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Supplementary Material

Article Title: High-Frequency Repetitive Transcranial Magnetic Stimulation Accelerates and Enhances the Clinical Response to Antidepressants in Major Depression: A Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials

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Supplementary eSection 1. ***PREVIOUS META-ANALYSES ON rTMS FOR MAJOR DEPRESSION***

1.1 ***Excluded Randomized Controlled Trials and Main Reasons for Exclusion (Supplementary eTable 1)***

Supplementary eTable 1. Previous meta-analyses on rTMS for major depression: excluded randomized controlled trials and main reasons for exclusion.

Reference	Reason for Exclusion (example)
2008	
Fitzgerald et al ¹	n=60, but active rTMS primed by twenty 5-second, 6-Hz trains of stimulation
Jorge et al ²	Only subjects with vascular depression
Mogg et al ³	n=59, but rTMS used as an augmenting strategy for major depression
2007	
Anderson et al ⁴	n=25, but rTMS used as an augmenting strategy for major depression
Bortolomasi et al ⁵	n=19, but rTMS used as an augmenting strategy for major depression
Loo et al ⁶	n=34, but rTMS used as either an augmenting strategy or a monotherapy for major depression
O'Reardon et al ⁷	n=301, but rTMS used as a monotherapy for major depression
Stern et al ⁸	n=25, but rTMS used as a monotherapy for major depression
2006	
Avery et al ⁹	n=68, but rTMS used as a monotherapy for major depression
Fitzgerald et al ¹⁰	n= 50, but only bilateral rTMS used as an augmenting strategy for major depression
Garcia-Toro et al ¹¹	n=30, but only bilateral rTMS used as an augmenting strategy for major depression
Januel et al ¹²	n=27, but rTMS used as a monotherapy for major depression
McDonald et al ¹³	n=62, but only bilateral rTMS used as an augmenting strategy for major depression
Moller et al ¹⁴	n=10, but rTMS used as an augmenting strategy for major depression
2005	
Miniussi et al ¹⁵	n=71, but rTMS used as an augmenting strategy for major depression
Rossini et al ¹⁶	n=54, but rTMS used as an augmenting strategy for major depression
Su et al ¹⁷	n=30, but rTMS used as an augmenting strategy for major depression
2004	
Hansen et al ¹⁸	n=15, but rTMS used as an augmenting strategy for major depression
Hausmann et al ¹⁹	n=41, unilateral and bilateral rTMS used as accelerating strategies, but no reported outcomes for

	unilateral rTMS
Hausmann et al ²⁰	n=41, but data overlap with Hausmann et al, 2004 ¹⁹
Holtzheimer et al ²¹	n=14, but rTMS used as a monotherapy for major depression
Jorge et al ²²	Only subjects with post-stroke depression
Kauffmann et al ²³	n=12, but rTMS used as an augmenting strategy for major depression
Koerselman et al ²⁴	n=55 but rTMS used as an augmenting strategy for major depression
Mosimann et al ²⁵	n=24, but rTMS used as an augmenting strategy for major depression
Poulet et al ²⁶	n=19, but insufficient data for this meta-analysis (e.g., age, gender, baseline depression scores)
2003	
Fitzgerald et al ²⁷	n=60, but rTMS used as an augmenting strategy for major depression
Herwig et al ²⁸	n=25, but 19 subjects received rTMS as an augmenting strategy for major depression
Hoppner et al ²⁹	n=21, but rTMS used as an augmenting strategy for major depression
Loo et al ³⁰	n=19, but bilateral rTMS used as either an augmenting strategy or a monotherapy for major depression
Nahas et al ³¹	n=23, but rTMS used as an augmenting strategy for major depression
2002	
Boutros et al ³²	n=21, but rTMS used as an augmenting strategy for major depression
Padberg et al ³³	n=30, but rTMS used as an augmenting strategy for major depression
2001	
Garcia-Toro et al ³⁴	n=35, but rTMS used as an augmenting strategy for major depression
Lisanby et al ³⁵	n=24, but unreported outcomes ³⁶ (i.e., response and/or remission rates); main author contacted by email but did no reply
Manes et al ³⁷	n=20, but rTMS used as a monotherapy for major depression
Szuba et al ³⁸	n=16, but rTMS used as a monotherapy for major depression
2000	
Berman et al ³⁹	n=20, but rTMS used as a monotherapy for major depression
Eschweiler et al ⁴⁰	n=12, but used as an augmenting strategy for major depression
George et al ⁴¹	n=30, but rTMS used as a monotherapy for major depression
Grunhaus et al ⁴²	n=40, but open-label
Pridmore ⁴³	n=22, but single-blind
1999	
Avery et al ⁴⁴	n=6, and rTMS used as an augmenting strategy for major depression
Kimbrell et al ⁴⁵	n=13, but rTMS used as either an augmenting strategy or a monotherapy for major depression
Klein et al ⁴⁶	n=70, rTMS used as an augmenting strategy for major depression
Loo et al ⁴⁷	n=18, but rTMS used as either an augmenting strategy or a monotherapy for major depression
Padberg et al ⁴⁸	n=18, but rTMS used as either an augmenting strategy or a monotherapy for major depression

Stikhina et al ⁴⁹	Written in Russian
1997	
George et al ⁵⁰	n=12, but rTMS used as a monotherapy for major depression
Haag et al ⁵¹	n=18, but rTMS used as an augmenting strategy for major depression
1996	
Conca et al ⁵²	n=24, but not sham-controlled
Pascual-Leone et al ⁵³	n=17, but rTMS used as either an augmenting strategy or a monotherapy for major depression
1995	
Kolbinger et al ⁵⁴	n=10, but rTMS used as either an augmenting strategy or a monotherapy for major depression

Supplementary eSection 2. *DATABASES SEARCH (1995-2012)*

2.1 *Electronic Databases – Selection*

- MEDLINE: October 2008 - May 7, 2012
- EMBASE: January 1st, 1996 - May 12, 2012
- PsycINFO: January 1st, 1995 - May 12, 2012
- Cochrane Central Register of Controlled Trials (CENTRAL): January 1st, 1995 - May 12, 2012
- SCOPUS: January 1st, 1995 – May 12, 2012
- ProQuest Dissertations & Theses (PQDT): January 1st, 1995 – May 12, 2012
- Web of Science’s Citations Index Expanded: Up to May 27, 2012

2.2 *Electronic Databases – Syntaxes*

2.2.1 MEDLINE (PubMed)

An advanced search was conducted on 2012/05/07 using the following search syntax (derived from Corrao et al⁵⁵):

("randomized controlled trial"[PT] OR ((randomized[TIAB] OR randomised[TIAB]) AND controlled[TIAB] AND trial[TIAB]))
AND ("magnetic stimulation"[TIAB] OR rTMS[TIAB]) AND depress*[TI]

This search retrieved 44 references (Figure 1).

