Additional file 1 (Methodological Appendix)

Kedzior, K, & Reitz, S (2014). Short-term efficacy of repetitive transcranial magnetic stimulation (rTMS) in depression - reanalysis of data from meta-analyses up to 2010. *BMC Psychology*.

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| Section/topic | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|--------------|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| TITLE        |   | **TITLE**                                                                                                                                                                                                       |                   |
| Title        | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                               | 1                 |
| ABSTRACT     |   | **ABSTRACT**                                                                                                                                                                                                     |                   |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1                 |
| INTRODUCTION |   | **INTRODUCTION**                                                                                                                                                                                                  |                   |
| Rationale    | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                     | 1-3               |
| Objectives   | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                           | 2-3               |
| METHODS      |   | **METHODS**                                                                                                                                                                                                       |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                          |                   |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                               | 3                 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                              | Tables S1-S2      |
| Search       | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                         | Table S1          |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                     | 3; Figure 1       |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                 | 3                 |
| Data items   | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                               | 3; Tables 1-2     |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4; 10             |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                       | 4                 |
| Section/topic                     | Checklist item | Reported on page # |
|----------------------------------|----------------|--------------------|
| Synthesis of results             | 14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 4; 10 |
| Risk of bias across studies      | 15 Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 10 |
| Additional analyses              | 16 Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 10 |

### RESULTS

| Section/topic                     | Checklist item | Reported on page # |
|----------------------------------|----------------|--------------------|
| Study selection                  | 17 Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 3-4; Figure 1, Table S2 |
| Study characteristics            | 18 For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Tables 1-2 |
| Risk of bias within studies      | 19 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Figures 2 S1-S8 |
| Results of individual studies    | 20 For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figures 2, S1, S6 |
| Synthesis of results             | 21 Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 10-11 |
| Risk of bias across studies      | 22 Present results of any assessment of risk of bias across studies (see Item 15). | 11; 13; Table 3; Figures 2, S4-S5 |
| Additional analysis              | 23 Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Figures 3, S2-S3, S6-S8 |

### DISCUSSION

| Section/topic                     | Checklist item | Reported on page # |
|----------------------------------|----------------|--------------------|
| Summary of evidence              | 24 Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 11; 13-16 |
| Limitations                      | 25 Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 15-16 |
| Conclusions                      | 26 Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 11; 13-16 |

### FUNDING

| Section/topic                     | Checklist item | Reported on page # |
|----------------------------------|----------------|--------------------|
| Funding                          | 27 Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 16 |
**Mathematical approach used in the current meta-analysis**

The approach to meta-analysis and all formulae in this document are based on the method of Hedges’ et al. (Borenstein et al. 2009).

**1. Combining of data from independent (active rTMS) subgroups within studies**

Some studies in the current meta-analysis compared one sham group with more than one active rTMS groups. Thus, for the purposes of the overall meta-analysis the data from the multiple active subgroups were combined into one active rTMS group to compute only one effect size for the study. Using one example study (Padberg et al. 1999), the mean \( (M) \) and standard deviation \( (SD) \) of depression scores for the two active subgroups (stimulation frequencies of either 10 Hz or .3 Hz) were combined into one group at each of the two points in time (pre and post-treatment) according to the following formulae (Borenstein et al. 2009 p. 222):

- The combined mean depression score for the ‘active-pre’ group \( (M_{1+2}) \) was computed by weighing the mean depression score of subgroup 1 \( (M_1; 10 \text{ Hz}) \) and subgroup 2 \( (M_2; .3 \text{ Hz}) \) based on the sample size of each subgroup \( (N_1 \text{ and } N_2) \):

\[
M_{1+2} = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}
\]

The combined mean depression score for the other group (‘active-post’) was computed the same way.

- The combined standard deviation of the mean depression scores for the ‘active-pre’ group \( (SD_{1+2}) \) was computed using individual \( SD \) and \( N \) values of subgroup 1 (10 Hz; \( SD_1 \text{ and } N_1 \)) and subgroup 2 (.3 Hz; \( SD_2 \text{ and } N_2 \)):

\[
SD_{1+2} = \sqrt{\frac{(N_1-1)SD_1^2 + (N_2-1)SD_2^2 + \frac{N_1N_2}{N_1+N_2}(M_1 - M_2)^2}{N_1 + N_2 - 1}}
\]

The combined standard deviation of the mean depression scores for the other group (‘active-post’) was computed the same way.
• The combined sample size for the ‘active-pre’ group \( (N_{1+2}) \) was computed by adding the sample sizes of the two subgroups \( (N_1 + N_2) \). The combined sample size for the other group (‘active-post’) was computed the same way.

The study by Stern and colleagues (Stern et al. 2007), was performed on three active subgroups (10 Hz left DLPFC, 1 Hz left DLPFC, and 1 Hz right DLPFC). Thus, the two left-stimulation subgroups (10 Hz and 1 Hz) were combined first and these (combined) scores were then combined with the scores of the right-stimulation subgroup according to the formulae described above.

2. Combining of data in dependent subgroups at different points in time (pre and post)

Since data were collected from the same groups (sham or active) twice (pre and post treatment) it was necessary to reduce them to one score/group for the purposes of meta-analysis. Following the approach of Holtzheimer and colleagues (Holtzheimer et al. 2001), such reduction in scores was performed by expressing the severity of depression scores as difference scores: mean depression at baseline (pre-treatment) – last session (post-treatment) in each group separately \( (M_S \text{ in sham or } M_A \text{ in active groups}) \).

