Universiteit
Leiden
The Netherlands

The role of BDNF in depression : will the neurothrophin hypothesis sparkle on, long after the glitter of the firework is gone?

Molendijk, M.L.

Citation
Molendijk, M. L. (2014, June 3). *The role of BDNF in depression : will the neurothrophin hypothesis sparkle on, long after the glitter of the firework is gone?*. Retrieved from https://hdl.handle.net/1887/25851

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/25851

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/25851 holds various files of this Leiden University dissertation

Author: Molendijk, M.L.
Title: The role of BDNF in depression : will the neurotrophin hypothesis sparkle on, long after the glitter of the firework is gone?
Issue Date: 2014-06-03

APPENDIX I

Chapter 1 General introduction

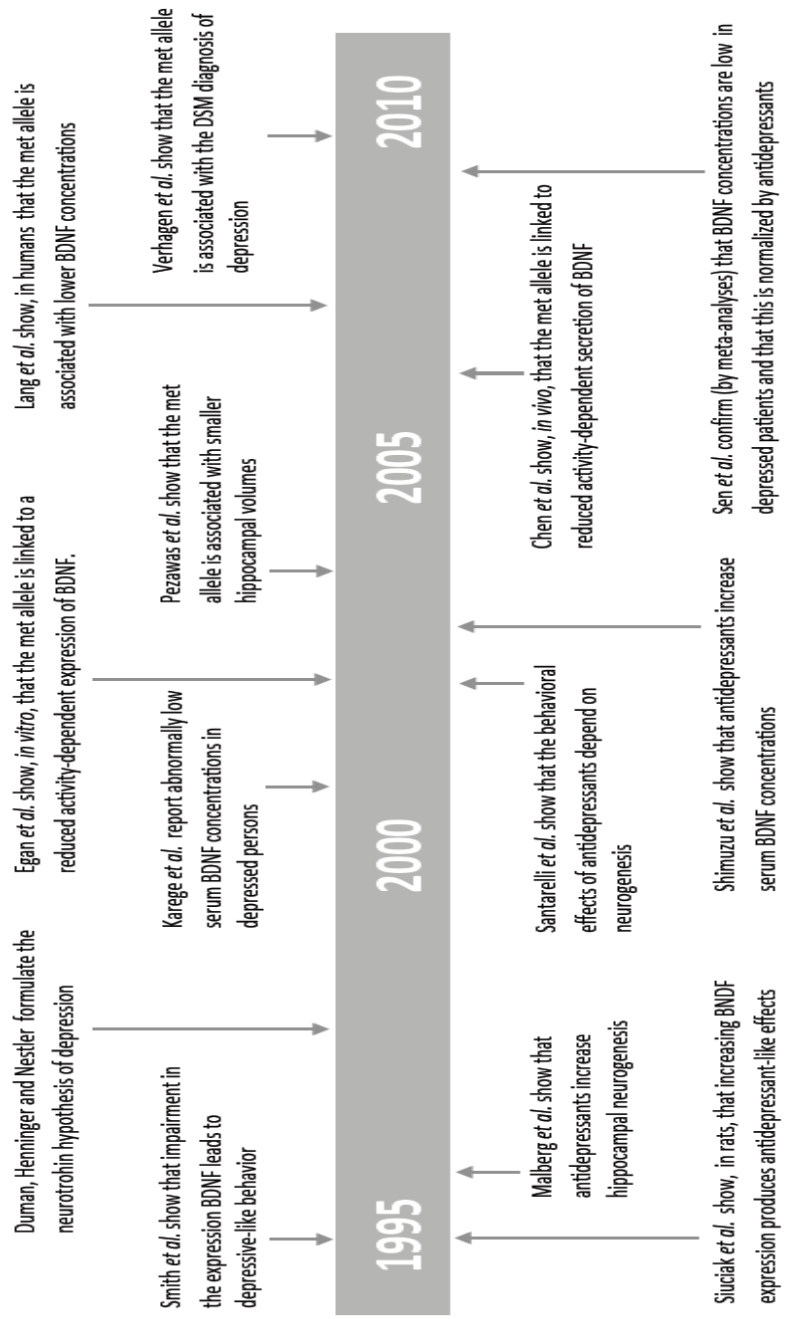

Figure S1. Overview of the breakthroughs in the research into the neurotrofin hypothesis

APPENDIX II

Chapter 3 BDNF concentrations show strong seasonal variation and are correlated with the amount of ambient sunlight

Table S1. *P*-values for pair-wise comparisons on covariate adjusted serum BDNF concentrations by month of sampling

	Jan *n* = 249	Feb *n* = 238	Mar *n* = 239	Apr *n* = 228	May *n* = 229	Jun *n* = 231	Jul *n* = 203	Aug *n* = 211	Sep *n* = 280	Oct *n* = 254	Nov *n* = 292	Dec *n* = 197
Jan	1	.19	.01 ↑	.74	.26	.001 ↓	.003 ↓	.001*↓	<.001*↓	.004 ↓	<.001*↓	.003 ↓
Feb	.19	1	.21	.35	.02↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓
Mar	.01 ↓	.21	1	.03 ↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓	<.001*↓
Apr	.74	.35	.03 ↑	1	.15	<.001*↓	.001 ↓	<.001*↓	<.001*↓	.001 ↓	<.001*↓	.002 ↓
May	.26	.02 ↑	<.001*↑	.15	1	.04 ↓	.06	.02 ↓	.001 ↓	.09	.006 ↓	.07
Jun	.001 ↑	<.001*↑	<.001*↑	<.001*↑	.04 ↑	1	.92	.78	.27	.69	.59	.87
Jul	.003 ↑	<.001*↑	<.001*↑	.001 ↑	.06	.92	1	.72	.25	.78	.53	.94
Aug	.001*↑	<.001*↑	<.001*↑	<.001*↑	.02 ↑	.78	.71	1	.44	.50	.81	.66
Sep	<.001*↑	<.001*↑	<.001*↑	<.001*↑	.001 ↑	.27	.25	.44	1	.12	.56	.22
Oct	.004 ↑	<.001*↑	<.001*↑	.001 ↑	.09	.69	.78	.50	.12	1	.33	.84
Nov	<.001*↑	<.001*↑	<.001*↑	<.001*↑	.006 ↑	.59	.53	.82	.56	.33	1	.48
Dec	.003 ↑	<.001*↑	<.001*↑	.002 ↑	.07	.87	.94	.66	.22	.84	.48	1

