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Serum S100B Represents a New Biomarker for Mood Disorders

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Abstract: Recently, mood disorders have been discussed to be characterized by glial pathology. The protein S100B, a growth and differentiation factor, is located in, and may actively be released by astro- and oligodendrocytes. This protein is easily assessed in human serum and provides a useful parameter for glial activation or injury. Here, we review studies investigating the glial marker S100B in serum of patients with mood disorders. Studies consistently show that S100B is elevated in mood disorders; more strongly in major depressive than bipolar disorder. Consistent with the glial hypothesis of mood disorders, serum S100B levels interact with age with higher levels in elderly depressed subjects. Successful antidepressive treatment has been associated with serum S100B reduction in major depression, whereas there is no evidence of treatment effects in mania. In contrast to the glial marker S100B, the neuronal marker protein neuron-specific enolase is unaltered in mood disorders. Recently, serum S100B has been linked to specific imaging parameters in the human white matter suggesting a role for S100B as an oligodendrocytic marker protein. In sum, serum S100B can be regarded as a promising *in vivo* biomarker for mood disorders deepening the understanding of the pathogenesis and plasticity-changes in these disorders. Future longitudinal studies combining serum S100B with other cell-specific serum parameters and multimodal imaging are warranted to further explore this serum protein in the development, monitoring and treatment of mood disorders.

Keywords: Astrocytes, bipolar disorder, DTI, glia, imaging, major depression, mania, mood disorder, MRI, oligodendrocytes, S100B.

MOOD DISORDERS ARE GLIAL DISORDERS

Mood disorders, comprising major depressive disorder (MDD) and bipolar disorder (BD), are often very severe illnesses [1-4]. Accordingly, understanding their pathomechanisms and exploring the potential of new treatment strategies deserve paramount scientific interest. What are the characteristic cellular alterations in mood disorders? Rajkowska [3] proposed that mood disorders are characterized by specific glial pathology. Histopathological *post mortem* studies [1, 5-7] consistently showed reductions in glial cell density or glial cell numbers in prefrontal brain regions, such as the (subgenual) anterior cingulate cortex, the orbitofrontal cortex, and dorsolateral prefrontal cortex in association with reduced prefrontal gray matter and alterations in metabolism in mood disorders [3, 8-11]. Changes were attributed histopathologically mainly to astrocytes [12-16] and oligodendrocytes [17-22] in these disorders. Specific reductions in oligodendrocytes have been reported for the amygdala in MDD [17]. Microglial alterations have also been observed in BD, including manic and depressive episodes [1].

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Are these glial changes only epiphenomena or are they causally involved? Several animal studies have addressed this question and provide evidence in support of a causal mechanism. Banasr & Duman [23] could provoke depressive-like behavior in rats that had undergone pharmacologic ablation of astroglial cells in the prefrontal cortex, whereas rats that were exposed to a neurotoxic did not show this behavior. Consistent with this hypothesis, antidepressive treatment has been shown to successfully reverse reduction in astroglial density in animal models of depression [24].

TOWARDS A DYNAMIC CONCEPT OF GLIAL MOOD DISORDERS

What are the dynamics of these changes? New conceptual approaches, based on evidence from histopathological *post mortem* studies, have challenged the view of mood disorders as 'static' glial disorders [7, 13, 14, 25]. Instead, they underline the dynamic aspect of mood disorders with regard to neuro- and glioplasticity. Rajkowska & Miguel-Hidalgo [7] have suggested in their concept of MDD that glial pathology with reductions in cell density and number occurs in early stages, whereas later on, as the disorder progresses, neurons are affected, presumably due to an excess of extracellular glutamate as caused by glial dysfunction. Finally, in elderly depressive subjects, neuronal injury may lead to

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reactive glial proliferation. Khundakar & Thomas [25] support this hypothesis by observing glial reduction consistently in younger groups with MDD and neuronal changes in studies with older subjects with a mean age of over 60 years, which might indicate a differing pathological basis in MDD, dependent on age.

How can this dynamic glial concept of mood disorders, in particular for MDD, be validated? Animal models are *per se* limited in their validity as models for human subjects, because psychiatric symptoms require approaches to first person perspective, phenomenological data, as in humans possible only [26]. *Post mortem* histopathological studies are based *per se* on cross-sectional approaches, making the investigation of longitudinal processes, and, consequently, the testing of the aforementioned dynamic hypotheses by observing intra-individual changes across the course of mood disorder almost impossible. Longitudinal *in vivo* studies in human subjects that combine specific serum biomarkers and neuroimaging data provide a promising approach to overcome these limitations.

S100B IS A GLIAL AND TROPHIC MARKER PROTEIN

S100 proteins are acidic proteins that can bind calcium and influence various cellular responses along the calcium-signal-transduction pathway [4, 27-30]. In the central nervous system, one member of the S100 family is of particular interest – S100B. It regulates cell shape, energy metabolism, contraction, cell-to-cell communication, intracellular signal transduction and cell growth [31]. S100B is located in the cytoplasm and can be actively released by astro- and oligodendrocytes [32, 33]. The effects of extracellular S100B depend on its concentration [29, 34]. Whereas in micromolar concentration it may induce apoptosis, nanomolar concentrations act as growth and/or differentiation factor for neurons and astrocytes. Due to these characteristics S100B can be regarded as a useful biomarker for glial alterations and neuro- and glioplasticity, easily obtained from human serum. Recent studies have suggested a crucial role for S100 proteins in the pathogenesis of depression and the action of antidepressive treatment, in particular for S100B [35-44] and for S100A10 or p11 [40, 41, 45-53]. Although S100A10 seems to be a very interesting candidate for a serum marker protein, to our knowledge no study has investigated this protein in serum in mood disorders to date. Consequently, we will focus our review on S100B in the following.

