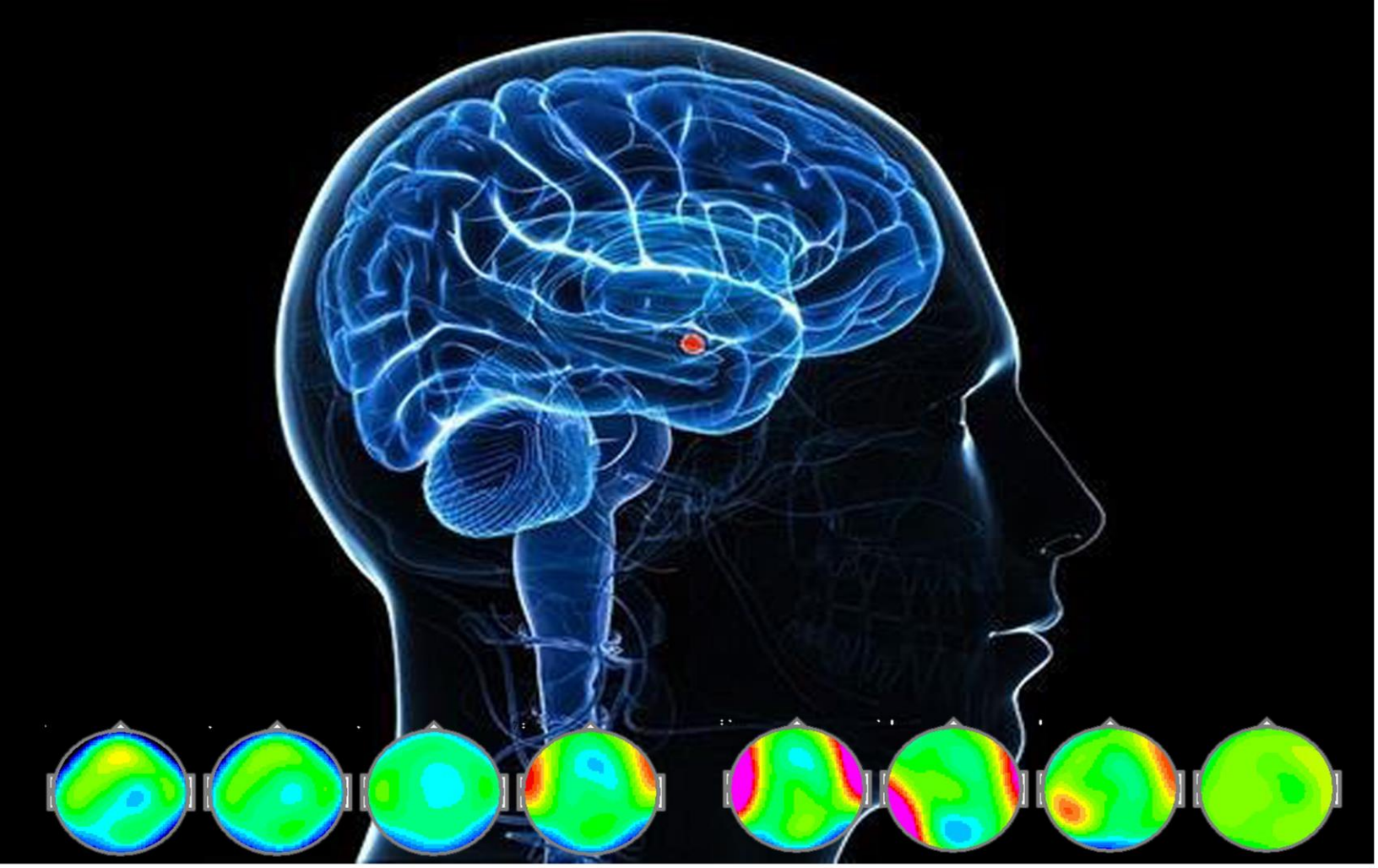

APJNT

ASIA PACIFIC JOURNAL OF NEUROTHERAPY

Vol. 1, No. 1 2019

APJNT Journal

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Message from APNA President

Greetings and welcome to this inaugural issue of **Asia Pacific Journal of Neurotherapy** (**APJNT)**. I am deeply honored to be the President of the Asia Pacific Neuro-Biofeedback Association (APNA) when this journal is launched. I would like to acknowledge our Founder President, the late Dr. Kenneth Kang for all the groundwork he has done to set up this Association. As the President of APNA, I have witnessed the Association's steady growth, thanks to the efforts of all practitioners and researchers who have come together to help make the dissemination of information possible.

APNA is a non-profit organization with the express purpose of providing a common platform for the dissemination of the results of practitioners and researchers who are involved in the research, technology and the clinical applications of neurofeedback and biofeedback in community healthcare. APNA is also involved in defining the qualities of neurofeedback practitioner through its training programmes and certification exercises.

APNA publishes a newsletter, Neuro-Eastern regularly since 2016. A conference is held every two years within the Asia Pacific Region. Every attending participant had noted the increased awareness of the health benefits of neurofeedback and biofeedback among the general public. As such, the demand for this type of intervention has increased. This awareness has created a need for dissemination of knowledge in the field.

As President of APNA, I recognized the need for an umbrella organization to bring together groups of practitioners in the diverse fields of neurofeedback and its technology into a global network for collaboration and mutual sharing of resources in order to provide a more evidence-based foundation for neurofeeedback applications.

The APNA journal aims to spread knowledge to and update members with the latest clinical applications of neurofeedback and biofeedback interventions. APNA would like to encourage our members who are certified practitioners of neurofeedback to contribute and share their experience. Publication of our results and experiences remain a fundamental function of the Association which will lead APNA into a recognized domain in neuroscience and its technology.

Finally, I want to express my gratitude to the editorial board and all authors who contributed to this inaugural publication. I look forward to working together with the Board, committees, and membership to strengthen APNA's role in neuroscience in general and neurofeedback in particular.

Dato' Prof Dr. See Ching Mey

APNA president

Message from ANSA president

What is ANSA?

The Applied Neuroscience Society of Australasia (ANSA) is a membership organization of health professionals from Australia, Australasia and New Zealand, who are involved in the promotion of professional excellence in the fields of Applied Psychophysiology, Neurotherapy and Nutrition. ANSA works to obtain broad acceptance of this combination of disciplines as a viable treatment approach in mental health care and for optimal performance.

ANSA aims to:

- advance the scientific study and professional practice of applied neuroscience (biofeedback, neurotherapy, applied psychophysiology and nutrition);
- function as a professional and educational society in the field of applied neuroscience;
- promulgate, foster, and maintain high ethical standards in the use of applied neuroscience;
- advocate and promote applied neurosciences to professionals in the community;
- establish/support the achievement of best practice for clinical applications of applied neuroscience;
- promote training and further education for health professionals in the application of biofeedback, neurotherapy, applied psychophysiology, nutrition and other self-regulator modalities as therapeutic tools;
- nurture and/or maintain interactions with similar international Societies such as ISNR, AAPB, etc.;
- increase public & professional awareness of applied neurosciences as integral to the health system;
- Encourage research and expansion of clinical and educational applications of applied neurosciences.

On behalf of the ANSA Executive Committee, I extend my sincere thanks to the APJNT Editorial Board for their efforts to bring you this first edition of the non-profit, on-line **Asia Pacific Journal of Neurotherapy (APJNT),** a joint initiative between ANSA and the Asia Pacific Neuro-Biofeedback Association (APNA). I further extend my thanks to those contributors who have given of their time to prepare manuscripts for this first release of the journal. Your work serves dual purposes for our readers: interpreting outcomes from research and practice; and modelling methodologies that may teach and encourage our peers to share their work.

Criticism of studies in our field may highlight sample sizes, randomization, control groups, and specificity of the treatment effects, however, well-designed single-case or uncontrolled studies may have valuable clinical utility. Furthermore, case studies may serve to test the feasibility of more systematic research of the efficacy of assessment and intervention methods. I strongly encourage clinicians to develop their confidence and capacity to contribute to our field as scientist-practitioners. Consider the following references:
Barlow, Nock & Hersen, (2009). Single Case Experimental Designs: Strategies for Studying Behavior Change, 3rd Edition, Pearson.
Kazdin, A. E. (2011). Single-case research designs: Methods for clinical and applied settings (2nd ed.). New York, NY, US: Oxford University Press.

Segool, N. K., Brinkman, T. M., & Carlson, J. S. (2007). Enhancing accountability in behavioral consultation through the use ofsingle-case designs. *International Journal of Behavioral Consultation and Therapy, 3*(2), 310-321. doi: 10.1037/h0100805
One proven strategy for developing work for publication is to share the topic as a presentation at a meeting of peers. In the context of an annual conference, for example the ANSA Annual Conference*, contributors tend to benefit from informal peer review and may subsequently refine their work for later submission to a peer-reviewed journal such as the APJNT. (*To learn more about the ANSA Conference being held in Cairns 22–27 August 2019, please visit Eventbrite at https://www.eventbrite.com.au/e/2019-ansa-conference-workshops-gateway-to-health-tickets-48189068802.

I trust that members of ANSA and APNA will come to value this journal as it promotes Neurotherapy research in clinical practice and provides a platform to showcase our knowledge and expertise.

Michelle Aniftos
ANSA President 2017 – 2109

Modulating Cortical Asymmetry: The Transdiagnostic Reduction of Depressive and Anxiety Symptoms Utilizing a Novel Therapeutic Approach

Randy Beck[a*], Johnathan Laugharne[b], Richard Laugharn[c], Wessel Woldman[d], Brendan McLean[e], Sajan Thapa[f], Ricardo Jorge[g], Michael Beck[h], Rohit Shankar[i]

[a]*Director, Institute of Functional Neuroscience, Perth, Australia.*
[b]*Associate Professor of Psychiatry, School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, Australia.*
[c]*Research Fellow, School of Maths, Exeter University, Exeter, England.*
[d]*Consultant Psychiatrist, Cornwall Partnership NHS Foundation Trust and University of Exeter Medical School, Exeter, England*
[e]*Lead Consultant Neurologist Royal Cornwall Hospital Trust, Cornwall, England.*
[f]*Research Fellow, Institute of Functional Neuroscience, Perth, Australia.*
[g]*Clinical Supervisor, Institute of Functional Neuroscience, Perth, Australia.*
[h] *Research Fellow and Clinical Supervisor, Institute of Functional Neuroscience, London, Canada.*
[i]*Consultant in Adult Developmental Neuropsychiatry – CFT Hon. Associate Clinical Professor, Exeter Medical School, Exeter, England*.

Abstract

A major theme emerging from recent studies of major depression and other psychiatric disorders encompasses the structural and functional changes in activity levels in a variety of brain regions which may be used as biomarkers to indicate levels of severity and location of dysfunction. Other studies have demonstrated that stimulation of a variety proprioceptive system components can reliably produce activation in cortical circuits and can be used to stimulate neuroplastic remodelling or correction of asymmetry of these circuits when applied in the appropriate manner. We present four cases of anxiety and MDD who have undertaken the new treatment paradigm involving EEG guided neuroplastic restructuring. All participants demonstrated significant improvement with respect to The Depression Anxiety Stress Scale (DASS) and general improvement in most categories of their World Health Organization Quality of Life Assessment (WHOQOL-BREF) scores. In every patient in all frequency ranges studied, a shift from a right dominant asymmetry to a left dominant asymmetry was observed.Our results indicate that specific peripheral stimulation can modulate cortical asymmetry across a variety of EEG frequency ranges and that this modulation is associated with a significant change in symptom presentation as measured by psychometric self-reporting tools.

Keywords: Cortical asymmetry; EEG; Depression; neuroplastic restructuring.

ARTICLE INFO	
RECEIVED	November 18
REVIEWED	January 19
ACCEPTED	February 19

** Corresponding author.*

Email: drrwbeck@me.com

1. Introduction

Major depression disorder (MDD) is characterized by dysphoric and irritable mood, rumination and self-referential thinking, anhedonia, a loss of motivation and interest in daily activities and impaired functioning in the social and occupational domains (American Psychiatric Association, 2013). MDD has also been shown to be associated with cognitive deficits, including impaired memory and concentration (Marazziti et al., 2010; Ravnkilde et al., 2002). MDD is a complex mental illness that can result in significant disability, reduced quality of life, and societal burden affecting 10%–15% of the population per year (Al-Harbi, 2012). A major theme emerging from recent studies is that structural and functional changes in activity levels in a variety of brain regions may be used as biomarkers to indicate levels of severity and location of dysfunction in MDD and other psychiatric disorders. For example, changes in activity levels in the hippocampus and/or prefrontal cortex produced by stress in genetically susceptible individuals have been identified as part of the pathophysiology of MDD (Malberg et al., 2000; Rajkowska, 2000a, 2000b; Sheline, 2000). Functional neuroimaging studies have shown that MDD is associated with hyperactivity of the amygdala and subgenual anterior cingulate gyrus (ACC), whereas the DLPFC and supragenual ACC are hypoactive in depressed individuals (Drevets et al., 1999; Mayberg et al., 1999; Siegle et al., 2007). Altered functional connectivity between these structures has also been reported in MDD. Electrical stimulation of the white tracks surrounding Cg25, which is located in the prefrontal cortex, has resulted in successful treatment of depression (Mayberg et al., 2005), as has stimulation of the nucleus accumbens (Bewernick et al., 2010). A recent review postulated that stimulation of the proprioceptive system components can reliably produce activation in cortical circuits and can be used to stimulate neuroplastic remodeling or correction of asymmetry of these circuits when applied in the appropriate manner (Beck et al., 2017). We utilized EEG imaging to identify and target asymmetrical cortical areas and exposed these areas to a variety of different peripheral stimulation techniques by applying repeated stimulation of specifically chosen modalities all of which have well established cortical target localisation including: unilateral interferential current, unilateral high velocity low amplitude adjustment, unilateral superficial vibration, novel cerebellar/vestibular stimulation, focused breathing, and listening therapy.A variety of research approaches have focused on individual differences in electroencephalogram (EEG) asymmetry patterns, following Davidson's conceptual model which suggested that individual differences in asymmetry patterns may be associated with a tendency towards certain affective styles and may be related to the individual's susceptibility to develop depression (Davidson, 1998; Fingelkurts & Fingelkurts, 2015; Thibodeau et al., 2006). Specifically, it has been suggested that relatively higher left compared to right frontal activity is associated with behavioral approach whereas relatively higher right than left frontal activity is related to behavioral withdrawal (Coan & Allen, 2004; Davidson et al., 1990). As such, individuals showing decreased left frontal activity or enhanced right frontal activity are more likely to experience feelings of sadness and anhedonia or to exhibit behavioral inhibition and withdrawal (Sutton & Davidson, 1997), all of which are known to be associated with depression, in addition to other psychiatric conditions. Along with regions of the brains such as the limbic system, the dorsolateral prefrontal cortex in particular seems to be heavily involved with the development of major depressive disorder (MDD). It is clear that damage, lesion or dysfunction in the DLPFC can lead to increased expression of depression symptoms (Koenigs, 2009). Other research hasdemonstrated that an asymmetry of function between the right and left DLPFC in which low levels of activity in the left dorsolateral prefrontal cortex but elevated levels of activity in the right dorsolateral prefrontal cortex can also result in major depressive disorder (Grimm et al., 2008). The DLPFC is not an anatomical structure, but rather a functional one. It lies in the middle frontal gyrus of humans (i.e., lateral part of Bradman's Area (BA) 9 and 46). Other sources consider that DLPFC is attributed anatomically to BA 9 and 46 and BA 8, 9 and 10 (Cieslik, 2013; Hoshi, 2006; Mylius et al., 2013).

1.1. Neuroplastic Reconstruction.

The dynamics of brain connectivity are complex in nature and involve the development of intricate network connection systems that can both maintain an appropriate level of integrity of synaptic connection and at the same

time express neuroplastic properties in response to the constant change of environmental stimulus (Beck, 2013; Boyer, 2016). These network connections are categorized as Structural, Functional and Effective (Friston et.al. 1993; Greenblatt et al. 2007; Sakkalis, 2011). Structural connectivity is based on detection of the axon fiber tracts that physically connect the regions of the brain. These are the anatomical network maps that indicate possible pathways that the signals can travel on in the brain (Le Bihan et al. 2001, Wedeena et al. 2008). Functional connectivity identifies actual activity levels in brain regions that have similar frequency, phase and/or amplitude of correlated activity. These areas may be involved in the resting state (i.e. task independent) or higher order information processing (i.e. task dependent) that is required for sensory responses, motor responses and intellectual or emotional processing. (Towle et al. 2007). Effective connectivity uses the functional connectivity information and then determines the magnitude and directness of influence that one neural system may have over another, more specifically the direction and magnitude of the dynamic information flow in the brain (Boyer, 2016; Cabral, 2014; Horwitz, 2003]. These projection system connections can be disrupted by a number of factors including neurotransmitter asymmetries (Harrison 2015), Hormonal asymmetries (Wittling & Scweiger 1993), immune dysregulation (Renoux et al. 1986) resulting in an inappropriate response patterns referred to as functional disconnections. Disconnection can present clinically as syndromes in at least two disruptive forms, disconnection and hyper-connection, which alter connectivity in different ways.

Hyper-connection causes the same neuronal pathways to be excited or inhibited over and over again which reduces the ability of the system to respond flexibly to altered states of activity. This results in a functional projection system that becomes functionally deficient, inflexible, debilitated, and incapable of reacting to environmental stimuli effectively. Hypo-connection or disconnection results in a slow inefficient transfer of information, which results in incomplete or slow thought formation diminishing the relevance of the systems' output to the environmental input received. Disconnection and hyper-connection syndromes also involve emotional responses and states and result in a variety of psychological and psychiatric conditions. It is important to understand that psychological and psychiatric disorders usually do not result from specific localizable lesions in the nervous system, in contrast to the relatively well-defined lesions that occur in stroke and trauma. Instead, these disorders are characterized by abnormalities in the network of connections forming the limbic, prefrontal and frontostriatal neural circuits that underlie motivation, perception, cognition, behavior, social interactions and regulation of emotion (Beauregardet al., 2001). Neuroplastic restructuring is the term we have applied to the neurorehabilitation therapies involved in the process of repairing functional disconnections and other disruptive pathologies such as cortical asymmetries utilizing the concepts of neuroplasticity. We have found a dramatic increase in the effectiveness of neuroplastic restructuring by utilizing EEG assisted targeted non-invasive stimulation (Beck 2013b).We present:

Four cases of anxiety and MDD who have undertaken the new treatment paradigm involving EEG guided neuroplastic restructuring.

2. Methodology

2.1. Materials and Methods For Participants

In this section, all information related to methods including experiment, data collection, protocol, techniques of data analysis, participants' information, detail of public dataset (if any), etc. Four patients clinically diagnosed as suffering from various levels of anxiety and depression, were recruited through clinician referral for specialized treatment (for detailed histories see table 1). Prior to entering the study, all participants were informed of the procedures and signed consent documents. All clinical investigators followed the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki ("Declaration of Helsinki", 2013).

Table 1. Short Histories of Participants

Case A
A 39-years old married woman with one infant child. Presents with long-term symptoms of anxiety and depression of a mild-moderate severity. Diagnosed with Dysthymia and Generalised Anxiety Disorder. Not keen on medications so undedicated but several brief periods of supportive counselling and CBT based psychotherapy in previous years.
Case B
A 52-years old unemployed divorced woman with 3 adult children. Presents with a 20yr history of symptoms of anxiety and depression. A significant trauma history and re-experiencing and avoidance symptoms noted. Diagnosed with chronic PTSD and Major Depressive Disorder. Currently prescribed Sertraline 200mg daily (for several months). Previous trials of several antidepressants and CBT based psychological interventions.
Case C
A 47-years old married woman with one adult daughter. Employed part-time as a nurse. Gives a 25yr history consistent with a diagnosis of Major Depression with psychotic symptoms. Multiple trials of medications over previous years and courses of CBT based psychotherapy. Current medications: Efexor SR 450mg, Mirtazapine 30mg, Quetiapine 325mg, Diazepam 5mg BD, Risperidone 4mg.
Case D
A 28-years old single unemployed woman living with her mother who acts as her career. She gives a 13yr history of psychotic symptoms and has been given clinical diagnoses of Schizophrenia, PTSD, Autism spectrum disorder and Major Depression. Ongoing psychological therapy and social supports are in place. Current medications: Olanzapine 25mg, Asenapine 20mg, Lamotrigine 450mg, Sertraline 100mg.

2.2. Study Design

The study was carried out in a private clinic to which all patients were referred to for treatment. The rooms were quiet and comfortably lighted. During the first session in the presence of a trained practitioner all subjects completed two self-administered neuropsychological measurement tools whose completion required about 30 minutes. The participant was then invited to the EEG room where the EEG cap was positioned. EEG recording was continuously performed for a period of 10 minutes while the participants were at rest with eyes open (5 Minutes) and eyes closed (5 minutes).Participants then received appropriate peripheral stimulation as determined by the activity measured on their EEG. They received peripheral stimulation 3 times per week for 18 weeks. The peripheral stimulation treatment protocols used have been outlined in detail in a previous publication by this group (Beck et al., 2017). EEGs, psychometric testing and treatment plan updates were performed at 18, 36 and 54 treatments.

2.3. Self-Administrated Checklists

We utilized two valid and reliable psychometric tests; the Depression Anxiety Stress Scale (DASS), the WHOQOL-BREF Assessment as objective measure questionnaires to measure symptoms of psychopathology.

A) The Depression Anxiety Stress Scale (DASS)

The DASS is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress. The DASS was designed to efficiently measure the core symptoms of anxiety and depression and

has demonstrated positive psychometric properties in adult samples of anxiety and depression patients (Brown et al., 1997).

B) World Health Organization Quality of Life Assessment (WHOQOL-BREF)

The WHOQOL-100 allows detailed assessment of each individual facet relating to quality of life. In certain instances however, the WHOQOL-100 may be too lengthy for practical use. The WHOQOL- BREF version has therefore been developed to provide a shorter form of quality of life assessment ("The World Health Organization quality of life assessment (WHOQOL): Position paper from the World Health Organization", 1995). The WHOQOL-BREF looks at Doman level profiles through a total of 26 questions and produces a quality of life profile. It is possible to derive four domain scores. There are also two items that are examined separately: question 1 asks about an individual's Z score overall perception of quality of life and question 2 asks about an individual's Z score overall perception of their health. The four domain scores denote an individual's Z score perception of quality of life in each particular domain. Domain scores are scaled in a positive direction (i.e. higher scores denote higher quality of life). The mean score of items within each domain is used to calculate the domain score. The mean scores are then multiplied by four in order to make domain scores comparable with the scores used in the WHOQOL-100.

2.4. EAG Procedure

A fitted electrode cap (electro-cap international) with leads placed according to the International 10/20 System was applied to achieve a standardized 19-channel qEEG recording. A Mitsar EEG –BT system 21 EEG and 4 poly channel EEG amplifier was used to perform a linked earlobes referential EEG recording. Electrode impedance of less than 5 Kilo ohms was required at all electrode contact sites prior to initiation of recording. EEG signals was digitized at a rate at or above 256 samples per second, band-pass filtered between 0.5 and 35 Hz and stored on a hard disk for subsequent analysis. Seated upright in a comfortable chair, the participant underwent 10 minutes of EEG recording composed of two standardized tests of five minutes duration; eyes open then eyes closed. Digitized data was subjected to a visual artefact detection routine and artefacts of subject movement and other non-brain generated signals were removed. All results met the required minimum reliability measurements of a split half score over 95% and a test retest score over 92%. A low pass filter was used at 37Hz to remove any external interference.

Representative samples of qEEG data was analyzed for frequency content using discrete Fourier transformation. Evaluation of this data employed various descriptive and statistical displays with a variety of frequency band formats including individual frequency band displays, topographic maps, and coherence analysis head map displays. The ranges of the frequency bands were established as follows: delta (d), 1.5–4 Hz; theta (h), 4–8 Hz; alpha (a), 8–12 Hz; beta 1 (b1), 12– 20 Hz; beta 2 (b2), 20–30 Hz; gamma (c), 30–45 Hz. Statistical analysis was used to compare client data with the FDA registered (K041263) Neuro-Guide normative database which has a total sample size N = 900 and spans the age range from 2 months to 82 years (Thatcher 1998; Thatcher et al. 2003) and corrected for time-of-day variations and state transition.

3. Results and Discussion

The participants in this study were all females ranging in age from 26-53 years of age with an average age of 40.5 years. All were examined by a registered psychiatrist (JL) and classified as described in table 1. Treatment periods ranged from 4-5 months with an average treatment period of 4.5 months. The participants each received a total of 54 clinical interventions during this period. Table 2 shows the EEG amplitude results (uV Sq) for the theta (4-8 Hz), alpha (8-12Hz), beta (12-25Hz), high beta (25-30Hz) and gamma (30-40Hz) frequency ranges from all four participants over the international 10/20 placements (Fp1, Fp2, F3 and F4) recorded.

Table 3 shows the average Fp1/Fp2 ratios of activity measured over all participants at those sights. An Fp1/Fp2 ratio less than 1 indicates a right frontal cortex dominant asymmetry and an Fp1/Fp2 ratio greater than 1 indicates a left frontal cortex dominant asymmetry. In all frequency ranges a shift from a right dominant asymmetry to a left dominant asymmetry was observed (figure 1 also). Table 4 shows the average F3/F4 ratios of activity measured

over all participants at those sights. An F3/F4 ratio less than 1 indicates a right dorsal lateral prefrontal cortex dominant asymmetry and an F3/F4 ratio greater than 1 indicates a left dorsal lateral prefrontal cortex dominant asymmetry. In all frequency ranges a shift from a right dominant asymmetry to a left dominant asymmetry was observed (figure 2 also).

Table 5 shows the average total left frontal cortical activity (Fp1+F3)/total right frontal cortical activity (Fp2+F4) measured over all participants at those sights. A left frontal/right frontal ratio less than 1 indicates a right cortex dominant asymmetry and a ratio greater than 1 indicates a left cortex dominant asymmetry (figure 3). Across the average ratio an overall shift from a right dominant asymmetry to a left dominant asymmetry was observed (p=.03).

Table 6 lists the depression, anxiety, and stress scores for each of the participants in the study. All participants reported an overall decrease in all categories over the duration of treatment.

Table 7 lists the average percentage change in scores of across all participants in the study. All participants demonstrated significant changes across all categories stress (p=0.05), depression (p=0.02) and anxiety (p=0.01). The greatest percentage change was observed in the depression category (54%), followed by anxiety (40%) and stress (34%) respectively (figure 4).

Table 2. Individual Participant EEG Activity Fast Fournier Transform Absolute Power (uVSq) EEG amplitude results (uV Sq) for the theta (4-8 Hz), alpha (8-12Hz), beta (12-25Hz), high beta (25-30Hz) and gamma (30-40Hz) frequency ranges from all four participants over the international 10/20 placements (Fp1, Fp2, F3 and F4) recorded.

