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Sex Differences in the Antidepressant and Neurocognitive Effects of Nonconvulsive Electrotherapy in Patients with Treatment-Refractory Depression

ABSTRACT

Objective: The objective of this study was to examine sex differences in the antidepressant and neurocognitive effects of adjunctive nonconvulsive electrotherapy (NET) in patients with treatment-refractory depression (TRD), which has not yet been thoroughly investigated.

Methods: The study enrolled 20 patients with TRD, comprising 11 males and 9 females, who underwent a series of 6 NET sessions. The 17-item Hamilton Depression Rating Scale (HAMD-17) was used to assess depressive symptoms, response, and remission at baseline and after the first, third, and sixth NET sessions. The Wisconsin Card Sorting Test (WCST) was used to assess neurocognitive function at baseline and after the sixth NET session.

Results: After completing 6 NET sessions, female patients experiencing TRD exhibited a higher inclination toward achieving an antidepressant response (77.8% vs. 45.5%, $P = .197$) and antidepressant remission (22.2% vs. 0%, $P = .189$) when compared to their male counterparts. No significant differences were observed in changes in the HAMD-17 and WCST subscale scores (all $P > .05$), including completing classification number, total error number, persistent error number, and random error number between males and females. Additionally, no significant correlations were observed between baseline WCST subscale scores and changes in HAMD-17 scores or endpoint scores, irrespective of sex (all $P > .05$).

Conclusion: These pilot findings suggest that female patients with TRD exhibited increased rates of achieving antidepressant response and remission after undergoing NET. However, further studies should be conducted to confirm these findings.

Keywords: Nonconvulsive electrotherapy, sex differences, treatment-refractory depression, response, remission

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Introduction

Major depressive disorder (MDD) is a common and severe psychiatric disorder worldwide, often resulting in chronic disability.[1] This not only impacts the affected individuals' social functioning but also places substantial burdens on families and society at large.[2] According to data from the China Mental Health Survey,[3] MDD was found to have a lifetime prevalence of 3.4% and a 12-month prevalence of 2.1%, ranking as the second leading cause of years lived with disability in China since 2010.[4] Approximately, 55.3% of patients with MDD were diagnosed with treatment-refractory depression (TRD).[5] Despite significant advances in treatment options over recent decades, effective strategies for TRD remain deficient.[6,7]

Recent studies on TRD have highlighted the influence of sex differences,[8,9] which hold significant relevance in epidemiology,[10] clinical characteristics,[11-13] and therapeutic outcomes associated with TRD.[14-16] Notably, large-scale epidemiological surveys have revealed a higher prevalence of depressive disorders in females compared with males,[17] although males might be predisposed to TRD.[10] Additionally, numerous studies have indicated that females with

TRD tend to experience more severe depressive and anxiety symptoms than males[11-13] due to different neuropathological mechanisms.[18,19] Furthermore, a substantial body of evidence indicated that sex-related factors possess the potential to influence the outcomes of treatments (both pharmacological and non-pharmacological treatments) for patients with TRD,[14-16] this underscores the significance of taking into account sex disparities when evaluating treatment effectiveness. For instance, males and females with TRD exhibit varying responses to antidepressant augmentation strategies, involving mood stabilizers, antipsychotics, or a combination of both, with females deriving significantly greater benefit in one study.[14] Another study reported that females exhibited a poorer responsiveness to tricyclic antidepressants relative to males.[11] With regard to non-pharmacological treatments, sex-specific research on TRD treatment effectiveness remains limited. While one study found that electroconvulsive therapy (ECT) for MDD yielded equally effective outcomes in both sexes,[20] another study identified interleukin-6 as a significant predictor of antidepressant effects for females but not males with TRD.[16]

Nonconvulsive electrotherapy (NET), a novel therapeutic approach for treating TRD, involves applying electrical brain stimulation similar to the standard ECT procedure. Unlike the standard ECT technique, NET is characterized by its reduced likelihood of causing adverse neurocognitive effects because the electric stimulation used does not reach the intensity required to induce convulsions.[21,22] Animal studies have provided preliminary evidence that the use of subconvulsive electrical stimulation can elicit similar antidepressant effects to ECT without causing seizures.[23] Moreover, a recent systematic review has demonstrated the safety and tolerability of adjunctive NET as an effective treatment option for patients with depression, without any occurrences of serious neurocognitive impairments.[24]

It has not been studied whether Chinese patients with TRD experience different antidepressant and neurocognitive effects in response to NET based on their gender. However, existing evidence suggests that NET holds promise as a therapeutic approach for individuals with TRD.[21,25] Hence, investigating potential disparities in sex could represent a significant step toward gaining insights into the underlying biological mechanisms of this treatment regimen. Furthermore, recent research findings indicate that the baseline neurocognitive performance does not serve as a prognostic indicator for the antidepressant efficacy of ECT in individuals with depression.[26,27] More importantly, our previous research has revealed that baseline neurocognitive performance does not predict NET antidepressant outcomes among patients with TRD,[21] however, it remains unclear whether there exist in-depth sex differences in the relationship between baseline neurocognitive performance and antidepressant outcomes.

