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Efficacy of Eeg Neurofeedback Training on Functional Networks in Patients with Depression – An F Mri Study

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ABSTRACT

Depression is one of the most prevalent mood disorders, which also causes significant disruptions in the socio-occupational life of an individual. Aberrant connectivity in the functional networks is an important predictor of vulnerability to depression. The aim of the present study was to examine the efficacy of EEG neurofeedback training (NFT) on functional networks in patients with depression. An experimental pre -post randomized control group design has been used. A sample of 10 patients with mild to moderate depression was taken purposively and assigned to a treatment group (TG) and treatment as usual group (TAU). Patients in the treatment group has received 20 sessions of NFT at the Occipital 1 and 2 scalp locations at a frequency of 3 days a week along with pharmacotherapy. Patients in the treatment as usual group received only pharmacotherapy. Clinical changes were documented on the Hamilton Depression Rating scale and rest state fMRI in TG group after 20 sessions and in TAU group after a period of 2 months. Results indicated that there is a trend in decreased connectivity in default mode network, executive control network, Left fronto-parietal network and right fronto parietal network in treatment group in comparison to treatment as usual group.

KEYWORDS :

Depression is one of the most prevalent mood disorders. It is characterized by diverse symptoms including sad mood, loss of interest, and unhappiness, and shows high co morbidity with other brain dysfunction (Currie and Wang, 2004, DeRubeis et al, 2008). Epidemiological studies have shown that depression is common throughout the lifespan of an individual, with 20% of the population worldwide experiencing a depressive episode during their lifetime and 2–5% of the population being affected by severe depression (Kessler & Berglund, 2005).

On a neural level, altered neural activation patterns have been reported in those areas responsible for processing emotional stimuli (limbic structures, prefrontal regions such as the ventromedial prefrontal cortex) and higher cognitive processes (dorsolateral prefrontal cortex). These havea been associated especially with the onset and persistence of mood disorders such as MDD (Phillips, Drevets, Rauch &, 2003).

Many studies have reported that numerous regions of the brain are affected by depression, and that the symptoms of depression are associated with the dysregulation of distributed neural networks, encompassing cortical regions, rather than the functional breakdown of a single discrete brain region. Thus, to explain the heterogeneous domains of depression symptoms, it is important to use methods that analyze the global functional networks rather than a single region or a local circuit. Functional connectivity, defined as the temporal correlation between spatially remote neurophysiological events is believed to serve as the mechanism for the coordination (or dis-coordination) of activity between different neural populations or systems across the cortex (Friston et al, 1993).

Functional magnetic resonance imaging (fMRI) is a functional neuro-imaging procedure using MRI technology that measures brain activity by detecting associated changes in blood flow. This technique relies on the fact that cerebral blood flow and neuronal activation are coupled. When an area of the brain is in use, blood flow to that region also increases. Resting state functional MRI (R-fMRI) is a relatively new and powerful method for evaluating regional interactions that occur when a subject is not performing an explicit task. According to *Beckmann (2005)* there are eight major functional networks in human brain when it is in resting state. They are *Medial visual cortical, lateral visual cortical, auditory system, Sensory–motor system, Visuo-spatial system*, default mode network*, Executive control and dorsal visual stream*. Recent resting-state functional connectivity magnetic resonance imaging studies have shown significant group differences in several regions and networks between patients with major depressive disorder and healthy controls such as decreased bilateral amygdala and left anterior insula connectivity in an affective network, reduced connectivity of the left frontal poles in a network associated with attention and working memory, and decreased bilateral lingual gyrus connectivity within ventromedial visual regions. (Illya et al, 2011). Increased functional connectivity in Default mode network is also an important biomarker for depression (Sheline Y, 2009) there is slower brainwave activity in the left frontal area in depression. This part of the brain is more inactive and the right frontal area is more dominant. In the left frontal area there is an excess of slow, alpha brainwave activity. This is the pattern that has been classically associated with a vulnerability to depression.

