Genetic Influences on Hippocampal Structure Mapped in 288 Twins

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Introduction: Here we created the first detailed 3D maps of genetic and environmental influences on the volume and shape of the hippocampus in a large twin sample. We used a novel segmentation method based on adaptive boosting to automatically create detailed surface-based maps of anatomy, on which we fitted quantitative genetic models. Based on prior studies suggesting that 40-69% of the variance in hippocampal volume is explained by genetics (i.e. heritability), we aimed to reveal the 3D profile of these genetic effects.

Methods: 81 monozygotic (MZ) twin pairs and 44 dizygotic (DZ) twin pairs underwent T_1-weighted structural imaging. Two independent raters manually defined both the left and right hippocampus in 20 unrelated DZ subjects and reliability measures were calculated. Our previously validated pattern recognition algorithm was trained on one rater's tracings and used to automatically trace the hippocampus of all the other subjects. The distance from a line through the center of the hippocampus to each point on its surface was used as a measure of shape. Covariance matrices were calculated (1) for the distance to each point on the surface, and (2) for the total volumes, separately for MZ and DZ twins. The covariance matrices were entered into an ACE structural equation model, which separated phenotypic variance into components attributed to additive genetic effects (A), common environment (C), and non-common environment/measurement error (E). Maps were created to show the value of the normalized coefficients. We also created separate maps of the intraclass correlation coefficients of each point on the surface of the hippocampus for the MZ and DZ twins separately. These measures were combined using Falconer's formula to give a separate measure of heritability.

Results: The reliability of the two raters was in line with previous literature values for manual hippocampal tracing (Sensitivity: Left = 0.897, Right = 0.882; Overlap: Left = 0.715; Right = 0.713). The heritability of the hippocampal volume was determined through ACE model fitting. Normalized path coefficients of a^2 (Left = 0.498, Right = 0.326), c^2 (Left = 0.025, Right = 0.156), and e^2 (Left = 0.477, Right = 0.518) agreed with prior results in a smaller sample of elderly subjects and confirm that the volume of this brain structure is moderately heritable. Novel maps of hippocampal shape illustrate which parts of the hippocampus are more or less environmentally influenced. Figure 1 shows the proportion of phenotypic variance explained by additive genetics (a^2), common environment (c^2), and non-common environment/measurement error (e^2). The maps show high values for non-common environment, consistent with the idea that the hippocampus is highly plastic, adapting in response to individual experiences. The maps also show hotspots of genetic influence. Figure 2 shows maps of the intraclass correlation coefficients for MZ and DZ twins. Figure 2 also shows Falconer's h^2, a separate measure of heritability which is largely consistent with a^2.

Conclusions: These results confirm previous studies illustrating that left and right hippocampal volumes have moderate heritability estimates. In addition, we extend these results by showing detailed maps of the heritability of hippocampal shape. These maps of genetic associations will assist in the search for specific genes affecting hippocampal structure.

References:

Gray, J.R. (2004), 'Neurobiology of Intelligence: Science and Ethics', *Nature Reviews Neuroscience*, vol. 5, no. 6, pp. 471-82.

Morra, J.H. (2008), 'Validation of a fully automated 3D hippocampal segmentation method using subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls', *NeuroImage*, vol. 43, no. 1, pp. 59-68.

Neale, M.C. (1997), '', *Mx: statistical modeling*, vol. , no. , pp. .

Pantel, J. (2000), 'A new method for the in vivo volumetric measurement of the human hippocampus with high neuroanatomical accuracy', *Hippocampus*, vol. 10, no. 6, pp. 752-8.

Peper, J.S. (2007), 'Genetic influences on human brain structure', *Human Brain Mapping*, vol. 28, no. 6, pp. 464-73.

Sullivan, E.V. (2001), 'Heritability of hippocampal size in elderly twin men: Equivalent influence from genes and environment', *Hippocampus*, vol. 11, no. 6, pp. 754-62.