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TRANS-AURICULAR VAGUS NERVE STIMULATION IN THE TREATMENT OF RECOVERED PATIENTS AFFECTED BY EATING AND FEEDING DISORDERS AND THEIR COMORBIDITIES

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SUMMARY

Introduction: *Eating and feeding disorders (EFD's) represent the psychiatric pathology with the highest mortality rate and one of the major disorders with the highest psychiatric and clinical comorbidity. The vagus nerve represents one of the main components of the sympathetic and parasympathetic nervous system and is involved in important neurophysiological functions. Previous studies have shown that vagal nerve stimulation is effective in the treatment of resistant major depression, epilepsy and anxiety disorders. In EFD's there are a spectrum of symptoms which with Transcutaneous auricular Vagus Nerve Stimulation (Ta-VNS) therapy could have a therapeutic efficacy.*

Subjects and methods: *Sample subjects is composed by 15 female subjects aged 18-51. Admitted to a psychiatry community having diagnosed in according to DSM-5: anorexia nervosa (AN) (N=9), bulimia nervosa (BN) (N=5), binge eating disorder (BED) (N=1). Psychiatric comorbidities: bipolar disorder type 1 (N=4), bipolar disorder type 2 (N=6), border line disorder (N=5). The protocol included 9 weeks of Ta-VNS stimulation at a frequency of 1.5-3.5 mA for 4 hours per day. The variables detected in four different times (t0, t1, t2, t3, t4) are the following: Heart Rate Variability (HRV), Hamilton Depression Rating Scale (HAMD-HDRS-17), Body Mass Index (BMI), Beck Anxiety Index (BAI).*

Results: *Data analysis showed statistically significant differences between recording times ($p>0.05$) in HAM-D ($t0=18.28\pm5.31$; $t4=9.14\pm7.15$), in BAI ($t0=24.7\pm10.99$; $t4=13.8\pm7.0$) the reported values show how during (T0-T4) the treatment there are a decay of the degree in the depressive state, in the state of anxiety and an improvement in the value of BMI. In particular, the BMI in the AN-BN sub-sample had a minimum gain of 5% and a maximum of 11%. The analysis of H.R.V. did not show a significant changes among subjects thus confirming the discordance of the activity of the sympathetic and parasympathetic nervous system in EFD's.*

Conclusions: *Although the sample does not possess a relevant value to determine long-term efficacy of Ta-VNS or on a larger number of patients, this study reports how the application of neuro-stimulation in EFD's may become an ADD-ON in therapeutic approach. Indeed, substantial improvements are highlighted in the results and confirmed hypotheses proposed by the study.*

Key words: *anorexia nervosa - bulimia nervosa – neurostimulation - eating disorders – anxiety - depression*

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INTRODUCTION

Eating and feeding disorder's (EFD's) in according with the Diagnostic and statistical manual of mental disorders (DSM-5) divides the diagnostic groups in: anorexia nervosa (AN) disorder characterized by a recurrent reduction in caloric intake, loss of weight, obsessive fear of weight gain, dysmorphophobia, egosyntonic with the disease and the denial of related disorders, a body mass index below 16-16.99 kg/m^2; bulimia nervosa (BN) characterized by episodes of binge-eating where subjects consume an excessive amount of food in a limited period of time, subsequently implementing compensatory behaviours to try to contain the fear of weight gain, such as use: of laxatives, induction of vomiting, phisical exercise in an obsessive-compulsive way; binge-eating disorder (BED) behaviour characterized by constant episodes over time of food, but episode of binge eating without compensatory methods, this diagnostic category was also identified as psychogenic obesity.(American Psychiatric Association 2014). The EFD's in particular anorexia nervosa represent the psychiatric pathology with the highest rate of suicidal death and related pathologies. These types of psychopathologies have a deep root in human history, in particular in the history of the female gender. In fact, eating disorders have always a typically female connotation, starting from ancient Greece, to the Roman Empire, until the late Middle Ages where we can find biographical traces of subjects who use this behaviours to represent an ascetic life, but today this behaviours, we could identify them within a psychopathological classification (Bell 1987). Certainly, Richard Morton's contribution in 1689, he diagnosed for the first time in the history of medicine a EFD's in a patient who showed how these behaviours are based on states of psychological alteration (Martin 2004). The scientific literature and the phenomenological construction of the EFD's, in particular of the AN, was defined by Ernest Charles Lasègue in France and W.W. Gull in Britain. The two physician report in the article "Anorexie histérique" 8 clinical cases from the prodromal stages to the most advanced stages of the pathology, it is interesting how the two physician highlighted the same