Neurofeedback (NFT) has emerged as one such technique aimed at altering processes in the brain to as to enhance certain cognitive functions. It works on brain waves to improve various aspects of functioning. It involves reinforcement of particular EEG frequencies thus increasing or reducing their occurrence. It is used to modify amplitude, frequency and even coherency of one's own brain waves using operant conditioning methods (Thatcher et al, 1999).

In neurofeedback training, sensors are placed on the scalp and devices are used to monitor and provide moment- to- moment information that is fed back to the individual about his/ her physiological brain activity for purposes of improving brain functioning (Hammond et al, 2011). Neurofeedback treatments for depression (Baehr, Rosenfeld, & Baehr 1997) appear very promising not only in bringing relief from depression, but in modifying the underlying biological predisposition for becoming depressed. Neurofeedback focuses on retraining the brain, for example, reversing the frontal brainwave asymmetry, with the goal of producing an enduring change that does not require people to remain on medication indefinitely. Training often requires about 15 to 20sessions. It is effective in the sense that it has direct access to the underlying vulnerability which can in turn affects the cognitive areas and mood.

Four major processes by which NFT effects changes in the brain are (Collura, 2003) are auto regulation, Operant conditioning, Intention to be still, focused and relaxed and Post reinforcement synchronization.

Aim:
The aim of the present study was to examine the effect of EEG Neurofeedback on fMRI in patients with depression.

Hypothesis:
There will be no significant difference on the pre- post EEG NFT fMRI results in the patients with depression.

Design:
An experimental pre- post randomized control group design will be used.

Sample:
Ten patients diagnosed with mild-moderate depression will be screened and referred by Department of Psychiatry, NIMHANS and 5 each will be randomly assigned to TG and TAU group. The TAU group will include those patients who have been diagnosed as mild to moderate depression and are on routine medication.

Tools:
Socio- demographic data sheet

Mini-international neuropsychiatric interview (MINI Screen) (Sheehan, et al., 1998).

Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960)

Rest state - Functional Magnetic Resonance Imaging for assessment of connectivity in the brain networks

Procedure
Pre training assessment
Assessment was carried out on all the ten patients using sociodemographic data sheet and the clinical scale for depression. Resting state fMRI also been carried out for all the ten patients.

Neurofeedback training
Twenty sessions of NFT were administered for 5 patients in the TG. The patients were given alpha theta training on the O1 (occipital 1) and O2 (occipital 2) channels of Neurofeedback in the 20 sessions. The brain wave pattern were amplified by the machine and gave feedback to the patients by way of visual signals. Each session was of the duration of 20-40 minutes, and 3 sessions per week. Initial 5 sessions were kept at 20 minutes each for the patients to get acquainted to the NFT. The next 15 sessions were of 40 minutes duration.

Post training assessment
The post assessment was done for the treatment group on the completion of the 20 sessions of neurofeedback training and for the treatment as usual group one and half months to two months after the pre assessment**.**

The scores were analyzed using descriptive statistics to compare the two groups on socio-demographical variables. For comparing independent means that is between TG and TAU group Mann Whitney U test was used. The *f* MRI scans were pre- processed using the FSL software library. The method of analysis used is referred to as MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) 3.0. This uses Independent Component Analysis to decompose a single or multiple 4D data sets (time x voxel) into different spatial and temporal components. For ICA group analysis, MELODIC used the temporal concatenation approach. Further dual regression was done.

Separately a repeated measures design was adopted and single group paired difference test (paired T- test) was conducted for to find if the average difference between the two treatment conditions is different .The scores were analyzed using descriptive statistics to compare the two groups on socio-demographical variables.

