug abuse	HDRS > 17 for inclusion	31 (6)	Yes	Not reported	Free of all medication for at least 5 half-lives; No psychotropics for at least 4 wk; No AIDs for at least 3 mo	PET	[¹⁸ F]FESP; Antagonist; Not clear; Test-retest data not found;	↑ in all regions in MDD subgroup with high (i.e., above median) dysfunctional attitude vs. controls
Meyer et al. [34]	29 controls	Screened for psychiatric illness, current suicidal ideation and history of self-harm	—	—	—	—	—	—	—	—	Binding positively correlated with Dysfunctional Attitude Scale score

Table 1. continued

Study	Sample	Diagnosis	Mean HDRS at baseline (SD)	Age matched?	Gender (M:F)	Medication status	Imaging modality	Binding in MDD relative to controls	Any correlation between binding and medication status, depression severity or suicidality?
Minturn et al. [50]	46 drug-free MDD	DSM-IV for MDD; No history of neurological disorder; No other medical illness potentially affecting the CNS	23.13 (4.31)	49.6 (15.6)	Yes	16.30	Yes	No psychotropics for at least 4wk; No fluoxetine for at least 6wk	PET [18F]altanserin; Inverse agonist; 0.36 nM in human brain [91]; Acceptable test-retest data [108]
	29 controls	No alcohol or substance abuse; No first-degree relative with mood disorder	0.31 (0.71)	45.8 (15.3)		9.20		No psychotropics for at least 3mo	–
Sheline et al. [51]	16 drug-free MDD aged over 50 yo (subgroup from Minturn et al. [50])	DSM-IV for MDD Screened for any psychiatric illness besides depression	22.6 (3.7)	66.0 (9.5)	Yes	7.9	Yes	No psychotropics for at least 2 wk; No other "potential CNS-active drugs"	[18F]altanserin; Inverse agonist; 0.36 nM in human brain [91]; Acceptable test-retest data [108]
	9 controls	No history of psychiatric illness or cognitive impairment	0.4 (1.1)	64.7 (8.5)		2.7		No psychotropics for at least 4 wk or 5 half-lives; No other "potential CNS-active drugs"	–
Baekken et al. [52]	21 AD-free, medication-resistant, unipolar MDD	MINI for MDE; No alcohol or drug dependence; No suicide attempts during current episode of illness; No history of epilepsy, neurosurgery or having metal or magnetic objects in the brain	25.57 (3.92)	45.3 (11.7)	Yes	8.13	Yes	9 patients were on BZDs; No other psychotropics for at least 2 wk	[123]I-[5- ¹¹ C]-Antagonist; 0.11 nM in rat brain [111]; Test-retest data not found
	21 controls	"Never depressed"	–	42.1 (12.6)		8.13		Free of all medication	–
Baekken et al. [53]	15 AD-naïve MDD (AND)	DSM-IV for unipolar melancholic MDE; No history of bipolarity or alcohol or drug abuse;	22.4 (6.8)	36.3 (9.8)	Yes	6.9	Yes	Unmedicated in current episode; Never prescribed ADs	[123]I-[5- ¹¹ C]-Antagonist; 0.11 nM in rat brain [111]; Test-retest data not found
								↓ in dorsal PFC and ACC in TRD vs. CTL; ↓ in dorsal PFC and ACC in TRD vs. AND; (↓) in FC, TC, OC, ventral	None found – post-hoc tests revealed no significant effect of current BZD or recent TCA use

Table 1. continued

Study	Sample	Diagnosis	Mean HDRS at baseline (SD)	Mean age (SD)	Age matched?	Gender (M:F)	Gender matched?	Medication status	Imaging modality	Radioligand; Activity at 5-HT _{2A} ; Dissociation constant (K _d) at 5-HT _{2A} ; Test-retest data	Binding in MDD relative to controls	Any correlation between binding and medication status, depression severity or suicidality?
		No suicide attempt during the current depressive episode									PFC, OFC and ACC in AND vs. CTL; (↑) in PC and dorsal PFC in AND vs. CTL	PFC, OFC and ACC in AND vs. CTL; (↑) in PC and dorsal PFC in AND vs. CTL
15 treatment-resistant MDD (TRD)		DSM-IV for unipolar melancholic MDE; No history of bipolarity or alcohol or drug abuse; No suicide attempt during the current depressive episode		26.5 (3.3)	38.6 (9.5)							
				6.9								
		6 patients were on BZDs; No ADs, APs or mood stabilisers for at least 2 wk										
15 controls		'Never depressed'; No history of alcohol or drug abuse		37.01 (9.8)	37.01 (9.8)							
				6.9	6.9							
		Not reported										
Eritzoe et al. [46]	11 AD-free MDD	MINI for MDE secondary to MDD; No other psychiatric diagnosis	21 (4)	40 (11)	No (included as covariate in analyses)	9.3	Not reported	AD-free for at least 6 mo; 6 of 12 original patients were antidepressant-naïve	PET	[¹¹ C]CIMB-36; Agonist; 1.3 nM in rhesus monkey brain [112]; Acceptable test-retest data [113]	↑ in TC; (↑) in FC, PC and OC	Not reported
	20 controls	Not reported		32 (9)		17.3		Never previously taken psychoactive medication including SSRIs				

↑ and ↓ denote significantly higher or lower values in MDD relative to controls, respectively. (↑) and (↓) denote non-significantly higher or lower values in MDD relative to controls, respectively.

Studies in bold font report full data for antidepressant-naïve MDD cohort. Studies in italicised font were not included in meta-analyses due to unavailability of data.

ACC anterior cingulate cortex; AD(s) antidepressant(s); AND antidepressant-naïve depressed; AP(s) antipsychotic(s); BZD benzodiazepines; C/MBl-36 centre for integrated molecular brain imaging-36; CNS central nervous system; CS central sulcus; CT computed tomography; ctx cortex; dPFC dorsolateral prefrontal cortex; DSM-IIIR diagnostic and statistical manual version 3 (Revised); DSM-IV diagnostic and statistical manual version 4; ECT electroconvulsive therapy; FC frontal cortex; FESP fluoroethylspiperone; Gf gyrus rectus; HC hippocampus; HDS Hamilton depression rating scale; ITG lateral temporal cortex; MDD major depressive disorder; MDE major depressive episode; MINI Mini-international neuropsychiatric interview; MFG medial frontal gyrus; mo months; MRI magnetic resonance imaging; ND no statistically significant difference; OC occipital cortex; OFC orbitofrontal cortex; PC parietal cortex; PET positron emission tomography; PFC prefrontal cortex; pgACC pregenual ACC; PHG parahippocampal gyrus; SCI structured clinical interview; sgACC subgenual ACC; SD standard deviation; sgPFC subgenual prefrontal cortex; SPET single photon emission computed tomography; SSRI selective serotonin reuptake inhibitor; TC temporal cortex; TCA tricyclic antidepressant; TRD treatment resistant depression; wk week(s); yr year(s); yo years old.

