Anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex improves anorexia nervosa: A pilot study

Eman M. Khedr, Noha Abo Elfetoh, Anwer M. Ali and Mostafa Noamany
Department of Neuropsychiatry, Assiut University Hospital, Assiut, Egypt

Abstract

Background: Existing treatments for adults with anorexia nervosa (AN) have limited proven efficacy. New treatments that have been suggested involve targeted, brain-directed interventions such as transcranial direct current stimulation (tDCS). We describe findings from seven individuals with treatment-resistant AN who received 10 sessions of anodal tDCS, over the left dorsolateral prefrontal cortex (DLPFC).

Material and method: In this open-label, single-arm study, seven patients received anodal tDCS (2mA) for 25 minutes over the left dorsolateral prefrontal cortex daily for ten days. Assessments pre-tDCS, post-tDCS and one month later included the Eating Attitude Test (EAT), Eating Disorder Inventory (EDI) and Beck Depression Inventory (BDI).

Results: Three patients improved in all three rating scales immediately after the treatment sessions and one month later. Two patients showed improvement at the end of treatment but returned to the baseline after one month. One subject improved only on the BDI scale but not eating scales. The scores in the three rating scales were unaffected by treatment in the remaining patient. There was a significant effect of time (pre, post and 1 month later) on the three rating scores; BDI ($P = 0.016$), EDI ($P = 0.018$) and EAT ($P = 0.016$) and a significant correlation between the percent improvement of BDI and EAT ($r = 0.01$), and between BDI and EDI ($r = 0.006$).

Conclusions: These findings suggest that tDCS has potential as an adjuvant treatment for AN and deserves further study.

Keywords: Anorexia nervosa, transcranial direct current stimulation, beck depression inventory, eating attitude test, eating disorder inventory

1. Introduction

Eating disorders (ED) are some of the most serious problems affecting adolescents and young adults today. Anorexia nervosa and bulimia nervosa are compulsive psychosocial, pathological disorders that affect people’s relationships with food and their own bodies. (Nicholus and Viner, 2005; Herzog and Copeland, 1985). Although eating disorders affect both men and women, the disorders are most common in adolescents and young adults and are 10 times more common in girls and women (Pritts and Susman, 2003; Casper et al., 1980). Anorexia nervosa is characterized by an intense fear of food, eating and gaining weight, severe food restriction and in some cases binge/purge behaviours, resulting in extremely low body weight. AN is associated with a myriad of physical and psychological comorbidities, high levels of mortality and disability (Arcelus et al., 2011). Despite the growing body of neuroimaging data and the emergence of neural models of ED, there is a lack of targeted treatment interventions. At present, the leading treatment for AN...
in adolescents is family based therapy (FBT); yet, there is still no ‘gold standard’ treatment for AN (Schmidt et al., 2012; Watson and Bulik, 2012).

Imaging research has identified a range of brain structures that are likely to be involved in the pathophysiology of eating disorders (Van den Eynde and Treasure, 2009). The lateral prefrontal cortex has been proposed to be part of dysfunctional fronto-striatal circuitry that underlies the impaired capacity for self-regulation seen in eating disorders. The problems in more dorsal neural circuits (which include the DLPPC) may also contribute to symptoms of AN as a result of an impaired balance between interoceptive and reward processing (Kaye et al., 2009). Finally, increased lateral prefrontal cortex activity during the processing of visual food stimuli in recovered AN patients, suggests that this may be associated with good outcome (Van Kuyck et al., 2009).

Electroencephalographic (EEG) measurements of anorexics have shown hyperactivity of the right hemisphere (Grunwald et al., 2004). Similarly, a positron emission tomography (PET) scan, of anorectics, aimed to map serotonergic activity around 5-HT1A receptors, found increased clusters of serotonergic bindings, predominantly, in right fronto-temporal regions (Galusca et al., 2008). When anorexic patients viewed images of their own body which they had themselves digitally distorted there was activity in the right amygdala, the right fusiform gyrus and brainstem region, as if a ‘fear network’ had been triggered (Seeger et al., 2002).