The total sample size \( N \) of each group \( (N_S \text{ or } N_A) \) was either the sample size at baseline or the mean sample size at baseline and last session if any patients dropped out of the study.

The \( SD \) of the mean difference scores was computed for each group separately \( (SD_S \text{ or } SD_A) \) as follows (Borenstein et al. 2009 p. 234):

\[
SD = \sqrt{SD_{pre}^2 + SD_{post}^2 - 2rSD_{pre}SD_{post}}
\]

The correlation coefficient \( r=.5 \), between the pre- and the post-treatment depression scores, was chosen as the most optimal coefficient that neither overestimates the \( SD \) \( (r=.0) \) nor underestimates the \( SD \) \( (r=1.0) \) (Borenstein et al. 2009 p. 237, Table 24.7). The value of .5 was also close to the mean of correlations between pre- and post-treatment scores conducted in studies that reported the scores for all individual patients (these studies are listed in the table below). Specifically, the correlation coefficients were \( r=.37 \) (all patients), \( r=.38 \) (sham), and \( r=.49 \) (active group).
Table. Pearson correlation coefficients \( r \) between mean severity of depression scores at baseline (pre) and after the last session (post) of rTMS (or sham) in studies that reported such scores for individual patients

| Study by first author and year | \( r_{\text{both}} \) | \( N_{\text{both}} \) | \( r_{\text{sham}} \) | \( N_{\text{sham}} \) | \( r_{\text{active}} \) | \( N_{\text{active}} \) |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1 Berkin 2000 HAMD25          | .28             | 20              | .48             | 10              | .20             | 10              |
| 2 Boutros 2002 HAMD25         | .50             | 18              | .02             | 7               | .57             | 11              |
| 3 George 1997 HAMD21          | .22             | 12              | .00             | 5               | .70             | 7               |
| 4 Kimbrell 1999 HAMD21        | .48             | 13              | .97             | 3               | .38             | 10              |
| Total                         | 4               | 4               | 4               | 4               | 4               | 4               |

Notes: All studies reported the scores on HAMD (different versions listed in the table). Abbreviations: HAMD, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation.

The \( M \) and \( SD \) of the difference scores and the total \( N \) per group (sham and active) were used to compute the effect sizes.

3. Effect size computation (standardised mean difference)- Cohen’s \( d \) and Hedges’ \( g \)

The standardised mean difference, Cohen’s \( d \), was computed for the sham and active rTMS groups in each study as follows (Borenstein et al. 2009 p. 26):

\[
d = \frac{M_S - M_A}{SD_{pooled}}
\]

where \( M_S \) and \( M_A \) refer to the mean severity of depression difference score (pre-post) in sham and active rTMS groups respectively, \( SD_{pooled} \) is the \( SD \) of the severity of depression difference score (pre-post) pooled for the two groups using the standard deviations of sham (\( SD_S \)) and active rTMS (\( SD_A \)) groups, and \( N_S \) and \( N_A \) are the sizes of sham and active groups respectively. The variance of \( d \) (\( V_d \)) was computed as follows (Borenstein et al. 2009 p. 27):

\[
V_d = SD_d^2 = \frac{N_S + N_A}{N_S N_A} + \frac{d^2}{2(N_S + N_A)}
\]

In addition to \( d \), the standardised mean difference, Hedges’ \( g \) (that is an unbiased version of \( d \) in small-\( N \) studies) and its variance (\( V_g \)) were computed for the sham and active stimulation groups in each study as follows (Borenstein et al. 2009 p. 27):

\[
g = d \times J = d(1 - \frac{3}{4(N_S + N_A) - 9})
\]

\[
V_g = V_d \times J^2
\]

where \( J \) is the correction factor.
4. Combining multiple outcomes within studies

Some studies in the current analysis utilised multiple scales to measure depression severity (HAM-D, BDI, and MADRS). In such cases, the effect sizes $d$ and their variance ($V_d$) were computed separately for each scale. Subsequently, one mean effect size $d$ was computed/study using an arithmetic mean. The variance of such a mean effect size ($V_{d_{\text{mean}}}$) was computed according to the following formula for combining multiple outcomes within the same studies (Borenstein et al. 2009 p. 227):

$$ V_{d_{\text{mean}}} = \frac{1}{4} \times \left( V_{d1} + V_{d2} + 2r\sqrt{V_{d1} V_{d2}} \right) $$

where $r=1.0$ (correlation coefficient between outcomes in the same cases). Subsequent meta-analysis was computed on such a mean effect size of multiple outcomes/study and its variance.

5. Meta-analysis: random-effects model with inverse-variance weights

The weight in each study ($W_d$) was computed according to the random-effects model as follows (Borenstein et al. 2009 p. 73):

$$ W_d = \frac{1}{V_d + T^2} $$

where $V_d$ is the within-study variance (variance of $d$) and $T^2$ is the between-study variance which was computed according to the method of moments (or the DerSimonian and Laird method (DerSimonian and Laird 1986)) and using $df=k-1$ ($k=$number of studies) as follows (Borenstein et al. 2009 p. 73-74):

$$ T^2 = \frac{Q - df}{C} \quad \quad C = \sum \frac{1}{V_d} \quad \quad Q = \sum \frac{(d - M_d)^2}{V_d} $$

