SEARCHING FOR PATOMECHANISMS OF LATE LIFE MINOR DEPRESSION – A COMBINED MRI, BIOMARKER AND META-ANALYTIC STUDY

Dissertation

for obtaining the academic degree

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at the medical faculty of the University of Leipzig

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Decision on the award of the academic title on: 16.04.2019

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1. INTRODUCTION

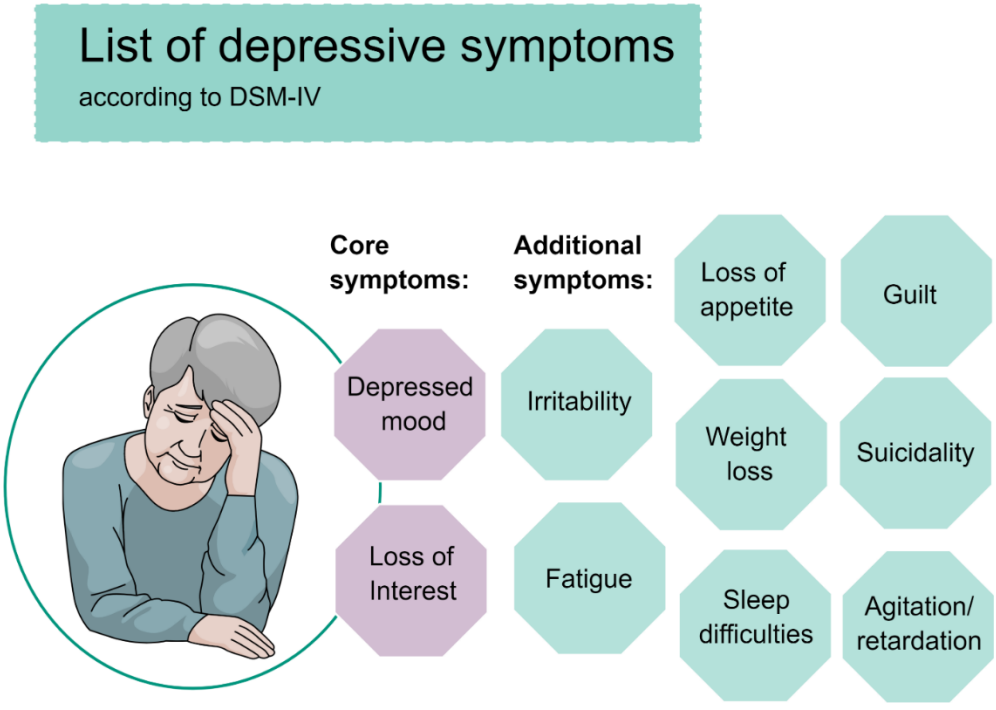
1.1 Motivation

1.1.1 Minor depression in the spectrum of psychiatric disorders

Depressive disorders belong to the most debilitating psychiatric disorders both for patients and for the healthcare system[1, 2]. As for many psychiatric disorders, the spectrum of depressive disorders is broad, starting from few subthreshold symptoms up to a full-blown major depression with suicidal thoughts or psychotic features[3, 4]. The prevalence of depressive disorders changes with gender, age and somatic status. In particular, depression more often affects females[1, 5]. With aging and accumulation of somatic diseases the incidence of minor depression prevails over major depressive disorder[6].

The American Psychiatric Association (APA) proposed a critical threshold of five depressive symptoms in order to distinguish between minor and major depressive episode[3, 4] (Figure 1, 2).

Figure 1 Depressive symptoms according to DSM-IV

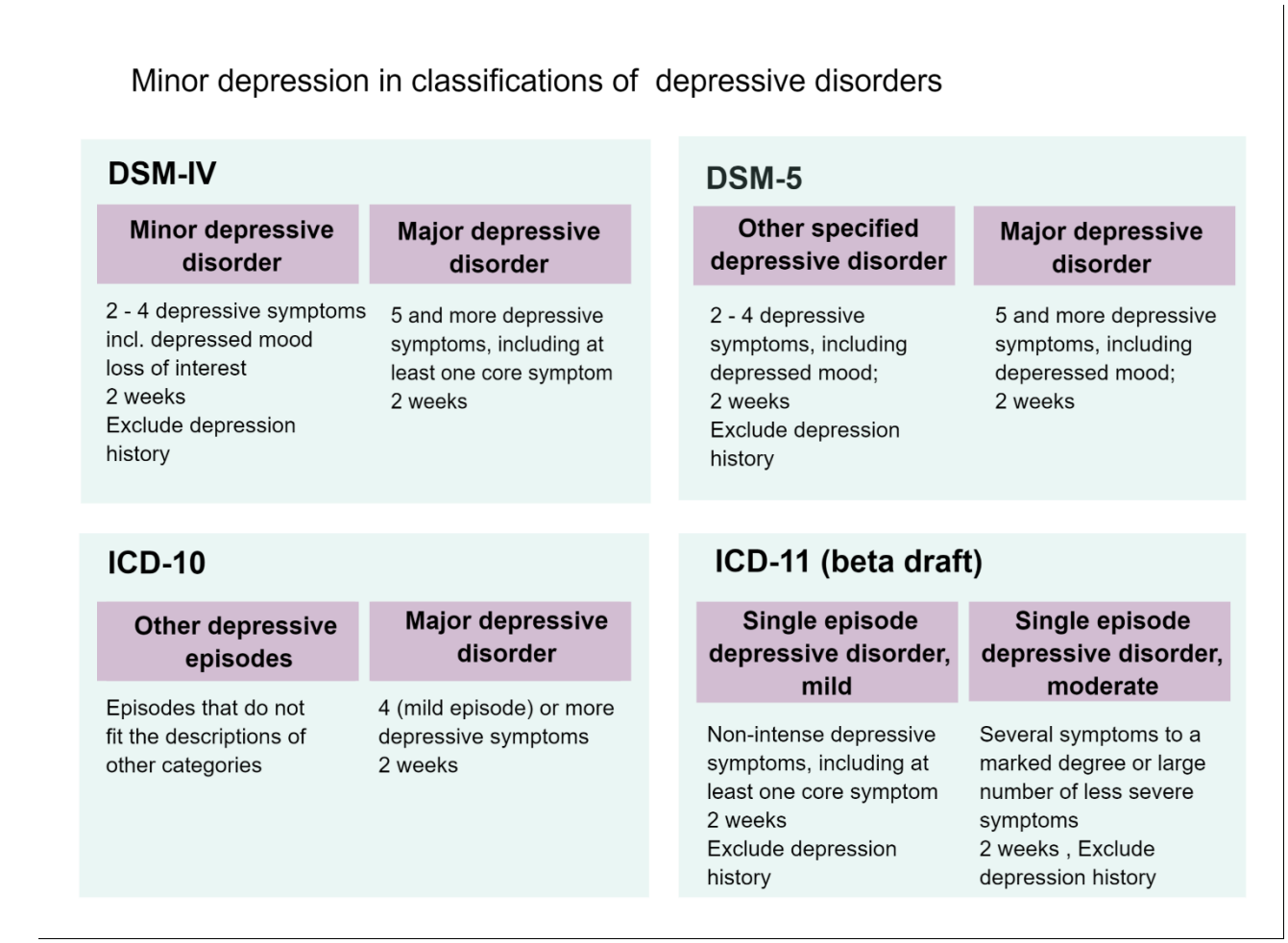


According to the fourth edition of the Diagnostic and Statistical Manual of mental disorders (DSM-IV) minor depressive episode is diagnosed when two to four depressive symptoms (including at least one core symptom, see Figure 1) disturb a patient for at least two weeks. Exclusion of depression history is required for the diagnosis of minor depressive disorder. In DSM-IV minor depressive disorder is listed under a category Depressive Disorder Not Otherwise Specified (NOS, code 311)[3].

The DSM-5 does not use the term “minor depression” anymore. A similar condition, where only one core symptom - depressed mood - is combined with up to three other depressive symptoms, is placed at the category “Other specified depressive disorders” (code 311[4]).

According to the 10th edition of the International Classification of Diseases (ICD-10) persons suffering from two core symptoms and two additional symptoms should be diagnosed with mild depressive episode (F32.0). Those having less than four symptoms qualify for F32.8 (Other depressive episodes) or F32.9 (Depressive episode, unspecified). The criteria for these categories are vague though. The beta-draft of ICD-11 (https://icd.who.int/dev11) tends to avoid counting the depressive symptoms focusing more on the severity of them (See Figure 2).

Figure 2. Minor depression in the categorization of depressive disorders according to international classifications, Diagnostic and Statistical Manual for psychiatric disorders (DSM)[3, 4] and International Classification of Diseases (ICD)[7].



Overall classification systems disagree on thresholds and diagnostic criteria for major and minor depression. Nevertheless, all of them leave space for a diagnosis of some kind of subthreshold depression with different number of symptoms per category. The need for such a category is clear due to high prevalence of subthreshold depressive symptoms, especially in the elderly population.

1.1.2 Minor depression is prevalent but unrecognized

When patients are examined thoroughly by the psychiatrist, it becomes obvious that minor depression is not rare. The majority of studies assessing prevalence of minor depression show that this condition is very prevalent especially in late life. Nevertheless,

the point prevalence ranges widely: from 0 % in community settings[8] to 26.5 % in patients with mild cognitive impairment[9]. Likely due to the high variation in the assessment methods, the prevalence of minor depression, its' clinical correlates and the most vulnerable groups were never systematically reviewed.

Insufficient information and inconsistencies in the classification systems reflect lack of understanding of the nature of minor depression. It is viewed either as an independent depressive disorder or as a prodrome of major depression[10]. The first view is supported by a single episode and relatively low conversion rates[11]. On the other hand, the conversion into major depressive disorder in some patients suggests that minor depression might be a first episode in the development of more severe depressive disorder[12, 13]. Both courses are possible and are likely orchestrated by, to date, unknown biological mechanisms. Identification of these mechanisms is crucial for understanding the nature and course of the disorder.

Despite two neuroimaging studies investigating cortical thickness[14] and volume[15] in minor depression, pathophysiology of this disorder is largely unexplored. In the course of this thesis, prevalence rates and biological correlates were systematically reviewed, and blood and imaging biomarkers of minor depression investigated.

1.2 Theoretical background

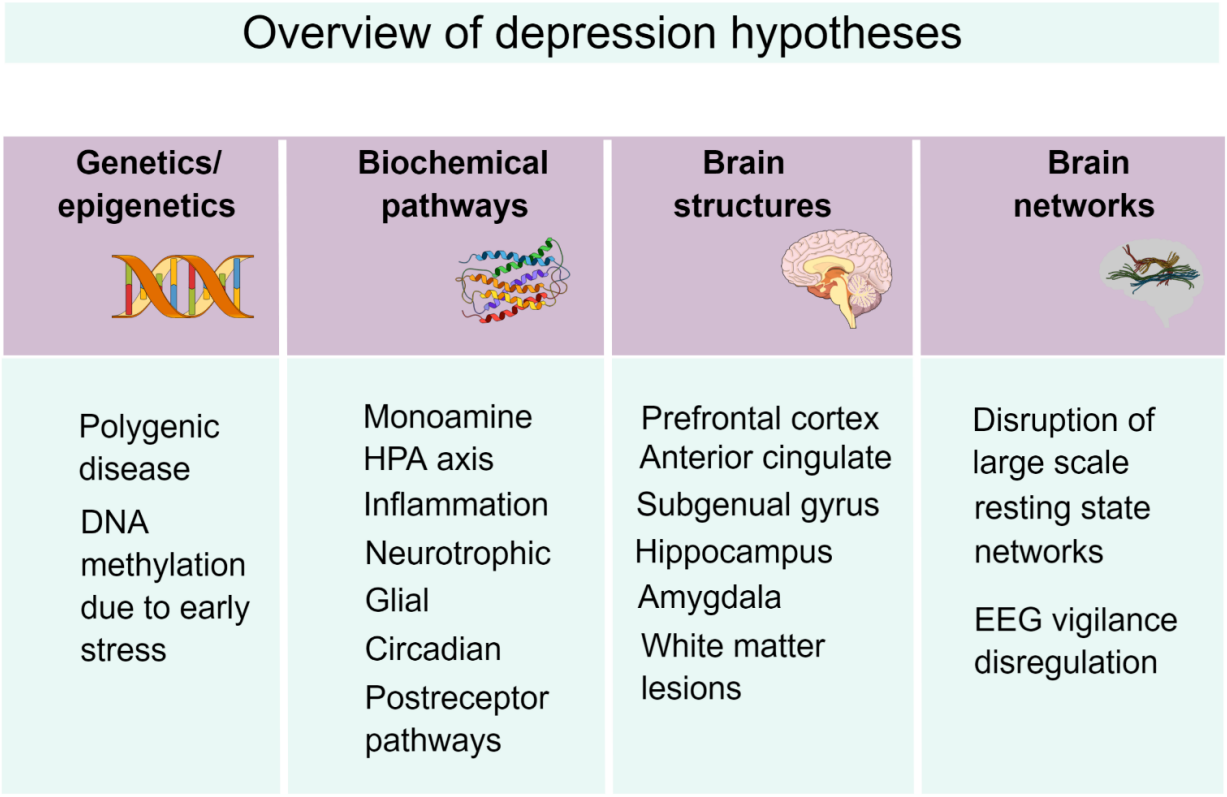
1.2.1 Overview of depression hypotheses

The spectrum of depressive disorders is broad and pathophysiological alterations of depression are even broader. The heritability of depression is estimated at 36-37%[16]. No single gene responsible for development of depression was found[17]. Rather depression is viewed as a polygenic disorder, sharing some genes with other psychiatric disorders[18] and having an "own" group of genes[19].

A large number of involved genes results in a number of altered biochemical pathways. Among the most studied ones are serotoninergic[20], neurotrophic[21] and glial[22] hypotheses

of depression (Figure 3). These hypotheses are grounded on animal and biomarker studies [23-25]. Human neuroimaging analyses in patients with major depression revealed reductions in gray matter density and cortical thickness (Figures 4, 5), white matter lesions[26], and alterations in structural and functional connectivity[27, 28]. The attempts to combine several levels of analysis are challenging and, therefore, still rare[29, 30]. Such combinations, however, build a promising link between imaging and biochemical theories.

Figure 3. Overview of depression hypotheses based on the level of analysis.



1.2.2 Neurotrophic hypothesis of depressive disorders

The neurotrophic hypothesis of mood disorders relies on a number of observations related to Brain Derived Neurotrophic Factor (BDNF), a protein responsible for synaptic plasticity and long-term potentiation. In animal models, increased cortisol levels due to

stress lead to reduced BDNF levels in the brain and induced depressive-like behavior in rodents[31, 32]. On the other hand, peripheral BDNF levels were consistently reduced in serum of patients with major depression[21, 33-36]. Together these findings gave rise to the neurotrophic hypothesis of depression[21]. This hypothesis postulates that in mood disorders reduced levels of neurotrophic factors due to the chronic stress result in diminished neuronal plasticity, loss of neuronal connections and apoptosis[21].

1.2.3 Glial hypothesis of depressive disorders

The glial hypothesis of depressive disorders is originally based on histopathological postmortem findings showing reductions in glial cell density or glial cell numbers in the subgenual anterior cingulate cortex, the orbitofrontal cortex, and dorsolateral prefrontal cortex[37, 38]. These reductions were mainly attributed to astrocytes and oligodendrocytes and preceded neuronal pathology in depression[39]. Furthermore, *in vivo* studies show that a marker of glial activation and injury - the calcium-binding protein S100B - is consistently elevated in serum and cerebrospinal fluid of patients with acute depression[40, 41]. At the same time a marker of neuronal injury, neuron-specific enolase, remains unchanged in patients with major depression[41].

1.2.4 Structural neuroimaging changes in major depression

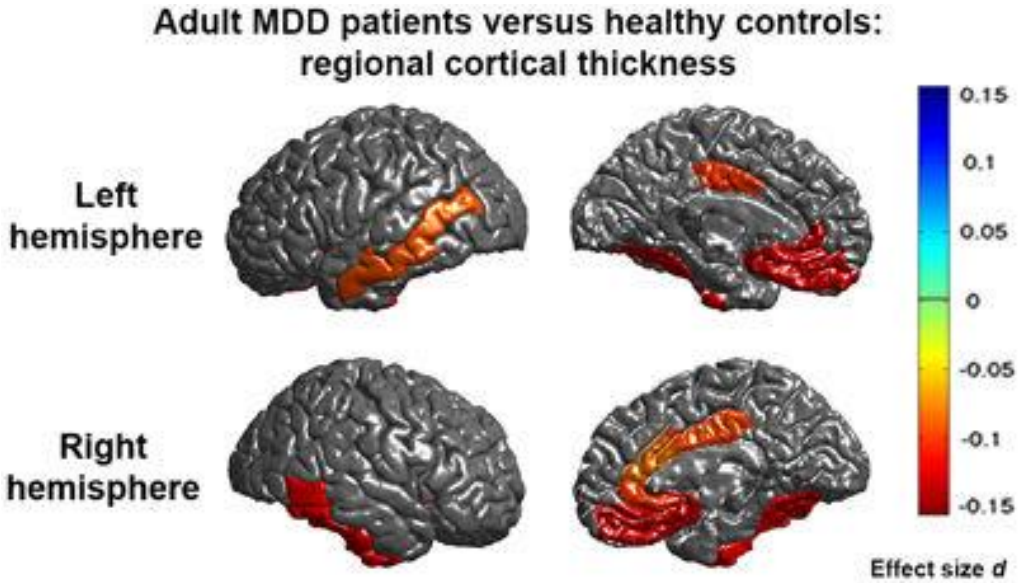
In vivo human neuroimaging evidence has linked major depressive disorder to white matter lesions[42] of, presumably, vascular genesis and to alterations in gray matter density and cortical thickness.

Gray matter density is consistently reduced in orbitofrontal and anterior cingulate cortex, hippocampus and amygdala across several meta-analytic studies[43-47]. The map of alterations in major depression as compared to healthy controls obtained by the most recent meta-analysis is presented in Figure 4[43].

Figure 4. Map showing alterations (orange – decrease, blue - increase) of gray matter density in major depression relative to control subjects, obtained by the meta-analysis of Wise et al.[43]

The cortical thickness has also been measured in a number of studies investigating major depression. The evidence was recently summarized by a large scale meta-analysis by the ENIGMA consortium[48]. Its results are depicted in Figure 5. The cortical thickness did not correlate with symptom severity[48], while hippocampal gray matter density was positively related to depression severity at the meta-regression analyses.

Figure 5. Map of cortical thinning in major depression, obtained by meta-analysis of Schmaal et al.[48]



Several neuroimaging findings related subthreshold depression to smaller medial prefrontal cortex[49] and (manually traced) amygdala[50]. One study has, surprisingly, shown

that gray matter volume in left operculum and superior temporal gyrus, and bilateral postcentral gyrus correlated positively with subclinical depressive symptoms (at FDR<0.05)[51]. These studies have diagnosed patients based on self-rating depression scales. Finally, one group selected patients with minor depression using the Structured Clinical Interview for DSM-IV (SCID). This group observed cortical thinning in the right cingulate cortex[14] and a negative association of the normalized prefrontal volume and the severity of depression[15]. This group, however, included only 18 patients and used 1.5 Tesla MRI-scans in the study. Therefore, their findings still need replication.

1.3 Rationale and hypotheses of the empirical studies

Due to high prevalence of minor depression in late life and absence of any data on pathophysiology of this disorder the rationale of the current thesis is to increase interest to the problem and understand whether there are any detectable pathophysiological alterations underlying this disorder.

1.3.1 Research questions:

In this thesis, we focused on the following research questions:

- What is the prevalence of late life minor depression in different populations?
- What are the biological correlates of minor depression?
- Is minor depression sufficiently detected by the medical personnel?
- Can serum BDNF serve as a biomarker for major depressive disorder?
- Are serum BDNF, S100B and NSE levels altered in minor depression, similarly to major depression?
- Are there any structural brain alterations in minor depression?

1.3.2 Research hypotheses

The systematic review on the prevalence rates and biological correlates of minor depression was performed in order to summarize the existing epidemiological data.

In order to develop hypotheses for the BDNF biomarker study in minor depression we performed a series of meta-analyses including studies assessing serum BDNF changes in major depression. These **meta-analyses were based on the following hypotheses:**

- We expected reduced peripheral BDNF concentrations in acute state of mood disorders as compared to healthy controls, and as compared to the euthymic state;
- Serum BDNF measurements were expected to be more consistent as compared to plasma measurements;
- We expected that serum BDNF concentrations are related to the response to the antidepressive treatment in depression;
- Central BDNF expression in rodents and peripheral BDNF concentrations in both rodents and humans were expected to increase in response to electro-convulsive treatment.

Based on the biomarker and imaging meta-analytical findings in major depression we developed further **hypotheses for our studies in minor depression:**

- We expected decreased serum BDNF, increased serum S100B levels and unaltered serum NSE levels in minor depression as compared to healthy subjects.
- In the whole brain analysis, we hypothesized a disease-specific decrease of gray matter density in bilateral anterior cingulate cortex (ACC), hippocampus, amygdalae and right dorsomedial frontal cortex.
- In the region of interest (ROI) analysis, we expected decreased gray matter density within the meta-analytically-derived mask (the largest cluster: left insula, temporal pole, inferior frontal, superior temporal gyrus) and cortical thinning in bilateral medial orbitofrontal cortex, fusiform gyrus, insula, rostral anterior and posterior cingulate

cortex, unilaterally in the left middle temporal, right inferior temporal gyrus and right posterior part of ACC.

2. EMPIRICAL STUDIES

2.1 The prevalence of minor depression in the late life

2.2 The Meta-analysis of BDNF changes in mood disorders

2.3 The Meta-analysis of BDNF changes following ECT in depression

2.4 Serum markers in minor depression

2.5 Structural brain imaging in minor depression

Journal of Affective Disorders 152-154 (2014) 28–38

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

Prevalence of minor depression in elderly persons with and without mild cognitive impairment: A systematic review

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ARTICLE INFO

Article history:
Received 24 May 2013
Received in revised form
8 August 2013
Accepted 17 September 2013
Available online 25 September 2013

Keywords:
Minor depression
Mild cognitive impairment
MCI
Elderly
Late life

ABSTRACT

Background: Minor depression (MinD) and mild cognitive impairment (MCI) are common disorders in late life that often coexist. The aim of the present review is to demonstrate prevalence rates of minor depression in older patients with and without MCI.
Methods: Electronic database searches were performed through Medline, ISI Web of Knowledge, Psycinfo, and Cochrane library. Two independent reviewers extracted the original studies based on inclusion criteria: representative study population aged 55 and older, diagnostics of MinD according to DSM. Data on prevalence rates, risk factors, comorbidity and health care usage were analyzed.
Results: Point prevalence for MinD is higher in medical settings (median 14.4%) than in the community-based settings (median 10.4%) and primary care patients (median 7.7%). Although minor depression is rarely investigated in elderly persons with MCI, nearly 20% of patients with MCI seem to suffer from MinD. No data was found on the prevalence of MCI in patients with MinD. Risk factors associated with MinD include female gender, history of cerebrovascular diseases, generalized anxiety disorder, loneliness, and long-term institutional care.
Limitations: Methodological differences of included studies resulted in a broad range of prevalence rates. No data is shown regarding the prevalence of MCI in MinD group due to insufficient evidence.
Conclusions: Our review indicates that MinD is frequent in elderly population. MCI among those subjects has not been sufficiently investigated. Future studies based on clinical structured interviews should be performed in longitudinal design in order to differentiate late-life depression from progressive MCI or early manifestation of Alzheimer's disease.

Contents

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http://dx.doi.org/10.1016/j.jad.2013.09.016

1. Introduction

Depression and dementia are among the most common psychiatric disorders in late life (Olivera et al., 2008; Rabins et al., 1996; Wancata et al., 2000). Due to the growth of the elderly population these conditions have recently become a focus of research. Most studies on depressive disorders in the elderly refer to major depressive disorder (MDD) although minor depression (MinD) was found to be the most prevalent mental disorder in primary care settings (Helmchen, 2001).

MinD includes clinically relevant symptoms of MDD without meeting the full criteria for this disorder. Approximately 1 in 10 patients seen in primary care has symptoms of MinD (Banazak, 2000) and prevalence seems to be highest in late life (Beekman et al., 1995; Newman, 1989). The prevalence has been estimated to be between 10% and 20% (Tannock and Katona, 1995). Nevertheless, older adults are significantly less likely than younger adults to receive specialized mental health care (Unutzer, 2002). Indeed, recognition of MinD in older adults is difficult due to their increased tendency to demonstrate alexithymia and somatisation which may mask depression (Tannock and Katona, 1995; Watts et al., 2002). Insufficient clinical diagnostics are also observed in most available studies—only a few of them used structural clinical interviews and applied a classification according to Diagnostic and statistical manual of mental disorders (DSM). Patients often fail to meet criteria for MinD because symptoms are not present for most of the day, nearly every day. That makes clinical interviews based on DSM-criteria essential. Clinical diagnostics based solely on self-administered questionnaires is not sufficient. All these factors contribute to the underestimation of the disorder by medical staff.

Evidence suggests that patients fulfilling criteria for MinD have an increased risk of developing MDD (Lyness et al., 2006) or other adverse outcomes such as substance abuse or dependence (Lewinsohn et al., 2000). About 25% of patients suffering from MinD will develop MDD within 2 years (Lyness et al., 1999). Eaton et al. (1995) regarded MinD as part of the prodromal phase of MDD and about 13% of MinD patients have attempted suicide at least once (Angst, 1995). These results show that MinD cannot be regarded as a “minor” condition at all.

The concept of mild cognitive impairment (MCI) is developed to describe subjective and neuropsychologically confirmed cognitive deficit in persons whose daily living is not altered. It is usually subdivided into amnestic (aMCI) and non-amnestic MCI subtypes (non-aMCI), also with respect to single or multi-domain deficits (Winblad, 2004). However, depending on the neuropsychological protocol used, aMCI is frequently discovered as multi-domain MCI when episodic memory tests are used. To this end, the aging-associated cognitive decline (AACD) (Levy, 1994) concept was first introduced to cover a broad range of cognitive deficits and nowadays is replaced by Petersen's multi-domain MCI concept (Schönknecht et al., 2005).

MCI is the transitional phase between unimpaired cognition and dementia and 10–15% of patients progress to dementia per year compared to 1–2% of healthy controls (Petersen et al., 1999; Petersen et al., 2001). Population-based studies document that with respect to different age ranges, 10–25% of the elderly suffer from MCI (Schönknecht et al., 2005). In general hospitals the prevalence may increase to about 36% (Bickel et al., 2006). Compared to the prevalence of dementia it is twice as high.

The common co-existence of depression and MCI in older persons is likely to increase the rate of adverse outcomes for physical health, functional status, and mortality and represents the most compelling reason for decreased quality of life (Bickel et al., 2006). In particular, in older adults co-existence is associated with an increased risk of dementia as 20–60% develop Alzheimer's disease (AD) within a few years after the onset of depression (Berger et al., 1999; Houde et al., 2008; Li et al., 2001; Modrego and Ferrandez, 2004; Paterniti et al., 2002; Teng et al., 2007). In their Italian Longitudinal Study on Aging (ILSA) Solfrizzi et al. (2007) found a 63.3% prevalence rate of depressive symptoms among people with MCI. Depressive symptoms included mild (49.3%) and severe (14.0%) forms. Houde et al. (2008) found a 52% prevalence of depression among the 60 MCI patients in a clinical sample. Sixty percent of these MCI patients progressed to AD within a mean period of 4.3 years resulting in an annual conversion rate of 14%. In another clinical sample Feldman et al. (2004) reported a 50% prevalence rate of depression in MCI. Paterniti et al. (2002) found that high baseline levels of depressive symptoms predicted cognitive decline because MMSE score was more likely to fall below 26 and to remain below the MMSE score of those without depressive symptoms. In a study by Starkstein et al. (2005), prevalence of MinD increased from 21% in the moderate stage of AD to 45% in the severe stage of AD.

A deep systematic review was published regarding the prevalence and risk factors of subthreshold by Meeks et al. (2011). However, the authors noted that studies assessing more than one type of subthreshold depression tend to show higher than median prevalence rates (Meeks et al., 2011). To date, studies on the co-existence of MinD and MCI are still rare. Depressive patients have often been excluded from MCI studies and vice versa. In a population-based epidemiological study by Lyketsos et al. (2002) 20% of the 320 MCI patients exhibited depression. A number of studies show that about half of the patients with MCI report depressive symptoms (Feldman et al., 2004; Forsell et al., 2003;

Houde et al., 2008; Solfrizzi et al., 2007). In contrast, in studies on MDD in MCI, prevalence rates were consistently low and in the range of 3.4–11.2% (Forsell et al., 2003; Levy, 1994). Two types of MinD were hypothesized by Park et al. (2010); MinD as a subsyndromal stage for recurrent MDD or an independent subsyndromal disorder in late life. Li et al. (2001) suggest that early depressive symptoms in patients with MCI may constitute a preclinical sign of dementia and predict the conversion to AD or vascular dementia (VaD). The main aim of this review is to summarize the findings concerning MinD in older patients with and without MCI and to look for the prevalence rates, factors, and comorbid disorders associated with them.

2. Methods

2.1. Systematic literature search

Two independent reviewers (NS, MP) performed the literature search using the electronic databases Medline, ISI Web of Knowledge, Psycinfo, and Cochrane library (last date 15/07/2013) with the following keywords: minor depression, minor depressive disorder, subsyndromal depression, subthreshold depression, cognitive impairment, mild cognitive impairment, cognitive impairment no dementia, MCI, and CIND in combination with elderly, older adults, geriatric, and late life. Searches were categorized by topic, title, title and abstract, keyword, or text word where applicable. We identified 2028 potentially relevant articles. All of them were independently screened by two reviewers (NS, MP) using title, abstract and—when available—full text to meet the inclusion criteria (see Fig. 1). References from the original articles were screened to reveal omitted papers. Whenever there was any doubt regarding inclusion of the paper a third reviewer (PS) was consulted. Studies reporting prevalence of other than MinD types of subsyndromal depression as well as those reporting combined rates were not included in the review. If two or more studies were performed on the same cohort of patients one of them was chosen. One exception was accepted: The studies by Mechakra-Tahiri et al. (2009) and Preville et al. (2008) used the same sample but covered different aspects in the data analysis. Mechakra-Tahiri studied the point prevalence, whereas Preville concentrated on the 12-month prevalence and comorbidity. In total, 23 original research publications were retrieved and included in the review.

2.2. Methodological quality assessment

The quality of included studies was assessed by the adapted criteria for methodological quality assessment published elsewhere (Luppa et al., 2012). Each criterion was rated from 0 to 2 points (see Table 1). Studies scoring 75% or more of the maximum score ($\geq$ 14 points) were rated as 'high quality', studies scoring between 50% and 75% (9–13 points) were considered 'moderate quality', and studies with lower than 50% (9 points) were considered 'low quality'.

2.3. Definition of minor depression (MinD)

According to DSM-IV research criteria (APA, 2000), MinD requires less than five, but at least two depressive symptoms during a two-week period with either depressed mood or loss of interest or pleasure being one of them. A history of MDD excludes the person from this category. Other studies use terms such as subsyndromal (Judd et al., 1994) or subthreshold (Heun et al., 2000) depression. Therefore, at least two depressive symptoms are decisive. It is necessary to distinguish other forms of depression (e.g., recurrent brief depression, atypical depression, seasonal

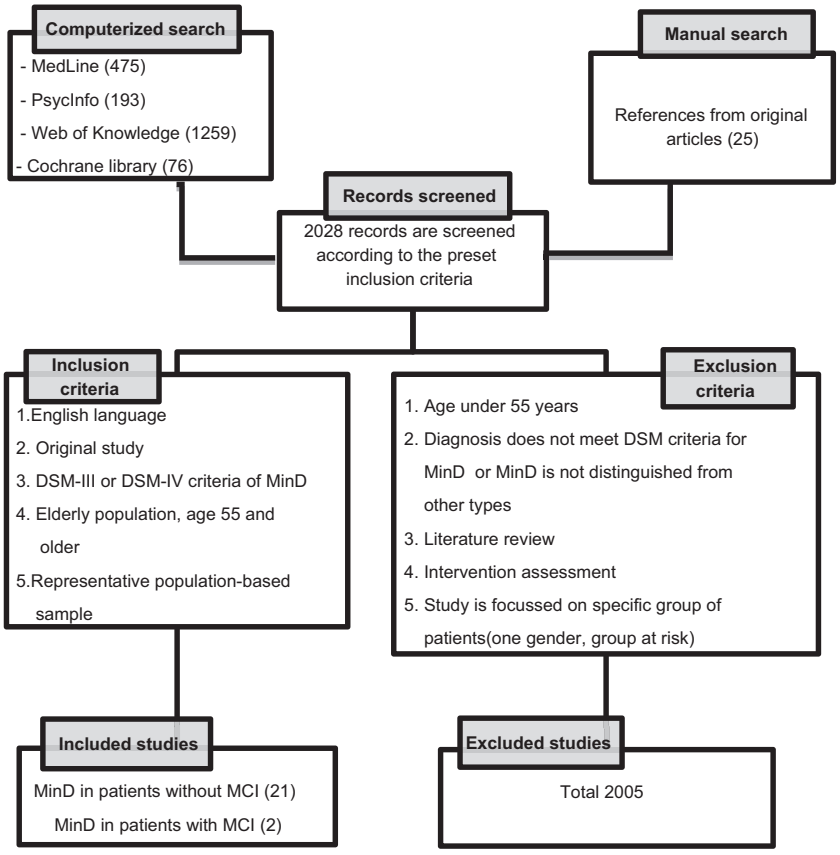

Fig. 1. Selection of the studies.

Table 1
Criteria for methodological quality assessment of epidemiologic studies.

Criteria	Not met	Partially met	Fully met
Socio-demographic and medical data is described (e.g., age, race, educational status, etc.)	0	1	2
Age groups are differentiated *	0	1	2
Inclusion and/or exclusion criteria are formulated	0	1	2
Detailed description of methods and instruments is given	0	1	2
Participation and response rates are described **	0	1	2
Information about cognitive status is given	0	1	2
Mean, SD, CI are reported for the most important outcome measures	0	1	2
Diagnostic procedure is described: a) **For categorical diagnosis: diagnostic algorithm, diagnostician.** b) **For dimensional diagnosis: valid cut-off score.**	0	1	2
The missing values are described	0	1	2
Total	0–18 points		

Annotations:

* Age groups: only one age group (0 points), two or more age groups (1 point), three and more groups described (2 points).
** Participation and response rates: below 50% or not described (0 points); 50–75% (1 point); more than 75% (2 points).

affective disorder, premenstrual dysphoric disorder, etc.), which do not meet criteria for MDD. In DSM-IV (APA, 2000) MinD was included in the depressive disorder NOS (Not Otherwise Specified) category where any depressive disorder not meeting criteria for a specific disorder can be found. The recently published DSM-V (APA, 2013) assigned MinD a new name 'Depressive episode with insufficient symptoms' under the category 311 'Other Specified Depressive Disorder'. This diagnosis requires the following criteria: depressed affect and at least one of the other eight symptoms of a major depressive episode associated with distress or dysfunction that persists for at least 2 weeks in an individual who has never met criteria for any other mood disorder, does not currently meet active or residual criteria for any psychotic disorder, and does not meet criteria for 'mixed subsyndromal anxiety–depressive disorder'.

2.4. Definition of mild cognitive impairment (MCI)

Predementia syndromes arising in elderly persons have received a multitude of descriptions: mild cognitive impairment (Petersen et al., 1999), late-life forgetfulness, age-consistent memory impairment (Blackford and Larue, 1989), cognitive impairment —no dementia (Graham et al., 1997), and age-associated memory impairment (Crook et al., 1986). Prevalence of the different predementia syndromes varies as a result of different diagnostic criteria (Schönknecht et al., 2005; Schroder et al., 1998; Toro et al., 2009). MCI began to gain popularity as it is thought to be a prodromal phase of Alzheimer's Disease (AD) (Petersen, 2000).

Criteria for MCI suggested by the American Academy of Neurology in 2001 correspond to the aMCI: (1) an individual's report of his or her own memory problems, preferably confirmed by another person, (2) measurable, greater-than-normal memory impairment detected with standard memory assessment tests (1.5 SD below age norms), (3) normal general thinking and reasoning skills, (4) ability to perform normal daily activities. Criteria used in different studies mostly include the above-mentioned features (Petersen, 2004; Petersen et al., 2001).

Most recently, the First Key Symposium held in Stockholm in 2003 adopted the following recommendations for MCI general diagnostic criteria: (i) a person is not normal but not demented, (ii) cognitive decline reported and impairment of objective cognitive tasks—not only amnestic—or there is evidence of cognitive decline with time, (iii) preserved activities of daily living (Winblad, 2004). MCI is divided into four subtypes and is attended by an increased risk of developing dementia:

(1) Amnestic MCI-single cognitive domain (memory impairment only).
(2) Amnestic MCI-multiple domain (memory impairment plus nonmemory deficits, such as in language, executive function, or visuospatial function)—corresponding to AACD.
(3) Non-amnestic MCI-single domain (nonmemory deficit).
(4) Non-amnestic MCI-multiple domain (impairment in at least two cognitive domains other than memory).

3. Results

3.1. Characteristics of the sample

The literature search described above revealed 2028 original articles. Of these, 2005 papers were disregarded because they met the exclusion criteria (see Fig. 1). For the subsequent analysis 23 original research articles were chosen (Tables 2 and 3). Among them, 13 studies were designed to be community-based, three were medical inpatient studies, three studies assessed patients in nursing homes, three assessed primary care patients, and another assessed home care patients. Only two studies were designed to assess depressive symptoms including MinD in patients with MCI. In total 19,876 patients of both sexes were included, aged 55 and older. They represented 10 countries (Australia, Austria, Brazil, Canada, Germany, Finland, Netherlands, South Korea, Spain, and USA). DSM-III or DSM-IV criteria were used for assessment of MinD, MDD, and subthreshold depressive disorder. Cognitive status was diagnosed using neuropsychological tools such as MMSE (Jongenelis et al., 2004), Clinical Dementia Rating (CDR); (Gabryelewicz et al., 2004; Teresi et al., 2001), global deterioration scale (Gabryelewicz et al., 2004) and others (Tables 2 and 3). MCI diagnosis was made according to Mayo Clinic diagnostic criteria.

