Medial Prefrontal Cortex Glutamate Is Reduced in Schizophrenia and Moderated by Measurement Quality: A Meta-analysis of Proton Magnetic Resonance Spectroscopy Studies

Supplement

Contents of the Supplement

Supplemental Methods – Empirical method for identifying quality thresholds.

We examined three metrics sensitive to the quality of the glutamate measurements for each study: mean + 2 SD for Cramer-Rao lower bound (CRLB), mean + 2 SD for singlet line width (FWHM), and mean COV for glutamate. For each metric, we averaged the values for the patient and control groups. We hypothesized that glutamate measurement quality would have a moderating effect on the meta-analytic results across studies comparing schizophrenia patients to healthy volunteers. Formally, we hypothesized there was a quality threshold Q, for which the meta-analytic result would be significantly stronger in studies surpassing Q than for those falling short of Q. To identify the quality threshold Q in an unbiased manner, we first ranked the studies for each metric. We then calculated the inverse variance-weighted pooled effect sizes from a moving sample of studies (k = 7) running from the lowest to the highest quality studies for each quality metric (analogous to a moving average). A best-fitting, 4-parameter, logistic function was fit to this series of pooled effect sizes using the computational resource at https://mycurvefit.com/ using the following equation:

$$Y = d + ((a - d)/(1+(X/c)^b))$$

Where Y = the pooled effect size (k=7) and X = the rank of the set of seven adjacent studies for the quality metric being examined. The best fitting four parameters (a, b, c, and d) for each of the quality metrics is shown below.

	a	b	c	d	Inflection point (Q)
CRLB	-0.1822	26.31	17.57	-0.5382	-.3602
FWHM	+0.0343	4.518	18.60	-0.8647	-.4152
COV	-0.0568	67.00	29.09	-0.4653	-.2610

Parameter “a” is the asymptote of the pooled effect size for the lowest quality datasets, and parameter “d” is the asymptote of the pooled effect size for the highest quality datasets for each metric. These best fitting parameters were used to generate a logistic transform of the ranks of each quality metric. The empirical quality threshold Q was identified as the inflection point in the logistic transform curve. The inflection point (Q) is the midpoint between parameters “a” and “d” (thus Q = (a + d)/2). This point Q was used to stratify studies into low and high quality subgroups for each metric. All studies included in a set of 7 ranked studies for which the moving pooled effect size (k = 7) was more negative than Q were stratified into the high quality subgroup for that quality metric. All other studies were stratified into the lower quality subgroup.

Supplemental Results – Exploratory analysis of signal-to-noise as a quality metric.

Spectral signal-to-noise (SNR) was not included as an *a priori* quality metric for testing the hypothesis that the meta-analytic result would be significantly stronger in studies surpassing an empirically identified threshold for measurement quality. We chose this approach in order to limit multiple comparisons for testing this hypothesis. It was our opinion, *a priori*, that SNR would be the least discriminating of the four quality metrics commonly reported (COV, CRLB, FWHM, and SNR). We reasoned that quality metrics based specifically on the glutamate measurement, such as CRLB and COV for glutamate, might have an advantage over those based on the whole spectrum, such as FWHM and SNR. With regard to the latter two, in our own lab we have consistently found low FWHM to be a better predictor of valid glutamate measurements than high SNR.

In response to a question about this issue during peer review, we searched for and extracted SNR mean and SD values from the 36 mPFC studies included in our meta-analysis. Only 23 studies reported these data, and only 20 used an equivalent method for calculating SNR (the LCModel default method). Applying the same procedure as for the other quality metrics, we identified 14 high quality datasets for SNR (mean minus 2 SD ≥ 13). Six studies were identified as having lower quality SNR values. The 16 studies not reporting SNR were included in the lower-quality subgroup. Moderator analyses showed that effect sizes were not significantly different between lower- and high-quality subgroups for SNR (omnibus model Q = 2.2, df =1, p = .13; heterogeneity: I^2 = 45, p = .002). When studies not reporting SNR were excluded altogether from the moderator analysis, there was trend for mPFC glutamate to be more reduced in the high-quality versus the lower-quality SNR subgroup, but it was not significant with our corrected alpha (omnibus model Q = 3.9, df =1, p = .048; heterogeneity: I^2 = 42, p = .02). Detailed statistics for each SNR subgroup are shown below. In agreement with our expectation, an empirical quality threshold based on SNR was less successful than the other quality metrics at identifying studies sensitive to reduced mPFC glutamate in schizophrenia.

Region	Subgroup	Datasets	Cases	Healthy Controls	Effect Size (95% CI)	P value	Heterogeneity I^2, %	P value
MPFC	All datasets	36	1022	1064	**-.19 (-.07 to -.32)**	**.003**	48	<.001
	SNR[a] ≥ 13	14	444	521	**-.30 (-.14 to -.47)**	**<.001**	33	.12
	SNR[a] < 13	6	251	231	-.02 (+.32 to -.36)	.91	67	.02
	SNR not stated	16	327	312	-.17 (+.04 to -.38)	.12	42	.04

[a]mean minus 2 standard deviations of SNR values, averaged across patients and controls

Table S1. Excluded studies and reason for exclusion. Abbreviations: glx = glutamate+glutamine, gln = glutamine, HC = healthy control group, MRS = Magnetic Resonance Spectroscopy, NR = Not Reported, SD = Standard Deviation.

Total Count	Count by Reason	Study	Reason for Exclusion
1	1	Atagun et al. (2017) [1]	no glutamate measure (also no gln or glx)
2	2	Bartolomeo et al. (2019) [2]	no glutamate measure (glx)
3	3	Bernier et al. (2016) [3]	no glutamate measure (glx)
4	4	Birur et al. (2020) [4]	no glutamate measure (glx)
5	5	Block et al. (2000) [5]	no glutamate measure (glx)
6	6	Bustillo et al. (2011) [6]	no glutamate measure (glx)
7	7	Bustillo et al. (2017) [7]	no glutamate measure (glx)
8	8	Bustillo et al. (2017) [8]	no glutamate measure (glx)
9	9	Bustillo et al. (2019) [9]	no glutamate measure (glx)
10	10	Cadena et al. (2018) [10]	no glutamate measure (glx)
11	11	Capizzano et al. (2011) [11]	no glutamate measure (glx)
12	12	Cen et al. (2020) [12]	no glutamate measure (glx)
13	13	Chang et al. (2007) [13]	no glutamate measure (glx)
14	14	Chiu et al. (2018) [14]	no glutamate measure (glx)
15	15	Choe et al. (1994) [15]	no glutamate measure (also no gln or glx)
16	16	Choe et al. (1996) [16]	no glutamate measure (also no gln or glx)
17	17	Chouinard et al. (2017) [17]	no glutamate measure (also no gln or glx)
18	18	Conus et al. (2018) [18]	no glutamate measure (also no gln or glx)
19	19	Curcic-Blake et al. (2017) [19]	no glutamate measure (glx)
20	20	Da Silva et al. (2018) [20]	no glutamate measure (also no gln or glx)
21	21	Da Silva et al. (2018) [21]	no glutamate measure (also no gln or glx)
22	22	Da Silva et al. (2019) [22]	no glutamate measure (also no gln or glx)
23	23	Dlabac-de Lange et al. (2017) [23]	no glutamate measure (glx)
24	24	de la Fuente-Sandoval et al. (2015) [24]	no glutamate measure (glx)
25	25	de la Fuente-Sandoval et al. (2018) [25]	no glutamate measure (glx)
26	26	Galinska et al. (2009) [26]	no glutamate measure (glx)
27	27	Galinska-Skok et al. (2018) [27]	no glutamate measure (glx)
28	28	Galinska-Skok et al. (2019) [28]	no glutamate measure (glx)
29	29	Gan et al. (2017) [29]	no glutamate measure (also no gln or glx)
30	30	Goto et al. (2012) [30]	no glutamate measure (glx)
31	31	Grent-'t-Jong et al. (2018) [31]	no glutamate measure (glx)
32	32	Hafizi et al. (2018) [32]	no glutamate measure (also no gln or glx)
33	33	Hasan et al. (2014) [33]	no glutamate measure (glx)
34	34	He et al. (2018) [34]	no glutamate measure (also no gln or glx)
35	35	Huang et al. (2017) [35]	no glutamate measure (glx)
36	36	Huang et al. (2019) [36]	no glutamate measure (glx)
37	37	Hugdahl et al. (2015) [37]	no glutamate measure (glx)