Supplementary eFigure 1. MEDLINE: search strategy.

History [Clear history](#)

Search	Add to builder	Query	Items found	Time
#1	Add	Search ("randomized controlled trial"[PT] OR ((randomized[TIAB] OR randomised[TIAB]) AND controlled[TIAB] AND trial[TIAB])) AND ("magnetic stimulation"[TIAB] OR rTMS[TIAB]) AND depress*[TI] Limits: English, Publication Date from 2008/10/01 to 2012/05/07	44	19:10:56

2.2.2 EMBASE (OVID interface)

An advanced search was conducted on 2012/05/12 using the following search syntax (derived from Wong et al⁵⁶):

(random\$.tw. or placebo\$.mp. or double-blind\$.tw.) and (magnetic stimulation.ti. or rtms.ti. or transcranial magnetic.ti.) and depress\$.ti. and (English language and yr="1996-Current")

This search retrieved 180 references (Figure 2).

Supplementary eFigure 2. EMBASE: search strategy.

<input type="checkbox"/>	# ▲	Searches	Results
<input type="checkbox"/>	1	(random\$.tw. or placebo\$.mp. or double-blind\$.tw.) and (magnetic stimulation or rtms or transcranial magnetic).ti. and depress\$.ti.	199
<input type="checkbox"/>	2	limit 1 to (english language and yr="1996 -Current")	180

2.2.3 PsycINFO (OVID interface)

An advanced search was conducted on 2012/05/12 using the following syntax (derived from Wong et al⁵⁶):

(random\$.tw. or placebo\$.mp. or double-blind\$.tw.) and (magnetic stimulation.ti. or rtms.ti. or transcranial magnetic.ti.) and depress\$.ti. and (English language and yr="1995-Current")

This search retrieved 137 references (Figure 3).

Supplementary eFigure 3. PsycINFO: search strategy.

<input type="checkbox"/>	# ▲	Searches	Results
<input type="checkbox"/>	1	(random\$.tw. or placebo\$.mp. or double-blind\$.tw.) and ("magnetic stimulation" or rtms or "transcranial magnetic").ti. and depress\$.ti.	147
<input type="checkbox"/>	2	limit 1 to (english language and yr="1995 -Current")	137

2.2.4 CENTRAL

An advanced search was conducted on 2012/05/12 using the following syntax:

depress*:ti AND (magnetic stimulation:ti OR rTMS:ti OR transcranial magnetic:ti), from 1995 to 2012 in Trials

This search retrieved 207 references (Figure 4).

Supplementary eFigure 4. CENTRAL: search strategy.

Current Search History

ID	Search	Hits
#1	depress*:ti AND (magnetic stimulation:ti OR rTMS:ti OR transcranial magnetic:ti), from 1995 to 2012 in Trials	207

2.2.5 SCOPUS

An advanced search was conducted on 2012/05/12 using the following syntax:

(TITLE(**depress***) AND TITLE(**"magnetic stimulation"**) OR TITLE(**rtms**) OR TITLE(**"transcranial magnetic"**) AND TITLE-ABS-KEY(**sham**) OR TITLE-ABS-KEY(**random***) OR TITLE-ABS-KEY(**controlled**) OR TITLE(**trial**) OR TITLE-ABS-KEY(**double-blind**) OR TITLE-ABS-KEY(**intention-to-treat**) AND LANGUAGE(**english**)) AND SUBJAREA(**mult** OR **agri** OR **bioc** OR **immu** OR **neur** OR **phar** OR **mult** OR **medi** OR **nurs** OR **vete** OR **dent** OR **heal**) AND PUBYEAR > 1994

This search retrieved 253 references (Figure 5).

Supplementary eFigure 5. SCOPUS: search strategy.

Search	Results
8 (TITLE(depress*) AND TITLE("magnetic stimulation") OR TITLE(rTMS) OR TITLE("transcranial magnetic") AND TITLE-ABS-KEY(sham) OR TITLE-ABS-KEY(random*) OR TITLE-ABS-KEY(controlled) OR TITLE(trial) OR TITLE-ABS-KEY(double-blind) OR TITLE-ABS-KEY(intention-to-treat) AND LANGUAGE(english)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 1994	253

2.2.5 PQDT

An advanced search was conducted on 2012/05/12 using the following syntax:

ti(depress*) AND ti(("transcranial magnetic" OR rTMS)) OR ti("magnetic stimulation")

This search retrieved 45 references (Figure 6).

Supplementary eFigure 6. PQDT: search strategy.

ti(depress*) AND ti(("transcranial magnetic" OR rTMS)) OR ti("magnetic stimulation")

Full text
 Additional limits - Language: English

45 Results * Search within

Create alert Create RSS feed Save search

2.2.6 Web of Science Citations Index

An advanced search was conducted on 2012/06/12.

