Vermis - to exclude or not exclude? Defining a proper reference region for PET modelling of the serotonin system

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Abstract:

VERMIS – TO EXCLUDE OR NOT EXCLUDE? DEFINING A PROPER REFERENCE REGION FOR PET MODELLING OF THE SEROTONIN SYSTEM

Objectives:

Reference-Tissue modelling (RTM) necessitates a proper reference region and for that purpose cerebellum is most commonly used. The cerebellum can, however, be subdivided into sub-regions that may vary in terms of their suitability as reference tissue. We investigate regional differences in binding within the grey matter of the cerebellar hemispheres (CH) and the cerebellar vermis (CV) for PET radioligands targeting the serotonin system.

Methods:

The following PET scans were available for analysis: 5-HT_{1A}R ([^{11}C]CUMI, n=8), 5-HT_{1B}R ([^{11}C]AZ10419369, n=12), 5-HT_{2A}R ([^{18}F]Altanserin, n=7) and ([^{11}C]Cimbi-36, n=29), 5-HT_4R ([^{11}C]SB207145, n=51), and 5-HTT ([^{11}C]DASB, n=63). All subjects were scanned on a HRRT scanner and corresponding T1-weighted MRI scans were also available. We employed the software packages SUIT [1] to segment CV and FreeSurfer [2] to delineate CH. We used mean standardized uptake values (SUV) weighted by frame-length as a measure of brain uptake. SUV is defined as the time-activity-curve in the region-of-interests divided by injected dose per kg bodyweight. Statistical difference was assessed with paired two-tailed t-tests.

Results:

Figure 1 shows the ratio (CV/CH) in mean SUV between CV and CH. A significant ($p<0.001$) difference between CH and CV was found for [^{11}C]CUMI, [^{11}C]AZ10419369 and [^{11}C]SB207145. No significant difference was found between CH and CV with the antagonist Altanserin, but uptake was significantly lower ($p<0.001$) in CV with the agonist [^{11}C]Cimbi-36. We found no significant difference between CH and CV for [^{11}C]DASB. All these data are consistent with the available literature on human post-mortem autoradiography [3][4][5][6], with the exception of 5-HT_4R, where Hall et al [7] reported no evidence for specific binding to 5-HT_4R in cerebellum.

Conclusions:

We demonstrate radioligand specific regional differences in cerebellar uptake, of relevance for its use as a reference region in PET imaging. These differences may be ascribed to differences in concentration of the receptor or transporter in question in CV vs. CH, could reflect off-target binding of the radioligands or – less likely – differences in the non-displaceable binding in the two tissue types. There is evidence from post-mortem autoradiography of the presence of 5-HT_{1A}Rs in CV [3] and we observe a significantly higher [^{11}C]CUMI uptake in the CV compared to CH. We also found significantly higher uptake of [^{11}C]AZ10419369 in CH compared to CV, which is consistent with an autoradiographic study showing presence of 5-HT_{1B}Rs in CH [6]. Additionally, we observed a CH-CV difference between the 5-HT_{2A}R agonist [^{11}C]Cimbi-36 and the 5-HT_{2A}R antagonist [^{18}F]Altanserin. Our data highlight the importance of validating each radioligand carefully with regard to the suitability of including or excluding CV in the reference region definition. Additionally, we recommend the use of automatic segmentation software based on individual structural MRIs to accurately delineate cerebellum subregions.

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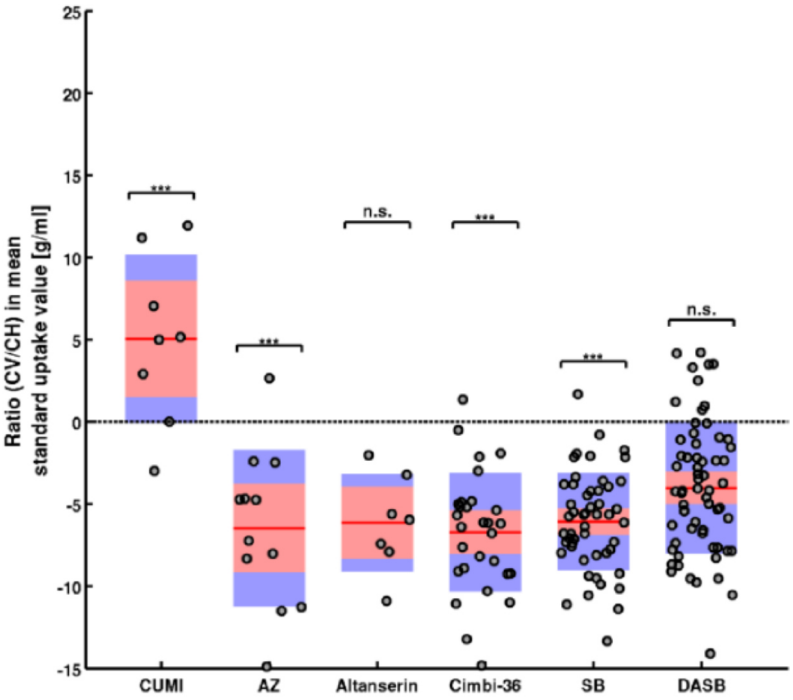

Figure1: Ratio (CV/CH) between mean standard uptake value in CV and CH

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