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

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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 remodeling 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

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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 has demonstrated 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 Brodmann'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).

Neuroplastic Restructuring

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 magnitiude 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 a 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, behaviour, social interactions and regulation of emotion (Beauregardet al., 2001).

Neuroplastic restructuring is the term we have applied to the neuorehabilitation 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 utilising 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

Participants

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 ("Delaration 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 unmedicated but several brief periods of supportive counseling 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 carer. 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 participant's 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-administered 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 EEG Procedure

A fitted electrode cap (electro-cap international) with leads placed according to the International 10/20 System was applied to achieve a standardised 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 Kohms was required at all electrode contact sites prior to initiation of recording. EEG signals was digitised 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 standardised tests of five minutes duration; eyes open then eyes closed. Digitised 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 analysed 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) NeuroGuide 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 transitions.

3. Results

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%

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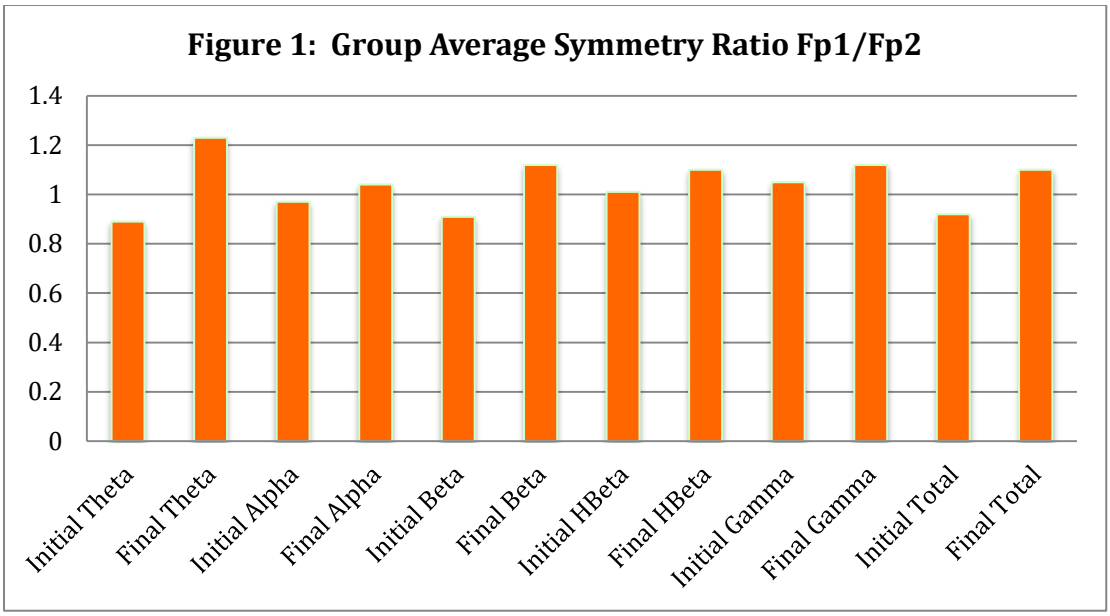

Figure 1 shows the average Fp1/Fp2 ratios of activity measured over all participants. An Fp1/Fp2 ratio less then 1 indicates a right prefrontal cortex dominant asymmetry and a Fp1/Fp2 ratio greater than 1 indicates a left prefrontal cortex dominant asymmetry. In all frequency ranges a shift from a right dominant asymmetry (less than 1.0) to a left dominant asymmetry (greater than 1.0) was observed.

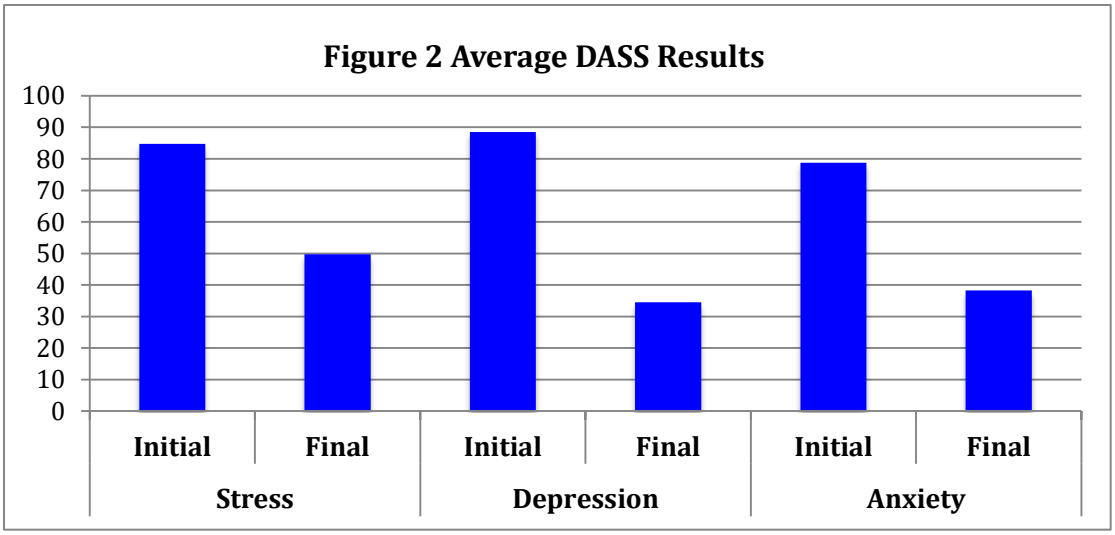

Figure 2: All participants demonstrated significant changes across all DASS categories; stress (p=0.05), depression (p=0.02) and anxiety (p=0.01).

