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Patterns of Hippocampal Shape and Volume Differences in Blind Subjects

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Abstract

Numerous studies in animals and humans have shown that the hippocampus (HP) is involved in spatial navigation and memory. Blind subjects, in particular, must memorize extensive information to compensate for their lack of immediate updating of spatial information. Increased demands on spatial cognition and memory may be associated with functional and structural HP plasticity.

Here we examined local size and shape differences in the HP of blind and sighted individuals. A 3D parametric mesh surface was generated to represent right and left HPs in each individual, based on manual segmentations of 3D volumetric T1-weighted MR images of 22 blind subjects and 28 matched controls. Using a new surface mapping algorithm described in [64], we created an average hippocampal surface for the controls, and computed its normal distance to each individual surface. Statistical maps were created to visualize systematic anatomical differences between groups, and randomization tests were performed to correct for multiple comparisons. Cumulative distribution functions for the *p*-values were also plotted to examine the magnitude of group differences in hippocampal data, and in data adjusted for brain scale differences.

In both scaled and unscaled data, the anterior right HP was significantly larger, and the posterior right HP significantly smaller in blind individuals. No significant differences were found for left HP. These differences may reflect adaptive responses to sensory deprivation, and/or increased functional demands on memory systems. They offer a neuroanatomical substrate for future correlations with measures of navigation performance or functional activations related to variations in cognitive strategies.

1. Introduction

Vision is unquestionably an important sense for allowing us to navigate through our environment. Blind subjects who lack this source of information must develop alternative strategies to map and navigate through the surrounding space and localize objects using the remaining senses. One of the most important cerebral structures involved in spatial mapping is the hippocampus. Animal studies [50] were the first to demonstrate the existence of ‘place cells’ in the hippocampus. Hippocampal cells activated by specific locations in space were

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subsequently found in humans via single cell recordings [14]. The hippocampus is also involved in encoding and retrieving episodic memories [77], path integration [78], spatial navigation tasks [39], and remembering spatial locations [26,35,37,42] (see for instance [5] for a review of the literature on this topic).

The hippocampal surface is also heterogeneous in function. For instance, spatial learning has been associated with the dorsal section of the hippocampus in rats [46], while in apes, anterior regions have been related to movement tasks and posterior ones to spatial memory [9]. In human subjects, the anterior part of the hippocampus and posterior right hippocampus were found through fMRI studies to be involved in wayfinding [25], while the medial part has been found to be activated during mental navigation [20].

Here we hypothesize that the increased demands on spatial cognition and memory due to blindness are associated with structural HP plasticity. Hippocampal plasticity has been demonstrated in numerous studies of sighted animals [7,30] and human subjects. In [38,39], the posterior regions of the hippocampi of London taxi drivers were found to be larger, compared to controls, and the volumetric difference was correlated with the number of years of experience as a taxi driver, suggesting structural plasticity that may be associated with navigational experience. Furthermore, hippocampal neurogenesis has been observed in studies of marsh tits [53], rats [21], primates [22] and in postmortem studies of human subjects [16], although the cellular basis of the volumetric differences in imaging studies is not yet known.

Furthermore, blind individuals exhibit widespread changes in brain anatomy [49,32]. In particular, in [17], a volumetric study revealed hippocampal volume differences in blind subjects, as compared to sighted controls. The hippocampus was segmented into head, body and tail regions, and a voxel count analysis was performed. Overall, the volume was larger for the blind individuals, with differences mostly located in the anterior right hippocampus.

The heterogeneous functional organization of the hippocampal surface suggests that accurate localization of hippocampal differences is crucial for understanding which functions are likely affected. In [17], the volumetric analysis used was not sensitive enough to detect effects separately in the left and right HPs, so HP volumes were pooled across hemispheres. A trend for an overall volume difference in the HPs was found at a level of $p = 0.10$ for the pooled left and right sides. For this pooled sample, the head of the HP was shown to be significantly changed ($p = 0.045$). However, as the posterior part of the HP is thought to be associated with visuospatial memory [59,67], we hypothesized that a more sensitive study, specifically one using a mapping technique, might find a smaller posterior region in the blind group. Furthermore, the right hemisphere is known to be dominant for visuo-spatial functions [27], and thus differences between blind and sighted subjects are expected to occur predominantly in the right HP. We thus turned to a more sensitive method to better localize the differences in size between the structures.

