Electrophysiological Neuroimaging using sLORETA Comparing 12 Anorexia Nervosa Patients to 12 Controls

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Abstract

Anorexia Nervosa (AN) is characterized by Diagnostic and Statistical Manual of Mental Disorders Volume 4 (DSM IV), as one's refusal to maintain a body weight that is above the calculated limit, which is determined by an algorithm involving one's height and weight. As more emphasis in society is placed on one's body image and appearance there has been an increase in the prevalence of this disease. Previously, the sole diagnostic imaging modality was fMRI. Studies determined that there was reduced blood flood in the Parahippocampal Gyrus, and Left Fusiform Gyrus, of those afflicted with AN. Electroencephalography (EEG) was utilized as an alternative imaging modality that was more cost effect. It was determined that the activated regions localized on the fMRI study coincided with those highlighted on the EEG report and previous fMRI studies. The goal of this study was to determine a more cost effective way to earlier detect a diagnosis of AN. The desired outcome would be for patients afflicted with AN to be diagnosed and treated at an earlier stage, increasing their overall long-term survival.

Keywords: Anorexia; Parahippocampal Gyrus; Fusiform Gyrus; sLORETA; Neuroimaging

1. Introduction

Anorexia Nervosa (AN) is classified as an eating disorder whose prevalence has increased in industrialized countries, particularly where there is a strong sociological correlation between attractiveness and thinness (Fairburn and Harrison, 2003). According to the Diagnostic and Statistical Manual of Mental Disorders Volume 4 (DSM IV), the criteria for the proper diagnosis of AN involves the refusal of one to maintain body weight at or above the minimally determined appropriate weight for one's age and height (Mitchell et al., 2005). The specified criteria in the DSM IV states that AN can be categorized as weight loss that leads to the maintenance of a body weight that is less than 85% of the standard calculated value. Additionally, AN can be diagnosed after a patient has failed to make expected weight gain during a crucial growth period which results in a weight that is less than 85% of the standard calculated value (Wilfley et al., 2007). Those afflicted with AN psychologically demonstrate an intense fear of gaining weight and becoming "fat;" even though, by every definition, this patient is underweight. Unfortunately, these patients often underestimate the severity of this condition and tend to not seek treatment in a timely manner and have concurring body shape disturbances.

As more emphasis has been placed on one's body image, the prevalence of AN has continued to increase (Simpson, 2002; Smink et al., 2012). Unfortunately, the distinctions between the rapid increase of afflicted patients and scientific breakthroughs in diagnostic testing have not been made. Although it is speculation that this large influx of afflicted patients is due to the increased ability of the medical community to identify cases, it can neither be confirmed nor ruled out.

Anorexia nervosa manifests across the world but in recurring demographics (Smink et al., 2013). There is a higher prevalence of AN in a child born to older parents rather than those in their prime childbearing years. People who tend to procreate later in life tend to be of a higher socioeconomic status (SES), but conversely these people have an increased risk of genetic mutations in their gametes. These mutations increase the prevalence of physical and psychiatric disorders such as AN (Bulik et al., 2007). Additionally, the age of onset usually begins before puberty and extends into early adulthood. AN patients tended to have a birth weight that was outside the normal range with a statistical ratio of females afflicted with AN exceeds male cases 4:1 (Halmi). AN can also be correlated with one's SES. Generally, race does not predominantly influence this disease; however, there is a positive correlation between the SES of a family and the risk for their child to develop AN (Andersen and Hay, 1985).

Anorexia Nervosa has illustrated a positive correlation with premature birth. Neonates born before week 32 of gestational pregnancy are at an increased risk of developing AN compared to those reaching full term. This risk is exacerbated when the premature birth is associated with a lower birth weight than normal (Cnattingius et al., 1999). Often times it is difficult to compile a care plan for patients afflicted with an eating disorder. There needs to be a proper balance between physical, psychological, and service interventions so that there can be a positive influence on the patient's long-term outcome. Due to the fact that the majority of one's treatment is specifically designed for the individual, many aspects like support system, age of the patient, level of risk, complications and motivation need to be taken into account. Patients diagnosed with anorexia nervosa tend to be treated in secondary care after an initial trial of out-patient care. The goal is to work in a step by step fashion until the patient is capable of taking care of themselves without the supervision of a health care provider ((NICE), 2009; Rosen, 2010).

