THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Electroencephalogram Resting State Frequency Power Characteristics of Suicidal Behavior in Female Patients With Major Depressive Disorder

Author(s): Lars Benschop, MSc; Chris Baeken, MD, PhD; Marie-Anne Vanderhasselt, PhD; Frederik Van de Steen, PhD; Kees Van Heeringen, MD, PhD; and Martijn Arns, PhD

DOI Number: 10.4088/JCP.18m12661

List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1

Participants

The study sample is comprised of a naturalistic open-label study, in which aspects unrelated to suicide have been published elsewhere[1]. The original sample consisted out of MDD patients who applied for rTMS treatment and were enrolled at three different sites between May 2007 and November 2016: neuroCare Clinic Nijmegen, neuroCare Clinic The Hague and Psychologen Praktijk Timmers Oosterhout. The current study constitutes a subsample of the original naturalistic open-label study: the MDD patients which were enrolled at neuroCare Clinic Nijmegen (N = 196). All participants signed an informed consent and agreed upon the data being used for research purposes. The primary diagnosis of non-psychotic MDD was confirmed using the Mini-International Neuropsychiatric Interview (MINI-Plus)[2], DSM-IV criteria and a score of ≥ 14 on the 21-item Beck Depression Inventory (BDI)[3].

In addition, suicide risk was assessed using the MINI questionnaire. Considering the suicide related items derived from the MINI questionnaire, we defined three distinct groups based upon suicide risk: a) MDD who attempted suicide within the previous 30 days (i.e. attempters), b) MDD with only SI (i.e. ideators) and c) MDD without SI and/or a history of suicide attempts (i.e. psychiatric controls). Since the present study's concern is in acute suicide risk, MDD patients with a suicide attempt outside the 1-month interval and with no reported ideation were excluded from the analysis. Forty participants were excluded from the dataset due to missing suicide-related data (N = 36) or not meeting the inclusion criteria (i.e. suicide attempt outside of the 1-month interval). Furthermore, we included only females for two reasons: a) male subjects were severely underrepresented within the attempter group (5 males vs 19 females) and b) several studies have found gender-specific EEG predictors and findings within MDD patient populations[4-6]. Consequently, the final study's sample size was 78, including 19 attempters, 36 ideators and 23 psychiatric controls.

EEG procedure & pre-processing

EEG procedure

The EEG recordings were acquired by adopting the standardized methodology and platform from Brain Resource Ltd., Australia. Details of this standardized procedure are described elsewhere[7,8]. The reliability and across-site consistency of this standardized EEG methodology has been demonstrated in multiple studies[9,10]. The procedure can be summarized as follows: subjects were seated in a light- and sound-controlled room with a fixed ambient temperature of 22°C. The EEG data were collected using a 26-channel Quikcap (NuAmps; 10-20 electrode extended international system). The acquisition of the continuous EEG resting state data consisted of two-minute eyes closed (EC) and eyes open (EO) segments. The experimenter did not intervene when drowsiness patterns were observed in the EEG. The EEG data was referenced to average mastoids with a ground at the AFz. Horizontal and vertical eye movements were also recorded. The electrode impedance was < 5K Ω for all the channels and the sampling rate was 500 Hz. A continuous acquisition system was used and subsequent artifact removal such as EOG-corrections was performed offline. Finally, a 100 Hz low pass filter was applied prior to digitization.

EEG pre-processing

A high pass filter of 1 Hz and a low pass filter of 100 Hz were applied. EOG corrections were performed based on a similar technique of Gratton and colleagues[11]. The continuous data were segmented into two second epochs. Individual epochs were marked as artifacts based on the following criteria: a) EMG detection, b) pulse and baseline shift detection, c) crosstalk detection, d) high kurtosis, e) extreme power level detection, f) residual eye blink detection and g) extreme voltage swing detection. The data was re-referenced to the average. The pre-processing steps are based on the pipeline of Arns and colleagues, who have published a detailed description and a validation of this automated EEG pre-processing procedure[4].

EEG Analysis

Cluster-based permutation method

Cluster thresholding for multiple comparisons correction (MCC) is based on the notion that EEG data auto-correlates (e.g. a specific significant time-point's neighbour will probably also be significant). These auto-correlations form clusters in the data, which may be expressed over time-points, frequencies and/or electrodes. Clusters observed in the data will be viewed as significant if they are larger than the typical data clusters one would expect to find under the null hypothesis. More specifically, a null hypothesis distribution of clustered *t*-values is generated by means of: a) shuffling condition labels (e.g. the study groups) at random, b) calculating t-statistics on these shuffled group differences, c) applying an alpha-level threshold (e.g. 0.05) on these t-statistics (i.e. pixel thresholding) and d) extracting the t-statistic clusters based on cluster mass (i.e. the sum of these supra-threshold pixels)[12]. This 4-step process (including the random shuffling) is repeated 1000 times. This will result in a null hypothesis distribution of clustered *t*-values which can subsequently be used as a comparison for the observed data clusters. If the observed data clusters are larger than the 95-percentile (i.e. alpha = 0.05) of the null hypothesis cluster distribution, it can be concluded that they represent a significant difference. Notably, cluster-based permutation methods provide adequate control over the family wise error rate[12,13].