The overall mean weighted effect size ($M_d$) and its variance ($V_{M_d}$) were computed for subgroups of studies as follows (Borenstein et al. 2009 p. 73-74):

$$ M_d = \frac{\sum W_d \times d}{\sum W_d} \quad \quad V_{M_d} = \frac{1}{\sum W_d} $$
The lower and upper 95% confidence intervals of $M_d$ ($LCI_{Md}$ and $UCI_{Md}$) were computed as follows (Borenstein et al. 2009 p. 73-74):

\[ LCI_{Md} = M_d - 1.96 \times \sqrt{V_{M_d}} \quad \quad UCI_{Md} = M_d + 1.96 \times \sqrt{V_{M_d}} \]

Finally, the $z$-score for $M_d$ was computed, to test the null-hypothesis that $M_d=0$ meaning that rTMS is not effective at reducing depression scores compared to sham, according to the following formula (Borenstein et al. 2009 p. 74):

\[ Z = \frac{M_d}{\sqrt{V_{M_d}}} \]

6. Computation of $R^2$ in meta-regression

Univariate linear meta-regressions were computed using the random-effects model to find out if the weighted effect sizes (outcome) could be predicted using the various study characteristics (clinical, demographic, and the rTMS parameters) in the current meta-analysis. The slope of the straight line (the line of best fit), $B^*$, was tested for statistical significance according to the following formula (Borenstein et al. 2009 p. 197):

\[ Z^* = \frac{B^*}{SE_{B^*}} \]

The null-hypothesis tested was that $B^*$ is not different from zero (meaning that the predictor does not predict the outcome). Since univariate regressions were conducted (using one predictor only), it was assumed that the statistical significance of the slope of the regression line was equivalent to the statistical significance of the regression model.

The practical significance of the statistically significant regression models was tested using the equivalent of the $R^2$ index in linear regression. The formula for $R^2$ in meta-regression takes into account the between-study variance in the weighted $d$ unexplained by the regression model containing the predictor ($T^2_{model}$ shown as ‘Tau-squared’ in the output of the meta-regression module in CMA) and the total within- and between-study variance among the weighted $d$ ($T^2_{total}$ that is computed together with other heterogeneity
statistics in the standard random-effects model of all studies involved in the meta-regression) as follows (Borenstein et al. 2009 p. 202):

$$R^2 = 1 - \frac{T^2_{model}}{T^2_{total}}$$

The $R^2$ in meta-regression shows the proportion of the between-study variance in weighted $d$ explained by the predictor.
### Table S1 Search strategy in the past 13 meta-analyses up to 2010

| Study | Database (Time frame) | Key words (search limits) | N studies |
|-------|-----------------------|---------------------------|-----------|
| (Dell'Ozzo et al. 2011) | PubMed (Jan 1980-Dec 2010) | Transcranial magnetic stimulation; TMS; rTMS; depression; major depression; depressive disorders; treatment resistant depression; dysthmic disorder (English) | 13 meta-analyses |
| 1. (McNamara et al. 2001) | Medline (1966- Jan 2000), Embase/Excerpta Medica (1980- Jan 2000), Biological Abstracts and Index of Scientific and Technical Proceedings, Meta-Register of Controlled Trials (www.controlled-trials.com), the National Register (www.doh.gov.uk/research/rrtr), Cochrane Library, Omni Biomedical Search Tool (www.omni.ac.uk), TMS Resources and Published Articles (www.music.edu/tmsmirror/TMSresrc), Avery-George Index (www.ists.unibe.ch/ists/TMSavery), the International Society of Transcranial Magnetic Stimulation (www.ists.unibe.ch/), TMS and Depression (www.psycnet.net/depression.central.transcranial), the Helsinki TMS (www.hiomap.helsinki.fi/tms/) | transcranial magnetic stimulation; TMS; rTMS; depression | N=5 |
| 2. (Holtzheimer et al. 2001) | Medline, International Society of Transcranial Magnetic Stimulation (www.ists.unibe.ch/) | – | N=12 |
| 3. (Rodriguez-Martin et al. 2001)* | Cochrane Collaboration Depression, Anxiety and Neurosis Review Group trials register (~June 2001), the Cochrane Controlled Trials Register (Issue 2, 2001), Medline (1966-2001), Embase (1974-2001), PsycLit (1980-2001) | – | N=16 |
| 4. (Kozel and George 2002) | PsyInfo (1887- April 2002), Medline (1966-April 2002), Current Contents (April 2001- April 2002), meta-analyses (Burt et al. 2002; McNamara et al. 2001) | TMS; rTMS; transcranial magnetic stimulat: and depression or depressive disorder (English) | N=12 |
| 5. (Burt et al. 2002) | Medline (1966-March 2002), Embase (1974- March 2002), PsycLit (1980-2001), the Register of Clinical Trials of the Cochrane Collaboration Depression, Neurosis and Anxiety Review Group (January 2002), Cochrane Controlled Trials Register (January 2002) | magnetic-stimulation; TMS; rTMS; depression; depressive disorder; dysthmic disorder | N=14 |
| 6. (Martin et al. 2003) | Medline, Cochrane Database of Controlled Trials, metaRegister of Controlled Trials (www.controlled-trials.com/mrct), abstracts from scientific meetings: the Society of Biological Psychiatry (2002-2003), the American Psychiatric Association (2000-2003) | transcranial magnetic stimulation; transcranial magnetic stimulation AND depression (review; randomised controlled trial) | N=6 |
| 7. (Couturier 2005) | Medline, Embase, Cochrane Database of Controlled Trials (www.controlled-trials.com/mrct), abstracts from scientific meetings: the Society of Biological Psychiatry (2002-2003), the American Psychiatric Association (2000-2003) | transcranial magnetic stimulation; transcranial magnetic stimulation AND depression (review; randomised controlled trial) | N=33 |
| 8. (Herrmann and Ebmeier 2006) | Medline, Embase, Cochrane Database of Controlled Trials | transcranial magnetic stimulation; TMS; depression | N=5 |
| 9. (Gross et al. 2007) | PsyInfo (~1966), Embase (~1980), Cochrane Central Register of Controlled Trials databases (~May 15, 2008) | major depression; depression; transcranial magnetic stimulation; rTMS; TMS | N=16 |
| 10. (Lam et al. 2008) | Medline (~1966), Embase (~1980), PsycINFO (~1974), Cochrane Central Register of Controlled Trials databases (~May 15, 2008) | transcranial; magnetic; depress* | N=24 |
| 11. (Schutter 2009) | PubMed, Web of Science (January 1980-November 2007) | depression; transcranial magnetic stimulation | N=30 |
| 12. (Schutter 2010) | PubMed, Web of Science (January 1994-July 2009) | depression; transcranial magnetic stimulation | N=9 |
| 13. (Slotema et al. 2010) | PubMed (1999- October 2008), Medline (1999- October 2008), Embase Psychiatry (1997- October 2008), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, PsycoINFO (1990-October 2008) | transcranial magnetic stimulation; TMS; repetitive TMS; psychiatry; mental disorder; psychiatric disorder; bipolar disorder; depression | N=34 |
| Year | Study (by year and first author) | 13 meta-analyses |
|------|---------------------------------|-----------------|
|      |                                 | 1. (McNamara et al. 2001) | 2. (Holzheimer et al. 2001) | 3. (Rodriguez-Martin et al. 2000) | 4. (Koecz and George 2002) | 5. (Burt et al. 2002) | 6. (Martin et al. 2003) | 7. (Courney 2005) | 8. (Herwig et al. 2006) | 9. (Gross et al. 2007) | 10. (Lam et al. 2008) | 11. (Schutter 2009) | 12. (Schutter 2010) | 13. (Sibem 2010) |
| 1995 | (Kolbinge et al. 1995)*         | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 1996 | (Conca et al. 1996)*           | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 1997 | (Fascial-Leone et al. 1996)*   | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 1999 | (Herwig et al. 1999)           | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2000 | (Avery et al. 2000)*           | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2001 | (Berman et al. 2000)           | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
|      | (Loo et al. 2003)              | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2002 | (Koerselman et al. 2004)       | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2003 | (Holtzheimer et al. 2004)      | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2004 | (Januel et al. 2006)           | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2005 | (Mamish and George 2005)       | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2006 | (Molier et al. 2006)           | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2007 | (Andersson et al. 2007)        | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2008 | (Bertolomasi et al. 2007)      | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2009 | (Herwig et al. 2009)           | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
| 2010 | (Loo et al. 2010)              | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                | +                |
Notes: There were 55 sources in total because data from two abstracts excluded from the current analysis ((Haag et al. 1997) and (Avery et al. 2000)) were later included in published articles included in the current analysis ((Padberg et al. 1999) and (Holtzheimer et al. 2004)).

