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Electroconvulsive therapy and aerobic exercise training increased BDNF and ameliorated depressive symptoms in patients suffering from treatment-resistant major depressive disorder

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ABSTRACT

Background: To treat patients suffering from treatment-resistant major depressive disorder (TR-MDD), research has focused on electroconvulsive therapy (ECT) and aerobic exercise training (AET). Brain derived neurotrophic factor (BDNF) seems to be key in MDD. The aims of the present study were therefore two-fold, to investigate in a three-arm interventional study the differential effects of ECT, ECT plus AET, and AET alone in patients suffering from TR-MDD on 1. depressive symptoms and 2. BDNF.
Methods: 60 patients with TR-MDD (mean age: 31 years; 31.6% female patients) were randomly assigned either to the ECT, ECT + AET, or AET condition. The AET condition consisted of treadmill exercise for 30 min, three times a week. Both depression severity and BDNF levels were assessed at baseline and 4 weeks later. All patients were further treated with an SSRI standard medication.
Results: BDNF levels increased over time in all three study conditions. After completion of the intervention program, the ECT group showed significantly higher BDNF levels compared to the ECT + AET and the AET conditions. Depressive symptoms decreased in all three conditions over time. The combination of ECT + AET led to a significantly greater decrease than in either the ECT or AET alone conditions. BDNF levels were not associated with symptoms of depression.
Conclusions: The pattern of results suggests that ECT, AET and particularly their combination are promising directions for treatment patients suffering from TR-MDD, and that it remains unclear to what extent BDNF is key and a reliable biomarker for TR-MDD.

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1. Introduction

Fifty to 70% of treated patients suffering from depressive disorders do not improve in the long-term (Greden, 2001; Sackeim, 2001; Jenkins and Goldner, 2012; Keitner and Mansfield, 2012), and residual depressive symptoms are associated with poor long-term outcomes and increased risk of relapse (Fava et al., 2002; Judd et al., 1998; Kennedy and Paykel, 2004). Accordingly, the economic costs of treatment-resistant major depression (TR-MDD) largely surpass those caused by MDD, thus representing a serious and costly public mental health problem (Olchanski et al., 2013). Therefore, adequate treatment and care of patients suffering from TR-MDD is highly desirable from both clinical and economic points of view. To address this issue, we investigated the impact of a 4-week electroconvulsive therapy (ECT) and aerobic exercise training (AET) in patients with TR-MDD.

Research on possible molecular pathways of MDD has shown that increased cellular dysfunction in limbic and cortical areas of the brain can be observed in patients suffering from MDD (cf. Guilloux et al., 2012; Sen et al., 2008), and it is strongly related to

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decreased neurotrophic activity (Duman and Monteggia, 2006). In this regard, the search for biomarkers, including nerve growth factors such as brain-derived neurotrophic factor (BDNF), that reliably predict and describe improvements in treatment of depressive disorders has become an increasingly important focus of research (Naert et al., 2011). BDNF is a protein mostly expressed in the central nervous system and has an importance in survival and maintenance of neuronal functioning (Binder and Scharfman, 2004). Indeed, low neurotrophic activity has been seen as a mechanism underlying reduced cell numbers in the frontal cortex (Cotter et al., 2001; Rajkowska et al., 2001), and the amygdala (Bowley et al., 2002; Hamidi et al., 2004) and also underlying hippocampal volume (Videbech and Ravnkilde, 2004; Campbell et al., 2004), thus indicating that nerve growth factors, and more specifically, changes in BDNF, may play a crucial role in the development of and recovery from MDD (Castrén et al., 2007; Karege et al., 2002; Sen et al., 2008; Molendijk et al., 2011; Sen et al., 2008; Guilloux et al., 2012; Wolkowitz et al., 2011; Matrisciano et al., 2009; Serra-Millàs et al., 2011; Mikoteit et al., 2014). In this context, Guilloux et al. (2012) were able to show reduced BDNF function in the amygdala of females suffering from MDD. Likewise, Sen et al. (2008) concluded from a meta-analysis that BDNF-levels were lower in people suffering from MDD than in controls. Following Hasselbalch et al. (2012) this holds also true even when patients are fully remitted. However, as a result, it is claimed that, among other factors, increasing the levels of plasma BDNF might be associated with improvements in MDD (cf. Siuciak et al., 1997; Shirayama et al., 2002).

There is a large body of evidence that electroconvulsive therapy (ECT, Haghighi et al., 2013) and aerobic exercise training (AET) both improve depressive symptoms (Josefsson et al., 2014; Lindwall et al., 2013) and boost secretion and the effect of BDNF (Cho et al., 2012; Seifert et al., 2010; Brunoni et al., 2014). Therefore, the aim of the present study was to investigate the impact of ECT and AET concomitantly on depressive symptoms and BDNF in patients suffering from TR-MDD.