38	38	Hutcheson et al. (2012) [38]	no glutamate measure (glx)
39	39	Jessen et al. (2013) [39]	no glutamate measure (gln and glx)
40	40	Kegeles et al. (2000) [40]	no glutamate measure (glx)
41	41	Kegeles et al. (2012) [41]	no glutamate measure (glx)
42	42	Keshavan et al. (2009) [42]	no glutamate measure (glx)
43	43	Kim et al. (2017) [43]	no glutamate measure (also no gln or glx)
44	44	Kim et al. (2017) [44]	no glutamate measure (also no gln or glx)
45	45	Kirtas et al. (2016) [45]	no glutamate measure (also no gln or glx)
46	46	Klauser et al. (2018) [46]	no glutamate measure (also no gln or glx)
47	47	Kraguljac et al. (2012) [47]	no glutamate measure (glx)
48	48	Kraguljac et al. (2019) [48]	no glutamate measure (glx)
49	49	Larabi et al. (2017) [49]	no glutamate measure (glx)
50	50	Lesh et al. (2019) [50]	no glutamate measure (also no gln or glx)
51	51	Liemburg et al. (2016) [51]	no glutamate measure (glx)
52	52	Liu et al. (2015) [52]	no glutamate measure (also no gln or glx)
53	53	Lotfi et al. (2018) [53]	no glutamate measure (glx)
54	54	Malaspina et al. (2016) [54]	no glutamate measure (also no gln or glx)
55	55	Marenco et al. (2016) [55]	no glutamate measure (also no gln or glx)
56	56	Mazgaj et al. (2016) [56]	no glutamate measure (also no gln or glx)
57	57	McQueen et al. (2020) [57]	no glutamate measure (glx)
58	58	Menschikov et al. (2016) [58]	no glutamate measure (glx)
59	59	Meyer et al. (2016) [59]	no glutamate measure (also no gln or glx)
60	60	Modinos et al. (2018) [60]	no glutamate measure (also no gln or glx)
61	61	Natsubori et al. (2014) [61]	no glutamate measure (glx)
62	62	Ohrmann et al. (2005) [62]	no glutamate measure (glx)
63	63	Ohrmann et al. (2007) [63]	no glutamate measure (glx)
64	64	Ohrmann et al. (2008) [64]	no glutamate measure (glx)
65	65	Ota et al. (2012) [65]	no glutamate measure (glx)
66	66	Ota et al. (2015) [66]	no glutamate measure (glx)
67	67	Piras et al. (2019) [67]	no glutamate measure (also no gln or glx)
68	68	Prasad et al. (2016) [68]	no glutamate measure (also no gln or glx)
69	69	Prasad et al. (2018) [69]	no glutamate measure (also no gln or glx)
70	70	Provenzano et al. (2020) [70]	no glutamate measure (glx)
71	71	Psomiades et al. (2018) [71]	no glutamate measure (also no gln or glx)
72	72	Rauchmann et al. (2020) [72]	no glutamate measure (glx)
73	73	Reid et al. (2016) [73]	no glutamate measure (glx)
74	74	Reyes-Madrigal et al. (2019) [74]	no glutamate measure (also no gln or glx)
75	75	Rogdaki et al. (2019) [75]	no glutamate measure (glx)
76	76	Rowland et al. (2009) [76]	no glutamate measure (glx)
77	77	Rowland et al. (2013) [77]	no glutamate measure (glx)
78	78	Rowland et al. (2016) [78]	no glutamate measure (also no gln or glx)
79	79	Shaw et al. (2020) [79]	no glutamate measure (also no gln or glx)
80	80	Sivaraman et al. (2018) [80]	no glutamate measure (glx)

81	81	Strzelecki et al. (2015) [81]	no glutamate measure (glx)
82	82	Strzelecki et al. (2015) [82]	no glutamate measure (glx)
83	83	Strzelecki et al. (2015) [83]	no glutamate measure (glx)
84	84	Szulc et al. (2004) [84]	no glutamate measure (glx)
85	85	Szulc et al. (2011) [85]	no glutamate measure (glx)
86	86	Tandon et al. (2013) [86]	no glutamate measure (glx)
87	87	Tarumi et al. (2020) [87]	no glutamate measure (glx)
88	88	Tasic et al. (2019) [88]	no glutamate measure (also no gln or glx)
89	89	Thomas et al. (1998) [89]	no glutamate measure (glx)
90	90	Tibbo et al. (2004) [90]	no glutamate measure (glx)
91	91	Ublinskii et al. (2015) [91]	no glutamate measure (also no gln or glx)
92	92	Vingerhoets et al. (2019) [92]	no glutamate measure (also no gln or glx)
93	93	Wang et al. (2016) [93]	no glutamate measure (glx)
94	94	Wijtenburg et al. (2019) [94]	no glutamate measure (also no gln or glx)
95	95	Wood et al. (2007) [95]	no glutamate measure (glx)
96	96	Wood et al. (2008) [96]	no glutamate measure (glx)
97	97	Xia et al. (2018) [97]	no glutamate measure (also no gln or glx)
98	98	Xiang et al. (2019) [98]	no glutamate measure (glx)
99	99	Yamasue et al. (2003) [99]	no glutamate measure (glx)
100	100	Yang et al. (2019) [100]	no glutamate measure (also no gln or glx)
101	101	Yoo et al. (2009) [101]	no glutamate measure (glx)
102	102	Yoon et al. (2020) [102]	no glutamate measure (also no gln or glx)
103	1	Bustillo et al. (2016) [103]	no HC group
104	2	Dempster et al. (2015) [104]	no HC group
105	3	Demro et al. (2017) [105]	no HC group
106	4	Kaur et al. (2019) [106]	no HC group
107	5	Kegeles et al. (2019) [107]	no HC group
108	6	Mouchlianitis et al. (2016) [108]	no HC group
109	7	Nussbaum et al. (2016) [109]	no HC group
110	8	Rowland et al. (2017) [110]	no HC group
111	1	Bustillo et al. (2014) [111]	either means or SDs NR
112	2	Chiappelli et al. (2015) [112]	either means or SDs NR
113	3	Goldstein et al. (2015) [113]	either means or SDs NR
114	4	Limongi et al. (2020) [114]	either means or SDs NR
115	5	Nussbaum et al. (2017) [115]	either means or SDs NR
116	6	Stanley et al. (1996) [116]	either means or SDs NR
117	1	Davies et al. (2019) [117]	intervention study with no baseline
118	2	McQueen et al. (2018) [118]	intervention study with no baseline
119	1	Jelen et al. (2019) [119]	MRS performed during a task
120	2	Taylor et al. (2015) [120]	MRS performed during a task
121	1	da Silva Alves et al. (2011) [121]	22q11.2
122	1	Chiappelli et al. (2016) [122]	participant overlap with other studies
123	2	Chiappelli et al. (2018) [123]	participant overlap with other studies