Supplementary eFigure 6. Garcia-Toro et al, 2001

Results Cited Author=(garcia-toro M*) AND Cited Title=(add on) AND Cited Year=(2001) AND Document Types=(Article)
Timespan=All Years. Databases=SCH-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

Results: 22

Supplementary eFigure 7. Rossini et al, 2005

Results Cited Author=(rossini D*) AND Cited Title=(hasten) AND Cited Year=(2005) AND Document Types=(Article)
Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

Results: **17**

Supplementary eFigure 8. Rumi et al, 2005

Results Cited Author=(Rumi D*) AND Cited Title=(severe) AND Cited Year=(2005) AND Document Types=(Article)
Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

Results: **47**


Supplementary eFigure 9. Herwig et al, 2007

Results Cited Author=(herwig U*) AND Cited Title=(augmentative) AND Cited Year=(2007) AND Document Types=(Article)
Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

Results: **34**

Supplementary eFigure 10. Bretlau et al, 2008

Results Cited Author=(Bretlau L*) AND Language=(English) AND Document Types=(Article)
Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

Create Alert /  RSS



Results: **17**

Supplementary eFigure 11. Huang et al, 2012

No register.

2.3 Excluded Studies and Reasons for Exclusion

2.3.1 MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT

Searches on MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT yielded 379 references (after discarding duplicates). Of these, only 1 was included in this meta-analysis⁵⁷ (please refer to Supplementary eTables 2 and 3 for information on excluded studies).

Supplementary eTable 2. MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT: reasons exclusion - non-randomized controlled trials.

REASON FOR EXCLUSION	n
No Primary Data	
Review	50
Book or book chapter	2
Erratum	1
Post-hoc and/or secondary analysis	18
Comment	10
Clinical trial registration	17
Non-Primary MDD Samples	
Bipolar depression	10
No separate results for subjects with MDD	1
Postpartum MDD	1
Secondary MDD (e.g., Parkinson's, obsessive-compulsive disorder)	20
Clinical Studies, but Non-RCT Design	
Randomized trial but no sham rTMS	20
Case report or series	11
Retrospective design	1
Open label trial	49
Other	
Non-treatment rTMS study in subjects with MDD (e.g., neuroimaging, neurochemistry, neurophysiology, coil positioning)	66
Other neuromodulation techniques (e.g., transcranial direct current stimulation, vagus nerve stimulation)	11
Theta burst stimulation	2
Stimulation of a region other than the DLPFC	2
Study in subjects with psychotic disorders	3
Study in subjects with anxiety disorders	1
Study in subjects with addiction disorders	1
Study in subjects with autistic disorders	1
Study in subjects with neurological illnesses	2
Study in animals	12
Study in healthy subjects or using computer/mathematical modeling	27
Study in subjects with > 75 years	2
Study on children and/or adolescents	3

Supplementary eTable 3. MEDLINE, PsycINFO, EMBASE, CENTRAL, SCOPUS and PQDT: reasons for exclusion - randomized controlled trials.

Reference	Reason for Exclusion (example)
2012	
Fitzgerald et al ⁵⁸	n=67, but rTMS used as an augmenting strategy for major depression
Hernandez-Ribas et al ⁵⁹	n=21, but rTMS used as an augmenting strategy for major depression
Peng et al ⁶⁰	n=30, but rTMS used as an augmentation strategy for major depression
2011	
Aguirre et al ⁶¹	n=34, but rTMS used as an augmenting strategy for major depression
He et al ⁶²	n=164, but only rTMS used as a monotherapy for major depression
Karamustafalioglu et al ⁶³	n=44, but unreported outcomes ³⁶ (i.e., response and/or remission rates); main author contacted by email but did not respond; nevertheless, their main findings were that “...in terms of response, study group was significantly superior to the control group. This significant superiority continued to the endpoint. By the second week, study group was superior to the control group in terms of remission...”
Lingeswaran et al ⁶⁴	n=23, but rTMS used as an augmenting strategy for major depression
Ray et al ⁶⁵	n=40, but single-blind, and rTMS used as a monotherapy for major depression
Zhang et al ⁶⁶	n=28, but rTMS used as an augmenting strategy for major depression
2010	
George et al ⁶⁷	n=190, but rTMS used as a monotherapy for major depression
Karamustafalioglu et al ⁶⁸	n=35, but rTMS used as an augmenting strategy for major depression
Lee et al ⁶⁹	n=14, but rTMS used as an augmenting strategy for major depression
Paillere-Martinot et al ⁷⁰	n=48, but rTMS used as an augmenting strategy for major depression
Pallanti et al ⁷¹	n=60, but rTMS used as an augmenting strategy for major depression
Triggs et al ⁷²	n=25, but rTMS used as an augmenting strategy for major depression
Zheng et al ⁷³	n=34, but rTMS used as an augmenting strategy for major depression
2009	
Bares et al ⁷⁴	n=60, but no sham rTMS group
Carretero et al ⁷⁵	n=28, but single-blind rTMS
Speer et al ⁷⁶	n=22, but rTMS used as a monotherapy for major depression
2008	
Fitzgerald et al ⁷⁷	n=50, but bilateral rTMS used as augmenting strategy for major depression
Jakob et al ⁷⁸	n=36, but rTMS used as either an augmenting strategy or a monotherapy for major depression

2005	
Chistyakov et al ⁷⁹	n=59, but no active rTMS + antidepressant group

2.3.2 Web of Science Citations Index

Searches on the Web of Science's Citation Index Expanded yielded 70 references (after discarding duplicates), but none of these were included in this meta-analysis (please refer to Supplementary eTables 4 and 5 for additional information).

