Research Paper

Alpha oscillations predict paroxetine response to low sexual desire in depression

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ABSTRACT

Background: Decreased sexual desire (libido) is one of the most common sexual complaints in patients with depression. It is known that antidepressants have certain effects on sexual life. Paroxetine is one of those antidepressants. However, the sexual adverse effects of paroxetine are unpredictable. This retrospective study aimed at determining the electrophysiological markers of paroxetine treatment effect on sexual desire in patients with depression ($N = 56$).
Methods: Quantitative electroencephalography (QEEG) spectral power across all frequency bands were examined in depressed patients with decreased or normal sexual desire. Analysis of covariance was conducted on baseline qEEG, taking attention condition and severity of depression (Hamilton Depression Rating Scale -HDRS) as covariates.
Results: Patients whose sexual desire did not improve had higher frontal alpha power and impaired attention function at baseline examination.
Limitations: The results could be taken as preliminary due to the modest sample size.
Conclusion: Based on the present findings, it can be concluded that frontal alpha power can be a biomarker of lack of libido improvement after treatment with paroxetine.

1. Introduction

Depressive disorders characterized by feeling of sadness, emptiness, irritableness with impaired cognitive and social functioning is one of the most commonly reported mental illness in psychiatry (American Psychiatric Association, 2013). Approximately 10% of the population reported a lifetime history of depression (Lim et al., 2018). It has become a global burden as its prevalence increased by from 1997 to 2017 (Liu et al., 2020).

It is known that depression has a wide range of effects on an individual ranging from somatic symptoms such as insomnia, loss or increase of appetite, decreased sexual desire to psychological symptoms, e. g., loss of interest, feeling of worthlessness and to cognitive problems such as difficulty in concentration, attention, memory, and processing speed (Zuckerman et al., 2018).

Sexual desire or libido, defined as the biological drive for sexual activity and sex-seeking behavior (Pfaus, 2009), is one of the most negatively affected behavior in depression. Approximately, 25–70% of depressed patients suffer from decreased sexual interest (Clayton et al., 2014). Indeed, the most commonly reported sexual problem for depressed patients before antidepressant treatment is low sexual desire (for women 50%, and for men 40%) (Kennedy and Rizvi, 2009).

Although decreased sexual interest is a characteristic of depression, a general concern for antidepressants is that they further may decrease libido. According to a large French population ELIXIR study (Bonierbale et al., 2003), the number of patients suffering from sexual problems in general is higher for patients treated with Selective Serotonin Reuptake Inhibitors (SSRIs) and tricyclic antidepressants (71%) than untreated depressed patients (65%). While some studies confirm the serious effects of SSRIs on sexual functioning such as delayed ejaculation, absent or

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delayed orgasm (Rosen et al., 1999), more studies are needed to understand the extent of SSRI related sexual dysfunction. Despite studies reporting negative effects of serotonergic antidepressant treatment on sexual functioning, another study (Baldwin et al., 2006) revealed that depressed patients receiving SSRI treatment, e.g., paroxetine exhibited an improvement in sexual satisfaction and sexual function.

The neurological mechanism underlying decreased sexual desire in depression should be clarified to develop the most appropriate treatment strategy. By the help of neuroimaging techniques, the neural correlates of sexual dysfunction can also be investigated. In an fMRI study (Abler et al., 2011), the paroxetine effect on sexual dysfunction was associated with decreased activation in anterior cingulate cortex (ACC) which is related to motivation, emotion, and erotic stimulation. Nonetheless, electrophysiological correlates of decreased sexual desire in depression are scarce. In one of those quantitative electroencephalography (qEEG) studies (Prause et al., 2014), the association between left frontal alpha power and decreased sexual desire was shown. Another study showed that, in depressed individuals, qEEG frontal alpha asymmetry was associated with somatic symptoms including decreased sexual interest (Imperatori et al., 2019).

Given the lack of empirical evidence regarding neurophysiological basis of decreased sexual desire in depression and its treatment, the present study aimed at determining the electrophysiological markers of paroxetine treatment effect on the sexual desire in patients with depression.

2. Methods

The study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonization/ Good Clinical Practice guidelines. All participants provided written informed consent, and the local ethics committee approved the study.

2.1. Participants and procedures

The present retrospective study included patients with depression admitted to Kemal Arıkan Psychiatry Clinic (Istanbul, Turkey). Subjects were examined by the same psychiatrist (M.K.A.) between May 2016 and October 2020. The diagnosis of depression was made in the first interview according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatry Association, 2013). Sexual desire was assessed in the first and second psychiatric interviews by asking participants the following question: "Have you felt a decrease in your level of sexual desire in the last few weeks?" Patients who reported a decrease in sexual desire deemed as having decreased libido. Based on the change in libido status over time subjects were divided into three groups: (1) From decreased to decrease (D-D); (2) From normal to normal (N—N); (3) From decreased to normal (D-N).