Participant A						
Electrode	Initial Theta	Final Theta	Initial alpha	Final alpha	Initial Beta	Final Beta
Fp1	4.6	32.5	11.3	22.1	5.5	13.5
Fp2	4.7	18.6	11.0	21.8	6.3	10.2
F3	7.0	14.3	15.5	23.2	9.1	10.2
F4	7.7	14.0	17.5	22.3	14.2	13.8
	Hbeta	Hbeta	gamma	gamma	Total	Total
Fp1	1.2	3.6	1.7	5.5	24.4	77.1
Fp2	1.5	2.1	2.4	3.7	25.8	56.4
F3	1.3	1.5	1.3	1.8	34.2	51.0
F4	1.3	1.9	1.6	2.2	42.3	54.3
Participant B						
Electrode	Initial Theta	Final Theta	Initial alpha	Final alpha	Initial Beta	Final Beta
Fp1	8.2	20.3	6.0	8.3	9.1	13.9
Fp2	10.9	19.4	6.4	7.3	9.5	12.0
F3	12.1	21.9	8.5	9.6	15.7	19.9
F4	13.6	21.9	11.3	11.9	23.9	25.3
	Hbeta	Hbeta	gamma	gamma	Total	Total
Fp1	2.0	4.1	1.8	4.2	27.1	50.8

Fp2	2.0	3.6	2.1	3.4	30.9	45.7
F3	3.8	7.7	3.3	4.9	43.3	64.0
F4	5.3	9.2	3.1	4.5	57.3	72.7

Participant C

Electrode	Initial Theta	Final Theta	Initial alpha	Final alpha	Initial Beta	Final Beta
Fp1	20.7	20.0	11.3	9.8	9.3	10.4
Fp2	22.2	18.0	11.0	9.0	9.1	8.8
F3	13.9	13.7	9.0	9.0	10.1	9.8
F4	12.9	11.5	10.4	8.7	12.0	11.5
	Hbeta	Hbeta	gamma	gamma	Total	Total
Fp1	2.6	1.8	4.1	2.0	48.1	43.9
Fp2	1.8	1.6	2.5	1.4	46.5	38.9
F3	2.5	2.1	2.0	1.4	37.5	36.0
F4	2.1	1.5	2.0	1.2	39.3	34.5

Participant D

Electrode	Initial Theta	Final Theta	Initial alpha	Final alpha	Initial Beta	Final Beta
Fp1	13.7	26.2	23.4	39.5	66.8	85.1
Fp2	15.1	26.1	27.2	42.6	86.9	106.4
F3	27.1	39.7	40.2	51.3	110.8	120.6
F4	26.3	27.8	40.3	45.4	92.3	98.6
	Hbeta	Hbeta	gamma	gamma	Total	Total
Fp1	6.9	8.7	4.6	5.6	115.4	165.1
Fp2	8.8	17.6	4.9	17.3	142.9	210.1
F3	8.9	12.5	4.8	9.3	191.8	233.4
F4	7.0	8.2	4.2	4.9	170.0	184.9

Table 3. Group Ave Symmetry Ratio Fp1/Fp2

Initial Theta	Final Theta	Initial Alpha	Final Alpha	Initial Beta	Final Beta
0.89	1.23	0.97	1.04	0.91	1.12
Initial Hbeta	Final Hbeta	Initial Gamma	Final Gamma	Initial Total	Final Total
1.01	1.10	1.05	1.12	0.92	1.10

Table 4 Group Ave Symmetry Ratio F3/F4

Initial Theta	Final Theta	Initial Alpha	Final Alpha	Initial Beta	Final Beta
0.98	1.16	0.88	1.00	0.83	0.90
Initial Hbeta	Final Hbeta	Initial Gamma	Final Gamma	Initial Total	Final Total
1.04	1.14	0.99	1.25	0.91	1.03

Table 5. Group Ave Symmetry Ratio Left/Right Frontal

Initial	Final	
0.91	1.06	p=.03

Table 6. Depression Anxiety Stress (DAS) Scores (% Change) lists the depression, anxiety, and stress scores for each of the participants in the study. All participants reported an overall decrease in all categories over the duration of treatment

Participant A	28/08/15	3/12/15	6/01/16	Difference
Stress	88%	45%	29%	-59%
Depression	86%	29%	7%	-79%
Anxiety	58%	10%	5%	-53%

Participant B	5/09/15	4/12/15	13/01/16	
Stress	67%	51%	55%	-12%
Depression	79%	69%	48%	-31%
Anxiety	64%	36%	38%	-26%

Participant C	19/09/15	17/11/15	11/01/16	
Stress	86%	80%	43%	-43%
Depression	93%	86%	50%	-43%
Anxiety	74%	88%	33%	-41%

Participant D	12/09/15	13/11/15	22/02/16	
Stress	98%	64%	76%	-22%
Depression	96%	31%	33%	-63%
Anxiety	100%	54.76%	60%	-40%

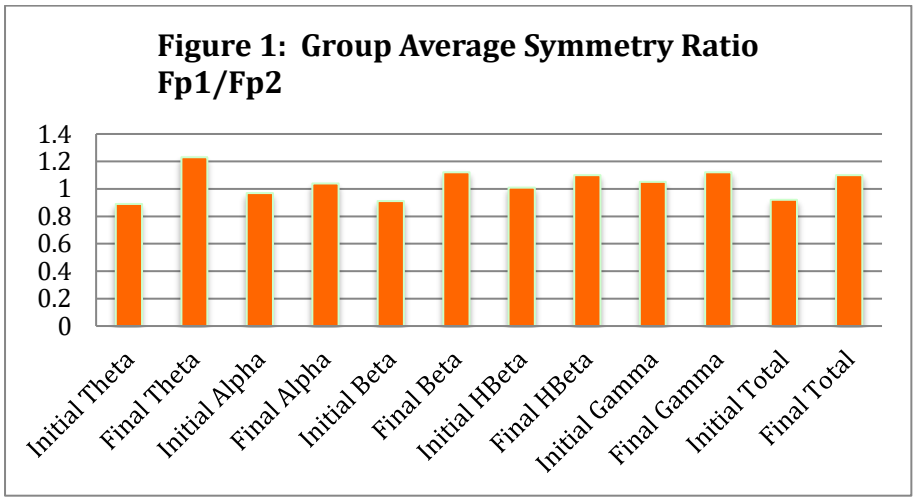

Fig 1. shows the average Fp1/Fp2 ratios of activity measured over all participants.

An Fp1/Fp2 ratio less than 1 indicates a right prefrontal cortex dominant asymmetry and a Fp1/Fp2 ratio greater than 1 indicates a left prefrontal cortex dominant asymmetry. In all frequency ranges a shift from a right dominant asymmetry (less than 1.0) to a left dominant asymmetry (greater than 1.0) was observed.

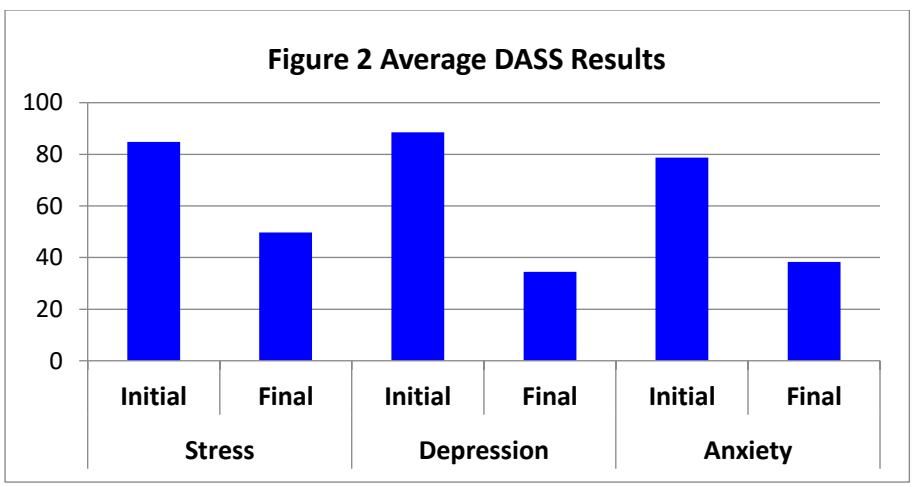

Fig 2. All participants demonstrated significant changes across all DASS categories; stress (p=0.05), depression (p=0.02) and anxiety (p=0.01).

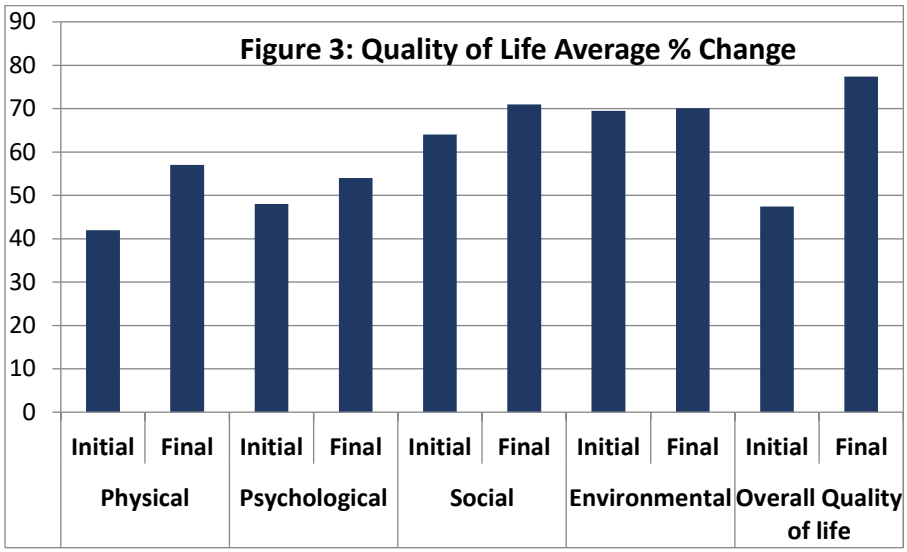

Fig 3. demonstrates the average percentage change in each WHOQOL-100 category. Positive changes were recorded in all categories.

Significant changes were recorded in the physical (p=0.04) and overall health categories (p=0.02).

Table 7. DASS Scores Group Average Change

(% ave change)	Stress	Depression	Anxiety
Participant A	-59.43	-78.86	-53.24
Participant B	-11.91	-30.95	-26.19
Participant C	-42.85	-42.86	-40.48
Participant D	-21.81	-62.67	-39.98
Total % change	-34.00	-53.84	-39.97

Table 7 lists the average percentage change in scores of across all participants in the study. All participants demonstrated significant changes across all categories stress (p=0.05), depression (p=0.02) and anxiety (p=0.01).

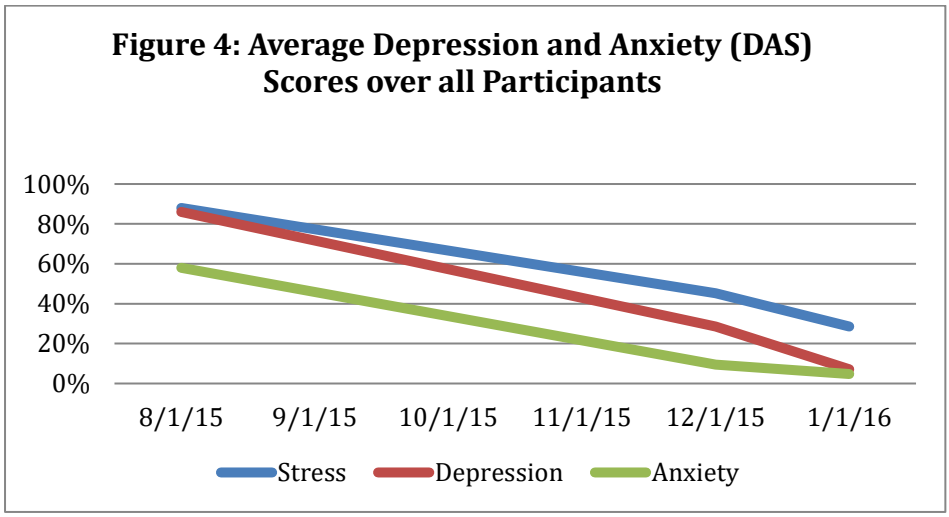

Fig 4. The greatest percentage change was observed in the depression category (54%), followed by anxiety (40%) and stress (34%) respectively.

Table 8. World Health Organization Quality of Life Checklist lists the World Health Organization Quality of Life Assessment (WHOQOL-BREF) scores reported by all participants in the study.

Participant A	28/08/15	3/12/15	6/01/16
Physical Health	69%	62%	62%
Psychological Health	53%	53%	53%
Social Relationships	73%	67%	67%
Environment	90%	90%	78%
Overall Quality of Life and General Health	60%	80%	90%

Participant B	5/09/15	4/12/15	13/01/16
Physical Health	46%	57%	63%
Psychological Health	47%	30%	47%
Social Relationships	60%	60%	60%
Environment	50%	53%	50%
Overall Quality of Life and General Health	30%	50%	50%

Participant C	19/09/15	17/11/15	11/01/16
Physical Health	43%	74%	74%
Psychological Health	37%	70%	57%
Social Relationships	67%	73%	80%
Environment	68%	85%	73%

Overall Quality of Life and General Health	40%	80%	80%

Participant D	12/09/15	13/11/15	22/02/16
Physical Health	42%	60%	60%
Psychological Health	55%	70%	60%
Social Relationships	58%	67%	60%
Environment	70%	78%	73%
Overall Quality of Life and General Health	60%	70%	90%

Table 9 lists the average percentage change and the p values associated with the group changes in each category. Positive changes were recorded in all categories with the exception of environmental which showed a slight regression of 1%. Significant changes were recorded in the physical (p=0.04) and overall health categories (p=0.02).

Table 9. World Health Organisation Quality of Life Checklist

	Ave%Change	p value
Physical	15	0.04
Psychological	6	0.13
Social	7	0.23
Environmental	1	0.40
Overall	30	0.02

4. Discussion

4.1. Comorbidity of Anxiety and Depression

There are several theoretical models that attempt to explain the emotional and motivational deficits underlying depression and anxiety (Clark, Watson, & Mineka, 1994; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Gray, 1994; Shankman & Klein, 2003). As previously discussed, anxiety is a common clinical feature of depressive disorders and in our study all of the participants exhibited a significant comorbidity. Most studies examining frontal EEG asymmetry in depression have utilized alpha power as an inverse measure of brain activity.Thus, increased alpha power over left relative to right frontal regions is inferred as decreased brain activation over left relative to right frontal regions. While the use of alpha power as an inverse measure of brain activity has been controversial (Allen, Coan, & Nazarian, 2004; Tenke & Kayser, 2005), several studies have shown that alpha power is inversely correlated with other measures of brain activity, such as functional magnetic resonance imaging (fMRI) (Goldman, Stern, Engel, & Cohen, 2002) and positron emission tomography (PET) (Oakes et al., 2004). In addition, alpha power has been shown to be inversely associated with performance on neuropsychological tasks mediated by specific cortical regions (Davidson, Chapman, Chapman, & Henriques, 1990). Bruder et al. (1997) compared EEG alpha asymmetries of patients having a major depressive disorder (MDD) and patients having both an MDD and an anxiety disorder. As expected they found that depressed patients showed relatively greater alpha power over left than right anterior sites, consistent with EEG evidence of left frontal hypo activation in depression. This finding was the same in depressed patients with or without an anxiety disorder (Bruder et al., 1997). The participants in our study, while demonstrating a reduced overall power in the left frontal regions and increased power in the right frontal regions, they did not exhibit

the expected pattern in the alpha frequency range as reported in EEG studies above (figure 1). Inconsistencies of results have emerged which have led to confusion and debate with regards to the meaning of these results. Pollock and Schneider (1990) reviewed eight studies comparing EEG differences among depressed and non-depressed participants. Three studies reported no between-group differences, whereas one described decreased alpha power (i.e., increased activation in depressed individuals similar to our results) relative to controls. Reid et al. (1998) found that data from two different samples of depressed individuals failed to replicate findings from previous studies of relatively increased left frontal alpha activity in depression. The absence of group differences in alpha band activity for the 8-minute baseline condition was consistent across three different reference montages, at both mid-frontal and lateral-frontal sites. Other studies have found results similar to ours when considering just the alpha frequency range (Heller & Nitschke, 1998; Kemp et al., 2010; Segrave et al., 2010).

We have considered several explanations that may have contributed to our results in the alpha band. Firstly, in this study EEG alpha asymmetry was solely calculated on the basis of data derived by a linked-earlobes reference montage. This reference has been critically discussed in the literature (Miller et al., 1991) however Debener (2000) compared linked earlobes-referenced data to computational Cz-referenced and common-average-referenced data (19-channel recording). The linked-earlobes reference channel comprised less alpha activity in a resting condition, and the corresponding data reflected more appropriately the basic occipitoparietal topography of EEG alpha activity in healthy individuals. The results in this report should be interpreted considering that the linked earlobes reference was utilized because asymmetry measures derived by different EEG reference montages may (Henriques & Davidson, 1990, 1991; Tomarken, 1992; Wheeler, Davidson, & Tomarken, 1993) or may not (Reid et al., 1998; Hagemann et al., 1998; Debener et al., 2000) provide similar results.

Secondly, all of our participants received pharmacological treatment during the course of the study. Although antidepressants are generally not known to alter

EEG alpha asymmetry (Kwon et al., 1996; Shagass et al., 1988) it is unknown what effect they would have on the other frequencies we have recorded in this study. A few studies have related therapeutic effects of antidepressants to a shift in anterior EEG alpha power asymmetry (Saletu, Grünberger, Anderer, Linzmayer, & Zyhlarz, 1996; Ulrich et al., 1993). However, since patient medication remained constant throughout the study, the possible influence of antidepressants on anterior EEG alpha asymmetry and its temporal characteristics was controlled in this study. Whether regionally restricted alteration of anterior EEG asymmetry is caused by antidepressant medication is not known yet. Future research may determine whether mood improvements in clinically depressed patients due to antidepressant medication are accompanied by a shift towards higher left anterior activation. Thirdly, Thibodeau (2006) performed a meta-analytic review to determine the association between depression, anxiety and resting frontal EEG activity. They found that three moderating variables predicted effect sizes: (a) shorter EEG recording periods were associated with larger effects among adults, (b) different operationalization of depression yielded effects of marginally different magnitudes, and (c) younger infant samples showed larger effects than older ones. In our study the average age was 40.5 years and the youngest participant was 26-years old, reducing the probability of younger age bias contributing to our findings. Fourthly, researchers have identified further possibilities for the inconsistencies observed across EEG studies on depression including data collection periods, which varied from one 8-minute measure of baseline EEG data (Reid et al., 1998) to 1-minute (two 30 second) baseline periods (Henriques & Davidson, 1990, 1991) and one 30 second baseline measurement (Allen et al., 1993). In this study we used 10 minutes of baseline data recordings (two 5-minute), one eyes open and one eyes closed.

We note that in one patient (participant C) in the study a slight reversal between initial and final FFT absolute power was recorded as compared to the other participants. One explanation for this observation involves the occurrence of comorbidies in this patient. We know there is considerable comorbidity of depressive and anxiety disorders (Maser and Cloninger 1990). Bruder et al (1997), compared EEG alpha asymmetries of patients having a major depressive disorder (MDD) and patients having both a MDD and an anxiety disorder. They found, as predicted on the basis of the model proposed by Heller et al (1995), depressed patients with an anxiety disorder had the opposite direction of alpha asymmetry in the posterior region when compared to depressed patients without an anxiety disorder. We did not include the activity of posterior regions in our study but it is possible that comorbidity of depressive and

anxiety disorders may act to heighten the abnormal direction of anterior alpha asymmetry that has generally been seen for depression and anxiety in some patients. We intend to further explore this concept in future investigations.

4.2. Asymmetric Index

The majority of the research on frontal EEG asymmetry has computed an asymmetry index (i.e., right alpha power minus left alpha power), which has been frequently related to depression. However, these findings have been inconsistent (i.e., Bruder et al., 1997; Kentgen et al., 2000). That is, for many studies the relationship between the frontal EEG asymmetry and depression is only seen with the asymmetry index and not with alpha power over a specific hemisphere as we found in our study. Furthermore, Allen and colleagues (2004) have suggested that earlier methods for calculating alpha power at individual electrodes may have magnified individual hemisphere effects. Thus, we suggest the asymmetry ratio that we have used in this study might be a more reliable metric of asymmetry, as it describes not only the location of the asymmetry but also the relative strength or size of the asymmetry which is a useful metric in clinical treatment.

The results of this study are consistent with the model proposed by Davidson's (1992; 1998) approach-withdrawal model, which posits two separate systems of emotion and motivation. The approach system controls appetitive behavior and sensitivity to reward, and is implemented by a neural circuit that incorporates left frontal regions. The withdrawal system underlies behavioral inhibition and avoidance, and is implemented by a neural circuit that incorporates the frontal regions. According to the approach-withdrawal model, depression and anxiety are associated with a hypoactive approach and hyperactive withdrawal system, respectively. As a result, the model hypothesizes that both conditions should be associated with an asymmetry in total frontal brain activation due to reduced relative left activity (depression) and increased relative right activity (anxiety). All of the participants in this study presented with an overall right dominant asymmetry in all frequency ranges. This dominance was also present in regional frontal and dorsal lateral frontal areas. Interestingly when analyzing individual frequency changes before and after treatment we found statistically significant changes in only one frequency range (Theta Fp1; $p=0.01$). All other frequency ranges did shift from a right to left dominance but not significantly. This implies that changes over all frequencies, not just alpha as previously thought, may contribute to the functional expression of depression and anxiety.

4.3. Therapeutic Approaches

As we have described in this paper, many studies have shown that socially anxious individuals exhibit greater relative right frontal EEG activity at rest, however, we have found only one other study which investigated whether improvements in symptoms as a result of treatment are associated with concomitant changes in resting brain activity. Moscovitch et al., (2011) measured regional EEG activity at rest in 23 patients with social anxiety disorder (SAD) before and after cognitive behavioral therapy (CBT). Results indicated that patients shifted significantly from greater relative right to greater relative left resting frontal brain activity from pre- to post-treatment. Greater left frontal EEG activity at pre-treatment predicted greater reduction in social anxiety from pre- to post-treatment and lower post-treatment social anxiety after accounting for pre-treatment symptoms. These relations were specific to the frontal alpha EEG asymmetry metric. Our results indicate that specific peripheral stimulation can also modulate cortical asymmetry across a variety of frequency ranges and that this modulation is associated with a significant change in symptom presentation as measured by psychometric self-reporting tools.

4.4. Underlying Physiological Mechanisms

The three symptom subtypes of depression and anxiety in Clark and Watson's model (1991)—negative affect, somatic hyperarousal, and anhedonia appear to involve specific patterns of regional hemispheric activity in which evidence that affective behavior is related to frontal activational asymmetries, with negative affect or withdrawal

behaviors being associated with right frontal activation, and positive affect or approach behaviors being associated with left frontal activation (for reviews see Davidson and Tomarken (1989) and Davidson (1992).

One weakness of many neuroimaging studies is that they do not provide specific physiological information regarding the mechanisms underlying the asymmetries observed. Insight into these mechanisms can be gained by utilizing the results of other studies utilizing different stimulation modalities and outcome measures that can provide a window into physiological processes. Paired-pulse TMS studies investigate intercortical excitability (Pascual-Leone et al., 1998). The effects obtained depend on the intensity of the conditioning and test stimuli and on the ISI (Pascual-Leone et al., 1998). These intensities influence the effects because different circuits are recruited by different intensities of stimulation. Motor threshold studies reflect neuronal membrane excitability, which is mainly dependent on ion channel conductivity (Hodgkin & Huxley, 1952; Ziemann et al., 1998a).

Inhibition seems to reflect the activity of inhibitory interneurons or inhibitory connections between cortical output cells (Wassermann et al., 1996). Facilitation seems to be partially due to facilitatory interaction between I-waves and is thought to take place in the motor cortex at or upstream from the corticospinal neuron (Ziemann et al., 1998b). Maeda et al found that MDD patients showed a significant interhemispheric difference in motor cortical excitability, with the left hemisphere having lesser and the right hemisphere having greater excitability than in controls. They postulated that a plausible explanation for their findings might be that by comparison with the right hemisphere, the left hemisphere in MDD patients during a medication-resistant major depressive episode has relatively low glutamatergic influence or excessive GABAergic tone. Recently, Larisch et al. (1999) have reported an abnormally low serotonin release in patients with a treatment-unresponsive major depressive episode. We propose that the critical factor in symptom generation may be the relative difference in EEG power between frontal regions or in other words the total magnitude of the asymmetry. We also propose that a critical threshold level of activity both a maximum and a minimum value may trigger a reversal of function in these frontal regions. This critical level of function may be related to metabolic capacity, chronicity of the situation, neurotransmitter production, or genetic limit controls present in the neurons. These processes may explain the variations in results found in the many studies we have presented including our own findings. Much more research aimed at exploring these concepts needs to be performed before a clear understanding of these functions can be presented.

5. Limitations of Study

The relevance of motor cortex abnormalities to depression is unknown. A larger sample size is needed to confirm this abnormality in depression. Different types of depression, both medication-responsive and refractory, need to be studied.

6. Conclusions

Our findings suggest the following conclusions:

- EEG guided peripheral stimulation can modulate cortical asymmetry across a variety of frequency ranges and that this modulation may be contributing to a significant change in symptom presentation as measured by psychometric self-reporting tools.
- The asymmetry ratio utilized in this study may be a more reliable metric of asymmetry in that it describes not only the location of the asymmetry but also the relative strength or size of the asymmetry which is a useful metric for the clinician applying therapy.
- The relative difference in EEG power between frontal regions, or in other words, the total magnitude of the cortical asymmetry may be one of the critical factors contributing to the generation of neuropsychiatric symptoms in these patients. We propose that a critical threshold level of activity at both a maximum and a minimum value may trigger a reversal of function in these frontal regions and that the resulting critical level of function may be related to metabolic capacity, chronicity of the situation, neurotransmitter production, or genetic limit controls present in the neurons.

- Our findings suggest that more research is needed to determine the clinical treatment parameters that would be most effective in different patient presentations and to further understand the generators and effects of cortical asymmetries on function.

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Developmental Trauma, LENS and Neural Regulation: Brain and Body

Ulrich Lanius*

Ph.D. Private Practice206A – 1571 Bellevue Avenue, West Vancouver, BCV7V1A6, Canada

Abstract

Individuals with a history of Developmental Trauma often have complex histories and symptom patterns that do not respond easily to therapeutic interventions. The addition of LENS Neurofeedback and its integration with other psychotherapeutic interventions for Developmental Trauma are discussed. LENS is unique in the field of neurofeedback in that it applies the concept of neural regulation not only to the brain but also to the body, reflecting both Top-down and Bottom-up interventions. Such an integrated body mind approach dovetails uniquely with other information processing interventions. Case studies of individuals that had previously had not responded to other interventions are presented who benefitted from the integration of LENS neurofeedback and associated neural regulation approaches into standard trauma treatment interventions. It is suggested that individuals with a history of Developmental Trauma benefit from the addition to LENS neurofeedback by directly intervening at the level of the electrical or frequency domain.

Keywords: neurofeedback; LENS neurofeedback; neuro therapy; alpha-theta; alpha feedback; posttraumatic stress disorder; developmental trauma; dissociative disorder, complex regional pain syndrome; EMDR; opioid antagonist; naltrexone; LDN;

ARTICLE INFO	
RECEIVED	November 18
REVIEWED	January 19
ACCEPTED	February 19

** Corresponding author.*

Email: ulanius@direct.ca

1. Introduction

The use of LENS Neurofeedback and its integration with psychotherapeutic interventions is discussed. Specifically, case studies are described of individuals with a history of developmental trauma that had not responded adequately to treatment as usual. Prior treatment commonly included multiple pharmacological interventions, as well as trauma-focused interventions including Cognitive Behavioural Therapy (e.g., Ehlers, 2013), EMDR (e.g. Shapiro, 2018), Sensorimotor Psychotherapy (e.g., Ogden & Fisher, 2015), as well as Ego-State Therapy (e.g., Watkins, 1997) including targeting dissociative symptoms (Boyd et al., 2018).

LENS lends itself to integration with other psychotherapeutic modalities due to the short duration of feedback, thus allowing time for additional interventions. Further, LENS is unique in the field of neurofeedback in that it applies the concept of neural regulation not only to the brain but also to the body, reflecting both Top-down and Bottom-up interventions. Such an integrated body mind approach dovetails uniquely with other information processing interventions, like mindfulness-based interventions, body-oriented psychotherapy, as well as EMDR.

2. Background and Literature:

2.1. Developmental Trauma

Developmental Trauma is a term used to describe childhood trauma that includes chronic abuse, neglect or other types of adversity while growing up. When a child is exposed to overwhelming stress and their caregiver does not help reduce this stress, or is the cause of the stress, the child experiences Developmental Trauma. While some of these children will go on to develop PTSD, many do not. Nevertheless, they are at risk for a host of complex emotional, cognitive and physical disorders that commonly affect them throughout their lives. Thus, individuals with a history of developmental trauma often present with a wide variety of mental and physiological symptoms, including significant dissociative symptoms (van der Kolk, 2005). They tend to be difficult to treat and frequently do not, or only minimally respond to standard trauma treatment approaches (Schmid et al., 2013).

2.2. Trauma, EEG, Abnormalities and Neurofeedback

EEG abnormalities are a common response to traumatic stress and include alterations in multiple frequency bands: gamma (Cohen et al. 2012; Huang et al. 2014), beta (e.g., Cohen et al. 2012; Huang et al. 2014), alpha (Jokić-Begić & Begić, 2003; Huang et al., 2014), theta (Todder et al., 2012; Huang et al., 2014) and alpha/theta ratio (Veltmeyer et al., 2006). Fisher (2014) has previously made a case for the use of neurofeedback in individuals with histories of developmental trauma. Operant-based neurofeedback has shown some promise (e.g., Fisher et al., 2016), but tends to be fairly time-intensive and thus difficult to integrate with standard trauma-focused treatment interventions that are typically delivered in 50-minute sessions.

2.3. Alpha Alpha-Theta and Trauma Treatment

One of the early neurofeedback studies with anxiety found both enhancement and suppression of alpha activity to have a beneficial effect (Plotkin & Rice, 1981). Neurofeedback research with regard to treatment of PTSD has frequently utilized alpha-theta feedback (e.g., Peniston & Kulkosky, 1991; Peniston et al., 1993). Kluetsch et al. (2014) in a group of individuals with PTSD related to childhood abuse used alpha desynchronizing feedback at Pz that resulted in initially decreased alpha amplitude during training that was followed by a significant increase or rebound in resting alpha synchronization. This rebound was associated not only with increased calmness but also in alterations in functional connectivity.