Additions are a set of subjective criteria that act as warning signs and symptoms so AN can be properly identified. These positive symptoms include dry skin that maintains a yellowish cast, hair and nails that become brittle, mild anemia, muscle wasting, which includes cardiac muscle, severe constipation, hypotension, decreased respiratory and heat rates, a decrease in one's overall core temperature, depression, lethargy, osteopenia, and osteoporosis. Most notably, patients with AN have been recorded with hypercholesteremia despite a diet of low cholesterol and fat (Ohwada et al., 2006). Statins, the appropriate standard of care, have been administered to lower the patients' cholesterol via inhibition of HMGCoA reductase, which is a responsible for the production of cholesterol (Edwards and Moore, 2003). Additionally, it is documented that these patients have taste aversion for foods containing both high cholesterol and fats, particularly meat (Blechert et al., 2011). This condition and prevalence of vegetarian diet among AN patients has been associated with low serum levels of zinc and iron (Casper et al., 1980). Low serum levels of zinc could be attributed to decreased absorption of dietary zinc in AN patients (Dinsmore, 1985). Administration of zinc has eradicated this taste aversion towards meat, and the patients have regained appetite and taste for these foods, resulting in zinc and iron serum returning to their normal range. This increase in appetite has led to weight gain in these patients (Esca et al., 1979). Although all of these symptoms and signs do not have to be present to confirm a case of AN, they are helpful clues in identifying this disease.

In order to better understand and confirm a diagnosis an imaging modality is often utilized. Functional magnetic resonance imaging, (fMRI) has been the preferred method regarding data analysis of AN patients due to the technique's ability to gather information concerning specific areas of the brain. This method is performed by measuring and monitoring changes in cerebral blood flow within a particular region. AN patients exhibit abnormal activity and neural processing in various regions of the brain. In order to delineate the circuitry dysfunction in these patients, a network based analysis is utilized. The goal of neuro-imaging in AN patients is to isolate the abnormal activity in specific regions to better understand how to diagnose and treat the disease.

Previous studies using fMRI have highlighted several regions and pathways that exhibit similar activity in the majority of AN patients (Sachdev et al., 2008; Santel et al., 2006; Suchan et al., 2013).

Aside from fMRI studies, localizer scan studies have indicated a high level of activation in the fusiform gyrus, as well as the inferior, temporal and occipital lobes of the brain. In a previous study by Lask et al. (Lask et al., 2005), seventy-five percent of patients that had early-onset AN demonstrated unilateral blood flow reduction within the temporal lobe of the brain. Even though no evidence directly correlated the decreased blood flow with the psychopathology of AN, there was a correlation between impairments of the visual system regarding complex visual memory and visio-spatial ability.

Secondary to these findings, activity has been indicated in the parietal lobe, inferior frontal gyrus, and middle occipital gyrus. A study conducted by Nico et. al. (Nico et al., 2010) highlighted that the abnormalities within the parietal cortex play a significant role in the progression of AN due to the fact that the parietal cortex controls body representation. Additionally, the insula cortex was observed to display abnormal activity in AN patients. The insula cortex, the hub of visceral memory, taste perception, and appetite regulation, lies inferior to the frontal lobes. This particular area displayed higher than baseline activity during times of hunger and before food intake. This documented activity indicates the role of these regions in relaying information regarding appetite between the hypothalamus and frontal lobes. It has been documented that AN patients display diminished or completely lack hunger cues, which could be linked to insula dysfunction. Unfortunately, screening for insula dysfunction in AN patients using fMRI is not a viable option. Other methods to assess insula dysfunction are essential to better diagnose AN patients.

The Standard Low Resolution Brain Electrotomography (sLORETA) using electroencephalography (EEG) was trialed as an alternative, more cost effective, way to accurately diagnose the affected cortical areas (Pascual-Marqui, 2002). It is necessary to quickly and accurately identify areas of the brain that correlate with specific characteristics of AN. In doing so, treatment options can be properly identified and targeted for a specific finding on the EEG report.

EEGs are generally recorded from nineteen electrode channels that monitor the neural oscillations of the brain by measuring the summation of the synchronous activity. This modality will record the differences in synchronized and desynchronized cortical activity. Nineteen individual leads are placed in a specific pattern on the patient's scalp, and the activity is monitored during rest or while the patient follows a protocol. Both are performed to monitor a cortical response. The three main waves seen on the EEG report are delta, theta, alpha frequencies, and beta frequencies. Theta waves, which are a focal point of this study, are increased in those patients afflicted with AN. The correlation between theta waves and AN have been associated with other abnormal findings, such as decreased alpha waves (Hatch et al., 2011). The authors of this study intend to facilitate the objective diagnosis of AN using the combination of fMRI and EEGs in order to expedite the treatment of patients and speed recovery. While long term recovery from AN ranges from 44% to 76%, a low baseline weight is among the most important factors in indicating a poor prognosis; therefore, it is beneficial to search for a more efficient diagnostic process in order to catch this disease before it leads to severe weight loss.