SERUM S100B IS ELEVATED IN MOOD DISORDERS

Are there studies that have investigated the glial marker protein S100B in mood disorders *in vivo*? In agreement with the aforementioned theoretical arguments, previous studies have shown that S100B, which is found in astro- and oligodendroglia, but not in microglia in the human brain [33], is altered in both serum [4, 54-56] and cerebrospinal fluid of patients with mood disorders. Cerebrospinal fluid changes have been reported for drug-free mild to moderate depressive patients compared with euthymic patients (increase) [57] and in rat animal models of mania (increase due to ouabain-induced hyperactivity) [58] and depression (decrease due to chronic unpredictable stress, reversed by antidepressive treatment with the selective serotonin reuptake inhibitor, SSRI, fluoxetine) [42]. No study has investigated S100B levels in the cerebrospinal fluid in mania in human subjects yet. The levels of the glial marker protein S100B have been found to be specifically altered in the lateral prefrontal and parietal cortices in BD, with a decrease in Brodmann's area 9 and increase in Brodmann's area 40 [59], without any available studies for MDD.

Furthermore, S100B has been identified as a susceptibility gene for BD, in particular if associated with psychosis [60]. Although Yang *et al*. [61, 62] did not find an association between S100B gene polymorphisms and MDD in a Chinese population, they revealed an influence on age of onset and subgroups (first-episode vs. recurrent episode depression) of MDD – A finding consistent with the dymanic glial concept of mood disorders. Remarkably, respective S100B polymorphisms are related to serum levels of this protein in healthy subjects and in patients with BD, and to messenger ribonucleic acid (mRNA) gene expression of S100B in the frontal cortex of healthy subjects [63, 64].

Systematic quantitative meta-analyses are essential to properly evaluate the relevance and validity of S100B as a useful biomarker for mood disorders. Recently, we have conducted such meta-analyses using MedLine and Current Contents search engines (search strategy: [S100 OR S-100] AND [depression OR mania]) [54-56]. Based on internationally recognized diagnostic criteria (International Classification of Diseases, ICD-10 [65]; Diagnostic and Statistical Manual of Mental Disorders, DSM-IV [66]) we identified eight studies involving 193 patients suffering from mood disorders and 132 healthy age-matched control subjects (for details see [54, 56]). Of these patients, 86 suffered from a major depressive episode, 63 from a manic episode, and 44 were euthymic at the time of investigation. To adjust for systematic measurement effects and to normalize S100B values, the effect size of each study (d) was calculated according to Cohen [67] as the difference of the means of the patient (m_p) and control group (m_c) divided by the standard deviation of the control group (SD_c).

Fig. **1A** shows the effect sizes for the studies involved. Cohen [67] defined values of $\geq$0.8 as large, $\geq$0.5 as medium and $\geq$0.2 as small. The mean effect size reached high values for all episodes of mood disorders [54], namely major depressive episode of MDD, manic episode of BD and currently euthymic mood disorder (2.6±0.7, 1.5±0.1, 2.5±2.5; mean±SD). For major depressive and manic episodes, values were significantly higher than zero, confirming high serum S100B in acute episodes of mood disorder, which was not the case for currently euthymic mood disorder.

Additionally, we compared serum S100B in BD and MDD as both subtypes of mood disorders are classified as separate nosological entities and because we did not detect any significant differences between depressive/manic episodes and remitted mood disorder *per se* [56]. As illustrated in Fig. **1A**, serum S100B reached high effect sizes in both MDD (3.0±1.0) and BD (1.4±0.4). Effect size was significantly larger in MDD than BD. For mania in BD and depression in MDD, only two studies with drug-free patients were available, each reporting high effect sizes (1.6, 3.3). In sum, there is considerable evidence in support of elevated serum

levels of S100B in mood disorders indicating glial involvement in the pathogenesis of these disorders, particularly MDD.

Remarkably, elevations of serum S100B have been replicated in translational studies, namely in two rat models of depression, olfactory bulbectomy and chronic unpredictable stress [38]. Although this study showed also reduced protein levels of S100B in the prefrontal cortex in the second model, it revealed no significant association between serum levels and protein expression in the brain. Of note, protein expression was investigated in this study in the prefrontal cortex, striatum and hippocampus only. Another animal study with rats extended reductions of S100B protein content due to chronic unpredictable stress to the hippocampus, which could be reversed by antidepressive treatment with the SSRI fluoxetine [42]. Increases of hippocampal S100B content due to fluoxetine could be replicated in mice [35].

SERUM S100B INTERACTS WITH AGE IN MOOD DISORDERS

As already discussed above, nowadays conceptual approaches of mood disorders have developed a dynamic concept for neuro- and glioplasticity, in particular for MDD [7, 13, 14, 22, 25]. Can serum biomarker studies of S100B prove these dynamic concepts *in vivo*? Are there any interactions of S100B with age in mood disorders? To answer these questions we conducted another meta-analysis on serum S100B in mood disorders [55]. We identified ten studies including a total of 165 patients with MDD and 119 with BD fulfilling inclusion criteria (for details see [55]). After checking for exclusion criteria and information available including age, the cohort entering the meta-analysis included four studies with 174 patients with mood disorders and 102 control subjects (MDD 89/70, BD 85/32). Again, effect sizes were calculated according to Cohen [67]. In the meantime, no other relevant studies on serum S100B in mood disorders have been published (literature search in PubMed 15th of March 2013).

Fig. **1B** shows the results of this meta-analysis. The influences of age, illness duration and age at onset on effect sizes of serum S100B were analyzed with a stepwise multiple regression analysis. A stepwise procedure was chosen to develop an optimal equation for predicting the dependent variable from several variables, and to isolate the most important factors. The analysis revealed a significant impact of age on S100B without significant effects of illness duration and age at onset. A subanalysis contrasting the three studies of older subjects with the three studies of younger subjects confirmed an impact of age – namely higher effect sizes for serum S100B in older (2.1±0.4) if compared with younger subjects (1.1±0.3). According to Cohen's assessment, both groups showed, as expected, high effect sizes, and, accordingly, elevated serum S100B levels if compared with healthy control subjects. Note that there were no significant differences between subjects with MDD and BD for effect sizes of S100B or mean age – a point we consider of particular relevance as we had to pool data from both MDD and BD patients for this analysis. However, patients with BD were characterized by longer mean illness duration in agreement with lower mean age at onset in BD compared with MDD. Replicating the aforementioned effect size analyses with Hedges' g, which provides an unbiased effect size adjusted for sample size, confirmed the results of the first analysis [68].