3.2. Methodological quality

According to the methodological quality criteria assessment described above, the 23 previously selected original research articles were given a total score ranging from 9 to 18. Among them, eight studies were rated as "high quality" (scores 14–18), the rest of the studies were rated as "moderate" methodological quality, two of which got a borderline score (9 points).

3.3. Prevalence of minor depression in the elderly

The point prevalence of late life MinD ranged from 0 to 18.6% depending on the study design. The prevalence was higher in the

Table 2
Studies on prevalence of MinD in older adults without MCI.

Reference	Study design, subjects	Diagnostic criteria and tools for MinD	Cognitive status assessment	Reported prevalence of MinD	Depressive Symptoms; risk factors, comments	Methodological Quality score
Brown et al. (2003)	Home care patients, New York, US $N=220$; Age ≥ 65	DSM-IV criteria SCID, CCI	MMSE	Point prevalence: 8.19%	Only 48.5% of the patients are identified by nurses. 20.6% of depressed patients were cognitively impaired.	13
Grabovich et al. (2010)	Primary care patients, New York, US $N=745$; Age ≥ 65	DSM-IV criteria SCID	MMSE, Trails A,B, Mattis dementia rating scale	Point prevalence: 6.9%	MinD and MDD were associated with poorer outcome in Trails B and ΔTrails time (but not in other cognitive tasks).	12
Han et al. (2008)	Medical inpatients, Montreal, Canada $N=281$; Age ≥ 65	DSM-IV criteria DIS, HAMD	MMSE	18.15% showed MinD at baseline, 17.5%—at 1 year follow-up	Patients with MinD at baseline showed 1 point lower performance in MMSE at 1 year follow-up.	11
Heun et al. (2000)	Community-based, Mainz, Germany $N=287$; Age ≥ 60	DSM-III-R criteria CIDI	SIDAM (includes MMSE, Hachinski Scale)	Point prevalence: 0%; Lifetime prevalence: 23%, (MD: 4.9%)	MinD is more frequent than MDD. MinD is not influenced by age or gender.	13
Jongenelis et al. (2004)	14 nursing homes AGED-Study, Netherlands $N=333$; Age ≥ 55 MMSE ≥ 15	DSM-IV criteria SCAN GDS	MMSE	14.1% (sub-clinical depression: 24.0%); Men: 18.3%; Women: 12.2%; prevalence 65–79 y. 17.7%; 80–99 y. 11.0%	63% of the population had mild dysfunction MMSE (15–23); prevalence highest for men 65–79 y. (26.7%); MinD was associated with presence of loneliness (OR=4.52) and age below 80 (OR=1.95) 22.1% of patients with CI had MinD.	14
Licht-Strunk et al. (2005)	GP attendees, 58 GPs in Netherlands, rural and urban $N=5686$; Age ≥ 55	DSM-IV criteria GDS-15 and diagnostic interview PRIME-MD	Not included	Point prevalence: 10.2% 65–74 y. rural 7.8%; urban 12.1%; >75 y. rural 13.5%; urban 15.5%	Prevalence increases with age. Prevalence is higher in urban areas.	17
Lyness et al. (1999)	Primary care patients, US $N=224$; Age ≥ 60	DSM-III-R criteria SCID,HAMD	MMSE	Point prevalence: 5.2%	46.2% of MinD patients were prescribed antidepressants.	9
Kramer et al. 2009	Nursing home's residents, Munich, Germany $N=97$; Age ≥ 65	DSM-IV criteria SCID	Not specified	Point prevalence: 14.4%	42.9% of the subjects with acute MDD were diagnosed as depressive by their attending physicians, and only half of them received an antidepressant; 17.5% received antidepressants without diagnosis of depression in their physician and nursing records.	11
McCusker et al. (2005)	Medical inpatients, from 2 hospitals in Canada $N=323$; Age ≥ 65	DSM-IV criteria DIS, CCI, ADL	MMSE	Point prevalence: 7.9% and 9.4%	History of depression, cognitive impairment, less tangible and emotional support, fewer friends seen are associated with MinD. 29% reported current treatment (almost all with antidepressants).	18
Mechakra-Tahiri et al. (2009)	Community-based, ESA longitudinal study of mental health Canada $N=2670$; Age ≥ 65	ESA computer diagnostic questionnaire based on DSM-IV criteria Social relationship questionnaire	MMSE <22—exclusion criteria	Point prevalence: 9.5%	Higher for females, higher in rural and urban areas, than in metropolitan areas.	14
Mossaheb et al. (2009)	Community-based, VITA study, Vienna Austria $N=331$; Age ≥ 75	DSM-IV criteria HAMD, Short GDS, self-rating scale for evaluation of depression in the old age	FOME, TMT	Point prevalence: 10.7%; 12.7% at 1 year follow-up; 12.0% among patients with MCI	Troubles with relatives—a significant variable for the onset of MinD ($p=0.02$) FOME showed significant influence on the newly occurred depression. None of the other factors were significant.	9
Newman et al. (1998)	Community-based, Edmonton, Canada (in conjunction with Canadian Study of Health and Aging CSHA) $N=1119$; Age ≥ 65	GMS-A3 AGECAT diagnostic system vs. DSM-IV	Included in GMS-A3 questionnaire	Point prevalence: 3.6%	Higher prevalence rates for GMS-AGECAT than DSM-IV based assessment.	13
Norton et al. (2006)	Community-based, Cache Country, Utah, USA $N=2877$; Age ≥ 65	DSM-IV criteria DIS; 'medicine chest inventory' for antidepressant use	Dementia–exclusion criteria	Point prevalence of MinD at baseline was 14.8%	Individuals with prior MinD episodes had significantly higher incidence rates of MD (23 per 1000 risk-years) than those with no prior episodes. Incidence of any depression increased when to the diagnostics by DIS the medication was added.	12

Ostbye et al. (2005)	Community-based +medical inpatients; Canadian Study of Health and Aging CSHA-Study $N=2341$ Age ≥ 65	Clinical examination using DSM-IIIR	Modified MMSE	4% (1.4% male, 6.0% female); 5.0% medical inpatients; 4.0% community; 4.7% in dementia; 4.0% without dementia	Prevalence was higher for females; increased with age for males; prevalence for women highest in youngest age group 65–74 years; little difference in prevalence rates among hospitalized subjects and those in the community (5.0% and 4.0%, respectively) slight difference between subjects with and without dementia (4.7% and 4.0%).	14
Paivarinta et al. (1999)	Community-based (87%)+ medical setting (13%), Vantaa, Finland $N=339$; Age ≥ 85	DSM-III-R criteria, DSI, Clinical interview	MMSE, dementia–exclusion criteria	Point prevalence: 18.6% (18.9% men, 18.5% women) Mean sum of MMSE score was 22.3 ± 5 for all MinD persons	Oldest-old; no differences between genders, MinD associated with long-term institutional care, frequent feelings of loneliness, poor physical health, poor ability to walk, poor functional abilities.	14
Park et al. (2010)	KLoSHA study Community-based, Korea $N=714$ Age ≥ 55	DSM-IV research criteria MINI GDS-K CES-D HAMD	MMSE FAB CERAD-K-C	Point Prevalence 5.52%	Depression as a single episode 57.6%, Late-onset (78.0% of MinD) depression was more prevalent than early onset. Prior MDD episodes, female gender, history of stroke or TIA are associated with MinD. MMSE scores were lower in MinD group than in control group, but did not reach statistical significance.	14
Preville et al. (2008)	Community-based; ESA-Study, Quebec, Canada $N=2798$; Age ≥ 65	ESA-Q, interview developed by research team, based on DSM-IV criteria;	MMSE <22–exclusion criteria	12-month-prevalence: 5.7% (men 4.0%; woman 6.9%)	MinD is the most prevalent mental disorder in the studied population. Prevalence of psychiatric disorders the most frequent comorbidity is observed with specific phobia (4.3%), generalized anxiety disorder (4.3%), obsessive-compulsive disorder (3.7%) and mania (1.3%) Used self-reported information, clinical validity of diagnoses is limited.	13
Steffens et al. (2009)	Community-based; ADAMS-Study (data from Health and Retirement Study),US $N=851$; Age ≥ 71	DSM-IV criteria CIDI-SF,	NPI	12-month-prevalence: 1.35% (CIDI)	Depression prevalence progressively increased with worsening cognitive impairment; 8% of the sample received medication for depression those cognitively intact reported less treatment than individuals with cognitive impairment.	13
Teresi et al. (2001)	Nursing homes, New York, US $N=319$; Age mean=84.5	DSM-III-R criteria Cornell Scale for Depression in Dementia, FTQ, HAMD, SCID , DIW	MMSE	Point prevalence: 16.8%	Patients with cognitive impairment included 37–45% of cases diagnosed by psychiatrists are recognized as depressed by nursing home staff.	12
Vilalta-Franch et al. (2012)	Community-based, Spain $N=451$; Age ≥ 70	DSM-IV criteria CAMDEX	Spanish adaptation of MMSE	Point prevalence: 16.8%	MinD is not associated with higher mortality risk.	14
Xavier et al. (2002)	Community-based, Veranopolis, Brazil $N=77$ Age ≥ 80	DSM-IV criteria GDS, SCID	MMSE, memory evaluation: MAC-Q, SC, FCSRT, Word-List from CERAD, CDR	Point prevalence: 12.1%	Small sample, all MinD subjects are female; lower life satisfaction, worse life quality; presence of generalized anxiety disorder associated with MinD (37%—6 month prevalence).	13

Abbreviations:
Depression diagnostic tools:
AGEGAT—Automated Geriatric Examination for Computer Assisted Taxonomy; CAMDEX—Cambridge Examination for mental disorders in elderly; CES-D—Centre of Epidemiologic studies depression scale; CIDI-SF—Composite International Diagnostic Interview—Short form; DIS—Diagnostic Interview Schedule; DIW—Diagnostic Impression Worksheet; DSI—Depression Status Inventory; FTQ—Feeling Tone Questionnaire; GDS—Geriatric Depression Scale; GMS—Geriatric Mental State; HAMD—Hamilton Depression Rating Scale; MADRS—Montgomery–Asberg Depression Rating Scale; MINI—Mini International Neuropsychiatric Interview; NPI—Neuropsychiatric Inventory; PRIME-MD—Primary Care Evaluation of Mental Disorders; SCAN—Schedule of clinical Assessment in Neuropsychiatry; SCID—Structured Clinical Interview.
Dementia diagnostic tools:
CERAD-K-C—Clinical assessment battery (Korean Version); CDR—Clinical Dementia Rating; FAB—Frontal Assessment Battery; FCSRT—Free and Cued Selective Reminding test; FOME—Fuld Object memory evaluation; GDS—Global Deterioration Scale; MAC-Q—Memory Complaint Questionnaire; MMSE—Mini Mental State Examination; SIDAM—Structured Interview for the diagnosis of Dementias; TMT—Trail Making Test part B.
Others:
ADL—Assessment Instrument for measuring instrumental Activities of Daily Living; ARIC—Atherosclerosis Risk in Communities; CCI—Charlson Comorbidity Index; GAF—Global Assessment of Functioning; HRQOL—Health related Quality of Life; KPSS—Karnofsky Performance Status Scale.

Table 3
Studies of MinD in patients with MCI.

Reference	Study design, subjects	Diagnostic criteria and tools for MinD	Cognitive impairment	Reported prevalence of minor depression	Depressive symptoms; risk factors, comments	Quality score
Gabryelewicz et al. (2004)	Longitudinal, hospital-based (3 years, 12-month intervals) $N=102$; Age Mean = 70;	DSM-IV criteria, MADRS, Clinical diagnostics by psychiatrist according to DSM-IV	Mayo Clinic Criteria for MCI; CDR; GDS	Point prevalence: 26.5%	MinD common in MCI 70.6% of participants were women.	11
Kumar et al. (2006)	Community-based PATH Project Canberra, Australia $N=549$; Age 60–64	DSM-IV criteria DIS Goldberg Depression scale; depression section of PRIME-MD patient Health Questionnaire	Mayo Clinic Criteria for MCI	17.2% of patients with MCI had MinD	MinD is found to be associated with MCI, as well as fewer years in education and such symptoms as feeling "slowed up" and "little interest or pleasure".	12

Abbreviations: see Table 2.

medical settings (median 14.4%) than in the community-based settings (median 10.4%) and primary care patients (median 7.7). Paivarinta et al. (1999) report association of MinD with long-term institutional care. In a community-based study in Canada (Preville et al., 2008) MinD was found to be the most prevalent mental disorder in old age. Table 2 summarizes the findings for the prevalence of MinD in the elderly without MCI.

3.4. Co-occurrence of MinD and MCI

Though depressive symptoms are a common observation in patients with MCI and preclinical dementia (Berger et al., 1999; Li et al., 2001; McCusker et al., 2005; Paterniti et al., 2002), MinD in elderly persons with MCI is rarely investigated. We found only two studies that focused on MinD in patients with MCI and made a clinical diagnosis according to DSM. Both studies defined MCI according to Mayo Clinic group diagnostic criteria published by Petersen et al. (1999). Gabryelewicz et al. (2004) found a MinD prevalence of 26.5% in MCI patients. Kumar et al. (2006) revealed that 17.2% of patients with MCI suffered from MinD. In a study by Jongenelis et al. (2004), 22% of patients with MinD showed cognitive impairment. Xavier et al. (2002) observed worse performance in the memory task measured by the CDR scale. However in this study, patients with MinD reported worse self-evaluation of the memory function, scoring equally to the healthy controls. Steffens et al. (2009) corroborate the hypothesis that the prevalence of depression progressively increases with worsening cognitive impairment. Paivarinta et al. (1999) showed slight decreases in MMSE scores in patients with MinD compared to control groups (22.3 ± 5 and 23.9 ± 4, respectively, $p=0.046$). McCusker (McCusker et al., 2005) demonstrated an association between cognitive impairment and MinD. On the other hand, Jongenelis et al. (2004) found no association between MinD and mild or moderate cognitive impairment.

3.5. Risk factors for minor depression in the elderly

3.5.1. Gender

The influence of gender data on the development of MinD is heterogeneous. Licht-Strunk et al. (2005), Ostbye et al. (2005), Xavier et al. (2002), Mechakra-Tahiri et al. (2009), as well as Park et al. (2010) revealed higher prevalence rates of MinD for women in late life. In studies by Heun et al. (2000), McCusker et al. (2005) and Gabryelewicz et al. (2004) no significant gender differences in the prevalence of MinD were found.

3.5.2. Age

As with gender, evidence for an impact of age on the development of MinD in late life is sparse. In most of the studies (Gabryelewicz et al., 2004; Heun et al., 2000; Jongenelis et al., 2004; McCusker et al., 2005) prevalence of MinD is not related to age. Nevertheless, Licht-Strunk et al. (2005) reported a continuous increase of MinD prevalence with growing age (in rural areas: 55–64 years 7.5%; 65–74 years 7.8%; >75 years 13.5%, in urban areas: 13.1%, 12.1%, 15.5%). In this study patients over the age of 55 years were included, whereas subjects in the other studies were mostly 65 years or older. A continuous rise with age was also found by Ostbye et al. (2005), but only for men. Jongenelis et al. (2004) found that the prevalence of MinD was higher in the group aged below 80 years (OR = 1.95, CI = 1.02–3.70). In the study by Mechakra-Tahiri et al. (2009), MinD prevalence was higher in the younger age group (65–69 years)—18.4% compared to 11.4—12.9% in older age groups—(70–75 years, 75–79 years, 80–84 years, 85+ years). One might conclude that impact of age depends

rather on the study design and cannot be considered an independent risk factor over the age of 65.

3.5.3. Other risk factors

A number of other risk factors were revealed in the reviewed studies. Loneliness and lack of tangible support were reported by Jongenelis (Jongenelis et al., 2004) and McCusker (McCusker et al., 2005) to accompany MinD. To this group of factors one can add long-term institutionalization reported by Ostbye et al. (2005). Mechakra-Tahiri et al. (2009) showed that the lack of conflict in intimate relationships was associated with lower prevalence of depression.

Licht-Strunk et al. (2005) included territorial factors in their research and revealed higher prevalence of MinD in urban areas. In contrast, during the ESA study in Canada (Mechakra-Tahiri et al., 2009), three types of locations were included and the finding was that the prevalence of depression was higher in the rural (17.0%) and urban areas (15.1%) than in the metropolitan areas (10.3%).

Paivarinta et al. (1999) found a group of physical health factors to be of significant influence: poor physical health, history of myocardial infarction for men, poor ability to walk, and smoking in women. Park et al. (2010) found an association between a history of stroke or transitory ischemic attack (TIA) with MinD. In contrast, Jongenelis et al. (2004) did not find any association between health-related factors and MinD, and Vilalta-Franch et al. did not reveal an association with higher mortality risk (Vilalta-Franch et al., 2012).

3.6. Comorbidity

In the reviewed studies, Xavier et al. (2002) and Preville et al. (2008) reported comorbidity with generalized anxiety disorder. Heun et al. (2000) showed a trend towards comorbidity with subthreshold anxiety disorder diagnosed during lifetime. Lyness et al. (2006) stated that MinD is a risk factor for MDD in itself, as patients with minor or subsyndromal depression had a 5.5-fold risk of developing MDD in the 12 subsequent months. Moreover, according to McCusker et al. (2005) and Park et al. (2010) MinD and MDD may be similar disorders but different in severity. Other possible comorbid disorders, one should mention, are specific phobias, obsessive compulsive disorder, and mania (Preville et al., 2008).

3.7. Usage of health care services and medication

Health care services usage for the patient's psychological distress varies between 8% and 39% in the studied populations (McCusker et al., 2005; Preville et al., 2008; Steffens et al., 2009). Though, MinD is associated with institutionalization of patients (Ostbye et al., 2005), Preville et al. (2008) revealed that 85% of health care attendees consulted a general practitioner for their probable active cases of psychological distress syndromes, 4.8% visited another general practitioner, only 11.5% visited a specialist, 9.8% first visited a psychologist, and 4.4% visited a social worker. McCusker et al. (2005) showed that almost all of those receiving treatment take antidepressants. Interestingly, Steffens et al. (2009) states that patients with cognitive impairment are more likely to receive antidepressive treatment than those without.

3.8. Recognition of minor depression by nonpsychiatric staff

Though MinD is associated with institutionalization of patients (Ostbye et al., 2005), only 37–45% of patients diagnosed by psychiatrists are recognized as depressed by nursing home staff (Teresi et al., 2001). For the home care nurses the sensitivity of recognition was 48.5% and the accuracy of recognition was higher in the nurses with geriatric experience (Brown et al., 2003). Among the treating physicians in two Montreal hospitals, the sensitivity of recognition was 31.1%. Herein, patients with a history of depression, low comorbidity (Charlson Comorbidity Index <1), long duration of hospitalization, and higher severity were more likely to be recognized as depressed (Cepoiu et al., 2007).

4. Discussion

The aim of the current review was to summarize the prevalence rates and risk factors of MinD in elderly patients with or without MCI. We have shown a great variation in the reported prevalence rates ranging from 0 up to 18.6% of the elderly population. Prevalence rates for MinD in the elderly population are higher than those reported for MDD—usually below 10%—(Boyle et al., 2010; Cole and Dendukuri, 2003; Heun et al., 2000; Meeks et al., 2011) and higher in medical settings than in community settings, that is consistent with finding of Meeks for all the subthreshold types of depression (Meeks et al., 2011). Though patients with cognitive impairment are often excluded from the studies of MinD, available studies show that 17.2% and 26.5% of patients with MCI suffer from MinD (Gabryelewicz et al., 2004; Kumar et al., 2006). It was outlined that female gender tends to be associated with MinD, while data on age impact seems to be insufficient and contradicting. Risk factors for MinD in late life include (i) physical health problems (such as myocardial infarction, history of stroke, or TIA); (ii) mental health disorders (generalized anxiety disorder, specific phobia, and obsessive compulsive disorder); (iii) psychological factors (loneliness, lack of tangible support, and conflict in intimate relationships). Medical service usage analysis revealed that about a half of the patients get medical help for their condition but most of them only visit general practitioner with their complaints. The recognition rates of MinD in the primary care services are below 50%, which decreases the amount of sufficient mental help to this group of patients.

The prevalence rate may depend on the number of factors: the coverage of studied population, its age, physical health, and to a large extent the diagnostic approach. A number of those included to review studies used a single diagnostic instrument (Grabovich et al., 2010; Heun et al., 2000; Kramer et al., 2009; Ostbye et al., 2005; Vilalta-Franch et al., 2012). Among them are SCID, CIDI, AGECAT, CAMDEX, ESA computer questionnaire (see Table 2 for abbreviations) and a single clinical examination. The range of prevalence rates across these studies is quite large (0–16.8%). However, the median prevalence is only 6.5%. In the studies using two or three diagnostic instruments the median prevalence rate is 10.7% (range 5.2–18.6%). This suggests that number and quality of tools may influence the revealed prevalence rate.

Structured clinical interviews may be less efficient compared to self-administered questionnaires, but provide more accurate findings. Since generalizations are hard to make across the variety of included populations we looked at the most frequently used diagnostic instruments. Studies using structured clinical tools (DIS, SCID) and depression rating scales (HAMD, MADRS) report higher prevalence rates for MinD. For DIS median prevalence rate is 12.1% (7.9–18.15%), for SCID median is 10.1% (5.2–16.8%), for HAMD median is 11.4% (5.2–18.15%), overall median prevalence rate for studies using one of abovementioned instruments is 10.7%. (5.2–18.15%). However, two studies that used CIDI reported the lowest prevalence rates—Heun (Heun et al., 2000) has shown 0% point prevalence and Steffens (Steffens et al., 2009) 1.35% lifetime prevalence. Composite International Diagnostic Interview (CIDI) is a tool developed by the world health organization according to the

definitions and criteria of ICD-10 and DSM-IV. One of the possible reasons for such low rates could be that ICD-10 does not contain the diagnostic category for MinD and such criteria are not taken into consideration in the interview. Similar low rates were shown using only clinical interview based on DSM criteria or automated geriatric examination (3.6–5.2%). Among the screening tools the most used was GDS and median prevalence rate estimated in these studies was 10.7% (5.52–14.1%) which is similar to the median in the elderly population.

An alternative explanation could also be considered: differences in the representativeness of the samples. To a large extent representativeness is achieved by the way patients are recruited. For example, Licht-Strunk et al. (2005) (point prevalence of 10.2%) cooperated with general practitioners (GPs) who invited the elderly to participate in the study, whereas Heun et al. (2000)) (point prevalence of 0%) selected a random sample of elderly subjects with the support of the city census office and contacted all subjects at home. When contacted via GP the participants suffering from MinD succeeded in overcoming the first barrier (seeking help) and were perhaps persuaded more easily to participate than the subjects who were contacted at home. Newman et al. (1998) obtained a point prevalence of 3.6% for MinD based on a random sample of subjects from a health insurance database. Their participants and the subjects from Ostbye et al. (2005) were contacted at home and conducted their study in conjunction with the same national prevalence study Canadian Study of Health and Aging (CSHA) and achieved similar point prevalence rates for MinD (4.0%). Considering those findings, one could conclude that point prevalence rates for MinD vary between 0 and 4.0% using representative community samples (in cooperation with city census offices or other population registers). As an argument for our previous explanation we would like to point out that the last two studies did not use standard diagnostic tools, but automated questionnaires and a clinical examination. For example, Norton et al. (2006) included the subjects Medicare enrollee list and Paivarinta et al. (1999) included all persons from one town born before 1906. Using DIS they achieved prevalence rates of 14.8% and 18.6%.

Demographical factors associated with MinD allowed us to identify only the female gender. Although this factor does not always show significant association (Heun et al., 2000; Jongenelis et al., 2004; McCusker et al., 2005), an association with MinD tends to be shown in a number of studies (Licht-Strunk et al., 2005; Meeks et al., 2011; Ostbye et al., 2005; Xavier et al., 2002). Association with female gender is controversial and not well understood so far, especially in late life. However, this tendency is also observed for MDD (Cole and Dendukuri, 2003; Meeks et al., 2011). The age difference in the prevalence rates of MinD seems to be inconsistent, confirming the previous findings (Buechtemann et al., 2012).

Symptoms of MinD are present in every fourth to fifth patient with MCI (Gabryelewicz et al., 2004; Jongenelis et al., 2004; Kumar et al., 2006), but so far this field has not been well investigated. A number of studies published on depression in MCI patients, either did not specify depressive symptoms or did not separate the severeness of MCI (Boyle et al., 2010; Forsell et al., 2003; Jessen et al., 2010; Solfrizzi et al., 2007). In the included MCI studies only aMCI criteria were used. Therefore patients suffering from non-aMCI were automatically excluded from the studies. That could lower the prevalence rates and alter the comorbidity with MinD rates.

According to Teng et al. (2007), who found depression to be the most prevalent predictor for a progression to AD, future longitudinal analyses should determine if depressive symptoms are a risk factor for developing AD from MCI or represent a part of the prodromal phase of AD. Berger et al. (1999) showed that the presence of depression with motivational and not mood-associated features predicted progression to dementia within 3 years. Interestingly, Jessen et al. (2010) demonstrated that subjective memory impairment was associated with a higher risk of conversion to any type of dementia. Hence, future studies are warranted to investigate the association between subjective memory or cognitive impairment and MinD.

Finally, the recognition rates of MinD among non-psychiatric staff remain pretty low (under 50%). That comes in agreement with Kramer et al. (2009) who demonstrated recognition levels for MDD at only 49%. They also demonstrated that only half of the patients receive treatment with antidepressant. As 85% of patients with MinD consult a GP with their complaints, the recognition of depressive symptoms in primary care services remains a problem for the elderly group of patients.

4.1. *Limitations of the present review*

No comparison with other types of depression in the elderly was made because we focused only on comorbidity with MCI. Additionally, we did not show the actual prevalence rate of MCI in patients with MinD as we were not able to find literature on this problem. Though all included studies are based on DSM criteria of MinD, they use different diagnostic tools and time frames. Here we decided to accumulate as much data as possible about this disorder in late life. Therefore, the presence of different sample settings makes meta-analysis not applicable for this review. Geographical and cultural differences were not included in the current analysis, though they may have an impact on prevalence rates.

5. Conclusion

MinD is the most prevalent mental disorder in old age (Preville et al., 2008). It is found to be a risk factor for MDD and MCI in late life. A number of factors are associated with MinD such as female gender, presence of somatic (stroke, myocardial infarction) and mental health disturbances (generalized anxiety disorder, history of MDD), and psychological problems. Our review, aiming to elucidate MinD, may enable easier recognition, treatment, and prevention of possible complications of this disorder in the future.

Role of funding source

No external funding was used for preparation of this publication.

Conflict of interest

Authors declare that they have no conflicts of interest.

Acknowledgments

We would like to thank Anja Lange and the Library team of Max-Plank Institute for cognitive neuroscience for assistance in retrieving literature sources. This publication is supported by LIFE – Leipzig Research Center for Civilization Diseases, Universität Leipzig. LIFE is funded by means of the European Union, by the European Regional Development Fund (ERDF) and by means of the Free State of Saxony within the framework of the excellence initiative. MLS is further supported by the German Consortium for Frontotemporal Lobar Degeneration.

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Journal of Affective Disorders 174 (2015) 432–440

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

BDNF as a biomarker for successful treatment of mood disorders: A systematic & quantitative meta-analysis

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ARTICLE INFO

Article history:
Received 28 July 2014
Received in revised form
20 November 2014
Accepted 23 November 2014
Available online 29 November 2014

Keywords:
Brain-derived neurotrophic factor
BDNF
Major depression
Bipolar
Response
Biomarker

ABSTRACT

Background: Peripheral brain-derived neurotrophic factor (BDNF) is decreased in acute major depressive disorder (MDD) and bipolar disorder (BD) and recovered after treatment. Here we validated on a meta-analytical level whether BDNF restores differentially according to treatment response and whose measurements could be used as a biomarker, plasma or serum.
Methods: Using strict inclusion criteria, we compared BDNF in healthy controls and patients with MDD (38 studies, $n=6619$), and BD (17 studies, $n=1447$). Pre- and post-treatment BDNF levels were meta-analyzed according to treatment response in patients from 21 MDD studies ($n=735$) and 7 BD studies ($n=88$). Serum and plasma subgroups were analyzed, publication bias was assessed and heterogeneity was investigated.
Results: Serum and plasma BDNF were decreased in acute MDD and BD, and did not differ in euthymia in comparison with control subjects. Antidepressive treatment increased serum BDNF levels in MDD in responders (Cohen's d (d)$=1.27$, $p=4.4E-07$) and remitters ($d=0.89$, $p=0.01$), significantly more than in non-responders ($d=0.11$, $p=0.69$). For plasma BDNF in MDD and for BD, the evidence was insufficient for a meta-analysis. Although no significant difference was found between serum and plasma ES, variance of plasma ES was higher.
Limitations: Between-study heterogeneity was explained only partially; signs of publication bias in serum studies.
Conclusion: Serum BDNF might be regarded as a biomarker for the successful treatment of MDD. Serum measurements seem more reliable than plasma ones. Further research should focus on defining optimal time points for BDNF measurements and increase evidence for the usage of BDNF as a predictive biomarker in BD.

Contents

Abbreviations: BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; BD, bipolar disorder; ES, effect size; SMD, standardized mean difference, Cohen's d; CI, confidence intervals

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http://dx.doi.org/10.1016/j.jad.2014.11.044
0165-0327/

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family. For over 30 years, research on BDNF has been fruitful in many fields, from basic to clinical. Through dendritic arborization and synaptic consolidation, BDNF mediates neuronal plasticity, migration, and survival in both the central and peripheral nervous system (Bramham and Messaoudi, 2005; Greenberg et al., 2009). It is secreted by neurons and peripheral cells such as leukocytes (Edling et al., 2004), endothelial cells (Nakahashi et al., 2000), and platelets (Yamamoto and Gurney, 1990), and passes the blood–brain barrier (Pan et al., 1998).

BDNF is involved in a wide range of neuropsychiatric and neurodegenerative diseases (Autry and Monteggia, 2012). A number of individual studies and later meta-analyses have demonstrated decreased BDNF levels in mood disorders (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Fernandes et al., 2014; Fernandes et al., 2011; Lin, 2009; Molendijk et al., 2012; Sen et al., 2008). The neurotrophin theory of mood disorders arose in 2006 (Duman and Monteggia, 2006); but the initial excitement has recently changed into a more balanced discussion (Groves, 2007; Molendijk et al., 2014). Major depressive disorder (MDD) and bipolar disorder (BD) are prevalent and disabling mood disorders (retrieved from 30.01.2014 from http://www.nimh.nih.gov/; Organization., 2008). Despite progress in pharmacotherapy, roughly half of MDD patients do not respond to the first antidepressant treatment (Dierckx et al., 2012; Undurraga and Baldessarini, 2012). Response rates for the second and third antidepressant remain even lower in patients who do not respond to the first prescription (Murrough and Charney, 2012). In non-responders, a clinical decision to switch medication is usually made during the second to fourth week of treatment (Bauer et al., 2007; Suehs B et al., 2008). Waiting several weeks until the treatment response or medication switch is burdensome for patients and leads to therapy dropout (Nakajima et al., 2010). In order to reduce this time window, BDNF was suggested as an early marker for treatment response (Tadic et al., 2011).

Today, it is well established that BDNF is decreased in mood disorders. Discussions remain only about the degree of reduction (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Molendijk et al., 2014). On a meta-analytical level it was also shown that BDNF increases with clinical improvement (Brunoni et al., 2008); but the treatment response was not taken into account. However, individual studies have shown differential BDNF restoration in responders and non-responders (Deuschle et al., 2013; Yoshimura et al., 2010a).

Although the relevance of BDNF for mood disorders is obvious, the source of measured BDNF is diverse. BDNF levels can be measured in whole blood, plasma, serum, or blood cells. Plasma and serum BDNF levels show at least a 100-fold difference (Radka et al., 1996; Rosenfeld et al., 1995) and may result from different processes. Plasma levels might be responsible for the immediate delivery of BDNF to the nervous system, while serum levels reflect the platelet pool of this protein, which can be released upon activation (Tamura et al., 2012). Changes in serum BDNF levels were addressed in a recent meta-analysis by Molendijk et al. (2014), while combined serum and plasma levels in their meta-analysis. Both reported decreased BDNF in acute mood episodes.

In the current meta-analysis, we aimed to elucidate three questions: i) Is there any difference between changes in plasma BDNF and in serum BDNF levels in mood disorders? (ii) Are there state-dependent differences in plasma and serum BDNF levels as suggested by other serum plasticity markers (Schroeter et al., 2008; Schroeter and Steiner, 2009)? iii) Does BDNF restore differentially depending on the treatment response? If so, this would help to establish BDNF as a predictive biomarker for successful antidepressive treatment.

We hypothesized that both plasma and serum BDNF levels are decreased compared with healthy control subjects in acute mood episodes and are not different from control subjects during the euthymic state of MDD and BD. In longitudinal studies we hypothesized that both serum and plasma levels increase only in responders to treatment of MDD and BD.

2. Methods

2.1. Literature search and inclusion criteria

Two independent reviewers (MP, KST) conducted a literature search through the electronic databases PubMed, ISI Web of Science, and PsycINFO. Keywords 'BDNF' or 'brain-derived neurotrophic factor' were combined with either 'depression', 'major depression', or 'bipolar', 'mania', 'euthymia', and 'remission' (last search-27.08.2013). We screened titles, abstracts, and full texts, when appropriate, according to predefined inclusion criteria: (i) original peer-reviewed article, (ii) adult patients with MDD or BD type I, (iii) absence of somatic comorbidity, (iv) BDNF serum or plasma levels assessed, (v) case-control design of the study comparing patients and control group or longitudinal therapy study of the same group of patients before and after treatment,

(vi) standardized treatment medications used (antidepressants for MDD, mood stabilizers for BD, with addition of antipsychotics when appropriate). We inspected reference lists of articles to identify further relevant articles. Studies including patients with somatic illnesses (cancer, diabetes), pregnant women, and studies using transcranial magnetic stimulation, electroconvulsive therapy or psychotherapy were excluded, as well as studies based on substantially overlapping samples.

2.2. Data extraction

Based on the inclusion criteria, 68 original articles were selected for subsequent analyses (Fig. 1). Information was extracted and structured. In the case of insufficiently reported data, we contacted the corresponding author via e-mail for additional information, and most of them provided it. When the author did not reply, we reviewed the study qualitatively only (Yoshimura et al., 2010b).

2.3. Risk of bias assessment

Based on the recommendations of the Cochrane collaboration handbook (Chang, 2011; Higgins JPT, 2009) and the Methods Guide for Comparative Effectiveness Reviews (Chang, 2011; Higgins JPT, 2009), we developed a risk of bias assessment tool for cross-sectional and longitudinal studies. All included questions were rated by the first author with "0", "1", or "2" according to the presence of specific criteria (Supplementary Tables 1, 2). The smaller the score, the higher the risk of bias. The total score of each study was tested as a covariate in the meta-regression.

2.4. Quantitative data synthesis

The software program comprehensive Meta-Analysis, version 2.2.064, (Borenstein et al., 2009) was used for statistical analysis. Since BDNF was measured with different kits, in different populations, and, accordingly, with different absolute values, data were normalized by calculating the standardized mean difference (SMD, Cohen's *d*), with 95% confidence intervals (CI) as an effect size (ES) estimate. According to Cohen, the magnitude of ES should be interpreted as small with an ES > 0.2, medium with an ES > 0.5, or large with an ES > 0.8. A random-effects model was chosen for the meta-analysis because it accounts for both within- and between-study variance. In cases where no heterogeneity is present, the random-effects model acts as a fixed-effects model.

Sensitivity analysis was performed, excluding each individual study from the meta-analysis. In cases where the meta-analysis results were driven by a single study, data were reported in the results section. Between-study heterogeneity was assessed using Q-statistics and I^2 estimate. An exploration of between-study heterogeneity was performed by a subgroup analysis for categorical predictors, and mixed-effect regression (unrestricted maximum likelihood) for continuous predictors.

We checked for a potential publication bias in the included analyses by visual assessment of funnel plots, Egger's test, and Begg and Mazumdar test. Duval and Tweedie's trim and fill method was used to correct for the funnel plot asymmetry arising from publication bias (Duval and Tweedie, 2000; Taylor and Tweedie, 1998).

Meta-analyses were performed separately for the cross-sectional and the longitudinal studies. Conventionally, clinical treatment response was defined as a 50% reduction in the scores of Young mania rating scale (YMRS), Hamilton depression rating scale (HDRS) and Montgomery–Asberg depression rating scale (MADRS) (Zajecka, 2003), remission as scores < 7 on HDRS, scores < 8 on MADRS or scores < 8 on YMRS (Aydemir et al., 2005; Deuschle et al., 2013; Gervasoni et al., 2005; Sousa et al., 2011).

For the subgroup analysis, we subdivided the cross-sectional studies according to the polarity of mood episode (depression, mania, and euthymia). The longitudinal MDD studies were subdivided according to the treatment response (remitters, responders, non-responders). Due to insufficient data, we review longitudinal studies in BD qualitatively only. Serum and plasma studies were analyzed separately. For both MDD and BD, we ran mixed-effects meta-regression analyses with the predictors that were previously described in the literature: number of patients (Molendijk et al., 2014), patients' mean age (Bus et al., 2011; Fernandes et al., 2011), gender (measured as percentage of males) (Bus et al., 2011), duration of illness (Fernandes et al., 2011), and risk of bias score.