RESULTS AND DISCUSSION
Comparison of Sociodemographic details of TG and TAU
The mean age of the patient in TG was 25.20 ± 2.28 and that of TAU group was 37.60± 5.32. There was a significant difference found between the TG and TAU group with regard to age. On statistical analysis no significant difference was found between the TG and TAU group on the basis of education. Similarly, there was no statistically significant difference between TG and TAU group based on gender.

Clinical details of depression
The level of depression for TG and TAU were 13.00± 2.64 and 14± 2.73respectively. Hence there is a significant difference in age of onset of illness there is no significant difference between TG and TAU with regard to mean duration of the episode and level of depression.

Pre -post fMRI results of TG and TAU group
Dual regression analyses (using 5000 permutations) for detecting connectivity differences in 5 resting state networks revealed trend-level differences ($p<0.05$ uncorrected) across the two time points (pre and post) in the experimental (TG) and control (TAU) groups. These results that depict interesting trends in alterations of connectivity following treatment in the various resting state networks are described below:

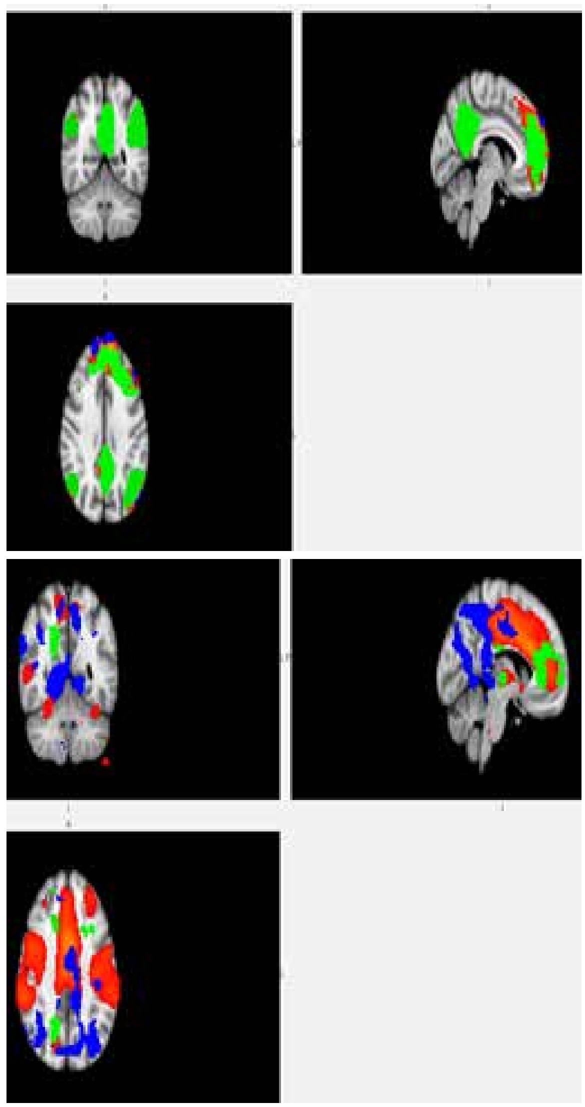


Figure 4.14 Reduced functional connectivity in DMN for TG (above, n=5) in comparison to TAU (below, n=5). Red-yellow color represents resting state of DMN for the whole group, green voxels represent clusters of decreased functional connectivity and blue voxels represent clusters of increased functional connectivity at P value of <0.05 (K=5 voxels), uncorrected. All the images are co-registered to MNI template, and images are shown in radiological convention.

In comparison to pre-treatment rsfMRI, the post-treatment rsfMRI revealed trend-level reductions in connectivity throughout all the nodes of the DMN in the experimental group (TG). However, such a trend was not visualized in the control group.

