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Journal of Affective Disorders

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Short communication

Plasma levels of soluble TNF receptors 1 and 2 after tDCS and sertraline treatment in major depression: Results from the SELECT-TDCS trial



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ARTICLE INFO

Article history:

Received 26 May 2015

Received in revised form

2 July 2015

Accepted 6 July 2015

Available online 29 July 2015

Keywords:

Major depressive disorder

Transcranial direct current stimulation

Sertraline

STNFR1

STNFR2

ABSTRACT

Background: The cytokine hypothesis of depression postulates that the pathophysiology of this illness incorporates an increased production of pro-inflammatory cytokines, which leads to an over-activation of the hypothalamic–pituitary–adrenal axis as well as monoaminergic disturbances. Nevertheless, it remains unclear whether the amelioration of depressive symptoms could decrease cytokine levels. Notwithstanding antidepressant drug therapy might exert anti-inflammatory effects, the effects of non-invasive neuromodulatory approaches like transcranial direct current stimulation (tDCS) on pro-inflammatory cytokine networks are largely unknown.

Methods: We evaluated, in the Sertraline vs. Electric Current Therapy for Treating Depression Clinical Study (SELECT-TDCS) trial, whether the plasma levels of the soluble TNF receptors 1 and 2 (sTNFRs) changed after antidepressant treatment in a sample of 73 antidepressant-free patients with unipolar depressive disorder in an episode of at least moderate intensity.

Results: Although both tDCS and sertraline exerted antidepressant effects, the plasma levels of sTNFRs did not change over time regardless of the intervention and clinical response. Also, baseline sTNFRs levels did not predict antidepressant response.

Limitations: Our negative findings could be a type II error, as this trial did not use an equivalence design.

Conclusions: To conclude, in this novel placebo-controlled trial prospectively evaluating the changes of sTNFRs in depressed patients, we found that these molecules are not surrogate biomarkers of treatment response of tDCS, whose antidepressant effects occurred regardless of normalization of immunological activity.

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1. Introduction

Several lines of evidence indicate that the activation of cell-mediated immunity and the increased production of pro-inflammatory cytokines are implicated in the pathophysiology of major depressive disorder (MDD), as postulated by the “cytokine

hypothesis of depression” (Maes et al., 2011). For instance, acute infections with intense inflammatory response are associated with psychological symptoms similar to depression such as anhedonia, lethargy, loss of appetite and apathy (i.e., sickness behavior); whereas acute increases in pro-inflammatory cytokines may lead to depressive episodes (DellaGioia and Hannestad, 2010). Studies have shown elevated serum levels of IL-1 β , IL-6 and tumor necrosis factor-alpha (TNF- α) in depressed patients (Young et al., 2014). Pro-inflammatory cytokines also lead to an enhanced consumption of serotonin and tryptophan via indoleamine 2,3-dioxygenase (IDO) activation (Muller and Schwarz, 2007).

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Furthermore, anti-inflammatory agents may have antidepressant effects (Kohler et al., 2014), while the therapeutic benefits of standard antidepressants may involve a decreased production of pro-inflammatory cytokines by the activated microglia (Raison et al., 2013).

TNF- α plays a pivotal role in the regulation of the inflammatory response, primarily exerting its effects by binding to its cognate membrane receptors TNFR1 and TNFR2, which are found in soluble forms (sTNFRs) in the blood. They are more stable than TNF- α and might be more reliable markers of inflammatory activity (Wajant et al., 2003), being increased in major depressive disorder (MDD) (Grassi-Oliveira et al., 2009).

However, no study evaluated whether sTNFRs change after treatment with transcranial direct current stimulation (tDCS), a novel antidepressant technique based on the application of a weak, direct electric current using two electrodes placed over the scalp (Brunoni et al., 2013b). Being non-invasive, tDCS exerts no direct effects on peripheral cells compared to antidepressant pharmacological therapy that might have direct peripheral anti-inflammatory effects (Hannestad et al., 2011). Conversely, antidepressant drugs display anti-inflammatory effects, according to *in vivo* (Lanquillon et al., 2000) and *in vitro* (Xia et al., 1996) studies.