Therefore, the objective of this study was to examine the impact of sex on the outcomes of antidepressant and neurocognitive measures after 6 NET sessions in patients diagnosed with TRD. Furthermore, the sex differences in the associations between neurocognitive performance at baseline and the antidepressant outcomes of NET were also examined. It was hypothesized that sex differences exist in the efficacy of 6 NET sessions for ameliorating depressive symptoms and enhancing neurocognitive performance as well as in the correlations between neurocognitive performance at baseline and the antidepressant outcomes among patients with TRD.

MAIN POINTS

- *Female patients with treatment-refractory depression (TRD) exhibited heightened responsiveness to 6-session nonconvulsive electrotherapy (NET) compared to their male counterparts.*
- *The effectiveness of NET in rapidly alleviating depressive symptoms was consistent between the sexes.*
- *No significant sex differences were observed in the impact on neurocognitive function after 6 sessions of NET.*
- *No sex differences were observed in the correlations between baseline neurocognitive function and the severity of depressive symptoms.*

Material and Methods

Participants

Between January 2017 and December 2017, a single-arm prospective study was conducted comprising 11 male and 9 female participants with TRD who had undergone NET. The research protocol for this single-arm prospective study was approved by the Research and Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University (Approval No: 2016-005). Notably, this university-affiliated teaching hospital in Guangdong Province has 1800 psychiatric beds and conducts up to 1500 ECT sessions per month. All participants provided written consent for their participation in the study.

The inclusion criteria for this study have been previously described.[21] In summary, all male (n = 11) and female (n = 9) inpatients met the following inclusion criteria: (1) ages ranging from 18 to 50 years; (2) a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria;[28] (3) currently experiencing a major depressive episode with 17-item Hamilton Depression Rating Scale (HAMD-17)[29] scores of ≥17 during the screening; (4) diagnosed with TRD, defined as a failure to respond to 2 courses of antidepressants;[30] and (5) not having undergone other non-pharmacological intervention (e.g., transcranial magnetic stimulation, ECT and psychotherapy) within the past 3 months.

The exclusion criteria employed in this study were as follows: (1) individuals meeting the DSM-IV criteria for any other serious mental disorders, including but not limited to unstable and severe somatic conditions (i.e., infectious disease or cancer), schizophrenia, or alcohol/substance use disorder; (2) participants who were breastfeeding or pregnant; (3) individuals with a previous history of seizures; and (4) patients with an implanted foreign body, such as an intracranial electrode or pacemaker.

Nonconvulsive Electrotherapy Parameters

The NET was delivered by the Physical Therapy Department at the Affiliated Brain Hospital of Guangzhou Medical University. Participants received a prescribed course of bilateral NET, as determined by their attending psychiatrists, administered thrice a week for 2 weeks, with the participant under general anesthesia. Comprehensive details regarding the NET parameters have been previously described.[21] In brief, NET was administered employing the following settings: pulse width of 0.5 ms, current intensity of 900 mA, and frequency of 20 Hz. This was conducted using a Thymatron IV system integrated with an ECT instrument (Somatics LLC, Lake Bluff, IL, USA). As recommended

previously,[25] the energy for NET in this study was set at 1/8 of the standard ECT dose using the "half-age" stimulation strategy for ECT dosing. Propofol anesthesia was administered at a dose of 1 mg/kg, along with succinylcholine at a dose of 1 mg/kg and atropine at a dose of 1 mg to induce muscle relaxation and suppress glandular secretion during each NET session. Electroencephalography was applied to monitor the seizures. A psychiatrist regularly recorded vital signs, including systolic and diastolic blood pressures, pulse rate, and respiratory rate, throughout each NET session. During NET, all patients with TRD continued their use of psychotropic medications.

