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Abstract

Purpose: Research applying the EEG to AN is still limited, even though in other psychiatric disorders it permitted to find out the allmarks of the disorder. The aim of the study was to explore whether EEG recorded basal activity and reactivity to musical stimulation differs in anorexia nervosa (AN) as compared to healthy subjects (HS).

Methods: Twenty female subjects (respectively 10 with AN and 10 HS) were administered a battery of psychometric tests and underwent EEG under three different conditions: 1) at baseline; 2) after a generic music stimulation; and 3) after a favorite music stimulation. EEGs of AN patients showed higher absolute amplitude of cortical slow waves (theta) in the parieto-occipital and temporal derivations, as far as for a deficit in the beta band.

Results: They showed a higher N100 latency and a reduced P300 latency compared to HS. While N100 and P300 latency was sensitive to the musical stimulus in HS group, the AN group showed no difference after music stimulation.

Conclusion: These data suggest that AN is accompanied by a state of brain hyperarousal with abnormal reactivity to environmental which is similar to the state of control subjects after musical stimulation. If confirmed, this finding may have treatment implications.

Keywords: *Anorexia Nervosa; EEG activity; slow waves; p300; hyperarousal; music therapy.*

Level of Evidence: Level III, Evidence obtained from well-designed cohort or case-control analytic studies

1. Introduction

According to the biopsychosocial model, Anorexia Nervosa (AN) results from the interaction of different factors, including biological, psychological and environmental ones [1]. The ever-increasing prevalence of the disease prompts more investigations in the search of innovative and more effective therapeutic strategies [2,3]. Experimental approaches of neurophysiological and neurofunctional neuroimaging, such as EEG or fMRI, have been applied to provide evidences for a greater understanding in the pathogenesis and evolution of these disease [4,5]. EEG studies in other psychiatric conditions, like schizophrenia, have shown some specific hallmarks of neuronal activity, such as an increased presence of delta (1-3 Hz) and theta (3.125-8 Hz) activity compared to the unaffected population [7]. Moreover, patients suffering from Major Depression showed a significant correlation between the subdomain of the motor slowdown and the presence of slow electroencephalographic activity, specifically alpha1 and theta 2 [8].

The evidence that some alterations in the frequencies of neuronal activity are specifically related to psychopathological alterations of mental disorders [9] may suggest that external stimulation that can interfere with these frequencies, like through TMS or tDCS, might be effective in modifying neuronal activity and possibly clinical symptoms [10, 11].

In recent years, the use of EEG methods has also been associated with experimental therapeutic protocols investigating the rationale for the use of music-therapy in patients with schizophrenia and major depression [12]. Specifically, the musical administration could have a therapeutic effect on the synchronization of encephalic rhythms and on the prefrontal-hippocampal plasticity involved in psychoticism and anxiety [13].

Concerning ED, research linking EEG with music-therapy is still limited. Some preliminary EEG studies in AN revealed theta waves patterns in frontal hemispheres of

these subjects, suggesting a cortical slow wave pattern in AN [14]. This alteration could be consequent to malnutrition as suggested by previous electroencephalographic studies [15]. Nevertheless, other authors hypothesized that the detection of low values in parieto-occipital delta waves and frontomedian alpha activity in AN patients compared to healthy controls may represent a specific neurobiological characteristic of this disorder and not exclusively a consequence of malnutrition [16]. This pattern could be connected to a slight frontal dysfunction or to a state of increased attention-vigilance [17]. Studies on Event-Related Potentials (ERPs) recording techniques showed second rate amplitudes and latency alterations in early and late ERPs evoked components among anorectic people [18], suggesting deficits in environmental stimuli categorization and selective attention shifting [19].

On the other hand, the evidence for therapeutic effects of music therapy in AN, is still limited even though there have been encouraging preliminiary reports 20). In particular, the use of music therapy in the treatment of AN may represent an useful adjunctive treatment to overcome resistances to treatment in these patients [2].

The aim of this preliminary study is to explore the EEG characteristics in a sample of female patients suffering from AN and to compare these features with those of healthy subjects. The second aim was to explore the effect of music stimulation on EEG activity in AN and healthy subjects and to examine the possible association between EEG and psychopathology characteristics.

