

Using Pre-treatment EEG Data to Predict Response to rTMS Treatment for Major Depressive Disorder

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INTRODUCTION

- Mental illnesses may account for about 16% of total health care costs and about 30% of disability claims
- Identification of patient subgroups based on objective biomarkers, may contribute to a more effective treatment prescription

- Objective procedures for selecting optimal treatments are lacking
- Personal preference, family history, symptom clustering, previous medication history.
- Non-response to the first medication puts an enormous amount of distress on the depressed patient and may even increase the risk of suicide.

PREDICTORS OF CLINICAL RESPONSE

- Neuroimaging, neurocognitive, and electrophysiologic measures: pre-treatment differences are related to subsequent clinical response to antidepressant drugs.
- Event-related potential
- Neuropsychological factors
- Genetic polymorphisms
- Sleep

Event-related potential research

- A stronger loudness dependence of the auditory evoked potential has been associated with a better response to SSRIs. [[Paige et al., 1994](#)], [[Juckel et al., 2007](#)], [[Mulert et al., 2007](#)]
- Smaller P300 amplitudes in a perceptual asymmetry task are related to a better treatment outcome. Smaller P300 amplitudes in schizophrenia related to trait marker [[Bruder et al., 1995, Boutros 2005](#)]
- A prolonged P300 latency in an auditory evoked potential is related to a better treatment outcome. [[Kalayam et al., 1999](#)]

Neuropsychological studies

- Generally better cognitive performance is predictive of better treatment response to antidepressants
- Executive functioning [[Kalayam et al., 1999](#), [Dunkin et al., 2000](#), [Gorlyn et al., 2008](#), [Bogner et al., 2007](#)]
- Working memory [[Gorlyn et al., 2008](#)]
- Psychomotor functioning [[Taylor et al., 2006](#)]
- Some have reported that relatively impaired performance was associated with a better response [[Herrera-Guzmán et al., 2008](#)]

Genetic Perspective

- Brain-derived neurotrophic factor (BDNF)
- Catechol-O-methyltransferase (COMT)
- 5-HT (serotonin) related polymorphisms
- TDM, Pharmacogenomic studies

Results to date have not been consistent

[\[Chen et al., 2001\]](#), [\[Tsai et al., 2009\]](#), [\[Domschke et al., 2009\]](#),
[\[Choi et al., 2006\]](#), [\[Benedetti et al., 2009\]](#), [\[Arias et al., 2006\]](#),
[\[Baune et al., 2008\]](#), [\[Peters et al., 2009\]](#)

- a favourable association with treatment outcome for carriers of the Met/Met genotype

[\[Benedetti et al., 2009\]](#) and [\[Tsai et al., 2009\]](#)

- others have found a negative effect of the Met COMT variant to antidepressant response to a TCA and SSRI

[\[Arias et al., 2006\]](#) and [\[Szegedi et al., 2005\]](#)

Metabolic Rate

- Subjects with higher metabolic rates respond better to sleep deprivation and antidepressive medication with paroxetine, sertraline or venlafaxine.

(Ebert et al., 1994; Smith et al., 1999; Wu et al., 1999, Brody et al., 1999; Saxena et al., 2003; Buchsbaum et al., 1997; Davidson et al., 2003)

EEG-QEEG FINDINGS IN DEPRESSION

- a decrease in slow (delta-theta bands) activity and increases in the beta range
- increase in alpha absolute power in clinical depression, consistent with a hypoactivation hypothesis
- patients show left frontal hypoactivation compared to healthy controls

(Allen et al 2004, Knott et al 2001, Lubar et al 2003).

- abnormalities of regional hemispheric asymmetries, as measured by the EEG alpha power over the left and right hemisphere sites.

[Pop-jordanova et al 2005]

- The abnormal EEG sources are most frequently found in the right hemisphere showing increase in current power densities in the alpha and the theta EEG bands.

[Ricardo-Garcell et al 2009]

However...