connotations of the contemporary clinical-symptomatic construct of AN (Martin 2004). The large presence in the history of these disorders underlines and confirms their expanding epidemiological significance. In Europe, the rates of women with EFD's are: AN 1-4%, BN1-2%, BED 1-4% of the general population; In the USA. about 20 million women and 10 million men suffer from nutrition and nutrition disorders (Keski-Rahkonen 2016). The latest epidemiological studies for Italy indicate that in the female population the frequency of presence is about 0.3-0.5% (one case for 200-300 people) for anorexia nervosa and 1-2% (one case per 50-100 people) for bulimia nervosa. The constant missing data is that of the submerged data, that is, the subjects who are not diagnosed by the health systems, thus remaining outside of the epidemiological investigations without being able to demonstrate the magnitude of these pathologies (Udo & Grilo 2018). The other relevant trend in this pathologies, is that, in the last 20 years the distribution of gender: women has changed for the EFD's, changing from the previous ratio of 1: 10-1:15 to 1: 4. This data suggests to us how these pathologies no longer exclude the male gender, also highlighting the subtypes of the DAN such as vigorexia and orthorexia (Strother et al. 2012). Thus, even the age of onset during the past 20 years has changed, lowering the age of onset from adolescence or late adolescence to the pre-pubertal stages (Preti et al. 2009). The EFD's as reported in the literature (Griton & Konsman 2018) they have a comorbidity with other psychiatric disorders such as (Godart et al. 2007) mood disorders in BN subjects with values between 24.1-90%, in the AN 31-88% (Jordan et al. 2014).

The hypothesis we developed on the treatment of EFD's with trans-cutaneous electrical stimulation of the vagus nerve (Ta-VNS) has moved from the previous work of its application in the major depressive disorder and in refractory epilepsy (Kong et al. 2018) and in obesity, where this treatment has had positive medium-term post-treatment results (Brunoni et al. 2010). The vagus nerve, the tenth cranial nerve plays a fundamental role in regulating mood and regulating appetite (Bodenlos et al. 2007). The function of the vagus nerve allows communication between the efferent pathways from the body to the brain that are distributed bilaterally in the cerebral cortex, in the diencephalon, in the limbic system and in the insula; consequently, towards the afferent pathways, from the brain to the organs of our body such as: heart, stomach, lungs, esophagus (Bodenlos et al. 2014). In fact, as we note some efferent pathways of the vagus nerve play a fundamental role in the regulation of food intake, so, electrical stimulation trials of the vagus nerve have shown through BOLD investigations the functional modulation of the orbital frontal cortex, hippocampus, cerebellum and the striatum; typically areas involved in psychiatric diseases such as addictions and abstinence from substances (Val-Laillet et al. 2015). Certainly, further animal studies have shown how invasive vagal nerve stimulation (VNS) produces results on eating behaviours, thus supporting the hypothesis proposed by us. Human studies, report how Ta-VNS have a reduction in food-craving effect, probably because vagal innervation engages the limbic and dopaminergic areas of pleasure and appetite regulation (Val-Laillet et al. 2015). Further studies converge on the efficacy of Ta-VNS where it is reported how its use increases the levels of G.A.B.A. and norepinephrine in the brain, thus confirming its neuro-modulatory action of some target areas involved in EFD's (Steenbergen et al. 2015). Our hypothesis therefore moves on a double asset, by the stimulation of the vagus nerve trans auricularly without any kind of invasiveness, we are going to modulate the activity connected to the areas responsible for regulating mood and in the areas of regulation of nutrition (Bodenlos et al. 2007). Not least, we took into account the fundamental action that the vagus nerve implements on the regulation of the autonomic system in areas and organs of the sympathetic and parasympathetic nervous systems, two essential systems in the regulation of hemogenic expressions, maintenance body homeostasis and vegetative functions (Kong et al. 2018).