Thus, the objective of this exploratory study was to compare the effects of tDCS and sertraline in sTNFRs plasma levels of depressed patients. This study is important because few placebo-controlled trials have prospectively assessed the impact of antidepressant treatments on sTNFRs levels and this issue has not been addressed yet for tDCS. Moreover, considering that tDCS and sertraline are, respectively, non-pharmacological and pharmacological interventions, they might exert different effects on sTNFRs, which would suggest distinct mechanisms of action of these treatments.

2. Methods

2.1. Study design

We used data from the Sertraline vs. Electric Current Therapy for Treating Depression Clinical Study (SELECT-TCS), a factorial, double-blind, sham-controlled trial enrolling 120 depressed participants that were randomized to receive placebo, sertraline, tDCS or the combined treatment, as described in Brunoni et al. (2011). The blood samples described here are the same as used in our previous studies evaluating biomarkers in the SELECT-TDCS trial (Brunoni et al., 2014a, 2014b, 2014c).

The study was conducted at the University Hospital, University of São Paulo, Brazil; being registered in clinicaltrials.gov (NCT01033084) and approved by the Local and National Ethics Committee. The trial was 6 weeks long; including an acute treatment period when ten consecutive weekday sessions of active/sham tDCS were performed, followed by two extra tDCS sessions delivered every other week. Sertraline (or placebo) was used in a fixed dose of 50 mg/day, starting and ending simultaneously with tDCS. Its main findings are described in Brunoni et al. (2013b).

2.2. Subjects

We recruited participants in a non-psychotic, acute depressive episode of at least moderate intensity, diagnosed by board-certified psychiatrists using the Mini International Neuropsychiatric Interview. Comorbid anxiety disorders were allowed. Exclusion criteria were other psychiatric disorders, personality disorders, neurological diseases, pregnancy or breastfeeding, suicidal ideation and previous or current use of sertraline.

Participants underwent physical examination, psychiatric and medical history, routine laboratory analyses, electrocardiogram (ECG) and assessment of vital signs. Subjects were excluded if not in good physical health or presenting medical disorders such as uncontrolled diabetes, hypertension, seizures, acute or chronic inflammatory conditions or other conditions that could affect inflammatory activity. They were gradually tapered off any psychotropic medications except benzodiazepine drugs that remained constant throughout the entire study.

We compared the sTNFRs levels of depressed patients with 22 healthy subjects from a previous study of our group (Teixeira et al., 2015). The healthy subjects lived in the same city of the depressed patients and all blood samples were analyzed in the same laboratory.

2.3. Procedures

We used standard, commercial tDCS devices (Chattanooga Ionto™ Dual Channel Devices, Chattanooga Group, Hixson, TN 37343 USA). The anode and the cathode were, respectively, placed over the left and the right dorsolateral prefrontal cortex (DLPFC). Brain areas were localized using the EEG 10/20 system. We used a current density of 0.8 A/m² (2 mA/25 cm²) per 30 min/day. For sham tDCS, the device was turned on for only 1 min. Trained nurses applied all sessions, guaranteeing patients' blinding. Raters were blind to the procedure being administered and raters and nurses were blind to study medication.

Blood samples were collected by venipuncture immediately before baseline and at endpoint assessments. Within 30 minutes of sample collection, samples were then spun at 3000g for 15 minutes at 5 °C. Plasma aliquots were collected and stored at –80 °C until assayed. All procedures were performed between 2 and 4 p.m. to minimize biological differences due to circadian rhythms.

The concentration of sTNFRs was determined using a sandwich enzyme-linked immunosorbent assay (ELISA) according to the procedures supplied by the manufacturer (DuoSet, R&D systems, Minneapolis, MN) at the Interdisciplinary Laboratory of Medical Investigation in the Federal University of Minas Gerais (Belo Horizonte, MG, Brazil). All samples were assayed in duplicate, and the intra- and inter-assay coefficients of variability were below 5% and 10%, respectively. The detection limit of these assays was 10 pg/mL. Concentrations are expressed as pg/mL. Analyses were performed blind to group assignment.