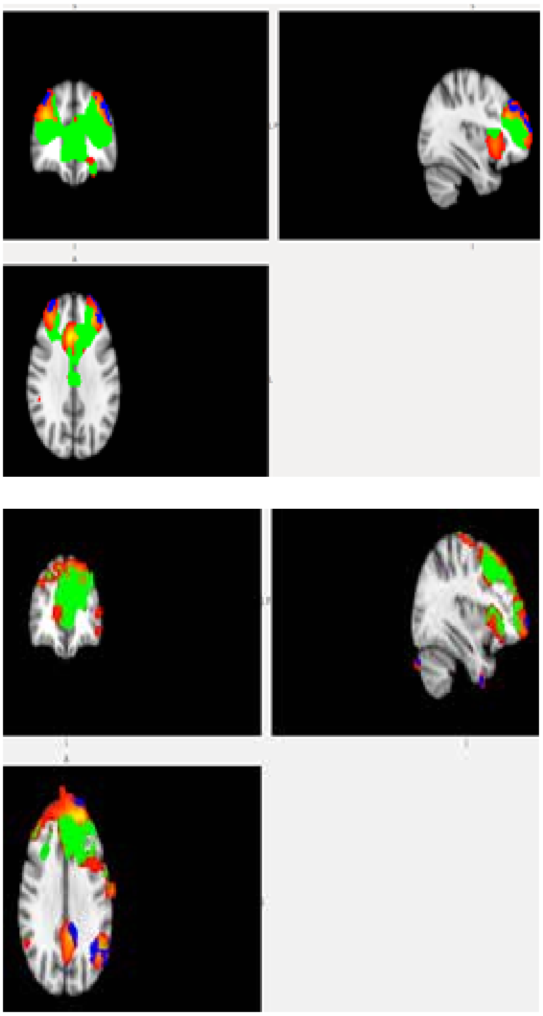
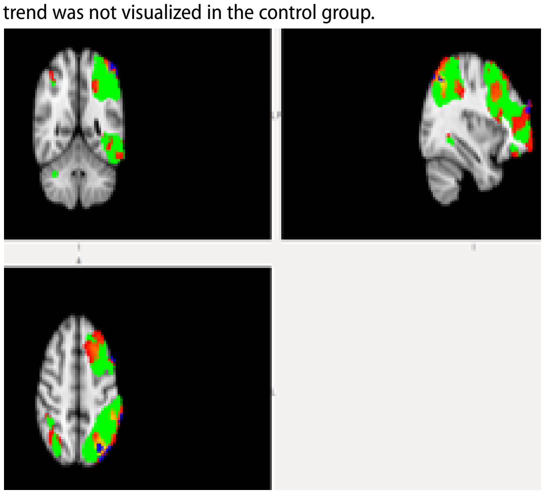


Figure 4.15 Reduced functional connectivity in Executive control network (ECN) for TG (above, n=5) in comparison to TAU (below, n=5). Red-yellow color represents resting state of ECN for the whole group, green voxels represent clusters of decreased functional connectivity and blue voxels represent clusters of increased functional connectivity at P value of <0.05 (K=5 voxels), uncorrected. All the images are co-registered to MNI template, and images are shown in radiological convention.

In comparison to pre-treatment rsfMRI, the post-treatment rsfMRI revealed trend-level reductions in connectivity throughout all the nodes of the ECN in the experimental group (TG). However, such a trend was not visualized in the control group.



