Identifying a Frontal Theta Network that Differentially Predicts Outcomes of Treatment with SSRI or Placebo in Depression: A CSD-PCA Approach to Analyze Sensor-Level EEG Connectivity

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BACKGROUND

- Improving patient-treatment matching can relieve patient suffering, lower health care costs, and also reveal psychiatric subtypes.
- Strength of EEG oscillations at rest, including midfrontal theta and posterior alpha, has been associated with responsiveness to antidepressants.
- Theta and alpha frequencies have also been linked to resting oscillatory networks that rely on phase-locking for interregional communication.
- Few studies have investigated oscillatory network dynamics in relation to antidepressant response, but phase-locked connectivity is understudied and existing endogenous phase-locked networks are not clearly specified.
- Methodological limitations related to (i) volume conduction and (ii) identification and quantification of EEG connectivity patterns hinder systematic progress.

METHODS

- Resting pretreatment EEG was obtained in a multisite randomized clinical trial (EMBARC) from 212 patients with major depressive disorder (MDD) and 35 healthy controls (HC).
- Patients were administered a selective serotonin reuptake inhibitor (SSRI; sertraline or citalopram) or placebo for eight weeks.
- EEG consisted of 2 eyes-closed and 2 eyes-open blocks (2 min/block; OCCO).
- EEG were transformed to current source density (CSD) estimates representing reference-free radial current flow at scalp with improved spatial resolution.
- We assessed functional connectivity (EEG synchronization) via debiased weighted phase lag index (dwPLI) within theta and alpha frequency range (3-16 Hz) between 69 (10/10 system) recording sites (2,346 pairs).
- **Two-step** principal components analysis (**unrestricted Varimax-PCA**) was used to systematically reduce the high-dimensionality of functional connectivity data into distinct spectral-spatial connectivity components (fcPCA).
- **PCA step #1**: To identify **latent connectivity spectra** (= spectral loadings; **Fig. 1**), dwPLI values were arranged with frequencies as variables and electrode pairs, subjects, and condition (eyes open/closed) as cases.
- **PCA step #2**: To identify **spatial connectivity patterns** (= spatial loadings; **Fig. 2**), each factor from step #1 was re-projected into dwPLI space and then arranged with electrode pairs as variables and frequencies, subjects, and condition as cases.
- Factors from step #2 represent spatial loading patterns of latent connectivity spectra. The corresponding factor scores reflect a **concise summary for** the strength of **a particular connectivity pattern** for each case, and thus for each participant and condition, which can be employed for subsequent analysis.
- This 2-step PCA procedure was applied separately to HC, MDD, and HC+MDD. The combined solution was used for further analysis.
- The **decline of symptom severity**, operationalized as the estimated individual **slope** of Hamilton Depression Rating Scale (**HAM-D**) scores across the 8 weeks of treatment, was the primary dependent variable.
- Robust linear regression examined relationships between connectivity factor scores of step #2 and treatment response, focusing on fcPCA component main effects and component × group interactions.

RESULTS

- The PCA solutions of step #1 revealed 5 spectral components for MDD and MDD+HC, and 6 for HC (**Fig. 1**). Three alpha (8-13 Hz peak frequencies) and one ~ 5 Hz theta component were highly consistent across solutions and thus the focus of our regression analyses.
- Step #2 identified high-variance spatial connectivity components (**Fig. 2**) for each of the spectral components identified in step #1.
- A marginally significant main effect of eyes-closed midfrontal theta (t = -1.92, p = .056) was qualified by a significant eyes-closed × treatment group interaction (t = 2.62, p = .01; R^2 = .06; **Tab. 1**). Separate correlations between treatment response and midfrontal theta for each group showed that *patients with strong midfrontal theta connectivity were less likely to improve with placebo* (r = -.23, p = .01) *and more likely to improve with SSRI* (r = .22, p = .03).
- Follow-up analyses included the above predictors of treatment response in a single model. Eyes-closed midfrontal 5.1 Hz theta interacted with eyes-open frontal-posterior 8.0 Hz alpha connectivity to predict treatment outcome (t = 2.15, p = .03; **Fig. 3**). *Participants with low 5.1 Hz **and** high 8.0 Hz connectivity had the most favorable response to treatment.*
- Eyes-closed midfrontal 5.1 Hz theta also interacted with an eyes-closed lateral-frontal 12.5 Hz alpha component to predict treatment outcome (t = 3.00, p = .003). *Participants with weak midfrontal theta **and** weak lateral-frontal high alpha showed the most rapid recovery* (**Fig. 4**).