Likewise, anorexic and bulimic patients were reported tally distorted there was activity in the right amygdala, of their own body which they had themselves digi- to resist food and a reduction in food cravings in 19 overweight subjects. Montenegro et al., (2012) repli- cated the reduction of the desire to eat in 9 overweight subjects following a single session of prefrontal tDCS. These studies on hyperphagia – the opposite of anorexia – linking overeating with a weakened and compromised RH (i.e. LH dominance), are consistent with the idea that restricted food intake is associ- ated with the opposite pattern of inter-hemispheric imbalance – a RH dominance. Given the relative

The lateral prefrontal cortex and cathode over the left prefrontal cortex tDCS caused a transient increase in the self-reported ability to resist food and a reduction in food cravings, as well as a reduction in snack consumption and eye gaze fixation to food follow- ing 20 min of tDCS applied over (anode right/cathode left) the prefrontal cortex. Similarly, Goldman et al. (2011) found that anode over the right prefrontal cortex and cathode over the left prefrontal cortex iDCS caused a transient increase in the self-reported ability to resist food and a reduction in food cravings in 19 overweight subjects. Montenegro et al., (2012) repli- cated the reduction of the desire to eat in 9 overweight subjects following a single session of prefrontal iDCS. These studies on hyperphagia – the opposite of anorexia – linking overeating with a weakened and compromised RH (i.e. LH dominance), are consistent with the idea that restricted food intake is associ- ated with the opposite pattern of inter-hemispheric imbalance – a RH dominance. Given the relative
ineffectiveness of present treatments for AN, and previous positive findings during treatment with tDCS in food-craving subjects, we decided to conduct a preliminary trial to test the acceptability of tDCS as a potential treatment for AN. Based on the concept of mutual balance between the hemispheres we hypothesized that anodal excitation of the hypoactive hemisphere would restore inter-hemispheric balance in AN. Patients attended 10 sessions of anodal tDCS delivered to the left DLPFC. We examined effects on the urge to restrict food intake and symptoms of depression associated with AN.

2. Material and method

2.1. Subjects

The anorexic group was composed of 7 patients (6 females). The mean age was 21.75 ± 7.8 with range 16–39 years. Diagnosis was established with the eating disorders module of the Structured Clinical Interview for DSM-IV– axis I Disorders/Patient version (First et al., 2002), and patients met the principal eligibility criterion required, that is, a body mass index between 14–17.5 kg/m². The patient subjects were asked not to take drugs that affect motor cortex excitability (dopaminergic, Psychotropic, antiepileptic, or hormonal drugs Estrogen) at least two weeks before the study. None of the patients suffered from any other clinically relevant disorders; however most of them had been receiving antidepressant serotonin reuptake inhibitors (SSRIs) for few months without improvement (6 patients). This medication was kept constant throughout the study. Height, weight and body mass index were measured for each subject. Demographic and clinical information for all patients were recorded.

Each subject underwent clinical tests including Eating Disorder Inventory (EDI) (Garner et al., 1983), Eating Attitude Test (EAT) (Garner and Garfinkel, 1979) and Beck’s Depression Inventory (BDI, II (Beck et al., 1996).

2.2. Eating Disorders Inventory (EDI)

The EDI described is a frequently used 64-item self-report measure of Eating related attitudes and behaviours divided into eight subscales.

1. Drive for thinness: an excessive concern with dieting and fear of weight gain.
2. Bulimia: episodes of binge eating and purging.
3. Body dissatisfaction: not being satisfied with one’s physical appearance.
4. Ineffectiveness: assesses feelings of inadequacy, worthlessness and lack of control over one’s life.
5. Perfectionism.
6. Interpersonal distrust: reluctance to allow close relationships.
7. Interoceptive awareness: measures the ability to discriminate between sensations and feelings, and between the sensations of hunger and satiety.
8. Maturity fears: the fear of facing the demands of adult life.

Options ranged from ‘always to never’. The most extreme eating disorder response earns a score of 3, the intermediate response scores 2, and the next Response scores 1; the other three responses receive no score. Scale scores are the sum of all items for that particular subscale. EAT is a 40-item measure of the symptoms in anorexia nervosa are reported. The scale (EAT) is presented in a 6-point, forced choice, self-report format which is easily administered and scored.

3. The BDI-II

Finally, participants were asked to rate how they had been feeling for the previous two weeks. The BDI-II contains 21 questions, each answer being scored on a scale value of 0 to 3. The cut-offs used are: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms.

These tests were repeated at post-treatment and at 1 month follow-up. The study was approved by the Institutional Ethical Committee of Assiut University Hospital. Prior to the investigation, patients gave their informed consent according to the declaration of Helsinki.