2.4. Low Energy Neurofeedback System (LENS)

The Low Energy Neurofeedback System (LENS) is an EEG biofeedback system that is unique in the field of neurofeedback in that rather than being based on operant conditioning, it uses tiny electromagnetic signals as a carrier wave for the feedback to assist in reorganizing brainwave activity (Ochs, 2006). The feedback frequency is linked to the momentary peak frequency detected by the system. "Subjects are not consciously learning to change brainwave activity; instead, the brainwave changes are the result of the brain continuously interacting with the resonant changes in the feedback pulses." (Nelson et al., 2010; p. 913). In comparison to typical operant-based neurofeedback, LENS sessions are typically much shorter and do not require attentional demands on the part of the client.

Empirical evidence for LENS is limited at this time. There are several case studies with the precursor of LENS, the Flexyx system being effective with traumatic brain injury, PTSD and traumatic stress symptoms (Nelson & Esty, 2012; 2015a; 2015b; 2018; Schoenberger et al., 2001). More recently, Larsen et al. (2006) provide supporting evidence for LENS using a sample of convenience. Further, a randomized, double-blind, placebo-controlled trial suggested a trend towards improvement with regard to fibromyalgia symptoms, potentially supporting its utility as an adjunctive intervention for fibromyalgia (Nelson et al., 2010). Finally, a single case study found LENS to be effective for anosmia associated with TBI (Hammond, 2007).

2.5. LENS and EEG Maps

LENS uses the 10/20 system with the addition of Fpz and Oz for a total of 21 sites. Different from a qEEG map, data are acquired sequentially, one site at a time. LENS uses both 'Standard Maps' and 'Suppression Maps' that provide information about EEG amplitude and variability. 'Standard Maps' order the electrode sites to be accessed by amplitude plus standard deviation or frequency and standard deviation at each site. 'Suppression Maps' are based on a coefficient of variation. The latter is determined by taking the standard deviation at a specific site and dividing it by the average amplitude and/or the standard deviation of the dominant frequency and dividing it by the average dominant frequency.

LENS typically defines a site as being suppressed if such coefficient of variation falls below a value of .35 – a number that has been found to be a useful heuristic for the notion of EEG suppression. With LENS treatment there is an initial release from suppression which results in both increased amplitudes, as well as increased variability, as measured by the standard deviation. While this typically correlates with improved behavioural functioning, as Ochs suggests, "the EEG at the end of a successful LENS treatment can look more typical of what accompanies impairment of functioning than it did at the beginning from the traditional qEEG point of view" (Lanius et al. 2015), raising questions about the reliability of qEEG maps in trauma survivors and basing treatment plans on those qEEG's.

2.6. Survivors Syndrome, Dissociative Symptoms and EEG Suppression

The concept of EEG suppression and 'Survivors Syndrome' is unique in the neurofeedback literature. Individuals with Trauma- and Stressor-related Disorders commonly exhibit what Ochs refers to as a 'Survivors Syndrome.' The latter is typically associated with an extreme lack of variability of the EEG that is hypothesized to be related to inhibitory neurotransmitter activity (Ochs, 2006). On the 'Standard Map', 'Survivors Syndrome' commonly presents as multiple electrode sites with low amplitudes with small standard deviations. On the 'Suppression Map' EEG variability is also limited: Commonly, the majority of electrode sites exhibit a low coefficient of variation.

Ochs' notion of suppression is related but not identical to the concept of burst suppression (e.g., Niedermeyer, 2009), an EEG pattern correlated with cerebral anoxia and anesthesia with mixed slow and fast electrical activity with decreasing amplitude as anesthesia deepens. This kind of EEG suppression in trauma

survivors with complex histories may be neurochemically related to the dissociative symptoms commonly experienced by this group (van der Kolk, 2005). Indeed, it has been suggested that dissociation is at least in part mediated by stress-related release of endorphins and endogenous opioids (e.g., Schore, 2001; Lanius, 2014).

2.7. LENS Feedback To Body and Brain

EEG biofeedback typically involves the use of sensors placed on the scalp only. While biofeedback approaches have used EMG, temperature, GSR, ECG and others, they typically do not use EEG on the body. LENS neurofeedback is different in that it uses a measurement of the dominant frequency and applies feedback not only to the scalp, but also to other locations of the body. The latter application is often preferred when using LENS to alleviate CNS dysfunction associated with pain activity or musculoskeletal issues.

While the use of EEG neurofeedback on the body seems unusual, it should be noted that the skeletal muscles operate at a frequency of about 10hz, similar to the dominant frequency of the human brain. As suggested by Horsley & Schäfer (1888): "Every prolonged contraction of the skeletal muscles which is provoked by excitation (…) is a titanic contraction (…) passing along the motor nerves at an average rate of about 10 per second. " This frequency is similar at multiple sites of the body. There is suggestion that it is not innervated by the brain's alpha rhythm, in that it continues if the brain is isolated from the body (Marshall & Walsh, 1956).

3. Methodology

Four non-randomly selected cases are described that were selected on the basis that they had not previously responded or incompletely responded to previous psychological, psychiatric, as well as in two cases previous neuro therapy intervention. All cases described were conceptualized in terms of a Developmental Trauma Disorder. Each client exhibited significant dissociative symptoms and met, among others, diagnostic criteria for a Dissociative Disorder, e.g. Dissociative Identity Disorder, Depersonalization/ Derealisation Disorder and/or Other Dissociative Disorder not specified.

All LENS neurofeedback to the head was conducted with Lensware 2 installed on a Toshiba laptop running Windows 7 64-bit software. Single channel LENS neurofeedback to the body also utilized Lensware 2. Two-channel LENS neurofeedback was conducted with Lensware 3 installed on the same laptop computer. The amplifier used on all occasions was an Alpha 200.

All scalp sites were prepared with Nuprep (Weaver) and standard EEG electrodes were attached with Ten20 conductive paste (Weaver), using A1 and A2 as reference and ground respectively. For body sites, ECG leads and electrodes (Kendall H124SG) were used. In case of LENS neurofeedback to the body, electrodes were affixed to their respective sites/locations in the shape of an equilateral triangle. In the case of bilateral 2-channel applications, the grounds for both sites were linked at the amplifier. For LENS neurofeedback to the brain, electrode sites were accessed in order based on topographic EEG maps that provide information about EEG amplitude and variability. In all cases, 'Suppression Maps' were utilized as long as suppression was evident.

The author had previously found that optimal dosing of the LENS neurofeedback in a population of clients with Developmental Trauma was difficult at times, in that the window for optimal amounts of feedback tended to be narrow, with clients having a tendency to exhibit symptoms of excessive stimulation that included 'wiredness', 'tiredness' and headache activity.

Encouraged by the findings of Kluetsch et al. (2014) the author developed a set of hybrid protocols that include the use of an alpha filter (8-12hz) when applying LENS neurofeedback – typically LENS feedback is based on 1-42hz activity. Apart from limiting feedback to 8-12hz and using 100% duty cycle, stronger or more aggressive feedback settings were used – increased duration, increased number of sites, decreased offset (smaller offsets tend to have more powerful effects), more frequent use of a narrow band rather than broad band carrier wave (narrow band has more powerful effects than broad band), etc. Rather than providing feedback at

Pz or another posterior site alone, LENS was administered to all 21 electrode sites (10/20 system), the approach commonly used when administering LENS.

3.1. Case 1-Depersonalization Disorder

The client was referred by a psychiatrist for neurofeedback to assist with an intractable Depersonalization Disorder. The client had a history of neglect with absent parents during early childhood including multiple and inadequate caregivers. There was suggestion of probable childhood sexual abuse by a substitute caregiver. Onset of depersonalization symptoms occurred after a recreational MDMA (Ecstasy) experience. A pre-existing history of Social Anxiety was noted. There had been a full medical and neurological work-up with CT-scan, MRI and EEG previously. Some CT scan anomalies were noted in the right temporal lobe but these were judged to be artifact on a later MRI. In addition, some right temporal lobe anomalies were noted on EEG but these were judged as not epileptiform in nature. Prior to referral, the client has undergone pharmacotherapy with antidepressants, Sensorimotor Psychotherapy and EMDR, all to little or no avail.

Subsequent to the referral, a course of neurofeedback with Neuroptimal was introduced that resulted in a mild decrease in anxiety but had no effect on depersonalization symptoms. In conjunction with the referral source, a course of low dose naltrexone (LDN) was started, an intervention that has been found helpful in Dissociative Disorders (Lanius & Corrigan, 2014; Pape & Wöller, 2015). A slight but functionally insignificant effect on depersonalization was noted. Subsequently, higher doses of naltrexone were introduced, as these had been demonstrated to be beneficial in Depersonalization Disorder specifically (Simeon & Knutelska, 2005). Starting dosage was 50mg per day that was titrated up in 50mg steps. The most notable therapeutic effect on depersonalization occurred at 150mg per day, with 200mg per day triggering significant anxiety. Nevertheless, depersonalization and social anxiety continued to interfere profoundly with both employment and social functioning.

A set of initial LENS maps, both a ‘Regular Map’ and a ‘Suppression Map’, was acquired. The ‘Regular Map’ was notable for low amplitudes on the majority of sites with the exception of elevated amplitudes with little or no standard deviation on P4, F4, C4, and O2. On those very sites an elevated dominant frequency was also noted with a lack of normal variability. On the ‘Suppression Map’, each and every one of the 21 sites accessed was suppressed, e.g., had a coefficient of covariation that fell below the .35 value.

LENS treatment - using standard LENS 100% duty cycle applications (100% duty cycle applications are generally recommended in seizure spectrum disorders) - proceeded slowly, as the client could only tolerate a limited number of sites (2-3) being accessed at a time without responding either with increased anxiety on one hand or increased depersonalization on the other. Amplitude suppression failed to lift significantly. In order to lift suppression more effectively, a LENS application that uses changeable offsets, commonly referred to as a Variable Pulse application, was utilized. While this resulted in a successful removal of suppression on the sites accessed, the client reported a panic attack in the week following treatment while travelling in a car with her family.

Subsequently, the author, based on theoretical notions discussed above and experience with other clients, used a LENS application (Appendix A) with an alpha bandwidth filter (8-12hz), 100% duty cycle, a relatively small offset of 10hz and narrow band. The client responded well to this new LENS application, with much less adverse effects. Indeed, the number of sites could be rapidly increased, with the client ultimately able to tolerate accessing all 21 sites in a single session. This application seemed to lift amplitude suppression quite effectively, while at the same time introducing decreased variability with regard to frequency. That is, it tended to lift the dominant frequency into the alpha range with decreased variability, thus introducing frequency suppression while lifting average amplitude suppression. This was correlated with significant improvement in depersonalization and social anxiety.

In addition to the 21 site sessions, multiple sessions where 7 sites were accessed at a time followed up by EMDR, were conducted. 7 sites was judged to be the maximum number of sites that would allow sufficient

time for conducting an EMDR session within a 50 minute-hour therapy session. Whereas the client had been unresponsive to EMDR treatment previously due to excessive levels of levels of depersonalization, the combination of naltrexone and LENS seemed to result in the client increasingly benefitting from EMDR treatment. Finally, a further application was written to assist with lifting frequency suppression (Appendix B). A variable pulse application with small offsets, narrow band, 100% duty cycle that was followed by a period of a 100% duty cycle with an alpha filter. This application lifted frequency suppression completely while re-introducing a limited amount of mean amplitude suppression. At the time the client had undergone 48 LENS sessions. At this point, depersonalization and social anxiety had massively decreased to a point where they no longer interfered with employment and social functioning and the patient terminated treatment.

3.2. Case 2-Other Dissociative Order not Specified

The client had a history of severe attachment issues that included parental abandonment and neglect and childhood sexual abuse. He was being treated pharmacologically with antidepressant and stimulant medication. He had a graduate degree in psychology. He was unable to work when he self-referred. He had previously been diagnosed with Major Depressive Disorder and Attention Deficit Disorder. He had a pornography addiction. He also presented with significant dissociative symptoms. He specifically requested a course of Sensorimotor Psychotherapy, as well as expressing an interest in EMDR.

Initial interventions included Sensorimotor Psychotherapy, EMDR, as well as Neuroptimal neurofeedback. There was only limited response to treatment, which was attributed to significant depersonalization and derealisation. The treating psychiatrist agreed to prescribe LDN. The addition of LDN resulted in a significant improvement in functioning - e.g. increased attentional functioning, decreased dissociative symptoms and improved mood - but response to psychotherapy remained limited.

The client reluctantly agreed to LENS neurofeedback due to beliefs about the nature of LENS, as compared to standard neurofeedback that he was familiar with. His initial LENS map again showed a ‘Survivor Syndrome’ on both the ‘Regular Map’ and the ‘Suppression Map’. The client was able to tolerate the use of 100% duty cycle application with an alpha filter (Appendix A) on all 21 sites, with a concurrent lifting of mean amplitude suppression on several sites that was correlated with further improvement in functioning.

At this time, response to EMDR therapy much improved. At the same time, on the regular map significant high delta amplitudes in the frontal region emerged (F8, F7, FZ, FP1, FP, FP2) with slightly higher amplitudes in the left hemisphere. An attempt to decrease delta activity in the frontal lobes, a LENS application using a delta filter was utilized. This was effective in reducing delta band activity but resulted in symptom re-instatement. A return to the application using the alpha filter resulted in the improvement of functioning to previous levels. After a total of about 40 LENS sessions, some of which were LENS only (all 21 sites accessed) and others were LENS (7 sites accessed) in combination with EMDR, the client found employment in another community and chose to move and subsequently terminated treatment.

3.3. Case 3-Complex Regional Pain Syndrome

A client who presented with Complex Regional Pain Syndrome (CPRPS) was experiencing intractable pelvic pain. She had undergone multiple interventions that had essentially been unsuccessful. The client had a history of severe attachment trauma, early sexual abuse, as well as multiple severe medical trauma. CRPS was triggered by a medical procedure during adulthood. The client was on antidepressant medication, gabapentin, lorazepam, cesamet prn, Sativex, as well as topical ketamine and gabapentin. She also had been prescribed LDN for her CRPS pain (Chopra & Cooper, 2013) by a specialist but was unable to tolerate the LDN prescription of 4.5mg per day, as it created massive activation and anxiety for her. As a result the client discontinued the medication and returned to relying on prn opiates for pain control. After a consultation, the client weaned herself of all opiates and it was decided to massively lower the LDN dose to less than a quarter of what had been

prescribed previously to 1mg per day. The client then underwent a combination of LENS neurofeedback to the scalp (all sites), as well as to the body.

The body location chosen was acupuncture spot Kidney 1 (K1) based on Oschman et al. (2015) who reported electrical grounding (earthing) of K1 to be effective in reducing inflammation in pelvic pain. A long body application (Appendix C) was utilized bilaterally on K1 on the soles of both feet three times for a total of 10 sessions. The client experienced being much more grounded (sic). There was noticeable decrease in perceived pain intensity after the first session that persisted and improved over time.

In addition, LED low level light therapy (LLLT) was used for brief durations on multiple occasions. LLLT has been shown to assist in decreasing pain activity (Cotler et al., 2015). The client could only tolerate short applications of LLLT, as again she had a tendency to become overstimulated. The combination of interventions resulted in a massive reduction in pain activity with much improved functioning. At the same time a diagnosis of a Dissociative Identity Disorder emerged. Psychological Treatment is ongoing. Naltrexone dosing has been slowly increased to 2mg per day in .1mg increments. While there remains ongoing pain activity in the pelvic area, the achieved pain reduction has been stable over two years and the client continues to make improvements in functioning.

3.4. Case 4-Early Childhood Medical Trauma

The client has early childhood medical trauma including severe birth complications including breech position, prolonged labour and uterine complications resulting in compression of the baby's neck. After 8 hours of labour an emergency C-section was conducted. APGAR score at birth was 1. At about 8 months of age, surgical hernia repair was conducted. The client was then put into daycare at 11 months of age. There is a history of significant attachment trauma due to multiple substitute caregivers prior to age one, as well as subsequently throughout childhood. Mother had a history of depression and alcohol abuse. Father was largely absent due to work. There were several incidents of sexual childhood sexual abuse by substitute caregivers. Previous diagnoses include Attention Deficit Disorder, learning disability, PTSD, as well as a Dissociative Disorder. He has also had a previous history of substance abuse. He has been maintained on antidepressants and LDN and has benefitted from both. On three occasions he has had flashbacks so severe that this resulted in a dissociative psychosis. He had undergone weekly LENS session over a period of three years, refusing other forms of psychotherapeutic interventions. The client made significant gains that have resulted in much improved educational functioning – he has been attending university, taking a part-time course load. However, he continued to suffer significant PTSD symptoms that include body tics like muscle tightening and grimacing around the face and neck, as well as pain and muscle spasms around the area of the hernia repair radiating into the groin.

At some point in time the client agreed to participate in other forms of psychotherapy, including EMDR. Sessions targeted multiple traumatic events - targeting the birth trauma using a narrative provided by the mother and focusing on the facial and neck sensations and tics – over 40 sessions in total. Sessions typically provided temporary relief at the time, usually lasting several days but did not hold over time with body tics returning with a similar level of severity and the SUD's level returning to previously elevated levels. In conjunction with the client, it was decided to give Body LENS a trial: Electrodes were placed in an equilateral triangle (approximately 2") arrangement on the area of the neck that was exhibiting the most severe muscle spasms. The previously utilized narrative was used to trigger muscle spasms and a LENS body application with a duration that was slightly longer than 30 minutes that was set to run the whole duration of the session (Appendix C; Periods 4, 6, 10 were set to 10 minutes respectively).

The client again experienced a significant calming effect, as soon as feedback was initiated. The client was asked to focus on the body sensation only using an EMDR bottom-up processing protocol (Lanius, 2009) and tactile bilateral stimulation (hand taps) was administered. The feedback seemed to allow the client to stay more easily in touch with the somatic sensations and seemed to result in the facilitation of somatic trauma discharging (e.g., Payne et al., 2015). For the first time, the therapeutic gains during the session were maintained over time

and the decreased SUD level remained over time. The client reported much decreased activation in the neck and face, likely reflecting decreased somatosensory flashbacks. After five sessions, the activation in the facial and neck area had largely disappeared and the patient requested to target the area of the hernia repair that produced similar results.

4. Results and Discussions

4.1. LENS Neurofeedback to the Brain Effects

All cases described here have in common that there was no further progress with regard to response to treatment until the addition of LENS neurofeedback that changed the trajectory of treatment response in only a few sessions. The treatment response seemed to be correlated to the removal of suppression that was related to a marked improvement in overall functioning including a reduction in dissociative symptoms.

Typically, individuals with 'Survivors Syndrome' only tolerate relatively slow removal of suppression. Further it has been the author's experience that clients with Dissociative Disorders typically tolerate removal of amplitude suppression more easily than the removal of frequency suppression. Based on clinical observations, the use of specifically developed LENS applications that included the use of an alpha bandwidth filter has a profound impact not only on how LENS was conducted, but also on the EEG and behavioural response.

Three of the clients had undergone LENS treatment with standard LENS applications and they typically were able to tolerate accessing 2-4 sites per session. Using an alpha bandwidth filter they were able to tolerate the accessing of all 21 sites during a session, without undue adverse effects. When using an application that utilized an alpha bandwidth filter for the entire duration of the feedback, typically amplitude suppression was effectively removed - it appeared, more easily so than with typical LENS applications. At the same time, this seemed to reliably introduce frequency suppression on each and every site accessed (99% of the time). Moreover, if one subsequently used a complex LENS application and added a period with the use of an alpha filter at the end, both amplitude suppression and frequency suppression were effectively removed without undue adverse effects.

In addition, when using an alpha filter, the raw EEG clearly showed brief reduction in alpha amplitude with a subsequent alpha rebound. Moreover, more often than not, there was also an increase of theta amplitude, with theta intermittently rising above alpha. This phenomenon occurred both with eyes open and closed, though more reliably so with eyes closed. It appeared, that applying LENS neurofeedback to the brain with an alpha filter resulted in triggering a similar response to what is typically achieved with operant-based alpha-theta neurofeedback.

Finally, the emergence of delta activity in the frontal lobe as specifically described in section 3.2 is a relatively common phenomenon in clients with Developmental Trauma. The author, with a number of other clients, used a delta filter to reduce delta activity. Consistently, in each and every case, this resulted in symptom reinstatement until another LENS application was run without the delta filter. This raises the question whether such an emergence of slow wave activity is an essential part of information processing therapies. A similar emergence of slow wave delta activity has been observed during EMDR bilateral stimulation and has been hypothesized to be involved in memory consolidation (Pagani et al., 2017).

4.2. LENS Neurofeedback to Body

Body LENS seems to have a significant role in reducing somatic reactivity, somatic flashbacks and pain activity. In both cases, a LENS application was utilized that included the use of an alpha filter at the end of the application. This was based on theoretical grounds that included the findings that the body resonates at a frequency in the alpha range and previous successful use when applying LENS neurofeedback to the brain, though I have no data or observations that support the use of that strategy with regard to Body LENS.

In both cases described, LENS neurofeedback was again administered for longer durations with more aggressive settings than is typically the case. It should be noted that the author has used the LENS approach discussed in section 3.3 with two further CRPS clients. In one case, where the client was not on opiates, this was also successful. In another, where the client continued to be on opioid medication, the first session seemed initially successful but did not hold with the client continuing to use opiates for pain control. In that case, further sessions did not seem beneficial, only leading to increased perceived pain, potentially suggesting the involvement of the opioid system in the effectiveness of LENS.

5. Conclusion

In clients that did not respond or had a limited response to other interventions, LENS seems to have utility in stabilizing clients, as well as facilitating psychotherapeutic response in clients with Developmental Trauma that did not respond to other treatment interventions. While LENS does not seem unique among different types of neurofeedback in facilitating increased response to psychotherapeutic interventions, (e.g., Gerge, 2018; Yordy, 2018), at least one other type of neurofeedback had been ineffective in two of the cases discussed here. While the reported results are encouraging, placebo effects cannot be ruled out. A trial of LENS with Developmental Trauma under double – blind conditions is desirable.

When compared to operant based neurofeedback, LENS, due to its short treatment duration, allows for easier integration with other psychotherapeutic interventions. In addition, the possibility to use LENS on the body that includes areas activated due to intractable somatosensory flashbacks, as well as the targeting of specific acupuncture sites, may provide additional venues for clients suffering from complex Developmental Trauma that are not responsive or only minimally responsive to the usual treatment interventions. This use of LENS is consistent with an information processing approach, allowing opportunity to integrate both bottom-up and top-down processing.

Ochs hypothesizes that LENS may affect the levels of inhibitory neurotransmitters. The notion that the level of inhibitory neurotransmitters – endogenous opioids, beta-endorphin in particular - being affected by neurofeedback was first noted by Peniston & Kulkosky (1989), who found increased beta-endorphin levels in individuals that underwent treatment as usual, and reduced levels in those that underwent neurofeedback. Inhibitory neurotransmitters are also involved in dissociative symptoms (e.g., Simeon & Knutelska, 2005) and may play a role in EEG suppression. Pharmacological interventions that target the opioid system may have additional and synergistic effects with regard to the effectiveness of neurofeedback. For instance, Lensing et al. (1995) suggested that excessive opioid activity interferes with cortico-thalamocortical processing of visual stimuli, finding that the opioid antagonist naltrexone reinstated selective alpha blocking, thereby increasing visual pursuit behaviour. Further research with regard to neurofeedback and the role of inhibitory neurotransmitters is indicated.

It has been suggested that alpha desynchronizing neurofeedback, while associated with decreased alpha amplitude during training, is followed by a significant increase (‘rebound’) in alpha amplitude (Kluetsch et al., 2016). That phenomenon bears much resemblance to what the release of suppression looks like during LENS neurofeedback. Moreover, this alpha rebound phenomenon may throw a different light on Plotkin and Rice (1981) notion of attributing neurofeedback effects to placebo, based on their findings that reducing alpha amplitude had similar effects to increasing alpha amplitude on anxiety reduction. Indeed, it seems that suppressing alpha activity, either with operant conditioning based neurofeedback, or targeting alpha with LENS, ultimately seem to have an effect that appears similar to that of rewarding alpha amplitude.

Klimesch (2012) has argued that alpha plays a significant role in information processing. Specifically, he suggests that alpha-band oscillations are involved in inhibition and timing that relates to fundamental functions of attention, enabling one’s ability to be consciously oriented in time, space, and context. As such, alpha-band oscillations reflect one of the most basic cognitive processes. Thus, targeting alpha activity may affect basic homeostatic processes essential to information processing.

While there is clear theoretical rationale for learning and operant based neurofeedback that is supported by an emerging field of research, (an) underlying functional mechanism(s) for LENS are at this time, for the most part, hypothetical and speculative. Nevertheless, LENS conceptualizations and effects raise some questions relevant for traditional operant based neurofeedback. At the same time, LENS may benefit from integrating alpha focused interventions, as suggested by relevant research with regard to traditional neurofeedback.