* Statistically significant after Bonferroni correction was applied (66 comparisons, critical *P* value = .00076)
↑ Higher serum BDNF levels in the month indicated in the row relative to the month indicated in the corresponding column
↓ Lower serum BDNF levels in the month as indicated in the row relative to the month as indicated in the corresponding column

Table S2. Zero-order and partial Pearson's correlation coefficients with corresponding *P*-values on the associations between the number weekly sunlight hours and serum BDNF concentrations

	Zero-order correlation	*P*-value	Partial correlation [1]	*P*-value
Number of sunlight hours in the:				
Week of blood draw	0.03	.08	0.04	.03
Week prior to blood draw	0.03	.07	0.04	.04
Two weeks prior to blood draw	0.02	.11	0.04	.03
Three weeks prior to blood draw	0.04	.01	0.06	.001
Four weeks prior to blood draw	0.07	< .0001	0.09	< .0001
Five weeks prior to blood draw	0.12	< .0001	0.13	< .0001
Six weeks prior to blood draw	0.14	< .0001	0.15	< .0001
Seven weeks prior to blood draw	0.15	< .0001	0.16	< .0001
Eight weeks prior to blood draw	0.16	< .0001	0.18	< .0001
Nine weeks prior to blood draw	0.15	< .0001	0.16	< .0001
Ten weeks prior to blood draw	0.12	< .0001	0.13	< .0001

[1] See the paper for covariates

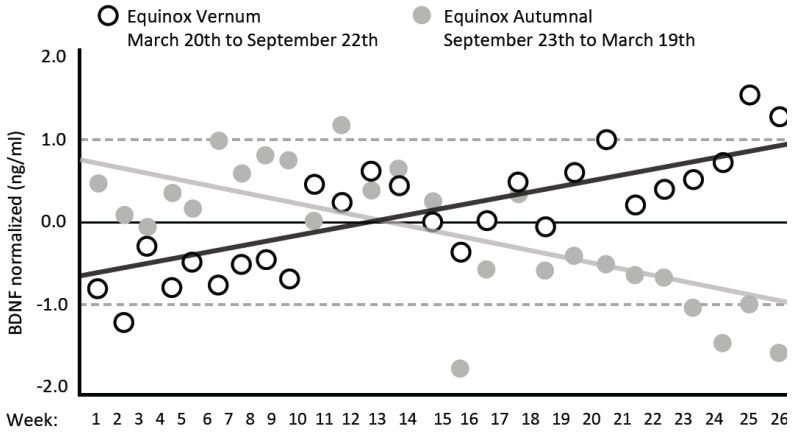

Figure S1. Mean normalized serum BDNF concentrations plotted as a function of each consecutive week of measurement in each equinox

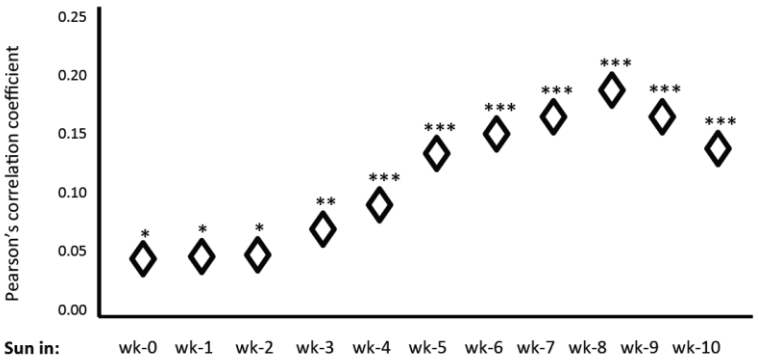

Figure S2. Partial Pearson's correlation coefficients (for covariates see the paper) on the relation between mean serum BDNF concentrations and the hours of sunlight in the week of blood draw (wk-0) and the 10 weeks prior to blood draw (wk-1 to wk-10). * $P < .05$, ** $P < .001$, *** $P < .0001$

APPENDIX III

Chapter 5 Serum BDNF concentrations as peripheral manifestations of depression: *evidence from a systematic review and meta-analyses on 179 associations (N = 9,484)*

