

Dear Miss Lian-Sheng Ma,

RE: Neuroimaging in Huntington's disease

(Ref.: 8015, ID 00474576)

Thank you for your interest in our manuscript and we would like to thank the Reviewers for the positive comments. We have now revised the manuscript taking into consideration the reviewer's suggestions.

Reviewer 1

This is a comprehensive review of neuroimaging studies on Huntington's disease. It is well written and covers the issues such as MRI and PET studies in this field. I think this review will provide comprehensive understanding of neuroimaging studies in HD to the related fields.

Response:

We would like to thank reviewer 1 for the positive comments.

Reviewer 2

1. The authors, Drs. Niccolini and Politis, reviews the current neuroimaging literature in Huntington's disease (HD) focusing on the ability of magnetic resonance imaging (MRI) and positron emission tomography (PET) to detect pre-symptomatic changes and to monitor disease progression in HD patients. These findings could be useful for assessing the efficacy of future disease modifying therapies. The manuscript need an impressive figure, which shows that there is an inadequate indication for the use of Acetyl Cholinesterase inhibitors for cognitive impairment in HD.

Response:

We would like to thank reviewer 2 for the positive comments. We have now addressed his/her suggestions.

2. The Authors might discuss about the possible role of symptomatic drugs (i.e. neuroleptic) in disease modifying and in detected neuroimaging changes.

Response:

We did not find any study on the possible role of symptomatic drugs such as neuroleptic in detecting neuroimaging changes.

3. A table could explain the changes detected on neuroimaging (especially on PET).

Response:

We have now added a table.

4. The setting of the sections needs to be improved.

Response:

We have now improved the sections.

5. References have not a uniform structure: a single criterion should be used.

Response:

We have now used a single criterion for the references.

Reviewer 3

1. This is an elegant and profoundly written manuscript which has its place in the current literature. I only found that the presentation of different modalities seems somewhat unbalanced given the state of the art. While the extensive description of PET studies using different ligands, one should extend the description of e.g. functional imaging studies. A big advantage of such studies is the application of specific task designs, which allow for a mechanistic interpretation of deviant BOLD responses in HD patients. This aspect seems largely missing in the current review and I suggest to include evidences such as from: 1: Unschuld PG, Liu X, Shanahan M, Margolis RL, Bassett SS, Brandt J, Schretlen DJ, Redgrave GW, Hua J, Hock C, Reading SA, van Zijl PC, Pekar JJ, Ross CA. Prefrontal executive function associated coupling relates to Huntington's disease stage. *Cortex*. 2013 Nov-Dec;49(10):2661-73. doi: 10.1016/j.cortex.2013.05.015. Epub 2013 Jun 26. PubMed PMID: 23906595. 2: Hua J, Unschuld PG, Margolis RL, van Zijl PC, Ross CA. Elevated arteriolar cerebral blood volume in prodromal Huntington's disease. *Mov Disord*. 2013 Jul 11. doi: 10.1002/mds.25591. [Epub ahead of print] PubMed PMID: 23847161; PubMed Central PMCID: PMC3834086. 3: Unschuld PG, Joel SE, Pekar JJ, Reading SA, Oishi K, McEntee J, Shanahan M,

Bakker A, Margolis RL, Bassett SS, Rosenblatt A, Mori S, van Zijl PC, Ross CA, Redgrave GW. Depressive symptoms in prodromal Huntington's Disease correlate with Stroop-interference related functional connectivity in the ventromedial prefrontal cortex. *Psychiatry Res.* 2012 Aug-Sep;203(2-3):166-74. doi: 10.1016/j.psychres.2012.01.002. Epub 2012 Sep 11. PubMed PMID: 22974690; PubMed Central PMCID: PMC3466385.

Response:

We would like to thank reviewer 3 for the positive comments. We have now reviewed these papers.

2. I also suggest that the authors at least mention recent evidence from direct metabolic imaging studies, which would potentially corroborate the very well written introduction on the cellular basis. I would suggest to include e.g. this reference : Unschuld PG, Edden RA, Carass A, Liu X, Shanahan M, Wang X, Oishi K, Brandt J, Bassett SS, Redgrave GW, Margolis RL, van Zijl PC, Barker PB, Ross CA. Brain metabolite alterations and cognitive dysfunction in early Huntington's disease. *Mov Disord.* 2012 Jun;27(7):895-902. doi: 10.1002/mds.25010. Epub 2012 May 30. PubMed PMID: 22649062; PubMed Central PMCID: PMC3383395.

Response:

We have now added Unschuld et al., 2012.

3. I also found the conclusion too short in terms of what the reader should make out of the abundance of information. What is the authors conclusion - next to stating that imaging methods are interesting. I would have expected that, after such a detailed description, one may read about some sophisticated judgement on what can currently be drawn from the existing studies and which next steps might be most promising.

Response:

We have now improved the conclusions.

Reviewer 4

1. In this article the authors present neuroimaging evidence related to Huntington's Disease. I have the following comments and recommendations.

Abstract: Please revise sentence: "Over the recent years,considerably advanced about HD."

Please include a results and conclusion sentence.

Response:

We would like to thank reviewer 4 for the positive comments.

We have now changed the sentence “over the recent years..” an added a results and conclusion sentence.

2. Introduction: What is the prevalence of HD? What method of search and article organization was used for the review? Please provide a summary of the number of studies per neuroimaging method that were considered. How is this review different from other reviews on HD?

Response:

We have now added the prevalence of HD and a small paragraph about the methods we used.

3. MRI: 1.Results on cortical thickness are consistent with evidence with recent fMRI meta-analyses of the functions of the basal-ganglia (Arsalidou et al., 2013). TFC – abbreviations need to be spelled out the first time they are introduced.

Response:

We have explained TFC abbreviation (please see page 3, line 14).

4. Brain activation and metabolism: Page 8: “ “transplantation” is that a typo? I believe the reader would greatly benefit from a table or graph that summarized the range of deficits detected and brain areas involved by neuroimaging method and which method is optimal for assessment at different stages of diagnosis.

Response:

We have corrected “transplantation” with “transplantation” and we have added a table.