2. Methods

2.1.Participants

Thirty female subjects (20 affected by AN and 10 healthy subjects) were enrolled for this study. Patients were recruited at the Outpatient Service of the Regional Expert Centre for the Eating Disorder of the University of Torino, AOU Città della Salute e della Scienza di Torino, between December 2016 and June 2017. All participants received a psychiatric examination to determine the presence or the absence of an eating disorder (specifically Anorexia Nervosa) using the Structured Clinical Interview for Diagnosis (SCID) for DSM-IV-TR, a tool that has fair to excellent inter-rater reliability on axis I and excellent on axis II diagnoses [21,22]. Inclusion criteria for the study were: 1) female sex; 2) BMI between 14 and 17; 3) age between 16 and 26 years; and 4) duration of illness < 1.5 years. Exclusion criteria were: a) intellectual disability, developmental or learning disorders; b) psychotic or neurological disorder (e.g., multiple sclerosis, stroke); c) history of dementia or severe head trauma; d) current acute psychotic condition or substance abuse; and e) history of hearing problems. The final group consisted of 10 patients affected by Anorexia Nervosa. A sample of 10 healthy controls matched for age and sociodemographic characteristics was recruited as control group.

Ethics

All recruited participants provided written informed consent to this study. All the procedures were conducted according to the 1995 Declaration of Helsinki as revised in Edinburgh in 2000. Study was approved by the Ethics Committee of AOU City of Science and Health, Turin (protocol number: 0089968).

2.2. Measures

All the participants completed a battery of self-administered psychometric tests including:

Toronto Alexithymia Scale (TAS--20) [23]: a 20-item questionnaire used to assess the level of alexithymia. This scale had a strong support for its reliability and factorial validity [24].

Barratt Impulsiveness Scale (BIS) [25]: used as a measure of the degree of subject's impulsivity. It showed good validity and reliability.

BDI-II [26]: this test is composed of two different scores, respectively related to the "Somatic--Affective" and to the "Cognitive" area of depressed mood. It shows a high internal consistency and content validity.

SCL-90 [27]: it is composed of 90 items assessing the presence and the severity of mental distress symptoms in different domains. Its psychometric properties support its validity as an instrument to assess the psychopathological profile [28].

Temperament and Character Inventory (TCI) [29]: this questionnaire provides an estimate of the personality structure of the subject, according to the neurobiological model proposed by Cloninger (1994). Its psychometric properties support its clinical usefulness in the assessing of personality psychopathology [30].

Emotion Regulation Questionnaire (ERQ) [31]: a 10-item questionnaire that evaluates the emotion regulation modalities implemented by the subject. It has shown acceptable validity and reliability.

Difficulty in the Emotion Regulation Scale (DERS) [32]: 36-item questionnaire measuring individual patterns of emotional regulation. It has shown excellent internal consistency and good test-retest reliability and construct validity.

2.3. EEG data acquisition

With the participant comfortably seated at a semi-recumbent position in a sound and light attenuated room, 40-minutes eyes-closed EEG recordings were obtained using a 19-channel EEG Analysis Station according to the Jasper International 10-20 System (33). According to this System, electrodes were placed at Fp2, F8, T8/T4, P8/T6, O2, F4, C4, P4, Fp1, F7, T7/T3, P7/T5, O1, F3, C3, P3, Fz, Cz, and Pz through a self-adhesive conductive paste.

First, a quantitative electroencephalographic (qEEG) recording was performed. Quantitative EEG (qEEG) is a method of analyzing electrical activity of the brain to derive quantitative patterns that may correspond to diagnostic information and/or cognitive deficits [33]. The peculiarity of qEEG is that it takes into account frequency and amplitude in a simultaneous and independent way. The qEEG allows 6 main frequency bands to be obtained, one for each electrode used, according to a Fourier spectral analysis. The electrodes record and transmit the surface potentials to a computer, which converts them (using an analog digital method) into graphic values and quantifies them (with spectral analysis on successive epochs of 2 sec) [34]. The qEEG recording was obtained in three different situations:

- at rest, with no musical stimuli;
- while listening to a standardized music, the same one for patients and controls [35];
- while listening to an individually selected track.

