



PEER-REVIEW REPORT

Name of journal: *World Journal of Psychiatry*

Manuscript NO: 67126

Title: Dysregulated cortical synaptic plasticity under MeC deficiency and its implication in motor impairments

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04536616

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

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|---------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |



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| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
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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. 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). 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. 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. 5. Similarly in line 52 -



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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. 6. Conversely on line 63 - citing a review or additional papers would be helpful. 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. 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. 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. 10. Line 154 typo "may reside it in" 11. "... correlation between MecP2 and motor function may reside



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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. 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. 13. Line 194 relieve - typo