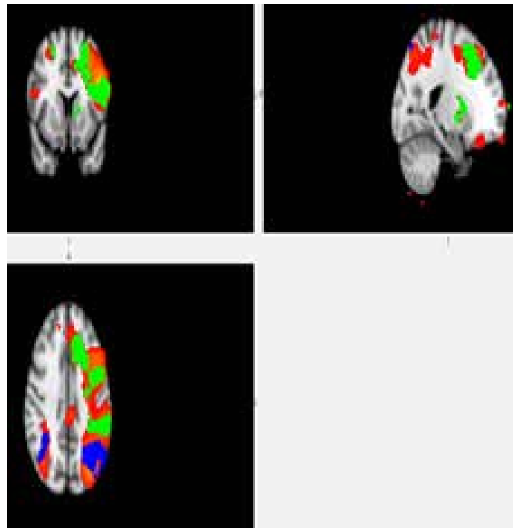


Figure 4.16 Reduced functional connectivity in Left Fronto-Parietal network for (FPN) TG (above, n=5) in comparison to TAU (below, n=5). Red-yellow color represents resting state of Left Fronto-Parietal network for the whole group, green voxels represent clusters of decreased functional connectivity and blue voxels represent clusters of increased functional connectivity at P value of <0.05 (K=5 voxels), uncorrected. All the images are co-registered to MNI template, and images are shown in radiological convention.

In comparison to pre-treatment rsfMRI, the post-treatment rsfMRI revealed trend-level reductions in connectivity throughout all the nodes of the left FPN in the experimental group (TG). However, such a trend was not visualized in the control group

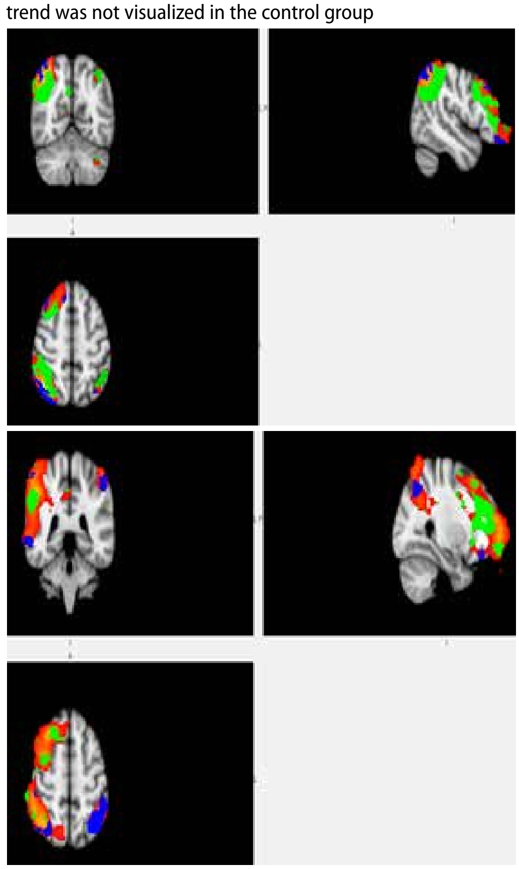


Figure 4.17 Reduced functional connectivity in Right Fronto-Parietal network for (FPN) TG (above, n=5) in comparison to TAU (below, n=5). Red-yellow color represents resting state of Right Fronto-Parietal network for the whole group, green voxels represent clusters of

decreased functional connectivity and blue voxels represent clusters of increased functional connectivity at P value of <0.05 (K=5 voxels), uncorrected. All the images are co-registered to MNI template, and images are shown in radiological convention.

In comparison to pre-treatment rsfMRI, the post-treatment rsfMRI revealed trend-level reductions in connectivity throughout all the nodes of the right FPN in the experimental group (TG). However, such a trend was not visualized in the control group.