*Studies excluded from the current analysis (13/53 or 24% studies excluded). The exclusion criteria were:

- $N=1$: DLPFC not stimulated (vertex, Cz location, stimulated) (Kolbinger et al. 1995)
- $N=3$: No sham group (Conca et al. 1996; Fitzgerald et al. 2008; Grunhaus et al. 2000)
- $N=2$: Sham at location other than DLPFC: parietal cortex (active stimulation) (Herwig et al. 2003), occipital cortex (active stimulation, coil tilted at 45°) (Moller et al. 2006)
- $N=1$: Cross-over design used (Pascual-Leone et al. 1996)
- $N=5$: Inadequate data reported and/or lack of response from authors:
  - baseline scores for individual groups and after treatment scores missing (Lisanby et al. 2001)
  - parallel stimulation applied only after all participants received active stimulation and $SD$ values for HAMD scores missing (Miniussi et al. 2005)
  - $SD$ values for HAMD scores missing (Rossini et al. 2005; Stikhina et al. 1999)
  - after treatment HAMD28 scores missing (Szuba et al. 2001)
- $N=1$: Depression secondary to stroke and $SD$ values for HAMD scores missing (Jorge et al. 2004)
Figure S1 Random-effects meta-analysis of N=40 studies

Notes: The data shown on this figure are also included in the meta-analysis of N=54 studies (N=40 studies from this analysis and N=14 new studies) shown on Figure S3 (Kedzior et al. 2014). ‘All’ refers to all patients in multiple active rTMS groups who received rTMS with different parameters. ‘Combined’ in the column ‘Outcome’ indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined into one. The mean number of patients per group was used in the final calculations if patients dropped out throughout the study between baseline and final sessions. The forest plot shows the weighted effect size $d$ (box) and its 95% CI (vertical line through the box) for each study in the analysis. The diamond depicts the overall mean weighted $d$ of all studies and its 95% CI (width of the diamond). The mean depression scores (baseline – final) were significantly reduced after rTMS compared to sham in 40 studies (overall mean weighted $d=-.54$, 95% CI: $-.68$, $-.41$).