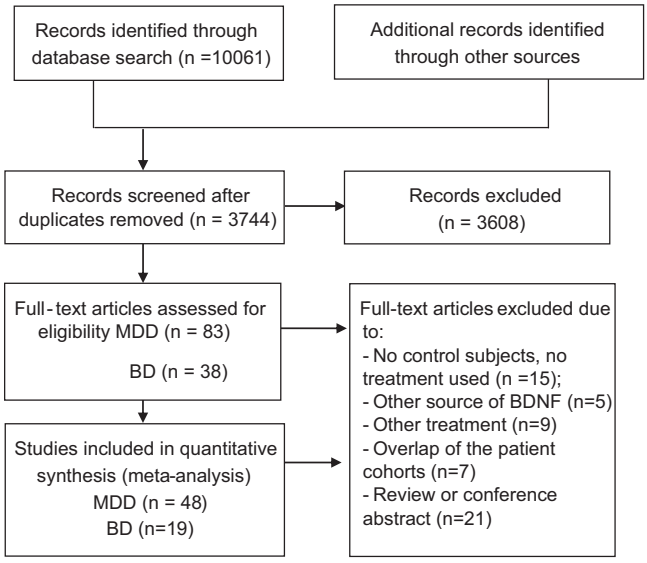

Fig. 1. PRISMA flow-diagram of the strategy for searching and selecting studies; BD bipolar I disorder, BDNF brain-derived neurotrophic factor, MDD major depressive disorder, n number of studies.

3. Results

3.1. Results of the systematic literature search

The PRISMA flow diagram summarizes the identification of the relevant studies (Fig. 1). Our inclusion criteria were satisfied by 48 studies with MDD patients and 19 studies involving BD patients (Supplementary Tables 3–6). In sum, the studies taken into account by the meta-analyses included a large group of 3365 and 758 patients with MDD and BD, respectively.

Thirty-eight studies were included in our cross-sectional MDD meta-analysis and 19 in our cross-sectional BD meta-analysis (Supplementary Figs. 13–19). BDNF values before and after treatment were assessed in 21 MDD studies and seven BD studies. The total score in the risk of bias assessment tool of cross-sectional studies varied from 15 to 20, and for longitudinal studies it varied from 11 to 18.

3.2. Group difference analysis based on cross-sectional studies

The first analysis investigated group differences for BDNF levels between the subtypes of mood disorders, MDD and BD, and their

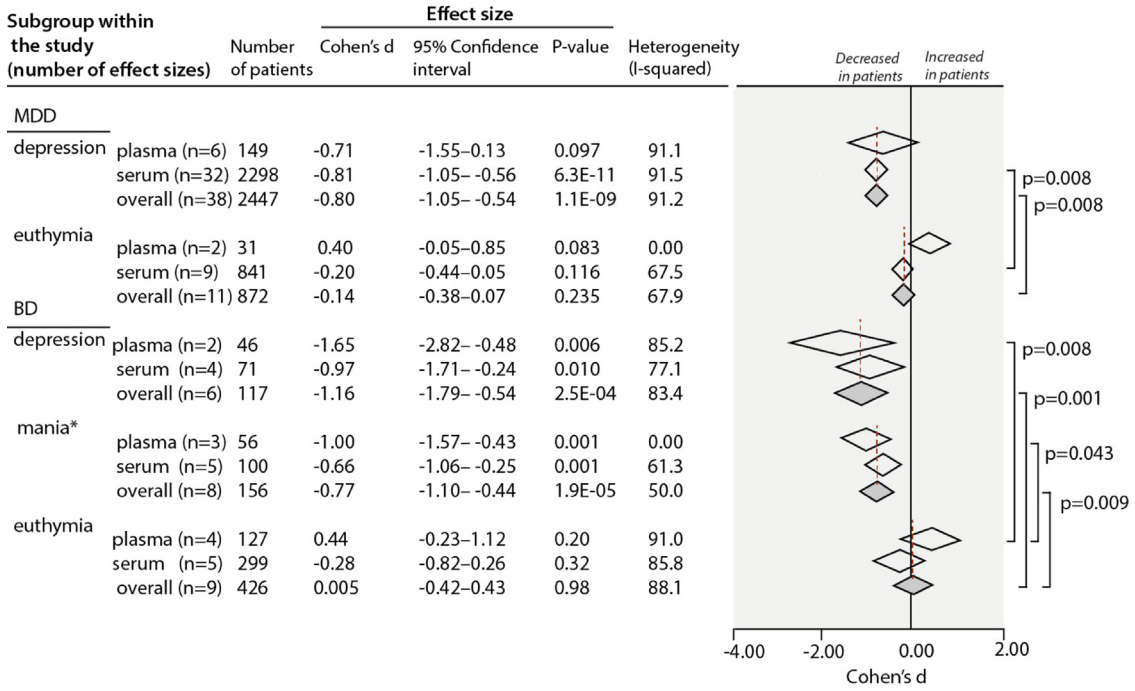

Fig. 2. Meta-analysis comparing plasma and serum levels of BDNF between major depressive disorder (MDD) and bipolar disorder (BD) in respective mood states. Cross-sectional studies. SMD standardized mean difference. *Study by Barbosa et al. (2010) was excluded from the meta-analysis as it investigated patients with long-term BD. SMD—Standardized mean difference. The dashed lines illustrate mean values for MDD and BD when compared with the control cohort. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

different states (depressive, manic, and euthymic episode) and the influence of the analysis approaches (serum vs. plasma levels). Results are illustrated in Fig. 2.

3.2.1. MDD meta-analysis: BDNF is decreased in acute mood episodes

Thirty-eight studies compared patients with MDD in depressive state with control subjects, including 2447 patients and 2147 controls. High overall between-study heterogeneity (I^2=91.2) remained despite grouping by source of BDNF and sensitivity analysis. When compared with healthy controls, BDNF was significantly decreased in acute MDD (d=−0.80, 95% CI −1.05 to −0.54, p=1.1E-09, 38 effect sizes, n=2447), but not in euthymia (d=−0.14, 95% CI −0.38 to 0.07, p=0.235, 11 effect sizes, n=872; Fig. 2).

To answer the question whether there is a difference in ES between serum and plasma studies, we compared ES in six plasma studies and 32 serum studies in acute MDD. One study was included in both analyses since it measured BDNF in both plasma and serum (Piccinni et al., 2008). Serum BDNF was significantly decreased in patients in a depressive state compared with controls (d=−0.81, 95% CI −1.05 to −0.56, p=6.3E-11, 32 effect sizes, n=2298). A similar trend was observed in plasma studies (d=−0.71, 95% CI=−1.55 to 0.13, p=0.097, 6 effect sizes, n=149; Fig. 2). BDNF levels of patients in euthymia did not differ significantly from healthy subjects in serum (d=−0.20, 95% CI=−0.38 to 0.07, p=0.116, 9 effect sizes, n=841) and were slightly increased in plasma studies (d=0.40, 95% CI −0.05 to 0.85, p=0.083, 2 effect sizes, n=31; Fig. 2).

While in acute state there was no significant difference between plasma and serum studies (p=0.91), in euthymia we observed a tendency for plasma BDNF to be higher than serum (p=0.076). Note that confidence intervals of plasma studies were always wider, thus less precise. Subgroup analysis according to the severity of depression also resulted in no significant differences (data not shown).

3.2.2. BD meta-analysis: BDNF is decreased in acute mood episodes

This random-effects meta-analysis comprised six depressive, eight manic, and nine euthymic state studies. BDNF levels were significantly decreased in patients with an acute depressive episode (d=−1.16, 95% CI −1.79 to −0.54, p=2.5E-04, 6 effect sizes, n=117) and an acute manic episode (d=−0.77, 95% CI −1.10 to −0.44, p=1.9E-05, 8 effect sizes, n=156; Fig. 2). No significant differences were found in BDNF levels of euthymic patients when compared with control subjects (d=0.05, 95% CI −0.42 to 0.43, p=0.098, 9 effect sizes, n=426; Fig. 2).

According to the sensitivity analysis, ES in the manic state might be driven by the study by Barbosa et al. (2010). In this study, mean illness duration was 19.5 years, in others it varied from 0.2 to 12.8 years (mean 8.4 years). The large positive ES in this study (Supplementary Fig. 18) increased the between-study heterogeneity by 41%. Based on these data, we excluded Barbosa et al.'s study from the respective subgroup (Fig. 2). No significant differences were observed between serum and plasma ES in any of the BD subgroups. ES in acute depression and mania subgroups were significantly lower than in the euthymic subgroup (p=0.001 and p=0.009, respectively); and this difference was driven by plasma studies (Fig. 2). Note that confidence intervals of plasma studies were again larger than in serum studies.

3.2.3. BD vs. MDD meta-analysis: no significant differences among disorders

Summarizing cross-sectional studies, we found decreased serum and plasma BDNF levels in all acute episodes of both MDD and BD when compared to control subjects. No significant differences were found between the acute mood episodes of both

Subgroup within the study (number of effect sizes)	Number of patients	Effect size: Cohen's d	95% Confidence interval	P-value	Heterogeneity (I-squared)
Serum levels					
Responders (n=11)	252	1.33	0.69–1.97	5.1E-05	90.5
Remission (7)	116	0.84	0.39–1.29	0.003	58.9
Non-responders (7)	118	0.15	-0.33–0.63	0.55	67.1
Pooled(n=1)	40	0.33	-0.89–1.56	0.14	0.00
Overall (n=26)	586	0.77	0.46–1.09	1.5E-06	84.3
Plasma levels					
Responders (n=4)	64	0.33	-0.13–0.79	0.03	19.2
Remission (n=1)	38	0.39	-0.07–0.84	0.09	0.00
Non-responders (n=1)	8	0.10	-0.88–1.08	0.84	0.00
Pooled(n=1)	39	0.20	-0.24–0.65	0.37	0.00
Overall (n=7)	149	0.30	0.03–0.63	0.08	0.00

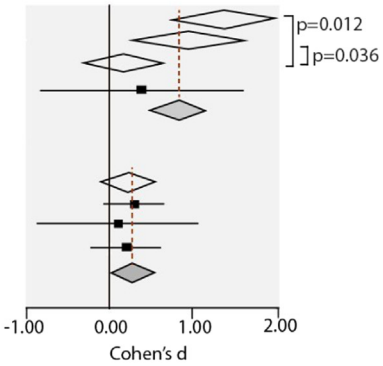

Fig. 3. Meta-analysis investigating treatment effects on serum and plasma levels of BDNF with regard to treatment efficacy in major depressive disorder (MDD). Longitudinal studies. SMD—Standardized mean difference. The dashed lines illustrate mean treatment effects for serum and plasma BDNF in MDD. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

disorders. In the euthymic state of BD and MDD, serum and plasma BDNF levels were similar to control subjects.

3.3. Treatment effect analysis based on longitudinal studies

The second analysis investigated the effect of treatment on BDNF levels in MDD and BD (depressive and manic states). Post-treatment levels of BDNF were compared between remitters, responders, and non-responders to treatment. Results are illustrated in Fig. 3.

3.3.1. MDD meta-analysis: BDNF is increased in responders and remitters in contrast to non-responders

Twenty-one studies satisfied inclusion criteria for the longitudinal MDD meta-analysis investigating treatment effects on serum BDNF. Four studies included only the responders group; six studies included both the responders and the non-responders groups. Six studies reported only the remitters group, and one study included the remitters and non-responders groups. One study reported pooled data. This meta-analysis included 553 patients. Median treatment duration was 6 weeks (range 2–8 weeks).

To investigate whether the treatment-related change in BDNF (post- vs. pre-treatment) is related to treatment response, we subdivided the whole MDD sample into remitters, responders, and non-responders to antidepressant treatment, according to the criteria mentioned in the Methods section. Indeed, the meta-analysis indicated that BDNF levels increased upon treatment in remitters ($d=0.85$, 95% CI 0.39–1.29, $p=0.003$, 7 effect sizes, $n=116$) and responders ($d=1.33$, 95% CI 0.69–1.97, $p=5.1E-05$, 11 effect sizes, $n=252$), whereas in the non-responders they remained stable ($d=0.15$, 95% CI −0.33 to 0.63, $p=5.1E-05$, 7 effect sizes, $n=118$) (Fig. 3). Serum BDNF changes in remitters and responders were significantly larger than in the non-responders ($p=0.036$ and $p=0.012$ respectively; Fig. 3). The data on the plasma BDNF changes are limited and the differences between different subgroups were not significant (Fig. 3). The overall meta-analysis (very likely driven by the responders and the remitters) indicated increasing BDNF values due to antidepressive treatment in serum (ES=0.77, $p=1.5E-06$) and in plasma (ES=0.30, $p=0.08$).

3.3.2. BD review: a trend for increased BDNF in responders in contrast to non-responders

We review the results of individual studies in this section, because subdivision of the seven identified studies by polarity and source of BDNF is not sufficient for meta-analysis.

In the mania group, we identified studies reporting remitters and responders to the treatment. Two of them observed increased BDNF levels in plasma: Palomino et al. (2006) ($d=0.56$, 95% CI= −0.19 to 1.3, $p=0.14$) and de Sousa et al. (2011) ($d=1.02$, 95% CI=0.09–1.95, $p=0.03$). Serum BDNF levels were assessed in four studies, reporting controversial findings. Yoshimura et al. (2006) ($d=0.27$, 95% CI= −0.53 to 1.07, $p=0.51$) and Huang et al. (2012) ($d=0.16$, 95% CI= −0.45 to 0.76, $p=0.61$) found no significant BDNF changes. Studies were conducted on 12 and 21 patients, respectively. Tramontina et al. (2009) found a statistically significant increment in BDNF upon treatment in the sample of 10 patients ($d=0.99$, 95% CI=0.06–1.92, $p=0.04$) and decreased BDNF levels were observed in the group of three patients by Grande et al. (2012) ($d=-2.4$, 95% CI= −4.5 to −0.30, $p=0.025$).

Serum BDNF in the depressive episode of BD was studied by Grande et al. (2012). They reported a trend for increased BDNF in responders to treatment ($d=0.85$, 95% CI= −0.17–1.89, $p=0.1$) and no change in the non-responders ($d=-0.001$, 95% CI= −1.39–1.39, $p=0.99$). Yoshimura et al. (2006) observed no significant difference in the serum BDNF in non-responders ($d=0.13$, 95% CI= −1.00 to 1.26, $p=0.81$). In a later study of BD and MDD patients, the same research group found significantly increased plasma BDNF levels in the responders ($d=1.0$, 95% CI=0.18–1.81, $p=0.037$) but not in the non-responders ($d=0.15$, 95% CI= −0.51 to 0.80, $p=0.66$) (Yoshimura et al., 2010b).

Overall, there seems to be a trend similar to MDD studies (peripheral BDNF is increased in responders and unchanged in non-responders to treatment) at least in the depressive state of BD, but at the moment evidence for meta-analytic conclusions is lacking.

3.4. Investigation of between-study heterogeneity

To ensure the validity of our meta-analyses, we analyzed between-study heterogeneity. Variation between studies revealed by a heterogeneity test was high in MDD meta-analyses, both cross-sectional ($I^2=91.2$) and longitudinal ($I^2=84.3$). For cross-sectional BD meta-analysis, heterogeneity was moderate to high ($I^2=50.0–88.1$). In order

to distinguish the source of between-study variation, we performed subgroup analysis and meta-regression.

3.4.1. Subgroup analysis

The subdivision of MDD studies according to BDNF source did not reduce the between-study heterogeneity (Figs. 2 and 3), which was in agreement with the assumption that signal-to-noise ratio analyses by calculating SMD eliminates, or at least reduces, this possible bias. In BD, such subgroup analysis decreased heterogeneity in mania, but did not affect the depressive and euthymic state analysis. In longitudinal MDD studies of serum BDNF, the heterogeneity was reduced in the remitters and the non-responders subgroups when compared to the overall heterogeneity.

3.4.2. Mixed effect meta-regression

Predefined moderator variables were patients' age, sex (measured as % of males), disease duration, and risk of bias score. We did not find any significant correlations across any of the meta-analyses.

3.5. Publication bias

The publication bias was detected and corrected by a trim and fill procedure in three out of 10 meta-analyses: i) meta-analysis of cross-sectional studies of serum BDNF levels in depressive state of MDD, ii) meta-analysis of longitudinal studies of serum BDNF levels in responders, and iii) non-responders subgroups in MDD (Supplementary Figs 2, 10, 11). In the meta-analysis of cross-sectional studies in the depressive state MDD, correction of pooled ES from serum studies led to its reduction from $d=-0.81$ (95% CI$=-1.05$ to -0.54) to $d=-0.48$ (95% CI$=-0.72$ to -0.22). In the responders subgroup from longitudinal meta-analysis of serum BDNF studies, correction increased pooled ES from $d=1.33$ (95% CI$=0.69$–1.97) to $d=1.52$ (95% CI$=0.86$–2.19). In the non-responders subgroup from longitudinal meta-analysis of serum BDNF studies, corrected ES decreased from $d=0.15$ (95% CI$=-0.33$ to 0.63) to $d=-0.12$ (95% CI$=-0.44$ to 0.20). Since correction for publication bias led to comparable results, we conclude that publication bias did not substantially affect the results of our meta-analysis.

4. Discussion

In the current meta-analysis we confirmed the previous findings of reduced BDNF levels in acute, but not in euthymic, mood episodes (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Fernandes et al., 2014; Fernandes et al., 2011; Lin, 2009; Molendijk et al., 2012; Sen et al., 2008). This was true for both MDD and BD, with no significant differences among their ES. Serum and plasma ES were not different in the cross-sectional studies, but the CI for plasma studies was always wider, and thus less precise.

Moreover, our meta-analyses revealed findings that, to our knowledge, have not been reported before. Analysis of longitudinal studies indicated that BDNF is differentially restored upon treatment, namely BDNF levels increase in remitters and responders, but remain unchanged in non-responders. This difference was significant for MDD and a trend was observed in BD, although more evidence is needed to draw meta-analytic conclusions in BD. Therefore, BDNF may become a useful treatment biomarker for MDD, whereas any inferences for BD are premature.

BDNF is involved in a wide range of psychiatric and neurological disorders (Autry and Monteggia, 2012). Fernandes et al. (2009) observed decreased serum BDNF levels in bipolar depression compared to MDD patients. Monteleone et al. (2008) found no significant differences between the groups of euthymic BD or MDD patients or the acute MDD group. On the meta-analytic level, there is no credible evidence that differences between the acute mood episodes of BD and MDD exist. However, a clear difference between BDNF levels in euthymic and acute mood states in both BD and MDD (Fernandes et al., 2013b) supports our finding that BDNF is restored as a result of successful treatment.

To establish BDNF as a biomarker for the successful treatment of mood disorders, three aspects should be discussed: Which BDNF source is preferable, at which time point is the BDNF change reliably detectable and clinically meaningful, and how strong is the association between BDNF and treatment efficiency?

By different estimations, BDNF levels in serum are 100–200-fold higher than in plasma (Radka et al., 1996; Rosenfeld et al., 1995). Plasma BDNF represents the circulating protein, and serum BDNF constitutes the sum of plasma levels and, mainly, BDNF released from platelets during clotting (Fujimura et al., 2002; Radka et al., 1996; Rosenfeld et al., 1995). Similar to other neurotrophins, BDNF is rapidly eliminated from plasma with a half-life time of 2.7 ± 1 min. The main clearance mechanisms are uptake and subsequent degradation in the liver; and to a lesser extent in the kidneys and lungs (Pardridge et al., 1994). To our knowledge, the lifespan of platelet BDNF has not yet been determined, but it is known that platelets remain in peripheral blood for about 10 days and are able to store and release BDNF upon activation (Fujimura et al., 2002; Harker et al., 2000). Therefore, plasma levels reflect a short-term BDNF content, and serum levels reflect a relatively long-lasting BDNF. The increased serum BDNF in the responders group should, in turn, reflect the BDNF accumulated by platelets during the treatment period. The underlying physiological mechanisms remain to be elucidated: the origin of platelet BDNF, the ration of BDNF isoforms, and the relation to antidepressants or to the pure disease physiology etc.

Relationships between serum and plasma BDNF levels are not well described. A high positive correlation ($r=0.73$) in healthy volunteers was reported by Yoshimura et al. (2010c). In this study the difference between plasma and serum levels was 14-fold, which is much smaller than previously reported by Radka et al. (1996) and Rosenfeld et al. (1995), but the authors did not control for potential platelet contamination of plasma samples (Yoshimura et al., 2010c). Bocchio-Chiavetto et al. (2010) did not find any correlation between plasma and serum BDNF in patients with MDD ($p=0.259$). Studies specifically focusing on the relations between serum and plasma BDNF levels are needed to understand if these levels are independent or not.

The interpretation of similar ES between the plasma and the serum cross-sectional studies should be done cautiously, and should account for a small number of included plasma studies, their large confidence intervals, and high heterogeneity. Moreover, determination of BDNF in serum is rather stable and reproducible (Elfving et al., 2010; Trajkovska et al., 2007; Tsuchimine et al., 2014), while plasma levels are more strongly affected by the handling of material (Elfving et al., 2010; Tsuchimine et al., 2014). The longer plasma samples are kept at room temperature (in hours), the higher their absorbance scores in the ELISA detection system (Elfving et al., 2010; Tsuchimine et al., 2014). For serum BDNF, storage in the freezer for more than 3 years was shown to decrease BDNF levels (Bus et al., 2011). In addition, anticoagulants used for plasma preparation may further alter BDNF plasma measurements (Tsuchimine et al., 2014); another potential reason for large variance in plasma levels of BDNF. Based on previous methodological findings and more narrow confidence intervals in serum studies, one might conclude that serum levels are generally more reliable.

Most interestingly, we found significantly higher BDNF levels in the serum of responders when compared with non-responders in MDD on

the meta-analytic level. This result clarifies partly controversial findings in the literature with differential BDNF changes in responders and non-responders in most original studies (Huang et al., 2008; Lee and Kim, 2008; Umene-Nakano et al., 2009; Yoshimura et al., 2010a), but opposite results in others (Basterzi et al., 2009; Yoshimura et al., 2007). In our longitudinal meta-analysis, BDNF levels were measured at different time points. Treatment time ranged from 2–8 weeks, with a median of 6 weeks. One may reasonably argue that in MDD, a marker which is significant during the sixth week of treatment cannot support clinical decisions, since clinically antidepressant response is obvious around week 3 or 4. This issue was addressed by one pilot study (Dreimuller et al., 2012; Tadic et al., 2011). Tadic et al. (2011) revealed that absence of clinical improvement combined with unchanged serum BDNF could predict non-response reliably at the end of the second week of treatment (between day 7 and 14, specificity increased from 67 to 100%). The combination of increased plasma BDNF levels and HDRS scores of the same patients could predict the treatment response already on day 7 with a sensitivity of 67% and a specificity of 93%. The best relative BDNF cut-off score for prediction of response on day 7 was 126% (Dreimuller et al., 2012). However, one has to be aware that these data are limited to 39 patients. Supporting this data, Rojas et al. (2011) observed an early parallel increase of serum BDNF and clinical improvement. An association between treatment response and serum BDNF levels on day 7 was also reported by Delini-Stula et al. (2012).

In order to develop a biomarker for the treatment response, additional studies addressing the strength of association between BDNF and treatment efficiency are required. Instead of comparing overall pre- and post-treatment BNDF, attention should be focused on the sensitivity and specificity of BNDF as a biomarker of treatment response, optimal time point, and source of BDNF measurement. Additional control for depression course may add valuable information, as patients with recurrent depression tend to show decreased BDNF over time even when reaching clinical remission (Bus et al., 2014). Since different ELISA kits use different measurement scales, the percent change of BDNF should be used for the sensitivity and specificity analyses. Using the kits sensitive to different BDNF isoforms would pave the way for a better understanding of the role of BDNF in treatment response.

Last but not least, we used the meta-regression to discriminate factors leading to high between-study heterogeneity. Based on the patients' average age, gender, illness, or treatment duration, meta-regression has its limitations. Most of the included cross-sectional studies were already controlled for age; excluding the effect of aging across the studies (Schroeter et al., 2011). Some of the studies were also controlled for gender. Therefore, we could observe gender effects between studies only partially. Mean illness duration for the study may be different from the true within-study distribution. The only precise factors were risk of bias scores and treatment duration for longitudinal studies, but we did not detect any relationship with BDNF change in our analysis. Since between-study relationships are observational by nature, inferences based on such meta-regression may be misleading and only individual patient level can resolve such discrepancies (Thompson and Higgins, 2002).

A major limitation of our study is the high heterogeneity between the included studies. We could not control for potential moderators: physical activities, body-mass index, handling, and storage of material; usually they were not reported in the clinical studies. However, a priori, we excluded a potential confound, physical comorbidity, and allowed only standard medications. In longitudinal MDD studies we were able to partially explain heterogeneity by the treatment response, and in mania cross-sectional studies the sensitivity analysis revealed a study that drove the whole result and increased heterogeneity by 41%. The second limitation, publication bias, was corrected by the trim and fill procedure, which even increased the difference between serum BDNF changes in the responders and non-responders.

In conclusion, meta-analytic evidence suggests that BDNF is a biomarker for the successful treatment of mood disorders, in particular MDD. Serum measurements seem to be more reliable than plasma measurements. Further research should focus on defining optimal time points for BDNF measurements to support early clinical decisions and increase evidence for the usage of BDNF in BD.

Conflict of interest

The authors declare no conflict of interest.

Role of funding source

This study has been supported by the International Max Planck Research School on Neuroscience of Communication (IMPRS NeuroCom; MP), by LIFE—Leipzig Research Center for Civilization Diseases at the University of Leipzig - funded by the European Union, European Regional Development Fund and by the Free State of Saxony within the framework of the excellence initiative (PS & MLS), by the German Consortium for Frontotemporal Lobar Degeneration, funded by the German Federal Ministry of Education and Research, (KST & MLS) and by the Parkinson's Disease Foundation (KM & MLS; Grant no. PDF-IRG-1307).

Acknowledgments

We would like to thank all the authors who replied to our enquiries regarding additional data, the library of Max Planck institute for their assistance in the literature retrieval, and Elizabeth Kelly for proofreading the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2014.11.044.

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SUPPLEMENTARY MATERIAL

Table 1 Risk of bias assessment tool for cross-sectional studies.

Risk of bias domain	Criteria	No	Partially or not known	Yes
Selection bias	Are two groups matched by age and gender?	0	1	2
	Are two groups similar by psychiatric and somatic comorbidity?	0	1	2
	Were patients and controls selected randomly from the target population?	0	1	2
Detection bias	Was the same diagnostic method applied to both groups?	0	1	2
	Did the same person assess two groups?	0	1	2
	Was diagnosis made in accordance with international classifications using standardized tools?	0	1	2
	Was normality of distribution checked and appropriate statistical test applied?	0	1	2
	Were the confounding variables assessed and treated appropriately (diurnal fluctuations, handling and storage of samples, joint ELISA measurements, body mass index)?*	0	1	2
Performance bias	Were the outcome assessors blinded to participants?	0	1	2
Attrition bias	Was attrition (dropout, exclusion of participants) a concern in the study?	2	1	0
Reporting bias	Are all prespecified outcomes reported?	0	1	2
	Total	0 to 22points		

- None of the confounding variables – 0 points; 1 – 2 variables – 1 point, 2 and more –2 points.

Table 2 Risk of bias assessment tool for longitudinal studies.

Risk of bias domain	Criteria	No	Partially or not known	Yes
Selection bias	Were patients selected randomly from the target population?	0	1	2
	Was medication assigned randomly?	0	1	2
	Was the group homogeneous by means of psychiatric and somatic comorbidity?	0	1	2
Detection bias	Did the same person assess all patients?	0	1	2
	Was diagnosis made in accordance with international classifications using standardized tools?	0	1	2
	Were the confounding variables assessed and treated appropriately (diurnal fluctuations, handling and storage of samples, joint ELISA measurements, body mass index)?*?*	0	1	2
Performance bias	Were the outcome assessors blinded to participants?	0	1	2
Attrition bias	Was attrition (dropout, exclusion of participants) a concern in the study?	2	1	0
Reporting bias	Are all prespecified outcomes reported?	0	1	2
	Total	0 to 18 points		

- None of the confounding variables – 0 points; 1 – 2 variables – 1 point, 2 and more –2 points.

Table3. Studies included in the MDD cross-sectional meta-analysis

Reference	*Source of BDNF*	*Patients*							*Controls*					**units**
		N	**Severity of depression (HDRS)**	**% male**	**Age mean**	**SD**	**BDNF mean**	**SD**	**N**	**Age mean**	**SD**	**BDNF mean**	**SD**	
Acute state														
Karege, 2002 (1)	serum	30	34.0 ±5.0 [a]	50.0	36.0	8	22.6	3	30	38.0	9	26.5	7	ng/ml
Shimizu,2003 (2)	serum	17	27.8±10.2	75.0	40.8	13.6	17.6	9.6	50	41.9	15.9	27.7	11.4	ng/ml
Aydemir, 2005 (3)	serum	10	23.02±4.6	20.0	31.8	14.3	17.9	9.1	10	39.8	7.1	31.6	8.6	ng/ml
Gervasoni, 2005 (4)	serum	26	32.8±4.9 [a]	42.3	40.5	10.7	22.6	3.6	26	39.6	12.2	26.4	3.6	ng/ml
Gonul, 2005 (5)	serum	28	27.3±3.5	25.0	35.5	8.1	20.8	6.7	18	35.7	5.8	26.8	9.3	ng/ml
Karege, 2005 (6)	plasma	43	32.0±4.0 [a]	37.2	36.0	10	1685	243	35	31.0	11.8	2165	349	pg/ml
Laske, 2005 (7)	serum	16	26.2	31.3	61.3	NA	19.7	3.3	30	58.1	NA	21.3	5.4	ng/ml
Aydemir, 2006 (8)	serum	20	39.75±7.4	0.0	35.6	7.5	27.68	13.74	20	34.6	7.86	41.16	15.14	ng/ml
Yoshimura, 2007 (9)	serum	42	23.5±6.7	35.7	47.0	19	9.51	6.49	40	45.0	15.0	23.4	10.1	ng/ml
Huang, 2008 (10)	serum	111	35.1±4.9	22.8	36.0	10.1	10.9	7.1	107	28.9	5.1	14.1	7	ng/ml
Lee, 2008 (11)	plasma	32	29.488.6	34.4	44.2	17.3	698.2	537.7	50	38.5	9.7	830.7	624.8	pg/ml
Monteleone, 2008 (12)	serum	11	19.9±3.5	18.2	45.7	13.6	29	15.9	22	40.1	16.4	42.5	12.5	ng/ml
Piccinni, 2008 (13)	plasma	15	22.8±5.3	13.3	44.2	10.8	2900	1900	15	38.5	9.2	5400	2300	pg/ml
	serum	15	22.8±5.3	13.3	47.0	10.8	19300	8800	15	36.9	16.4	33600	8600	pg/ml
Basterzi, 2009 (14)	serum	45	25.7±5.5	33.3	32.0	11.0	42005	12630	15	36.0	10.0	47727	7698	pg/ml
Fernandes, 2009 (15)	serum	10	26.3	40.0	44.8	17.0	0.35	0.08	30	41.0	11.9	0.38	0.12	pg/µg
Gorgulu, 2009 (16)	serum	42	24.3±4.7	26.8	36.4	11.3	20.49	4.31	31	35.0	12.2	33.83	7.14	ng/ml
Matrisciano, 2009 (17)	serum	21	19.0±5.3	52.4	42.4	8.0	35.4	15.2	20	31.8	5.9	64.1	13.1	ng/ml
Ozan, 2010 (18)	serum	66	24.1±1.06	28.8	33.0	2.3	22.13	6.47	56	34.0	?	27.27	6.5	ng/ml
Umene-Nakano, 2009 (19)	plasma	20	>15	75.0	45.0	9.0	9.8	5.2	20	43.0	7.0	21.1	7	ng/ml
Diniz, 2010 (20)	serum	29	18.0(14-22)	20.7	71	NA	603.43	276.87	42	69.5	NA	1016.14	902.61	pg/l
Eker, 2010 (21)	serum	25	24.4±4.8	28.0	32.1	9.3	21.7	6.6	22	29.7	6.4	27	5.7	ng/ml
Hung, 2010 (22)	serum	25	32.7±0.82	34.5	38.4	2.15	21.7	6.6	22	33.0	1.17	27	5.7	ng/ml
Bocchio-Chiavetto,2010 (23)	serum	55	22.7±4.6[a]	20.0	43.4	10.0	5.24	3.7	53	42.6	10.1	5.5	3.58	pg/ml
Shi, 2010 (24)	plasma	25	28.6±6.8	37.5	69.2	6.4	29.6	12.4	59	70.0	6.2	40.7	11.3	pg/ml
Molendijk, 2011 (25)	serum	962	33±12.9 [b]	66.8	42.6	11.0	9.14	3.51	382	45.7	12.3	9.4308	3.1755	ng/ml
Satomura, 2011 (26)	serum	109	19.4±8.7	41.3	39.8	14.5	20321.2	8180	163	45.7	16.9	27105.5	8310.2	pg/ml
Serra-Millas, 2011 (27)	plasma	14	24.0±4.35	16.7	54.4	16.1	496.8	132.3	14	52.5	14.1	311.5	90.6	pg/ml
Su, 2011 (28)	serum	18	NA	100.0	21.9	2.0	5.7	6.5	21	25.0	3.0	12.5	3	ng/ml

Sozeri-Varma, 2011 (29)	serum	30	17.1±4.92	80.0	39.8	16.3	1453.4	144.51	40	34.6	7.6	1632.23	252.93	pg/ml
Wolkowitz, 2011 (30)	serum	29	26.1±8.3	34.5	39.1	10.0	14.88	5.41	28	39.0	10.0	20.91	7.07	ng/ml
Karlovic, 2013 (31)	serum	122	27.3±5.6	45.9	46.5	12.4	37.5	13.3	142	44.8	14.2	56.8	6.3	ng/ml
Chu,2012 (32)	serum	12	NA	100.0	82.4	4.4	115.1	57.2	122	81.8	5.0	548.8	370.6	Pg/ml
Deuschle, 2013 (33)	serum	56	23.0±4.2	67.4	52.2	15.9	7.73	5.005	14	56.7	11.6	6.64	2.11	ng/ml
Elfving, 2012 (34)	serum	162	NA	16.7	46.5	9.6	31206	7280	289	45.7	10.4	29274	6806	pg/ml
Oral , 2012 (35)	serum	39	30.0±8.3 [c]	28.2	26.3	4.0	1.75	0.35	40	27.2	4.0	1.91	0.36	ng/ml
Yoshida, 2012 (36)	serum	69	11.8 ±5.5 [d]	35.4	40.5	9.7	21.09	5.6	78	37.2	9.8	23.11	5.9	ng/ml
Papakostas, 2013 (37)	serum	36	21.4±4.4	25.0	42.5	9.8	15174	8163	43	30.0	8.6	10096	6946	pg/ml^{-1}
Ristevska-Dimitrovska, 2013 (38)	serum	23	28.52±4.02	52.2	44.22	NA	13.15	6.75	23	44.04	NA	25.95	9.17	ng/ml
	serum	10	NA	0	51.2	NA	26.84	8.66	10	38	NA	25.04	2.88	ng/ml
Euthymia														
Aydemir, 2005 (3)	serum	10	<25% on HDRS	20.0	31.8	14.3	34.6	7.1	10	39.8	7.1	31.6	8.6	ng/ml
Gervasoni, 2005 (4)	serum	26	<8 [a]	42.3	40.5	10.7	24.40	3.6	26	39.6	12.2	26.4	3.6	ng/ml
Neumeister, 2005 (39)	serum	25	1.1±1.2	33.3	39.8	12.7	8.206 [*]	1.6491[*]	20	33.7	12.8	7.885[*]	1.3000[*]	pg/ml
Monteleone, 2008 (12)	serum	24	3.3 ±2.6	20.8	49.2	12.7	29.4	11.9	22	40.1	16.4	42.5	12.5	ng/ml
Matrisciano, 2009 (17)	serum	7	≤ 7	57.2	42.4	7.5	52.3	12.7	20	31.8	5.9	64.1	13.1	ng/ml
		7	≤ 7	57.2	43.7	9.5	54.9	12.2	20	31.8	5.9	64.1	13.1	ng/ml
		7	≤ 7	42.8	41.3	7.9	41.6	14.1	20	31.8	5.9	64.1	13.1	ng/ml
Molendijk, 2011 (25)	serum	539	16.8±10.3[b]	28.9	43.1	12.9	9.2	3.2	382	45.7	12.3	9.4308	3.1755	ng/ml
		161	20.3±10.6[b]	29.2	43.1	45.4	9.2	3.4	382	45.7	12.3	9.4308	3.1755	ng/ml
Serra-Millas, 2011 (27)	plasma	14	3.93±3.95	16.7	54.4	16.1	369.9	151.5	14	52.5	14.1	311.5	90.6	pg/ml
Pillai, 2012 (40)	plasma	17	according to SCID	NA	67.1	5.7	248.90	117.55	43	67.0	5.3	210.12	103.55	pg/ml
Deuschle, 2013 (33)	serum	11	≤ 7	31.8	50.5	18.0	8.5	5.54	14	56.7	11.6	6.64	2.11	ng/ml
	serum	14	≤ 7	42.1	54.1	13.8	8.61	6.91	14	56.7	11.6	6.64	2.11	ng/ml
Ristevska-Dimitrovska,	serum	23	≤ 7	52.2	44.22	NA	24.73	11.8	10	44.04	NA	25.95	9.17	ng/ml
2013 (38)	serum	10	≤ 7	0	51.2	NA	30.33	9.25	10	38	NA	25.04	2.88	ng/ml

Abbreviations: HDRS – Hamilton depression rating scale; [a] MADRS – Montgomery- Asberg depression rating scale; [b] IDS - inventory of depressive symptoms ; [c] BDI – Beck's depression inventory; [d] SIGH-D - structured interview guide for the HDRS; [*]log-transformed data.

