Genes correlated with increases in neuroanatomical variabilitythrough evolution are implicated in neuropsychiatric disorders: A comparative chimpanzee-human neuroimaging and transcriptomic study

Gabriel A. Devenyi[1,2](gabriel.devenyi@mcgill.ca), Chet Sherwood[4], William D. Hopkins[5], Armin Raznahan[6] and M. Mallar Chakravarty[1,2,3]

[1]Cerebral Imaging Center, Douglas Mental Health University Institute, Montreal, Canada. [2]Department of Psychiatry, McGill University, Montreal, Canada. [3]Department of Biomedical Engineering, McGill University, Montreal, Canada. [4]Department of Anthropology and Center for the Advanced Study of Human Paleobiology, The George Washington University, Washington, DC 20052. [5]Department of Comparative Medicine, University of Texas MD Anderson Cancer Center, Bastrop, TX, 78602 [6]Developmental Neurogenomics Unit, Human Genetics Branch, National Institute of Mental Health, Bethesda, MD, 20892, USA

Introduction

- Chimpanzees, among the closest living relatives of humans, have remarkably similar brain structure despite 6-8 million years of divergent evolution.
- Prior work investigating genetic expression differences between chimps and humans identified a relationship between cortical expansion and "Human Accelerated Regions" of the genome[1].
- Cortical expansion regions, and HAR genes have been previously implicated in neuropsychiatric disorders in humans[2].
- We hypothesize that individual brain structure variability is a signature of brain regions with relaxed genetic control
- Genetic expression differences correlated with variability may differ between chimpanzees and humans, exposing underlying genetic mechanisms for brain evolution, and consequently, neuropsychiatric disorders

Data

- DICOM data of 261 T1-weighted MRIs of 216 individuals (87 M, 129 F) ages 6 to 53 from the National Chimpanzee Brain Resource, along with basic demographic information of age and sex.
- Scans were collected on a large variety of scanners, at numerous sites, with varying resolution (voxel dimensions 0.3 -- 1.2 mm) and TR/TEs, 139 at 1.5 T and 77 at ~3 T.
- A human comparison dataset was constructed by combining 4 individual datasets, 2 public, the HCP and PNC, and 2 from within the Douglas Hospital, Healthy Aging, and LAM, totaling 2943 subjects (1407M), aged 9-81.

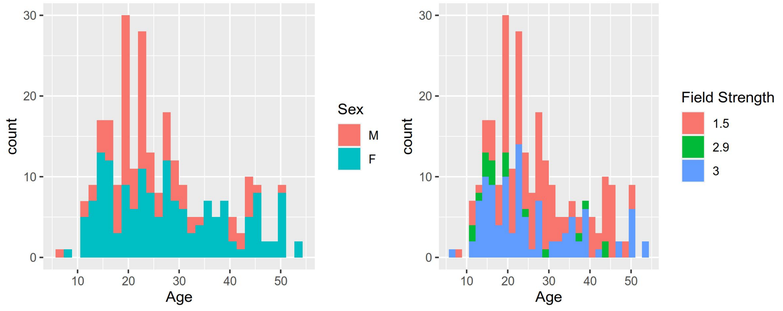


Figure 1: Sex/age, and Field Strength/age distribution of chimpanzee MRI scans included during template construction.

