



Enriched environment enhances β -adrenergic signaling to prevent microglia inflammation by amyloid- β

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ORIGINAL PUBLICATION DATE: 9th August 2018

EMBO Molecular Medicine (2018) 10: e8931 <https://doi.org/10.15252/emmm.201808931>

Correction timeline:

Journal contacted authors:	2 nd of August 2022
Authors' response to journal:	2 nd of August 2022
Authors' response to journal:	12 th of August 2022
Journals' response to authors.	16 th of August 2022
Journals' response to authors.	12 th of September 2022
Authors' response to journal:	13 th of September 2022

Staff: Karin Dumstrei, Bernd Pulverer, Jingyi Hou, Erica Wilfong Boxheimer, Christopher Rickerby.

Report:

Journal contacted authors **02.08.2022**

Dear Dr. Selkoe,

The journal was recently notified of a potential duplication in Figure 6A of your 2018 paper with EMBO Mol Med (DOI: 10.15252/emmm.201808931). We perform our own image analysis and assessment of any issues raised and decide whether the journal needs to follow up.

We have evaluated the claim that there are duplicated, rotated confocal images in Figure 6A:

<https://pubpeer.com/publications/BD983CC0C4350D7003E8E73B7EA5C6>. Our analysis shows that the images appear nearly identical. We checked the other figures in the paper and noted that the duplication in Figure 6A persists within the images shown in Figure S5. We invite you to comment on these aberrations and request source data for these panels.

We would appreciate hearing back from you by Monday, the 15th of August.

Sincerely,

Erica Wilfong Boxheimer
Data Integrity Analyst | EMBO Press

Authors' response to journal

02.08.2022

Dear Ms. Boxheimer:

I am surprised to hear about this and was unaware of any issue with the figures of this paper. I will immediately review these figures (and all others in the paper) with my former HMS graduate student, Huixin Xu, the first author. We will then report back to you. We will make every effort to accomplish our review of the images and obtain the source data for these panels by August 15, but that depends on the availability of Dr. Xu at this time.

We look forward to responding in a full and timely fashion.

Sincerely,

Dennis Selkoe

Authors' response to journal

12.08.2022

Dear Dr. Boxheimer:

Thank you again for your letter of inquiry. I attach a detailed report explaining the source of this error and our correction thereof.

After you have considered our response, we stand ready to discuss any further questions you may have about this inadvertent image selection error on our part.

Sincerely,

Dennis J. Selkoe, MD

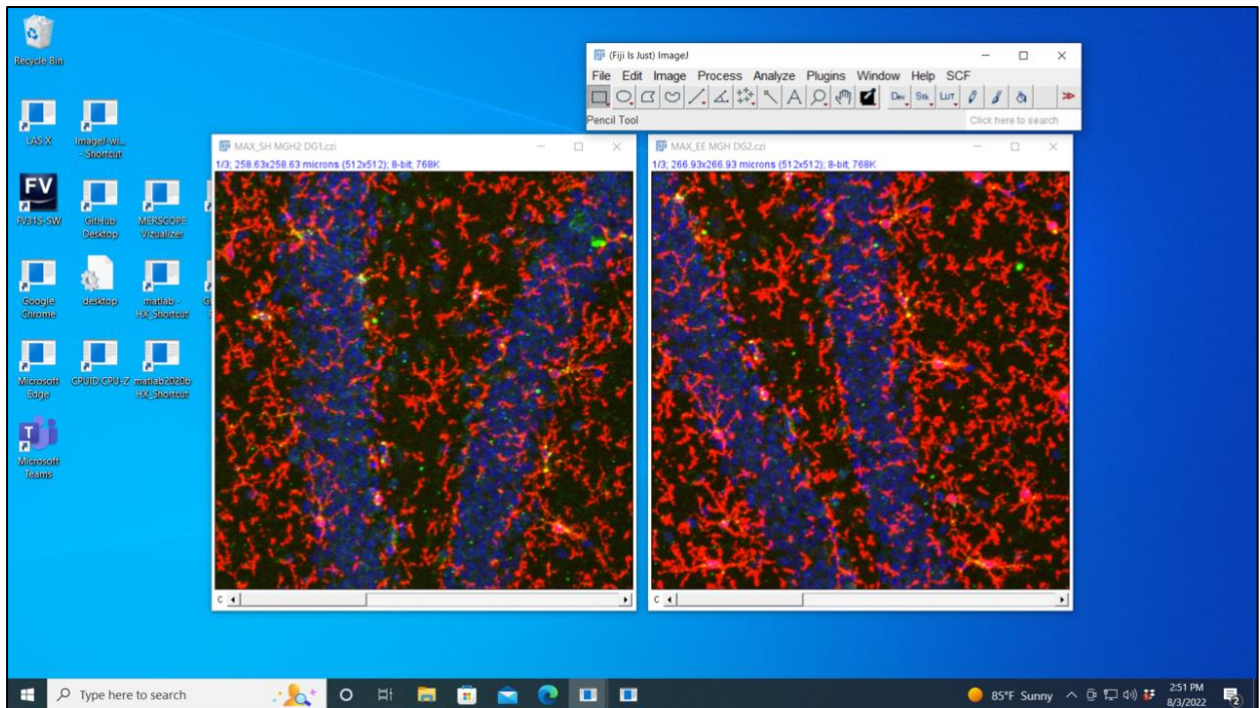
Dear Dr. Boxheimer:

