**Psychiatry research: Neuroimaging**

*Title:* Relationship between the COMT val108/158met genotype and brain volume in treatment naïve major depressive disorder: voxel-based morphometry analysis by Watanabe et al..

*Overall:* the authors investigate the relationship between the COMT val/met polymorphism and brain volumes in depression. The study is novel as no previous study investigated COMT and brain size in relation to depression. The results are compelling and worth being published in this journal. Major revisions are however required.

*Abstract:* it provides sufficient information but the authors should provide the refSNP (rs) numbers associated to the SNP included in this manuscript (this applies to the introduction of the manuscript too).

*Introduction:* I would recommend a major reorganization of the introduction, for instance by talking about COMT polymorphisms and depression prior to describining the VBM technique. Benefits of this technique in comparison to Freesurfer for instance would be helpful. Further, the authors could improve their explanation of the relationship between dopamine and depression and COMT and depression (for instance there a few studies on white matter and neural activity in relation to COMT variants and mood disorders). The authors mention the effects of medication on the brain at the very end of the introduction. This should be addressed when discussing the brain abnormalities associated with depression. For instance, could medication affect the brain morphology and expression of the COMT gene? The authors may mention the connection between illness chronicity and brain volume, and possibly the relationship between COMT gene expression levels. Age and gender related differences in MDD and genetic influence should also be briefly discussed. Further, could the authors please state their main hypotheses.

*Methods:* it is unclear whether the authors included participants of all ages. What was the age range of the participants? Please include in the participant description. Within the Genotyping section: more information should be provided in terms of assay for genotyping, reference to the taqman technique and amplification processes. Relative references should be included. In the statistical analyses seciton the authors should explain whether the genotype x diagnoses analyses were performed on brain region volumes found to be difference between HC and MDD patients or on the whole brain. Also why did the authors consider the ratio between the caudate volume and the total GM volume? Also how did the authors deal with intracranial volume differences across participants given the possibly large age range?

*Results:* Section 3.7 could be transformed in a table and doesn’t need to be included.

*Discussion:* I would recommend to change the structure of the discussion, by talking about **1**. Abnormalities in brain regions associated with striatal regions in depression, **2.** Results of lesion studies in the caudate (please define what kind of lesions if you do, trauma? Illness-related?). Also please provide a more recent reference than Mendez et al. 1989 or Parashos (references from 2000 onwards are preferable). **3.** discuss the relationship between emotional regulation/processing and striatal regions. Also please provide a more critical appraisal of the current findings in reference to Pizzagalli et al for example. It is unclear why the authors provide such reference when they do not discuss how the “genetic” populations differed in relation to their clinical presentation**. 4.** Discuss what the current findings mean for MDD or mood. **5.** I would encourage the authors to address the topic of other genetic variants associated with dopamine and MDD further.

Overall I could encourage the authors to shorten the section on dopamine and rather focus on val vs met carriers-related findings. Specifically when the authors talk about “COMT” genotype they could mention whether it’s val/val or val/met that affect the dopaminergic flux (see Carr and Sesack, 2000). When the authors mention that “the neurotoxic damage associated with the environmental factors that causes MDD” it would be good to know “which factors” the authors are referring to.

I would shorten the very last section starting from “a previous study…” as it appears to be a repetition of the results section and rather focus on the strengths and relevance of the current findings. The last paragraph of this paragraph deserves to be at the beginning of the discussion and not at the end.

*Language:* please proofread the paper (there are a few typos e.g. abrrations) and the last page of the discussion needs to be rewritten. In the highlights please change “MDD grey matter” for example by saying “in MDD patients” or “in MDD”. The authors should use the term valine/methionine just before using the acronyms val and met at the beginning of the abstract, not at the end of it. In the abstract would recommend to say “volume is comparable between MDD patients and HS” rather than talk about “same reduction”. In the results section please change the sentence “no voxel could survive after correction” and state “no voxel survived the correcton for multiple comparisons”.