Original Article

Study of Frontal Alpha Asymmetry in Mild Depression: A Potential Biomarker or Not?

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Abstract

Background: Depression, despite being the most common of mental illness lacks any quantifiable and absolute biomarker. Frontal alpha asymmetry (FAA) is proposed as biomarker of depression both in resting and activated state. Yet, the location of extraction of alpha, clinical utility as well as validity of FAA is uncertain. With aim of obtaining clarity on this confusion we conducted this study. **Methodology:** Electroencephalographic frontal alpha power was calculated in patients of depression (n = 24) and compared with healthy controls (n = 17) for the assessment of FAA. Both groups were studied for resting phase and activation phase changes in FAA. For activation phase, auditory stimuli in the form of Indian classical music were used. **Results:** Frontal alpha power was measured across FP1, FP2, F3, F4, F7, and F8. Mean powers were compared in resting (before), activated (during) and postactivated resting stage (after). FAA was statistically significant in F7–F8 pair of electrodes and on F7 electrode when compared between cases and controls. **Conclusion:** Quest for biomarker for depression churned out FAA as frontrunner. Despite of vast amount of research on it, practical utility eludes us. We need to revisit our approach from conventional search of the diagnostic biomarker; as FAA might reflect component of depression but not totally disorder. In our opinion, we are not yet ready for it and have a road ahead to travel.

Keywords: *Alpha rhythm, biomarker, depressive disorder, electroencephalography, frontal alpha asymmetry*

Introduction

Depression is one of the most taxing mental illness regarding global burden and days affected life years.[1] Regarding remission, it is interesting to observe that we have some space left for "normalcy of illness", and rating scales for depression do not have cutoff of zero for remission. The clinical endpoint of depression is often chosen by the patient by stating how he/she feels or back to functioning.[2] Even score on rating scale are subjective account of patient measured objectively. In other branches of medicine, biomarkers are invariably used to measure outcome of treatment or define remission. We have seen many such biomarkers especially in the field of cancer. These biomarkers are either reflection of normalcy or underlying pathological changes in person.[2] Use of biomarker brings more of objectivity in understanding and management. However, many response or remission indicated by biomarker does not coincide with clinical response or remission.[3] In mental health, this holds true due to heterogeneity of disorders, differential response to treatments and varied subjective interpretation for what remission or response means. Hence, search of biomarker in psychiatry has been difficult. There is ongoing research for the quest of biomarkers of depression.

Peripheral biomarkers hold some promise, but with limited utility due to lack of specificity and sensitivity.[4,5] Similarly, functional imaging and electroencephalography (EEG)

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also has shown variable results.[6] Considering all the research ongoing in the field of biomarkers of depression, EEG is one of the most cost-effective, noninvasive and largely available tool for clinicians.

There is evidence to suggest predictive the value of alpha and theta band as well as alpha asymmetry and theta asymmetry in depression.[7,8] There are certain measures calculated from quantitative assessment of EEG which are proposed as biomarkers.[8,9] Frontal lobe of brain especially midline region, is highlighted in the quest for physiological correlates of depression.[10] Lower alpha activity in the right prefrontal cortex and higher alpha activity in the left prefrontal cortex is assumed to be associated with depression where higher alpha activity reflects resting, nonactive state.[11]

For what sounds so promising in a theoretical sense may not always translate into actual findings. There is no clear evidence yet to put frontal alpha asymmetry (FAA) as biomarker of depression. Meta-analysis[12] suggests moderate level of correlation (r = 0.19) between depression score and FAA measure at F3-F4; however, it was convenient to include only F3-F4 and exclude other scalp site. There is further need of research and across all frontal electrode. We additionally also explore correlation of resting and activated alpha activity as well. With all this in mind, we devised current study and aimed to explore these lacunae.

Methodology

Site and study design

It's an unblinded case control study with consecutive sampling. Samples were recruited from psychiatry outpatient department of a tertiary care municipal teaching hospital in suburban Mumbai, Maharashtra, India.