In [64], we designed a new method to automatically register hippocampal surface models and statistically compare groups of subjects at the vertex level. The method in [64] built on the level-set based direct cortex-to-cortex mapping described in [??0]. The method in [64] maps hippocampal surfaces based on their intrinsic geometry and is pose invariant, and the whole mapping process is completely automatic. The use of a mapping method which can pinpoint local size differences offers a potentially more precise anatomical localization for effects that are subtle and hard to detect using conventional measurements of the overall volume, as in [17]. The improved localization offered by mapping is useful as it makes it possible to relate morphometric differences to known functionally differentiated systems within and along the anterior-posterior extent of the hippocampus. Here we used this technique to study local differences in hippocampal volume and shape in a group of 22 blind individuals versus 28

matched healthy controls. A preliminary version of this work can be found as an abstract [31]. As the right HP is involved in the processing of visuo-spatial information, we postulated that greater differences would be present on that side. Even so, we did not expect to be able to predict in advance the precise location of subregional changes in the HP, as they may result from distributed reorganization. In formulating tests on the maps, we used a supra-threshold area statistic (the area of the surface with p -values smaller than the threshold value of 0.05). We note that in general, it is possible to quantify the distribution of suprathreshold features in statistical maps using either the peak height (maximum statistic), extent (i.e., volume or area) of suprathreshold clusters, or the total extent of the suprathreshold voxels [18]. The last of these (also known as $\hat{O}$ setlevel inference $\hat{O}$) was chosen here as it has good sensitivity to distributed effects that may affect numerous locations at once.

2. Design and Methods

1. Data

We acquired 3D T1-weighted brain MRI data from 22 blind but otherwise healthy subjects (14 men/8 women, age: 36.9 ± 11.0 SD, 17 right-handed, 4 left-handed and one ambidextrous) and 28 age, gender, education and laterality-matched controls (17 men/11 women, age: 34.1 ± 10.6 , 24 right-handed and 4 left-handed), as assessed by the Edinburgh Handedness Inventory. Age of onset varied from 0 to 33 years old (see Table 1), and in all cases, blindness was attributable to peripheral damage and led to either total blindness or at most light perception.

The research protocol was approved by the ethics committees of the Center for Interdisciplinary Research in Rehabilitation, which coordinates research with blind participants in the Province of Quebec and is sponsored by the Institut Nazareth & Louis Braille, the principal advocacy agency promoting the well-being of blind individuals in the Province, by the Centre Hospitalier de l'Université de Montréal (CHUM), where the MRI scans were collected, and by the Université de Montréal, where the project originated. All participants provided written informed consent prior to testing.

For each subject in the study, a high-resolution volumetric MRI was performed on a Siemens 1.5 Tesla Magnetom Vision MRI scanner (Siemens Electric, Erlangen, Germany) at the Notre-Dame Hospital (CHUM). Each subject was scanned with a volumetric high-resolution T1-weighted 3D sagittally oriented MRI gradient echo sequence, with the following parameters: TR: 1100 ms; TE: 4.38 ms; flip angle: 15 degrees; 256×256 matrix and field of view (FOV) 250 mm. Each image was corrected for intensity non-uniformity (Sled 1998), and registered using minctracc [8] to compute a 9-parameter transformation aligning individual scans to the ICBM-152 standard template from the International Consortium for Brain Mapping. The hippocampi were manually segmented as binary maps [55] using the MNI-Display software from the McConnell Brain Imaging Centre, Montreal Neurological Institute. Details of this procedure are described in Appendix A. See [17] for more details on the segmentation and the anatomical protocol. The scaling in the 9-parameter registration allows us to remove the effect of total brain volume on the results. In order to be able to compute absolute differences in the local displacement from the template to each shape, we also generated an unscaled hippocampal dataset by rescaling the segmented volumes back to their original sizes in native space. We computed the ratio of mean brain volume between the two groups using voxel counting on the skull stripped data, and found a difference of 5.0%. A t -test was performed to assess the significance of volume differences between the two groups, and yielded a non-significant p -value of $p = 0.45$.

As an input to the algorithm, a triangular mesh representation of the HP surfaces used was constructed by first obtaining the signed distance function from the binary volume using the

fast marching algorithm [61,76]. To obtain the zero level set of the signed distance function with genus zero topology, the fast level set from [62] was used. The final mesh representation was obtained from the Marching Cubes algorithm described in [33].