The intention of this study would like to facilitate the objective diagnosis of Anorexia Nervosa using routine EEG recordings in order to expedite the identification of biomarkers in these patients and therefore hopefully decrease recovery time. Long-term recovery from AN ranges from 44% to 76%, with an important indicator for a poor prognosis being a low baseline weight (Rosen, 2010; Smink et al., 2012, 2013). The earlier the medical community can properly diagnosis this disease and avoid an excessive loss of weight in the patient, the higher the possibility that those afflicted will have a better prognosis regarding long term recovery.

2. Methodology

This study was a retrospective chart review of the electroencephalogram database at the Neurophysiology Unit at the Medical University of Lublin's Department of Psychiatry. All patients were diagnosed by a board-certified Psychiatrist using the diagnostic criteria from the International Statistical Classification of Diseases and Related Health Problems (ICD-10) section on Mental, Behavioral, and Neurodevelopmental Disorders.

During the patient's electroencephalogram selection, we selected EEG records from 15 patients, all females, diagnosed with Anorexia Nervosa (ICD-10 Code F50.00) with an average age (standard deviation) of 24 ± 8.2, and compared them to 12 healthy controls with an average age of 23.5 ± 5.9 years. This research protocol was approved by the Bioethical Commission of the Medical University of Lublin.

All patients and control participants were comfortably seated at a semi-recumbent position in a sound and lighted attenuated room, while 20-minutes or more of routine eye-open and eyes-closed resting EEG data were recorded using the 19-channel EEG Analysis Station (ELMIKO Medical, Poland) and Ag/AgCl electrodes. Patients EEG recordings were in accordance to the international 10/20 system with electrodes 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. Electrodes were referenced to linked earlobes and impedances were kept below 5 kΩ. The data sampling rate was 250 Hz, and the acquired signals were filtered with a band-pass filter of 0.15–70 Hz after sampling. Prior to data analysis, artifact detection was performed, visually, 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.

Following the export of the ASCII formatted data from the ELMIKO EEG acquisition system; 3-minutes of eyes-open EEG signals were recomputed to the average reference. Subsequently, spectral analysis was performed for the same 3-minutes of artifact-free data of each ICD-10 diagnostic group. The cross-spectra were averaged across the 50% overlapping windows, which yielded 7 EEG frequency bands: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18 Hz), beta-2 (18.5–21 Hz) and beta-3 (21.5–30 Hz) (Kubicki et al., 1979). Lastly, LORETA was used to estimate the 3-dimensional intracerebral current density distribution (Pascual-Marqui, 2002; Pascual-Marqui et al., 1994).

3. Results

The findings of the sLORETA analysis indicated that, the difference is statistically significant (p=0.03) using a one-tailed t-test: Anorexia > Controls. The brains of the patients with Anorexia Nervosa illustrated decreased neuronal activity in the Left Fusiform Gyrus and the Left Parahippocampal Gyrus (p=0.03) in the resting-state brains when Anorexia Patients were sitting for 3min, as compared to the Controls sitting for 3minutes. The identified Montreal Neurological Institutes three-dimensional and Talairach coordinate systems, the Voxel-value, Brodmann Area, Lobe, and Structural results are identified in Table 1 below.

Results from the sLORETA imaging indicates decreased neuronal activation within the Left Fusiform Gyrus located in the Temporal lobe and Parrahippocampal gyrus, which is located in the Limbic Lobe (Table 1). This correlates with other fMRI findings where patients with early onset AN have exhibited reduced unilateral blood flow in the temporal lobe. The Parahippocampal and Fusiform Gyri are centers that process emotions. Previous studies in which these regions have shown activation involve women that have distorted perceptions of their bodies from a cognitive perspective (Santel *et al.*, 2006). It is apparent from our findings that the Fusiform Gyrus may play a vital role in the processing of visual appearance of the human body. There is also a correlation with the somatosensory limbic pathway in the limbic lobe, due to the similarity of function.

Table 1: sLORETA results of Montreal Neurological Institute (MNI) coordinates, the voxel t-statistc, Brodmann Area, and neuroanatomical location in the Anorexia Nervosa patients.