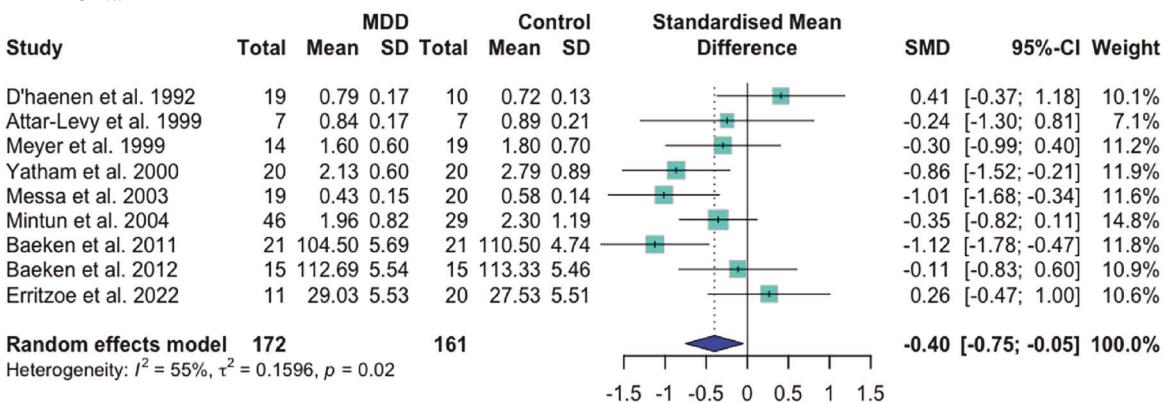
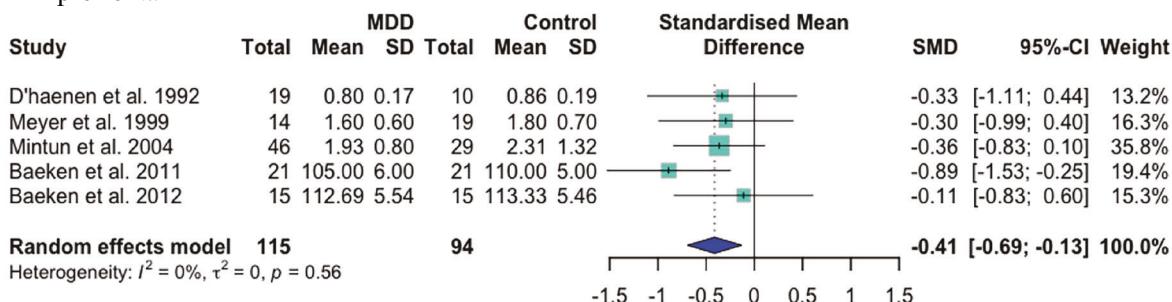
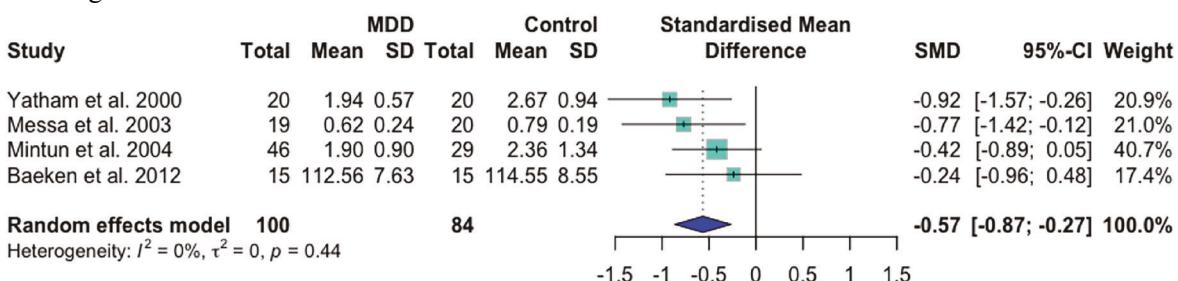
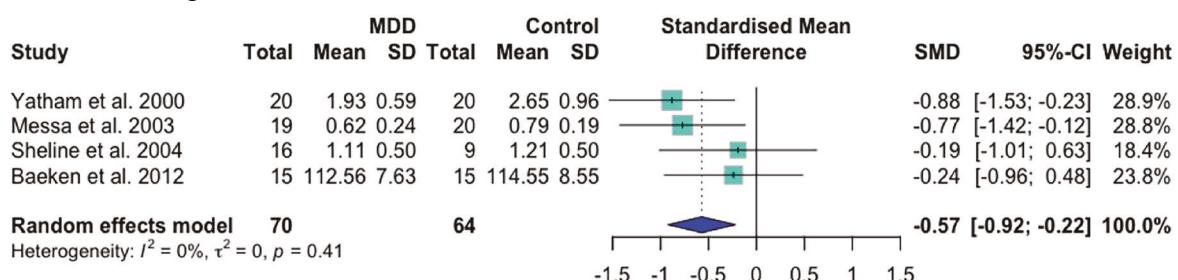
A – frontal**B – prefrontal****C – cingulate****D – anterior cingulate**

Fig. 3 Case-control PET/SPECT studies: forest plots. Mean 5-HT_{2A} binding was significantly lower in MDD patients than controls in frontal (A), prefrontal (B), cingulate (C) and anterior cingulate (D) cortex.

undertook sensitivity analyses excluding data from Erritzoe et al., 2022, as this was the only study to use an agonist tracer and to have groups unmatched for age (although age was included as a covariate in analyses) [46]. With this study excluded, 5-HT_{2A}R binding was

significantly lower in MDD in temporal cortex ($g = -0.45$ [-0.81, -0.09], $p_{uncorrected} = 0.015$, $p_{corrected} = 0.045$; $I^2 = 39\%$, $p = 0.15$; $N = 6$) (see Fig. 4D for this forest plot) and there were no significant changes to results in other regions ($p > 0.10$, data not shown).

