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DOTTORATO DI RICERCA IN FISIOLOGIA
Ph.D. in Physiology

Novel computational clectroencephalographic methodologies for autism management and epileptic seizure prediction

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To my dearly missed father
My future wife Krystle, for believing in me
My mother and the rest of my family,for their ongoing support
And to my mentor Prof Paolo Cavallari, for being there all along

SUMMARY

FOREWORD

During my PhD studies I have dealt with a number of novel methodologies associated with electroencephalography and their use in order to help both children and adults on the Autism Spectrum and to aid people suffering from Epilepsy. This study has built on a very wide collection of literature from a number of allied disciplines ranging from computing to psychiatry and physiology.

This dissertation was conceived with three different sections in mind, these being the Recording of brain activity in humans, Autism and Epilepsy. In order to better arrange the information presented and to create emphasis, a supplementary section on history was enclosed in a grey box and more technical section on EEG was put in a red box.

The dissertation delved into the background of each of the three sections, with a thoroughly analyzed literature review, before exploring a novel methodology for neurofeedback based on a sonified principle, in order to help patients on the Autism Spectrum. This method is based on a number of previous studies that clearly show a very complex neurophysiological picture in people with ASD, including very high delta wave activity retrieved from EEG recordings in *awake* autistic children (Wang et al, 2013). Adopting the same approach of EEG analysis and clustering, we also looked at the correlation of autism and the high incidence of epileptic discharge of these subjects. We looked separately at patients with Epilepsy and worked on a novel methodology to analyse epileptic seizures with a very similar methodology of clustering data and building neural networks to be able to predict/anticipate these seizures by looking at the accumulative power of these intertwining networks. In this case we built on previous studies by Scaramelli and Braga (2009) that defined seizure specific features.

This study will hopefully lay the foundations for a new way of looking at electroencephalographic representations and to be able to more effectively use such data for therapeutic and predictive measures, having faster and more reliable monitoring outcomes.

RECORDING OF BRAIN ACTIVITY IN HUMANS

Electroencephalography (EEG)

The electroencephalogram (EEG) is defined as electrical activity of an alternating type recorded from the scalp surface after being picked up by metal electrodes and conductive media (Deco, Jirsa, & McIntosh 2011). An electroencephalography or the EEG is measured directly from the scalp's surface. The depth probes are called electrograms. Thus, electroencephalography can be applied repeatedly to patients, healthy adults, and children with virtually no risk or limitation as it is a non-invasive procedure (Deco, Jirsa, & McIntosh 2011).

Local current flows are produced when brain cells (neurons) are activated. EEG measures the currents that flow during synaptic excitations of the dendrites of many pyramidal neurons in the cerebral cortex. Differences of electric potentials are due to the summed post synaptic graded potentials from pyramidal cells that create electrical dipoles between soma (body of neuron) and apical dendrites (neural branches). Brain electrical current consists mostly of Na^+, K^+, Ca^{++}, and Cl^- ions that are pumped through channels in neuron membranes in the direction governed by membrane potential (Deco, Jirsa, & McIntosh 2011). The comprehensive microscopic picture is more sophisticated, including different types of synapses involving variety of neurotransmitters. Recordable electrical activity on the head surface can only be generated with large populations of active neurons. Between electrode and neuronal layers the current penetrates through skin, skull and several other layers (Deco, Jirsa, & McIntosh 2011).

Even weak electrical signals detected by the scalp electrodes are massively amplified, and displayed on paper or stored to computer memory. EEG has been found to be a very powerful tool in the field of neurology and clinical neurophysiology, due to its capability to reflect both the normal and abnormal electrical activity of the brain (Deco, Jirsa, & McIntosh 2011).

History
Throughout more than a hundred years of its history, encephalography has undergone immense progress. The existence of electrical currents in the brain was discovered in 1875 by an English physician Richard Caton. He observed the electrical currents from the exposed brains of rabbits and monkeys (Herrmann et al. 2015). In1924 Hans Berger, a German neurologist, used his ordinary radio equipment to amplify the brain's electrical activity measured on the human scalp. He reported that even weak electric currents generated in the brain can be recorded without opening the skull, and illustrated graphically on a strip of paper. He further observed the activity that changed the functional status of the brain, such as in sleep, anaesthesia and lack of oxygen in certain neural diseases, such as in epilepsy (Herrmann et al. 2015).
Hans Berger laid the foundations for many of the present applications of electroencephalography. He also used the word electroencephalogram as the first for describing brain electric potentials in humans. He was correct when he suggested that brain activity changes in a consistent and recognisable way when the general status of the subject changes, as from relaxation to alertness (Herrmann et al. 2015).

EEG recording Techniques

Encephalographic measurements employ a recording system which consists of electrodes with conductive media, amplifiers with filters, A/D converter and recording devices (Allen, Josephs, & Turner 2000). Electrodes read the signal from the head surface. Microvolt signals are amplified into the range where they can be digitalised accurately. Analog signals are changed to digital form by a converter, and personal computer (or other relevant device) stores, and displays obtained data (Allen, Josephs, & Turner 2000). Scalp recordings identified as the EEG of neuronal activity in the brain, allow measurement of potential changes over time in the basic electric circuit conducting between a signal (active) electrode and reference electrodes. An extra third electrode, called ground electrode, is needed for getting differential voltage by subtracting the same voltages showing at active and reference points (Allen, Josephs, & Turner 2000).

Minimal configuration for mono

Channel EEG calculation consists of one functioning electrode, one (or two specially linked together) reference and one ground electrode. The multi-channel configurations can be of up to 256 active electrodes (Allen, Josephs, & Turner 2000).

Recording electrodes

The EEG recording electrodes and their proper function are critical for acquiring appropriately high quality data for interpretation. Many types of electrodes exist, often with different characteristics (Allen, Josephs, & Turner 2000). Basically there are the following types of electrodes: disposable (gel-less, and pre-gelled types), reusable disc electrodes (gold, silver, stainless steel or tin), head bands and electrode caps. Others include saline-based electrodes and needle electrodes (Allen, Josephs, & Turner 2000). Electrode caps are preferred for multi-channel montages with a number of electrodes installed on its surface. The scalp electrodes, commonly used consist of Ag-AgCl disks, 1to 3mm in diameter, with long flexible leads that can be plugged into an amplifier. The AgCl electrodes can record the very slowest changes in potential. Needle electrodes are used for long recordings and are invasively inserted under the scalp (Allen, Josephs, & Turner 2000).

Brain Wave Classification

To obtain basic brain patterns of individuals, subjects are advised to close their eyes and relax. The patterns of waves in the brain are commonly sinusoidal. Usually, they are measured from peak to peak and range from 0.5 to100 microvolts in amplitude, which is about a hundred times lower than ECG signals. By applying Fourier transform, the power spectrum from the raw EEG signal is derived (Shaker 2007). In power spectrum contributions of sine waves with different frequencies are visible. Although the spectrum is continuous, up to one half of sampling frequency, the brain state of the individual may make certain frequencies more dominant (Shaker 2007). Brain waves have been categorised into four basic groups as below.

The famous and heavily studied pattern of the human brain is the alpha rhythm (Williamson, 1997). Alpha waves can be usually observed better in the dorsal occipital regions with typical size about 50 µV peak to peak. Alpha wave activity was observed to also significant between axial and inner regions in comparison to other regions (Shaker 2007). Alpha activity is instigated by closing the eyes and by relaxation, and stopped by becoming alert and by any

mechanism like thinking, calculating or eye opening. "Eye closing" instances, are remarkably sensitive to the occurrence of alpha waves for most human beings. For example, when they close their eyes their wave pattern significantly changes from beta to alpha waves (Shaker 2007). The exact origin of the alpha rhythm is still not recognised. Alpha waves are generally held responsible for summated dendrite potentials. Summed up potentials (e.g. generated in brain stem) often include of fibre potentials (axonal) and synaptic elements (Shaker 2007).
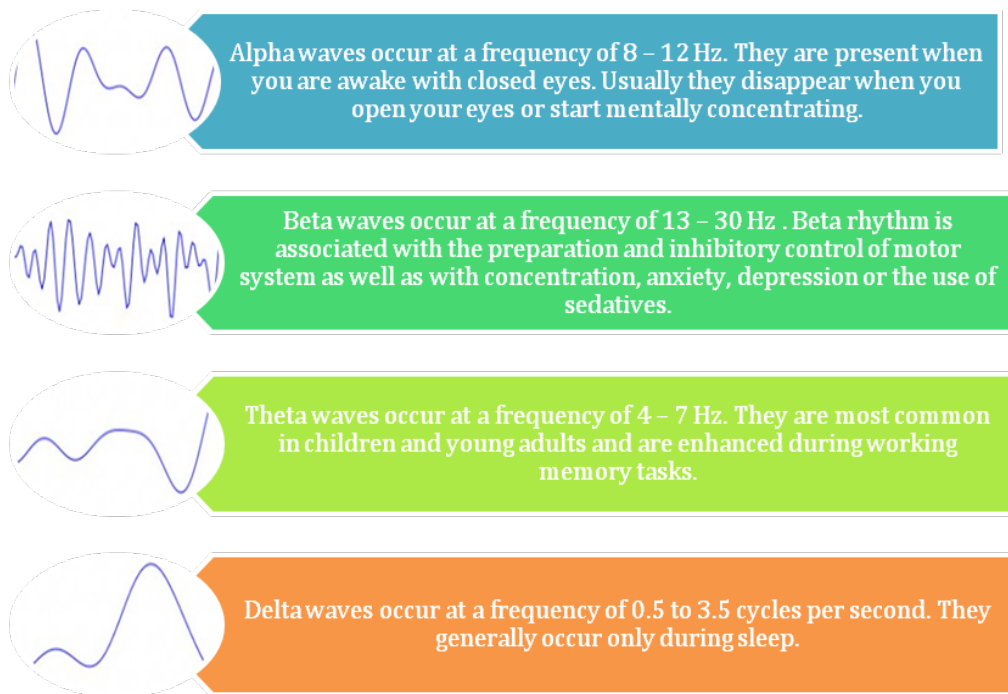
Alpha waves occur at a frequency of 8 – 12 Hz. They are present when you are awake with closed eyes. Usually they disappear when you open your eyes or start mentally concentrating.

Beta waves occur at a frequency of 13 – 30 Hz . Beta rhythm is associated with the preparation and inhibitory control of motor system as well as with concentration, anxiety, depression or the use of sedatives.

Theta waves occur at a frequency of 4 – 7 Hz. They are most common in children and young adults and are enhanced during working memory tasks.

Delta waves occur at a frequency of 0.5 to 3.5 cycles per second. They generally occur only during sleep.

figure 1: brainwave classification of Alpha , Beta , Theta and Delta wave frequencies

EEG is responsive to a continuum of states ranging from a stress condition to awareness, relaxing, hypnosis, and sleep. Beta waves are dominant during the normal state of wakefulness with open eyes. During sleep the power of lower frequency band increases due to relaxation or drowsiness. Sleep is commonly divided into two types: non rapid eye movements sleep (NREM) and rapid eye movement REM sleep. NREM and REM happen in alternate cycles. NREM is further divided into stage I, stage II stage III, and stage IV. The last two stages correspond to deeper sleep, where slow delta waves show higher magnitude. With slower dominant frequency responsiveness to stimuli subsides.

Different regions of the brain do not emit the same brain wave frequency synchronously. An EEG signal between electrodes placed on the scalp consists of many waves with different characteristics. Large amount of data received from even one single EEG recording presents a difficulty for interpretation. Individual's brain wave patterns are unique. In some cases, it is

possible to differentiate persons only according to their typical brain activity. For example, a higher activity in their frontal left and frontal right hemisphere is demonstrated among subjects who value themselves as rational types or as holistic / intuitive types (Ergenoglu et al. 2004).

Applications

EEG's biggest benefit is speed. Within fractions complex patterns of neural activity can be recorded a second after a stimulus has been administered. EEG provides fewer spatial resolutions compared to MRI and PET. Thus for better measures within the brain, EEG images are often integrated with MRI scans. EEG can establish the relative intensities and locations of electrical activity in different brain regions (Allen, Josephs, & Turner 2000). According to R. Bickford (1989) research and clinical applications of the EEG in humans and animals are used to monitor alertness, coma and brain death; find areas of damage following head injury, stroke, tumour, etc.; examine afferent pathways (by evoked potentials); and observe cognitive engagement (alpha rhythm). Others include showing of biofeedback situations, alpha, etc., check anaesthesia depth ("servo anaesthesia"); and examine epilepsy and locate seizure origin (Allen, Josephs, & Turner 2000). It further reveals test on epilepsy drug effects; aid in experimental cortical excision of epileptic focus; observe human and animal brain development; check drugs for convulsive effects; and examine sleep disorder and physiology (Allen, Josephs, & Turner 2000).

Within the brain hemispheres the balance of alpha activity can be observed. In cases of constrained lesions such as tumour, haemorrhage, and thrombosis, it is usual for the cortex to originate lower frequencies. EEG signal abnormality can be manifested by reduction in amplitude; reduction of dominant frequencies beyond the normal limit; production of spikes or specific patterns. Epileptic conditions produce stimulation of the cortex and the presence of high-voltage waves referred to as "spikes" or "spike and wave" (Allen, Josephs, & Turner 2000).

EEG patterns have been shown to be modified by aide range of variable quantities, including biochemical, metabolic, circulatory, hormonal, neuroelectric, and behavioural factors. By tracking changes of electric activity duringa drug abuse-related phenomena as euphoria and craving, brain areas and patterns of activity that mark these phenomenon can be ascertained (Allen, Josephs, & Turner 2000).

As the EEG method is non-invasive and pain free it is being widely used to study the brain organisation of cognitive actions such as perception, memory, attention, language, and emotion in normal adults and children. For this intention, the most practical application of EEG recording is the ERP (event related potential) method (Allen, Josephs, & Turner 2000).

Quantitative Electroencephalography (QEEG)

Technical advances improved the ability of encephalography to read brain activity information from the entire head at the same time. Quantitative EEG (QEEG) applies multi-channel assessments that can better ascertain spatial structures and localise areas with brain activity or

irregularity. The results are often used for topographic brain mapping represented with colour maps in 2D and 3D to enhance the visual image (Vallabhaneni, Wang, & He 2005).

Quantitative EGG is actively used in psychology and neuroscience, as it is aimed to measure the brain activity. Nonetheless, it is also actively applied in neurology, psychophysiology, and brain development (Harmony, 2008). For instance, it is a potential medical tool to identify the presence of cerebral ischemia (Friedman & Claassen, 2010). This approach is utilized as a "predictive biomarker for Parkinson disease dementia" (Klassen et. Al, 2011). The last example is the fact that quantitative EEG contributes to the sufficient planning of the surgeries, for instance, in the context of epilepsy (Krsek et al, 2015). It could be said that its area of application is vast, and its role in the medical research and treatment is significant.

Nonetheless, is evident that role and significance of quantitative EEG cannot be underestimated, as it is actively used to identify the suitable treatment for the various illnesses and diseases. Moreover, it contributes to the advancement of the clinical research and new discoveries in the medical sphere. QEEG is a helpful tool for the treatment of various illnesses and diseases. It helps propose appropriate treatment, as the problems are clearly identified. It is evident that its role cannot be underestimated, as it is actively applied in various medical spheres in the context of clinical research. Nonetheless, some risks have a tendency to exist. However, it is widely known that continuous technological progress allows development of the particular techniques and technologies, which reduce the potential risks.

Event-related potentials (ERPs)

Aroused potentials or event-related potentials (ERPs) are significant voltage variations resulting from evoked neural activity. Evoked potential is initiated by an external or internal stimulus. ERPs are the appropriate scientific methods for studying the aspects of cognitive processes of both normal and abnormal nature (neurological or psychiatric disorders) (Vallabhaneni, Wang, & He 2005).

Mental operations, such as those concerned with perception, selective attention, language processing, and memory, advance over time ranges in the order of the tenth of milliseconds. Whereas, PET and MRI can localise regions of operation during a given mental task, ERPs can help in defining the time course of these operations (Teplan 2002). Magnitudes of ERP components are often much shorter than spontaneous EEG components, so they are not to be identified from raw EEG trace. They are extracted from a set of single recordings by digital averaging of epochs (recording periods) of EEG time-locked to repeated incidents of sensory, cognitive, or motor events. The spontaneous background EEG fluctuations, which are random in relation to time point when the stimuli occurred, are averaged out, leaving the event-related brain potentials (Teplan 2002).These electrical signals reveal only that activity which is regularly associated with the stimulus processing in a time-locked way. The ERP exhibits high temporal resolution, the patterns of neuronal activity evoked by a stimulus (Teplan 2002).

Brain Computer Interface (BCI)

A brain computer interface (BCI) is an information system that recognises user's command only from his or her brain waves and responds according to them. For this intention PC or / and subject is trained to do an uncomplicated task which can consist of the required motion of a narrow displayed on the screen only through the subject's imagining of the motion of his or her left or right hand (Vallabhaneni, Wang, & He 2005). As the result of this algorithmic process, certain characteristics of the brain waves are raised and can be used for user's command recognition, e.g. motor mu waves (brain waves of alpha range frequency associated with physical movements or intention to move) or certain ERPs (Vallabhaneni, Wang, & He 2005). BCI uses signals from neurons with the assistance of programs and computer chips that enable a patient to translate various signals to actions. This system ensures that patients write and control limbs and motor wheelchairs using their thoughts. Although the emergence of the BCI technology is currently encouraged to improve the recovery of patients in hospitals, some challenges are encountered. These drawbacks include the development of electrodes as well as various surgical methods that are invasive at minimal levels (Vallabhaneni, Wang, & He 2005). The BCI reliability and validity is still poor due to its ineffective real life use which is not as reliable as the muscle base movements. The usefulness of BCI is still in the communication basis in severe disability patients. In order to make BCI reliable, the main features that need further development include the central role in adopting interactions in the BCI and its operations, the design and desirability that perfectly imitate the distributional functions of the central nervous system and the way of combining additional signals of brain as well as the signals of sensory feedback (Vallabhaneni, Wang, & He 2005).

Brain machines are designed to work using the brain waves that are monitored in required frequency bands. This produces stimuli that are repetitive on either touch, visual or audio. Biofeedback methods are thus essential in training patients to effectively use such machines. Changes in finger movements, skin resistance and temperatures can be monitored. The EEG biofeedback thus uses EEG signals to effectively provide feedback in training processes (Pop-Jordanova et al. 2010).

AUTISM

Overview on Autism Spectrum Disorder

There is a significant overlie amid the dissimilar kinds of autism. The broad scope of symptoms amongst autistic children, nevertheless, has created the concept of autism spectrum conditions. The word spectrum denotes the broad scope of symptoms, proficiencies, and rates of impact or disability that autistic children could demonstrate. Some autistic individuals show minor signs while others are critically affected. Though autism spectrum conditions seem to be highly increasing, it is not clear whether the rising number of diagnoses expresses an actual augment or emanates from enhanced recognition (Roelfsema et al. 2012). Early identification of autism is crucial as it plays a vital role in assisting autistic children make noteworthy gains in social and language proficiencies. At times, the growth of children is retarded from delivery. However, some children appear to grow typically prior to their abruptly losing communication or social proficiencies. Other children express normal development till they have adequate language to illustrate abnormal interests and ideas.

Autism spectrum disorder (ASD), also referred to as autism, denotes an array of intricate neurodevelopment disorders typified by social problems, communication challenges, and constrained, recurring, and stereotyped forms of conduct (Ruta et al. 2011). The autism spectrum depicts a scope of conditions categorized as neurodevelopmental disorders. Such conditions along the spectrum encompass a mild kind of Asperger disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), and pervasive developmental disorders encompassing Autism and childhood disintegrative disorder. There is a range of numerous illnesses that are similar to autistic disorder, for instance, epileptic attacks, mental retardation, sensory integration difficulties, and seizure disorders. On this note, comorbidity expresses the impact of other illnesses that a patient could suffer apart from the primary ailment of concern, which is autism in this case.

From around 1960, there seems to have been a constant rise in the rate of autistic children, which is alleged to be an outcome of enhanced diagnostic techniques, broadening of diagnostic measures, less stigmatisation of the conditions, and better enlightenment from medical professionals. The prevalence rates for autism spectrum conditions in the UK have demonstrated a constant increase in the course of the last 40 years (Baron-Cohen, et al. 2009). The consensus approximation for the prevalence of autism was 4 in 10,000 people in 1978. The current prevalence rate for autism is one percent of the population. There is no record or accurate count, but the data regarding the likely prevalence rates in the UK is anchored in epidemiological investigations. The recent frequency studies of autism spectrum conditions signify that more than 695,000 (1%) individuals in the United Kingdom have autism spectrum conditions. If the family members are to be included, it means that autism affects close to three million individuals daily.

Autism spectrum conditions do not only affect children since they develop to be autistic grownups (Lai et al. 2011). The prevalence rates are anchored in a couple of reasonably recent kinds of research, one of the autistic children, and the other grownups. The huge rise is probable of reflecting seven aspects, which encompass enhanced identification, modifications in study methodologies, an augment in existing diagnostic services, augmented awareness amid

parents and medical specialists, rising acceptance that autism(can coexist with a variety of other conditions, and a broadening of the diagnostic criteria. The yearly prevalence of autism was approximated at about 4 per 1,000 males and 1 per 1,000 females, which was steady from 2004 to 2010. There is convincing proof that a great increase in prevalence rates of autistic spectrum conditions cropped up around the 1990s but got to a plateau in the early 2000s and has been steady since then (World Health Organization).

Autism is normally believed to be a condition that occurs only in childhood as public concentration centres mainly on children and the significance of early identification (Bird, Press, and Richardson 2011). Nevertheless, autism spectrum disorders are lifetime conditions, and the accessible, essential assistance, as well as treatment, vary as individuals on the spectrum progress through key stages of life. With the high prevalence rate, there is a need to accommodate the pressing requirements and programs for individuals on the spectrum across the natural life. Similar to everybody else, individuals with autism progress through considerable stages of development in life. Their value of existence relies not just on the aid offered in childhood, but as well on ongoing assistance that is in line with their learning, social, recreational, health, family, and job requirements. Autistic individuals and their family members are mainly supported through three crucial phases of life.

The first stage is the early identification and the start of successful treatments prior to three years of age (Tavassoli and Baron-Cohen 2012). Autistic behaviours could turn evident as early as one and a half years of age, and parents ought to assess once they suspect autistic spectrum conditions or any other developmental problem. Timely recognition of autism disorder could lessen lifelong care outlays by up to 60% since it enables parents, health professionals, and other stakeholders to start treatment early enough. Learning greatly aboutautistic spectrum conditions is significant at this phase.

The second stage entails the creation of a strong foundation from childhood to adolescence (Cook and Bird 2012). Different organizations work to assist parents and health professionals design educational and treatment programs to ensure that every autistic child and adolescent can realize their utmost potential. During this stage of life, it is vital to comprehend the manner in which the school system can assist (for instance, via a personalized learning plan) and the way to prepare for the development of life in adulthood. The school years generate countless difficulties for autistic children though they also bear incredible opportunities for development. The parents are faced with the challenge of determining and leveraging resources with the purpose of enhancing the children's possibilities of academic learning, social encounters, and physical well-being. The existence of a team of experts is vital all through this stage since receiving aid from the people that are aware that the system can lessen distress on the family and advance results for the autistic children. Apart from numerous educational programs targeting dissimilar needs and capabilities there are several treatment approaches for school going autistic children that encompass Applied Behaviour analysis among others.

The third stage entails a life of happiness and dignity. Some autistic individuals mature devoid of their condition being identified, at times through preference (Stewart et al. 2013). Irrespective of age, it is never overdue to be diagnosed with autism though it is sometimes challenging as some National Health Service authorities do not offer financing for diagnosing the condition in grownups. With a suitable diagnosis, grownups with autism could have the ability to access available support services. Different organizations currently operate to make

sure that all autistic grownups have access to services and assistance that ascertain independence and secure the maximum value of life.

The diagnosis of autism spectrum does not occur through a single test but normally entails a scope of examinations and evaluations, which often engages numerous professionals. Through tests and involvement of specialists, a perfect diagnosis and suitable treatment arrangement for autism spectrum disorder are realized (Clare and Woodbury-Smith 2009). Diagnosis is anchored in observing the manner in which children play and interrelate with others (present development), engaging parents in interviews, and analysing the developmental account of the children (past development). Through the application of numerous tools, health professionals establish the position in the spectrum in which the children fall. While diagnosing autism spectrum, specialists such as psychologists and psychiatrists make reference to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). DSM-5 assists in grouping the signs and symptoms of autism spectrum disorder. Diagnosis assists in ascertaining the subdivision that fits the patient, for instance, autistic disorder, Asperger syndrome, and PDD-NOS. The diagnosis of autism spectrum establishes a severity ranking, level 1 to 3, depending on the intensity of support that the patient requires.

Currently, professionals diagnose ASD based on problems in two areas, and a child must have challenges in both to be diagnosed with the autism spectrum disorder (Golan, Baron-Cohen, and Golan 2008). This method substitutes the preceding technique that was based on three areas: repetitious and limited conducts and concentrations, social interrelation, and language and communication. Communication and social difficulties have been combined into one area called deficits in social communication. Problems in this area seldom encompass making use of language to communicate with others, not talking by any means, not reacting when talked to, or not imitating the actions of others, for instance, clapping. The other area is the fixed concerns and repetitive conducts, for instance, arranging toys in a given manner repetitively or showing narrow and extreme involvements.

Patients on the autism spectrum can further have some unique restrictions as well as stereotype behaviours. Researchers have noted that ASD affect about 1 in 88 children of which 1 in every 54 males are affected. The disease is hereditary between 80 to 90 percent with a greater percentage of its recurrence rate of about 20 percent in children (Levy et al. 2010). There are minimal researches that have been conducted regarding both etiological and pathophysiological mechanisms on the ASD condition. The various ways through which this condition is occur include various gene disorders such as the fragile X tuberous sclerosis and the rare copy number variants that occur either when 16p11 are deleted or when 15q13 are replicated in the brain. These gene combinations have been noted to associate with the ASD (Volkmar, State, &Klin 2009). Other researchers have also noted that mutation; genetic syndrome as well as the single-gene aetiologies account for only 20 percent of cases that are related to the ASD and majority of individuals with such cases do not necessarily have ASD. There seem to be more complexities surrounding cases of ASD in relation to abnormalities of genetic and epigenetic conditions that are associated with highly penetrant, less penetrant rare mutations and other variants (Volkmar, State, &Klin 2009).

Various post-mortem studies have noted that there are indeed abnormalities in the patients with ASD especially in the limbic system and cerebellum. Researchers through the neuroimaging studies have noted abnormalities in the brain and the size of heads together with the structures of limbic and cerebellum. These studies have indicated differences in early brain over growth,

and different activities among others (Volkmar, State, &Klin 2009). Reports on functional MRI (fMRI) indicate that there are abnormalities in patients with ASD when they perform tasks such as communication, recognition of faces, and movement of their eyeballs, communication and comprehension of languages among others (Newschaffer et al. 2007). This study had a comparison with the normally developing participants and noted that patients with ASD have a kind of network that is unclear and diffuse patterns with frequently diminishing activity in regions that are related to activities and increased activities in the regions that are not related to activities (Newschaffer, et al. 2007). In their anterior-posterior connections, such patients with ASD show increased functional under-connectivity, while the medial prefrontal cortex and the angular gyrus on the left indicate reduced functional connectivity. These patients with ASD furthermore do not indicate that they have no deactivation in regions related to task when they are at rest when tested (Newschaffer et al. 2007).

The various clinical evidences have indicated that conditions of patients with ASD vary greatly from regression developments especially on behaviour challenges, conditions among others. Examples of such traits include sensory complications, hyperactivity, intellectual and impairment among others. These studies have not clearly linked whether there is an existing link between clinical symptomatology to the disorder thus it cannot be concluded that indeed ASD is due to abnormality in the brain (Newschaffer et al. 2007). Diagnoses of the ASD are a challenge to many doctors since most of them conduct observation of the behaviours of patients and then assess their symptoms. These doctors then give verdict on such combinations of the behaviours and symptoms.

EEG in Autism

The physiological parameters of children on the autism spectrum has been studied since the early 90s (Teplan , 2002) . Currently, there is an improved use of the EEG to detect how the brain responds to the sights and sounds. The EEG thus could offer a more accurate way of identifying whether a patient has ASD or not (Guastella et al. 2010). The EEG basically identifies how the brain categorises information that can either be in the form of speech, listening, facial expressions and voices. The EEG examines the regions of the brains and their activities (Guastella et al. 2010). For example, a region of the brain is responsible for processing information that are auditory in nature while another region is responsible for procession visual incoming information (Guastella et al. 2010). A normal human being must make sense and relevance when the two regions communicate to each other. Researchers have noted that the two hemispheres of the brain cannot communicate well in the ASD patients thus they become less effective. This was compared to the normal patients when EEG was used in the study. The EEG is specifically designed to record brain waves of both the left and right hemispheres of the brain. The brain waves that are recorded are those of sound, vision and touch which occur less rapidly to the ASD patients of which should otherwise be rapid in the normally developing patients (Guastella et al. 2010).The complexity in the neurophysiological changes that are related to post synaptic activity in the neocortex of the ASD is the EEG due to its capability of capturing abnormal activity by detecting focal spikes, which occur with increased frequency in ASD patients. There must be an earlier detection and biomarkers of the ASD as indicated by various retrospective studies in children. The various features of ASD are noted in children as early as 12 months (Guastella et al. 2010). These children are normally diagnosed at the age of four years.

Biomarkers are therefore needed for early detection to ensure that in time interventions are done. With application of the EEG, selective alterations can be identified between 4 and 6 months. The EEG also indicate reduced power of delta, alpha, beta, theta and gamma frequencies in the high risk children of four to six months with ASD (Guastella et al. 2010). A research conducted by Elsabbagh et al. (2012) indicated an increase in the gamma wave activity in the midline anterior and the right cortex of high-risk children (Elsabbagh et al. 2012). Another study by Foxe et al. (2013) revealed that brain waves can be monitored through EEG recording thus can indicate ASD in patients. Their findings revealed that children with Autism indicated less rapidity in processing sensory information of vision, sound and touch when compared with normally developing children (Foxe et al. 2015). Most researches have not indicated uniform and consistent diagnostic approaches to ASD. This is attributed to small numbers of electrodes, their analysis such as qualitative, quantitative among others.Researchers have identified two basic methods of examining resting EEG recordings (Pelphrey et al. 2002). The first method is the visual inspection method. This method is capable of detecting and recording vocals of wakefulness frequencies and detection of forms of paroxysmal activity (Pelphrey et al. 2002). The second methodology is the measure and recording of focal and diffuse slowing of waves in the EEG through the use of computer-analysed reading (Boutros et al. 2015). The visual inspection method can be used to detect epileptiform activity, especially when the epileptic discharges areinfrequent (Pelphrey et al. 2002). The use of computerised EEG allows for the increase of number of sensors recording (electrodes) from 21 to 256 and above. It also ensures accurate analysis of data, assessing the topography of any detected mapping.This allows for detection and assessment of cerebral abnormalities.

Other methods such as coherence are used in the resting EEG signals. This method is used to record and assess similarity that exists between the signals recorded between two electrodes (Boutros et al. 2015). With the combination of computerised techniques, it registers the information regarding wave signals.To effectively understand the conditions that are exhibited in the ASD, an integration of data from observations of clinical, electrophysiological, genetic, neuroimaging and neuropharmacological studies are required (Boutros et al. 2015).The use of eye-closed (EC) and eye-open (EO) conditions are also preferred in diagnosing ASD. The EO condition requires that participants are viewing a quiet stimuli. Moving bubbles across the screen are monitored and recorded (Pelphrey et al. 2002). A study conducted by Barry et al. (2008) indicated reduction in amplitude in delta (lateral-frontal0, theta (posterior), alpha and beta frequency waves in EO status relative to those of EC conditions. The researcher indicated an increase in frontal beta in EC condition. The conductance in skin levels were also recorded at higher frequencies in the EO conditions. This result was negatively correlated with alpha power thus showed high levels of arousal.

Chen et al. (2008) reported an increased core frontal delta and reduced frontal midline theta in the EO conditions. There were also low alpha and beta waves at lower levels in the posterior areas in the EO conditions (Chen et al. 2008). There were no higher beta and gamma waves recorded in the ASD in both conditions.Another study by Mathewson et al. (2012) indicated that people with ASD did not show difference from those who are healthy on the alpha power levels in the EC statuses. These people however, as indicated by the researchers indicated less alpha suppressions at the EO state (Mathewson et al. 2012).

QEEG in Autism

The current and most rising growing technique to measure ASD is a computer analysed derivative of the quantitve EEG recordings(C-EEG). This is because of its high sensitivity to the minute variations in both time and amplitudeduringits operations when compared with the standardised EEG methods. Most abnormalities are detected using this method other than the normally used techniques (Kozma& Freeman 2002). The C-EEG is useful in detecting the malfunctions of the brain or physiological alterations in the brain activity. A study conducted by Pop-Jordanova et al. (2010) introduced a technique of calculation of spectrum weight frequency that determines the brain rate (Pop-Jordanova et al. 2010).

A study was conducted to compare raw data on EEG from 430 with ASD and 554 control participants of age between 2 and 12. The findings indicated that participants with ASD indicated a consistent EEG patterns due to their altered connectivity between the brain hemispheres (Duffy &Als 2012). There was a reduced connectivity as compared to those of participants under control section.The left hemispheres language of the ASD patients indicated reduced connectivity as compared with neurotypical children (Duffy &Als 2012).