- However, not all studies have found the frontal asymmetry to be consistently related to emotions and depression [Reid et al 1998].
- Some studies have found frontal EEG asymmetry in both the depressed patients and the healthy controls [Debener et al 2000].
- Evidence of changes in the EEG alpha asymmetry scores have not been significantly related to changes in depressive severity and clinical state [Allen et al 2004].

Inter-hemispheric coherence

- Depression has been characterized by the reduced coherence values in each EEG frequency band

[Knott et al 2001]

- Absolute and relative power in the EEG beta band appeared to differentiate the depressive patients

[Knott et al 2001]

EEG FOR PREDICTING TREATMENT OUTCOME

- Increased posterior alpha in depressed patients who subsequently responded to amitriptyline. (Ulrich et al, 1986)
- Fluoxetine responders had greater alpha than nonresponders (Bruder et al, 2001)
- They also found SSRI responders to differ from nonresponders in alpha symmetry, with responders showing relatively **less cortical activity over the right posterior region.**

- Lower pretreatment Theta power ([Knott et al., 1996](#)),
- Decreased Theta cordance 48 hrs to 2 weeks after start of medication ([Cook et al., 2002](#); [Bares et al., 2007](#))
- Decreased Beta power, slower Beta frequencies, greater interhemispheric Beta coherences ([Knott et al., 2000](#)),
- Increased Theta in the rostral anterior cingulate ([Pizzagalli et al., 2001](#))

- Increased Theta and Delta power: poor treatment response ([Knott et al., 2000](#)).
- Theta power measures at Fz loaded can be a significant predictor, ([Knott et al., 1996](#)).
- However, [Spronk et al \(2010\)](#) did research showing a result in the opposite direction, i.e., higher pretreatment Theta power was predictive of a higher decrease in depressive symptoms.
- Higher Theta activity at baseline could be interpreted as an electrophysiological manifestation of higher activation within the anterior cingulate ([Pizzagalli et al., 2001](#))

Cordance

- Cordance is a QEEG method which combines complementary information from absolute (the amount of power in a frequency band at a given electrode) and relative power (the percentage of power contained in a frequency band relative to the total spectrum) of EEG spectra ([Leuchter et al., 1994a](#)).

Cordance Computation

$$\text{CORDANCE}(s,f) = (\text{ANORM}(s,f) \cdot 0.5) + (\text{RNORM}(s,f) \cdot 0.5)$$

Electrode site

Frequency band

Normalized
absolute power

Normalized
relative power

If the site is discordant associated with white-matter lesions, cordance is negative,

If the site is concordant, cordance is positive.

(Leuchter et al., 1994a)

- Cordance values are correlated with regional cerebral blood flow, findings with this measure could be interpreted within the same conceptual framework as other functional neuroimaging studies. ([Leuchter et al., 1999](#); [Cook, 2008](#))
- An abnormal pattern of metabolism or perfusion in the prefrontal cortex and the anterior cingulate was found in depressed patients ([Drevets, 1998](#); [Mayberg et al., 2000](#))
- Higher pretreatment theta activity of the anterior cingulate was associated with clinical response to nortriptyline and citalopram treatment ([Asada et al., 1999](#); [Mulert et al., 2007](#); [Pizzagalli et al., 2001](#))

Knott et al. found that depressed patients who responded to imipramine showed a trend for **more alpha** but had significantly **less theta** compared with nonresponders.

Cook et al. did not find pretreatment differences between fluoxetine responders and nonresponders in theta but did find group differences in **“cordance.”**

There is an increased current source density in the anterior cingulate cortex in responders to nortriptylin in the **theta-frequency range** (**Pizzagalli et al., 2001**).