Clinical Interview and Assessments

Two attending physicians conducted face-to-face interviews for all assessments. A self-reported questionnaire was specially designed for this study to collect patients' basic demographic and clinical data, including age, body mass index (BMI), and marital status. The primary outcome measure focused on the improvement of depressive symptoms as measured by the HAMD-17 after a course of NET. As secondary outcomes, "antidepressant response" was defined after a course of NET as a reduction of ≥60% from baseline HAMD-17 scores,[31,32] and "antidepressant remission" as achieving HAMD-17 scores of ≤7.[33] Assessments using the HAMD-17 scale were conducted at baseline and a day after the first, third, and last NET session. A trained neuropsychological technician employed the Wisconsin Card Sorting Test (WCST)[34] to evaluate the neurocognitive effects of NET at baseline and the last NET session. The WCST encompasses 4 subscales, namely completing classification number, total error number, persistent error number, and random error number. It is designed to measure neurocognitive performance and is widely used in the assessment of major mental disorders, particularly for MDD.[35]

Statistical Analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences version 24.0 (IBM SPSS Corp.; Armonk, NY, USA), and statistical significance was set at $P < .05$. Descriptive statistics were reported as median (minimum–maximum) for non-normally distributed variables, mean ± SD for the normally distributed variables. Categorical variables were presented as frequencies and percentages. The Student's *t*-test or the Mann–Whitney *U*-test was used for continuous variables to compare the differences in demographic and clinical variables between the male and female groups, as appropriate. Fisher's exact tests were used for categorical variables.

The linear mixed model analysis was performed to compare the HAMD-17 scores and the 4 subscales scores of the WCST between the female and male groups following 6 NET sessions. More specifically, groups (males versus females), each assessment time point, and time by group interaction were entered as explanatory variables (fixed effects), each assessment time point was entered as random effects, and the HAMD-17 scores and the 4 subscale scores of the WCST were entered as response variables. This analysis controlled for baseline levels of these measurements. We used a linear mixed model analysis to compare the baseline with the first, third, and sixth NET periods within each group. Similarly, group differences in changes in depressive symptoms from the baseline to the first, third, and sixth NET periods were also compared using a linear mixed model analysis. Finally, group differences in the correlations between WCST subscales at baseline and HAMD-17 change/endpoint scores were analyzed using the Pearson correlation coefficient.

Results

Twenty inpatients, comprising 11 males and 9 females, were included in this study. No significant differences were observed between the male and female patients in terms of demographic and clinical characteristics, including age, BMI, marital status, and baseline HAMD-17 and WCST subscale scores (Table 1).

Sex Differences in Antidepressant Effects of Nonconvulsive Electrotherapy

Following the completion of 6 NET sessions, the response rates for males and females were 45.5% and 77.8% ($P = .197$), respectively,

Table 1. Comparisons of Demographic and Clinical Characteristics Between Male and Female Patients at Baseline

	Males (n = 11)		Females (n = 9)		
Variables	**Mean**	**SD**	**Mean**	**SD**	***P***
BMI (kg/m^2)	20.7	1.1	20.3	1.6	.450
Baseline HAMD-17 scores	26.2	2.1	26.2	2.8	.971
WCST at Baseline					
Total error number	9.4	2.3	8.2	3.5	.388
Random error number	7.1	1.8	6.8	3.2	.785
Variables	**Median**	**Minimum–Maximum**	**Median**	**Minimum–Maximum**	***P***
Age[a] (years)	29	21-43	27	21-57	.882
WCST at Baseline					
Completing classification number[a]	7	5-8	6	2-7	.824
Persistent error number[a]	1	0-3	1	0-4	.412
Variables	**n**	**%**	**n**	**%**	***P***
Married[b]	4	36.4	4	44.4	1.000
Antidepressant responders[b]	5	45.5	7	77.8	.197
Antidepressant remitters[b]	0	0	2	22.2	.189

BMI, body mass index; HAMD-17, 17-Item Hamilton Depression Rating Scale; WCST, Wisconsin Card Sorting Test.
[a]Mann–Whitney *U*-test.
[b]Fisher's exact test.

Table 2. Comparisons of the 4 Subscales Scores of the Wisconsin Card Sorting Test and 17-item Hamilton Depression Rating Scale Between Male and Female Patients Using Linear Mixed Model Analysis

	Group-By-Time Interaction		Time Main Effect		Group Main Effect	
Variables	*F*	*P*	*F*	*P*	*F*	*P*
HAMD-17 scores	0.69	.564	187.97	**<.001**	3.31	.085
WCST						
Completing classification number	0.11	.739	10.98	**.004**	2.03	.171
Total error number	0.02	.893	17.46	**.001**	1.05	.320
Persistent error number	0.15	.707	7.27	**.015**	1.68	.211
Random error number	0.01	.924	6.53	**.020**	0.20	.657

Bolded values indicate $P < .05$.
HAMD-17, 17-Item Hamilton Depression Rating Scale; WCST, Wisconsin Card Sorting Test. Note: each baseline variable serves as a covariate.

whereas the remission rates were 0% and 22.2% ($P = .189$) (Table 1). In the linear mixed model analysis, a significant main effect over time was identified for HAMD-17 scores ($P < .001$). No significant interactions were observed in terms of group-by-time ($P = .564$) and group main effect ($P = .085$) (Table 2).