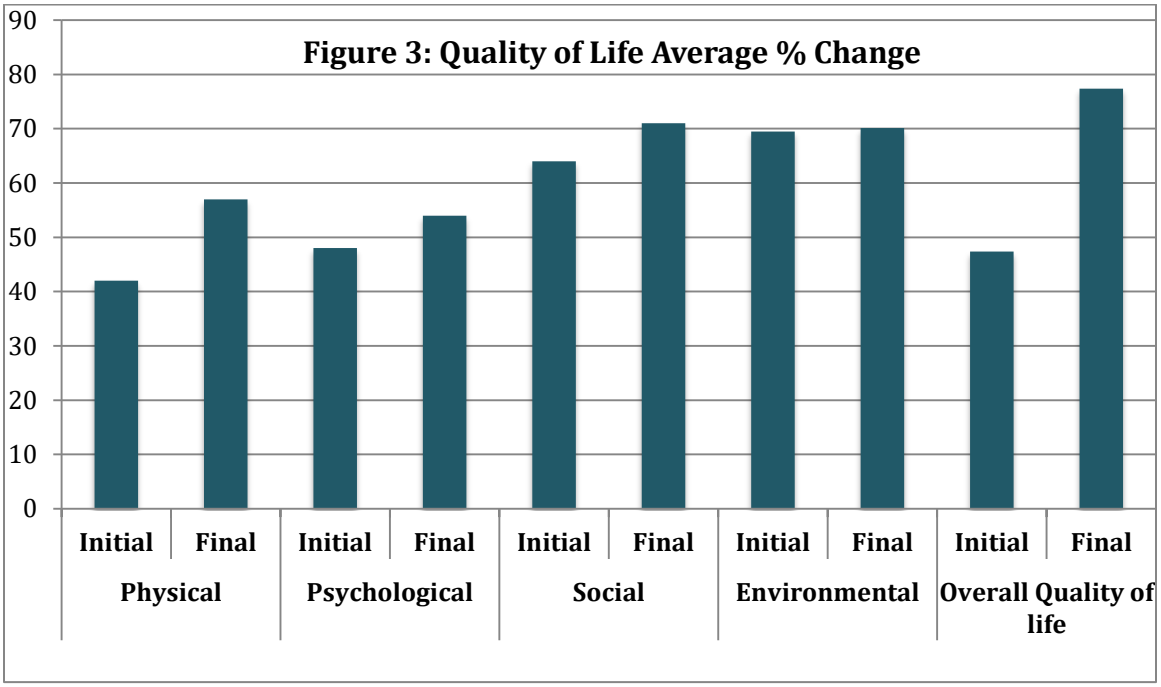

Figure 3 demonstrates the average percentage change in each WHOQOL-100 category. Positive changes were recorded in all categories.
Significant changes were recorded in the physical (p=0.04) and overall health categories (p=0.02).

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).

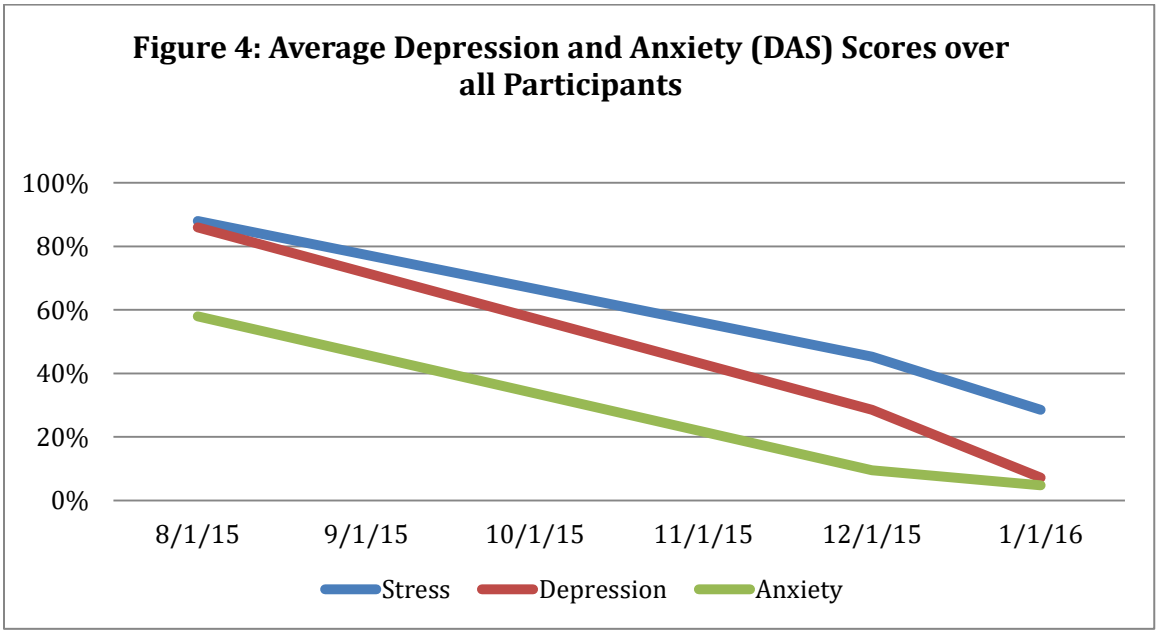

Figure 4: The greatest percentage change was observed in the depression category (54%), followed by anxiety (40%) and stress (34%) respectively.

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
World Health Organisation Quality of Life Checklist 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).

	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 hypoactivation 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 lead 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 utilised 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 operationalizations 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 occurance 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 Asymmetry 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 utilising different stimulation modalities and outcome measures that can provide a window into physiological processes. Paired-pulse TMS studies investigate intracortical 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 the 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:

1. 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.
2. The asymmetry ratio utiilised 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.
3. 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.
4. 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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