These results indicate higher levels of the glial marker protein S100B in older compared with younger subjects suffering from mood disorders, without an impact of illness duration or age at onset. As patients were compared with age-matched control subjects in each single study included in the meta-analysis the calculated effect sizes of S100B have been adjusted for age-related changes in normal healthy populations. These data provide *in vivo* support for the dynamic glial hypothesis of mood disorders that has originally been postulated based on histopathological findings in MDD [7, 14, 25]. Because serum S100B findings were detected in a mixed cohort consisting of MDD and BD, whereas histopathological evidence exists for MDD only, the dynamic glial hypothesis has to be reinvestigated with future meta-analyses if more studies are available to disentangle changes in MDD and BD.

The age range of the subjects included (range of mean age in the various studies 34 – 49 years) reveals a younger study population compared to most of the histopathological studies (mean age in young vs. elderly groups approximately 50 vs. 75 years [25]). Accordingly, the meta-analysis has not been confounded by late-life ('vascular') mood disorders (MDD), disorders with a typical age of onset above approximately 50-60 years, that have been related to other etiological mechanisms – a potential bias that might be relevant for the interpretation of these histopathological observations [7, 25].

Based on meta-analytic serum S100B studies, one might conclude that S100B has a modifying effect in mood disorders in the interaction with age. More precisely, data suggest that the role of S100B becomes more prominent across the lifespan. This result is supported by recent genetic studies demonstrating gene polymorphisms of S100B to influence age of onset and to differ between subgroups (first-episode vs. recurrent episode depression) of MDD [62]. Accordingly, future studies on serum S100B shall control for age and numbers of depressive or manic episodes. Furthermore, they should exclude any impact of gender, because a former study in a rat model of posttraumatic stress disorder showed sex-specific effects upon serum S100B levels [69] in agreement with a study of MDD [70] and gender-specific associations between serum S100B and brain imaging parameters in humans [71].

SERUM S100B INDICATES SPECIFICALLY GLIAL ALTERATIONS IN MAJOR DEPRESSION

As discussed above numerous studies show that serum S100B indicates glial involvement in the pathogenesis of mood disorders, particularly MDD. Using serum S100B as a biomarker for these disorders requires high validity and high specificity. What about these characteristics? Disease specificity has been questioned by a recent meta-analysis investigating serum S100B with the same meta-analytic method in 420 patients with schizophrenia (Fig. **1A**). This meta-analysis showed elevated levels of S100B in schizophrenia

(effect size 2.0±1.8) without clear distinction to MDD or BD samples [56, 72]. One interpretation of this study is that serum S100B is not a valid diagnostic marker for mood disorders *per se*, rather for the prediction of their course and the understanding of their pathophysiology.

On the other hand, the specificity for cell type is an important property to consider in this context. Are there any serum biomarkers for other cell types available in the current literature? For neurons, neuron-specific enolase (NSE) can be measured in serum samples. NSE is located mainly in the cytoplasm of nerve cells and is not actively secreted [73, 74]. Hence, it has been regarded as a marker for neuronal injury or brain damage [75]. Recently, we measured S100B simultaneously with NSE in the serum of patients with MDD and healthy age- and gender-matched control subjects [54]. If mood disorders are mainly glial disorders as suggested by Rajkowska [3], one would expect elevated serum levels of S100B paralleled by unaltered levels of the neuronal marker protein NSE. Indeed, S100B concentrations were higher in depressive patients at admission and discharge compared to control subjects, whereas NSE was not statistically different between patients and control subjects for both time points [54]. Antidepressive treatment did not show any significant effect on NSE serum levels. Results were in agreement with three other studies investigating NSE serum levels in MDD ([76-78], for details see [4]).

In sum, the aforementioned studies suggest that, in MDD, S100B is elevated while NSE remains unaltered, providing substantial support for Rajkowska's glial hypothesis for mood disorders [3]. In contrast, the situation is less clear for mania, because only one study has investigated NSE in mania so far, showing decreased values in unmedicated and lithium treated patients in comparison with healthy control subjects [79]. Accordingly, the hypothesis of specific glial pathology cannot be generalized to all mood disorders to date.

INCREASED SERUM S100B SEEMS TO BE RELATED TO FUNCTIONAL SECRETION IN MOOD DISORDERS

The mechanisms underlying an increase in serum S100B in mood disorders require further discussion. Which kind of glial alterations do these changes indicate? At least two options have to be considered. Brain damage of astrocytes and/or oligodendrocytes [80] or functional secretion of S100B by astrocytes and/or oligodendrocytes could drive an S100B elevation [32, 33]. Mathematical models suggest that levels of serum S100B exceeding approximately 350 ng/l indicate brain damage [81]. Mean serum levels of S100B as reported in previous studies of mood disorders do not reach this threshold [54]. As discussed above, former studies exclude possible neuronal damage in MDD and mania as indicated by normal or decreased serum NSE values [77-79]. One might conclude that elevated serum S100B in mood disorders indicates functional secretion by glial cells, rather than substantial brain damage. Whether increases of serum S100B also indicate dysfunctions of the blood-brain barrier that is supported by astrocytes [82-84] is still an issue of debate in the current literature [81, 85-90].