2. Surface Mapping, Morphometry and Statistics

The method described in Shi et al. (2007b) was used to map the hippocampal surfaces. Briefly, a set of common landmarks was determined automatically based on the intrinsic geometry of the HP surface on each of the parametric meshes describing the hippocampal surfaces. Correspondence between vertices was found using the direct hippocampal mapping from [64,??]. An average shape was then determined, and the component of the translation locally orthogonal to the surface was computed from each vertex on the average shape to the corresponding one on every image. A t-test was applied at each vertex to obtain a local significance map between the blind and sighted groups. The process is related to other ongoing work on hippocampal shape averaging [23,70,11] but uses automatically defined intrinsic geometric landmarks on the hippocampal surface to enforce higher-order correspondences across subjects when averaging anatomy across a group.

More specifically, a set of four longitudinal and four latitudinal landmark curves was determined automatically on each hippocampal surface model using an intrinsic property of the surface, namely the entropy of the intrinsic shape context (ISC) at each surface vertex. To compute the ISC, a histogram was created at each vertex p by dividing the surface into K bins each containing all vertices with a geodesic distance d in a given range to p . The intrinsic shape feature at each surface point expresses the variation of the shape of the remaining surface relative to this point of reference. This variation in shape is expressed as the amount of surface on the shape within a particular distance from the reference point, up to the point on the shape that is the farthest away. The distance is not the Euclidian but the geodesic distance, which is the minimum distance between two points along the surface. Thus, the ISC is a histogram describing in bins of geodesic distances from the point of reference the amount of surface area within particular distance ranges of the point of reference. Because only features intrinsic to the surface itself is used in this histogram, the ISC feature is invariant to rigid body transformation (translation, rotation), as well as rescaling, because these transformations do not change the relative geodesic distance between points.

In the next step for each vertex of the surface the variability in the ISC feature is computed as the amount of entropy over the bins in the histogram. This entropy value is highest for vertices near the tail and head and lowest at the body of the hippocampus surface. By using percentile 75 and 50 thresholds iso-entropy lines on the surface, 5 distinct regions are automatically defined. These iso-entropy lines are the four latitudinal landmarks. The longitudinal ones were then determined as weighted geodesics (i.e. shortest paths on the surface) connecting those curves.

To match two hippocampal surfaces, each surface was represented implicitly as the zero level set of a signed distance function [52] and a map u from the first surface to the second one that minimizes a harmonic energy, with the constraint that equivalent landmarks on each surface should be mapped into one another. The minimization was performed via a gradient descent algorithm [43,44,??]. The boundary conditions were maintained by blocking the flow of the diffusion term across the landmarks.

To create the average hippocampus, one of the controls was chosen and mapped to a new surface by adding to it the average displacement field from it to all the other controls. Maps from that control to all the other images were found, and a rigid transformation (translation and rotation) was applied to each of the controls. The rotational and translational components may be removed after estimating the harmonic mappings, as the solutions to the harmonic maps

are independent of rotations of the data, as they only contain spatial gradients and intrinsic parameters. The reference image was transformed by moving each vertex by the average displacement field. This process is repeated iteratively until the change of the average shape between iterations is below certain threshold.

For all the results described below, the hippocampal atlas, or reference surface with respect to which displacements were computed, was constructed as the mean of the hippocampal surfaces in the control group. Because we have point correspondences resulting from the mapping process, the atlas was constructed for both the left and right hippocampus as the average of the point coordinates after factoring out rigid transformations. The component of the translation locally orthogonal to the surface d_n between the average hippocampus and each of the shapes was then computed at each vertex after the rotation and translation were factored out. T-tests were performed between the blind and sighted subjects with d_n as a statistic, to analyze group differences. The left and right hippocampi were analyzed separately. In order to be able to compute absolute differences in the local displacement from the template to each shape, we also generated an unscaled hippocampal dataset by rescaling the segmented volumes back to their original sizes in native space. An analysis of the displacement or contraction of the hippocampal surface projected onto outward normal vectors has also been used by [10] as an index of local atrophy in Alzheimer's disease.