Imaging Methods

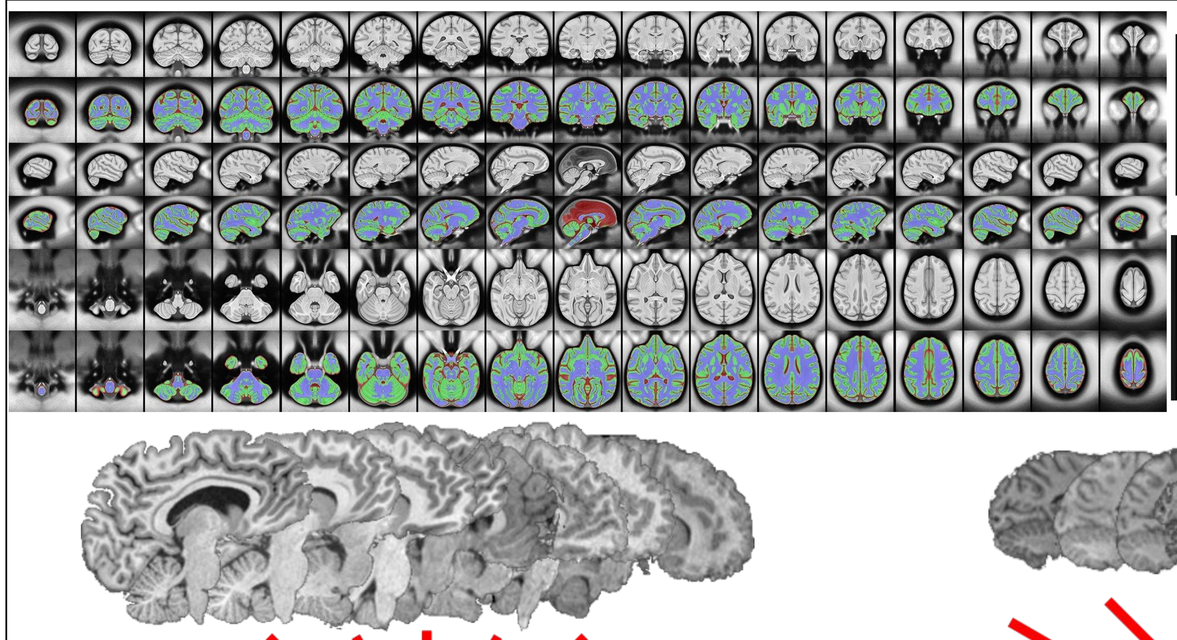
- Raw DICOMs were converted to MINC2 and pre-registered rigidly to the MNI ICBM 09c symmetric model.
- Scans were preprocessed using an iterative implementation of the ITKN4 algorithm, where a brain mask and tissue classification was estimated along with the bias field correction using the MNI ICBM 09c priors.
- Scans were extracted and flipped left-right to produce 432 scans, averaged, upsampled to 0.4 mm^3 and used as the starting target for `antsMultivariateTemplateConstruction2.sh`[2] to produce an symmetric unbiased average of the population.
- Jacobian determinants of nonlinear warp fields with residual affine effects removed (denoted relative jacobians) were smoothed with a 1.2 mm FWHM 3D Gaussian and used as the measure of local brain volume.
- Human brain scans underwent similar preprocessing and model construction procedures.
- Both chimpanzee and human population averages were then registered to the MNI ICBM 09c symmetric model.

Analysis Methods

- Voxel-wise mixed-effect linear models for relative Jacobians were computed in R/3.6.3 using RMINC/1.5.2.2 with fixed effects of sex, second order natural spline of age, and random intercept effect of subject and MRI field strength.
- Multiple comparisons were corrected for using false discovery rate (FDR) with degrees of freedom estimated with Satterthwaite's approximation and thresholded at 5%.
- Chimpanzee subjects were weighted in lmer models using the contrast-to-noise ratio (CNR) of the scan.

- Voxel-wise sum-of-square residuals (which we denote residual variability) were extracted for chimpanzee and human and z-scored in the cortical gray-matter.
- Residual variability maps, transformed into MNI space, were correlated with gene expression from the Allen Human Brain Atlas Microarray data and ordered by t-value.
- Rank-Rank Hypergeometric Overlap of the human and chimpanzee ordered gene lists was used to extract uniquely correlated and anti-correlated genes with the residual variability map
- Uniquely correlated and anti-correlated genes were then subjected to Gene Ontology, and Disease Enrichment Analysis in WEBgestalt and DisGenNet

Results



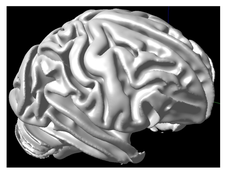


Figure 2: Representative slices of the minimum deformation average of the chimpanzee, with consensus CSF/GM/WM segmentation (left). The full field of view model (below), and cortex surface (left).