SERUM S100B IS A BIOMARKER FOR PLASTICITY IN MAJOR DEPRESSION

Recently, it has been suggested that a loss of neuroplasticity and cellular resilience may underlie the pathophysiology of mood disorders and that effective long-term treatment can only be achieved by early neurotrophic and/or neuroprotective intervention [1, 2]. What about serum S100B in this context? Extracellular S100B may act as a growth and/or differentiation factor for neurons and astrocytes *via* various intracellular signal cascades [1, 29, 91-93]. Astrocytes express serotonin receptors [44, 94, 95]. Antidepressants have been reported to influence the secretion of S100B by astrocytes *via* the serotonergic system: The 5-HT(1A) agonists buspirone and ipsapirone increased mRNA expression in the developing rat brain, and augmented astroglial release of S100B in rat cell cultures, the latter without effects on protein content [96]. Other rat studies replicated this effect on S100B release for ipsapirone in astroglial cell cultures [43], and for the SSRI fluoxetine in hippocampal astrocyte cultures and hippocampal slices [97]. These literature reports are in agreement with other animal studies showing that fluoxetine increases S100B content in the mouse [35] and rat [42] hippocampus. S100B may even induce neurogenesis [98], which is considered specifically relevant to behavioral effects of antidepressants [99]. It has also been suggested that S100 proteins may play an essential role in the pathogenesis of depression and its treatment [37, 40, 50], and that S100B-related mechanisms could be explored as potential targets for novel antidepressive therapeutics [36, 39]. Interestingly, higher levels of serum S100B have been found to predict more efficient response to antidepressive treatment in MDD after 4 or 6 weeks [100, 101] and normalization of visually evoked event-related potentials in MDD after antidepressant treatment [102].

To validate the impact of serum S100B as a plasticity biomarker in mood disorders we conducted a meta-analysis to assess S100B levels during the course of pharmacological antidepressive treatment including three studies of 46 patients with MDD in total (for details see [54]). The treatment effect size (d) for S100B and the severity of clinical symptoms was calculated for each study according to Cohen [67] as the difference of the means of the patient group at admission (m_{ad}) and discharge (m_{dis}) divided by the standard deviation at admission (SD_{ad}). This treatment effect size represents a normalized measure for changes from baseline. The mean treatment effect size reached a large value for changes on the Hamilton Depression Rating Scale (HAMD) scale (3.5±1.8), with a lower impact on serum S100B (0.4±0.4). As illustrated in Fig. **1C**, effect sizes for clinical improvement and respective changes of the serological marker S100B during treatment were significantly correlated with each other. This significant positive correlation between clinical treatment effects (HAMD) and serological treatment effects (S100B) indicates that serum S100B may be a reliable marker for treatment in major depression if clinical improvement is sufficient. To date for mania only one study has examined changes of S100B during treatment and failed to detect any significant effects [103]. Although this data provides preliminary evidence for the role of serum S100B as a plasticity marker, a conclusive assessment is limited by the small subject sample, varying antidepressive treatment protocols and