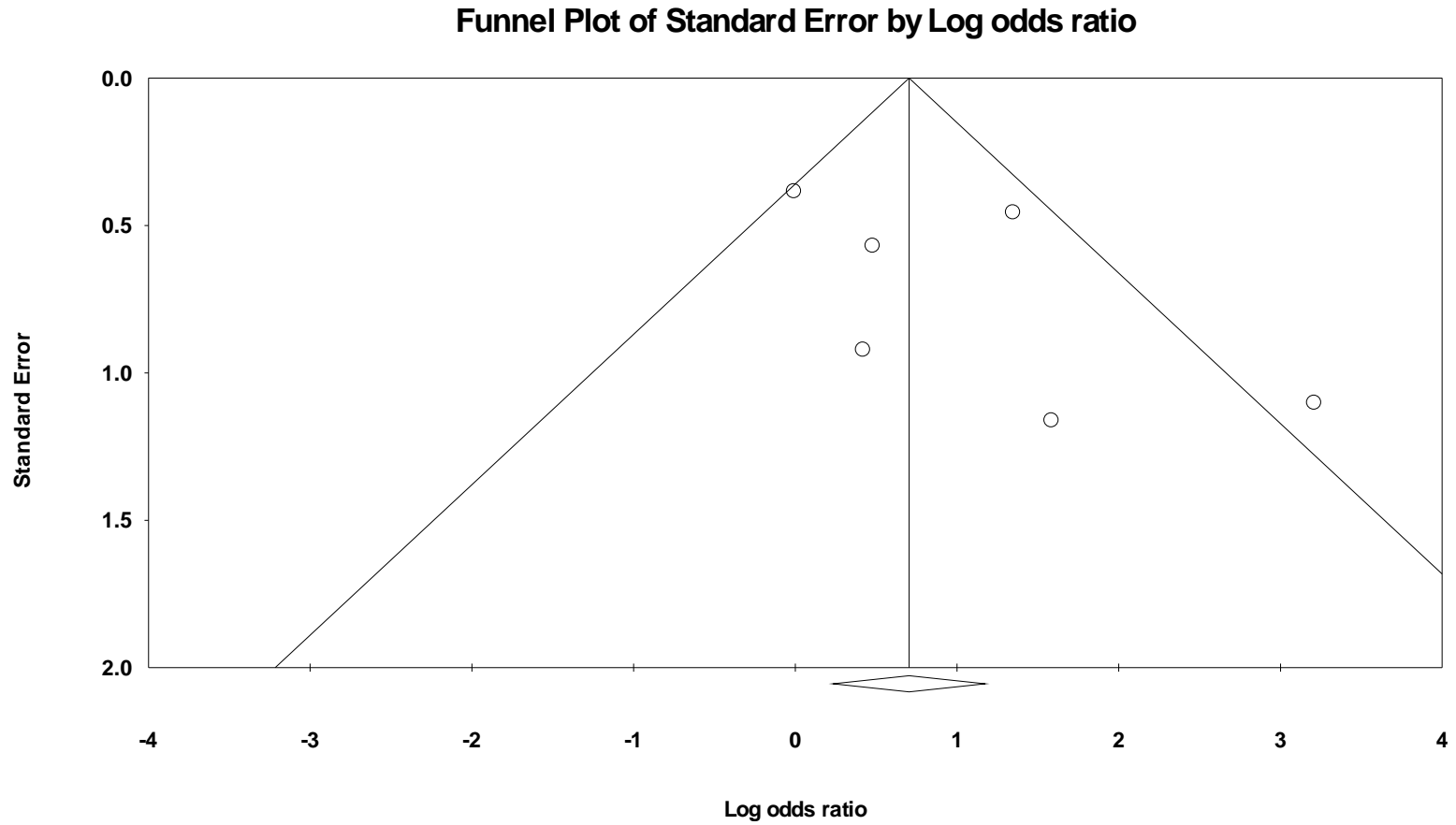
Supplementary eTable 4. Web of Science's Citations Index Expanded: reasons for exclusion - non-randomized controlled trials.

REASON FOR EXCLUSION	n
No Primary Data	
Review	26
Post-hoc and/or secondary analysis	4
Clinical Studies, but Non-RCT Design	
Randomized trial but no sham rTMS	5
Case report or series	4
Retrospective design	2
Open label trial	9
Other	
Other neuromodulation techniques (e.g., transcranial direct current stimulation, vagus nerve stimulation)	3
Theta burst stimulation	2
Study in subjects with mania	1
Study in subjects with psychotic disorders	1
Study in subjects with anxiety disorders	1
Study in subjects with neurological illnesses	5
Study in animals	1
Study in healthy subjects, using computer/mathematical modeling or describing new equipment	5
TOTAL	69

Supplementary eTable 5. Web of Science's Citations Index Expanded: reasons for exclusion - randomized controlled trials.

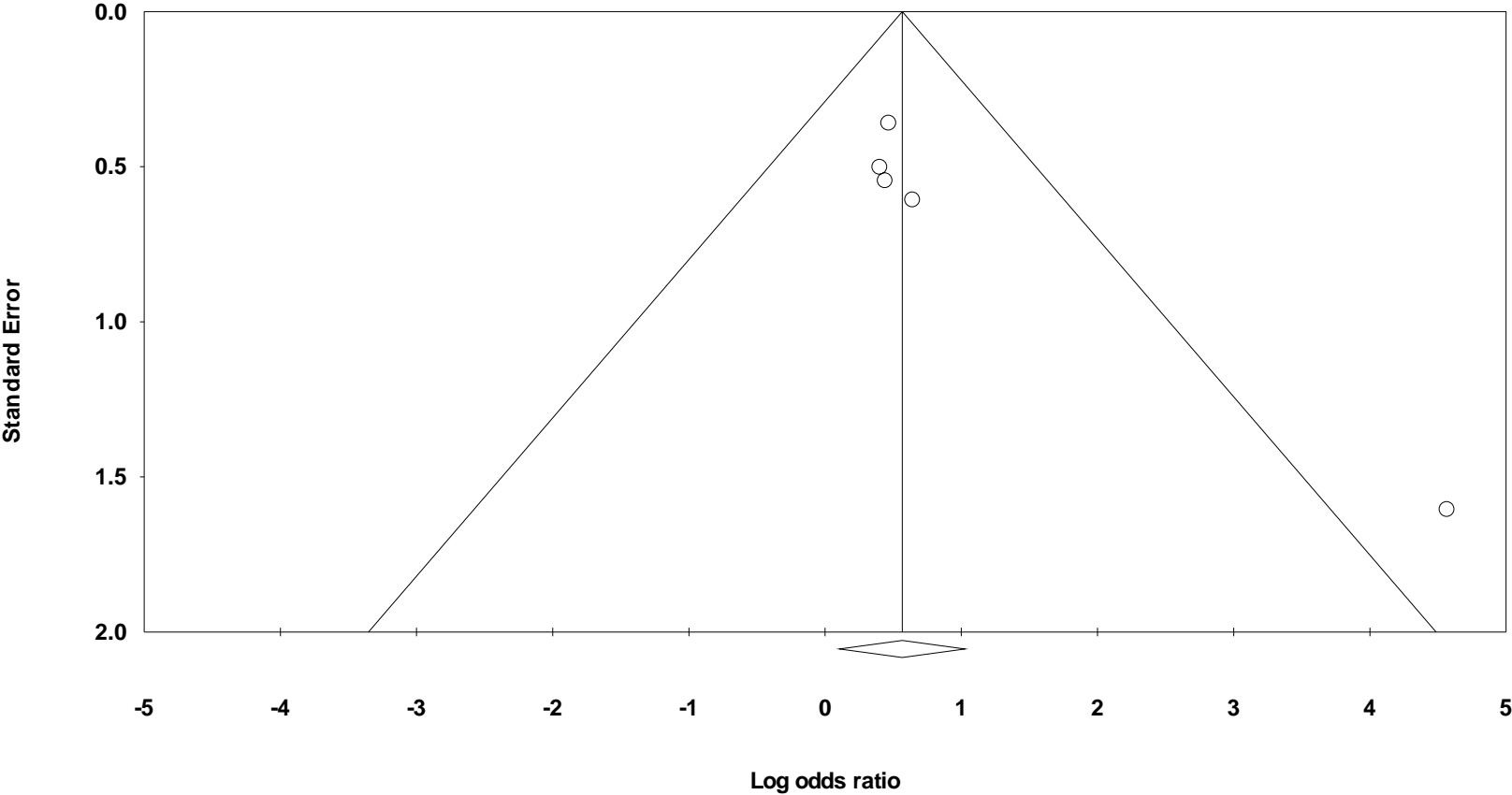
Reference	Reason for Exclusion (example)
2010	
Hoepfner et al ⁸⁰	n=30, but data overlap with Herwig et al, 2007 ⁸¹