Thank you for pointing out this error in an image displayed in Figure 6A and corresponding Figure S5 of our 2018 *EMBO Molecular Medicine* paper. Huixin Xu (then an HMS graduate student in my lab and now a senior postdoctoral fellow at Boston Children's Hospital) and I looked through the original source data from this study and identified the source of this error in image selection. We have established that while performing the confocal microscopy, the representative image we chose for the SH AD-TBS animal, as displayed on the left in published Fig. 6A, was indeed mistakenly acquired from the same brain section as the image for the EE AD-TBS animal displayed on the right in published Fig. 6A. We attach a screenshot of our original data folder below (**Display item 1**). The two images intended as representative images for published Fig. 6A (among the 25 images total in this table) are marked in red in

Name	Date modified	Type	Size
EE MGH DG1	11/30/2017 10:39 AM	TIF File	5,715 KB
EE MGH DG2.czi	11/30/2017 10:43 AM	CZI File	8,630 KB
EE MGH DG2	11/30/2017 10:43 AM	TIF File	5,715 KB
EE MGH DG3.czi	11/30/2017 10:50 AM	CZI File	11,669 KB
EE MGH DG3	11/30/2017 10:50 AM	TIF File	5,715 KB
SH 94182 1 DG1.czi	11/30/2017 11:11 AM	CZI File	10,919 KB
SH 94182 1 DG1	11/30/2017 11:12 AM	TIF File	5,715 KB
SH 94182 1 DG2.czi	11/30/2017 11:17 AM	CZI File	10,923 KB
SH 94182 1 DG2	11/30/2017 11:46 AM	TIF File	5,715 KB
SH 94182 1 DG3.czi	11/30/2017 11:24 AM	CZI File	11,678 KB
SH 94182 1 DG3	11/30/2017 11:46 AM	TIF File	5,715 KB
SH 94182 2 DG1.czi	11/30/2017 10:56 AM	CZI File	8,627 KB
SH 94182 2 DG1	11/30/2017 11:03 AM	TIF File	5,715 KB
SH 94182 2 DG2.czi	11/30/2017 11:02 AM	CZI File	9,380 KB
SH 94182 2 DG2	11/30/2017 11:02 AM	TIF File	5,715 KB
SH AD3 DG1.czi	11/30/2017 11:32 AM	CZI File	10,159 KB
SH AD3 DG1	11/30/2017 11:46 AM	TIF File	5,715 KB
SH AD3 DG2.czi	11/30/2017 11:38 AM	CZI File	8,648 KB
SH AD3 DG2	11/30/2017 11:46 AM	TIF File	5,715 KB
SH Control 2 DG1.czi	11/30/2017 12:33 PM	CZI File	8,612 KB
SH Control 2 DG1	11/30/2017 12:33 PM	TIF File	5,715 KB
SH ctrl 2-1 re-exp	11/30/2017 12:23 PM	TIF File	5,715 KB
SH ctrl 2-2 re-exp	11/30/2017 12:22 PM	TIF File	5,715 KB
SH MGH1 DG1.czi	11/30/2017 12:12 PM	CZI File	10,148 KB
SH MGH1 DG1	11/30/2017 12:23 PM	TIF File	5,715 KB
SH MGH2 DG1.czi	11/30/2017 12:19 PM	CZI File	8,634 KB
SH MGH2 DG1	11/30/2017 12:33 PM	TIF File	5,715 KB