4. Experimental design and tDCS procedure

Anodal tDCS for 25 minutes at 2mA (15 s ramp in and 15 s ramp out) was applied daily for 10 consecutive days (5 session/week) (CX - 6650 Model TRCU - 04A Rolf Schneider Electronics, D-37130 E.M. Khedr et al. / Therapeutic effect of direct current stimulation on anorexia nervosa 791
Gleichen, Germany). The anodal electrode (24 cm² with current density of 0.08 mA (2 mA/24 cm²) was placed over the left DLPFC (6 cm anterior to the left primary motor cortex (M1) along a parasagittal line (Fitzgerald et al., 2009; Moschioni et al., 2004; Boros et al., 2008; Nitsche et al., 2007) in the anodal group, and the reference electrode (100 cm² with current density 0.02 (2 mA/100 cm²) was fixed over the contralateral arm (extracephalic). The large surface area reference electrode (100 cm²) reduces current density, and consequently the efficacy of stimulation at that location, making it functionally inert (Fregni et al., 2008; Knoch et al., 2008). In addition, an extracephalic reference avoids the confounding effects of two electrodes with opposite polarities over the brain (Accorto et al., 2007; Ferrucci et al., 2008). Because brief exposure to tDCS has no after-effects whereas we used 25 min duration in order to produce robust after-effects. However, since other successful clinical studies have used multi-day application of 20–30 min anodal TDCS over frontal cortex for depression (e.g., Brunoni et al., 2013). Daily tDCS was given to prolong and stabilize these long-lasting after-effects (Boggio et al., 2007; Fregni et al., 2006).

5. Data analysis

All data were analyzed with the aid of the SPSS ver. 16 (http://www.spss.com). The results were expressed as mean ± SD. Statistical analysis of the scores in each test was done with a Non –parametric Friedman Test with TIME (pre and post tenth session and then at 1 month follow up) as the within subject factor. Wilcoxon Test was used to compare the improvement at different assessment points (post sessions and one month later). Percent improvement in each rating scale (BDI, EAT, and EDI) was calculated as [Pre session – one month follow up/pre session score] × 100 for each subject. Spearman correlation was performed between base line data of the different rating scales, as well as between the percent improvements of different rating scales at one month follow up. P < 0.05 was considered significant for all statistical analysis.

6. Results

Demographic and clinical rating scales are shown in Table 1. The mean duration of illness was 3.4 ± 0.78 years with age of onset ranging from 12–35 years. At the start of treatment, two patients had minimal depression; 2 patients had mild depression; and 3 patients had severe depression. All patients except one (7th patient) were taking the SSRI citalopram 10 mg/day throughout the study. There was a significant positive correlation between BDI and EDI (r = 0.581 and p = 0.005), and between BDI and EAT (r = 0.47 and p = 0.027).

There was considerable variation in the response to treatment between the patients. Figures 1–3 show changes in the three rating scales (BDI, EAT and EDI respectively) for each subject at each time of assessment. The 1st, 3rd, and 4th patients improved in all three rating scales post session and one month later. The 2nd subject improved only on the BDI scale but not eating scales. The 5th and 6th patients showed improvement at the end of session but returned to the base line after one month. The 7th patient recorded no changes in the three rating scores either post session or one month later. Interestingly patient number 7, the only patient who was not receiving treatment with SSRIs, had no improvement.

Non –parametric Friedman test showed a significant effect of time (mean ± SD pre, post sessions and 1 month later; 22.4 ± 12.4, 14.9 ± 7.6 and 13.3 ± 5.3 respectively) for BDI with P = 0.016, EDI (72.3 ± 15.7, 56 ± 9.6 and 50.1 ± 12.9 respectively) with P = 0.018 and EAT (60.9 ± 7.4, 41.1 ± 14 and 39.4 ± 19.1 respectively (with P = 0.016). Post hoc comparisons using the Wilcoxon test showed that there was significant improvement compared with base line in the different rating scales at post session and also at one month after the end of treatment (P = 0.028, and 0.043 respectively) (Fig. 4).

The largest changes in subscales of the Eating Disorder Inventory were: Body dissatisfaction, interpersonal distrust, interoceptive awareness, and ineffectiveness (Table 2).

There was a significant positive Spearman correlation between the percent improvement of BDI and EAT (r = 0.87 p = 0.01), and between BDI and EDI (r = 0.89 and P = 0.006).