Table 4. Studies included in the BD cross-sectional meta-analysis

Reference	Medication status	Source of BDNF	Patients						Controls					
			N	Severity of mood episode (YMRS; HDRS)	% male	Age mean	SD	BDNF mean	SD	N	Age mean	SD	BDNF mean	SD	units
Mania															
Laske, 2005 **(7)**	Medicated	serum	8	NA	25	50.9	NA	15.7	03.07.	30	58.1	NA	21.3	5.4	ng/ml
Cunha, 2006 **(41)**	Medicated	serum	32	34.5±7.06	56.25	40.2	12.6	0.14	0.04	32	40.69	12.1	0.2	0.07	pg/µg protein
Palomino, 2006 **(42)**	Drug-free	plasma	14	29.5±11.6	57.14	25.93	6.9	3.78	1.99	12	26.27	7.3	7.92	3.75	ng/ml
Yoshimura, 2006 **(43)**	Medicated	plasma	12	22±5.0	44.4	34.0	15.0	24.3	7.9	20	30.0	11.0	25.4	11.7	pg/ml
Machado-Vieira, 2007 **(44)**	Drug-free	plasma	30	36.9±0.5	23.0	26.0	4.0	224.8	76.5	30	26.5	5.2	318.5	114.2	pg/ml
Tramontina, 2009 **(45)**	Medicated	serum	10	26.2±9.6	50.0	34.9	13.8	0.26	0.1	10	34.41	4.0	0.31	0.05	pg/µg protein
de Oliveira, 2009 **(46)**	Drug-free	serum	12	31.9±9.7	33.3	41.8	13.5	0.25	0.08	22	42.84	11.5	0.4	0.12	pg/µg protein
de Oliveira, 2009 **(43)**	Medicated	serum	12	32.5±11.0	33.3	43.8	9.5	0.33	0.14	22	42.84	11.5	0.4	0.12	pg/µg protein
Barbosa, 2010 **(47)**	Drug-free	plasma	34	28.5±6.2	38.2	49.6	14.2	3161.1	1409.3	38	42.9	9.7	1211	1043.4	pg/ml
Huang, 2012 **(48)**	Drug-free	serum	26	42.1±7.5	46.15	33.2	11.7	4.2	4	56	32.5	5.7	6.7	10.1	ng/ml
Depression															
Cunha, 2006 **(41)**	Medicated	serum	21	22.81±4.4	28.57	40.7	9.3	0.15	0.13	32	40.69	12.1	0.2	0.07	Pg/µg protein
Mackin, 2006 **(49)**	Medicated	serum	20	18.1±9.0	95	48.6	10.8	13755.2	7932.2	14	43.7	12.9	13400.4	9107	pg/ml
Yoshimura, 2006 **(43)**	Medicated	plasma	6	24±6.0	44.4	34.0	15.0	16.1	8.5	20	30.0	11.0	25.4	11.7	ng/ml

de Oliveira,2009 **(43)**	Drug-free	serum	10	23.4±7.5	11.0	35.0	11.2	0.21	0.1	22	35.24	8.1	0.4	0.12	pg/µg protein
de Oliveira,2009 **(43)**	Medicated	serum	10	19.5±7.7	11.0	35.4	5.7	0.24	0.24	22	35.24	8.1	0.4	0.12	pg/µg protein
Fernandes, 2009 **(15)**	Medicated	plasma	40	23.4±7.5	24.5	41.32	8.5	0.15	0.08	30	41.0	11.9	0.38	0.12	pg/µg protein
Su, 2011 **(28)**	Drug-free	serum	10	NA	100	22.7	2.9	5.4	4.7	21	25.0	3.0	12.5	3.0	ng/ml
Euthymia															
Cunha, 2006 **(41)**	Medicated	serum	32	3.16±5.44; 4.28 ±4.16	54.5	40.3	12.0	0.19	0.08	32	40.69	12.1	0.2	0.07	pg/µg protein
Monteleone, 2008 **(12)**	Drug-free	serum	28	3.92±3.29; 9.27±3.74	39.3	42.54	11.5	27.9	14.8	22	44.08	13.8	42.5	12.5	ng/ml
Tramontina, 2007 **(50)**	NA	serum	114	NA	28.07	44.42	10.8	0.14	0.08	137	40.1	16.4	0.16	0.08	pg/µg protein
Kauer-Sant' Anna, 2009 (early stage)**(51)**	Medicated	serum	30	1.53 ±2.8; 3.80±7.10	43.3	22.4	3.9	0.91	0.22	30	22.1	3.4	0.77	0.2	pg/ml
Kauer-Sant' Anna, 2009 (late stage) **(48)**	Medicated	serum	30	3.6 ±4.1; 9.20±6.00	30	41.4	8.4	0.33	0.16	30	43.2	6.4	0.57	0.24	pg/ml
Dias, 2009 **(52)**	Medicated	serum	65	1.0±1.72; 2.6±2.36	36.9	37.8	10.5	0.28	0.21	50	33.6	9.7	0.24	0.21	pg/ml
Barbosa, 2010 **(47)**	Medicated	plasma	19	1.3±2.5; 1.9±1.8	42.1	44.5	10.9	2695.8	1570.1	38	42.9	9.7	1211	1043.4	pg/ml
Rybakowski, 2010 **(53, 54)**	Medicated	plasma	60	0.6 ±0.9/ 2.6±1.8	41.6	52.6	10.2	23.6	13.3	60	52.1	13.6	28.9	10.9	ng/ml
Barbosa, 2012 **(53)**	Medicated	plasma	25	1.08 ±1.53 / 1.52 ±1.64	32	50.88	9.1	3991.542	2358.264	25	48.04	7.1	1752.191	1358.96	pg/ml
Chou, 2012 **(55)**	Medicated	plasma	23	3.1±0.9/ 6.1±1.8[a]	26.1	36.5	8.9	328	242.4	33	37.6	7.8	334.5	343.6	pg/ml

Abbreviations: HDRS – Hamilton depression rating scale; YMRS – Young mania rating scale; [a]MADRS - Montgomery-Asberg depression rating scale;

Table 5. Studies included in MDD longitudinal meta-analysis.

Reference	Response to treatment	Source of BDNF	N of patients	Severity of depression (HDRS)	Duration of treatment	Type of medication	% male	Age		BDNF pretreatment		BDNF post-treatment		units
								mean	SD	mean	SD	mean	SD	
Aydemir, 2005 (3)	remitters	serum	10	23.2±4.6	8w	VNL	20.0	31.8	14.3	17.90	9.10	34.60	7.10	ng/ml
Gonul , 2005 (5)	responders	serum	28	27.28±3.53	8w	VNL, SER, FLX, PRX	25.0	35.5	8.1	20.80	6.70	33.30	9.89	ng/ml
Gervasoni, 2005 (4)	remitters	serum	26	32.8±4.9[a]	13.5 ±6w	PRX, PRX+Li, Clm, VNL	42.3	40.5	10.7	22.60	3.60	24.40	3.6	ng/ml
Aydemir, 2006 (8)	responders	serum	20	39.75±7.4	6w	ES	0	35.55	7.6	27.68	13.74	38.57	15.3	ng/ml
Yoshimura, 2007	responders	serum	14	24 ± 7	8w	PRX	37.7	47	19	9.10	7.70	22.00	8.5	ng/ml
(56)	non-responders		12							9.60	8.00	13.80	6.70	ng/ml
	responders		7	23 ± 6		MLN				9.90	9.00	18.20	9.10	ng/ml
	non-responders		9							9.60	4.60	13.40	7.10	ng/ml
Huang, 2008 (57)	responders	serum	58	34.8 ± 4.7	4w	FLX, PRX, VNL, MIR	18.0	37.4	10.3	11.70	7.70	13.10	9.10	ng/ml
	non-responders		21	28.4 ± 4.8				37.0	10.2	7.80	5.50	8.80	7.30	ng/ml
Lee, 2008 (58)	responders	plasma	24	29.5±8.6	6w	CTP, PRX, VNL	34.4	46.6	16.7	733.00	512.20	1153.6	766.00	pg/ml
	non-responders		8	29.9±7.9				36.7	17.6	593.50	634.00	654.70	559.80	pg/ml
Piccinni, 2008 (59)	responders	serum	9	22.8 ± 5.3	4w	CTP, SER, PRX, AMT, IMI, TrIMI, DesIP	13.3	47.0	10.8	19300.0	8800.00	22089.00	8 373.00	pg/ml
		plasma	9							2900.00	1900.00	4448.00	2 095.00	pg/ml
Yoshimura, 2008	responders	serum	5	22±6	4w	SER+ RIS	28.5	54.0	10.0	8.10	2.70	11.50	0.90	ng/ml
(60)	non-responders		5							7.80	2.20	7.90	2.40	ng/ml
Hellweg, 2008	pooled	serum	20	23.8±5.1	5w	AMT	22.5	49.7	14.4	13.00	3.70	15.10	5.90	pg/ml
(61)	pooled		20	22.6±3.		PRX		51.4	14.4	13.20	5.10	12.00	4.80	pg/ml
Basterzi, 2009	responders	serum	17	26.5 ± 4.9	6w	VNL, FLX	26.8	31.0	14.0	43280.0	13932.0	50011.00	12060.00	pg/ml
(14)	non-responders		12	25.7 ± 3.5				32.0	11.0	39214.0	11439.0	44362.00	14369.00	pg/ml
Matrisciano, 2009	remitters	serum	7	19 ±5.3	6 month	SER	52.4	42.4	7.5	29.40	12.60	52.30	12.7	ng/ml
(17)			7	19.4±4.5		VNL		43.7	9.5	32.20	14.00	54.90	12.2	ng/ml
			7	14.3± 5.9		ES		41.3	7.9	44.40	16.40	41.60	14.1	ng/ml
Umene-Nakano,	responders	serum	37	<15	8w	SER	40.7	55.0	16.0	7.28	7.65	10.46	10.51	ng/ml

2009 (19)	non-responders		22								14.42	12.53	14.76	13.59	ng/ml
Gorgulu, 2009	responders	serum	22	24.3±5.0	6w	SER	26.8	33.3	11.2	19.54	4.26	52.29	6.76	ng/ml
(16)	responders		19	25.5±4.5		SER+ Total sleep deprivation		40.0	11.7	21.59	4.34	45.20	8.85	ng/ml
Shi, 2010 (24)	responders	plasma	15	28.6±6.8	6w	FLX, SER	37.5	69.2	6.5	859.83	211.36	906.94	145.44	pg/ml
Rojas, 2011 (62)	responders	serum	26	23.5 ±5.2	6w	VNL	29.4	42.5	11.5	8.1	7.8			pg/ml
	non-responders		8	22.1 ±2.				39.6	10.8	16.3	12.1	5.6	1.23	pg/ml
Serra-Millas, 2011 (27)	responders	plasma	16	24±4.35	8w	ES	16.7	38.5	16.0	496.8	132.3	454.39	167.75	pg/ml
Wolkowitz, 2011	responders	serum	9	26.1 ±8.3	8w	ES	64.0	39.0	10.1	16.88	5.81	18.14	4.71	ng/ml
(30)	non-responders		6							12.7	4.5	16.42	2.49	ng/ml
Kurita, 2012 (63)	remitters	plasma	38	33.7±8.9[a]	8w	AMT, CLM; IMI, FLX, MPT, MLN, PRX, SER, TRZ, SLP	50.0	44.3	18.6	1827.0	1340.0	2402.0	1610.0	pg/ml
	non-responders		10	35.1±6.5[a]			30.0	50.4	15.2	2932.0	2373.0	2117.0	2042.0	pg/ml
Dreimuller, 2012 (64)	pooled	plasma	39	20.8±4.5	2w	ES, SER, FLX, VNL, DLX, MIR, AMT	48.7	44.8	13.2	298.00	196.00	334.00	157.00	pg/ml
Deuschle,2013 (33)	remitters	serum	11	22.7±4.2	4w	MIR	75.9	50.5	18.0	6.21	4.22	8.5	5.4	ng/ml
Ristevska-Dimitrovska, 2013 (38)	remitters	serum	23	28.52±4.02	3w	SER, PRX, VEN	52.2	44.22	NA	13.15	6.75	24.73	11.80	ng/ml
	remitters	serum	10	NA	3w	NA	0	51.2	NA	26.84	8.66	30.33	9.25	ng/ml

Abbreviations: HDRS – Hamilton depression rating scale; [a]MADRS - Montgomery-Asberg depression rating scale; ES -escitalopram; SER - sertraline; FLX-fluoxetine; VNL - venlafaxine; DLX - duloxetine; MIR - mirtazapine; AMT - amitriptyline; CLM – clomipramine; MPT - maprotiline; MLN - milnacipran; PRX - paroxetine; TRZ- trazodone;SLP - sulpiride; IM – imipramine; TrIMI – trimipramine; DesIP – desipramin; CTP – citalopram; RIS – risperidone; Li - lithium sulfate

Table 6. Longitudinal studies on BDNF in bipolar disorder.

Reference	Response to treatment	Source of BDNF	N of patients	Severity of depression (YMRS, HDRS)	Duration of treatment	Type of medication	% male	Age		BDNF pretreatment		BDNF post-treatment		
								mean	SD	mean	SD	mean	SD	units
Mania														
Palomino, 2006 **(42)**	responders	plasma	14	NA	4	Li + aa/p	na	23.7	1.0	3.78	1.9	5.12	2.78	ng/ml
Yoshimura, 2006 **(43)**	responders	serum	12	22±5.0	4	RSP; RSP + VA	44.4	34	15.0	23.4	11	26.5	12	pg/ml
Tramontina, 2009 **(45)**	responders	serum	10	26.2±9.6		Li + aa/p	50	34.9	13.85	0.26	0.1	0.38	0.14	pg/µg protein
De Sousa, 2011 **(65)**	responders	plasma	10	37.3±9.5	4	Li	60	25.4	7.5	406.3	69.5	510.9	127.1	pg/ml
Grande, 2012 **(66)**	responders	serum	3	16(13-20)	16	QTP	50	42	(29-55)	57.7163	2.25684	40.5984	9.82605	pg/ml
Huang, 2012 **(67)**	responders	serum	21	42.1±7.5	4	VA or Li + A/P	38	33.2	11.7	4	4	4.6	3.7	ng/ml
Depression														
Yoshimura, 2006 **(43)**	non-responders	serum	6	24.0±6.0	4	RSP; RSP+ VA	44.4	34	15.0	16.1	8	17.1	7	pg/ml
Grande, 2012 **(66)**	responders	serum	8	22(18-26)	16	QTP	33	42	(29-55)	50.7786	10.46884	61.5087	14.35482	pg/ml
Grande, 2012 **(66)**	non-responders	serum	4	22(18-26)	16	QTP	33	42	(29-55)	48.0348	12.96763	48.0481	12.66159	pg/ml

Abbreviations: YMRS – Young mania rating scale; HDRS – Hamilton depression rating scale; Li – lithium; VA – valproic acid; a/p – antipsychotics; aa/p – atypical antipsychotics; a/d – antidepressants; m/s - mood stabilizer; QTP – quetiapine; RSP – risperidone.

Funnel plots for cross-sectional meta-analyses

Figure 1. Funnel plot for cross-sectional studies of BDNF plasma levels in patients with MDD in acute state versus control subjects.

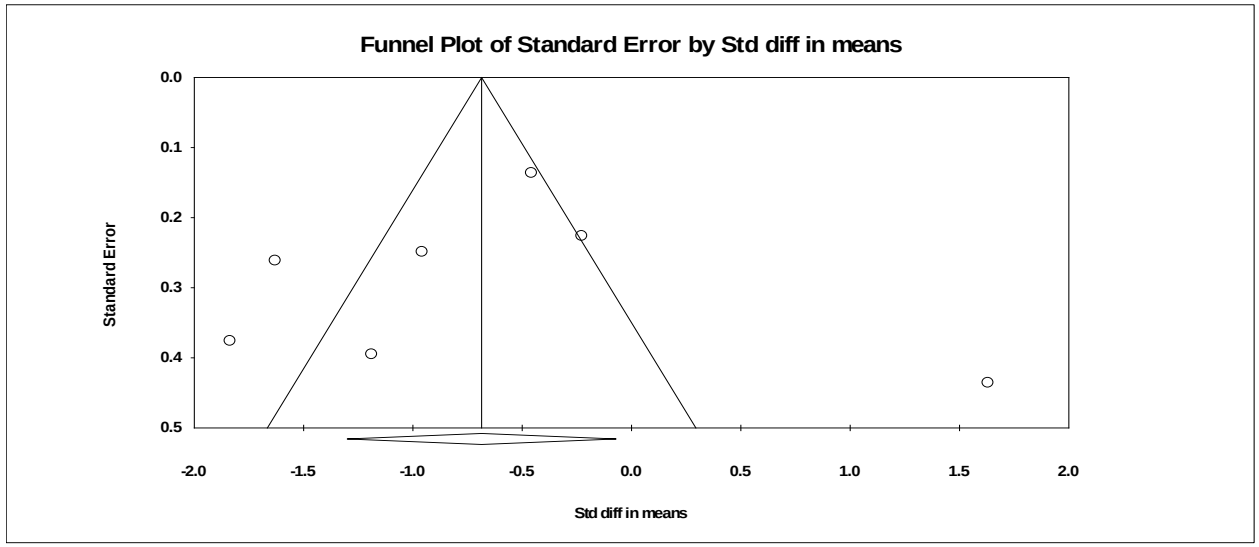


Figure 2. Funnel plot for cross-sectional studies of BDNF serum levels in patients with MDD in acute state versus control subjects. Reflects signs of publication bias.

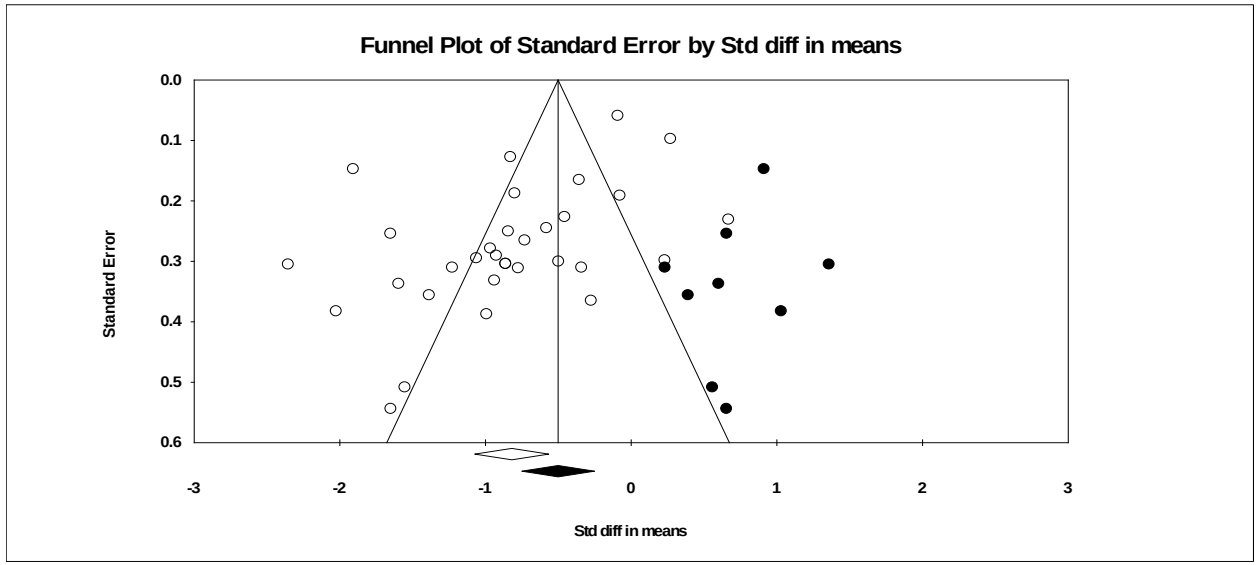


Figure 3. Funnel plot for cross-sectional studies of BDNF serum levels in patients with MDD in euthymic state versus control subjects.

Figure 4. Funnel plot for cross-sectional studies of BDNF serum levels in patients with BD depressive state versus control subjects.

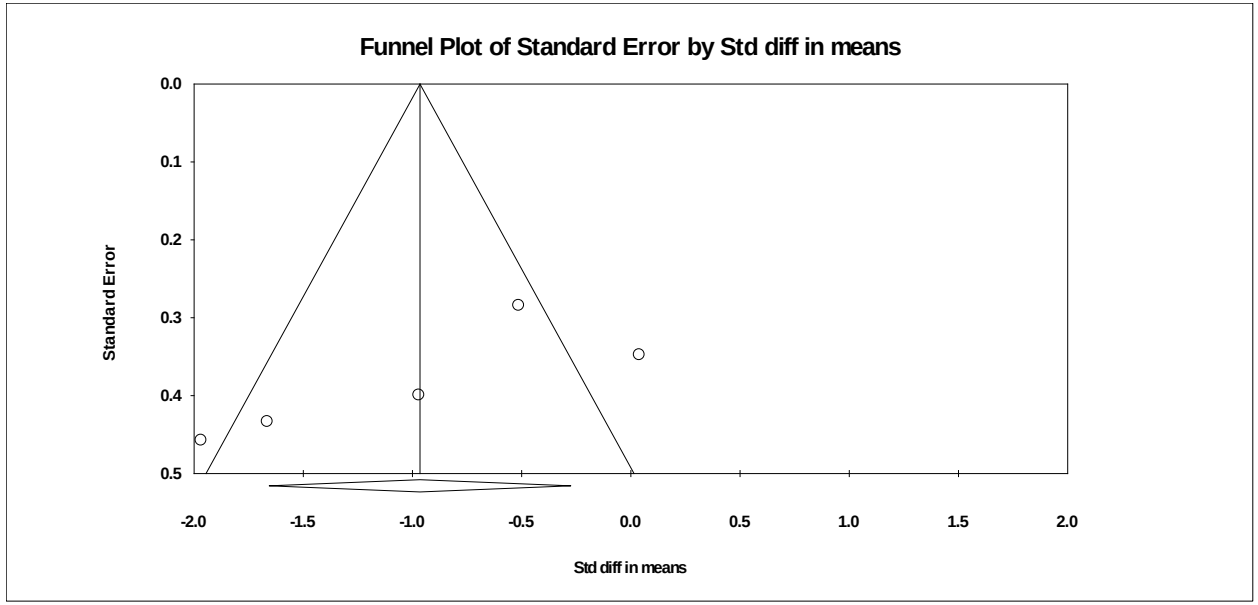


Figure 5. Funnel plot for cross-sectional studies of BDNF plasma levels in patients with BD manic state versus control subjects.

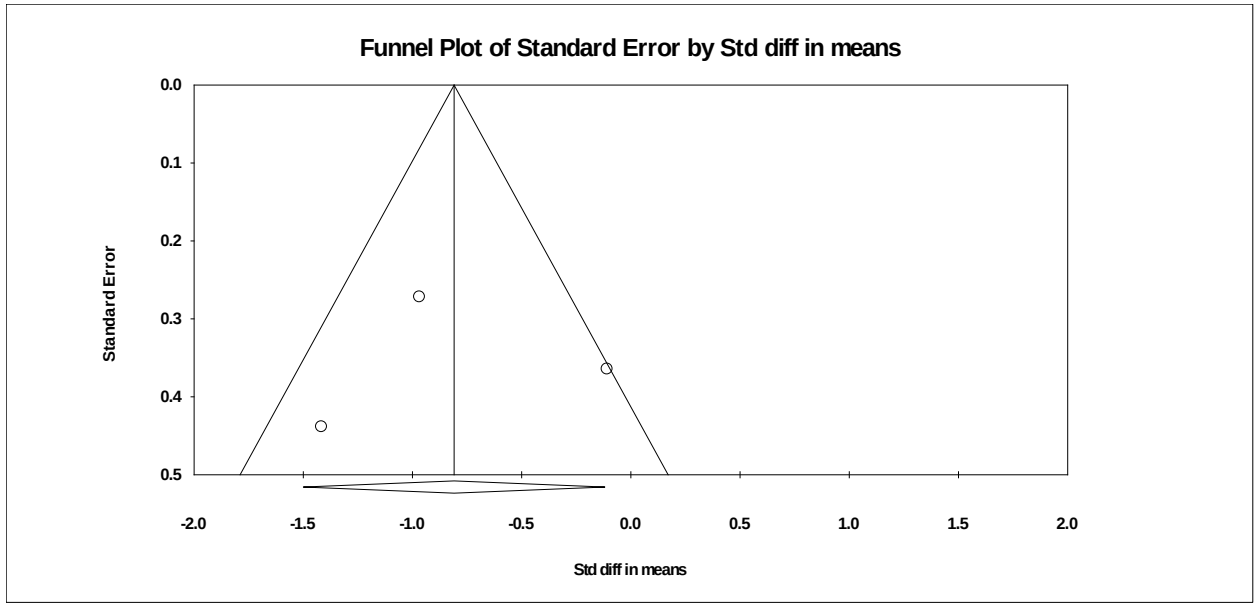


Figure 6. Funnel plot for cross-sectional studies of BDNF serum levels in patients with BD manic state versus control subjects.

Figure 7. Funnel plot for cross-sectional studies of BDNF plasma levels in patients with BD euthymic state versus control subjects.

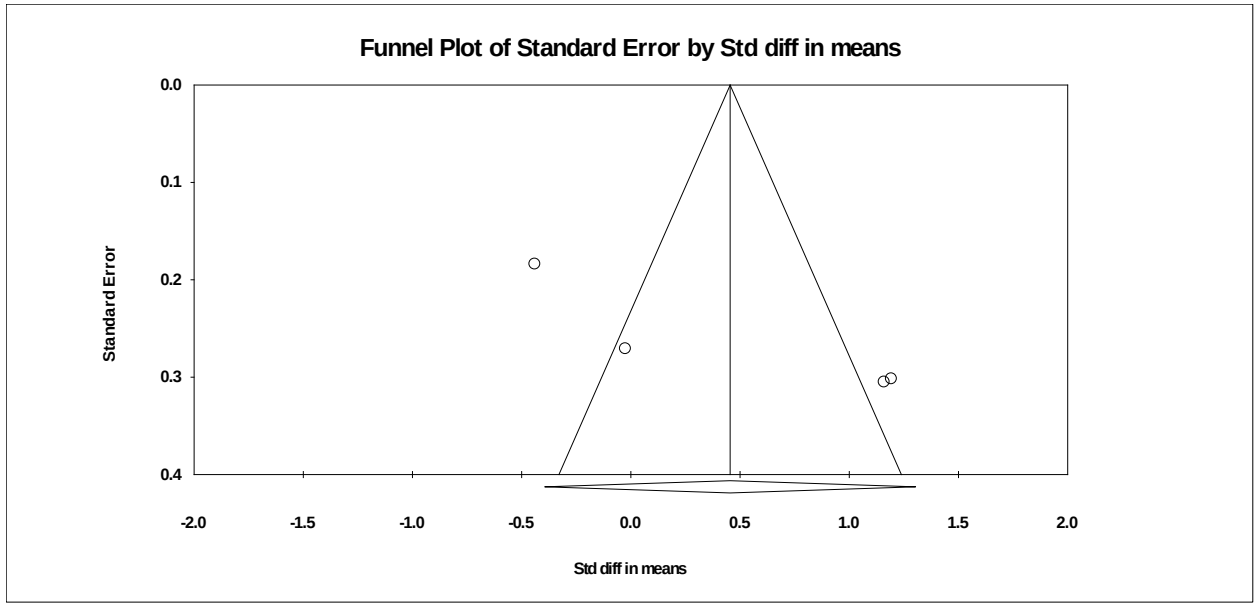


Figure 8. Funnel plot for cross-sectional studies of BDNF serum levels in patients with BD euthymic state versus control subjects.

Funnel plots for longitudinal studies

Figure 9. Funnel plot for longitudinal studies of BDNF levels change in serum of patients with MDD who reached remission.

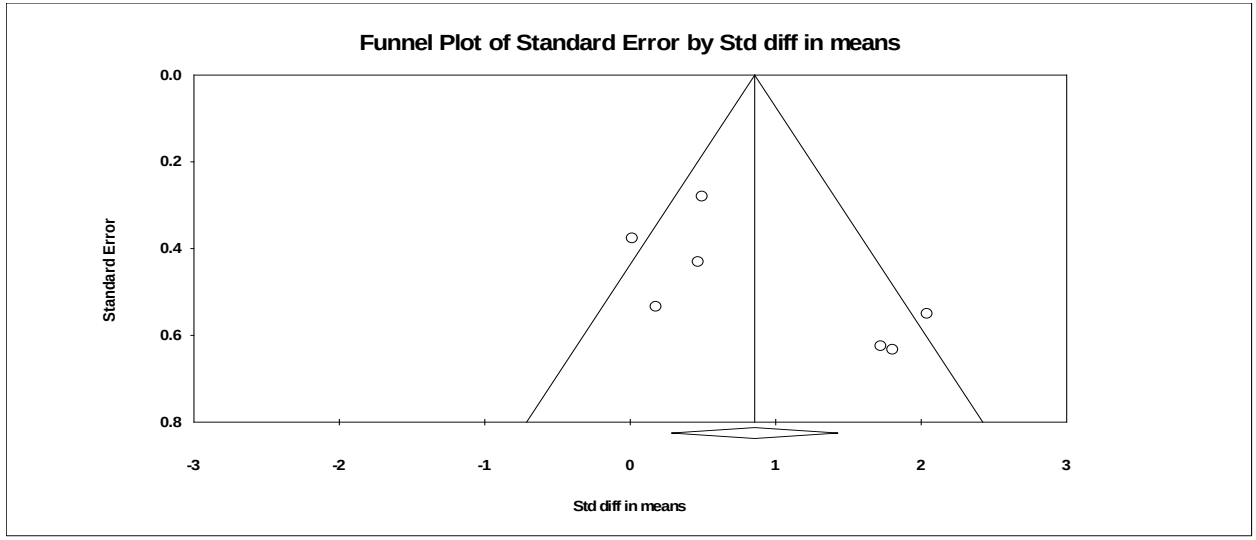


Figure 10. Funnel plot for longitudinal studies of BDNF levels change in serum of patients with MDD who responded to treatment. Reflects signs of publication bias.

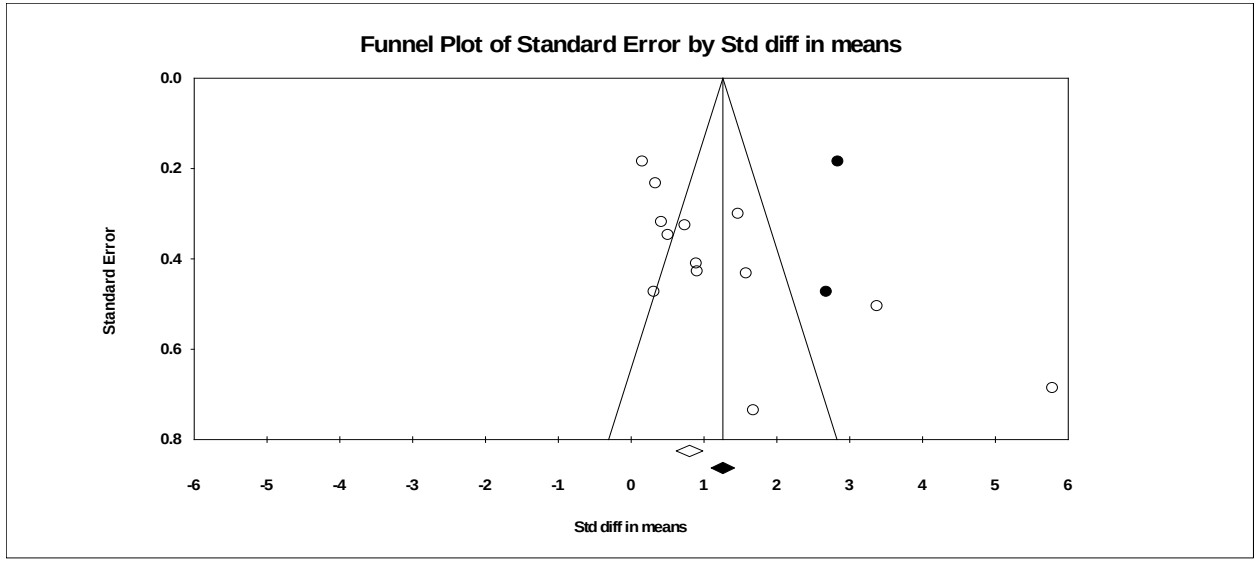


Figure 11. Funnel plot for longitudinal studies of BDNF levels change in serum of patients with MDD who did not respond to treatment. Reflects signs of publication bias.

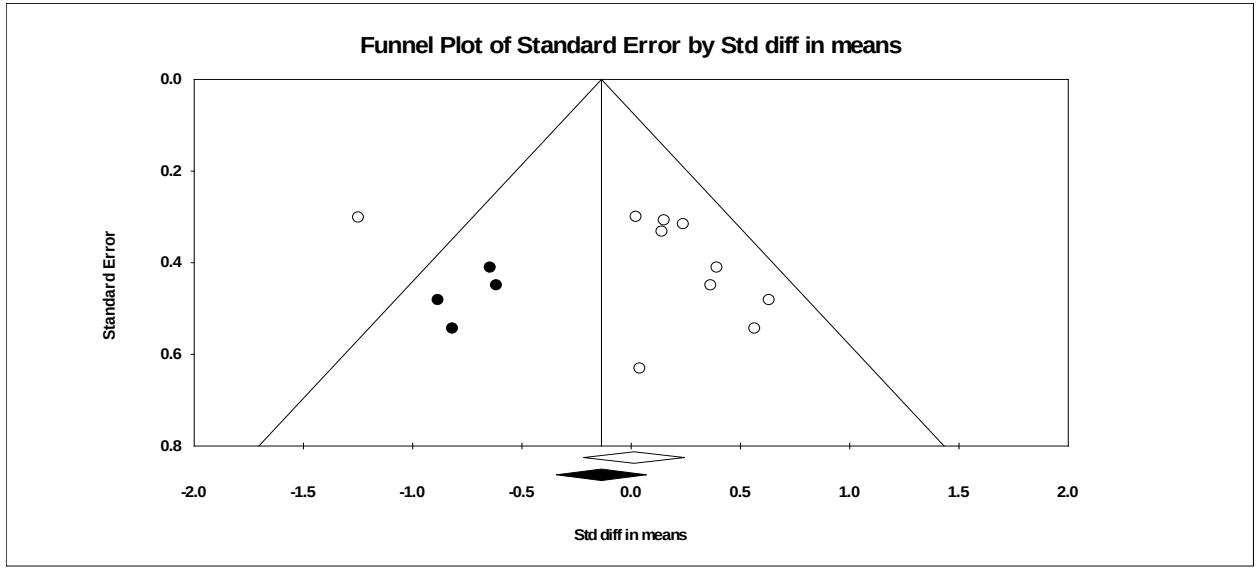


Figure 12. Funnel plot for longitudinal studies of BDNF levels change in plasma of patients with MDD who responded to treatment

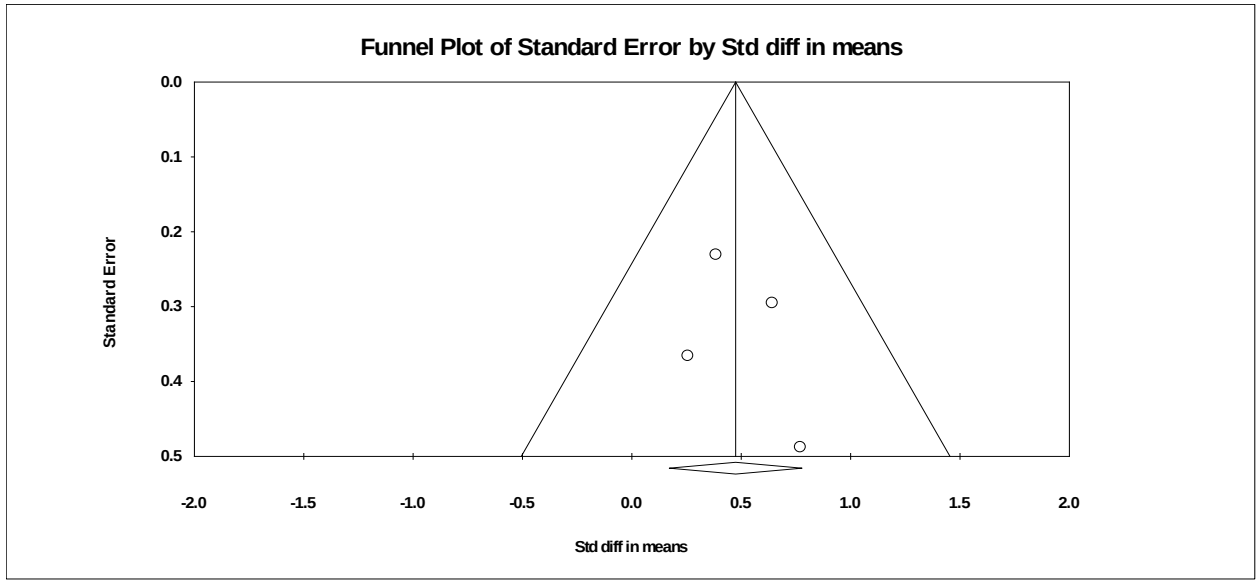


Figure 13. Forest plot for meta-analysis of cross-sectional studies of serum BDNF levels in depressive state of MDD.