Display item 1 and are then shown side by side in **Display item 2** below. There was no image editing performed at any time on these original files. Rather, we have now confirmed from our source data that the image from the brain section named SH MGH2 DG1 had been intended (lower red box in the table), but a section from EE MGH DG2 brain tissue (upper red box in the table) was imaged by mistake under this file name. The EE section had been imaged at an earlier time but was later mistaken by us as a section of SH tissue and inserted a second time into our confocal holder, as shown by the time stamps in the table, which is why the two otherwise identical images have slightly different fields of view and angles.

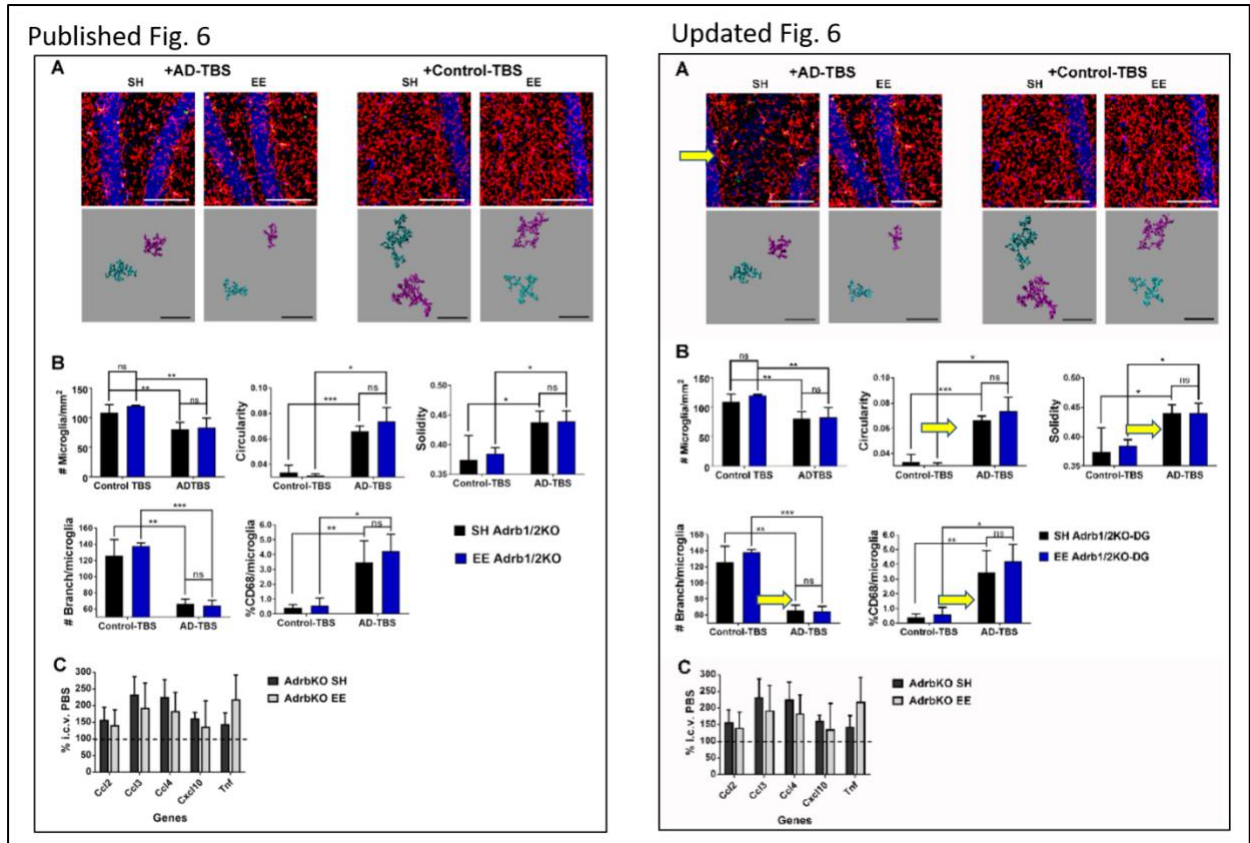
Display item 1. A screenshot of our original data folder, showing the listings of the two different representative images (marked in red) that we had meant to choose for Figure 6A.