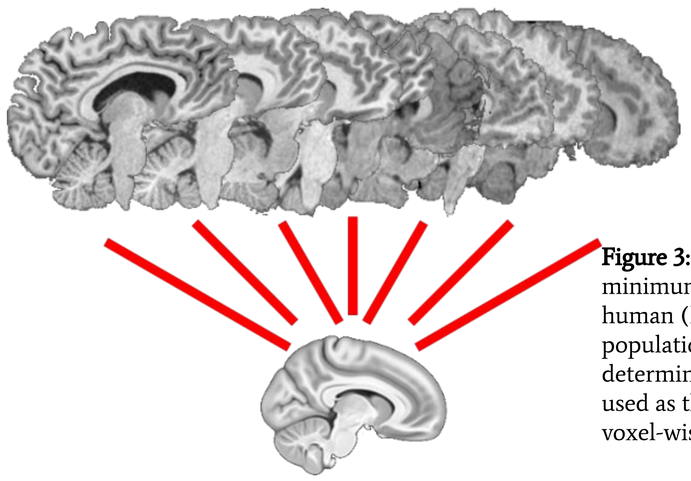


Figure 3: Construction of unbiased minimum deformation averages from human (left) and chimpanzee (right) populations. Resulting Jacobian determinants of deformation fields are used as the volume measure for voxel-wise modelling.

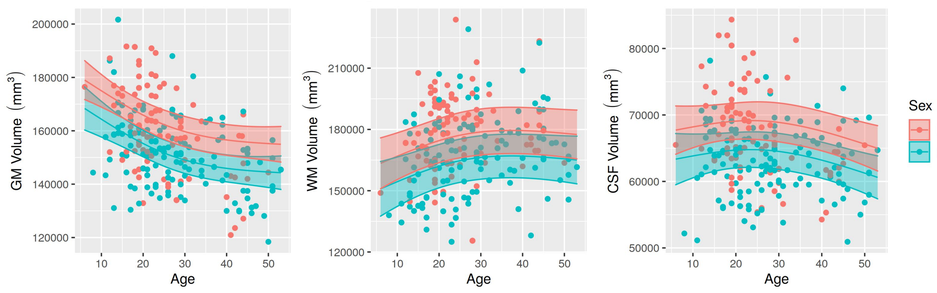


Figure 4: Chimpanzee GM/WM/CSF modelling, illustrating voxel-wise volumetric modelling curves. Modelled with fixed effect of Sex, with second order natural spline fitting Age.

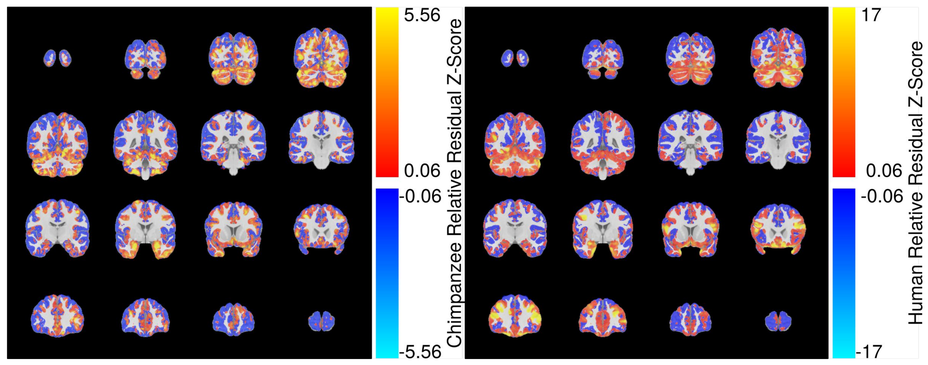
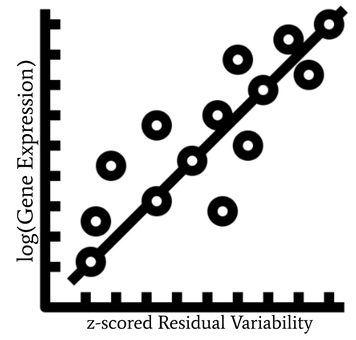
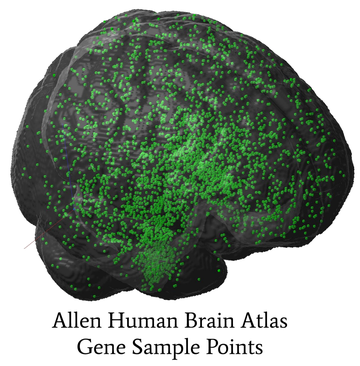