Abbreviations: CI, confidence interval; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference (Cohen’s $d$).
Figure S2 Cumulative random-effects meta-analysis of N=40 studies

| Study name       | Outcome | Cumulative statistics | Cumulative std diff in means (95% CI) |
|------------------|---------|-----------------------|-------------------------------------|
|                  |         | Point | Lower | Upper | Std diff | CI      | p-value | Sham | rTMS |
| George et al. (1997) | HA MD | -1.44 | -2.73 | -0.16 | 0.028 | 5 7     | 0.007   |
| Avery et al. (1999) | Combined | -1.14 | -0.08 | 0.025 | 0.11    |
| Kveder et al. (1999) | HA MD | -1.05 | -1.94 | -0.16 | 0.028 | 5 7     | 0.007   |
| Loo et al. (1999) | Combined | -1.07 | -0.28 | 0.020 | 0.11    |
| Podsiadlo et al. (1999) | HA MD | -0.07 | -0.35 | 0.25 | 0.77 | 0.00    |
| Berman et al. (2000) | HA MD | -1.04 | -0.29 | 0.000 | 0.07 | 0.87 | 0.007   |
| Eschelard et al. (2000) | Combined | -1.07 | -0.26 | 0.000 | 0.02 | 0.94 | 0.007   |
| George et al. (2000) | Combined | -1.01 | -0.41 | 0.000 | 0.14 | 114    | 0.007   |
| Klein et al. (1999) | Combined | -1.17 | -0.32 | 0.000 | 0.05 | 0.12 | 0.039   |
| Loo et al. (1999) | Combined | -0.56 | -1.07 | -0.05 | 0.030 | 142    | 0.007   |
| Padberg et al. (1999) | All | -0.58 | -1.07 | -0.08 | 0.031 | 152    | 0.007   |
| Berman et al. (2000) | HA MD | -0.67 | -1.04 | -0.29 | 0.000 | 0.07 | 0.87 | 0.007   |
| Eschelard et al. (2000) | Combined | -0.72 | -0.30 | 0.000 | 0.02 | 0.94 | 0.007   |
| George et al. (2000) | Combined | -0.71 | -0.41 | 0.000 | 0.22 | 131    | 0.007   |
| Klein et al. (1999) | Combined | -0.94 | -0.41 | 0.000 | 0.11 | 142    | 0.007   |
| Loo et al. (1999) | Combined | -0.79 | -0.36 | 0.000 | 0.19 | 221    | 0.007   |
| Padberg et al. (1999) | Combined | -0.85 | -0.41 | 0.000 | 0.13 | 173    | 0.007   |
| Loo et al. (2000) | Combined | -0.57 | -0.36 | 0.000 | 0.18 | 222    | 0.007   |
| Khan et al. (2000) | Combined | -0.54 | -0.31 | 0.000 | 0.20 | 243    | 0.007   |
| Buchholz et al. (2004) | HA MD | -0.62 | -0.86 | -0.38 | 0.000 | 163    | 0.007   |
| Hausen et al. (2004) | Combined | -0.96 | -0.29 | 0.000 | 0.21 | 274    | 0.007   |
| Holthauer et al. (2004) | Combined | -0.85 | -0.36 | 0.000 | 0.21 | 281    | 0.007   |
| Kudlow et al. (2004) | HA MD | -0.86 | -0.29 | 0.000 | 0.20 | 288    | 0.007   |
| Kurose et al. (2004) | HA MD | -0.86 | -0.37 | 0.000 | 0.24 | 314    | 0.007   |
| Loo et al. (2005) | Combined | -1.02 | -0.50 | 0.000 | 0.20 | 288    | 0.007   |
| Podsiadlo et al. (2005) | Combined | -0.86 | -0.25 | 0.000 | 0.21 | 288    | 0.007   |
| Romal et al. (2005) | Combined | -0.86 | -0.33 | 0.000 | 0.20 | 288    | 0.007   |
| Su et al. (2005) | Combined | -0.95 | -0.37 | 0.000 | 0.19 | 243    | 0.007   |
| Avery et al. (2006) | Combined | -0.65 | -0.37 | 0.000 | 0.20 | 243    | 0.007   |
| Kudlow et al. (2006) | HA MD | -0.67 | -0.37 | 0.000 | 0.20 | 288    | 0.007   |
| Januel et al. (2006) | Combined | -1.02 | -0.50 | 0.000 | 0.20 | 288    | 0.007   |
| Anderson et al. (2007) | MDRS | -0.55 | -0.71 | -0.40 | 0.000 | 311    | 0.007   |
| Bortolomasi et al. (2007) | Combined | -0.52 | -0.65 | -0.42 | 0.000 | 329    | 0.007   |
| Botsford et al. (2007) | Combined | -0.57 | -0.72 | -0.43 | 0.000 | 329    | 0.007   |
| Herwig et al. (2007) | Combined | -0.54 | -0.68 | -0.41 | 0.000 | 329    | 0.007   |
| Loo et al. (2007) | Combined | -0.53 | -0.67 | -0.40 | 0.000 | 329    | 0.007   |
| Fitzhugh et al. (2007) | Combined | -0.53 | -0.68 | -0.42 | 0.000 | 311    | 0.007   |
| Stern et al. (2007) | Combined | -0.54 | -0.68 | -0.41 | 0.000 | 329    | 0.007   |
| Bretlau et al. (2008) | HA MD | -0.55 | -0.68 | -0.42 | 0.000 | 311    | 0.007   |
| Mogg et al. (2008) | Combined | -0.54 | -0.68 | -0.41 | 0.000 | 329    | 0.007   |

Notes: The data shown on this figure are also included in the cumulative analysis of N=54 studies (N=40 studies from this analysis and N=14 new studies) shown on Figure S5 (Kedzior et al. 2014). ‘All’ refers to all patients in multiple active rTMS groups who received rTMS with different parameters. ‘Combined’ in the column ‘Outcome’ indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined into one. ‘Point’ refers to the overall mean weighted $d$ of all studies before and including the study listed in each row. Abbreviations: CI, confidence interval; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference (Cohen’s $d$).
Figure S3 One-study removed random-effects meta-analysis of N=40 studies

