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

Supplement

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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:

\[ Y = d + \frac{(a - d)}{1+(X/c)^b} \]

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 | -0.3602              |
| FWHM  | +0.0343 | 4.518 | 18.60 | -0.8647 | -0.4152              |
| COV   | -0.0568 | 67.00 | 29.09 | -0.4653 | -0.2610              |

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: I² = 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: I² = 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 | P value |
|--------|----------|----------|-------|------------------|----------------------|---------|---------------|---------|
| MPFC   | All datasets | 36       | 1022  | 1064             | -0.19 (-0.07 to -0.32) | .003    | 48            | <.001   |
|        | SNR ≥ 13     | 14       | 444   | 521              | -0.30 (-0.14 to -0.47) | <.001   | 33            | .12     |
|        | SNR < 13     | 6        | 251   | 231              | -0.02 (+0.32 to -0.36) | .91     | 67            | .02     |
|        | SNR not stated | 16   | 327   | 312              | -0.17 (+0.04 to -0.38) | .12     | 42            | .04     |

amean 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               | Atagu et al. (2017)                        | no glutamate measure (also no gln or glx)                |
| 2          | 2               | Bartolomeo et al. (2019)                   | no glutamate measure (glx)                              |
| 3          | 3               | Bernier et al. (2016)                      | no glutamate measure (glx)                              |
| 4          | 4               | Birur et al. (2020)                        | no glutamate measure (glx)                              |
| 5          | 5               | Block et al. (2000)                        | no glutamate measure (glx)                              |
| 6          | 6               | Bustillo et al. (2011)                     | no glutamate measure (glx)                              |
| 7          | 7               | Bustillo et al. (2017)                     | no glutamate measure (glx)                              |
| 8          | 8               | Bustillo et al. (2017)                     | no glutamate measure (glx)                              |
| 9          | 9               | Bustillo et al. (2019)                     | no glutamate measure (glx)                              |
| 10         | 10              | Cadena et al. (2018)                       | no glutamate measure (glx)                              |
| 11         | 11              | Capizzano et al. (2011)                    | no glutamate measure (glx)                              |
| 12         | 12              | Cen et al. (2020)                          | no glutamate measure (glx)                              |
| 13         | 13              | Chang et al. (2007)                        | no glutamate measure (glx)                              |
| 14         | 14              | Chiu et al. (2018)                         | no glutamate measure (glx)                              |
| 15         | 15              | Choe et al. (1994)                         | no glutamate measure (also no gln or glx)               |
| 16         | 16              | Choe et al. (1996)                         | no glutamate measure (also no gln or glx)               |
| 17         | 17              | Chouinard et al. (2017)                    | no glutamate measure (also no gln or glx)               |
| 18         | 18              | Conus et al. (2018)                        | no glutamate measure (also no gln or glx)               |
| 19         | 19              | Curcic-Blake et al. (2017)                 | no glutamate measure (glx)                              |
| 20         | 20              | Da Silva et al. (2018)                     | no glutamate measure (also no gln or glx)               |
| 21         | 21              | Da Silva et al. (2018)                     | no glutamate measure (also no gln or glx)               |
| 22         | 22              | Da Silva et al. (2019)                     | no glutamate measure (also no gln or glx)               |
| 23         | 23              | Dlabac-de Lange et al. (2017)              | no glutamate measure (glx)                              |
| 24         | 24              | de la Fuente-Sandoval et al. (2015)        | no glutamate measure (glx)                              |
| 25         | 25              | de la Fuente-Sandoval et al. (2018)        | no glutamate measure (glx)                              |
| 26         | 26              | Galinska et al. (2009)                     | no glutamate measure (glx)                              |
| 27         | 27              | Galinska-Skok et al. (2018)                | no glutamate measure (glx)                              |
| 28         | 28              | Galinska-Skok et al. (2019)                | no glutamate measure (glx)                              |
| 29         | 29              | Gan et al. (2017)                          | no glutamate measure (also no gln or glx)               |
| 30         | 30              | Goto et al. (2012)                         | no glutamate measure (glx)                              |
| 31         | 31              | Grent-'t Jong et al. (2018)                | no glutamate measure (glx)                              |
| 32         | 32              | Hafizi et al. (2018)                       | no glutamate measure (also no gln or glx)               |
| 33         | 33              | Hasan et al. (2014)                        | no glutamate measure (glx)                              |
| 34         | 34              | He et al. (2018)                           | no glutamate measure (also no gln or glx)               |