CONCLUSIONS

- High-dimensional functional connectivity (fc) EEG datasets can be comprehensively summarized by a combination of CSD and two-step PCA (**CSD-fcPCA**).
- The resulting **functional connectivity components** are readily interpretable.
- This **systematic, unbiased approach** avoids applying arbitrary thresholds.
- MDD and HC showed qualitatively similar EEG connectivity patterns at rest.
- **Interactions** between **oscillatory networks predicted** depression **outcomes**.
- Consistent with prior research, a **midfrontal theta network** revealed **differential prediction of** depression outcomes as a **function of treatment arm**.
- **Parallel analyses of theta and alpha networks** may help **to improve** prediction of MDD treatment outcomes **and optimize treatment selection**.

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Poster available in high resolution at
http://psychophysiology.cpmc.columbia.edu/mmedia/SoBP2020/CSDfcPCA_SoBP2020.pdf

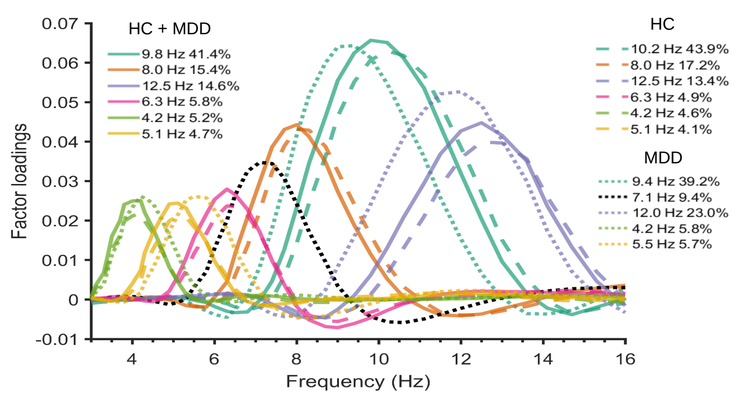


Fig. 1. Spectral factor loadings from **PCA step #1**. PCA solutions were obtained for HC, MDD, and HC+MDD samples. Spectral loadings were highly consistent across samples (i.e., at least "fair similarity" via Tucker's congruence coefficients) except for a 7.1 Hz factor observed for MDD participants (black dotted line) that did not align well with the HC solution. This factor was not present in the combined MDD+HC solution.