3.1 Supplementary eFigure 12. Response rates at T_1

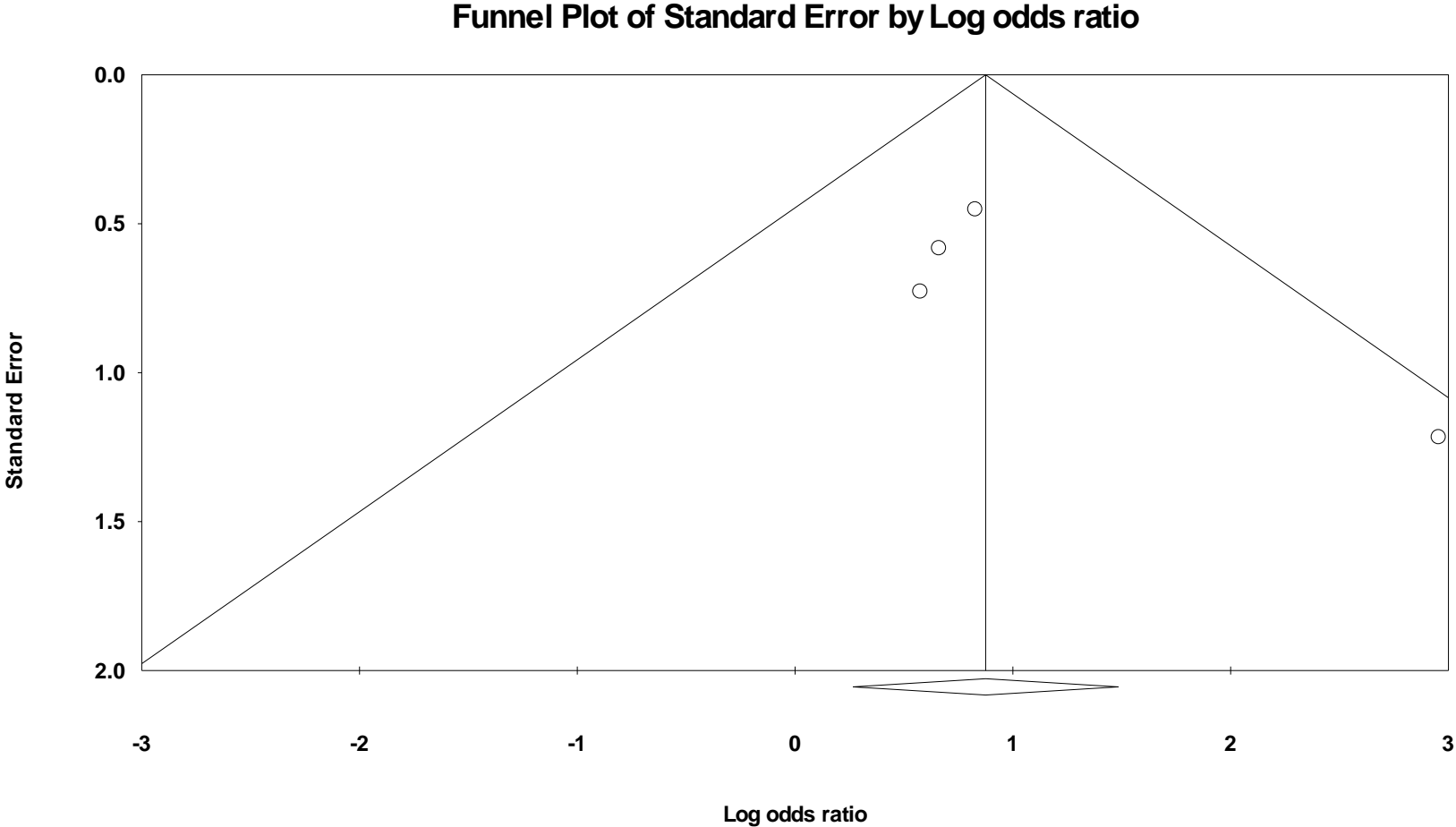


3.2 Supplementary eFigure 13. Response rates at T_2

Funnel Plot of Standard Error by Log odds ratio



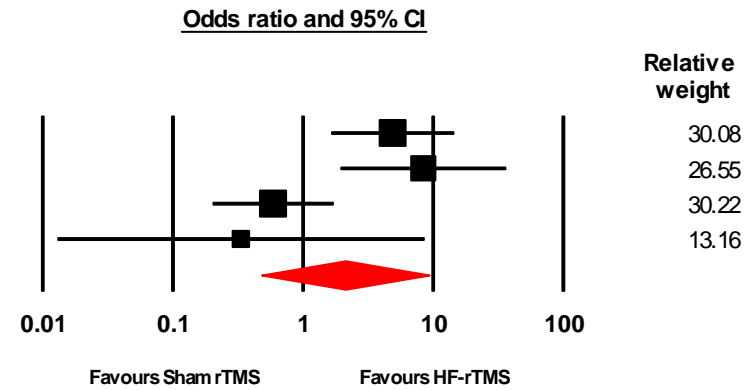
3.3 Supplementary eFigure 14. Remission at T_2