Prior to data analysis, artifact detection was performed to exclude eye-movements, head-movements, muscle-movements, and segments of decreased alertness. EEG recordings

were then exported using ELMIKO's EEG DigiTrak Analysis Software to the ASCII format for later processing.

2.4. P300 analysis

The P300 wave is an event related potential (ERP) component elicited in the process of decision making. It is considered a possible index of attention and processing capacity. According to literature, Odball Paradigm Method has been used to elicit event related potentials (ERP) [36]. According to this method, mix low-probability target items are mixed with high-probability non-target (or "standard") items: a P300 wave manifests itself in response to rare stimuli, called targets, dispensed in a random sequence that sees them alternated with more frequent stimuli, called non-target. The detection of P300 evoked potentials was performed in basal conditions, after listening to the standard musical stimulus, and finally after the individualized musical stimulus, using the Oddball Paradigm method.

2.5. Statistical Analysis

A parametric comparison of sociodemographic, clinical, personality and psychopathological characteristics was carried out with Student's t test to test for differences between patients with Anorexia Nervosa (AN) and Healthy Subjects (HN).

A nonparametric test using independent Mann-Whitney analysis was then performed on the qEEG variables, assuming as a null hypothesis the non-variation within the distribution between the absolute amplitude averages in patients and controls. A global measurement survey was initially carried out, including the set of measurements taken at

baseline, during standard musical stimulus and during individual musical stimulus. With regard to the event-related evoked potentials (p300), we conducted a Student's t test between patients and healthy controls concerning p300 in three different conditions according to our aim: 1) at baseline; 2) after a common musical stimulus; 3) after preferred individual musical stimulus. The intra-group variability was verified separately for both patients and controls using Student's t test for repeated measurements, in the three different phases of detection in order to verify a variation that should confirm or refuse the normalization observed in the intergroup comparisons. Finally, we performed a Pearson linear correlation between psychometric, clinical and EEG variables in order to detect possible correlations.

We considered the significance threshold of $p < 0.001$ for psychometric measures and $p < 0.05$ for EEG analysis.

3. Results

3.1. Clinical and psychopathological variables

Table 1 shows significant differences between patients and controls in cinical and psychopathological indices.

[Insert Table 1 here]

3.2. Quantitative EEG (qEEG) analysis and comparison between patients and controls

Significant differences in qEEG were found between AN and HS with higher values reported in AN regarding the following electrodes and waves: T3 (wave theta: $p<0.02$), T5 (wave alpha: $p<0.02$ and beta: $p<0.02$), P3 (wave theta: $p<0.05$), T6 (wave beta: $p<0.04$) e O1 (wave theta: $p<0.03$ and wave beta 1: $p<0.02$). (see Table 2).

[insert Table 2 here]

3.3. ERPs comparison between AN patients and controls in different conditions

ERPs comparison between AN and HS showed significant differences (see Table 3) at baseline in Lat Fz N1 ($t=3.18$; $df=2$; $p<0.000$) and p300 ($t=-1.99$; $df= 2$; $p<0.05$), after standard musical stimuli in Lat Fz N1 ($t=4.65$; $df= 2$; $p<0.01$) and p300 ($t=-2.54$; $df=2$; $p<0.02$) and after Individual Preferred musical stimulus in Lat Fz N1 ($t=3.36$; $df=2$; $p<0.001$).

[insert Table 3 here]

3.4. ERP intragroup comparison after musical stimulum

ERP intragroup comparison of different conditions showed significant differences between baseline condition and individual stimuli condition in HS group specifically in LatP3 Fz ($t= 2.32$; $df=2$; $p<.0.03$), Cz ($t=2.40$; $df=2$; $p<0.03$) and Pz ($t=2.03$; $df=2$; $p<0.05$), no significant difference was found in AN group (see Table 4).

