**Relationship between the catechol-O-methyl transferase Val108/158 met genotype and brain volume in major depressive disorder**

*By Watanabe et al.*

The authors addressed my concerns in a satisfactory manner, there are however a few additional revisions to be made.

Introduction: please reformulate “the VBM using SPM”. One has to explain the acronym before mentioning e.g. Statistical parametric mapping (SPM). A good formulation could be “using the VBM of the Statistical Parametric Mapping SPM) software”.

Reply 4:

The authors mention “a few studies of MDD have reported the influences of COMT”. This statement is vague, the authors should mention if it is positive or negative influence. If mixed findings, please state so.

Reply 6

Did the authors have more precise hypotheses? The reader is otherwise left wondering “how is it affected, positively or negatively?”

Reply 12: authors improved their discussion but there are not enough references in the paragraph mentioned here. Please address.

Reply 14: I find this statement confusing, misleading and largely unreferenced. Please provide a reference connecting neurotoxic damage to stressful life event, a reference connecting MDD to stressful life events. Also do the authors perceive stressful life events, MDD and brain abnormalities in adults? One cannot talk about neurodevelopmental change in this case.

Discussion:

Page 1: I find the sentence “in addition, a blood plasma…antidepressant treatment” concerning because the authors appear to mix the concept of genetic expression and levels of DA. Although the two concepts may indeed be related the authors should be more careful before connecting the two in such a simplistic way.

Also how do they link peripheral DA levels to DA levels in the brain? I would recommend either deleting this sentence or providing additional evidence.

Page 2: :”plays a causal role in MDD”. I would suggest that the authors delete the word “causal”. Overall I would recommend that the authors use a more cautious type of language when associating brain related measures to genetics. Words such as “link to”, “associated with” are the best choice in this context.

Further down: ”Therefore, the genetic variants…MDD”. This statement is confusing and misleading. The authors provide no evidence that these DA polymorphisms may be associated with the caudate volume”. What I asked in my previous revision was to generally discuss other DA polymorphisms that have been associated with neuroanatomical abnormalities in MDD. I think it would be wrong to generalize all MDD-related DA polymorphisms to the caudate volume. Please either delete or re-write statement.

Further on: neurodevelopmental differences and DA levels: I support the idea of discussing the chronically high DA levels and possibly neurodevelopmental differences in MDD. I think it is wrong to use the term “cause”, rather use “link”. Also highlight the longitudinal component of this “link”.

At the end of the discussion I would recommend reformulating the very last sentence as it is a bit confusing (from a language point of view) “an estrogen and a primary female sex hormone down-regulated”. For instance by saying “female hormones such as estrogen may down-regulate the expression of the COMT”.

Overall: the authors talk about DA polymorphisms and changes in DA levels. They also mention that these changes differ across brain regions. So I assume it would be more correct to talk about not only neurodevelopmental differences in the caudate but also about the effects of these varying DA levels in the fronto-striatal circuits and a neurodevelopmental abnormality in the circuit rather than in a single brain region such as the caudate.

References: I couldn’t find Frodl et al. please check it

Overall I would recommend that a native English speaker proofread this manuscript. It contains grammar and syntax mistakes.