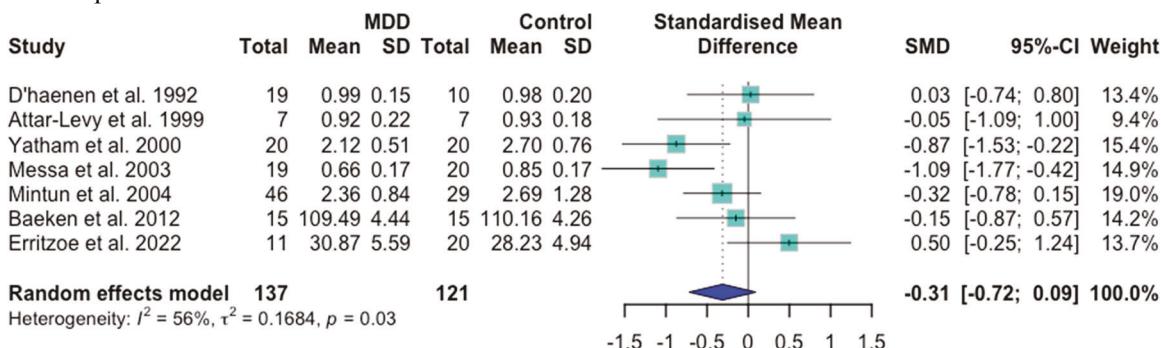
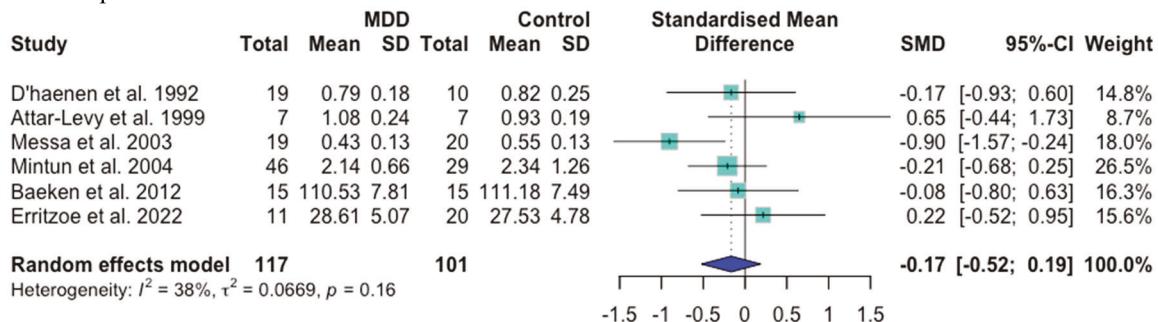
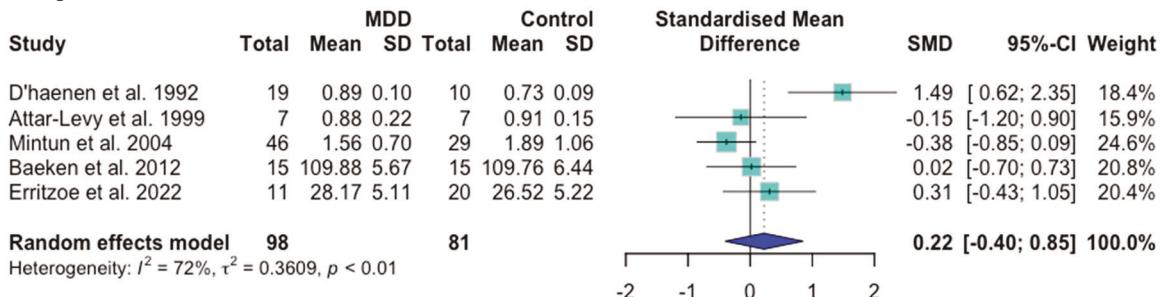
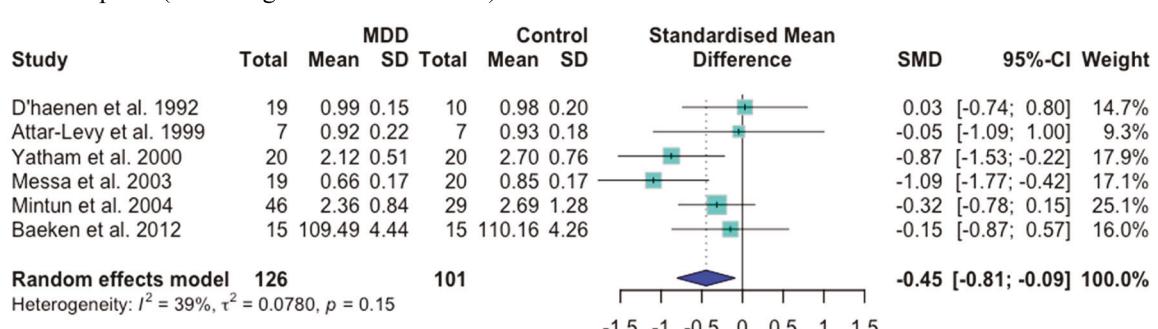
A – temporal**B – occipital****C – parietal****D – temporal (excluding Erritzoe et al. 2022)**

Fig. 4 Case-control PET/SPECT studies: forest plots. Mean 5-HT_{2A} binding was not significantly different between MDD patients and controls in temporal (A), occipital (B), parietal (C) or temporal (not shown) cortex. When data from Erritzoe et al. 2022 were excluded from analyses, binding was significantly lower in temporal cortex (D).

Two case-control studies included cohorts of MDD patients who had never taken antidepressants. Messa et al. [44] found significantly lower 5-HT_{2A}R binding in antidepressant-naïve MDD than controls in frontal, anterior cingulate, temporal and occipital cortex [44].

Meanwhile, Baeken et al. [53] found non-significantly lower binding in antidepressant-naïve MDD in frontal, ventral prefrontal, orbitofrontal, anterior cingulate, temporal and occipital cortex, and non-significantly higher binding in dorsal prefrontal and parietal cortex [53]. In

