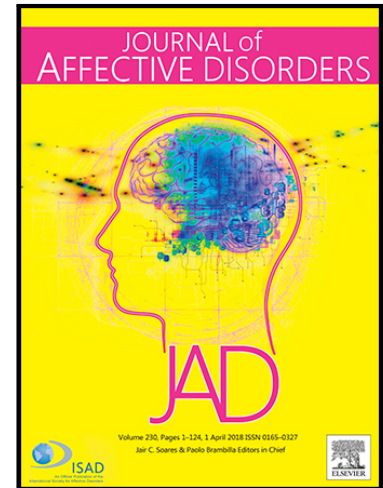


Accepted Manuscript

EEG Gamma Synchronization Is Associated with Response to Paroxetine Treatment

Mehmet Kemal Arikan , Baris Metin , Nevzat Tarhan

PII: S0165-0327(18)30169-1
DOI: [10.1016/j.jad.2018.04.041](https://doi.org/10.1016/j.jad.2018.04.041)
Reference: JAD 9695



To appear in: *Journal of Affective Disorders*

Received date: 25 January 2018
Revised date: 7 March 2018
Accepted date: 4 April 2018

Please cite this article as: Mehmet Kemal Arikan , Baris Metin , Nevzat Tarhan , EEG Gamma Synchronization Is Associated with Response to Paroxetine Treatment, *Journal of Affective Disorders* (2018), doi: [10.1016/j.jad.2018.04.041](https://doi.org/10.1016/j.jad.2018.04.041)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Highlights

- EEG gamma power is related to cognitive-affective processing
- Baseline gamma power is significantly associated with change in depression severity
- Gamma power could be used as a potential biomarker to predict antidepressant response

EEG Gamma Synchronization Is Associated with Response to Paroxetine Treatment

Authors: Mehmet Kemal Arikan, Baris Metin, Nevzat Tarhan

Affiliation: Uskudar University, Department of Psychology (all authors)

Corresponding author: Baris Metin

**Address: Uskudar Universitesi, Haluk Turksoy sok, no: 14, 34662, Altunizade Istanbul,
Turkey**

Email: baris.metin@uskudar.edu.tr

Abstract

Background: Resistance to medication is a significant problem in psychiatric practice, and effective methods for predicting response are needed to optimize treatment efficacy and limit morbidity. Gamma oscillations are considered as an index of the brain's general cognitive activity; however, the role of gamma oscillations in disease has not been studied sufficiently.

Aim: This study aimed to determine if gamma power during rest can be used to predict response to anti-depressant medication treatment. **Method:** Hamilton Depression Rating Scale (HDRS) score and resting state gamma power was measured in 18 medication-free patients during an episode of major depression. After 6 weeks of paroxetine monotherapy HDRS was administered again. **Results:** Baseline gamma power at frontal, central and temporal electrodes before treatment was significantly related to post-treatment change in HDRS scores. **Conclusion:** The results indicate that gamma oscillations could be considered a marker of response to paroxetine treatment in patients with major depression.

Keywords: Quantitative EEG; personalized medicine; paroxetine; treatment response

Introduction

Depression is the most common mental health problem (Kessler and Bromet, 2013) and among all mental health problems is associated with the greatest disease burden (US Burden of Disease Collaborators, 2013). Failure to respond to a single major anti-depressant is referred to as stage 1 resistance, which has an estimated prevalence of approximately 50% (Nemeroff et al., 2007). Generally, response is defined as %50 reduction in symptom severity and remission is defined as Hamilton Depression Rating Scale score <7. Resistance to medication is an important healthcare issue because it prolongs disease duration and greatly increases the cost of treatment (Crown et al., 2002). Treatment-resistant patients access healthcare services more often than non-resistant patients and the annual cost of psychiatric care is about 80% higher for resistant patients (Lepine et al., 2012). In addition, treatment-resistant depression (TRD) is associated with a decrease in quality of life (QoL) (Saad al-Harbi et al., 2012) and an increased risk of suicide (Pfeifer et al., 2013).

The above-mentioned data suggest that TRD is a serious mental health problem that should be managed proactively. As the treatment approach to TRD would be different than treatment responsive depression, a proactive strategy should include not only a management plan for resistance, but an attempt to predict TRD before it manifests. Current predictors of resistance include a history of resistant episodes, early age of onset, multiple episodes and bipolarity (Dudek et al., 2010), and a number of clinical and genetic factors including anxiety, neuroticism and serotonin receptor gene polymorphism (Benabi et al., 2015). Nonetheless, the accuracy of predicting TRD remains inadequate therefore, more accurate and reliable markers of TRD that could inform treatment before resistance emerges are needed.