Participants

The research proposal was approved by the Institutional Ethics Committee before commencing the study. A total of 24 right-handed participants diagnosed with Major Depressive Disorder as per DSM 5,[13] rated mild on Hamilton Depression Rating Scale (Score range 8–13) were enrolled in study. Age range of sample was 18–45 years, with age, gender and handedness-matched controls. Out of 24 participants in control group, 7 had to be excluded due to multiple interfering artifacts. All participants underwent participatory introductory session, providing aims, and objective of the research. Participants were given information sheet and their doubts were clarified about study. Participants were given appointment for recording data after getting written informed consent and screening for study criteria. Only right-handed individuals were included for study and Chapman and Chapman was used to determine handedness.[14] Participants with a history of significant head injury, epilepsy, concussion, electro-convulsive therapy, personality disorder, being treated with mood stabilizer, benzodiazepines or any other psychotropic medications, and patient with suicidal ideation (although participation in current psychotherapy was allowed). For cases, a patient diagnosed with major depressive disorder (DSM5) without any other psychiatric comorbidity by two independent psychiatrists was recruited. Controls were also interviewed for screening for any psychiatry illness and rated on Hamilton Depression Rating Scale (Score <07)). Controls with diagnosis of lifetime depression on Mini International Neuropsychiatric Interview 6.0 were also excluded.

Procedure

EEG were recorded at resting phase and activated phase using a noninvasive 32-channel EEG machine and international electrode placement system of 10–20. Both phase recordings were done in one setting, activation phase was recorded using music as stimuli. Participants were seated in a sound-attenuated, dimly light room with ambient temperature with the experimenter. Noise canceling headphones were used for listening to music. EEG was recorded before, during and after session of listening music. Music session lasted for 20 min against before and after recording of EEG lasted for 10 min only. For uniformity, during whole process subjects were asked to close the eyes.

Stimulus

Music was selected for activation phase. Music is complex stimuli, hence simpler form, instrumental musical was selected. Indian classical music uses basic eight tone of music in simplest form. Another uniqueness of Indian classical music is assignment of specific time of day to sung respective "raga", which is based on musical valance of respective "raga". Owing to these reason we selected Indian classical music as stimuli. To avoid bias, Rag Bhairavi was chosen as it is most time neutral. Raga Bhairavi uses "KDha and KNe" as soft notes.

EEG data collection and reduction: a set of data was collected using a 32-channel EEG machine (Nmx 32 series, Medicaid Systems, Mohali, India) using the international 10–20 system electrode placement. For ocular artifact rejection, during resting state, two electrooculogram channels, vertical, and lateral were used. The impedances were kept below 10K Ω. Amplification and filtering of data was done before digitization. EEG data were acquired with auricle as reference point. Epoch with movement and signal discontinuities were removed by visual inspections of

each data file. Custom scripts in Matlab (The Mathworks Inc., Natick, MA) were used for data reduction and artifact rejection algorithm was used for segments with large fast deviations in amplitude that missed manual inspections. Each 1-min block was epoched using Hamming window followed by the application of Fast Fourier Transform to artifact-free epochs. Total alpha power (8–13 Hz) extraction was done from power spectrum for each 10-min resting state session (before and after) and all 20 min of activated session. Alpha asymmetry was calculated by the subtraction of right natural log transformed score from homologous right score, i.e., FP1 and FP2, F3 and F4, and F7 and F8. Higher asymmetry score is assumed to reflect greater left activity or relatively greater right alpha.[15] We analyzed specific subset pairs (frontal: F3-F4, F7-F8) corresponding to regions commonly studied.[16]

Results

We evaluated 24 cases (15 females, 09 males) and 17 controls (11 females. 06 males). Mean age of the cases was 34.82 (±11.05) years and that of controls was 29.52 (±09.80) years. Frontal alpha power was measured across FP1, FP2, F3, F4, F7, and F8. Mean frontal alpha power was compared while resting (before), activated (during), and post activated resting stage (after). There was no statistically significant difference between the corresponding frontal electrode when compared before, during and after in both cases as well as controls [Table 1]. Further, we calculated alpha power asymmetry in cases between respective paired electrode (FP1–FP2, F3–F4, F7–F8). Alpha power calculated were compared on respective electrodes and difference of power was statistically significant across F7-F8 and not across FP1-FP2; F3-F4. In pair F7-F8, significance was observed on all three phases of recording (Before activation, during activation and after activation) [Table 2]. Comparison of difference of alpha power across pair of electrodes in controls did not reveal any statistical difference across any pair or any phase of recording [Table 3]. Subsequently, we compared respective electrode's mean alpha power difference between cases and control, revealing no statistical difference across any electrode except F7. Electrode F7 had statistically significant difference in all before activation, during activation, and after activation phase [Table 4].