X (MNI)	Y (MNI)	Z (MNI)	Voxel Value t-value	BA	Lobe	Neuroanatomical Location
-30	-35	-15	-1.15E+00	37	Temporal Lobe	Fusiform Gyrus
-30	-50	-20	-1.14E+00	37	Temporal Lobe	Fusiform Gyrus
-35	-35	-25	-1.14E+00	20	Temporal Lobe	Fusiform Gyrus
-35	-35	-20	-1.14E+00	20	Temporal Lobe	Fusiform Gyrus
-30	-45	-15	-1.14E+00	37	Limbic Lobe	Parahippocampal Gyrus
-25	-45	-15	-1.14E+00	37	Limbic Lobe	Parahippocampal Gyrus
-30	-30	-20	-1.14E+00	36	Limbic Lobe	Parahippocampal Gyrus
-45	-80	-15	-1.13E+00	18	Occipital Lobe	Middle Occipital Gyrus
-45	-85	-5	-1.13E+00	19	Occipital Lobe	Middle Occipital Gyrus
-45	-80	-10	-1.13E+00	19	Occipital Lobe	Inferior Occipital Gyrus
-40	-85	-15	-1.12E+00	18	Occipital Lobe	Inferior Occipital Gyrus
-35	-25	10	-1.12E+00	13	Sub-lobar	Insula
-35	-25	15	-1.10E+00	13	Sub-lobar	Insula
-35	-30	15	-1.10E+00	13	Sub-lobar	Insula

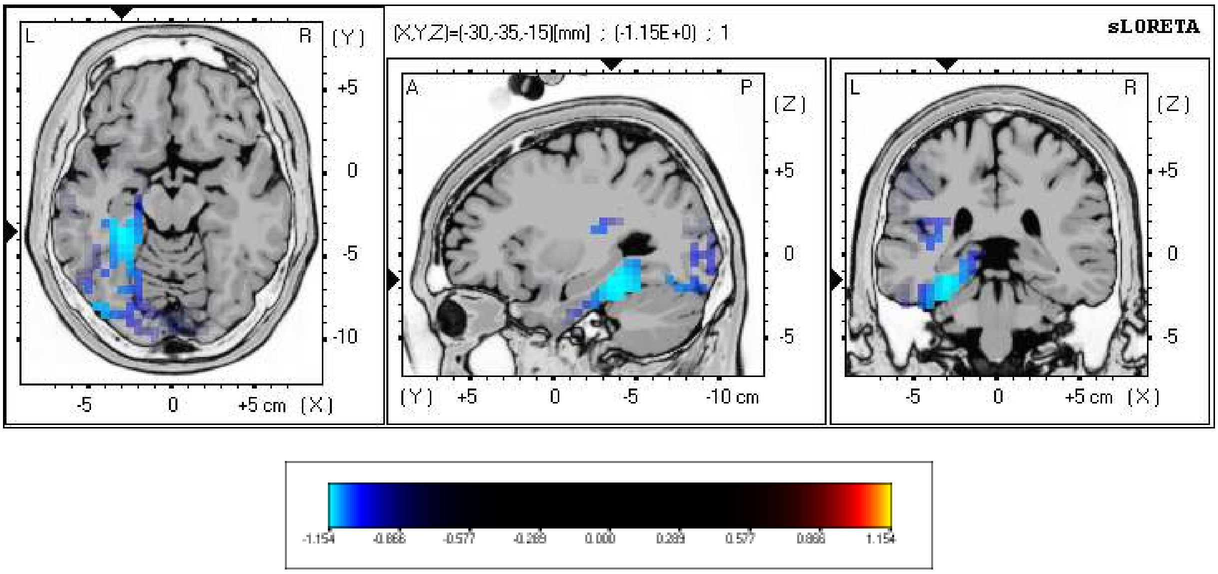

Figure 1: sLORETA imaging results of Resting State EEG Supra-Threshold Voxels in both the Parahippocampal (limbic) and Fusiform (temporal) Gyri illustrating decreased neuronal activity in the Anorexia Nervosa patients relative to Control participants.