Study name	Subgroup within study	Diagnosis	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aydemir, 2005	depression	MDD	-1.547	0.510	0.260	-2.547	-0.548	-3.036	0.002
Aydemir, 2006	depression	MDD	-0.932	0.333	0.111	-1.585	-0.280	-2.800	0.005
Basterzi, 2009	depression	MDD	-0.492	0.302	0.091	-1.083	0.099	-1.631	0.103
Bocchio-Chiavetto, 2010	depression	MDD	-0.071	0.193	0.037	-0.449	0.306	-0.371	0.711
Chu,2012	depression	MDD	-1.221	0.312	0.097	-1.832	-0.610	-3.918	0.000
Deuschle, 2012	depression	MDD	0.237	0.299	0.090	-0.350	0.824	0.792	0.428
Diniz, 2009	depression	MDD	-0.575	0.246	0.061	-1.058	-0.092	-2.335	0.020
Eker, 2010	depression	MDD	-0.855	0.305	0.093	-1.454	-0.257	-2.801	0.005
Elfving, 2012	depression	MDD	0.277	0.099	0.010	0.084	0.470	2.808	0.005
Fernandes, 2009	depression	MDD	-0.268	0.366	0.134	-0.986	0.450	-0.732	0.464
Gervasoni, 2005	depression	MDD	-1.056	0.296	0.088	-1.636	-0.475	-3.566	0.000
Gonul, 2005	depression	MDD	-0.768	0.313	0.098	-1.381	-0.156	-2.459	0.014
Gorgulu, 2009	depression	MDD	-2.348	0.306	0.094	-2.948	-1.747	-7.665	0.000
Huang, 2008	depression	MDD	-0.454	0.137	0.019	-0.723	-0.185	-3.308	0.001
Hung, 2010	depression	MDD	-0.855	0.305	0.093	-1.454	-0.257	-2.801	0.005
Karege, 2002	depression	MDD	-0.724	0.267	0.071	-1.247	-0.202	-2.717	0.007
Karlovic, 2012	depression	MDD	-1.901	0.149	0.022	-2.192	-1.610	-12.793	0.000
Laske, 2005	depression	MDD	-0.334	0.312	0.097	-0.945	0.276	-1.073	0.283
Matrisciano, 2009	depression	MDD	-2.019	0.384	0.147	-2.771	-1.267	-5.260	0.000
Molendijk, 2011	depression	MDD	-0.085	0.060	0.004	-0.204	0.034	-1.406	0.160
Monteleone, 2008	depression	MDD	-0.986	0.389	0.151	-1.748	-0.224	-2.537	0.011
Oral , 2012	depression	MDD	-0.451	0.228	0.052	-0.897	-0.004	-1.977	0.048
Ozan, 2009	depression	MDD	-0.793	0.189	0.036	-1.162	-0.423	-4.202	0.000
Papakostas, 2013	depression	MDD	0.675	0.232	0.054	0.220	1.130	2.907	0.004
Piccini, 2008(1)	depression	MDD	-1.644	0.545	0.297	-2.712	-0.575	-3.015	0.003
Satomura, 2011	depression	MDD	-0.822	0.129	0.017	-1.074	-0.569	-6.386	0.000
Shimizu,2003	depression	MDD	-0.919	0.292	0.085	-1.491	-0.348	-3.151	0.002
Sozeri-Varma, 2011	depression	MDD	-0.837	0.252	0.063	-1.331	-0.344	-3.327	0.001
Su, 2011	depression	MDD	-1.380	0.357	0.128	-2.080	-0.680	-3.864	0.000
Wolkowitz, 2011	depression	MDD	-0.960	0.280	0.078	-1.509	-0.412	-3.432	0.001
Yoshida, 2012	depression	MDD	-0.351	0.167	0.028	-0.677	-0.024	-2.105	0.035
Yoshimura, 2007	depression	MDD	-1.645	0.256	0.065	-2.146	-1.144	-6.436	0.000
Ristevska-Dimitrovska, 2013	depression	MDD	-1.590	0.338	0.114	-2.253	-0.927	-4.700	0.000
			-0.806	0.123	0.015	-1.047	-0.564	-6.536	0.000

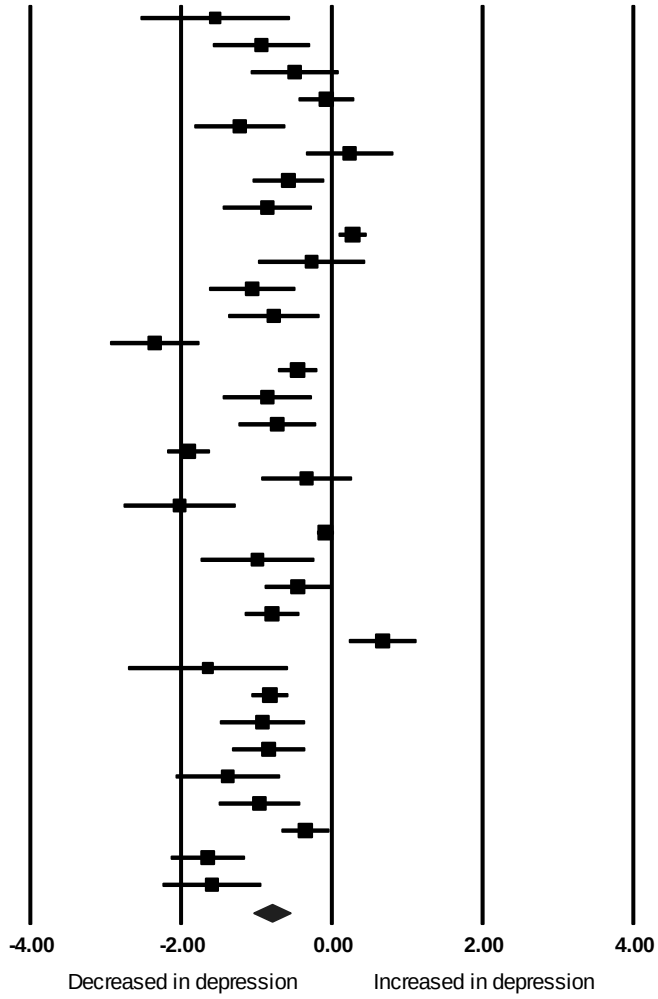


Figure 14. Forest plot for meta-analysis of cross-sectional studies of plasma BDNF levels in depressive state of MDD.

Study name	Subgroup within study	Diagnosis	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Karege, 2005	depression	MDD	-1.626	0.262	0.069	-2.140	-1.112	-6.201	0.000
Lee, 2008	depression	MDD	-0.224	0.227	0.052	-0.669	0.221	-0.985	0.325
Piccini, 2008	depression	MDD	-1.185	0.511	0.261	-2.187	-0.183	-2.319	0.020
Serra-Millas, 2011	depression	MDD	1.634	0.437	0.191	0.779	2.490	3.744	0.000
Shi. 2010	depression	MDD	-0.954	0.250	0.062	-1.444	-0.465	-3.821	0.000
Umene-Nakano, 2008	depression	MDD	-1.833	0.377	0.142	-2.571	-1.094	-4.864	0.000
			-0.713	0.429	0.184	-1.554	0.128	-1.662	0.097

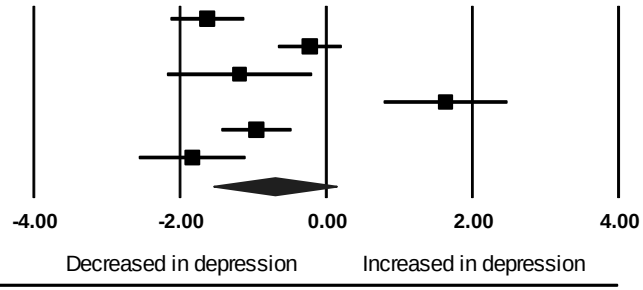


Figure 15. Forest plot for meta-analysis of cross-sectional studies of serum BDNF levels in euthymic state of MDD.

Study name	Subgroup within study	Diagnosis	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aydemir, 2005	remission	MDD	0.380	0.451	0.204	-0.504	1.265	0.843	0.399
Gervasoni, 2005	remission	MDD	-0.556	0.283	0.080	-1.110	-0.002	-1.966	0.049
Matrisciano, 2009	remission	MDD	-0.907	0.456	0.208	-1.801	-0.013	-1.989	0.047
Monteleone, 2008	remission	MDD	-1.075	0.316	0.100	-1.693	-0.456	-3.404	0.001
Neumeister, 2005	remission	MDD	0.210	0.301	0.090	-0.380	0.799	0.697	0.486
Matrisciano, 2009 (1)	remission	MDD	-0.714	0.450	0.202	-1.595	0.168	-1.587	0.113
Matrisciano, 2009 (2)	remission	MDD	-1.686	0.495	0.245	-2.657	-0.715	-3.402	0.001
Molendijk, 2011 (1)	remission	MDD	-0.072	0.067	0.004	-0.203	0.059	-1.081	0.279
Molendijk, 2011 (2)	remission	MDD	-0.071	0.094	0.009	-0.255	0.113	-0.757	0.449
Deuschle, 2013	remission	MDD	0.467	0.408	0.167	-0.333	1.267	1.144	0.253
Deuschle, 2013 (1))	remission	MDD	0.386	0.381	0.146	-0.362	1.133	1.011	0.312
Ristevska-Dimitrovska, 2013	remission	MDD	-0.110	0.379	0.144	-0.853	0.633	-0.290	0.772
Ristevska-Dimitrovska, 2013 (1)	remission	MDD	0.772	0.464	0.215	-0.136	1.681	1.666	0.096
			-0.197	0.125	0.016	-0.442	0.048	-1.573	0.116

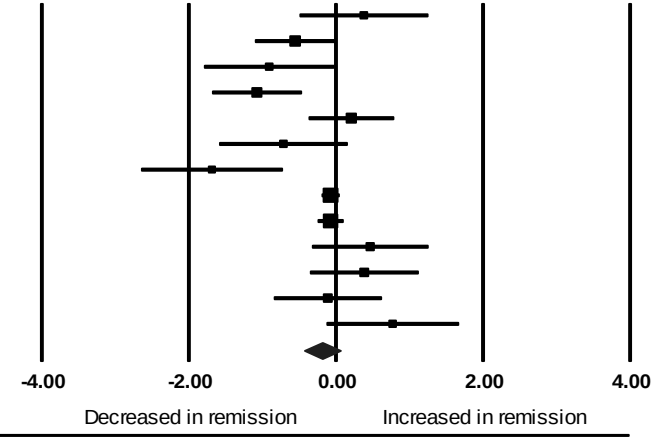


Figure 16. Forest plot for meta-analysis of cross-sectional studies of plasma BDNF levels in euthymia state of major depression.

Study name	Subgroup within study	Diagnosis	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Serra-Millas, 2011	remission	MDD	0.468	0.383	0.147	-0.283	1.219	1.221	0.222
Pillai, 2012	remission	MDD	0.360	0.288	0.083	-0.205	0.926	1.250	0.211
			0.399	0.230	0.053	-0.052	0.851	1.733	0.083

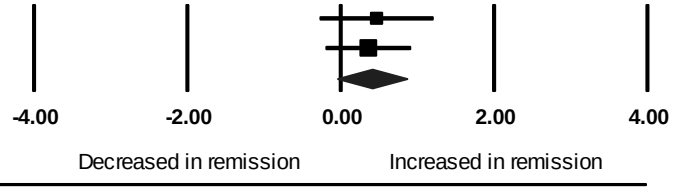


Figure 17. Forest plot for meta-analysis of cross-sectional studies of plasma and serum BDNF levels in depressive state of BD.

Group by Source	Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
plasma	Fernandes, 2009	depression	-2.322	0.311	0.097	-2.932	-1.712	-7.461	0.000
plasma	Yoshimura, 2006(1)	depression	-0.837	0.480	0.230	-1.777	0.103	-1.745	0.081
plasma			-1.648	0.597	0.356	-2.818	-0.479	-2.763	0.006
serum	Su, 2011(1)	depression	-1.964	0.458	0.210	-2.862	-1.067	-4.288	0.000
serum	Cunha, 2006	depression	-0.510	0.285	0.081	-1.069	0.049	-1.789	0.074
serum	de Oliveira, 2009	depression	-1.661	0.434	0.189	-2.512	-0.810	-3.826	0.000
serum	de Oliveira, 2009(1)	depression	-0.967	0.400	0.160	-1.751	-0.183	-2.418	0.016
serum	Mackin, 2006	depression	0.042	0.349	0.121	-0.641	0.725	0.121	0.904
serum			-0.971	0.375	0.141	-1.706	-0.236	-2.588	0.010
Overall			-1.163	0.318	0.101	-1.785	-0.541	-3.662	0.000

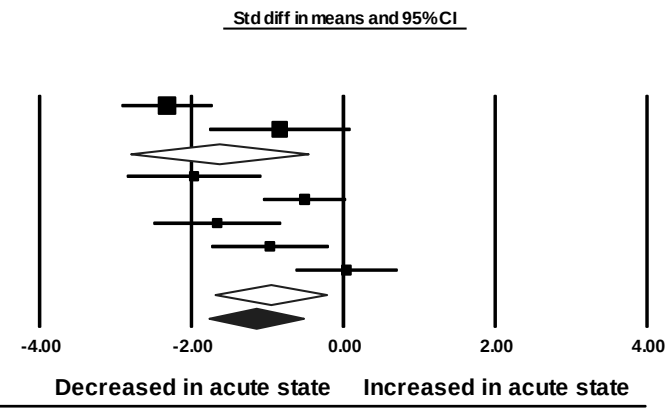


Figure 18. Forest plot for meta-analysis of cross-sectional studies of plasma and serum BDNF levels in manic state of BD (including a study of Barbosa, 2010).

Group by Source	Study name	Subgroup within study	Diagnosis	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
plasma	Barbosa, 2010	mania	BD	1.586	0.271	0.073	1.056	2.116	5.862	0.000
plasma	Machado-Vieira, 2007	mania	BD	-0.964	0.273	0.074	-1.499	-0.429	-3.534	0.000
plasma	Palomino, 2006	mania	BD	-1.413	0.439	0.193	-2.274	-0.551	-3.214	0.001
plasma	Tramontina, 2009	mania	BD	-0.632	0.458	0.210	-1.531	0.266	-1.380	0.168
plasma				-0.317	0.518	0.268	-1.333	0.698	-0.612	0.540
serum	Cuncha, 2006(1)	mania	BD	-1.052	0.267	0.071	-1.575	-0.530	-3.946	0.000
serum	De Oliveira, 2009	mania	BD	-1.390	0.396	0.157	-2.167	-0.613	-3.505	0.000
serum	De Oliveira, 2009(1)	mania	BD	-0.550	0.365	0.133	-1.266	0.165	-1.507	0.132
serum	Huang, 2012	mania	BD	-0.288	0.238	0.057	-0.756	0.179	-1.210	0.226
serum	Yoshimura, 2006	mania	BD	-0.105	0.365	0.134	-0.821	0.611	-0.288	0.774
serum				-0.673	0.458	0.210	-1.571	0.225	-1.469	0.142
Overall				-0.517	0.343	0.118	-1.189	0.156	-1.506	0.132

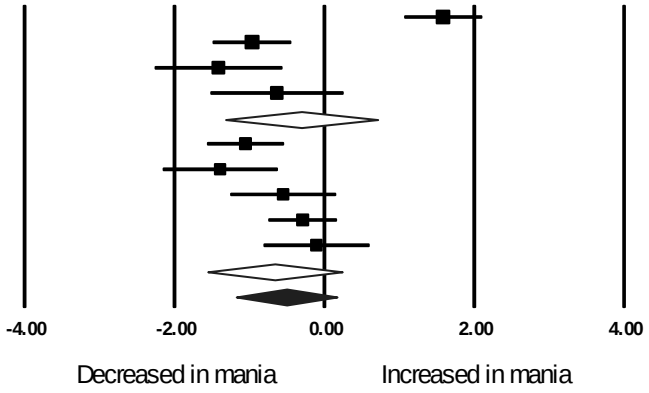


Figure 18a. Forest plot for meta-analysis of cross-sectional studies of plasma and serum BDNF levels in bipolar mania (excluding a study of Barbosa, 2010).

Group by Source	Study name	Subgroup within study	Diagnosis	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
plasma	Machado-Vieira, 2007	mania	BD	-0.964	0.273	0.074	-1.499	-0.429	-3.534	0.000
plasma	Palomino, 2006	mania	BD	-1.413	0.439	0.193	-2.274	-0.551	-3.214	0.001
plasma	Tramontina, 2009	mania	BD	-0.632	0.458	0.210	-1.531	0.266	-1.380	0.168
plasma				-1.001	0.290	0.084	-1.569	-0.433	-3.456	0.001
serum	Cuncha, 2006(1)	mania	BD	-1.052	0.267	0.071	-1.575	-0.530	-3.946	0.000
serum	De Oliveira, 2009	mania	BD	-1.390	0.396	0.157	-2.167	-0.613	-3.505	0.000
serum	De Oliveira, 2009(1)	mania	BD	-0.550	0.365	0.133	-1.266	0.165	-1.507	0.132
serum	Huang, 2012	mania	BD	-0.288	0.238	0.057	-0.756	0.179	-1.210	0.226
serum	Yoshimura, 2006	mania	BD	-0.105	0.365	0.134	-0.821	0.611	-0.288	0.774
serum				-0.657	0.206	0.042	-1.061	-0.254	-3.194	0.001
Overall				-0.773	0.168	0.028	-1.102	-0.444	-4.605	0.000

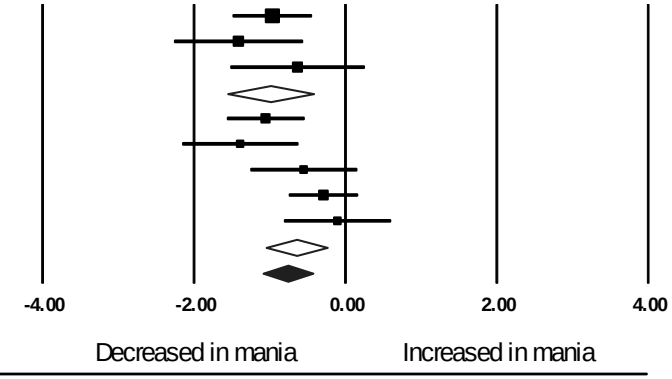


Figure 19. Forest plot for meta-analysis of cross-sectional studies of plasma and serum BDNF levels in euthymic state of bipolar disorder.

Group by Source	Study name	Subgroup within study	Medication	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
plasma	Barbosa, 2010(1)	euthymia	Medicated	1.197	0.303	0.092	0.604	1.790	3.956	0.000
plasma	Rybakowski, 2010	euthymia	Medicated	-0.436	0.185	0.034	-0.798	-0.074	-2.360	0.018
plasma	Barbosa, 2012	euthymia	Medicated	1.164	0.306	0.094	0.564	1.763	3.804	0.000
plasma	Chou, 2012	euthymia	Medicated	-0.021	0.272	0.074	-0.554	0.511	-0.078	0.938
plasma				0.442	0.344	0.118	-0.232	1.116	1.285	0.199
serum	Cunha, 2006(2)	euthymia	Medicated	-0.133	0.250	0.063	-0.624	0.357	-0.532	0.595
serum	Monteleone, 2006	euthymia	Drug-free	-1.055	0.304	0.092	-1.650	-0.459	-3.472	0.001
serum	Tramontina, 2007	euthymia	NA	-0.250	0.127	0.016	-0.499	-0.001	-1.964	0.049
serum	Kauer-Sant'Anna, 2009	euthymia	Medicated	0.666	0.265	0.070	0.146	1.186	2.510	0.012
serum	Kauer-Sant'Anna, 2009(1)	euthymia	Medicated	-1.177	0.280	0.078	-1.725	-0.629	-4.208	0.000
serum	Dias, 2009	euthymia	Medicated	0.190	0.189	0.036	-0.179	0.560	1.010	0.312
serum				-0.278	0.276	0.076	-0.819	0.264	-1.004	0.315
Overall				0.005	0.215	0.046	-0.417	0.427	0.023	0.982

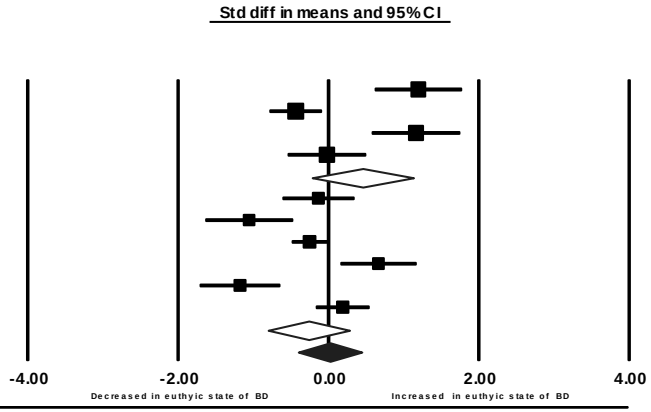


Figure 20. Forest plot for meta-analysis of longitudinal studies of serum BDNF levels in patients with major depression who responded to treatment.

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Aydemir, 2006	Responders	0.749	0.327	0.107	0.108	1.390	2.289	0.022
Basterzi, 2009	Responders	0.517	0.349	0.122	-0.167	1.200	1.482	0.138
Gonul , 2005	Responders	1.480	0.302	0.091	0.889	2.071	4.906	0.000
Gorgulu, 2009	Responders	5.796	0.688	0.473	4.449	7.144	8.431	0.000
Piccinni, 2008	Responders	0.325	0.475	0.225	-0.605	1.255	0.684	0.494
Umene Nakano, 2009	Responders	0.346	0.234	0.055	-0.113	0.805	1.477	0.140
Wolkowitz, 2011	Responders	0.238	0.473	0.224	-0.689	1.165	0.504	0.615
Yoshimura, 2008	Responders	1.689	0.737	0.543	0.246	3.133	2.293	0.022
Gorgulu, 2009 (1)	Responders	3.387	0.506	0.256	2.395	4.380	6.692	0.000
Huang, 2008 (1)	Responders	0.166	0.186	0.035	-0.198	0.531	0.893	0.372
Yoshimura, 2007 (3)	Responders	1.591	0.434	0.188	0.741	2.441	3.668	0.000
Yoshimura, 2007 (4)	Responders	0.917	0.429	0.184	0.076	1.758	2.137	0.033
		1.327	0.327	0.107	0.685	1.969	4.051	0.000

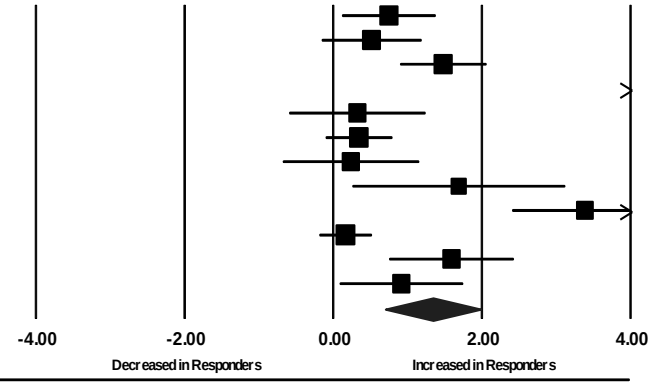


Figure 21. Forest plot for meta-analysis of longitudinal studies of serum BDNF levels in patients with major depression who reached remission.

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Matrisciano, 2009 (2)	Remission	0.183	0.536	0.287	-0.867	1.233	0.342	0.732
Matrisciano, 2009 (1)	Remission	1.729	0.626	0.392	0.501	2.957	2.760	0.006
Deuschle,2012 (2)	Remission	0.020	0.378	0.143	-0.721	0.760	0.052	0.959
Matrisciano, 2009	Remission	1.810	0.635	0.403	0.566	3.054	2.852	0.004
Gervasoni, 2005	Remission	0.500	0.282	0.079	-0.052	1.052	1.775	0.076
Deuschle,2012	Remission	0.473	0.432	0.187	-0.375	1.320	1.093	0.274
Aydemir, 2005	Remission	2.046	0.552	0.305	0.964	3.128	3.707	0.000
Ristevska-Dimitrovska, 2013	Remission	1.205	0.321	0.103	0.576	1.833	3.759	0.000
Ristevska-Dimitrovska, 2013 (1)	Remission	0.390	0.451	0.204	-0.495	1.274	0.863	0.388
		0.837	0.228	0.052	0.389	1.285	3.663	0.000

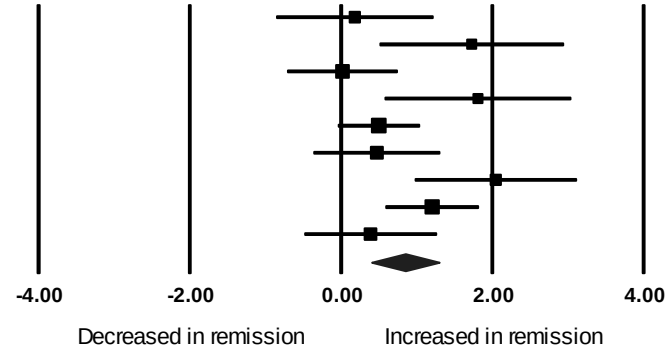


Figure 22. Forest plot for meta-analysis of longitudinal studies of serum BDNF levels in patients with major depression who did not respond to treatment.

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Basterzi, 2009 (1)	Non-responders	0.396	0.412	0.170	-0.412	1.204	0.962	0.336
Huang, 2008	Non-responders	0.155	0.309	0.096	-0.451	0.760	0.501	0.617
Kurita,2012 (1)	Non-responders	0.368	0.451	0.203	-0.516	1.252	0.816	0.414
Rojas, 2011	Non-responders	-1.244	0.303	0.092	-1.838	-0.650	-4.106	0.000
Umene Nakano, 2009(1)	Non-responders	0.026	0.302	0.091	-0.565	0.617	0.086	0.931
Wolkowitz, 2011 (1)	Non-responders	1.023	0.614	0.377	-0.180	2.226	1.666	0.096
Yoshimura, 2007 (1)	Non-responders	0.569	0.545	0.297	-0.499	1.638	1.044	0.297
Yoshimura, 2007 (2)	Non-responders	0.635	0.483	0.233	-0.312	1.582	1.315	0.189
Yoshimura, 2008 (1)	Non-responders	0.043	0.633	0.400	-1.196	1.283	0.069	0.945
		0.147	0.244	0.060	-0.331	0.626	0.604	0.546

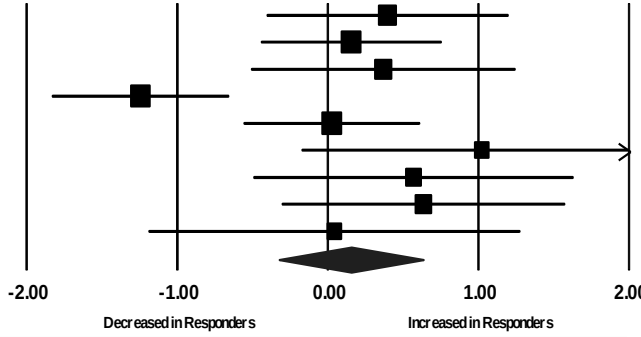


Figure 20. Forest plot for meta-analysis of longitudinal studies of plasma BDNF levels in patients with major depression who reached remission.

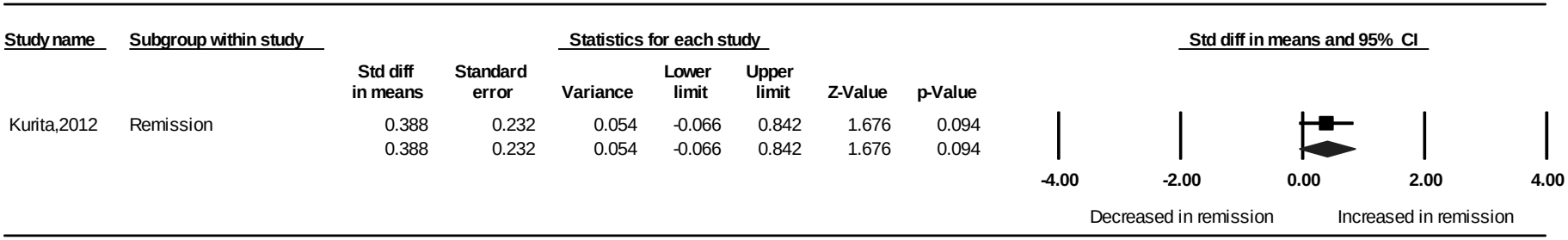


Figure 23. Forest plot for meta-analysis of longitudinal studies of plasma BDNF levels in patients with major depression who responded to treatment.

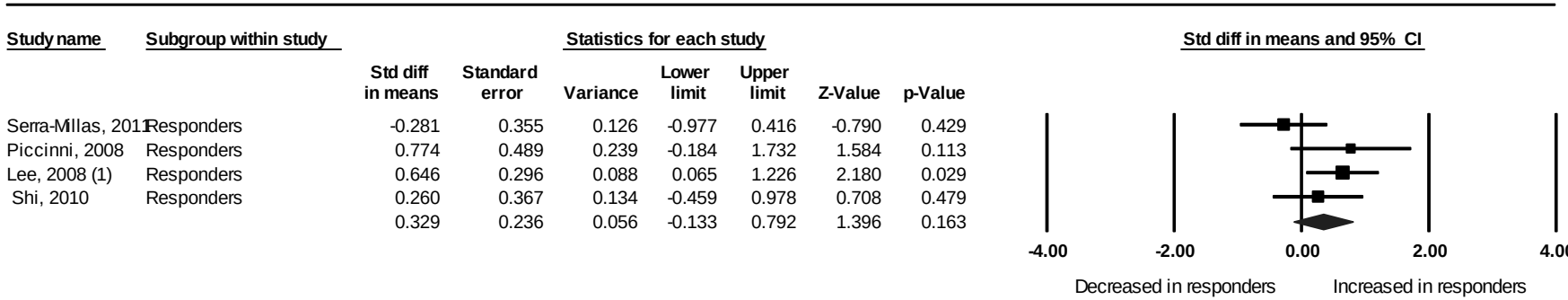
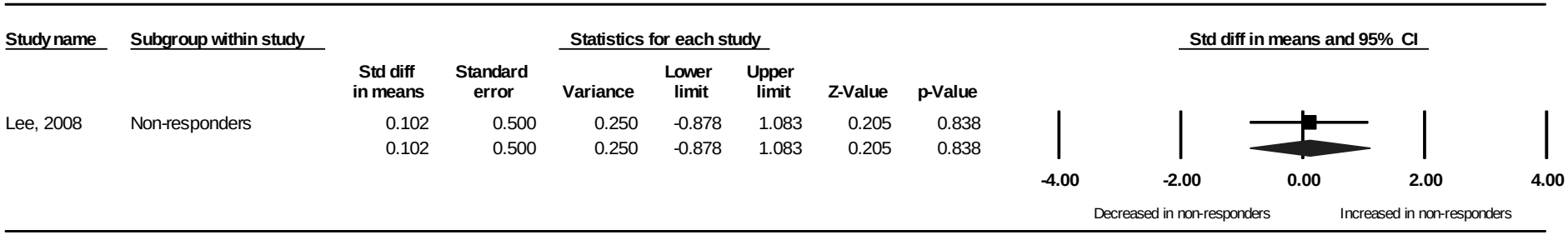


Figure 24. Forest plot for meta-analysis of longitudinal studies of plasma BDNF levels in patients with major depression who did not respond to treatment.



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RESEARCH ARTICLE

Brain-Derived Neurotrophic Factor and Antidepressive Effect of Electroconvulsive Therapy: Systematic Review and Meta-Analyses of the Preclinical and Clinical Literature

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Citation: Polyakova M, Schroeter ML, Elzinga BM, Holiga S, Schoenknecht P, de Kloet ER, et al. (2015) Brain-Derived Neurotrophic Factor and Antidepressive Effect of Electroconvulsive Therapy: Systematic Review and Meta-Analyses of the Preclinical and Clinical Literature. PLoS ONE 10(11): e0141564. doi:10.1371/journal.pone.0141564

Editor: Lin Lu, Peking University, CHINA

Received: April 16, 2015

Accepted: October 10, 2015

Published: November 3, 2015

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Emerging data suggest that Electro-Convulsive Treatment (ECT) may reduce depressive symptoms by increasing the expression of Brain-Derived Neurotrophic Factor (BDNF). Yet, conflicting findings have been reported. For this reason we performed a systematic review and meta-analysis of the preclinical and clinical literature on the association between ECT treatment (ECS in animals) and changes in BDNF concentrations and their effect on behavior. In addition, regional brain expression of BDNF in mouse and human brains were compared using Allen Brain Atlas. ECS, over sham, increased BDNF mRNA and protein in animal brain (effect size [Hedge's g]: 0.38–0.54; 258 effect-size estimates, $N = 4{,}284$) but not in serum ($g = 0.06$, 95% $CI = -0.05$–0.17). In humans, plasma but not serum BDNF increased following ECT ($g = 0.72$ vs. $g = 0.14$; 23 effect sizes, $n = 281$). The gradient of the BDNF increment in animal brains corresponded to the gradient of the BDNF gene expression according to the Allen brain atlas. Effect-size estimates were larger following more ECT sessions in animals ($r = 0.37$, $P < .0001$) and in humans ($r = 0.55$; $P = 0.05$). There were some indications that the increase in BDNF expression was associated with behavioral changes in rodents, but not in humans. We conclude that ECS in rodents and ECT in humans increase BDNF concentrations but this is not consistently associated with changes in behavior.

Introduction

Electro Convulsive Treatment (ECT) has been used as a treatment for mood disorders for years. There is little doubt on the clinical efficacy of ECT [1, 2], yet, how it improves mood

remains unclear [3, 4]. Emerging data have led to the idea that ECT may reduce depressive symptoms by increasing the expression of Brain-Derived Neurotrophic Factor (BDNF), a key regulator of neuronal functioning [5]. This idea rests on the *neurotrophin hypothesis*, which posits that depressive disorders are secondary to a stress-induced lowered expression of BDNF [6]. Complementary, it predicts that antidepressants are efficacious, because they increase BDNF expression and herewith boost neuronal plasticity [7–9].

Preclinical and clinical studies both have provided support for the neurotrophin hypothesis. Nibuya *et al.* [10], for instance, showed in rats that Electro-Convulsive Shocks (ECS, the equivalent of ECT in animals) increases the expression of hippocampal BDNF mRNA. This has been replicated and extended to other brain regions (*e.g.*, the amygdala [11]) and was shown for BDNF protein levels [12]. Interestingly, and in line with the neurotrophin hypothesis, some studies show that the increase in BDNF following ECS is associated with a decrease in depression-like behaviors.

Measurements in brain tissue, as they are applied in preclinical studies, obviously cannot be pursued in humans. Clinical studies usually measure the change in peripheral (*e.g.*, blood serum) BDNF protein concentrations over treatment with ECT. The validity of this approach is based on the observation that the brain is in part the source of BDNF in peripheral tissues [12, 13]. Clinical studies show that peripheral BDNF concentrations increase following treatment with ECT, as evidenced by a recent a meta-analysis (Hedge's $g = 0.38$, 11 studies, 221 subjects) [14]. In contrast to some individual preclinical (*e.g.*, Li *et al.* [15]) and clinical studies (*e.g.*, Hu *et al.* [16]), this meta-analysis did not find evidence for the notion that changes in BDNF concentrations over treatment are related to the clinical efficacy of ECT. This omission may be due to a limited number of trials and patients and the use of group-level statistics [17]. An additional factor explaining the lack of association may be that serum and plasma BDNF measurement were merged in the analyses. Plasma levels are likely to reflect momentary BDNF protein expression, while serum levels reflect accumulated (over a period of about 10 days) BDNF [18–20]. The combination of plasma and serum measurement in a single meta-analysis, as was done by Brunoni *et al.* [14], therefore may not be biologically plausible.

Notwithstanding some contradictory findings, the data above suggest a relation between ECT treatment and BDNF expression. The goal of this study, then, was to evaluate, through systematic review and meta-analyses, the preclinical (*i.e.*, rodent) and clinical (*i.e.*, human) literature on changes in BDNF concentrations and behavior over the course of ECS and ECT respectively. To fulfill this translational aim, we first will pool the preclinical literature on the relationships between ECS, BDNF and depression-like behavior. Next, we will aggregate effect-sizes of ECT treatment on BDNF concentrations and clinical improvement as they are reported in the human literature. This will be done partially using meta-analysis on individual data because this better suits the questions at hand given a limited number of trials and patients that are available [17].

Materials and Methods

We adhered to the guidelines that are recommended by the preferred reporting items for systematic reviews and meta-analyses statement [21].

Search Strategy

We searched PUBMED, Embase, and PsychInfo through December 1st 2014 to identify eligible studies on changes in peripheral and central BDNF concentrations as a function of treatment with ECT. The following keywords were used: 'electroconvulsive' or 'ECT' or 'ECS' in combination with 'BDNF' or 'brain derived neurotrophic factor'. This was supplemented by

backward searches in which the references to the seminal papers of interest were screened for preclinical and clinical studies and by examining the reference sections of the retrieved papers. The literature search, decisions on inclusion, data extraction, and quality control were performed independently by two of the authors (MP and MM).

Inclusion and Exclusion Criteria

We included peer-reviewed preclinical and clinical studies that reported data on BDNF concentrations as a function of ECS/ECT (*i.e.*, ECS/ECT *versus* sham and pre *versus* post treatment). Inclusion was independent of ECS/ECT characteristics (*e.g.*, number of sessions) and methodological characteristics of the study (*e.g.*, tissue in which BDNF was sampled). For the clinical studies diagnosis of major- or bipolar depression had to be based on international classifications.

Non-empirical studies such as reviews were excluded according to review protocol, as were case studies, studies that were not peer reviewed, and studies that were not written in Dutch, English, French, German or Spanish. Where study samples overlapped we excluded the study that reported on the fewest number of subjects.