Notes: The data shown on this figure are also included in the one-study removed analysis of N=54 studies (N=40 studies from this analysis and N=14 new studies) shown on Figure S4 (Kedzior et al. 2014). ‘All’ refers to all patients in multiple active rTMS groups who received rTMS with different parameters. ‘Combined’ in the column ‘Outcome’ indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined into one. ‘Point’ refers to the overall mean weighted $d$ of all studies except the study listed in each row. Abbreviations: CI, confidence interval; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference (Cohen’s $d$).
Figure S4 Funnel plot of the random-effects meta-analysis of N=40 studies

Notes: The funnel plot shows the effect size $d$ versus standard error for each study in the analysis. The plot was asymmetrical around the overall mean weighted $d$ and $N=7$ studies (filled circles) were theoretically missing from the analysis. The overall mean weighted effect size corrected for these seven studies indicated that antidepressant effect was still present in the data favouring rTMS over sham (corrected overall mean weighted $d^*=-.42$, 95%CI: -.57, -.28). Thus, there was little evidence that publication bias affected the results of the current meta-analysis. Abbreviations: CI, confidence interval; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference (Cohen’s $d$).
Figure S5 Random-effects meta-analysis of N=33 HFL studies with one outlier

| Study name           | Outcome | Std diff in means | Lower limit | Upper limit | p-Value | Std Residual | P-Value |
|----------------------|---------|-------------------|-------------|-------------|---------|--------------|---------|
| George et al. (1997) | HAMD   | -1.44             | -2.73       | -0.15       | 0.028   | -1.29        | 0.098   |
| Avery et al. (1999)  | Combined | -0.50             | -2.23       | 1.23        | 0.922   | 0.23         | 0.67    |
| Kimble et al. (1989) | HAMD   | -0.24             | -1.33       | 0.86        | 0.741   | 0.07         | 0.67    |
| Loo et al. (1999)    | Combined | 0.02             | -0.97       | 1.89        | 0.932   | 1.41         | 0.194   |
| Robine et al. (1998) | HAMD   | 0.04             | -1.14       | 0.74        | 0.463   | 0.19         | 0.046   |
| Berman et al. (2000) | HAMD   | -1.21             | -2.17       | -0.26       | 0.019   | -1.23        | 0.227   |
| Eschweiler et al. (2000) | Combined | -1.05        | -2.86       | -0.08       | 0.038   | -1.17        | 0.344   |
| George et al. (2000) | all HAMD | -0.70             | -1.46       | 0.08        | 0.880   | -0.35        | 0.173   |
| Garcia-Torralba et al. (2004) | Combined | 0.01             | -1.89       | 1.89        | 0.932   | 0.42         | 0.073   |
| Garcia-Torralba et al. (1999) | Combined | -0.44             | -1.39       | 0.41        | 0.339   | 0.16         | 0.673   |
| Manivel et al. (2001) | Combined | -0.30             | -1.19       | 0.59        | 0.306   | 0.49         | 0.036   |
| Berman et al. (2000) | HAMD   | 0.02             | -1.20       | 0.70        | 0.806   | 0.31         | 0.043   |
| Eschweiler et al. (2000) | Combined | -0.59             | -1.92       | -0.08       | 0.038   | -0.94        | 0.403   |
| Fitgen et al. (2003)  | Combined | 0.19             | -0.72       | 1.08        | 0.826   | 1.34         | 0.152   |
| Nahas et al. (2003)   | HAMD   | -0.29             | -0.97       | 0.41        | 0.797   | 1.22         | 0.223   |
| Burchardt et al. (2004) | Combined | 0.14             | -0.56       | 1.24        | 0.756   | 1.07         | 0.286   |
| Hotzler et al. (2004) | Combined | -0.22             | -1.34       | 0.85        | 0.324   | 0.01         | 0.007   |
| Kranzler et al. (2004) | Combined | 0.01             | -1.70       | 0.40        | 0.881   | 0.02         | 0.007   |
| Kranzler et al. (2004) | Combined | -0.42             | -1.17       | 0.71        | 0.374   | 0.03         | 0.037   |
| Posavac et al. (2004) | Combined | 0.03             | -1.20       | 1.04        | 0.772   | 1.02         | 0.224   |
| Rusin et al. (2003)   | Combined | -0.63             | -2.05       | 0.80        | 0.300   | -0.64        | 0.100   |
| Suck et al. (2003)    | Combined | 0.00             | -1.24       | 1.04        | 0.772   | 1.23         | 0.223   |
| Aye et al. (2006)     | Combined | -0.97             | -1.96       | -0.00       | 0.000   | -0.88        | 0.376   |
| Ambram et al. (2007)  | Combined | -0.57             | -1.15       | 0.00        | 0.352   | 0.07         | 0.717   |
| Bortolomasi et al. (2007) | Combined | -0.74             | -2.25       | 0.00        | 0.326   | 0.39         | 0.558   |
| Hayami et al. (2007)  | Combined | -0.97             | -2.05       | 0.10        | 0.326   | 1.04         | 0.319   |
| Low et al. (1999)     | Combined | -0.89             | -2.16       | 0.40        | 0.308   | 1.02         | 0.319   |
| O'Sullivan et al. (2007) | Combined | 0.00             | -1.25       | 1.01        | 0.772   | 1.02         | 0.319   |
| Borm et al. (2007)    | Combined | -0.28             | -1.17       | 0.60        | 0.330   | 0.39         | 0.558   |
| Bots et al. (2008)    | Combined | -0.26             | -1.16       | 0.64        | 0.256   | 0.70         | 0.474   |
| Mogg et al. (2008)    | Combined | 0.13             | -0.56       | 0.83        | 0.256   | 0.70         | 0.474   |

