Dear Editor,

We are grateful for the comments of the reviewers. All required changes have been implemented and highlighted in red. Where possible

Round-1

Reviewer 1

1. I have the following comments: -In the whole topic is interesting but as a reader it appear to me as not well-coordinated. In the section 1.1.2 Endogenous brain glutamate and depression-The entire manuscript has been proof read for grammar and sections rewritten and rearranged to improve the flow
2. Authors might add more information on the studies alterations in glutamatergic neurotransmission and depression: such as methodology, study population, tools the primary outcome for each study. The information are often redundant so that I suggest to shortened this version. This has been done the sections have been beefed up for more clarity
3. REFERENCES: THE AUTHORS APPEALED 12 SELF-CITATIONS. This has ben reduced to 10 however it is important to mention that only articles relevant to this subject matter were cited

Reviewer 2

1. Initially, The authors should correct some minor errors in English. – This has been done
2. Additionally, the manuscript would deeply enrich by incorporating tables that condense the information on molecules, receptors, and effects with their corresponding bibliographic citations-This has been included
3. And one point that I consider essential is the inclusion of a diagram that presents the reader with the molecular steps of glutamate interaction, pointing out its sources, the receptors with which it interacts, and its effects, specifying the site of action of the drugs described. in review Additionally, I consider that the authors must review the number of self-citations in this review. the remaining points adequately comply with what is expected- An image has been included that tries to describe the subject matter being discussed in this review. Table 4 has been included to show the receptor subtypes that are being studied for their antidepressant effects This has been done however, I would like to mention that only articles relevant to this subject matter were cited

Reviewer 3

The regulation of GLU pathway has rapidly become a key target for the development of neuropsychiatric drugs. Future new drugs may regulate the GLU signaling pathway to treat mental and somatic comorbidities, such as schizophrenia comorbid diabetes, depression comorbid body pain. It is worth noting that patients with schizophrenia already have glucose metabolism disorders at the time of onset, which may be due to GLU excitotoxicity in both the

body and the brain. The main reason why depression is not easy to cure and easy to relapse is that psychological factors are not removed. Drugs only control some symptoms of the disease and may relapse when stimulated by psychosocial factors. We should further elaborate on the classification of glutamate receptors, and then focus on the biochemical and pharmacological changes of glutamate receptors induced by antidepressants, as well as the clinical and animal models of glutamate dysfunction. Thank you for your comments and contributions

Round-2

Q: After reviewing the new version of manuscript ID: 65474, I believe that the requested points have been partially covered. 1. I did not see the Figure 1 mentioned in the paper; in the last revision, this figure was requested.

A: It has been uploaded. I apologize for the omission

Q: 2, Likewise, and even though two reviewers agree on an excessive number of self-citations in this manuscript. The number of self-citations has only been reduced from 12 to 10, so seven more self-citations should be replaced or removed to have a number less than or equal to 5 self-citations,

A: While I acknowledge that the scientific community frowns at unjustified and irrelevant self-citations, which is definitely not the case here, there is no scientific data that backs your request to limit self-citations to 5. Please see the link below "To cite or not to cite: author self-citations and the impact factor" hartley2011.pdf I cited other scientists and researchers who have worked in this field (some as many as 8 times), I would wonder why citing our work relevantly in this paper 10 times out of a total of 146 (6.9%) references is wrong. To the best of our knowledge there have been suggestions that up to 14% relevant self-citation is appropriate for neuroscience articles The authors would be pleased if the reviewer could oblige us by giving us more clarification on the subject matter The scientific editor requested that the title be shortened -This has been done