2.4. Statistical analysis

Stata 12 (Statacorp, College Station, TX, USA) was employed for all analyses. We described clinical and demographic variables across groups using one-way analysis of variance (ANOVA) for continuous variables and the χ^2 tests or Fisher's exact tests for categorical variables. Normality of data distribution was verified using the Shapiro–Wilk test. All tests were two-sided at the 5% significance level. As this was an exploratory study, we did not correct for multiple comparisons.

The dependent variables were not normally distributed. Few participants (< 1% of the sample) presented extreme values (up to one-hundred times of the sample mean) of sTNFR1 or sTNFR2. To handle with these extreme outliers, these values were trimmed to the mean + 3SD of the variable. After that, the dependent variables underwent natural logarithmic transformation, achieving Gaussian distribution. Finally, we calculated the change (pre minus post-levels) of sTNFRs blood levels in order to obtain the dependent variables for our models.

We used paired *t*-tests to investigate whether sTNFRs changed over time and to compare sTNFRs levels of the depressed patients

vs. healthy controls. For the primary outcomes, we carried out two (one for each sTNFR) mixed-model ANOVAs. In these analyses, significant interactions were followed by *t*-tests. Whenever sphericity was violated, the Greenhouse–Geisser correction was applied. The independent variables were group (4 levels: placebo, sertraline, tDCS and combined treatment) and clinical response (defined as $\geq 50\%$ improvement from baseline to endpoint MADRS scores).

Additional analyses were performed to assess whether other factors such as gender, age, obesity (body mass index ≥ 30 kg/m²), smoking status, physical activity, melancholic depression, atypical depression, severe depression (baseline MADRS ≥ 30), refractory depression (therapeutic failure to two or more antidepressants in the current depressive episode) and benzodiazepine use influenced the primary outcomes. Each variable was explored in a separate model.

Finally, to investigate whether baseline sTNFRs levels were predictors of response, analyses of covariance (ANCOVAs) were performed using depression improvement as the dependent variable, group as the independent variable and each sTNFR as the covariate (each one in a different model).

3. Results

We collected blood samples of 73 participants out of 103 completers; other samples were not collected due to technical reasons or patient refusal. The results observed in SELECT-TDCS were reproduced in the present subsample (Table 1). All other cytokines, except TNF- α , decreased over time in the four groups, as described elsewhere (Brunoni et al., 2014c) (Supplementary material).

Blood levels of sTNFRs were higher in MDD ($t_{1,94}=2.19$, $p=0.03$; $t_{1,94}=2.63$, $p=0.01$, respectively) compared to healthy controls. The plasma levels of sTNFRs did not significantly change over time ($t_{1,75}=-1.02$, $p=0.3$ and $t_{1,75}=-0.69$, $p=0.49$, respectively) (Fig. 1).

The changes of sTNFR1 were not significantly different according to treatment group ($F_{3,69}=1.32$, $p=0.27$), clinical response ($F_{1,71}=1.07$, $p=0.3$) or both ($F_{3,65}=0.38$, $p=0.71$). Also for sTNFR2, changes were not significantly different according to treatment group ($F_{3,69}=0.33$, $p=0.8$), clinical response ($F_{1,71}=0.03$, $p=0.85$) or both ($F_{3,65}=0.33$, $p=0.81$). Also, no other variable moderated these results (Supplementary Table). Finally, neither sTNFR1 nor

sTNFR2 were identified as predictors of depression improvement ($F_{1,72}=0.13$, $p=0.72$ and $F_{1,72}=0.51$, $p=0.47$, respectively).