- **A reduction of prefrontal QEEG theta cordance** values after 1 or 2 weeks of treatment with selective serotonin reuptake inhibitors (SSRI) and selective serotonin–norepinephrine reuptake inhibitors (SNRI) can predict clinical response to an 8-week treatment. ([Cook & Leuchter, 2001](#); [Cook et al., 2002](#); [Cook et al., 2005](#)).
- These changes were different from those observed in placebo responders ([Leuchter et al., 2002](#)).
- The reduction of prefrontal QEEG cordance value in **theta frequency** band after one week of bupropion treatment predicted clinical response to a 4-week treatment ([Bares et al 2010](#)).

rTMS AND PREDICTORS OF TREATMENT RESPONSE

- TMS manifests antidepressant properties when delivered to the left or right dorsolateral prefrontal cortex [[Avery et al 2005](#)], [[Fitzgerald et al 2003](#)], [[George et al 1997](#)], [[George et al 2000](#)], [[Klein et al 1999](#)], [[Loo et al 1999](#)].
- Magnetic pulses of rTMS enter the brain **unimpeded** and cause neuronal depolarization in a localized area under the coil. They also cause distal effects in relevant networks ([Lisanby and Belmaker, 2000](#)).

- Younger and less treatment resistant patients seem to respond better to rTMS treatment. (Fregni et al, 2006)
- Patients with low level therapy resistance, short depression episode durations, and a high level of sleep disturbance respond better to rTMS treatment. ([Brakemeier et al., 2007](#))

USING PRE-TREATMENT EEG DATA TO PREDICT RESPONSE TO rTMS

- Study was based on naturalistic open label design.
- All subjects received 25 Hz rTMS over the left DLPFC, at 110% MT, 30 trains of 2 seconds, each train being 20 times at 30-second intervals.
- Concurrent SSRI.
- Hamilton depression scale before and after 20 sessions.
- Pre-treatment QEEG
- Exclusion: Paroxysmal EEG, comorbidity.

Exclusion Criteria

- Bipolar disorder
- Any psychotic symptoms (e.g. depression with psychotic features or an Axis I psychotic illness)
- Dementia, delirium, substance-related disorders
- Cluster A or B Axis II disorders
- Treatment with electroconvulsive therapy (ECT) in the prior year.
- Any past history of craniotomy, skull fracture, seizures, or significant neurological illness
- Past history of suicidal intent, plan, or attempt.







- The subjects were divided into three groups: remission, responder, non-responder.
- Response was defined as a **50% reduction** in the HAMD score.
- Patients with HAMD scores of **less than 8** were considered to be in remission.

Results

Depressed Patients	Remission	Responder	Non-responder
N (male/female): 73	26 (18/8)	18 (9/9)	29 (19/10)
Mean±S.D.Age	43,35 ± 15,50	36,17 ± 14,64	41,62 ± 15,39
Pre-treatment HAMD	21,03 ± 4,10	25,00 ± 7,20	23,34 ± 3,66
Post-treatment HAMD	6,11 ± 2,33	11,28 ± 2,80	15,4 ± 2,74

Results I

- The most serious side effect that has been reported with TMS is a seizure ([Anderson et al. 2006](#)), and none were observed in this study.
- No adverse effects on mood in terms of either treatment-emergent suicidality or treatment-emergent mania or hypomania were observed.