| 35         | 35              | Huang et al. (2017)                        | no glutamate measure (glx)                              |
| 36         | 36              | Huang et al. (2019)                        | no glutamate measure (glx)                              |
| 37         | 37              | Hugdahl et al. (2015)                      | no glutamate measure (glx)                              |
| Page | Page | Study Reference | Glutamate Measure |
|------|------|-----------------|-------------------|
| 38   | 38   | Hutcheson et al. (2012) | no glutamate measure (glx) |
| 39   | 39   | Jessen et al. (2013) | no glutamate measure (glx) |
| 40   | 40   | Kegeles et al. (2000) | no glutamate measure (glx) |
| 41   | 41   | Kegeles et al. (2012) | no glutamate measure (glx) |
| 42   | 42   | Keshavan et al. (2009) | no glutamate measure (glx) |
| 43   | 43   | Kim et al. (2017) | no glutamate measure (also no gln or glx) |
| 44   | 44   | Kim et al. (2017) | no glutamate measure (also no gln or glx) |
| 45   | 45   | Kirtas et al. (2016) | no glutamate measure (also no gln or glx) |
| 46   | 46   | Klauser et al. (2018) | no glutamate measure (also no gln or glx) |
| 47   | 47   | Kraguljac et al. (2012) | no glutamate measure (glx) |
| 48   | 48   | Kraguljac et al. (2019) | no glutamate measure (glx) |
| 49   | 49   | Larabi et al. (2017) | no glutamate measure (glx) |
| 50   | 50   | Lesh et al. (2019) | no glutamate measure (also no gln or glx) |
| 51   | 51   | Liemburg et al. (2016) | no glutamate measure (glx) |
| 52   | 52   | Liu et al. (2015) | no glutamate measure (also no gln or glx) |
| 53   | 53   | Lotfi et al. (2018) | no glutamate measure (glx) |
| 54   | 54   | Malaspina et al. (2016) | no glutamate measure (also no gln or glx) |
| 55   | 55   | Marenc et al. (2016) | no glutamate measure (also no gln or glx) |
| 56   | 56   | Mazgaj et al. (2016) | no glutamate measure (also no gln or glx) |
| 57   | 57   | McQueen et al. (2020) | no glutamate measure (glx) |
| 58   | 58   | Menschikov et al. (2016) | no glutamate measure (glx) |
| 59   | 59   | Meyer et al. (2016) | no glutamate measure (also no gln or glx) |
| 60   | 60   | Modinos et al. (2018) | no glutamate measure (also no gln or glx) |
| 61   | 61   | Natsubori et al. (2014) | no glutamate measure (glx) |
| 62   | 62   | Ohrmann et al. (2005) | no glutamate measure (glx) |
| 63   | 63   | Ohrmann et al. (2007) | no glutamate measure (glx) |
| 64   | 64   | Ohrmann et al. (2008) | no glutamate measure (glx) |
| 65   | 65   | Ota et al. (2012) | no glutamate measure (glx) |
| 66   | 66   | Ota et al. (2015) | no glutamate measure (glx) |
| 67   | 67   | Piras et al. (2019) | no glutamate measure (also no gln or glx) |
| 68   | 68   | Prasad et al. (2016) | no glutamate measure (also no gln or glx) |
| 69   | 69   | Prasad et al. (2018) | no glutamate measure (also no gln or glx) |
| 70   | 70   | Provenzano et al. (2020) | no glutamate measure (glx) |
| 71   | 71   | Psomiades et al. (2018) | no glutamate measure (also no gln or glx) |
| 72   | 72   | Rauchmann et al. (2020) | no glutamate measure (glx) |
| 73   | 73   | Reid et al. (2016) | no glutamate measure (glx) |
| 74   | 74   | Reyes-Madrigal et al. (2019) | no glutamate measure (also no gln or glx) |
| 75   | 75   | Rogdaki et al. (2019) | no glutamate measure (glx) |
| 76   | 76   | Rowland et al. (2009) | no glutamate measure (glx) |
| 77   | 77   | Rowland et al. (2013) | no glutamate measure (glx) |
| 78   | 78   | Rowland et al. (2016) | no glutamate measure (also no gln or glx) |
| 79   | 79   | Shaw et al. (2020) | no glutamate measure (also no gln or glx) |
| 80   | 80   | Sivaraman et al. (2018) | no glutamate measure (glx) |
| Page | Line | Reference                                      | Additional Information           |
|------|------|-----------------------------------------------|----------------------------------|
| 81   | 81   | Strzelecki et al. (2015)                       | no glutamate measure (glx)       |
| 82   | 82   | Strzelecki et al. (2015)                       | no glutamate measure (glx)       |
| 83   | 83   | Strzelecki et al. (2015)                       | no glutamate measure (glx)       |
| 84   | 84   | Szulc et al. (2004)                            | no glutamate measure (glx)       |
| 85   | 85   | Szulc et al. (2011)                            | no glutamate measure (glx)       |
| 86   | 86   | Tandon et al. (2013)                           | no glutamate measure (glx)       |
| 87   | 87   | Tarumi et al. (2020)                           | no glutamate measure (glx)       |
| 88   | 88   | Tasic et al. (2019)                            | no glutamate measure (also no gln or glx) |
| 89   | 89   | Thomas et al. (1998)                           | no glutamate measure (glx)       |
| 90   | 90   | Tibbo et al. (2004)                            | no glutamate measure (glx)       |
| 91   | 91   | Ublinski et al. (2015)                         | no glutamate measure (also no gln or glx) |
| 92   | 92   | Vingerhoets et al. (2019)                      | no glutamate measure (also no gln or glx) |
| 93   | 93   | Wang et al. (2016)                             | no glutamate measure (glx)       |
| 94   | 94   | Wijtenburg et al. (2019)                       | no glutamate measure (also no gln or glx) |
| 95   | 95   | Wood et al. (2007)                             | no glutamate measure (glx)       |
| 96   | 96   | Wood et al. (2008)                             | no glutamate measure (glx)       |
| 97   | 97   | Xia et al. (2018)                              | no glutamate measure (also no gln or glx) |
| 98   | 98   | Xiang et al. (2019)                            | no glutamate measure (glx)       |
| 99   | 99   | Yamasue et al. (2003)                          | no glutamate measure (glx)       |