SUBJECTS AND METHODS

The participants involved in this study are subjects suffering from EFD's, patients hospitalized at "Villa Miralago" center for the treatment of eating disorders in Cuasso al Monte (VA). 15 volunteer patients from 19 to 51 years of age were recruited, they read and signed the informed consent. The exclusion criteria applied: heart problems such as bradycardia or hypotension, no cardiac implant and no other neuro-stimulation implant, no changes during trial of psycho-drug therapy. The subjects involved in the study following the diagnostical criteria in accordance with DSM-5: AN (N=9); BN (N=5), binge eating disorder (BED) (N=1) with psychiatric comorbidities: bipolar disorder type 1 (N=4), bipolar disorder type 2 (N=6), border line disorder (N=5). The device used for the Ta-VNS is the NEMOS of Cerbomed G.m.b.h. composed by a portable device that generates 0.8 mA-4.5mA electric current in accordance with previous experiments, the stimulation is carried out only in the left ear cup by means of a mobile electrode. The intensity of the discharge is based on the patient's skin sensitivity, the discharge is set at 200-300 μs at 25 Hz, with 30 seconds of activity and 30 seconds of pause with 4h sessions per day between meals and not during sleep. The protocol provides 2-month treatment with five examination (T0=recruitment; T1=first week; T2=5 weeks; T3=7 weeks; T4=9 weeks) in each examination the variability of heart function is recorded in two conditions: 4 min at rest and 4 min under cognitive stress, using linguistic and mathematical reasoning tests. The measurement of cardiac variability is carried out through a photopletysmograph on the index finger

of the left hand, so as to capture the pressure variation of the capillaries through infrared, representing the heart rate. Dedicated hardware and software for data recording are property of ELEMAYA s.r.l. specifically, the Heart & Emotion is a small computerized instrument that performs the analysis of the Heart Rate Variability (HRV), the Heart Rate, the balance between the Sympathetic and Parasympathetic system. The collected and extrapolated data are: the VLF (Very low frequency) frequencies from 0.001-0.04 Hz representing a part of the activity of the sympathetic nervous system; LF (Low frequency) 0.04-0.15 Hz which mainly corresponds to the regulation of baroreceptor activity; HF (High frequency) considered as the representative data of the parasympathetic system (Peschel et al. 2016). Following this recording, we administer the Beck anxiety inventory scale (BAI), a psychometric test for the assessment of the anxiety state, composed of 21 items, scores based on a 4-point likert-scale with values from 0-3, with a total score from 0 to 63. It is a self-administered test, with a high internal consistency (Cronbachs α=0.92) and an efficacy in the test-retest between weeks of 0.75. The guidelines for scoring the score report as follows: 0-9 anxiety-free state; 10-18 medium moderate state of anxiety; 19-29 moderate severe anxiety; 30-63 severe anxiety (Muntingh et al. 2011). Further investigation of mood disorder assessment, was investigated through the administration of the semi-structured interview of the Hamilton Depression Rating Scale (HDRS-17- HAM-D) with an internal consistency of 0.76 and a test-retest value of 0.74 (Virginia Guilléna et al. 2014). This test consists of 17 questions that investigate various symptoms of the depressive state with a score of 0-3 or 0-5 per question (Virginia Guilléna 2014). The scoring of the test is represented by the following indices: 0-9 no depressive state; 10-13 medium depressive state; 14-17 medium moderate depressive state; 18> moderate severe depressive state (Zimmerman et al. 2004). The data analysis was prepared through the use of the statistical analysis software S.P.S.S. v25 using the single-sample and coupled-sample T-test, setting the statistical significance to 0.05.