One extensively used method for aiding diagnosis and monitoring treatment is quantitative EEG (qEEG). qEEG involves calculating the spectral power of EEG bands after applying fast Fourier transformation (FFT), which converts signals from the time domain to

frequency domain. The most commonly calculated bands include delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-25). qEEG is used for numerous applications in psychiatric practice. For instance, it is well known that depression is accompanied by an increase in left frontal alpha activity, as is anxiety (Thibodeau et al., 2006). Kandilarova et al. (2017) reported that left parietal alpha power predicted response to pharmacological treatment in patients with major depression and that treatment responders had higher baseline alpha power than non-responders. Another study reported an association between prefrontal theta activity and response to venlafaxine treatment (Bares et al., 2008). In addition to the delta, theta, alpha, and beta bands, a less commonly explored wave band is gamma, which includes frequencies >25 Hz (Basar, 2013). While the gamma band is commonly defined as 30-100 Hz, the range can be subdivided into low gamma (30-50) and high gamma bands (above 70 Hz) (Seeber et al., 2015). Gamma oscillations are associated with sensory and cognitive processes (Basar, 2013).

Although gamma oscillations are commonly investigated during cognitive activity, their clinical significance is not well known. It is known that gamma activity is correlated more than other oscillations to BOLD fmri responses during cognitive processing (Deligianni et al., 2014). Evoked gamma oscillations have been studied most commonly in schizophrenia patients and it is observed that they have a reduced gamma response to auditory tones in addition to altered phase locking in the gamma band (Basar 2013). Oribe et al (2010) reported that patients with bipolar disorder have increased evoked gamma oscillations in response to listening to speech. Similar results in schizoaffective patients were also reported (Brealy et al., 2015). Regarding depression, Roh et al. (2016) reported that fronto-central beta and low-gamma oscillations are associated with symptoms of inattention. In addition, alterations in resting gamma power in depression were reported following repetitive transcranial magnetic stimulation (Kito et al., 2014; Noda et al. 2017). In terms of event-related gamma

oscillations, patients with bipolar disorder have increased gamma power in the posterior temporal regions, whereas unipolar depression patients have increased gamma power in the anterior temporal regions during an implicit emotion task (Liu et al., 2012). The authors interpreted these results as an alteration in emotional information processing. These earlier studies indicate that whereas classical EEG bands are generally associated with basic brain functions, the gamma band is generally associated with cognitive-emotional functions and information processing. As such, the present study aimed to determine if gamma power during rest is associated with response to anti-depressant medication paroxetine.

Materials and Methods

The study included 18 patients (9 females) identified retrospectively from our outpatient clinic database that were diagnosed with a major depressive episode and met the following criteria: 1. Medication free for ≥ 3 weeks; 2. A 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) score for before and 6 weeks after the initiation of paroxetine treatment; 3. An qEEG before starting paroxetine treatment. None of the patients were considered to have TRD based on their previous medication history. Mean patient age was 46.4 years (range: 17-72 years). The mean pre-treatment HDRS score was 25.4 (range: 11-41), versus 11.5 (range: 0-36) 6 weeks after starting treatment. Local ethics committee approved the study protocol.

EEG

All qEEGs were recorded in a quiet dim room, with patients in the sitting position with eyes closed. Recording time was 3 min and 19 scalp electrodes were placed according to the 10-20 system. Linked mastoid electrodes (A1-A2) were used for reference. The data sampling rate was 500 Hz, and the acquired signals were bandpass filtered at 0.15-70 Hz and notch filtered at 50 Hz. Patient data were also individually checked for the absence of muscle

artifacts. Each patients' data were averaged across the recording epochs for each electrode, and the absolute power was computed for the gamma band (30-50 Hz).

Statistical analysis

Data were analyzed using Neuroguide Deluxe v.2.5.1 (Applied Neuroscience, Largo, FL). First, average gamma power was calculated for the 11 electrodes representing multiple brain regions (F3, F4, Fz, P3, P4, Pz, C3, C4, Cz, T3, and T4). These electrodes were chosen because they cover the frontal, central, temporal, and parietal regions, and are not contaminated by eye movement artefacts. The correlation between average gamma and change in HDRS score (absolute pre-post difference) was calculated using non-parametric correlation analysis. Benjamini-Hochberg procedure was implemented to correct for multiple comparisons.