In order to correct for multiple comparisons, we applied a randomization test consisting of randomly assigning subjects to the two groups, and performing vertex-wise t-tests on the new data. For each randomization, the area with p -values < 0.05 was computed and compared to that of the data. We note that in performing a test on the supra-threshold area, it is possible to select any statistical threshold, t , even one greater than 0.05 (e.g. 0.1) and if the observed area of suprathreshold statistics exceeds the 95th percentile of those observed by chance in the random permutations, then the pattern of effects can be declared significant at the 0.05 level, i.e. controlling for false positive conclusions at the standard rate. The primary threshold is generally set to match the effect size that might be expected at any given voxel. When weak but distributed effects are expected, it is generally ideal to set a weak primary threshold, such as $t = 0.05$, and then perform permutation on the supra-threshold extent to confirm that the pattern of effects would not be expected to occur by chance. A weak primary threshold can always be justified if needed as the permutation test on the area enforces the conventional expected false positive rate, regardless of the voxel-level threshold. We used 100000 randomizations (which is sufficient to control the variance in the p -value derived from the randomization test [12,47] to test the overall significance of the map.

We did not recompute the reference surface during every iteration of the randomization testing. As the variance in the mean surface is approximately $\sigma(x) / \sqrt{N}$, where $\sigma(x)$ is the variance of the data (Fig. 5), there is minimal variation expected in the reference surface.

3. Results

To better understand any dependencies on overall brain scale, we determined shape and size differences among the hippocampi both before and after global scaling. The structures were first segmented from the 9-parameter registered (scaled) whole brain images, i.e., after all hippocampi had been normalized for overall brain scale. Figure 1 and Figure 2 show maps of shape differences computed by applying the analysis described above to the hippocampal surfaces manually traced on these registered images. We also inverted the scaling from the whole brain 9-parameter registration, to compare the actual relative sizes of the structures (Fig. 3 and 4).

In Fig. 1, we mapped the average displacement of the blind group to the control average atlas. At each point of the atlas, we examined group differences with an independent *t*-test and the resulting map of *p*-values is shown in Fig. 2. We also performed a randomization test using the suprathreshold statistic in order to assess the significance of the local changes and correct for multiple comparisons over the whole area of the HP (*p*-value = 0.52, left HP, *p*-value = 0.021, right HP). Positive displacements from the average shape were found in the blind group for the anterior ventral HP (CA1 + subiculum), while to a lesser extent, negative ones were found in the posterior CA2 - CA3 - dental gyrus complex. After visual inspection by comparing the right HP surface of each blind subjects to the atlas, no bending effect was observed. For the scaled results, two smaller clusters of negative displacements were also found in the dorsal side of the right hippocampal head, though these effects were not present in the unscaled HPs as we describe below.

We next repeated the above analysis on the unscaled HP surfaces, by first inverting them to their native scale via the 9-parameter transform obtained in the registration process. We then re-computed the left and right HP atlas from the unscaled HP surfaces in the control group. In Fig. 3, we show the average displacement of the blind group with reference to the control average surface. Using the unscaled HP surfaces, we see a similar trend to the map in Fig. 2. We also applied a *t*-test pointwise on the HP atlas and the corresponding map of uncorrected *p*-values is shown in Fig. 4. The randomization test was also applied with 1,00000 random assignments of blind subjects and controls to groups, to assess the overall significance of the map. This yielded a corrected overall *p*-value for the unscaled left HPs of 0.55, while that for the unscaled right HPs is 0.018. For the unscaled HP, changes were similar to those found in the scaled case, with the addition of the posterior ventral CA1/subiculum regions. In the unscaled case, both the anterior and posterior results have similar effect sizes, though part of the posterior effect is washed out with brain scaling.

We also divided the subjects into two groups, one group with 12 early-blind subjects (age of onset < 5 years old), and one group of 8 late-blind subjects (age of onset > 14 years old). Overall (corrected) *p*-values were found for both groups. We also determined two sets of control groups by matching each blind subject to a control by age and sex. We did not expect meaningful results due to the small sample sizes. In fact, we found corrected *p*-values of 0.34 (early blinds, left scaled HPs), 0.30 (early blinds, right scaled HPs), 0.29 (early blinds, left unscaled HPs), 0.43 (early blinds, right unscaled HPs), 0.13 (late blinds, scaled left HPs), 0.027 (late blind, scaled right HP), 0.22 (late blinds, unscaled left HPs), 0.16 (late blinds, unscaled right HPs)