Discussion

We examine the relationship between frontal alpha power asymmetry and depression during a resting state and a musically valance task using Indian classical music with aim to assess the feasibility of FAA (resting and activated) as biomarker in depression.

We made three hypotheses for assessment of FAA as biomarker in depression

1. FAA (left <right) would be specific for patients of mild depression when compared with controls
2. Frontal alpha activity would differ in resting and activated state in patients with mild depression
3. Frontal alpha power difference would be significant on respective electrodes of cases and controls.

Many researchers studied FAA in perspective of neuroanatomical correlation in search to pinpoint anatomical basis of depression. Zotev *et al*.[16] compared electroencephalographic FAA with functional magnetic resonance imaging using blood oxygen level–dependent concurrently on same patient to understand neuroanatomical correlation. Study found spatial correlation in the left lateral orbitofrontal cortex, the left middle temporal gyrus, the left amygdala, the right medial frontotempolar cortex, the left insula, the right hippocampus, the right parahippocampal gyrus,

Table 1: Mean alpha power across various electrode among case and control

Electrode	Before activation	During activation	After activation	χ^2	*P* (Friedman test)
Cases					
FP1	3.12±4.62	2.84±4.32	3.17±5.28	1.75	0.417
F7	2.41±2.50	2.29±2.66	2.47±2.98	4.00	0.135
F3	3.21±3.53	3.14±3.52	3.30±3.47	2.083	0.353
FP2	2.89±3.78	2.21±2.30	3.00±5.05	1.583	0.453
F8	1.78±1.53	1.83±2.24	1.80±2.28	0.250	0.882
F4	3.46±3.38	2.94±3.01	3.11±3.26	3.083	0.214
Control					
FP1	2.38±1.73	3.85±4.59	2.67±1.96	0.118	0.943
F7	1.12±0.49	1.32±0.71	1.19±0.66	0.471	0.790
F3	2.57±1.34	2.93±2.26	2.51±1.80	0.824	0.662
FP2	2.60±1.49	2.59±1.57	2.62±1.66	0.825	0.661
F8	1.50±1.41	1.49±1.31	1.48±1.39	0.118	0.943
F4	2.43±1.31	2.44±1.49	2.48±1.58	1.529	0.45

Table 2: Mean of difference in alpha power across pair of electrodes in patients of depression

Stage of EEG recording	FP1	FP2	Difference	df	*P* (*t*-test)
Before activation	3.12±4.62	2.89±3.78	0.23±1.46	23	0.45
During activation	2.84±4.32	2.21±2.30	0.63±4.10	23	0.46
After activation	3.17±5.28	3.00±5.05	0.17±0.69	23	0.22
Stage of EEG recording	**F3**	**F4**	**Difference**	**df**	***P* (*t*-test)**
Before activation	3.21±3.53	3.46±3.38	−0.23±2.13	23	0.58
During activation	3.14±3.52	2.94±3.01	0.21±1.40	23	0.48
After activation	3.30±3.47	3.11±3.26	0.18±1.05	23	0.41
Stage of EEG recording	**F7**	**F8**	**Difference**	**df**	***P* (*t*-test)**
Before activation	2.41±2.50	1.78±1.53	0.63±1.48	23	0.04*
During activation	2.29±2.66	1.83±2.24	0.46±1.06	23	0.04*
After activation	2.47±2.98	1.80±2.28	0.67±1.51	23	0.04*

