Dear editor and reviewers

Thank you for your letter and reviewers' comments concerning our manuscript entitled "The functional role of frontal EEG alpha asymmetry in the resting state in patients with depression: A review" (NO: 81459). These suggestions and questions gave us a lot of inspiration and thinking, making this article more complete We've read the comments carefully, highlighted their questions and suggestions in red, and responded to each of them below.

We would love to thank you for allowing us to resubmit a revised copy of the manuscript and we highly appreciated your time and considera

Sincerely,

Yu-Hong Xie, Ye-Min Zhang, Fan-Fan Fan, Xi-Yan Song, Lei Liu

The following is the review comments and corresponding replies:

Reviewer #1:
Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Rejection
Specific Comments to Authors:

First, the title says "a review", the text states that this is a systematic review. This is a significant difference.

Response: Thanks for your suggestion. This is a general review, and the word "systematic review" used in the article is not accurate. The relevant description has been deleted according to your suggestion.

Second, the abstract does not do justice to the complex facts and shows a lack of method awareness. The difficulties in clinical diagnosis are pointed out, and EEG mapping is recommended as a solution. Clinical and basic research are mixed here. However, the authors themselves concede that their depression marker "right frontal EEG alpha asymmetry" disappears in older patients. The fact that right frontal EEG alpha asymmetry persists with antidepressants and clinical improvement suggests that it may be a trait marker that indicates vulnerability to depressive disorders (and not depressive symptomatology). However, a trait marker is not very helpful for the clinical diagnosis,

since the current condition is to be evaluated here. Therefore, a state marker would be more helpful. Regrettably, up to now, there are no reliable depression markers that surpass the fairly valid diagnosis based on diagnostics such as the DSM-5 in terms of accuracy.

Response: Thanks for your question. As you said, at present, DSM-5 clinical diagnoses are indeed the most authoritative, widely used and accurate methods. However, in the process of using DSM-5, the subjective experience judgment of psychological counselors is still needed, and misdiagnosis may occur inevitably in this process. This paper proposes that FFA may be a diagnostic indicator of depression. The purpose is not to surpass DSM-5 in accuracy, but to use this indicator as an aid to minimize the misdiagnosis rate of psychological counselors. Just like the diagnosis and treatment of physiological diseases, it needs the subjective judgment of the doctor, as well as the objective indicators provided by various instruments. This subjective judgment and objective physiological indicators are not incompatible, but complement each other.

The conclusions from a positive right frontal EEG alpha asymmetry finding in patients with maternal depression are also formulated somewhat imprecisely. Does this mean that the right frontal EEG alpha asymmetry in this case depends on genetic factors or on a life event? Or both? This was not spelled out clearly. In any case, these patients are affected by both, genetic factors and a life event, which makes an etiological assignment particularly difficult in this case.

Response: Thank you for your question. Based on previous studies we can observe an abnormal pattern of alpha asymmetry in the resting frontal EEG of newborns of depressed mothers, indicating a genetic preference for greater right-side asymmetry on cross-sectional assessments. This highlights the importance of genetics in an individual's early development, but the pattern of depression and FFA may change as acquired factors such as life experiences play a role. This paper also emphasizes the importance of the influence of acquired factors, and there is no relevant research at present. In the future, longitudinal studies can be focused to examine whether there are long-term and lasting changes in the psychological risks faced by children. Therefore, genetic factors and life events may play a role in the development of depression in individuals, but how and the trend of development are questions that need to be discussed in the future.

Third, the main problem, however, is the methodology that the authors have not made sufficiently transparent. Systematic reviews should currently be carried out in accordance with the PRISMA guidelines (available at https://www.prisma-statement.org). In the following I quote some items from the PRISMA checklist as an example: (1) specify the inclusion and exclusion criteria for the review and how studies were grouped for the

syntheses; (2) specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies; (3) specify the date when each source was last searched or consulted; (4) present the full search strategies for all databases, registers and websites, including any filters and limits used; (5) specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record. and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process; etc. In addition, I recommend using the PRISMA Flow Diagram (confer: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71). Regrettably, your work does not follow the PRISMA guidelines, nor was a similar or comparable methodology used.

Response: Thanks for your advice. This article is a general review. As in the reply above, the relevant expressions of "systematic review" have been deleted.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: Depression is a leading cause of disability worldwide and contributes greatly to the global burden of disease. At present, the diagnosis of depression depends on interviews and various mental scales. This method is very subjective, time-consuming and with poor consistency. The objective biological markers of depression are worth studying. The author selects a very specific subdivision field, FAA (front EEG alpha asymmetry), which is of great significance and demonstrates its potential. This article reviews various studies of FAA from multiple perspectives, including rest-state clinically depressed individuals, children inherited from generation to generation, the influence of aging, the stability of FAA indicator and so on. Based on all of these, conclusions are presented for future researches. The review is rigorous, inspiring and with adequate details. In my opinion, further improvements can be made in the following fields.