The reference surface on which we computed the normal distances is the mean surface of the controls used afterwards in the statistical tests. Though the bias induced by this fixed control-only template is expected to be small, we verified this by re-running the randomization tests for each of the 4 cases (left and right, scaled and unscaled HPs), and recomputing the mean shape at each iteration. For this test, we reduced the number of randomizations to 10000, as these took 1000 CPU hours to perform. When $N = 10,000$, the approximate margin of error (95% confidence interval) for *p* is approximately 5% of *p*, so this adequately controls the standard error SE_p of the omnibus probability *p*, which follows a binomial distribution $B(N, p)$ with known standard error (Edgington, 1995). We obtained corrected *p*-values of $p = 0.5139$ (left scaled), $p = 0.5980$ (left unscaled), $p = 0.0212$ (right scaled) and $p = 0.0183$ (right unscaled), which are similar to the ones computed with the fixed template that was not re-computed during the randomizations. This shows that there are no major differences incurred by computing the reference surface and measuring distances to the new surface during each randomization.

To assess the influence of handedness on the results, we pooled all blind and sighted subjects, and we separated the dataset into a left-handed and a right-handed group. Our vertex-wise

statistical analysis was performed to compare the two sets. We found randomization p -values of $p = 0.50$ (scaled right), $p = 1.00$ (scaled left), $p = 0.50$ (unscaled right), $p = 1.00$ (unscaled left). We repeated this procedure by dividing the data into a male and female group. For these we obtained p -values of $p = 0.60$ (scaled right), $p = 1.00$ (scaled left), $p = 0.38$ (unscaled right), $p = 1.00$ (unscaled left).

In order to further assess the validity of the results, we then computed the positive False Discovery Rate (pFDR) as an exploratory post hoc test. The pFDR measures the rate at which findings are positive when the null distribution is true, conditioned on there being positive findings (see Storey and (2001) and Storey (2002) for more details). The pFDR and randomization tests are both widely used methods for multiple hypothesis testing, but each may be more or less powerful depending on the data. A trend was found in the right HPs for both scaled and unscaled case (right scaled HPs: pFDR = 0.0792, right unscaled HPs: pFDR = 0.0882, left scaled HPs: pFDR = 0.8036, left unscaled HPs: pFDR = 0.5263). The pFDR value indicates the expected rate of reported effects that are in fact false positives if we consider a p -value of $p = 0.05$ as significant at the voxel level. For instance, this is 7.92% for the right scaled HPs. These results are consistent with the p -values we obtained from the randomization test. In addition, the pFDR values are much more conservative in this case.

To examine the potential effects of variability on the results, we also plotted the standard deviation at each vertex for the left and right HP (Fig. 5). There was no group difference in the displacement variability between the two sides. This suggests that the failure to detect a difference on the left HP may reflect a biologically lateralized effect, rather than a reduction in power to detect a true effect due to higher anatomical variability.

In order to verify that there was no significant difference in the displacement variability between the two hemispheres, we computed the ratio of variances of the displacement fields from the left and right sides. The variance ratio between two groups is distributed approximately as an F-statistic with $N-1$ and $M-1$ degrees of freedom, where N is the sample size for the numerator group and M is the sample size for the denominator group. Vertex-wise p -values from the F-statistic are shown in Fig. 6. No significant differences were found between the two sides.

4. Discussion

Here we show the first maps, to our knowledge, of local structural differences in the hippocampus of blind individuals, relative to sighted individuals. Significant anatomical differences were detected, but only in the right hippocampus. Anterior regions (head/body) showed increased displacement in the blind with respect to the average template while more posterior ones (body/tail) showed decreased displacement compared to sighted controls, though this second effect was not as strong as the result in the anterior regions. These results are corroborated by two recent studies examining structural alterations of the hippocampi in the blind. Pooling left and right HPs, [17] showed that the rostral portion (head) of the hippocampus was larger in blind individuals, [6] showed that the caudal portion (tail) of the right hippocampi was smaller in the blind. Here, using the new method designed in [64], we were able to visualize significant structural differences in the right hippocampus between blind and sighted individuals, pinpointing their location using maps. In particular, differences were localized to the anterior and tail portion of the hemisphere, and no significant changes were seen on the left, despite comparable anatomical variance in each hemisphere.