A significant reduction in HAMD-17 mean scores was observed from baseline to any of the indicated times in either male (all $P < .001$) or female patients (all $P < .001$) (Figure 1 and Supplementary Table 1). There were no significant sex differences regarding changes in depressive symptoms from the baseline to the first ($P = .295$), third ($P = .332$), and sixth NET periods ($P = .587$) (Figure 1 and Supplementary Table 2).

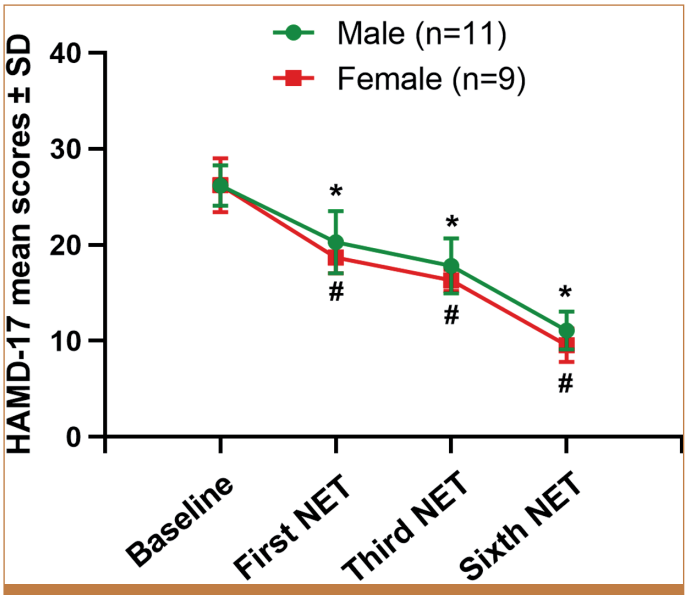

Figure 1. Comparisons of depressive symptoms from baseline to the sixth NET session in male and female patients with TRD.
***Significant differences were found at any of the indicated times when compared to baseline among males ($P < .001$).**
#Significant differences were found at any of the indicated times when compared to baseline among females ($P < .001$).
No significant difference was found between males and females at any of the indicated times ($P > .05$).
HAMD-17, 17-item Hamilton Depression Rating Scale; NET, nonconvulsive electrotherapy; TRD, treatment-refractory depression.

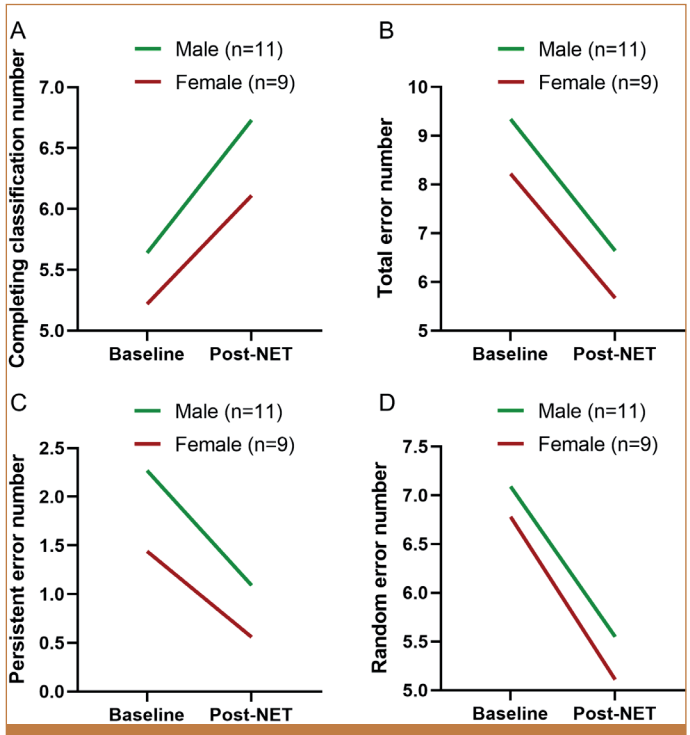

Figure 2. Comparisons of the 4 subscales scores of the WCST from baseline to the sixth NET session in male and female patients with TRD.
Note: no significant differences were found regarding the 4 subscales scores of WCST between males and females at any of the indicated times ($P > .05$).
NET, nonconvulsive electrotherapy; TRD, treatment-refractory depression; WCST, Wisconsin Card Sorting Test.