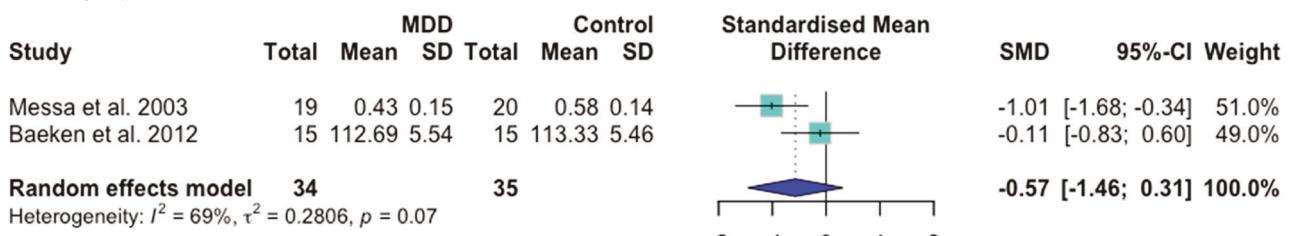
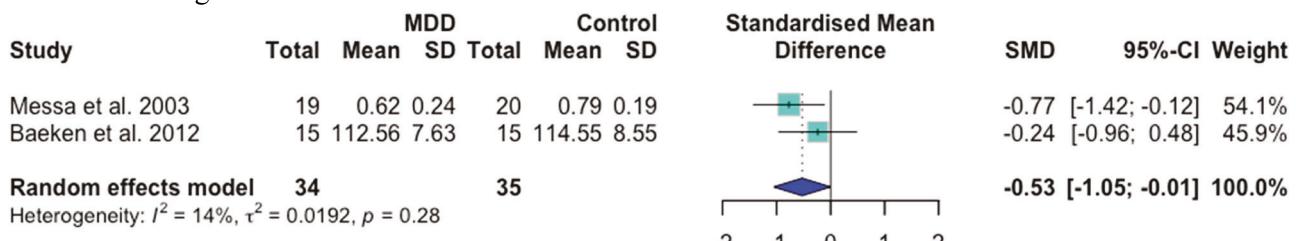
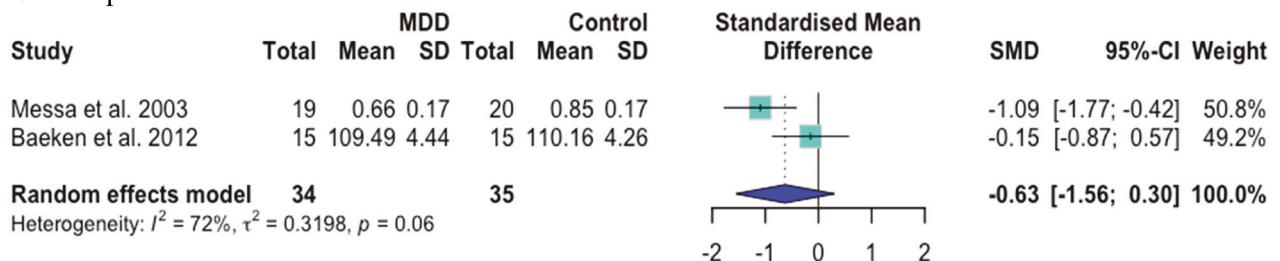
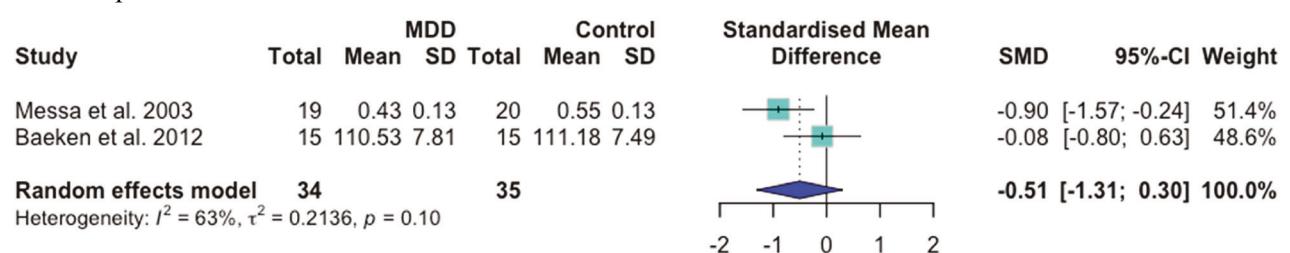
A – frontal**B – anterior cingulate****C – temporal****D – occipital**

Fig. 5 Case-control PET/SPECT studies: exploratory forest plots. Mean 5-HT_{2A} binding was significantly lower in antidepressant-naïve MDD patients than controls in anterior cingulate cortex (**B**) only. There was no significant difference between antidepressant-naïve MDD patients and controls in frontal (**A**), temporal (**C**) or occipital (**D**) cortex.

exploratory analyses, 5-HT_{2A}R binding was significantly lower in antidepressant-naïve MDD patients than controls in anterior cingulate cortex ($g = -0.53$ [-1.05, -0.01], $p_{uncorrected} = 0.047$, $p_{corrected} = 0.047$, $I^2 = 14\%$, $p = 0.28$; $N = 2$) only. There were no significant differences in frontal ($g = -0.57$ [-1.46, 0.31], $p_{uncorrected} = 0.20$, $p_{corrected} = 0.20$; $I^2 = 69\%$, $p = 0.07$; $N = 2$), temporal ($g = -0.63$ [-1.56, 0.30], $p_{uncorrected} = 0.18$, $p_{corrected} = 0.18$; $I^2 = 72\%$, $p = 0.06$; $N = 2$) or occipital ($g = -0.51$ [-1.31, 0.30], $p_{uncorrected} = 0.22$, $p_{corrected} = 0.36$; $I^2 = 83\%$, $p = 0.10$; $N = 2$) cortex. See Fig. 5 for these four forest plots.

Meta-analysis of group differences in binding variance. The variability of 5-HT_{2A}R binding was not significantly different between MDD patients and controls in any region. See Supplementary Figure 7

for InVR, InCVR, VR, CVR and associated p values. See Supplementary Figure 8 for seven InVR and seven InCVR forest plots.

Meta-regression of mean baseline HDRS score against binding effect size. Data from Attar-Lévy et al. [45] were excluded because the authors reported using the 26-item questionnaire; accordingly, the mean baseline HDRS score in the patient group was more than two SDs above the population mean ($z = 2.79$).

There was a significant negative correlation between mean baseline HDRS score and 5-HT_{2A}R binding effect size in MDD patients in frontal (adjusted $R^2 = 0.70$, $F(df \text{ regression } 1, df \text{ residual } 6) = 17.6$, $p_{uncorrected} = 0.0057$, $p_{corrected} = 0.006$; number of studies, $N = 8$), prefrontal ($R^2 = 0.92$, $F(1,3) = 48.83$, $p_{uncorrected} = 0.006$,

$p_{corrected} = 0.006$; $N = 5$), cingulate ($R^2 = 0.95$, $F(1,2) = 61.8$, $p_{uncorrected} = 0.016$, $p_{corrected} = 0.025$; $N = 4$) and anterior cingulate ($R^2 = 0.93$, $F(1,2) = 38.25$, $p_{uncorrected} = 0.025$, $p_{corrected} = 0.025$; $N = 4$) cortex. No significant correlation was seen in temporal cortex (excluding data from Erritzoe et al. 2022 [46]) ($R^2 = 0.67$, $F(1,3) = 9.06$, $p = 0.057$; $N = 5$). See Fig. 6 for these five regressions.

Publication bias. It was not possible to assess funnel plot asymmetry visually in any region due to the small number of included studies (see Supplementary Figure 9 for all seven funnel plots). However, Egger's test was non-significant in all regions; that is, frontal ($p = 0.42$), prefrontal ($p = 0.18$), cingulate ($p = 0.72$), anterior cingulate ($p = 0.13$), temporal ($p = 0.46$), occipital ($p = 0.42$) and parietal ($p = 0.40$) cortex.

Study-level risk of bias. We found four studies to be of good quality, five studies to be of fair quality and two studies to be of poor quality. See Supplementary Table 3 for the full Newcastle–Ottawa Scale ratings.