Results

Gamma power in the frontal and central regions was significantly correlated with post-treatment change in HDRS scores. The direction of the correlation indicated that patients with less gamma power at baseline had a greater decrease in post-treatment HDRS score (Table 1). The strongest correlation between gamma power and post-treatment change in the HDRS score was for the Cz electrode (see Figure). The difference at C3, F3 and T3 were also significant. There wasn't a relationship between baseline HDRS score, age, gender and post-treatment change in HDRS scale ($P > 0.4$). To examine whether gamma power predicted significantly the change in HDRS scores we performed a regression analysis. Average gamma power at Cz, C3, F3 and T3 electrodes significantly predicted HDRS change scores (beta=0.54, p=0.02).

Table 1. Correlations between gamma power and post-treatment change in HDRS score.

	F3	F4	Fz	C3	C4	CZ	P3	P4	PZ	T3	T4
HDRS change	-0.45	-0.32	-0.28	-0.45	-0.32	-0.46	-0.32	-0.19	-0.19	-0.43	-0.12
P	0.009*	0.06	0.1	0.009*	0.06	0.007*	0.06	0.271	0.271	0.01*	0.47

Note: All correlation coefficients are non-parametric Kendall's tau * indicates significance after FDR (Benjamini-Hochberg) correction (corrected p value=0.05)

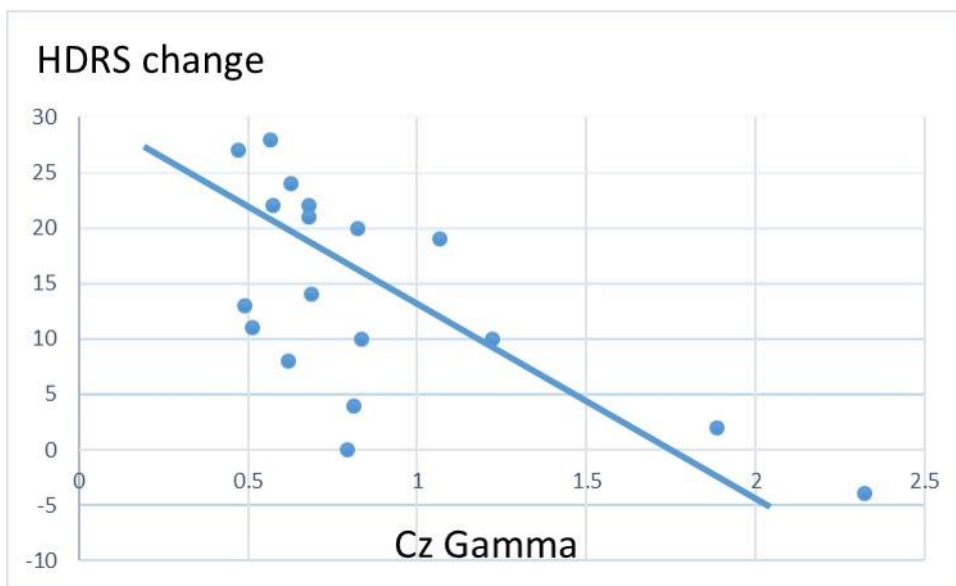


Figure. Scatter plot shows the relationship between post-treatment change in HDRS score and gamma power.

Discussion

The present study aimed to determine if gamma power is associated with response to paroxetine by measuring the response to paroxetine in a group of patients with an episode of major depressive. Patient qEEG recordings were made before starting paroxetine treatment and patients were reevaluated after 6 weeks of treatment. The findings indicate that baseline left fronto-central gamma power was significantly associated with post-treatment change in the HDRS score. Other factors, such as the baseline severity of depression and age were not associated with response to paroxetine.