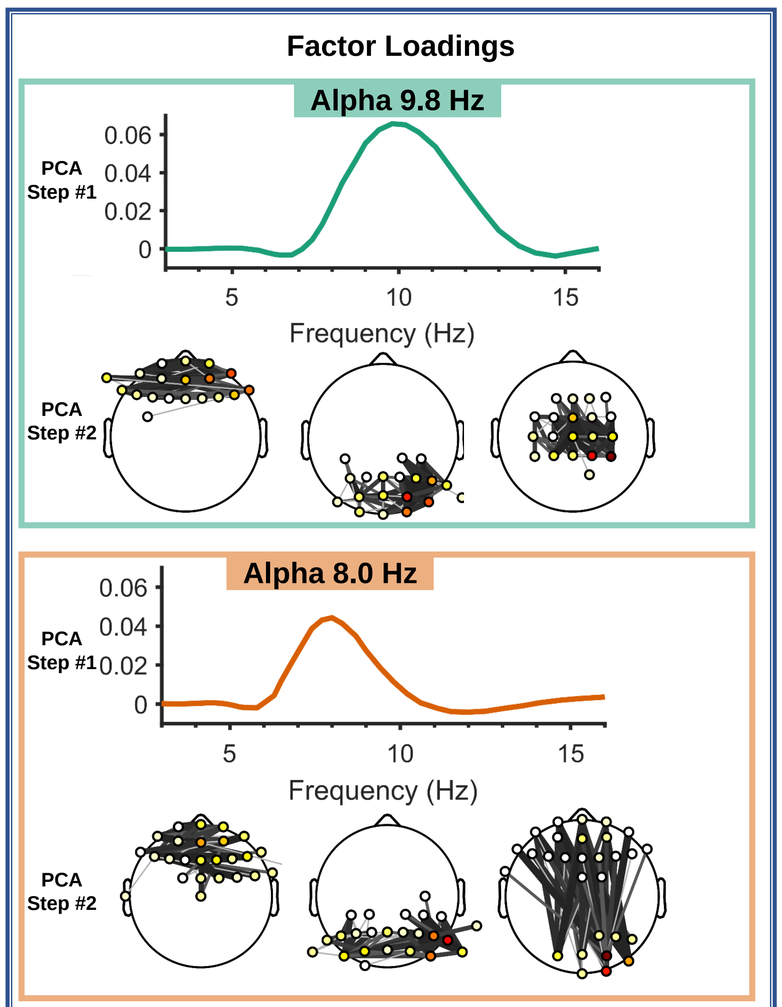


Fig. 2. Spatial factor loadings from **PCA step #2** (plotted below associated spectral loadings from PCA step #1). Lines (thickness) mark connection strength between dots (colors) marking electrodes with suprathreshold connections (count). Components within the canonical theta and alpha ranges displayed above were of particular interest given previous literature on oscillatory networks.

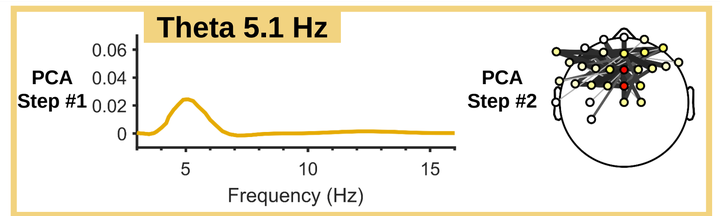
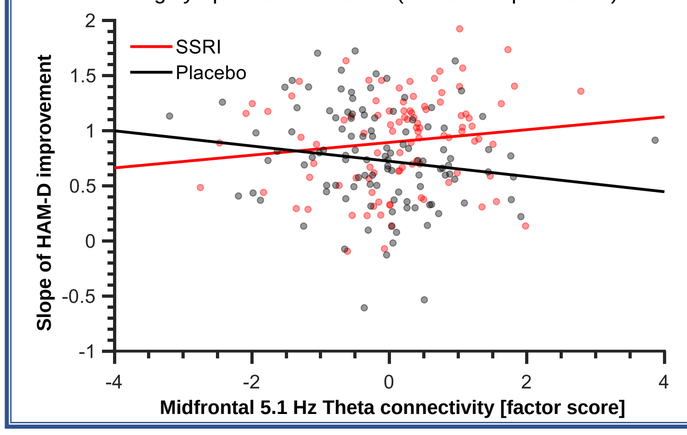


Table 1. Linear regression summary for fcPCA theta 5.1 Hz component.

	B	*SE*	*t*	*p*	
Intercept	.76	.04	17.62	< .001	
EC	- .09	.05	- 1.92	.06	(*)
EO	.02	.04	.50	.62	
Group	.14	.06	2.26	.03	*
EC*Group	**.18**	**.07**	**2.62**	**.01**	*
EO*Group	- .04	.07	- .49	.62	

Note. The strength of a connectivity pattern is effectively summarized by the mean fcPCA factor score for each participant and condition. These scores were regressed on HAM-D slopes. A 5.1 Hz midfrontal fcPCA component interacted with treatment arm (SSRI/Placebo) to predict improvement in depression symptoms (HAM-D slope), and this effect was driven by the eyes-closed condition. Correlation analyses split by treatment group showed that strong connectivity between midfrontal sites predicted more rapid symptom improvement for SSRI, but worsening symptoms for Placebo (see scatterplot below).