Sex Differences in Neurocognitive effects of Nonconvulsive Electrotherapy

In the linear mixed model analysis, a significant main effect over time was observed for each domain of the WCST, including completing classification number ($P = .004$), total error number ($P = .001$), persistent error number ($P = .015$), and random error number ($P = .020$) (Table 2). However, no significant interactions were observed in terms of group-by-time or group main effect in each domain of the WCST (all $P > .05$) (Table 2). Furthermore, the improvement in neurocognitive performance, assessed using each domain of the WCST exhibited no differences between males and females when comparing improvements from baseline to the endpoint (Figure 2).

Sex Differences in the Correlations Between Neurocognitive Performance at Baseline and the Antidepressant Effects of Nonconvulsive Electrotherapy

As presented in Table 3, no significant correlations were observed between baseline WCST subscale scores and HAMD-17 change/endpoint scores among females or males (all $P > .05$).

Table 3. Correlation Analysis Between the 4 Subscales Scores of the Wisconsin Card Sorting Test at Baseline and the Antidepressant Outcomes of Nonconvulsive Electrotherapy

	Males (n = 11)		Females (n = 9)	
Variables	HAMD-17 Scores After Post-NET	Change in HAMD-17 Scores	HAMD-17 Scores After Post-NET	Change in HAMD-17 Scores
WCST at Baseline				
Completing classification number	$r = -0.094$	$r = -0.431$	$r = 0.017$	$r = -0.200$
	$P = .783$	$P = .185$	$P = .965$	$P = .606$
Total error number	$r = 0.588$	$r = -0.496$	$r = -0.238$	$r = 0.423$
	$P = .057$	$P = .120$	$P = .537$	$P = .257$
Persistent error number	$r = 0.467$	$r = -0.034$	$r = -0.289$	$r = 0.358$
	$P = .147$	$P = .920$	$P = .451$	$P = .344$
Random error number	$r = 0.090$	$r = -0.202$	$r = -0.177$	$r = 0.232$
	$P = .793$	$P = .551$	$P = .648$	$P = .548$

HAMD-17, 17-item Hamilton Depression Rating Scale; NET, nonconvulsive electrotherapy; *r*, Pearson coefficient of correlation; WCST, Wisconsin Card Sorting Test.

Discussion

To the best of our knowledge, this is the first study to investigate sex differences concerning the antidepressant and neurocognitive effects of 6 NET sessions among patients with TRD. Additionally, it delves into the correlations between baseline neurocognitive function and the severity of depressive symptoms. The primary findings of the study were as follows: (1) female patients with TRD exhibited a heightened responsiveness to 6-session NET compared with their male counterparts; (2) the effectiveness of NET in rapidly alleviating depressive symptoms, as measured by the HAMD-17, was consistent between sexes in patients with TRD; (3) no significant sex differences were observed in the impact on neurocognitive function, as measured by the WCST after 6 sessions of NET; and (4) no sex differences were observed in the correlations between the baseline neurocognitive function and the severity of depressive symptoms.

While previous research had already indicated the effectiveness of NET in treating patients with TRD,[21] our study extends these findings by revealing that the response rates and remission rates achieved through 6 NET sessions were significantly higher in female patients with TRD compared with their male counterparts, indicating that sex might influence the response to NET. This finding aligns with a recent study on ECT, which reported a higher antidepressant response rate in females (78.0%) compared with males (54.0%).[36] The findings of previous studies examining sex differences in patients with MDD undergoing other treatments, such as transcranial magnetic stimulation[37] and ketamine[38] were inconsistent. For instance, a recent study found that clinical outcomes were superior in females who received transcranial magnetic stimulation compared to males.[37] However, a randomized controlled trial (RCT) did not find differential antidepressant efficacy (assessed by the 6-item HAM-D), among males and females receiving varying doses of ketamine (i.e., 0.1, 0.2, 0.5, and 1.0 mg/kg) for TRD treatment.[38] The inconsistency of these findings might be attributed, in part, to variations in study design, adopted treatments, study duration, selected measurements, and other factors.