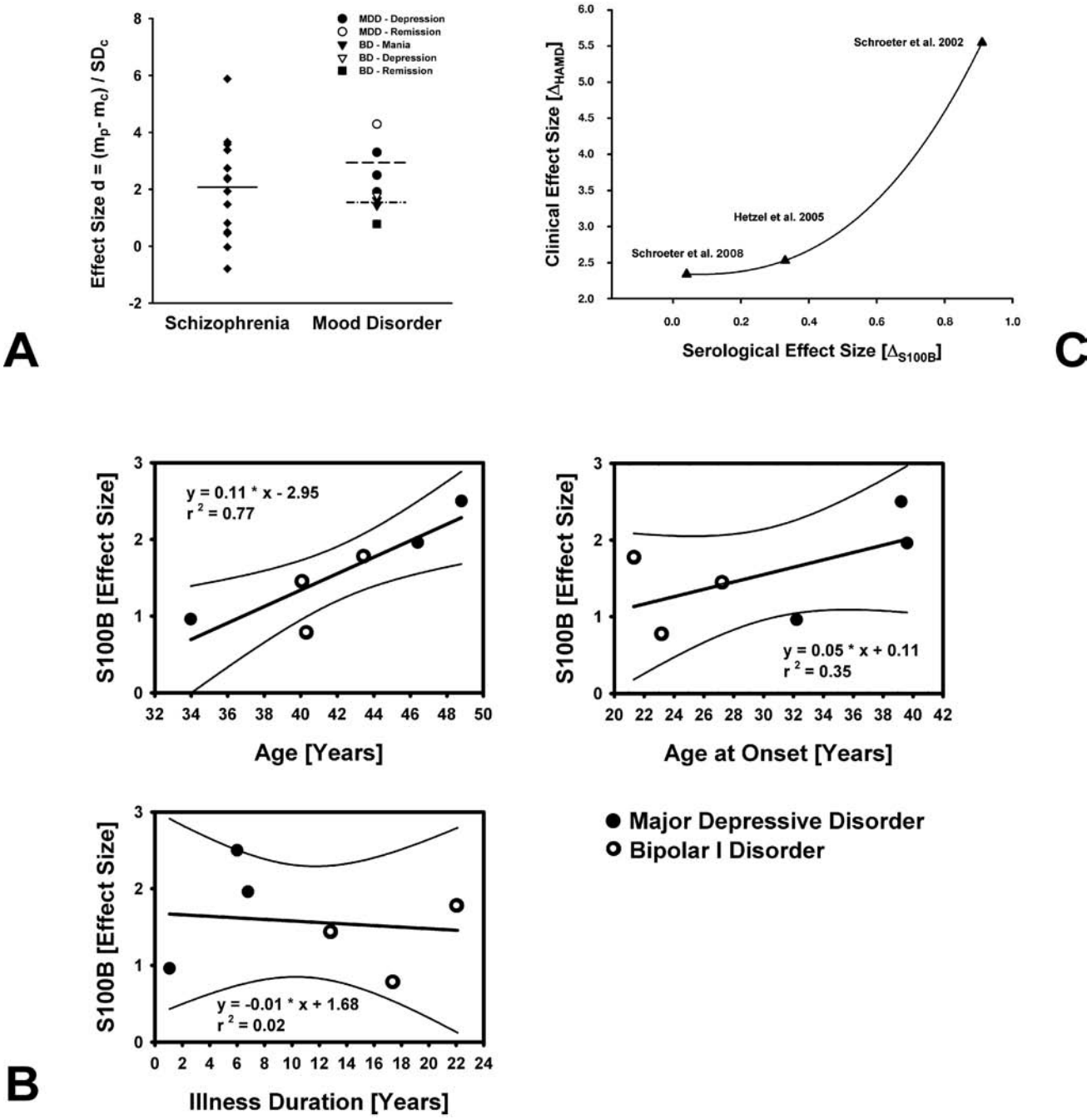

Fig. (1). S100B serum concentrations in mood disorders as identified by systematic meta-analyses. Calculation of effect sizes according to Cohen [67]. **A** Values for mood disorders in comparison with schizophrenia [56]; median is shown for schizophrenia (solid), major depressive disorder MDD (dashed), and bipolar disorder BD (dashed and dotted line). **B** Serum S100B in relation to age, illness duration and age at onset in mood disorders [55]; results of linear regression analyses with 95% confidence intervals are shown. **C** Changes of serum S100B versus clinical improvement in major depression [54]; effect sizes were calculated for clinical (HAMD scores) and serological (serum S100B) treatment effects in major depression as changes between admission and discharge. HAMD Hamilton Depression Rating Scale.

potentially confounding concomitant medication, such as antipsychotics when psychotic symptoms were present. Hence, future well-powered clinical studies are necessary to overcome these limitations. Furthermore, *in vitro* (cell culture) studies are required to examine effects of different antidepressive treatment strategies on S100B with regard to specific signaling pathways of the neurotransmitter system.

SERUM S100B IS ASSOCIATED SPECIFICALLY WITH WHITE MATTER PARAMETERS IN THE HUMAN BRAIN

Thus far we have argued that S100B represents a useful serum biomarker for the pathogenesis of mood disorders and a valid indicator of antidepressant related changes in neural

plasticity. Moreover, if combined with other cell-specific serum biomarkers, for instance NSE, one might be able to disentangle glia- and neuron-specific alterations in mood disorders. Yet, not much is known regarding the use of serum S100B assessment to link glial changes to a specific brain region. Can serum S100B be related to specific imaging markers in the human brain? To address these questions we combined measurements of serum S100B with magnetic resonance imaging (MRI), histological and gene expression data [71].

Two different imaging methods were applied – voxel based morphometry (VBM) based on T1-weighted images to identify regional structural changes in the gray matter, and diffusion tensor imaging (DTI) to analyze white matter changes. In addition to the most commonly assessed DTI parameter fractional anisotropy, an index for global white matter integrity, we analyzed axial and radial diffusivity as markers for axonal and myelin degeneration, respectively [104]. We hypothesized S100B as an astro- and oligodendrocytic marker to be associated with gray and white matter parameters. For the white matter, we expected the strongest signal in the corpus callosum, because this structure has an abundance of oligodendrocytes according to histological studies [33] and shows the highest signal-to-noise ratio due to parallel orientation of numerous fibers [105]. Additionally, we hypothesized NSE as a neuronal marker to be associated with gray matter density. To avoid any confounding factor related to pathological MRI findings, we limited our study population to healthy subjects.

As illustrated in Fig. **2A** serum S100B was specifically related to white matter structures in the healthy human brain as it correlated negatively with the parameter fractional anisotropy. We observed this effect in female subjects only, which might be related to higher serum levels of S100B, higher variance and wider range of values of this glial protein in the female study group compared to male subjects in our cohort. Note that mean serum S100B and NSE were in the normal range of healthy subjects, excluding glial or neuronal damage. A secondary analysis revealed that correlations of serum S100B with fractional anisotropy in women had to be attributed to a positive correlation with radial diffusivity in the same regions without significant effects for axial diffusivity. For the gray matter we did not obtain any significant correlations with S100B. For NSE, we did generally not detect any significant correlations with DTI parameters, rather with gray matter density in the amygdalae and both most anterior hippocampi (see [71]). In a later study, we found an association between serum NSE and gray matter density in the cerebellum specifically in subjects with overweight/obesity [75].

Additionally, we validated the imaging results by investigating gene expression of S100B in the whole human brain genome wide atlas of the Allen Institute for Brain Sciences and by histological co-localization studies in human *post mortem* brain tissue and in cell culture (Fig. **2B** - **2D**) [71]. The Allen Human Brain Atlas (www.human.brain-map.org [106]) characterizes gene expression in human brain tissue with genome wide microarray-based gene expression profiles including over 62,000 gene probes for 500 samples covering the whole brain. As shown in Fig. **2D**, S100B was most abundantly expressed in the human corpus callosum, followed by the globus pallidus. The bar chart illustrates normalized z scores for these brain regions. Both regions showed elevated S100B expression in comparison with the whole brain, and higher expression in the corpus callosum than the external and internal globus pallidus. The positive correlation of serum S100B with radial diffusivity fits well with *post mortem* histological double immunofluorescence data demonstrating high concentration of S100B in oligodendrocytes in the healthy human brain, particularly in the corpus callosum, and is in line with *in vitro* (cell culture) findings (see Fig. **2B** & **2C**, and [33]).

Our results are very relevant for MDD that is also characterized by white matter changes (reviewed in [107]). Deep white matter hyperintensities have been demonstrated particularly in late life MDD and have been associated with clinical severity, lower treatment responsiveness and vascular ischemic markers in agreement with a vascular hypothesis of late life depression [107-113]. Although serum S100B and NSE have also been shown to be elevated in arterial hypertension, the main risk factor for vascular dementia originating from small vessel disease, serum S100B was not associated with white matter lesions, in contrast to serum NSE [114]. Interestingly, increasing serum S100B further indicated progression of vascular mild cognitive impairment into subcortical vascular dementia, and decreased if therapy had been effective [115]. These mechanisms are particularly relevant for the dynamic glial hypothesis of mood disorders, namely MDD, and the higher serum S100B values in elderly compared with young subjects with mood disorder (see above). Moreover, prefrontal regions show decreased oligodendrocyte density and reductions in the expression of oligodendroglial genes in MDD [107]. Although a few studies showed reduced fractional anisotropy also in younger subjects with DTI, there is a particular dearth of studies in this age subgroup.