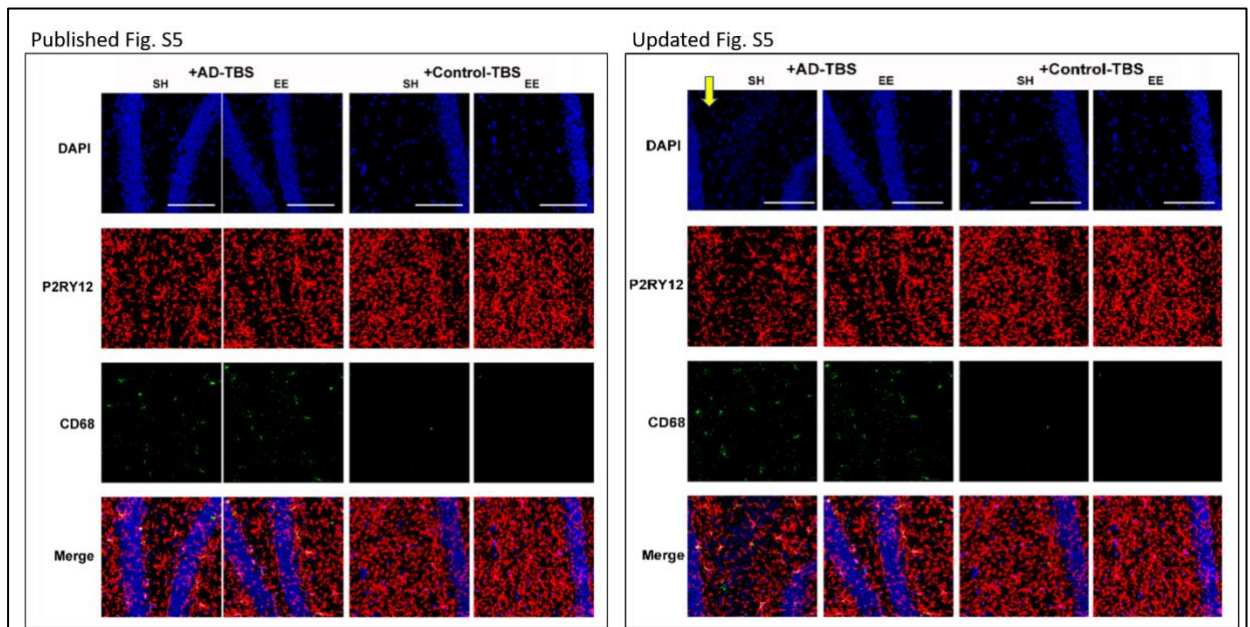
Display item 2. A screenshot showing the two representative images as they were displayed in published Figure 6A

In light of this inadvertent figure selection error, we now decided to repeat the related quantitative analysis (as per Figure 6B: microglial circularity, solidity, #branches/microglia, and %CD68/microglia) but with the cells from the wrong “SH” image now removed. A total of 20 or more cells across at least 3 different brain sections have now been analyzed for each animal. (The image in question had contributed 5 cells to our original analysis.) While the absolute numerical values have changed very slightly after removing these 5 cells, as expected, the final conclusion and statistical analysis outcomes remain the same. We attach the image below (**Display item 3**) showing the original published figure (on the left) compared to the new figure (on the right) that has an updated and correct representative image for the SH condition and the corresponding correct graphic analysis. 3D reconstructed cells (lower part of the figures) were selected from all images and did not involve the erroneously selected image in question. Of note, our Figure 6B (microglia density study) was conducted at a later time during manuscript revision from a separate set of tissue sections and therefore was not affected by the error. We also attach an updated and correct Figure S5, which displays the individual channels of images from Figure 6A, in comparison to the published version (**Display item 4**).