Potential powers of the C-EEG

The EEG powers can be determined in terms of relative or absolute powers. A relative power can be determined by getting the EEG activity in a frequency wave divided by the amount of activities in all frequency waves (Fatemi et al. 2012). The absolute power is derived at by determining the amount of EEG activity of one wave band independent of the activity of those of the other bands (Fatemi et al. 2012). The relationships between the frequencies of wave bands can thus be determined using the relative power. This alone cannot be used to identify the degree or presence of abnormality or abnormal electrophysiological activity in a specific frequency wave band (Fatemi et al. 2012). The ASD vary in the degree of the presence of absolute power of bands. It is therefore relevant to interpret a relationship that exists between frequency bands to ensure proper comparisons of frequencies. The use of absolute power is advantageous in determination of and understanding of electrophysiological alterations in patients with ASD (Fatemi et al. 2012). Electrophysiological abnormalities have been noted from a resting-state EEG studies.These electrophysiological disorders have been present across the different patients. Excessive powers of delta and theta have been noted at low-frequencies and high-frequencies of beta and gamma waves. On the other hand, reduced powers have been indicated in the middle-range frequency waves of alpha. These have been identified in the various developmental stages in children with ASD (Fatemi et al. 2012).

Both relative and absolute powers have been indicated to have excessive delta powers and in the various brain regions such as parietal, dorsal midline and frontal cortical regions. This is an evidence of distributed patterns of abnormality (Fatemi et al. 2012). In the same way, an increased low frequency of relative and absolute theta of about 5 to 7 Hz have been detected in some adults and children with ASD in the frontal and right posterior positions of the cortex. Increased powers have also been detected in relative high-frequency beta of about 14 and 35 Hz and absolute gamma of more than 35 Hz waves in patients with ASD. It is noted that a significant alteration exist in gamma power over the occipital, parietal and midline regions within the higher-frequency waves (Fatemi et al. 2012).

Patients with ASD in most cases indicate reduced relative and absolute powers in the alpha frequencies across various regions in the brain such as the frontal, occipital, parietal and temporal cortex. This movement indicate an electrophysiological power that is U-shaped and are alternated in the ASD patients thus increasing their abnormalities. It is thus clear that monitoring the power indicated in EEG can be used to determine abnormality (Fatemi et al. 2012).

The U-shaped electrophysiologicalprofile happens due to the abnormal function of gamma-aminobutyric acid (GABA) which further leads to the functioning and development of plasticity of the brain. This ensures modulation of power in high and low frequency wave bands as well as enhancing the power in alpha waves. The visible activity of gamma waves in the EEG recordings is responsible for the impairment of dendritic GABA inhibitions. When GABA concentrations are increased through administration of the GABA antagonist vibration increases the resting power of delta in patients (Fatemi et al. 2012).It is thus concluded that ASD abnormalities result from numerous and complex patterning of neurochemical changes that affect the inhibitory GABAergic inter-neurons as well as their activities in the brain cells. In ASD patients, the GABAergic interneuron connectivity is disrupted at the prefrontal cortex thus an abnormality occurs (Fatemi et al. 2012).

Abnormality in GABAergic has been noted to have some consequences due to its excitatory trophic factor that ensures normal growth and development of dendrites. The abnormality may lead to the development of abnormal inhibitory circuit which may lead to long term alterations of oscillatory activity at numerous frequencies (Fatemi et al. 2012). This situation can lead to biasness in the neural network system towards higher frequencies.When both delta and theta frequencies are stimulated, an increase in GABA precursors expression in inhibitory cortical systems is detected (Fatemi et al. 2012). Due to such activities, a lower frequency activity can be used as a compensatory mechanism in patients with ASD to counter the rate of high-frequency excitatory being produced by GABAergic dysfunction. This abnormality in the GABAergic activity is noted in patients with ASD.

A study done by Fatemi et al. (2012) indicated that interactions between GABA receptors, their densities and GABRA4 and GABRB1 genes in the cerebellum and Brodmann's areas 9 and 40 are to diagnose ASD (Fatemi et al. 2012). This is because they increase the rate of neuronal excitability during the development of the brain. An alpha wave power has been indicated to ensure the control of to-down control of sensorimotor responses. This has been inclusive of its role in ensuring voluntary blocking of contextual responses that are inappropriate (Fatemi et al. 2012). When children with ASD are examined, they indicate an increased level of inattention and inhibitory errors as well as impulsiveness. A conclusion can be drawn of an existing association between Alpha powers and inhibitory control problems to patients with ASD. If such cases occur, a person can suffer from ASD (Fatemi et al. 2012).

The concentration of power differences among the patients with ASD have been noted to constantly change in the hemispheres in asymmetrical way. When examining the resting-state EEG, more enhanced power is exhibited in the left hemisphere as compared to the right across all the frequency bands (Rojas, Becker, & Wilson 2015). A study conducted by Cantor and Chabot (2009) confirm that participants with ASD tend to have increased power of delta waves in the posterior-temporal, midline and the occipital areas of the left hemisphere (Cantor & Chabot 2009). Another study by Stroganova et al. (2007) indicated an enhanced delta powers at

the left hemisphere of patients with ASD in temporal, frontal and partial sections (Stroganova et al. 2007). It can be concluded that resting-state EEG in the ASD patients indicate abnormalities in low-frequency and higher frequency wave band power, lateralisation in the brain and connectivity functions.

The problematics and advantages of EEG in Autism

When one uses the EEG method, a specific consideration should be noted on the diffusing sources of neutral activities being recorded on the scalp. This is because of the conductivity of the scalp due to conductivity of the brain, cerebrospinal fluid and the skull (Wang et al. 2013). The diffusion and blurred information indicated always makes it difficult to specifically identify a source of a particular information or an activity. This is noted when few electrodes are used in the EEG (Wang et al. 2013). In normal circumstances, a U-shaped pattern is recorded for a spectral power that is more relative to healthy controls. An example has been noted in experiments whereby delta waves have shown differences in power at the frontal, midline, temporal and other regions (Wang et al. 2013). The differences are due to the longer distribution of deficits that exist within the frequency of waves and due to blurred data. This problem can be corrected through comparison of densities of the waves at the source for the groups of waves (Wang et al. 2013).

A study on the source localisation on EEG indicates that focal sources reported different frequencies of wave bands. For example the anterior delta source and the most posterior sources of alpha. Resting frequencies of waves are always noted to be distributed at the source network when simultaneous recording of EEG –fMRI are done. Coherence analysis also becomes difficult due to the blurred or diffuse waves. This is normally seen in the short range coherences (Wang et al. 2013).

A technique called surface Laplacian transformation is used to estimate current source density (CSD). Power and coherence can then be estimated and evaluated using the EEG method. The CSDtransformation can then be used to compute derivative of voltage between two close electrodes. This contributes to the elevation of local electrical activity as well as eases the contribution of remote activity. Some studies have indicated reduction in short-range connectivity in the ASD where large sample size was included to solve the problem of blurred or diffuse waves (Wang et al. 2013).

A second technique was designed by Crespo-Garcia et al. (2010) where they used regional sources. This method requires that surface potentials are to a source space using multiple discrete equivalent current dipoles. Coherence analysis is then calculated between the two source regions rather than electrodes. Another issue that can occur is the method of calculating coherence of wave bands. A research conducted by Murias et al. (2007) on the measurement of coherence in the short distances was biased in powers due to the classic coherence frequency of calculation in a resting state of EEG studies. The calculations are arrived at due to the complex spectrum of power decomposition. This method is however critical to both phase relationships and amplitude between signals (Crespo-Garcia et al. 2010). Multiple electrodes when close to each other can easily detect power modulation at a specific single source. This leads to induction of the confounding factors of the strength of local source. This leads to limitation of the surety of the cause of relationship when more than two concurrent modulating powers are detected. In order to solve such limitations, a phase synchrony analysis is used. This approach

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requires analysis and assessment of relationships indecently (Crespo-Garcia et al. 2010). In the study, a method of phase synchrony was used. In this technique, two EEG signals were first made to pass a ± 2 Hz frequency target, and then used with Gabor wavelet function. A comparison of two signal outputs from wavelet decomposition was done (Isler et al. 2010).The use of EEG in studying brain development disorders such as the ASD comes with some benefits compared to other techniques such as the MRI. The EEG can be used in a wider group range with developmental disabilities due to its ability to tolerate higher movements. It also indicates high temporal resolutions and can further record repeated measurements due to its non-invasive nature (Murias et al. 2007). The technique uses resting state approaches that do not need responses made by the subjects. This technique is advantageous in handily patients with severe impairment or younger children who cannot perform activities accurately due to physical, cognitive and other development challenges at a tender age. This ensures that abnormal maturation trajectories in ASD patient can successfully be identified in younger children (Pop-Jordanova et al. 2010).Some researchers have indicated that a resting-state EEG in individuals indicates an increase in alpha powers and coherence in patients with ASD. They further indicate a relatively reduced power in low-frequency of delta and theta in adults in relation to children. This is an indication of long range cortico-cortical connections (Stroganova et al. 2007). A treatment outcome can also be indicated by the resting-state EEG on the quantitative aspect thus a proper approach of monitoring treatment outcome can be deduced (Chan, Sze, & Cheung 2007).

The above statement indicated that patients with ASD who were given neurofeedback training on control of neural oscillatory activities in the alpha, displayed relatively greater reduction of power and coherence and improved performance on their attention tests thus a reduction in the Autism Treatment Evaluation Checklist (Chan, Sze, & Cheung 2007). A neurofeedback training helps in reducing theta activities and increasing the beta activity in the ASD patients (Chan, Sze, & Cheung 2007).

The research has elaborated on the relationship that exists between the EEG and the ASD. It has been noted from the essay that at the resting-state EEG, ASD can be diagnosed especially based on the computer based C-EEG. The ASD condition must be examined in advance to aid in possible ways of treatment. More researches and development should therefore be conducted towards the development of three-dimensional pictures of the brain by use of records from the EEG. This attempt is still not successful due to swapping of deeper information by the surface information gathered at the near surface and lack of hormogeneity of the conductors to locate accurate measurements.

NeurophysiologicalPatterns in Autism

Progress in neuropsychology, neurobiology, and brain imaging has enabled fresh perceptiveness into the likely brain foundation of autism (Falkmer et al. 2015). Different sections of the brain that range from the medial lobe parts and cerebellum to the prefrontal cortex have been established as likely core segments of the anomaly in autism spectrum conditions. Moreover, it is established that dysfunction in a given section of the brain possibly influences functioning and progress of associated sections of the brain. Indeed, autism spectrum disorders most certainly entail dysfunction of brain circuits that back the operations of different brain sections. Neurophysiological patterns demonstrate that lower-functioning

autistic children are affected on a visual identification recall test exploiting medial temporal lobe structures. (Falkmer et al. 2015)
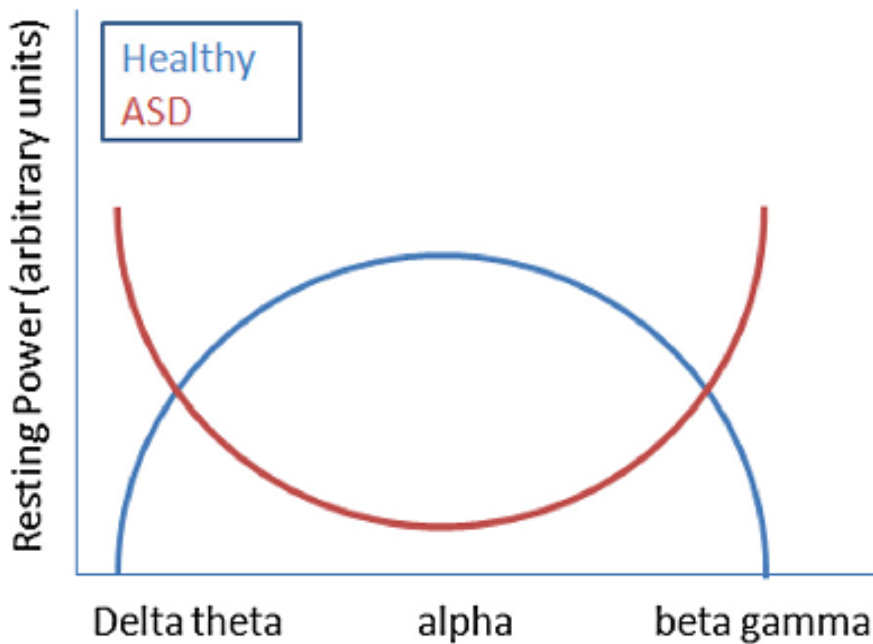

figure 2: U-Shaped profile of abnormal power pattern in autism spectrum disordersas illustrated byWang et al2013

Neurophysiological studies have a tendency of evaluating mechanism as compared to etiology and have embarked on two general directions, one underscoring the interruptions of cognition and language and the second highlighting the disorders of sensory modulation and motion. The disorders of cognition and language imply subcortical dysfunction (Izawa et al. 2012). Neurophysiological studies concerning cortical patterns are pertinent to the disorders of communication and language in autism. The neurophysiological studies that have centred on cortical mechanisms have encompassed electroencephalographic studies, event-associated potential studies, and radiological studies (encompassing numerous computerized tomography explorations). Though the proof of an unusual pattern of hemispheric lateralization is incoherent, and the basis of any likely abnormal or deficient irregularity might or might not be cortical, abnormal right or left cortical function in autism is a likely explanation of diverse facets of autistic conduct.
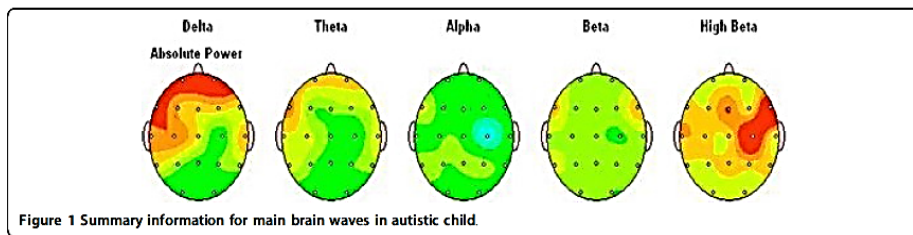
Figure 1 Summary information for main brain waves in autistic child.

figure 3: *QEEG characteristics and spectrum weighted frequency for children diagnosed as autistic spectrum disorder*, as illustrated byPop-Jordanova et al. 2010

Working Hypothesis

Neurofeedback denotes a greatly promising and novel therapy for autistic spectrum conditions (Wright et al. 2011). Neurofeedback presents a tool for the direct training of brain function and that has been found triumphant in handling a broad scope of mental medical interests. Similar to the occurrence with different forms of therapy, its use to the autism disorders has been made difficult by the inherent complication of the condition. Nevertheless, researchers have reviewed the advancement of neurofeedback for the autistic disorders and offered some direction to both parents and physicians in terms of the alternatives open to them. Whilst other behaviour disorders for children, for instance, Attention Deficit Hyperactivity Disorder (ADHD), have gone through neurofeedback attention, it may seem that autism spectrum disorder will soon have its time in the sun.

The current studies are demonstrating that children with autism spectrum conditions are reacting in an excellent manner to both the haemoencephalographic (HEG) and electroencephalographic neurofeedback. In addition, recent studies indicate that neurofeedback could be a successful intervention for school-aged children with autistic disorders. Neurofeedback acts as an intervention meant to train people to control the biological operations in their brain effectively (Cook, Blakemore, and Press 2013). This has generally engaged the self-regulation of electroencephalographic rhythmic activity, also known as electroencephalographic biofeedback, neurotherapy, or neurofeedback. Nevertheless, inpresent times, the perception of neurofeedback has expanded to encompass self- regulating of different neural substrates.

The identification of successful treatment is directly associated with the studies concerning the real reasons behind autism (Barnes and Baron-Cohen 2012). Different studies are yet to establish every likely source fully. Nevertheless, many scientific research works ascertain that autism spectrum conditions mainly have genetic sources. Such genetic mutations could be high-risk aspects for an anomalous advancement of the brain, for instance, through inhibition of the development of significant neuronal linkages or generating insufficient brain wave actions. The abnormal patterns could result in severe shortfalls in neuropsychological operations and capacities, for example, executive operations, the theory of mind, central coherence, intelligence, language, and imitation proficiencies. Children normally begin copying facial expressions, gestures, or activities encompassing objects at an extremely young age. This denotes a considerable precondition for the advancement of the theory of mind, which acts as the capacity to be responsive of and understand internal deliberations and

sentiments, as well as the ones of other people. In autistic children, these capacities frequently are developed in a limited manner.

People with autism normally express problems in designing and controlling their conduct or identifying intricate social conditions (Golan, Sinai-Gavrilov, and Baron-Cohen 2015). It could be extremely difficult to establish and comprehend feelings, deliberations, or objectives. Several research studies assess the neuropsychological performance of autistic individuals, and presently numerous professionals concur that a mirror neuron dysfunction network is amid the major sources of restricted neurocognitive capacities. The network checks identification and perception of fundamental motor activities but is apparently also engaged in more intricate cognitive practices and thus could result in a range of problems. In addition, researchers have identified that some brain sections of individuals with autism are differently aroused in the course of cognitive practice when judged against normally working brains. From time to time, completely dissimilar sections become stimulated for cognitive endeavours, for instance, functional memory or executive tasks. This implies the advancement of indemnified policies in the autistic mind. A different occurrence normally stated in many studies depicts that cerebral operations are not adequately incorporated and thus dissimilar psychological operations cannot be synchronized accurately. This leads to the frequently apparent discrepancies in incorporating, developing, or responding suitably to insights, feelings, or conducts.

It seems practical to study neurofeedback as a kind of intervention that is meant to modify the operations of the mind essentially (Luke et al. 2012). Through obtaining immediate information regarding the neuronal patterns, people have the chance to learn to control the action of their brain waves anchored in influential training. With time, researchers have come up with numerous neurofeedback training plans that partially vary in their recording and likely guiding techniques. Contrary to numerous other treatment programs, neurofeedback training seeks to transform the person's brain action essentially, rather than just addressing the signs and symptoms of a condition. Since neurofeedback is a noninvasive practice, the mind cannot become reliant on external influences such as electrical impulses and medicines. Attributable to such explanations, it is possible that neurofeedback can generate lasting impacts, which can stay unrelenting even following the end of the training.

Neurofeedback training programs are totally personalized as they are anchored in the individual's recorded mind action and the associated symptoms, which is a fundamental necessity particularly regarding treatment methods for autism spectrum conditions. Furthermore, neurofeedback training could be modified at any instance such as in the occurrence of the deterioration of symptoms or similar incidences (Wing, Gould, and Gillberg 2011). Besides, so far no fallouts from neurofeedback training have been established. Another significant advantage is the option of merging neurofeedback training with different treatment techniques to possibly augment the therapy development.

Neurocognitive Theories

The mind-blindness theory affirms that children with ASD have hindered the development of the theory of mind (ToM), the capacity to assume being in another individual's shoes, and envisaging of deliberations and opinions. The mind-blindness theory implies that individuals that have autistic disorder or Asperger disorder have hindered the advancement of their theory of mind, making them have a measure of mind-blindness. Consequently, they view the

conducts of others as puzzling and impulsive, even dreadful (Auyeung et al. 2009). Proof for this hails from the challenges they demonstrate at every position on the progress of the capability to mind construe. Autistic children and children with Asperger disorder demonstrate decreased rate of joint interest in toddlerhood. For instance, the typical 2-year-old baby is involved in pretend play while utilizing their mind-construing proficiencies to comprehend that in the other individual's mind, they are only feigning. On the contrary, autistic children and children with Asperger disorder express minimal pretend play, or their make-believe is restricted to more rule-anchored plans.

While a typical 9-year-old can construe a different individual's manifestations from their eyes, to discover what they could be considering or feeling, children that have Asperger disorder perceive such tryouts far more intricate and similarly when the adult assessment of interpreting the mind in the eyes is employed (Wakabayashi et al. 2007). Autistic grownups and those with Asperger disorder score less than the typical ones on the assessment of enhanced mind construing. The mind-blindness theory has been proved triumphant in explaining the communication and social challenges that typify such circumstances but cannot clarify the non-social aspects (the narrow concerns, requirement for similarity, and concentration to detail). On the other hand, the empathising-systemising (E-S) theory affirms that two aspects are required to elucidate non-social and social facets of the autism spectrum conditions. The E-S theory is linked to other neurocognitive hypotheses, for instance, the weak central coherence theory (WCC) and male brain theory.

The E-S theory elucidates the communication and social challenges in people with Asperger disorder and autism by orientation to delays and deficits in empathy, while clarifying the points of strength by consultation to integral or even advanced proficiency in systemising. Therefore, it is the difference between E and S that establishes whether an individual is probable of developing autism (Happé and Frith 2006). Similar to the weak central coherence theory, the empathising-systemising theory concerns a cognitive approach and conceives superb attention to detail (in insight and remembrance), because when one systemizes he/she has to consider fine details.

The weak central coherence theory anticipates that individuals with Asperger syndrome or autism will be everlastingly mislaid in the detail and by no means realize a comprehension of the system in its entirety (because this would necessitate an international impression). In contrast, the E-S theory expects that, with time, the individual could attain a brilliant comprehension of the entire system, given the chance to examine and manage every variable in the structure. The empathising-systemising theory, being a two-aspect theory, seems better fitting to elucidate the entire set of the attributes typifying autism spectrum conditions (von demHagen et al. 2012). The theory also appears more germane when judged against the executive dysfunction description or WCC theory, which have drawbacks in terms of descriptive or catholicity scale.

Neuroplasticity and Neurofeedback efficacy

Neurofeedback, also referred to as electroencephalographic biofeedback, denotes an automated treatment technique for the neurobiological disorder that seeks to transform anomalous brain activities (Tavassoli et al. 2011). Neuroplasticity denotes the capacity of the mind to rewire or restructure itself through creating or transforming neural links and varying the operations of

dissimilar sections of the brain. On this note, neurofeedback training acts as the use of neuroplasticity through providing brain information regarding its latest conduct. Therefore, neurofeedback enables the brain to utilize its plastic quality to modify the way it operates with the purpose of acting more successfully and ably, even in cases of damage, for instance, brain injury and stroke. In twenty neurofeedback patterns that have response twice in a minute, a person gets 72,000 opportunities of learning. This entails much of performance and recurrence.

The study of the brain has indicated that recurrent exercise of its systems leads to alteration, which is termed as neuroplasticity. To get to the bottom of the matter and restructure the brain, neurofeedback permits an individual to harness neuroplasticity. Neurofeedback training ensures the application of the mind's remarkable capability for change, its aptitude to reform the manner in which it operates, and assists people to tackle their challenges. Though everyone is born with hard-wiring systems of connecting fibres and neurons, the human brains are continuously being formed through experience. Frequent encounters lead to enhanced linkages amid neurons and in greater potency in the extant correlations (Eriksson et al. 2013). Such small modifications, normally repeated, result in adaptations in the operations of the brains. Hence, it is possible to transform brain action models through response directed learning.

Brief History of Neurofeedback

The management of autistic conditions with the help of neurofeedback dates back to about 25 years (Holtmann et al. 2011). During such early times, the utilization of neurofeedback was mainly for Attention-Deficit Hyperactivity Disorder, though such similar techniques were evidently also supportive for a range of other concerns. Therefore, it was a natural consequence to attempt using the techniques also with children having autistic disorder. Such early endeavours were only as probable of making conditions worse the same way that they could make matters better, thus researchers rapidly situated a virtual enclosure around autism and resolved that they did not identify much to embark thereon. Years afterward, a number of researchers in the field identified some excellent outcomes with novel approaches thus the barrier was once again removed to enable trying neurofeedback in the management of autistic conditions. (Holtmann et al 2011)
Neurofeedback approaches have proliferated in form in the course of the years, and with an extensive set of medical devices, it is as well beneficial to be consistent with an expansive scope of medical difficulties in the autistic disorders. The point was being realized where people could practically anticipate valuable progress with almost every child with autism. Simultaneously, scientific comprehension of the concerns was advancing to the point where the neurofeedback operation could presently be comprehended with respect to an established model. Prior to progressing into greater depth on the neurofeedback advance, it is useful to take that model into consideration. Therapies for autistic disorders could be mainly grouped into techniques that tackle biomedical matters that are in the causal chain and techniques that try to improve the behavioural effects (Hurt, Arnold, and Lofthouse 2014).

Looking at a glance, neurofeedback suits the latter group, and certainly neurofeedback practitioners have a tendency of belonging to the mental medical camp. Through tackling conduct at the phase of the brain, the novel ground that does not fit suitably either in the ideal biomedical model, the idyllic mental fitness, or behavioural representation is opened up. When observed from the view of brain conduct, the most obvious limitation in autistic spectrum

conditions is at the level of integration of task. Furthermore, such a shortfall is not consistent across functional domains but instead bothers particularly the psychological hub that enables people to operate in socially-associated habits (Hurt, Arnold, and Lofthouse 2014). At the position of the brain, even the psychological operation is systemized by neural systems. It is evident that there are developmental errors in the structural connectedness of such systems. Past that, nevertheless, there are as well shortfalls in the operational linkages that function on the faulty style. By just studying the structural discrepancies in the white matter, researchers establish no explanation to believe that psychological systems ought to be selectively influenced. Neurofeedback occurs at the position of the operational linkage. Researchers have to fundamentally function in the restrictions of what is available with respect to structural connectedness, but the good thing is that psychological linkage in the children with autism lies mainly in the practical field and is hence medically reachable. Electroencephalographic neurofeedback enables this in an effective manner, and there is currently, fundamentally no other equivalent way of making it possible (Hurt, Arnold, and Lofthouse 2014). There is no apparent final point to training in autism since the progressively proficient brain only keeps on developing fresh skills. The society requires ensuring that all children with autism have the chance to enlarge their mental perspectives with neurofeedback.

Autism Management Using EEG and Neurofeedback

Approximately 1% of children across the globe have autism. Nevertheless, the diagnosis of autism spectrum conditions is still in the dark times since it remains a perplexing and biased practice where physicians convey their judgment following observation of the behaviours of a child and evaluating past signs and symptoms. The symptoms of autism spectrum conditions fluctuate noticeably from one individual to another, varying from mild communication and social challenges to intense cognitive problems (Catarino et al, 2013). Amid the difficulties in autism is that there is no simple and perfect method of categorizing patients into groups or what such groupings could constitute. However, researchers have established and are refining novel and objective methods of diagnosing autism, the electroencephalographic (EEG) methodologies. Determining through EEG methodologies how rapid the mind reacts to sounds and sights could be the explanation for a perfect and clear-cut recognition of autism.

The EEG methodologies are anchored in scientific understanding of the way human brains classify the received information (Catarino et al, 2013). When a person listens to another, he/she collects input concerning what they are saying not just from perceiving their words but as well watching their facial expression. In the meantime, a given section of the brain is acting on the auditory message while another section is working on the visual information. To add up what has been stated, the two dissimilar brain sections have to communicate with one another. Via earlier studies, researchers have found that the communication involving the brain sections is in some way impaired, or merely less efficient amid children with autism when compared with normally developing children. This was established while researchers were employing an electroencephalogram (EEG) to determine the brainwaves of a number of children. Evaluating the recordings of every child, they found out that children with autism processed a sensory message (touch, visual, and audio) less quickly when compared to their normally developing counterparts.

Many neuroimaging pieces of research have illustrated brain abnormalities in autistics when judged against healthy controls. The electroencephalogram has been crucial in the management

of autism, for instance, attributable to its capacity to examine the neurobiology of autism. The identification of an elevated occurrence of electroencephalographic anomalies and seizure disorders in people with autism indicates a biologic foundation for the disorder (Ingudomnukulet al. 2007). Additionally, the electroencephalographic methodologies are premier instruments in the evaluation of neural dysfunctions associated with autism and seizures because of their noninvasive quality, accessibility, and usefulness in detailing such forms of problems. In the electroencephalographic methodologies, spikes could denote causal morphological brain anomalies or metabolic disorders thus ensuring that they are addressed in a timely manner.

Brainwave electroencephalographic recordings could possibly express the manner in which people with severe cases of autism are affected (Golan et al. 2007). Furthermore, such recordings could assist in the early diagnosis of autism spectrum disorder. Early diagnosis enables opportune treatment, which plays a key role in ensuring the possibility of better results. Being novel and objective, EEG methodologies are vital for the identification of autism at an early stage thus leading to better treatment and ultimately offering great optimism of an industrious existence. Nevertheless, only less than fifteen percent of autistic children are currently diagnosed before attaining four years of age. There is a great need to adapt this technology extensively to enable early autism identification, therapy, and management of a higher proportion of children.

Publications

This section contains a number of articles published as part of my PhD

A Portable Sonified Neurofeedback Therapy for Autism Spectrum Disorder Patients-An Initial Evaluation

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Abstract

A novel sonified Neurofeedback management therapy for children diagnosed with Autism Spectrum Disorder (ASD) is explored and tested. ASD is a condition in children which effects their social interaction, language and communication and behaviours. Literature suggests that people diagnosed with ASD tend to have higher levels of Delta (δ) waves and less levels of Alpha (α) and Beta (β) waves in their brain activity. This paper studies how the use of sonified Neurofeedback produced by a two channel EEG device headband and the Brain Music System (BMS), can successfully suppress the δ waves while at the same time promote α and β waves. The two channel EEG device headband records EEG activity and the BMS converts the EEG activity into sonified binaural signals feeding them back to the user. Results recorded showed a relevant δ wave suppression clearly indicating that children subjected to this study made significant progress in managing symptoms associated with ASD. This was also confirmed by feedback from the parents of the respective subjects.

Keywords: EEG; Sonified neurofeedback; Autism spectrum disorder

Introduction

Problem statement

In this paper, a research study is performed on an experimental management treatment possibility to Autism Spectral Disorder (ASD) making use of musical Neurofeedback (NF). The Brain Music System (BMS) was used in conjunction with a two channel electroencephalography (EEG) device headband with the intent to suppress Delta (δ) waves in the subject's brain.

Autism spectral disorder

ASD is a disorder characterized by impairments in social interaction, verbal communication and repetitive behaviours (European Commission [1]). It affects around 60 children out of 1000 [2], of which mostly are below the age of 8 years. No treatment has been found to cure ASD, however, the disorder is controllable with the use of several treatment methodologies [1]. In the literature reviewed we see how several treatments tend to improve the patients' life leading to the point where the child grows up to live a normal or near normal life [1].

There are two main types of treatments for ASD; Ingestible (orally administered e.g. taking pills) and noningestible (externally administered e.g. psychiatry) [3]. Studies indicate that the most effective noningestible treatments are specialized and supportive educational programs tailor-made for children suffering from ASD [3,4]. In fact, one of the most effective specialized programs is speech and language therapy [5].

The only Food and Drug Administration (FDA) approved medication for ASD treatment are Risperidone and Aripiprazole and are only approved to be used in children between the ages of 5 and 16 [3]. Any other medication used in treating ASD are targeted to treat secondary effects caused by ASD such as sleep deprivation, hyperactivity, anxiety, aggression, disruptive behaviour and self-injuries [3]. However, these sort of ingestible therapies are known to cause several other problems and side effects [3].

Literature suggests that children diagnosed with ASD have different brain activity levels when compared to normally developing children. A study on 50 children (27 diagnosed with ASD and 23 controls) concluded that children with ASD have higher levels of δ waves amongst other abnormalities which support the imbalance of neural excitation in an Autistic brain [6].

Neurofeedback

NF has now been used for several years in research, clinical trials and as treatment for several conditions and disorders [7]. NF makes use of the user's EEG gathered data to modify the neurophysiological and neurological basis for a number of neurological based disorders [7]. NF proved to be helpful for a number of neurological disorders [8,9]. Research on the effects of NF performed on patients diagnosed with ASD show that improvements in social behaviour and electrophysiological behaviour are obtained in several cases [3,10]. Other research studies imply that NF has no or little effect in treating ASD [11].

Two channel EEG device and the Brain Music System

As a preamble to the analysis of obtained results a general introduction on the two channel EEG device headband and the BMS is presented. The two channel EEG device headband developed by AAT Research, is a portable two electrode EEG signal acquisition device which uses a modified version of the low resolution brain electromagnetic tomography (LORETA) to obtain estimates of subcortical activity. This device can connect to a computer via Bluetooth such that it can be interfaced to the BMS application running on the same machine. The BMS is a software application that uses Sonified Neurofeedback to convert the EEG signals obtained from the headband into Sonified

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signals (binaural beats). These musical waveforms are presented back to the user forming a loop in attempt to level the brainwaves in real-time according to the respective mental state [12]. The NF music trains the brain in attaining a pleasant frequency of brain activity [13,14].

The basic composition of the whole system used as therapy is represented by a detailed block diagram in Figure 1.

EEG is the measure of the electrical activity of the brain and is widely represented using the LORETA algorithm [15]. The LORETA algorithm was first introduced in 1994 as 3D, linear solution to the inverse EEG/MEG problem [16].

The two-channel EEG headband device makes use of just two dry electrodes; one placed on the frontal left hemisphere and the other placed on the frontal right hemisphere of the subject's head to collect EEG data [13,14]. The signal gathered from the electrodes is processed using a modified version of the LORETA algorithm [13,14]. The latter mentioned algorithm uses the EEG data gathered from the two electrodes to predict, estimate and virtually create 14 other channels. The output data from the EEG headband device is saved in EDF file format (which is the European Standard EEG data file format) [13,14].