Gamma oscillations reflect brain activity due to cognitive processing (Deligianni et al., 2014). In addition, several studies showed that they play a role in a number of cognitive functions including focused attention, perception, and arousal (Basar-Eroglu et al., 1996; Freeman, 1975). Gamma abnormalities have been observed in patients with bipolar disorder and schizophrenia; however, gamma alterations in patients with depression are not well described. The present findings merely indicate that gamma power is related to change in HDRS scores after selective serotonin reuptake inhibitors. As such, the pathophysiological significance of gamma alterations in patients with depression should be more clearly discerned via additional research. It is possible that depressed individuals with increased gamma oscillations represent a distinct subtype with a unique clinical profile. Furthermore, gamma oscillations have been linked to emotional memory (Headley and Paré, 2013), which indicates that individuals prone to concern about emotional memories are more resistant to depression; however, this is yet to be adequately studied.

The present study has some limitations. The small patient population yielded insufficient power for sensitivity and specificity analyses. In addition, only 1 medication was used, but this ensured homogeneity. Additional research is required to determine the predictive ability of gamma oscillations with different medications. Furthermore, only resting qEEG power was measured. Earlier studies primarily investigated event-related gamma

oscillations in schizophrenia and Alzheimer's disease (Herrmann and Demiralp, 2005; Uhlhaas and Singer, 2013). The relationship between treatment response and evoked gamma oscillations is a topic that warrants further research. The present study's primary strengths are that all the patients were medication free at the time baseline qEEG recordings were made, which eliminated the confounding effects of different medications. The present study's findings should be considered preliminary and should be evaluated cautiously. The findings do indicate that gamma oscillations can be considered a potential biomarker for predicting response to treatment during episodes of depression. If confirmed by future studies, gamma power could be used as a predictor of treatment response. Patients with high gamma activity could represent a subgroup with inadequate treatment response, which should be treated more aggressively. In such patients initial treatment may include augmentation with antipsychotics, with neuromodulatory techniques such as transcranial magnetic stimulation or with psychotherapy in addition to medication.

References

- Al-Harbi, K.S. 2012. Treatment-resistant depression: Therapeutic trends, challenges, and future directions. *Patient Preference and Adherence* 6, 369–388.
<https://doi.org/10.2147/PPA.S29716>
- Bares, M., Brunovsky, M., Kopecek, M. et al. 2008. Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder. *European Psychiatry* 23(5), 350–355.
<https://doi.org/10.1016/j.eurpsy.2008.03.001>

- Başar, E. 2013. A review of gamma oscillations in healthy subjects and in cognitive impairment. *International Journal of Psychophysiology* 90(2), 99–117.
<https://doi.org/10.1016/j.ijpsycho.2013.07.005>
- Başar, E. 2013. A review of gamma oscillations in healthy subjects and in cognitive impairment. *International Journal of Psychophysiology* 90(2), 99–117.
<https://doi.org/10.1016/j.ijpsycho.2013.07.005>
- Başar-Eroglu, C., Strüber, D., Schürman, M., Stadler, M., Başar, E. 1996. Gamma-band responses in the brain: A short review of psychophysiological correlates and functional significance. *International Journal of Psychophysiology* 24(1–2), 101–112.
[https://doi.org/10.1016/S0167-8760\(96\)00051-7](https://doi.org/10.1016/S0167-8760(96)00051-7)
- Brealy, J.A., Shaw, A., Richardson, H., Singh, K.D., Muthukumaraswamy, S.D., Keedwell, P.A. 2015. Increased visual gamma power in schizoaffective bipolar disorder. *Psychological Medicine* 45(4), 783–794. <https://doi.org/10.1017/S0033291714001846>
- Crown, W.H, Finkelstein, S., Berndt, E.R., Ling, D., Poret, A.W., Rush, A.J., & Russell, J.M. 2002. The impact of treatment-resistant depression on health care utilization and costs. *The Journal of Clinical Psychiatry* 63(11), 963—971.
- Deligianni, F., Centeno, M., Carmichael, D., Clayen, J. 2014. Relating resting-state fMRI and EEG whole-brain connectomes across frequency bands. *Front. Neurosci.* 8, 258.
10.3389/fnins.2014.00258
- Dudek, D., Rybakowski, J.K., Siwek, M., Pawłowski, T., Lojko, D., Roczeń, R., & Kiejna, A. 2010. Risk factors of treatment resistance in major depression: Association with

bipolarity. *Journal of Affective Disorders* 126(1–2), 268–271.

<https://doi.org/10.1016/j.jad.2010.03.001>

Freeman WJ (1975) *Mass Action in the Nervous System*, Academic Press, New York.

Hamilton, M. 1960. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*. 23: 56-62

Headley, D.B., & Paré, D. 2013. In sync: gamma oscillations and emotional memory.