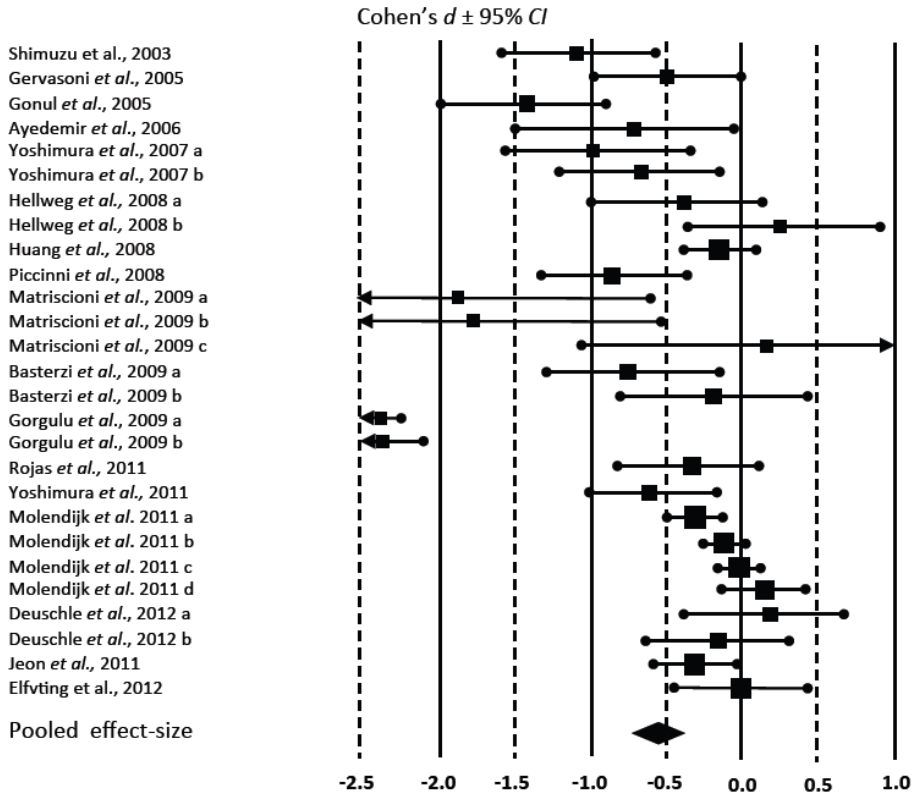

Figure S1. Forest plot for random effect meta-analysis on differences in serum BDNF concentrations between antidepressant-free and antidepressant treated depressed patients. The sizes of the squares are proportional to sample size.

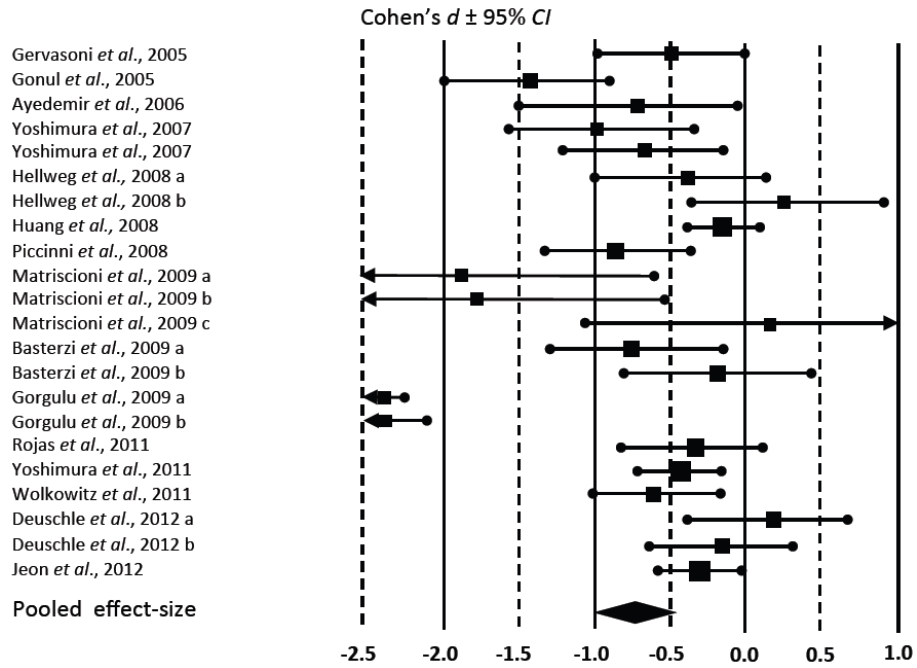

Figure S2. Forest plot for random effect meta-analysis on differences in serum BDNF concentrations between antidepressant-free and treated depressed patients (within-subjects data only, that is treatment studies applying a pre- and post-treatment design). The sizes of the squares are proportional to sample size.

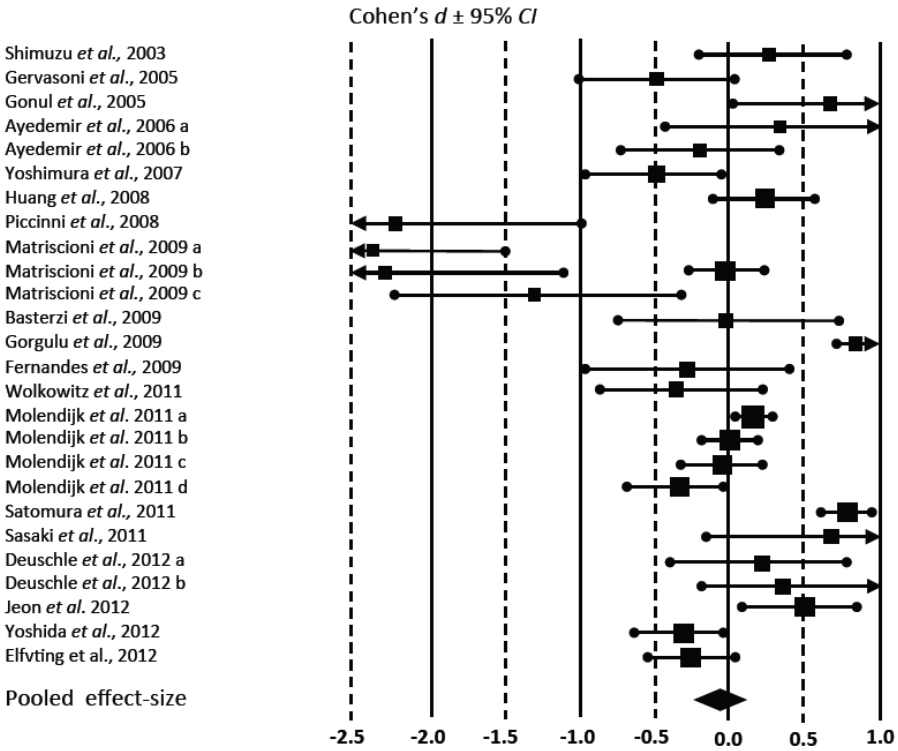

Figure S3. Forest plot for random effect meta-analysis on differences in serum BDNF concentrations between healthy controls and antidepressant-treated depressed patients. The sizes of the squares are proportional to sample size.