124	3	Jauhar et al. (2018) [124]	participant overlap with other studies
125	4	Maddock et al. (2018) [125]	participant overlap with other studies
126	5	Merritt et al. (2019) [126]	participant overlap with other studies
127	6	Overbeek et al. (2019) [127]	participant overlap with other studies
128	7	Rowland et al. (2016) [128]	participant overlap with other studies
129	8	Shah et al. (2020) [129]	participant overlap with other studies
130	9	Shukla et al. (2019) [130]	participant overlap with other studies
131	10	Theberge et al. (2002) [131]	participant overlap with other studies
132	1	Ongur et al. (2008) [132]	no internal reference
133	1	Smesny et al. (2015) [133]	multivoxel MRSI acquisition
134	1	Kim et al. (2018) [134]	sex ratio group imbalance
135	1	Girgis et al. (2019) [135]	CT-PRESS sequence
136	1	Bloemen et al. (2011) [136]	high risk participants only
137	2	Bossong et al. (2019) [137]	high risk participants only
138	3	Egerton et al. (2014) [138]	high risk participants only
139	4	Howes et al. (2020) [139]	high risk participants only
140	5	Modinos et al. (2018) [140]	high risk participants only
141	6	Purdon et al. (2008) [141]	high risk participants only
142	7	Stone et al. (2009) [142]	high risk participants only
143	8	Wenneberg et al. (2020) [143]	high risk participants only

Table S2. Included studies of regions for which < 10 datasets are available.

Region	Reference
Thalamus	Aoyama et al. (2011) [165]
Thalamus	Bojesen et al. (2019) [166]
Thalamus	Bustillo et al. (2010) [167]
Thalamus	Egerton et al. (2018) [168]
Thalamus	Legind et al. (2019) [169]
Thalamus	Taylor et al. (2017) [170]
Thalamus	Theberge et al. (2003) [171]
Thalamus	Wang et al. (2019) [151]
Dorsolateral Prefrontal Cortex	Iwata et al. (2019) [145]
Dorsolateral Prefrontal Cortex	Kaminski et al. (2020) [146]
Dorsolateral Prefrontal Cortex	Ragland et al. (2020) [147]
Dorsolateral Prefrontal Cortex	Rusch et al. (2008) [148]
Dorsolateral Prefrontal Cortex	Stanley et al. (2007) [149]
Dorsolateral Prefrontal Cortex	van Elst et al. (2005) [150]
Dorsolateral Prefrontal Cortex	Wang et al. (2019) [151]
Striatum	de la Fuente-Sandoval et al. (2011) [144]
Striatum	Plitman et al. (2016) [161]
Striatum	Plitman et al. (2018) [162]
Striatum	Tayoshi et al. (2009) [163]
Striatum	Thakkar et al. (2017) [158]
Frontal White Matter	Chiappelli et al. (2015) [152]
Frontal White Matter	Lutkenhoff et al. (2010) [153]
Frontal White Matter	Tunc-Skarka et al. (2009) [154]
Frontal White Matter	Wang et al. (2019) [151]
Occipital Cortex	Balz et al. (2018) [156]
Occipital Cortex	Kumar et al. (2020) [155]
Occipital Cortex	Marsman et al. (2014) [157]
Occipital Cortex	Thakkar et al. (2017) [158]
Cerebellum	de la Fuente-Sandoval et al. (2011) [144]
Cerebellum	Piras et al. (2019) [67]
Parietal Cortex	Korenic et al. (2020) [159]
Parietal Cortex	Lee et al. (2018) [160]
Superior Temporal Cortex	Atagun et al. (2015) [164]
Superior Temporal Cortex	Balz et al. (2018) [156]
Inferior Frontal Cortex	Kumar et al. (2020) [155]
Lateral Orbitofrontal Cortex	Wang et al. (2019) [151]
Ventromedial Prefrontal Cortex[a]	Yang et al. (2015) [172]

Table S2. Included studies of regions for which < 10 datasets are available.
The Legind et al. (2019) [149] and Stanley et al. (2007) [157] studies each had 2 datasets. [a]Ventromedial Prefrontal defined as having the midpoint of voxel inferior to the most rostral point of the corpus callosum.

Table S3 Medial Prefrontal Glutamate - Study Characteristics, Glutamate Data, and Quality Metrics.

1st Author/Year/Parameters	HC N	HC Mean	HC STD	PT N	PT Mean	PT STD	Hedges g	95% CRLB	95% FWHM	mean CoV
Bartha 1997 1.5T ST-20	10	11.75	2.75	10	10.3	2	-0.576	NR	NR	0.214
Theberge 2003 4T ST-20	21	15.89	2.81	21	13.31	3.82	-0.755	NR	NR	0.232
Terpstra 2005 4T ST-5	9	10	0.7	13	10.2	0.9	0.233	NR	NR	0.079
Tayoshi 2009 3T ST-18	25	11.5	3.6	30	9.8	2.7	-0.534	NR	NR	0.294
Bustillo 2010 4T ST-20	10	15.82	2.59	14	14.55	1.37	-0.624	0.105	NR	0.129
Lutkenhoff 2010 3T PR-30	21	11.83	3.81	9	8.11	3.34	-0.982	0.229	0.10	0.367
Ongur 2010 3T M-PR-68	17	0.804	0.152	19	0.889	0.21	0.449	0.22	NR	0.213
Shirayama 2010 3T PR-30	18	1.275	0.088	19	1.256	0.15	-0.150	0.082	NR	0.094
Aoyama 2011 4T ST-20	17	15.6	6	15	15.6	5.7	0.000	NR	NR	0.375
Tibbo 2013 3T ST-240	41	7.83	1.8	33	8.05	1.91	0.118	0.149	0.09	0.234
Demjaha 2014 3T PR-30	10	8.62	1.02	14	9.49	2.18	0.467	NR	NR	0.174
Marsman 2014 7T S-LAS-28	18	8.65	1.14	14	8.48	1.34	-0.135	0.042	0.038	0.145
Brandt 2016 7T ST-14	24	9.05	0.72	24	9.16	1.66	0.085	NR	NR	0.130
Gallinat 2016 3T PR-80	27	15.17	1.11	29	14.46	1.56	-0.514	0.158	NR	0.091
Rowland 2016 7T ST-14	29	8.1	0.67	27	7.9	0.85	-0.259	NR	0.0405	0.095
Xin 2016 3T SPEC-6	33	14.18	0.98	25	13.47	1.59	-0.548	0.03	0.043	0.094
Chen 2017 3T M-PR-68	24	6.54	1.99	24	6.07	2.48	-0.206	NR	NR	0.356
Taylor 2017 7T ST-10	18	10	1.3	15	10.7	1.2	0.543	NR	NR	0.121
Wijtenburg-1 2017 3T ST-6.5	54	9.54	0.7	48	9.25	0.8	-0.384	0.065	0.066	0.080
Wijtenburg-2 2017 3T ST-6.5	39	8.71	0.8	47	8.16	1	-0.596	0.077	0.062	0.107
Chiappelli 2018 3T ST-6.5	21	13.62	0.96	20	12.9	1.25	-0.635	0.063	0.0585	0.084
Egerton 2018 3T PR-30	60	1.339	0.137	70	1.335	0.164	-0.028	0.088	0.06	0.113
Kumar 2018 7T ST-17	45	6.21	0.81	27	6.01	0.66	-0.261	NR	0.085	0.120
Posperilis 2018 7T ST-15	20	1.33	0.14	20	1.29	0.1	-0.322	0.025	0.058	0.091
Rigucci 2018 3T SPEC-6	33	14.2	0.9	35	13.28	1.52	-0.719	0.03	NR	0.089
Bojesen 2019 3T PR-30	36	1.55	0.1	37	1.51	0.14	-0.325	0.064	0.098	0.079
Borgan 2019 3T PR-30	65	13	2.2	46	13.2	2	0.094	NR	0.0586	0.160
Hjelmervik 2019 3T PR-35	33	16.55	1.69	33	17.09	1.8	0.306	NR	0.09	0.104
Iwata 2019 3T PR-35	26	15.98	1.74	74	16.94	1.66	0.568	NR	0.0678	0.103
Legind-1 2019 3T PR-30	49	10.36	1.03	28	10.44	1.1	0.075	0.072	0.075	0.102
Legind-2 2019 3T PR-30	36	10.26	0.9	22	10.43	1.65	0.136	0.074	0.07	0.123
Pillinger 2019 3T PR-30	18	1.33	0.21	19	1.25	0.18	-0.401	0.099	NR	0.151
Reid 2019 7T ST-5	21	6.93	0.5	21	6.57	0.5	-0.706	0.029	0.038	0.074