| 100  | 100  | Yang et al. (2019)                             | no glutamate measure (also no gln or glx) |
| 101  | 101  | Yoo et al. (2009)                              | no glutamate measure (glx)       |
| 102  | 102  | Yoon et al. (2020)                             | no glutamate measure (also no gln or glx) |
| 103  | 1    | Bustillo et al. (2016)                         | no HC group                      |
| 104  | 2    | Dempster et al. (2015)                         | no HC group                      |
| 105  | 3    | Demro et al. (2017)                            | no HC group                      |
| 106  | 4    | Kaur et al. (2019)                             | no HC group                      |
| 107  | 5    | Kegeles et al. (2019)                          | no HC group                      |
| 108  | 6    | Mouchlianitis et al. (2016)                    | no HC group                      |
| 109  | 7    | Nussbaum et al. (2016)                         | no HC group                      |
| 110  | 8    | Rowland et al. (2017)                          | no HC group                      |
| 111  | 1    | Bustillo et al. (2014)                         | either means or SDs NR          |
| 112  | 2    | Chiappelli et al. (2015)                       | either means or SDs NR          |
| 113  | 3    | Goldstein et al. (2015)                        | either means or SDs NR          |
| 114  | 4    | Limongi et al. (2020)                          | either means or SDs NR          |
| 115  | 5    | Nussbaum et al. (2017)                         | either means or SDs NR          |
| 116  | 6    | Stanley et al. (1996)                          | either means or SDs NR          |
| 117  | 1    | Davies et al. (2019)                           | intervention study with no baseline |
| 118  | 2    | McQueen et al. (2018)                          | intervention study with no baseline |
| 119  | 1    | Jelen et al. (2019)                            | MRS performed during a task      |
| 120  | 2    | Taylor et al. (2015)                           | MRS performed during a task      |
| 121  | 1    | da Silva Alves et al. (2011)                   | 22q11.2                         |
| 122  | 1    | Chiappelli et al. (2016)                       | participant overlap with other studies |
| 123  | 2    | Chiappelli et al. (2018)                       | participant overlap with other studies |
| Study Reference | Participant Overlap | Details |
|-----------------|---------------------|---------|
| Jauhar et al. (2018) | participant overlap with other studies |
| Maddock et al. (2018) | participant overlap with other studies |
| Merritt et al. (2019) | participant overlap with other studies |
| Overbeek et al. (2019) | participant overlap with other studies |
| Rowland et al. (2016) | participant overlap with other studies |
| Shah et al. (2020) | participant overlap with other studies |
| Shukla et al. (2019) | participant overlap with other studies |
| Theberge et al. (2002) | participant overlap with other studies |
| Ongur et al. (2008) | no internal reference |
| Smesny et al. (2015) | multivoxel MRSI acquisition |
| Kim et al. (2018) | sex ratio group imbalance |
| Girgis et al. (2019) | CT-PRESS sequence |
| Bloemen et al. (2011) | high risk participants only |
| Bossong et al. (2019) | high risk participants only |
| Egerton et al. (2014) | high risk participants only |
| Howes et al. (2020) | high risk participants only |
| Modinos et al. (2018) | high risk participants only |
| Purdon et al. (2008) | high risk participants only |
| Stone et al. (2009) | high risk participants only |
| Wenneberg et al. (2020) | 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                       |
| DorsolateralPrefrontal Cortex       | Iwata et al. (2019) 145                      |
| DorsolateralPrefrontal Cortex       | Kaminski et al. (2020) 146                    |
| DorsolateralPrefrontal Cortex       | Ragland et al. (2020) 147                    |
| DorsolateralPrefrontal Cortex       | Rusch et al. (2008) 148                      |
| DorsolateralPrefrontal Cortex       | Stanley et al. (2007) 149                    |
| DorsolateralPrefrontal Cortex       | van Elst et al. (2005) 150                   |
| DorsolateralPrefrontal 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                    |
| FrontalWhite Matter                 | Chiappelli et al. (2015) 152                 |
| FrontalWhite Matter                 | Lutkenhoff et al. (2010) 153                 |
| FrontalWhite Matter                 | Tunc-Skarka et al. (2009) 154                |
| FrontalWhite Matter                 | Wang et al. (2019) 151                       |
| OccipitalCortex                     | Balz et al. (2018) 156                       |
| OccipitalCortex                     | Kumar et al. (2020) 155                      |
| OccipitalCortex                     | Marsman et al. (2014) 157                    |
| OccipitalCortex                     | Thakkar et al. (2017) 158                    |
| Cerebellum                          | de la Fuente-Sandoval et al. (2011) 144      |
| Cerebellum                          | Piras et al. (2019) 67                       |
| ParietalCortex                      | Korenic et al. (2020) 159                    |
| ParietalCortex                      | Lee et al. (2018) 160                        |
| SuperiorTemporalCortex              | Atagun et al. (2015) 164                     |
| SuperiorTemporalCortex              | Balz et al. (2018) 156                       |
| InferiorFrontalCortex               | Kumar et al. (2020) 155                      |
| LateralOrbitofrontalCortex          | Wang et al. (2019) 151                       |
| VentromedialPrefrontalCortex\textsuperscript{a} | Yang et al. (2015) 172                   |

