

Specific Comments to Authors:

Zhang et al. provide an interesting overview of neural plasticity, focusing mostly on the effects of knocking out MECP2 function. Overall this is useful review that summarizes important information for the field. One aspect that can be improved is the quality of the English in the manuscript which would benefit greatly from expert editing. Below I list some comments point by point:

1. The review provides good basic information on the effects of MeCP2 deficiency on plasticity. It does not discuss sufficiently the effects of MeCP2 over-expression. I would therefore suggest changing the title to reflect the focus on MeCP2 deficiency. Alternatively, a considerably more extensive discussion of the MeCP2 duplication would be warranted.

Thank you for the valuable suggestion. We have changed the title accordingly to "Dysregulated cortical synaptic plasticity under MeCP2 deficiency and its implication in motor impairments".

2. Along the same vein it would be useful to discuss the effect that mosaic loss of MeCP2 function (i.e. Rett) has on cell function (ie autonomous versus non-autonomous plasticity effects).

We appreciate your advice and added one paragraph describing the autonomous vs non-autonomous effect under MeCP2 mutant (line 112-120, page 6-7).

3. Line 58+ : a more nuanced discussion of transcriptional regulatory effects that might be related to plasticity would be useful. MeCP2 effects on synaptic plasticity are mostly indirect via transcriptional regulation, so there are many pathways that are potential mediators of the dysregulation of homeostasis and plasticity. This could be discussed more thoroughly. A figure that may depict schematically upregulated vs downregulated pathways that may affect plasticity would add a lot to the overview of potential mechanisms. Adding the recently emerging information that MeCP2 post-translational modifications may modulate some of these functions would be a useful addendum.

Thank you for the valuable suggestion. We have added one paragraph describing different transcriptional and post-transcriptional mechanisms of MeCP2 in mediating neuronal genes (line 75-94, page 5). Moreover, a relevant graphic illustration has been added as Figure 1.

4. It would be preferable to quote primary sources (rather than reviews), and this is not always the case. For example, in line 50 – references by Bedogni et al Cerebral Cortex 2015, and Kishi and Macklis, Molecular and Cellular Neuroscience, 2004 could be added.

We appreciated your advice, and have added the relevant references (line 50, page 3).

5. Similarly in line 52 – Banerjee et al. PNAS 2016, Dani et al. PNAS 2005, Lo Blue and Erzurumlu J Neurophysiology 2016 could be cited. Also it would be good to expand more in

depth about how E/I balance fails and in particular in discussing separately and in more detail the abnormalities noted in the E versus the I parts of the transmission.

Yes we have added those refs in the manuscript (line 52-53, page 3-4). Moreover, we added some descriptions of detailed neurophysiological changes of cortical E/I balance under MeCP2 dysfunction (line 53-64, page 4).

6. Conversely on line 63 – citing a review or additional papers would be helpful.

Yes we have added a new ref (#18) to state the spatial pattern of MeCP2 regulation (line 74, page 4).

7. The authors largely ignore the brain-wide mechanisms that may affect synaptic plasticity in motor cortex. Noradrenergic and dopaminergic modulation of motor learning and plasticity by locus coeruleus and VTA are also affected by disruption of MeCP2 function in Rett syndrome. Discussing the effects of MeCP2 on neuromodulatory pathways (particularly NE and dopaminergic pathways) which also impact plasticity would be useful. Line 120 – 122: “Although site-specific gene knockout study has suggested the role of MeCP2 in mediating motor behaviors across different neural networks such as the noradrenergic transmission [40], motor cortex remains as the prominent brain region in which fine motor control is regulated.” The way noradrenaline and dopamine affect motor cortex plasticity and execution needs to be discussed, as parkinsonian symptoms and Rett pathology are also linked to the disruption of these systems. In the rest of this section, authors could also add some information on the influence of lowered noradrenergic and dopaminergic tone onto function of SST, VIP and PV interneurons.

We appreciated your suggestions, and have added the relevant description of monoaminergic system under MeCP2 deficiency scenario (line 172-179, page 9). Moreover, the possible connection between subcortical modulatory system and cortical GABAergic neurons has been discussed in line 203-211 (page 10-11).

8. In line 90 + – the roles of neurotrophic factors such as BDNF should be discussed to provide a more well rounded viewpoint. Regarding IGF-1 additional studies could be cited – ie Castro et al. PNAS vol 111, 2014. Also I believe reference 25 of the manuscript could be also cited here.

Thank you for the suggestion. We have added descriptions of BDNF (ref 48, line 133, page 7) and new citation of IGF-1 therapy (Ref 50, line 135, page 7).

9. Line 102 is confusing: “ excitability … probably due to enhanced postsynaptic GABA receptor mediated response” If I am not mistaken reference 30 also reported impaired excitatory transmission and a more nuanced discussion on post-synaptic, pre-synaptic inhibitory and excitatory effects would be desirable here.

We agree your advice and have corrected those descriptions. Moreover, discussions for the synaptic mechanism of MecP2 has been added (line 145-152, page 8).

10. Line 154 typo “may reside it in”

This has been corrected (line 219, page 11).

11. “. correlation between MecP2 and motor function may reside in the inhibitory neurons of the motor cortex” This is a strong claim that requires a strong defence. It is true that MecP2 -KO in pyramidal neurons causes milder syndrome but it is too strong to say that it is without effect. Additional references that can be used for a more nuanced discussion are: Meng et al. Elife 2016. Ure et al. Elife 2016.

Thank you for the kind suggestion. We agree that the E/I balance is a complex process that can not be solely dependent on either excitatory or inhibitory pathway. We thus updated the statement and added relevant descriptions for pyramidal neurons and excitatory synapse (line 224-230, page 11-12).

12. Regarding the effects of exercise and training on learning this has been studied elsewhere implicating BDNF-TrkB-mTOR pathways. It would be good to reference these studies more generally. Some studies that could be cited include: Skriver et al Neurobiol Learn and Memory 116, 2014; Wrann et al. Cell Metabol 2013, Chen et al. Transl Psychiatry 2017.

Yes we have added relevant descriptions of more exercise-induced BDNF effects (line 261-262, page 13).

13. Line 194 relieve – typo

This has been corrected (line 267, page 13).

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes a Minireviews of the Motor dysfunction of Rett syndrome. The topic is within the scope of the WJP. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: Overall this is useful review that summarizes important information for the field. Some points need to be clarified and English need a polish. The questions raised by the reviewers should be answered; (3) Format: There is no table or figure; (4) References: A total of 67 references are cited, including 20 references published in the last 3 years; (5) Self-cited references: There is no self-cited reference. 2 Language evaluation: Classification: Grade B. The manuscript is reviewed by a

native English speaker. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by National Natural Science Foundation of China (General Program). The topic has not previously been published in the WJP.

5 Issues raised:

(1) The "Author Contributions" section is missing. Please provide the author contributions;

[We have added the Author Contributions section at the end of revised manuscript.](#)

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

[Ye we have attached approval documents for funding.](#)

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

[Yes we have added PMCID and doi into each reference.](#)

6 Recommendation: Conditional acceptance.

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Psychiatry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Before final acceptance, the author(s) must add a table/figure to the manuscript.

[Yes a relevant graphic illustration has been added as Figure 1.](#)