1st Author/Year/Parameters	HC N	HC Mean	HC STD	PT N	PT Mean	PT STD	Hedges g	95% CRLB	95% FWHM	mean CoV
Wang 2019 7T ST-14	87	8.16	0.57	75	7.83	0.65	-0.540	0.03	0.042	0.076
Dempster 2020 7T LAS-100	27	8.35	2.3	26	8.51	2.05	0.072	0.066	NR	0.258
Korenic 2020 3T PR-30	22	13.3	1.3	19	13.2	1.2	-0.078	NR	NR	0.094

Table S3: Studies ordered by year of publication. First author, year, field strength, sequence and TE are shown in first column. ST = STEAM; PR = PRESS; LAS = LASER; M-PR = MEGA-PRESS; SPEC = SPECIAL; HC = healthy controls; PT = patients; N = sample size; Mean = mean glutamate value; STD = standard deviation of glutamate values; 95% CRLB = mean + 2SD CRLB values averaged across patient and control groups; 95% FWHM = mean + 2SD FWHM values in PPM averaged across patient and control groups; mean COV = coefficient of variation of glutamate values (STD/mean) averaged across patient and control groups.

Table S4 Hippocampal Glutamate - Study Characteristics, Glutamate Data, and Quality Metrics

1st Author/Year/Parameters	HC N	HC Mean	HC STD	PT N	PT Mean	PT STD	Hedges g	95% CRLB	95% FWHM	mean CoV
Bartha 1999 1.5T ST-20	11	7.58	1.67	11	6.83	2.32	-0.356	NR	NR	0.280
van Elst 2005 2T PR-30	16	2.37	0.8	8	4.34	2.83	1.100	NR	NR	0.495
Olbrich 2008 2T PR-30	32	2.37	1.13	9	3.91	0.87	1.395	NR	NR	0.350
Rusch 2008 2T PR-30	12	2.67	0.7	14	3.56	1.44	0.742	NR	NR	0.333
Lutkenhoff 2010 3T PR-30	21	9.26	5.67	9	7.54	1.9	-0.341	0.264	0.10	0.432
Nenadic 2015 3T PR-30	42	9.878	2.628	18	10.095	2.53	0.082	NR	NR	0.258
Stan 2015 3T M-PR-70	16	0.88	0.08	18	0.82	0.09	-0.685	0.063	NR	0.100
Gallinat 2016 3T PR-80	29	10.42	1.53	29	12.1	1.47	1.105	NR	NR	0.134
Singh 2018 3T PR-33	28	1.24	0.21	28	1.15	0.16	-0.475	NR	NR	0.154
Korenic 2020 3T PR-30	21	8.5	1.3	19	8.2	1.3	-0.226	NR	NR	0.156
Shakory 2020 3T PR-35	31	10.51	1.4	10	10.12	1.15	-0.284	0.09	.092	0.123

Table S4: Studies ordered by year of publication. First author, year, field strength, sequence and TE are shown in first column. ST = STEAM; PR = PRESS; M-PR = MEGA-PRESS; HC = healthy controls; PT = patients; N = sample size; Mean = mean glutamate value; STD = standard deviation of glutamate values; 95% CRLB = mean + 2SD CRLB values averaged across patient and control groups; 95% FWHM = mean + 2SD FWHM values in PPM averaged across patient and control groups; mean COV = coefficient of variation of glutamate values (STD/mean) averaged across patient and control groups.

Moderator effects

Meta-regression analysis showed no effect of either field strength or log TE. The distributions of these regressors, however, were very limited. There were no studies above 3T, and 8 of the 11 studies used TE between 30 and 35 ms. Three datasets were categorized as ≥ 80% unmedicated and 6 datasets as all medicated (2 datasets excluded). Medication status did not significantly moderate effect size (omnibus model Q = 2.2, df =1, p = .14; heterogeneity: I^2 = 75, p < .001). Similarly, 4 datasets were categorized as recent onset and 7 as chronic. Neither phase of illness nor mean patient age significantly moderated effect size (omnibus model Q = 0.0, df =1, NS; heterogeneity: I^2 = 80, p = .001; and omnibus model Q = 2.5, df =1, p = .114; heterogeneity: I^2 = 74, p = .001, respectively).

Table S5 Thalamic Glutamate - Study Characteristics, Glutamate Data, and Quality Metrics

1st Author/Year/Parameters	HC N	HC Mean	HC STD	PT N	PT Mean	PT STD	Hedges g	95% CRLB	95% FWHM	mean CoV
Theberge 2003 4T ST-20	19	13.11	1.74	19	12.88	1.37	-0.144	NR	NR	0.120
Bustillo 2010 4T ST-20	10	11.5	4.26	12	12.29	3.38	0.200	0.275	NR	0.323
Aoyama 2011 4T ST-20	17	13.89	2.69	16	13.71	1.79	-0.076	NR	NR	0.348
Taylor 2017 7T ST-10	18	7.4	0.60	15	7.4	1.00	0.0	NR	NR	0.108
Egerton 2018 3T PR-30	60	1.09	.15	70	1.09	.20	0.0	0.165	0.075	0.1623
Bojesen 2019 3T PR-30	32	1.22	.15	38	1.29	.15	0.461	0.13	0.057	0.120
Legind-1 2019 3T PR-30	52	7.07	.84	23	7.55	.84	0.565	0.185	0.075	0.115
Legind-2 2019 3T PR-30	36	7.34	.92	22	7.45	1.13	0.108	0.155	0.075	0.139
Wang 2019 7T ST-14	74	6.36	0.54	66	6.24	0.63	-0.204	0.10	0.0705	0.093

Table S5: Studies ordered by year of publication. First author, year, field strength, sequence and TE are shown in first column. ST = STEAM; PR = PRESS; HC = healthy controls; PT = patients; N = sample size; Mean = mean glutamate value; STD = standard deviation of glutamate values; 95% CRLB = mean + 2SD CRLB values averaged across patient and control groups; 95% FWHM = mean + 2SD FWHM values in PPM averaged across patient and control groups; mean COV = coefficient of variation of glutamate values (STD/mean) averaged across patient and control groups.