Data Extraction

From each paper we extracted, as primary outcomes, mean BDNF concentrations (and *Standard Deviation* [*SD*]) in treatment conditions *versus* sham and/or before and after ECS/ECT or indices on this change (*e.g.*, the standardized mean difference). We also extracted data on mean age, gender distribution, specifics of the ECS/ECT treatment, and the method that was applied to quantify the amount of BDNF (*e.g.*, RT-PCR).

From the preclinical studies we further extracted data on the strain of animal that was used, the weight and age of the animals, the brain-region in which BDNF was measured, and the amount of time between ECS treatment and decapitation. Data on behavioral changes due to ECS were extracted where provided.

From the clinical studies we in addition extracted data on depression severity pre- and post ECT, whether participants exhibited a clinical response to ECT, the antidepressant that were used, and the amount of time between the last ECT session and blood draw for BDNF determination. In order to perform subgroup comparisons according to treatment response we contacted the authors of the clinical studies and asked them to provide anonymised Individual Patients Data (IPD) [17]. In those cases where non-significant results were reported (*e.g.*, $P>.05$) and authors did not reply to our request for exact outcome data, we set the association at $P = .50$, indicating no association.

We assessed the methodological quality of the preclinical and clinical studies using the ARRIVE guidelines[22] and the Newcastle-Ottawa Scale (NOS) [23] respectively. In addition we used the risk of bias assessment tool for the longitudinal studies [24]. We refer to the Supplement for detailed information on quality assessment (S1 Text, S1 Table, S2 Table, S3 Table).

Statistical Analysis

Analyses were performed using Comprehensive Meta-Analyses 2.0 [25] and SPSS version 21.0 [26].Random effects models (*i.e.*, models that include sampling- and study level error) were applied to calculate pooled effect-sizes on changes in central and peripheral BDNF concentrations as a function of ECS/ECT. As effect-size measure we chose to use Hedges' *g*, a standardized metric that corrects for bias related to small sample sizes [27]. All outcomes were weighted using inverse variance methods [25]. Statistical significance was assessed using a *Z*-statistic at a Confidence Interval (*CI*) of 95%. The amount of between-study heterogeneity in outcomes was

quantified using the I^2 measure [28] and assessed for statistical significance using the *Q*-statistic[25].

The stability of our results was evaluated through meta-analyses that were run in specific subgroups: (**I**) by brain region in which BDNF was assessed (clustered as follows: Dentate Gyrus [DG], hippocampus not DG, cortex, other brain regions, and in serum [S4 Table], (**II**) single *versus* multiple ECT sessions, and (**III**) the type of BDNF that was measured (*i.e.*, BDNF mRNA *versus* protein and BDNF in serum *versus* in plasma). The possible moderating effects of between-study differences on outcomes were evaluated by calculating correlation coefficients between the values for the moderator and the outcome of the studies.

For the analyses on preclinical data, the animal strain that was used, duration of treatment, the amount of time between the last ECT session and decapitation for BDNF measurements, and the quality score were considered as potential moderators. For clinical data analysis, obtained IPD were combined with the aggregated data using a two-step approach. In a first step summary statistics were calculated for each subgroup from single studies. In the second step summary statistics from the IPD were combined in meta-analysis as described above. Treatment response was considered as reduction of depression severity scores by $\geq$50%. Duration of treatment and the quality score were considered as potential moderators of the effect-sizes retrieved from clinical studies.

Visual inspection of funnel plots and the Egger test were used to assess publication bias [29]. In case of publication bias we used trim-and-fill procedures to estimate effect-sizes after bias has been taken into account [30].

Results

Preclinical Studies

Our search generated 97 papers of which 23 [10–11,15,33–51] fulfilled the inclusion criteria (see Fig 1 for a flow-chart). From these we could extract 280 effect-size estimates (*k*) on a total of 4,670 animals (mean $n = 17$ per effect-size, range 8–30) on changes in BDNF concentrations in animals that were subjected to ECS as compared to sham treatment or, in one case, to baseline.[31] Mean number of ECS sessions was 5 (range: 1–14). Mean time that passed between last ECS session and decapitation was 40 hours (range: 1–504 hours). We refer to Table 1 for the included studies and general information on them. S5 Table and S6 Table provide additional information on the animals that were used and the methods that were applied.

Meta-analysis over preclinical findings

ECS was associated with increased BDNF concentrations in comparison to sham treatment ($g = 0.40$, 95% $CI = 0.35–0.44$, $P < .0001$; 280 effect-sizes, $N = 4{,}284$). Meta-analyses by specific brain region showed a larger effect-size ($P < .05$) when BDNF was assessed in the DG ($g = 0.54$) as compared to assessments in the hippocampus and the cortex (*g*: 0.38–0.41 respectively). Yet, effect-sizes were significant regardless in which brain area BDNF was sampled (see **Table 2**). Interestingly, the observed gradient of ECS induced increases in BDNF protein corresponds to the gradient of BDNF gene expression across the whole brain in mice and humans as assessed in the genome wide atlas of the Allen Institute for Brain Sciences (Seattle, WA, USA, see www.brain-map.org) [52]. Results of this analysis are illustrated in **Fig 2** with highest gene expression in DG, followed by hippocampus and other brain regions.

Evidence for increases in serum BDNF concentrations (*i.e.*, in blood serum) following ECS was not found in the preclinical data ($g = 0.06$, 95% $CI = -0.05–0.17$). In fact, the pooled effect-size on serum measurement was smaller as compared to the ones calculated on central BDNF (*P*-values all $< .001$). Studies that subjected animals to multiple ECS's yielded larger effect-size

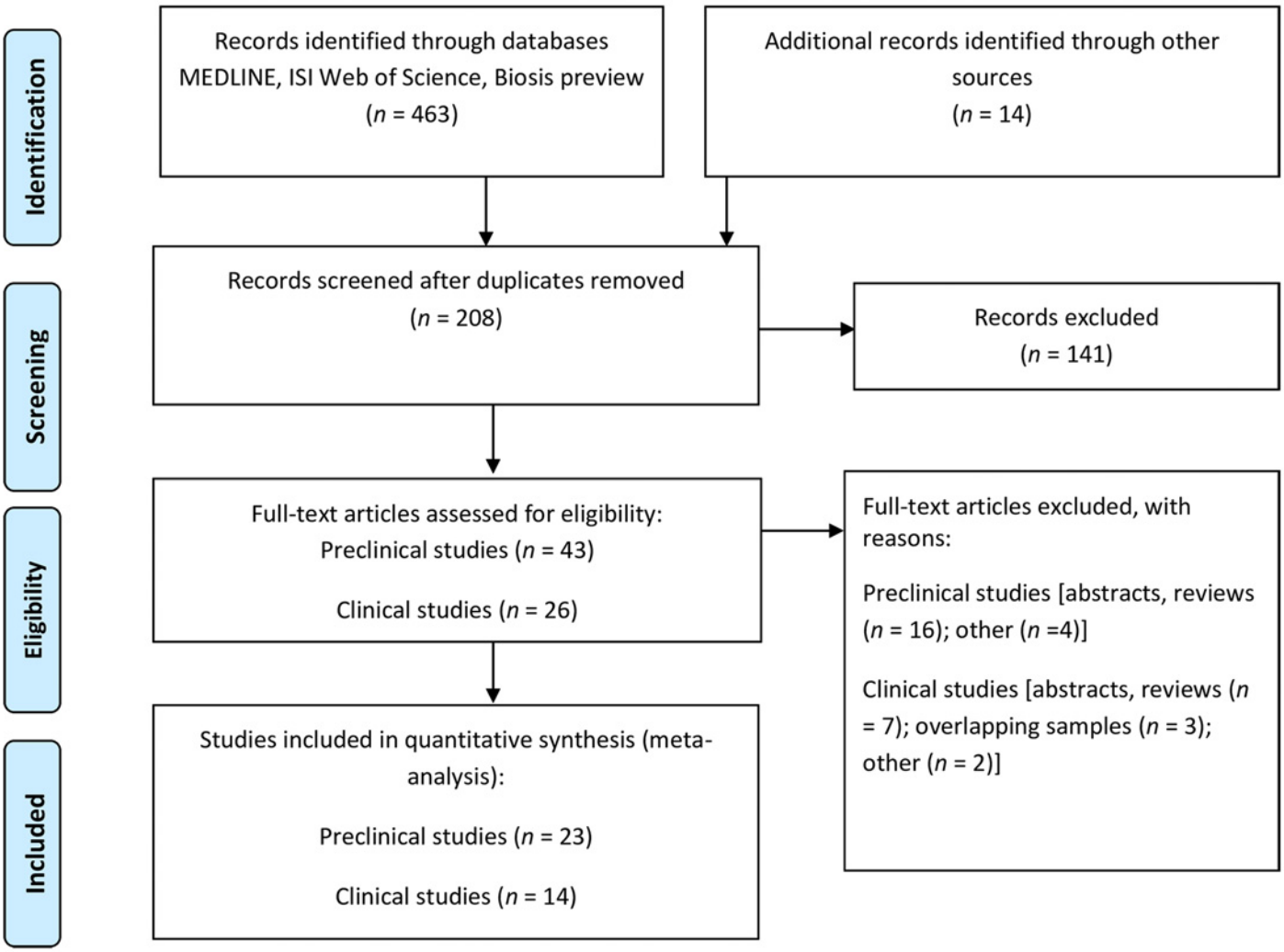

Fig 1. Prisma flow diagram of the search strategy and its results.

doi:10.1371/journal.pone.0141564.g001

as compared to studies that applied single ECS ($P < .0001$). Yet, also a single ECS session was associated with an increase in BDNF (see Table 2). The pooled effect size that was derived from studies that measured BDNF mRNA was larger as the one from studies that measured BDNF protein ($P < .0001$) although the latter also was statistically significant (see Table 2).

Between-study heterogeneity in outcomes was identified ($I^2 = 51\%$, $Q = 572.13$, $P < .00001$). The number of ECS sessions that was applied and the time that passed between the last ECS session and measurement appeared to be sources of the observed heterogeneity. A larger number of treatment sessions, in general was associated with larger effect size estimates ($r = 0.36$, $R^2 = 0.13$, $P < .0001$) and a longer gap in time between the last ECS session and decapitation with smaller effect-size-estimates ($r = -0.27$, $R^2 = 0.07$, $P < .0001$). The correlation between the number of ECS and ECS induced increase in BDNF was also present within the multiple treated animals ($r = 0.35$, $R^2 = 0.13$, [202 data points], $P < .0001$). The methodological quality of a study was unrelated to outcome.

Table 1. Basic information on the preclinical studies included in the meta-analysis.

Study	Animal [A]	ECT	*n* [B]
Lindefors *et al*.[32]	Sprague-Dawley rats	*Single*: 1 p/d for 1 d	6
Nibuya *et al*.[10]	Sprague-Dawley rats	*Single*: 1 p/d for 1 d and *Multiple*: 1 p/ for 10 d	8
Zetterström *et al*.[33]	Sprague-Dawley rats	*Single*: 1 p/d for 1 d and *Multiple*: 5 over 10 d	5
Chen *et al*.[34]	Sprague-Dawley rats	*Multiple*: 1 p/d for 10 d	6
Altar *et al*. [11]	Wistar rats	*Single*: 1 p/d for1, 2 and 3 d and *Multiple*: 1 p/d for 4, 6, 10 d	7–9
Angelucci *et al*.[35]	FRL and FSL rats	*Multiple*: 1 p/d for 10 d	7
Dias *et al*.[36]	Sprague-Dawley rats	*Single*: 1 p/d for1, 2 and 3 d, and *Multiple*: 1 p/d for 10 d	5
Newton *et al*. [37]	Sprague-Dawley rats	*Single*: 1 p/d for1 d and *Multiple*: 1 p/d for 10 d	5
Jacobsen *et al*.[38]	Wistar rats	*Multiple*: 1 p/d for 10 d	8
Li *et al*.[39]	Wistar rats	*Multiple*: 6 or 14 for 6 or 14 d	15
Ploski *et al*. [40]	Sprague-Dawley rats	*Multiple*: 1 p/d for 14 d	8
Conti *et al*. [41]	Sprague-Dawley rats	*Multiple*: 8 for 2 d	8
Li *et al*. [15]	Wistar rats	*Multiple*: 14 for 14 d	7–8
Sartorius *et al*.[31]	Sprague-Dawley rats	*Single*: 1 p/d for1 d and *Multiple*: 1 p/d for 5 d	8
Gersner*et al*. [42]	Sprague-Dawley rats	*Multiple*: 1 p/d for 6–14 d	10
Kyerematenng *et al*. [43]	Wistar-Kyoto rats, Wistar rats	*Multiple*: 5 p/d for 5 d	10
Luo *et al*.[44]	Wistar rats	*Multiple*: 1 p/d for 6–14 d	10
O'Donovan *et al*.[45]	Sprague-Dawley rats	*Multiple*: 10 sessions over 3–4 weeks	8
Ryan *et al*.[46]	Sprague-Dawley rats	*Single*: 1 p/d for 1 d and *Multiple*: 10 sessions over 21–28 d	8
Segawa *et al*. [47]	Sprague-Dawley rats	*Single*: 1 p/d for1 d and *Multiple*: 1 p/d for 10 d	8
Segi-Nishida *et al*. [48]	C57BL/6N mice	*Single*: 1 p/d for 1 d and *Multiple*: 1 p/d for 6 and for 14 d	4
Dyrvig *et al*. [49]	Sprague-Dawley rats	*Single*: 1 p/d for 1 d	6
Kyerematenng *et al*. [50]	Wistar-Kyoto rats, Wistar rats	*Multiple*: 5 p/d for 5 d	9–10

[A] all studies assessed male animals. Sartorius *et al*.[31] and Gersner *et al*.[51] did not specify the sex of the animals they used.

[B] *n* is given per group and, in general can be doubled for the experimental vs sham comparison.

All studies applied sham ECT as the control condition, except for the study by Sartorius *et al*.[31] in which *baseline* was considered as the control condition.

In the S5 Table we present additional information on the included preclinical studies (*e.g*., age and weight of the animals).

doi:10.1371/journal.pone.0141564.t001

The funnel plot and the Egger's test suggested evidence for publication bias in the overall analysis ($t_{[278]} = 10.41$, $P < .0001$). Imputation of 15, presumed missing, effect-size estimates resulted in a symmetric funnel-plot. The pooled effect-size estimate that was recalculated after imputation was only slightly smaller as compared to the one derived in the original analysis ($g = 0.38$, 95% $CI = 0.35–0.41$). Between-study heterogeneity, correlations between outcomes and moderators, and publication bias in outcomes were rather similar in analyses that were run separately in the subgroups (see **Table 3**).

ECS, BDNF and changes in behaviour. There was too little comparable data on behavioral tests (*e.g*., the open-field test) to perform meta-analysis on. In case similar behavioral paradigms were applied, often the outcome measures over studies were different. This was for

Table 2. Pooled effect-size estimates, heterogeneity and publication bias for the animal studies by sub-group meta-analyses indicated in the row.

	k	*N*	Hedges' *g* (95% *CI*)	Heterogeneity		Publication bias
				I^2	*Q*	Egger's *t*
BDNF sampled in: [A]						
DG	25	384	0.54 (0.42–0.67) ***	23.6%	31.4	3.1 *
Hippocampus	124	2,032	0.38 (0.32–0.45) ***	49.3%	242.8 ***	5.2 ***
Cortex	57	982	0.41 (0.32–0.51) ***	51.5%	115.6 ***	3.3 **
Other	61	976	0.44 (0.34–0.54) ***	56.8%	138.9 ***	6.9 **
Serum	13	296	0.06 (-0.05–0.17)	0.1%	6.7	0.3
Number of sessions: [B]						
Single treatment	78	1,282	0.22 (0.12–0.29) ***	44.3%	138.3 ***	5.5 **
Multiple treatment	202	3,388	0.46 (0.38–0.48) ***	49.6%	398.9 ***	8.8 **
BDNF type: [C]						
BDNF protein	147	2,795	0.35 (0.29–0.41) ***	49.0%	286.5 ***	8.2 **
BDNF mRNA [D]	133	1,875	0.46 (0.39–0.53) ***	51.0%	224.8 ***	7.5 **

[A] Effect-size estimates were of a larger magnitude in studies that measured central- as compared to serum BDNF (all *P*-values < .001). Furthermore, larger effect-size estimates were found in the DG as compared to those found in the hippocampus and the cortex (*P*-values < .05). There were no statistically significant differences in pooled effect-size estimates derived from the hippocampus, the cortex and other brain regions (all *P*-values > .5).

[B] Chronic ECS yielded larger effect-size estimates as compared to single ECS ($P < .0001$).

[C] Studies that sampled BDNF mRNA yielded larger effect-size estimates as compared to studies that sampled BDNF protein ($P < .01$).

[D] Among the studies that are characterized as measuring BDNF mRNA were 3 effect-sizes on BDNF RNA and 9 on the precursor protein pro-BDNF. Excluding these effect-sizes did not change the results.

* Statistical significant at $P < .05$

** Statistical significance at $P < .01$

*** Statistical significance at $P < .001$.

doi:10.1371/journal.pone.0141564.t002

instance so for swimming time in the FST for which we could extract 48 effect-size estimates (910 animals, range: 11–30 per effect-size) on total swimming time in the FST. Together, these showed that ECS, over sham, increased swimming time ($g = 0.26$, 95% $CI = 0.19–0.32$, $P < .0001$). The increase in swimming time correlated positively with the increase in BDNF ($r = 0.37$, $R^2 = 0.14$, $P < .001$). Note though that these effect sizes came from only four studies that widely differed in for instance in time of sacrifice after ECS and other variables that potentially can confound the observed relation. The association, thus, should be interpreted with caution.

Sensitivity analyses. None of the study findings was unduly driven by the effect of a particular study (data not shown). Furthermore, effect-size estimates were not related ($P = .49$) to whether or a particular study used a stress paradigm (*e.g.*, chronic unpredictable mild stress). Method of BDNF measurement was not associated with the amount of change in detectable BDNF ($P = .17$; see S6 Table for the methods of measurement by study). Animal strain was tested as a potential effect modifier (see S6 Table for the animal strain that was used in each individual study). Analyses showed that there were no differences in ECS induced increases in BDNF as a function of strain of animal that was used in the experiment ($P = .18$).

Clinical Studies

Our search for clinical studies generated 111 publications of which 14 fulfilled the inclusion criteria (see Fig 1 for a flow-chart). From these papers we obtained 23 effect-size estimates on changes in BDNF concentrations over the course of ECT ($N = 250$ subjects a [mean $n = 13$ per

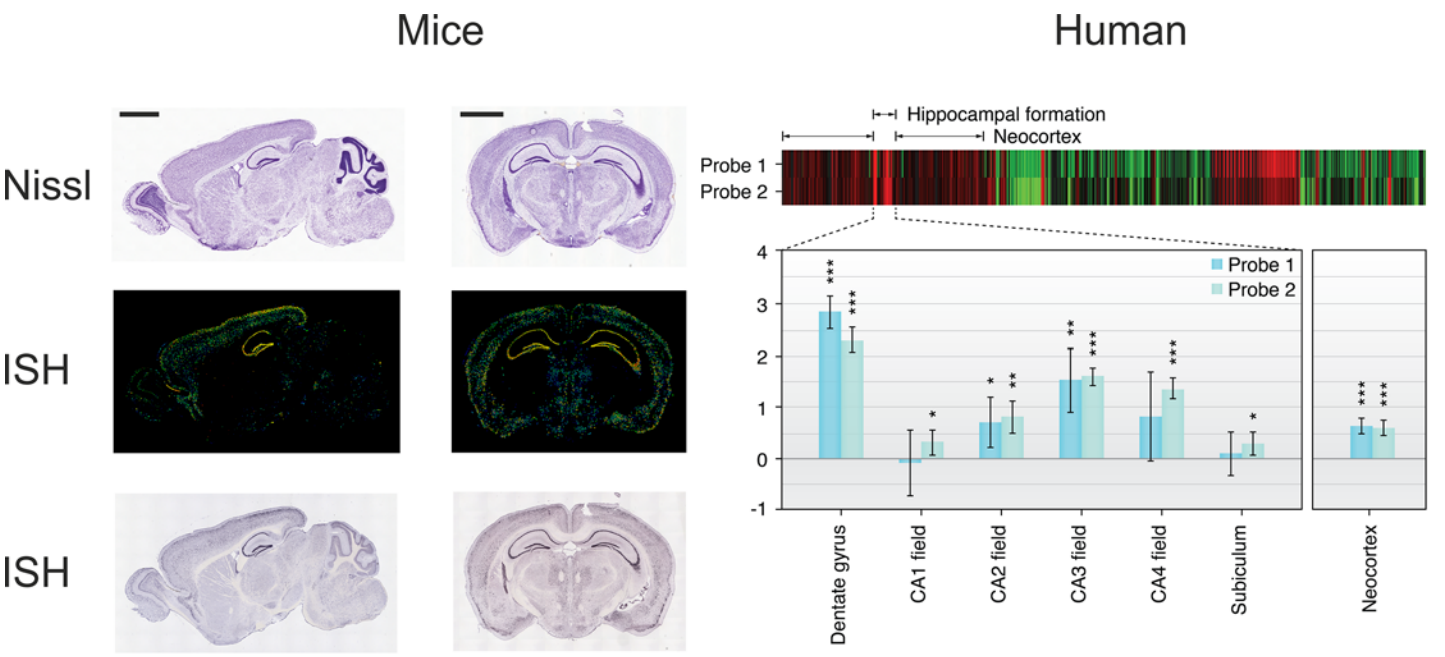

Fig 2. Gene expression of BDNF across the whole brain as assessed in Allen Brain Atlas (Seattle, WA, USA). In mice, gene expression was the highest in the DG/hippocampus as investigated by In Situ Hybridization (ISH), where warm colors indicate high expression. Note that contrast and brightness were enhanced in original images to increase visibility of the effects here. Black bars correspond to 2 mm. Gene expression in humans is shown as individually normalized gene expression (*Z*-scores normalized to whole human brain expression). The heat map shows scores across the whole human brain and for each of the six subjects contained in the database beside each other, where red indicates high and green indicates low expression. Bars represent mean normalized gene expression and standard deviation across one female and five male subjects included. Search conducted on 17th October 2014 for human and on 9th October 2014 for mice data. *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$, two-tailed Student's *t*-test against 0. For details on the methods we refer to Mueller *et al*.[53]

doi:10.1371/journal.pone.0141564.g002

Table 3. Pearson's correlation coefficients on the relation between study characteristics and study effect size (by meta-analysis indicated in the columns).

	All	DG	Hippocampus	Cortex	Other
BDNF mRNA and protein	*k* = 267, *n* = 4,374	*k* = 25, *n* = 384	*k* = 124, *n* = 2,032	*k* = 57, *n* = 982	*k* = 61, *n* = 976
Number of treatments [A]	0.36***	0.10	0.43***	0.46***	0.28*
Time of measurement after last ECT	-0.22***	-0.38	-0.17	-0.30*	-0.35**
BDNF mRNA	*k* = 133, *n* = 1,489	*k* = 25, *n* = 384	*k* = 65, *n* = 933	*k* = 17, *n* = 222	*k* = 26, *n* = 336
Number of treatments	0.29**	0.10	0.29*	0.41	0.20
Time of measurement after last ECT	-0.39**	-0.38	-0.24	-0.29	-0.38
BDNF protein	*k* = 147, *n* = 2,795	*k* = 0, *n* = 0	*k* = 59, *n* = 1,099	*k* = 40, *n* = 744	*k* = 35, *n* = 640
Number of treatments	0.48***	*NA*	0.61***	0.54***	0.25
Time of measurement after last ECT	-0.21*	*NA*	-0.10	-0.32*	-0.33*

[A] The correlation between number of treatments and outcome was also present in studies that applied multiple treatments ($r = .35$ (202 data points) $P < .0001$).

Abbreviation. *NA*; Not Applicable.

* Statistically significant at $P < .05$

** statistically significant at $P < .01$

*** statistically significant at $P < .001$.

NOTE. There was no evidence for between-study heterogeneity in the meta-analyses on serum BDNF levels. Correlational analyses therefore were not performed in this sub-group.

doi:10.1371/journal.pone.0141564.t003

Table 4. Basic information on the clinical studies included in the meta-analysis.

Study	Diagnosis	Source	Response	*N* (f/m)	BDNF levels				Unit
					Pre-treatment		Post-treatment		
					mean	SD	mean	SD	
Bocchio-Chiavetto *et al*.[54]	MDD	serum	Yes	20 (14/6)	27.10	9.31	27.95	8.03	ng/ml
			No	3 (2/1)	31.2	8.42	31.2	8.3	pg/ml
Marano *et al*.[63]	MDD, BD	plasma	Yes	13 (3/10)	83.1	63.0	202.5	179.1	pg/ml
			No	2 (1/1)	119.5	33.3	265.5	236.6	pg/ml
Okamoto *et al*.[55]	MDD, BD	serum	Yes	12 (6/6)	7.9	9.9	15.1	11.1	ng/ml
			No	6 (3/3)	11.5	11.0	9.4	7.5	ng/ml
Fernandes *et al*.[56]	MDD, BD	serum	Yes (73.33%)	15 (10/5)	0.3	0.1	0.3	0.1	pg/ml
Gronli *et al*.[57]	MDD, BD	serum	Yes	10 (NA)	1242.5	187.0	1395.7	517.7	pg/ml
Piccinni *et al*. [64]	MDD, BD	plasma	Yes	8 (5/3)	2.9	1.3	5	1.8	ng/ml
			No	10 (4/6)	1.5	0.5	2.7	1.4	ng/ml
Hu *et al*.[16]	MDD	serum	Yes	24 (20/4)	5.5	1.9	8.08	3.5	ng/ml
			No	4 (3/1)	6.5	3.4	6.9	3.1	ng/ml
Gedge *et al*.[58]	MDD	serum	Yes	5 (2/3)	13.3	6.7	12.4	4.3	ng/ml
			No	6 (5/1)	7.2	5.2	12.2	3.1	ng/ml
Haghighi *et al*.[65]	MDD	plasma	Yes (75%)	20 (5/15)	151.0	174.7	376.7	299.3	pg/ml
Lin *et al*.[66]	MDD, BD	plasma	Yes	48 (38/10)	3652.8	2372.6	3512.6	2104.9	pg/ml
	MDD, BD		No	7 (6/1)	3085.3	2005.6	4190.7	1917.9	pg/ml
Stelzhammer *et al*.[59]	MDD	serum	Yes	3 (3/0)	20.4	13.5	8.2	4.5	ng/ml
			No	4 (2/2)	22.7	7.01	14.3	5.4	ng/ml
Bilgen *et al*.[60]	MDD	serum	Yes	30 (19/11)	1990.5	510	2713.3	382.8	pg/ml
Bumb *et al*.[61]	MDD	serum		20 (10/10)	2596.7	1101.5	3001.8	1118.5	pg/ml
Kleimann *et al*.[62]	MDD	serum	Yes	6	541.2	294.9	342.8	134.4	pg/ml
			No	5	721.8	364.1	506.3	142.0	pg/ml

Abbreviations: MDD, major depressive disorder; BD, bipolar disorder

doi:10.1371/journal.pone.0141564.t004

effect-size, range 3–48]). Ten studies [16, 54–62] reported on serum BDNF alternations (16 effect sizes) and 4 studies [63–66] (7 effect sizes) on plasma BDNF alterations. Table 4 and S7 Table provide details of the included studies.

Meta-analysis over clinical findings. Overall peripheral BDNF was significantly increased after ECT as compared to baseline ($g = 0.35$, 95% $CI = 0.034–0.67$, $P = 0.03$; 23 effect sizes, $n = 281$). BDNF levels increased in plasma ($g = 0.72$, 95% $CI = 0.22–1.23$, $P = 0.004$; 7 effect sizes, $n = 108$) but not in serum ($g = 0.14$, 95% $CI = -0.29–0.56$, $P = 0.67$; 16 effect sizes, $n = 173$). However, the difference between serum and plasma subgroups did not rich the significance threshold ($P = 0.10$; Table 5). When subdivided into responders and non-responders subgroups, BDNF increased non-significantly in both the responders- ($g = 0.40$ 95% $CI = 0.02–0.82$, $P = 0.06$; 13 effect sizes, $n = 214$) and non-responders subgroups ($g = 0.22$ 95% $CI = -0.38–0.82$, $P = 0.48$; 9 effect sizes, $n = 47$). There was no different pattern of results when comparing the pooled effect sizes from studies that measured BDNF in serum versus plasma (Table 5). However, significant differences could be observed between plasma and serum BDNF in the non-responders subgroups ($P = 0.05$).

Sensitivity analysis showed that the results were not substantially affected by a single study. We observed overall high heterogeneity in outcomes between the studies ($Q = 63.11_{[22]}$ $P<0.001$, $I^2 = 65.14\%$). This appeared to be driven by the responder subgroups in both serum

Table 5. Pooled effect-size estimates, heterogeneity and publication bias for the clinical studies by sub-group meta-analyses indicated in the row.

	k	*n*	Hedges' *g* (95% *CI*)	Heterogeneity		Publication bias
BDNF in serum and plasma [A]				I^2	*Q*	Egger's *t*
Responders to ECT	13	214	0.40 (0.02–0.82) *	75.6%	44.8 ***	0.7
Non-responders to ECT	9	47	0.22 (-0.38–0.82)	40.5%	14.5	1.1
Overall	23	281	0.37 (0.034–0.67) *	65.1%	63.1 ***	1.1
BDNF in plasma [A]						
Responders to ECT	4	89	0.66 (0.06–1.26) *	74.7%	11.9 **	4.0
Non-responders to ECT	3	19	0.87 (-0.04–1.78)	0.0%	0.63	0.2
Overall	7	108	0.72 (0.22–1.23) **	57.9%	14.3*	2.5
BDNF in serum [A]						
Responders to ECT	9	125	0.22 (-0.36–0.80)	78.4%	37.0***	2.7*
Non-responders to ECT	6	28	-0.13 (-0.94–0.68)	35.8%	7.8	0.7
Overall	16	173	0.14 (-0.29–0.56)	69.1%	48.6***	3.1**

[A] Effect size estimates were medium and significant in studies that measured BDNF in responders subgroup and non-significant in non-responders subgroup. However, there were no statistically significant differences in pooled effect-size estimates between the responders and non-responders subgroups (all P-values > .5).

* Statistical significance at P < .05

** Statistical significance at P < .01

*** Statistical significance at P < .001

doi:10.1371/journal.pone.0141564.t005

and plasma (see Table 5). In line with the rodent findings, the number of ECT treatments was positively correlated with the effect sizes in combined serum and plasma subgroup ($r = 0.55$; $P = 0.05$). The number of subjects and methodological quality of the study was not associated with outcomes (data not shown).

Publication bias was detected in the serum subgroup and induced by the studies by Stelzhammer *et al. [59]* and Kleimann *et al. [62]*, two negative studies with particularly low power. Correction for publication bias by Trim-and-Fill procedure led to an increased effect size ($g = 0.57$, 95% $CI = 0.11–1.04$; 11 effect sizes, $n = 101$). Overall, and in the plasma subgroup, no publication bias was detected.

Discussion

Our systematic review and meta-analyses investigated changes in BDNF concentrations as a function of ECS and ECT. Our main findings are: (**A**) in rodents, ECS increases BDNF mRNA and protein concentration (or synthesis/release) in the brain, with largest effect sizes measured in the DG, (**B**) the increase in BDNF is positively correlated with number of treatments and negatively with the time between the last ECT and BDNF measurement, (**C**) BDNF concentrations do not increase in the course of treatment in rodent and human serum, yet they increased in human plasma, and (**D**) the increase in BDNF following ECT is also related to the number of treatment sessions but not to clinical outcome in human studies.

In preclinical studies ECS increased BDNF secretion throughout the brain. Activation of distinct promoters of the BDNF gene is responsible for a differently regulated BDNF expression over brain regions [67, 68]. Four out of nine possible BDNF transcripts are expressed in the rat brain [69]. While in most brain regions one or two transcripts are produced, all four are activated in the DG following ECT [36]. Interestingly, BDNF expression as elicited by ECS appeared to be highest in the DG. This relates well to what the Allen brain atlas shows: BDNF expression in the DG of mice and human brains is highest in this region. A constant supply of

BDNF here is not restricted to effects of ECS. This may serve neurogenesis, as the DG is one of the main sources of progenitor cells [70, 71].

The effect of single ECS on BDNF concentrations seems to be short-lived (6–8 hours [10, 49]) and does not involve a hard reset after which BDNF expression remains at a constant higher level. The effect of multiple ECS lasted longer as compared to single treatment: up to 14 days post-ECS [15, 31, 39, 45]. On the meta-analytical level this was reflected by a positive correlation between number of treatments and BDNF levels in rodents, and a trend towards such an association ($P = .06$) in humans.

Interestingly, effect sizes were larger for BDNF mRNA as compared to protein concentrations. Several posttranscriptional mechanisms can be responsible for this. First, protein synthesis may be inhibited by a specific class of microRNA molecules, that bind target mRNA and induce its degradation. Several microRNAs are associated with BDNF depletion [72, 73], one of them, microRNA-212, was increased after ECS in rat's DG [46]. Second, there is evidence of activity-dependent mRNA trafficking of BDNF to dendrites, where it can be stored and translated on demand [74]. Third, an increased BDNF turnover after ECS was proposed[38] and makes sense in light of findings of neurogenesis after ECT [71, 75].

Once BDNF is synthesized it can act locally, be transferred to neighboring brain areas through axonal anterograde transport or secreted to the blood stream. The later property allowed scientists to make inferences about central BDNF secretion from peripheral measurements. However, initial findings of a high positive correlation between central and serum BDNF [76] were not confirmed [77, 78] or at least depended on animal strain and brain region [31]. Neither a correlation between CSF and serum BDNF in humans was demonstrated [79]. In rodents we demonstrated increments in brain but not in the serum BDNF levels.

In clinical studies, ECT increased peripheral BDNF levels with a small to moderate effect size ($g = 0.35$). Compared to a previous meta-analysis on this topic [14], we included newly published studies, obtained individual patient data and took the source of BDNF (*i.e.*, plasma versus serum) into account. This approach revealed significantly enhanced BDNF after ECT in plasma and not in serum.

Although both plasma and serum BDNF levels are decreased in acute major and bipolar depression [24, 80], they seem to restore differently following antidepressant treatment [24]. The difference between responders and non-responders that we observed in serum BDNF after pharmacological antidepressant treatment was not demonstrated after ECT. Neither did we observe an increase in serum BDNF after ECT. This differs for plasma measurements, where ECT seems to lead to an increase of BDNF but antidepressant treatment did not [24]. Such difference may point to different mechanisms of action of ECT and antidepressants on BDNF synthesis and release.

Limitations

Our study has a number of limitations. First, obviously we could not match the preclinical and clinical studies according to depressive state, only (roughly) according to the treatment applied. Most of the animal studies used healthy male animals and did not account for the effects of sex and disease on BDNF. The clinical studies, in turn, included both sexes and were based on treatment-resistant depression cases. Furthermore, none of these studies controlled for relevant confounders in longitudinal studies assessing BDNF, such as seasonality [81]. Plasma BDNF studies could be further confounded by measurement errors [24]. Secondly, due to limited data we had to combine treatment effects on major- and bipolar depression even though imaging studies show differential response to ECT for these two groups [82]. Thirdly, most of the clinical studies included antidepressants and ECT premedication which may have affected BDNF

concentrations. Fourthly, while meta-analysis of preclinical data had enough power and showed small to medium heterogeneity, the meta-analysis of clinical data was underpowered and showed signs of publication bias. Due to the limited power we could not control for the impact of ELISA kit manufacturer on effect sizes. Finally, effect-size estimates for the preclinical data may have been suboptimal in terms of precision because they were often estimated based on *P*-value and *N*.

Conclusions

Despite the limitations, animal and human studies seem to complement each other with regard to effects of ECT on BDNF: ECT increases brain BDNF in animals and plasma BDNF in humans. In animals regional BDNF increments after ECT (*i.e.*, the DG) corresponded to areas with distinct expression shown in the Allen brain atlas. Besides, multiple treatments as compared to single ECT were associated with a larger increase in BDNF in both animals and humans, which is suggestive for a dose-response effect of ECS on BDNF.

Future Directions

The questions that remain unsolved are: (1) why plasma but not serum BDNF increased in human studies, (2) what is the relationship between BDNF and behavior, and (3) are increments in BDNF after ECT/ECS related to neurogenesis?

The potential differences between serum and plasma may arise from several aspects. Firstly, plasma BDNF levels reflect momentary BDNF content whereas serum levels reflect BDNF that has been accumulated over several days or even weeks [18 – 20]. Secondly, plasma measurements are very sensitive to the laboratory conditions and, thus, error prone [24]. Future studies (following strict methodological recommendations) should clarify whether plasma increment is not an artifact and further investigate the nature of plasma and serum BDNF.

A larger number of studies is needed to understand the relation of behavioral outcomes to BDNF levels. For clinical studies such outcome measurement is well established: response to treatment or clinical remission. Preclinical studies, however, reported rather different, in terms of timeframe and behavioral assessment, data. Therefore, for the later at least partial overlap in outcome variables with previous studies is needed.

Though the behavioral data is still mixed, neurogenesis is required to achieve antidepressive effect of ECS [83]. Survival of newborn neurons is supported by BDNF [84]. The causality and the dose-response relationships between ECS, BDNF, neurogenesis and behavior are the next questions to adress. Moderators of BDNF functioning, most notably the common genetic variant val66met that has been associated with activity dependent BDNF expression [85], might be considered. Relating variation at this locus to hippocampal morphology [86] and functioning [87] however has thus far led to mixed results.