[Insert Table 4 here]

3.5. Correlation between ERPs and psychopathological characteristics of the AN group.

A significant correlation was found between ERPs (see Table 5) and some psychopathological variables: TAS-20 ($r=0.60$; $p<0.001$), Expressive Suppression ($r=0.60$; $p<0.000$), Cognitive Instability ($r=0.60$; $p<0.000$), Impulsivity ($r=0.56$; $p<0.01$), and SCL-90 ($P=-0.46$; $p<0.04$).

[Insert table 5 here]

4. Discussion

4.1.Electroencephalographic baseline quantitative features of AN patients

Participants with AN differed from healthy controls for a higher absolute amplitude of cortical slow waves (theta) diffused in the parieto-occipital and temporal derivations, as far as for a deficit in the beta band. These may be a sign of brain suffering possibly due to reduced blood perfusion with respect to controls [37]. According to previous studies, this may be due to the low BMI [38], which has also be related to deficits in executive functions as reduced perfusion of temporal cortical areas has been associated with performance in visual-spatial executive tasks [39]. Neuroimaging studies have highlighted functional alteration of parieto-temporal regions in subjects with AN at the level of the left parahippocampal gyrus and the left fusiform gyrus [40]. Moreover, recent studies suggested a role of the parietal lobe in the development and maintenance of body image [41, 42]. Thus, as sustained by Smeets and Kosslyn [43], the temporal-parietal asymmetry observed in our AN sample may relate to distorted body image perception.

4.2. The baseline differences in N100 latency and the musical effect on N100 wave

Participants with AN displayed a significantly greater N100 latency at baseline, which may be related to a deficit in selective attention [44, 45] or to an increased state of arousal [46]. The latter interpretation would be consistent with the correlation of higher N100 latency to a dysfunction in the catecholamine production as evidenced by literature [47]. The basic between-group difference is maintained throughout the experiment and it is not significantly affected by the two musical stimulations, thus indicating that higher N100 latency is a stable characteristic of this population. This is consistent with the evidence of

high harm avoidance in our AN participants, which is a typical marker of trait-hyperarousal related to stable temperament features [48, 49].

The concomitant presence of time distribution differences and of a left asymmetry index supports the hypothesis of a difference in the processing of emotional information related to the musical stimulus in the AN participants. This would be consistent with the evidence of alterations in the functional limbic circuits involved in the processing of emotional information in anorexia nervosa [50]. A previous reports suggests that, in healthy subjects, musical stimuli produce an intense activation of the reward system at the limbic level [51]. Recent evidence ascribes this action to the recruitment of the accumbens nuclei [52], an area involved in the pathogenesis of affective manifestations of patients with AN [53]. However, in our study, the intra-group comparisons refutes the hypothesis that such activation can be effective in re-approaching the latency of N100 of the AN participants to that of controls by reducing their arousal level. The lack of pre- and post-stimulus differences also within the control group suggests a poor sensitivity of the N100 latency to the musical stimulus per se and reducing its relevance as a distinctive marker of AN participants emotional elaboration anomalies.

P300 wave between group differences

The latency of the P300 is significantly reduced in AN participants, in contrast with what found with the N100 latency. Multiple reports has linked this finding with hyper-arousal in cortical state and increased obsessiveness [54], traits which are both associated with AN. Indeed, some researchers have suggested that high obsessiveness and Increased vigilance constitute true and proper endophenotypes of the anorexic pathology that are present early at the subclinical level [55]. This means that healthy subjects in baseline conditions display low levels of vigilance and pay attention to different stimuli in a

different manner, proportionate to their relevance [56]. Instead, AN patients, and possibly also at-risk but not yet affected youngsters, tend to process stimuli with faster categorizations due to an increased state of vigilance. Their high alert levels bring their functioning closer to that of patients with Compulsive Obsessive Disorder and Panic Attack Disorder [54, 57].

AN subjects, therefore, would be more efficient in the categorization of external stimuli, but, in the long term, this increased level of activation could lead to a reduction in their ability to discriminate stimuli [58]. This discriminative deficit may include the subjects with AN in the ADHD spectrum, a frequently comorbid diagnosis which shares the hyperactivity as a common symptom [59].