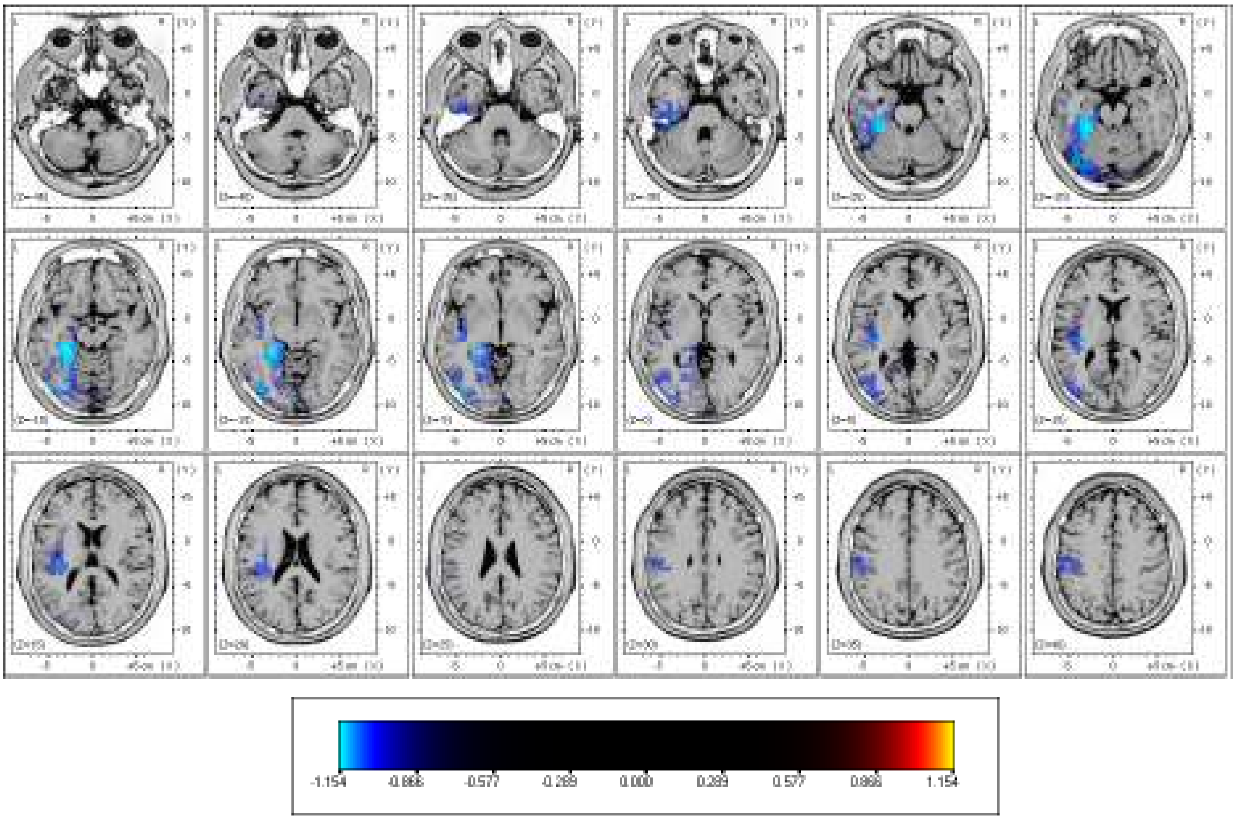

Figure 2: All axial slices of sLORETA imaging results of Resting State EEG Supra-Threshold Voxels in both the Parahippocampal (limbic) and Fusiform (temporal) Gyri illustrating decreased neuronal activity in the Anorexia Nervosa patients.

4. Discussion

Anorexia Nervosa is a disease that is becoming more prevalent within societies that link one's beauty with a low weight and small figure. There have been a number of correlative studies that address socioeconomic status, premature birth, DSM IV criteria, along with care plans for those diagnosed, in an effort to pinpoint diagnosis and treatment of this disease at an earlier stage. Although this data has led to a revolutionary understanding of this disease, it has not been the diagnostic breakthrough that is necessary. Normally, an fMRI study was used to highlight the cortical areas that displayed reduced blood flow in AN patients. However, this method tends to be costly and has not demonstrated early detection of the disease. After this research had been conducted it was discovered that, like fMRI studies, the Parahippocampal Gyrus and Left Fusiform Gyrus showed high activation. This allows the authors to conclude that similar results can be calculated using an EEG to display reduced blood flow in the cortical areas associated with Anorexia Nervosa. It is our hope that with this more cost effective diagnostic tool, patients afflicted with AN can be diagnosed and treated in a more timely manner, therefore increasing their chances for long-term survival.

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6. Conflicts of Interest

The authors declare no conflict of interest.

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