Supporting Information

S1 Table. Quality of the included preclinical studies.
(DOCX)

S2 Table. Quality of the included clinical studies as measured with the Newcastle-Ottawa Scale.
(DOCX)

S3 Table. Quality of the included clinical studies as measured with the RBLS.
(DOCX)

S4 Table. Brain regions in which BDNF was sampled in the preclinical studies that we included.
(DOCX)

S5 Table. Basic information on the animals that were used in the preclinical studies that were included in our meta-analysis.
(DOCX)

S6 Table. Basic methodological information on the preclinical studies that were included in our meta-analysis.
(DOCX)

S7 Table. Basic information on the patients that were included in the clinical studies that were included in our meta-analysis.
(DOCX)

S8 Table. PRISMA checklist.
(PDF)

S1 Text. Quality assessment of the included studies.
(DOCX)

Author Contributions

Conceived and designed the experiments: MP MLS BME SH PS ERK MM. Performed the experiments: MM MP SH MLS. Analyzed the data: MM MP SH MLS. Wrote the paper: MP MLS BME SH PS ERK MM.

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S1 Table. Quality of the included preclinical studies

Between-Group Studies	**Introduction** [3 max]	**Methods** [21 max]	**Results** [6 max]	**Discussion** [5 max]	**Total** [35 max]
Lindefors *et al.* (1995)	1.5	8.0	5.0	3.0	17.5
Nibuya *et al.* (1995)	2.0	10.5	4.5	2.0	19.0
Zetterström *et al.* (1998)	2.0	6.0	5.0	1.0	14.0
Chen *et al.* (2001)	3.0	10.0	5.0	3.0	21.0
Altar *et al.* (2003)	2.0	15.0	5.0	2.0	24.0
Angelucci *et al.* (2003)	2.0	14.0	4.0	3.0	23.0
Dias *et al.* (2003)	3.0	11.0	5.0	3.0	22.0
Newton *et al.* (2003)	2.0	11.0	5.0	2.0	20.0
Jacobsen *et al.* (2004)	2.0	12.0	5.0	3.0	22.0
Li *et al.* (2006)	3.0	9.0	5.0	2.0	19.0
Ploski *et al.* (2006)	2.0	8.0	5.0	3.0	18.0
Conti *et al.* (2007)	2.0	8.0	4.0	3.5	17.5
Li *et al.* (2007)	3.0	11.0	5.0	3.0	22.0
Sartorius *et al.* (2009)	3.0	10.0	4.0	3.0	20.0
Gersner *et al.* (2010)	2.0	11.0	4.0	2.0	19.0
Kyeremanteng *et al.* (2012)	2.0	15.0	4.0	3.0	24.0
Luo *et al.* (2012)	2.5	13.0	5.0	2.5	23.0
O'Donovan *et al.* (2012)	3.0	14.0	5.0	3.0	25.0
Ryan *et al.* (2013)	1.0	8.0	5.0	3.0	17.0
Segawa *et al.* (2013)	3.0	12.0	5.0	3.0	23.0
Segi-Nishida *et al.* (2013)	2.5	11.0	5.0	2.0	22.5
Dryvig *et al.* (2014)	2.0	9.0	5.0	1.0	17.0
Kyeremanteng *et al.* (2014)	3.0	13.0	4.0	3.0	23.0
Mean	**2.3**	**10.8**	**4.7**	**2.6**	**20.5**

Quality Assessment

Quality of the preclinical studies

Based on the ARRIVE guidelines for reporting animal research (Kilkenny *et al.,* 2010), two of us (MP and MLM) evaluated the methodological- and reporting quality of the included studies. Overall quality of a study was defined as the number of items that was met by the particular study. Agreement among the raters was excellent (Cohen's Kappa = 0.95, Standard Error [SE] = 0.1). Overall, the included studies met on average 20 of the 35 quality items (range 14.0 – 25.0). See **Table S4** for the quality of each study (overall, and subdivided by introduction, method, results, and discussion). The quality-score of an individual study was unrelated to the effect-size of the study (r = -0.005, P = .93). The quality score was related to sample size (r = 0.22, P = .002) and year of publication (r = 0.57, P < .0001), indicating that studies that used a larger number of animals and/or that were more recently published were in general of a higher quality.

Quality of the clinical studies

Based on the Newcasltle-Ottowa Scale (NOS; Wells *et al,* 2014; The Cochrane Collaboration, 2014), the quality assessment tool that is recommended by the Cochrane collaboration (2014) and the Risk of Bias tool for Longitudinal Studies (RBLS) (Polyakova *et al,* 2014), two of us (MP and MLM) evaluated the quality of the included clinical studies. Overall quality of a study was defined as the number of items that was met by the particular study on each of these scales individually. Agreement among the raters was high (Cohen's Kappa = 0.90, SE = 0.05 for the NOS and Cohen's Kappa = 0.76, SE = 0.06 for the RBLS). The included studies met on average 2 of the 8 NOS quality items (range 1 – 4) and 14 of the 35 RBLS items (range 11 – 16). See **Table S5** and **S6** for the NOS and RBLS quality score of the included studies respectively. Both, the NOS and the RBLS quality-score were unrelated to the effect-size of the study (r = 0.15, P = .61 and r = 0.09, P = .76 respectively. The NOS quality score was unrelated to sample size (r = -0.17, P = .56) and year of publication (r = 0.10, P = .74). The RBLS quality score also was unrelated to year of publication (r = -0.16, P = P = .60) but it was related to sample size (r = 0.64, P = .02), so that studies that used a larger number of subjects were in general of a higher quality.

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The Cochrane Collaboration Handbookhttp://www.cochrane.org/, accessed 9 November 2014

S3 Table Quality of the included clinical studies as measured with the RBLS

	Selection [4 max]	**Detection** [8 max]	**Performance** [2 max]	**Attrition** [2 max]	**Reporting** [2 max]	**Total** [18 max]
Bocchio-Chiavetto *et al.* (2006)	3	7	1	2	1	15
Marano *et al.* **(**2006**)**	3	5	2	2	2	14
Okamoto *et al.* **(**2008**)**	3	7	1	2	2	15
Fernandes *et al.* **(**2009**)**	2	6	1	2	2	13
Gronli *et al.*2009	3	5	1	0	2	11
Piccinni *et al.* **(**2009**)**	3	6	1	2	2	14
Hu *et al.* **(**2010**)**	3	6	1	2	2	14
Gedge *et al.* **(**2012**)**	3	4	1	2	2	12
Haghighi *et al.* **(**2013**)**	3	4	1	2	2	12
Lin *et al.* **(**2013**)**	3	8	1	2	2	16
Stelzhammer *et al.* **(**2013**)**	3	6	1	2	2	14
Bilgen *et al.* **(**2014**)**	3	7	1	2	2	15
Bumb *et al.* **(**2014**)**	2	6	1	2	2	13
Kleinmann *et al.* **(**2014**)**	2	6	1	2	2	13
Mean	**2.8**	**5.9**	**1.1**	**1.9**	**1.9**	**13.6**

S4 Table. Brain regions in which BDNF was sampled in the preclinical studies that we included. Brain regions are presented alphabetically. The third column: '*Unit of analyses*' indicates in which 'analysis' unit the region was clustered.

Tissue sampled	Frequency	Unit of analyses	References
Anterior olfactory nucleus	1	Other	Conti *et al.* (2007)
Basolateral amygdaloid nuclei	1	Other	Conti *et al.* (2007)
Brainstem	4	Other	Kyeremanteng *et al.* (2014)
CA1	14	Hippocampus	Nibuya *et al.* (1995), Zetterström *et al.* (1998), Chen *et al.* (2001), Conti *et al.* (2007)
CA2	1	Hippocampus	Conti *et al.* (2007)
CA3	15	Hippocampus	Nibuya *et al.* (1995), Zetterström *et al.* (1998), Chen *et al.* (2001), Jacobsen *et al.* (2004), Conti *et al.* (2007)
Cerebellum	8	Other	Kyeremanteng *et al.* (2012, 2014)
Claustrum	1	Other	Conti *et al.* (2007)
Dentate gyrus	17	Hippocampus	Nibuya *et al.* (1995), Zetterström *et al.* (1998), Chen *et al.* (2001), Jacobsen *et al.* (2004), Ryan *et al.* (2013)
Dorsal endopiriform nucleus	1	Other	Conti *et al.* (2007)
Dorsal hippocampus	1	Hippocampus	Li *et al.* (2007), Gersner *et al.* (2010)
Dorsal raphe nucleus	1	Other	Conti *et al.* (2007)
Enthorinal cortex	2	Other	Altar *et al.* (2001), Conti *et al.* (2007),
Frontal cortex	29	Cortex	Nibuya *et al.* (1995), Altar *et al.* (2001), Angelucci *et al.* (2003), Altar *et al.* (2004), Jacobsen *et al.* (2004), Kyeremanteng *et al.* (2012, 2014)
Frontal parietal cortex	6	Cortex	Zetterström *et al.* (1998)
Granual layer the dentate gyrus	1	Hippocampus	Conti *et al.* (2007)
Granule layer cerebellum	1	Other	Conti *et al.* (2007)
Hippocampus	75	Hippocampus	Altar *et al.* (2001), Newton *et al.* (2003), Altar *et al.* (2004), Angelucci *et al.* (2003), Li *et al.* (2006), Ploski *et al.* (2006), Sartorius *et al.* (2009), Kyeremanteng *et al.* (2012, 2014), Luo *et al.* (2012), O'Donovan *et al.* (2012), Segawa *et al.* (2013), Segi-Nishida *et al.* (2013), Dryvig *et al.* (2014)
Hypothalamus	8	Other	Kyeremanteng *et al.* (2014)
Medial amygdaloid nucleus	1	Other	Conti *et al.* (2007)
Medial prefrontal cortex	3	Cortex	Chen *et al.* (2001)
Neocortex	8	Cortex	Kyeremanteng *et al.* (2012, 2014)
Nucleus accumbens	1	Other	Gersner *et al.* (2010)
Occipital cortex	1	Cortex	Angelucci *et al.* (2003)
Paraventricular thalamic nucleus	1	Other	Conti *et al.* (2007)

Table SI *continues on the next page*

Table SI *continued*

Parietal cortex	1	Cortex	Nibuya *et al.* (1995), Altar *et al.* (2001)
Pirfiform cortex	4	Other	Zetterström *et al.* (1998)
Pirfiform gyrus	7	Other	Conti *et al.* (2007)
Polymorph layer of the dentate gyrus	1	Hippocampus	Conti *et al.* (2007)
Posterior cortical amygdaloid nucleus	1	Other	Conti *et al.* (2007)
Prefrontal cortex	10	Cortex	Conti *et al.* (2007), Sartorius *et al.* (2009)
Prefrontal cortex layer III	1	Cortex	Conti *et al.* (2007)
Peripheral serum	13	Periphery	Sartorius *et al.* (2009), Kyeremanteng *et al.* (2012)
Septum	1	Other	Altar *et al.* (2001)
Striatum	13	Other	Altar *et al.* (2001), Angelucci *et al.* (2003); Gersner *et al.* (2010), Kyeremanteng *et al.* (2014)
Thalamus	4	Other	Kyeremanteng *et al.* (2014)
Ventral hippocampus	1	Hippocampus	Gersner *et al.* (2010)
Ventral tegmental area	1	Other	Gersner *et al.* (2010)
Ventromedial hypothalamic nucleus	1	Other	Conti *et al.* (2007)

S5 Table. Basic information on the animals that were used in the preclinical studies that were included in our meta-analysis.

Study	Animal	Age in weeks	weight
Lindefors *et al.* (1995)	Male Sprague-Dawley rats	N.K.	150 - 200 gr
Nibuya *et al.* (1995)	Male Sprague-Dawley rats	N.K.	150 - 200 gr
Zetterström *et al.* (1998)	Male Sprague-Dawley rats	N.K.	N.K.
Chen *et al.* (2001)	Male Sprague-Dawley rats	N.K.	160 - 180 gr
Altar *et al.* (2003)	Male Wistar rats	N.K.	230 - 250 gr
Angelucci *et al.* (2003)	Flinders Sensitive Line rats Flinders Resistant Line rats	10	N.K.
Dias *et al.* (2003)	Male Sprague-Dawley rats	N.K.	200 - 250 gr
Newton *et al.* (2003)	Male Sprague-Dawley rats	N.K.	160 - 180 gr
Jacobsen *et al.* (2004)	Male Wistar rats	N.K.	200 - 300 gr
Li *et al.* (2006)	Male Wistar rats	8 - 10	N.K.
Ploski *et al.* (2006)	Male Sprague-Dawley rats	N.K.	180 - 220 gr
Conti *et al.* (2007)	Male Sprague-Dawley rats	8 - 10	N.K.
Li *et al.* (2007)	Male Wistar rats	8 - 10	300 - 330 gr
Sartorius *et al.* (2009)	Sprague-Dawley rats (no sex specified)	8	N.K.
Gersner *et al.* (2010)	Sprague-Dawley rats (no sex specified)	8	N.K.
Kyerematenteng *et al.* (2012)	Male Wistar-Kyoto rats Male Wistar rats	7 - 8 7 - 8	250 - 350 gr 150 - 250 gr
Luo *et al.* (2012)	Male Wistar rats	N.K.	200 - 240 gr
O'Donovan *et al.* (2012)	Male Sprague-Dawley rats	N.K.	150 - 200 gr
Ryan *et al.* (2013)	Male Sprague-Dawley rats	N.K.	150 - 200 gr
Segawa *et al.* (2013)	Male Sprague-Dawley rats	N.K.	250 - 300 gr
Segi-Nishida *et al.* (2013)	Male C57BL/6N mice	9 - 12	N.K.
Dryvig *et al.* (2014)	Male Sprague-Dawley rats	N.K.	270 - 350 gr
Kyerematenteng *et al.* (2014)	Male Wistar-Kyoto rats Male Wistar rats	7 - 8 7 - 8	150 - 200 gr 200 - 300 gr

S6 Table. Basic methodological information on the preclinical studies that were included in our meta-analysis

Study	Method	BDNF type	Other condition	Behavioral tests	Sacrificed after
Lindefors *et al.* (1995)	In situ hybridization	BDNF mRNA	None	None	immediately
Nibuya *et al.* (1995)	in situ hybridization, Northern blot	BDNF mRNA	None	None	2 and 18 hours
Zetterström *et al.* (1998)	In situ hybridization	BDNF mRNA	None	None	6, 24, 48 and 504 hours
Chen *et al.* (2001)	In situ hybridization	BDNF mRNA	Ketamine add-on conditions	None	2 hours
Altar *et al.* (2003)	ELISA	BDNF mRNA, BDNF protein	None	None	6, 15, 36, 72, 134, and 240 hours
Angelucci *et al.* (2003)	ELISA	BDNF protein	None	None	24 hours
Newton *et al.* (2003)	RT PCR	BDNF RNA	None	None	2 and 6 hours
Jacobsen *et al.* (2004)	ELISA, in situ hybridization	BDNF mRNA	None	None	18 hours
Li *et al.* (2006)	ELISA	BDNF protein	ACTH add-on conditions	Forced swim, locomotor activity, rearing behavior, wet-dog response	6 hours
Ploski *et al.* (2006)	In situ hybridization	BDNF RNA	None	None	6 hours
Conti *et al.* (2007)	In situ hybridization	BDNF mRNA	None	None	6 hours
Li *et al.* (2007)	ELISA	BDNF protein	None	Forced swim test, open-field test: locomotor activity	24, 48, and 168 hours
Sartorius *et al.* (2009)	ELISA	BDNF protein	None	None	3, 8, 24, 72, 168, and 336 hours
Gersner *et al.* (2010)	ELISA	BDNF mRNA	None	Home-cage locomotion, exploration/novelty induced behavior, forced swim test, Morris water maze, sucrose preference test,	1 hour
Kyeremanteng *et al.* (2012)	ELISA	BDNF protein	None	None	24 and 168 hours
Luo *et al.* (2012)	ELISA	BDNF protein	Saline-proponol conditions	Sucrose preference, open-field test	24 hours
O'Donovan *et al.* (2012)	ELISA	BDNF protein	None	Forced swim test, water plus maze	336 hours
Ryan *et al.* (2013)	qRT PCR	BDNF mRNA	None	None	96 hours
Segawa *et al.* (2013)	Western blot, qRT PCR	BDNF mRNA, protein, Pro-BDNF	None	None	1, 2, 4, 8, and 24 hours
Segi-Nishida *et al.* (2013)	In situ hybridization, qRT PCR	BDNF mRNA	None	Food intake	2, 4, and 24 hours
Dryvig *et al.* (2014)	qRT PCR	BDNF mRNA	None		1, 4, 8, 16, 24, and 48 hours
Kyeremanteng *et al.* (2014)	ELISA	BDNF protein	None	Conditioned emotional response, forced swim test, open field test	24 and 168 hours

S7 Table Basic information on the patients that were included in the clinical studies that were included in our meta-analysis.

Study	Characteristics of subjects			Sub-group	N (f/m)	ECT		Depression ratings	
	Diagnosis	Treatment resistance	Age			Number of sessions	Time point of measurement	Pre-ECT	Post-ECT
Bocchio-Chiavetto *et al.,* (2006)	MDD	yes	54.0±16.2	responders	20 (14/6)	7	day after the last ECT	34.90±7.31#	8.10 ± 3.24
		yes	45.0±27.0	Non- responders	3 (2/1)			29.67±2.01#	14.00±13.11
Marano *et al.,* (2006)	MDD, BD	NA	55.9±21.7	Responders	13 (3/10)	7	day after the 4th ECT	27.5±6.3	7.9±3.5
		NA	62.0±24.0	Non-responders	2 (1/1)			29.0±1.4	16.0±0
Okamoto *et al.,* (2008)	MDD, BD	yes	58.6±13.9	Responders	12 (6/6)	12	1 week after last ECT	25.0 ± 8.2*	10.3± 3.4
		yes	62.4±15.1	Non-responders	6 (3/3)			20.6 ± 4.4*	na
Fernandes *et al.,* (2009)	MDD, BD	yes	52.7±15.9	Responders (73.33%)	15 (10/5)	11.23	day after the last ECT	24.15 ± 6.32*	24.15±6.32*
Gronli *et al.,* (2009)	MDD, BD	yes	70 (40-85)	Responders	10 (NA)	12	immediately prior to discharge	23.1*	6.0*
Piccinni *et al.,* (2009)	MDD, BD	yes	47.4±16.7	Responders	8 (5/3)	8.6	1 week after last ECT	24.1 ± 5.3**	6.8 ± 3.1
		yes	42.9± 17.9	Non-responders	10 (4/6)	8		24.1 ± 5.3**	6.8 ± 3.1
Hu *et al.,* (2010)	MDD	Not known	43.9±13.8	Responders	24 (20/4)	6	day after the last ECT	31.6±4.79 *	6.5±3.7
		Not known	23.3±4.2	Non-responders	4 (3/1)			30.0±3.9*	18.0 ± 4.1
Gedge *et al.,* (2012)	MDD	yes	45.7±12.2	Responders	5 (2/3)	12	1 week after ECT	25.6 ±4.93*	7.8±1.3
		yes	47.7±7.9	Non-responders	6 (5/1)			22.17 ±4.40*	17.83 ± 4.79

Table SI *continues on the next page*

Haghighi *et al.,* (2013)	MDD	no	30.7±5.8	Responders (75%)	20 (5/15)	12	na	39.35±10.46**	35.10 ±7.18
Lin *et al.,* (2013)	MDD, BD	yes	47.4±12.0	Responders	48 (38/10)	9.2	after the last ECT	31.5±8.6*	5.8±3.6
	MDD, BD	yes	40.1±8.7	Non-responders	7 (6/1)			26.1±6.5*	17.3±8.1
Stelzhammer *et al.,* (2013)	MDD	yes	49.7**±7.2**	Responders	3 (3/0)	12	6h after last ECT	32.3±5.7	17.7±10.7
		yes	58.0±7.7	Non-responders	4 (2/2)			22.8±4.6	21.3 ±6.6
Bilgen *et al.,* (2014)	MDD	Not known	33.0±5.9	responders	30 (19/11)	5.06	At the day of response	30.66±4.11**	15.73±3.36**
Bump *et al.,* 2014	MDD	Not known	51.7±13.7	NA	20 (10/10)	11.25	Varies	31.2±8.1**	NA
Kleinmann *et al.,* 2014	MDD	yes	47±16.5	NA	11(6/5)	10	24 h after 1st, 4th, 7th and 10th ECT	34±8.3#	NA

Abbreviations: MDD – major depressive disorder; BD – bipolar disorder; " – HDRS-6; * - HDRS-17; **- HDRS-21; ***- HDRS-24; # - MADRS

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
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.	4
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	4,6
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.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
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.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
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.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	5, S1-S3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
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.	6
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.	7,11,12,S5-S7
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).	S1-S3
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.	8-10,12-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10, 12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	S1-S3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11, 13
DISCUSSION			
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).	13
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
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
FUNDING			
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.	1, no special funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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frontiers in Cellular Neuroscience

ORIGINAL RESEARCH
published: 09 October 2015
doi: 10.3389/fncel.2015.00406

First evidence for glial pathology in late life minor depression: S100B is increased in males with minor depression

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Minor depression is diagnosed when a patient suffers from 2 to 4 depressive symptoms for at least 2 weeks. Though minor depression is a widespread phenomenon, its pathophysiology has hardly been studied. To get a first insight into the pathophysiological mechanisms underlying this disorder we assessed serum levels of biomarkers for plasticity, glial and neuronal function: brain-derived neurotrophic factor (BDNF), S100B and neuron specific enolase (NSE). 27 subjects with minor depressive episode and 82 healthy subjects over 60 years of age were selected from the database of the Leipzig population-based study of civilization diseases (LIFE). Serum levels of BDNF, S100B and NSE were compared between groups, and correlated with age, body-mass index (BMI), and degree of white matter hyperintensities (score on Fazekas scale). S100B was significantly increased in males with minor depression in comparison to healthy males, whereas other biomarkers did not differ between groups ($p = 0.10$–0.66). NSE correlated with Fazekas score in patients with minor depression ($r_S = 0.436$, $p = 0.048$) and in the whole sample ($r_S = 0.252$, $p = 0.019$). S100B correlated with BMI ($r_S = 0.246$, $p = 0.031$) and with age in healthy subjects ($r_S = 0.345$, $p = 0.002$). Increased S100B in males with minor depression, without alterations in BDNF and NSE, supports the glial hypothesis of depression. Correlation between white matter hyperintensities and NSE underscores the vascular hypothesis of late life depression.

Keywords: minor depression, late life depression, S100B, BDNF, NSE, glia, white matter hyperintensities, biomarker

OPEN ACCESS

Edited by:
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Received: *31 July 2015*
Accepted: *25 September 2015*
Published: *09 October 2015*

Citation:
Polyakova M, Sander C, Arelin K, Lampe L, Luck T, Luppa M, Kratzsch J, Hoffmann K-T, Riedel-Heller S, Villringer A, Schoenknecht P and Schroeter ML (2015) First evidence for glial pathology in late life minor depression: S100B is increased in males with minor depression. Front. Cell. Neurosci. 9:406. doi: 10.3389/fncel.2015.00406

INTRODUCTION

Minor depression is a widespread phenomenon in late life (Hegerl and Schoenknecht, 2009; Polyakova et al., 2015). According to the fourth edition of the diagnostic statistical manual of mental disorders (DSM-IV) a person suffering from two to four depressive symptoms for at least 2 weeks has a minor depressive episode. For diagnosis of minor depressive disorder one additionally has

to exclude a history of major depression (American Psychiatric Association, 2000). In clinical practice patients with minor depressive symptoms may represent an independent minor depressive episode or a subsyndromal stage of major depression (Park et al., 2010). Every fourth patient with minor depression develops major depression within 2 years after diagnosis (Lyness et al., 1999) and 13% of subjects with minor depression have attempted suicide at least once (Eaton et al., 1995). With regard to these data proper diagnosis and management of minor depression might become an approach to prevent a more severe depressive disorder.

Although plenty of studies have been conducted to elucidate the etiology of major depression, the pathophysiology of minor depression is still unknown. Possible research directions include the glial, neurotrophic and vascular hypotheses of depression. Alterations of peripheral biomarkers of brain structure and function might shed light on the pathological changes in central mechanisms. Brain derived neurotrophic factor (BDNF), S100B and neuron specific enolase (NSE) are among the most studied biomarkers in affective disorders, in particular major depressive disorder (Schroeter et al., 2002; Hetzel et al., 2005; Andreazza et al., 2007; Schroeter and Steiner, 2009; Kalia and Silva, 2015).

BDNF, associated with plasticity in the central and peripheral nervous system, is decreased in serum in acute major depressive episodes and restored in remission (Molendijk et al., 2014). The glial marker protein S100B is elevated during major depressive episodes and decreased following successful treatment (Schroeter et al., 2013). Thus, fluctuations in serum levels of BDNF and S100B seem to be state markers for major depression. This is supported by powerful meta-analyses including a very high number of subjects (Schroeter et al., 2008; Polyakova et al., 2015). NSE is a marker for neuronal injury. In contrast to BDNF and S100B, serum NSE levels seem to be stable in depression suggesting mainly glial dysfunction (Schroeter et al., 2013). However, a recent publication reported increased NSE levels in cerebrospinal fluid (Schmidt et al., 2015), leaving more space for discussion.

Due to clinical similarities with major depression, we expect similar biomarker changes in minor depression. Since BDNF levels do not correlate with depression severity (Molendijk et al., 2011), decreased serum BDNF might also be observed in minor depression. In this disorder it might reflect impaired constitutive or activity-dependent BDNF expression, resulting in impaired brain plasticity. Increased S100B in minor depression may indicate early glial pathology that precedes specific neuronal changes such as in major depression (Rajkowska, 2000). Unaltered (comparing to healthy controls) NSE should confirm that there is no neuronal damage in minor depression.

To further explore the etiology of minor depression we analyzed serum levels of BDNF, S100B and NSE in subjects with minor depression and healthy control subjects from the Leipzig population-based study of civilization diseases (LIFE). Serum levels of BDNF, S100B and NSE were considered as primary outcomes. In analogy to major depression we hypothesized a decrease of BDNF and an increase of S100B, without changes of NSE in minor depression.

An association between late life minor depression and the vascular hypothesis of depression (Taylor et al., 2013) was investigated in explorative analyses by correlating white matter hyperintensities to serum markers. In order to control for confounding variables we correlated age and body mass index (BMI) with serum markers. Correlation of serum markers with clinical and imaging parameters, such as age, BMI and extent of white matter hyperintensities were considered as secondary outcomes.

MATERIALS AND METHODS

Participants

Twenty seven subjects 60 years and older satisfying the DSM-IV criteria for minor depressive episode and eighty two healthy control subjects were selected from the LIFE study. LIFE study includes a representative sample from the Leipzig population (Loeffler et al., 2015). All of the participants provided their written informed consent in accordance with the Declaration of Helsinki before participation in the study. The study was approved by the ethics board of the Medical Faculty of the University of Leipzig. At the moment of subjects' selection the LIFE study database included 1617 subjects over 60 years of age. Every subject underwent structured psychiatric interview, neuropsychological testing, clinical examination, blood sampling and scanning with multimodal magnetic resonance imaging (MRI).

Diagnostic Criteria and Laboratory Procedures

Minor depressive episode according to DSM-IV criteria was diagnosed based on the structured clinical interview for DSM-IV axis I disorders (SCID). White matter hyperintensities were rated by experienced neuroradiologists using the Fazekas scale (Fazekas et al., 1987) in fast fluid-attenuated inversion recovery (FLAIR) images.

Blood samples were collected from the subject's cubital vein at the first day of the study. The mean time between blood sampling and psychiatric interview was 10.0 (4.3) days for subjects with minor depression and 13.0 (9.0) for healthy subjects. All samples were collected uniformly in the morning, following overnight fasting. Serum was prepared using the standard operating procedures. In brief, samples were left for 45 min for clotting, followed by a centrifugation step (10 min, 2750 g, 15°C). Samples were then filled in straws (CryoBioSytems IMV, France) by an automatic aliquoting system (DIVA, CryoBioSytems IMV, France). After that serum samples were stored at −80°C. To minimize freeze-thaw cycles, samples were sorted in a cryogenic work bench (temperatures below −100°C) and automatically stored in tanks with a coolable top frame in the gas phase of liquid nitrogen (Askion, Germany; Loeffler et al., 2015).

S100B and NSE were measured with monoclonal 2-site immunoluminometric assays performed on the fully mechanized system LIAISON (Diasorin, Dietzenbach, Germany). The detection limit for the assays was 0.02 μg/l and 0.04 μg/l (described in detail elsewhere (Streitbuerger et al., 2012). BDNF

was measured in serum with an ELISA manufactured by R&D systems (Wiesbaden, Germany). The sensitivity of the assay was 20 ng/L leading to a measuring range of 62.5 until 4000 ng/L. Interassay coefficients of variation were between 9.4 and 11.1% for mean BDNF concentrations between 362 and 2079 ng/L. Note that serum samples were diluted 1:20 before measuring them with the assay.

Statistical Analyses

Statistical analyses were performed using SPSS version 22 (IBM, Chicago, IL, USA). Complex assessment of the data distributions were performed including visual assessment of the histograms, skewness and kurtosis of the data, as well as by Kolmogorov–Smirnoff and Shapiro-Wilk test. Since the protein levels were non-normally distributed and different numbers of subjects were included in patients' and controls' groups we applied non-parametric Mann-Whitney U test for evaluation of group differences. The differences in demographic factors were assessed by independent *t*-test or by chi-square test. The impact of sex differences and a history of depression were assessed by subgroup analyses. The correlation analyses between serum markers, clinical/imaging and demographic data were performed by calculating Spearmen correlation coefficients. We expected directed changes for BDNF and S100B in minor depression in comparison with control subjects, therefore one-tailed α-level for statistical significance was set at 0.05 for these biomarkers. For NSE and the correlation analyses two-tailed α-level at 0.05 was chosen. The statistical power was calculated using G-power 3.1.9.2. (Faul et al., 2009). Generally, data are presented as means and standard deviations (SD). Dot plots represent the distributions of the protein levels and their medians.

RESULTS

The demographics, clinical and imaging data, and serum marker levels of the patients and healthy control subjects are presented in **Table 1**. Both cohorts were matched for age, education, BMI and the extent of white matter hyperintensities as measured with the Fazekas scale.

BDNF, S100B and NSE did not differ between patients in minor depressive episode and healthy control subjects (**Table 1**). Since the two groups differed with regard to sex, we conducted additionally sex-specific analyses. **Figure 1** illustrates results with dot plots for the three serum marker proteins across the whole groups, and specifically for each sex. When the analysis was stratified by sex we observed significantly increased S100B ($p = 0.034$) in males with minor depressive episode (0.092 μg/l [0.012]) in comparison with healthy male controls (0.067 μg/l [0.004]).

As depicted in the **Figure 2**, serum S100B levels were significantly lower in healthy males (0.067 μg/l [0.004]) in comparison with healthy females (0.115 μg/l [0.029]; $p = 0.01$), whereas there was no sex difference in the minor depression group (male: 0.091 μg/l [0.12]; female: 0.088 μg/l [0.011]; $p = 0.53$). Removal the abovementioned female outlier did not affect the differences between healthy males and females for S100B. BDNF and NSE did not differ neither between the groups stratified by sex (males $p = 0.13$–0.95; females $p = 0.40$–0.42), nor when male and female subjects were compared within the minor depression subgroup ($p = 0.10$–0.98).

Similarly, presence of the history of major depression did not affect the levels of BDNF, S100B or NSE in the minor depression group ($p = 0.10$–0.50); neither in comparison with healthy controls ($p = 0.13$–0.38; **Figure 3**).

As presented on **Figure 1** one female control subject presented with extremely high S100B value, above three SD of the group. To control for the impact of this subject on the analysis of S100B we performed an additional analysis of S100B excluding this subject's data. In this analysis we observed a trend, $p = 0.078$, for increased S100B in the whole minor depression group (0.088 μg/l [0.043]) in comparison with healthy controls (0.074 μg/l [0.032]).

We observed a positive correlation between S100B and BMI in the whole sample ($r_s = 0.204$, $p = 0.04$), and in healthy subjects ($r_s = 0.246$, $p = 0.03$), and a positive correlation between S100B

TABLE 1 | Demographical, clinical/imaging data and serum markers in patients and healthy control subjects.

	Whole group		Males		Females	
	MinD	HC	MinD	HC	MinD	HC
Number (with a history of depression)	27 (14)	82	7 (3)	58	21 (11)	24
Age	71.2 (4.5)	70.0 (4.1)	71.4 (4.8)	70.3 (4.1)	71.1 (4.5)	69.6 (4.3)
Sex (male/female)	7/21***	51/31***				
Education (<12years/>12 years)	24/4	58/24	5/2	37/15	19/2	22/9
Fazekas score (0/1/2/3)	6/16/5/0	25/45/12/0	2/4/0/0	17/27/7/0*	4/12/5/0	8/18/5/0
BMI (kg/m^2)	27.1 (4.9)	28.1 (4.6)	26.7 (2.1)	27.8 (3.7)	27.2 (5.7)	28.7 (5.9)
BDNF (μg/L)	25.8 (5.4)	25.2 (5.9)	29.6 (14.2)	24.7 (4.3)	26.1 (4.9)	26.1 (7.8)
NSE (μg/L)	11.8 (2.6)	11.9 (2.1)	11.9 (2.9)	11.7 (2.3)	11.7 (2.6)	12.2 (1.7)
S100B (μg/L)	0.088 (0.043)	0.086 (0.11)	0.088 (0.03)*	0.067 (0.03)*†	0.088 (0.05)	0.12 (0.16)†

*MinD, minor depression; HC, healthy controls; BMI, body-mass index; BDNF, brain derived neurotrophic factor; NSE, neuron specific enolase; †Significant difference between males and females at p < 0.05; *Significant difference between minor depression and healthy controls group at p < 0.05; ***Significant difference between minor depression and healthy controls group at p < 0.001; Student's t-test for age and body mass index, chi-square test for categorical data, Mann-Whitney U test for BDNF, NSE, S100B.*

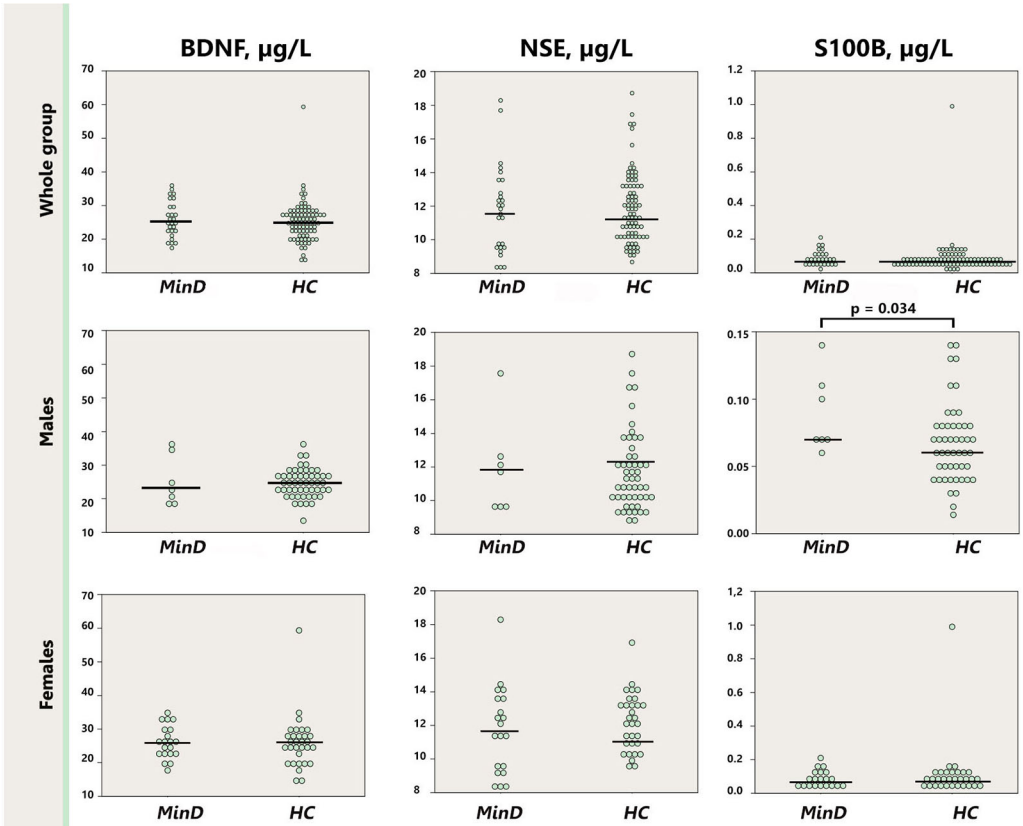

FIGURE 1 | Dot plot for the distribution of serum markers' levels in subjects and healthy controls (first row), separately for males (second row), and females (third row). Median levels of the serum markers are depicted with black horizontal lines. Note that the distribution of S100B in males is depicted on a zoomed scale. MinD, minor depression; HC, healthy controls; BDNF, brain derived neurotrophic factor; NSE, neuron specific enolase.

and age in the whole sample ($r_s = 0.229$, $p = 0.02$) and in healthy control subjects ($r_s = 0.345$, $p = 0.002$).

A significant positive correlation was found between age and the degree of white matter hyperintensities as measured with the Fazekas score both, in the whole sample ($r_s = 0.425$, $p < 0.001$), and in subgroups (minor depression: $r_s = 0.462$, $p = 0.04$; healthy controls: $r_s = 0.421$, $p < 0.001$). With regard to serum markers, Fazekas score correlated positively with NSE in the whole sample ($r_s = 0.252$, $p = 0.02$) and in patients with minor depression ($r_s = 0.436$, $p = 0.048$). In the healthy control sample the Fazekas score correlated positively only with S100B ($r_s = 0.261$, $p = 0.04$).

Finally, we examined whether our groups were large enough to detect the predicted impact of minor depression on serum BDNF and S100B. The statistical power calculations using G-Power for Mann-Whitney tests were based on the previous meta-analyses of BDNF and S100B alterations in major depression (Schroeter et al., 2013; Polyakova et al., 2015). These calculations lead to required sample sizes of $n = 36$ per group for BDNF and $n = 5$ per group for S100B.