4. Discussion

Compared to a concurrent healthy control sample, sTNFRs levels were higher in depressed patients. However, sTNFRs blood levels did not significantly change according to treatment group, response status and over time and baseline sTNFRs levels did not predict antidepressant response. Hannestad et al. (2011) also found that TNF- α did not change after MDD treatment, suggesting that inflammatory cytokines contribute to depressive symptoms and that antidepressants block the effects of these molecules on the brain. This rationale is also supported by a recent meta-analysis of longitudinal studies showing that increased levels of inflammatory proteins subsequently predicted depression (Valkanova et al., 2013). Thus, one hypothesis for our findings is that tDCS/sertraline may have improved depression by blocking the effects of cytokines on the brain rather than by directly reducing inflammation. Other explanations for our findings are: (1) the relatively small, selective contribution of inflammation to MDD (Howren et al., 2009) and (2) the existence of particular MDD subgroups where the contribution of inflammation is significant; e.g., those with high C-reactive protein levels (Raison et al., 2013).

In previous studies, we found that the blood levels of several cytokines (IL-2, IL-4, IL-6, IL-10, IL-17a, IFN- γ) decreased after tDCS treatment, but also in the placebo arm (Brunoni et al., 2014c) and that heart rate variability did not change after tDCS treatment, regardless of treatment response (Brunoni et al., 2013a). Thus, neither the HPA axis nor the autonomous nervous system are majorly implied in the antidepressant mechanisms of tDCS, at least during the MDD acute phase.

TDCS was applied over the DLPFC, a brain area where, in MDD vs. controls, levels of transmembrane TNF α , TNF α and TNFR2 mRNA are respectively increased, similar and decreased (Dean et al., 2013). Thus, our non-significant findings do not necessarily indicate that tDCS does not modulate TNF α activity, as other signaling pathways might be implicated. Further tDCS studies could explore TNF α mRNA activity and transmembrane TNF α levels and, the effects of tDCS in cortical TNF α pathways in animal models of depression.

Table 1

Clinical and demographic characteristics of the study sample.

	Placebo	Sertraline-only	tDCS-only	Combined treatment	<i>p</i>	Total	Total from the original study	<i>p</i>
<i>Clinical characteristics</i>								
Sample size	19	18	15	21	0.79	73	120	–
Age, years (SD)	50 (12)	41 (1)	41 (12)	41 (13)	0.1	41 (12)	42 (12)	0.58
Women, <i>n</i> (%)	12 (63)	11 (61)	10 (66)	18 (85)	0.3	51 (70)	82 (68)	0.77
Using BZD (%)	2 (10)	2 (11)	1 (7)	5 (23)	0.53	10 (14)	23 (20)	0.3
BMI, kg/m ² (SD)	26 (6)	25 (3)	25 (6)	27 (5)	0.54	26 (5)	26 (5)	0.92
<i>Depression characteristics at baseline, <i>n</i> (%) or mean (SD)</i>								
Refractoriness	7 (37)	9 (50)	6 (40)	7 (33)	0.75	29 (40)	50 (42)	0.78
Severity	12 (63)	11 (61)	11 (73)	12 (57)	0.8	46 (63)	70 (58)	0.49
MADRS	31.5 (6)	31 (7)	32 (6)	31 (6)	0.92	31 (6)	31 (6)	0.5
HDRS17	22 (4)	22 (4)	22(4)	22 (4)	0.99	22(4)	22(4)	0.75
<i>Depression endpoint scores, mean(SD) and response, <i>n</i> (%)</i>								
MADRS	24 (9)	19 (13)	19 (12)	10 (6)	< 0.01	18 (11)	19 (11)	0.38
HDRS17	17 (7)	14 (8)	13 (7)	9 (5)	0.01	14 (8)	15 (7)	0.34
Response	4 (21)	7 (39)	7 (46)	16 (76)	< 0.01	34 (46)	47 (39)	0.52

tDCS, Transcranial direct current stimulation; MADRS, Montgomery–Asberg depression rating scale; HDRS17, Hamilton Depression Rating Scale, 17-items; BMI, body mass index; SD, standard deviation. Refractory depression: patients who had failed to respond to two or more antidepressants in the current major depressive episode. Severe Depression: MADRS ≥ 30 . Significant *p* values (< 0.05) are highlighted in bold.