There are several reasons to perform global anatomical normalization in a morphometric study and, as it is standard to do so, we presented results both with and without normalization of brain scale to understand the effects of scaling. Brain scale and overall brain volume are so

variable across individuals that it is common to perform some covariation for brain scale or scaling of the data, to control for variability that depends on factors other than those being studied. If results are found in scaled images, it can be asserted that there is a difference in regional anatomy as a proportion of overall brain scale. In addition, with brain scale variations discounted, it can be easier to detect more localized neuroanatomical differences, although this is not always the case. Even so, there are some arguments for either avoiding brain scaling, and for understanding potential confounds that can affect the interpretation of findings in scaled data. For example, normalization may introduce systematic bias to the extent that brains of blind people differ from brains of normal people through extended differential use of this structurally plastic organ. Parts of the cerebrum or cerebellum may have a different shape or volume in blind persons and if so, this will systematically affect the linear normalization of the brain and hence the resizing of the hippocampus. Second, there is some argument that brain substructures scale nonlinearly with overall volume, which makes it difficult to compare regional anatomy in groups with overall differences in brain scale (see [73], and [34] for a discussion). The scaled and unscaled maps display similar patterns of changes, and thus the results seem to be somewhat independent of total brain volume. However, the scaled results were more powerful, as may be expected from the removal of variability associated with differences in total brain volume.

The specific neural mechanisms underlying the morphological changes found in this work are unknown, but there are several hypothesis regarding their origins and consequences. The right hemisphere is well known to be dominant, in general, in terms of visuo-spatial skills [27]. Furthermore, an extensive literature supports a relationship between the hippocampus and spatial functions [36,5]. Human neuroimaging studies show hippocampal activation during navigational tasks [36,42,26,25]. The importance of the temporal lobe as a whole for path integration has been clearly established by studies of humans with temporal lobectomy [79]. In addition, circumscribed hippocampal lesions can impair spatial learning in human patients [29]. Within a given species, hippocampal volume also varies as a function of experience: in general, the more important spatial memory is for the survival of a species, the larger is the hippocampus. For instance, studies of birds have shown that increases in hippocampal volume occur concomitantly with increased use of spatial skills [30,3,7]. Furthermore, a reduction in volume is observed when these skills are not required, suggesting that the increased volume of the hippocampus may be causally related to its use, rather than attributable to general developmental factors or effects of aging. Therefore similar changes may be hypothesized in humans who are expert in spatial navigation. [38] were the first to examine this relationship in London taxi drivers. Taxi drivers showed a bilateral excess (compared to control participants) in gray matter density in the posterior hippocampus and a bilateral deficit in gray matter density in the anterior hippocampus. Moreover, a positive correlation was found between the number of years spent driving taxis and the gray matter density of the right posterior hippocampus. This excess tissue with greater experience is in the opposite direction to any typically expected age-related change, i.e., a reduction in hippocampal volume with age, which would otherwise be a confound in the design. In [39], the volume of the hippocampus of normal controls was shown to be independent of the degree of navigational expertise, thus suggesting that experience and not innate navigational ability accounted for the increased size of the posterior HP in London taxi drivers. There is no *a priori* reason to expect that the blind group selected here is innately better at navigation than the sighted group, nor that innate HP sizes differ in the two groups. Thus, our results also suggest, as in [38,39], that at least some of the differences found here were acquired as a result of the difference in environment between blind and sighted controls. In a future study, it would be interesting to correlate the results found here with navigational ability in our group of subjects.

Like taxi drivers in some respects, blind individuals require an extensive mapping and understanding of their environment. Even so, they cannot rely on vision to understand the

spatial organization of their immediate surroundings. Our findings however, along with those of [17] and [6], do not match those of [38] anatomically. We found local increase in size in the anterior HP and local decreases in size in the posterior HP. These results, and those of [6] and [17] are at first glance contradictory to those observed in taxi drivers compared to controls. The posterior HP is associated with visuospatial memory [59,67], and this may partially explain its decreased size in the blind when compared to sighted individuals. However, if the presence or absence of visual memories was the only explanation for the size discrepancy between the two groups, one would expect that HP volumes would be similar in all sighted subjects, including taxi drivers. The most obvious explanation for the discrepancy between the blind and sighted groups is the absence of vision which affects the type of spatial representations available to each group of individuals. Blind individuals tend to navigate better when they use an ideothetic (or egocentric) frame of reference when encoding spatial information in large-scale environments [48] - especially if they have lost sight at an early age [45,72]. Taxi drivers, on the other hand, are thought to use a more integrated (allocentric) representation of space than normal controls [38]. It was suggested in [39] that the right posterior HP is used to store an allocentric spatial map representing known locations. Therefore, the greater gray matter volume in the posterior hippocampus of taxi drivers may be linked to their increased use of an allocentric frame of reference. The negative displacements found here in the posterior HP may reflect the diminished use for such a map. In [39], anterior HP gray matter volumes were found to be smaller in London taxi drivers when compared to London bus drivers. These results were correlated with a poorer neuropsychological performance in tests measuring the acquisition and retrieval of new visuo-spatial memories. The blind individuals in our study have to memorize a great deal of spatial information, as they lack immediate feedback from the environment, which may explain the greater displacements found in the anterior HP.