*$P<0.05$

Table 3: Mean of difference in alpha power across pair of electrodes in controls

Stage of EEG recording	FP1	FP2	Difference	df	*P* (*t*-test)
Before activation	2.38±1.73	2.60±1.49	0.28±1.36	16	0.40
During activation	3.85±4.59	2.59±1.57	1.27±4.51	16	0.26
After activation	2.67±1.96	2.62±1.66	0.05±0.08	16	0.73
Stage of EEG recording	**F7**	**F8**	**Difference**	**df**	***P* (*t*-test)**
Before activation	1.12±0.49	1.50±1.41	−0.37±1.26	16	0.24
During activation	1.32±0.71	1.49±1.31	−0.18±1.30	16	0.57
After activation	1.19±0.66	1.48±1.39	−0.29±1.18	16	0.32
Stage of EEG recording	**F3**	**F4**	**Difference**	**df**	***P* (*t*-test)**
Before activation	2.57±1.34	2.43±1.31	0.13±0.73	16	0.46
During activation	2.93±2.26	2.44±1.49	0.48±2.18	16	0.37
After activation	2.51±1.80	2.48±1.58	0.03±0.75	16	0.88

the left pregenual anterior cingulate cortex, and the right amygdala.[16] Above findings displays widespread anatomical basis of depression. Clinically, depression in itself is heterogeneous entity, differing in its presentation patient to patient; both could explain inconsistency of FAA findings obtained in our study.

Our finding on FAA is inconsistent across electrode not only in case but also in control. Similar inconclusive results were also found in many previous studies, where the comparison between depressed and nondepressed individual was made by measuring frontal alpha activity at resting stage;[17-21] in addition, inconsistent pattern of findings was also reported in frontal alpha activity when calculated from average, Cz, and lateral mastoid references.[22] A recent metanalysis[23] discusses the FAA research in depression to be very heterogeneous with small effect size. Although we used auricular reference only, we failed to obtain consistent finding with respect to FAA. In an interesting study by Sun *et al*.,[24] it is concluded that, the neuromodulation which impacts affective circuits, modulates FAA, which in turn modulates emotions and behavior. We investigated only cases with mild depression and our finding to certain extent suggest that FAA association with depression may be relevant to subsyndromal cases of depression.[25]

Statistically significant finding at F7–F8 level is partially in line with two meta-analyses[10,12] where analysis of 26 and 19 (respectively) studies shown mild-to-moderate correlation (r = 0.26 and r = 0.19, respectively). However, same time both meta-analyses could not explain heterogeneity of FAA across various pair of electrodes. Most of the study chosen for meta-analysis had statistically significant difference across F3–F4 in contrast with our result. However, few studies also have shown significant difference in F7–F8 and not in other. In addition, Thibodeau *et al*.[10] point out that such inconsistent finding may be due to publication bias, journal or researcher favoring positive studies for publication. A recent EEG research in depression[26] finds inconclusive evidence, and further hypothesized of different reference electrodes and possible gender differences which held true at static recording in recent study.[27] The emotional challenge task assumes statistically significant consistency across reference modes, concurring hypothesis that emotional challenge produces frontal alpha activity asymmetry in patients of depression.[27] While our study gives evidence that musical valance does not produce asymmetry in patients of depression. Meaning FAA in activated state is not consistent across various stimuli but largely dependent on nature of stimulus, and in turn processing area of brain.

Our study found statistical difference in FAA across F7-F8 pair, but failed to find on PF1-PF2 and F3-F4 pairs, partially accepting first hypothesis. Testing second hypothesis, there was no statistical difference in any electrode (FP1, FP2, F3, F4, F7, and F8) in resting as well as stimulated stage could be found. This finding is replicated in cases as well as controls. Final hypothesis was also partially acceptable, as mean alpha activity on F7 electrode had statistically significant difference in cases and controls. Summarizing, on basis on our hypothesis, we could not be certain about specificity of FAA as diagnostic indicator of depression. Resent meta-analysis suggests limited value of FAA in diagnosis and as biomarker for depression.[23] Yet, consistent F7-F8 asymmetry in resting and activated state should not be prematurely invalidated.