In our study, an initial investigation into potential neurocognitive differences between sexes in terms of NET was conducted and no significant sex differences were observed in the impact on neurocognitive function after 6 sessions of NET. However, sex-based differences in the neurocognitive effects of ECT have been examined in previous research.[39,40] Several studies have demonstrated that the adverse effect of ECT on neurocognitive function is more pronounced in females compared with males.[39,40] For instance, Sinclair et al[39] observed that after 4 ECT sessions, females exhibited more significant cognitive deficits than males, as assessed using the Spatial Recognition Memory task from the Cambridge Neuropsychological Test Automated Battery. Another study reported that ECT resulted in greater impairment in autobiographical memory in females compared with males, as measured by the Autobiographical Memory Interview-Short Form.[40] This observed pattern of sex differences might be attributed to the fact that the electrical dosage is not adjusted according to sex in clinical practice, despite females having markedly lower seizure thresholds than their male counterparts.[40,41] As a result, females might receive higher electrical doses relative to their seizure thresholds, potentially leading to more severe cognitive deficits compared with males. Unlike ECT, our study reported that NET does not produce sex-specific adverse effects on cognitive function. This suggests that NET might represent a safe treatment option to a certain extent. One plausible explanation for this finding is that the electrical stimulation used in NET is of a small magnitude insufficient to elicit discernible impacts on neurocognitive function in males or females. Nevertheless, it is imperative to interpret these results with caution, and further research will be necessary to validate our findings.

No sex differences were observed in the correlations between the baseline neurocognitive function and the antidepressant effects after 6 NET sessions. One study reported that interactions between neurocognitive function and childhood maltreatment could serve as predictors of antidepressant outcomes in individuals with MDD, and these predictors were associated with activities of the right dorsolateral prefrontal cortex.[42] However, whether such sex-specific differences exist in this context remains unclear. Furthermore, a 4-year longitudinal study involving 285 never-depressed adolescents reported a sex difference between baseline neurocognitive function and depressive episodes.[43] Specifically, the study found that the baseline neurocognitive performance was predictive of the first onset of depressive episodes in boys but not in girls.[43] However, our study focused on a distinct sample comprising patients with TRD undergoing NET and did not find a similar sex-related difference between neurocognitive performance and depressive symptoms, regardless of symptom severity or change.

This study has several limitations. First, the observed sex-related disparities in the antidepressant and neurocognitive effects of NET might be influenced by the relatively small sample size of this preliminary study. Second, existing medications might affect the antidepressant and neurocognitive effects of NET. Third, due to the lack of follow-up visits after treatment, it was not possible to investigate whether sex differences of NET require a longer time to manifest. Fourth, subjective evaluations are inevitable without a control group. Fifth, no additional data pertaining to the medications was collected. However, it is noteworthy to emphasize that the individuals involved in this study can be regarded as representative of patients with TRD in real-world settings, as they continued with medication usage to address their depressive symptoms. Finally, this study employed

an open-label real-world design instead of an RCT, and the present study was a post hoc secondary analysis of a sample of patients with TRD. Therefore, future research in this area should aim to address these limitations.

In conclusion, the present preliminary study indicated that female patients with TRD exhibit higher rates of antidepressant response and remission after undergoing NET. However, to establish the robustness of these findings, further research of a larger sample is warranted.

Availability of data and materials: *The data that support the findings of this study are available from the corresponding author upon reasonable request.*

Ethics Committee Approval: *This study was approved by Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University, (Approval No: 2016-005, Date: January 16, 2016).*

Informed Consent: *Written informed consent was obtained from the patients who agreed to take part in the study.*

