OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-22-00145
Title: Decreased GDNF in the PFC potentially evokes the cognitive impairment of Parkinson disease by blunting dopamine transmission
Reviewer's Name: Xavier d'Anglemont de Tassigny
Reviewer's country: Spain

COMMENTS TO AUTHORS

General comments:
In this paper, the authors present a study split in two parts. First, a clinical study that sought to link serum GDNF level in the bloodstream to cognitive performance in patients with Parkinson's disease and healthy controls. This was measured with the help of two cognitive evaluation scales and contrasted with demographic, medical and lifestyle parameters, and conclude that low serum GDNF correlates with some cognitive decline. The second part of the paper is a preclinical study whereby authors induced midbrain dopaminergic neurons degeneration with the neurotoxic drug MPTP and assessed cognitive function in the mice with artificial decrease or increase of GDNF content in the prefrontal cortex (PFC), a brain region associated to cognitive behavior that receives innervation from midbrain (VTA) DA neurons as experimentally demonstrated in this work. From their results, the authors conclude that a decrease of GDNF level in the PFC may worsen the cognitive alterations associated to DA denervation of the PFC. The authors provide some mechanistic insights by showing that GDNF regulates dopamine activity in the PFC by modulating the postsynaptic density at the dopaminergic synapse as well as tuning the presence of dopamine transporter (DAT).

The study is well conducted and the experimental design is sound and appropriate to answer the hypothesis. The material and methods sections are detailed and thorough and the results are in general well presented in 6 comprehensive figures and a table, as well as supplementary figures and tables.

Please find below my comments on several aspects of the manuscript.
Major comments:
The mouse prefrontal cortex is normally devoid of GDNF as shown in Ortega de San Luis et al. Front Neuroanat 2016. How do the authors argue for the use of AAV-RNAi-driven reduction of GDNF production in a cerebral region (at least in the mouse brain) that has been reported to be devoid of endogenous GDNF?
Along to the above comment, do the authors have information regarding the cellular origin of GDNF (if any) in the PFC region? Since the expression of GDNF in the PFC is the angular stone of the study, it seems important to discuss this aspect thoroughly.
Antibodies anti-GDNF have repeatedly given false positive for GDNF. The anti-GDNF used in this article is not referenced. Authors should provide the manufacturer and catalog number of the antibody used as well as they should provide evidence for the specificity of this antibody for GDNF.
Could the authors explain which neural cells are target by AAV2-CaMKIIa-DA1h in the PFC region and what exactly occurs when electrical stimulation is applied to the VTA.
From my own understanding, the VTA stimulation leads to DA fibers firing at the axon terminal in the PFC, resulting in DA release. Then, I suppose that DA binds to specific DA receptors expressed, thus activating DA1h which emits fluorescence in the postsynaptic terminal of different neurons than the projecting DANs in the PFC region. I just need to confirm that I understand it right.
Could the authors introduce the "degree centrality" concept? I am not familiar with this concept and I

quite struggle to figure out what information this brings to the study. Since those results are not shown in the main paper (but mentioned in the abstract and discussion) and the contribution of these data to the study does not seem essential (to my opinion), perhaps it might be better to remove these data from the study.
Moreover, in supplementary Fig 6. A, the green coloring is incorrect for the hypothalamus as it actually shows brainstem (or medulla). The blue coloring in fact corresponds to the thalamus and not to the medulla. Finally, the hypothalamus is not colored.
Authors should include in the Introduction, or Discussion, a paragraph where they would discuss the relation between plasma GDNF and brain GDNF. How can we rely on peripheral GDNF as a marker for brain GDNF, especially cortical GDNF? Is there a clinical evidence for this? Preclinical evidence?

Comments on Results.
Table S1: p value should not be zero (last column).
Supplementary table 2: Change "Person" for "Pearson". Some Sig (2-tailed) values are 0.000. I reckon that they cannot be equal to zero.
Table 1: Some P values for significance between groups are indicated as zero. However, a P value cannot be zero. Authors should indicate the real P value, or indicate if the P value is inferior to a certain threshold value (for example $P < 0.001$).
Since I am not familiar to the ROC curve analysis (fig. 1 C-D), I am not sure how this data should be read and interpreted. Therefore, I am wondering whether the authors could add a brief explanation on how they perform the ROC curve analysis and how to read the graphs prior to providing the results description.
I also think that the lines and panel have too dark colors which makes the graph quite difficult to read at first glance. Authors may consider increasing the color contrast between the different curves.
Fig.6 E and F. Why having two Y-axis in a same bargraph? Unless well justified, the relative ratio axis on the right side could be cropped out.

Some sentences are difficult to clearly understand. Authors may consider some further editing.
Example (line 50): "As a result, several contradictory studies exist, such as those that indicate no change in CSF such as tau levels and so little utility in predicting progression."
Other example (line 279): "38 patients with PD and 25 healthy controls had received blood sampling collection and complete measurements eventually."
Other example (line 425): "The PFC region totals PSD95 level presents decline as well"

In general, Elisa should be written ELISA and, since this assay is normally performed on blood plasma or serum, "Plasma GDNF ELISA" should replace "GDNF Elisa of blood" everywhere it is mentioned in the paper (figures and text).
Authors switch between the use of "MPTP mice" and "PD mice" (example line 413). They should maintain a consistent style, thus keep MPTP mice and avoid PD mice when they refer to MPTP-treated mice.