Aims and objectives

The aim of combining the two channel EEG device and BMS is to create a user friendly, portable and reduced cost platform as an aid to people diagnosed with ASD. Such a person would generally have increased levels of δ waveforms when awake, which are normally found in a healthy person's brain activity sleep patterns. The BMS aims to suppress δ waveforms while promoting Alpha (α) and Beta (β) waves, which are respectively associated with focus and mental activity. The intention of this study is to analyse the effect of the two channel EEG device and the BMS combined together over a group of subjects diagnosed with ASD.

Testing

Two channel EEG device SNR testing

A coherence test was carried out on the two channel EEG device headband in a sterile clean room environment. The test was performed using the in-house clean room for a sterile environment, a dBA (sound Amplitude) meter, a set of speakers which could be calibrated to produce a certain dBA sound and tailor-made software designed to produce pure tone sounds at various frequencies while recording the response from the two channel EEG device sensors.
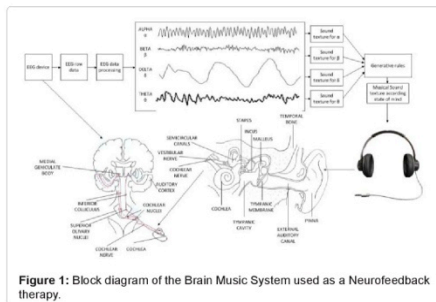

Figure 1: Block diagram of the Brain Music System used as a Neurofeedback therapy.

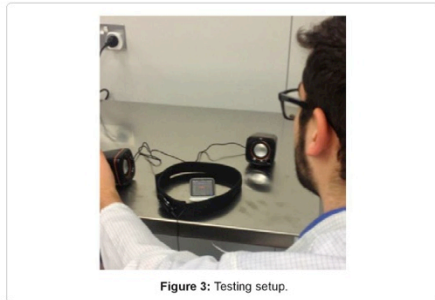**Figure 2:** Sterile environment used for testing procedure.

Figure 3: Testing setup.

The test was carried out by recording readings from the headband while pure tones at frequencies 256 Hz, 512 Hz 1 kHz, 3 kHz, 5 kHz, 7 kHz and 10 kHz were played sequentially. The whole testing procedure was repeated twice at 80 dB amplitude and 92 dB amplitude. In addition, a reading was also taken of background noise since perfect silence in the clean room could not be obtained and thus the background noise was common in all readings. This background noise was found to have an amplitude of 57 dB. The recorded signals from the two channel EEG device sensors were saved and used for analyses.

Seven plots were obtained from the results gathered. Each plot was constructed from background noise data and the response of the device at 80 dBA and 92 dBA for each frequency respectively (Figures 2-4).

Figure 5 shows some of the several plots constructed. These prove that the output recorded with respect to different dBA and same frequency input tone, is coherent. This validates the results that the sensor produces.

Participant selection

For a subject to be considered to participate in this long term
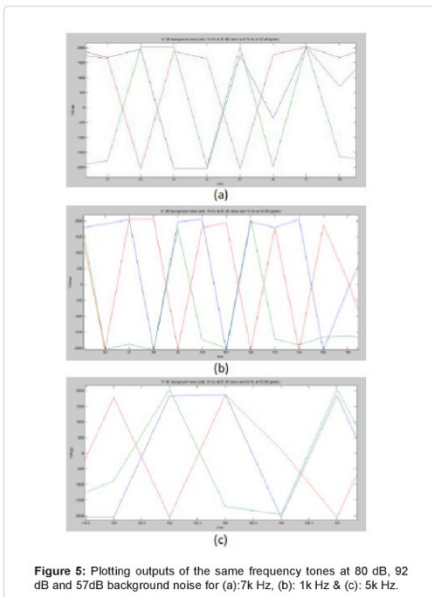
26

Figure 4: Testing procedure.

Figure 5: Plotting outputs of the same frequency tones at 80 dB, 92 dB and 57dB background noise for (a):7k Hz, (b): 1k Hz & (c): 5k Hz.

clinical trial a number of requirements had to be met. This was done with reference to participant selection done for Autistic clinical trials performed by the U.S. National Institutes of Health [17] and a similar clinical trial selection process to that performed by the Yukon Government (Canada) for clinical trials [18].

To be eligible for the clinical trial presented, the following requirements had to be met:

Age: Between 2 Years and 40 Years

Gender: both

The participant had to be diagnosed with ASD or Asperger's Disorder.

Participants were considered as non-eligible if they suffered from hearing impairment.

Presentation of test data

The test considered in this paper is based on nine subjects using the two channel EEG device and BMS in unknown non-controlled environment such as the test subject's personal household. Participants in this study signed a disclaimer and submitted their reports daily. No remuneration was given to the subjects in this study. Also, none of the members of the staff had direct access to both the subjects and their reports respectively.

Participants in this study are all aged between 6 and 18 years and have all been diagnosed with ASD, although the severity of the condition's diagnosis varies from Pervasive, Asperger's Syndrome to Classical Autism. Since the subjects submitted their reports voluntarily, the regularity of BMS report submission, as well as the total amount of reports submitted varies with the test subject. Due to possible variability in the data and amount of data sets between subjects, the obtained BMS reports are not analysed across subjects but analysis of test results is performed on each data set independently.

Nine subjects were in accordance to the participant selection policy employed in this study; however, only eight were accepted while the other subject was eliminated due to the lack of reports submitted. The first 10 session reports of each participant were not considered for analysis in order to give the participants enough time for adaptation.

Furthermore, from all eight accepted subjects, the focus of analysis was done on a particular one of them. This is due to the highest testing data reports obtained from the subject. A total of 124 reports were submitted for analysis from this particular subject.

Procedure

Each session accepted for analysis in this paper involves the test subject's usage of the two channel EEG device and the BMS for a fixed 40 minute pre-programmed session for not more than once per day. Such a session involves the user wearing the two channel EEG device headband with the two electrodes placed symmetrically on the frontal lobe. The user then connects to the BMS and undergoes a session while sitting down and wearing headphones. Furthermore the user was asked to minimize eye blinking and movement in order to reduce artefact generation on the EEG signal obtained. As the session ends, the user is provided with a report in Portable Document Format (PDF). This document is conveyed to AAT Research and analysis is performed on the waveforms presented in this report. These PDF type reports were converted to a Portable Network Graphics (PNG) type of image in order to extract data from the PNG images using image processing techniques. To do this, an algorithm was built in which a set of PNG report images were selected for analysis. Each report was cropped in such a way that only α, β and δ waves are left of the original report image. The image now obtained, has a binarization procedure performed on the respective red (R), green (G) & blue (B) images using a threshold of 0.86. This provided us with images of α, β & δ waveforms independently. The respective waveform images' bounding box coordinates were detected and each image was scanned horizontally to detect the amount of voltage peaks occurred during the respective session of every wave type i.e. α, β & δ. A peak is defined as a rapid change in voltage from baseline voltage exceeding a certain threshold set.

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Moreover, parents of the children participating in this study were given a question to answer to have direct feedback on the progress of the child using the two channel EEG device headband and BMS system.

Results

Refer to (Tables 1-4) and (Figures 6-22).

Analysis and Discussion

δ waves, which in a healthy normal person are recorded during deep sleep (stage 3 & stage 4) [19], tend to be at high levels at all times in persons diagnosed with ASD, even while they are awake [19]. In a study done to compare normally developing children and children diagnosed with ASD, it was concluded that brain asymmetry activity in children with ASD is caused by higher δ wave activity [20]. With reference to this result, in the presented study, δ waves are being suppressed. Suppression of these δ waves could be seen in Figure 22.

Results displayed in Figures 14,15 and 22 show how δ wave peaks tend to have lowered in peak levels in the respective time in which the respective subject is using the 2 channel EEG headband with the BMS. A significant improvement could be seen when comparing the δ peak levels in the first session to that in the last session reported.

Analyzing Figures 16,17 and 20, we can conclude that during the periods in which the subjects are being analyzed, all participants tend to have increased levels of α wave peaks over time. α waves are produced in state of relaxation and closing eyes [19]. As a result, it could be concluded that the subjects being studied in this paper tend to be more relaxed over time. With reference to the cause of lateral asymmetry in

Gender	Medical Condition	Specify your experience on the therapy's effectiveness
Male	Autism	More attention, more calm, less tantrums, but zero improvement in speech
Female	Autism	Longer concentration span, happier, calmer, shows affection, acceptance of peers and siblings respects parents, Obedient etc...
Male	ASD	Our son seems to have calmed down after several sessions
Female	Mild Asperger's Syndrome	Needs more time to see effectiveness
Male	ASD	I noticed that our son has increased in his vocabulary a lot and is now communicating much better. Now he can also describe a situation that happened when we were not present. Actually he is now enjoying communicating. In the past few days he also started to decide what he wants and communicate his decisions too, which is a very positive step.
Female	PDD	Increased academically

Table 1: Parents feedback.

Subject	Alpha Before	Alpha After	Beta Before	Beta After	Delta Before	Delta After
1	652	1960	801	1452	506	322
2	515	775	1066	789	1235	1019
3	15	6	28	78	164	149
4	917	140	850	653	857	107
5	6	309	50	1201	729	470
6	640	251	586	981	535	377
7	907	28	166	160	946	206
8	1088	485	1514	631	984	441

Table 2: Before and after Alpha, Beta and Delta peak levels. This data was used for statistical analysis to test the significant change over the period of time the BMS was used.

Paired t-Test for Before and After Alpha		
	Alpha Before	Alpha After
Mean	592.5	494.25
Variance	162717.4286	414583.9286
Observations	8	8
Pearson Correlation	0.098090614	
Hypothesized Mean Difference	0	
df	7	
t Stat	0.383037635	
P (T<=t) one-tail	0.356529119	
t Critical one-tail	1.894578605	
P (T<=t) two-tail	0.713058238	
t Critical two-tail	2.364624252	
Paired t-Test for Before and After Beta		
	Beta Before	Beta After
Mean	632.625	743.125
Variance	280739.125	224851.8393
Observations	8	8
Pearson Correlation	0.237225587	
Hypothesized Mean Difference	0	
df	7	
t Stat	-0.502800961	
P(T<=t) one-tail	0.315267166	
t Critical one-tail	1.894578605	
P(T<=t) two-tail	0.630534333	
t Critical two-tail	2.364624252	
Paired t-Test for Before and After Delta		
	Delta Before	Delta After
Mean	744.5	386.375
Variance	112743.1429	83050.83929
Observations	8	8
Pearson Correlation	0.604452096	
Hypothesized Mean Difference	0	
df	7	
t Stat	3.608078927	
P (T<=t) one-tail	0.004323133	
t Critical one-tail	1.894578605	
P (T<=t) two-tail	0.008646265	
t Critical two-tail	2.364624252	

Table 3: Paired t-Test results for data from Table 2.

Figure No.	Figure description
Figures 6-13	These figures represent the data analysis obtained from using the algorithm created. Three figures show mean voltage of all sessions, number of peaks and standard deviation from mean for Alpha, Beta and Delta waves for all subjects respectively.
Figure 14 and 15	These figures represent lines showing how peak levels of Delta waves change throughout the sessions
Figure 16 and 17	These figures represent lines showing how peak levels of Alpha waves change throughout the sessions
Figure 18 and 19	These figures represent lines showing how peak levels of Beta waves change throughout the sessions
Figures 20-22	All the data collected was represented as a percentage and all subject's data was plotted in one graph for comparison.

Table 4: Figure explanation.

the brain presented by Stroganova et al. [20], increasing α waves apart from decreasing δ waves helps to compensate for the lower activity and higher activity from the respective hemispheres.

β waves are associated with focusing activities [19]. Results illustrated in Figures 18,19 and 21 demonstrate how the subjects' levels of β wave peaks increase over time while using the two channel EEG device and BMS device. Due to this promotion of β waves, subjects
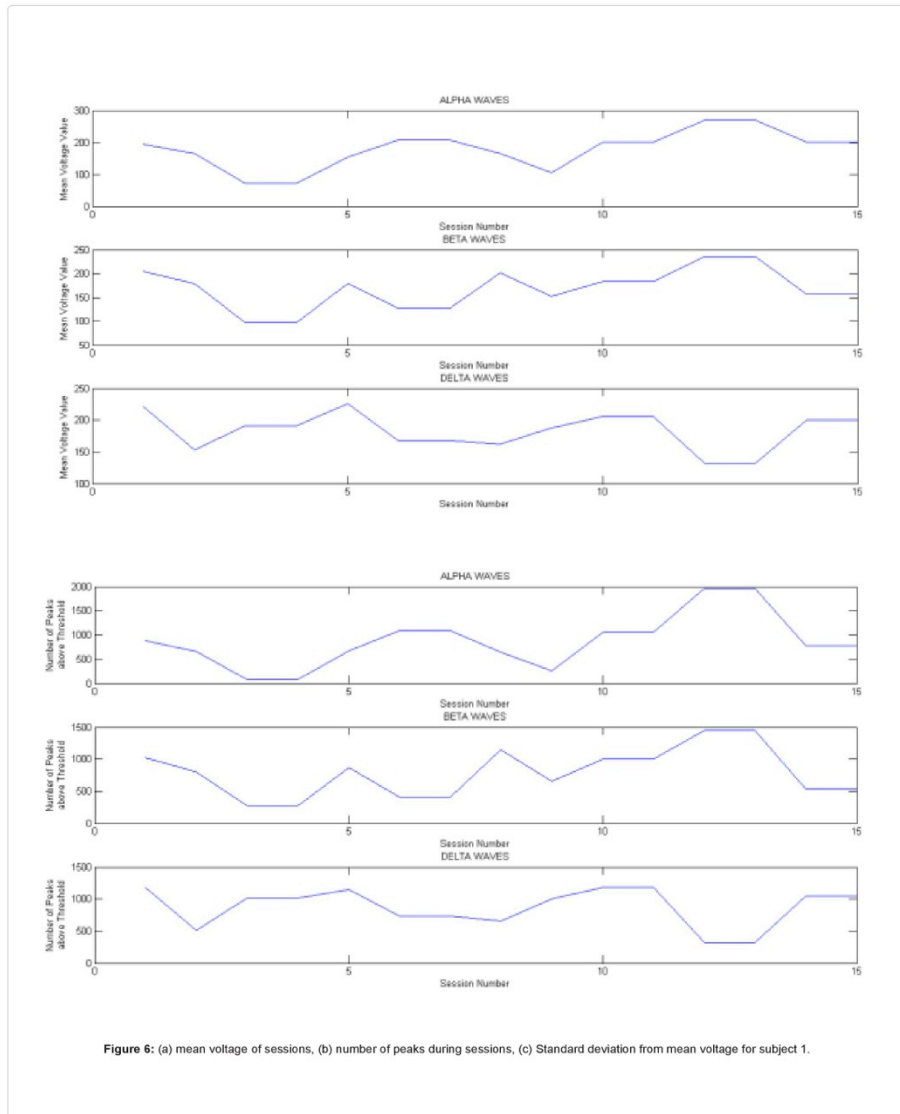
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Figure 6: (a) mean voltage of sessions, (b) number of peaks during sessions, (c) Standard deviation from mean voltage for subject 1.
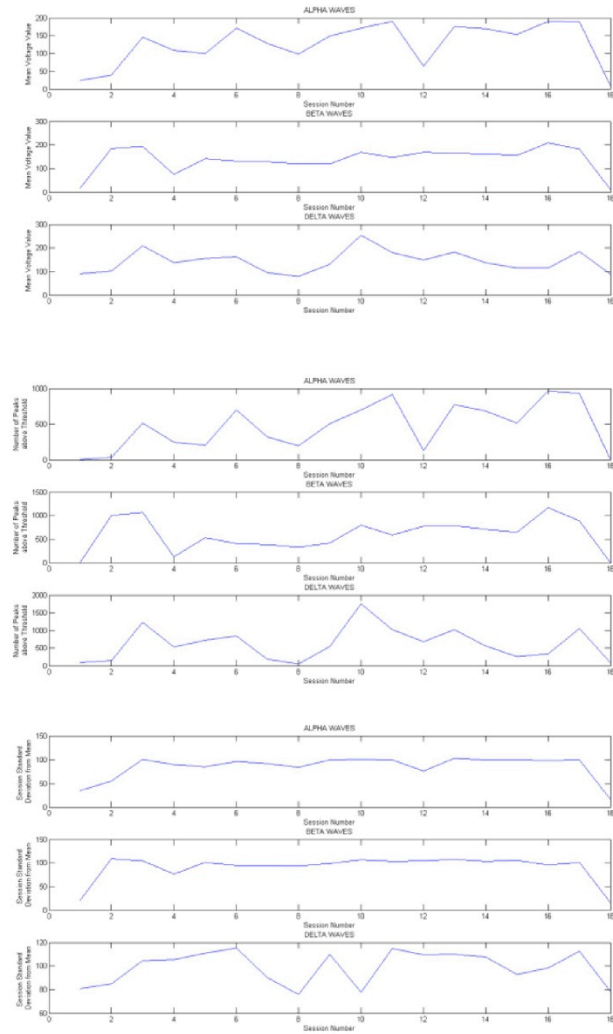
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Figure 7: (a) mean voltage of sessions, (b) number of peaks during sessions, (c) Standard deviation from mean voltage for subject 2.
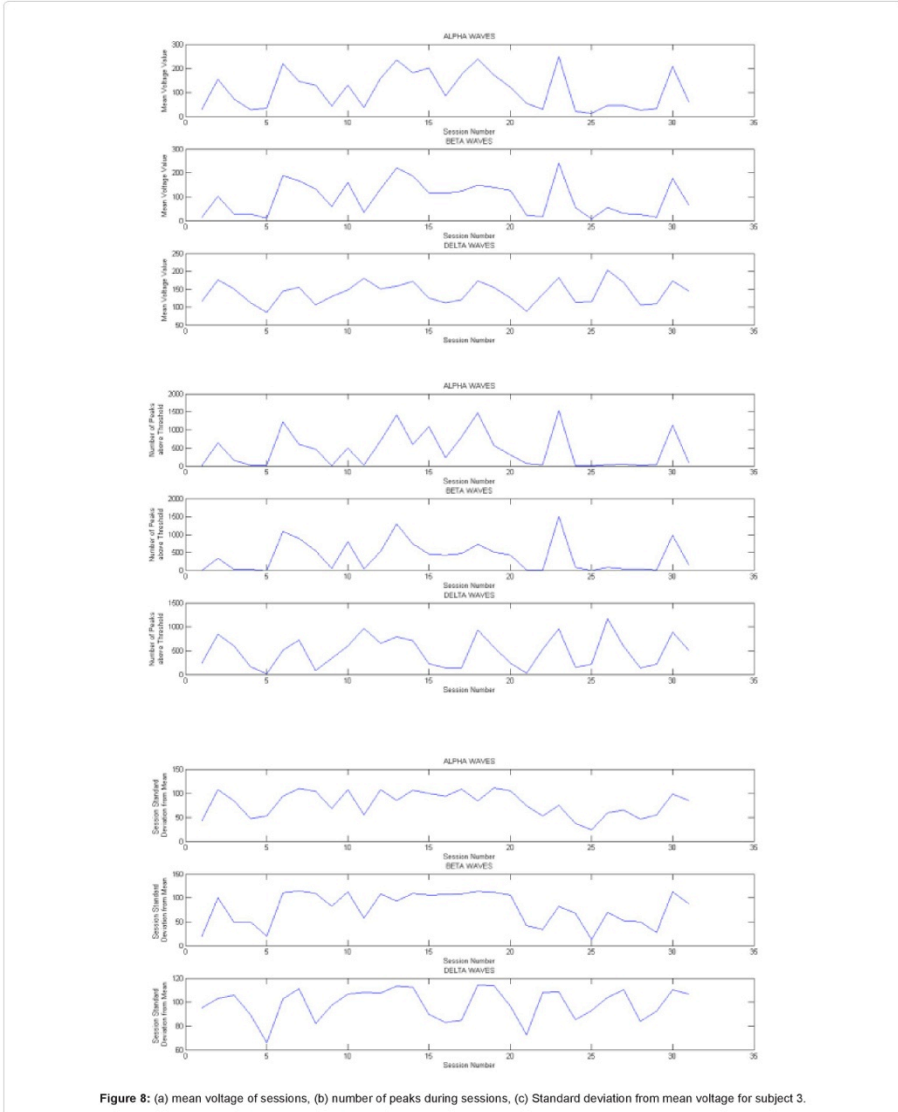
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Figure 8: (a) mean voltage of sessions, (b) number of peaks during sessions, (c) Standard deviation from mean voltage for subject 3.

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Figure 9: (a) mean voltage of sessions, (b) number of peaks during sessions, (c) Standard deviation from mean voltage for subject 4.
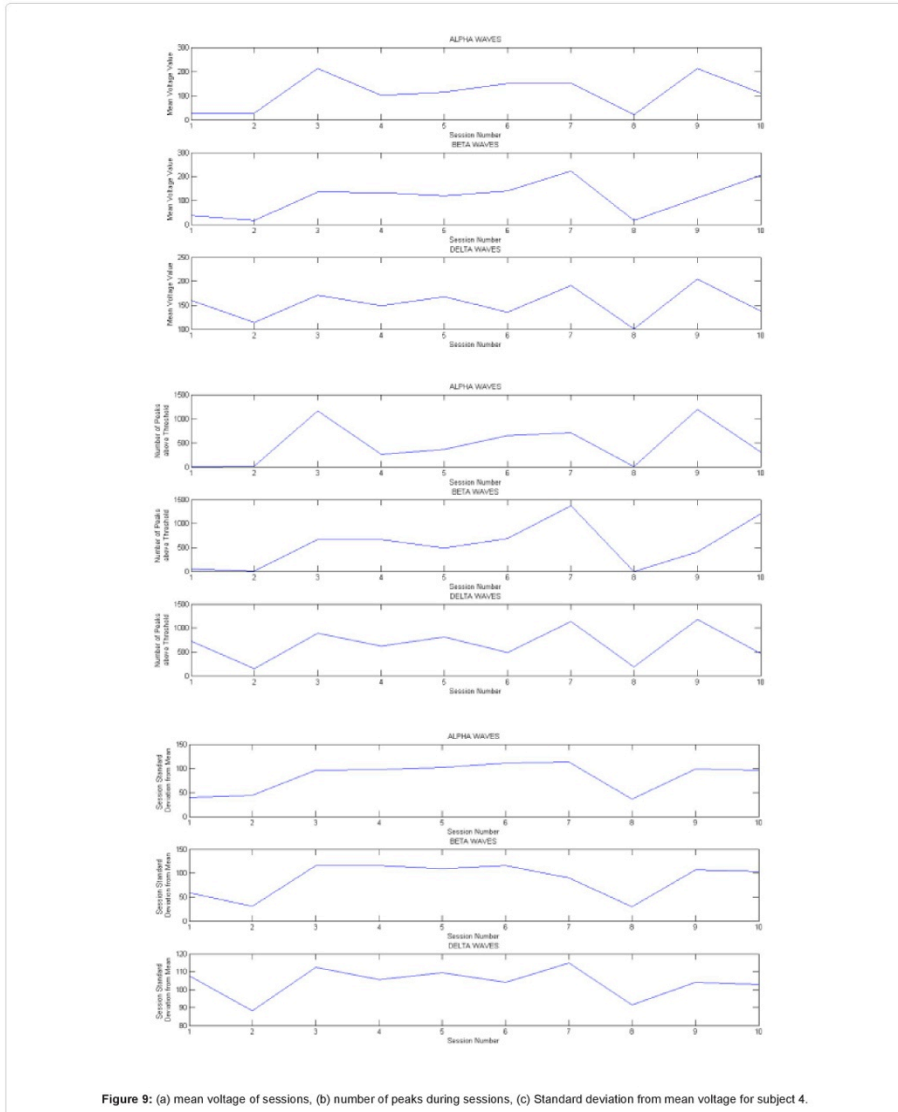
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Figure 10: (a) mean voltage of sessions, (b) number of peaks during sessions, (c) Standard deviation from mean voltage for subject 5.

Figure 11: (a) mean voltage of sessions, (b) number of peaks during sessions, (c) Standard deviation from mean voltage for subject 6.
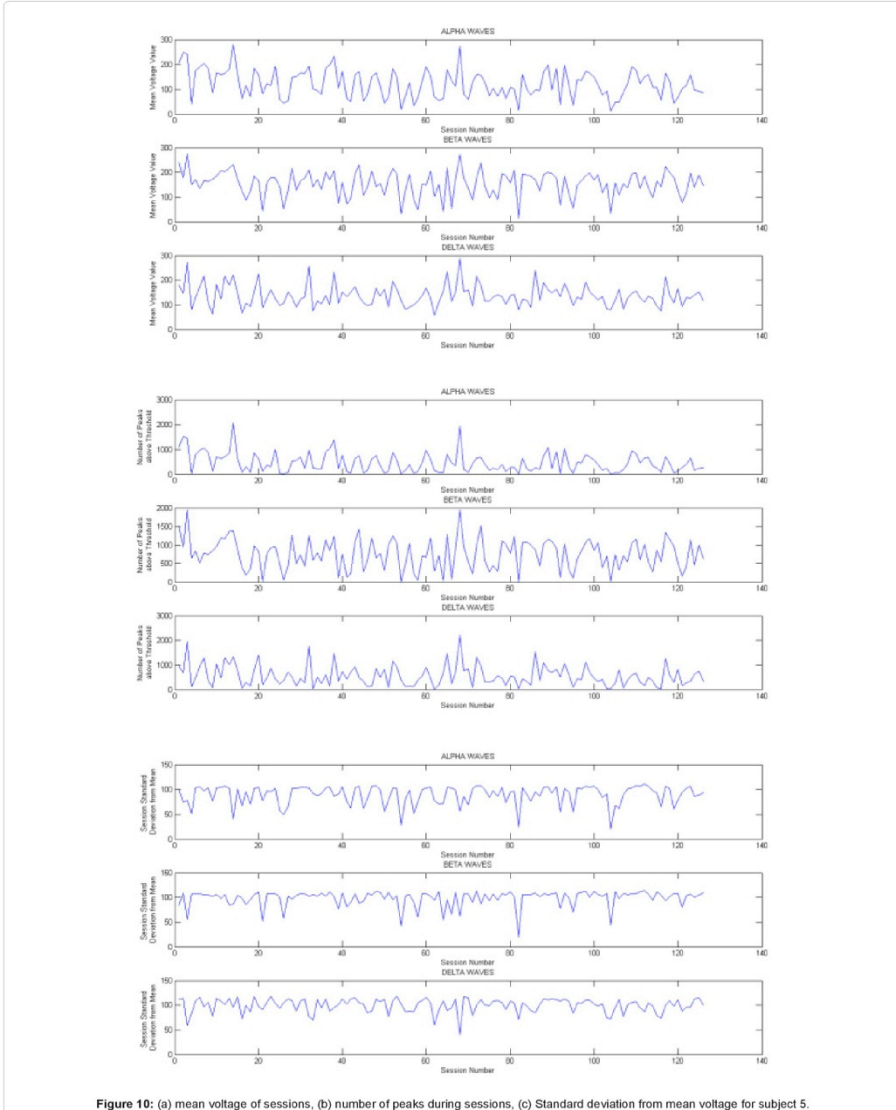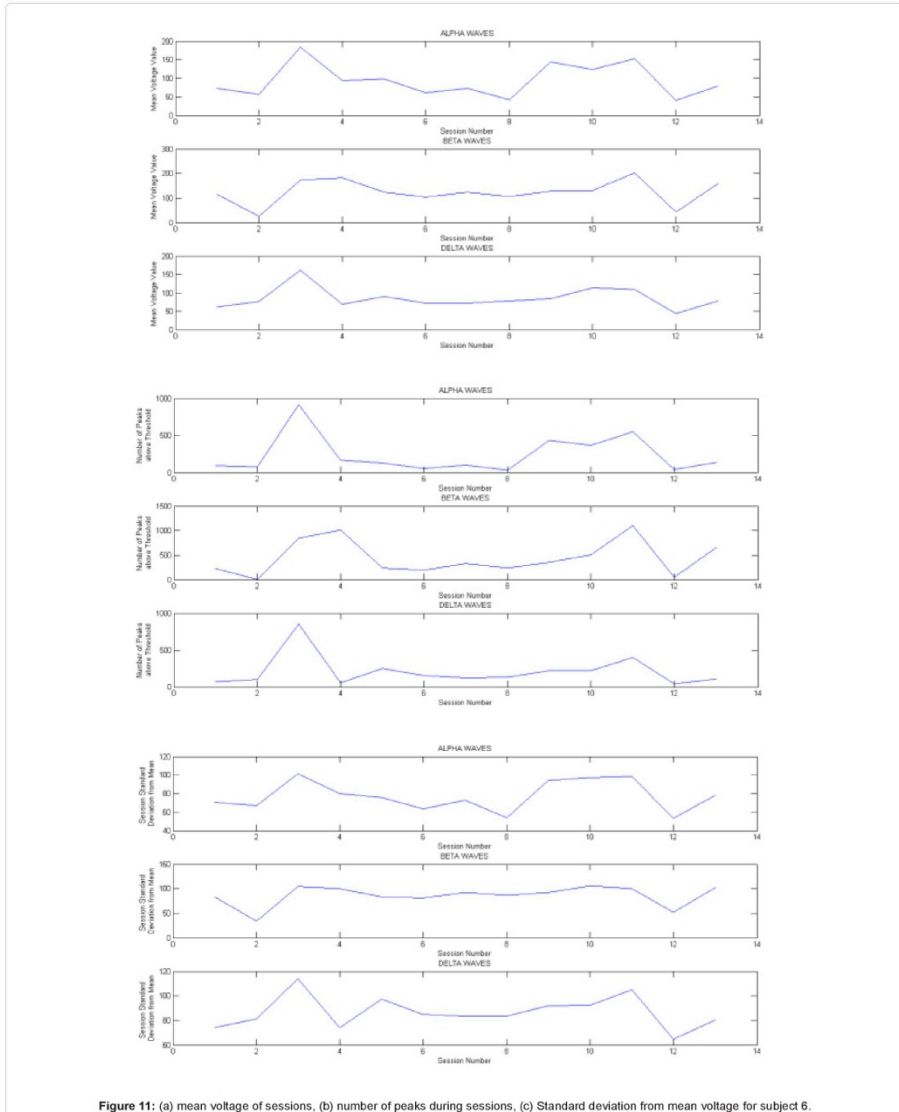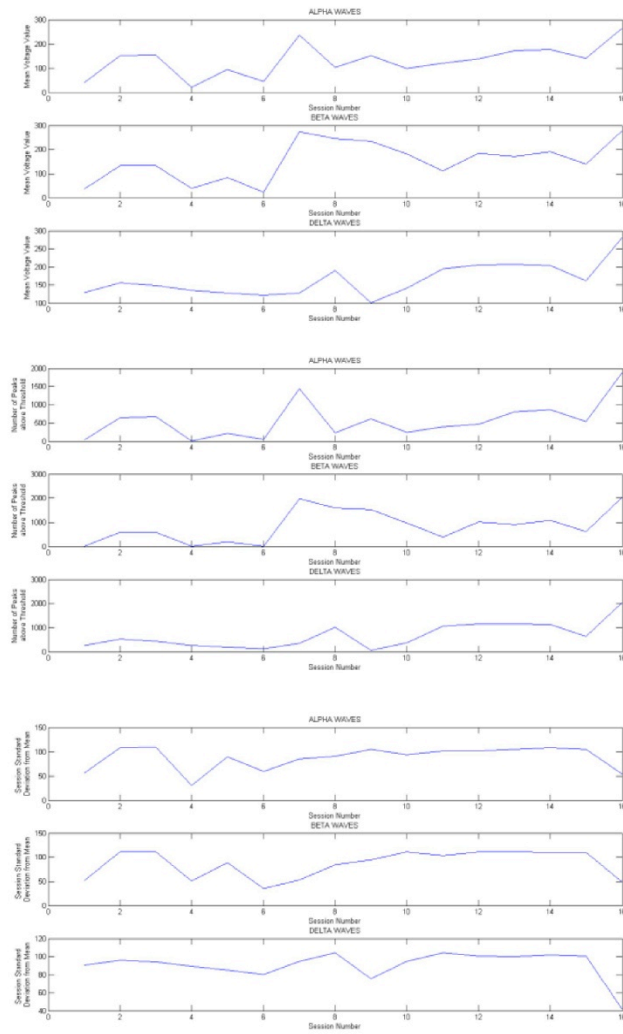
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Figure 12: (a) mean voltage of sessions, (b) number of peaks during sessions, (c) Standard deviation from mean voltage for subject 7.
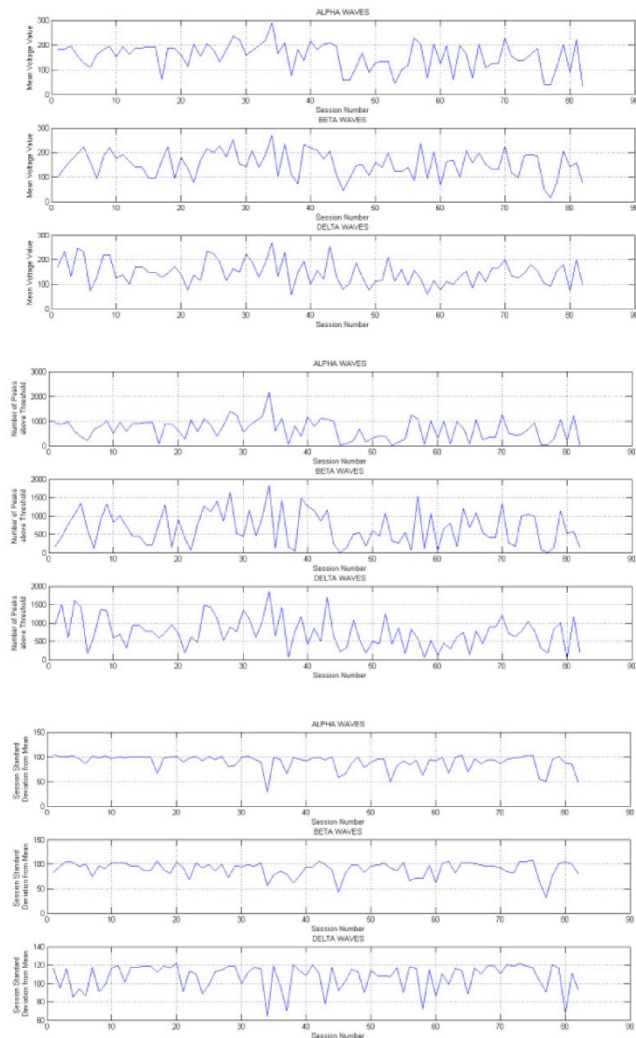
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Figure 13: (a) mean voltage of sessions, (b) number of peaks during sessions, (c) Standard deviation from mean voltage for subject 8.
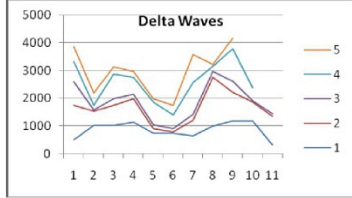
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Figure 14: Delta waves in 5 of the subjects in this study(should u label the axis? Hz vs what?).
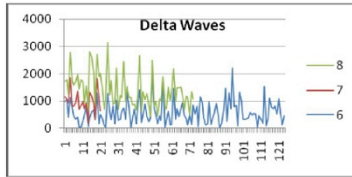

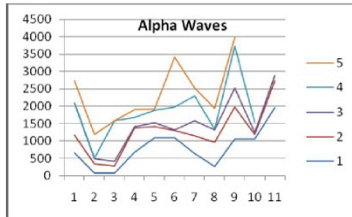**Figure 15:** Delta wave peaks in the 3 other subjects.