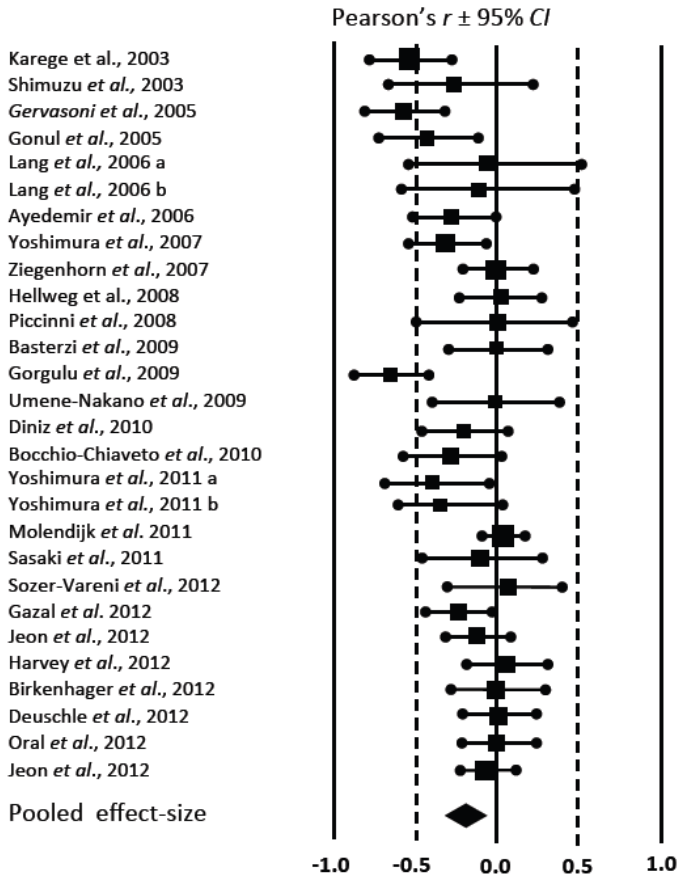

Figure S4. Forest plot for random effect meta-analysis on the continuous relation between serum BDNF concentrations in antidepressant-free depressed persons. The sizes of the squares are proportional to sample size.

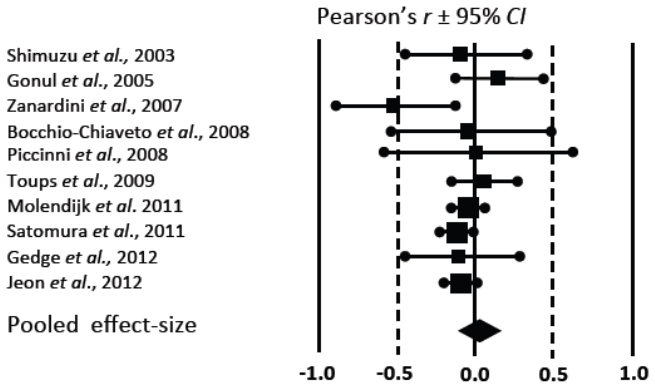

Figure S5. Forest plot for random effect meta-analysis on the continuous relation between serum BDNF concentrations in antidepressant-treated depressed persons. The sizes of the squares are proportional to sample size.

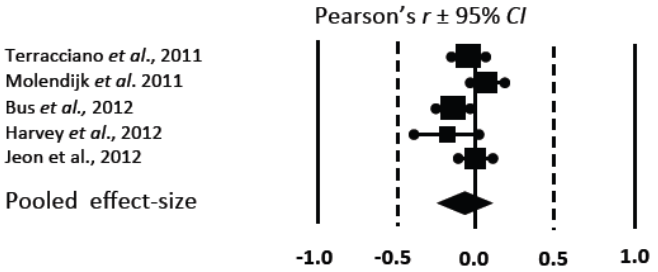

Figure S6. Forest plot for random effect meta-analysis on the continuous relation between serum BDNF concentrations in healthy control subjects. The sizes of the squares are proportional to sample size.

