

Review Form 3

Journal Name:	Asian Journal of Pediatric Research
Manuscript Number:	Ms_AJPR_126643
Title of the Manuscript:	The Role of Synaptic Cargo Transporters in Regulating Neuronal Excitation/Inhibition Balance: The Molecular Fingerprint to Autism Spectrum Disorders?
Type of the Article	Review Article

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PART 1: Review Comments

Compulsory REVISION comments	Reviewer's comment	Author's Feedback (Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<p>Please write a few sentences regarding the importance of this manuscript for the scientific community. Why do you like (or dislike) this manuscript? A minimum of 3-4 sentences may be required for this part.</p>	<p>It was my pleasure to review the above article. This review article explores the role of Synaptobulin-Syntaxin system in synapse development, pruning and functionality and how disruption of this axis can lead to ASD-related phenotypes.; however, in my opinion, the article could benefit from streamlining the type(s) of synapses – for example CNS or PNS. ASD is extremely heterogeneous and so are the synapses. While discussing about the general perspectives of synapse development and functionality are critical, specific CNS synapses share their own set of structural and functional specificity. It seemed to this reviewer that the authors have focussed on Ach-ergic synapses under the section ‘Synaptohgenesis’. However, there are also some explanation round excitatory glutamatergic synapses. I think this article will benefit from streamlining around this idea. Additionally, excitatory GABA plays a crucial role in developing brain. Given ASD is a neurodevelopmental disorder, discussion around instances of the Synaptobulin-Syntaxin -axis in shaping the GABA-ergic neurons will benefit the article especially how it manifests in the E-I imbalance in autism. Given the title of the article it seems that it would be focussed on the CNS, coming across the NMJ was challenging to follow.</p>	
<p>Is the title of the article suitable? (If not please suggest an alternative title)</p>	<p>Yes (provided synapses of the CNS is in the focus of the review article)</p>	
<p>Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here.</p>	<p>The abstract is comprehensive. However, it would benefit from the following modifications;</p> <ul style="list-style-type: none"> - ‘synaptic loss’ is an ambiguous term. I would suggest omission of the first sentence - I would suggest using the term ‘neuronal’ over nerve. Since it is not obvious in the abstract whether the authors are focusing on CNS or PNS - The acronyms are not explained in the abstract - If the abstract talks about hippocampus, the article would need more instances on how disruption in this specific axis manifests in ASD-like phenotypes by affecting the hippocampal synaptic functionality. If the article focuses on more general synaptic functions, I would recommend omitting the hippocampus-specific from the abstract - Overall, I recommend the abstract to have more focus on synaptic disruptions in autism and why it is important to study (for example, how studying synaptopathy in ASD can open new arenas for pharmaceutical interventions). 	
<p>Are subsections and structure of the manuscript appropriate?</p>	<p>Yes. The discussion could benefit from more specific subsections such as how atypical synapse formation cause disruption in E-I inhibition/ intracellular trafficking/ how it affects the directionality of cargo transport / receptor expression and recycling etc.</p>	
<p>Please write a few sentences regarding the scientific correctness of this manuscript. Why do you think that this manuscript is scientifically robust and technically sound? A minimum of 3-4 sentences may be required for this part.</p>	<p>The article discusses the synapse-specific causes of E-I dysbalance in ASD-related disorders with a key focus on synaptic proteins. The authors have carefully analysed a wide range of relevant studies, providing balanced insights that reflect the field's consensus and identifying gaps for future research. The inclusion of well-organized summaries and critical evaluations enhances the article's reliability and value as a resource for researchers. This approach ensures that the review is both informative and grounded in scientific rigor.</p>	
<p>Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form. -</p>	<p>No.</p> <ul style="list-style-type: none"> - The introduction part has no citation. This reviewer was not sure if that is some formatting issue of the word document. Every phenotype of autism should be cited from both human and animal models since the article takes both into account - More discussion around the complexity of synapses is warranted. For instance, in the context of feeding, the review by Deem et al 2022 would provide some valuable insight. Linking it with atypical feeding in autism in both humans and animal models would also be beneficial for the article. Similarly, context-specific synaptic orchestration on every 	

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	<p>aspect discussed – such as sleeping disturbances, restricted interests, anxiety-like behaviour should be explored in details.</p> <ul style="list-style-type: none"> - Behaviours like socialization and feeding also intersects with the central reward processing. How synaptic disruption in the central reward circuits (dopamine, oxytocinergic synapses) manifests in ASD-like traits 	
<p><u>Minor REVISION</u> comments</p> <p>Is the language/English quality of the article suitable for scholarly communications?</p>	<ul style="list-style-type: none"> - 'engage in repetitive irritating behaviours' – consider omitting/ substituting the term 'irritating' - 'A human missense variant of syntabulin identified in an autism patient fails to rescue synaptic deficits in mice lacking syntabulin.' – this sentence is grammatically wrong. Obviously a missense mutation is not expected to rescue an altered phenotypic behaviour - Instead of 'recent research suggests' consider 'current findings suggest' . the word 'research' appears many times in the article and sounds repetitive 	
<p><u>Optional/General</u> comments</p>	<ul style="list-style-type: none"> - Disruption in synaptic pruning is relevant to autism. Can the authors elaborate on what happens to the synaptic cargo transporters in the context of disrupted synaptic pruning and/ or how disruption in synaptic cargo transports affect pruning - 'Neurons lacking syntabulin exhibit impaired transport' – this term is ambiguous. Does lacking mean complete knockout of the gene or producing truncated protein? - There are quite a few instances of ambiguous statements in the article that warrants specificity. For example : 1. 'The role of SNAP47 is to date not well ruled out in the context of autism spectrum disorder.' Does not discuss whether any instance have been found or whether it is merely plausible. 2. ASD in the context of GRIA 3 / 4 is not discussed 3. 'have shown brain abnormalities consistent with ASD' - exactly how 	

PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Are there ethical issues in this manuscript?	<i>(If yes, Kindly please write down the ethical issues here in details)</i>	

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