1) In the review, “Frontal EEG alpha asymmetries are usually calculated by subtracting the EEG power in the right frontal cortices from the EEG power in the left frontal cortices”. It is the core problem in the review and more details of the calculations should be presented and discussed.

Response: Thank you for your suggestions, we have made supplements in the paper according to your suggestions to enrich more details of FFA calculation. The specific content is as follows：Frontal EEG alpha asymmetries are usually calculated by subtracting

the EEG power in the right frontal cortices from the EEG power in the left frontal cortices. However, different researchers may use different methods of calculation. The first common equation uses channel "F4" to denote right frontal alpha power at or around the F4 10−20 position and channel "F3" to denote left frontal alpha power at or around the F3 10−20 position in scalp regions of interest (ROIs). Equations to calculate FAA involve taking the difference between or the ratio of alpha power at F3 and F4. Two equations for FAA are commonly used in the literature. Most developmental studies have used the difference in the natural log (ln) of absolute power, that is, ln(F4) – ln(F3) [1]. The second common equation takes the ratio of the difference between frontal power in the left and right hemispheres to their sum, that is, (F4 – F3)/(F3 + F4), which is thought to normalize the difference value [2]. A third, less common approach is to log-transform the ratio, resulting in (ln(F4)–ln(F3))/(ln(F3) + ln(F4)) [3]. FAA has also been calculated with relative frontal alpha power, which is calculated as the percentage of power in the alpha band divided by the total power in all frequency bands[4]. Relative power may be advantageous over absolute power in testing paediatric populations due to its improved test–retest reliability[5] and its ability to distinguish among changes in the frequency makeup of EEGs across development[6]. A recent paper by Harrewijn et al. calculated FAA in a fourth way: by computing the difference between the natural log of the relative power in both hemispheres, that is, ln(rel(F4)) – ln(rel(F3)) [7]

1 **Fox NA**, Rubin KH, Calkins SD, Marshall TR, Coplan RJ, Porges SW, Long JM, Stewart S. Frontal activation asymmetry and social competence at four years of age. *Child Dev* 1995; **66**: 1770-84 [PMID: 8556898]

2 **Allen JJ**, Coan JA, Nazarian M. Issues and assumptions on the road from raw signals to metrics of frontal EEG asymmetry in emotion. *Biol Psychol* 2004; **67**: 183-218 [PMID: 15130531 DOI: 10.1016/j.biopsycho.2004.03.007]

3 **O'Reilly MA**, Bathelt J, Sakkalou E, Sakki H, Salt A, Dale NJ, de Haan M. Frontal EEG asymmetry and later behavior vulnerability in infants with congenital visual impairment. *Clin Neurophysiol* 2017; **128**: 2191-2199 [PMID: 28950152 DOI: 10.1016/j.clinph.2017.08.016]

4 **Marshall PJ**, Bar-Haim Y, Fox NA. Development of the EEG from 5 months to 4 years of age. *Clin Neurophysiol* 2002; **113**: 1199-208 [PMID: 12139998 DOI: 10.1016/s1388-2457(02)00163-3]

5 **John ER**, Ahn H, Prichep L, Trepetin M, Brown D, Kaye H. Developmental equations for the electroencephalogram. *Science* 1980; **210**: 1255-8 [PMID: 7434026 DOI: 10.1126/science.7434026]

6 **Clarke AR**, Barry RJ, McCarthy R, Selikowitz M. Age and sex effects in the EEG: development of the normal child. *Clin Neurophysiol* 2001; **112**: 806-14 [PMID: 11336896 DOI: 10.1016/s1388-2457(01)00488-6]

7 **Harrewijn A**, Buzzell GA, Debnath R, Leibenluft E, Pine DS, Fox NA. Frontal alpha asymmetry moderates the relations between behavioral inhibition and social-effect ERN. *Biol Psychol* 2019; **141**: 10-16 [PMID: 30599209 DOI: 10.1016/j.biopsycho.2018.12.014]

2) Many EEG datasets have been provided for training and validation. Take [1] as an example. [1] Cai, H., Gao, Y., Sun, S., Li, N., Tian, F., Xiao, H., Li, J., Yang, Z., Li, X., Zhao, Q., Liu, Z., Yao, Z., Yang, M., Peng, H., Zhu, J., Zhang, X., Hu, X., & Hu, B. (2020). MODMA dataset: a Multi-modal Open Dataset for Mental-disorder Analysis. arXiv preprint arXiv:2002.09283

Response: Thanks for your advice, more EEG details have been added to the article *p*32.