DISCUSSION

In this study, for the first time to our knowledge, we evaluated serum levels of BDNF, S100B and NSE in subjects with minor depressive episode. We found evidence for increased S100B in males with minor depression without any alterations of NSE, which was in agreement with our hypotheses. BDNF was unchanged, although we expected a decrease in analogy to major depression. In assessment of the secondary outcomes we observed a positive correlation between NSE and Fazekas score in minor depression and in the whole sample. S100B correlated positively with age and BMI in the whole sample and in healthy controls.

Our hypotheses were initially built on data derived from major depression studies. In minor depression we didn't detect the hypothesized difference for BDNF. One explanation of such a negative finding might be that neurotrophic functions are not impaired at the subthreshold level of depression. Then the substantial differences in the pathophysiology of these disorders arise. Nevertheless, one might also argue that the sample size was too low. The calculation of the required sample size using G-Power for BDNF indeed showed that our minor depressive group might have been underpowered (27 subjects instead of the 36 required). In this study we reached only 75% of statistical power. To solve the power issue future studies should involve larger sample size.

For S100B the sample size was obviously large enough to detect the expected group effects (27 subjects instead of five

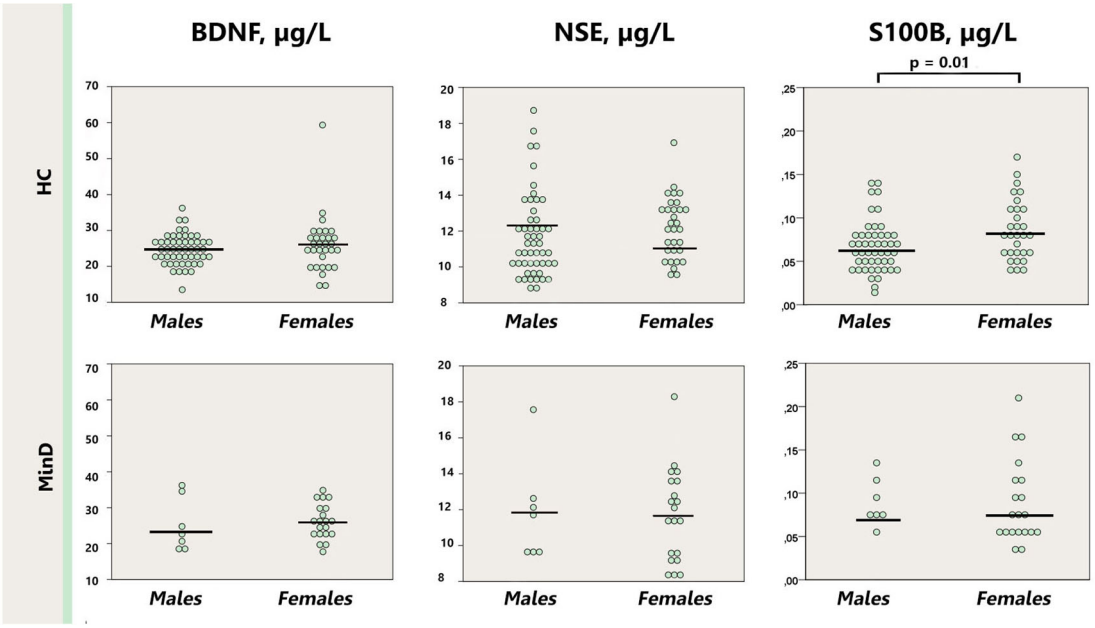

FIGURE 2 | Dot plot for the distribution of serum markers' levels in healthy males and females (first row), and males and females with minor depression (third row). Median levels of the serum markers are depicted with black horizontal lines. Note that the outlier from the healthy females group is not depicted on the S100B plot. MinD, minor depression; HC, healthy controls; BDNF, brain derived neurotrophic factor; NSE, neuron specific enolase.

required). Indeed, we observed a trend for increased S100B in the whole minor depression group and significantly increased S100B in males with minor depression in comparison with control subjects. Though we did not rule out potential non-brain sources of S100B in our study, this finding points to the similarities between major and minor depression. Moreover, the fact that differences in S100B are less prominent than in major depression suggests that clinical presentation mirrors to some extend molecular changes.

The findings we describe are based on the concept that serum S100B changes are related to alterations in the brain. However, S100B, as well as BDNF, and NSE might originate from non-brain sources. For instance, various subtypes of leukocytes can secrete S100B (Miki et al., 2013; Fujiya et al., 2014; Moutsatsou et al., 2014). Thrombocytes are the largest source for serum BDNF (Fujimura et al., 2002), adipocytes produce both S100B and BDNF (Fujiya et al., 2014; Huang et al., 2014), finally NSE may originate from damaged peripheral nerves (Li et al., 2013). Because we did not assume relevant biases related to these potentially confounding sources in minor depression, we did not control for potential non-brain sources of the serum markers in our study. Note that we compared subjects with minor depression to matched healthy control subjects and considered, therefore, differences and not absolute values of

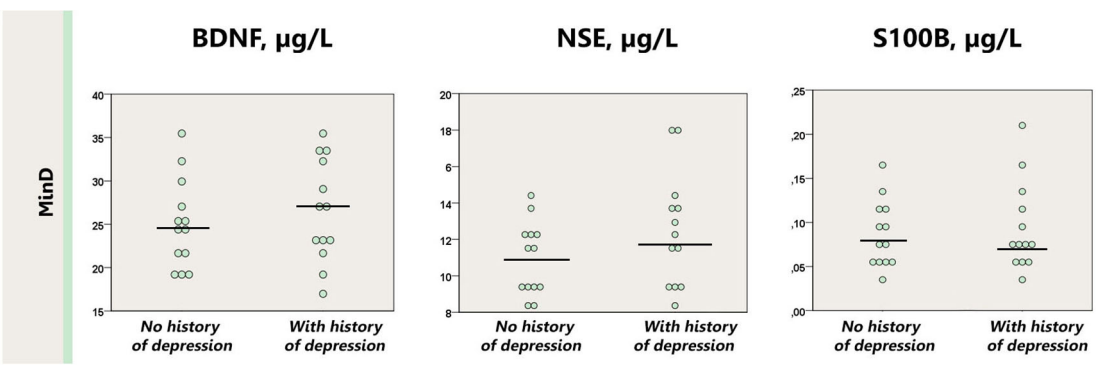

FIGURE 3 | Dot plot for the distribution of serum markers' levels in subjects with minor depression with or without a history of depression. Median levels of the serum markers are depicted with black horizontal lines. MinD, minor depression, HC, healthy controls; BDNF, brain derived neurotrophic factor; NSE, neuron specific enolase.

S100B. Moreover, changes of S100B in leukocytes have been shown only in bipolar disorder (Moutsatsou et al., 2014), whereas for unipolar depression, which is more relevant for our data, no studies are available in the literature so far. Future studies might transcend these limitations by including larger and more strictly selected cohorts and controlling for non-brain sources of these markers.

The concept of leakage from the brain obviously has its limitations. S100B, as well as BDNF, and NSE might originate from non-brain sources. Various subtypes of leucocytes can secrete S100B (Miki et al., 2013; Fujiya et al., 2014; Moutsatsou et al., 2014), thrombocytes are the largest source for serum BDNF (Fujimura et al., 2002), adipocytes produce both S100B and BDNF (Fujiya et al., 2014; Huang et al., 2014), finally NSE originate from damaged peripheral nerves (Li et al., 2013).

Interestingly, S100B was not different between males and females with minor depression, rather it differed between healthy males and females. This finding is in line with previous studies showing no sex differences in major depression (Arolt et al., 2002; Hetzel et al., 2005), but contradicts another one showing increased S100B in females with major depression (Yang et al., 2008). The differences between our and the former study might be attributed to the differences in the studied samples with regard to disease severity and age. Further studies are in agreement with our finding for healthy subjects by showing higher S100B in healthy female than male adults (Streitbuerger et al., 2012) and children (Gazzolo et al., 2003). Overall, the literature on effects of gender on S100B did not reach consensus so far. Whether gender differences in S100B reflect the differences in susceptibility to disease and whether S100B is a gender-specific marker of minor depression needs more systematic assessment.

S100B, as an index for glial alterations, is modified by age in major depression (Schroeter et al., 2011). In minor depression we did not find a correlation between S100B and age. Instead, S100B correlated positively with age in healthy controls. This finding is in line with cerebrospinal fluid studies (van Engelen et al., 1992; Nygaard et al., 1997), but contradicts later serum studies (Wiesmann et al., 1998; Portela et al., 2002). One potential reason for these differences is again the different disease severity. According to Rajkowska's observations development of depressive disorder starts with glial alterations and progresses with age (Rajkowska, 2000). If late life minor depression is a subtle manifestation of major disorder, absence of correlation between S100B and age in minor depression might add to Raikowska's hypothesis.

A weak positive correlation between S100B and BMI was not surprising. S100B is secreted by adipocytes and is involved in the pathogenesis of obesity as shown *in vitro* (Fujiya et al., 2014) and *in vivo* (Buckman et al., 2014). Positive correlation of serum S100B with BMI was previously reported in a combined sample of cognitively intact lean and obese subjects (Steiner et al., 2010a) and in subjects with schizophrenia (Steiner et al., 2010b). In our study the positive correlation in the whole sample was likely driven by the healthy subgroup, with no such association in minor depressive episode. As correlations between S100B and age/BMI were detected only in healthy subjects but not in the minor depression group, and both cohorts were matched regarding mean age and BMI, we assume that age and BMI did not drive the S100B effects in minor depression.

The finding of positive correlation between S100B and white matter hyperintensities in healthy subjects is in agreement with a study by Streitbuerger et al. (2012). These authors reported an association between serum S100B and the diffusion tensor imaging parameters fractional anisotropy and radial diffusivity in white matter tracts in healthy females. From the biological point of view increased secretion of S100B might reflect neuroinflammation that accompanies neuronal damage (Kabadi et al., 2015).

We detected also a positive correlation between serum NSE and Fazekas score in the whole sample and in the minor depression subgroup. NSE, a peripheral marker of neuronal damage, might be either of central (Cheng et al., 2014) or peripheral origin (Li et al., 2013). In major depression a central origin is suggested by the correlation with white matter hyperintensities. Finally, the extent of white matter hyperintensities correlated with age in both cohorts, healthy and minor depressive subjects, which is in line with the literature (Nyquist et al., 2015). In combination with the correlation between white matter hyperintensities and the neuronal injury marker NSE in minor depression, our data might support the vascular hypothesis of late life depression (Taylor et al., 2013; Taylor, 2014).

Limitations

As already discussed our study was limited by a relatively small sample size, which might have hampered, in particular, the detection of BDNF effects. Another limitation might be the inclusion of patients having a history of depression. Thus, not all patients could be qualified as having minor depressive disorder. We addressed this issue in the subgroup analysis and found that inclusion of the subjects with a history of depression did not affect our results. In fact, such a sample mirrors a real life situation when psychiatrists need to make a clinical judgement and select a treatment strategy. Note, moreover, that our subjects were chosen from a representative population study.

The findings we describe are based on the concept that serum S100B changes are related to alterations in the brain. However, S100B, as well as BDNF, and NSE might originate from non-brain sources. For instance, various subtypes of leukocytes can secrete S100B (Miki et al., 2013; Fujiya et al., 2014; Moutsatsou et al., 2014). Thrombocytes are the largest source for serum BDNF (Fujimura et al., 2002), adipocytes produce both S100B and BDNF (Fujiya et al., 2014; Huang et al., 2014), finally NSE may originate from damaged peripheral nerves (Li et al., 2013). Because we did not assume relevant biases related to these potentially confounding sources in minor depression, we did not control for potential non-brain sources of the serum markers in our study. Note that we compared subjects with minor depression to matched healthy control subjects and considered, therefore, differences and not absolute values of S100B. Moreover, changes of S100B in leukocytes have been shown only in bipolar disorder (Moutsatsou et al., 2014), whereas for unipolar

depression, which is more relevant for our data, no studies are available in the literature so far. Future studies might transcend these limitations by including larger and more strictly selected cohorts and controlling for non-brain sources of these markers.

CONCLUSION

In this study we made a first attempt to assess serum levels of BDNF, S100B, and NSE in minor depression. We found evidence for increased glial marker S100B in males with minor depression and a similar trend in the whole minor depressive group, but no significant evidence of BDNF and NSE alterations. The positive correlation of NSE with Fazekas score as a measure for white matter hyperintensities in minor depression supports the vascular hypothesis of late life depression.

AUTHOR CONTRIBUTIONS

MP, PS, MLS have designed the study, analyzed and interpreted the data, drafted and revised the manuscript content; MP and CS selected the subjects from LIFE study database, JK was responsible for the laboratory detection of the serum markers; LL and KTH were responsible for ratings of white matter hyperintensities, CS, KA, ML, TL, SRH, AV contributed to data acquisition. All authors have critically reviewed the manuscript and approved its final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This study has been supported by the International Max Planck Research School on Neuroscience of Communication (IMPRS NeuroCom; MP), by LIFE—Leipzig Research Center for Civilization Diseases at the University of Leipzig—funded by the European Union, European Regional Development Fund and by the Free State of Saxony within the framework of the excellence initiative (CZ, KA, TL, SRH, AV, PS and MLS), by the German Consortium for Frontotemporal Lobar Degeneration, funded by the German Federal Ministry of Education and Research (MLS), and by the Parkinson's Disease Foundation (MLS; Grant No. PDF-IRG-1307).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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3. GENERAL DISCUSSION

In the framework of the current thesis significance and biological correlates of minor depression, a subthreshold depressive disorder, as categorized by the DSM-IV were investigated. The experimental results are discussed in detail in respective sections. The discussion section will summarize important findings of our studies. Thereafter, the discussion will focus on limitations of this work, implications for research, clinical practice and general conclusions.

3.1 Summary of results

Prevalence of minor depression

Results of the systematic review showed that minor depression is highly prevalent in late life. It often accompanies somatic and cognitive disorders. The highest prevalence of minor depression is observed in institutionalized patients (14.4%) and patients with mild cognitive impairment (20-26%). At the same time, only about half of the minor depression cases are recognized by medical staff (nurses and general practitioners)[52-54]. Patients with minor depression have a higher risk for developing a major depressive disorder[55] or even progression of the comorbid cognitive impairment to dementia[56-58].

Biomarker of neurotrophic and glial function in major and minor depression

BDNF, a biomarker of neurotrophic function, is one of the most consistent biomarkers of mood disorders. In our meta-analytical study, significantly decreased peripheral BDNF levels were observed in acute major depression and acute states of bipolar disorder as compared to healthy controls. This difference was not anymore significant when patients reached euthymic state. Furthermore, for the first time on the meta-analytical level, the exclusive increment of serum BDNF in responders to antidepressive medication was shown, while in non-responders BDNF levels did not change as compared to baseline.

Therefore, *serum BDNF may be considered a state marker and a marker of treatment response in major depression.*

In clinical practice, one of the most efficient treatment methods for non-responders to antidepressive drugs is electro-convulsive therapy (ECT). We performed a translational meta-analysis investigating effects of ECT on BDNF. We demonstrated a similar pattern of BDNF expression in mouse and human brains, based on the data from the Allen Brain Atlas (www.brain-map.org/). Further, we showed that ECT leads to increased BDNF expression in the rodent brain without impact on peripheral BDNF concentrations. We could not observe changes of peripheral BDNF concentrations in patients that underwent electro-convulsive treatment. Based on the animal studies we conclude, that *absence of peripheral BDNF changes does not imply that there are no changes in the brain and even if we do not see changes of peripheral BDNF in humans, some changes can still occur in the brain*.

Serum biomarkers in minor depression

The analysis of serum biomarkers of depression did not reveal any major alterations in subjects with minor depression. Contrary to the main hypothesis we did not see any significant decrease of BNDF in minor depression. The increment of S100B was observed only in a small group of men with minor depression. Serum NSE levels were comparable between the groups as expected. These results confirm *absence of neuronal damage and major alterations of neurotrophic function in the brain. Along with our hypothesis signs of early glial dysfunction were observed in men.* However, this finding still needs further replication in larger samples.

Structural brain correlates of minor depression

In the fifth chapter structural brain scans of patients with minor depression and healthy controls were compared. Several parameters such as whole brain gray matter density,

region of interest analysis of gray matter density and cortical thickness. Despite thorough analyses no significant differences were detected between the groups. Therefore, the conclusion is - there is not enough evidence for structural brain alterations in late life minor depression.

Implications for research

The limitations of the experimental work were described in detail in each individual study. Accordingly, this chapter focuses more on general issues that were faced during this work, and on future directions.

Subjects' selection

Firstly, data from the population-based LIFE study were used. The study involved two days of extensive clinical assessments, cognitive tests and multi-modal MRI. After completion of the first round of assessments a selection bias became evident, with the predominant selection of high functioning elderly individuals in LIFE cohort. This led to lower than expected prevalence of minor depression (about 5% of the population). Furthermore, two thirds of subjects with minor depression did not complete the MRI scanning. In the end the expected number of 200 participants shrank to 38 subjects with minor depression. In future studies on minor or subthreshold depression other sources and ways of recruitment would be recommended. These could be patients recruited at ambulatory psychiatric clinics, hospitalized patients or patients from nursing homes.

Biomarkers

Due to time constraints we measured serum biomarkers only in half of the subjects with minor depression. As the LIFE study recruitment was finished, and new subjects arrived, it was difficult to quantify serum biomarkers in remaining subjects reliably exactly fitting first measurements. In the biomarker studies it is very important to use exactly the same

measurement procedures, including laboratory kits, standard proteins etc. Minor changes due to laboratory conditions might influence statistical analysis. Therefore, we recommend to measure serum biomarkers in one batch as soon as all probes are collected.

Statistics

In our small population all biomarkers were non-normally distributed. Blood biomarker levels often have non-normal distribution even in large populations. In case of any additional variable (such as sex in our case), that is needed to be controlled in the model, statistical test selection becomes very difficult. Therefore, accounting for a non-normal distribution and controlling for all confounding variables is necessary already at the study design level.

In our experimental work we faced the multiple comparisons problem and learned multiple opinions on this issue. For future studies interested in multiple parameters we recommend to state clearly whether the study is exploratory or not and use the False Discovery Rate (FDR) correction. This correction is appropriate from the statistical point of view and clearly informs the reader about evidence level of the study.

Neuroimaging

Current neuroimaging has a wide range of modalities. For example, gray matter density, volume, surface or the cortical thickness can be measured in the same scan. The selection of the imaging modality remains to be at a certain point intuitive. However, the evidence shows that not every modality is suitable for every study[59]. In case of minor depression, the available neuroimaging data was very limited. In such cases we recommend to use the exploratory approach with several modalities and clearly state it in the publication. Replication of these findings will be the task of further research.

The power of neuroimaging studies is a well-known issue. Nevertheless many studies are planned without power estimation. During our work we understood that, while in the

regular statistics the tools are available to calculate the power, for the neuroimaging analyses such tools are still scarce and very difficult to implement. Therefore, such tools are an unmet need in the light of the current replication crisis in neuroimaging.

3.2 Implications for clinical practice

In our study we observed a number of non-significant findings. Still, there are some implications that could be proposed for clinical practice.

First of all, it is necessary to inform medical staff of nursing homes and somatic departments of the frequent co-occurence of minor depression, train them to diagnose it and provide help. For this, special trainings should be organized and printed materials distributed.

Though our results are partly negative and, from a statistical point of view, uninterpretable, they might also show that no major pathology is present in minor depression. In the light of absent clinical studies for the biologically driven treatment of minor depression[64] our study suggests such easy accessible and cheap intervention as physical exercise might be of choice.

3.3 Conclusions

The nature and course of minor depression is not yet understood. However, the clinical significance is substantial. The clinical closeness to major depression makes minor depression a good candidate model for the search of early alterations related to depressive disorders. Heterogeneity, disagreement on thresholds and poor diagnostics, on the other hand, cause difficulties in research.

In this thesis we used a systematic approach to determine clinical features and neural correlates of minor depression. We used the best available diagnostic interview and identified subjects from the general population. Despite benefits of the screening of large population, the missing neuroimaging data has substantially reduced our sample size.

Nevertheless, our cohort was the largest to date investigating minor depression. We formed our hypotheses based on large scale meta-analyses of biomarker studies and neuroimaging data in major depressive disorder. However, in minor depression only few features resembled the pathology observed in major depressive disorder. While no structural changes were observed in minor depression, our data indicate that subtle changes of glial and neurotrophic function might be present.

Current classification systems have stepped away from the term “minor depression”, shifting to a dimensional approach in case of ICD-11, or refining earlier categorical thresholds in case of DSM-5. Regardless of the future categorization of subthreshold depressive disorders, minor depression provides a valuable model for early clinical research due to the inclusion of core depressive symptoms. We recommend adhering to this feature in future studies, along with rigorous clinical diagnostics. Our contributions to the glial and neurotrophic hypotheses of depression might become a starting point for replication and further research in subclinical depressive disorders.

SUMMARY

Cumulative doctoral Dissertation submitted in fulfillment of the requirements for the academic grade Dr. rer. med.

Looking for pathomechanisms of late life minor depression – a combined MRI, biomarker and meta-analytic study

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August 2018

Our first study shows that, the minor depression affects nearly ten percent of elderly population. Its median prevalence increases in hospitalized and institutionalized patients and, especially, in patients with co-morbid mild cognitive impairment. Nearly half of minor depression cases are not recognized by the medical staff, and its pathophysiology remains largely unexplored. To address the latter, in the current thesis we tested the neurotrophic and glial hypotheses of mood disorders

in subjects with minor depression. Further, we looked for structural brain changes and markers of neuronal damage in subjects with minor depression.

In the second study, we addressed the neurotrophic hypothesis of mood disorders. This hypothesis attributes an onset of depressive disorder to the impaired secretion of Brain Derived Neurotrophic Factor (BDNF), leading to reduced neuronal plasticity. Our meta-analyses confirmed that serum and plasma BDNF levels decreased in acute depressive episodes, and were similar between healthy subjects and patients in euthymic state. The unique finding of our meta-analysis is that serum BDNF increased only in responders to antidepressant treatment and remained stable in non-responders. Therefore, serum BDNF is of interest as a potential marker of clinical response to the antidepressant treatment.

In the third study, we investigated whether BDNF may also mark the response to the Electro-Convulsive Therapy (ECT), which is widely used for the treatment resistant depression. Since, BDNF has a similar topographic pattern of gene expression in rodent and human brains; we investigated BDNF changes following ECT in human and rodens. In series of translational meta-analyses peripheral BDNF did change significantly following ECT, neither in rodents and nor humans. However, despite the unchanged BDNF in the blood, its brain synthesis (both mRNA and protein) had significantly increased. Hence, the absence of BDNF changes in the blood does not mean the absence of BDNF changes in the brain.

In the fourth study, we assessed the serum levels of markers of neurotrophic (BDNF) and glial (S100B) function, and neuronal damage (Neuron Specific Enolase, NSE) in subjects with minor depression and healthy controls. Serum levels of BDNF and NSE were not altered in subject with minor depression. In this study, we

observed increased serum levels of glial marker S100B in a subgroup of males with minor depression. This finding is in line with the described early glial changes in depressive disorders, and should be investigated further.

In the fifth study, we applied three different methods to assess structural gray matter changes in minor depression. Neither in the Voxel-Based Morphometry (VBM) analysis, nor in the Region-of-Interest (ROI) approach within the meta-analytically derived mask, nor in the analysis of cortical thickness had we observed gray matter alterations. In the statistical sense, our finding cannot be interpreted, as “the absence of evidence is not the evidence of absence”. However, taking the broader perspective and very small effect sizes of cortical atrophy in major depression (the largest g=0,138 as reported by a recent powerful meta-analysis), one may speculate that clinical symptoms precede visible on the Magnetic Resonance Imaging (MRI) gray matter alterations in depressive disorders.

Taken together, the minor depression is highly prevalent in the late life and, thus, should not be ignored. The construct of minor depression provides an in vivo model for detection of early changes in depressive disorders. In the current thesis, we did not find any significant evidence for decreased serum BDNF, NSE or gray matter parameters. However, we found an increment of serum S100B, supporting the glial hypothesis of depression.

Future studies on minor and subthreshold depression should aim for larger sample sizes. Classification systems should seek agreement on definitions. Together, these improvements will build a reliable base for the search of pathomechanisms and testing early interventions in depression.

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APPENDIX A

In accordance with the Promotionsordnung of the medical faculty of the Leipzig University for the cumulative doctoral dissertation. I hereby confirm, that the the International Committee of MedicalJournal Editors (ICMJE) authorship criteria were followed for the following article:

Prevalence of minor depression in elderly persons with and without mild cognitive impairment: a systematic review

By signing the following co-authors confirm that, the first author, Maryna Polyakova, was responsible for

- Designing the conception of the work, the literature search, data extraction, analysis, and interpretation ; AND
- Drafting the work and revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Name of co-author	Signature
Nadene Sonnabend	
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Christian Sander	
Matthias L. Schroeter	
Peter Schönknecht	

In accordance with the Promotionsordnung of the medical faculty of the Leipzig University for the cumulative doctoral dissertation. I hereby confirm, that the the International Committee of MedicalJournal Editors (ICMJE) authorship criteria were followed for the following article:

BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis.

The first author, Maryna Polyakova, was responsible for

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Katharina Stucke

Katharina Schuemberg

Karsten Mueller

Peter Schönknecht

Matthias L. Schroeter

In accordance with the Promotionsordnung of the medical faculty of the Leipzig University for the cumulative doctoral dissertation. I hereby confirm that the International Committee of Medical Journal Editors (ICMJE) authorship criteria were followed for the following article:

Brain-Derived Neurotrophic Factor and Antidepressive Effect of Electroconvulsive Therapy: Systematic Review and Meta-Analyses of the Preclinical and Clinical Literature

The first author, Maryna Polyakova, was responsible for:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Matthias L. Schroeter 17.7.2018

Bernet M. Enzinga

Stefan Holiga 17.7.2018

Ron de Kloet

Marc L Molendijk

In accordance with the Promotionsordnung of the medical faculty of the Leipzig University for the cumulative doctoral dissertation. I hereby confirm that the International Committee of Medical Journal Editors (ICMJE) authorship criteria were followed for the following article:

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- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Matthias L. Schroeter

Bernet M. Enzinga

Stefan Holiga

Ron de Kloet Leiden, The Netherlands, july 12, 2018

Marc L Molendijk

In accordance with the Promotionsordnung of the medical faculty of the Leipzig University for the cumulative doctoral dissertation. I hereby confirm that the International Committee of Medical Journal Editors (ICMJE) authorship criteria were followed for the following article:

Brain-Derived Neurotrophic Factor and Antidepressive Effect of Electroconvulsive Therapy: Systematic Review and Meta-Analyses of the Preclinical and Clinical Literature

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Matthias L. Schroeter

Bernet M. Enzinga

Stefan Holiga

Ron de Kloet

Marc L Molendijk July 13 2018

In accordance with the Promotionsordnung of the medical faculty of the Leipzig University for the cumulative doctoral dissertation. I hereby confirm, that the the International Committee of MedicalJournal Editors (ICMJE) authorship criteria were followed for the following article:

First evidence for glial pathology in late life minor depression: S100B is increased in males with minor depression.

The first author, Maryna Polyakova, was responsible for

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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In accordance with the Promotionsordnung of the medical faculty of the Leipzig University for the cumulative doctoral dissertation. I hereby confirm, that the the International Committee of MedicalJournal Editors (ICMJE) authorship criteria were followed for the following article:

No Changes in Gray Matter Density or Cortical Thickness in Late-Life Minor Depression.

The first author, Maryna Polyakova, was responsible for

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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APPENDIX B

STATEMENT OF AUTHORSHIP

I confirm that, to the best of my knowledge, the doctoral dissertation represents my own work and was prepared independently without any impermissible help or sources. I assure that third parties have not received indirect or direct monetary incentives for work in connection the contents of the present dissertation, and that the doctoral dissertation contains no material which has been presented for the award of any other degree or diploma in any other university, tertiary education institution, and national or foreign examination board. I certify that to the best of my knowledge and belief, this doctoral dissertation contains no material previously published or written by another person, except where due reference has been made in the text. All persons directly involved in the present work have been indicated by name. The current legal standards with regard to clinical studies, animal welfare, genetic engineering as well as data protection regulations have not been violated. I assure to know and to adhere to the regulations of good scientific practice of the University of Leipzig.

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

Leipzig, May 2018

Maryna Polyakova

APPENDIX C

CURRICULUM VITAE

Personal Information

Name	Polyakova Maryna
Date of birth	November, 23rd, 1984
Place of birth	Khmelnytskyi, Ukraine

Work Experience

Since 12/2012	Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, Research group Cognitive Neuropsychiatry University Clinic for psychiatry and Psychotherapy, Leipzig University, Leipzig, Germany *Doctoral student*
06/2011-11/2012	Vienna medical University, Vienna, Austria Neuroproteomics laboratory of Prof. Gert Lubec *Research Fellow*
02/2011 – 05/2011	Khmelnytskyi Regional Psychiatric Hospital, Khmelnytskyi, Ukraine *Psychiatrist*

Education

08/2009 – 01/2011	Juschenko Winnytsya Regional Psychiatric Hospital, Winnytsya, Ukraine *Specialization in Psychiatry*
09/2003 – 06/2009	Winnytsya National Medical University named after M. Pyrogov, Winnytsya, Ukraine *Medicine*
09/2000 – 06/2003	Khmelnytskyi Medical College, Khmelnytskyi, Ukraine *Nursing*
09/1996 – 05/2000	Khmelnytskyi Gymnasium #1 , Khmelnytskyi, Ukraine
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APPENDIX D

ACADEMIC CONTRIBUTIONS

Articles

1. Polyakova M, Sonnabend N, Sander C, Mergl R, Schroeter ML, Schroeder J et al. Prevalence of minor depression in elderly persons with and without mild cognitive impairment: A systematic review. Journal of Affective Disorders 2014; 152: 28-38.

2. Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: A systematic & quantitative meta-analysis. Journal of Affective Disorders 2015; 174: 432-440.

3. Polyakova M, Schroeter ML, Elzinga BM, Holiga S, Schoenknecht P, de Kloet ER et al. Brain-Derived Neurotrophic Factor and Antidepressive Effect of Electroconvulsive Therapy: Systematic Review and Meta-Analyses of the Preclinical and Clinical Literature. Plos One 2015; 10(11).

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5. Schumberg K, Polyakova M, Steiner J, Schroeter ML. Serum S100B Is Related to Illness Duration and Clinical Symptoms in Schizophrenia - A Meta-Regression Analysis. Frontiers in Cellular Neuroscience 2016; 10.

6. Polyakova M, Schlogl H, Sacher J, Schmidt-Kassow M, Kaiser J, Stumvoll M et al. Stability of BDNF in Human Samples Stored Up to 6 Months and Correlations of Serum and EDTA-Plasma Concentrations. International Journal of Molecular Sciences 2017; 18(6).

7. Polyakova M, Sander C, Arelin K, Lampe L, Luck T, Luppa M et al. First evidence for glial pathology in late life minor depression: MOB is increased in males with minor depression. Frontiers in Cellular Neuroscience 2015; 9.

8. Polyakova M, Mueller K, Sander C, Beyer F, Witte V, Lampe L et al. No Changes in Gray Matter Density or Cortical Thickness in Late-Life Minor Depression. The Journal of clinical psychiatry 2018; 79(2).

9. Schroeter ML, Pawelke S, Bisenius S, Kynast J, Schuemberg K, Polyakova M et al. A Modified Reading the Mind in the Eyes Test Predicts Behavioral Variant Frontotemporal Dementia Better Than Executive Function Tests. Frontiers in Aging Neuroscience 2018; 10.

Poster presentations

1. Exploring the neural correlates of minor depression: a combined serum marker, VBM, DWI and resting state MRI study. M. Polyakova K. Mueller, C.Sander, N.Sonnabend, N.Mauche, R.Mergl, P. Schoenknecht and M. L.Schroeter IMPRS summer school, Leipzig 2013
2. Computer - assisted volumetry of mammillary bodies in vivo using high resolution 7 Tesla MRI in major depression and bipolar disorder S. Schindler, M. Polyakova, M. Kleinsorge, N. Freund, M. Strauß, P.-L. Bazin, U. Hegerl, R. Turner, S. Geyer, P. Schönknecht, DGPPN Congress, Berlin 2013
3. Brain Derived Neurotrophic factor in mood disorders: meta-analysis of serum and plasma studies M.Polyakova, K.Stucke, K.Mueller, P.Schoenknecht and M.Schroeter, Research Festival, Medical Faculty of the Leipzig University, Leipzig 2014
4. Brain Derived Neurotrophic factor in mood disorders: meta-analysis of serum and plasma studies M.Polyakova, K.Stucke, K.Mueller, P.Schoenknecht and M.Schroeter, DGPPN Congress, Berlin, 2014
5. Prevalence of minor depression in elderly persons with and without mild cognitive impairment: a systematic review M. Polyakova, N. Dreimueller, C. Sander, R. Mergl, ML Schroeter, J. Schroeder, P. Schoenknecht, European Psychiatry Association Congress (EPA), Munich, 2014

6. Brain-derived neurotrophic factor and antidepressive effect of electroconvulsive therapy: systematic review and meta-analyses of the preclinical and clinical literature M. Polyakova, M. L. Schroeter, B. M. Elzinga, S. Holiga, P. Schoenknecht, E. R. De Kloet, M. L. Molendijk, DGPPN Congress, Berlin 2015
7. Serum neuron-specific enolase is increased in mild neurocognitive disorder / mild cognitive impairment and related to white matter hyperintensities M. Polyakova, C. Sander, K. Arelin, L. Lampe, T. Luck, M. Luppa, J. Kratzsch, KT. Hoffmann, S.Riedel-Heller, A. Villringer, P. Schoenknecht and ML. Schroeter, FTLD 10th International Conference on Frontotemporal Dementias, Munich, 2016
8. First evidence for glial pathology in late life minor depression: S100B is increased in males with minor depression M. Polyakova, C. Sander, K. Arelin, L. Lampe, T. Luck, M. Luppa, J. Kratzsch, KT. Hoffmann, S.Riedel-Heller, A. Villringer, P. Schoenknecht and ML. Schroeter, EPA Congress, Madrid, 2016
9. Insufficient evidence for structural gray matter alterations in late life minor depression: results from LIFE-adult study. Maryna Polyakova, Christian Sander, Karsten Mueller, Katrin Arelin, Leonie Lampe, Karl-Titus Hoffmann, Arno Villringer, Matthias L. Schroeter, Peter Schoenknecht, Deutsche Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung (DGKN), Leipzig, 2017
10. First evidence for glial pathology in late life minor depression: S100B is increased in males with minor depression. Results from LIFE-adult study. Maryna Polyakova, Christian Sander, Katrin Arelin, Leonie Lampe, Tobias Luck, Melanie Luppa, Jürgen Kratzsch, Karl-Titus Hoffmann, Steffi Riedel-Heller, Arno Villringer, Peter Schoenknecht and Matthias L. Schroeter, Deutsche Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung (DGKN), Leipzig, 2017
11. Does the DSM-5 neglect unaware patients with neurocognitive disorder? Maryna Polyakova, Jana Kynast, Francisca Then, Tobias Luck, Steffi Riedel-Heller, Arno Villringer, Peter Schoenknecht, Matthias L. Schroeter, 24th International Symposium on Current Isues and Controversies in Psychiatry, "Crisis in Psychiatry?", Barcelona, 2017

Awards

1. A stipend from the Medical University of Vienna for the project “Protein kinases and phosphatases network in Alzheimer’s Disease”, Vienna, Austria 2011
2. IMPRS NEUROCOM stipend for the PhD thesis “Neural correlates of lte life minor depression|, Leipzig, Germany, 2012

3. Poster Prize for the Poster “Brain Derived Neurotrophic factor in mood disorders: meta-analysis of serum and plasma studies” Research Festival, Medical Faculty of the Leipzig University, Leipzig 2014
4. Second Poster Prize for the Poster “Does the DSM-5 neglect unaware patients with neurocognitive disorder?” 24th International Symposium on Current Isues and Controversies in Psychiatry, "Crisis in Psychiatry?", Barcelona, 2017

APPENDIX E

AKNOWLEDGEMENTS

I want to thank people directly involved into this work, and those who supported me on the way to PhD.

First of all to my supervisors. To Prof. Peter Schoenknecht, for choosing my CV from many others, for his support and optimism, despite obstacles. To Prof. Matthias Schroeter for guiding me during my work, for his attention to details and being responsive to my needs. I'm appreciate to Prof. Karsten Mueller for his methodological advice, openness and sharing his knowledge. I further thank Steffanie Schindler for always being critical and honest, listening to and commenting on my presentations. I thank my collaborator Dr. Marc Molendijk, for scientific discussions and joint projects.

I thank all the people involved in LIFE project: Dr. Christian Sander and Dr. Roland Mergl; Dr. Veronica Witte, Frauke Beyer and Dr. Leonie Lample; Dr. Franzisca Then and Dr. Tobias Luck. As well as its permanent leaders Prof. Arno Villringer, Prof. Steffi Riedel-Heller and Prof. Marcus Loeffler. I thank our research coordinators Dr. Antje Niven and Dr. Veronika Krieghoff, their advice and support. I also thank our research group members, the very encouraging environment of Max Planck Institute. Finally, I thank LIFE study participants for giving their time for the science. Many theses would not be possible without their help

I am also very appreciate my family members for their support. First of all, to my husband for sharing all my worries, being my closest reviewer and advisor, and especially for taking care of our three little girls, when I was out for work. I thank my girls for inspiration; my mom, for giving me the education and providing space for dreams. And one last thank goes to my granddads,both examples of striving for knowledge men, who would be very happy to know that I have earned a doctorate.