Clinical implication

All branches of medicine use various biological measures as a tool for diagnosis, response, and prognosis. This

Table 4: Mean of difference in alpha power across various electrodes of control compared with cases

Stage of EEG recording	Mean alpha power		Mean of difference in alpha power	df	*P* (*t*-test)
	FP1 (cases)	FP1 (controls)			
Before activation	3.12±4.62	2.38±1.73	−0.40±0.74	16	0.53
During activation	2.84±4.32	3.85±4.59	0.39±7.37	16	0.83
After activation	3.17±5.28	2.67±1.96	1.14±6.53	16	0.48
Stage of EEG recording	**FP2 (cases)**	**FP2 (controls)**	**Mean of difference in alpha power**	**df**	***P* (*t*-test)**
Before activation	2.89±3.78	2.60±1.49	0.78±4.94	16	0.52
During activation	2.21±2.30	2.59±1.57	−0.13±2.99	16	0.86
After activation	3.00±5.05	2.62±1.66	0.86±6.07	16	0.57
Stage of EEG recording	**F7 (cases)**	**F7 (controls)**	**Mean of difference in alpha power**	**df**	***P* (*t*-test)**
Before activation	2.41±2.50	1.12±0.49	1.78±2.90	16	0.02*
During activation	2.29±2.66	1.32±0.71	1.52±2.94	16	0.04*
After activation	2.47±2.98	1.19±0.66	1.82±3.24	16	0.03*
Stage of EEG recording	**F8 (cases)**	**F8 (controls)**	**Mean of difference in alpha power**	**df**	***P* (*t*-test)**
Before activation	1.78±1.53	1.50±1.41	0.50±2.33	16	0.39
During activation	1.83±2.24	1.49±1.31	0.66±2.83	16	0.35
After activation	1.80±2.28	1.48±1.39	0.57±3.02	16	0.45
Stage of EEG recording	**F3 (cases)**	**F3 (controls)**	**Mean of difference in alpha power**	**df**	***P* (*t*-test)**
Before activation	3.21±3.53	2.57±1.34	0.64±4.50	16	0.26
During activation	3.14±3.52	2.93±2.26	0.63±4.50	16	0.59
After activation	3.30±3.47	2.51±1.80	1.10±3.70	16	0.24
Stage of EEG recording	**F4 (cases)**	**F4 (controls)**	**Mean of difference in alpha power**	**df**	***P* (*t*-test)**
Before activation	3.46±3.38	2.43±1.31	1.47±4.06	16	0.16
During activation	2.94±3.01	2.44±1.49	0.74±3.26	16	0.36
After activation	3.11±3.26	2.48±1.58	0.89±3.61	16	0.32

*$P<0.05$

makes mental health clinician eager to have an objective measure of diagnosis or response for their patients. Many researchers use EEG biomarkers (such as FAA and FM theta) as outcome measures independently or in combination.[28,29] Although it is quite fascinating to have biomarker, however validity, consistency, and reliability of FAA as EEG biomarker in patients of depression is not yet well established. Hence, use of FAA as biomarker in clinical practice or research is cautioned. Investigations with FAA as outcome measure are advised to carefully monitor its relation with more robust outcomes. Further, evidence is required to investigate biomarkers of depression as FAA might be related to certain aspect of depression instead of per say diagnosis.

Limitations and future directions

Like no exception, our study too has limitations. Selection of the sample was not randomized and from tertiary care hospital; future study with random sampling from general population would provide more robust result. Study with higher sample size is encouraged. We did cross-sectional EEG assessment which limits us in understanding of role of FAA in course of depression. Another limitation of study was use of antidepressant in case group. As per theoretical context, there is no interference of use of selective serotonin reuptake inhibitor in EEG, but possibility of antidepressant being reason for inconclusive results cannot be denied. Future studies to investigate FAA for assessing response in patients of depression are recommended. Future studies should also take in consideration of genetic predisposition, family history, depression being endogenous or reactive and early neuronal changes.

Conclusion

Quest for biomarker for depression churned out FAA as frontrunner. Despite of vast amount of research on it, practical utility eludes us. We need to revisit our approach from conventional search of diagnostic biomarker; as FAA might reflect component of depression but not the syndrome which is termed depression. In our opinion we are not yet ready for it and have a road ahead to travel.

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Conflicts of interest

There are no conflicts of interest.

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