In sum, our findings for S100B and white matter integrity in healthy subjects validate and underline the specificity of the glial protein S100B for brain changes *in vivo*. The close correlation with radial diffusivity and histological data suggest serum S100B as an oligodendrocytic biomarker. Together with evidence for an involvement of oligodendrocytes in the pathogenesis of mood disorders [17, 19-21, 116] in interaction with age as suggested by the dynamic glial model [22], our findings underline the importance of S100B as a biomarker for these disorders and open new perspectives for future studies.

LIMITATIONS IN THE USAGE OF SERUM S100B AS A BIOMARKER FOR MOOD DISORDERS

After exploring and stressing the potential of serum S100B as a biomarker for mood disorders, possible limitations have to be acknowledged. Are there any arguments that limit the usefulness of S100B as a biomarker for mood disorders? Firstly, S100B has also been detected in numerous other tissues in the human body besides glial cells, for example, in adipocytes, melanocytes, chondrocytes, myocardium, and Schwann cells [29, 31, 117]. Changes based on adipocytes are at least theoretically possible in mood disorders [118, 119]. Furthermore, obesity might interact with white

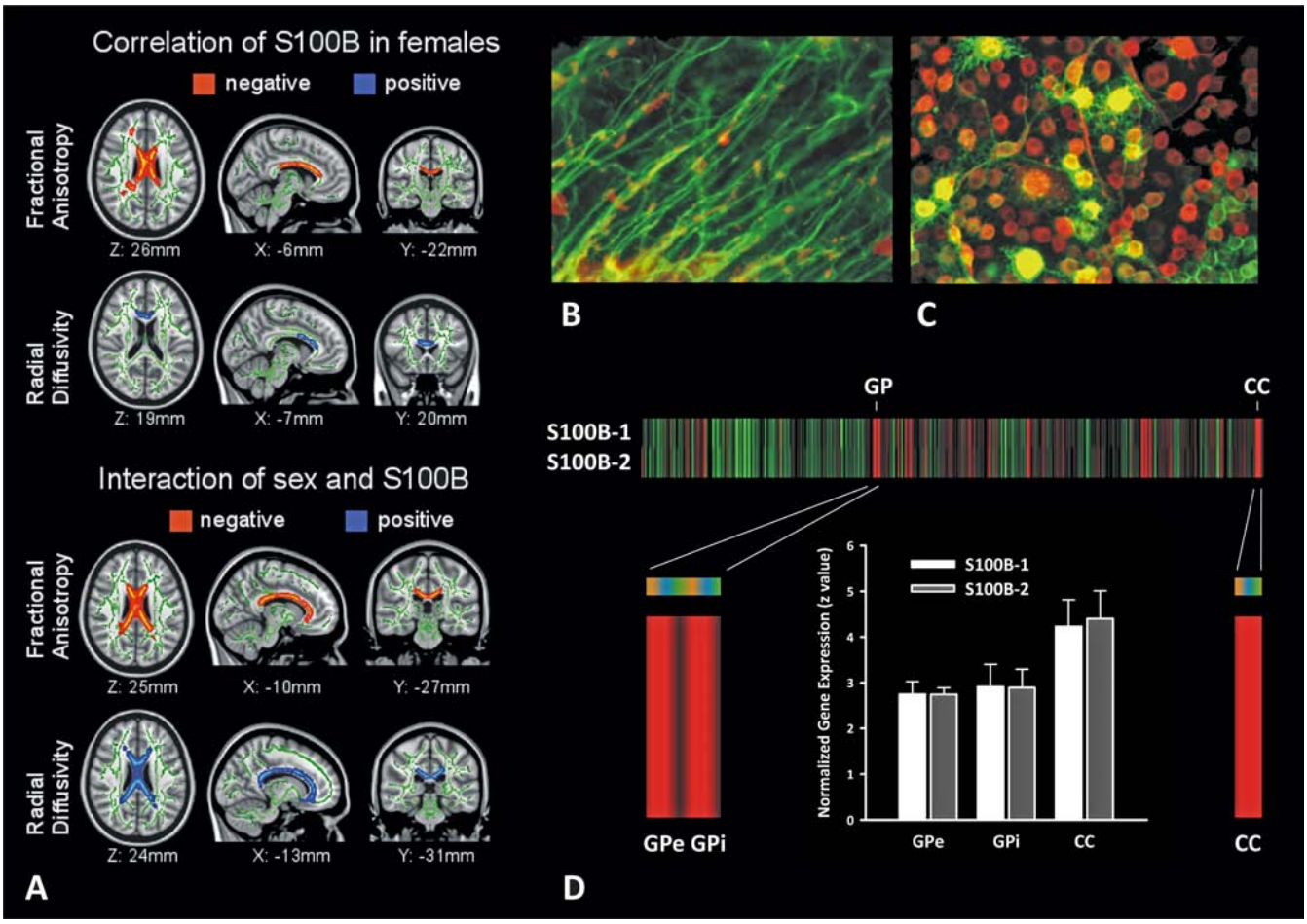

Fig. (2). Associations between S100B and the brain. For details see Streitbürger *et al.* [71]. **A** Diffusion tensor imaging parameters correlate with serum S100B in the corpus callosum, anterior forceps, and the right superior longitudinal fasciculus of the female brain (upper row) and in comparison with male brains (lower row). **B-D** Expression & localization of S100B in the human brain and in cultured oligodendrocytes. **B** Co-localization (yellow) of S100B (red) and myelin basic protein (MBP)-positive (green) myelinated fibres in the human corpus callosum. **C** Co-localization (yellow) between S100B (red) and the oligodendroglial marker p75 neurotrophin receptor (green) in the oligodendrocyte cell line OLN-93. **D** Individual normalized gene expression of S100B in heat map in z scores normalized to whole human brain expression, where green indicates relatively low and red relatively high expression. Highest expression was detected in the corpus callosum (CC), followed by globus pallidus (GP). Bar chart shows quantitative values in CC and external/internal (e/i) GP (mean±SD).