eLORETA analysis

eLORETA (exact low-resolution electromagnetic tomography, http://www.uzh.ch/keyinst/loreta.htm) calculates the cortical 3-dimensional distribution of current density, which is based on the scalp-recorded electric potential distribution. The mathematical foundation of LORETA has been described elsewhere[14]. eLORETA is the latest improvement of the standardized sLORETA[15] which was an improvement of the original LORETA[16]. eLORETA is a non-adaptive distributed source imaging method and a solution to the inverse problem, with exact and zero localization errors. eLORETA's statistical methodology for evaluating group differences is based on nonparametric permutation tests for functional neuroimaging, which has been published by Nichols

and Holmes[17]. In the current study, 14 frequency bands have been defined a priori (delta: 1.5 Hz – 3.5 Hz; theta: 4 Hz – 7.5 Hz; theta I: 4 Hz – 5 Hz; theta II: 5 Hz – 7.5 Hz; alpha: 8 Hz – 13 Hz; alpha I: 8 Hz – 11 Hz; alpha II: 11 Hz – 13 Hz; SMR: 12 Hz – 15 Hz; beta: 14.5 Hz – 30 Hz; beta I: 14.5 Hz – 20 Hz; beta II: 20 Hz – 25 Hz; beta III: 25 Hz – 30 Hz; gamma I: 31 Hz – 49 Hz; gamma II: 50 Hz – 100 Hz).

Confirmatory post-hoc localization analyses were applied based on the findings (i.e. the specific frequency band and direction of the effect) of the spatial-frequency cluster MCC analysis performed in MATLAB. Since the data concerns group differences of EEG resting state, baseline correction and data normalization were not employed. An alpha level of 0.05 was set.

Results

The effect of study group on age, BDI-scores and MINI-diagnosis

Table 1: Patient demographics. BDI, Beck depression inventory, M, mean, MINI, Mini international neuropsychiatric interview, SD, standard deviation.

Patient demographics	Attempters	Ideators	Psychiatric controls
Age (P = 0.11)	M = 37.26, SD = 10.85	M = 45.00, SD = 13.31	M = 44.13, SD = 13.50
BDI (p < .001)	M = 42.16, SD = 10.10	M = 31.28, SD = 9.30	M = 28.61, SD = 9.00
MINI-diagnosis (p = 0.432)			

References

1. Donse L, Padberg F, Sack AT, Rush AJ, Arns M. Simultaneous rTMS and psychotherapy in major depressive disorder: Clinical outcomes and predictors from a large naturalistic study. *Brain Stimul.* 2018;11(2):337-345.
2. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998;59 Suppl 20:22-33;quiz 34-57.
3. Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry.* 1974;7(0):151-169.
4. Arns M, Bruder G, Hegerl U, et al. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. *Clin Neurophysiol.* 2016;127(1):509-519.
5. Iseger TA, Korgaonkar MS, Kenemans JL, et al. EEG connectivity between the subgenual anterior cingulate and prefrontal cortices in response to antidepressant medication. *Eur Neuropsychopharmacol.* 2017;27(4):301-312.
6. van Dinteren R, Arns M, Kenemans L, et al. Utility of event-related potentials in predicting antidepressant treatment response: An iSPOT-D report. *Eur Neuropsychopharmacol.* 2015;25(11):1981-1990.
7. Arns M, Gunkelman J, Breteler M, Spronk D. EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *J Integr Neurosci.* 2008;7(3):421-438.
8. Williams LM, Rush AJ, Koslow SH, et al. International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol. *Trials.* 2011;12:4.
9. Williams LM, Simms E, Clark CR, Paul RH, Rowe D, Gordon E. The test-retest reliability of a standardized neurocognitive and neurophysiological test battery: "neuromarker". *Int J Neurosci.* 2005;115(12):1605-1630.

10. Paul RH, Gunstad J, Cooper N, et al. Cross-cultural assessment of neuropsychological performance and electrical brain function measures: additional validation of an international brain database. *Int J Neurosci.* 2007;117(4):549-568.

11. Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol.* 1983;55(4):468-484.

12. Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Meth.* 2007;164(1):177-190.