7. Discussion

Although previous studies have applied short bursts of tMS to the DLPFC in patients with ED and in healthy controls, to our knowledge this is the first report of a prolonged course of anodal tDCS applied over the left DLPFC on cases with treatment-resistant AN.
Table 1
Demographic and clinical data of anorexia nervosa

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>BMI</th>
<th>Age of onset of illness (years)</th>
<th>Duration of illness</th>
<th>Eating Attitude Test (EAT)</th>
<th>Eating Disorder Inventory (EDI)</th>
<th>Beck depression Inventory (BDI)</th>
<th>SSRI</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>23</td>
<td>F</td>
<td>15</td>
<td>20</td>
<td>3</td>
<td>64</td>
<td>80</td>
<td>39</td>
<td>10 mg/day</td>
<td>Anemia; GIT symptoms; nutritional deficiency; severe depression and fear of marriage</td>
</tr>
<tr>
<td>Patient 2</td>
<td>39</td>
<td>F</td>
<td>15</td>
<td>35</td>
<td>3</td>
<td>63</td>
<td>53</td>
<td>19</td>
<td>10 mg/day</td>
<td>Headache; anxiety; menorrhagia; nausea; vomiting; and mild depression</td>
</tr>
<tr>
<td>Patient 3</td>
<td>16</td>
<td>F</td>
<td>12</td>
<td>12</td>
<td>4</td>
<td>64</td>
<td>91</td>
<td>36</td>
<td>10 mg/day</td>
<td>Anemia; GIT symptoms; nutritional deficiency; and severe depression</td>
</tr>
<tr>
<td>Patient 4</td>
<td>24</td>
<td>F</td>
<td>17</td>
<td>20</td>
<td>4</td>
<td>61</td>
<td>90</td>
<td>29</td>
<td>10 mg/day</td>
<td>Severe depressive symptoms; intractable colon and fear of marriage</td>
</tr>
<tr>
<td>Patient 5</td>
<td>16</td>
<td>F</td>
<td>14</td>
<td>12</td>
<td>4</td>
<td>68</td>
<td>53</td>
<td>8</td>
<td>10 mg/day</td>
<td>Anxiety and headache</td>
</tr>
<tr>
<td>Patient 6</td>
<td>17</td>
<td>F</td>
<td>16</td>
<td>13</td>
<td>2</td>
<td>61</td>
<td>71</td>
<td>10</td>
<td>10 mg/day</td>
<td>Headache and anxiety</td>
</tr>
<tr>
<td>Patient 7</td>
<td>16</td>
<td>M</td>
<td>15</td>
<td>12</td>
<td>4</td>
<td>45</td>
<td>68</td>
<td>16</td>
<td>–</td>
<td>GIT symptoms; diastolic-delayed pulse; sense of neglect from his father and mild depression</td>
</tr>
</tbody>
</table>

GIT symptoms; Gastro-intestinal tract symptoms.
Fig. 1. shows the changes in the BDI score at the three assessment points; at base line (pre-session), after the end of the 10th session (post-session) and one month later (1 month). The 1st, 3rd and the 4th patients apparent decrease in BDI score post session, and continuous improvement month later was recorded. The 2nd, 5th and 6th patients show mild improvement at the end of session but returned to the base line after one month. The 7th patient records no changes in his score either post session or one month later.

Fig. 2. shows the changes in the EAT score at the three assessment points; at base line (pre-session), after the end of the 10th session (post-session) and one month later (1 month). The 1st, 3rd, 4th and 5th patients apparent decrease in EAT score post session, and continuous improvement month later was recorded. The 6th patient shows improvement at the end of session but returned to the base line after one month. The 2nd and 7th patients recorded no changes in their score either post session or one month later.

A part from transient local itching during the initial sessions of treatment in 2 patients there were no other adverse effects.

The main finding was that 10 daily sessions of anodal tDCS over the left DLPFC improved symptoms of both depression and AN for up to one month. Although the trial was not designed to examine the mechanism of any effect, our results support the initial hypothesis that excitatory anodal tDCS increased the excitability of the left DLPFC and restored interhemispheric balance with the overactive right DLPFC that has previously...
Table 2

| Eating disorders inventory subscales: baseline and follow up assessment post sessions and one month later |
|---------------------------------------------------------------|-----------------------------|-----------------------------|
|                                                                  | Presessions mean ± SD       | Post sessions mean ± SD      | 1 month mean ± SD         | Friedman test P value |
| Drive for Thinness                                              | 8.9 ± 2.9                  | 6.6 ± 2.9                   | 5.6 ± 4.4                 | 0.050                |
| Interpersonal distrust                                          | 11.3 ± 7.2                 | 7.9 ± 4.1                   | 6.7 ± 3.5                 | 0.024                |
| Perfectionism                                                   | 11.9 ± 4.3                 | 11.4 ± 4.4                  | 10.4 ± 4.4                | 0.15                |
| Bulimia                                                        | 15.0 ± 9.0                 | 15.0 ± 9.0                  | 15.0 ± 9.0                | --                  |
| Maturity fears                                                  | 7.7 ± 5.1                  | 6.7 ± 3.6                   | 5.4 ± 2.8                 | 0.07                 |
| Interoceptive awareness                                         | 9.3 ± 5.2                  | 6.6 ± 4.7                   | 5.4 ± 3.7                 | 0.006                |
| Body dissatisfaction                                            | 11.7 ± 3.5                 | 9.9 ± 4.3                   | 8.7 ± 5.1                 | 0.024                |
| Ineffectiveness                                                | 10.4 ± 6.6                 | 6.4 ± 5.7                   | 4.4 ± 6.1                 | 0.007                |