matter parameters that are associated with serum S100B levels, in particular in the female brain [105], and are altered in late life depression [107-113]. Although no study has yet reported changes in S100B due to the aforementioned extracranial cell types, results for S100B in mood disorders have to be validated by independent methods ranging from cell culture, gene expression to combination with different imaging modalities or with more cell-specific serum markers, such as glial fibrillary acidic protein for astrocytes or myelin basic protein for oligodendrocytes [74]. Future analyses shall control for vascular risk factors such as obesity or arterial hypertension, in particular if late life depression is studied.

Furthermore, cross-sectional serum S100B studies cannot disentangle the influence of antidepressive, mood stabilizing and antipsychotic treatment from the spontaneous course of mood disorders. Recent studies have revealed an impact of these drugs on S100B [30, 54, 72, 120, 121]. Accordingly, medication effects have to be generally controlled for in cross-sectional studies. Future longitudinal studies are warranted to overcome this limitation. For such study-design, the *in vivo* measurement of serum S100B offers crucial advantages over histopathological *post mortem* studies. Finally, investigating one serum value per subject does not deliver any information about its regional concentrations in the brain – a decisive bias if one considers the concentration dependent action of S100B ranging from glio- and neurotrophic to apoptotic.

SERUM S100B AS A BIOMARKER FOR MOOD DISORDERS – CONCLUSIONS AND PERSPECTIVES

A substantial body of literature supports serum S100B as a relevant biomarker for mood disorders. Here, we provide an overview of key findings and the future directions in this emerging field of research.

Serum S100B is a useful biomarker for mood disorders: Concentrations of the glial marker protein S100B are elevated in patients with mood disorder, major depression and

mania, when compared with healthy control subjects; Serum S100B is higher in major depressive disorder than bipolar disorder.

Serum S100B is an indicator of plasticity in major depression: Effective antidepressive treatment reduces S100B levels in major depression. While only one study investigated treatment effects in mania, such an effect was not found for this disorder.

Serum S100B is a cell-specific biomarker for mood disorders, at least for major depression: In contrast to glial S100B, the neuronal marker protein NSE is unaltered in major depression and its treatment. NSE is not increased in mania; the only study in the literature reported mildly reduced serum levels.

Serum S100B supports the dynamic glial hypothesis of mood disorders.

Serum S100B is related to active secretion by astrocytes and/or oligodendrocytes in mood disorders and not cellular destruction.

Serum S100B is associated specifically with white matter parameters in the human brain, in particular oligodendrocytic measures.

Summarizing the literature on S100B in mood disorders, one might develop a framework for S100B's role in these disorders and their treatment. Main findings and concepts are illustrated in Fig. **3**.

(i) Highest (meta-analytic) evidence is available for elevated values of *serum S100B* in acute episodes of mood disorders in human subjects, higher in MDD than BD, and for at least partial reduction with antidepressive treatment in MDD [54-56]. There is no evidence for antimanic treatment effects on serum S100B. Serum S100B values are higher in elderly subjects in comparison with young subjects with mood disorders [55]. Higher serum levels of S100B in MDD have been confirmed with two rat depression models without investigating treatment effects [38]. No animal study has been performed for serum S100B in mania so far.

(ii) Evidence is limited and controversial for *cerebrospinal fluid S100B*. The only study in human subjects reported elevated levels in acute episodes of MDD [57], whereas there is no study for mania in humans at all. For animal (rat) studies, one study demonstrated higher values in a mania model [58]; another study showed lower values in a depression model, where antidepressive treatment with the SSRI fluoxetine normalized values again [42].

(iii) *Regional S100B protein levels in the brain* have been shown to be reduced in the prefrontal cortex in humans suffering from BD [59], without data for MDD. As this study was performed *post mortem*, it could not disentangle effects of the disorder *per se* and treatment. Two studies in rats revealed reductions of S100B protein content in prefrontal regions [38] and the hippocampus [42], whereas the latter could be reversed by antidepressive treatment with the SSRI fluoxetine. Another study replicated an increasing protein content of S100B after administration of fluoxetine in mice [35].

What about local molecular mechanisms that are presumably involved in S100B alterations in mood disorders? Concerning reductions in local S100B content in acute episodes we refer to the glial hypothesis suggested by Rajkowska [3, 7] showing reductions in glial cell density or glial cell numbers mainly in prefrontal brain regions in mood disorders, and attributed histopathologically to astrocytes and oligodendrocytes (see for a detailed discussion above), although one has to keep in mind that these *post mortem* studies could not dissociate effects of drugs and the natural course of the disease.

(iv) The situation becomes much more interesting, if one considers drug effects during acute episodes of mood disorders on a cellular/molecular level. Here, it was hypothesized that effective long-term treatment can only be achieved by early neurotrophic and/or neuroprotective intervention [1, 2]. It is well known that extracellular S100B may act as a growth and/or differentiation factor for neurons and astrocytes *via* various intracellular signal cascades [1, 29, 91-93]. *S100B secretion* studies in rat cell culture and hippocampal slice models have shown that antidepressants, in particular serotonergic agents, increase the release of S100B from astrocytes [43, 96, 97], finally leading to higher S100B content, as shown for the hippocampus in mice and rats [35, 42]. However, nothing is known for S100B secretion by other (antimanic or mood-stabilizing) agents and with regard to the secretion of S100B during acute episodes of mood disorders – obviously due to the fact that acute episodes of mood disorders might not be modelled in cell culture studies.