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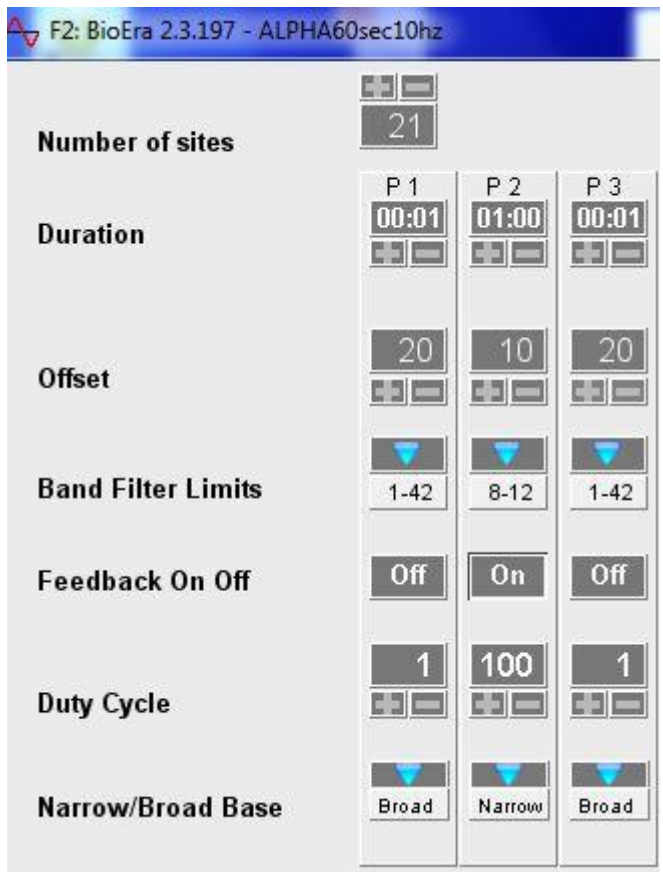
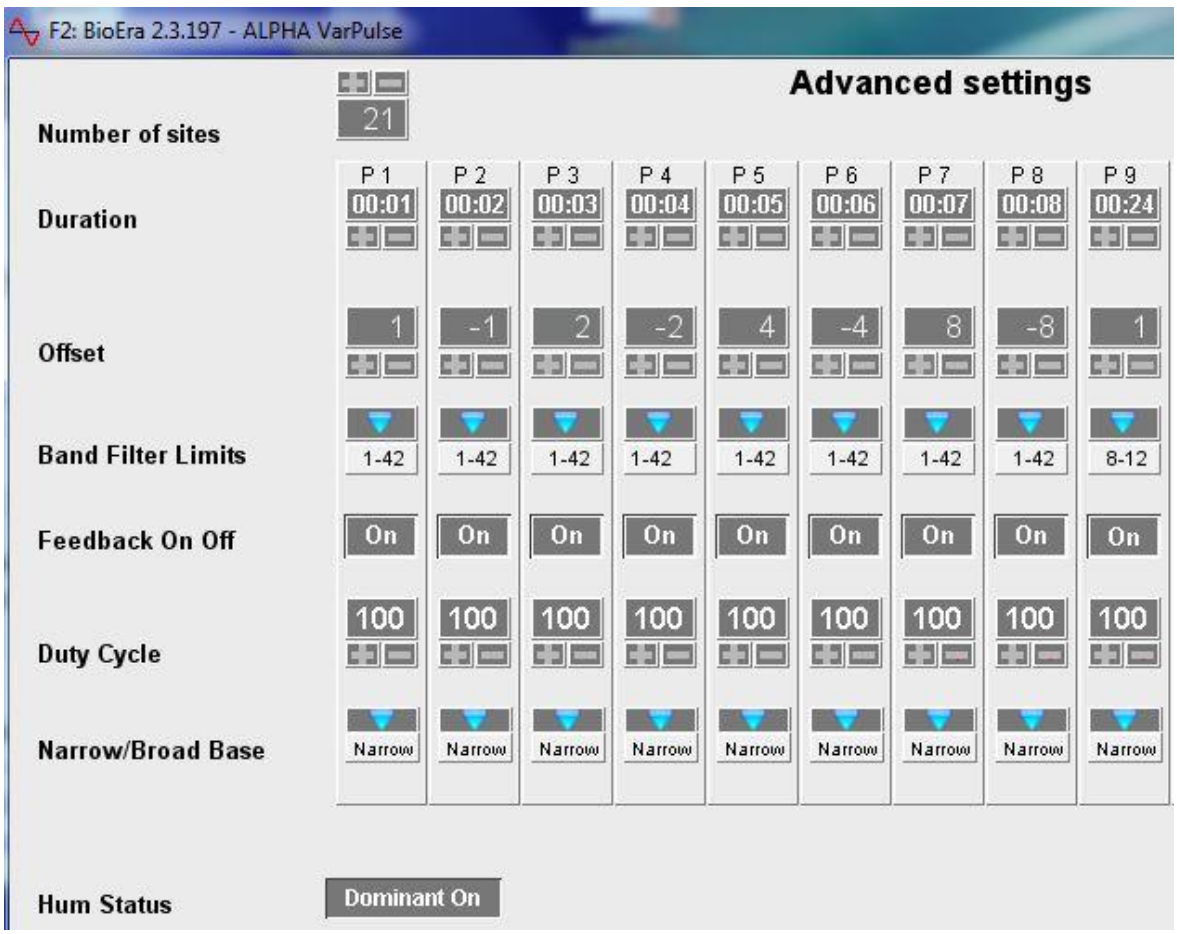
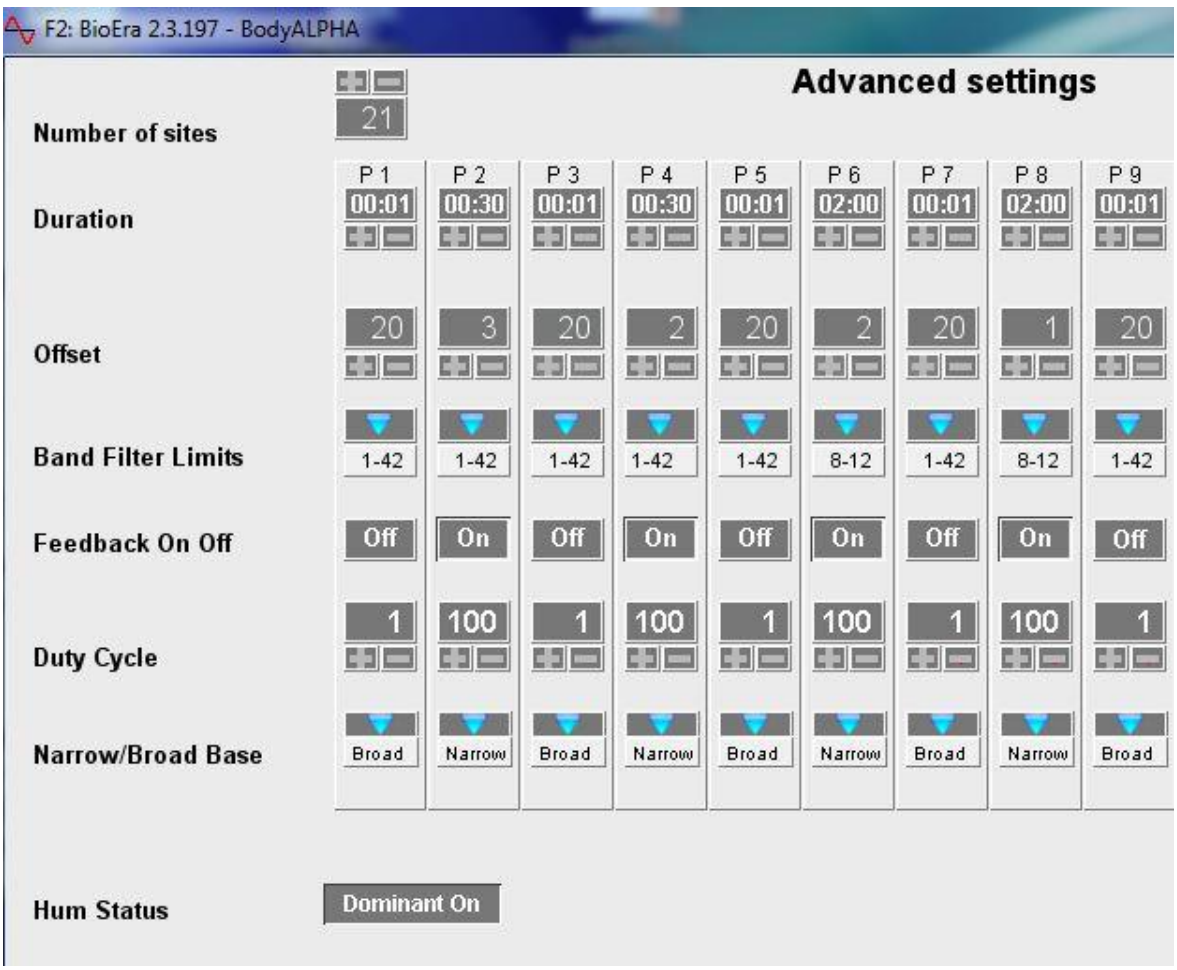
Appendix A: Initial LENS alpha filter application



Appendix B: Variable Pulse alpha filter application



Appendix C: Body application



Multi-modality based diagnosis: A Way Forward

Hafeez Ullah Amin*

Centre for Intelligent Signal and Imaging Research, University Technology PETRONAS, 32610 Seri Iskandar, Perak, Malaysia

Abstract

The Human brain is our most complex organ and responsible for controlling all bodily functions. The brain is also implicated in many psychiatric disorders and diseases such as Dementia, Depression, Epilepsy, Parkinson, Stroke, Tumour, and so on. Researchers from different fields including Neuroscience, Neurosurgery, Psychiatry, Psychology, Pharmacology, Engineering, and Computing, are continuously working to investigate and develop novel techniques to diagnose and treat the brain's disorders using neuroimaging modalities. Today, many different modalities are currently used such as electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), functional near infrared (fNIR), Magnetoencephalography (MEG), positron emission tomography (PET), and computed tomography (CT). Each technique has its own strengths and limitations and thus is suited to a specific area of study. However, these modalities can be used simultaneously to reduce the limitations of using one technique and enhance the accuracy of disease diagnosis. Multi-modality-based diagnosis will help clinicians to identify both early and accurately those individuals who are at risk of many conditions including brain tumor, tumor recurrence, and Alzheimer's disease.

Keywords: Multimodal approach, treatment, neurofeedback, and neurotherapy.

ARTICLE INFO		
RECEIVED	November 18	
REVIEWED	January 19	
ACCEPTED	February 19	

** Corresponding author.*

Email: hafeezullahamin@gmail.com

1. Introduction

The brain is an extremely complex organ, which is responsible for controlling all activities such as sensation, perceptual inference, planning, execution, evaluation, movements and decision making. It consumes approximately 20% of the energy in the entire body (K. Uludağ, 2014). The structure of the brain consists of different types of cells (including pyramidal neurons, interneurons and glia), which relate to each other through biological pathways. Modern neuroimaging techniques probe the structure and functions of the human brain and expose neuro-glial bases of human cognition and behavior in healthy subjects as well its dysfunctions in patients. Every imaging technique has its strength and limitations; hence, a multi-modal approach can give important insights into the brain functions and structure in addition to improving spatiotemporal resolution (including quantification, generalization and normalization) (K. Uludağ,2014).

The multimodality approach combines two or more data sets collected with different imaging techniques with the objective of enhancing our understanding of brain structure and functions. It provides a fusion of different data sets. While there are advantages of a multimodal approach, there are also challenges, including cost, wide knowledge of multiple instrumentations, and data quality of one modality being compromised over another, and so on. In this paper, the existing studies utilizing the multimodal approach for studying the brain in healthy subjects and brain disorders are described.

2. EEG-fMRI

Understanding the neural basis of brain functions needs awareness regarding the spatial and temporal aspects of the underlying mechanisms in information processing in the brain. Electroencephalography (EEG) and Functional Magnetic Resonance Imaging (fMRI) are two non-invasive imaging techniques (V. Menon, 2005). However, neither of these techniques alone can provide spatiotemporal information processing. EEG is a widely used brain imaging modality in research as well as in clinical practice due to its good temporal resolution. The recording of EEG requires electrodes to be placed over the scalp to capture neural activity in terms of electrical voltage potential. The captured signal from the brain region will show a pattern, and this data can be interpreted. However, the diagnosis with EEG technique lacks spatial resolution. The actual cerebral sources of the recorded EEG over the scalp is not known. The solution to this issue is to estimate the sources, but the solution of estimating sources from EEG signals is quite complex (the inverse problem). The existing methods of source localization are either dipole-based, which assumes that sources are localized, or distributed source analysis, which also relies on some assumptions such as smoothness (J. Gotman, 2006). Hence, both the source analyses are based on assumptions, which are difficult to confirm because to know the complete distribution of the intracerebral potential is almost impossible. Therefore, researchers and clinicians have begun diagnoses of brain functions by combining EEG with functional magnetic resonance imaging (fMRI) technique. FMRI measures the changes in the blood oxygen level of the brain with high spatial resolution.

There are a number of studies that have utilized simultaneous EEG-fMRI measures. For example, Hoppstädter and colleagues conducted a simultaneous EEG-fMRI study for recognition memory using event-related potentials (ERPs) in old/new effect (M. Hoppstädter, 2015). Their findings showed that the right dorsolateral prefrontal cortex and right intraparietal sulcus were linked with the amplitude of the frontal old/new effect between 350ms to 550 ms. Gorka et al., also conducted simultaneous EEG-fMRI techniques in their investigation into reward anticipation (S. M. Gorka, 2015). Their results suggested that increased left frontal activity was linked with increased activity in the left anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC). The fusion of EEG and fMRI data is likely to enhance our understanding of brain functions and structure (S. Debener, 2011).

3. PET-MRI

PET and MRI are brain imaging modalities which are well established in clinical practice. Standard MR imaging technique plays an important role in the diagnosis of brain disease, such as brain tumours, due to its capability of capturing anatomic detail of the brain. However, MRI only gives the structural information of the brain and no detail about the tissue and its functioning. Position emission Tomography (PET) is another imaging technique which uses a radioactive substance (tracer) to look for injury or disease in the brain. The PET scan provides information about the brain size, shape and functions (tissues and its working). Catana and colleagues reviewed methodologic enhancement and neurologic applications of PET/MRI data acquisition (C. Catana, 2012). Combined PET and MRI provide the spatial and temporal correlation of the measured changes in the brain, which are impossible with a single modality. With the advent of combined PET/MRI scanners, the relationships of different elements of tumour metabolism can be explored simultaneously.

Moodley and colleagues employed simultaneous PET-MRI to compare patterns of cerebral hypo metabolism and atrophy in six different syndromes of both Alzheimer's disease (AD) and frontotemporal dementia (FTD) (K. K. Moodley, 2015). Their findings suggested that the concordance of atrophy and hypo metabolism differ significantly across syndromic variants of AD and FTD, reflecting underlying molecular pathologies as well as operational differences employed in the criteria to diagnose these syndromes.

The application of PET/MRI includes, but is not limited to diagnosis of tumour, dementia, stroke injury, cerebrovascular disorders, Parkinson disease and epilepsy. For workflow and protocol design for PET/MRI combined data acquisition, see (F. de Galiza Barbosa, 2015). The combination of MRI with PET improved quantification and tissue characterization as compared to PET/CT imaging. The advantages of simultaneous PET/MRI data include enhancement of diagnostic accuracy and it is likely to have benefits for planning surgery and radiation therapy.

4. EEG-fNTRS

FMRI, EEG and PET are in practice modalities to study the functions of brain in humans. These modalities have improved and enhanced our knowledge of the neural networks that impair emotional and mental processes (C. J. Price,2012), (R. J. Huster, 2012). However, these neuroimaging technologies each have advantages and restrictions. FMRI is non-invasive and has exceptional spatial resolution, but is expensive, exceptionally sensitive to movement artefact, confines the participants into limited positions within the magnet, is difficult to incorporate with other imaging methods [like (EEG)], and also necessitates that participants endure loud noises. PET also requires a limited range of movement and confinement and requires the injection of radioactive substances. These factors make these imaging techniques unsuitable for many applications such as the assessment of children, and the observation of cognitive activities under working stress.

A decade ago, functional near-infrared (fNIR) spectroscopy was introduced as a neuroimaging modality to run functional neuroimaging experiments. fNIR Technology employs wavelengths of light over the entire scalp, to allow the measurement of changes non-invasively at the relative ratios of deoxygenated haemoglobin (Deoxy Hb) and oxygenated haemoglobin (Oxy Hb) from the capillary beds during brain action. This technology allows the layout of mobile, safe, cheap, non-invasive, and more intrusive tracking systems. These attributes make fNIR acceptable for investigation of hemodynamic changes because of emotional and cognitive brain action under many working conditions.

Concurrent recording of fMRI with EEG/MEG is difficult to apply, because of technical limitations; however, NIRS is suited to concurrently recorded EEG measurements (M. E. Pflieger, 2012). The reason is that NIRS uses near-infrared light, and the EEG signals are not contaminated by light as in the case of fMRI-EEG with gradient and ballistocardiogram artefacts (T. Zama, 2015). In addition, the EEG-NIRS recordings are relatively cost effective, portable, and tolerable to participants' movement, which make it suitable for long-term recording, and it's easy to use with infants and patients and is suitable for naturalistic human motor control studies.

5. EEG-MEG

Magnetoencephalography (MEG) enables us to assess the continuing brain activity using millisecond time resolution. Considering that 300 detectors dispersed over the head detect the neural activity, it's likely to identify where, with moderate accuracy, the activity is generated in the brain. This makes MEG suited to analysing the human brain as a system of interacting brain regions during the operation of different tasks. The key applications of MEG are in clinical and cognitive neuroscience research and analyses.

MEG technology relies on SQUID. The superconducting quantum interference device (SQUID), which was introduced in the late 1960s, and is a more sensitive detector of magnetic flux. Now whole-head MEG techniques have a high number of SQUIDs (involving 100 to 300) attached to detector coils in a configuration approximating the curvature of the human head. It measured the magnetic field produced by neuronal activity in the brain and records signals in a millisecond time. This high temporal resolution makes the MEG different from fMRI, which records blood flow changes over much longer periods of time. MEG records signals, which may be in response to visual stimulation, or spontaneous brain activity.

Simultaneous EEG-MEG data acquisition improves the accuracy of source localization, because MEG signals are not distorted by concentric heterogeneities in conductivity. Thus, in epileptic activity combined EEG-MEG is recommended to increase reliability of results (Ü. Aydin, 2014).

6. Discussion and Conclusion

The first step for a researcher is to look into the single modality results and derive inferences for diagnosis of a mental condition. However, single modality results may not provide a clear and effective picture of the mental health of an individual. Hence, the use of multimodality may be valuable in situations once the researcher has already exhausted the option of a single modality. In addition, the multimodal approach can provide a better map of neural activities and hence aid not only in diagnosis but also treatment of a mental health condition. Hence, the objective of multimodality wouldn't be to unite information but to supplement the results of single modality. The supplementary information may provide additional biomarkers which allows the clinician to assess the neural condition and assist in the interpretation for intra- and inter-subject variability. In addition, EEG signals can provide information about the drowsiness of the subject and other peripheral information based on the external stimulus (K. Rosenkranz, 2010).

In case of non-repeatable and non-standard experiments, this is particularly important. As an instance, combined EEG--fMRI experiment has found its way to cognitive neuroscience studies (C. S. Herrmann, 2008), in which it is helpful when the subject performance (such as attention, errors, learning and trial-by-trial evaluation processes) must be equivalent and the order effects must be avoided. The existence of a subject performance condition could compensate the expenses of combined EEG-fMRI recording discussed previously and make such experimentation an essential requirement. EEG is typically used as the biomarker in EEG/fMRI research. It will be interesting to look at a change in opposite direction of this multimodality investigation asymmetry. An example of such investigation is presented by De Martino et al. (F. De Martino, 2010), where they utilized multivariate prediction approaches to estimate single-trial EEG using fMRI images of the whole brain. Recent exciting findings of combined use of EEG-fMRI is the modulation of human cortical responses in the behavioral experiments by state of ongoing occipital alpha oscillations (Becker et al., 2011; Scheeringa et al., 2011)

Multimodality methods can serve various purposes including investigation of brain functions and structures based upon the processing of their information. Several functional studies utilized two or more modalities to attain the most effective spatial and temporal resolution. They assumed that the recorded data has exactly identical sensory sources. Nevertheless, the imaging techniques may differ not just in the data acquisition, but the way neuronal activities and structures bring about the image contrasts. This presents, on the one hand, a problem in fusion of multimodality data without a model describing the series of physiological and bodily

events leading to the signals. On the other hand, the advantage is that it enables one to receive a perspective on the neuronal processes more comprehensively.

Therefore, it is important to discover the sources of discrepancies in multimodality approaches which can lead to an improved perspective on cognitive processes and structural composition than that of a single modality (K. Uludağ, 2014). To this end, in order to solve the discrepancies, biophysical generative units need to be developed. Multimodal imaging is also helpful if one is simply interested in the outcomes of a single modality as another modality can confirm the interpretation of the data (in case of biomarkers derived from one modality). One example can be of a learning experiment, when variability of mind states can't be avoided. At length, multimodality approach may be utilized to measure parameters that may be used to generalize the outcomes from specific methods and algorithms. Though, use of multimodality, data acquisition and their fusion need to address several challenges, such as additional software applications, setup time, subject discomfort, extra cost etc., and the merits of multimodality approach make it a very useful and an essential tool to explore neuronal processes and structural composition. Besides data acquisition techniques and analysis methods, the number of research studies using multimodality approach will continue to grow, particularly in the application of neurotherapy (neurofeedback) to treat the patients non-invasively and with more precision.

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EEG amplitude neurofeedback: a review of the research

Moshe Perl & David Perl*

Neurotherapy Institute of Australasia (NIA), 55B Kooyong Road, Caulfield North, Victoria 3161, Australia

Abstract

Studies published on neuromodulation for the past 50 years were analyzed for neuromodulation technique, research design, condition or disorder investigated and outcome. 314 relevant studies were found, involving over 9,500 research subjects. EEG amplitude neurofeedback contributed over 70% of all studies. 62 randomized controlled design studies were found (and two utilizing an ABA crossover design), and of those, over 75% involved amplitude neurofeedback. Outcomes for amplitude neurofeedback were overwhelmingly positive, as they also were for other techniques with a reasonable research base. For some neuromodulation techniques the research data is meagre, and more research is needed to confirm efficacy.

Keywords: EEG; amplitude; neurofeedback; neurotherapy; neuromodulation; review; research; study; modality; comparison; RCT; case

ARTICLE INFO		** Corresponding author.*
RECEIVED	November 18	E-mail address: info@neurotherapy.com.au
REVIEWED	January 19	
ACCEPTED	February 19	

1. Introduction

Over the past 10 years much has been made of new and innovative neuromodulation methodologies, with claims of efficacy exceeding that of the traditional mainstay of the neuromodulation field, single or double channel EEG amplitude neurofeedback training (henceforth referred to as amplitude neurofeedback or simply amplitude). While this can be seen as a marketing strategy, it nevertheless raises the question as a matter of science. Does evidence exist that amplitude neurofeedback is inferior to more recent neuromodulation methodologies? If so, are there particular conditions or disorders that respond more favorably to more recently developed methodologies (such as Slow Cortical Potential training, LENS training, 19-channel training and stimulation techniques)? In order to address this question, the literature on neuromodulation was reviewed. Of the research studies published, how many used amplitude neurofeedback as opposed to other modalities? What was the experimental design of the studies? What was the outcome of the studies? Is there still research being conducted on amplitude neurofeedback or has it been consigned to the museum of neuromodulation – figuratively speaking.

This review was first presented at the Applied Neuroscience Society of Australasia 2018 annual conference and was expanded and reformatted for journal publication. The project of collating and classifying neuromodulation research is planned to be an ongoing one, with the database of studies made available on an ongoing basis.

2. Methodology

a. Sourcing studies

The search for neuromodulation studies began at ISNR (International Society for Neurofeedback and Research) – reviewing their comprehensive bibliography - https://www.isnr.org/isnr-comprehensive-bibliography. Studies were classified according to publication year, neuromodulation technique, condition treated, study type/research design, number of subjects, and outcome.

ISNR's bibliography contains not only experimental studies, but also, studies on proof of concept – showing that a particular modality was having some effect on brain function, usually not directly clinically relevant. Additionally, the bibliography has references to books and book chapters as well as review studies (e.g. meta-analyses of several studies). Our interest was limited to experimental studies that were relevant to clinical outcomes for a condition/disorder or for peak performance training.

We expanded the search beyond ISNR's bibliography to include additional Slow Cortical Potential neurofeedback (SCP) and Low energy neurofeedback system (LENS) studies from the following websites:

- https://www.neurocaregroup.com/adhd-neurofeedback-and-sleep.html
- https://www.site.ochslabs.com/lens-references

As we searched further, we came upon additional articles, usually given from references at the end of previously found studies which we then sourced through PubMed:

- https://www.ncbi.nlm.nih.gov/pubmed

We then decided to search PubMed for neurofeedback studies from 2017 and 2018 (that were not already included) and added those as well.

We decided to only consider peer reviewed studies (i.e. studies that were published in a peer reviewed journal). When a study is peer reviewed, one has some assurance that the author of the study has employed at least a modicum of scientific rigor in the preparation of the study, that the outcomes reported seem reasonable and that the methodology is given in enough detail to allow replication.

We note that our search criteria may have had a negative bias towards including non-neurofeedback neuromodulation techniques. We plan on incorporating additional studies in future updates to this review.

b. Classification of studies - modality

For purposes of clarity, all amplitude neurofeedback modalities were grouped together. These included: Beta/SMR neurofeedback, Alpha neurofeedback, Alpha-Theta neurofeedback, Theta/beta ratio neurofeedback and other ratio trainings as well as one case study using Neuro Optimal methodology. Other modalities included Slow Cortical Potential neurofeedback (SCP); QEEG guided neurofeedback - where both amplitudes and coherences were trained (sometimes the term "QEEG-guided" was used to mean that results from a QEEG informed which amplitude neurofeedback protocols were used, in these cases the studies were classified as amplitude); Coherence neurofeedback; Low energy neurofeedback system (LENS) training; 19 channel Z-score training (including LORETA based training); Infra low frequency training; hemoencephalography (HEG) training and ffunctional magnetic resonance imaging (fMRI) neurofeedback. Stimulation methodologies included direct current stimulation (tDCS) and transcranial magnetic stimulation (rTMS) which were each given their own category, while the following stimulation methodologies were grouped together: Audio-visual entrainment (AVE), Roshi, Alpha stimulation, Photic stimulation, Vagus stimulation, and Neurofield magnetic stimulation.

We found two studies where two modalities were used, in direct comparison – head to head. These studies utilized a randomized control methodology (RCT) and compared SCP and amplitude neurofeedback. Both modalities were counted in our tallies as both studies found both modalities beneficial – see Table 3, Table 4 and Table 6.

There were also seven studies where two or more neuromodulation modalities were used in combination to treat subjects, (e.g. rTMS and amplitude neurofeedback). These were not counted for either modality as it could not be determined which modality drove the outcome of the study. It should be noted that all seven of these studies utilized amplitude neurofeedback as one of the methodologies. Whenever a study employed a neuromodulation modality in conjunction with another treatment or exercise which was not neuromodulation (e.g. another form of biofeedback or mindfulness meditation) then that study was counted for the single neuromodulation modality employed.

c. Classification of studies – study type / research design

We settled on four categories:

- Case study (1 – 3 cases).
- Case series, (more than 3 cases) with pre and post measures. Cherry-picking only positive outcome cases was not accepted. When it was not clear how many subjects were involved, a case series was classified as a case study.
- Control – some experimental controls, such as a waiting list control group, two groups – one clinical one non-clinical and/or partial randomization. Review of past records for somewhat matching clients who received different treatment was not accepted as a control group. Such studies were counted as case studies or series.
- RCT – Randomized Control Trial – contrasting two effective modalities, or a control condition considered efficacious by naïve subjects, all with random assignment to experimental or control groups, sometimes with cross over repeated measures with alternate treatments.
- Additionally, there were two studies which employed an ABA crossover design which we classified as RCTs as we took this study design to be of at least equivalent rigor to a RCT.

d. Classification of studies – outcome

This is a high-level study, so we simply classified outcomes as:

- Positive – researchers deemed results of the neuromodulation treatment to be positive, regardless of whether the effect was larger for a competing treatment (e.g. medication).
- Negative – researchers deemed results of the neuromodulation treatment to have no positive effect. It must be noted that some of these studies utilized training protocols that are contrary to accepted standard practice in the industry, e.g. reinforcing 18 Hz to treat epilepsy, or smaller numbers of training sessions.

e. Classification of studies – date

We classified studies into three time periods:

- 2009 – The present.
- 1999 – 2008.
- 1998 and earlier.

3. Results

690 articles were listed on ISNR's bibliography as of April 5, 2018 (see Table 1). There were 141 duplicate entries to the bibliography – studies belonging to more than one condition, and 4 double entries (i.e. same study for the same condition). For purposes of our analysis these studies are listed only in their first location – i.e. for only one condition or disorder. However, there were many studies in which we felt that they should be categorized differently (e.g. if subjects were selected due to presentation of a learning disorder, we changed the category to "Learning disorders" instead of "ADHD") and we changed the category as we saw appropriate. Of those left, 175 were book chapters, reviews, or theoretical papers. 77 studies were excluded as they did not involve treatment of a condition or peak performance training (or the measured outcomes were unknown or not directly linked to clinical improvement). Two studies were excluded as they were papers presented at a conference. The bibliography also contained 33 articles which could not be located, not even an abstract (27 of these studies were published prior to 1999 and six prior to 2009). This left 258 studies for review. Seven studies were added from the SCP and LENS websites and 49 studies were added from the PubMed search (see above and Table 2). This gave 314 studies in total. For 83 studies, only their abstract was found and reviewed. Also, there were two studies where two modalities (SCP and amplitude) were used in direct comparison – head to head (as noted above). In Table 3, Table 4 and Table 6 these studies were added to both modalities as both studies found both modalities beneficial, but they were not double counted in the totals (bottom row of the tables). For 17 studies, it was not completely clear which modality was used (often as the researchers just said "neurofeedback" in the abstract). For these we used our best judgement to determine which modality was studied (12 amplitude, three QEEG guided, one LENS and one Infra-low).