Post-mortem studies

MDD patients versus controls

Meta-analysis of group differences in mean binding. Three studies reported separate data for medicated and unmedicated MDD patients [58, 65, 72]. When unmedicated patient data from these three studies were used, no patient–control differences in 5-HT_{2A}R binding were seen in frontal cortex ($g = -0.16$ [-0.44 , 0.12], $p_{uncorrected} = 0.26$, $p_{corrected} = 0.26$; $I^2 = 0\%$, $p = 0.55$; $N = 7$), temporal cortex ($g = -0.34$ [-0.75 , 0.08], $p_{uncorrected} = 0.12$, $p_{corrected} = 0.23$; $I^2 = 16\%$, $p = 0.30$; $N = 3$) or hippocampus ($g = -0.52$ [-1.05 , 0.01], $p = 0.053$, $p_{uncorrected} = 0.053$, $p_{corrected} = 0.106$; $I^2 = 47\%$, $p = 0.15$; $N = 3$). See Supplementary Figure 10 for these three forest plots. When medicated patient data from these three studies were used, 5-HT_{2A}R binding was only significantly lower in MDD in frontal cortex before correction for multiple comparisons ($g = -0.30$ [-0.59 , -0.00], $p_{uncorrected} = 0.0498$, $p_{corrected} = 0.0996$; $I^2 = 0\%$, $p = 0.56$; $N = 7$) and there was no significant change to the results in any other region. See Supplementary Figure 11 for these three forest plots.

All meta-analysed studies used [³H]ketanserin as their radioligand.

Meta-analysis of group differences in binding variance. The variability of 5-HT_{2A}R binding was not significantly different between MDD patients and controls in any region. See Supplementary Figure 12 for InCVR, InVR, CVR, VR and associated p values. See Supplementary Figure 13 for three InVR and three InCVR forest plots.

Publication bias. It was not possible to assess funnel plot asymmetry visually in any region due to the small number of included studies (see Supplementary Figure 14 for these three funnel plots). However, Egger's test was non-significant in all regions; that is, frontal ($p = 0.54$), temporal ($p = 0.74$) and occipital ($p = 0.069$) cortex.

Study-level risk of bias. We found four studies to be of fair quality and three studies to be of poor quality. See Supplementary Table 3 for the full Newcastle–Ottawa Scale ratings.

Post-mortem studies

Suicide victims versus controls

Meta-analysis of group differences in mean binding. Two studies reported separate data for medicated and unmedicated suicide victims [58, 65]. When unmedicated patient data from these two studies were used, no patient–control differences in 5-HT_{2A}R

binding were seen in frontal cortex ($g = 0.22$ [-0.07 , 0.50], $p_{uncorrected} = 0.14$, $p_{corrected} = 0.23$; $I^2 = 61\%$, $p < 0.01$; $N = 17$), prefrontal cortex ($g = 0.48$ [-0.17 , 1.13], $p_{uncorrected} = 0.15$, $p_{corrected} = 0.19$; $I^2 = 74\%$, $p < 0.01$; $N = 7$), temporal cortex ($g = 0.04$ [-0.38 , 0.45], $p_{uncorrected} = 0.22$, $p_{corrected} = 0.43$; $I^2 = 53\%$, $p = 0.05$; $N = 7$) or hippocampus ($g = -0.29$ [-0.75 , 0.17], $p_{uncorrected} = 0.87$, $p_{corrected} = 0.87$; $I^2 = 50\%$, $p = 0.09$; $N = 5$). See Supplementary Figure 15 for these four forest plots. There was no significant change to results in any region when medicated patient data from these two studies were used instead. See Supplementary Figure 16 for these four forest plots.

Four studies reported separate data for suicide victims who died and who did not die by violent means [58, 59, 64, 65]. In no region was 5-HT_{2A}R binding significantly different between victims of either violent or non-violent suicide and controls. See Supplementary Figure 17 and 18 for these six forest plots. There was no significant difference in binding between victims of violent and non-violent suicide in frontal cortex ($p = 0.77$; number of studies, $N = 4$) (see Supplementary Figure 19 for this forest plot), and there were too few data to complete direct comparisons for other regions.

Of the studies meta-analysed, three used a 5-HT_{2A}R antagonist ([³H]spiperone), eleven used an inverse agonist (2-[¹²³I]ketanserin) and three used an agonist ([¹²⁵I]lysergic acid diethylamide, LSD) as their radioligand. There was no significant change to the results in any region when studies using the agonist [¹²⁵I]LSD [60, 62, 68] were removed from analyses ($p > 0.10$, data not shown).

Meta-analysis of group differences in binding variance. The variability of 5-HT_{2A}R binding was significantly higher in suicide victims than controls in frontal cortex ($VR = 1.21$, $p_{uncorrected} = 0.0026$, $p_{corrected} = 0.0052$), but this did not survive controlling for mean scaling ($CVR = 1.10$, $p_{uncorrected} = 0.20$, $p_{corrected} = 0.40$). There were no significant case–control differences in group variability in any other region. See Supplementary Figure 20 for InCVR, InVR, CVR, VR and associated p values. See Supplementary Figure 21 for four InVR and four InCVR forest plots.

Publication bias. Funnel plot inspection indicated a degree of publication bias in frontal cortex but there were too few studies for visual assessment in other regions (see Supplementary Figure 22 for these four funnel plots). Egger's test was non-significant in all regions; that is, frontal cortex ($p = 0.75$), prefrontal cortex ($p = 0.82$), temporal cortex ($p = 0.15$) and hippocampus ($p = 0.73$).

Study-level risk of bias. We found three studies to be of good quality, five studies to be of fair quality and ten studies to be of poor quality. See Supplementary Table 3 for the full Newcastle–Ottawa Scale ratings.

PET and SPECT studies

Within subjects data

Six within-subjects studies, looking at whether antidepressant treatment altered 5-HT_{2A}R binding in MDD and if this was related to clinical outcome, are summarised in Supplementary Table 4. Four of these studies reported significant reductions in cortical binding post-treatment: by 18% across frontal, temporal, parietal and occipital cortex following clomipramine treatment [45]; by 8.1% across frontal, temporal, parietal and occipital cortex following desipramine treatment [75]; by 10% across various frontal, cingulate and temporal subregions following paroxetine treatment in young, but not middle-aged, adults [33]; and by 3.8% across various frontal, temporal and occipital subregions following ECT [77]. One study reported significantly increased cortical binding post-treatment: by 31% across frontal and occipital cortex following fluvoxamine treatment [76]. One study reported mixed findings post-treatment: reduced binding in right and left