Figure 16: Alpha wave peaks in 5 of the subjects in this study.
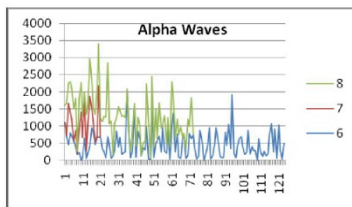

Figure 17: Alpha wave peaks in the other 3 subjects.

two subjects submitted more daily reports than others thus we have more data on the effect of the BMS device. These two subjects are of more clinical interest due to the opportunity to analyze the long-term effect of the BMS. α and β wave peak levels tend to be promoted and increase with respect to previous levels in most of the sessions as demonstrated by the respective figures. However, of more interest in this study is the result obtained in Figure 15 which demonstrates how δ wave peaks tend to be lowered over time.

A paired t-Test was done on data recorded before and after a period of NF training to test if the Null hypothesis could be rejected [21]. This data represents the peak levels of α, β and δ respectively and is shown in Table 2. Results for this test are shown in Table 3 and it could be concluded that for α before and after, the Null-Hypothesis is not rejected since t-Stat is <t Critical one-tail [21]. This implies that statistical difference could or could not have occurred in the period of time. On the other hand, the results demonstrate very positive
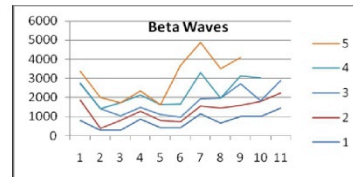
Figure 18: Beta wave peaks in 5 of the subjects in this study.
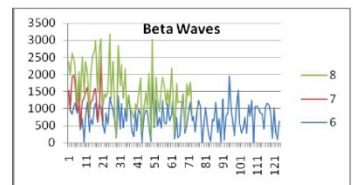
Figure 19: Beta wave peaks in the other 3 subjects in this study.
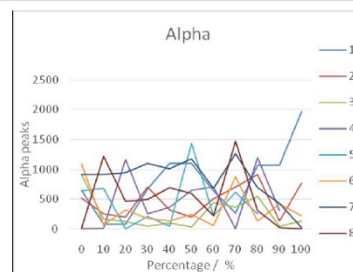
Figure 20: Graph representing Alpha wave peaks of all subject with respect to the percentage of the duration in which analysis was done.

tend to be more focused since their levels of β wave peaks increase.

Figures 15,17 and 19 represent how α, β and δ wave peaks tend to behave over a longer period of time while using the NF device. These

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Figure 21: Graph representing Beta wave peaks of all subject with respect to the percentage of the duration in which analysis was done.

Figure 22: Graph representing Delta wave peaks of all subject with respect to the percentage of the duration in which analysis was done.

statistical relevance for β and δ wave peak levels before and after the NF training period. For the β wave peak levels, the Null-Hypothesis is rejected since t-Stat is >t Critical one-tail and therefore there is statistical difference [21] i.e. β wave levels have increased over the period of time. The most important result from this study shows that δ wave levels have been suppressed and there is statistical difference before and after NF training. In fact, the Null-Hypothesis is rejected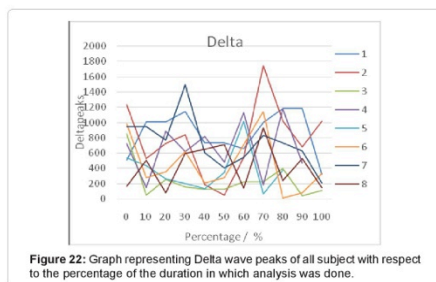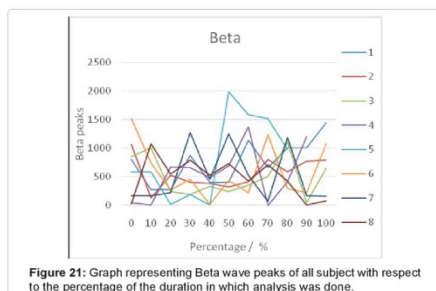 since t-Stat is >t Critical one-tail & P (T<=t) two-tail is smaller than alpha (0.05) which demonstrates that there is statistical difference between before and after data [21].

To summarize the results of this study performed on children diagnosed with ASD, all participants in this trial demonstrated behavioral improvement. Literature states that patients suffering from ASD tend to have atypical functional brain asymmetries which are the cause of different activity in hemispheres causing lower α and β waves while keeping high δ waves activity. The children who participated in this study used the BMS device and the result was that δ waves were suppressed and α and β waves were promoted leading to a lower peak count of δ waves and higher peak counts of α and β waves respectively.

Conclusion

The presented study gave positive and coherent results. The use of the BMS for children suffering from ASD showed significant improvement of the child's behaviour and interaction. A paired t-Test also supported the main aim of the study, i.e. to suppress δ waves in the subject's brain activity. The results show that there is statistical difference before and after the NF training period. To support this statement, apart from all

the analysis done, close relatives of the children subjected to this paper also confirmed the significant improvement in their children's social behaviour. As for future work, comparing the BMS music therapy together with other complimentary therapies should be encouraged.

Conflict of Interest

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Brain Music System :Brain Music Therapy Based on Real-Time Sonified Brain Signals

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Abstract

The paper discusses a standardized therapeutic treatment using the Brain Music System, a system that uses Sonified Neurofeedback accurately and cost effectively to convert brainwaves into musical sound using Digital Signal Processing algorithms. A standard course of sonified neurofeedback therapy (for example 15 sessions), tailored specifically to individual patients suffering from a number of neurological conditions such as Autism Spectrum Disorder is a realistic possibility due to the inexpensive and portable nature of the system, and could be used both inside or even outside of a traditional clinical setting for subjects suffering from a wide array of mental and neurological conditions including Autism Spectrum Disorder. In a pilot study to test the algorithms and output of the Brain Music System, the distribution of the Alpha, Beta and Theta waves in normal subjects corresponds closely to that in published studies using standard high-end equipment (confined to expensive clinical setups). These results allows the Brain Music System to align its protocol to practice standards, and to better associate standard algorithmic tasks to each of the three mentioned brainwave types.

1 Introduction

Listening to music is a personal experience which is influenced by a variety of factors. Music and other mental activities share the same cognitive functions as well as operations. These other mental activities include among others language as a means of expression and communication. However, listening to music for the majority of people is mostly of a receptive nature. The arousing feeling by music and the appreciation of music are essentially the interaction of the musical piece with the emotional and mental status of the listener. Without the expression of this receptive process, exploration of its neuroanatomical substrate is difficult. Nevertheless, the interaction of music with the brain may be reflected in alterations in brain electrical activity, recorded by the electroencephalogram (EEG) as demonstrated by Satoshi et al. A brief exposure to music can lead to an instant improvement in spatial duty performance, correlating with alterations in the EEG power spectrum.

1.1 EEG Waves and Sound Waves

We know that "Sound is a regular mechanical vibration that travels through matter as a waveform" which exhibits all characteristics of longitudinal waves. (Kurtus).Sound waves with specific characteristics can be viewed as music. Alterations of ordinary sound in tone, note, time durations etc. create melody or music. The words of N'Diaye "a distributed network of brain areas has been repeatedly evidenced in timing tasks" identify musical touch of brain waves and activities. (N'Diaye, Garnero and Pouthas). Each state of brain is represented by certain waves called brain waves of which Gamma, Beta, Alpha, Theta and Delta are the recognized brain waves. Gamma waves (30 to 70 Hz) are produced while processing of various attended stimuli…. From an EEG point of view, they will be present mostly while a subject is awake, but they will always be supported by other waves in the beta, alpha, theta, or delta ranges. Usual considerations are given to main brain waves excluding supporting gamma waves. Brainwave activity tends to fall into four groups: beta, alpha, theta and delta. These categories are associated with the rapidity of oscillation (frequency) of brainwaves. It may be asked why usage of sound waves itself are adopted, rather than light or visual rays. This can be resolved by understanding that EEG signals can be easily represented by sound waves due to similarity of both in many of their characteristics. The selection of sound waves instead of light or visual rays is due to the properties of light itself. "Light is composed of transverse waves in an electromagnetic field....The denser the medium, the greater the speed of sound. The opposite is true of light.... Sound travels through all substances, but light cannot pass through opaque materials." (Comparison of Light Waves with Sound Waves). The stated properties of light makes it inappropriate to be compared with EEG signals which are more alike sound waves.

1.2 Brain Structure and Music

It was important to identify the part of brain responsible for creating music. The two hemispheres make up major portion of brain , the right hemisphere is associated with creativity and the left hemisphere is associated with

logic abilities (Brain Structures and Their Functions). The functions of right and left hemispheres make it clear that both are involved while the brain creates music. "Accepted neurological theories suggest that the right hemisphere deals with special elements like pitch whereas the left is responsible for the structure and progress of the melody (Heslet, 2)." Studies of relations between neural regions and music (Levitin, 2006) illustrate the involvement of both hemispheres in creating music.
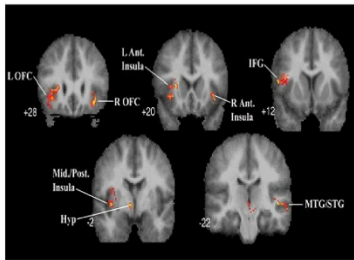

Figure 1.0 (Levitin ,2006)

"Images from an experiment to locate the neural regions of the brain involved in listening to music. Dr Levitin scanned the brains of 13 people as they listened to scrambled and unscrambled versions of a tune." (Levitin , 2006)

Several studies have sought out the points on the brain linked to meditation or music. This research has shown the scope of meditating music for neurological treatment. "Activity in the left prefrontal cortex (the seat of positive emotions such as happiness) swamped activity in the right prefrontal (site of negative emotions and anxiety), something never before seen from purely mental activity." (Meditation Alters Brain Structures). The linking of brain structuring to meditational music experienced is a realistic success for neurology.

1.3 Sonification of Neural Signals

There are various distinct processes involved in converting neural signals to sound signals or sonification of neural signals. It is a fact that "analyzing multichannel EEG signals using sounds seems a natural method: using a sonification of EEG signals.... perceive simultaneously every channel, and analyze more tractably the time dynamics of the signals – hoping to gain new insights about the brain signals." (Vialatte and Cichocki). The sonification of neural signals is done in various steps having separate set of procedures. This process will consist of the following stages:

1. Data acquisition
2. Data pre-processing
3. The creation of visual and

sonic map
4. Visualization and sonification

Usually, Data acquisition process is defined as the phase of data handling that begins with the sensing of variables and ends with a magnetic recording or other record of raw data. The data recorded then undergoes preprocessing during data preprocessing stage. Data preprocessing describes any type of processing performed on raw data to prepare it for another processing procedure. In sonification activity, data preprocessing is done to get relevant input to represent data before creating the actual visual and sonification output. Visualization can be defined as a tool or method for interpreting image data fed into a computer and for generating images from complex multi-dimensional data sets which is responsible for representing recorded data into visual patterns. Visualization is accompanied by sonification which "is the transformation of data relations into perceived relations in an acoustic signal for the purposes of facilitating communication or interpretation" where in our application music is produced at the end. (Hermann).

Various experiments were carried out for deducing some efficient approach for sonification process. Researchers from Georgia Institute of Technology in Atlanta were among those. They were in search of "aesthetically satisfying and educationally useful representation of complex datasets of neural activity through hands-on interaction" sonification procedures. They succeeded in it by their reach to introduce the triumph project on "framework of the "Fish and Chips" project (in collaboration with the Symbiotic Research Group, Perth ,Australia), where they sonified low resolution audio signal from an in-vitro culture of fish neural cells." (Weinberg and Thatcher 246).

3 Impacts of Neuro feedback Music

"Neuro feedback training is brainwave biofeedback." (Hammond). The brain waves are fed back to brain cells so that it helps in attaining a pleasant frequency of brain activity. This method can be viewed as "exercising or doing physical therapy with the brain, enhancing cognitive flexibility and control." (Hammond). By doing this, variations to brain waves can be achieved. But, it is a fact that brain waves are responsible for various activities and moods of an individual. So, through keen analysis and investigation, it becomes possible to change a mood to another by employing neuro feedback. There is extensive experimentation carried out to analyse impacts of Neuro feedback Music. Department of Cognitive Neuroscience and Behaviour within the Faculty of Medicine at Imperial College in London , is an association that explored on the matter through their experiments. They mainly relied on two separate experiments they conducted. "In experiment 1, a group of students was trained on the SMR, Beta1, and a/t protocols and performance changes were compared to a no-training control group and a group receiving additional interventions." (Egner and Gruzelier 1221). The variations in performance brought about by three

different neuro feedback protocols were evaluated. "In experiment 2, different neuro feedback protocols were trained in separate groups and performance changes were contrasted with comparison groups undergoing alternative interventions." (Egner and Gruzelier 1221-1222). Both the experiments dug out the positive impacts of neuro feedback.

4 Brain Music System

The Brain Music System delivers electroencephalographic data as modulated MIDI. It is similar to the brain-computer interface (BCI) system created and amply documented by Professor Eduardo Miranda, but runs optimally even on a 2 channel EEG since it does not depend on the collecting end for the processing functions but uses computational methods which can be supported by regular modern office computers (making its uses different and more accessible due to its cheaper running costs).

4.1 Brain Waves Conversion

A number of methods are available to be employed in analysing the various factors involved in transforming brain waves to music. Power spectrum analysis (PSA) and Discrete Fourier Transform (DFT) techniques are suitable in our context. "The Fourier Transform of the Auto correlation Function is the Power Spectrum." (Nyack). Power spectrum is used in analysing various images which finds application in this investigation as well. The first step in PSA is to Fourier transform the image $I(x, y)$ and calculates the square modulus of the FT to generate the power spectrum, $p(u, v)$.

$$p(u,v) = |FT[I(x, y)]|2$$

In order for us to obtain the active PSA , the FT array is rearranged according to frequencies in a way that the zero frequency is in the centre of the array, the 1st quadrant is in the upper right, the second in the upper left, etc. .

The resulting array was later converted to get values from 1.0 to 10.0 whose logarithm to base 10 is obtained. The array obtained was then used to obtain the required equivalent; here brain waves underwent power spectrum analysis to get music equivalent for them. Discrete Fourier Transform (DFT) is another procedure carried out. "The Discrete Fourier Transform (DFT) allows the computation of spectra from discrete-time data... in discrete-time we can exactly calculate spectra." (Johnson). This definition itself explains the relevance of this method in our analysis of brain waves. Accurate computation is significant for conversion of brain waves to music waves so that least redundancies result.

4.2 System Design

The system used in the current project is built on the basis of the LORETA algorithm discussed about by Filatriau et al. (2007, p. 2). In more detail, the system design includes three major stages, i. e. EEG collection, digital signal processing, and MIDI representation. Graphically, the system design progress is identified in figure 2.0
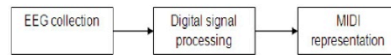

Figure 4.0

This system design permits collection of the EEG waves of the participants' brains with the help of electrodes placed on their both hemispheres. Next, the data collected is processed with the help of the LORETA algorithm (Filatriau et al., 2007, p. 2), and after this the system produces MIDI files on the basis of analogies between the qualities of EEG waves and specific musical notes. As seen from the above statement (Filatriau et al., 2007, p. 2)., the LORETA algorithm plays a crucial role in the operation of the system design This algorithm is based on four major criteria defined and calculated as first, it is necessary to measure the potential of EEG wave occurrence, Φ. Second, the value of the sources producing those EEG waves, φ, is measured. The third and the fourth criteria that help in estimating the second point are the lead field matrix, G, and the rate of additional noise, η (Filatriau et al., 2007, p. 2):

$$\Phi = G \varphi + \eta$$

At the same time, Ito et al. (2006, p. 1153) propose a slightly different formula that includes the role of mental change in sound stimulation, S, and the additional noise, N, for the calculation of Y, the time series data:

$$Y = S + N$$

In any case, both formulae require additional calculations, and Filatriau et al. (2007, p. 2) provide rationale for them, arguing that the bayesian formalism fits the goal of defining the value of the sources producing those EEG waves from the above formula. So, the design system discussed here uses the following formula to obtain the final data that are later sent to the sound synthesis module (Filatriau et al., 2007, p. 2)

$$P(\varphi/\Phi) = P(\Phi/\varphi)P(\varphi) / P(\Phi)$$

The data obtained through the above formula are ready for processing with the help of the LORETA algorithm

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that includes four stages:

1. Sending the data to the sound synthesis module;
2. Associating the brain zones with cognition,
visualization, and movements;
3. Creation of dipoles from the calculated data;
4. Computing the dipoles and using them as
features for creating the respective MIDI files

Thus, the use of the LORETA algorithm is the basis on which the performance of the discussed system design is founded and the scheme described in figure 4.1 becomes possible with the use of this cheaper technology :
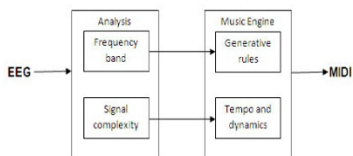

Figure 4.1(Filatriau et al., 2007)

At this point, the system's design performance follows this scheme and uses the LORETA algorithm to enable the researchers to convert the EEG waves into MIDI music files.

4.3 Musical Engine

The transformation of Brainwaves into Sound (Sonification of Neural Signals) is the major task to be tackled by the Brain Music System . The topic itself is arguable and literature does leave a lot of open ended questions as to which methodology to adopt and the success that such algorithmic solutions might have ,

There are various distinct processes involved in converting neural signals to sound signals . It is a fact that "analyzing multichannel EEG signals using sounds seems a natural method: using a sonification of EEG signals.... perceive simultaneously every channel, and analyze more tractably the time dynamics of the signals - hoping to gain new insights about the brain signals." (Vialatte and Cichocki)..

This topic is mainly discussed by 2 peers of neuroscientists that both focus on their distinct interests .1) The Engineering neuroscientists ,2) The Biological neuroscientists . The first peer is more interested in obtaining a functional system that functions in a way that is functional but not necessarily compliant perfectly to what happens during the Brainwave

formation , whilst the 2nd peer is more focused on to representing all the processes that occur during the brainwave formation , in most cases the problem with latter ground being that the designed systems "lack stability " (Miranda 2003)

Miranda and Hofstadter argues that the biological representation of music needs to be linked to 3 important features , these being the timbre , pitch and tempo (Miranda 2003) . We managed to build our system basing ourselves on this concept and keeping in mind the power limitation that our low-end system got (including the fact that the collected EEG data are only collected from limited parts of the scalp and then augmented)
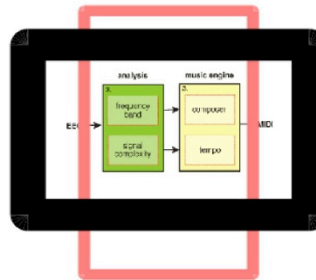
Figure 4.2 illustrates the adapted musical engine and the analysis section adopted by the BMS

The Brain Music System's musical engine is built on the theoretical works by Hofstadter (Hofstadter, K , 2009) and Miranda (Miranda 2003) and adapted and simplified in order to work with a 2 channel EEG , allowing the frequency bands emitted by the different brainwave types to control a purpose built Generative System with the signal complexity controlling the music interpretation .The mathematical formula adopted in this case is

Difference in Signal = Difference in tempo + Musical
Grammar

4.4 Musical Generative Rules

With the system being an "online" one it is difficult to be able to gather the initial musical representation (as the brain signals will need to be stimulated in order to start reacting and sending synchronized signals for processing) . The BMS musical engine does generate computer generated music (not biological music) for the first 2.0 seconds . During this short time frame the music generated by the system does not hold any biological importance and just after that time frame. After that , the system will use the N100 rule (a standard

EEG collection rule that enables a particular collecting algorithm) , with a data collection sample being taken every 80-120 milliseconds as a result of the previous musical representation . Each representation will serve as an auditory stimulus triggering the response used for the next data collection point.

Figure 4.3 illustrates the generative system's sample collection and processing (Miranda,2003)

5 Brain Music Therapy

Neurological   studies show that temporary co-ordination between different and often distant neural assemblies play a vital role in higher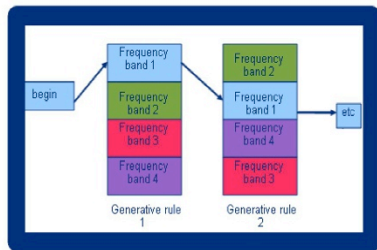 cognitive phenomena. Multiple cortical regions may become co-active during cognitive tasks and also functionally interdependent. For instance, most of information processing most likely takes place in the rear brain regions containing the visual cortex when eyes are open, whereas the principal processing occurs in the frontal brain when eyes are closed (Bhattacharya et al.). It has been shown that listening to music helps to arrange the cortical patterns so that they may not wash out at the expense of other pattern development functions, and particularly, the right hemisphere processes, music is important for excitation and priming of the common repertoire and orderly flow of the cortical patterns responsible for higher brain functions, and helps in the enhancement and facilitation of the cortical symmetry operations among the inherent patterns.   "The cortex's response to music can be thought as the 'Rosetta Stone' for the 'code' or internal language of higher brain function". (Rauscher et al)
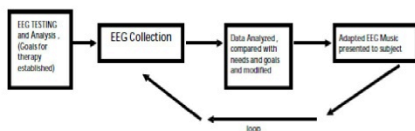

Figure 1 . Brain Music Therapy Diagram

By analyzing the components of an EEG output ; namely alpha, Beta, Delta, and Theta waves, a system can be developed to convert these waves into music by a number of computational methods (modified LORETA in the case of Brain Music System). Various studies show that alteration of this process and presenting to an altered musical representation to the subject in a loop form can help in leveling the brainwaves as a structured type of therapy as shown in "Brain Music Therapy diagram" . This type of therapeutic adaptation can be successfully applied   to a range of clinical conditions such as epilepsy, attention deficit hyperactivity disorder and the locked-in syndrome, and to optimise performance in healthy subjects. "In healthy individuals, neurofeedback has been shown to improve artistry in music students and dance performance".(Egner et al.)

6 Pilot Study

The results for ten subjects undergoing a regular recording of 15 second active blocks using the Brain Music System (as described by Attard Trevisan and Jones) with a Pendent EEG collecting device were collected and presented in the table below. The four different brain waves i.e., Alpha, Beta, Delta, and Theta were color-coded as green, red, yellow, and blue respectively. The table below presents the average values of the four forms of EEG waves for ten subjects undergoing 15 seconds of useful recording blocks.

Objectives of the Study

1. **Check if there are common patterns and levels of Brainwave activity in EEG outputs which can be optimally used in the musical process of the Brain Music System**
2. **Compare Output Brainwave levels by the"modified LORETA" with published literature studies**

6 Results

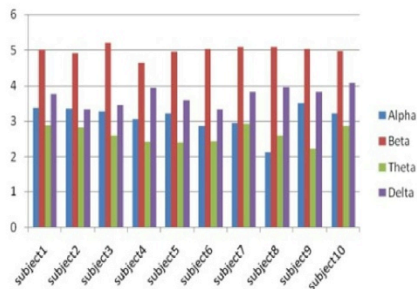| EEG	subject 1	subject 2	subject 3	subject 4	subject 5	subject 6	subject 7	subject 8	subject 9	subject 10
Alpha	3.37	3.36	3.29	3.06	3.23	2.88	2.95	2.13	3.52	3.22
Beta	5	4.91	5.21	4.64	4.95	5.03	5.09	5.09	5.02	4.97
Delta	2.89	2.83	2.61	2.42	2.41	2.45	2.93	2.61	2.23	2.88
Theta	3.76	3.34	3.45	3.94	3.59	3.34	3.83	3.97	3.83	4.07

Table 1: Results Table
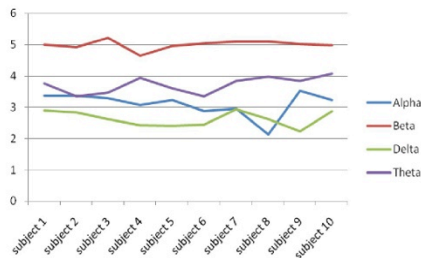
Figure 6.0 : Band Frequency Graph 1

Figure 6.1: Band Frequency Graph 2

The linear Band Frequency Graph 2 shows that throughout the analysis of brain waves, the Beta wave presented as the most significant form of brain with the highest mean wave followed by Theta and Alpha waves respectively. The least form of brain

wave was the Delta wave which had consistently lower figures in most of the subjects.

According to the linear graph, Delta is statistically insignificant in this study in awake subjects and is thus deemed not relevant to include it. The means of the relevant bands recorded in the table above were analyzed and the results presented as Band Frequency Graph 1 and Band Frequency Graph 2. They clearly indicate which of the bands had the most stable output, in order to further confirm which bands should be given priority for its role in the system. The results show that the Beta waves have the most stable output, followed by the Alpha and the Theta waves.

Throughout the analysis of brain waves, the Beta wave presented as the most significant form of wave with the highest mean wave followed by Theta and Alpha waves respectively. The least form of brain wave was the Delta

wave which since the experiment needed subjects to remain assertive had consistently lower figures in each of the ten subjects .

In this study, the Beta wave provides the best avenue for the study of the interaction between a musical piece and the brain. The results indicate that the left frontal regions of the brain are more involved in processing as shown by the higher mean of the Beta range. The right hemisphere may also be increasingly engaged with higher frequencies of the Beta wave. The Beta range can be used to indicate the part of brain that is involved in processing a particular kind of music. The Theta band showed coherence in pattern in the ten subjects and that coherence increased symmetrically, except in just few cases. The Alpha band was characterized by more coherence decreases and extending over longer distances than other bands.

The interpretation of increases in coherence advances the theory of increasing cooperation between two regions of the brain. Decreases on the other hand indicate that mental process under investigation requires lower collaboration between the two regions in order to perform optimally.

Changes in gravity centers of coherence clearly indicate particular significance of the regions involved for processing information and how other cortical regions are involved. In the case of decreases, the region concerned may decouple from other cortical regions. Visual data processing studies have substantiated this view and can be applied to the alpha band as is the case in this study. In other words, attentive listening needs increased attention and suspends the freely floating thinking that could be assumed to take place upon EEG at rest; the two processes lead to parcellation of the cortex in that frequency band that is concerned in general attention processes. Moreover, it could also be that cortical coherence is reduced for an increased information exchange with subcortical sites. "As far as the behaviour in the Theta band is concerned, it was found to be fairly characteristic in processes where memory takes a momentous part (in this case, the violoncellist knew the piece by heart and thus, mentally anticipated every single phrase)" (Hellmuth et al.).

Conversely, emotion is also reflected by coherence. Machleidt et al shows that different bands may be adjacent to different domains of sensory signal processing. It is worthy noting that the extensive twisting of the cortex and the electrical conductivities of tissue layers may cause the electric features of the surface EEG not to be displayed fully. However, characteristic coherence patterns can be found.

7 Conclusion

From this study, common patterns and levels of Brainwave activity in EEG outputs can be optimally used in the musical process of the Brain Music System. The stratification of the different elements of the EEG can help to find out which band is most significant in the musical process of the Brain Music System . The ability of having a standard protocol for a "Brain Music Therapy" program developed on the patient's

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individual needs while rehabilitating from a number of Neurological conditions has been eased and is now possible without incurring excessive clinical expenses. Another area of utilization of such a structured therapy is rehabilitation. People suffering from paralysis and diseases of the degenerative nervous system and who cannot effectively communicate with the outside world without the help of prosthetic devices can benefit from these findings.

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A Home-Based, EEG-Neurofeedback Device for the Management of Children on the Autism Spectrum

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ABSTRACT

Autism Spectrum Disorder (ASD) is characterized by increased levels of delta (δ) electroencephalographic waveform levels, while alpha (α) and beta (β) waveforms tend to be present at lower levels, particularly in the frontal and temporal regions. Non-invasive methods for the management and treatment of ASD have attracted a lot of interest in recent years. We hereby present a system – Mente™ – allowing real-time brain stimulation in the form of a sonified neurofeedback treatment, derived from a portable, 4-channel EEG system. Our results indicate that this system vastly improves behavioral aspects in children with ASD. Statistically significant positive changes were observed in attention levels, physical behavior, and social behavior, indicating that the portable, neurofeedback treatment device can be successfully used in the treatment and management of autism. Normalization of EEG waveforms was also observed following treatment. In conclusion, the methodology proposed in this study using the Mente™ system, has been shown to bring about potential improvements in children with ASD, and can thus be of value in the treatment of patients with this condition.

Keywords: *autism spectrum disorder, EEG biofeedback, sonified neurofeedback, Mente™*

AUTISM SPECTRUM DISORDER (ASD) is a complex developmental disorder characterized by various impairments in physiological, cognitive, social communication and social interaction. Other important characteristics crucial to the diagnosis of ASD are restricted repetitive behaviors, interests, and activities (RRBs) (Lai, Lombardo, & Baron-Cohen, 2014). ASD is nowadays defined by the American Psychiatric Association's Diagnosis and Statistical Manual of Mental Disorders (DSM-5) as a single condition that includes four disorders that were previously considers separately, namely autism, Asperger's syndrome, childhood disintegrative disorder and pervasive developmental disorder unless otherwise specified (American Psychiatric Association, 2013). Prevalence rates of autism vary between 0.62% (Elsabbagh et al. 2012) to 1.47%, with the condition being at least 4 times more common in males (US Centers for Disease Control and Prevention 2014).

Neurophysiological perspective

From a neurophysiological point of view, it has been well-established that frontal lobe activity is associated with higher executive functions such as working memory, sentence comprehension, attention gating, decision-making, social awareness, empathy and emotions (Schultz W, 2015). A separate part of the brain, the amygdala, contributes to emotional response, integrating input signals and initiating activities related to them (Rasia et al, 2000). LORETA and fMRI studies report irrational social and emotional behaviour in subjects with either hypofunctioning or hyperfunctioning amygdalae (Budzynski et al, 2009). Furthermore, bilateral amygdala damage results in remarkably reduced affective responding to both positive and negative external stimuli (Bliss-Moreau et al, 2011). Data from animal and human studies point to a specific amygdala–frontal circuit of emotion generation and regulation. Moreover, anatomical tracing studies demonstrate strong reciprocal connections between the amygdala and the frontal lobes, that is, anterior cingulate cortex, ventro-lateral prefrontal cortex and dorso-medial prefrontal cortex (Banks et al, 2007).

In their study, (Wang et al. 2013) argue how electroencephalographic (EEG) profiles in ASD have altered excessive power in low-frequency waves (such as delta and theta), and high frequency (beta, gamma), but reduced power in the middle-range frequency band (largely alpha). (Figure 1).
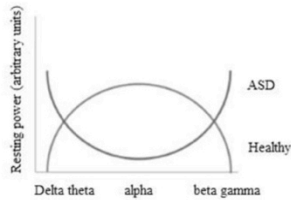
Fig. 1. Graph showing waveform irregularities in Autistic Spectrum Disorder. (Adapted from Wang et al., 2013).

Similarly, a qEEG (quantitative EEG) study performed on children on the autism spectrum showed a high increase in delta absolute power in the frontal and temporal areas of the cortex. This increase in slow wave power is accompanied by a significantly lower alpha power in the autistic brain (Pop-Jordanova et al. 2010).

Management of autism

Management of autism is a complex topic that has gathered a lot of interest in recent years, particularly as to what interventions are most effective, the variables affecting the outcomes of treatment, and the degree of short- and long-term improvements that can be expected (Rogers and Vismara 2008). A survey carried out over the internet by Green et al., highlighted the therapies that parents frequently select for their children with ASD (Green et al. 2006). On average, as many as seven different treatment modalities are used to ameliorate the symptoms of autism in these children. Speech therapy was the most commonly reported intervention. Interestingly, 52% of parents were currently using at least one medication to treat their child, 27% had implemented special diets, and 43% were increasing vitamin supplements in the children's diets. The authors emphasized the need to promote greater use of evidence-based practice by parents in the treatment of their children (Green et al. 2006).