The CA1 regions of the hippocampus may be involved in sequence memory and navigation [28,58]. The improved navigational skills might explain the increased displacements with respect to the average template found here in the blind group compared to controls. Furthermore, the posterior region of the HP is thought to be involved in spatial memory [9], which may explain the smaller posterior CA1 and subiculum regions. However, it is likely that the changes found here reflect a global reorganization of the HP. It would be interesting in the future to compare the anatomical results above to the functional activation of the HP in blind individuals during navigational and spatial memory tasks. To our knowledge, no such studies exist to date.

[50] were the first to show the existence of place cells in the rat hippocampus. These cells have the characteristic of being activated only when the rat is at a specific location in space. The field of activation of the place cells is formed using multimodal information derived from the vestibular, visual, proprioceptive and motor systems [41,51,19]. Studies of blind and sighted rats have shown that place cells were present and functional even when the rats became blind early in life [60]. These cells had characteristics comparable to those in the sighted rats and had similar fields of activation. A recent study in humans found that 24% of hippocampal cells were *bona fide* place-responsive cells [14]. This finding coupled with that of the significantly larger anterior hippocampus in blind individuals could explain the preservation [17] and even improvement [75] of navigational skills observed across a wide variety of tasks despite the absence of vision. In some instances, blind individuals even show superior skills to those observed in the sighted [17]. The hippocampal head has also been typically associated with verbal memory [24]. Thus, a greater volume in this region of the hippocampus could also be related to an enhanced use of memory by blind individuals, as often observed in previous studies [1,2,57,56]. These questions are likely to be resolved by using functional imaging, perhaps in conjunction with anatomical surface mapping, to understand the activation of the hypertrophied regions found here and relate their altered structure to measures of navigational performance, strategy, and other cognitive parameters.

As is often debated in studies of hippocampal neurogenesis, it is strictly speaking unknown whether the extra tissue observed here contributes to improved function or not. For example, in Williams syndrome [74] and fetal alcohol syndrome [2002], there is excess gray matter in cortical regions known to be involved in the altered behaviors, but it is not known whether this is a functionally beneficial adaptation or merely dysfunctional tissue. Even so, it is fair to hypothesize that it may be an adaptive response to sensory deprivation, and may be experience-dependent and beneficial. To establish this conclusively, larger studies would be required with sufficient power to correlate the excess tissue volume with specific measures of navigation performance or with functional activation, and to relate them to differences in the cognitive strategy employed.

Appendix

Appendix A

The anatomical boundaries used for segmentation have been described in detail elsewhere [55]. In short, the procedures described below for delineation of the hippocampus were employed:

The most posterior part of the hippocampus was defined as the first appearance of ovoid mass of gray matter inferomedial to the trigone of the lateral ventricle (TLV). The lateral border at this point was the TLV, whereas medially, the border was identified by the presence of white matter. Further anteriorly, an arbitrary border was defined for the superior and medial border of the hippocampus, in order to differentiate hippocampus gray matter from the gray matter of the Andreas Retzius gyrus, the fasciolar gyrus, and the crus of the fornix.

For the hippocampus body, the most visible inferolateral layer of gray matter was excluded, assuming that it actually represents entorhinal cortex. Next, the white matter band at the superomedial level of the hippocampus body, the fimbria, was included. If gray matter was found superior to the fimbria, the first row of gray matter was also included. The dentate gyrus, located in between the four CA regions in the hippocampal formation, together with the CA regions themselves and part of the subiculum, were included. The subiculum was divided by drawing a straight line with an angle of approximately 45deg from the most inferior part of the hippocampus medially to the cistern if no white matter delineation was visible between these two structures. The lateral border at this point was identified by the inferior horn of the lateral ventricle.