Supplementary eSection 4. Forest Plots

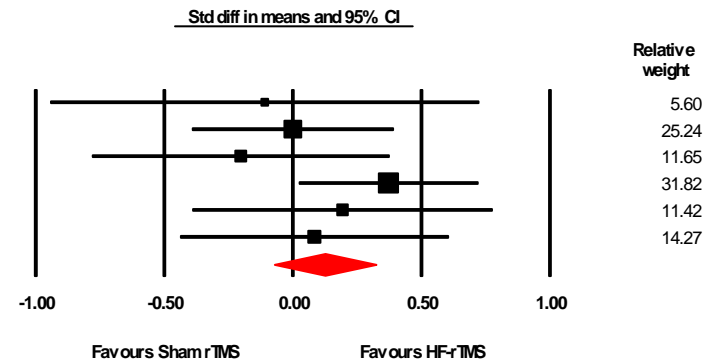
4.1 Supplementary eFigure 15. Remission Rates at T₁

Study name	Statistics for each study					Remitters / Total	
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Active rTMS	Sham rTMS
Rossini et al, 2005	4.877	1.633	14.567	2.839	0.005	18 / 49	5 / 47
Rumi et al, 2005	8.400	1.927	36.618	2.833	0.005	12 / 22	3 / 24
Herwig et al, 2007	0.589	0.200	1.732	-0.961	0.336	6 / 62	10 / 65
Bretlau et al, 2008	0.333	0.013	8.627	-0.662	0.508	0 / 22	1 / 23
	2.090	0.475	9.197	0.975	0.329	36 / 155	19 / 159



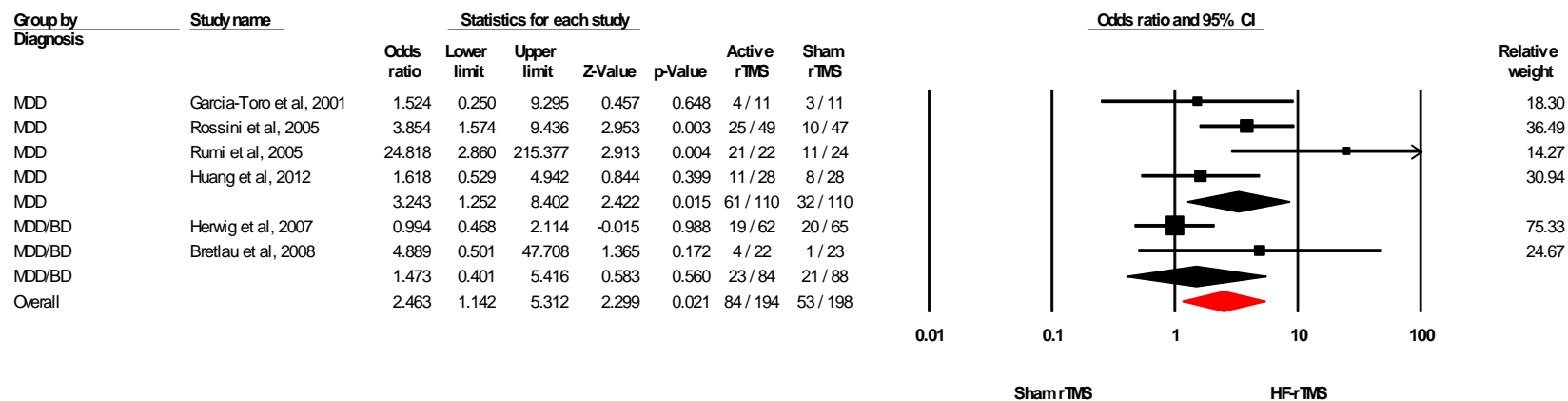
4.2 Supplementary eFigure 16. Baseline Depression Scores

Study name	Statistics for each study						Sample size		
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Active rTMS	Sham rTMS
Garcia-Toro et al, 2001	-0.109	0.427	0.182	-0.946	0.727	-0.256	0.798	11	11
Rossini et al, 2005	0.000	0.201	0.040	-0.394	0.394	0.000	1.000	50	49
Rumi et al, 2005	-0.203	0.296	0.088	-0.783	0.377	-0.685	0.494	22	24
Herwig et al, 2007	0.372	0.179	0.032	0.021	0.723	2.080	0.038	62	65
Bretlau et al, 2008	0.193	0.299	0.089	-0.393	0.779	0.647	0.518	22	23
Huang et al, 2012	0.084	0.267	0.071	-0.440	0.608	0.314	0.753	28	28
	0.123	0.101	0.010	-0.075	0.321	1.216	0.224	195	200