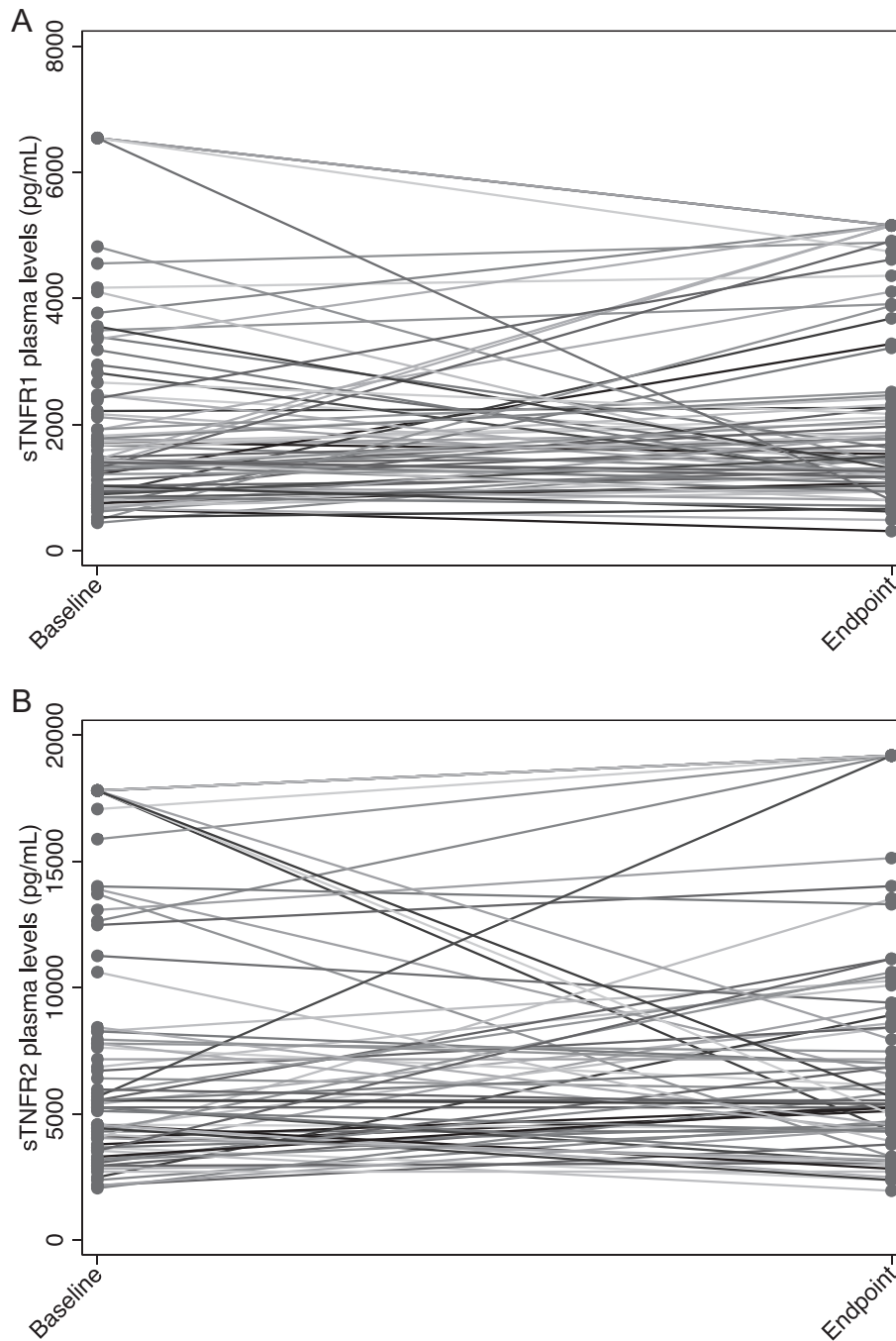


Fig. 1. Absence of changes in sTNFR1 (A) and sTNFR2 (B) plasma levels over time.