Research has suggested that ASD may be associated with functional disconnectivity between different regions of the brain, pointing to the need for therapeutic interventions that tackle ASD as a neuro-developmental and brain disorder (Baron-Cohen 2004).

Neurofeedback for the management of autism

EEG biofeedback, better known as neurofeedback, aims to modify the brain's altered patterns and neurophysiological state into more desirable waveforms (Pineda et al. 2014). This form of treatment

generally consists of real-time gathering of neuro-physiological data using non-portable equipment and presenting the patient with a stimulus feedback derived from the same physiological data (Kouijzer 2011). In contrast with other modes of treatment, neurofeedback is a non-invasive therapeutic intervention that has been shown to effectively reduce core ASD symptoms (Coben and Padolsk 2007). Most of these studies use suppression of the slow EEG waves, including delta and theta, in order to alleviate ASD symptoms with .success (Thompson et al, 2010) In such studies, the positive effect derived from the neurofeedback treatment, indicated that maintenance of improvement of executive functions and social behavior was maintained for an average of 12 months (Kouijzer 2011). This is in contrast to other modes of treatment such as drug therapy or diet supplementation, which show a reversal in clinical outcome as soon as the treatment is withdrawn.

Binaural beats

When a tone of one frequency and steady intensity is presented to one ear and a slightly different frequency is presented to the other ear, a perception of beats is experienced. This beat would possess a frequency corresponding to the difference in frequency between the two ears. These beats do not reflect a physical property of the sound, but probably the convergence of neural activity from the two ears in the central binaural auditory pathways of the brain. The intensity changes in the perceived sound are therefore called "binaural beats". (Pratt et al. 2009).

Binaural beats are known to elicit neural phase locking firing patterns in the cortex, detectable on the EEG (Schwarz et al, 2005; H Pratt et al, 2009), and can also act as cognitive or neural entrainment (Reedijk et al, 2015), affecting cognitive functioning and mood (Lane et al, 1998). Low-frequency binaural beats are also associated with mental relaxation and high-frequency beats with alertness and attentional concentration (Reedijk et al, 2015).

Portable neurofeedback technology

The need for mobile and portable devices that support quantitative measurements in natural settings in the field of neuroscience has long been recognized (Makeig et al. 2009; Blankertz et al. 2010; Gramann et al. 2011). One of the advantages of small, portable units is that they extend care into the home of the patients, easily treating conditions, while prolonging monitoring of chronic conditions. Moreover, one cannot ignore the fact that smaller, portable devices greatly improve compliance and end-user acceptance of brain-computer interface (BCI) systems (Casson et

al. 2010). Traditional BCI systems are bulky and impractical to use in real-life applications on a daily basis, necessitating the need of portable, wearable wireless systems. This need is being increasingly met by the several wireless BCI systems being introduced by leading research groups and commercial companies (Lee et al. 2013).

A portable neurofeedback device aimed to be worn by children suffering from ASD can help in the early treatment of such a condition, preventing or slowing disease progression more effectively.

MATERIAL AND METHODS

Participants

A power analysis using the Gpower computer program (Erdfelder et al. 1996) indicated that a total sample of 33 people would be needed to detect medium effects (d = 0.5) with 80% power using a t-test between means with alpha at 0.05.

Children with a medical diagnosis of ASD through Autism Diagnostic Observation Screening (ADOS) or a similar diagnostic test were eligible for participation. Children with a history of hearing impairment were excluded from the study since the treatment makes use of auditory pathways. Children with neurological comorbidities were also excluded. Sixty children were registered as being eligible for participation, of which 33 children were randomly selected for participation as part of the intervention group, after obtaining appropriate written consent from parents and/or guardians. Of the 33 participants, 32 were male and 1 was female, with a mean participant age of 5 years ± 4 years. All necessary information was given in writing to the parents and guardians, prior to commencement. A total of eight (8) participants were not in a position to finalize the trial due to usability issues.

Experimental Protocol

The proposed methodology for this research has been reviewed, accepted, and supported by the Università degli Studi di Milano. (Figure 2).

Fig. 2. Methodology used for the clinical evaluation. Participants underwent a series of baseline tests, followed by a 15-week period of neurofeedback treatment delivered daily for 40 minutes at home. After the intervention period of 15 weeks, the participants underwent the same series of tests to identify and quantify any progress made.

Standard tests used to quantify, behavioral, social, and cognitive skills of participants were selected to be performed before and after the intervention phase. These allowed for quantifiable differences between the two phases and acted as a measure of therapeutic effect between the active and control group. All testing was endorsed by third-party psychologists and/or medical professionals with no knowledge of the interventions the children were undergoing. The pre-treatment and post-treatment tests carried out were:

- Electroencephalography;
- QABF test;
- Reynell Developmental Language Scales; and
- PEP-3 test.

QABF (Questions about Behavioral Function classification) test.

The QABF is a measure designed for the functional assessment of behavior problems in persons with developmental disabilities. The rating instrument yields five categories reflecting the behavioral functions of Attention, Escape, Physical, Tangible, and Non-social.

Verbal comprehension of language (Reynell Developmental Language Scales; RDLS).

The new Reynell Developmental Language Scales (RDLS) is used to identify speech and language delays and impairments in young children, aged two or more. It is intended to give an overview of the child's linguistic ability, for guiding intervention, and for evaluating the effectiveness of intervention. The comprehension scale explores the child's understanding of selected vocabulary and grammar and the production scale examines the child's production of the same features of language.

Psychoeducational Profile (PEP-3) tests.

The PEP-3 test assesses skills and behaviors of children, aged 2-7 years old, with autism and communicative disabilities. Results from the PEP-3 provide valid clinical insight into uneven and idiosyncratic development, emerging skills, and autistic behavioral characteristics. They also offer an understanding of the child's unique learning strengths and individual characteristics (communication, motor, maladaptive behaviors) important for learning and education.

The treatment, in the form of a portable, easy to use medical device aimed for home-use, makes use of a wireless 4-channel EEG headband that collects data and transmits it in real-time to accompanying software running on smartphones, tablets, or PCs. This specialized software computes the neurological data in real-time to create additional virtual channels on the scalp, and then use the same computed information to form a sonified, binaural beat interpretation of the neurological data. This binaural beat output is then presented back to the users closing the loop, to allow modulation and induction of the brain into attaining better performance through reduction of excessive delta activity and subsequently increasing levels of alpha and beta wave activity. This process is repeated daily for the 40 continuous minutes, and carried out as early as possible during the day (Figure 3).

Binaural Beat Generation

The neurological data gathered and transmitted to the software is used for computation and eventual binaural beat creation aimed at levelling brainwave activity; specifically the suppression of delta activity and the subsequent increasing of alpha and beta activity. Data is initially pre-processed and prepared for sonification. A number of automated filtering techniques are used to eliminate unwanted readings and then the modified low-resolution brain electromagnetic tomography (LORETA) algorithm is used to compute a more detailed representation of the data available. Power spectral analysis work together with a set of generative rules, which discriminate between power and spectral frequencies of each channel. These create different sound textures and a sonification map of the real-time EEG data.
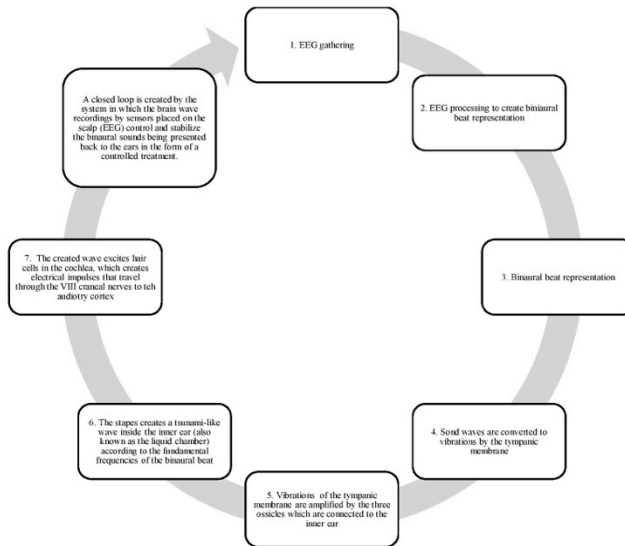

Fig. 3. Chart depicting the steps involved in treatment.

The latter are warbled together to create a sonified, binaural beat output which is now fed back to the patient, stimulating the brain through auditory pathways into interrupting disruptive, excessive delta activity (Attard Trevisan and Jones 2010). This is repeated continuously for 40 minutes, at each given

time, having a binaural beat representation that is derived from the real-time EEG representation of the patient (Trevisan et al. 2013). (Figure 4).
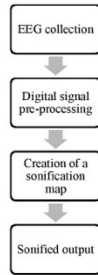
Fig. 4. Methodology used, and steps taken in creating a binaural beat representation used as therapeutic means.

The modified LORETA algorithm

The creation of an additional twelve (12) virtual channels from an existing four (4) real channels on the scalp is achieved through a modified LORETA algorithm as described by (Attard Trevisan and Jones, 2010). The LORETA algorithm is based on the work of (Pascual-Marquiet al. 1994) and the data gathered is used in real-time to get estimations of other brain areas in between the channels. This was shown to be clinically comparable to other 16 channel EEG systems (Trevisan and Jones 2011). (Figures 4 & 5).
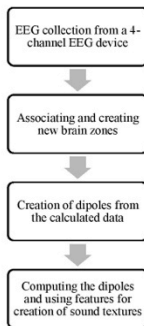
Fig. 5. Methodology used for creation of 12 virtual channels in between the existing 4 channels.
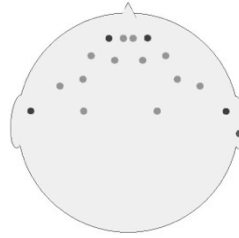
Fig. 6. Final montage obtained after the modified LORETA algorithm.

RESULTS

Neurophysiological data via EEG

Neurophysiological (EEG) readings were automatically derived daily before and after each treatment session. Data collection carried on until May 2015. Any test participants who for some reason or other had five or less data recordings, were not considered for data analysis and interpretations. For eligible data, a paired-samples t-test was conducted to compare waveform activity levels before and after treatment was received.

Results indicate that there is a significant increase in the alpha (α) waveform score post-treatment (M 15.89, SD 15.8); t(-2.931)=, p = 0.003, from baseline levels (M 14.16, SD 14.7). A significant increase in the beta (β) waveform score was also observed, from pre-treatment (M 32.36, SD 24.7) to post-treatment levels (M 37.9, SD 26.6); t(5.9)=, p $\geq$ 0.001. On the other hand, delta (δ) waveforms showed a significant decrease with pretreatment levels (M 53.56, SD 27.5) going down to post-treatment levels (M 46, SD 28.8); t(7.2)=, p $\geq$ 0.001. (Figure 7).

EEG Activity Level Scores
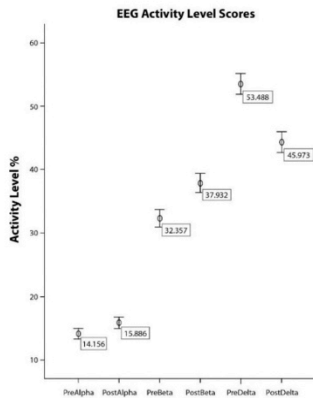
PreAlpha, α-wave pre-treatment; PostAlpha, α-wave post-treatment; PreBeta, β-wave post-treatment; PostBeta, β-wave post-treatment; PreDelta, δ-wave post-treatment; PostDelta, δwave post-treatment

Fig. 7. Graph representing the difference in EEG activity level scores for Pre- and Post-treatment sessions against waveform types.

QABF

Treatment effectiveness was gauged using paired-samples t-test results comparing QABF scores before and after treatment was carried out. The QABF tests gives an indication of any reduction in negative behaviors exhibited by the children taking part in the study. These behaviors were exclusive to hand-flapping, item-throwing, sitting on adults, echolalia, screaming, pushing, imitating others' behaviors, crying, verbalizing instead of answering, and running. Each child was tested for only one behavior at a time. Using the QABF test sheet (Table 1) professionals recorded under which situations the negative behavior was observed.

Scores were based on occurrence, with ratings ranging from never occurring behavior (score = 0) and often occurring behavior (score = 3) across a four-level Likert scale. Since the behaviors under observation were of a negative nature, a reduction in score following treatment was taken to indicate improved overall behavior. Based on the 25 items mentioned in Table 1, the QABF produces scores in five distinct categories:

- Attention;
- Escape;
- Physical;
- Non-social; and
- Tangible.

Results showed that for the attention condition there was a significant reduction in behavior when comparing scores before treatment (M 1.2, SD 1.003) with scores following treatment (M 0.89, SD 99); $t_{(64)}$ = 2.756, p = 0.008.

Table 1. QABF test sheet with list of situations under which maladaptive behavior might be observed.

No.	Behavior
1	Engages in the behavior to get attention
2	Engages in the behavior to escape work or learning situations
3	Engages in the behavior as a form of 'self-stimulation'
4	Engages in the behavior because he/she is in pain
5	Engages in the behavior to get access to items such as preferred toys, food, or beverages
6	*Engages in the behavior because he/she likes to be reprimanded.*
7	Engages in the behavior when asked to do something (get dressed, brush teeth, work, etc.)
8	Engages in the behavior even if he/she thinks no one is in the room
9	Engages in the behavior more frequently when he/she is ill
10	Engages in the behavior when you take something away from him/her
11	Engages in the behavior to draw attention to himself/herself
12	Engages in the behavior when he/she does not want to do something
13	Engages in the behavior because there is nothing else to do
14	Engages in the behavior when there is something bothering him/her physically
15	Engages in the behavior when you have something that he/she wants
16	Engages in the behavior to try to get a reaction from you
17	Engages in the behavior to try to get people to leave him/her alone
18	Engages in the behavior in a highly repetitive manner, ignoring his/her surroundings
19	Engages in the behavior because he/she is physically uncomfortable
20	Engages in the behavior when a peer has something that he/she wants
21	Does he/she seem to be saying, "come see me" or "look at me" when engaging in the behavior?
22	Does he/she seem to be saying, "leave me alone" or "stop asking me to do this" when engaging in the behavior?
23	Does he/she seem to enjoy the behavior, even if no one is around?
24	Does the behavior seem to indicate to you that he/she is not feeling well?
25	Does he/she seem to be saying, "give me that (toy, food, item)" when engaging in the behavior?

Following treatment in these situations negative behaviors decreased by 25.6%. Reduced negative behavior was also evidenced by a significant reduction in escape situations before treatment (M 1.28, SD 1.10) compared to the post-treatment phase (M 1.03, SD 0.98); $t_{(64)}$ = 2.159, p = 0.035. Incidence of behavior following treatment decreased by 19.25% in these conditions. When it came to physical aspects of the condition, there was a significant difference before treatment (M 0.98, SD 0.98) compared to after treatment (M 0.63, SD 0.76); $t_{(64)}$ = 3.407, p ≥ 0.001. Negative symptoms in these cases were 36% less prevalent following treatment. A significant difference in the scores for the non-social condition was also observed, with a 23.3% reduction in maladaptive behavior post-treatment (M 1.06, SD 1.17) when compared to baseline (M 1.38, SD 1.23); $t_{(64)}$ = 3.207, p = 0.002. For the tangible condition a significant difference was reported ($t_{(64)}$=2.04, p =0.046) between pretreatment (M 1.6, SD 1.07) and post-treatment (M 1.3, SD 0.99) with an 18.8 % reduction in negative behavior. The below figures summarize the mean scores differences from baseline to post-testing for the above-mentioned conditions (Figure 8) and mean differences for each of the QABF's 25 listed items (Figure 9).
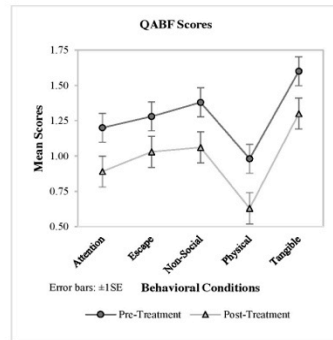

Fig. 8: Graph depicting mean QABF pre-treatment and post-treatment scores for each of the distinct category situations: Attention, Escape, Non-Social, Physical, and Tangible.
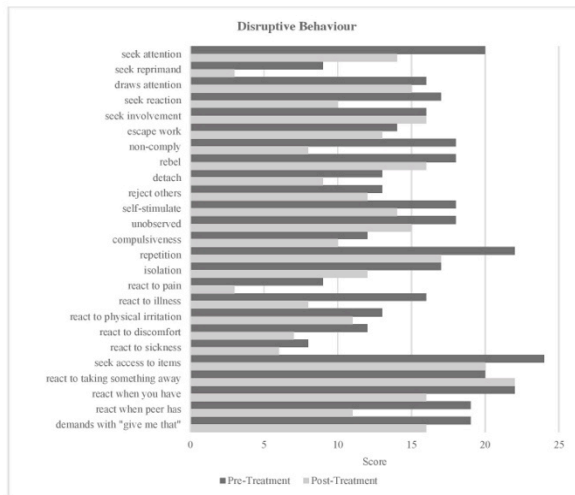

Fig. 9. Mean score differences from baseline (pre-treatment) to post-treatment for communication, motor, and maladaptive response.

Psychoeducational Profile (PEP-3) Test

Improvements in behavior, skills, and communicative disabilities following treatment were further assessed using a Psychoeducational Profile (PEP-3) test. Pre-treatment and post-treatment scores were compared for three categories: communication, motor behavior, and maladaptive behavior. Each category further consisted of three, three, and four subtests respectively, each assessing child performance for a particular task

Paired samples t-tests indicated a significant difference in communication behavior ($t_{(8)}$ = -2.37, p = 0.45) following treatment administration (M 118.3, SD 44.4) when compared to baseline (M 70.89, SD 58.7), with a 66% improvement rate. Although improvements for motor behavior and maladaptive behavior were observed, these were non-significant ($t_{(8)}$ = 0.793, p = 0.45 and $t_{(8)}$ = -1.6, p = 0.138 respectively). For motor behavior, a 15.6% increase in score was observed in post-treatment (M 72.6, SD 30.4) when compared to pre-treatment (M 62.8, SD 29.1), while for maladaptive or behavior an improvement of 20.5% was observed (pre-treatment (M 65.56, SD 21.8; post-treatment (M 79, SD 20.8)). The figure below summarizes the mean scores differences from baseline to post-testing for the three mention conditions above (Figure 10).
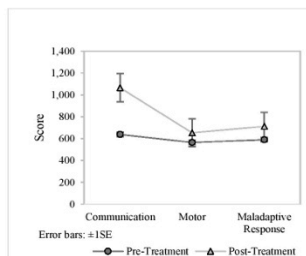
Figure 10. Mean score differences from baseline (pre-treatment) to post-treatment for communication, motor, and maladaptive response.

Individually six out of the nine participants (66.67%) showed a significant difference for all tests overall when a paired sample t-test was carried out comparing pre- and post- test scores. This is indicated in the table below (Table 2). Five of these participants showed improvement differences of 13.8%, 248%, 64.8%, 77.1% and 19.4% respectively. One participant showed a decrease of 5.9% (Table 3).

Table 1. Paired samples test

		Paired Differences							
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	T	df	Sig. (2-tailed)
Pair 1	Part1pre Part1post	-4.000	2.867	0.907	-6.051	-1.949	-4.411	9	0.002
Pair 2	Part2pre Part2post	-21.800	10.528	3.329	-29.331	-14.269	-6.548	9	0.000
Pair 3	Part3pre Part3post	-11.222	14.034	4.678	-22.009	-0.435	-2.399	8	0.043
Pair 4	Part4pre Part4post	1.900	2.514	0.795	0.101	3.699	2.390	9	0.041
Pair 5	Part5pre Part5post	-10.889	4.649	1.550	-14.462	-7.316	-7.027	8	0.000
Pair 6	Part6pre Part6post	0.600	6.501	2.056	-4.051	5.251	0.292	9	0.777
Pair 7	Part7pre Part7post	-1.700	2.830	0.895	-3.725	0.325	-1.899	9	0.090
Pair 8	Part8pre Part8post	2.700	9.056	2.864	-3.778	9.178	0.943	9	0.370
Pair 9	Part9pre Part9post	-5.200	5.160	1.632	-8.891	-1.509	-3.187	9	0.011

Table 2. Paired samples statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Part1pre	29.900	10	14.067	4.448
	Part1post	33.900	10	15.695	4.963
Pair 2	Part2pre	8.800	10	5.731	1.812
	Part2post	30.600	10	13.517	4.274
Pair 3	Part3pre	17.440	9	10.549	3.516
	Part3post	28.670	9	10.344	3.448
Pair 4	Part4pre	31.800	10	13.045	4.125
	Part4post	29.900	10	12.749	4.032
Pair 5	Part5pre	14.110	9	4.457	1.486
	Part5post	25.000	9	7.176	2.392
Pair 6	Part6pre	19.900	10	10.225	3.233
	Part6post	19.300	10	14.780	4.674
Pair 7	Part7pre	30.700	10	14.111	4.462
	Part7post	32.400	10	15.284	4.833
Pair 8	Part8pre	12.300	10	9.889	3.127
	Part8post	9.600	10	6.415	2.029
Pair 9	Part9pre	26.700	10	10.166	3.215
	Part9post	31.900	10	13.486	4.265

Reynell Developmental Language Scales (RDLS)

The children's production and understanding of spoken language was further tested using the RDLS. Test scales are divided into a Comprehension and Production Scale, each containing their own subtests. Of the designated 12 children, nine completed the test.

Paired samples t-tests carried out for the Comprehension scale showed that only two of the eight subtests had significantly different pre- and post-treatment scores. Children showed significant improvements in sentence building ($t_{(8)}$ = -2.3, p = 0.5) after treatment (M 7.2, SD 3.4) when compared to baseline (M 7.9, SD 3.21), as well as significantly improved complex sentence comprehension ($t_{(8)}$ = 2.8, p = 0.22) when comparing post-treatment scores (M 3.0, SD 3.2) to baseline (M 5.0, SD 2.6) (Figure 11).

None of the sub-tests for the Production Scale showed significant differences when the pre- and post-treatment scores were compared using a paired sample t-test. (Figure 12).

DISCUSSION

Based on our results, we can conclude that generally, significant positive changes were observed following therapy sessions using the portable auditory neurofeedback device. These positive changes were evidenced by significant neurophysiological improvements as well as significant behavioral improvements.
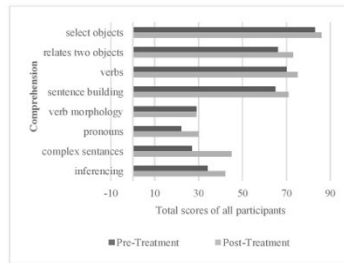

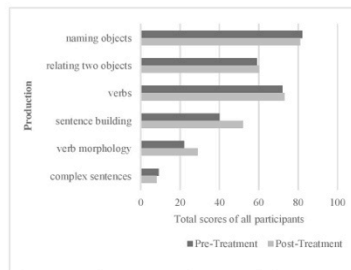Figure 11. Reynell Developmental Language Scales (RDLS): Comprehension scale

Figure 12. Reynell Developmental Language Scales (RDLS): Production scale

Electroencephalography showed a significant increase in both alpha and beta waveforms and a significant decrease in delta waveforms were observed in participants following therapy sessions using the auditory feedback device. In their review, Wang et al., 2013 suggest a U-shaped pattern of abnormalities in individuals with ASD (Figure 8) (Wang, et al., 2013), which pattern was confirmed by our baseline tests. The changes documented post-treatment can be thus interpreted as a reversal of the autism effects and a return to normal, healthy levels.

QABF scores showed that the children tested exhibited less maladaptive behavior across all situations, which was previously used to gain attention, as an escape solution, in non-social settings, and through physical situations. This was evident from the lower behavior scores recorded in the post-treatment condition compared to the pre-treatment ones. These results are in line with other published studies of Jarusiewicz (2002), Coben & Padolsky (2007), Pineda et al. (2008), and Kouijzer (2011) who found improvement in social behavioral and communication skills after neurofeedback training as well. In Kouijzer et al., (2009), significant improvements in social interactions, communication, and stereotyped and repetitive behavior, were reported by parents of children undergoing neurofeedback.

None of the sub-tests for the Production Scale showed significant differences when the pre- and post-treatment scores were compared using a paired sample t-test. We attribute this lack of significance to the fact that the number of participants was low, some sections were missing as participants refused to collaborate.

PEP-3 results showed a significant improvement of 66% in communication behavior, while non-significant improvements in motor behavior and maladaptive behavior were also observed (15.6% and 20.5% respectively).

Reynell scores also show a significant improvement in comprehension scale tests dealing with sentence structure and sentence building. Changes observed in the Production scale were deemed non-significant. This could be due to the low number of participants who have complete the test, which could have affected the testing outcome. This limitation, also gives an indication of the general limitations of this study, which are mainly participant based.

These encouraging results can be backed by data on the neurophysiological effects and behavioral changes of binaural-beat neurofeedback. It has already been established that both frontal lobe and the amygdala are associated with higher executive functions, social awareness, empathy and emotions (Schultz, 2015; Rasia et al, 2000). Budzynski et al. report irrational social and emotional behaviour in subjects with either hypo-functioning or hyper-functioning amygdalae (Budzynski et al, 2009).

Furthermore, bilateral amygdala damage results in remarkably reduced affective responding to both positive and negative external stimuli (Bliss-Moreau et al, 2011). Data from animal and human studies point to a specific amygdala–frontal circuit of emotion generation and regulation. Moreover, anatomical tracing studies demonstrate strong reciprocal connections between the amygdala and the frontal lobes, that is, anterior cingulate cortex, ventro-lateral prefrontal cortex and dorso-medial prefrontal cortex (Banks et al, 2007).

Although amygdala-frontal connectivity is beyond the scope of this study, we can conclude that the neurocircuitry of emotion and behaviour regulation is dependent on this connectivity (i.e. temporal correlations of activity across spatially distributed brain regions). Binaural beats elicit neural phase locking firing patterns in the cortex, detectable on the EEG (Schwarz et al, 2005; H Pratt et al, 2009), and they act as cognitive or neural entrainment (Reedijk et al, 2015), affecting cognitive functioning and mood (Lane et al, 1998). Low-frequency binaural beats are also associated with mental relaxation and high-frequency beats with alertness and attentional concentration (Reedijk et al, 2015). The stimulation induced by the binaural beats could further be extended to other parts of the brain, including the amygdala (amygdala-frontal connectivity). This would fit with the amygdala theory of autism (Baron-Cohen et al, 2000) and the observed behaviour and emotional changes seen in this clinical trial. Though we are not in position to give evidence for a direct connection between our results and modulation of amygdala–frontal circuits, it appears that connections between the temporal lobes and circuits that mediate emotions may be the pathways by which Mente™ produces its results. After these promising results, it is probably arrived time to investigate thoroughly and in detail this hypothesis.

As with most studies, study power could have the participants taking part in the study. Moreover, the specific inclusion criteria related to neurological co-morbidities made the recruiting stage challenging, resulting in limitations such as the much higher male to female subject ratio in our study compared to the normal 4:1 ratio found in the general population. We also encountered difficulty in convincing children and their parents to participate and complete the study, which has put restrictions on the sample size. Dropout rate was also high, because some of the participant or their immediate carers found it difficult to adhere to the daily treatment. This study had originally aimed at collecting QEEG physiological data as part of the pre- and post-treatment but the majority of children refused to wear the EEG cap and we had thus to rely on the headband device to record the relevant data. We intend to eventually carry out a larger study with a larger sample size and a control group and with a

male to female ratio, which better reflects the natural prevalence of the condition.

To conclude, results indicate that behavioral aspects were vastly improved with neurofeedback treatment, particularly in the case of attention, physical and non-social aspects; changes were statistically significant. This is in line with recent literature considering neurofeedback as a potential treatment for autism. EEG waveforms were also normalized following treatment. This supports the theory that the neurofeedback device being tested offers good individual neurofeedback response in children lying in different parts of the ASD arc. In conclusion, the device proposed in this study can bring about potential improvements in children with ASD.

DISCLOSURES

AUTHOR CONTRIBUTIONS

A. Attard-Trevisan designed and supervised the study, and analyzed the data. P. Cavallari supervised the study. N. Caruana designed the study, collected and analyzed the data, and wrote the paper. R. Mallia extracted the data, wrote the paper, and edited the final manuscript. R. Micallef coordinated the study participants and collected data.

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EPILEPSY

Overview on Epilepsy

For numerous patients, anticonvulsant medicines could be offered at adequately higher dosages to hinder seizures though the patients normally experience fallouts (Engel et al. 2012). For twenty to forty percent of epileptic patients, medicines are not successful, and even following the surgical elimination of epilepsy-causing tissue of the brain, numerous patients keep on encountering spontaneous ictuses. Regardless of the reality that seizures seldom happen, individuals with epilepsy experience constant anxiety because of the likelihood of their occurrence. Seizure prediction methods have the ability to assist people with epilepsy have more typical lives.

There is rising indication that the temporal kinetics of brain action could be grouped into four classes that encompass Interictal (amid seizures), Ictal (seizure), Preictal (before seizure), and Post-ictal (following seizures). The prediction of epileptic seizures requires the capacity to determine a preictal situation that could be distinguished from the other three consistently. The major difficulty lies in distinguishing the preictal and interictal occurrences (Thomas et al. 2014). The instances of epilepsy could be classified into different epilepsy syndromes by particular present aspects. Such aspects encompass the age that ictuses start, the kind of seizure, and electroencephalogram results to mention a few. Recognizing epilepsy syndromes is helpful in establishing the causes, in addition to the anti-seizure medicines that ought to be taken.

The capability to classify an instance of epilepsy into a given syndrome happens more frequently in children because the onset of ictuses is normally early. Predicting (diagnosing) epilepsy could be a difficult task. On this note, specialists and health professionals have to carry out many tests and collect much information from the patients and family members for a sure diagnosis (Hao et al. 2014). Some tests that the professionals can arrange for the patients to have are electroencephalographic tests, computerised tomography (CT), and magnetic resonance imaging (MRI) scans. The prediction of epilepsy is complicated by the fact that no single test could give a certain diagnosis.

Epileptic seizures occur as succinct occurrences of signs and symptoms because of anomalous extreme or synchronic neuronal action in the brain (Vezzani et al. 2011). The external impact could differ from unrestrained twitching movements to as slight as a short-lived loss of consciousness (absence seizure). The malady of the brain typified by a lasting inclination to produce epileptic seizures is termed as epilepsy. Nevertheless, seizures could as well arise in individuals that do not have epilepsy. It might be exceedingly hard to diagnose seizures since the professionals and specialists are seldom able to witness them at the time of the clinic visit; it is thus crucial to have an accurate account of the events or occurrences. The initial occurrence of seizure normally does not necessitate treatment except when there is a particular impairment of brain imaging or EEG. Five to ten percent of individuals that live past eighty years have had at least a single epileptic seizure and the likelihood of having a second one is between forty and fifty percent. Approximately half of the patients with an evident first seizure have had other slight seizures; thus, their diagnosis could be epilepsy.

EEG in Epilepsy

The cells in the brain continually send information to one another and that could be collected as minute electrical pulsations on the scalp (Fisher et al. 2014). The practice of gathering and recording the pulsations could be through electroencephalographic methodologies. A standard EEG record signifies that a person has a normal pattern of brainwave action while an atypical recording indicates that anomalous patterns of brain activity are being generated and collected. For people with epilepsy, the brain at times does not function normally, which results in seizures, also referred to as epileptic fits. Individuals experiencing seizures could have normal brain activities (as indicated on EEG outcomes) or some minor anomalies in the middle of the attacks; hence, professionals and specialists are crucial during the observation and assessment of the EEG results. The EEG results will assist the health professional determine the kind of epilepsy that an individual has and the factors that could be evoking the seizures, which will establish the most successful kind of medication for the prescription. In uncommon instances, treatment could necessitate brain operation (neurosurgery).

Electroencephalography denotes a fundamental section in the assessment of epilepsy (Heron et al. 2012). The Electroencephalogram offers significant results concerning background recording and is vital for the diagnosis of some electroclinical syndromes. This form of diagnosis bears significant prognostic details, directs choice of antiepileptic medicine, and proposes when to stop the medication. Neurologic evaluation in addition to imaging in the fundamental idiopathic, characteristically genetic, epilepsies are generally normal. After experiencing a seizure (that is, in the course of postictal phase), the electroencephalographic background could be sluggish. Nevertheless, interictal background electroencephalographic frequencies that are greatly sluggish with respect to age denote symptomatic epilepsy. Typical electroencephalographic background implies primary epilepsy (that is, idiopathic or probably genetic epilepsy) (Berényi et al. 2012). Therefore, the electroencephalographic background provides significant prognostic and categorization details, and epileptiform discharges assist medical professionals to distinguish generalized from central (that is, partial) seizures.

In the course of electroencephalographic tests, the electrical indications of the brain are registered (Morrell 2011). The signals generated by the brain neurons are collected by the sensors and when sent to the instrument draw different graphs on a moving sheet traced in ink or on the monitor of a computer. While undertaking the EEG test, the patient lies on the examining bench and approximately twenty sensors are fixed on the scalp. He is then told to calm down and first lie with the eyes open and afterwards closed. The patient could be told to breathe intensely and quickly or gaze at a blinking light, and both actions could generate modifications in the brainwave activities. When being assessed for sleep disorder, the test could be carried out at night when the patient is sleeping. The recordings that entail analysis of body functions when the patient is asleep, for instance, pulse rate, are called polysomnography. A neurologist then analyses the recorded electroencephalographic patterns for anomalies in the brainwave activities that could reveal maladies of the nervous system.