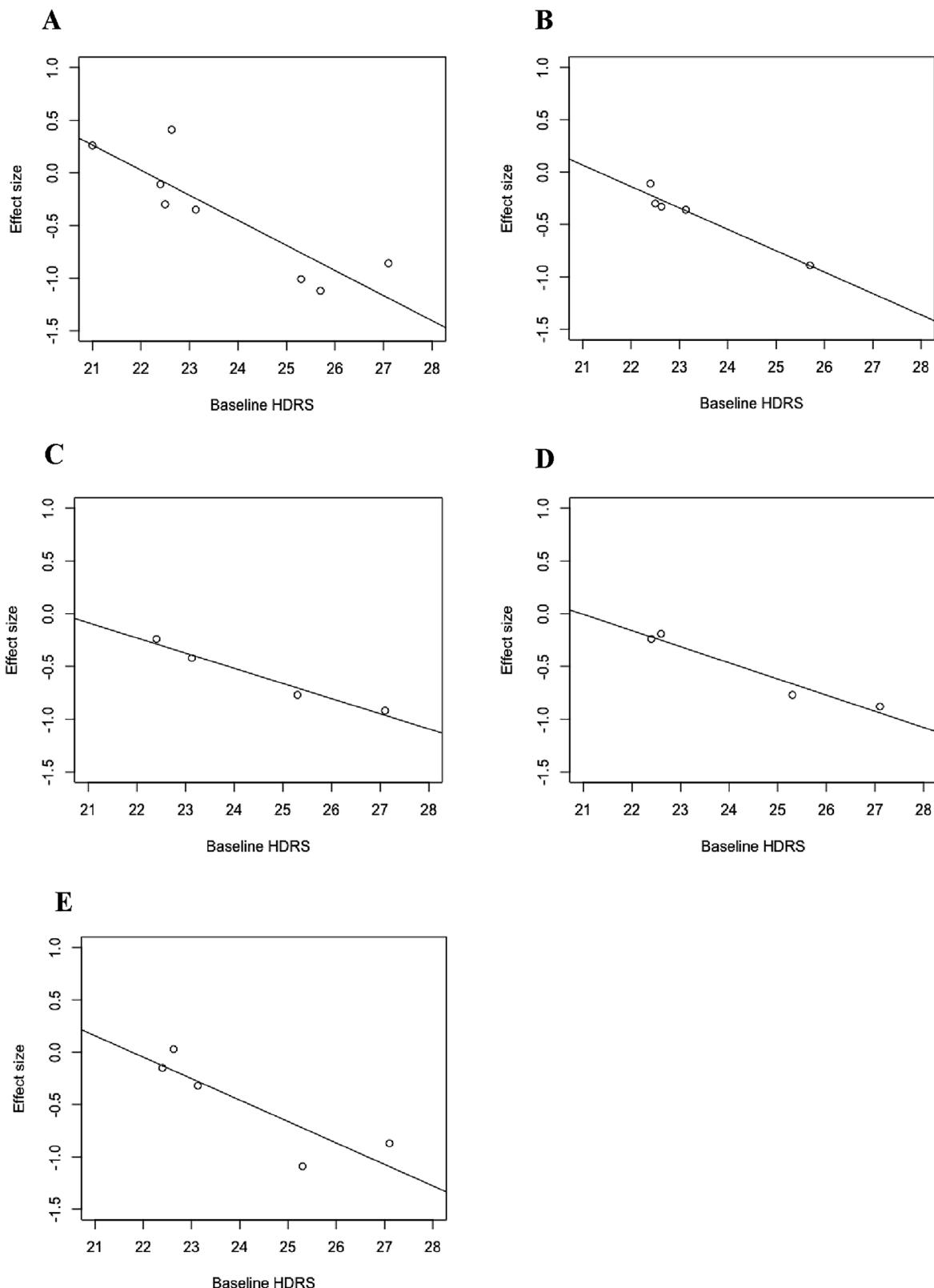


Fig. 6 Case-control PET/SPECT studies: meta-regressions of mean baseline HDRS score against study-level regional effect size. A significant negative correlation was seen in frontal (A), prefrontal (B), cingulate (C) and anterior cingulate (D) cortex. A non-significant ($p = 0.057$) negative correlation was seen in temporal cortex (excluding Erritzoe et al. 2022) (E).

dorsolateral prefrontal cortex, but increased binding in left hippocampus, following high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) [52]. Only one study found a significant correlation between changes in HDRS scores and changes in regional binding [52]: in right and left dorsolateral prefrontal cortex, where improvements in HDRS correlated with increased binding, and in right hippocampus, where improvements in HDRS correlated with reduced binding. Pre- and post-treatment binding data from three studies [45, 75, 76] could be included in meta-analyses below.

Supplementary Table 5 summarises three within-subjects studies looking at whether 5-HT_{2A}R binding prior to antidepressant treatment predicts subsequent clinical response. No significant associations were found between baseline 5-HT_{2A}R binding and antidepressant response to clomipramine [45], paroxetine [33] or HF-rTMS [52].

Meta-analysis of mean binding pre- versus post-treatment. 5-HT_{2A}R binding was not significantly different before versus after antidepressant drug treatment in the same patients in frontal ($g = 0.78 [-0.95, 2.50]$, $p = 0.38$; $I^2 = 86\%$, $p < 0.01$; $N = 3$), temporal ($g = 0.98 [-1.12, 3.07]$, $p = 0.36$; $I^2 = 88\%$, $p < 0.01$; $N = 3$) or occipital ($g = 1.37 [-1.61, 4.36]$, $p = 0.37$; $I^2 = 91\%$, $p < 0.01$; $N = 3$) cortex. See Supplementary Figure 23 for these three forest plots.

DISCUSSION

We found that *in vivo* cortical 5-HT_{2A}R binding was lower in unmedicated MDD patients than in healthy controls, as measured using mostly antagonist or inverse agonist tracers. Binding was significantly lower in frontal, prefrontal, cingulate, anterior cingulate and, upon sensitivity analysis, temporal cortex, with medium effect sizes (Hedges' $g = -0.40$ to -0.57). These findings are broadly, though not entirely, consistent with previous reviews [18, 27, 28]. Discrepancies may be due to differences in review methodology. Unlike Nikolaus et al. [27, 28], we completed meta-analyses of mean difference and excluded studies of remitted patient cohorts, as significant differences in 5-HT_{2A}R binding have been demonstrated between euthymic and currently depressed MDD patients [75–78]. We additionally searched multiple databases, included more studies and data, and analysed a greater number of subregions.

