EXPLORING ANTERIOPOSTERIOR DIFFERENCES OF HIPPOCAMPUS PERFUSION RESPONSE TO PHYSOSTIGMINE USING ASL

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Introduction: A substantial literature (1-6) indicates distinct yet integrated anatomy and function along the longitudinal hippocampus (HPO) axis (anterior-posterior (A-P) in primates and humans, ventral-dorsal or temporal-septal in rodents). Some diseases also selectively affect A-P HPO regions (7-8). The anterior HPO has more afferent and efferent connections associated with cholinergic signaling, whereas the posterior HPO has more connections associated with serotonergic and dopaminergic signaling (1). Cholinergic selectivity along the longitudinal axis of the HPO (4) as well as higher acetylcholinesterase (AChE) and choline acetyltransferase (ChAT) level in ventral than in dorsal HPO (5) have been observed in the rat. Studies also suggest that the cholinergic projections to ventral but not dorsal HPO contain the neuropeptide galanin, which inhibits acetylcholine release (6). To test the hypothesis of A-P differences in human HPO rCBF response to cholinergic challenge with physostigmine (PHYSO), a short-acting cholinesterase inhibitor often used to test the functional integrity of the cholinergic system, HPO perfuson studies were performed with normal healthy adults at baseline and with cholinergic challenge.

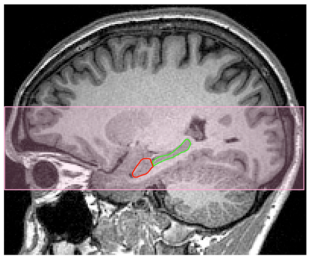

Figure 1. Anatomic images with overlaid imaging slab (pink) and contours showing the definition of anterior (red) and middle plus posterior (green) ROIs of the hippocampus.

Materials and Methods: Eleven normal male subjects (59 ± 5 years, mean ± S.D.) who had clinical and psychiatric tests to check for medical, neurological, and psychiatric disorders participated in this study. Subjects provided written informed consent prior to being studied according to a research protocol approved by the local Institutional Review Board. Subjects refrained from caffeine-containing drinks the night before and day of experiments and kept their eyes closed but remained awake during the imaging sessions. Semi-blinded perfusion studies (subjects did not know what agent would be given in which session) consisted of two sessions, the first with infusion of saline as a placebo control and the second, two days later, with infusion of PHYSO. They were performed in early afternoon, to coincide with maximal cholinergic sensitivity. The saline or PHYSO infusion rate was controlled at 1.0 mg/hour, and the infusion duration was 35-40 minutes. To counteract the peripheral autonomic effects of PHYSO, 0.3 mg of glycopyrrolate, a peripheral cholinergic antagonist, was injected IV over one minute prior to the beginning of PHYSO infusion.

Studies were performed on a 3T Siemens TIM Trio whole-body MR scanner with body coil for RF transmission and a Siemens 12-channel phased array head coil for signal reception. Axial imaging slices were aligned parallel to the anterior commissure (AC) to posterior commissure (PC) line, with the first inferior imaging slice covering the inferior edge of the temporal lobe (Fig. 1) and T_1-weighted high-resolution anatomic images for accurate reference. A FAIR (9) with Q2TIPS (10) sequence was used with gradient echo EPI: TR/TE = 3 s/9.2 ms; FOV = 230 x 230 mm^2; matrix size = 66 x 66; resolution = 3.5 x 3.5 mm^2; 16 axial imaging slices of thickness = 3.5 mm with 20% gap; 110 measurements; GRAPPA parallel imaging to reduce acquisition time and distortion from magnetic susceptibility with acceleration factor = 2 and 24 reference lines; partial Fourier (PF) = 7/8; ascending slice acquisition order, temporal bolus width/post-bolus delays = 0.6/1.2 s, and Q2TIPS inferior saturation pulse interval/size/number = 25 ms/20 mm/48.