RESULTS

The scores shown in table 1 refer to the data collected in the recording of the average values of the HAM-D of the subjects during the treatment. As we can see, the variation of the initial values represent a "severe" depressive state within the sample, subsequently, at the end of the treatment the subjects report an average result of 9.14 per day below the clinical cut-off with a statistically variation significant within the sample ($p<0.015$). A percentage normalization of the data was also created, where 79% of the subjects in the time span of the treatment report a symptomatic remission of the depressive state.

Table 1. Average values of the HAM-D

HAM-D - t0	18.28±5.31
HAM-D - t1	14.00±5.16
HAM-D - t2	10.14±5.63
HAM-D - t3	10.40±7.59
HAM-D - t4	9.140±7.15

Table 2. Average values of the B.A.I.

B.A.I. - t0	24.70±10.99
B.A.I. - t1	19.80±11.00
B.A.I. - t2	17.28±11.64
B.A.I. - t3	16.00±10.21
B.A.I. - t4	13.80± 7.00

We used the same statistical method for the analysis of the B.A.I. It is also clear that in Table 2 the values of the variation within the group subjected to the treatment show a deflection of the anxiety state data with statistical significance ($p<0.01$). In the recruiting phase, the average group score is "moderate severe anxiety", but during the treatment we see a linear lowering of the test score, up to a "low average anxiety level" score. By applying a further statistical analysis, we were able to verify that within the individual recordings of each evaluation meeting, there is a significant variation in the score from the clinical cut-off set to score N=9, thus indicating an effective improvement during treatment and not only at the end of the treatment. The same normalization of the values of the change in the depressive state has been applied to the analysis of the B.A.I, where 84% of the subjects report a symptomatic remission of the anxiety state. The further analysis done for HRV did not report significant changes in the balancing of autonomic system, even if in some subjects between the beginning and the end of the treatment there is a decrease in the activity of the sympathetic nervous system during resting conditions, an index that it might make us suppose, as other articles report (Peana et al. 2014), that the Ta-VNS regulates the activation of the sympathetic system by inhibiting the hyper activation response that is manifested in subjects affected by the EFD's (Ogbonnaya & Kaliaperumal 2013). In addition, the regularization of parasympathetic activity in experimental stress conditions is recorded in particular at the end of the treatment, even without statistical significance. Other data that could suggest to us how in the states of emotional dysregulation and emotional disperception, in particular as reported in the literature, the hyperactivity of the parasympathetic system is an index present in subjects affected by BN - AN where there is an aberrant and chronic response in autonomic responses to emotional states (Meyer et al. 2016). Our data on the H.R.V. confirm the analysis of the Mazurak literature of 2011 where a lack of homogeneity of the HF/LF values is reported within the studies without a common agreement on which part of the autonomic system is most elicited or inhibited in the DAN.

CONCLUSIONS

This study has structural and methodological limitations, in fact we have a limited sample of subjects, without a control group and a gender bias. Another bias within the group is that the subjects involved being hospitalized in a psychiatric facility, carry out psychopharmacological and psychotherapy treatments; activities that could affect the data we collect. Also, it is true that the rapidity with which the subjects benefited from the treatment given by the Ta-VNS, usually does not occur in the subjects who did not participate in the study, but unfortunately, having not created a sham control group, we cannot say it but only suppose it. It has certainly been evident that our hypotheses based on previous works have occurred concluding that an add-on of a neuro-stimulation treatment can increase symptomatic remission in chronic patients with EFD's. This pilot study represents only the beginning of a possible consolidation in neuro stimulation treatments in hospitalization structures.

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Human rights statements and informed consent:

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients for being included in the study

Conflict of interest: *None to declare.*

Contribution of individual authors:

Yuri Melis wrote the manuscript, conducted the patient interviews and conducted all statistical analyses.

Emanuela Apicella, Marsia Macario & Giuseppina Bentivoglio are contributors.

Eugenia Dozio reviewed the final manuscript.

Leonardo Mendolicchio contributor and reviewed the final manuscript.

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