Peer-review: *Externally peer-reviewed.*

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References

1. Johansson C, Jansson M, Linnér L, et al. Genetics of affective disorders. *Eur Neuropsychopharmacol*. 2001;11(6):385-394. [CrossRef]
2. Monroe SM, Harkness KL. Major depression and its recurrences: life course matters. *Annu Rev Clin Psychol*. 2022;18:329-357. [CrossRef]
3. Huang Y, Wang Y, Wang H, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *Lancet Psychiatry*. 2019;6(3):211-224. [CrossRef]
4. Yang G, Wang Y, Zeng Y, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;381(9882):1987-2015. [CrossRef]
5. Thomas L, Kessler D, Campbell J, et al. Prevalence of treatment-resistant depression in primary care: cross-sectional data. *Br J Gen Pract*. 2013;63(617):e852-e858. [CrossRef]
6. Kverno KS, Mangano E. Treatment-resistant depression: approaches to treatment. *J Psychosoc Nurs Ment Health Serv*. 2021;59(9):7-11. [CrossRef]
7. Stimpson N, Agrawal N, Lewis G. Randomised controlled trials investigating pharmacological and psychological interventions for treatment-refractory depression. Systematic review. *Br J Psychiatry*. 2002;181:284-294. [CrossRef]
8. Millard SJ, Weston-Green K, Newell KA. The Wistar-Kyoto rat model of endogenous depression: a tool for exploring treatment resistance with an urgent need to focus on sex differences. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;101:109908. [CrossRef]
9. Carlberg L, Schosser A, Calati R, et al. Association study of CREB1 polymorphisms and suicidality in MDD: results from a European multicenter study on treatment resistant depression. *Int J Neurosci*. 2015;125(5):336-343. [CrossRef]
10. Lähteenvuo M, Taipale H, Tanskanen A, Rannanpää S, Tiihonen J. Courses of treatment and risk factors for treatment-resistant depression in Finnish primary and special healthcare: a nationwide cohort study. *J Affect Disord*. 2022;308:236-242. [CrossRef]
11. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):18-25.
12. Bangasser DA, Cuarenta A. Sex differences in anxiety and depression: circuits and mechanisms. *Nat Rev Neurosci*. 2021;22(11):674-684. [CrossRef]
13. Strawn JR, Aaronson ST, Elmaadawi AZ, et al. Treatment-resistant depression in adolescents: clinical features and measurement of treatment resistance. *J Child Adolesc Psychopharmacol*. 2020;30(4):261-266. [CrossRef]
14. Moderie C, Nuñez N, Fielding A, Comai S, Gobbi G. Sex differences in responses to antidepressant augmentations in rreatment-resistant depression. *Int J Neuropsychopharmacol*. 2022;25(6):479-488. [CrossRef]
15. Haq AU, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ. Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. *J Clin Psychiatry*. 2015;76(10):1374-1384. [CrossRef]
16. Kruse JL, Congdon E, Olmstead R, et al. Inflammation and improvement of depression following electroconvulsive therapy in treatment-resistant depression. *J Clin Psychiatry*. 2018;79(2) [CrossRef]
17. Lu J, Xu X, Huang Y, et al. Prevalence of depressive disorders and treatment in China: a cross-sectional epidemiological study. *Lancet Psychiatry*. 2021;8(11):981-990. [CrossRef]
18. Sun J, Luo Y, Ma Y, et al. Sex differences of the functional brain activity in treatment-resistant depression: a resting-state functional magnetic resonance study. *Brain Sci*. 2022;12(12) [CrossRef]
19. Amiri S, Arbabi M, Kazemi K, Parvaresh-Rizi M, Mirbagheri MM. Characterization of brain functional connectivity in treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;111:110346. [CrossRef]
20. Blanken MAJT, Oudega ML, Hoogendoorn AW, et al. Sex-specifics of ECT outcome. *J Affect Disord*. 2023;326:243-248. [CrossRef]
21. Zheng W, Jiang ML, He HB, et al. A preliminary study of adjunctive non-convulsive electrotherapy for treatment-refractory depression. *Psychiatr Q*. 2021;92(1):311-320. [CrossRef]
22. Perciaccante A, Coralli A, Cambioli L, Riva MA. Nonconvulsive electrotherapy in psychiatry: the treatment of the mental disorders of the Norwegian painter Edvard Munch. *Bipolar Disord*. 2017;19(2):72-73. [CrossRef]
23. Gersner R, Toth E, Isserles M, Zangen A. Site-specific antidepressant effects of repeated subconvulsive electrical stimulation: potential role of brain-derived neurotrophic factor. *Biol Psychiatry*. 2010;67(2):125-132. [CrossRef]
24. Cai DB, Zhou HR, Liang WN, et al. Adjunctive nonconvulsive electrotherapy for patients with depression: a systematic review. *Psychiatr Q*. 2021;92(4):1645-1656. [CrossRef]
25. Regenold WT, Noorani RJ, Piez D, Patel P. Nonconvulsive electrotherapy for treatment resistant unipolar and bipolar major depressive disorder: a proof-of-concept trial. *Brain Stimul*. 2015;8(5):855-861. [CrossRef]
26. Bjølseth TM, Engedal K, Benth JŠ, Dybedal GS, Gaarden TL, Tanum L. Baseline cognitive function does not predict the treatment outcome of