The rCBF was estimated by using the single blood compartment model (11). Image processing operations were performed within SPM, and the HPO was segmented into two A-P regions of nearly equal volume and approximately 1:2 length ratio corresponding roughly to head and body plus tail (1) using the suggested segmentation mode of the FIRST tool from the FSL package. Since the correspondence to head and body plus tail is not exact, the two regions are referred to as anterior and middle plus posterior. Conservative HPO ROIs were obtained by excluding co-registered ROI mask voxels that extended beyond the HPO region. To further reduce partial volume effects and regional bias due to subtraction errors from residual motion and physiological noise, trimmed mean of rCBF (excluding the 5% of voxels with the lowest values and the 5% with the highest values, based on the histogram from each ROI) was used for the following statistic analysis.

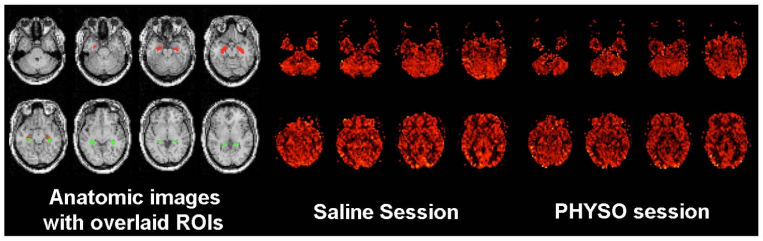

Figure 2. Co-registered anatomic images with overlaid ROIs for the anterior (red) and middle plus posterior (green) regions of the hippocampus and perfusion-weighted images from saline and physostigmine infusion sessions.

A single general linear model of rCBF was used for statistical comparisons of HPO segments, hemispheres, infusion types and all second and third order interactions among these factors. Since multiple measurements were taken on subjects and on two separate days in the same subject, the statistical model incorporated separate variance components across subjects, within subjects, and over the repeated measure. In addition, age was included as covariate. P-values were generated by specific contrasts of interest after estimating the model parameters, using SAS.

Results and Discussion: Bilateral rCBF results are reported since rCBF differences between right and left hippocampus were small and insignificant for all session-location conditions ($p = 0.81$). Hippocampus rCBF was lower in the anterior region than in the (middle plus posterior) region for both saline ($p = 0.00073$) and PHYSO ($p = 0.00047$) sessions. Compared to the saline session, rCBF was 10.0% lower in the PHYSO session in the anterior HPO ($p = 0.0157$) and 5.8% lower in the combined middle plus posterior HPO ($p = 0.0077$). PHYSO-induced rCBF changes are presented in Figure 3. However, the trend for greater effect of physostigmine on anterior than on (middle plus posterior) hippocampus rCBF was insignificant whether tested in absolute ($p = 0.30$) or percentage ($p = 0.17$) terms.

The observed trends for greater absolute and percentage reductions of rCBF by PHYSO in anterior than in (middle plus posterior) human HPO is consistent with a number of literature reports suggesting specificity of cholinergic effects along the longitudinal axis of the rodent hippocampus (1-6). That the observed trends did not reach significance may be due to: 1) insufficient spatial resolution, especially for the radial dimensions of the hippocampus and 2) the limited number of subjects in this study. This preliminary study suggests that a larger study with more subjects and higher spatial resolution along the radial axis of the hippocampus should be performed for an improved test of the hypothesis.

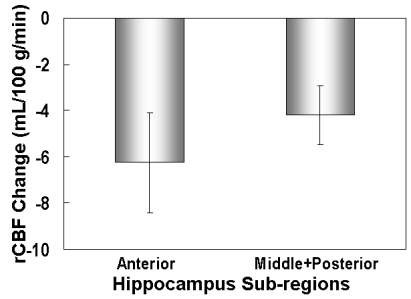

Figure 3. PHYSO-induced rCBF changes. Error bars represent standard errors.

Conclusions: In agreement with literature reports of cholinergic specificity along the longitudinal axis of the hippocampus in rodents, this preliminary human study found a larger (but not significant) rCBF response to PHYSO challenge in anterior HPO than in the rest of the HPO.

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