Table S6 Dorsolateral Prefrontal Glutamate - Study Characteristics, Glutamate Data, and Quality Metrics

1st Author/Year/Parameters	HC N	HC Mean	HC STD	PT N	PT Mean	PT STD	Hedges g	95% CRLB	95% FWHM	mean CoV
van Elst 2005 2T PR-30	33	2.9	0.7	21	7.49	8.4	0.876	NR	NR	0.682
Stanley-1 2007 1.5T ST-20	27	6.91	1.31	8	5.82	.92	-0.858	NR	0.080	0.174
Stanley-2 2007 1.5T ST-20	34	6.45	1.48	10	6.42	1.11	-0.021	NR	0.080	0.202
Rusch 2008 2T PR-30	22	3.04	0.64	20	3.82	1.43	0.702	NR	NR	0.292
Iwata 2019 3T PR-35	26	13.94	1.32	21	13.55	1.6	-0.264	0.058	0.077	0.106
Wang 2019 7T ST-14	84	6.65	0.52	72	6.41	0.75	-0.375	0.044	0.049	0.162
Kaminski 2020 3T PR-80	35	8.22	0.9	55	7.92	1.1	-0.289	NR	NR	0.124
Ragland 2020 3T PR-80	49	0.906	0.091	38	0.894	0.104	-0.123	0.072	0.056	0.108

Table S6: Studies ordered by year of publication. First author, year, field strength, sequence and TE are shown in first column. ST = STEAM; PR = PRESS; HC = healthy controls; PT = patients; N = sample size; Mean = mean glutamate value; STD = standard deviation of glutamate values; 95% CRLB = mean + 2SD CRLB values averaged across patient and control groups; 95% FWHM = mean + 2SD FWHM values in PPM averaged across patient and control groups; mean COV = coefficient of variation of glutamate values (STD/mean) averaged across patient and control group

Figure S1: PRISMA Flow Diagram[173]