4.3. Musical effect on P300 wave

The musical stimulus, therefore, seems not to act on AN participants who maintain the left hemispheric filter as general operation [60]. The absence of any specific response to individualized musical stimuli is further evidence of a poor discrimination ability in AN participants [58]. This alteration of the self-related functioning has been correlated to an altered resting-state activity in schizophrenic subjects. In particular the lack of sensibility to a stimulus related to the self supports the hypothesis of a poorer self-development in these subjects [61–63]. Possibly, therefore, the individual musical stimulus do not produce relaxation in subjects with AN, because of their high levels of alert. As a difference from controls, AN participants are more efficient in categorizing external stimuli as they are hypersensitive, not more relaxed. This could explain why in the long run the increased level of activation leads to a reduction in the ability to discriminate

between the external stimuli according to the neuropsychological theories that correlate the deficit in shifting selective attention to prolonged hyperstimulation conditions [5].

4.4. Correlation between the event-evoked components and AN features

Participants with AN showed a strong positive correlation between the latency of the N1 component at the frontal level and both the overall alexithymia and cognitive instability. The latency of the N1 component also positively correlates with increased impulsivity and emotional suppression. This supports the evidence that in eating disordered subjects the altered control of the selective attention is related with troubles in the management of emotional states [61]. Subjects affected with AN display a lack of confidence in managing and modulating negative emotions because of their deficit mechanisms of regulation and containment of negative affects [64]. Subjects with AN suppress the external manifestations of their emotions displaying a dysfunctional emotional regulation strategy. This is also consistent with the findings concerning the left asymmetry in quantitative analysis and in the typical characteristics of neurocognitive rigidity [65].

4.5.*Conclusions*

Our study reveals differences in the functioning of the left hemisphere of AN participants compared to healthy controls confirming the presence of some type of asymmetry in this population [60]. In parallel, the differences in N100 and P300 latency of the event-related evoked acoustic potentials assimilate the functioning of patients with AN to psychiatric disorders such as OCD because of the alterations in the shift of selective attention to external stimuli [2]. Such procedural dysfunction may represent an endophenotype of the AN that evoked potentials may precociously detect before diagnosis and track after treatments [55]. Their generalized hyperarousal and hypersensitivity that we called "the song of anorexia nervosa" may impair the responsiveness to those positive relational stimuli within the therapeutic relationship which should increase their self-esteem and favor the development of their self [61].

The combination of a higher latency of N100 and a low latency in P300 in front of the musical stimulus may represent a specific diagnostic marker for AN disorder. If further studies will confirm this result, it may potentially be used in prevention and early diagnosis and in addressing therapeutic approaches identifying subjects at risk of resistance or relapse [2].

Finally, the present results provide some neurophysiologic evidence to support the use music therapy to enhance traditional therapies in AN patients, but also point to some objective difficulties. Some recent report suggest a possible anxiolytic role of music therapy in AN patients [20]. Music therapy stimulates the frontal and limbic areas in the processing of the musical stimulus, activates the emotional and cognitive functions related to the reward system and may increase the inter-hemispheric connectivity [37].

Nevertheless, resistance mechanisms related to the hyperarousal and the difficulty in selective attention may oppose these effects. Thus it could be necessary to use specific frequency stimulation to overcome them.

4.6.Limitations

Our study is exploratory and preliminary. The results are promising, but a number of limitations must be taken into account, including the small sample size, uncertainty of localization and interpretation, which are typical of surface methods. Similarly, the lack of reference about electroencephalographic studies in psychiatry, and in the study of AN in particular, increases the interpretative difficulties of the findings. The study does not investigate the therapeutic effects of music therapy on AN or the possible beneficial implications of the addition of music therapy with respect to conventional psychotherapeutic or psychopharmacological methods. Future more structured research projects are needed to further test the efficacy of this adjuvant therapy. However, this is the first study exploring the effects of the music stimulation from a neurophysiologic point of view and correlating cognitive evoked potentials to psychopathology in participants affected by AN.

Author contribution

FA and AVS contributed to the conception and design of the study, patients' recruitment and data collection. FA, AVS, MM and SV contributed to the acquisition and to the analysis of data. FA, MM, BV, GAD and SF and contributed to the draft and revision of the manuscript.

Disclosure statement

The authors declare no conflict of interest.

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