The representative images used in all the published figures were selected from a total of over 350 confocal images. We apologize for this inadvertent single error in image selection and hope that our updated figure and its proper analysis (seen on the right in **Display Items 3 and 4**) do clarify the issue and confirm that our quantitative conclusions about microglial morphology remain unchanged after this correction. *We emphasize that there is no statement about the data and their interpretation in the original published paper that is incorrect because of this one figure selection error.* We would be pleased to answer any other questions that you and your colleagues may have about this matter. Sincerely, Dennis Selkoe, MD and Huixin Xu, PhD



Display item 3. Published vs. updated Figure 6A. Yellow arrows indicate updates of new image and graphs.



Display item 4. Published vs. updated Figure S5. Yellow arrow indicates updates of new image.

Journals' response to authors**16.08.2022**

Dear Dr. Selkoe,

Thank you for your detailed response. We would like to discuss your response with Bernd Pulverer, our head of publications, before we make any decisions on the next steps. However due to summer travel schedules, we aren't able to have the first discussion until Monday. I have my colleague Chris Rickerby in CC who will continue the discussion in my absence.

Sincerely,
Erica Boxheimer

Journals' response to authors**12.09.22**

Dear Prof. Selkoe,

Firstly, let me introduce myself. My name is Christopher Rickerby and I am taking over as data integrity analyst from Erica Boxheimer. Erica has transitioned into a new position outside of EMBO press and we are very proud of what she has achieved.

I am taking over all her current accounts and we will be working together to finish off your corrigendum.

Thank you for your reply to our email regarding the paper "Enriched environment enhances Beta-adrenergic signaling to prevent microglia inflammation by amyloid-Beta." We have now had a chance to carefully look at your response.

Since some of the data shown in Figures 6A&B and S5 is incorrect, we will use the "retract and replace" modality to correct the raised issues. This means that the original images and graphs for Figures 6A, 6B and Appendix figure S5 will be "retracted" and the corrected images and graphs based on data generated at the time of the original experimentation will be "replaced" in the original article with a footnote in the legend linking to the corrigendum; The retracted and corrected panels will be displayed side-by-side in the correction notice.

When presenting the updated figures in the corrigendum we require only the image of the updated section. Please see (<https://www.embopress.org/doi/full/10.15252/embr.202154145>) to illustrate what this looks like.

Please send us the updated figures for Figures 6A, 6B and Appendix figure S5

as individual figure files. For the quantification in 6B please display each data point in line with our general policy to show individual data points in cases of a small number of replicates.

It is standard practice for all corrigendum to display the corresponding source data. Please provide the source data for all images, graphs and show the 3 brain slices used for the quantification.

We would also recommend creating a process file for the corrigendum. This will be published alongside the corrigendum and will work to highlight the transparency of the corrigendum process. The process file itself will show the timeline and display all key correspondence between the journal and yourself.

Please find the editor approved corrigendum notice attached to this e-mail. Please read over the attached text and send us your agreement to the text at your earliest convenience.

Since we are retracting panels and replacing them with correct data generated at the time of the original experimentation, we encourage you to contact your institute and to inform them of this matter.

Yours sincerely,

Christopher Rickerby

Authors' response to journal

13.09.22

Dear Mr. Rickerby:

I have read your letter below in detail. We have begun to assemble all of the figures, images, and source data you have requested below, and we have most of this in hand and will now gather the rest. My colleague and first author, Dr. Huixin Xu, is working closely with me to complete all items. She will be away from her lab (Children's Hospital, Boston) beginning tomorrow (9/13/22) on a professional and personal trip and will return to her lab on 9/28/22. As I need her involvement to complete the request in full, I ask that we be allowed to send all the materials to you by October 4?

I have read the editor-approved corrigendum notice in its entirety and hereby send you my agreement to this text.

I had already informed my institution of the figure selection error and the exchange with EMBO Molecular Medicine (Erica Boxheimer) a few days ago.

I look forward to providing our final dossier of all that you ask for on or likely before October 4.

Sincerely,

Dennis J. Selkoe, MD