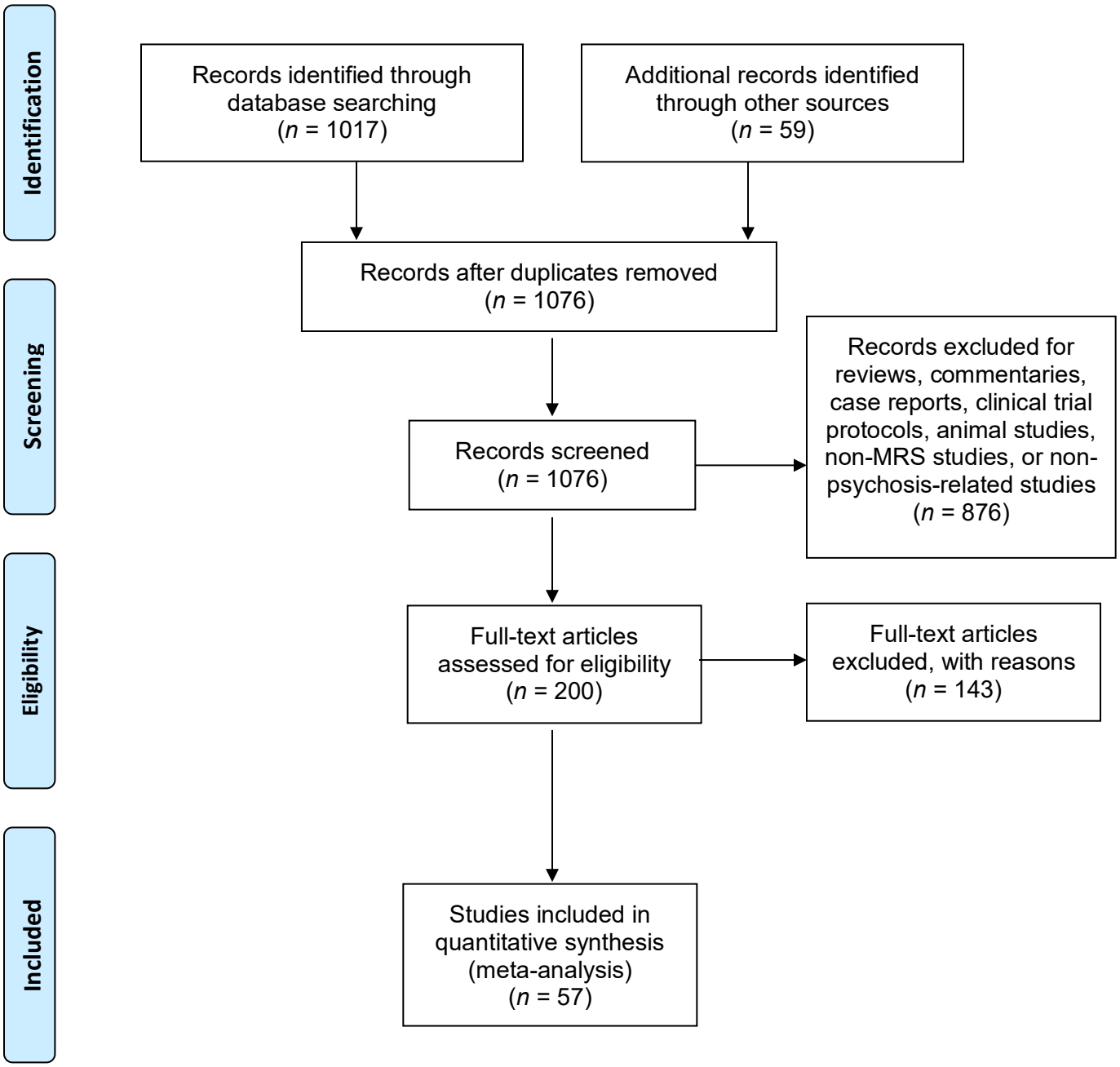

Figure S2
Hippocampal Glutamate

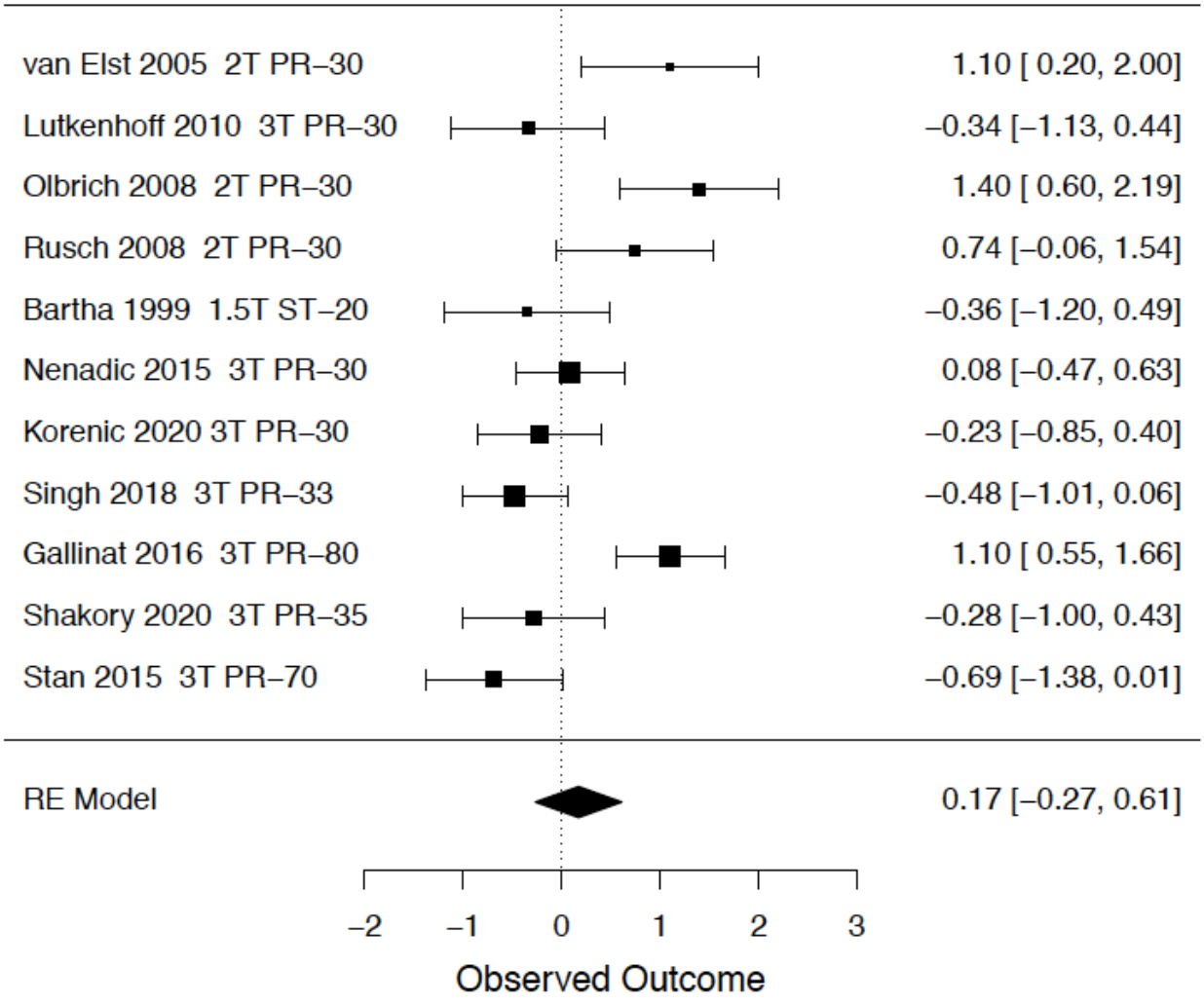

Figure S2: Meta-analysis forest plot for 11 datasets reporting hippocampal glutamate in schizophrenia patients and healthy control subjects. Datasets are listed in order of coefficient of variation (COV) of glutamate averaged across patient and control groups, with lowest COV at bottom. First author, year, field strength, sequence and TE are listed at left. Hedge's *g* and 95% CI are at center and right. ST = STEAM; PR = PRESS; RE = random effects.

Figure S3
Thalamic Glutamate

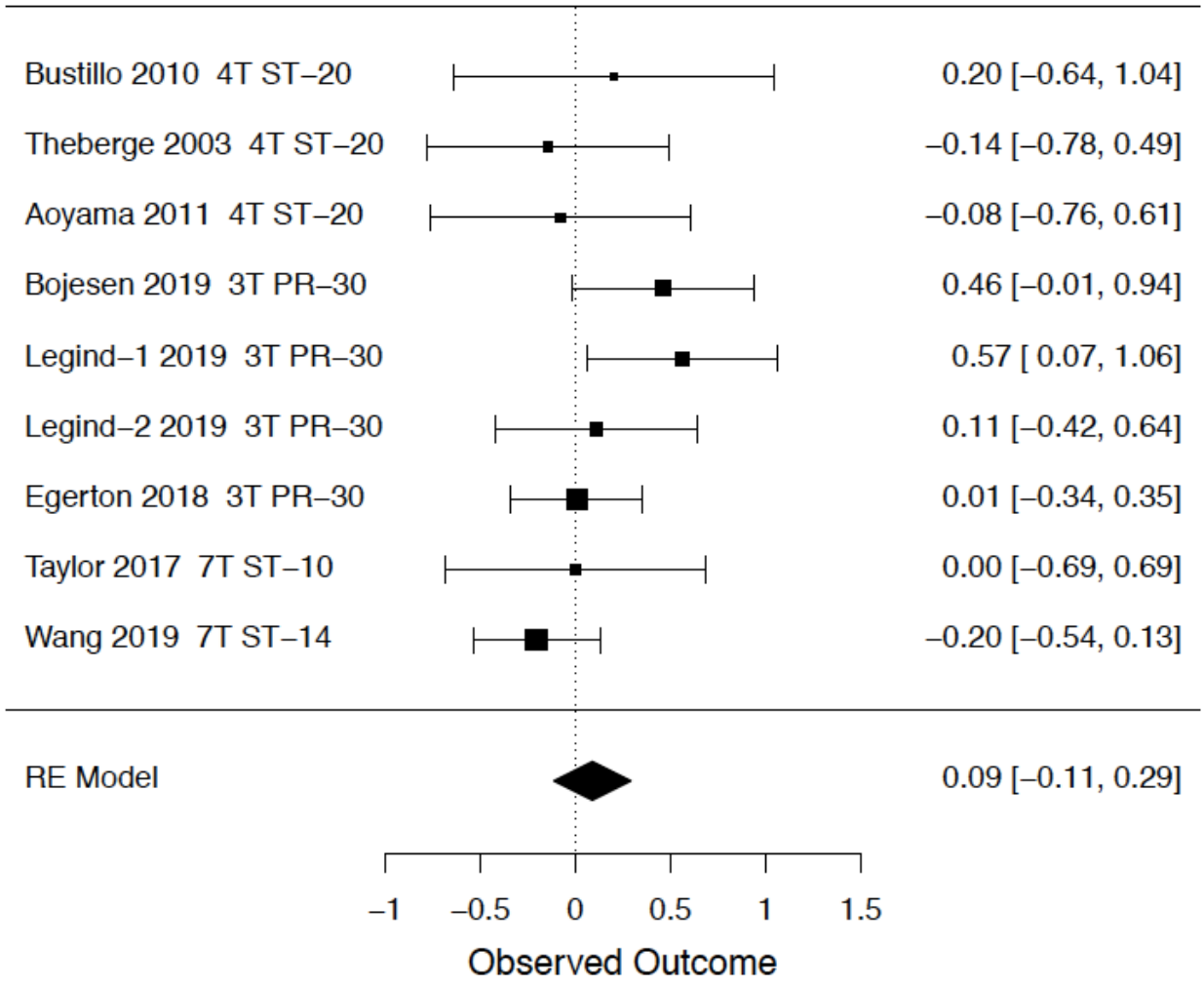

Figure S3. Meta-analysis forest plot for 9 datasets reporting thalamic glutamate in schizophrenia patients and healthy control subjects. Datasets are listed in order of coefficient of variation (COV) of glutamate averaged across patient and control groups, with lowest COV at bottom. First author, year, field strength, sequence and TE are listed at left. Hedge's *g* and 95% CI are at center and right. ST = STEAM; PR = PRESS; RE = random effects.