4.1. Limitations and strengths

Study limitations include: (1) the relative short time interval between blood measurements; (2) the relative low dose of sertraline (although a higher dose would probably induce a greater depression improvement, and we did not observe changes in sTNFRs levels comparing responders vs. non-responders); (3) negative findings due to a type II error; (4) although sertraline represented the “pharmacological” arm of our study, different antidepressant drugs, such as citalopram, escitalopram and mirtazapine present distinct effects on cytokine production of depressed patients *in vitro* (Munzer et al., 2013); (5) only two blood samples were collected – additional blood samples would allow to disentangle specific patterns of TNF α serum levels vis-à-vis depression response, as observed in a duloxetine trial (Fornaro et al., 2013).

Study strengths are its placebo-controlled design, comparison of two therapeutic interventions and the recruitment of antidepressant drug-free patients.

To conclude, sTNFRs levels did not change despite an adequate course of antidepressant treatment; moreover, baseline sTNFRs levels did not predict antidepressant response. Therefore, the antidepressant effects of tDCS and sertraline may not likely to involve the peripheral inflammatory activity.

Role of the funding sources

The funding sources played no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, and preparation, review or approval of the manuscript.

This study was partially funded by FAPESP (São Paulo Research Foundation, Grant number: 2009/05728-7), FAPEMIG and CNPq.

Contributors

ARB and ALT designed the work and drafted the initial manuscript. BSJ, LV, IMB, PAL collected study data. ELM and ALT performed blood analysis. ARB, RMV, AFC, HJC and WFG performed the statistical analyses and interpreted the data. All authors revised the work and provided important intellectual content. All authors approved the final version of the manuscript.

Conflicts of interest

None.

Acknowledgments

This study was partially funded by FAPESP (São Paulo Research Foundation, Grant number: 2009/05728-7), FAPEMIG and CNPq. The sponsors played no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, and preparation, review or approval of the manuscript. A.R.B. is supported by the following grants: 2013 NARSAD Young Investigator from the Brain & Behavior Research Foundation (Grant Number 20493), 2012 FAPESP Young Researcher from the São Paulo State Foundation (Grant Number 20911-5) and National Council for Scientific and Technological Development (CNPq, Grant Number 470904). The Laboratory of Neuroscience receives financial support from the Associação Beneficente Alzira Denise da Silva (ABADHS) and from JNK Empreendimentos e Incorporações.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2015.07.006>.