3) What about the number of EEG electrodes for FAA? If there are only a few electrodes for signal recording, does it work well? If too many electrodes are required, it will lead into more cost.

Response: Thank you for your question. In the FFA experiment, Number of electrodes in use is 128, 64, 32 in commom. Of course, there are also caps with 3 leads as you added in the literature above. However, as you said, too few electrodes may not be able to explain the problems of the research or record more relevant data. Too many electrodes will also lead to the increase of the cost of the experiment. In order to balance this problem, in the research of FFA, electrode caps with 32 electrodes were used as research tools which could not only explain research problems but also save costs [8,9].

8 **Dharmadhikari AS**, Jaiswal SV, Tandle AL, Sinha D, Jog N. Study of Frontal Alpha Asymmetry in Mild Depression: A Potential Biomarker or Not? *J Neurosci Rural Pract* 2019; **10**: 250-255 [PMID: 31001013 DOI: 10.4103/jnrp.jnrp_293_18]

9 **Koo PC**, Berger C, Kronenberg G, Bartz J, Wybitul P, Reis O, Hoeppner J. Combined cognitive, psychomotor and electrophysiological biomarkers in major depressive disorder. *Eur Arch Psychiatry Clin Neurosci* 2019; **269**: 823-832 [PMID: 30392042 DOI: 10.1007/s00406-018-0952-9]

4) FAA can differentiate depressive patients and healthy controls. We are wondering whether it can be used to quantify the degree of depression.

Response: Thank you for your question. This is a somewhat progressive question, although we studies from clinical research found that compared with individuals without

depression, those with depression showed greater right frontal EEG alpha asymmetry in the resting state. However, the pattern of frontal EEG alpha asymmetry at rest in depressive individuals seemed to disappear with age. Therefore, the current research on the relationship between FFA and depression is not very clear, and this issue can be discussed as the direction of future research. The conclusion has been made to supplement p17.

Reviewer #3:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)

Specific Comments to Authors: 1. Title: The title reflects the subject well. 2 Abstract: abstract summarize and reflected the work well 3 Key Words: focus of the manuscript and key words are appropriate. 4 Background: The manuscript adequately described the background, present status and significance of the study well. 5 Methods. It was a general review; would have been better with a systematic review. Authors provided comparison of methods of various studies they reviewed which appears sufficient. 6 Results. Not applicable 7 Discussion. Are good on topic and review is well summarized with adequate number of studies. Review covered various areas including adults, adolescents, children and older adults; prenatal and post-natal depression addressed research aspects needed a d touched up on genetics. 8 Illustrations and tables: Tables sufficient, good quality and appropriately illustrative, with labelling of figures using arrows, asterisks, etc., and are the legends adequate and accurately reflective of the images/illustrations shown. 9 Biostatistics. Not applicable. 11 References. Appropriate and adequate references were provided. 12 Quality of manuscript organization and presentation. the manuscript is well, concisely and coherently organized and presented. The style, language and grammar accurate and appropriate. 14 Ethics statements. Is not important in this article. Recommendations to authors:

This is a well written article and covered many aspects of frontal EEG in depression. It is of interest of good readers. They may add a discussion on availability/non availability of studies on other antidepressants including conventional and other newer antidepressants.

Response: Thank you very much for your question. Based on the review of previous studies, Neither escitalopram, sertraline or venlafaxine nor serotonin norepinephrine reuptake inhibitor (SNRI) changes the FFA pattern in depressed patients. This result does not indicate that medication is ineffective in the treatment of patients with depression, but rather that the short course of medication is unable to cure patients with depression,

resulting in no significant difference in FFA pattern between the depressed group and the healthy control group. Drug therapy has been playing a very important role in the treatment of depression and is the most commonly used treatment for depression. People with depression can still take medication under the guidance of a psychotherapist.

I would also suggest the authors discuss effect of ECT on a frontal EEG asymmetry. Studies if available may be summarized, if not available this may be mentioned briefly and makes the article more complete.

Response: Thank you very much for your suggestion. ECT, as a treatment method for depression, has also attracted much attention from researchers. However, there is no relevant literature that uses FFA as an indicator to investigate the relationship between ECT and depression, which has been added to the conclusion as a future prospect p17.

I would recommend to add a few sentences on future research needs in conclusion of this article.

Response: Thank you very much for your advice. We have already outlined the direction of future research in the conclusion.