Figure S4
Dorsolateral PFC Glutamate

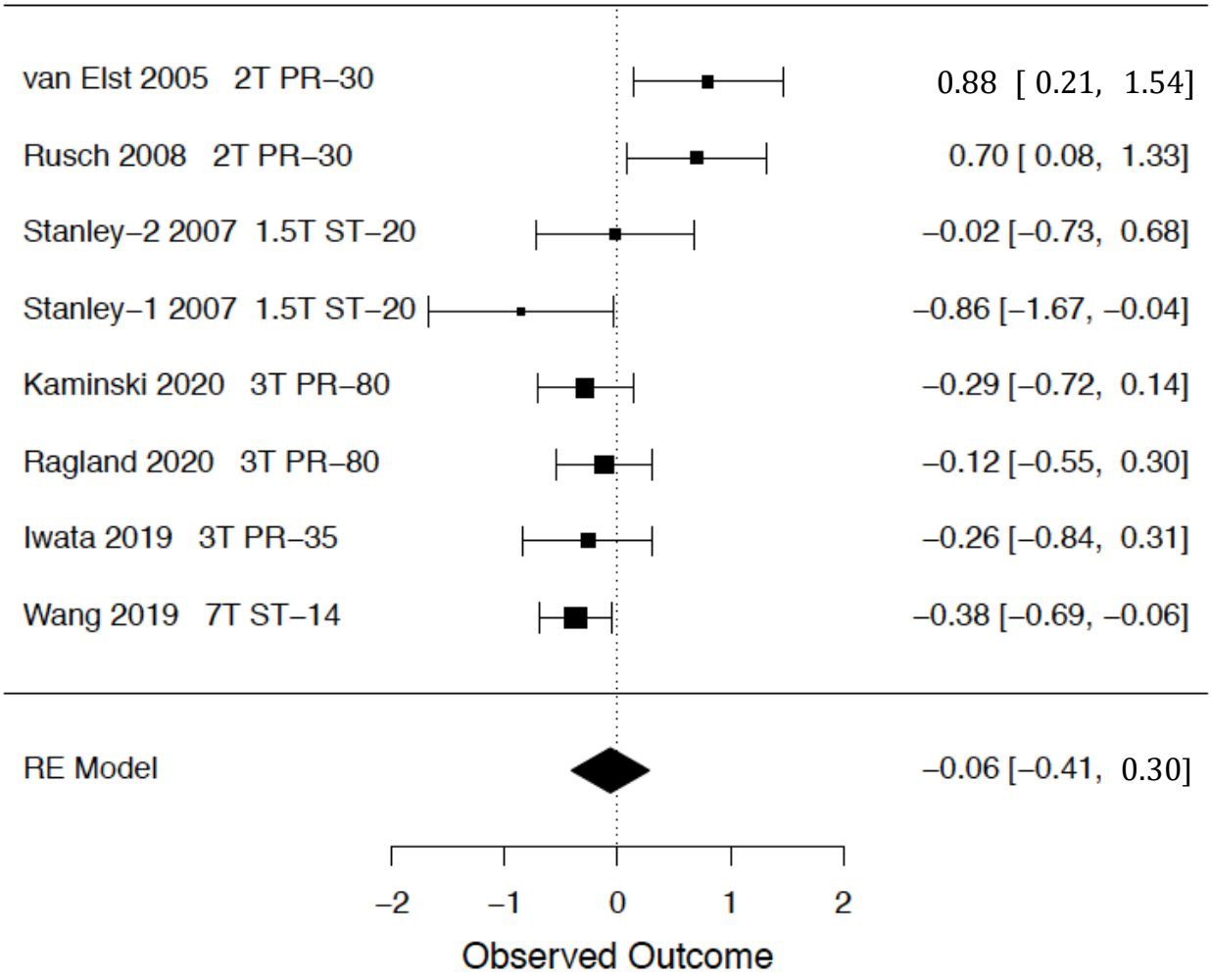

Figure S4. Meta-analysis forest plot for 8 datasets reporting dorsolateral PFC glutamate in schizophrenia patients and healthy control subjects. Datasets are listed in order of coefficient of variation (COV) of glutamate averaged across patient and control groups, with lowest COV at bottom. First author, year, field strength, sequence and TE are listed at left. Hedge's *g* and 95% CI are at center and right. ST = STEAM; PR = PRESS; RE = random effects.

Figure S5
Striatal Glutamate

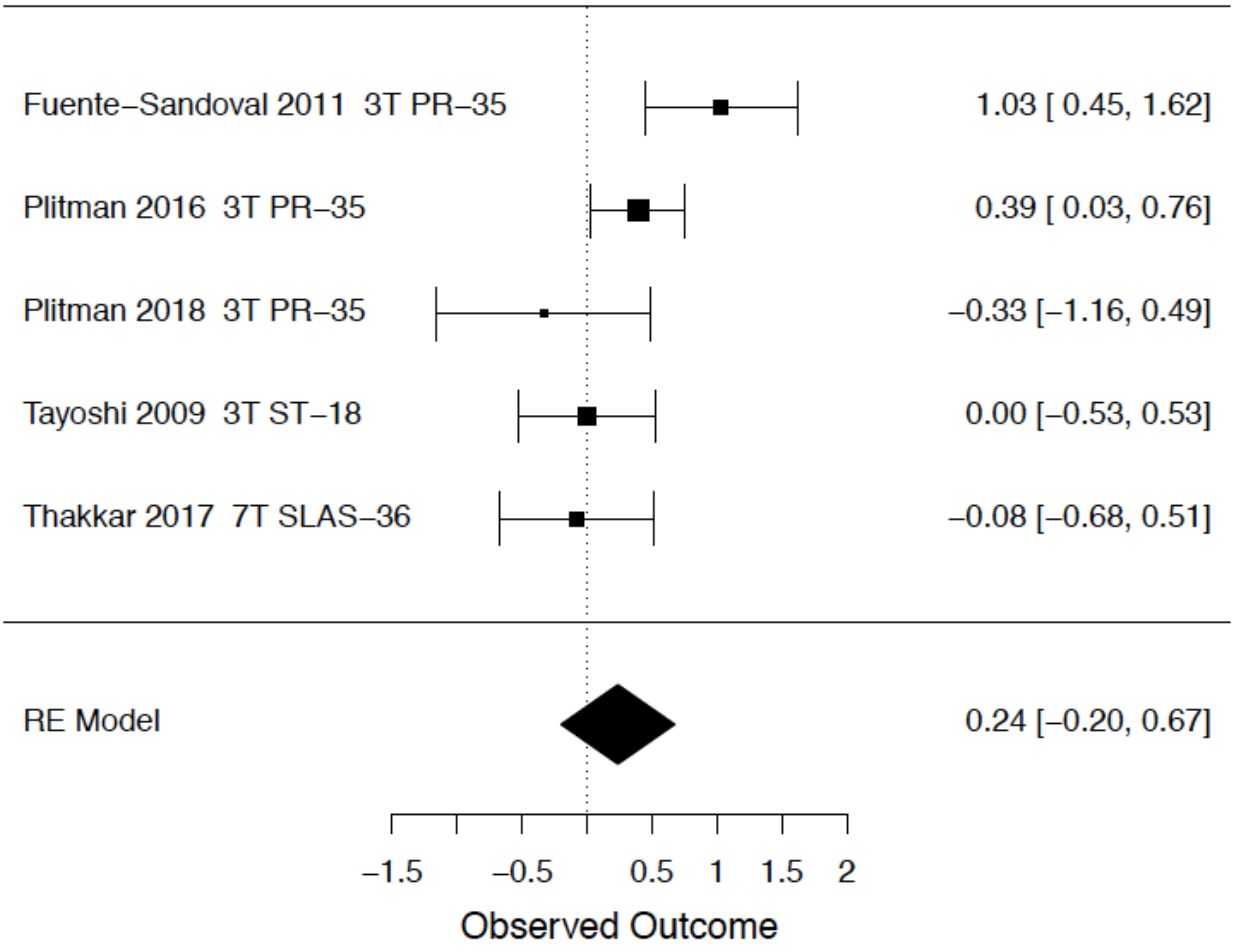

Figure S5. Exploratory meta-analysis forest plot for 5 datasets reporting striatal glutamate in schizophrenia patients and healthy control subjects. Datasets are listed in order of coefficient of variation (COV) of glutamate averaged across patient and control groups, with lowest COV at bottom. First author, year, field strength, sequence and TE are listed at left. Hedge's *g* and 95% CI are at center and right. ST = STEAM; PR = PRESS; SLAS = Semi-LASER; RE = random effects.