The results of post-mortem analyses were not consistent with *in vivo* findings. Frontal 5-HT_{2A}R binding was only significantly lower in MDD patients than controls when medicated patient data were included and before correction for multiple comparisons, whilst the results of all other post-mortem analyses were negative. We also found no significant effect of suicide on 5-HT_{2A}R binding. There are several possible methodological reasons for these results. First, not all studies matched cases and controls for post-mortem delay (the interval between time of death and sample processing). Second, there were between-study differences in how samples were stored: brains were variably stored whole (e.g., [55]), as cortical regions (e.g., [69]) and as slices (e.g., [60, 62, 70, 71]); storage temperatures ranged from -80°C (e.g., [54, 58, 65, 66, 69, 70, 72]) to -40°C (e.g., [55]); and storage times were seldom reported. Third, there were between-study differences in assay parameters: most studies homogenised brain tissue but some used sectioned slides (e.g., [60–62, 66, 67, 70, 71]); incubation temperatures ranged from 21°C (e.g., [62]) to 37°C (e.g., [56–59, 63, 65, 68, 72]); and incubation times ranged from 15 min (e.g., [58, 65]) to 180 min (e.g., [63, 64, 69]). Fourth, we must consider the pharmacological profile of the radioligand. All post-mortem MDD studies used [³H]ketanserin, which has classically been considered a 5-HT_{2A}R antagonist [79], although there is recent evidence that it may act as a partial agonist [80]. Studies in suicide victims used either [³H]ketanserin, the antagonist [³H]spiperone or the agonist [¹²⁵I]LSD and their different profiles may

account for some of the between-study variance in binding values. Similarly, the fact that PET and SPECT MDD studies used antagonist, inverse agonist and agonist tracers might, at least in part, explain why *in vivo* findings were not supported by the results of post-mortem MDD analyses, as we will discuss in more detail later. Fifth, some studies employed a saturation binding assay (e.g., [54, 56, 58, 64, 65, 68, 69])—an approach generally favoured for estimating maximal binding—whereas others studied receptor binding at a fixed concentration of radioligand (e.g., [55, 57, 60–62, 66, 70]). Finally, most post-mortem studies compared group means and SEMs, whereas meta-analysis using Hedges' g requires first converting study-level SEMs to SDs. As $SD = SEM \times \sqrt{n}$, and sample sizes ranged from seven to 73 subjects per group, SD was always several times larger than SEM, which reduced the likelihood of significant study-level observations being significant at the meta-analytical level. There are also sources of biological variability within the post-mortem literature. Suicide victims had a wide range of neuropsychiatric diagnoses, including MDD, bipolar affective disorder, schizophrenia, schizoaffective disorder, personality disorder and Parkinson's disease (e.g., [57, 63, 66]). Also, whilst all patients in included PET and SPECT studies had been antidepressant-free for at least a week, in several post-mortem MDD (e.g., [66, 71, 72]) and suicide (e.g., [57, 59, 64, 66, 68]) studies, patients were still taking antidepressants or other psychotropics at the time of death. These important limitations impact the robustness of our post-mortem analyses. The rest of our discussion will therefore focus on insights from the PET and SPECT literature.

When do alterations in cortical 5-HT_{2A}R binding occur in MDD? Lower *in vivo* 5-HT_{2A}R binding appears to result from the effects of chronic depressive illness. Baeken et al. [53] found that 5-HT_{2A}R binding in frontal, dorsolateral prefrontal and anterior cingulate cortex was significantly lower in treatment-resistant MDD than both first episode MDD and controls. Meanwhile, Schins et al. [81] reported a greater case-control difference in cortical 5-HT_{2A}R binding in depressed post-myocardial infarction patients who had previously experienced depression than in those who had not. This could point towards some effect of antidepressant treatment on 5-HT_{2A}R binding. Accordingly, most included within-patient studies reported regional reductions in 5-HT_{2A}R binding following antidepressant treatment (and whilst accompanying meta-analyses did not reach significance, they only included three studies and heterogeneity was high). Crucially, however, studies examining 5-HT_{2A}R binding in never-medicated MDD also found reduced binding relative to controls, in frontal, anterior cingulate, temporal, occipital and hippocampal regions [44, 51]. When data were combined in exploratory meta-analyses, binding was significantly lower in MDD in anterior cingulate cortex, where our primary analyses found the largest binding effect size ($g = -0.57$). This suggests that, in at least some cortical areas, case-control differences in mean binding are somewhat independent of medication effects. This idea is supported by our finding that baseline HDRS scores correlated with 5-HT_{2A}R binding in frontal, prefrontal, cingulate and anterior cingulate cortex, after all patients had been off antidepressants for at least a week. (Notably, the only study to include patients who had been antidepressant-free for under two weeks found no significant difference in binding between those who had been off antidepressants for less than three weeks versus more than three weeks [47].) We therefore conclude that cortical 5-HT_{2A}R binding, as measured using antagonist and inverse agonist tracers, is reduced during the course of MDD—partly, but not entirely, due to the effects of antidepressant medication.

Why is cortical 5-HT_{2A}R binding reduced in depression? Based on the findings of their own [¹⁸F]setoperone studies [49, 75, 77], Yatham and colleagues proposed that cortical 5-HT_{2A}R s are downregulated as a compensatory mechanism in MDD. They suggested that endogenous 5-HT_{2A}R downregulation is sufficient

to induce remission from depression in some individuals, whereas treatment is required to further reduce receptor density below a critical threshold in others [49]. This idea was also put forward to explain how ECT induces response in treatment-resistant MDD: by superimposing further reductions in 5-HT_{2A}R binding on reductions due to antidepressant drug treatment [77]. Whilst this explanation offers a coherent account of dynamic changes to 5-HT_{2A}R densities in vivo, it is at odds with a popular view that postsynaptic 5-HT receptors should *upregulate* when synaptic 5-HT concentrations are low [82], as is thought to be the case in MDD (e.g., [46]).

The ternary complex model of receptor–ligand binding provides an alternative account. The model states that G-protein coupled receptors (GPCRs) exist in coupled (active) or uncoupled (inactive) states, where the proportion of a fixed number of receptors in each state is in equilibrium, maintained by the availability of ligand [83–86]. It is said that agonists preferentially bind the active receptor, inverse agonists preferentially bind the inactive receptor and antagonists bind both equally [83–85]. Whilst this model appears to fit the activity of agonists and antagonists at the 5-HT_{2A}R [87, 88], some authors have questioned whether inverse agonists even exist at 5-HT_{2A}Rs in human brain. A decade ago, Nutt and colleagues highlighted that inverse agonists had, up until that point, only been characterised at mutant 5-HT_{2A}Rs [89]. Recent post-mortem studies appear to have addressed this knowledge gap, however, finding that altanserin, pimavanserin, ritanserin, volinanserin, eplivanserin and nelotanserin all act as inverse agonists at 5-HT_{2A}Rs in healthy human brain [80, 90]. Of note, one post-mortem study using the agonist [¹²⁵I]LSD, inverse agonist [¹⁸F]altanserin and antagonist [³H]MDL100907 recently reported higher, lower and unchanged 5-HT_{2A}R binding, respectively, in the same unmedicated schizophrenia patients compared to controls [91].