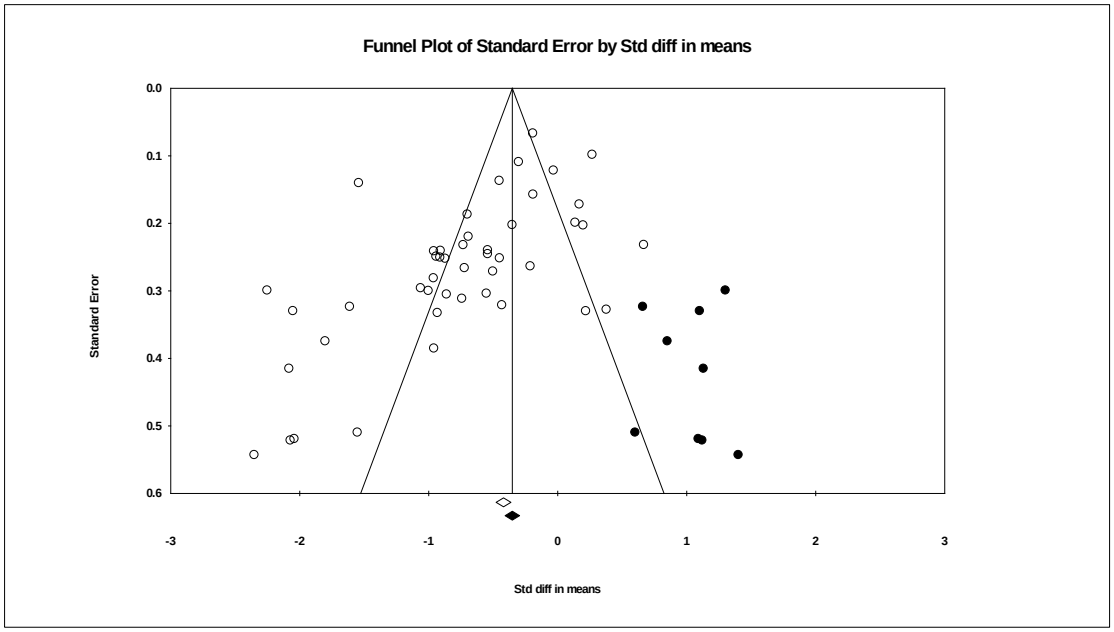

Figure S7. Funnel plot and trim-and-fill estimation showing the typical pattern of publication bias in the meta-analyses on differences in serum BDNF concentrations among healthy controls and antidepressant-free depressed patients. White data points depict observed associations and black data points imputed values. The white diamond depicts the aggregated point estimate (d = -0.71, 95% CI = -0.89 — -0.53, P < .00000001) and the black diamond the aggregated point estimate after the imputation of 10 studies (d = -0.47, 95% CI = -0.64—-0.27, P < .000001), resulting in a symmetrical funnel-plot.

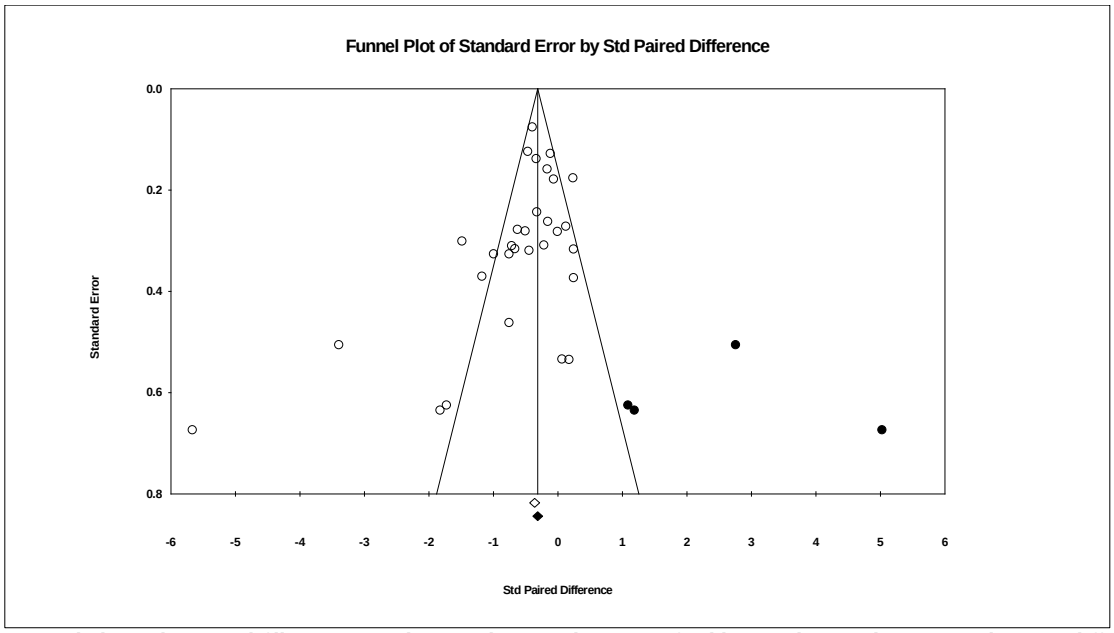

Figure S8. Funnel plot and trim-and-fill estimation showing the typical pattern of publication bias in the meta-analyses on differences in BDNF concentrations among antidepressant-free and treated depressed patients. White data points depict observed associations and black data points imputed values. The white diamond depicts the aggregated point estimate (d = -0.56, 95% CI = -0.77 — - 0.35, P < .000001) and the black diamond the aggregated point after the imputation of 4 studies (d = -0.34, 95% CI = -0.59 — - 0.09, P < .0001), resulting in a symmetrical funnel-plot.