Results 2

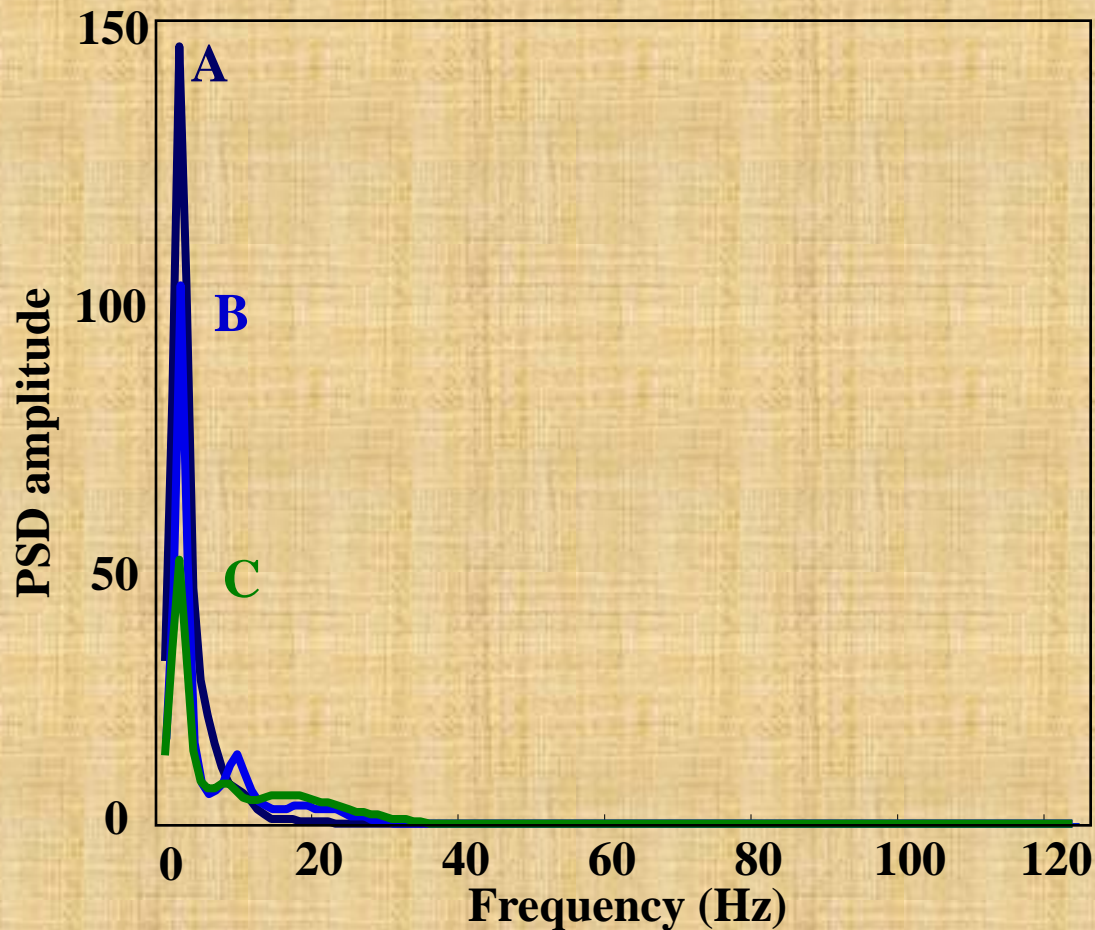
- EEG data collected from depressed patients were analyzed using the Burg Method to obtain Power Spectral Density (**PSD**) estimations.
- The spectral results are shown with respect to the three groups as follows:
 - **Group A** consists of **remissions**,
 - **Group B** consists of **responders**,
 - **Group C** includes **non-reponders**.

Results 3

- In the prefrontal and frontal regions, delta powers are dominant in comparison to theta powers,
- Therefore, EEG power spectra intervals were computed in association with delta and theta powers,
- Cordance values of all EEG bands will be calculated as a secondary step of our study in near future.

Results 4

EEG power distributions computed for a single channel at pre-frontal regions of each group are shown. It is observed that delta powers are dominant.