Further inclusion criteria were as follows:

(1) Being between 18t65 years of age.
(2) Not using any psychopharmacological agent for at least in the last three weeks.
(3) Measurement of the severity depression by Hamilton Depression Rating Scale (HDRS-17) before and after paroxetine treatment.
(4) Examination of attention by counting backwards from 100 by seven or alternatively spelling "world" backwards.
(5) Prescription of only paroxetine at first interview.
(6) QEEG data recorded before paroxetine treatment.

The first psychiatric examination and qEEG recordings of patients were performed at the same day with the start of paroxetine treatment during when all the patients were drug-free. The second evaluation was done after the paroxetine treatment. Time interval between clinical examination varied depending on symptom severity. In the case of non-response, it may need to wait twelve weeks to make a final clinical decision of treatment response to medication. The present study followed that rule. Patients with a comorbid condition, such as epilepsy, organic mental disorders, intellectual disability (or mental retardation), neurological diseases, any medical illness, and a history of head injury were excluded from the study. As for the treatment, paroxetine was preferred for several reasons. Firstly, it has a strong antidepressant effect. In addition, it is the first line treatment choice in depression in our clinic.

2.2. Data collection and filtering

The files of patients were retrospectively reviewed using information obtained from electronic medical records. Data collection which includes sociodemographic and clinical feature was done by the same experienced psychiatrist. Inclusion criteria were applied as filters. The remaining 56 patients with depression (29 females and 27 males) were included to the statistical analyses.

2.2.1. QEEG recordings

The resting-state qEEG recordings of patients were obtained in a silent room with dim light. A 19-channel (FP1, F7, T3, T5, F3, C3, P3, O1, FZ, CZ, PZ, F4, C4, P4, O2, FP2, F8, T4, and T6) electro-cap was used (Fig. 1). Approximately, 7-minute recording were acquired (3- minute background recording, 30-*sec* open eyes condition, and 3.00-minute closed-eyed condition). Detailed procedures of qEEG recordings and calculation of absolute power can be reached from the previous study (Arıkan et al., 2020).

2.1.2. Statistical analyses

Statistical analyses were performed in SPSS (Version 24.0). Change in libido status was taken as an independent variable while absolute power of each electrode-band pair was taken as dependent variable. Response to paroxetine treatment were determined by minimum 50% decrease in post-treatment HDRS-17 scores. A non-parametric independent sample Kruskal-Wallis test was selected due to the small sample size. Mean difference across three groups were explored. As the difference was found in frontal regions, attention and the severity of depression HDRS-17 were added as covariates to the analysis of covariance test (ANCOVA) Only attention was found to be significant across groups. Finally, pairwise Kruskal-Wallis post-hoc test was applied to the significant electrode-qEEG band pairs adjusted for attention.

3. Results

Participants grouped by change in libido status were homogenous with respect to age, gender, change in attention, dose, and duration of paroxetine but not to pre-treatment HDRS-scale (Table 1). Subjects with normal libido have had lower HDRS scores compared to the groups with decreased libidos at first visit. Decreased libido groups (decreased-to-decreased and decreased-to-normal [D-N]) did not differ in pre-treatment in HDRS-17 scores (Table 1).

3.2. QEEG band powers

Non-parametric Kruskall-Wallis test revealed that libido status groups differed in alpha and beta powers at frontal regions ($p < .05$) (Table 2). After analysis of covariance was applied to significant electrode-band pairs for changed libido status by taking percentage reduction in HDRS-17 and change in attention as covariate, most of the alpha bands preserved to remain significant ($p < .05$) (Table 2). Pairwise comparisons revealed that patients with no change in decreased sexual desire have greater alpha and beta power before paroxetine treatment compared to patients whose libido changed from decreased to normal ($p < .05$) (Table 2). The difference between these two groups were observed at FP1, FP2, F3, F4, Fz, F7, F8 electrodes (Table 2).
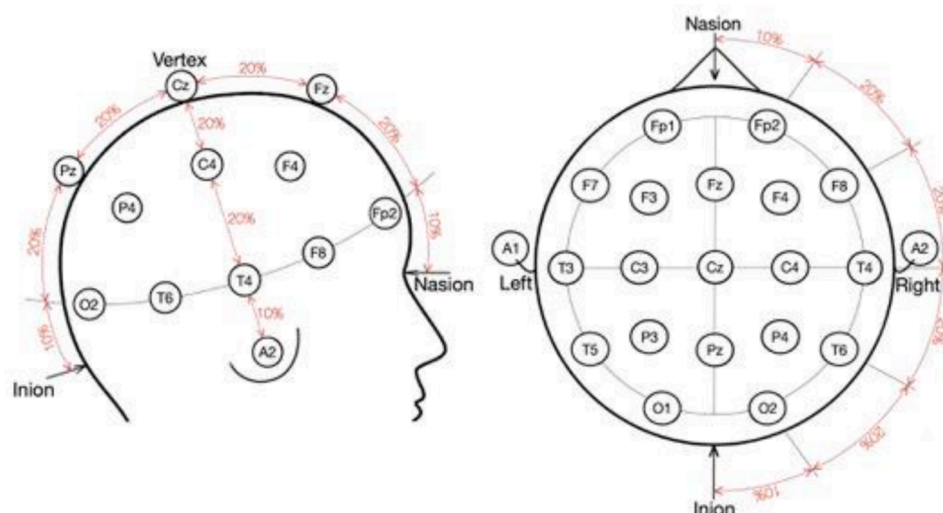
Fig. 1. Electrode placements of international 10–20 system for quantitative electroencephalography (EEG) from side and top views.