electroconvulsive therapy (ECT) in late-life depression. *J Affect Disord*. 2015;185:67-75. [CrossRef]
27. Luccarelli J, Forester BP, Dooley M, et al. The effects of baseline impaired global cognitive function on the efficacy and cognitive effects of electroconvulsive therapy in geriatric patients: a retrospective cohort study. *Am J Geriatr Psychiatry*. 2022;30(7):790-798. [CrossRef]
28. American Psychological Association, American Psychiatric Association. *Structured Clinical Interview for DSM-IV*. Washington, DC: American Psychiatric Press; 1994.
29. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56-62. [CrossRef]
30. Zheng W, Zhou YL, Liu WJ, et al. Investigation of medical effect of multiple ketamine infusions on patients with major depressive disorder. *J Psychopharmacol*. 2019;33(4):494-501. [CrossRef]
31. Heijnen WT, Birkenhäger TK, Wierdsma AI, van den Broek WW. Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. *J Clin Psychopharmacol*. 2010;30(5):616-619. [CrossRef]
32. Lin CH, Chen MC, Yang WC, Lane HY. Early improvement predicts outcome of major depressive patients treated with electroconvulsive therapy. *Eur Neuropsychopharmacol*. 2016;26(2):225-233. [CrossRef]
33. Lin HS, Lin CH. Early improvement in HAMD-17 and HAMD-6 scores predicts ultimate response and remission for depressed patients treated with fluoxetine or ECT. *J Affect Disord*. 2019;245:91-97. [CrossRef]
34. Channon S. Executive dysfunction in depression: the Wisconsin Card Sorting Test. *J Affect Disord*. 1996;39(2):107-114. [CrossRef]
35. Gardizi E, King JP, McNeely HE, Vaz SM. Comparability of the WCST and WCST-64 in the assessment of first-episode psychosis. *Psychol Assess*. 2019;31(2):271-276. [CrossRef]
36. Magid M, Truong L, Trevino K, Husain M. Efficacy of right unilateral ultrabrief pulse width ECT: a preliminary report. *J ECT*. 2013;29(4):258-264. [CrossRef]
37. Sackeim HA, Aaronson ST, Carpenter LL, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with transcranial Magnetic Stimulation. *J Affect Disord*. 2020;277:65-74. [CrossRef]
38. Freeman MP, Papakostas GI, Hoeppner B, et al. Sex differences in response to ketamine as a rapidly acting intervention for treatment resistant depression. *J Psychiatr Res*. 2019;110:166-171. [CrossRef]
39. Sinclair JE, Fernie G, Bennett DM, Reid IC, Cameron IM. Assessing the association between electrical stimulation dose, subsequent cognitive function and depression severity in patients receiving bilateral electroconvulsive therapy for major depressive disorder. *J ECT*. 2016;32(3):159-163. [CrossRef]
40. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology*. 2007;32(1):244-254. [CrossRef]
41. Sackeim H, Decina P, Prohovnik I, Malitz S. Seizure threshold in electroconvulsive therapy. Effects of sex, age, electrode placement, and number of treatments. *Arch Gen Psychiatry*. 1987;44(4):355-360. [CrossRef]
42. Miller S, McTeague LM, Gyurak A, et al. Cognitive-childhood maltreatment interactions in the prediction of antidepressant outcome in major depressive disorder patients: results from the iSPOT-D trial. *Depress Anxiety*. 2015;32(8):594-604. [CrossRef]
43. Stange JP, Connolly SL, Burke TA, et al. Inflexible cognition predicts first onset of major depressive episodes in adolescence. *Depress Anxiety*. 2016;33(11):1005-1012. [CrossRef]

Supplementary Table 1. Comparisons of HAMD-17 scores between the baseline and the first, third, sixth NET period

	Males (n = 11)		Females (n = 9)	
Time	**mean±SD**	***P*** [a]	**mean±SD**	***p*** [a]
Baseline	26.18 ± 2.01	NA	26.22 ± 2.82	NA
First NET	20.27 ± 3.23	<.001	18.67 ± 1.66	<.001
Third NET	17.82 ± 2.86	<.001	16.32 ± 1.12	<.001
Sixth NET	11.09 ± 1.97	<.001	9.56 ± 1.74	<.001

[a]The differences between baseline and the first, third, and sixth NET period within each group.
Abbreviations: HAMD-17=The 17-item Hamilton Depression Rating Scale; NA=not applicable; NET=nonconvulsive electrotherapy.

Supplementary Table 2. Comparisons of changes in HAMD-17 scores in male and female patients with TRD

		Males (n = 11)	Females (n = 9)	
Variables	**Time**	**Mean±SD**	**Mean±SD**	***p***
Change in HAMD-17 scores	Baseline - first NET	5.9±4.2	7.6±3.6	.295
	Baseline - third NET	8.4±3.9	9.9±3.2	.332
	Baseline - sixth NET	16.2±2.1	15.3±3.3	.587

Abbreviations: HAMD-17=The 17-item Hamilton Depression Rating Scale; NET=nonconvulsive electrotherapy.