Group by Outliers

| Study name | Outcome | Std diff in means | Lower limit | Upper limit | p-Value |
|------------|---------|-------------------|-------------|-------------|---------|
| outlier    | -2.93   | -4.09             | -1.77       | 0.000       |
| study      | -0.41   | -0.66             | -0.15       | 0.000       |
| Overall    | -0.51   | -0.65             | -0.37       | 0.000       |
Notes: The forest plot (top) shows that one study (Stern et al. 2007) was a statistical outlier because the weighted $d$ in this study (-2.93) was significantly higher ($p<.001$) than the overall mean weighted $d$ of all other 32 studies (-.47; bottom plot). Thus, this study was removed from all analyses to prevent the inflation of effect sizes in the analysis of the high frequency studies. ‘All’ refers to all patients in multiple active rTMS groups who received rTMS with different parameters. ‘Combined’ in the column ‘Outcome’ indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined into one. Abbreviations: CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; HAMD, Hamilton Depression Rating Scale; HFL, high-frequency rTMS of the left DLPFC; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std, standardised; Std diff, standardized mean difference (Cohen’s $d$).
Figure S6 Cumulative random-effects meta-analysis of N=32 HFL studies

| Study name          | Outcome | Cumulative statistics | Lower limit         | Upper limit         | p-Value | Sham rTMS |
|---------------------|---------|-----------------------|---------------------|---------------------|---------|-----------|
| George et al. (1997)| HAMD    | -1.44                 | -2.73               | -0.16               | 0.028   | 5         |
| Avery et al. (1999)| Combined| -1.11                 | -2.44               | 0.26                | 0.006   | 7         |
| Kothare et al. (1999)| HAMD   | -0.52                 | -1.86               | 0.14                | 0.020   | 10        |
| Lucal et al. (1999) | Combined| -0.51                 | -1.83               | 0.22                | 0.020   | 19        |
| Raberg et al. (1999)| HAMD   | -0.21                 | -0.94               | 0.33                | 0.036   | 25        |
| Barmalak et al. (1999)| HAMD | -0.12                 | -0.72               | 0.49                | 0.036   | 35        |
| Bachalar et al. (2003) | Combined| -0.63                 | -1.15               | 0.06                | 0.006   | 40        |
| George et al. (2003)| HAMD    | -1.05                 | -1.31               | 0.26                | 0.006   | 53        |
| Garcia-Torron et al. (2003)| HAMD | -0.21                 | -0.51               | 0.09                | 0.036   | 98        |
| Garcia-Torron et al. (2003)| Combined| -0.01            | -0.33               | 0.31                | 0.006   | 98        |
| Marsal et al. (2003)| HAMD    | -0.47                 | -0.97               | 0.03                | 0.006   | 100       |
| Raberg et al. (2003)| Combined| -0.56                 | -0.96               | 0.06                | 0.006   | 106       |
| Fitzgerald et al. (2003)| Combined| -0.26            | -0.66               | 0.14                | 0.006   | 147       |
| Higginson et al. (2003)| Combined| -0.36                 | -0.74               | 0.06                | 0.006   | 157       |
| Nahal et al. (2003)| HAMD    | -0.46                 | -0.86               | 0.02                | 0.006   | 168       |
| Burtin et al. (2004)| HAMD    | -0.43                 | -0.83               | 0.03                | 0.006   | 185       |
| Holzheier et al. (2004)| Combined| -0.32                 | -0.74               | 0.06                | 0.006   | 185       |
| Kwan et al. (2004)| HAMD    | -0.38                 | -0.78               | 0.08                | 0.006   | 188       |
| Majer et al. (2004)| Combined| -0.57                 | -0.97               | 0.05                | 0.006   | 222       |
| Prasert et al. (2004)| Combined| -0.34                 | -0.74               | 0.06                | 0.006   | 222       |
| Reind et al. (2004)| HAMD    | -0.41                 | -0.81               | 0.03                | 0.006   | 222       |
| Ruvic et al. (2004)| MDRS    | -0.65                 | -1.06               | 0.03                | 0.006   | 277       |
| Sper et al. (2004)| Combined| -0.38                 | -0.78               | 0.08                | 0.006   | 325       |
| Avery et al. (2005)| Combined| -0.30                 | -0.70               | 0.07                | 0.006   | 325       |
| Anderson et al. (2005)| MDRS| -0.69                 | -1.11               | 0.03                | 0.006   | 389       |
| Botzian et al. (2005)| Combined| -0.30                 | -0.70               | 0.07                | 0.006   | 389       |
| Hanaj et al. (2005)| Combined| -0.49                 | -0.99               | 0.02                | 0.006   | 438       |
| Lucal et al. (2005)| Combined| -0.49                 | -0.99               | 0.02                | 0.006   | 438       |
| O’Connor et al. (2005)| Combined| -0.26                 | -0.66               | 0.02                | 0.006   | 438       |
| Bhatia et al. (2005)| HAMD    | -0.48                 | -0.88               | 0.02                | 0.006   | 497       |
| Moseli et al. (2005)| Combined| -0.47                 | -0.87               | 0.02                | 0.006   | 497       |