The Legind et al. (2019) 149 and Stanley et al. (2007) 157 studies each had 2 datasets. \textsuperscript{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    |
| Galli 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   | 9.8     | 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    |
| Wijnenburg-1 2017 3T ST-6.5| 54   | 9.54    | 0.7    | 48   | 9.25    | 0.8    | -0.384   | 0.065     | 0.066    | 0.080    |
| Wijnenburg-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     | 0.043    | 0.094    |
| 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    |
| Legid-1 2019 3T PR-30      | 49   | 10.36   | 1.03   | 28   | 10.44   | 1.1    | 0.075    | 0.072     | 0.075    | 0.102    |
| Legid-2 2019 3T PR-30      | 36   | 10.26   | 0.9    | 22   | 10.43   | 1.65   | 0.136    | 0.074     | 0.07     | 0.123    |
| Pilling 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    |
### Table S3: Studies ordered by year of publication.

| 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: 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.

| 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   |
| 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

Records identified through database searching ($n = 1017$)

Additional records identified through other sources ($n = 59$)

Records after duplicates removed ($n = 1076$)

Records screened ($n = 1076$)

Records excluded for reviews, commentaries, case reports, clinical trial protocols, animal studies, non-MRS studies, or non-psychosis-related studies ($n = 876$)

Full-text articles assessed for eligibility ($n = 200$)

Full-text articles excluded, with reasons ($n = 143$)

Studies included in quantitative synthesis (meta-analysis) ($n = 57$)
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. 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. 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. 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. 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

| Dataset             | Hedge's $g$ and 95% CI       |
|---------------------|------------------------------|
| Marsman 2014 7T SLAS–28 | -0.02 [-0.72, 0.67]          |
| Balz 2018 3T SP–8.5    | 0.05 [-0.57, 0.67]           |
| Thakkar 2017 7T SLAS–36 | -0.69 [-1.33, -0.06]        |
| Kumar 2018 7T ST–17    | -0.19 [-0.68, 0.29]          |
| **RE Model**          | **-0.22 [-0.51, 0.08]**      |

**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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