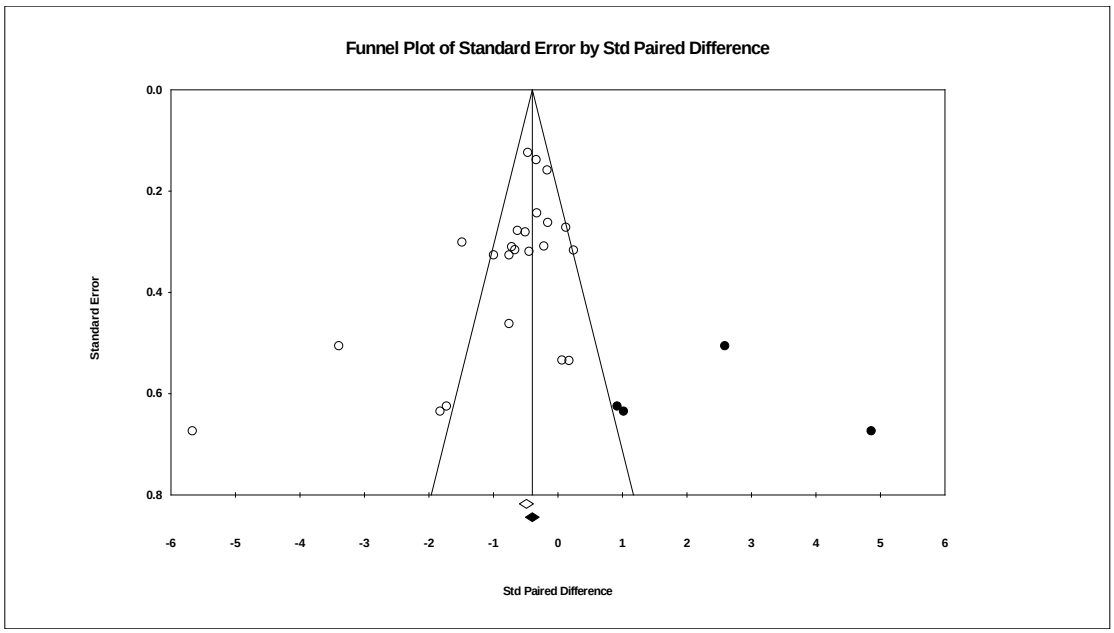

Figure S9. Funnel plot and trim-and-fill estimation showing the typical pattern of publication bias in the meta-analyses on differences in serum BDNF concentrations in treatment studies that reported on serum BDNF concentrations. White data points depict observed associations and black data points imputed values. The white diamond depicts the aggregated point estimate (d = -0.74, 95% CI = -1.04 — -0.45, P < .0000001) and the black diamond the aggregated point estimate after the imputation of 4 studies (d = -0.41, 95% CI = -0.76 — - 0.06, P < .001), resulting in a symmetrical funnel-plot.

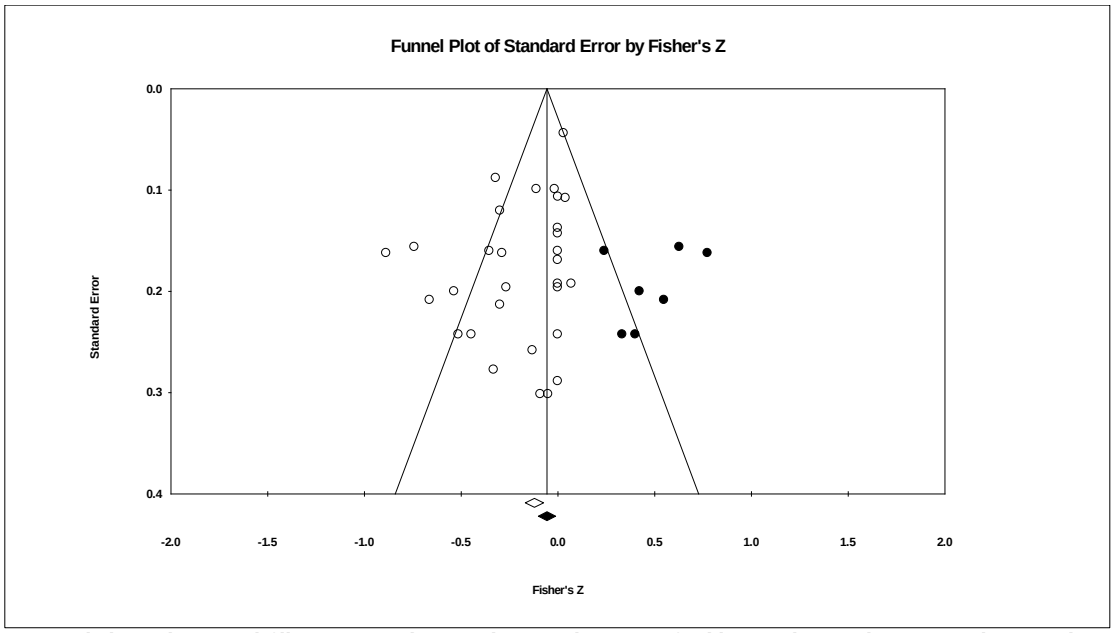

Figure S10. Funnel plot and trim-and-fill estimation showing the typical pattern of publication bias in the meta-analyses on the correlation between serum BDNF concentrations and the symptom severity of depression in antidepressant-free depressed patients. White data points depict observed associations and black data points imputed values. The white diamond depicts the aggregated point estimate (r = -0.19, 95% CI = -0.28 — - 0.10, P < .00001) and the black diamond the aggregated point estimate after the imputation of 7 studies (r = -0.08, 95% CI = -0.09 — 0.03, P = .42), resulting in a symmetrical funnel-plot.

APPENDIX IV

Chapter 9 A systematic review and meta-analysis on the association between BDNF val^{66}met and hippocampal volume – a genuine effect or a winners curse?

Table S1. Evaluation of the included records according to the Strenghtening the Reporting of Genetic Association Studies (Little *et al*., 2009) and Strenghtening Reporting of Observational Studies in Epidemiology (von Elme *et al*., 2007).