As to the impact of ECT on BDNF-levels when treating MDD, in an attempt to summarize the state of play, Haghighi et al. (2013), in a very brief review on the topic, reached the following conclusions: (1) in sample sizes ranging from 15 to 40 in-patients suffering from MDD, during a depressed episode of unipolar or bipolar disorder, BDNF increased exclusively in plasma (pBPNF), but not in serum BDNF (sBDNF) in response to ECT applied either bifrontal, unilateral, or bilateral; (2) two or three sessions per week were performed, (3) lasting for 2.5–5 weeks; (4) patients were assessed with concomitant antidepressants (SSRIs, NASSAs, tryzyclic antidepressants), antipsychotics, or benzodiazepines, or during the wash-out phase; (5) in most studies, the association between change in BDNF and psychopathology remained unclear; (6) only Haghighi et al. (2013) reported explicitly having treated patients suffering from TR-MDD. To conclude, given the heterogeneity with respect to the factors mentioned above, the mixed results are not surprising (see also Scott et al., 2000). In a previous study (Haghighi et al., 2013), we showed that sBDNF levels increased by 101% in patients with TR-MDD, compared to sBDNF levels of patients with TR-MDD treated with a citalopram, though the increase in sBDNF was not associated with increased symptom reduction or with treatment outcome. The latter observation is in accord with a recent meta-analysis and review in this field: Specifically, Brunoni et al. (2014), analyzing 11 different ECT studies covering 221 subjects suffering from mood disorders during an acute phase of depressive episode, concluded that (1) different algorithms (unilateral vs. bilateral), (2) different topographic placements (e.g. frontal vs. temporal), (3) a different number of trials, while (4) assessing plasma or serum BDNF were employed. However, two robust key results could be observed: First, regardless of the differences mentioned above, ECT did markedly improve levels of BDNF; second, BDNF levels and depressive symptoms were not associated; accordingly, Brunoni et al. (2014) concluded that this lack of correlation between BDNF increasing and depression improvement seemed to reflect that ECT induces neurotrophic effects regardless of clinical response in depression.

Aerobic exercise training has a positive impact on patients suffering from burnout (Beck et al., 2013), on cardiorespiratory fitness (Gerber et al., 2013), and on depression, stress and burnout (Lindwall et al., 2013). Most importantly, Mota-Pereira et al. (2011) showed, that compared to the control condition, 50% of female patients suffering from TR-MDD were remitted after a 12-week walking AET. In brief, there is evidence that AET has a beneficial impact on patients suffering from a broad variety of psychiatric disorders (see also Josefsson et al., 2014; Rethorst and Trivedi, 2013), and more specifically on patients suffering from affective disorders (Stanton et al., 2014).

Aerobic exercise training (AET) increases sBDNF, pBDNF and platelet BDNF (Cho et al., 2012). Of particular note, Seifert et al. (2010) showed that brain BDNF increased in seven healthy males after 3-months with AET, compared to five healthy males in a sedentary condition.

To the best of our knowledge, only one study has examined the association between BDNF and AET in patients suffering from MDD. Toups et al. (2011) assessed 104 patients suffering from MDD and found no association between BDNF and the efficacy of an exercise augmentation treatment.

To summarize, TR-MDD dramatically reduces individuals' quality of life and increases costs and burden for public expenditure. Both ECT and AET have the potential to successfully treat patients suffering from TR-MDD, and a key factor seems to be the release of circulating BDNF. However, surprisingly, no study has so far considered to the extent of positive impact of the combination of ECT and AET on both circulating BDNF and symptoms of depression. The aims of the present study were therefore two-fold: to investigate in a three-arm interventional study the differential effects of ECT alone, ECT with AET, and AET alone in patients suffering from TR-MDD on (1) depressive symptoms, and (2) BDNF concentrations. We believe the results have the potential to optimize treatment of patients suffering from TR-MDD.

Three hypotheses and one research question were formulated. First, following Haghighi et al. (2013) and Brunoni et al. (2014), we expected that ECT would improve both symptoms and sBDNF in patients suffering from TR-MDD. Second, following Mota-Pereira et al (2011) and Josefsson et al. (2014), we hypothesized that AET would improve symptoms in patients suffering from TR-MDD. Third, following Seifert et al. (2010) and others, we expected increased sBDNF levels following AET. Last, we treated as exploratory the extent to which the combination of ECT and AET has additive effects. To the extent that it does we would expect greater symptom improvement and higher sBDNF levels among TR-MDD patients following ECT in combination with AET.

2. Method

2.1. Sample

A total of 70[2] inpatients suffering from treatment-resistant major depressive disorders (TR-MDD) and meeting the inclusion

[2] Initially, 104 patients were approached; of these, 34 (32.7%) did not meet the inclusion and exclusion criteria: 30 (88.24%) suffered from comorbid disorders such as substance abuse disorders, personality disorders, anxiety disorders, and bipolar disorders; 25 (73.53%) were out of the range of age, and 31 (91.18%) had BDI and/or HDRS scores (see Method section) below the defined cut-off value.

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