The hippocampus head was defined by the emergence of the uncus recess in the superomedial region of the hippocampus. The most important structures for identification of lateral, anterior and superior borders of the head were the uncus recess of the inferior horn of the lateral ventricle and the alveus. Besides the coronal view, the sagittal and horizontal views were employed for identification of the anterior border of the hippocampus.

The intra-rater intra-class reliability coefficients ranged between 0.81 and 0.84 for one rater measuring the hippocampus structures in four participants two subsequent times, with at least one month elapsing between consecutive measurements. The intra-rater intra-class reliability coefficients ranged between 0.86 and 1.00 for one rater dividing the hippocampus in three parts for the same four participants. The inter-rater intra class reliability coefficients range between 0.99 and 1.00 for two raters dividing the hippocampus in three parts for the same eight participants.

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Figure 1.

Average displacement at each vertex from the scaled blind group to the atlas made of an average of the controls. The results are displayed as a colormap on the surface of the atlas, with red representing highly positive displacements and blue highly negative ones. The HP surface is shown from both a top view (top row) and bottom one (bottom row) for the left and right HPs (left and right columns, respectively).

Figure 2. Maps of the uncorrected p -values (logarithmic scale) at each vertex for the scaled HP surfaces, from vertex-wise t -tests between the displacements in the control and blind groups. The colormap is again displayed on the surface of the atlas with the same views as in Figure 1. Here values green and below represent vertices with p -values significant at a level equal or better than $p = 0.05$.

Figure 3.

Average displacement at each vertex from the unscaled blind group to the atlas made of an average of the controls. The results are displayed as a colormap on the surface of the atlas, with red representing highly positive displacements and blue highly negative ones. The HP surface is shown from both a top view (top row) and bottom one (bottom row) for the left and right HPs (left and right columns, respectively).

Figure 4. Maps of the uncorrected p -values (logarithmic scale) at each vertex for the unscaled HP surfaces, from vertex-wise t-tests between the displacements in the control and blind groups. The colormap is again displayed on the surface of the atlas with the same views as in Figure 3. Here values green and below represent vertices with p -values significant at a level equal or better to $p = 0.05$.

Figure 5. Standard deviation of the displacements from the average control HP atlas to the scaled HPs at each vertex. High standard deviations are shown in red, while low ones are in blue. The views are as in Figure 1–Figure 4.

Figure 6. Significance map for the ratio of variances of the displacements from the average control HP atlas to the scaled HPs at each vertex. Low p -values are shown in red, while high ones are in blue. Left: top view, right: bottom view.

Table 1

Information about the blind participants. Rows: subject id, age of onset of blindness (yrs), age (yrs), gender (m=male, f=female).

Subject	001	008	010	011	012	019	022	024	025	027	031	037	039	040	042	044	045	047	053	054	056	057
Onset	7	5	0	8	0	0	17	21	27	0	22	2	33	0	19	15	20	0	0	0	3	0.5
Age	36	36	19	49	22	46	24	40	47	35	16	55	57	39	42	42	47	31	35	22	26	39
Gender	m	m	m	f	m	f	f	m	f	m	m	m	m	m	f	m	f	m	m	f	f	m

Table 2

List of clusters and their locations for the scaled and unscaled right HP. The first column shows the location of the center of the cluster; columns 2–3/4–5 are for scaled/unscaled blinds, resp; the second and fourth columns are the p-values, and the third and fifth columns are the direction of the differences (bigger or smaller in the blind compared to controls)

(x,y,z) Coordinates	scaled p-value	scaled direction	unscaled p-value	unscaled direction
(24.5, -16.5, -16.5)	0.0043	bigger	0.0014	bigger
(20.5, 11.5, -31.5)	0.0093	smaller	0.0740	smaller
(30.5, 11.5, -38.5)	0.0064	bigger	0.0370	bigger
(20.5, -20.5, -18.5)	0.0060	bigger	0.0014	bigger
(14.5, 6.5, -37.5)	0.0119	smaller	0.0478	smaller
(27.5, 3.5, -46.5)	0.0052	bigger	0.0040	bigger
(31.5, -13.5, -29.5)	0.0082	smaller	0.0005	smaller
(36.5, 1.5, -86.5)	0.0023	bigger	0.0046	bigger