Table 1

Number of patients included into the study.

Demographics	Libido Groups		N	M	SD	P
Gender	D-D	Female	12	N/A	N/A	0.856[a]
		Male	11			
	N-N	Female	9			
		Male	10			
	D—N	Female	8			
		Male	6			
	Total	Female	29			
		Male	27			
Age	D-D		23	39.09	12.98	0.119[b]
	N-N		19	34.88	17.71	
	D—N		14	45.36	16.67	
	Total		56	39.04	15.64	
Attention	D-D		23	N/A	N/A	0.640[a]
	N-N		19			
	D—N		14			
	Total		56			
Dose (paroxetine)	D-D		23	30.86	13.11	0.458[b]
	N-N		19	27.65	9.70	
	D—N		14	32.72	10.10	
	Total		56	30.19	11.40	
Duration (weeks)	D-D		23	11.83	22.60	0.717[b]
	N-N		19	8.0	10.09	
	D—N		14	6.50	3.15	
	Total		56	9.73	16.33	
Pre-treatment HDRS-17	D-D		23	27.08	7.62	0.033[b]
	N-N		19	22.68	5.86	
	D—N		14	30.07	8.77	
	Total		56	26.33	7.81	
Post-treatment HDRS-17	D-D		23	6.69	6.31	0.373[b]
	N-N		19	7.11	8.20	
	D—N		14	4.57	5.73	
	Total		56	6.30	6.83	

Note: D-D = From decreased sexual desire to decreased sexual desire. N—N =From normal sexual desire to normal sexual desire. D-N=From decreased sexual desire to normal sexual desire. N/A = Not available.

[a] Pearson Chi-square test result.
[b] Independent Sample Kruskall-Wallis test result.

4. Discussion

The present study revealed that decreased libido is closely correlated with depression and approximately 9–12 weeks of paroxetine therapy is related with the improvement in decreased libido. The major concern was which parameters were effective in this process. So, we found that regardless of the severity of depression, there was a close relationship

between frontal alpha frequencies and attention capacity. Apart from alpha bands, there was only one statistically different beta band which was an alpha variant. If the baseline alpha frequencies are higher and the attention capacity is lower, the treatment response to sexual desire seems very poor.

Electroencephalographic alpha oscillations play a role in depression (Henriques and Davidson, 1991), sexual desire and motivation. Greater alpha power at left hemisphere, alpha asymmetry, and coherence were associated with sexually motivated states (Prause et al., 2014). As for the attention, it is known that libido or sexual desire is a process that is significantly affected by cognition (de Jong, 2009). Electroencephalographic studies measure P300 amplitude, an event related potential component, to explore how individuals with normal or low sexual desire pay attention to auditory or visual sexual stimuli. These studies suggest that subjects with low sexual desire pay less attention to sexual stimuli than those with higher sexual desire (Prause et al., 2008; Vardi et al., 2009).

In our study, there was no significant difference between the groups (D-D, N—N and D-N) in terms of age. However, when female participants were considered, the mean age of the N—N group (34.8) was in the premenopausal period, and the mean age of the D-N group (45.36) was in the perimenopausal period. Some studies report that perimenopausal or postmenopausal women have lower sexual interest or desire than women who have not yet entered the menopausal transition (Dennerstein et al., 1994; Woods et al., 2010). In this context, it can be thought that SSRI treatment has a positive effect on mental problems in the perimenopausal period and normalizes sexual desire in this population. While percentage of premenopausal women in groups were different and this should be mentioned as a limitation, On the other hand, it should be mentioned that no significant difference was found in other studies (Dennerstein et al., 1997; Hawton et al., 1994) between premenopausal and postmenopausal women in terms of sexual desire after age difference was controlled.