Figure S6
Frontal White Matter Glutamate

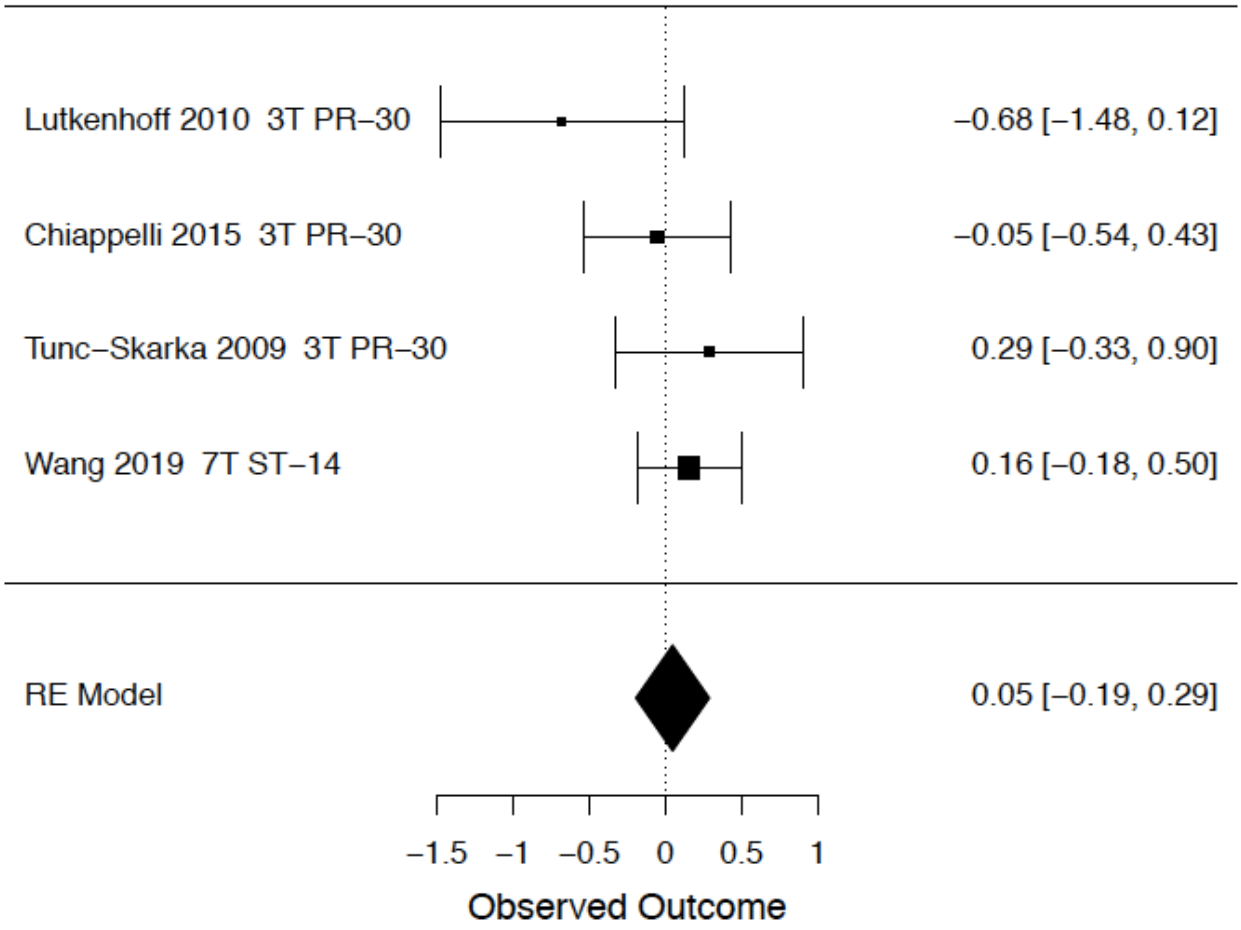

Figure S6. Exploratory meta-analysis forest plot for 4 datasets reporting frontal white matter glutamate in schizophrenia patients and healthy control subjects. Datasets are listed in order of coefficient of variation (COV) of glutamate averaged across patient and control groups, with lowest COV at bottom. First author, year, field strength, sequence and TE are listed at left. Hedge's *g* and 95% CI are at center and right. ST = STEAM; PR = PRESS; RE = random effects.

Figure S7
Occipital Cortex Glutamate

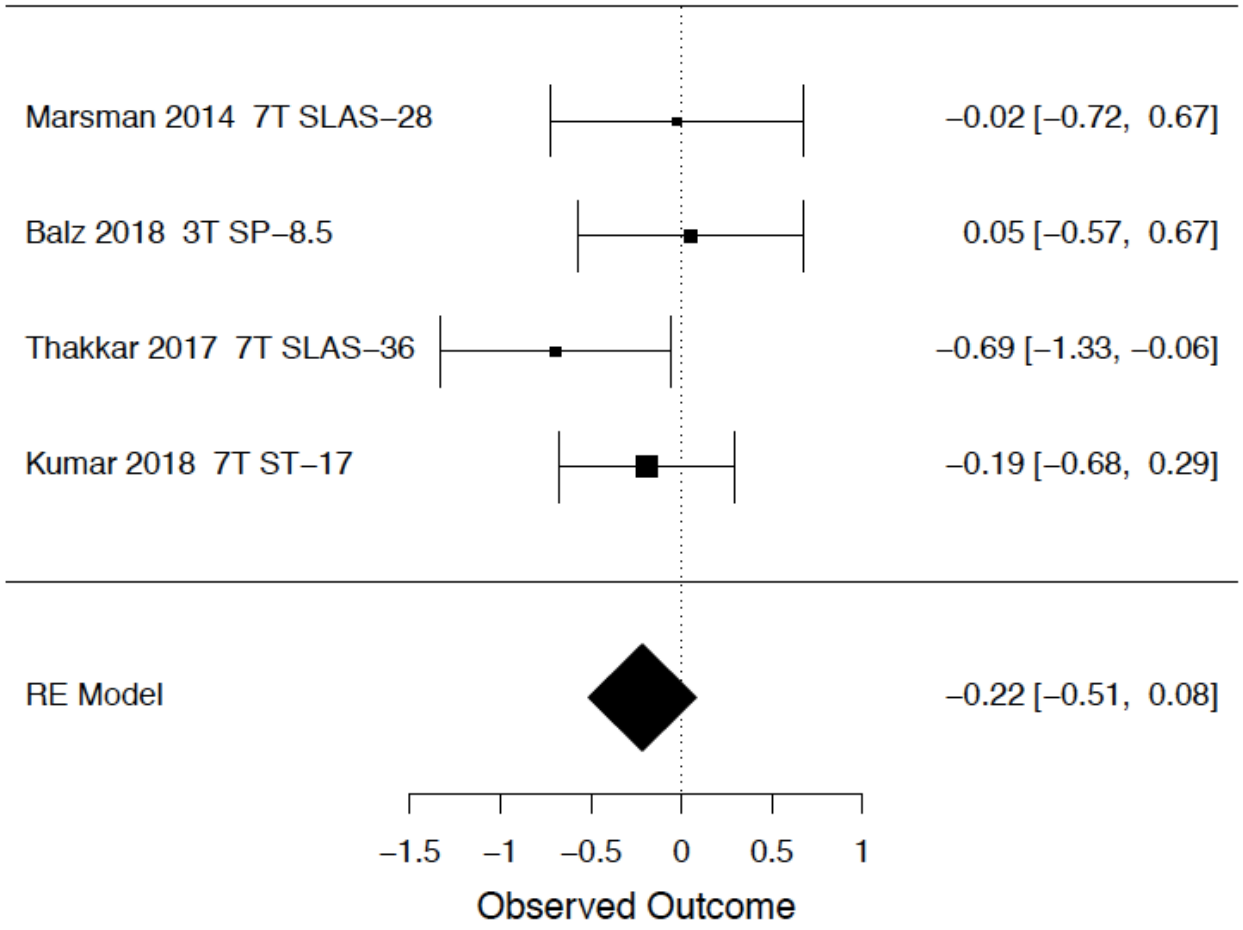

Figure S7. Exploratory meta-analysis forest plot for 4 datasets reporting occipital cortex glutamate in schizophrenia patients and healthy control subjects. Datasets are listed in order of coefficient of variation (COV) of glutamate averaged across patient and control groups, with lowest COV at bottom. First author, year, field strength, sequence and TE are listed at left. Hedge's *g* and 95% CI are at center and right. ST = STEAM; PR = PRESS; SLAS = Semi-LASER; RE = random effects.

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