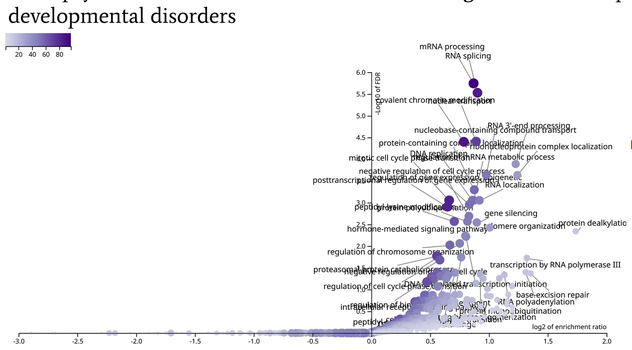
Figure 5: z-scored residuals from chimpanzee model (left) and human model (right). Humans have substantially larger residual variability than chimpanzees. Residual variability is primarily in frontal cortex

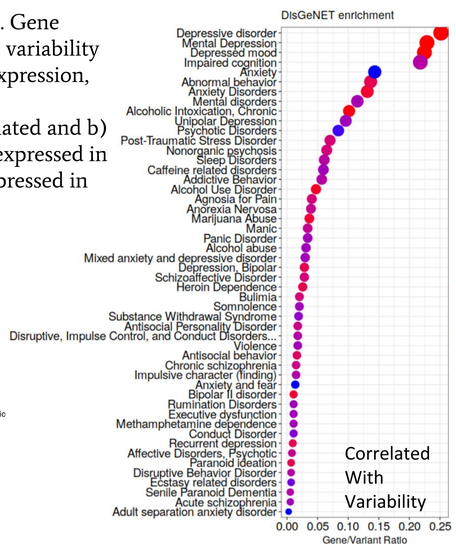


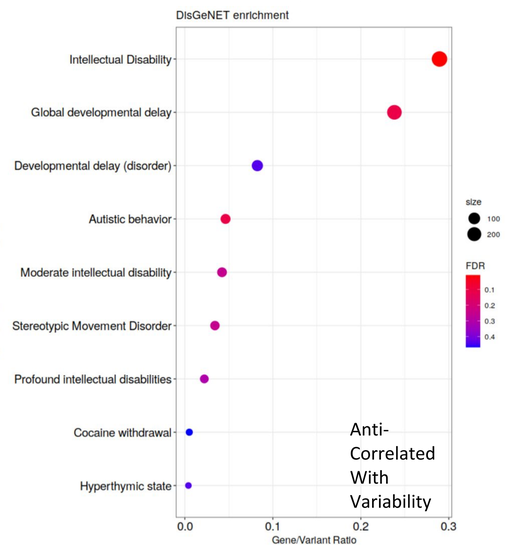


Allen Human Brain Atlas Gene Sample Points

Figure 6: Gene Ontology (below), and Disease Enrichment (right). Gene Ontology of human gene expression uniquely anti-correlated with variability is enriched for genes controlling DNA and RNA replication and expression, revealing a potential mechanism for individual brain variation.
Disease Enrichment for human gene expression uniquely a) correlated and b) anti-correlated with residual variability. Correlated genes are overexpressed in neuropsychiatric disorders, while anti-correlated genes are overexpressed in developmental disorders







References

[1] Wei, Y., de Lange, S.C., Scholtens, L.H., Watanabe, K., Ardesch, D.J., Jansen, P.R., Savage, J.E., Li, L., Preuss, T.M., Rilling, J.K., et al. (2019). Genetic mapping and evolutionary analysis of human-expanded cognitive networks. Nat. Commun. 10, 4839.