Spatial-Temporal Dynamics in Epilepsy

The emergence of seizures is the major aspect across the scale of epileptic disorders. The epileptic seizures are amid the most common disturbances of the nervous system (Kellermann et al. 2015). In epileptic individuals, a highly synchronized action of neural action is observed and could be recorded with the use of electroencephalographic methodologies. Through the use of analytical methods initiated for the evaluation of intricate nonlinear systems, it was possible to illustrate and measure specific variations in spatial-temporal dynamics in the electroencephalogram that start some minutes prior to and stop a few minutes following a seizure. Such variations seem to develop in a distinctive pattern, ending in a seizure. The developments show that in the near future it will be possible to achieve a signal handling technique with the ability of measuring the EEG more precisely and in finer aspects as compared to the possibility in the course of medical assessment. This will not occur as a surprise since there will be the outstanding evaluation of dynamical patterns on a spatial-temporal course; that is, details that are not directly available through observing the electroencephalographic recordings.

In line with the theory of nonlinear dynamics, state scope denotes the usual domain for the measurement of the attributes of nonlinear dynamics (Hesdorffer et al. 2012). It is evident that the incidence of epileptic seizures indicates a spatial-temporal state of transition involving extensive sections of the hippocampus, as well as the neocortex. Such a transition seems to arise over a greater time range as compared to what can be elucidated by existing theories of epileptogenesis. Anchored in multiple analyses of epileptic seizures from the recordings and neuron modelling, the condition could be divided into different spatial extents to demonstrate that the spatial degree of every patient expresses numerous time scope actions.

Detection and Prediction of Seizures on Scalp-EEG Data

EEG has acted as the most commonly employed tool for medical assessment of brain action hence making the categorization of epileptic seizures a possibility (Tomson et al. 2011). EEG data denotes the amount of current that is produced in the course of synaptic fervours of the dendrites of numerous neurons in the cerebral mantle. They are measured by multiple sensor electroencephalographic instruments that could be placed either inside the brain, on the cerebral mantle beneath the skull, or some positions on the scalp and could be expressed in dissimilar styles. The majority of the traditional techniques for the evaluation of epilepsy, anchored in the electroencephalogram, are centred on the recognition and categorization of epileptic seizures. Amongst them, the most excellent technique of assessment is the visual examination of the electroencephalographic recordings by a professional. Nevertheless, with the initiation of novel data analysing techniques founded on the mathematical hypothesis, there is an augmented concern in the study of the electroencephalogram for detecting and predicting epileptic seizures effectively.

Surges and Sandler have established five conditions (which encompass active alertness, quiet wakefulness, desynchronized electroencephalogram, phasic electroencephalogram, and sluggish electroencephalogram) for the detection of spike and devised a technique for automatic categorization of the condition. The researchers then created practices for detection

of nonepileptic episodes through the evaluation of different factors, for instance, sharpness and period of electroencephalographic waves. There has been an extensive application of artificial neural networks for the identification of seizures (Surges and Sander 2012). The prediction of epilepsy identifies the period of development of the slow signal greater that a number of predetermined standards from scalp-EEG data.

Amid contemporary methods, time-frequency (TF) techniques successfully employ the reality that the origins of seizures are expressed by the TF field. Among the inclinations for effective prediction of seizures is the nonlinear approach. The brain is alleged to be a dynamical system, because epileptic neuronal systems are fundamentally intricate nonlinear formations and a nonlinear conduct of their dealings is, therefore, anticipated. On this note, the approaches have verified the assumption that measurement of the variations in the brain's dynamics from the electroencephalogram may facilitate prediction of epileptic seizures. On the contrary, traditional techniques of evaluation have not succeeded in the recognition of specific alterations before the occurrence of seizures.

Some of the nonlinear approaches that have been initiated include the dynamical similarity index, which quantifies resemblance of electroencephalographic kinetics involving recordings carried out at different periods (Lutas and Yellen 2013). Some techniques initiate factors of standard energy scalp-EEG data. Such techniques state that when seizures occur, there are ruptures of complex epileptiform action and subclinical seizure, in additional to progressive augments in energy in the epileptic centre. The detection and prediction of seizures on scalp-EEG signals is mainly employed in health facilities. However, scalp-EEG data is more exposed to environmental noise and artefacts when judged against intracranial EEG, and the consequential waves are weakened and blended in their processing through bone and soft tissue.

Linear and Nonlinear Measures to Predicting of Seizures

Proof of a steady change was established around 1970 when researchers, utilizing linear data processing measures, found variations in EEG recordings starting a short while before the commencement of seizures (Lin, Mula, and Hermann 2012). Several researchers established alterations in interictal signal or period before the start of seizures though others did not find constant alterations in the recorded patterns. These analyses were carried out through evaluation of moderately brief electroencephalographic samples in a restricted number of epileptic individuals (Devinsky et al. 2013). Even at the point of analysis, the researchers found that the occurrence of preictal modifications in the electroencephalogram increased the likelihood of predicting seizures. Linear measures, for instance, consistency, spectrogram, and energy necessitate the presumption of a linear wave.

Before the end of the 1980s, quicker computers with broader storage capacities ensured the possibility of methodically assessing longer fragments of electroencephalographic recordings before and after seizures from a huge number of epileptic individuals and using more advanced techniques of data processing. Stimulated by assumptions that seizures could emanate from spontaneous conditions in a disorganized nonlinear coordination, researchers like Larson and Halton started employing mathematical approaches initiated for the study of intricate nonlinear systems to evaluate EEGs for qualities unique to the changes prior to and following seizures. In this regard, there was the initiation of ways of reporting quantifiable alterations in the

electroencephalographic dynamics (spatial-temporal and temporal) that occurred before seizures. Such alterations were measured with respect to signal arrangement, wave intricacy, time dependence, and resemblance, all predicted through the creation of multidimensional stage space (Russ, Larson, and Halfon 2012). The actual significance of the measured signals was excellently comprehended when employed in computer-created yield from independent representations of deterministic self-directed intricate nonlinear measures. The restrictions of nonlinear measures have resulted in many researchers regenerating endeavours to predict seizures with linear techniques.

Seizures Control

The objective of treatment in people experiencing epileptic seizures is the realization of a seizure-free position devoid of unpleasant outcomes (Walker et al. 2014). This objective is attained in over sixty percent of the people that desire treatment with anticonvulsants. The majority of epileptic individuals encounter negative impacts from the drugs, nevertheless, and several of them have seizures that are stubborn to medical treatment. Monotherapy is beneficial since it lessens the possibility of negative impacts and prevents the interaction of drugs. Furthermore, monotherapy could be cheaper when judged against polytherapy since most of the older drugs have hepatic enzyme-stimulating qualities that reduce the serum degree of associated medication hence augmenting the needed dosage of the drugs. Patients with seizures encounter psychosocial changes following their diagnosis; hence, social and occupational rehabilitation could be required. Some doctors underrate the impact that an epilepsy diagnosis could have on the individuals. For instance, epileptic patients could live in dread of having the next seizure, and might be incapable of driving or working at high heights. The epileptic individuals with stubborn spells ought to be referred to epileptologists or other health professionals for further treatment, encompassing video-EEG examination, to typify the aetiology of the seizures with the purpose of controlling them. When the likelihood of surgical treatment is mulled over, a neurosurgical professional should be consulted (Heck et al. 2014).

Taking medication has at all times been a fact for the majority of individuals that live with epilepsy (Kwan, Schachter, and Brodie 2011). Before 1990, the selection of epilepsy medication was relatively simple because just a few types were in the market. In the course of the last fifteen years, epilepsy treatment meant for seizures control has had numerous developments. The number of epilepsy medication in the market has increased almost threefold thus enhancing treatment but, resulting in their selection being more intricate. The realization of the most effective medication to a patient involves a bit of presumption. Though it might not be guesswork, there is certainly an issue of testing and making a mistake. Health professionals take into consideration a good deal of information (such as kind of seizure, age, gender, and health conditions) concerning the patient prior to the recommendation of an initial medication. Nevertheless, eventually, the choice of epilepsy medication turns out to be a learned leap of conviction. There is no dependable means of predicting whether an epileptic patient will react to a given drug negatively or the level of fallout that will be encountered.

The new assumption in the treatment of epilepsy is that every means of seizure control has its side effects (Lehnertz and Dickten 2015). Though some health professionals might differ with the assumption, every medicine has its side effects that many individuals experience. However, shifting to an epilepsy medicine with lesser side effects could also be risky though worth it in

terms of the quality of life; some of the risks for such drugs are tiredness, insomnia, and confusion. When it comes to selecting the most excellent medicine, the number of alternatives for controlling seizures could be overpowering even to physicians. Although inaccurate, the control of seizures is at times realized. 50% of individuals with the recent diagnosis of seizure are seizure-free after the initial attempt of epilepsy medication.

Slow Cortical Potentials

Slow cortical potentials(SCPs) denote the unconstructive or constructive polarizations of the magnetic field alterations in the magnetoencephalogram or electroencephalogram that occur for a short time (Breshears et al. 2012). They emanated from the depolarizations of the dendrites in the cerebral cortex and are initiated by synchronous firing. Functionally, they form a standard regulation system for restricted excitatory adoption (unconstructive SCPs) or suppression (constructive SCPs) cortical systems. SCPs could appear as slow unconstructive direct current alterations quantifiable at the scalp. They fit in the group of event-associated potentials, varying from the spontaneous activity achieved from predictable electroencephalographic capacities.

The neurophysiological foundations of slow unconstructive direct current alterations are long-term excitatory postsynaptic thresholds at the dendrites. Slow cortical potentials are linked to intricate cognitive and emotional processing, revealing a broad scope of tasks encompassing intent, motor development, communication, item and occurrence handing, and psychological orientation; eventually, it entails all consciously propelled, attentional, and operating memory tasks. Human beings could discover the means of voluntarily regulating the potentials subsequent to operant training with the aid of immediate feedback and constructive reinforcement for spontaneous slow potential alterations. Following the discovered self-adjustment of unconstructive SCPs, cognitive, as well as motor undertaking of diverse roles are reliant on the particular cortical position of the discerned response. Discovered lessening of cortical negativity augments the rate of seizures and facilitates medicine-resistant epileptic attacks (Peñagarikano et al. 2011). In this regard, the discovered self-adjustment of SCPs is anchored in the redistribution of attentional resources and relies significantly on a prefrontal, in addition to thalamic attention organization.

Working Hypothesis

Nearly a third of all patients who suffer from epilepsy experience seizures despite the presence of advanced epilepsy management tools (Bethesda National Institute of Neurological Disorders and Stroke 2013). Many researchers agree that the development of advanced techniques to detect seizures before they happen is an effective way for customizing epilepsy therapies to different groups of patients (Watson 2014). Similarly, such methods may play an important role in preventing accidents. However, the process of predicting seizures before they happen has not characterized epilepsy management for many decades because doctors always believed that it was impossible to predict seizures because of their randomly occurring nature (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). However, recent advancements in medical research studies have shown that it is possible to predict seizures from the analysis of different brain and nerve cell patterns, which

vary uncontrollably during a seizure. When experiencing a seizure, a patient could manifest different symptoms that include convulsions, rigid muscles, and unconsciousness. Such episodes could lead to fatalities or serious injuries when patients are alone. This is why it is important to predict seizures before they happen to allow patients and caregivers to prepare for such episodes. This chapter delves into explaining the working hypothesis of the mobile epilepsy predictive system, which is an instrument for helping patients to predict these seizures. However, before doing so, it is, important to clarify two terms that lead to confusion regarding this process – prediction and detection.

Prediction vs. Detection

Although there are many volumes of literature that explain what happens during the pre-ictal stage (before a seizure), the terminology is not uniform (Scaramelli& Braga 2009). There has been confusion regarding the use of prediction and detection techniques during the management of epilepsy cases. Although many researchers use the term interchangeably, they do not mean the same thing. Prediction refers to the identification of seizure before it occurs (before some measure of ictal manifestation). Comparatively, detection occurs when identification of a seizure occurs at its initial stage. The Bethesda National Institute of Neurological Disorders and Stroke (2013) says that although this distinction is simple, it is not always clear to many people. The confusion often occurs through different manifestations of EEG data (Binder 2013). For example, data obtained through EEG changes may represent true pre-ictal states, but at the same time, they may denote the earliest manifestations of a seizure. To demystify some of these issues, Binder (2013) proposes the development of a conceptual model that would use different intervention strategies for highlighting the differences between prediction and detection processes. Furthermore, he argues that this approach will show that the prediction of seizures can only occur during the pre-ictal period (Binder 2013). This is the time "when either the clinical, electrographic and/or physiological milieu represents a risky state where the likelihood of progression to a seizure is high" (Binder 2013). Haut (2013) says it is unwise to propose the use of different interventions at this stage because they would be pre-emptive. However, many researchers do not always accept this suggestion because detection usually occurs at the earliest physiological detection of an ictal state (when a seizure starts occurring) (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Such detections may occur before any EEG manifestation. In line with this observation, Lasemidis and Shiau (2003) say that any intervention introduced at this stage would be abortive.

Lipton (2009) says that many researchers have tried to classify different types of epilepsy detection and prediction methods. The most common groups are the linear and nonlinear methods. For example, variance-based and correlation-based methods for epilepsy prediction are linear methods (Lasemidis&Shiau 2003). With the exception of the simple power spectrum-based method, Schulze-Bonhage (2011) believes that all other seizure prediction and detection methods are non-linear. According to Sackellares (2003), researchers could also classify prediction and detection techniques according to the types of EEG used. For example, one category of seizure prediction is the scalp EEG method (Lipton 2009). The iEEG is also another category of prediction methods (Lipton 2009). Although researchers commonly use this classification to understand different types of epilepsy detection and prediction techniques (Bethesda National Institute of Neurological Disorders and Stroke 2013), this paper did not

adopt this classification because the mobile epilepsy predictive system is a non-linear technique.

How the Mobile Epilepsy Predictive System Works

Based on recent advancements in medical technology, researchers developed the electroencephalography (EEG) which can detect rapid changes in brain activity before a seizure occurs (Scaramelli& Braga 2009). It does so by measuring electrical activity in a patient's brain, which is a possible sign that a patient may be about to experience a seizure. Conventional methods of measuring brain wave patterns involve attaching electrodes to the scalp, which turn electrical signals into readable patterns (Scaramelli& Braga 2009). For a long time, experts have used EEG technology to diagnose seizures before they happen (Lasemidis&Shiau 2003). However, this process has often resulted in disastrous consequences, especially when people lose their lives or sustain injuries after a seizure. Therefore, there has been a new push to detect seizures before they happen. This push yielded to further advancements in technology that allowed researchers to use the EEG to do so. In this regard, it has been able to detect abnormal brain patterns, which is a possible sign that a patient could be about to suffer a seizure.

The challenge with EEG is its practicality because it is impossible for epileptics to carry around an EEG machine to know when their next seizure would occur (Lasemidis&Shiau 2003). Instead, experts have embarked on renewed efforts to make the technology work by using portable devices, such as smart-phones, which could integrate the EEG technology (Bethesda National Institute of Neurological Disorders and Stroke 2013). Such devices should detect abnormal brain waves and relay the same to an electronic device. Heart rate and breathing changes are common physiological symptoms that these devices use to detect changes in the nervous system, to predict when the next seizure could occur (Watson 2014). To come up with an accurate understanding of when the next seizure would occur, the EEG uses mathematical formulas to calculate the probability of a seizure occurring. These advanced detection methods used complex algorithms that infuse future computation techniques for detecting seizures. Some common methods used to detect seizures include the scalp and intracranial EEG. Other methods include electrocardiography, accelerometry and motion sensors (Watson 2014). This chapter advances the use of the mobile epilepsy predictive system as another method for detecting epilepsy. This method is unique to other tools for detecting epilepsy because it is non-invasive. Its efficacy in doing so comes from its ability to detect a seizure, 40 minutes before it occurs. The instrument also allows a patient to know of an attack through a smart-phone.

The working hypothesis of this predictive instrument has three main stages. The ability of a headset to detect brain waves is a common characteristic of the first stage. The second stage involves the relay of the brain waves (through Wi-Fi data) to a mobile device, personal computer (PC) or tablet. These devices integrate with other stages of the instrument through a signal relay process that raises an alarm to the user, 40 minutes before a seizure occurs. The diagram below illustrates these step
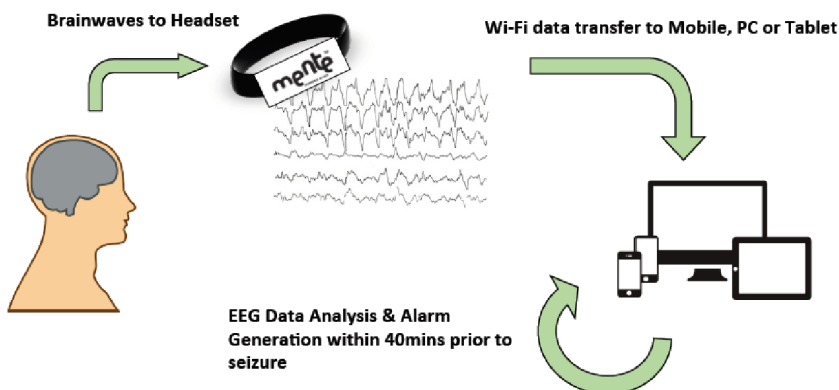
figure 4: how the proposed mobile Predictive System works

The third stage of the above model is the time between the inter-ictal stage and the pre-ictal stage. The latter stage lasts for 40 minutes as described earlier.

Signal Processing

There have been many developments in the field of processing signals for purposes of seizure prediction (Lasemidis&Shiau 2003). For example, there have been several discrete transformations and signal decomposition techniques that have revolutionized how researchers process signals from EEG data (Scaramelli& Braga 2009). In line with these developments, the discrete Fourier transform (DFT) has emerged as a popular signal processing technique. Similarly, the discrete wavelet transform (DWT) technique has cut a name for itself as a popular method for processing signals (Scaramelli& Braga 2009).

Ictal Stage

The inter-ictal state refers to the period between seizures. It also refers to periods between convulsions. According to Eftekhar (2013), many epileptic patients have inter-ictal periods that correspond to 99% of their lives. Experts use statistics from the inter-ictal period to diagnose epilepsy (Schuyler 2007). They do so because the EEG will only show small inter-ictal spikes, which are insufficient in detecting, or diagnosing, epilepsy. EEGs also show mere abnormalities (subclinical seizures) that most experts cannot use to diagnose the condition. For example, some EEG discharges only refer to abnormal waveforms that have little, or no, association with seizures, or convulsions, that occur from epileptic symptoms (Bethesda National Institute of Neurological Disorders and Stroke 2013). When a seizure occurs (inter-ictal stage), it could last for up to two minutes as described in the diagram below
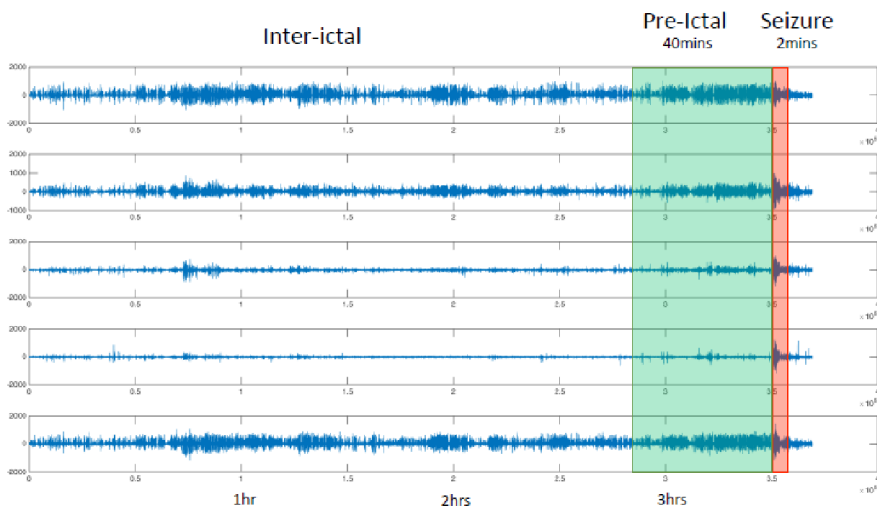
figure 5:different stages of a seizure

The lag between the inter-ictal and pre-ictal period depends on several factors. According to Scaramelli and Braga (2009), understanding these factors is a matter of understanding what somebody is looking for. The mobile epilepsy predictive system chooses to focus on two things – finding the evidence and learning that algorithms find the evidence (Scaramelli& Braga 2009). The first stage involves understanding that transformation evidence of the pre-ictal state involves transforming pre-ictal evidence into EEG features. The last stage involves designing tentative features and allowing the learning process to establish if it is evidence or not. The learning algorithm works as shown below
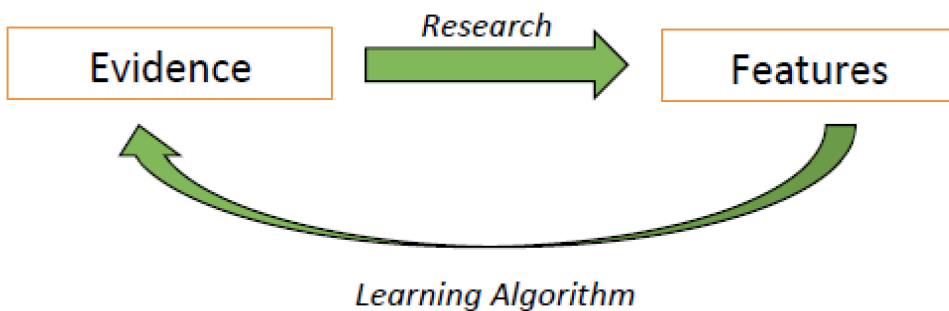
figure 6: proposed learning algorithm

Although the above diagram represents the learning algorithm of how researchers could use evidence to describe unique features of analysis, Ozdemir and Yildirim (2014) say that the body's transition into the inter-ictal stage is unclear. Nonetheless, some researchers claim that the synchronization of a large neuronal population by inhibitory inter-neurons could help

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demystify some of the unresolved issues (Arizona State University 2008). Studies designed to investigate the transition from the pre-ictal stage to the inter-ictal stage have involved humans and animals alike. For example, researchers have used slices of rat hippocampus's brains to investigate this issue (Fricker 2000). Their studies have revealed that GABA actions could be inhibiting (Arizona State University 2008). "Previously it was shown that the hyper-excitable state during transition to seizure could be a consequence of alterations in glutamatergic and/or GABAergic synaptic input in both animal and human tissues" (Zhang and Koifman 2012). This statement led many observers to believe that inhibitory and excitatory synaptic transmissions could potentially affect how patients transition from the pre-ictal state to the inter-ictal state. However, several issues still cloud this belief. For example, researchers still do not understand the extent that excitement and inhibiting factors affect the transition between these two states (Arizona State University 2008). They also do not understand the mediating mechanisms across the two stages. Lastly, Elsevier (2015) says there is little knowledge to explain whether transitions are cell-type dependent or not. Some researchers have strived to explain most of these issues. For example, Watson (2014) investigated the relative contributions of synchronized GABAergic inputs in the process and found that the shifting balance between excitatory and inhibitory inputs affected the transition between the pre-ictal and inter-ictal stages. Zhang and Koifman (2012) did a separate study to investigate the same issue using glutamatergic inputs and their functional roles during ictogenesis and found out that inhibitory GABAergic IPSPs and IPSCs often disappear (lessen) during the pre-ictal stage. This process happened because there was a lower GABA release from presynaptic terminals (Amy 2005). Relative to this discussion, Zhang and Koifman (2012) also "found that this synaptic mechanism of transition occurs in CA3 non-fast-spiking (non-FS) and FS interneurons and pyramidal cells".

EEG Milieu in the Pre-ictal State

The term pre-ictal state emerged in the early 1970s, when researchers struggled to find new ways of detecting and preventing seizures (Drury 2003). In line with this goal, the same researchers used surface or intracranial electroencephalography (EEG) to gather information about seizures. Recent studies have improved the use of computational algorithms to predict and detect seizures. Particularly, researchers have used them to analyse the characteristics of the pre-ictal state using the modalities derived from the EEG (Drury 2003). Recent attempts by researchers to improve the quality of information obtained from EEG modalities have mainly followed two distinct strategies. The first strategy involves improving the detection algorithms for predicting when imminent seizures are likely to occur (Neapolitan 2003). The second strategy involves improving the EEG spatial and temporal resolutions (Neapolitan 2003). These advanced algorithms are supposed to detect patterns that occur in the EEG. Information obtained in this way is supposed to help gather information about impending, or early, seizure activities. At a later stage, they are supposed to provide a trigger for alerting a patient about an impending seizure. In line with this trend, investigators have used different mathematical models to investigate EEG trends (Scaramelli& Braga 2009; Neapolitan 2003). Their attempts have mainly strived to predict the onset of seizures or muscle convulsions. Despite the numerous research studies conducted on this topic, Haut (2013) says there is no better algorithm method that predicts seizures better than chance.

The second strategy for learning EEG patterns involves improved spatial and temporal EEG sampling. Developments that have occurred in this sector have come from advancements in

engineering techniques and the use of new monitoring tools for the pre-ictal stage (Bethesda National Institute of Neurological Disorders and Stroke 2013). For example, recent advancements in electrode designs have helped researchers to improve spatial sampling. Indeed, such advancements have helped to discover new micro-seizures (Lasemidis&Shiau 2003). In particular, individual microelectrodes have been instrumental in helping to make such discoveries. Recent advancements in temporal sampling have also had the same impact because they have helped researchers to detect high frequency EEG oscillations (Lasemidis&Shiau 2003). Such information is useful in predicting the onset of seizures.

According to Reynolds (1861), new technological developments and advancements in algorithms will improve the quality of information pertaining to understanding the onset of seizures and muscle convulsions. Particularly, they would explain how these effects occur in the brain. Such advancements are important because available information quality has several drawbacks (Lasemidis&Shiau 2003). Besides having poor spatial resolutions, many EEG systems also have poor temporal resolutions, which incapacitate them from detecting HFOs (Reynolds 1861). These limitations have elevated the need to develop EEG systems with high spatial and temporal resolutions. In line with this observation, Dzhala (2003) claims that current paradigms require offline retrospective analysis to allow researchers to have a more reliable metric for predicting seizures and convulsions before they occur. This recommendation comes from the errors reported from inconsistencies in detection rates that emerged from previous human trials where patients had recording electrodes implanted in their bodies (Amy 2005; Beenhakker (2009). Cohen (1995) and Binder (2013) claim that they have assessed most of the issues discussed here and recommend "that a more important conceptual problem is that the synchronized neuronal discharges which EEG measures are the end result of a preceding physiologic cascade, making early seizure detection or seizure prediction difficult with EEG modalities" (Binder 2013). As researchers still ponder on whether to adopt these recommendations, or not, no real-time methods of EEG analysis could accurately predict when a seizure would occur (Dzhala 2003). However, the introduction of the mobile epilepsy predictive system is a useful step towards this direction (formulating an accurate and real-time instrument for predicting the onset of a seizure).

Clinical Milieu during the Pre-Ictal State

Researchers have often struggled to find the correct understanding of a clinical pre-ictal state because they use different data to describe this category. For example, some of them argue that constellations of symptoms provide the best data for describing this stage (Schuyler 2007; Scaramelli& Braga 2009). Others argue that the presence of precipitants provide the best data for describing the pre-ictal state, especially because they are more likely to provide a clearer likelihood of an imminent seizure (Lasemidis&Shiau 2003). Cohen (1995) says that many patients have often known that they are bound to have a seizure, hours or even days before the seizure occurs. However, tests show that such characteristics are implicit to specific cases because studies have shown that some patients have unique characteristics that allow them to know of an impending seizure (Bethesda National Institute of Neurological Disorders and Stroke 2013). Therefore, using findings from such patients is unreliable. Furthermore, the data obtained from research that includes such respondents is vulnerable to recall bias. Therefore, the best type of data to use is that which includes information from a large cohort of respondents. The same data should consist of time-stamped information that researchers have

collected over long periods. Many studies have collected information from this area, but few of them meet these criteria (Bethesda National Institute of Neurological Disorders and Stroke 2013).

The presence of prodromal or premonitory symptoms in epilepsy patients is becoming a new centre of focus for many researchers because these symptoms could provide sufficient data to describe a clinical milieu in the pre-ictal stage (Scaramelli& Braga 2009). "Both questionnaire studies and prospective diary studies have identified symptoms such as irritable mood, headache, dizziness, visual changes and concentration difficulties, to name a few, as being reliably prodromal" (Binder 2013). However, this finding is contestable because some researchers have opposed it (Cohen 1995; Schuyler 2007). For example, a recent electronic study contained data obtained from a seizure prediction workshop, which showed that some symptoms are not reliably prodromal (Schuyler 2007).

According to Neapolitan (2003), precipitating factors are a fairer metric for describing the clinical pre-ictal milieu. He says so because they believe that these factors relate to a time when there is a high risk of seizures (Neapolitan 2003). Such precipitated factors may vary according to patients' demographics. However, the most common factors to consider are stress, sleep, and menstrual status (Neapolitan 2003). Litt (2002) reports that the ability of patients to self-report a seizure depends on their ability to be aware of these precipitants and the associated prodromal features. Nonetheless, intriguing, clinical research studies have not predicted pre-ictal milieu with the sensitivity it deserves. For example, pre-emptive pharmacological trials require sensitive predictions of pre-ictal milieus (Litt 2002). According to Drury (2003), this study area is important because f unique prodromal characteristics of predictive symptoms characterized the pre-ictal period, understanding them would enhance ongoing efforts to develop effective instruments for understanding the pre-ictal state.

Physiological Milieu of the Pre-Ictal State

Based on the failure of some researchers to predict the onset of seizures using the EEG methods, experts have looked outside the EEG to find ways of giving them specific and sensitive EEG data (Scaramelli& Braga 2009; Neapolitan 2003). In line with this quest, many of these experts have undertaken animal studies to understand the neurochemical, histological, and behavioural properties of acquired epilepsy (Scaramelli& Braga 2009; Neapolitan 2003). Despite the nobility of this effort, many of these studies are still unable to predict what happens to a patient's brain right before the ictal stage. Based on this challenge, many of the available studies have only focused on identifying the physiological processes that occur before the ictal stage (Bethesda National Institute of Neurological Disorders and Stroke 2013). Several experiments, such as the 1989 rat hippocampus study revealed that electrical resistance often manifests in the rodents before a seizure occurs (Fricker 2000). This resistance often occurred through tissue resistance. The process is synonymous with decreased extracellular space during the ictal period (Bethesda National Institute of Neurological Disorders and Stroke 2013). Researchers have extrapolated these findings and applied them to people. They have suggested that a reduction in brain extracellular space could be an indication of an impending seizure (Fricker 2000). In a different set of studies, a separate group of researchers (Dudek's group) found that the reduction in brain extracellular space (ECS) could increase through hypoosmolartreatment (Fricker 2000). They say so because they found that the treatment

caused epileptiform bursting in the CA1 region of rat hippocampal slices (Fricker 2000). Nonetheless, Lopantsev (1998) reveals that mannitol could reverse this effect.

The above findings have further prompted the creation of new questions in this area of research because researchers, such as Carney (2011), ask if the constriction in the extracellular brain space occurs in vivo. To answer this question, the Arizona State University (2008), says that "Early pioneering studies of ECS parameters using the iontophoretic TMA+ method demonstrated significant constriction of the ECS during seizure activity in vivo, but the temporal onset of ECS constriction relative to seizure onset remained unclear". To explore some of these issues, Shiau (2003) and Lopantsev (1998) have taken upon themselves to conduct further tests using the cortical fluorescence recovery technique. They used photo bleaching to establish the real-time extracellular space that occurs before a seizure happens. They then applied this model to the PTZ model of general seizures and found that "The photo-bleaching technique involves in vivo loading of fluorescein-dextrans into the extracellular space (ECS) of intact brain, followed by laser-induced spot photo-bleaching and measurement of fluorescence recovery using confocal optics" (Binder 2013). Similar to the processes observed during cytotoxixexema, changes in the extracellular space brought further changes in diffusion rates within the brain cavity (Shiau 2003; Lopantsev 1998). Stated differently, there has been slowed diffusion rates associated with this process. The Bethesda National Institute of Neurological Disorders and Stroke (2013) has used these findings to argue that the decreased ECS diffusion could be a predictor of an impending seizure. These findings have shown the proof of concept concerning the use of water movements to detect seizure activity (Shiau 2013; Lopantsev 1998).