Table 1. Summary of ISNR studies

Total	Duplicates	Books, Reviews, Theoretical	No Treatment	Conference presentations	Not Found	Total Used
690	145	175	77	2	33	258

Table 2. Source of studies used

Source	Studies used	Abstract Only
ISNR	258	70
SCP	3	-
LENS	4	-
PubMed	49	13
Total	314	83

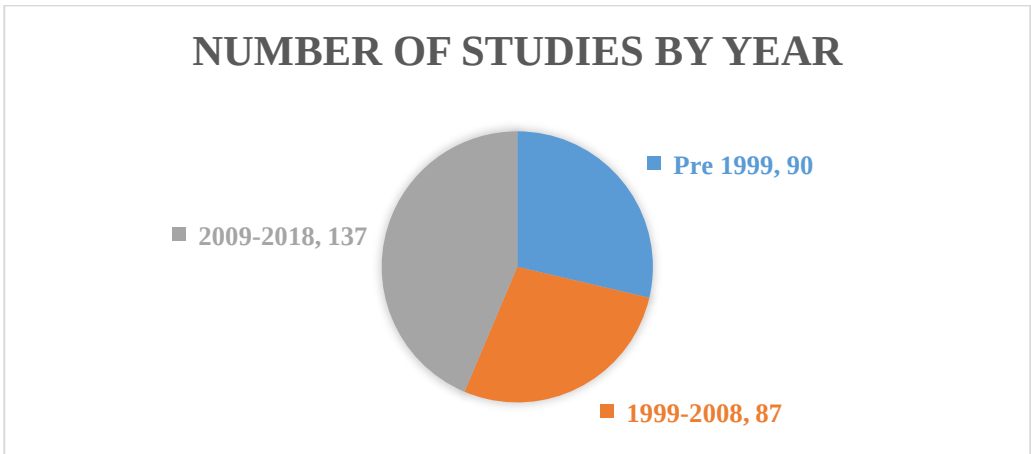

Fig. 1. Studies by year of publication

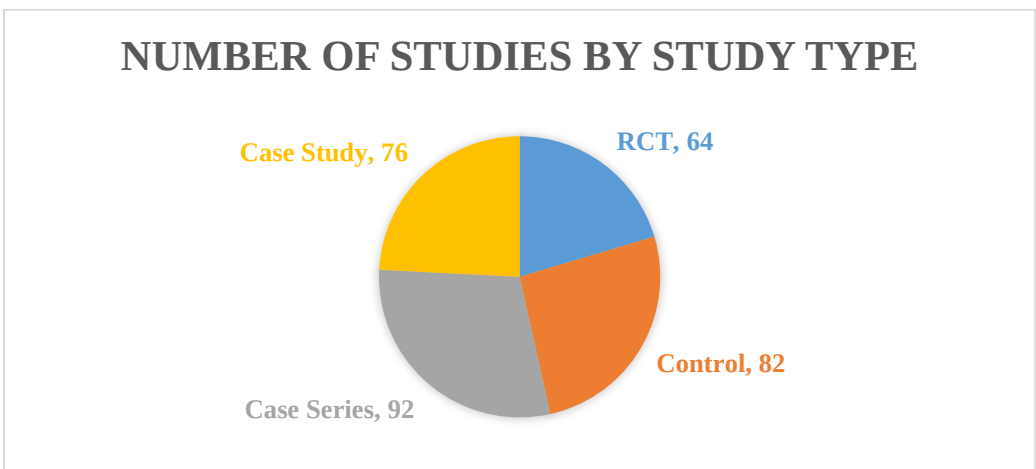

Fig. 2. Studies by study type

Figure 1 shows a breakdown of studies by time category. The trend is for studies in neuromodulation to be increasing. Figure 2 shows a breakdown into study types, with RCT studies comprising over 20% of published studies.

Table 3. Studies by modality

Modality	No. Studies	No. Successful
Amplitude (including head to head studies)	232	219
SCP (including head to head studies)	18	17
Stimulation	11	11
fMRI	8	8
LENS	7	6
HEG	7	7
QEEG guided	7	7
Z Score (19-channel including LORETA)	6	6
Coherence	5	4
Infra-low	3	3
rTMS	3	3
tDCS	2	2
Combined	7	7
Head to head	2	2
Total (does not include extra amplitude and SCP studies)	314	298

Table 3 shows a breakdown of studies by neuromodulation modality. Over 70% of all published studies used amplitude neurofeedback

Table 4. Studies by modality vs study type or research design

Modality	No. Studies	RCT	Control	Case Series	Case Study
Amplitude (including head to head studies)	232	50	64	62	56
SCP (including head to head studies)	18	5	6	7	-
Stimulation	11	1	2	4	4
fMRI	8	4	3	1	-
LENS	7	1	1	1	4
HEG	7	-	3	2	2
QEEG guided	7	-	-	6	1
Z Score (19-channel including LORETA)	6	-	-	4	2
Coherence	5	2	1	1	1
Infra-low	3	1	-	-	2
rTMS	3	-	1	2	-
tDCS	2	1	-	1	-
Combined	7	1	1	1	4
Head to head	2	2	-	-	-
Total (does not include extra amplitude and SCP studies)	314	64	82	92	76

When breaking down modality by research design, amplitude neurofeedback continues to account for the majority of studies in each category, reaching over 75% of all RCTs and control studies.

Table 5. Studies by condition treated

Condition	No. Studies	No. Studies with Positive Outcome	Modality Most Studied	No. Studies for Most Studied Modality
ADHD	82	78	Amplitude*	66†
Addiction (including alcohol)	21	20	Amplitude	19
Anger	2	2	Amplitude, LENS	1
Anxiety / Stress	13	11	Amplitude	11
ASD	18	18	Amplitude	13
Cognitive Decline	5	5	Amplitude	4
Depression	17	17	Amplitude	10
Dissociation	3	3	Amplitude	3
Epilepsy	35	32	Amplitude	26
Immune System (fibromyalgia and chronic fatigue)	6	6	Amplitude	4
Learning Disorders	15	15	Amplitude	11
Medical (Lyme's disease, angioedema, tinnitus, diabetes, and Chemotherapy Induced Neuropathic Symptoms)	7	7	Amplitude	6
OCD	4	4	Combined	2
Pain / headache	11	11	Amplitude	6
Parkinson's	4	3	Amplitude	2
Peak performance	26	25	Amplitude	20
Personality disorder	1	1	QEEG guided	1
Prison Inmates	3	3	Amplitude	3
PTSD	9	8	Amplitude	6
Schizophrenia	5	5	Amplitude	3
Sleep	5	4	Amplitude	4
Traumatic Brain Injury (TBI)	13	12	Amplitude	8
Tourette's	1	1	Amplitude	1
Stroke	8	7	Amplitude	4
Total	314	298	Amplitude	232†

*For ADHD, SCP studies are also impressive (see Table 6)

These include the two head to head studies previously discussed.

Table 6. ADHD studies by modality and study type –head to head results have been added to amplitude and SCP results

Modality	RCT		Control		Case Series		Case Study		Total	
	Studies	Subjects	Studies	Subjects	Studies	Subjects	Studies	Subjects	Studies	Subjects
Amplitude	22	1,360	20	805	15	1,460	9	11	66	3,636
SCP	5	416	3	70	3	72	-	-	11	558
HEG	-	-	1	51	-	-	1	1	2	52
Stimulation	-	-	1	32	1	40	-	-	2	72
fMRI	1	31	1	13	-	-	-	-	2	44
Head to head	2	85	-	-	-	-	-	-	2	85
Combined	1	72	-	-	-	-	-	-	1	72
Total	27	1,794	26	971	19	1,572	10	12	82	4,349

Table 7. Epilepsy studies by modality and study type

Modality	RCT		Control		Case Series		Case Study		Total	
	Studies	Subjects	Studies	Subjects	Studies	Subjects	Studies	Subjects	Studies	Subjects
Amplitude	2	16	4	60	11	164	9	16	26	256
SCP	-	-	2	54	3	44	-	-	5	98
QEEG guided	-	-	-	-	1	25	-	-	1	25
Stimulation	-	-	-	-	1	7	-	-	1	7
Z score	-	-	-	-	1	6	-	-	1	6
Infra-low	-	-	-	-	-	-	1	3	1	3
Total	2	16	6	114	17	246	10	19	35	395

Table 8. Combined studies by modality and study type for anxiety, stress, depression and PTSD

Modality	RCT		Control		Case Series		Case Study		Total	
	Studies	Subjects	Studies	Subjects	Studies	Subjects	Studies	Subjects	Studies	Subjects
Amplitude	3	129	9	265	7	271	8	10	27	675
Stimulation	1	16	1	74	-	-	3	4	5	94
fMRI	3	110	-	-	-	-	-	-	3	110
LENS	1	17	-	-	1	7	-	-	2	24
Coherence	-	-	-	-	1	132	-	-	1	132
Infra-low	-	-	-	-	-	-	1	3	1	3
Total	8	272	10	339	9	410	12	17	39	1,038

In Table 6, Table 1, Table 7 and Table 8 we introduce numbers of subjects to give a sense of the cumulative large numbers of subjects involved in the studies, adding validity to the positive outcomes reported. In total, over 9,500 subjects have been involved in neuromodulation research.

Both amplitude neurofeedback and SCP neurofeedback show very positive outcomes for ADHD (Table 6). In Table 8 we combined PTSD with disorders often associated with PTSD to give a perspective on a group of disorders not directly related to ADHD. In this smaller subset amplitude neurofeedback still plays a dominant role.

4. Discussion

EEG amplitude neurofeedback constitutes the vast majority of all neuromodulation studies, over 70%. This high percentage is ongoing. In 2018, of 26 studies reviewed, 19 involved amplitude neurofeedback, which is still greater than 70%. We only found and reviewed two head-to-head studies and these found that both amplitude neurofeedback and SCP neurofeedback were efficacious in the treatment of ADHD. We did not find evidence that one treatment modality is superior to any other for any of the conditions/disorders reviewed. However, for almost all conditions/disorders, amplitude neurofeedback had the most empirical support in terms of studies and numbers of subjects.

While it is beyond the scope of this review to analyze studies in depth regarding efficacy, several articles are of interest in this area (pro neurofeedback: Van Doren et al, 2018 and Piggott et al, 2018; against neurofeedback: Gelade et al, 2017 and Thibault & Raz, 2017). See also Coben, Hammond & Arns (2018) which takes issue with claims of efficacy of LORETA-based and Z-Score 19-channel training. Another interesting study explored improvements in functioning post neurofeedback training (Rance et al., 2018).

With neuromodulation methodologies diversifying, we need good studies so that we know which technique works best for which condition.

- We need case studies, especially for clients with unusual presentations.
- Where possible, case series give stronger support to a methodology, especially if the author is very specific on the "how to" component, which is critical to replicability. In clinical practice, if several practitioners, practicing independently validate a particular approach, with a particular client group, that is a very powerful endorsement. It is important to not cherry-pick cases that gave positive outcomes – to have unbiased selection criteria for which cases to include (e.g. all clients with particular characteristics seen between two dates). To not do so limits what can be learned from the case series as well as how much one can trust their findings.

- Clinic studies with controls eliminate some of the non-specific/unspecified elements (some say placebo) of the intervention as the cause of change. We need studies that are done with controls in a clinical setting for several reasons. Firstly, as clinicians, we do not seek to eliminate non-specific effects, we seek to maximize them. Furthermore, we do not randomly accept clients – they choose us, so the issue of random assignment to treatments is contrary to clinical practice. In addition, clients in clinic studies reflect real world conditions and comorbidities – the same as that which walks through our doors.
- RCTs are best for indicating the specific effect of a treatment. They are also needed to help gain mainstream recognition of neuromodulation.

Amplitude training still works, and still works well. It never didn't work well. In terms of research support, it is by far the strongest of the neuromodulation methodologies.

Regardless of which modality/form of neuromodulation practitioner's use, they are working to help their clients. Mutual support, rather than competitiveness and exclusivity will help the field grow. We look forward to a time when we know which neuromodulation methodology works best for which client group and which condition.

We plan on continually updating this review with additional studies (some that we were not yet able to locate, some that we have inadvertently excluded, and those that are yet to be published). We invite people to submit studies to be included in our database, and we aim to make the database we developed for this review available for general use.

5. Disclosures

The authors would like to disclose the following:

- Dr. Moshe Perl:
  - Has been practicing neurofeedback since 1998. He has predominantly used amplitude neurofeedback in his practice, and on occasion uses LENS. Additionally, he has studied and used a variety of coherence-based trainings including surface and LORETA 19-channel training.
  - Has been training and mentoring neurofeedback practitioners since 2001 in amplitude neurofeedback.
  - Has been a representative of EEG Education and Research (EEGer) (previously EEG Spectrum) for Australasia since 2001.
  - Is Board Certified in Neurofeedback by BCIA
  - Is a current member and past president of The Applied Neuroscience Society of Australasia (ANSA).
  - Is the director of the Neurotherapy Institute of Australasia (NIA)
- David Perl is a business manager of the Neurotherapy Institute of Australasia (NIA).

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QEEG AS A BASE FOR NEUROFEEDBACK TREATMENT: IS IT RELIABLE ENOUGH?

Rivi Sela*

CEO at BetterFly Neurofeedback, 24 Beit-El st, Tel-Aviv 6908720, Israel

Abstract

In the last two decades, qEEG has turned from a purely research tool into an important, basic part of the work of many neurofeedback clinicians. The analysis of EEG samples requires extensive knowledge and experience, which up until a decade ago were the province of a few experts in the neurofeedback community. Unlike the deep knowledge that is required in order to analyze raw EEG, performing an FFT analysis and creating qEEG maps and graphs is computerized and relatively straight forward. This article presents examples that explain the importance of surveying the raw EEG before starting the qEEG analysis, and combining raw EGG analysis with a close reading of the qEEG report in order to perform a reliable analysisof the information and to make proper decisions regarding the treatment protocol. In this article, we will use a few different softwares and technologies, and try to illustrate the common factors and common ideas that underlie each of these technologies.

Keywords: qEEG; neurofeedback; EEG biofeedback; EEG; EEG artifacts; automated qEEG reports

ARTICLE INFO		* *Corresponding author*
RECEIVED	November 18	E-mail address: drrivi@btr-fly.com
REVIEWED	January 19	
ACCEPTED	February 19	

1. Introduction

EEG was invented in 1924 by Hans Berger, however it was only inspected visually when computers became available to scientists in the late 1960's. The new developments in technology made it possible to apply spectral analysis (Fast Fourier Transform; FFT) on the recorded EEG data in order to define the frequency content of the signal.

This has eventually led to the appearance of graphs and brain maps, as we know them today. As that change was taking place, scientists and therapists began to collect normative data on the EEG and began to analyze the EEG quantitatively by comparing test results to a control group or normative database.

This quantitative EEG (or qEEG) has since been scientifically researched in more recent years to try and determine whether certain characteristic of the EEG be used as biomarkers of neuropsychiatric conditions. Since the 1990's, the neurofeedback community accepted the use of 19 channel qEEG as a comprehensive, scientific, objective assessment tool for deciding on a treatment protocol and as an objective way of looking at the outcomes of treatment (by making pre- and post-training comparisons).

There have been more publications of peer-reviewed research-studies that showed the effectiveness of qEEG guided neurofeedback versus training based on quantitative evaluations of the EEG at only a limited number of electrode sites (miniQ's) or on protocols derived from symptoms, solely from clinical experience (Bounias et al., 2001; Hammond, 2003; Hoffman et al., 1996; Thornton 2000, 2002).

In 2004, a position paper on the standards of use of qEEG in neurofeedback was published by a group of leading therapists in the field (Hammond et al., 2004). This position paper was accepted by the ISNR board as an official position paper of the ISNR.

The following is a quote from that position paper:

"The committee reached the following conclusions:

1. Although clinical research indicates that a full 19 channel QEEG does not appear necessary for conducting successful neurofeedback training, an increasing number of clinicians are using comprehensive QEEG evaluations to guide their neurofeedback training.
2. An impressive body of peer reviewed scientific literature attests to the utility of the QEEG in providing a scientifically objective and clinically practical assessment of a wide range of psychiatric, psychological and medical conditions.
3. Many of the significant contributions to the field of QEEG have come from psychologists, and the Board of Professional Affairs of the American Psychological Association has concluded that QEEG is within the scope of practice of psychologists trained in this specialty.
4. Unlike neurology and psychiatry, where QEEG is principally used for purposes of diagnosing medical pathology, neurotherapists who use QEEG primarily do so to guide EEG biofeedback training.
5. It is not necessary for a physician to screen raw EEG data as part of a QEEG evaluation for neurofeedback training."

The attitude which the committee displays in this position paper, according to which there is no need to specialize in inspecting the raw EEG in order to reach a decision about a neurofeedback treatment protocol, made the necessary expertise needed to read the EEG redundant, and provided an opening for a wide use of automatic qEEG report generators, which have become accessible and available to all neurofeedback clinicians.

2. Purpose and aim:

This paper will review examples of raw EEG and compare them with the qEEG graphs and maps to show the importance of screening and understanding the raw EEG as a part of qEEG evaluation for neurofeedback training.

This paper will discuss the following topics:

- The ease of automatic reports: fast, but are the outcomes reliable?
- Artefacts and automatic artefact detectors
- The importance of looking at the morphology of brainwaves
- Epileptic discharges and qEEG

The ease of automatic reports: Fast, but are the outcomes reliable?

Z-Score maps serve many clinicians not just to decide on a treatment protocol, but also to perform a follow-up of treatment results and to show their clients the significant change in their brain function with a scientific, objective tool. The colourful maps show the differences visually even to those who do not know how to read them, and websites of many clinics present them in order to show the efficiency of neurofeedback treatment. However, these maps do not always represent reality accurately. We will present a few examples here, to demonstrate this point:

Example 1:

This example is taken from a neurofeedback clinic ad, showing the pre- and post-training of a 15-year-old autistic boy. The Z-Score FFT maps were produced by an automatic report generator, and show some incredible outcomes attributed to neurofeedback training.

Pre-Training Post-Training

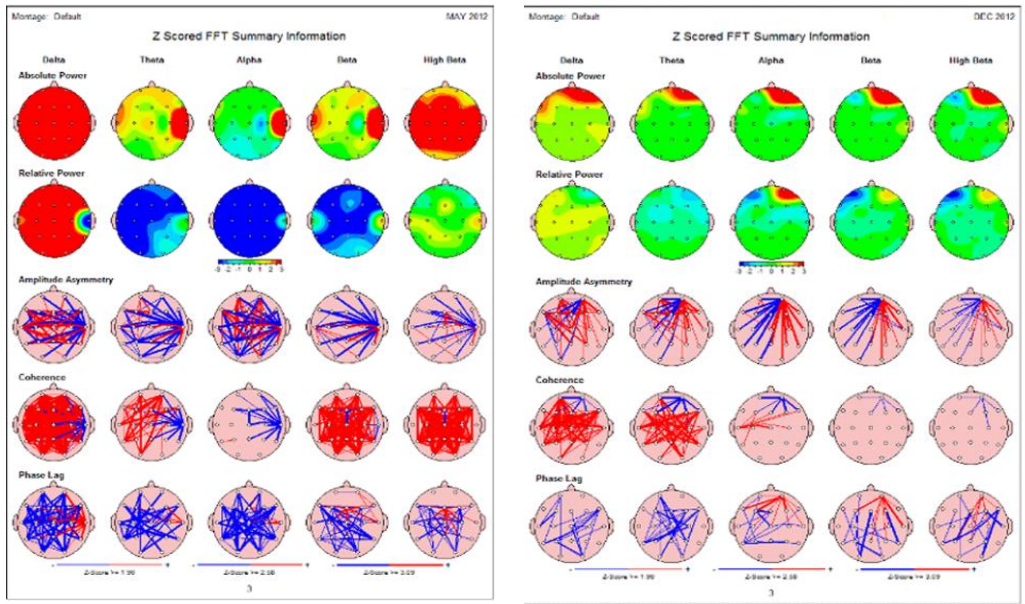

Fig. 1. A Z-Score FFT map of a 15-year-old autistic boy, (a) Pre and (b) Post neurofeedback training.

The pre-training map reveals an excess of Delta waves and an excess of high Beta waves in all cortical areas, as well as hyper-coherence of Delta, Beta and high Beta in intra- and inter-hemispheric connectivity. The post-training map reveals a frontal excess of Delta, Theta, Alpha and high Beta, but still, it is an incredible improvement from the pre-training map.

A Delta wave is a high amplitude wave with a frequency of oscillation between 0.5–4 Hz. Delta waves are usually associated with the deep stage 3 of NREM sleep. Delta-waves are also the predominant wave-form of infants. Analysis of the waking EEG of a newborn infant indicates that Delta wave activity is predominant in that age, and still appears in the waking EEG of five-year-old children.

Delta wave disruptions may present as a result of physiological damage, changes in nutrient metabolism, chemical alteration, or may also be idiopathic. Disruptions in Delta activity are seen in adults during states of intoxication or delirium and in those diagnosed with various neurological disorders such as dementia, schizophrenia or TBI.

A trained practitioner will know that although studies of qEEG in autism show generally increased Delta-Theta activity in the frontal region of the brain (Pop-Jordanova et al., 2010), the excessive Delta in all areas of the cortex, as shown in the pre- training map, cannot appear in the waking EEG of a 15-year-old boy.

Automated report generators should be used only on a clean, artifact removed, raw EEG. Automated report generators are simply not able to distinguish between artifacts and actual brain waves. The excess of Delta and high Beta activity all over the brain, as presented in the pre-training maps, are the outcomes of artifacts. The hyper-coherence of Delta, Beta and high Beta shown in the

pre-training maps are also the outcome of artifacts. As for the post-training map, the excess of Delta, Theta, Alpha, Beta and high Beta waves on the exact same area indicates that the source is an artifact.

Artifacts and Automatic Artifact Detectors

The EEG data are typically contaminated with artifacts such as those generated by eyeblinks, eye movements, muscle activity, ECG and pulse artifacts, as well as electrode artifacts. The elimination of artifacts from the raw EEG is of substantial importance for analyzing the EEG correctly and obtaining clinical information related to pathology.

Some automated qEEG report generators use artifact removal algorithms, combining a few research methods. The most common methods are based on Independent Component Analysis (ICA) that separates EEG data into neural activity and artifacts. Most ICA methods are performed using theoretic learning algorithms, and different software tools use different variants of the learning algorithms, such as Jade and FastICA. Once identified, artifactual components can be .deleted from the data.

In the following exampels I used the WinEEG software with the HBI database. The first step was using the ICA algorithm. The ICA algorithm can be used to separate neural activity from muscle and blink artifacts in spontaneous EEG data. The basic assumption of ICA applying to EEG artifact removal is that the time courses of the EEG activity and artifacts are statistically independent. However, some real EEG activity might be correlated temporally with particular artifacts and will also be removed from the raw EEG.

The next step was applying the search and rejection artifacts option, using the default parameters of the database.

Example 2 and 3 below will demonstrate the problem that occurs when clinicians rely on the automatic artifact removal tools to distinguish between artifacts and actual brain wave activity.

Example 2: A 24-year-old student with symptoms of ADHD:

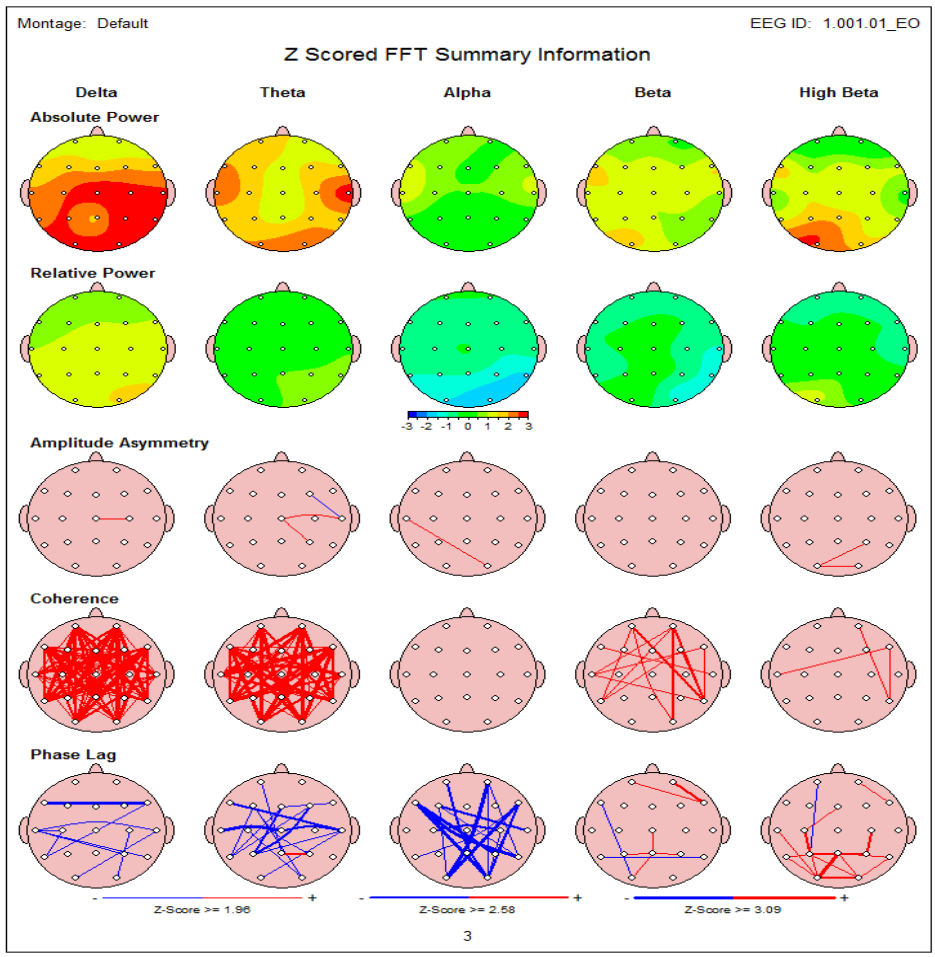

Fig. 2: A Z-Score FFT map of a 24-year-old student with symptoms of ADHD (example 2)

The map presented in Fig. 2 above reveals an excess of Delta and Theta wave activity in the central, parietal and occipital areas, and hyper-coherence of Delta and Theta in intra- and inter-hemispheric connectivity.

Looking at the raw EEG presented in Fig. 3 below, we can see that the recording contains many artifacts. I used an automatic artifact detector software to identify and mark the artifacts. The artifacts that were identified are marked in a blue underline.

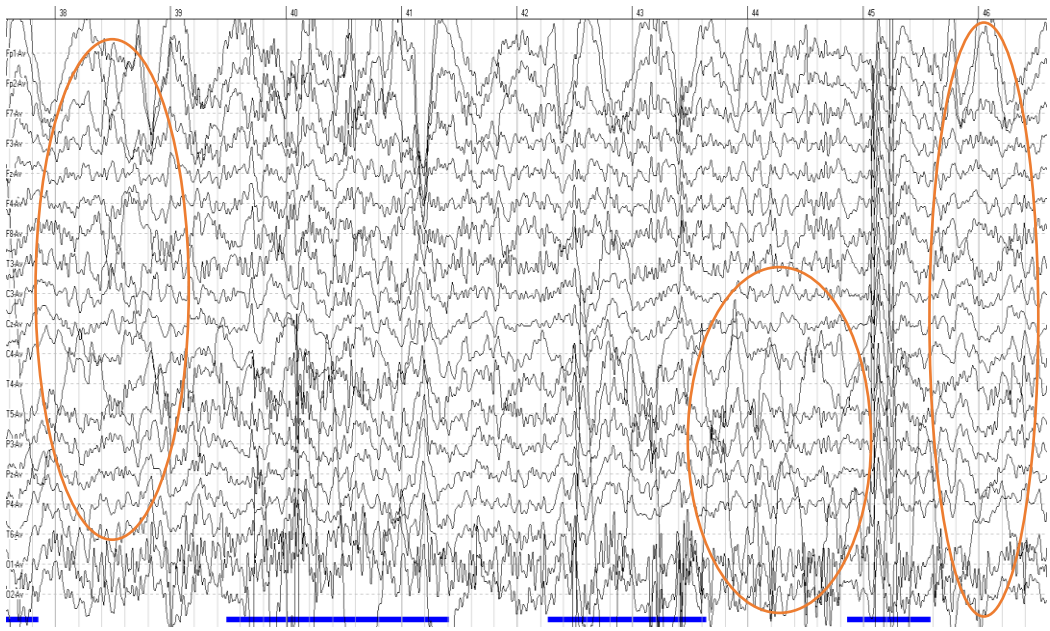

Fig. 3: The raw EEG of the 24-year old-student (example 2). The artifacts that were detected by the software are underlined in blue. The electrode artifact (circled) was not detected by the software.

Only a part of the artifacts were recognized by the software. The artifacts that were not recognized by the software are marked with red circles. These artifacts will be mistaken as an abnormally slow Delta and Theta brain waves and will be visible in the topographic maps as such.

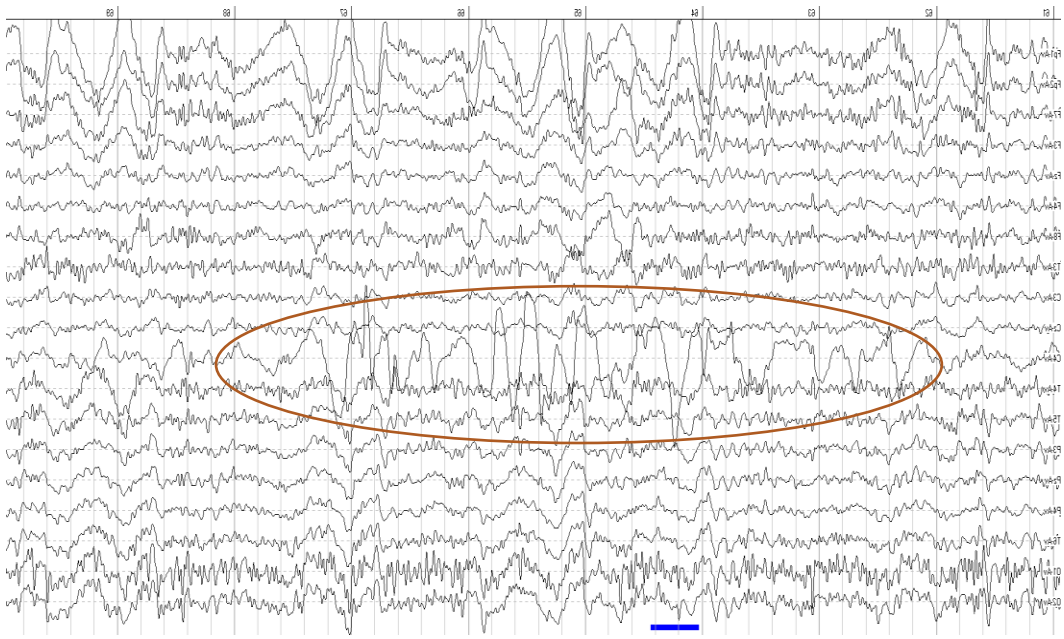

Fig. 4: The raw EEG of a 24-year-old student (example 2). The electrode artifact (circled), was not detected by the software.