Notes: ‘All’ refers to all patients in multiple active rTMS groups who received rTMS with different parameters. ‘Combined’ in the column ‘Outcome’ indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined into one. ‘Point’ refers to the overall mean weighted d of all studies before and including the study listed in each row. Abbreviations: CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; HAMD, Hamilton Depression Rating Scale; HFL, high-frequency rTMS of the left DLPFC; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference (Cohen’s d).
Figure S7 One-study removed random-effects meta-analysis of 32 HFL studies

| Study Name             | Outcome | Statistic with study removed | Std diff in means (95% CI) with study removed |
|------------------------|---------|------------------------------|---------------------------------------------|
|                        |         | Point                        | Lower Limit | Upper Limit | p-Value |
| George et al. (1997)   | HAMD    | -0.46                        | -0.60      | -0.32      | 0.000   |
| Avery et al. (1999)    | Combined| -0.47                        | -0.62      | -0.32      | 0.000   |
| Kirdal et al. (1999)   | HAMD    | -0.48                        | -0.62      | -0.34      | 0.000   |
| Loo et al. (1999)      | Combined| -0.49                        | -0.62      | -0.35      | 0.000   |
| Padberg et al. (1999)  | HAMD    | -0.47                        | -0.62      | -0.33      | 0.000   |
| Berenbaum et al. (2003)|        | -0.46                        | -0.59      | -0.32      | 0.000   |
| Eschweiler et al. (2003)|        | -0.46                        | -0.60      | -0.32      | 0.000   |
| Garcia-Torres et al. (2004)| | -0.47                        | -0.61      | -0.32      | 0.000   |
| Garcia-Torres et al. (2004)| | -0.47                        | -0.62      | -0.35      | 0.000   |
| Menard et al. (2001)   | HAMD    | -0.48                        | -0.62      | -0.33      | 0.000   |
| Stahel et al. (2002)   |        | -0.48                        | -0.62      | -0.34      | 0.000   |
| Pool et al. (2002)     | Combined| -0.46                        | -0.60      | -0.32      | 0.000   |
| Fitzgibbon et al. (2003)|        | -0.46                        | -0.62      | -0.35      | 0.000   |
| Hopp et al. (2003)     | Combined| -0.46                        | -0.62      | -0.35      | 0.000   |
| Nahas et al. (2004)    |        | -0.46                        | -0.63      | -0.35      | 0.000   |
| Butholtz et al. (2004) | HAMD    | -0.46                        | -0.62      | -0.34      | 0.000   |
| Holthuism et al. (2004)|        | -0.46                        | -0.62      | -0.34      | 0.000   |
| Konior et al. (2004)   | HAMD    | -0.46                        | -0.63      | -0.35      | 0.000   |
| Maier et al. (2004)    | Combined| -0.46                        | -0.62      | -0.34      | 0.000   |
| Phakalane et al. (2004)|        | -0.46                        | -0.62      | -0.34      | 0.000   |
| Rees et al. (1999)     | HAMD    | -0.45                        | -0.60      | -0.31      | 0.000   |
| Ruvio et al. (2003)    | MADRS   | -0.43                        | -0.58      | -0.29      | 0.000   |
| Sturt et al. (2003)    | Combined| -0.46                        | -0.62      | -0.32      | 0.000   |
| Avery et al. (2004)    | Combined| -0.46                        | -0.61      | -0.32      | 0.000   |
| Andersson et al. (2005)| MADRS   | -0.47                        | -0.61      | -0.32      | 0.000   |
| Berntson et al. (2005) | Combined| -0.46                        | -0.60      | -0.33      | 0.000   |
| Hopp et al. (2005)     | Combined| -0.46                        | -0.64      | -0.35      | 0.000   |
| Loo et al. (2005)      | Combined| -0.48                        | -0.62      | -0.35      | 0.000   |
| Ofarrell et al. (2007) |         | -0.30                        | -0.58      | -0.34      | 0.000   |
| Beilavsky et al. (2008)| HAMD    | -0.46                        | -0.60      | -0.32      | 0.000   |
| Marini et al. (2008)   | Combined| -0.47                        | -0.61      | -0.33      | 0.000   |

Notes: ‘All’ refers to all patients in multiple active rTMS groups who received rTMS with different parameters. ‘Combined’ in the column ‘Outcome’ indicates that more than one depression scale was used in a study and the effect sizes according to the multiple scales were combined into one. ‘Point’ refers to the overall mean weighted $d$ of all studies except the study listed in each row.

Abbreviations: CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; HAMD, Hamilton Depression Rating Scale; HFL, high-frequency rTMS of the left DLPFC; MADRS, Montgomery Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference (Cohen’s $d$).
Figure S8 Meta-regression of % female on weighted $d$ in $N=31$ HFL studies

Notes: The figure shows a scatterplot of weighted $d$/study (Y-axis) versus proportion of female patients/study (X-axis) according to a univariate meta-regression of 31 high-frequency studies. The removal of the study with the largest weight (O’Reardon et al. 2007) did not change the outcome of this analysis ($B=-.01$, slope $p_{two-tailed}=.006$). Thus, depression scores were significantly reduced after high-frequency rTMS compared to sham in studies with higher proportion of female patients after exclusion of the largest study from the analysis. Abbreviations: DLPFC, dorsolateral prefrontal cortex; HFL, high-frequency rTMS of the left DLPFC; rTMS, repetitive transcranial magnetic stimulation; Std diff, standardized mean difference (Cohen’s $d$).
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