Similar to the above studies, Binder (2013) has also undertaken independent research to predict the onset of seizures through electrical impendence monitoring. In this study, the researcher treated animals using picrotoxin and kainic acid (Binder 2013). In some cases, he also used fluorocitrate on the animals. Similar to the 1989 findings of Traynelis and Dingledine's (cited in Carney 2011), Binder (2013) found small instances of electrical tissue impedance in the animals before the onset of a seizure. He also found that the electrical tissue impedance increased with an increase in non-ictal high-frequency EEG activity (Binder 2013). According to this analysis, there may be a direct correlation between ECS changes and pre-ictal HFOs. Similarly, there may be a direct correlation between detectable tissue impedance and pre-ictal HFOs (Bethesda National Institute of Neurological Disorders and Stroke 2013). These findings show that different levels of constriction in the brain extracellular environment have led many researchers to ask questions about ECS constriction. Their focus has mainly been before and during seizure activity. Here it is pertinent to mention the work of some researchers, such as McBain, Traynelis, and Dingledine (cited in Zhang &Koifman 2012), who have used high-K+ models on animals to answer these questions. Their findings have revealed that the ECS volume could reduce by up to 30% before the onset of a seizure (Zhang &Koifman 2012). They also highlight a direct correlation between cell mass increase and ECS constriction (Zhang &Koifman 2012). Experts have often strived to know the cell type that is responsible for the swelling, but researchers have provided little information to answer this question (Binder 2013). Nonetheless, Binder (2013)says that "astrocytes but not neurons express aquaporin water channels that allow rapid facilitated water transport and swelling in response to osmotic gradients". Relative to this statement, Beenhakker (2009) says evidence has shown that osmotic processes often lead to the swelling of astrocytes and not their associated neurons. However, there is insufficient evidence surrounding the prediction of astrocyte or neuron swelling during the pre-ictal stage (Binder 2013). Nonetheless, some independent research

studies have hinted at pre-ictal calcium signalling before the onset of seizures (Arizona State University 2008). Their findings suggest that astrocyte activation may occur before the onset of seizures. Modern instruments for predicting the onset of epilepsy often use such information to alert a patient of an impending seizure (Arizona State University 2008).

System Design

For a long time, people always thought that epileptic seizures occurred randomly and there was no way of predicting its occurrence. While some people still hold this belief today, scientific advancements in medical research has proved otherwise (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). These research studies have stemmed from episodes of patients reporting specific periods when they believed seizures were most likely to occur. However, they have been unable to specify dates or times when they would occur. This paper has capitalized on the need to predict seizures because the unpredictability of seizures could lead to fatalities or injuries, especially if the patients are alone, or are engaged in "life-threatening" activities, such as swimming or driving. The mobile epilepsy predictive system relies on EEG recordings to predict the onset of a seizure. Although there are still many issues regarding the applicability of EEG readings for this purpose, advancements in computer technology and digital EEG technology have allowed researchers to understand EEG recordings and put them to good use using mathematical algorithms to predict the onset of seizures (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Although this paper has shown that, the mobile epilepsy predictive system could predict seizures 40 minutes before it occurs, studies from the 1970s show that these seizures may occur for long periods (Dzhala 2003). Hemodynamic studies have brought a new twist to this assessment by showing that increased blood flow within the epileptic hippocampus is synonymous with the onset of seizures or their associated muscle convulsions (Fricker 2000). To come up with accurate assessments for predicting seizures, it is prudent to have an effective set of algorithms for easy interpretation of EEG data.

Algorithms

Over several decades, different people have developed different sets of algorithms for predicting the onset of seizures. Most of the researchers who have developed them have done so retrospectively (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Stated differently, although people from different parts of the world have their unique versions of these algorithms, few of them have demonstrated clinical usefulness. According to Rajesh (2013), this drawback is the biggest challenge associated with seizure prediction. It mainly stems from the inconsistencies associated with reading EEG data. Varied sensitivity and specificity of statistical testing methods have also compounded this problem because they have caused a lack of uniformity in reading EEG data (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Researchers have used several algorithms to improve the efficiency of the mobile epilepsy predictive system during the pre-ictal period (Bethesda National Institute of Neurological Disorders and Stroke 2013). For example, the method used in the CHB-MIT database includes data from 22 patients, 22 EEG channels, and the number of seizures per patient (Haut 2013). The number of seizures per patient emerges from using statistics from the pre-ictal, post-

seizures and normal states of patients before they experience seizures. The methods for calculating the pre-ictal period also include a set of univariate time and frequency domain features (Haut 2013). They are calculated on 5s time-chunks 264 features, which include 12 features and 22 channels (Haut 2013). The pre-ictal period also uses data from cluster TCs by checking the number of TCs from each class (Bethesda National Institute of Neurological Disorders and Stroke 2013). The classes comprise of the pre-ictal, inter-ictal, and seizure stages. The diagram below represents the holistic understanding of the pre-ictal period.
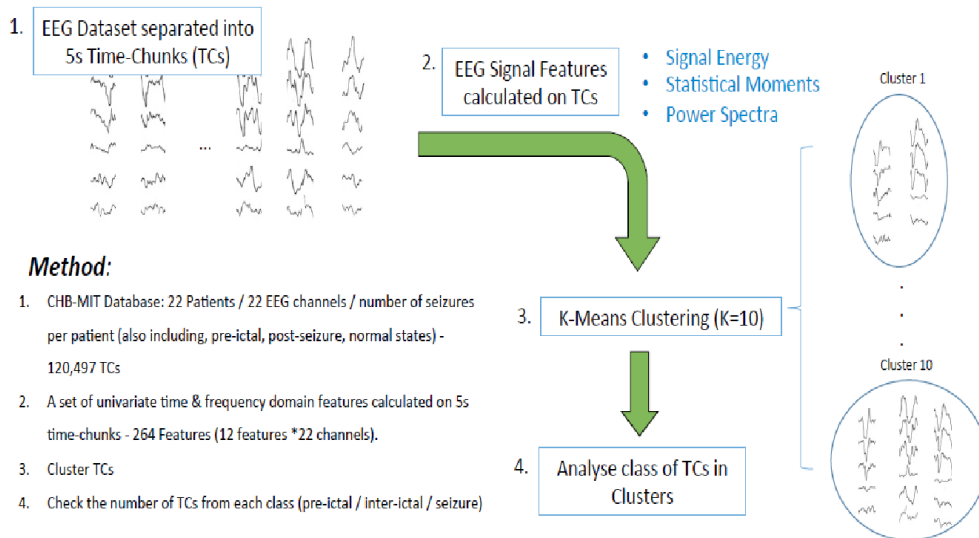

figure 7:pre-ictal period

According to Lasemidis and Shiau (2003), extraction and machine learning techniques have been instrumental tools for developing effective algorithms for managing epilepsy. Bethesda National Institute of Neurological Disorders and Stroke (2013) supports this narrative. Extracting the information obtained from EEG machines is a difficult process because it requires advanced methods for doing so. As such, Alotaiby and Alshebeili (2014) say the use of neural networks and support network machines are effective tools for extracting information from EEG segments. Haut (2013) adds that some researchers have started using Bayesian-based methods to predict seizures. The importance of using these methods and instruments comes from the complex nature of reading EERG signals. In line with this observation, Huang (1996) says, "EEG signals are spontaneous electrical brain activities that exhibit dynamic, stochastic, nonlinear, non-stationary and also complex behaviour". Traditional time analysis techniques have also assumed a linear or stationery approach to the analysis of EEG data. However, new researchers who believe their techniques could provide a more effective way of reading EEG data have proposed new techniques. For example, Ozdemir and Yildirim (2014) propose the use of the Hilbert-Huang transform (HHT) technique to process EEG signals. Their method is more accustomed to read non-linear and no-stationary information. This technique is not only a powerful tool for reading EEG signals because it can read ECG signals as well. According to Lipton (2009), "A recent study was conducted on a method for implementation of

EMD for computationally efficient and accurate real-time analysis and the method's efficiency was shown for EEG and ECG datasets".

Clustering Analysis

In an ideal state, it is easy to dominate each cluster of the algorithm by using one stat. However, this rarely happens because in many instances, there are many inter-ictal and pre-ictal TCs. This analysis shows that, given the current data and features outlined in the algorithm, it is difficult to ascertain the pre-ictal and inter-ictal states. Nonetheless, a learning procedure would help to do so (Ozdemir&Yildirim 2014). The diagram below shows how different clusters appear through the inter-ictal and pre-ictal TCs.
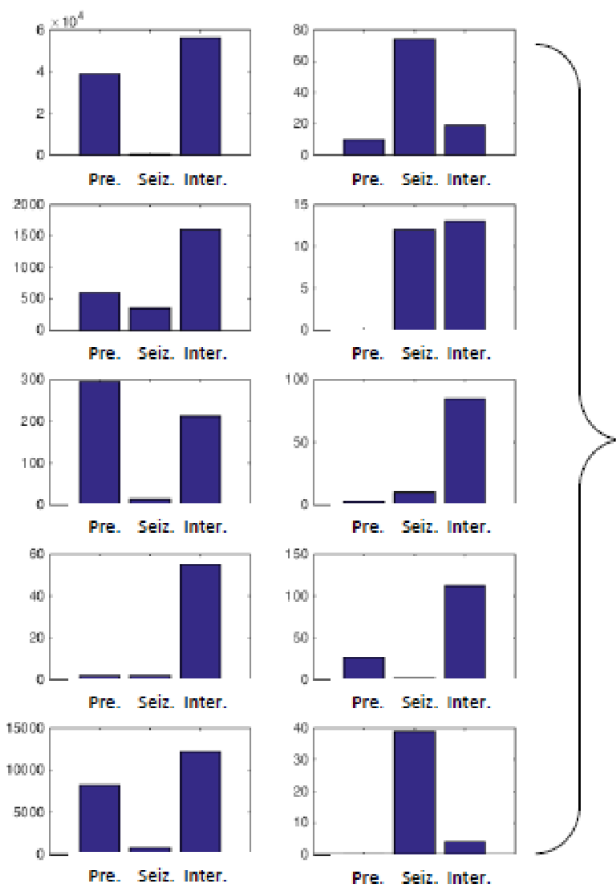

figure 8: Cluster Generation

Based on the diagram above, the TCs emerging in each of the above cluster follow their respective classes. The length of the bar in each cluster depicts the number of TCs in each category.

The Pre-Ictal Period

This paper has already shown that pre-ictal period refers to a patient's status before he experiences a seizure. The method used to calculate data in the pre-ictal period is almost similar to the methods used to do the same in the working hypothesis segment. For example, the CHB-MIT database includes 22 patients, 22 EEG channels, and the number of seizures reported from each patient (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). The number of seizures will include the pre-ictal, post-seizure, and normal states of every patient. Calculations in the system design process also include information from a set of univariate time and frequency domain features, which are calculated using 5s time-chunks. The 264 features emerge from multiplying 12 features and 22 channels (Scaramelli& Braga 2009). The pre-ictal period also includes information from the random classifier, which are separate for every patient received. The method also includes leave-seizure-out cross-validation, which assess the accuracy of the prediction. The following diagram summarizes these processes.
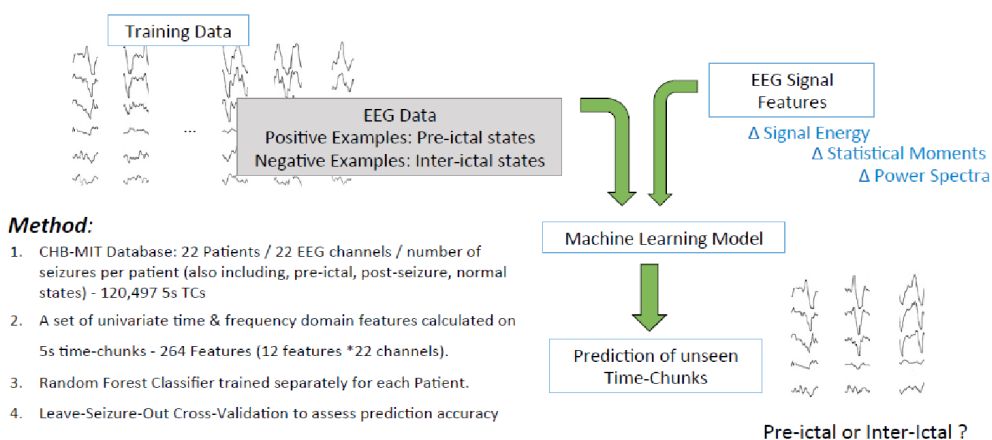
figure 9:the pre-ictal period analysis

When exploiting multivariate causal information in the pre-ictal period, discriminating between the pre-ictal and inter-ictal states require the exploration of two avenues. The first avenue is causality, which assesses the information flow in the pre-ictal state (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). This stage uses causality inference methods (Granger causality). In this state, we are starting to build directed networks, which show information flow across the time and frequency domains (Lasemidis&Shiau 2003). These domains cover both the pre-ictal and inter-ictal states. Using the flow of information described above, it is easy to develop network related features for shoring the distinctions between the pre-ictal and inter-ictal states (Lasemidis&Shiau 2003). For example, information obtained from social networks and genetic networks could distinguish between pre-ictal and inter-ictal states (Lasemidis&Shiau 2003).

Besides accounting for information from the pre-ictal state to distinguish between the inter-ictal and pre-ictal stages, another way of doing so is to account for clinical and physiological seizure variables (Scaramelli& Braga 2009). By doing so, we would answer several questions surrounding the pre-ictal stage, such as understanding whether it exists or not. This way, we would also answer questions that are more fundamental to the development of the mobile epilepsy predictive system, such as understanding how the pre-ictal stages differ from different types of seizures detected using the mobile epilepsy predictive system. This need emerges from the difficulty of looking for general patterns during the pre-ictal stages (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Sackellares (2003) says evaluating this need is important because there are different kinds of clinical seizures, which may occur because of different physiological factors. Through this analysis, the fundamental question we would be asking in this context is "how does the pre-ictal period change for different types of seizures?" In line with this narrative, it is important to understand that there are different categories of seizures that include partial seizures and generalized seizures (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013).

Partial seizures often occur from localized sources. According to Schuyler (2007), they often do not lead to the loss of consciousness because they are simple. However, in some cases, they may be complex and include a loss of consciousness. The second category of seizures includes general seizures that often emerge from non-localized sources. "Absence," which manifests through daydreaming or sudden seizures that may take only a few seconds characterizes them (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Such seizures may also manifest through myoclonic effects, often characterized by sudden muscle jerks. Schuyler (2007) also says that they are "tonic" because a patient's muscles stiffen and they lose consciousness. However, sometimes, these cases may be atonic, where the muscles stiffen and the patient crumbles to the ground. These features may appear through the following steps
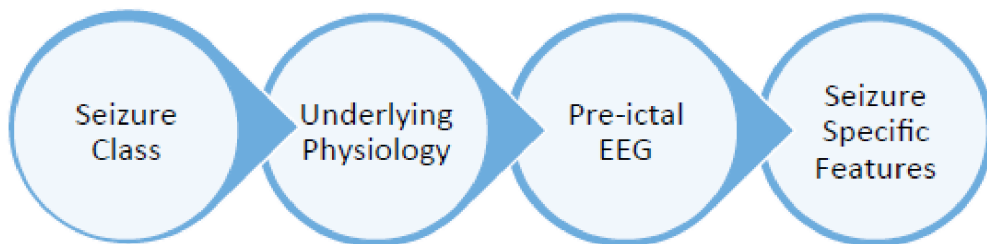
figure 10:stages of manifestation of seizures

The process between the underlying physiology and the pre-ictal EEG shows how class and physiological differences often emerge through EEG data. The interlude between the seizure class and the underlying physiology denotes the process whereby health practitioners understand the physiology behind different classes of seizures (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 1). Lastly, the stage between

the pre-ictal EEG stage and the seizure specific features denote the process of mapping the EEG realizations into seizure-specific features. The following figure presents this flow.
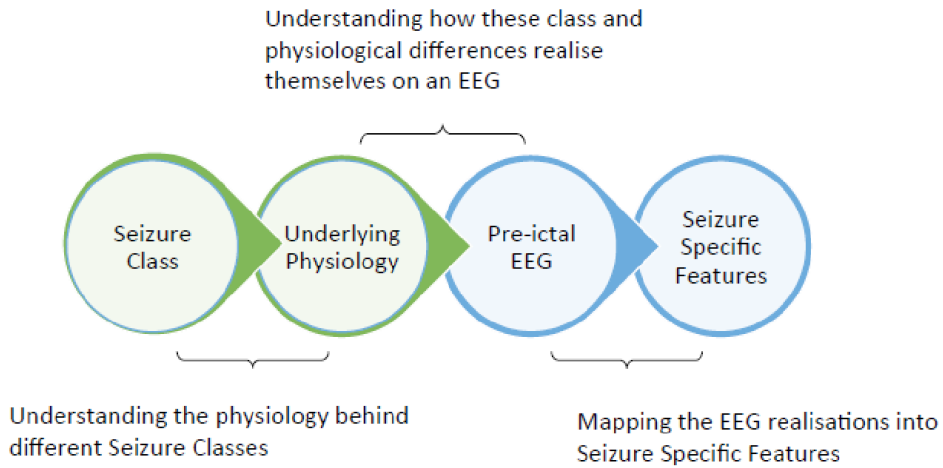
figure 11:seizure-specific features

Collectively, the above steps account for clinical and physiological seizure variability.

The wireless predictive system highlighted in this paper should predict the occurrence of seizures among epileptic patients. With the aid of such a predictive system, patients could lead normal lives because they could minimize the possibility of injury of death during a seizure, or prevent its occurrence altogether (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Nonetheless, Eftekhar (2013) insists that although such mechanisms may reduce the incidence of fatal seizures, it is still wise to make sure that a patient is not alone when a seizure occurs.

Many researchers have developed different types of technologies for reading signals from the patient's body (Rajesh 2013; Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). For example, many devices contain sensors that could detect abnormal brain activity, or involuntary muscle contractions that are synonymous to epilepsy. For example, pulse oximetry is an advanced technique used by researchers to measure a patient's pulse rate. Using such a technique, patients could monitor their heart rates and know when there are abnormal activities. Micro electromechanical sensors (MEMS) are other mechanisms used by researchers to measure muscle contractions, as another predictive indicator of an imminent seizure (Scaramelli& Braga 2009). The device is small and uses small sensors attached to a patient's body to detect abnormal muscle movements. Observers say it is an accurate and precise instrument for detecting muscle contractions (Scaramelli& Braga 2009).

To provide effective wireless tools for predicting seizures, it is important to provide wireless communication channels, such as the Mi-Wi protocol. The selected mobile epilepsy predictive system often uses Wi-Fi for this purpose. The MEMS signal has a good record in monitoring variations in a patient's heartbeat rate. When the device detects abnormal activities, it relays

the same to external devices for immediate remedial action (Scaramelli& Braga 2009). The mobile epilepsy predictive system uses the same mechanism, except for the fact that it uses Wi-Fi to communicate bodily signals to electronic devices (Neapolitan 2003). Besides mobile phones that relay epilepsy warnings, researchers have also used wearable electronic devices, such as watches and bracelets, to serve the same purpose (Scaramelli& Braga 2009; Neapolitan 2003). Recent advancements in technology have increased the device's capability to make them environmentally safe for patients. This is why Huang (1996) says, "The device can sense the aura of pre-ictal stage in a few minutes and take the necessary safety measures automatically". In this regard, patients do not require technical assistance when they have such devices. This advantage increases the appeal of such devices to young people who may be suffering from epilepsy, but want to live an active life. Indeed, the user gets to enjoy the benefits of having a wireless and portable device (properties that would allow them to live an uninhibited life). Based on these dynamics, implementing the mobile epilepsy predictive system would require several considerations. First, there should be a known criterion for sensing biometric signals.

Although two biological signals are ideal in detecting abnormal body movements (heartbeat and muscular movements), the mobile epilepsy predictive system would mainly focus on using brain wave activities to predict the occurrence of a seizure (Scaramelli& Braga 2009; Neapolitan 2003). Nonetheless, Cohen (1995) says there is nothing wrong with complementing this approach with the addition of a pulse oxymeter to measure heart rates and MEMS sensors for measuring muscle movements because they only add to the accuracy of predicting seizures.

Processing information and making decisions are also other considerations for implementing the mobile epilepsy predictive system. An electronic device (mostly a tablet, PC or smart-phone) should be able to do so (Rajesh 2013). However, such devices should correctly know which signals relate to a seizure and which ones do not. Thirdly, there should be a communication medium for relaying biological signals to the electronic devices. This means that for the mobile epilepsy predictive system to work there should be a Wi-Fi signal. According to Rajesh (2013), there should be a controlling mechanism for the patient to know of the presence of an imminent seizure. This addition means that all users should integrate an alarm device to the smart-phone to alert them of a seizure. Without such integrations, the patient would not understand what is happening, thereby rendering the entire apparatus useless (Rajesh 2013; Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Lastly, although using the mobile epilepsy predictive system is beneficial in detecting seizures before they happen, it has constraints that could limit their application. For example, patients should always be around places that have power because their mobile devices require frequent charging.

Originality of the proposed predictive system

The mobile epilepsy predictive system differs from other types of instruments for predicting the occurrence of seizures because of its non-invasive design. For a long time, researchers have used invasive procedures that involve planting a device in the patient's chest or head to detect the occurrence of a seizure (Rajesh 2013; Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). For example, an Australian research group recently did a study to integrate chest-implanted devices with the patient's brain through

electrodes that connect the two body parts (Scaramelli& Braga 2009; Neapolitan 2003). This method also used a handheld device that flashed "red" to warn the patient of an imminent seizure. Its efficacy level was 65% (Scaramelli& Braga 2009; Neapolitan 2003). However, the main drawback of this method was its failure to cater to patients' individual needs. This is why proponents of the system are still trying to understand the best patient profile that could use the system.

Other Types of Seizure Prediction Systems

Global Seizure Prediction System

The global seizure prediction model is a one-size-fits-all model. It has a less complex implementation process and it is similarly difficult to account for patient variability. These features make it less desirable for managing epilepsy because the mobile epilepsy predictive system is more effective in managing epilepsy among anomalous patients (Rajesh 2013; Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). The global seizure predictive system also distinguishes itself from other types of predictive systems because it uses offline data sets. Stated differently, there is no use for data from the actual patient. The global seizure prediction system is often synonymous with the adaptive seizure prediction algorithm (ASPA). Unlike researchers who believe that the global seizure prediction system does not have a high efficacy rate, studies conducted by Arizona State University (2008) reveal that it could predict up to 80% of seizures. It only has a false prediction rate of 0.16 per hour (Arizona State University 2008). In fact, unlike the mobile epilepsy predictive system, which can predict seizures 40 minutes before they happen, Beenhakker (2009) argues that the global seizure prediction system could predict a seizure, 70 minutes before it happens.

This efficacy shows that medical researchers could use the global seizure prediction system to develop therapies (Rajesh 2013; Scaramelli& Braga 2009). Similarly, its reliability is useful in developing and using implantable devices to predict the onset of seizures. Although researchers have synonymously used the ASPA in global seizure prediction systems, Lopantsev (1998) reveals that there have been improvements made in its application through improved seizure prediction algorithms. These improvements emerge from spatial synchronizations of all entrained pairs of sites.

Individual Seizure Prediction System

Details emerging in this study show that the mobile epilepsy predictive system relies on a set of algorithms to predict the onset of a seizure. These algorithms often use different sets of information to predict when a seizure will occur, such as the assessment of the seizure occurring and the EEG recordings (Rajesh 2013; Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). These pieces of information are reliable measures of a person's brain activity before the onset of seizures. However, they are abstract and inapplicable in developing patient-specific instruments for seizure detection. For example, Carney (2011) says that most experts cannot use such information (reliably) to develop implantable devices, or to develop individual therapies. The importance of having a patient-

specific seizure detection technique stems from the use of time-domain methods to predict when seizures would occur (Rajesh 2013; Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). This method shows that different patients have different forms of brain wave lengths for predicting the onset of seizures. Using this understanding, Schuyler (2007) argues that seizure detection and prediction algorithms should be sensitive to the differences noted across different types of patients. The time domain technique is one among many other types of seizure detection methods. The diagram below will place it among its peers.
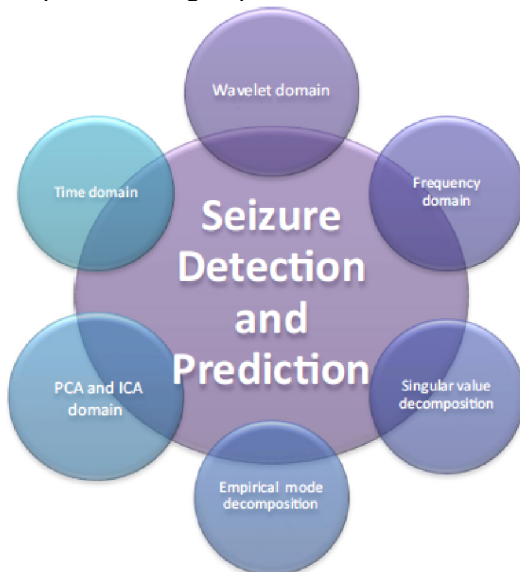
figure 12:seizure and detection prediction

The above diagram shows that wavelet domain, frequency domain, singular value decomposition, empirical mode decomposition, and PCA domain are other seizure prediction methods. Different patients are bound to report different statistics for ictal prediction using any of the above-mentioned methods. This is why the individual seizure prediction method is important in developing sensitive EEG prediction instruments.

As its name suggests, the individual seizure prediction system is tailor-made to suit only one patient. The individual seizure prediction system is important in predicting epileptic seizures because, as the Bethesda National Institute of Neurological Disorders and Stroke (2013) suggests, different patients have different EEG Signals. It has a complex implementation process that uses data from actual patients using the system, unlike the general system, which does not need data from actual patients. The individual seizure prediction system can also account for patient variability because the accuracy for the system's information for each patient is unlimited. Stated differently, it is easy to retrain on new EEG data that comes in the prediction system.

Type-Specific Seizure Prediction System

The type-specific seizure prediction system is different from other forms of epilepsy predictive systems because it is tailor-made for specific types of seizures (Rajesh 2013; Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Using this predictive system requires clearly annotated datasets to use during training. Similarly, it is easy to learn about a patient's medical history offline. Stated differently, the need for data from actual patients is low. The mobile epilepsy predictive system also uses such results to understand the different characteristics of different seizure types.

Summary

Despite the problems highlighted by some researchers surrounding the reading of EEG data, there are many benefits associated with an early warning system such as the mobile epilepsy predictive system (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). Already this paper has shown that such a system could warn patients and caregivers about an imminent seizure and help them to take precautionary actions to minimize the risk of injury. This paper has also explained how the mobile predictive system works. It has also compared this predictive system with other types of systems that manage epilepsy. In particular, it has compared it to the type-specific seizure predictive system, the individual seizure predictive system, and the global seizure predictive system. An ideal mobile epileptic predictive system should be non-invasive and monitor a patient's epileptic state, constantly. It should also suit individual needs because different epileptic patients have different types of needs. The mobile epilepsy predictive system has many of these characteristics. Its usefulness lies in the efficiency of its evolving prediction algorithm, which uses new EEG data and feeds it back to the system for retraining. This algorithm is sensitive to different states of the patient. For example, it could use information about a patient's sleeping patterns, frequency of anger conversational exchanges, and exercising patterns to develop a new algorithm for monitoring a patient's epileptic state. Indeed, different states would evoke different sub-algorithms to predict different epileptic states. The seizure prediction and suppression ability of the mobile epilepsy predictive system also makes the system unique to other types of predictive systems because it could turn on the seizure prediction system for high TP rates because FP is not an issue.

Lastly, smart-phones are not new additions to the management of epileptic seizures because patients have used them in the past to know how well their medicines are working (Rajesh 2013; Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013). In line with the goal of using smart-phones to predict when seizures would occur, researchers have learned to integrate them with the EEG technology. For example, dialog is a new app that has emerged from this push because experts have learned that it could help patients to get a better handle of their condition. By using this app, patients could know when a seizure would occur and take the appropriate actions to prepare for it. The mobile epilepsy predictive system outlined in this chapter uses the same mechanism to predict the onset of a seizure.

The Future of Epilepsy Prediction

The electronic system highlighted in this paper is a portable device that could alert a patient about the possibility of a seizure occurring, 40 minutes before it does. The device works by detecting and interpreting brain waves to know when a seizure is likely to occur. When the device detects abnormal brain activity, it sends a signal to an electronic device, which later relays the same to a digital mobile device, which alerts a patient about its occurrence. The coded signal detected from the brain is often decoded using a wireless device that pairs with a smart-phone. Future developments of this device should focus on creating a GPS device to pinpoint a patient's location (Scaramelli& Braga 2009; Bethesda National Institute of Neurological Disorders and Stroke 2013).

Although this paper shows the potential for detecting seizures before they happen, using the mobile epilepsy predictive system, the field of research underlying its use is still underdeveloped. Therefore, currently, many devices in the market include mechanisms that could help patients to get help when they experience a seizure, but they cannot properly detect one, at least accurately, before it happens. Nonetheless, the development of an effective and accurate epilepsy predictive system would help patients to prevent potentially harmful incidents that would occur when a seizure occurs. In fact, there is a high probability that the advancement of such methods could help to prevent a seizure, entirely, before it happens because patients could take medications to prevent their occurrence. Nonetheless, it is pivotal to understand that most of the technologies highlighted in this paper are still under development and it may take a long time before researchers produce instruments that could effectively predict seizures before they happen. Meanwhile, it may be beneficial for patient to follow their doctors' treatment regimen.

GENERAL DISCUSSION

Autism and epilepsy can be serious mental health problems although an early detection of these health complications can lead to proper management and control of the symptoms associated with them (Pop-Jordanova et al. 2010). Over the years, autism and epilepsy have been psychological conditions that have persistently subjected families to untold frustrations. Whereas people are aware of the medical complications and the problems associated with the late detection and interventions towards the control of autism and epilepsy, the healthcare systems have been falling short of ideas on how to incorporate early detection methods and systems for proper management of these mental health complications (Pop-Jordanova et al. 2010). As explained in this project, the aim of this report is to establish the manner in which Novel Computational Electroencephalographic solutions may help in autism management and prediction of epileptic seizures. This section of the report focuses on discussing how these computational disease management and control technologies work. In the end, the section proposes future work on these methodologies.

EEG methodologies for Autism Management

Autism is a serious mental health problem that has posed grievous challenges to the health care professionals (Pop-Jordanova et al. 2010). According to the intended project for the mobile epilepsy predictive system, the first aim of the proposed project was to establish Novel Computational Electroencephalographic for autism management. Based on the results established through the extant research is that Autism Spectrum Disorder (ASD) is a common problem affecting the autism patients, although there are EEG remedies for its management and control (Sichel, Fehmi, and Goldstein 2008). The ASD mental health problem is a form of a complex developmental disorder and psychological disorder that manifests in children through various characteristics of impairments associated with cognitive and psychological impairments (Pop-Jordanova et al. 2010). The disease also affects the social communication and interaction abilities of the affected children, and it sometimes presents characteristics such as restricted, repetitive behaviours, activities, and interests during its diagnosis (Sichel, Fehmi, and Goldstein 2008). One of the modern technologies or methodologies that can help to manage autism is the Brain Music System.

The Brain Music System works with a technology that supports the management of the Autism Spectrum Disorder (ASD) using real-time sonified brain-analysis signals (Sichel, Fehmi, and Goldstein 2008). The Brain Music System is a form of an EEG therapeutic remedy and a structured system that uses sonified neurofeedback accurately and cost effectively to convert brainwaves into musical sound using Digital Signal Processing algorithms (Trevisan and Jones 2013). For treatment of individual patients suffering from autism that presents multiple characteristics and numerous neurological conditions, the Brain Music System can offer efficient remedies that also offer a cost-effective approach. The inexpensive and easily portable Brain Music System is a computerised neuropathic treatment solution for the autism patients across different hospital settings as the health care professionals can use it in both the external and the internal environment of the traditional clinical environments (Coben and Myers 2010). The Brain Music System offers therapeutic solutions to the autism patients suffering from various mental and neurological conditions.

The aim of the intended project was to offer reliable and cost-effective remedies for management of the autism forms of disorders through a portable platform. Trevisan and (2013) state that the Brain Music System acts as a form of a sonified system for detecting and analysing Brain Signals. When tested through the "pilot studies that test for the behaviour of the Beta, Alpha, and Theta sound waves, the Brain Music System works comparatively well with the high-end confined equipment that are available in the expensive clinical setups" (Trevisan and Jones 2013). The technology that supports the use of the Brain Music System believes that there exists a very big association between music sensations and the cognitive functions of the brain in human beings. According to Trevisan and Jones (2013), the Brain Music System delivers a physiological notion that "the arousing feeling of music and the appreciation of music are essentially the interaction of the musical piece with the emotional and mental status of the listener".

Neurofeedback for Autism Management

Audio is normally a sensational aspect in the social life of human beings, and it often associates with mental relaxation and cognitive development in human beings. Neurofeedback music training is a strategy that helps neurologists to provide cognitive support to the autism patients through the science of brainwave biofeedback (Trevisan and Jones 2013). The biofeedback science involves a situation whereby the brainwaves remain fed into the brain system through the brain cells to help attain a pleasing rate of recurrence of the brain activity. Neurological studies have insisted that the association between the brain and music therapy exists where the neurofeedback plays an imperative role in determining the communication between the brain and the musical signals. Trevisan and Jones (2013) posit, "Brainwaves are responsible for various activities and moods of an individual, and through a keen analysis and investigation, it can be possible to change a mood to another by employing neurofeedback".

Studies carried out in London to analyse the impact of neurofeedback Music on the functioning of the human brain through the Cognitive Neuroscience and Behaviour Department show that brain music therapy can help in alleviating psychological problems associated with the Autism disorder (Schuyler 2007). Using the brain to alleviate problems associated with autism works perfectly with the science of cognitive neuroscience as research reveals that temporary harmonisation between the isolated neural assemblies contributes positively to the achievement of higher cognitive phenomena. Scientists believe that the multiple cortical regions of the brain often become co-active when the brain is working on a cognitive task. According to Sichel, Fehmi, and Goldstein (2008), neuroscientists have discovered that listening to music has a great impact on cognitive development as music provides a sensational feeling to the listeners and helps to arrange and coordinate the cortical brain patterns. Trevisan and Jones (2013) posit, "Music is important for excitation and priming of the common repertoire and orderly flow of the cortical patterns responsible for higher brain functions".