Thus, lower binding of inverse agonist tracers to 5-HT_{2A}Rs in MDD may reflect a reduction in the density of inactive 5-HT_{2A}Rs. If there were no change to the overall number of receptors, this would signify a complementary increase in the density of active 5-HT_{2A}Rs, relative to controls. It would follow that further reductions in 5-HT_{2A}R binding after antidepressant drug treatment and ECT represent further decreases and increases, respectively, in the densities of inactive and active 5-HT_{2A}Rs. This model could account for Erritzoe and colleagues' observation of significantly higher cortical 5-HT_{2A}R binding in MDD patients than controls: their agonist tracer, [¹¹C]CIMBI-36, may have been preferentially bound to active 5-HT_{2A}Rs. However, application of the ternary complex model here relies on the assumption that the total number of (both active and inactive) receptors is stable [86], which is unlikely to always be the case. Factors such as receptor mutation, trafficking and phosphorylation may affect receptor numbers, as well as the proportion of GPCRs in active and inactive states [92]. Importantly, we have noted that antagonist tracers may not distinguish between active and inactive GPCRs [87, 91]. Yet, most studies, including those of Yatham and colleagues, employed antagonist tracers and reported lower 5-HT_{2A}R binding in MDD than controls. Whilst lower binding might reflect a reduction in the density of all active and inactive 5-HT_{2A}Rs in MDD, it could alternatively be that some 5-HT_{2A}R "antagonists" preferentially bind inactive 5-HT_{2A}Rs. Recall that altanserin and other 5-HT_{2A}R ligands previously thought to be antagonists have recently been redescribed as inverse agonists [80, 90, 93, 94]. In summary, lower 5-HT_{2A}R binding in MDD could reflect a reduced density of all 5-HT_{2A}Rs and/or an increase in the proportion of active relative to inactive receptors; however, both these interpretations involve important assumptions or caveats.

Interestingly, several studies have found 5-HT_{2A}R binding to be higher in individuals with personality risk factors for depression than in healthy controls [18, 95]. This has been best demonstrated in neuroticism [96–98], where the neurotic traits vulnerability [99],

negativism [100] and pessimism [34] positively correlate with 5-HT_{2A}R binding. All of these studies report similar results despite employing various agonist [98], antagonist [18, 34] and inverse agonist [96, 97, 99, 100] tracers, challenging the applicability of the ternary complex model to 5-HT_{2A}R dynamics here. We therefore suggest that higher 5-HT_{2A}R binding in neuroticism reflects higher densities of both active and inactive receptors, relative to controls. This may occur as an adaptation against environmental risk factors for MDD, possibly via reduced 5-HT release.

We acknowledge four main limitations of our review of the case–control PET and SPECT literature. First, we included studies regardless of psychotropic drug use and screening. Washout durations were too highly variable to standardise; however, all patients were off antidepressants and antipsychotics at the time of scanning. The most commonly continued psychotropics—benzodiazepines—may affect 5-HT_{2A}R density; however, they likely increase receptor binding [101, 102], which would not have contributed to the patient–control differences we report. Second, we did not weight subregions according to size. Whilst such weighting would offset the greater impact of noise in smaller regions, it would be inappropriate to ascribe all larger regions more statistical influence in the context of MDD. Our approach is consistent with that of a prior meta-analysis of 5-HT receptors in MDD [103]. Third, some of our calculations were underpowered. There were too few data to correlate 5-HT_{2A}R binding with antidepressant or psychotropic washout durations, and whilst we did not find any significant evidence of publication bias, we included fewer studies than is recommended to visually inspect funnel plots or run Egger's test reliably [104]. Although there were sufficient data to run some additional analyses and regressions, more data are required to confirm or refute associations of borderline significance, such as the correlation between temporal cortical binding and baseline HDRS score. Finally, studies may have used different versions of the HDRS questionnaire. Some studies clearly reported using the 17- [47, 50, 52, 53] or 21-item [49] versions, which should both produce the same mathematical total and are therefore comparable [42]. Whilst not explicitly stated, we assume that Sheline et al. [51] used 17-item scale scores, as was the case for its parent study [50]; that Erritzoe et al. [46] used the 17-item questionnaire, as this is the version they reference [105]; that Meyer et al. [48] used the 21-item questionnaire, as this is the version they reference [106]; and that Messa et al. [44] used the 17- or 21-item scale, because of the required cut-off score given for study inclusion (at least 18 points), but we cannot be certain.

Conclusion and future directions

We found that *in vivo* cortical 5-HT_{2A}R binding was significantly lower in unmedicated MDD patients than control subjects, as measured using mostly antagonist or inverse agonist tracers. This effect was seen in frontal, prefrontal, cingulate, anterior cingulate and, upon sensitivity analysis, temporal cortex (Hedges' $g = -0.40$ to -0.57). Meanwhile, study-level binding effect size correlated with mean HDRS score at baseline in frontal and cingulate regions. Some authors reported lower regional binding in antidepressant-naïve MDD patients than controls, and exploratory meta-analyses found that binding was lower in these patients in anterior cingulate cortex. The results of within-patient studies indicated that antidepressants further reduce 5-HT_{2A}R binding in MDD. These findings were not supported by analyses of the corresponding post-mortem literature, which were almost entirely negative. We suggest that this is at least in part due to methodological and biological differences across studies.

Further longitudinal studies, reporting complete medication histories, are required to fully disentangle psychotropic effects from illness effects at the 5-HT_{2A}R. Ideally, these studies would recruit individuals at high risk of MDD prior to the onset of clinical depression and would follow them up throughout illness and

treatment. We also encourage PET or SPECT investigations of 5-HT_{2A}R binding within clinical trials of classical psychedelics for MDD and other mental health conditions, such as addictions and anxiety disorders. These studies should specifically investigate relationships between baseline 5-HT_{2A} binding, changes in 5-HT_{2A} binding with treatment and treatment outcomes. Finally, ambitious studies should seek to scan the same subjects with two or more radiotracers with different pharmacodynamic properties, to compare the differential effects of agonist, antagonist and inverse agonist tracers in PET and SPECT studies of 5-HT_{2A}Rs in MDD.

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AUTHOR CONTRIBUTIONS

GEC: conceptualisation, data curation, investigation, formal analysis, writing—original draft, writing—review and editing, visualisation. GT: investigation, formal analysis, writing—review and editing. APN: investigation, formal analysis, writing—review and editing. TB: investigation, formal analysis, writing—original draft, writing—review and editing. RZ: investigation, formal analysis, writing—original draft, writing—review and editing. RAM: conceptualisation, writing—review and editing, supervision. DE: conceptualisation, writing—original draft; writing—review and editing, supervision.

COMPETING INTERESTS

RAM has received speaker/consultancy fees from Boehringer Ingelheim, Janssen, Karuna, Lundbeck, Newron, Otsuka, and Viatris, and co-directs a company that designs digital resources to support treatment of mental ill health. DE is currently a paid scientific advisor for Aya Biosciences, Lophora ApS, Clerkenwell Health and Mindstate Design Lab. GEC, GT, APN, TB and RZ have declared no relevant conflicts of interest.

REQUIRED ETHICS STATEMENT

Ethical approval was not sought or required, as this review solely included previously published, publicly available data.

ADDITIONAL INFORMATION

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