	STREGA and STROBE quality checklist items Y; meets the criterion, N; does not meet the criterion, NA; not applicable											
Author, year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Overall quality score**
Pezawas *et al*., 2004	Y	Y	Y	Y	Y	Y	NA	Y	N	NA	Y	7 Y, 2 N, 2 NA = 0.78
Szeszko *et al*., 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11 Y, 0 N, 0 NA = 1.00
Agartz *et al*., 2006	Y	Y	Y	Y	Y	Y	NA	N	N	Y	Y	8 Y, 2 N, 1 NA = 0.80
Bueller *et al*., 2006	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	8 Y, 3 N, 0 NA = 0.73
Frodl *et al*., 2007	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	N	8 Y, 2 N, 1 NA = 0.80
Miyajima *et al*., 2008	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	9 Y, 0 N, 2 NA = 1.00
Takahashi *et al*., 2008	Y	Y	Y	Y	Y	Y	NA	N	Y	Y	NA	9 Y, 1 N, 2 NA = 0.89
Chepenik *et al*., 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11 Y, 0 N, 0 NA = 1.00
Dutt *et al*., 2009	Y	Y	Y	Y	Y	Y	NA	N	N	Y	NA	7 Y, 2 N, 2 NA = 0.78
Gatt *et al*., 2009	Y	Y	Y	Y	Y	Y	NA	N	N	Y	NA	7 Y, 2 N, 2 NA = 0.78
Jessen *et al*., 2009	Y	N	Y	Y	N	Y	NA	N	N	Y	NA	5 Y, 4 N, 2 NA = 0.56
Joffe *et al*., 2009	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	9 Y, 0 N, 2 NA = 1.00
Schofield *et al*., 2009	Y	N	Y	Y	Y	N	NA	Y	Y	Y	NA	7 Y, 2 N, 2 NA = 0.78
Toro *et al*., 2009	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	9 Y, 0 N, 2 NA = 1.00
Benjamin *et al*., 2010	Y	N	Y	Y	N	Y	NA	N	N	Y	NA	5 Y, 4 N, 2 NA = 0.56
Karnik *et al*., 2010	Y	Y	Y	Y	N	Y	N	N	Y	Y	N	7 Y, 4 N, 0 NA = 0.64
Koolschijn *et al*., 2010	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	9 Y, 0 N, 2 NA = 1.00
Cole *et al*., 2011	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	9 Y, 0 N, 2 NA = 1.00
Gerritsen *et al*., 2011	Y	Y	Y	Y	Y	Y	NA	N	Y	Y	NA	8 Y, 1 N, 2 NA = 0.89
Gonul *et al*., 2011	Y	Y	Y	Y	N	Y	NA	Y	Y	Y	NA	8 Y, 1 N, 2 NA = 0.89
Gruber *et al*., 2011	Y	Y	Y	Y	Y	Y	NA	N	Y	Y	NA	8 Y, 1 N, 2 NA = 0.89
Kanellopoulos *et al*., 2011	Y	Y	Y	Y	Y	Y	NA	N	Y	Y	NA	8 Y, 1 N, 2 NA = 0.89
Richter *et al*., 2011	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	9 Y, 0 N, 2 NA = 1.00
Milan Sanchez *et al.,* 2012	Y	Y	Y	Y	Y	Y	NA	N	Y	Y	NA	8 Y, 1 N, 2 NA = 0.89
Molendijk *et al.,* 2012	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	9 Y, 0 N, 2 NA = 1.00

Criteria were assessed independently by 2 of the authors. Inconsistencies were evaluated in consensus meetings. Agreement among the raters proved to be excellent with Cohen's Kappa = 0.83, standard error = 0.04. Please contact the corresponding author for information about the actual reason for scoring a yes, a no, or a not applicable

STREGA (Little *et al*., 2009) and STROBE (von Elme *et al*., 2007) criteria: (**1**) Clear statement of the objectives and the hypothesis (**2**) Clear eligibility criteria for study participants (**3**) Clear definition of all variables (**4**) Replicability of Statistical methods (**5**) Assessment of Hardy-Weinberg equilibrium (**6**) Assessment of ethnicity (**7**) Addressing the problem of mixed ethnicities (**8**) Sufficient descriptive data (**9**) Statement of genotype frequencies (**10**) Sample in Hardy-Weinberg equilibrium (**11**) Consideration of population stratification (if applicable)

APPENDIX V

Chapter 10 General discussion: The poll

Two know more than one: a poll

The conventional option to prove association is observation and experimentation. However, and notwithstanding the fact that some experiments have been performed on the relation between peripheral and central BDNF functioning, the literature on this topic appears confusing to me. Therefore, I chose to run a poll among experts/researchers from around the world.

Through PUBMED I identified the 50 most recently published papers that had *BDNF* and *depression* in their title (regardless whether it were studies on humans, rats,). From each paper I extracted the email address of the corresponding author and I wrote an email to him/her. I asked the following question: *What do you think, how relevant are serum BDNF concentrations with regard to (human) depression*? I prompted them to give a short answer by adding answer options: (A) *relevant, will add to our knowledge on depression*, (B) *irrelevant*, (C) *don't know yet, but the future probably will tell* or (D) *I do not believe in a biological basis of depression whatsoever*. I added that a short explanation could be given but that this was not necessary for my current concerns. While doing this I reckoned that a poll like this could yield biased results because all the persons work on the *topic* and therefore their responses could well be overly positive. To overcome this at least a little I set out a second poll. I identified the 50 most recently published papers that had *cognitive-* or *interpersonal theory* and *depression* in their title (again regardless their exact topic). I asked the corresponding authors of these papers the same question as I asked the BDNF oriented authors and I provided them with the same answer categories. A full version of the e-mail and the list of authors that was contacted can be found below.

Seventy-two percent (*n* = 36) of the BDNF oriented researchers and 48 percent (*n* = 24) of the cognitive/interpersonal-oriented researchers responded to my request. This difference in response rate was statistically significant (χ^2_1 = 6.01, *P* = 0.01). Of the BDNF oriented authors who responded, 56 percent (*n* = 26) agreed with the proposition that peripheral BDNF concentrations are relevant parameters for depression, 6 percent (*n* = 3) disagreed, and 36 percent (*n* = 13) suggested that for now there is too little knowledge on the topic to come to conclusions. The interpersonal/cognitive-oriented authors who responded to the poll were somewhat more pessimistic. In this group, 25 percent (*n* = 6) agreed with the proposition, 25 percent (*n* = 6) disagreed and 50 percent (*n* = 12) suggested that the future probably would inform us. The pattern of responses between the two groups of authors differed significantly (χ^2_2 = 6.44, *P* = 0.04) such that more of the BDNF oriented authors agreed with the proposition that peripheral BDNF concentrations are relevant parameters for depression. The response frequencies of both polls are provided in the **Table ↓**.