References

- Brunoni, A.R., Kemp, A.H., Dantas, E.M., Goulart, A.C., Nunes, M.A., Boggio, P.S., Mill, J.G., Lotufo, P.A., Fregni, F., Bensenor, I.M., 2013a. Heart rate variability is a trait marker of major depressive disorder: Evidence from the Sertraline vs. Electric Current Therapy to Treat Depression Clinical Study. *Int. J. Neuropsychopharmacol.* (Epub ahead of print)
- Brunoni, A.R., Machado-Vieira, R., Zarate Jr., C.A., Vieira, E.L., Valiengo, L., Bensenor, I.M., Lotufo, P.A., Gattaz, W.F., Teixeira, A.L., 2014a. Assessment of non-BDNF neurotrophins and GDNF levels after depression treatment with sertraline and transcranial direct current stimulation in a factorial, randomized, sham-controlled trial (SELECT-TDCS): an exploratory analysis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 56C, 91–96.
- Brunoni, A.R., Machado-Vieira, R., Zarate Jr., C.A., Vieira, E.L., Vanderhasselt, M.A., Nitsche, M.A., Valiengo, L., Bensenor, I.M., Lotufo, P.A., Gattaz, W.F., Teixeira, A.L., 2014b. BDNF plasma levels after antidepressant treatment with sertraline and transcranial direct current stimulation: Results from a factorial, randomized, sham-controlled trial. *Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol.* 24, 1144–1151.
- Brunoni, A.R., Machado-Vieira, R., Zarate, C.A., Valiengo, L., Vieira, E.L., Bensenor, I.M., Lotufo, P.A., Gattaz, W.F., Teixeira, A.L., 2014c. Cytokines plasma levels during antidepressant treatment with sertraline and transcranial direct current stimulation (tDCS): results from a factorial, randomized, controlled trial. *Psychopharmacology* 231, 1315–1323.
- Brunoni, A.R., Valiengo, L., Baccaro, A., Zanao, T.A., de Oliveira, J.F., Vieira, G.P., Bueno, V.F., Goulart, A.C., Boggio, P.S., Lotufo, P.A., Bensenor, I.M., Fregni, F., 2011. Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Trial—SELECT TDCS: design, rationale and objectives. *Contemp. Clin. Trials* 32, 90–98.
- Brunoni, A.R., Valiengo, L., Baccaro, A., Zanao, T.A., Oliveira, A.C., Goulart, A.C., Boggio, P.S., Lotufo, P.A., Bensenor, I.J., Fregni, F., 2013b. The sertraline versus electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry* 70, 383–391.
- Dean, B., Gibbons, A.S., Tawadros, N., Brooks, L., Everall, I.P., Scarr, E., 2013. Different changes in cortical tumor necrosis factor-alpha-related pathways in schizophrenia and mood disorders. *Mol. Psychiatry* 18, 767–773.
- DellaGioia, N., Hannestad, J., 2010. A critical review of human endotoxin administration as an experimental paradigm of depression. *Neurosci. Biobehav. Rev.* 34, 130–143.
- Fornaro, M., Rocchi, G., Escelsior, A., Contini, P., Martino, M., 2013. Might different cytokine trends in depressed patients receiving duloxetine indicate differential biological backgrounds. *J. Affect. Disord.* 145, 300–307.
- Grassi-Oliveira, R., Brietzke, E., Pezzi, J.C., Lopes, R.P., Teixeira, A.L., Bauer, M.E., 2009. Increased soluble tumor necrosis factor-alpha receptors in patients with major depressive disorder. *Psychiatry Clin. Neurosci.* 63, 202–208.
- Hannestad, J., DellaGioia, N., Bloch, M., 2011. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol.* 36, 2452–2459.
- Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom. Med.* 71, 171–186.
- Kohler, O., Benros, M.E., Nordentoft, M., Farkouh, M.E., Iyengar, R.L., Mors, O., Krogh, J., 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 71, 1381–1391.
- Lanquillon, S., Krieg, J.C., Bening-Abu-Shach, U., Vedder, H., 2000. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol.* 22, 370–379.
- Maes, M., Ruckoanich, P., Chang, Y.S., Mahanonda, N., Berk, M., 2011. Multiple aberrations in shared inflammatory and oxidative & nitrosative stress (IO&NS) pathways explain the co-association of depression and cardiovascular disorder (CVD), and the increased risk for CVD and due mortality in depressed patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 769–783.
- Muller, N., Schwarz, M.J., 2007. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol. Psychiatry* 12, 988–1000.
- Munzer, A., Sack, U., Mergl, R., Schonherr, J., Petersein, C., Bartsch, S., Kirkby, K.C., Bauer, K., Himmerich, H., 2013. Impact of antidepressants on cytokine production of depressed patients in vitro. *Toxins* 5, 2227–2240.
- Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 70, 31–41.
- Teixeira, A.L., de Souza, R.T., Zanetti, M.V., Brunoni, A.R., Busatto, G.F., Zarate Jr., C.A., Gattaz, W.F., Machado-Vieira, R., 2015. Increased plasma levels of soluble TNF receptors 1 and 2 in bipolar depression and impact of lithium treatment. *Hum. Psychopharmacol.* 30, 52–56.
- Valkanova, V., Ebmeier, K.P., Allan, C.L., 2013. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J. Affect. Disord.* 150, 736–744.
- Wajant, H., Pfizenmaier, K., Scheurich, P., 2003. Tumor necrosis factor signaling. *Cell. Death Differ.* 10, 45–65.
- Xia, Z., DePierre, J.W., Nassberger, L., 1996. Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. *Immunopharmacology* 34, 27–37.
- Young, J.J., Bruno, D., Pomara, N., 2014. A review of the relationship between proinflammatory cytokines and major depressive disorder. *J. Affect. Disord.* 169, 15–20.