been reported in AN. The effects of tDCS might also be partially related to effects on distant structures connected with the site of stimulation and which are also involved in the pathophysiology of AN.

For example, one possibility is that effects of tDCS on dopamine release in striatum. Specifically, mesolimbic dopaminergic (DA) projections into striatum are hypothesized to regulate food intake by modulating appetitive motivational processes. Dopaminergic modulation through cortical stimulation has been shown before with tDCS (Nitsche et al., 2006) and rTMS (Strafella, et al., 2001). However, animal models of the role of dopamine in controlling appetite suggest that if tDCS had a similar effect it would be expected to reduce appetite and augment symptoms rather than lessen them.

A more likely link is that the improvement in symptoms is explained by reduced depression following treatment with tDCS. Anxiety, depression and obsessive compulsive disorder (OCD) are significant comorbidities with AN, and there is now a good deal of evidence suggesting that stimulation of DLPFC is an effective treatment for depression (Ferrucci et al., 2009; Loo et al., 2010; Nitsche et al., 2009). Indeed we found a significant positive correlation between the percent improvement in BDI and both eating rating scales (EDI and EAT). Interestingly the six patients who received SSRIs throughout the study improved in at least one scale while patient number 7, the only patient who was not receiving SSRIs had no improvement.

A possible confound is that SSRIs may themselves increase the response to tDCS. Facilitatory plasticity in visual cortex was increased by chronic selective serotonin reuptake inhibitor (SSRI) intake in healthy subjects, whilst inhibitory plasticity was converted into facilitation (Normann et al., 2007). A similar effect is seen in motor cortex. Citalopram increases and prolongs facilitatory plasticity induced by anodal tDCS, and converts inhibitory plasticity induced by cathodal tDCS into facilitation (Nitsche et al., 2009a). It is therefore possible that the patients here who received SSRIs were more likely to show an enhanced response to tDCS and therefore a more prominent treatment effect.

An important caveat to these data is that since this was an exploratory trial we did not include a control group and therefore any effect cannot be distinguished from a possible placebo. Nevertheless, given the difficulty in treating adolescence and adult AN, the positive results so far are reassuring and deserved to be followed by a future placebo controlled trial. Nevertheless the data do confirm other reported preliminary data. Van den et al., (2011) found reduced levels of feeling full, feeling fat and feeling anxious after single session of rTMS (10 Hz) delivered to the left DLPFC. The same was observed by McClelland et al., (2013) in two AN patients after 19–20 sessions. Finally, Downar et al., (2012) reported that a woman with severe, refractory bulimia nervosa (BN) underwent treatment for comorbid depression using rTMS of the dorsomedial prefrontal cortex. Unexpectedly, there was a rapid, dramatic remission from BN.

7.1 Limitations and recommendations of the study

This is a first pilot experiment with important limitations (no sham condition, small sample size, lack of body weight monitoring, and differences in baseline scores of outcome measures). However the results are promising. More work is needed with double blind randomized clinical trials and optimized protocols (for example the parameters of tDCS, the time of application, as well as identification of patients who may benefit the most) with longer follow-up.

8. Conclusion

Daily treatment with anodal tDCS over left DLPFC is feasible and safe in patients with AN. It may improve
symptoms of both AN and depression. The results suggest that it would be worthwhile conducting a larger double blind placebo controlled trial of DCS in AN.

Contributors

EMK contributed to study concept and design, acquisition of data, draft and revision of the report, statistical analyses, and interpretation of data. NAFl, AMN and MN contributed to study design, acquisition of data, statistical analyses and interpretation of data.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments

We are grateful to Dr. John Rothwell (Head of Sobell Research Department of Motor Neuroscience and movement Disorders, National Hospital for Neurology and Neuroscience, Queen Square, London, UK) for revision and comments on the manuscript.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References