Table. Results from the poll by research orientation

	Biologically oriented colleagues			Cognitive oriented colleagues		
	n = 50	% *n* [1]	% *responders* [2]	*n* = 50	% *n* [1]	% *responders* [2]
A - *agree*	20	40%	56%	6	12%	25%
B - *disagree*	3	6%	9%	6	12%	25%
C - *future will tell*	13	26%	36%	12	24%	50%
D - *non-believer*	0	0%	0%	0	0%	0%
No response	14	28%	*NA*	26	52%	*NA*

Abbreviations: NA; Not Applicable
[1] Percentage of the *n* = 50 to which I send out the poll
[2] Percentage of the persons that actually responded on the poll

The main lesson to learn from this poll is that the large majority of researchers either agrees (43 percent) with the proposition that serum BDNF concentrations are relevant with regard to depression *or* expresses the belief that the future will inform us on this issue (42 percent). Only 15 percent explicitly disagrees with the notion that serum BDNF concentrations are relevant with regard to

depression. In this sense, the poll was helpful in that most authors see either relevance in the use of serum BDNF concentrations as parameters for depression or suggests that more research will bring definite answers. Tentatively, this strengthens the belief that serum BDNF concentrations are relevant with regard to depression – but again, a systematic exploration would suit the question better and therefore is be very welcome.

The e-mail that was sent out

Topic: Question: BDNF in the periphery, how relevant is that for central processes?

Dear Dr. *name corresponding author, dear colleague,*

I have a question for you. I'm writing my PhD thesis on serum BDNF concentrations – a topic related to your research interests (attached you can find one of our papers on serum BDNF levels in depressed persons). I'm in the middle of wrapping it all together and writing the final thesis discussion. Already for a while I noticed debate in the literature on the use of peripheral BDNF levels as a reliable mirror of neurotrophic functioning in the central nervous system. For my thesis discussion I wanted to know how other scientists, who work in related fields [but not necessarily the exact same], think about this issue. So, I decided to send out a poll to the corresponding authors of the 50 most recent papers that have BDNF in their title (regardless the precise topic) to learn about the opinion of the authors on this topic. You happen to be in that group with your paper in *the Journal in which the paper is published*.

My question to you is: *What do you think, how relevant are serum BDNF concentrations with regard to (human) depression*?

The corresponding letter A, B, C, or D is enough for me as response
A '*Relevant, will ad to our knowledge on depression and neuronal plasticity in the brain*'
B '*Irrelevant, won't add a lot to our knowledge on depression and neuronal plasticity in the brain*'
C '*Don't know, maybe the future will tell*'
D *'I do not believe in a biological basis of depression whatsoever*'

You can add a short explanation if you wish. I'm interested in that but it is not necessary for my current purpose.

Thank you in advance for your response, all the best,

Marc Molendijk

Note. Attached you can find one of our papers on serum BDNF concentrations in depressed persons that has been published in *Molecular Psychiatry*.

Authors in the poll -- authors who responded are underlined

BDNF oriented authors
C Duarte (Portugal), M Miquel (Spain), K Felmingham (New Zealand), K Iqbal (USA), H Scharfman (USA), D Jon (Korea), M Fawzi (Egypt), M Shamsul Ola (Saudi Arabia), S Vivekanandhan (India), G Morton (USA), X Zhang (China), F Lotrich (USA), N Perroud (Switzerland), L Ricceri (Italy), J Luykx (the Netherlands), R Ting-A-Kee (Canada), G Hasler (Switzerland), R Rodríguez-López (Spain), E Ottem (USA), L-M Wu (China), N Mechawar (Canada), K Ressler (USA), X Xiayixiayi (China), M Soleimani (Iran), S Cramer (USA), D Carlino (Italy), D Srivastava (UK), J-M Kim (Korea), G Réus (Brazil), T Sakharnova (Russia), E McNay (USA), Y Hung (Taiwan), J Charoenphandhu (Thailand), K Kauppi (Sweden), D Carbone (USA), M Gilbert (USA), D Ron (USA), M Dmitrzak-Weglarz (Poland), J Yang (USA), W Umene-Nakano (Japan), S Miller (USA), J-H Chae (Korea), V Stelzhammer (UK), Z-Y Chen (China), F Fumagalli (Italy), R Dalle Molle (Brazil), N Cardoner (Spain), T Endres (Germany), C Ernst (Canada), Y Tizabi (USA), E Tongiorgi, (Italy).

Cognitive/inter-personal oriented authors
P Pössel (USA), F Jollant (Canada), J Johnstone (New Zealand), Melitta Fischer-Kern (UK), P Thoma (Germany), M Constantino (USA), H O'Mahen (UK), M van Hees (the Netherlands), J Ogrodniczuk (Canada), M Hochberg (USA), R Auerbach (USA), S Winkeljohn Black (USA), E Sheets (USA), F Peters (the Netherlands), M Flynn (USA), K Mclaughln (USA), N Wongpakaran (Thailand), B D'Antono (Canada), J Ehrenreich-May (USA), M Constantino (USA), G Stein (USA), A Forsman (Finland), M Power (Scotland), F Renner (the Netherlands), J Stewart (Canada), T Kühnen (Germany), T Berger (Switserland), J Jakobsen (Danmark), J McCullough (USA), G Tasca (Canada), L Hides (Australia), L Lemmens (the Netherlands), J Goodman (USA), M Serfaty (UK), F Doyle (Ireland), M McKinnon (Canada), L Sockol (USA), S Rueger (USA), D Klein (USA), L Rood (the Netherlands), L Wolkenstein (Germany), K Iverson (USA), G Pomaki (Canada), R Trivedi (USA), Pauline Slade (UK), H Teunissen (the Netherlands), C Beevers (USA), S Hollon (USA), E Schramm (Germany), D Dozois (Canada).