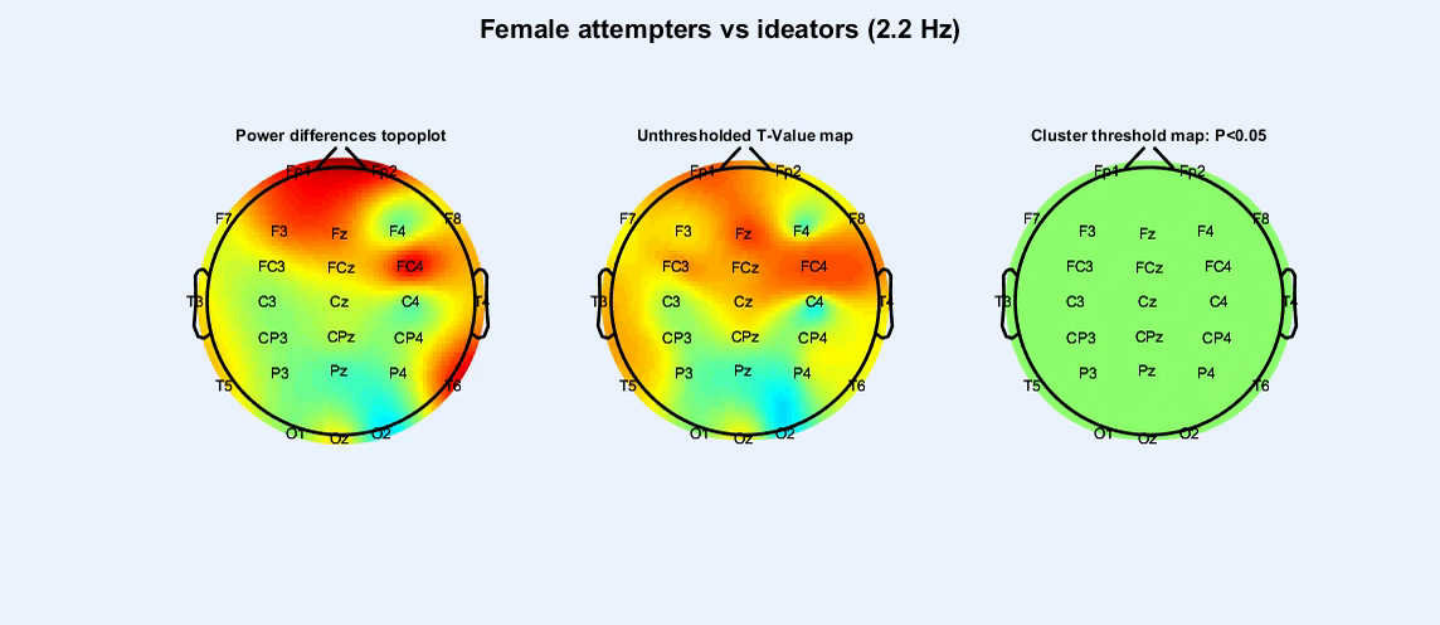
13. Pernet CR, Latinus M, Nichols TE, Rousselet GA. Cluster-based computational methods for mass univariate analyses of event-related brain potentials/fields: A simulation study. *J Neurosci Methods.* 2015;250:85-93.

14. Pascual-Marqui RD. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. *arXiv preprint arXiv:07103341.* 2007.

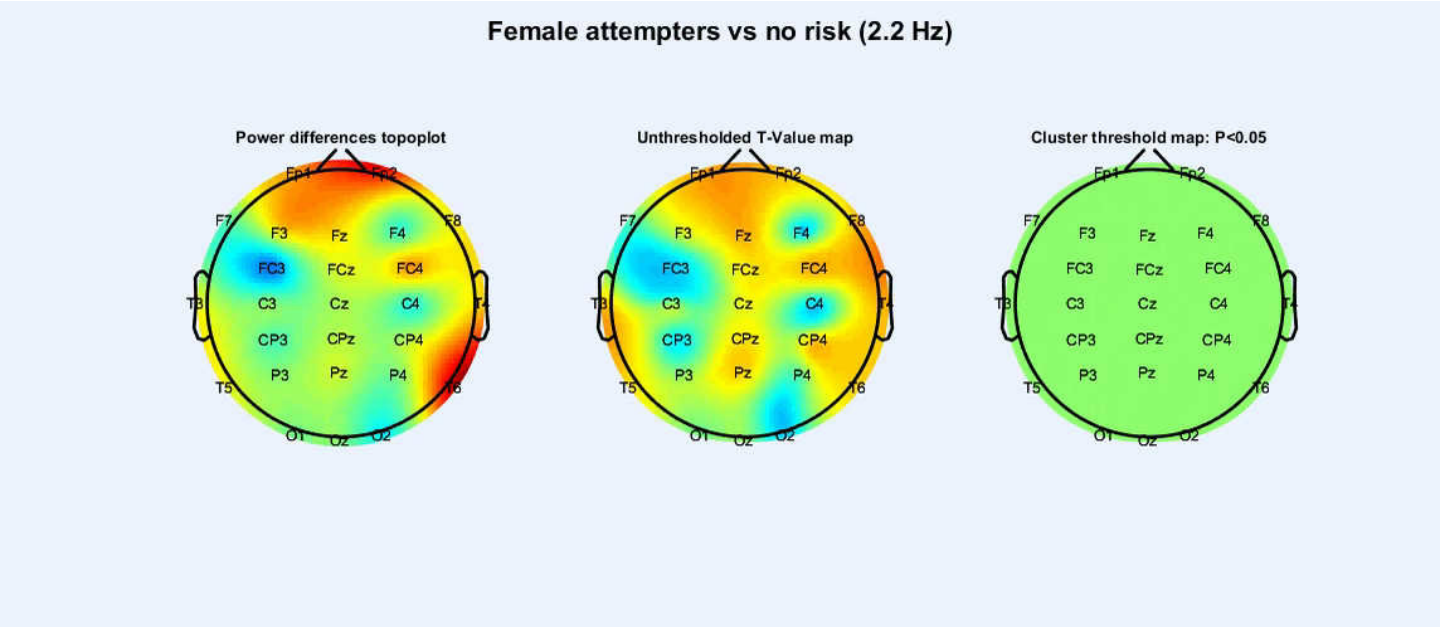
15. Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol.* 2002;24 Suppl D:5-12.