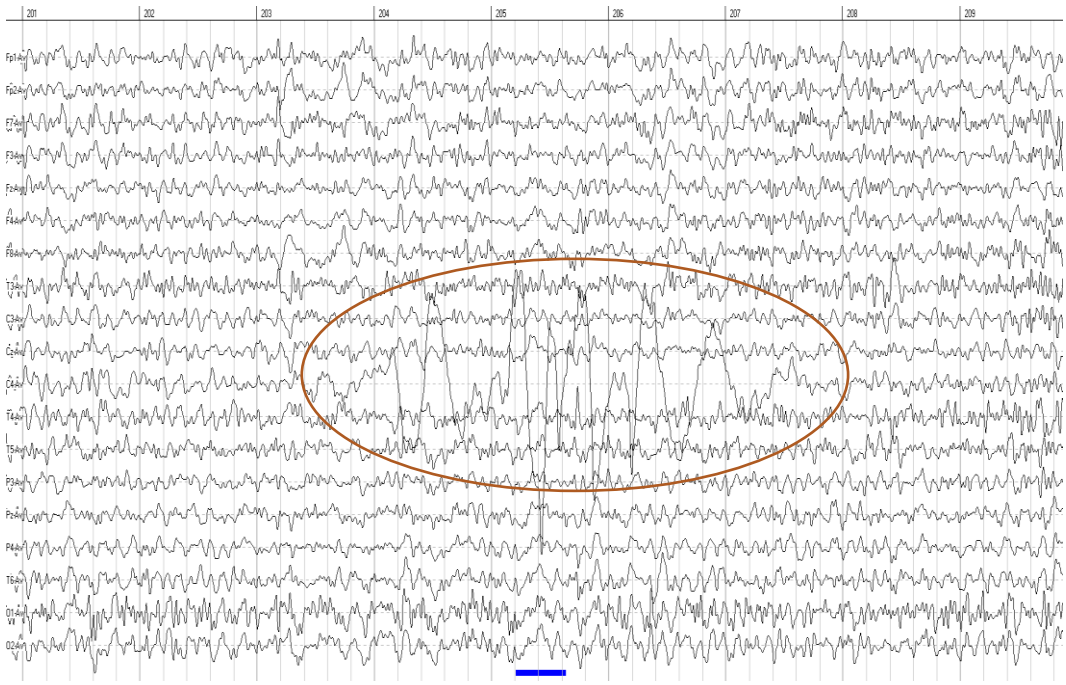

Fig. 5: The raw EEG of a 24-year-old student (example 2). The electrode artifact (circled), was not detected by the software.

Fig. 4 and Fig. 5 above present more shots from the same raw EEG. Again the automatic artifact detector software identified just a small part of the electrode artifact in C4. The artifacts that were identified are marked in blue.

Example 3: An 11-year-old with symptoms of ADHD:

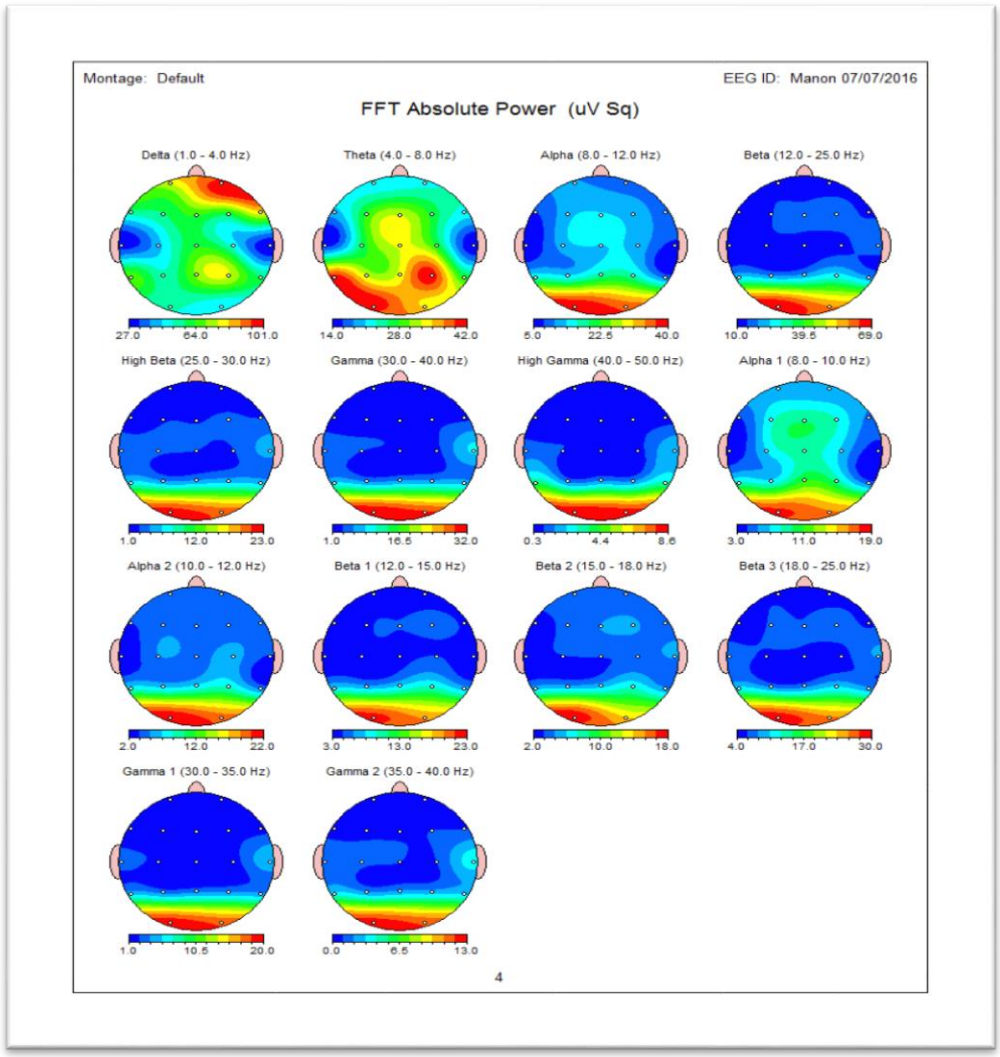

Fig. 6: Spectral analysis (Fast Fourier Transform) of an 11-year-old with symptoms of ADHD (example 3). The map shows Delta activity and a focal slow activity in the Theta range in the parietal-tempotal right side (P4/T6).

The spectral map in Fig. 6 above shows a focal slow activity in P4/T6.

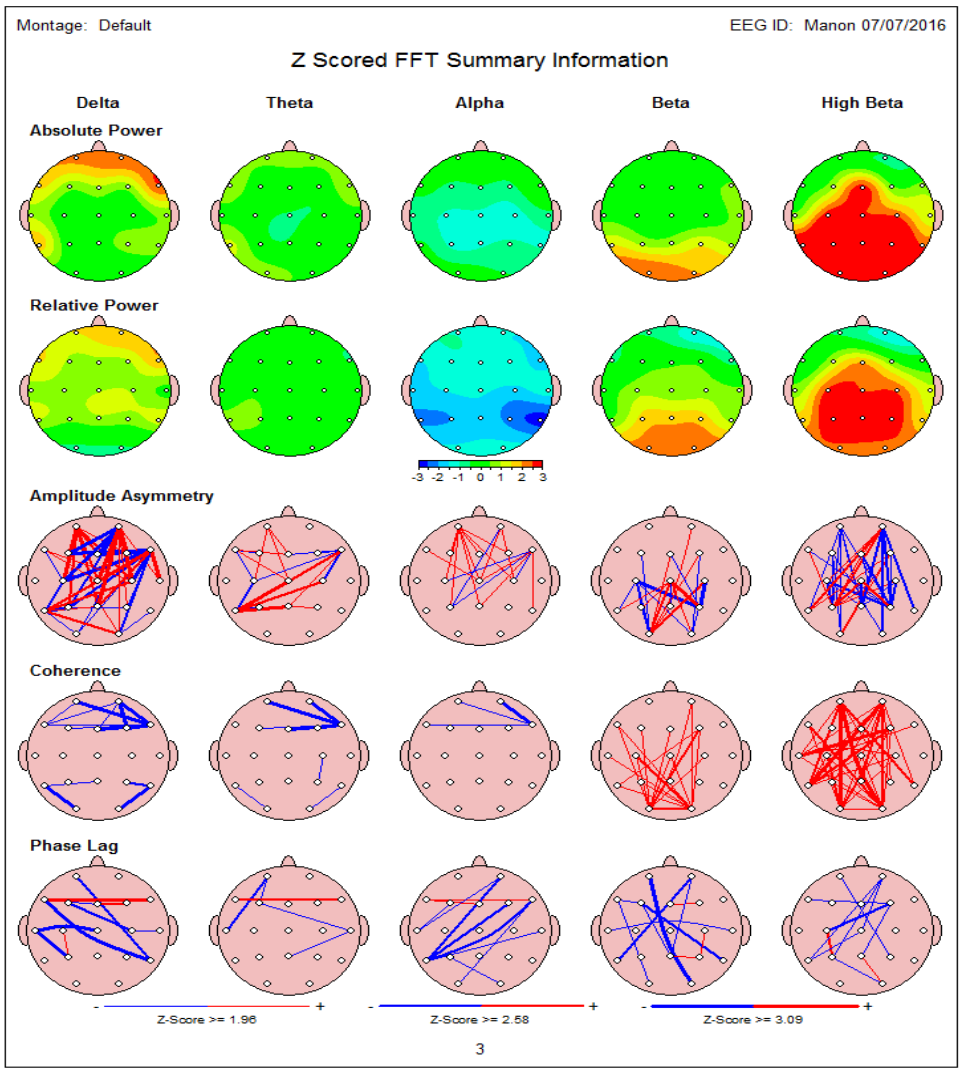

Fig. 7: A Z-Score FFT map of a 15-year-old with symptoms of ADHD (example 3). The maps show an excess of frontal Delta and an excess of Beta activity in the occipital head region in addition to excesses of high Beta in the central, parietal and occipital brain regions. There is hipercoherene in the Beta and high Beta range.

The map in Fig. 7 above reveals an excess of frontal Delta and an excess of Beta activity in the occipital head region in addition to excesses of high Beta in the central, parietal and occipital brain regions. Please note that the focal slow activity in P4/T6 that was shown in the spectral map in Fig. 6 left no trace in the Z-Score map shown in Fig. 7.

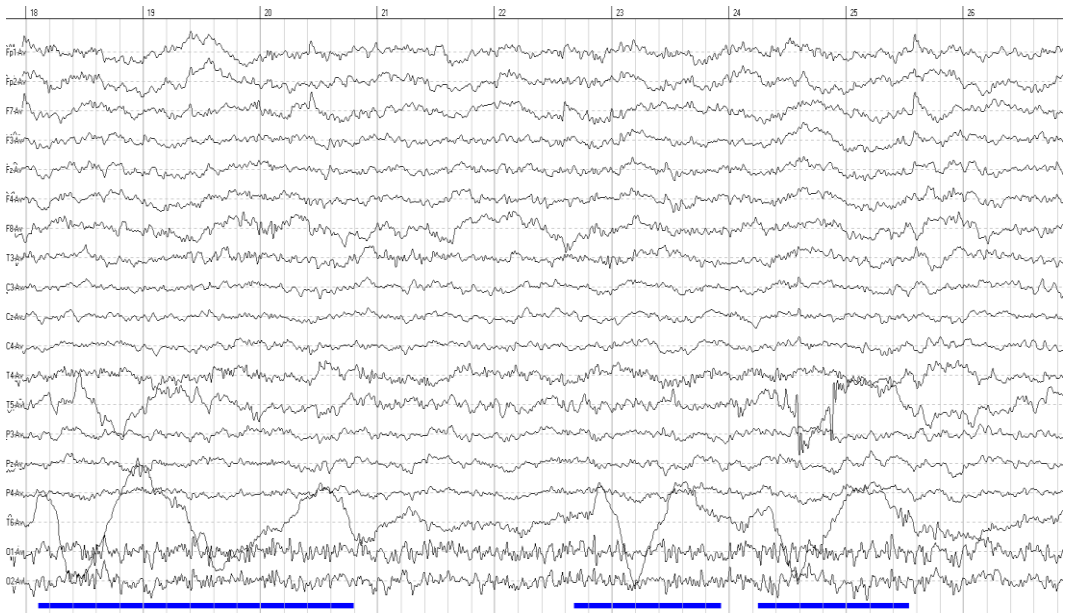

Fig. 8: The raw EEG of a 15-year-old (example 3). The artifacts that were detected by the software are underlined in blue. The electrode artifacs on T5, T6 were detected by the software. .

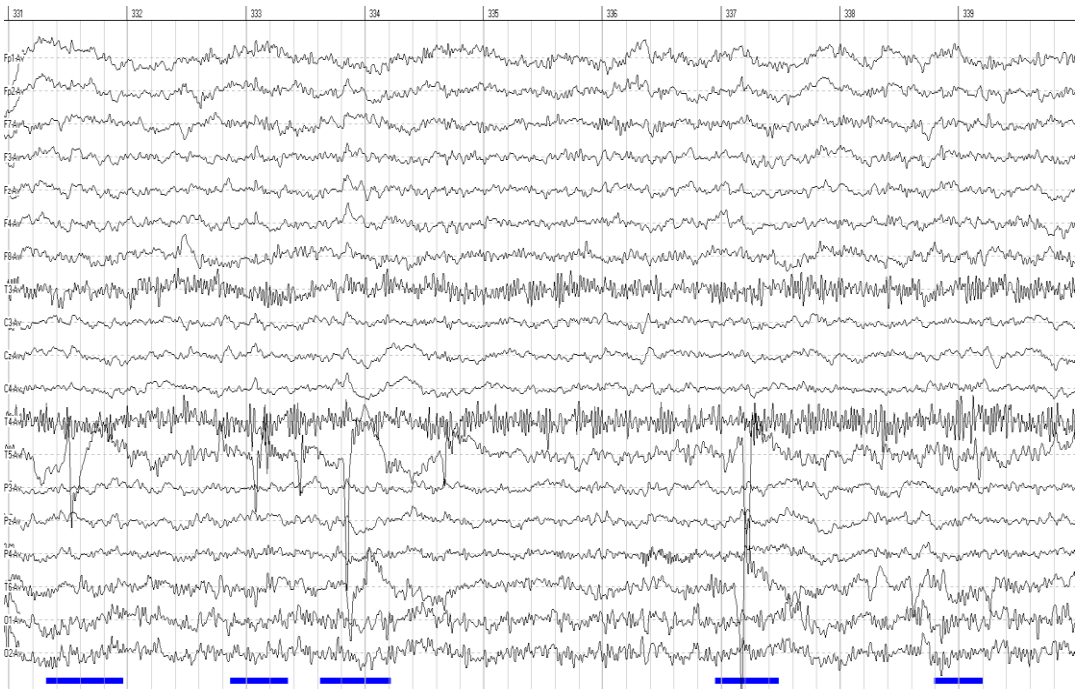

Fig. 9: The raw EEG of a 15-year-old (example 3). The artifacts that were wrongly detected by the software (underlined in blue) are epileptiform discharges.

Fig. 8 and Fig. 9 above show the raw EEG of the 15-year-old patient. We used an automatic artifact detector software to identify and mark the artifacts. The artifacts that were identified are marked in blue underline. Fig. 8 shows an electrode artifact in T6 that was identified by the artifact detector. In Fig. 9 we can see that the artifact detector marked the spike-and-wave discharges shown in T5 and T6 as artifacts. These spike-and-wave discharges are the source of the focal slow activity on T6,that was shown in the FFT map in Fig. 6. The Spectral Analysis in Fig. 7 is compared with norms. Since the spikes were excluded as artifacts in the raw EEG and in the Z-Score compared with norms, we cannot see the abnormal activity in this map.

Example 4: The raw EEG of a 21-year-old epileptic patient with generalized seizures.

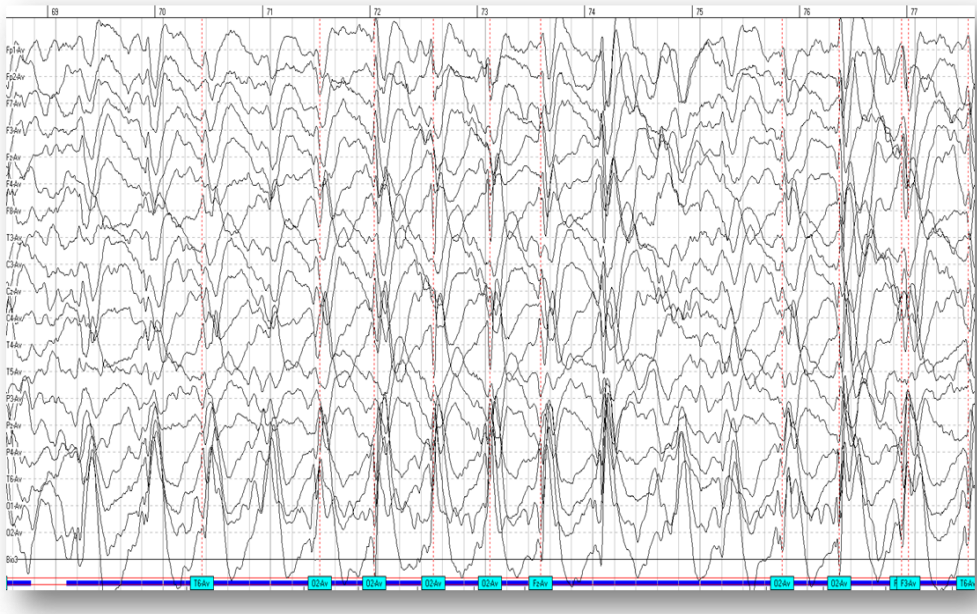

Fig. 10: The raw EEG of an epileptic patient (example 4). The EEG backround high amplitude activity was wrongly recognized as artifacts.

Patients who have a generalized seizure disorder frequently have higher amplitude background rhythms, as demonstrated in Fig. 10.above. The automatic artifact detector recognized the high amplitude activity as an artifact and marked it with a blue underline. The marked parts will not be included in the qEEG that will be calculated from this raw EEG, and the critical pathological information will be lost.

As demonstrated in examples 3 and 4, the ability to distinguish artifact from pathological epileptiform discharges requires an EEG professional expert that is to provide the essential identification of an abnormal EEG.

The importance of looking at the morphology of brainwaves

Raw EEG provides us with information of amplitude versus time. When we mathematically convert the raw information to qEEG, we lose relevant information about changes over time and the morphology of the brainwaves. The qEEG maps divide the brainwave bands according to predefined band widths, but the frequency of any of the brainwave bands varies from person to person. In order to correctly recognize pathological states, we must know the type of the brainwave, its frequency, its morphology, and its location on the scalp. *Example 5:*

Fig. 11 and Fig. 12 below (courtesy of Dr. Ron Swatzyna) show the qEEG maps and graphs of a 55-year-old woman who suffers from a significant reduction in her language skills: she forgets words, is unable to express herself coherently (confused discourse), and has difficulty understanding things that are being said to her.

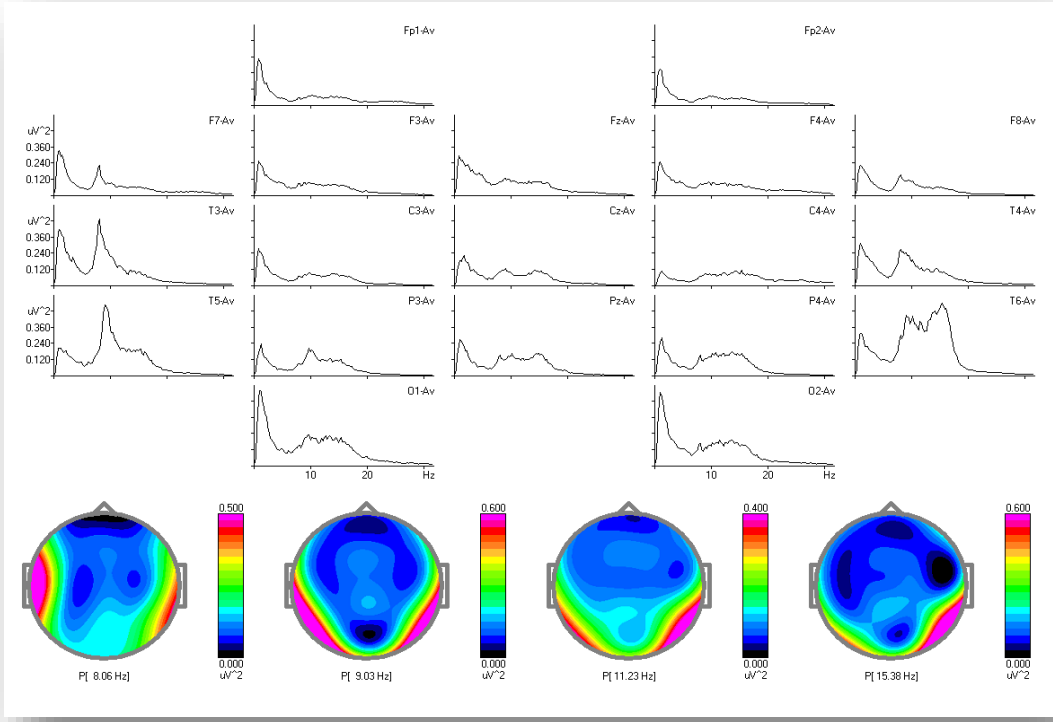

Fig. 11: Spectral Analysis (Fast Fourier Transform; example 5, courtesy of Dr. Ron Swatzyna)

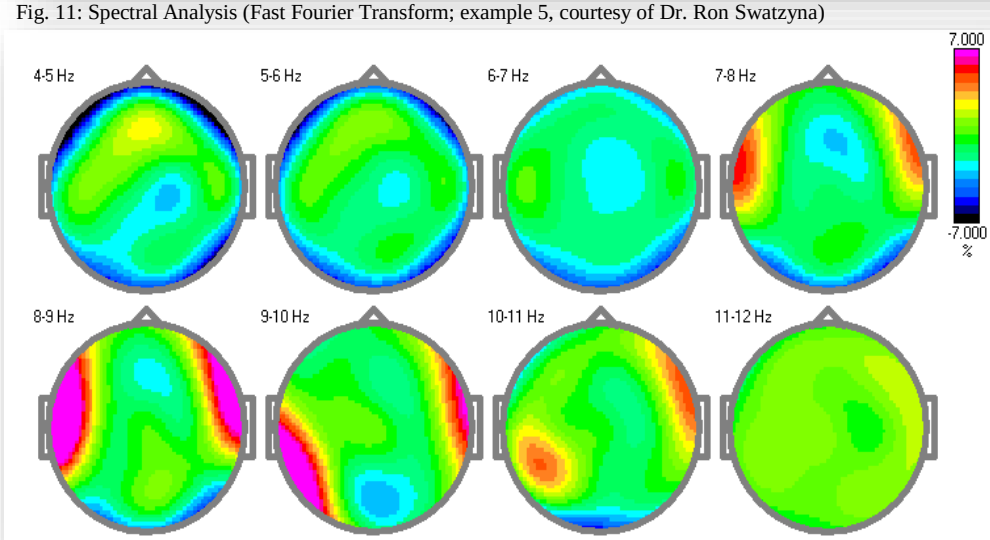

Fig. 12: Z-Score FFT map (spectral analysis compared with norms; example 5, courtesy of Dr. Ron Swatzyna)

The maps in Fig. 11 and Fig. 12 above reveal a slow activity 7-9 Hz on the left temporal lobe.

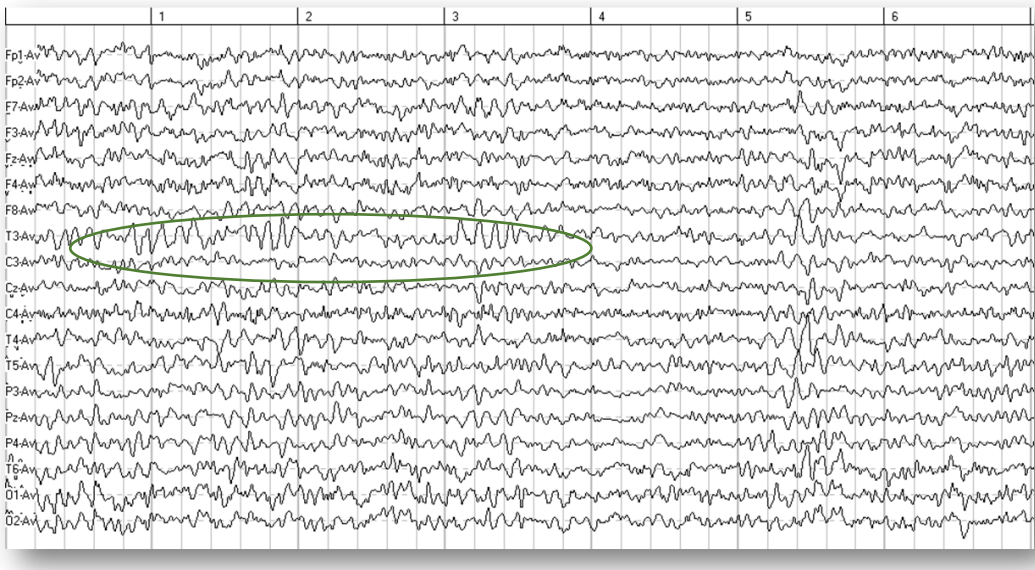

Fig. 13: Raw EEG for example 5 (courtesy of Dr. Ron Swatzyna)

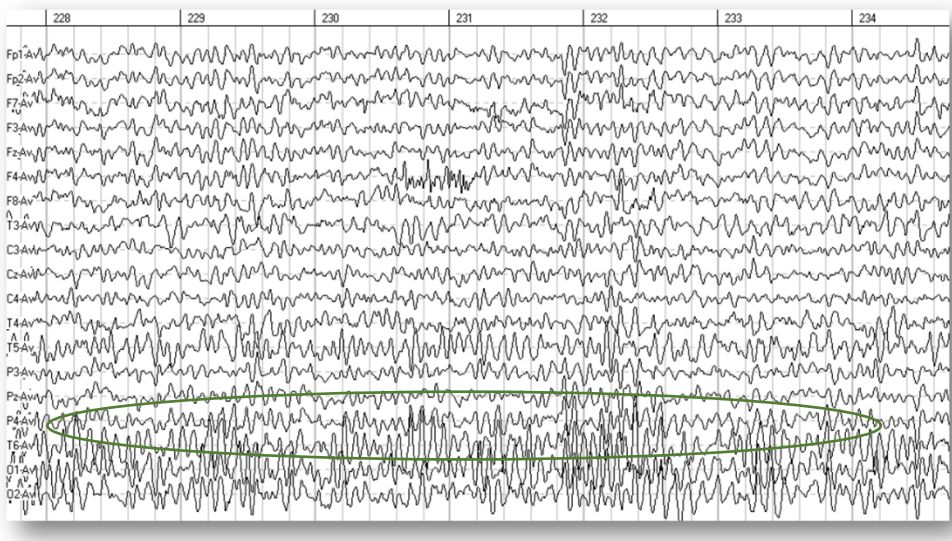

Fig. 14: Raw EEG for example 5 (courtesy of Dr. Ron Swatzyna)

Looking at the raw EEG of this woman in Fig. 13 and Fig. 14, we can see the background Alpha is at 9-11 Hz posteriorly, with excessive slower Alpha content at 7-9 Hz seen left-temporally. The slower Alpha on the left suggests low activity of this cortical area, such as seen in cases of brain trauma, tumor and cerebral vascular issues. In this case MRA identified a 7mm aneurysm on her left internal carotid artery. This example demonstrates the importance of identifying the brainwave type by looking at its morphology.