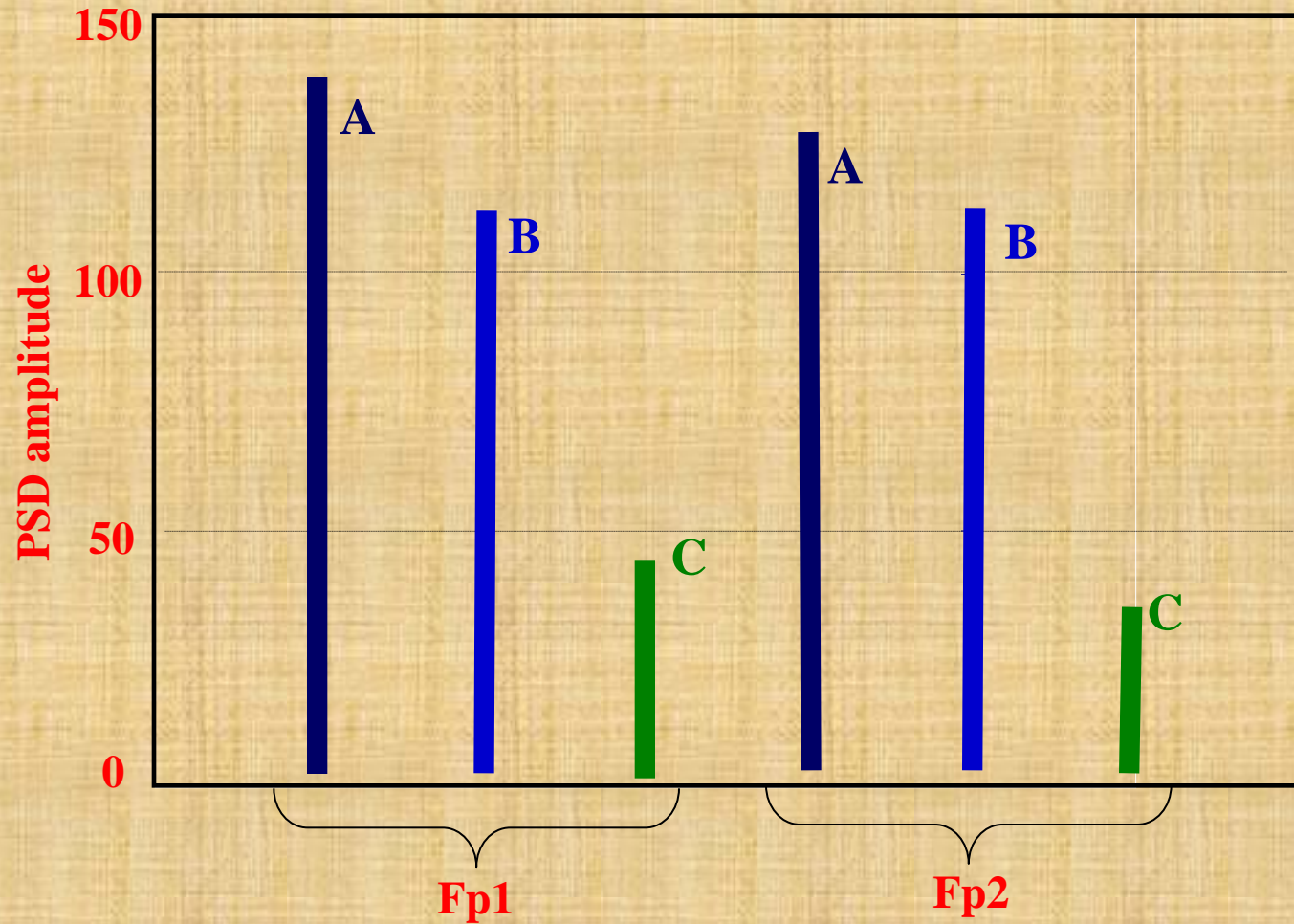
Sampling frequency is 250 Hz in our measurements.

Results 5

- Both minimum and maximum values of delta powers are calculated for all measurements and,
- PSD intervals were obtained for each group,
- All computations were performed for 16-electrode placements,
- Most spectral differences among groups were observed at frontal regions as shown with the following figures.
- Results were analysed by visual inspection