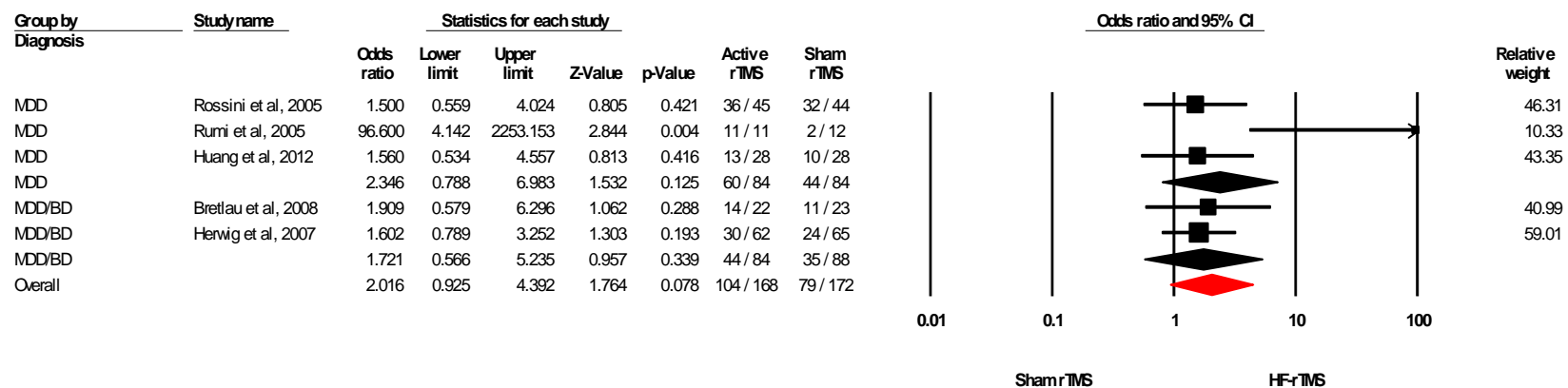


4.4 SENSITIVITY ANALYSES

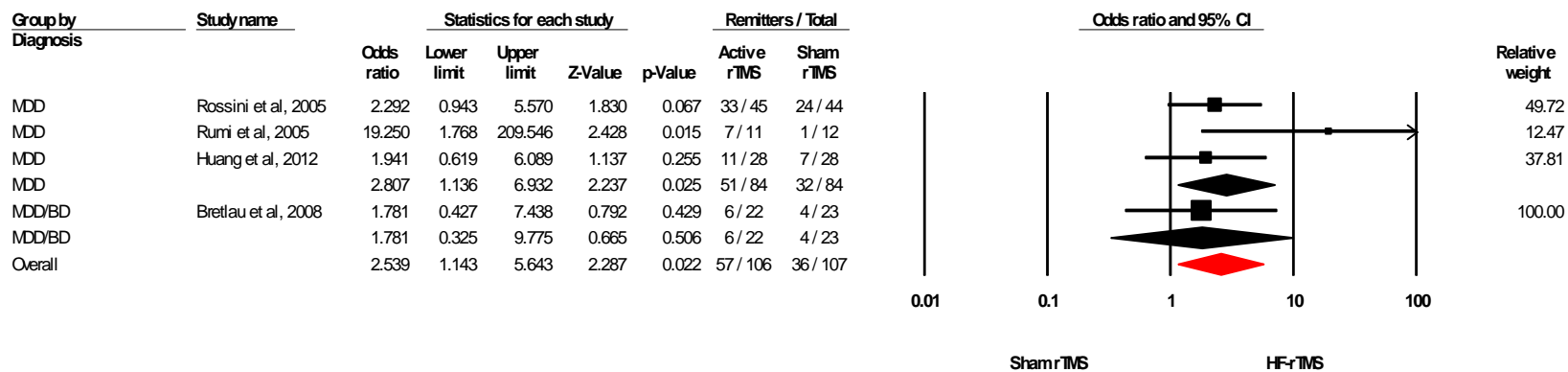
4.4.1 *Supplementary eFigure 17. Unipolar vs. Mixed (Unipolar/Bipolar) Samples: Response Rates at T₁*



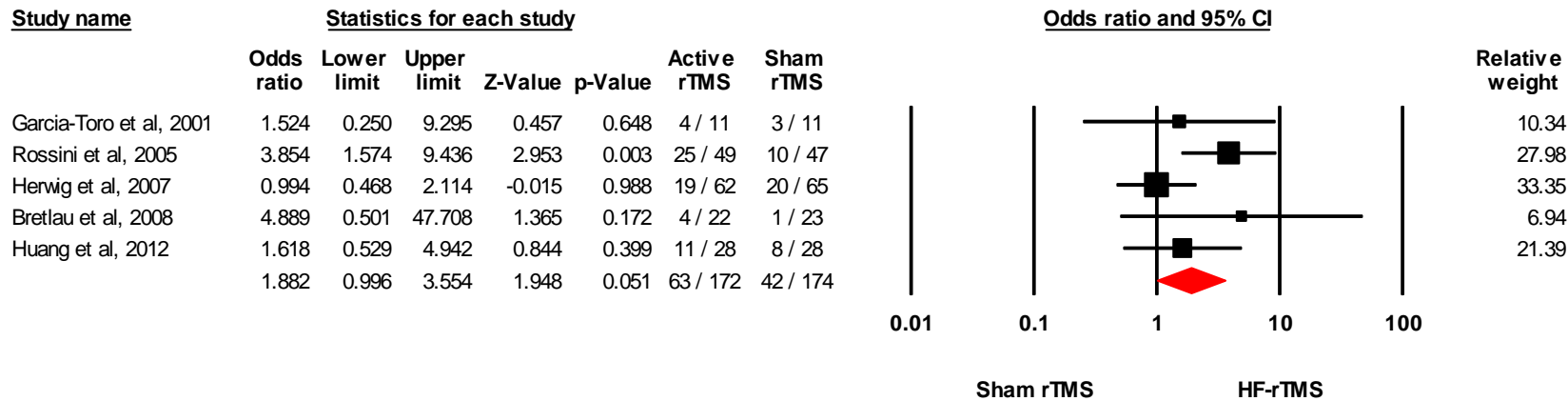
4.4.2 *Supplementary eFigure 18. Unipolar vs. Mixed (Unipolar/Bipolar) Samples: Response Rates at T₂*