In mood disorders, extracellular S100B may act as a growth and/or differentiation factor for neurons and astrocytes [1, 29, 91-93], protect them from possible apoptosis [122], and induce neurogenesis [98], which has been considered specifically relevant to behavioral effects of antidepressants [99]. Although effects of extracellular S100B depend on its concentration with micromolar concentrations inducing apoptosis and nanomolar concentrations acting as growth and/or differentiation factor for neurons and astrocytes [29, 34], theoretical assumptions support a rather neuro- and gliotrophic role in mood disorders. Reiber [123, 124] has suggested that ventricular cerebrospinal fluid may give an orientation for extracellular concentrations of S100B in brain tissue. Former studies reported lumbar cerebrospinal fluid levels of S100B between 1.9 ± 0.6 [125] and 2.3 ± 0.7 μg/l [57] in MDD (mean±standard deviation), which would correspond to 6.6 ± 2.1 and 8.0 ± 2.4 μg/l, or 0.3 ± 0.1 and 0.4 ± 0.1 nmol/l in ventricular cerebrospinal fluid, with an assumed ventricular to lumbar cerebrospinal fluid ratio of 3.5/1 [123, 124]. As stated before, no studies examined mania. Accordingly, extracellular levels seem to be in the nanomolar range and far below micromolar concentrations, supporting S100B's neuro- and gliotrophic role in mood disorders. How, at least partly conflicting, alterations of S100B in serum, cerebrospinal fluid, protein content, and secretion in mood disorders and their treatment (see Fig. **3**) can be interconnected, has to be investigated in future translational animal models that might monitor all levels in analogy to two recent studies in rats [38, 42].

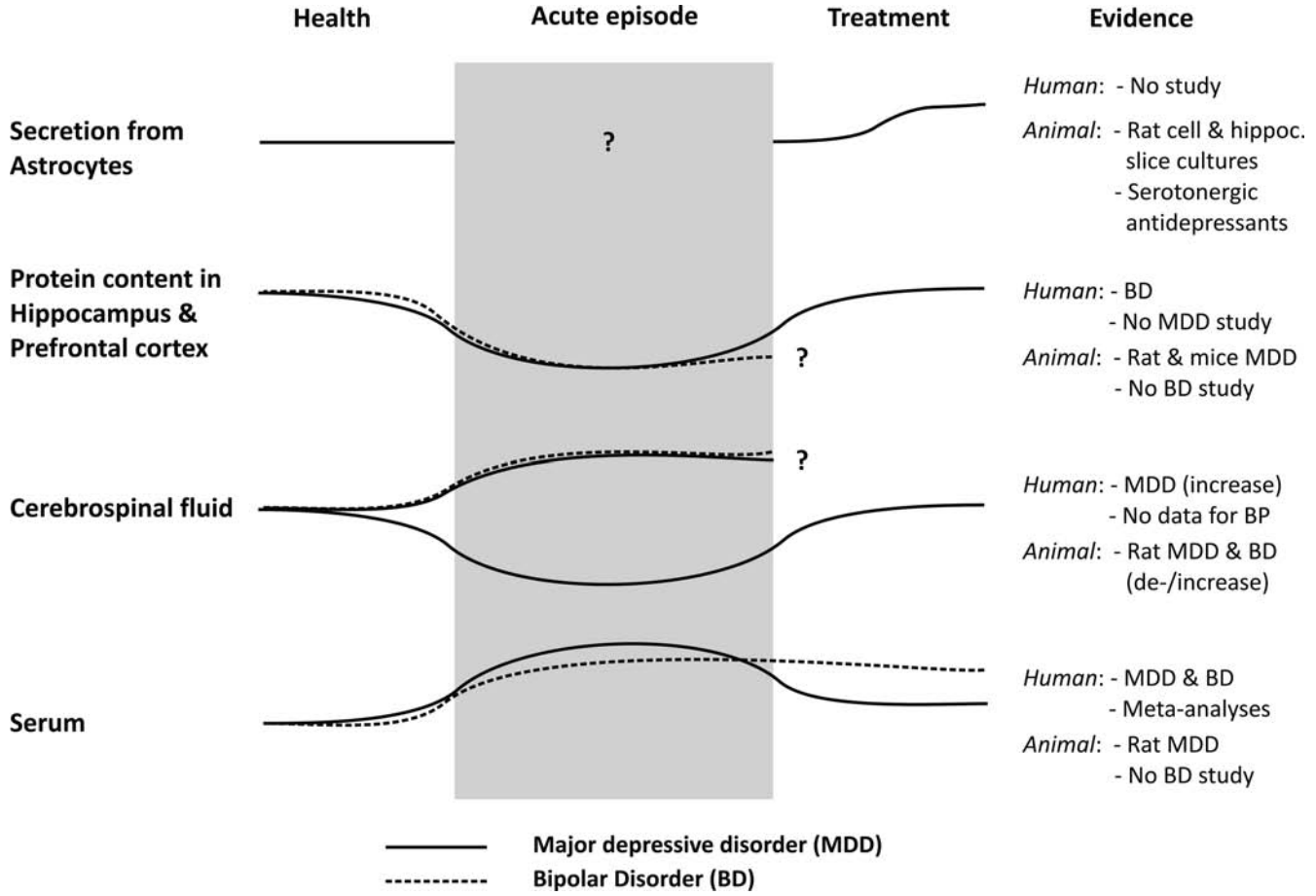

Fig. (3). Framework for S100B's role in mood disorders and their treatment. The figure summarizes evidence from human, animal and cell culture studies for the involvement of S100B in the pathogenesis and treatment of mood disorders. hippoc. hippocampal.

In conclusion, findings strongly support the concept of serum S100B as a reliable and sensitive biomarker for mood disorders to deepen the understanding of their pathogenesis, treatment and plasticity. Longitudinal studies combining serum S100B with other cell-specific serum parameters, cell-culture/gene-expression methodology and multimodal imaging modalities are warranted in patients with major depressive and bipolar disorder to evaluate a possible implementation of S100B in clinical practice.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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