Although the present retrospective study has modest sample size, libido status groups were homogenous for several sociodemographic and clinical features, and this should be regarded as a strength of the study. Despite the variation in treatment duration and medication dosage due to individual differences, there were no major confounding variables in the analyses. Further, only the patients who had no co-morbid disorders, were examined by the same psychiatrist, and took paroxetine as monotherapy were included in the retrospective analysis. The main limitation of this study are modest sample size and the lack of control condition to the treatment group; therefore, the present findings should not be evaluated as showing a causal relationship between

Table 2

Descriptive statistics of qEEG absolute powers based on patients' changed libido condition.

QEEG bands	Libido Change	N	M	SD	ANCOVA (p*) HDRS change	Attention change	Libido change	Kruskal Wallis Pairwise (p*) DN -NN	DN - DD	NN - DD
AP FP1 Alpha 2	D-D	23	2,38	0,65	0,47	**0,01**	**0,00**	0.778	**0.012**	0.190
	N-N	19	1,91	0,80						
	D—N	14	1,65	0,55						
	Total	56	2,04	0,74						
AP FP1 Beta 1	D-D	23	1,64	0,47	0,49	**0,04**	**0,02**	0.628	**0.006**	0.146
	N-N	19	1,40	0,50						
	D—N	14	1,22	0,31						
	Total	56	1,45	0,47						
AP FP2 Alpha 2	D-D	23	2,41	0,65	0,51	**0,01**	**0,00**	0.684	**0.008**	0.159
	N-N	19	1,94	0,79						
	D—N	14	1,68	0,52						
	Total	56	2,07	0,73						
AP FP2 Beta 1	D-D	23	1,68	0,48	0,70	0,10	**0,02**	0.962	**0.008**	0.090
	N-N	19	1,38	0,51						
	D—N	14	1,26	0,36						
	Total	56	1,48	0,49						
AP F4 Alpha 2	D-D	23	2,43	0,67	0,46	**0,02**	**0,02**	1.000	**0.040**	0.193
	N-N	19	1,95	0,86						
	D—N	14	1,80	0,53						
	Total	56	2,11	0,75						
AP Fz Alpha 2	D-D	23	2,47	0,78	0,84	0,09	**0,03**	1.000	0.095	0.127
	N-N	19	1,97	0,82						
	D—N	14	1,89	0,61						
	Total	56	2,16	0,79						
AP F8 Alpha 2	D-D	23	2,02	0,64	0,45	**0,01**	**0,01**	1.000	**0.047**	0.018
	N-N	19	1,60	0,74						
	D—N	14	1,47	0,48						
	Total	56	1,74	0,67						
AP F3 Alpha 2	D-D	23	2,45	0,67	0,50	**0,05**	**0,02**	1.000	**0.043**	0.018
	N-N	19	2,00	0,86						
	D—N	14	1,83	0,60						
	Total	56	2,14	0,76						
AP O1 Beta 3	D-D	23	1,86	0,44	0,37	0,88	0,06	N/A		
	N-N	19	1,64	0,48						
	D—N	14	1,48	0,35						
	Total	56	1,69	0,46						
AP F7 Alpha 2	D-D	23	2,08	0,62	0,32	**0,02**	**0,01**	0.857	**0.021**	0.246
	N-N	19	1,69	0,74						
	D—N	14	1,48	0,52						
	Total	56	1,80	0,68						
AP F7 Beta 1	D-D	23	1,41	0,35	0,39	0,11	0,10	N/A		
	N-N	19	1,32	0,51						
	D—N	14	1,11	0,31						
	Total	56	1,31	0,41						
AP T4 High Gamma	D-D	23	0,02	0,03	0,20	0,46	0,15	N/A		
	N-N	19	0,04	0,07						
	D—N	14	0,02	0,02						
	Total	56	0,03	0,05						

Note: AP = Absolute Power, DD = From decreased sexual desire to decreased sexual desire. NN =From normal sexual desire to normal sexual desire. DN=From decreased sexual desire to normal sexual desire.

* $p < .05$.

N/A = Not available. QEEG bands losing statistical significance after adjused for change in HDRS and in attention were excluded from post-hoc test.

paroxetine therapy and the improvement in decreased libido in depressed patients. Another limitation is that sexual desire was not evaluated with a standard rating scale, but only on a single question.

Consequently, the findings suggest that to decide whether to insist on the same medication, a clinician should consider the above-mentioned electrophysiological and cognitive parameters. We did not have a chance to consider pharmacogenetic parameters for this study. However, if pharmacogenetic parameters point that paroxetine is the only choice for treating depression, other attention enhancing therapies efficient in treating low-sexual desire, such as cognitive behavior therapy and mindfulness therapy (Arora and Brotto, 2017) could be considered as adjuvant attempts to paroxetine treatment.

Contributors

Author 1 and author 6 designed the research and wrote the protocol. Author 2, author 4, and author 5 conducted literature searches and provided summaries of previous research studies. Author 3 conducted the statistical analysis. Author 4 designed the Fig. 1. Author 2 wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Declaration of Competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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