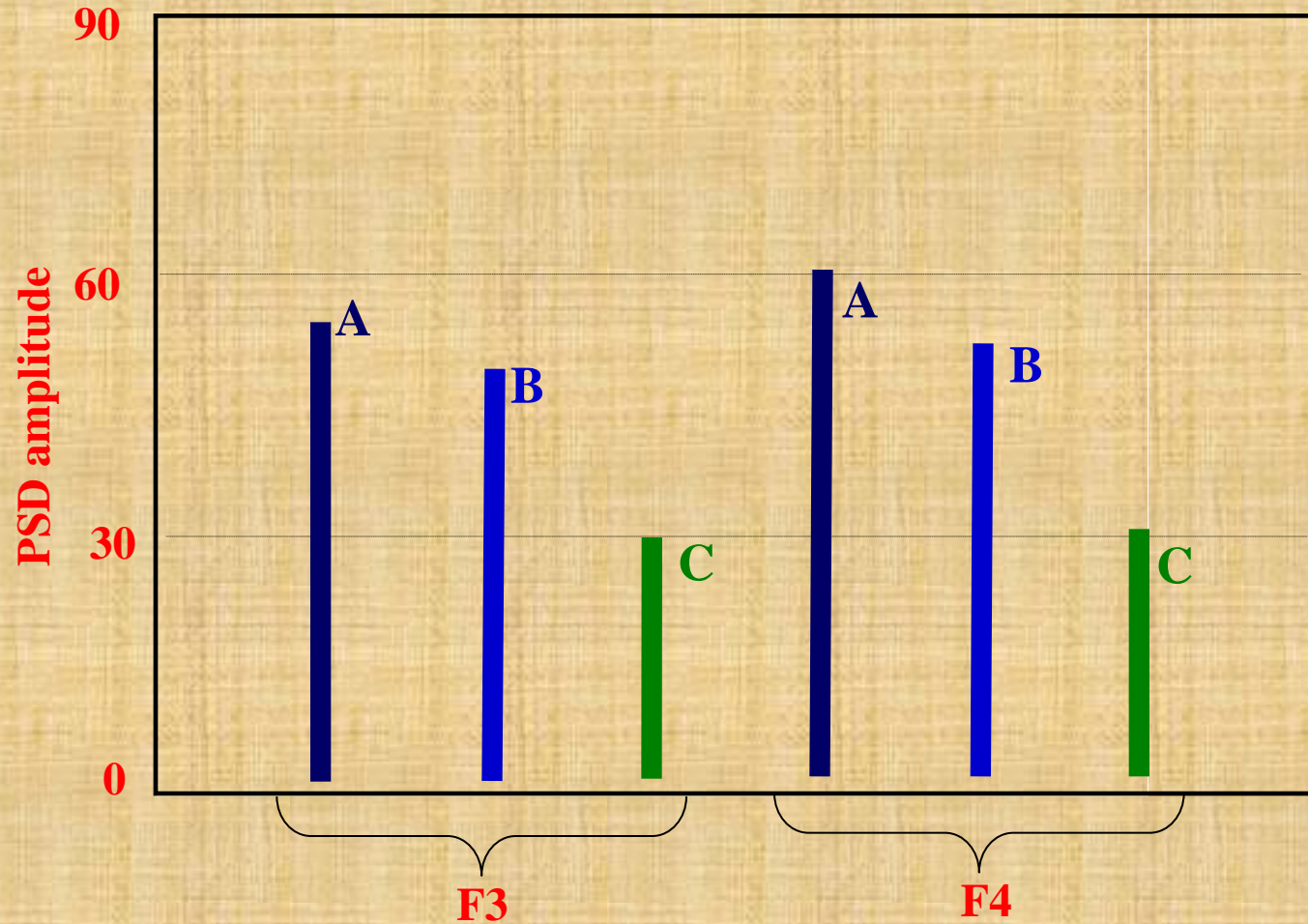
Results 6

EEG Spectral intervals in association with **delta** band



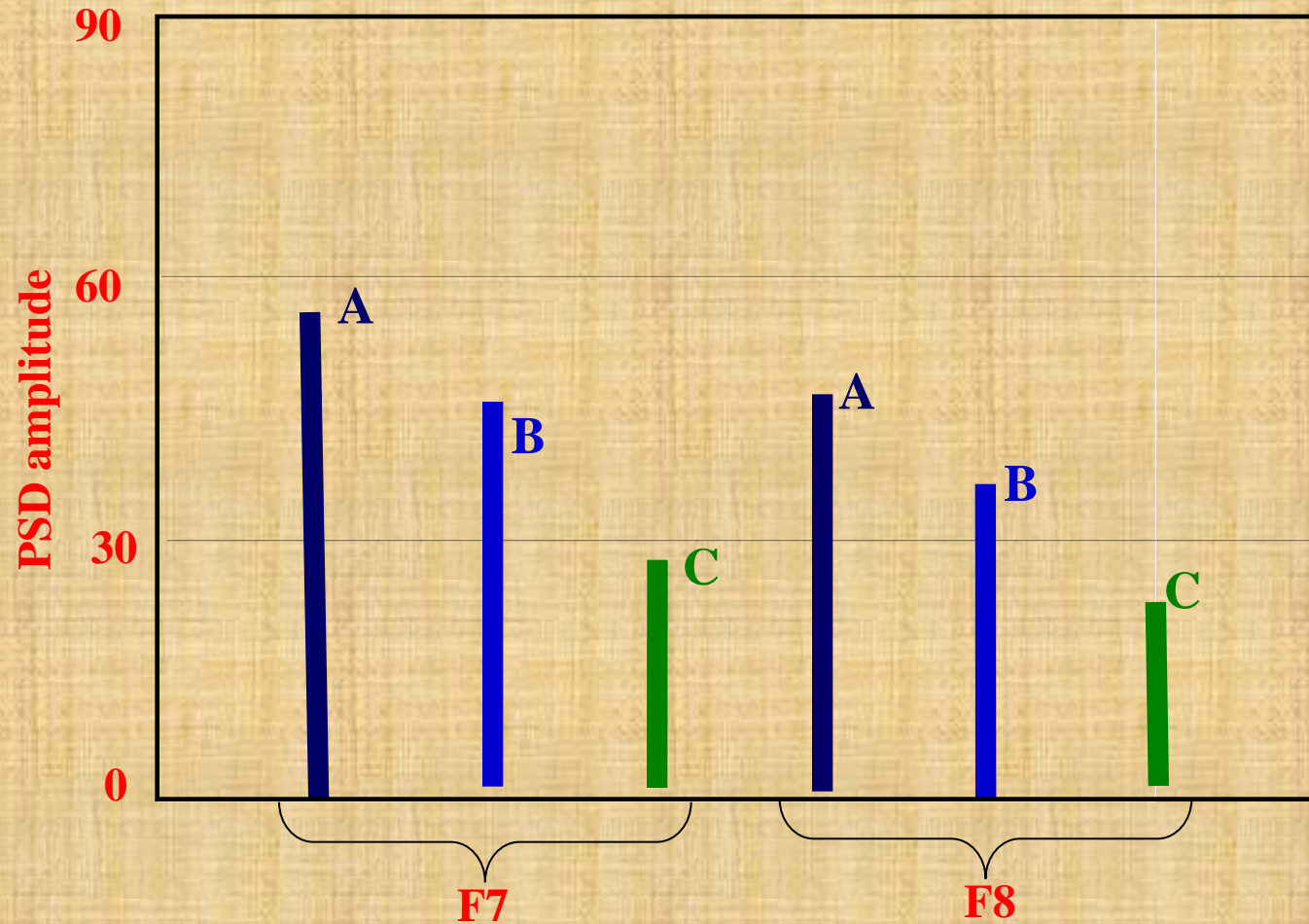
Results 7

EEG Spectral intervals in association with **theta** band



Results 8

EEG Spectral intervals in association with **theta** band



Conclusion

- The remission group had higher delta powers in the prefrontal regions as compared to non-responders.
- The delta powers of responders were slightly lower than the delta powers of the remission group in the prefrontal regions.
- rTMS could be proposed for depressed patients having high delta and high theta powers in the frontal regions.
- These show that the QEEG could find state marker values for rTMS treatment in depression

Future Work

- EEG powers at both pre-frontal and frontal regions will be computed before and after treatment so called rTMS,
- Then all possible changes on EEG band powers will be detected by using the cordance quantity,
- In particular, we will investigate the differences on EEG powers among three groups denoted by A, B and C in our study for 19-channel measurements.

RESEARCH TEAM



■ Thank you...