The Brain Music System As Form of Neurofeedback In Autism

The Brain Music System is a form of a neurofeedback remedy for the autism patients as it delivers a medical approach that comes in the form of an electroencephalographic data that produces modulated MIDI. The Brain Music System resembles the Brain-Computer Interface

(BCI) system that Professor Eduardo Miranda created during the early days of testing mental health complications with sound technology. The Brain Music System is a two-channel EEG methodology that uses the ordinary computational methods, which can easily remain supported by the standard modern office computers. Such characteristics make the Brain Music System more accessible, reliable and cost-effective in terms of offering therapeutic solutions to the patients suffering from the autism disorder (Sheikhani et al. 2010). The Brain Music System works efficiently using the brainwaves conversion model, which specialises in providing solutions on how transforming brainwaves to music works in the analysis of the Autism disorder. The technology uses the Discrete Fourier Transform (DFT) and the Power spectrum analysis (PSA).

The initial stage of "Power Spectrum Analysis (PSA) is the stage where the analysts calculate the Fourier transform indicated as I(x, y) and the square modulus of the Fourier Model using the format to form the power spectrum with a model p (u, v)" (Trevisan and Jones 2013). The general format for acquiring the power spectrum is p (u, v) = |FT [I(x, y)] |2. The format for power spectrum allows the Brain Music System to analyse various computerised images that provide significant data for assessing the brain functions. During the process of assessing the power spectrum, it is important to find the actual Power spectrum analysis (PSA) to establish the real values that can help determine the brainwaves. The process of transforming brainwaves into music signals also involves the process of determining the Discrete Fourier Transform (DFT), which is a process that allows an easy computation of the spectral rays from a discrete-time data.

According to Trevisan and Jones (2013), Discrete Fourier Transform (DFT) is a format that believes that computation of the spectral rays from a discrete-time data is imperative in assessing brain signals because discrete-time data enables the analysts to calculate the exact spectral in the computerised images. Additionally, Trevisan and Jones (2013) postulate that an "accurate computation of spectral rays is significant for conversion of brainwaves to music waves so that least redundancies result". While demonstrating the manner in which the brain works to create music and rhythmic activities, Trevisan and Jones (2013) note that the brain has two hemispheres that compose the main portion of the brain. The first hemisphere is the right hemisphere, which associates with the creativity aspect of human beings, and the second one known as the left hemisphere, which deals with the logic abilities of the human beings. The local abilities in the field of neuroscience are the brain structures and their relative functions.
The distinctive functions of the two hemispheres, the right and left hemispheres, demonstrate the manner in which the two spheres are relevant in understanding how the brain creates music or responds to music. To help understand how the two hemispheres work concurrently to support the brain to create or meditate music, Levitin (2013) developed a mental health study to analyse the functionalities of the right and the left hemispheres in music creation and music reception. Levitin (2013) then discovered that an activity carried out in the prefrontal cortex of the brain (a place where positive emotions such as happiness or joy exist) affected an activity in the right prefrontal cortex of the brain (a site where negative emotions and wild anxieties occur. Such occurrences explain how the Brain Music System works for accessing, diagnosing and managing children suffering from mental health disorders such as the autism disorder of the brain.

The technology that supports the use of a sonified neurofeedback therapy entails the use of brainwaves to determine the intelligence and different abilities of the children suffering from the Autism Spectrum Disorder. The neurofeedback therapy provides the neuroscientists with

medical remedies associated with musical signals while dealing with children suffering from Autism Spectrum Disorders. The sonified neurofeedback therapy uses four major steps namely the data acquisition phase, the data pre-processing phase, the development of visual and sonic maps, and finally, the visualisation and sonification phase. In the technology of using the sonified neurofeedback therapy, the first step that is known as the "data acquisition process entails a process of data handling that starts with the detection of the variables and ends with the process of magnetic recording and other relevant data recording processes" (Trevisan and Jones 2013). The data recorded then undergoes some syntheses in the pre-processing phase of the neurofeedback therapy.

The second important process in the technology of using the sonified neurofeedback therapy is the pre-processing phase. The data pre-processing stage of the sonified Neurofeedback therapy is a process of sorting data or pre-processing the collected raw data to get the appropriate input to represent the required data before developing the actual sonification and visual output for the neurofeedback therapy. In the process of dealing with the neurofeedback therapy, "visualisation acts as a process of interpreting the image data available and computerising the data to develop images from the available multi-dimensional data" (Fuchs et al. 2003). The complicated multi-dimensional data provides the system with a platform to create visual patterns from the recorded data in the third stage of a neurofeedback therapy. After visualisation, the sonification process terminates the fourth stage by transforming the recorded data into an acoustic signal to enable the communication and interpretation of the coded data.

How the Brain Music System Works

The computerised Brain Music System reveals a form of technology that aims at boosting and equalising the brain activities in which four major brainwaves act as important elements of understanding how the human brain works. Patients suffering from autism-related disorders such as the Autism Spectrum Disorder tend to have abnormalities in the functioning of the brain whether when awake or sleeping (Fuchs et al. 2003). The brain works in such a way that the four brainwaves involved in the psychological well-being of humans must function in normalcy. The four brain waves known as Alpha (denoted with a greekletter (α)), Theta, Beta (denoted with a letter β), and Delta brainwaves (denoted with a letter δ), must work without any alterations during the brain activity. In the Neuroscience studies, the Beta and the Theta brainwaves are responsible for proper concentration and mental activity in normal human beings, while the delta brainwaves associate with mental relaxation and inactiveness.

When the brain activities ofnormal healthy persons are analysed during a deep sleep period, the delta brainwaves tend to be higher than the Alpha and the Beta brainwaves (Fuchs et al. 2003). This assessment reveals that when human beings are asleep, the brain tends to be inactive or dormant during the sleeping sessions. Nonetheless, the trends in the brain activity for people suffering from autism spectrum disorder are different as these patients have the tendency of having high levels of delta brainwaves while awake(Fuchs et al. 2003). Studies carried out to compare the brain function and symmetry activity in normally developing children and in children suffering from the Autism Spectrum Disorder, reveal that ASD resulted with higher delta wave brain activity. Currently, there is no cure for patients suffering from the Autism Spectrum Disorder (Fuchs et al. 2003). As one of the computerised electroencephalography (EEG) solutions, the Brain Music System provides a remedial platform to balance the brainwaves.

A Discussion of the Actual Research with the Brain Music System

To determine the effectiveness of the Brain Music System as a sonified neurofeedback therapy, Trevisan and Jones (2013) conducted research for this technological model with two distinct objectives. The first objective of the research was to determine if there exist common patterns and levels of brainwave processes in the EEG outputs, which are essential in the musical process of the Brain Music System (Trevisan and Jones 2013). The second objective of their research was to compare the levels of output brainwaves or the modified LORETA, with the prevailing literature in the neuroscience studies (Fuchs et al. 2003). The two objectives primarily wanted to examine the existing relationship between the actual human brain, the Brain Music System, and its ability to generate music as one of the computational electroencephalography (EEG) systems. In testing the common patterns, the levels of brainwaves, and the presence of the output brainwaves, researchers can identify how the sonified neurofeedback therapy works in children with autism.

While trying to understand how a portable sonified neurofeedback therapy can help children with autism to communicate despite their impairments associated withspeaking abilities, it is important to consider the four sound components of the computerised Brain Music System influence the development of a communication. According to Kouijzer et al. (2009), the four components of sound that emerge vital in understanding the workability of the Brain Music System are the beta, alpha, theta, and delta sound waves that help when the brain is communicating with the body parts that make speaking possible. The beta, delta, theta, and alpha are brainwaves that determine the achievement of an effective communication between the brain and the sound-producing organs of the body. These four brainwave components also support the rates of brain oscillations or the rapidity of oscillation (popularly known as the brainwaves). The research recorded the behaviours of the four output components of the brainwave signals and delivered its results as follows.

EEG	subject 1	subject 2	subject 3	subject 4	subject 5	subject 6	subject 7	subject 8	subject 9	subject 10
Alpha	3.37	3.36	3.29	3.06	3.23	2.88	2.95	2.13	3.52	3.22
Beta	5	4.91	5.21	4.64	4.95	5.03	5.09	5.09	5.02	4.97
Delta	2.89	2.83	2.61	2.42	2.41	2.45	2.93	2.61	2.23	2.88
Theta	3.76	3.34	3.45	3.94	3.59	3.34	3.83	3.97	3.83	4.07

Table 1: shows the results of 10 subjects and relative recordings as publishedby Trevisan and Jones

The above results are recording of brain waves achieved from 10 research subjects associated with the research. The four components of the EEG system presented different recordings in the Brain Music System, and their results appeared as described below. Throughout the analysis of the brainwaves and the frequency signals, the results show that the band frequency varied between different subjects but presented similar results when put into a comparative analysis. In the research, the Beta brainwave "recorded the highest mean wave, the Theta

brainwave and the Alpha brainwave then followed in a respective manner" (Trevisan and Jones 2013). The least form of brainwave achieved in the analysis was the delta brainwave, which recorded lower figures in several instances among the present research subjects. The first EEG component in the computerised Brain Music System is the Beta brainwave component that gave the highest recordings. The Beta wave gives this research an "avenue for assessing the interaction between music and the brain" (Trevisan and Jones 2013).

The results of the research reveal that the left frontal areas of the human brain get more involved in the processing and distribution of information across the system (Kouijzer et al. 2009). Additionally, the "right hemisphere may experience higher frequencies and higher engagements across the spectrum of the Beta wave" (Trevisan and Jones 2013). Therefore, the Beta wave in this case helps the neurologists to understand how a portion of the human brain, whether from the left frontal part or from the right hemisphere, helps in processing a certain kind of music or musical sensations (Kouijzer et al. 2009). In a different study conducted to analyse how a portable Sonified Neurofeedback Therapy can support patients with Autism Spectrum Disorder, Trevisan, Cavallari, and Attard (2013) provided a significant portion of research that explains this association. In a study of 10 research subjects, the three researchers analysed the behaviour of the three main brainwaves coupled with how they help people understand the association between music and the Brain Music System.

Neuroscience studies believe that people diagnosed with Autism Spectrum Disorder (ASD) have the tendency of portraying greater levels of Delta brainwaves, and lower levels of the Beta and Alpha brainwaves. According to the findings of Trevisan et al. (2013), the Beta brainwaves are significantly high in the computerised Brain Music System, while the Theta and the Alpha brainwaves follow respectively.In their findings, the three researchers discovered that since children and patients suffering from autism tend to portray low levels of Beta and Theta brainwaves, are significant elements of the brain that associate with peak focus levels. The Brain Music System can help alleviate concentration problems among the ASD patients. In the above readings, the Beta brainwave tends to enhance the brain focus and mental activity tend to demonstrate how the computerised Brain Music System can reduce the levels of mental impairments and support cognitive development in the patients suffering from the Autism Spectrum Disorder.

While reviewing the behaviours of the brainwaves, Trevisan and Jones (2013) discovered that the theta band showed a coherent appearance in the 10 subjects and this coherence occurred in a symmetrical manner except in a few cases between the subjects. The Alpha band demonstrated a "more coherent decrease in the ten (10) subjects and stretched on longer distances compared to the other bands" (Trevisan and Jones 2013).Interpretively, "increases in the coherences can be best explained by the theory that explains the increasing cooperation between the two hemispheres of the brain" (Trevisan and Jones 2013). According to Trevisan and Jones (2013), "the two hemispheres that make up the major portion of brain, is the right hemisphere which is associated with creativity and the left hemisphere which is associated with logic abilities such as creativity and mental focus".On the other hand, "decreases indicate that the brain activity in the assessment requires lower levels of collaboration between the two hemispheres to perform with normalcy" (Trevisan and Jones 2013).
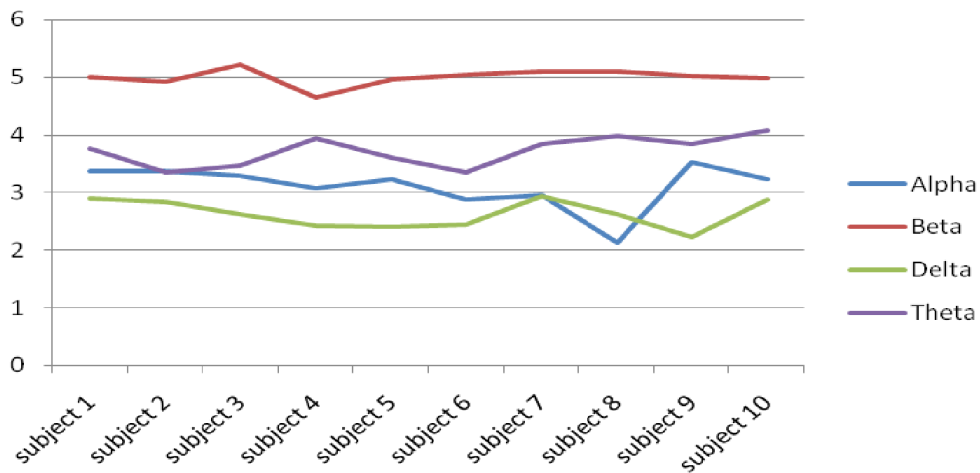
figure 13:band frequency graph as published by Trevisan and Jones

The above results are similar to several pieces of literature that have dealt with the understanding how the neurologists can use a sonified neurofeedback therapy to help children with autism to balance their brainwaves through the computerised platforms. In a study to examine the impact of Electroencephalographic Biofeedback in the treatment of people suffering from attention deficiency and hyperactivity disorders, Monastra et al. (2005) examined how hyperactivity and attention deficiency disorders occur, and how the human EEG can alleviate the problems. These researchers discovered that attention-deficit/hyperactivity disorder (ADHD) is characterised by a situation where there is increased relative theta power, reduced alpha and beta brainwaves and increased theta/alpha and theta/beta brainwave ratios. Alterations in the frontal, mid-line and central regions of the brain highly relate to the development of the attention-deficit/hyperactivity disorder (ADHD). The research of Monastra et al. (2005) delves much on bringing an understanding of how musical signals and brain waves can work to produce Electroencephalographic Biofeedback.

In their research, Monastra et al. (2005) reveal that an EEG biofeedback provides significant remedies for supporting people with mental disorders as it provides a platform for understanding how the thalamocortical mechanism develops in the human brain and how it plays a role in analysing the formation of rhythms and frequency modulations in the human brain.Like the Brain Music System, the thalamocortical mechanisms help to form rhythms and frequency modulations that support the formation of Electroencephalographic Biofeedback that neutralises the actions of the brainwaves during the brain activity (Coben 2009). In a similar study of the relationship between the science of neurofeedback training and the autism spectrum disorders, Wang et al. (2013) discovered that patients who suffer from the Autism Spectrum Disorder normally demonstrate high levels of delta brainwaves than the alpha and beta brainwaves. Therefore, to assess this relationship, Wang et al. (2013) decided to break down the oscillatory brain patterns into musical bands or sound frequencies that share common physiological properties in the brain activity.

Studies about the association of neurofeedback and better mental statuses in patients with autism have repeatedly revealed that music can form a significant part of mental healing in several cases of autism (Trevisan, Cavallari, and Attard 2013). In a different study conducted to investigate the manner in which neurofeedback training influences behaviours in persons suffering from Asperger's Syndrome, which is one of the numerous mental and neurological conditions associated with the Autism Spectrum Disorder, Thompson and Thompson (2010) unveiled some unique findings. The two researchers discovered that patients who suffer from the Asperger's Syndrome have low-frequency beta activity and high-frequency delta activity in the functions of their brains (Thompson and Thompson 2010). According to Coben (2009), the fluctuations in the behaviours of the beta and the delta brainwaves determine the mental status of people, regardless of whether they are normal or have some abnormalities.

EEG methodologies for Epileptic Seizure Prediction

Epilepsy is another seriousmental health problem that has caused psychological distresses in many modern families across the world. Epilepsy is still a challenge to the health care professionals and the healthcare fraternity due to its complex nature in the brain systems. In the field of medical technology, the role of the human electroencephalogram (EEG) continues to be imperative in the prediction, detection and management of the epilepsy conditions in human beings. More importantly, the human electroencephalogram (EEG) technology is becoming increasingly important in the early detection and prediction of the epilepsy condition in people suffering fromepileptic seizures (Coben and Myers 2010). Based on the scientific evidences developed concerning the relevance of the electroencephalograph technologies in determining the prediction and detection of seizures in epileptic patients, neuroscientists have discovered that an electroencephalograph is capable of recording the spontaneous electrical activities that occur in the cerebral cortex.

Although epilepsy has a long history, Epilepsy practitioners have historically established that many patients who suffer from the epilepsy disorder understand that their seizures do not occur abruptly (Coben and Myers 2010). Most epileptic patients understand that their seizures do not occur abruptly in onset, but they do occur in predictable periods throughout their lifetimes. Portable electroencephalographic technologies are currently the most advanced in the field of neuroscience across the world. In dealing with epileptic conditions associated withchildren andyoungsters, the portable electroencephalographic technologies play a significant role in determining the levels of seizure focus, accessing the nature of epileptic attacks, and determining the levels at which the epileptic attacks occur in the different scientific findings. According to Karimi, Haghshenasb, and Rostamic(2011) repeated studies show that the use of electroencephalographic technologies has significant impact on the prediction and detection of the seizures as this technology deals directly with the brain activity and the various brain functions.

The predictable nature of the onset of epileptic seizures makes the use of portable electroencephalographic technologies a relevant concept in the field of Neuroscience. Epileptic seizures are periodic in nature, as scientists have discovered that changes in the blood flow of the epileptic patients occur 12 minutes even before the seizures begin. Clinical prodromes of such occurrences have revealed in at least more than fifty percent of the epileptic patients tested for the study about the occurrence of seizures (Ozdemir and Esen 2014). Further studies on the occurrence of the epileptic seizures through the technology of the Magnetic Resonance

Imaging (MRI) show that before the occurrence of seizures, signals of blood oxygen levels have been reported (Karimi, Haghshenasb, and Rostamic 2011). Therefore, with the use of human electroencephalographic, biofeedback can be imperative in predicting, detecting, and managing epileptic seizures.

How the EEG helps in Epilepsy Detection and Management

As an effective methodology for detecting and managing the epileptic seizures, the human electroencephalogram (EEG) has several ways in which it supports in the prediction, detection, and management of the epileptic patients who demonstrate seizure characteristics (Moghim and Corne 9). The human electroencephalogram (EEG) technology helps the Neuroscientists to find efficient ways of diagnosing the epilepsy disorder and managing the epilepsy disorder through a series of medical strategies (Moghim and Corne 2014). According to Tripathi and Mehendiratta (2014), the human electroencephalogram is a technology that helps in the diagnosis of the epilepsy disorder through various processes. These processes include the diagnoses carried out in neurological paroxysmal events, the distinction between the generalised and the focal seizure disorders, investigation of the specific syndrome changes and the recognition of photosensitivity problems in epilepsies (Binder 2013). A portable or mobile epilepsy predictive system can offer significant assistance in the diagnosis of the epilepsies.

One of the mentioned diagnosis procedures for epilepsy is the differential diagnosis that often takes the science of analysing the paroxysmal neurological events (Moghim and Corne 2014). In a study of the human electroencephalogram (EEG) and its influence on the diagnosis of the epileptic seizures experienced by the epileptic patients, Tripathi and Mehendiratta(2014) sought to investigate the performance of electroencephalogram (EEG) equipment known as the Video EEG monitoring. According to the research of Tripathi and Mehendiratta (2014, the diagnosis of the epileptic seizures is very intricate and the values sometimes yield poor results due to the inability of some EEGs to detect and measure the actual events or attacks. This assertion holds because confirming seizures on actual attacks or events sometimes becomes a rare achievement during the standard 20-30 minutes of recording the brainwaves and the frequencies (Binder 2013). The diverse role of the VEEG technology spans from the period of diagnosis to the period of epilepsy management.

The Visual EEG monitoring technology is an appropriate tool for measuring the epilepsy seizures as it can operate during the normal inpatient treatment hours, around the workplaces or home environments and even with the use of an ambulatory EEG (Drury 11). The Visual EEG monitoring technology provides several important mechanisms through which the EEG technology works during the assessment of the epileptic seizures in the patients suffering from epilepsy (Drury 2003). The Visual EEG can allow for the confirmation of the various types of epilepsy attacks and the none-epileptic occasions such as the paroxysmal movement disorders, the pseudo-seizure problems, and the sleep disorders. The VEEG technology also supports the determination of seizure attention in epileptic patients with nonconforming features such as the frontal lobe seizures and the gelastic seizures that probably require pre-surgical assessments (Tripathi, Yadav, and Kumar 2011). Further analysis shows that the VEEG technology supports the exact classification of seizures prior to appropriate therapies.

The Actual use of the Portable EEG technologies

The proposed project on the development of the mobile epilepsy predictive system focussed on the use of the EEG technologies in assessing the onset of an epileptic seizure (Drury 2003). The EEG technology is still the central tool for the diagnosis and management of the epilepsy patients due to its ability to provide cheap remedies and convenient procedures for analysing the abnormal cortical excitability that associates with the epilepsy disorder (Tripathi, Yadav, and Kumar 2011). The technology of measuring the seizures is the same as the one used in the management of autism patients through the Brain Music System, as the technology of assessing the behaviours of the brainwaves also applies to the detection and prediction of the occurrence of seizures (Tripathi, Yadav, and Kumar 2011). The EEG technology relies on the use of the beta, theta, delta and the alpha brainwave technology to predict the possibility of having seizures in patients suffering the epilepsy psychological disorder (Tripathi, Yadav, and Kumar 2011). Extant studies have shown how this technology works.

In a research of the functions of the Video EEG monitoring, Tripathi and Mehendiratta(2014) discovered that the beta, the alpha, the theta, and the delta brain waves or brain signals have an important role in developing an understanding of how the EEG technology predicts and detects the epileptic seizures. Tripathi and Mehendiratta(2014) add that the four brainwaves provide the neurologists with an opportunity to access the brain activity through a system known as a spike-wave pattern. Nonetheless, the behaviours and occurrences of the brainwaves in the EEG technology rely on the type of seizures involved and the nature of the seizure when viewed from the neurological paradigms. While dealing with the temporal lobe seizures, the alpha and the theta brainwave play a significant role in the prediction and detection of the seizures in the epileptic patients. Alessandro et al. (2003) conducted research to examine the behaviours of electromagnetic seizures.

In their study, Alessandro et al. (2003) employed an intelligent genetic search procedure to analyse the multiple contacts of intracranial electrodes and the several quantitative characteristics obtained from the electromagnetic signals. The method involved the collection of electromagnetic data from multiday recordings achieved from the four selectively targeted patients with intracranial electrodes planted on their heads while they were undergoing assessment for epilepsy surgeries. The study came up with an estimated 6.5% record in seizure block sensitivity and an average block false positive of 0.2775 False Positive (FP) predictions. What appeared real in this electromagnetic brain study, just like in other studies, was the behaviour of the brainwaves that provided space for the calculation of signals and frequencies. There was a presence of the theta brainwaves in this analysis. According to this research, Alessandro et al. (2003) discovered that the theta brainwaves play an important role in the assessment of the epileptic seizures. See the diagram below.The prediction and detection of the epileptic seizures rely on the detection of the brainwaves such as the theta brain signal was imperative in determining the behaviours associated with the short and the long temporal spiking during the occurrence of the epileptic seizures in the epileptic patients. Using four categories of patients subjected to an electrode test where some intracranial electrodes were implanted in their heads, the research discovered that the theta rhythmic signals are essential in determining the longevity of the epileptic seizures. Just as Tripathi and Mehendiratta(2014) noted in their research, "most often the initial frequency of temporal lobe seizures is in the alpha or theta range with slower frequencies occurring in a lesser proportion". In an empirical research on the four patients named as Patient A, Patient B, Patient C, and Patient D, during the

assessment of the electromagnetic signals in detecting epileptic seizures, the theta brainwaves played a significant role.
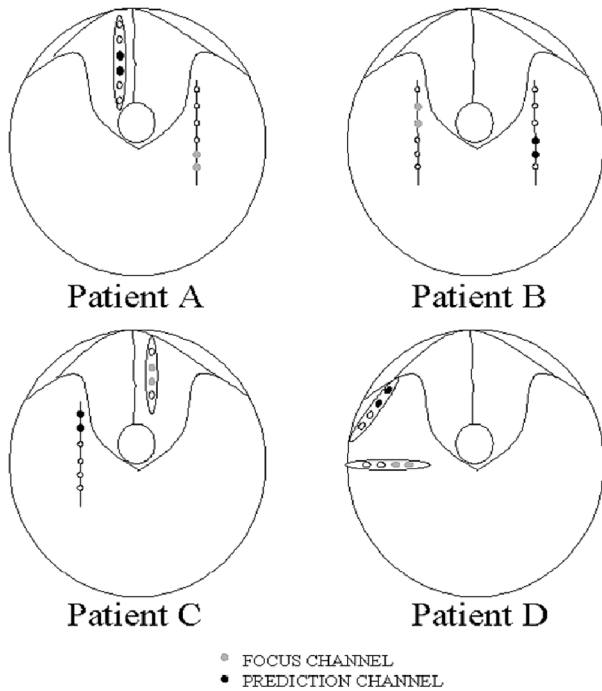

figure 14 : a view of the outcomes ofAlessandro et al

In their analysis, Alessandro et al. (2003) discovered that the theta signals or the rhythmic theta were responsible for the occurrence of the long epileptic periods that involved stopping of the left temporal spiking and an involvement of a suppression within the EEG background. In the same instance, some theta brainwaves had amplitude of 4-7.5Hz that prevailed for about 5-second durations in each of the four patients placed on the electromagnetic implants. The beta brainwaves are also part of the EEG technology especially in instances where the technology is trying to estimate the occurrence or predict the prevalence of the epileptic seizures in the epileptic patients. The research of Alessandro et al. (2003) revealed that the beta brainwaves are part of the brain activity during the occurrence of the epilepsy seizures. According to Alessandro et al. (2003), the four patients demonstrated the presence of the beta brainwaves in the assessment of the occurrence of the epileptic seizures.

Alessandro et al. (2003) noted that in most cases of the electrode activity, most seizures remain accompanied by some few seconds of the focal beta activity that occurs in the posterior electrodes on the right hemisphere of the brain (RT4-6) then a rhythmic activity spreads instantly through the various regions of the brain. Alessandro et al. (2003) posit that the rhythmic activity across the inferior frontal, the right temporal and the inferior temporal areas during the time at which the EEG was recording. The delta brainwaves are also part of the EEG prediction and detection system for the occurrence of the epileptic seizures in the epileptic patients. According to their findings, Alessandro et al. (2003) also discovered that most of the

patient seizures originated from the right hemisphere of the brain and in the areas where there were posterior contacts with the brain.

A Common Data Processing Approach For Both Autism and Epilepsy

A significant factor that stands out in the two systems of solving mental health complications is the use of the neurofeedback strategies in assessing the brain activity coupled with how it coordinates its rhythmic waves in relation to the music technology (Lipton 2009). According to the presented research, neurofeedback training can form an imperative solution to the children suffering from autism as it provides autistic spectrum solutions to the patients (Dzhala 2003). Since the delta brainwave seems to be the foremost aspect in the behaviours of children suffering from autism, using neurofeedback training solutions can help the affected children to balance their brainwaves and communicate through the Brain Music System (Lipton 2009). The two technologies for providing solutions to the autism and epileptic patients also involve the use of the electromagnetic technology, where the electrodes play a vital role in assessing the behaviours of the brainwaves in the experiments.

Thescience that seems to dominate in the two systems of providing solutions to the autism and the epileptic patients is the science of human electroencephalogram (EEG). While the neurofeedback technique in the Brain Music System provides an approach whereby the neuroscientists analyse the behaviour of the brainwaves from a dire perspective, the portable epilepsy-detecting device uses an indirect approach to the assessment of the brainwaves (Hughes and Bromfield 1993). According to researchers, the two technological components of the neuroscientists use an assessment of the behaviours of the brainwaves to detect changes in the behaviours of the individuals suffering from either the autism disorder or the epileptic seizures. Four major brainwaves characterised the development of the two EEG technologies for the autism patients and the epileptic patients (Lipton 2009). In the issue of autism spectrum disorder, children suffering from this kind of a disorder tend to have more delta brainwave and low alpha and beta brainwaves.

The human electroencephalogram (EEG) technology for developing the mobile epilepsy predictive system has similar traits as the human electroencephalogram (EEG) used in developing the portable Brain Music System that would help children suffering from autism (Hughes and Bromfield 1993). The two technologies have persistently used the beta, alpha, theta, and delta brainwaves to demonstrate how the brain activity operates and how the EEGs can help to reduce the instances of epilepsy occurrences and the autism impairments. Both the portable Radio Music System and the portable epilepsy predictive system rely on the beta, delta, alpha and theta brainwaves to explain the behaviours of the brain activity across the right temporal regions of the brain, the inferior frontal brain areas and the inferior temporal brain areas (Hughes and Bromfield 1993). The two EEGs demonstrate how the brain or the neural signals associate with music, sound waves, and brain sound waves interrelate. They highly recognise the contribution of brainwaves with the functioning of the systems.

Autism Spectrum Disorder and epilepsy continue to be among the serious mental health problems that are constantly causing psychological problems and distresses those affected. Autism is among the world's most irritating neurological and developmental disorders due to the psychological impact it has on many children attacked by its various complications. Nonetheless, since neurologists have fallen short of the required medical health solutions to

offer complete treatments to patients suffering from autism and epilepsy due to the complex nature of these neurological and developmental disorders, modern technology has come up with some effective remedies. The proposed project of designing portable neurofeedback training solutions and mobile epilepsy predictive system specifically relies on the human electroencephalogram (EEG). The human electroencephalogram (EEG) is an effective technology that helps the neurologists to offer therapeutically driven solutions to the patients who portray symptoms of autism and those who demonstrate seizure disorders. Given the fact that the clinical manifestations of the two mental health disorders are complex to control using the ordinary treatment options, neurofeedback solutions are very effective.

Future Work on Portable Epileptic and Autistic EEGs

Future work on the severity of autism and other mental health issues - While trying to understand the work of the human electroencephalogram (EEG) technology and the Brain Music System in managing the conditions of children and patients with autism through the balancing of brainwaves, it is important to note that autism has different levels of severities (Haut 2013). In the future, neurologists should attempt to investigate the likelihood of using the neurofeedback training options and the human electroencephalogram (EEG) technology in dealing with patients suffering from chronic autism and other severe impairments related to the brain such as lower brain functioning for the psychologically-upright individuals.

The nature of autism and epilepsy in human beings- Autism and Epilepsy are neurological and developmental disorders that normally begin during the plasticity stages of the children before they fully manifest in patients at their mature stages of life. Excessive promotion of the use of the human electroencephalogram (EEG) technology may result in circumstances whereby ordinary people can no longer predict even the simplest symptoms of autism and epilepsy (Schulze-Bonhage,Feldwisch-Drentrup, and Ihle 2011). Therefore, future investigations should concentrate on developing and understanding how the human electroencephalogram (EEG) technology will affect the ability ofordinary people to continue detecting autism and epilepsy symptoms.

The neurofeedback training and other interventions- Since medical technologies are meant to provide reliable solutions and help in improving the nature of treatment options and the related outcomes, future clinical research should establish the connection between the uses of human electroencephalogram (EEG) technology and other medical interventions (Scaramelli and Braga 247). For instance, research should focus on establishing how the human electroencephalogram (EEG) technology can work with other mental health interventions to analyse the synergistic effects that exist between other remedies and the neurofeedback training intervention (Scaramelli and Braga 2009). Other combinable interventions that can work with the human electroencephalogram (EEG) technology may include the hyperbaric oxygen therapy (HBOT) and the behaviour therapy.

CONCLUSIONS

Efforts to optimise seizure prediction- the current technological strategies meant to develop solutions for the autism and epilepsy patients are lacking the ultimate solutions for deterring the occurrence of seizures in patients. The mainstream EEG technology has only offered solutions on the detection and prediction, and slightly on the controlling of the seizures, but has failed to offer options to deter or abort the seizures in the epileptic patients. According to Fricker, this aspect means that the antiepileptic devices developed through the human electroencephalogram (EEG) technology are only offering solutions that even ordinary people can detect using physical assessment skills.

Seizure prediction and the future of the epileptic patients- Future investigations and research should focus on establishing how the human electroencephalogram (EEG) will affect the human beings and how the same technology can be useful in providing permanent solutions to the prevention of the occurrence of seizures. Future Neuroscience research should focus on analysing how the human electroencephalogram (EEG) can use permanent technologies such as the implantable devices to predict the occurrence of seizures in the epileptic patients. The future research should also focus on establishing how these implantable devices or technologies will affect the overall brain activity of the patients suffering from epilepsy.

Clarity of some neurofeedback training techniques- future research on the use of neurofeedback training technique on the autism patients should focus on several issues. One is explaining the prevailing relationships between the concepts of the rostral and dorsal ACC, and the involvement of the two concepts and the posterior cingulated cortices in the use of the neurofeedback treatment as a remedy used to treat patients suffering from autism. This assertion holds because the use of the neurofeedback training technique seems to have several complex strategies that are either confusing in nature or made up of mere exaggerations just to endorse the use of neurofeedback treatment in autistic patients.

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