Epileptic discharges and QEEG

Neurofeedback, from its inception, has dealt with epilepsy, and there are numerous articles that testify to the efficacy of this treatment (Sterman and Egner, 2006; Cott et al., 1979; Kaplan, 1975; Finley et al., 1975; Lantz and Sterman, 1988; Tan et al., 2009; Sela and Shaked-Toledano, 2014). The question is whether in cases of epilepsy, we should trust the qEEG alone to lead us to the right protocol decision. In some cases, the qEEG may give us information that is insufficient (and sometimes even confusing) in order to make a proper treatment protocol decision. Nevertheless, it may help us follow-up on the treatment results.

The examples below will show spectral graphs and maps of Z-Score spectra. The graphs show the difference from normality for each channel. The horizontal (X) axis presents the frequency, the vertical (Y) axis shows the amplitude, and the small vertical bars show the confidence level of deviation from normality (starting from p=0.05).

In the maps of the Z-Score spectra, the frequencies are defined by the peak of the EEG spectra. Please note that the graphs and maps give us a different point of view.

Example 6: Rolandic epilepsy is a benign epilepsy with central temporal spikes and is a localized form of epilepsy. The Raw EEG in Fig. 15 below reveals spike-and-wave discharges located at T6 and T4.

Fig. 15: Raw EEG characteristic of Rolandic epilepsy (example 6

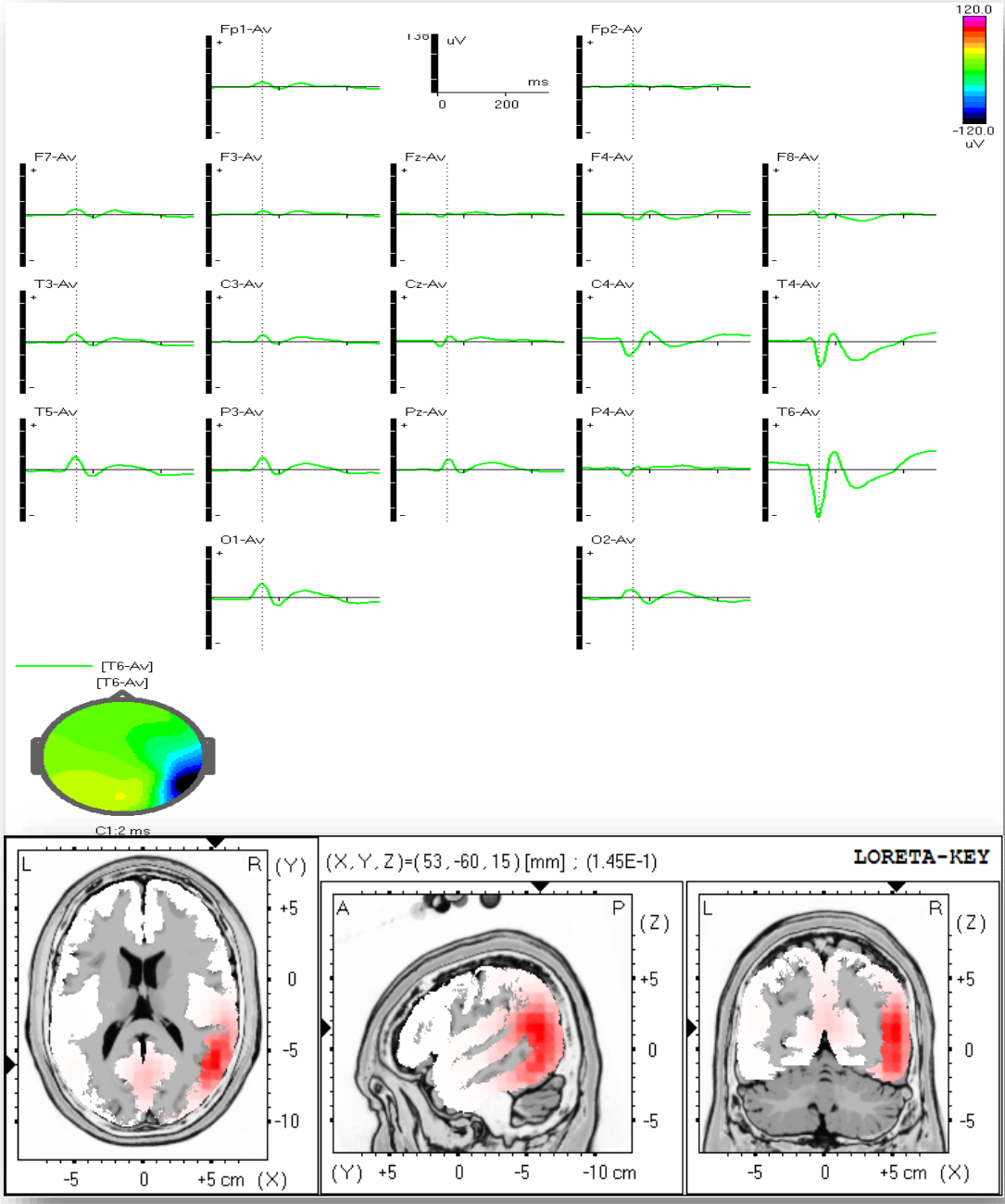

Fig. 16: Spike averaging (a) and source distribution (b) - example 6

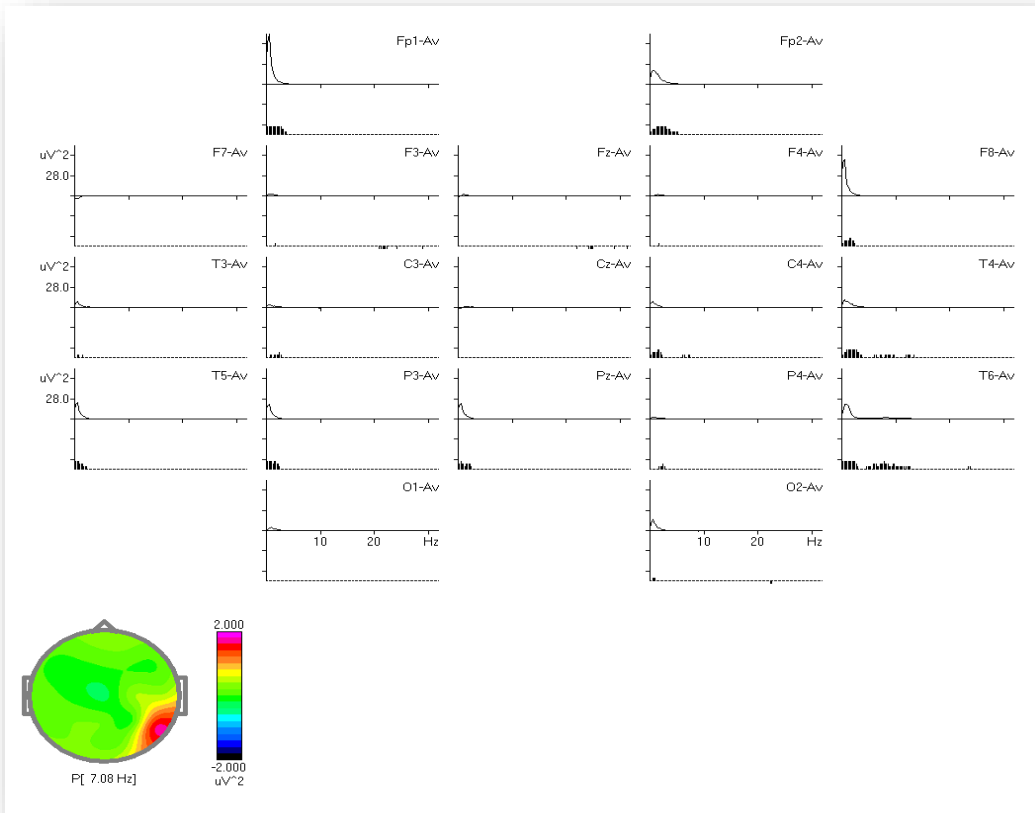

Fig. 17: Z-Score spectra (example 6)

The spectra compared with norms (Fig. 17) reveals increased activity in all frequency bands at the site of the focus (T4/T6). The information that the qEEG gives us in this case can be helpful at least for deciding on the electrode placements for the treatment protocol.

Example 7:

Epileptic patient who suffers from generalized epilepsy.

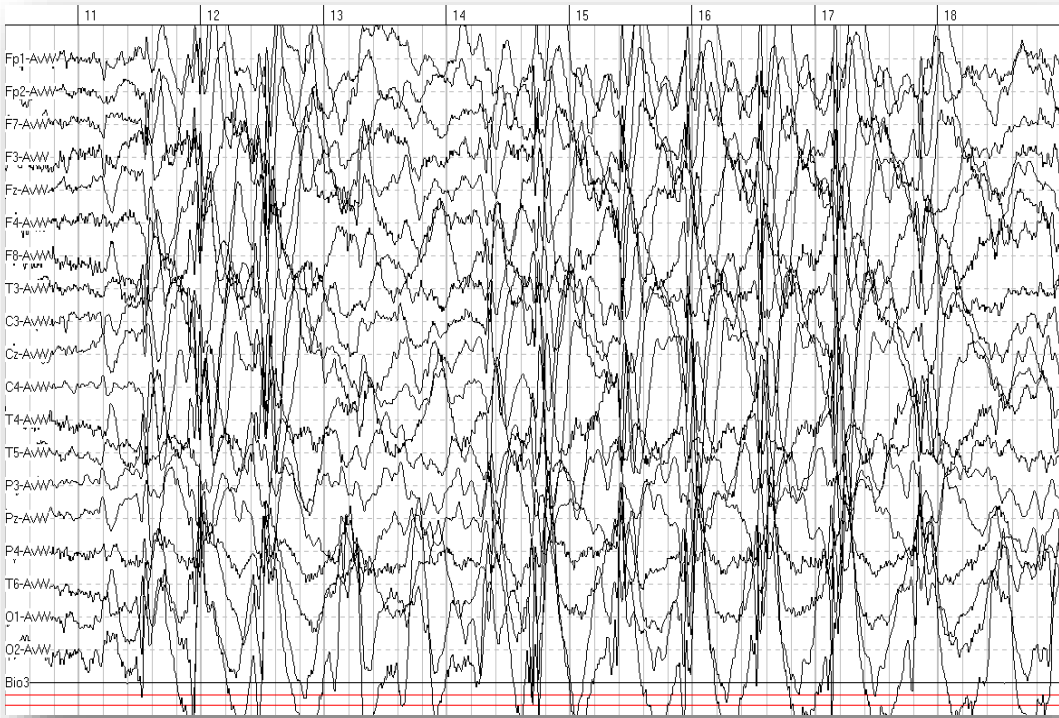

Fig. 18: Raw EEG of a patient who suffers from generalized seizures (example 7)

The Raw EEG in Fig. 18 above reveals epileptic discharges with higher amplitude background rhythms.

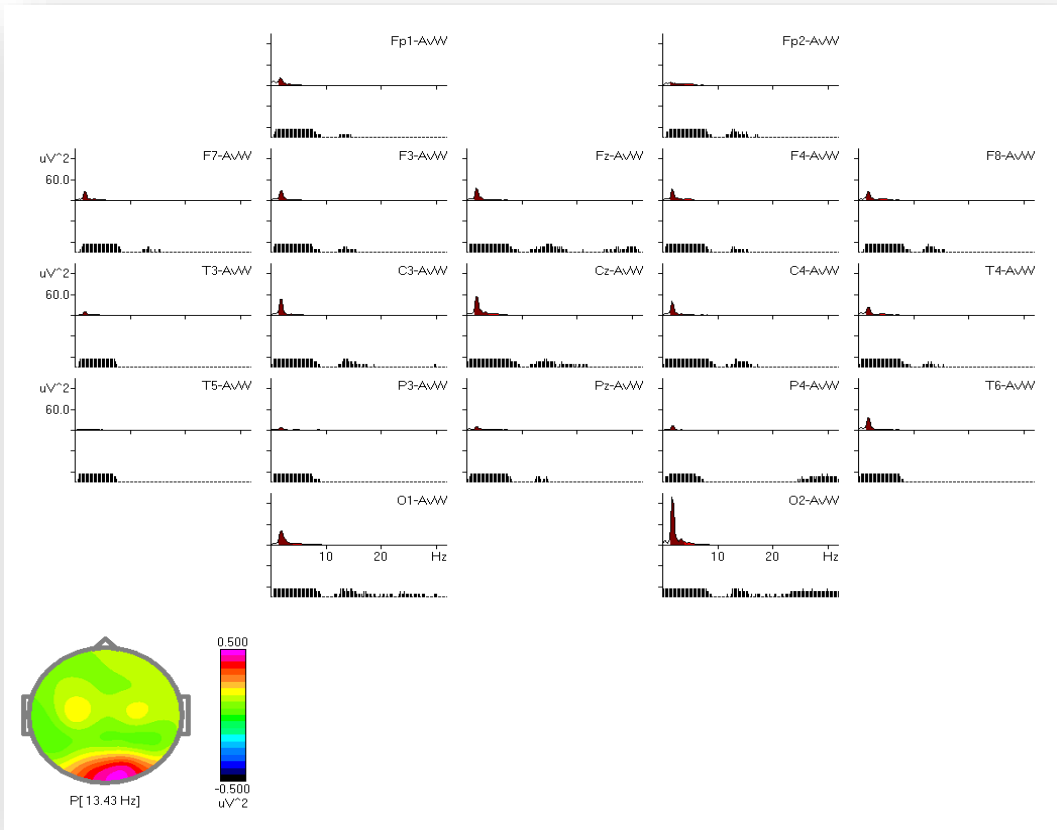

Fig. 19: Z-Score spectra (example 7)

In Fig. 19 above, which shows the FFT compared with norms, we can see that the higher amplitude background rhythms obscure additional focal changes. In this case the information that the qEEG gives us is insufficient and confusing and does not assist in guiding us in the protocol decision.

Example 8:

Epileptic patient who suffers from generalized epilepsy.

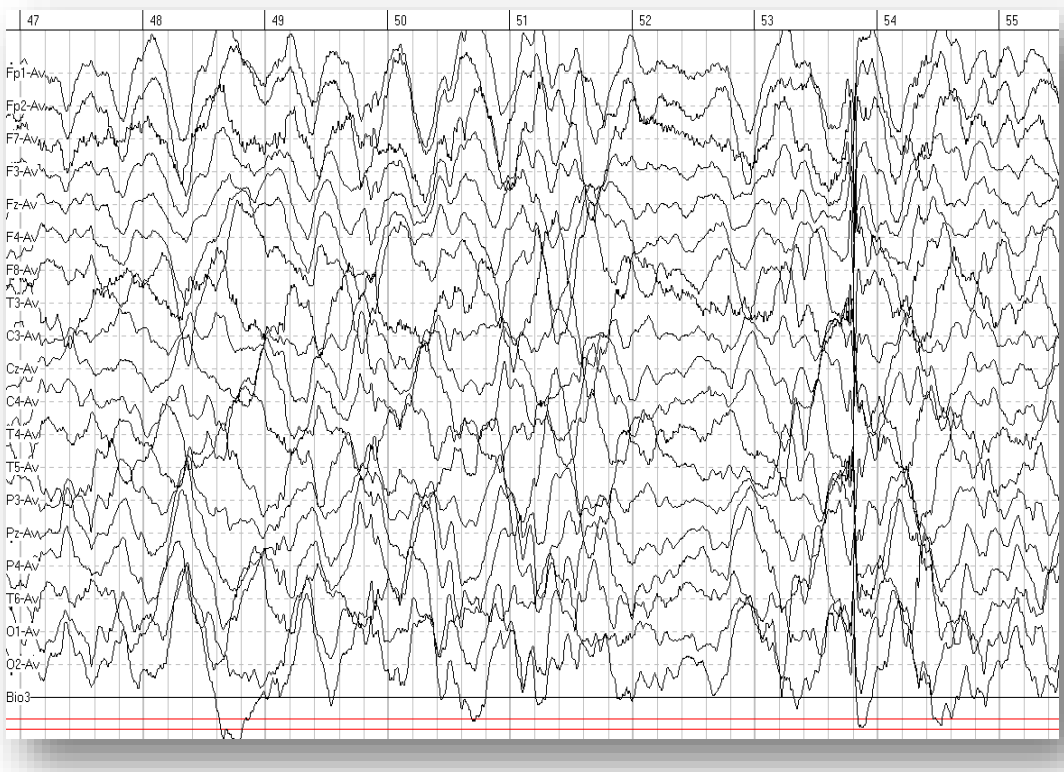

Fig. 20: EEG of an epileptic patient (example 8)

Looking at the raw EEG in Fig. 20 above, we see abnormal slow activity on the right side of the brain followed by a spike-and-wave pattern on the left side.

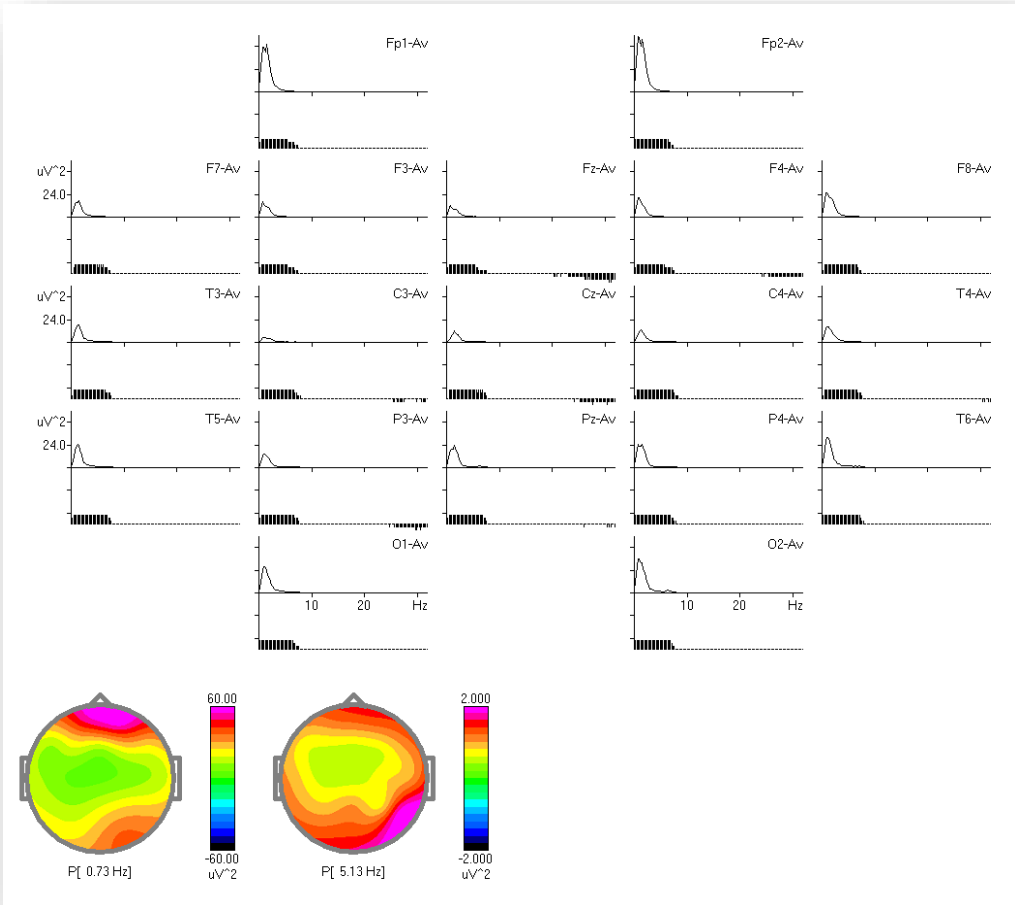

Fig. 21: Z-Score FFT of the epileptic patient (example 8)

In Fig. 21 above, which shows the FFT compared with norms, we can see the slow wave activity in all recording sites. In this case the information that the qEEG gives us does not help in guiding us in the protocol decision.

Example 9:

In Fig. 22 below we see the raw EEG of another epileptic patient, and in it we see a spike-and-wave pattern that occur relatively rarely (only 2 events over a 20 minute recording).

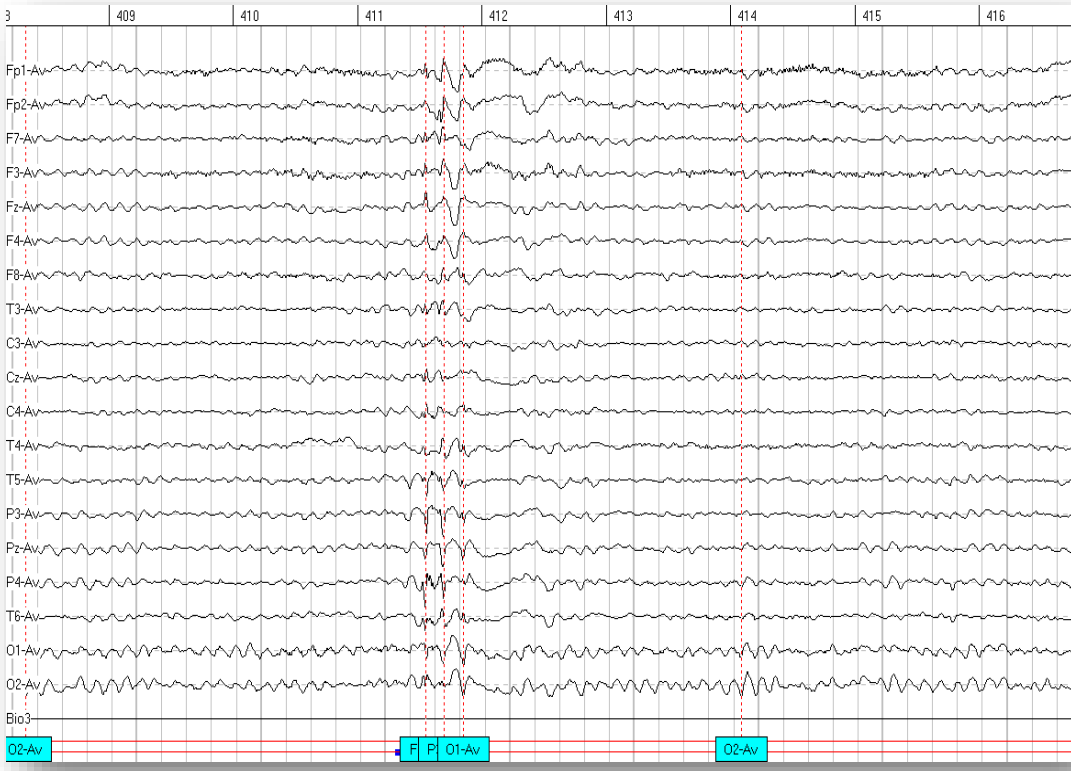

Fig. 22: EEG of an epileptic patient (example 9)

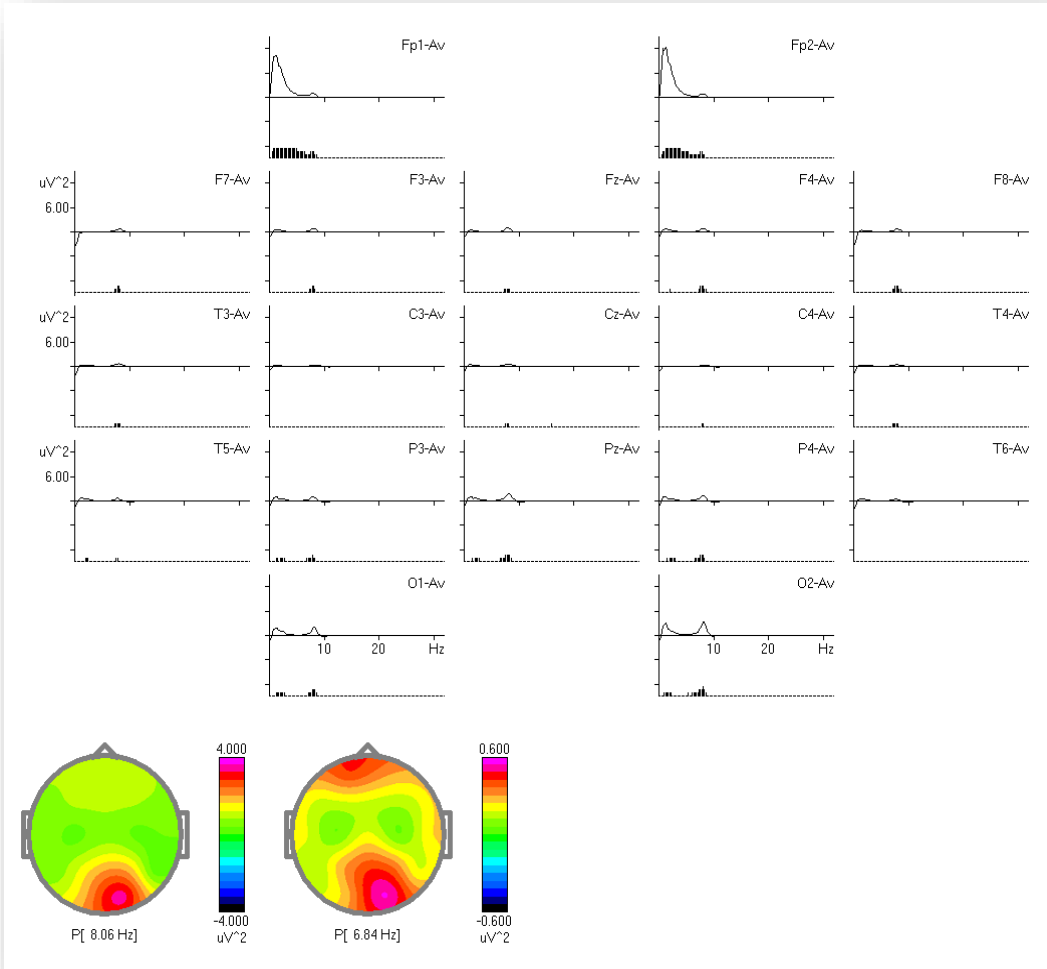

Fig. 23: Z-Score FFT of epileptic patient (example 9)

The Z-Score FFT in Fig. 23 (above) reveals slow activity in all electrode placements. In this case, when the discharges occur relatively rarely, the focus of the discharge is not indicated by the qEEG, and therefore the qEEG is not particularly helpful in deciding on the electrode-placements for the treatment protocol.

3. **Discussion**:

Brainwaves are generally classified according to their frequency, amplitude, and morphology. The FFT divides the raw EEG into brainwave bands according to frequency**,** and even thaen only by fixed frequencies that were pre-defined in the software (Delta, Theta, Alpha, Beta, High Beta,

and Gamma). Other waveforms can be identified only by visual inspection of the raw EEG by shape, some by shape and location on the scalp and some by shape and state at recording: These include K complexes, Vertex (V) waves, lambda waves, and positive occipital sharp transients of sleep (POSTS), spindles, mu rhythm, spikes, and sharp waves. These waveforms that can only be seen in the raw EEG are crucial for the diagnosis of abnormalities.

There are many different types of artifacts: eye blinks, eye movements, muscle activity, ECG and pulse, as well as electrode artifacts. Artifacts can only be identified by examining the raw EEG.

Automatic artifact detection technologies are still limited in their abilities to distinguish special wave forms from artifacts. Often, artifact rejection algorithms require a human element to review and confirm their accuracy. Analyzing data that contain artifacts may lead to a wrong treatment protocol decision.

A trained Therapist can benefit from using advanced algorithms such **as** ICA in the process of cleaning artifacts from the raw EEG. The ICA can be used to separate neural activity from muscle and blink artifacts in spontaneous EEG data. But in using this option, one should keep in mind that:

- The basic assumption of ICA applying to EEG artifact removal is that the time courses of the EEG activity and artifacts are statistically independent. However, some real EEG activity might be correlated temporally with particular artifacts and will therefore also be removed from the raw EEG.
- The correction of the data can change the phase and that will affect the coherence analysis.

Artifacts that accompany epileptic spikes are a regular occurrence and are usually seen with the same polarity in many electrodes. Also, patients who have a generalized seizure disorder frequently have higher amplitude background rhythms, which may be wrongly detected as artifacts by the automatic artifact detection technologies.

In cases of epilepsy, the QEEG is not particularly helpful in deciding on a treatment protocol, for the following reasons:

- When the recorded EEG shows frequent spikes, the QEEG will present a picture of increased activity in all frequency bands in the location of the focus.
- In cases of abnormal slow activity, or a higher-amplitude background activity, the QEEG will present a picture of slow wave activity in all recording sites.
- If the recorded EEG shows rarely occurring epileptiform discharges, the QEEG will not present a picture of increased activity in the location of the focus.