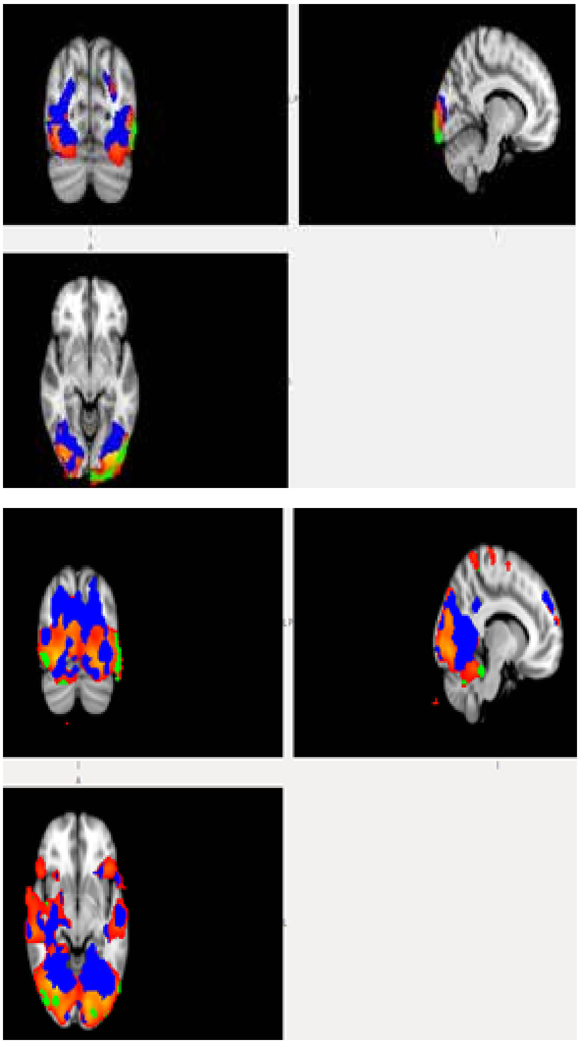


Figure 4.18 Reduced functional connectivity in Lateral visual network for both TG (above, n=5) and TAU (below, n=5). Red-yellow color represents resting state of Lateral visual network network for the whole group, green voxels represent clusters of decreased functional connectivity and blue voxels represent clusters of increased functional connectivity at P value of <0.05 (K=5 voxels), uncorrected. All the images are co-registered to MNI template, and images are shown in radiological convention.

In comparison to pre-treatment rsfMRI, the post-treatment rsfMRI revealed trend-level reductions in connectivity of the lateral visual network in the experimental group (TG) as well as in TAU group.

In the pre-post fMRI of Default mode network (DMN) a trend towards more reduced functional connectivity was seen in the TG group comparing to TAU. Literature reveals that ruminative aspects of depression such as pervasive feelings of sadness, guilt, and worthlessness would be associated with abnormally hyper connected default-mode network (Greicius et al, 2007). Increased functional connectivity in medial prefrontal portions of the network implicated in self-referential and emotional processing (Fossati et al 2003; Gusnard et al 2001) .In the TG group more widespread reduction in connectivity could be seen along with connecting all nodes of DMN. Since decreased connectivity was more in TG than in TAU, this could be hypothesized that the trend for reversal of abnormal connectivity in TG is a result of NFT.

Executive control network (ECN) ECN is involved in cognitive control and decision-making and is known to be impaired in depression (zeng, 2012) .Increased resting-state functional connectivity in the ECN is seen depression (Sheline Y, 2010). In the pre-post fMRI of ECN a trend towards more reduced functional connectivity was seen in the TG comparing to TAU group. In the TG more widen and spacially well organized decrease could be seen comparing to TAU. This trend in decrased connectivity is in line with the significant improvement in executive functions in TG comparing to TAU group.

Increased connectivity within a frontoparietal–posterior cingulate cortex–precunous network was specifically associated with cognitive anxiety and is related to increased spontaneous negative cognition (e.g., worry, pessimistic cognitions) (Bijsterbosch et al, 2014). In the pre-post fMRI of FPN a trend towards more reduced functional connectivity was seen in the TG comparing to TAU, which tends to be related to decrease in the worry cognitions associated with depression. Since the trend toward reversal of abnormal connectivity could be seen more in TG than TAU, it could be attributed to NFT.

Lateral visual network included the occipital pole extending laterally towards the occipito-temporal junction, encompassing non-primary regions of visual cortex, which has an important role in visuo-spatial attention. In the current study both TG and TAU had decrease in functional connectivity in Lateral visual network.

Hence in conclusion, fMRI results indicate that there was more widespread decrease in DMN, ECN, right and left FPN functional connectivity in TG in comparison to TAU.

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