Frontiers in Behavioral Neuroscience 7, 1–12. <https://doi.org/10.3389/fnbeh.2013.00170>

Herrmann, C.S., Demiralp, T., 2005. Human EEG gamma oscillations in neuropsychiatric disorders. *Clin. Neurophysiol.* 116, 2719–2733.

<https://doi.org/10.1016/j.clinph.2005.07.007>

Iosifescu, D.V., Greenwald, S., Devlin, P. et al. 2009. Frontal EEG predictors of treatment outcome in major depressive disorder. *European Neuropsychopharmacology* 19(11):

772–777. <https://doi.org/10.1016/j.euroneuro.2009.06.001>

Kandilarova SS, Terziyski KV, Draganova AI et al. 2017. Response to Pharmacological Treatment in Major Depression Predicted by Electroencephalographic Alpha Power – a

Pilot Naturalistic Study. *Folia Medica* 59(3), 318–325. <https://doi.org/10.1515/folmed-2017-0040>

Kessler, R.C., & Bromet, E.J. 2013. The Epidemiology of Depression Across Cultures.

Annual Review of Public Health 34(1), 119–138. <https://doi.org/10.1146/annurev-publhealth-031912-114409>

Kito, S., Pascual-Marqui, R.D., Hasegawa, T., Koga, Y. 2014. High-frequency left prefrontal transcranial magnetic stimulation modulates resting EEG functional connectivity for

gamma band between the left dorsolateral prefrontal cortex and precuneus in depression. *Brain Stimul.* 7, 145–146. <https://doi.org/10.1016/j.brs.2013.09.006>

Knott, V.J., Telner, J.I., Lapierre, Y.D., Browne, M., & Horn, E.R. 1996. Quantitative EEG in the prediction of antidepressant response to imipramine. *Journal of Affective Disorders* 39(3), 175–184. [https://doi.org/10.1016/0165-0327\(96\)00003-1](https://doi.org/10.1016/0165-0327(96)00003-1)

Lepine, B.A., Moreno, R.A., Campos, R.N., & Couttolenc, B.F. 2012. Treatment-resistant depression increases health costs and resource utilization. *Revista Brasileira de Psiquiatria*, 34(4): 379–388. <https://doi.org/10.1016/j.rbp.2012.05.009>

Liu, T.Y., Hsieh, J.C., Chen, Y.S., Tu, P.C., Su, T.P., & Chen, L.F. 2012. Different patterns of abnormal gamma oscillatory activity in unipolar and bipolar disorder patients during an implicit emotion task. *Neuropsychologia* 50(7), 1514–1520. <https://doi.org/10.1016/j.neuropsychologia.2012.03.004>

Nemeroff, C.B. 2007 Prevalence and management of treatment-resistant depression. *Journal of Clinical Psychiatry* 68(8), 17–25. <https://doi.org/WOS:000248487100003>

Oribe, N., Onitsuka, T., Hirano, S. et al. 2010. Differentiation between bipolar disorder and schizophrenia revealed by neural oscillation to speech sounds: An MEG study. *Bipolar Disorders* 12(8), 804–812. <https://doi.org/10.1111/j.1399-5618.2010.00876.x>

Roh, S.C., Park, E.J., Shim, M., Lee, S.H. 2016. EEG beta and low gamma power correlates with inattention in patients with major depressive disorder. *Journal of Affective Disorders*, 204, 124–130. <https://doi.org/10.1016/j.jad.2016.06.033>

Seeber, M., Scherer, R., Wagner, J., Solis-Escalante, T., Müller-Putz, G.R. 2015. High and low gamma EEG oscillations in central sensorimotor areas are conversely modulated during the human gait cycle. *NeuroImage* 112, 318–326.
<https://doi.org/10.1016/j.neuroimage.2015.03.045>

Thibodeau, R., Jorgensen, R., Kim, S. 2006. Depression, anxiety, and resting frontal EEG asymmetry: A meta-analytic review. *Journal of Abnormal Psychology* 115(4), 715–729.
<https://doi.org/10.1037/0021-843X.115.4.715>

Uhlhaas, P.J., Singer, W., 2013. High-frequency oscillations and the neurobiology of schizophrenia. *Dialogues Clin. Neurosci.* 15, 301–313. <https://doi.org/24174902>

US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA.* 310(6), 591-608, 2013.