The main point of this paper is that neurofeedback therapists that are using QEEG should have the training and knowelege in interpretation of raw EEG. Reading the raw EEG data in addition to looking at QEEG brain maps and the information obtained in the clinical intake will lead to a good decision regarding neurofeedback treatment protocols.

No software, as sophisticated as it may be, is able to recognize all artifacts and abnormalities. Our suggestion for therapists that want to benefit from the automatic reports is to first learn to scan and interpret raw EEG. For beginners who just started using QEEG, it is strongly recommended to work under the supervision of a QEEG specialist until they feel comfortable in scanning the raw EEG by themselves.

4. Conclusions:

QEEG analysis techniques can provide additional measurements of EEG, including: graphic displays of frequency and voltage, statistical comparisons to normative databases, evoked potentials and coherence.

The QEEG alone as a source for making treatment protocol decisions is insufficient. Consulting the QEEG requires clinicians to also perform at the same a thorough examination of the raw EEG. We, as clinicians, cannot and should not reach any conclusions based on the QEEG alone without referring to its source, the raw EEG. The raw EEG is a source of important information that can be lost in the averaging process. Studying the raw EEG must be done by a qualified expert. The automated tools, sophisticated as they may be, are still incapable of recognizing pathologies like a skilled professional.

Acknowledgements

- To Jay Gunkelman, a great teacher who taught me to look for the story behind every EEG
- To Prof. Juri Kropotov for many years of guidance and continuous support.
- To Dr. Ron Swatzyna for sharing knowledge and EEG samples

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WHAT'S SLEEP GOT TO DO WITH IT? CIRCADIAN RHYTHM SLEEP DISORDER, ADHD AND NEUROFEEDBACK.

Mark Ryan[a*], Trevor Brown[b], Madelon A. Vollebregt[c,d], Martijn Arns[e]

[a] *neuroCare, Sydney, Level 19, 56 Pitt Street Sydney. NSW. 2000. Australia*
[b] *neuroCare, Melbourne, Level 8, 372 Albert Street, East Melbourne. VIC. 3012. Australia*
[c] *Research Institute Brainclinics Nijmegen, The Netherlands*
[d] *Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Centre, Nijmegen, The Netherlands*
[e] *Dept of Experimental Psychology, Utrecht University, Utrecht, The Netherlands*

Abstract

Recent evidence points to the increasingly important role of sleep disturbance in ADHD. Circadian phase delay, resulting in delayed sleep onset, has been consistently described with causality implied for a large subgroup with Attention Deficit Hyperactivity Disorder (ADHD). The likelihood of varied and numerous causations in ADHD, the high prevalence of sleep disorders and the likely etiological/pathogenetic role of sleep disorders for a large subgroup with ADHD encourages a personalized medicine approach, particularly by assessing sleep and identifying biomarkers to assist in identifying subgroups which can enable a more personalized treatment. Psychostimulants are the mainstay of pharmacological treatment of ADHD, but do not assist sleep problems and can in fact exacerbate them. In a large subgroup with ADHD, psycho-education and sleep hygiene, CBTi and chronotherapy also have an important role to play in treating ADHD symptoms associated with sleep disturbance. Neurofeedback (operant conditioning of EEG), may have specific and lasting effects on sleep, and in turn ADHD symptoms, with the effect shown to be mediated via the normalization of sleep. This review article summaries and reports on some of the accumulating evidence for the role of sleep in ADHD and outlines various methods for assessment and intervention.

Keywords: sleep; delayed phase sleep disorder; circadian rhythm; dopamine; vigilance arousal; hypocretins; ADHD; neurofeedback

ARTICLE INFO	
RECEIVED	November 18
REVIEWED	January 19
ACCEPTED	February 19

** Corresponding author.*

Email: mark.ryan@neurocaregroup.com

1. Introduction

Psychostimulant medication remains the mainstay of treatment for Attention Deficit Hyperactivity Disorder (ADHD). Nevertheless, the positive effects on ADHD symptoms often diminish over time (Molina et al., 2009), side effects are common (Wang et al., 2013) and the medications can reduce sleep duration and increase sleep onset latency in some. Concurrent sleep problems have been shown to attenuate the response to stimulants, while conversely longer sleep duration is associated with a better response to ADHD medication (Santisteban et al., 2014; Morash-Conway et al., 2017). Longer duration of sleep is also associated with better response to antidepressant medications in people suffering from major depressive disorder (Arnedt et al., 2016), suggesting to a role for sleep in treatment efficacy.

There is a similarity in the symptoms of sleep disorders and those observed during jet lag, shift-work etc, and the symptoms of ADHD – that is, an inability to maintain focus and attention; impaired learning; behavioral difficulties manifesting as impulsivity and reactivity with a bias towards habitual or auto-regulatory behaviors and mental health symptoms such as anxiety and depression (Wolfson A, Carskadon M, 1998) and self harm (Lui X, 2004)). Children with ADHD are reported to have altered sleep architecture, spending comparatively more time in stage 1 sleep (Diaz-Roman et al., 2016) and also a reduced amount of sleep spindles have been reported (Saletin et al., 2017). More daytime sleepiness is also reported in this group (Langberg et al., 2017). The severity of sleep problems has been shown to correlate with cognitive dysfunction (Sciberras et al., 2015), while delayed sleep onset and poor sleep efficiency has been associated with impulsivity in particular (McGowan and Coogan., 2018). Persistence of childhood ADHD into adolescence and adulthood is predicted by the persistence and severity of sleep problems (Gregory et al., 2017; Cadman et al., 2016). In a recent study, shorter sleep duration correlated with more internalizing and externalizing behavior problems in children and adolescents, with shortened sleep duration being causal of such ADHD symptomatology as inattention, daytime sleepiness and oppositionality (Becker et al., 2018). Conversely, longer sleep duration is correlatively associated with better school performances and cognitive functioning (Astil et al., 2012). Sleep restriction is associated with poorer academic performance (Zerbini and Merrow., 2017) and interventions that have enabled increased sleep duration (e.g. delayed school start times) have reported improvements in mood and academic performance (Boergers et al., 2014; Owens et al., 2010) . Restricted sleep duration is causally linked to inattention in both those with ADHD (Becker et al., 2018; Arns and Vollebregt, in press) and without ADHD (Axelsson et al., 2008; Belenky et al., 2003: van Dongen et al., 2004). Sleep restriction is also linked to mood dysregulation, self-harm and impulsivity (Bernert and Joiner. 2007; O'Brien, 2009.; McGowan and Coogan., 2018) suggesting an important role of sleep interventions in the treatment and prevention of self-harm behaviours and mood disorders. Walker (2017, pages 147-148) suggests that the sleep restriction is associated with both hyper-activation of the dopaminergic striatum and hypo-activation of the prefrontal areas (resulting in emotional and hedonic instability) which may be an aspect of the underlying neurophysiological process manifesting in emotion dysregulation and impulsive behaviour. Disordered breathing in sleep, snoring (e.g., due to enlarged adenoids) and obstructive sleep apnoea (OSA) are associated with both inattention (Sedky et al., 2014) and hyperactivity (Silvestri et al., 2009) with the same relationship also shown in a general population sample (Bonuck et al., 2012). Treatment with tonsillectomy/cpap results in improvement of the ADHD symptoms (Sedky et al., 2014; Johnstone et al., 2001).

2. ADHD and sleep

A clear relationship between ADHD and sleep disturbances has been reported (Diaz-Roman et al., 2008) and on the group level, an association between ADHD and the delayed onset of sleep has been described (Coogan and McGowan, 2017) with delayed onset of sleep being shown as an important factor for at least some

with ADHD (Arns and Kenemans, 2012). Sleep onset insomnia has even been noted in the majority of ADHD patients before the age of three (Van der Heijden et al., 2005) with the strong suggestion that it is the persistence of this sleep disruption over time that eventually manifests in the clinical syndrome of ADHD. Disruption of brain network organisation and functioning involved in sleep and cognitive functioning, may lead to persistence of the symptoms and behaviours identified with ADHD into adolescence and adulthood (Kurth et al., 2016). A psycho-educational intervention to address sleep onset insomnia reported a decrease in ADHD symptoms (Corkum et al., 2016).

One of the causes of a delay in sleep onset is thought to be the absence of strong zeitgebers. Variation in natural daylight is the strongest zeitgeber of the circadian rhythm [for review, see (Roenneberg & Merrow, 2016). Note that the prevalence of ADHD has been shown to vary with daytime natural light exposure, i.e. with solar intensity (Arns et al., 2013). Lighting factors such as domestic lighting sources (LED, halogen and fluorescent lights) and the use of blue light emitting devices shortly before bedtime are associated with suppression and delay of production/release of melatonin (Wood et al., 2012; Cajochen et al., 2011) resulting in delayed sleep onset (Custers et al., 2012; Walch et al., 2016), and night-time blue light exposure has an effect even if eyes are closed (Figueiro et al., 2014). Fixed school/work starting times invariably means that delayed onset of sleep results in shorter duration of sleep (van don Bulch et al., 2004; Walch et al., 2016).

Children's sleep duration has declined by an average of 75 minutes over the past 100 years (Matricciani et al., 2012) and sleep restriction is associated with reduced school performance, impaired executive functioning and behavioural impulsivity (van Dongen et al., 2003). A recent study (Becker et al, 2018) was able to conclude that shortened sleep duration had a causal role in sleepiness, inattention and other features of ADHD symptomatology. Chronic sleep disruption of less than six hours a night is associated with cumulative, significant cognitive and behavioural deficits, of which the person is unaware (van Dongen et al., 2003).

A recent study demonstrated a pathway where evening blue light exposure delays sleep, thereby reducing sleep duration, which, in turn, results in increased teacher-rated symptoms of inattention (figure 1) (Vollebregt et al., Under Review).

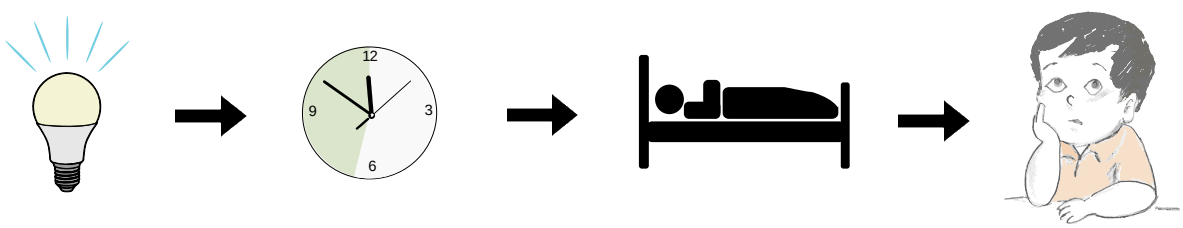

Figure 1. A pathway is depicted where LED light exposure is positively associated with amount of sleep onset delay, which in turn is negatively related to sleep duration, which ultimately leads to worsening of attention.

There are high rates of a range of sleep disorders in the child and adult ADHD patient populations; a 20% prevalence of OSA (Silvestri et al., 2009); a 20% prevalence of restless legs (Konofal et al., 2010; Silvestri et al., 2009) and a 73-78% prevalence of delayed onset circadian rhythm sleep (van der Heijden et al., 2005, 2007; van Veen et al., 2010; Arns et al., 2014). Both snoring (e.g., due to enlarged adenoids) and OSA are associated with core features of ADHD - inattention (Sedky et al., 2014) and hyperactivity (Silvestri et al., 2009; for subclinical disordered breathing sleep, Vollebregt et al., under review)), and specific treatment has been

shown to result in the improvement of ADHD symptoms (Sedky et al., 2014; Johnstone et al., 2001; Huang et al., 2007).

In line with children's declining sleep duration, indicators of drowsiness have increased over recent years; excess theta (4-8Hz) activity or an increased theta to beta ratio (TBR), often described as EEG slowing, have been reported (Arns et al., 2012). An increased absolute power in the theta band is a consistent reported EEG finding in ADHD (eg, Bresnahan et al., 1999; Clarke et al., 1998) and this slower EEG rhythm can be regarded as indicating impaired vigilance regulation and hypo-arousal (Sander et al., 2010). Other EEG phenotypes, such as frontal alpha, also reflecting impaired vigilance, have also been reported in ADHD (Arns, 2012). Sleep onset insomnia and inattention are linked to the excess theta and frontal alpha and spindling excessive beta (SEB) is linked to sleep maintenance problems and impulsivity (Arns et al., 2015). The EEG vigilance model is based on the progressive slowing of the EEG as one drifts towards sleep, with several phenotypes being described (Hegerl and Hensch, 2014) which can be related to a range of clinical conditions. It is this labile or unstable pattern that is often apparent in ADHD (Sander et al 2010), indicating significant drowsiness, and is thought to be the outcome of persistent sleep restriction over time (Beebe et al., 2010).

3. The Visual System and The Circadian System

The circadian rhythm orchestrates the temporal pattern of all biological processes – neuropsychological, behavioral, gene expression, metabolic, hormonal, immunological etc. Genetic variations in clock genes are reflected in individual chronotypes. It is important to consider whole of body entrainment of the circadian rhythm. Entrainment is the process of synchronisation between external/environmental time of day as signalled by zeitgebers, especially light-dark, and internal time. Optimal entrainment is when external time and internal time are approximately equal. Internal timing is orchestrated by the SCN entraining the peripheral cellular and organ clocks, developing a phase relationship between the central and peripheral clocks. Entrainment is readily disrupted by the weak zeitgebers of our urban lifestyle and further disrupted by the social/work demands and other non-sleep promoting behaviours etc, and the related required use of alarm clocks so that internal misalignments and sleep deprivation are common, resulting in social jetlag. Problems with circadian entrainment at any/all levels of the whole body resulting in suboptimal phase misalignment is considered to be related to most of our current health problems (Zee P, 2015)

As indicated above, variation in natural daylight is the strongest of a range of zeitgebers of the circadian rhythm [for review, see (Roenneberg & Merrow, 2016)]. Besides the well-known rods and cones photoreceptor cells in the retina that are responsible for night and color vision, there are also retinal photoreceptor cells that are responsible for the non-image forming perception of light intensity. These cells modulate, among others, the pupillary reflex, the release of melatonin and dopamine, and project via the retinohypothalamic tract to the suprachiasmatic nuclei (SCN) (Schmidt and Kofuji 2009). With this, the retina has a key role in circadian rhythmicity with both melatonin and dopamine being produced in small amounts in the retina (relative to pineal melatonin production), at night and in the day respectively. The retinal and brain regulation of dopamine and melatonin are related. Melatonin and dopamine function as neuromodulators of retinal physiology (e.g. dopamine adjusting for daytime vison, melatonin for night-time vision), with melatonin having the dominant role (Tosini et al., 2012). Retinal melatonin must be suppressed during the day to prevent melatonin intensified photoreceptor oxidation and damage to the retinal cells thought to contribute to macular degeneration, with melatonin also playing a role in the regulation of intraocular pressure. At night melatonin also influences retinal cell replacement and renewal (Tosini et al., 2012).

It is well known that retinal ganglion cells are involved in the pupillary response, respond to blue light intensity and project to the suprachiasmatic nucleus (SCN), resulting in melatonin release from the pineal gland, and the sleep promoting GABAergic neurones in the ventrolateral preoptic nucleus and superior colliculus (part

of the dialectic regulation of the vigilance arousal system), thereby playing a key role in circadian rhythm entrainment of the many physiological body clocks.

The retinal ganglion cells are interconnected with the retinal dopaminergic amacrine cells (Mendoza and Challet, 2014; Stone et al., 2013). Retinal dopamine is thought to play a role in ocular development which in turn may be related to the visual problems reported in ADHD (see below). The DRD4 7R allele is considered to be a genetic risk marker of ADHD (Nikolaidis and Gray, 2010) and is related to a significantly lower affinity for dopamine at the post-synaptic membrane (Ding et al., 2002) and a reduced capacity in the cellular processing in response to illumination (Ashargi et al, 1995). Carriers of this allele are also reported to have greater daytime sleepiness (Jawinski et al, 2016). The expression of DRD4 receptors, which occur in both the retina and pineal gland, varies with the circadian cycle (Kim et al., 2010).

At both the retinal and central levels, melatonin and dopamine are under circadian influence (Parekh et al., 2015) with opposing roles in the regulation of the circadian rhythm (Mendoza and Challet, 2014; Mundey et al., 2005; Iuvone et al., 1978). Dopamine which is predominately synthesised and released in the morning (Iuvone et al., 2005; Doran et al., 1990) inhibits melatonin release and vice versa (Green and Besharse, 2004). Impaired retinal dopamine synthesis is associated with circadian rhythm fluctuations (Wirz-Justice, 1984) suggesting an important role of dopamine in sleep-wake regulation.

Retinal dopamine is produced in the retinal amacrine cells and its synthesis and release are triggered by blue light activation of D2 receptors which also signals CLOCK and BMAL 1 activation (Yujnovsky et al., 2006). Melatonin, however, controls the amacrine sensitivity to blue light. In nocturnal mice for instance, light exposure inhibits behaviour and promotes sleep (Hubbard et al., 2013). Sleep deprivation is linked to HPA-axis activation and reduced sleep duration and slow wave sleep, and increased awakenings. The morning peak of the diurnal variation of cortisol is driven by the suprachiasmatic nucleus (SCN) via corticotropin releasing factor (CRF) signalling which also activates the locus coeruleus (LC) and striatum resulting in increased noradrenaline and dopamine release. This reflects the diurnal control of the Hypothalamic Pituitary Adrenal Axis (HPA axis) which is also has a role in the regulation of sleep and wakefulness. Corticotropin releasing factor (CRF) and cortisol are normally suppressed by melatonin as part of the process of enabling sleep to emerge and melatonin is also involved in the emergence of slow wave sleep and the related growth hormone surge (Buckley and Schatzberg, 2005). The hypocretin neuronal system which receives input from other hypothalamic areas, the environment, the homeostatic state and the limbic system has a key modulating and orchestrating role of these many signals for arousal and sleep, and widespread projections throughout the brain, to enable situation/task appropriate vigilance/arousal – apparent in REM and NREM sleep and sleep to wake transitions as well as appropriate arousal in the awake condition, and thus also providing a systems account of the daytime hypo-arousal and the night time hyperarousal and disordered sleep that are considered core aspects of ADHD (de Lecea L and Huerta R, 2014; Eban-Rothschild A et al, 2017; de Lecea Let al, 2012; de Lecea L, 2012).

There is a complex relationship between the dopaminergic amacrine cells, the retinal ganglion cells, the SCN and the LC, striatum, melatonin and sleep spindles. The LC plays a role in vigilance regulation and there are connections between the SCN and the LC, with the latter also having a role in the generation of sleep spindles (Sinha, 2011). Noradrenaline binding to receptors on the pineal gland promotes the synthesis and release of melatonin by the pineal gland. D4 receptors are expressed in the pineal only when there are increased levels of noradrenaline and, in relation to light exposure and dopamine binding to these receptors, modifies noradrenergic signalling, inhibiting synthesis and release of melatonin, contributing to waking up (Gonzalez et al., 2012).

Genetic influences are also relevant. In addition to the above mentioned DRD4 7R genotype, other genes have been linked to both ADHD and the circadian rhythm. The CLOCK gene is linked to lengthening of the sleep/wake cycle as well as ADHD, bipolar and depressive disorders (Xu et al., 2010; Benedetti et al., 2003); the BMAL1 and PER2 genes are also linked to delayed sleep onset and ADHD, and a decrease in circadian

rhythmicity in those with ADHD compared to healthy individuals (Baird et al., 2012). CLOCK and BMAL1 genes are also diurnally expressed in dopaminergic areas of the brain (ventral tegmental area and substantia nigra) with the SCN clock, via various connections, having the entraining role in modulating diurnal variation in dopamine levels (Mendoza and Challet, 2014). Prenatal and postnatal influences (e.g., long term maternal psychostimulant use) disrupts the developmental alteration in the SCN's progressive reduction of responsivity to dopamine and increased responsivity to blue light and melatonin, disrupting the capacity to adequately set the diurnal rhythm.

CLOCK genes have a role in the modulation of response to dopamine (Roybal et al., 2007). Any change in dopaminergic processes, including those related to psychostimulant use, have the potential to alter aspects of this complex system, including SCN functioning, and CLOCK gene expression both in the SCN and the striatum. Methamphetamine strongly activates dopaminergic and noradrenergic systems in the brain (Chio V, Schenk J, 2012), although there may be a dose dependent variable impact on the circadian rhythm (Honma K, Honma S, 2009). Psychostimulants also alter the expression of CLOCK genes in the ventral striatum and the SCN, potentially contributing to a disruption of circadian control by the SCN (Antle et al., 2012; Baird et al., 2013). Of note is that the striatum is heavily populated with melatonin receptors (Uz et al., 2005). In Parkinson's Disease, a dopamine related degenerative neuropathology, circadian rhythm disruptions with increased SOL, excessive daytime sleepiness and restless legs are prominent (Videnovic and Golombek, 2013; Palma et al., 2013), further supporting the idea that rhythmic diurnal dopamine-melatonin synchronization is important in the 'proper' regulation of the circadian sleep-wake cycle.

Other ocular issues reported in ADHD include glare sensitivity (Kooij and Bijlenga, 2014) with more frequent and longer use of sunglasses; refractive errors such as myopia, astigmatism and impaired depth perception (Gronlund et al., 2007; Granet et al., 2005; Mezer et al., 2012; Kim et al., 2014; Banaschewski et al., 2006). Both dopamine and melatonin have a role in optimising diurnal variations in visual acuity (Tosini et al., 2012) and retinal dopamine deficiency is associated with impaired visual acuity (Jackson et al., 2012). Of particular note, visual acuity has been reported to be improved on stimulant medication (Martin et al., 2008). Disruption in the complex circadian control of retinal melatonin and dopamine has also been implicated in a range of ocular abnormalities such as increased intraocular pressure, susceptibility to photoreceptor degeneration from light damage as in macular degeneration as well as the degree of refractive errors in myopia (Ruan et al., 2006).

Circadian dysregulation of dopamine is linked to a range of impulsive behaviors and actions and vulnerabilities as diverse as sexual activity, substance abuse (Parekh et al., 2015) and drug overdose (Baltazar et al., 2014; Raymond et al., 1992). So, there are a range of peptides, melatonin, corticotrophin releasing factor, noradrenaline and dopamine that have a complex relationship and widespread effects that need to be adequately synchronized for optimal functioning. There is a close relationship between circadian rhythm disruptions and substance abuse and dependence. Alcohol dependence disrupts circadian gene expression (Huang et al., 2010) and circadian genes regulate behavioral responses to drugs of abuse, which directly act on the dopaminergic reward systems also regulated by the circadian system. This suggests an additional mechanism of alcohol's sleep disrupting effects, such as its effects on REM sleep via its metabolite aldehyde.

The reports of melanopsin retinal ganglion and retinal amacrine dysfunction highlights the complexity of the interacting, recursive processes involved and encourages a more complex, whole body account of circadian entrainment and the pathophysiological processes accounting for the circadian sleep dysregulation, dopamine dysregulation and ADHD symptoms, particularly within the largest subgroup of ADHD.

4. Personalised Assessments and Individualised Treatments

Symptoms and diagnostic labels are imprecise indicators of causal processes and the corresponding treatments. Hence treatment guidelines based on diagnosis and symptoms lack precision, resulting in a 'stab in the dark/trial and error' approach to treatment. Typically, such an approach also features a profusion of comorbidities, each requiring different treatments and not necessarily beneficial when combined.

Considering the likelihood that ADHD is the result of heterogeneous pathophysiology and is thus likely to comprise several subtypes, this encourages a personalized assessment approach in order to define the most appropriate treatment.

Given that a large proportion of ADHD involves a sleep disorder, sleep assessments are essential. Sleep can be assessed clinically, using a range of questionnaires, actigraphy assessment and EEG/quantitative EEG (QEEG). Where indicated, an overnight sleep study can also be performed. These methods enable identification of possible sleep problems that might be playing a role in the aetiology/pathophysiology of ADHD and its specific impact on each individual. The markers identified in these assessments can enable greater precision in treatment planning with the likelihood of achieving a better outcome. This process of identifying neuromarkers and biomarkers is a feature of the 'personalized' or 'precision medicine' approach (Olbrich et al., 2015). Such assessments are then used to guide a range of chrono-medical interventions including neurofeedback, psychoeducation about sleep hygiene, CBT for insomnia, advice about caffeine and chronotherapy, cpap and other methods to address obstructive sleep apnoea, melatonin supplementation, medication for restless legs to name just a few.

5. Neurofeedback and sleep

Psycho-education, sleep hygiene, CBTi and chronotherapy play an important role in ADHD treatment. However, melatonin (which also increases sleep spindle density during sleep (Dijk et al 1995) and reduces sleep onset latency (Van der Heijden et al 2007)), and chronotherapy have only medium effect sizes and need to be continued in order to achieve any benefit (Rybak et al., 2006; Hoebert et al., 2009). The largest subgroup of sleep disorders in ADHD features a delayed sleep onset and other markers of failure to adequately establish circadian rhythm sleep. Neurofeedback, the operant training of EEG activity, has been shown to have a specific effect on sleep and ADHD symptoms (Arns et al., 2014). Arns et al (2009) have reported that at the group level, both Frequency Band and Slow Cortical Potential (SCP) neurofeedback for ADHD achieve a large effect size for inattention and impulsivity and medium effect sizes for hyperactivity. A more recent meta-analysis (van Doren et al., 2018) indicates that the effects of standard neurofeedback protocols (SMR, Theta-beta and SCP) are maintained at 3-12 month follow up, suggesting persistent effects of this intervention. This latter study noted further improvement in the follow up period after neurofeedback treatment was finished, supporting the notion that cognitive impairments continue to improve following a sustained period of adequate sleep. The effects of SMR neurofeedback in ADHD have been demonstrated to be mediated by the normalisation of sleep prior to the improvement of ADHD symptoms (Arns et al., 2014). A QEEG informed approach would use neurofeedback to target, as indicated, theta, alpha and/or SEB (Arns et al., 2012).

Effective neurofeedback requires strict adherence to the principles of learning and conditioning – so variables such as latency and specificity of reinforcement, shaping and generalisation are essential for learning to take place. In training sleep spindles in sensory motor rhythm (SMR) neurofeedback, training both amplitude and duration is necessary. SMR neurofeedback increases sleep spindle density during sleep, is associated with reduced sleep onset latency (Hoedlmoser et al., 2008), and increased total sleep time (Cortoos et al., 2010), similar to the effects of melatonin. It is considered that both SCP and SMR neurofeedback train the sleep spindle networks (Arns and Kenemans, 2012), although this finding needs to be replicated in well designed and well

powered clinical trials. The density of sleep spindles shows a circadian rhythmicity similar to that of melatonin (De Gennaro and Ferrare, 2003; Dijk et al., 1997).

6. Conclusion

The converging evidence on ADHD suggests there is most often a delayed phase circadian sleep disorder and, at least for some in this group, there may be a combination of genetic variants determining dysfunction in melanopsin photosensitive retinal ganglion cellular functioning and also genetically-related dysfunction in the amacrine and dopaminergic system. These systems alter the dynamics of the interaction with the light-dark cycle and the adequate entrainment of sleep-wake and arousal regulation physiological processes. The role of neurofeedback is clearly becoming more important for this subgroup with ADHD as understanding and specification of this method and supporting evidence of its efficacy continue to emerge.

Given that there is not just one, but several ADHD related sleep disorders playing a pathophysiological role in ADHD symptomatology, there is a need for comprehensive and personalized assessment of sleep in all patients with ADHD. Such a personalized assessment approach allows for a better characterization of the ADHD subgroup, enabling a more individualized treatment with the expectation of achieving better outcome from a more specific treatment.

An appreciation of the complexity of the neurobiology of sleep, wakefulness and arousal also encourages attention to the role of lifestyle/sleep behaviors and habit factors and the likelihood of dysfunction/dysregulation of a wide range of arousal regulation-related systems, such as the hypocretin system, the retinal ganglion- and amacrine dopaminergic cells, resulting in a systemic disruption of sleep-wake and arousal regulation. This should also encourage a fresh and nuanced look at the model of understanding ADHD, at current methods of treatment and a revision of the dominant approach of psychostimulant medication being the only treatment.

A future article will provide an overview of the model of vigilance/arousal regulation involving hypocretins and the relevance of dysfunction in this complex system manifesting in a range of psychiatric disorders including ADHD. Placing sleep and wakefulness and arousal into the complex system of vigilance regulation will potentially provide more of the jigsaw pieces that enable a more adequate apprehension and comprehension of the many variables and their relationships involved in consolidation of sleep and enabling appropriate wakefulness and arousal and foster further personalization of understanding and intervening in ADHD and psychiatric disorders as a systems/network dysregulation problem, rather than consideration of just one neurotransmitter system.

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