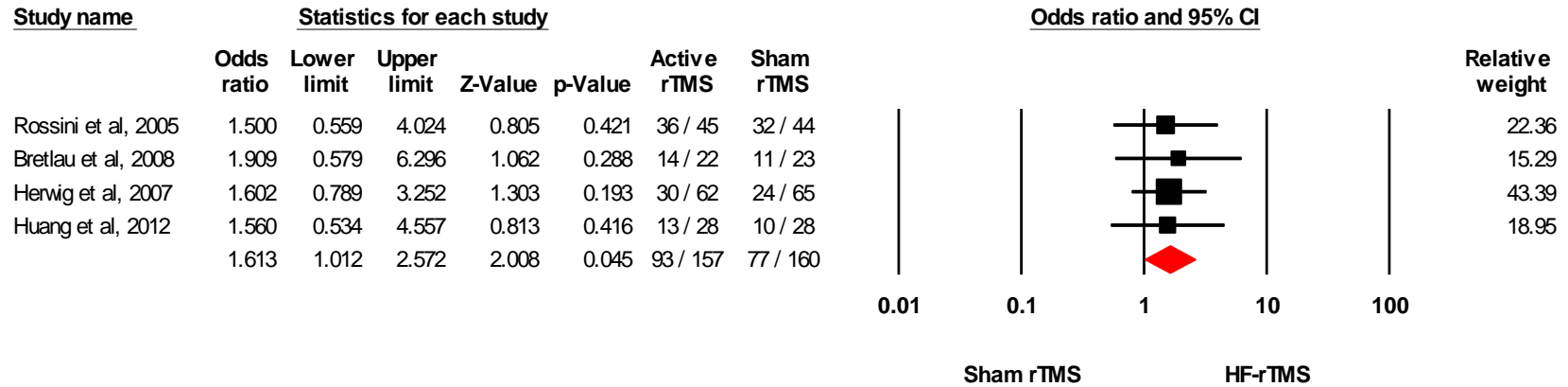
4.4.3 Supplementary eFigure 19. Unipolar vs. Mixed (Unipolar/Bipolar) Samples: Remission Rates at T₂



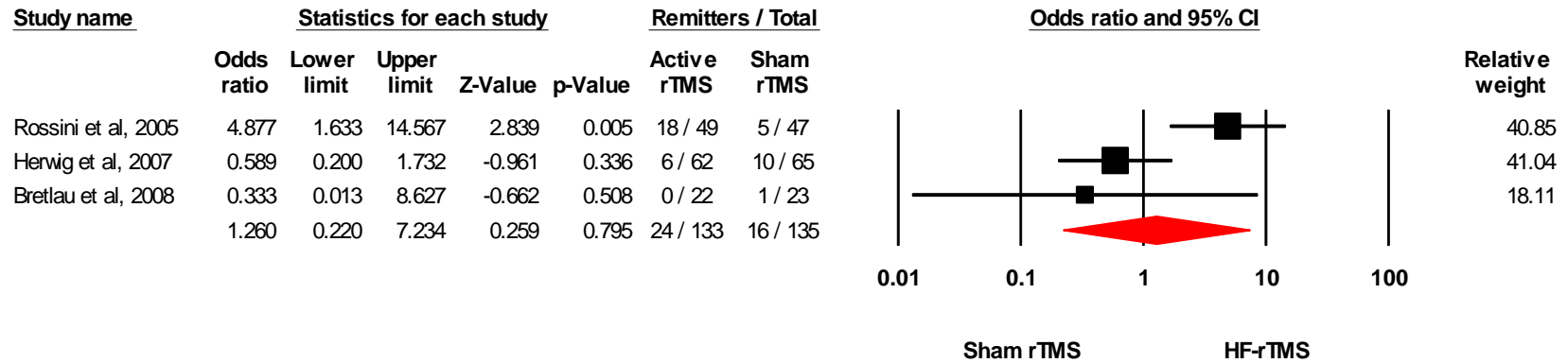
4.4.4 Supplementary eFigure 20. Response Rates at T₁ Excluding Rumi and colleagues⁸²



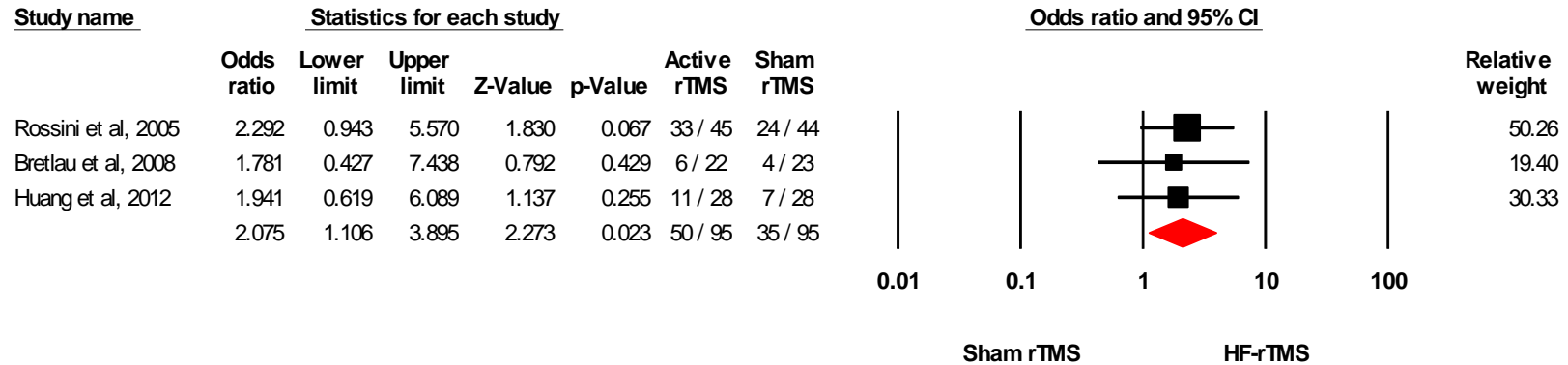
4.4.5 Supplementary eFigure 21. Response Rates at T₂ Excluding Rumi and colleagues⁸²



4.4.6 Supplementary eFigure 22. Remission Rates at T₁ Excluding Rumi and colleagues⁸²



4.4.7 Supplementary eFigure 23. Remission Rates at T₂ Excluding Rumi and colleagues⁸²



5. REFERENCES

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