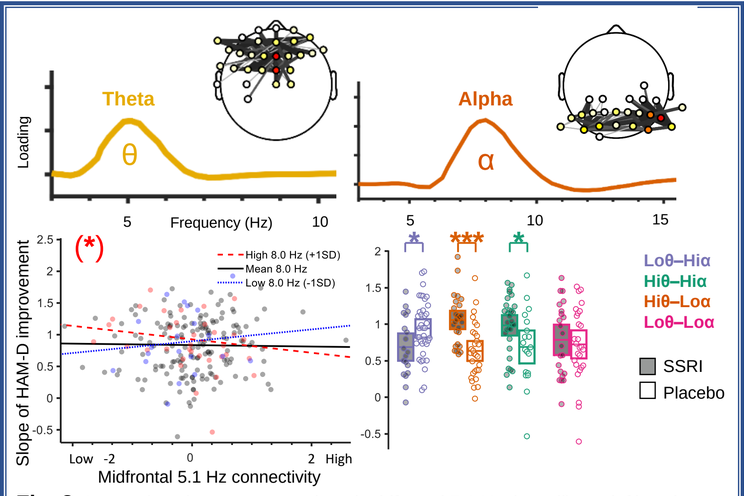


Fig. 3. Interactions between eyes-closed midfrontal 5.1 Hz theta (**θ**; top left) and eyes-open frontal-posterior 8.0 Hz alpha (**α**; top right) connectivity patterns predicted treatment response. Depression improvement as a function of connectivity pattern strength (bottom left) and when also taking treatment into account (bottom right). Patients with low midfrontal theta connectivity and strong frontal-posterior 8.0 Hz connectivity (red dashed line, bottom left) demonstrated the most favorable response overall. Post-hoc tests indicated that *participants with low theta and high alpha* (i.e., median splits) *were particularly responsive to placebo*, whereas *participants with strong theta and weak alpha were more likely to respond to SSRI*. (*) p < .10, *p < .05, *** p < .001

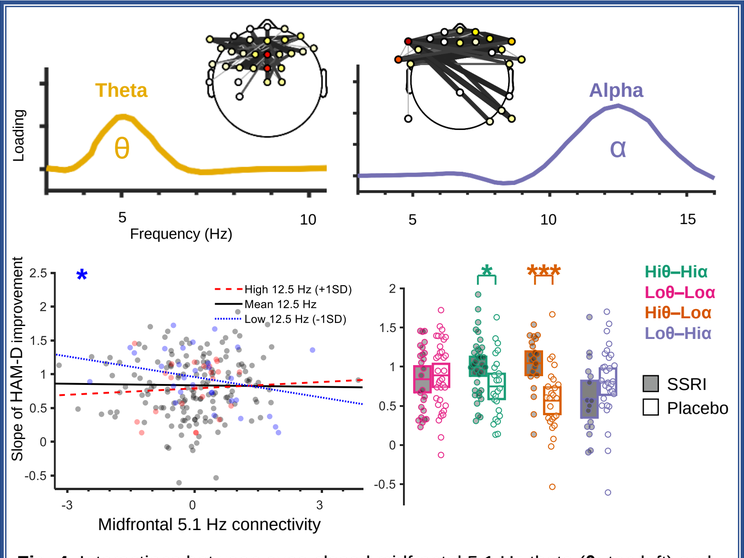


Fig. 4. Interactions between eyes-closed midfrontal 5.1 Hz theta (**θ;** top left) and eyes-closed lateral-frontal 12.5 Hz alpha (**α**; top right) connectivity patterns predicted treatment response. Depression improvement as a function of individual connectivity pattern strength (bottom left) and after also separating by treatment group (bottom right). *Patients with low midfrontal theta and low lateral-frontal high alpha showed the best response overall, independent of treatment arm.* Post-hoc tests indicated that *patients with high midfrontal theta responded better to SSRI than placebo*, this was *especially* the case *for participants with high midfrontal theta and low alpha*. (*) p < .10, *p < .05, *** p < .001

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