16. Pascual-Marqui RD, Michel CM, Lehmann D. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *Int J Psychophysiol.* 1994;18(1):49-65.

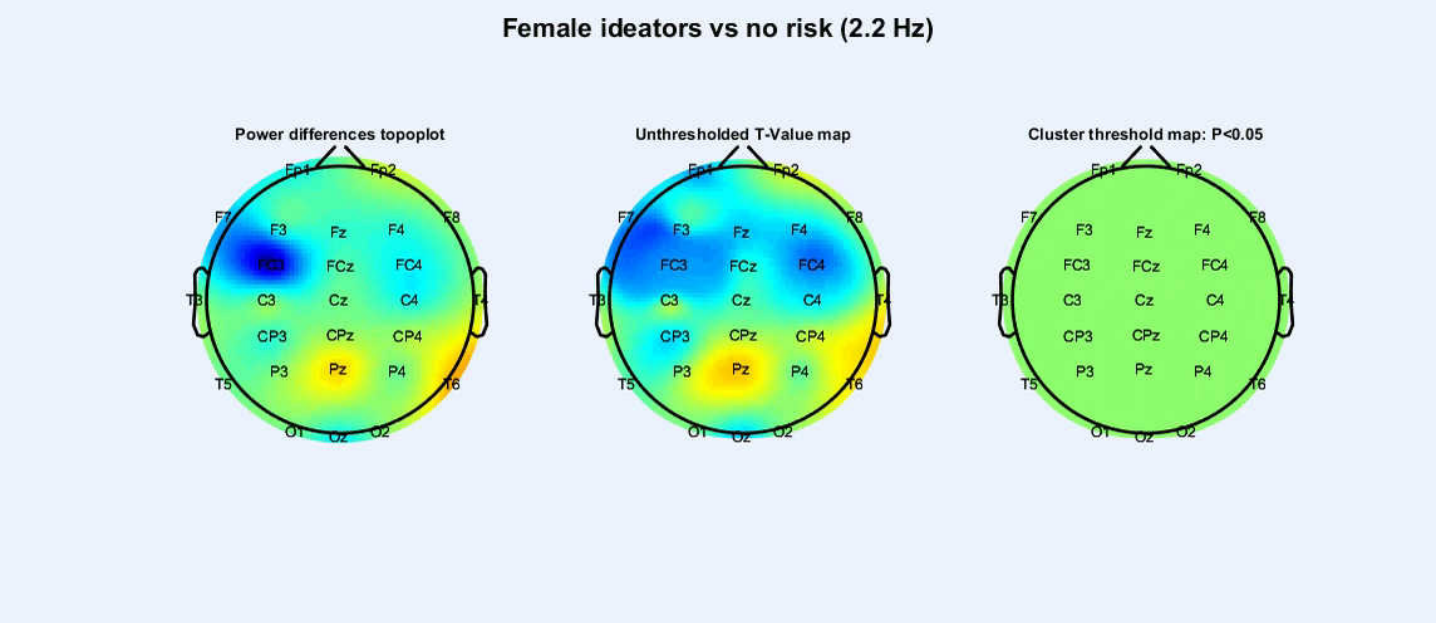
17. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp.* 2002;15(1):1-25.



To view Supplementary Figure 1, click here.



To view Supplementary Figure 2, click here.



To view Supplementary Figure 3, click here.