[2] van den Heuvel, M.P., Scholtens, L.H., de Lange, S.C., Pijnenburg, R., Cahn, W., van Haren, N.E.M., Sommer, I.E., Bozzali, M., Koch, K., Boks, M.P., et al. (2019). Evolutionary modifications in human brain connectivity associated with schizophrenia. Brain 142, 3991–4002.

[3] Avants, B.B., Tustison, N.J., Song, G., Cook, P.A., Klein, A., Gee, J.C., 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage 54, 2033–2044. https://doi.org/10.1016/j.neuroimage.2010.09.025

[4] Qureshi, I.A., and Mehler, M.F. (2012). Emerging roles of non-coding RNAs in brain evolution, development, plasticity and disease. Nat. Rev. Neurosci. 13, 528–541.

Conclusions

The comparison of residual variability of the age and sex trajectory of brain volume between chimpanzees and humans reveals that genes uniquely assoicated in humans are enriched for RNA/DNA regulation, along with being assoicated with neuropsychiatric disorders[4]. This result points to a mechanistic origin for genetic risk of neuropsychiatric disorders, where dysregulation of RNA/DNA control genes disrupts genetic programming of cortical development, leading to excess (or insufficient) response to environmental stimuli. Future work with this dataset will examine sex differences in residual variability in humans versus chimpanzees, and whether chimpanzee life history has an impact on residual variability.

Hello, and good day. My name is Gabriel Devenyi, and thank you for visiting my poster. I'll now give you a quick overview of our work and results.

Chimpanzees along with bonobos are our closest living non-human primate relatives. With approximately 8 million years since our last common ancestor they share approximately 99% of genes and have surprisingly similar brain anatomy. Genes in human accelerated regions of the genome have been associated with the expansion of frontal brain structures in humans compared to chimpanzees, as well as implicated in neuropsychiatric disorders.

We were interested in investigating how the chimpanzee brain differs by sex, and changes across the lifespan, in comparsion to humans, and furthermore, how and where the brain structure of individual chimps cannot be adequately described by common age trajectories and sex effects.

We hypothesized that such regions are hot spots of environmental sensitivity, where individual variation is high. We further suspected, that there would be underlying genetic differences impacting these regions.

In this work, we took the largest publicly available dataset of chimpanzee structural T1-weighted scans from the National Chimpanzee Brain Resource (and a complementary human dataset) and constructed a average brain through an iterative registration process, yielding voxel wise measures of brain volume for every input subject compared to the population average. We modelled the cross-sectional age and sex trajectory at every voxel, as exemplified in the gray matter, white matter, and CSF curves in Figure 4, and then extracted the sum of squared residuals at every voxel. This residual variability in brain structure was masked in the gray matter, z-scored, and transformed into MNI space, you can see coronal sections of said maps in Figure 5.

We then correlated the residual variability for the chimpanzee and human populations separately with the Allen Human Brain Atlas Gene Expression maps, gene-wise, to generate ordered lists of genes for chimpanzees and humans. We then compared those gene lists and extracted the unique genes from the human list for the most correlated and anti-correlated with with the residual variability maps.

We subjected those gene lists to gene enrichment analysis, to see if they were associated with biological, molecular or cellular processes, or they were previously reported to be associated with disease. Gene enrichment for genes anti-correlated with residual variability were strongly enriched for DNA and RNA regulatory and expression processes as seen in the volcano plot of Figure 6.

Meanwhile, a surprising result emerged disease enrichment analysis, were genes which correlated with residual variability are implicated in neuropsychiatric disorders which emerge in adolescence and later, while simultaneously anti-correlated genes are implicated in neurodevelopmental disorders, which arise early in development or shortly after birth.

This surprisingly clean split between disorders, along with mechanism associations hints at a tantalizing hypothesis for future research, in which genetic control of RNA and DNA processes may be controlling the environmental susceptibility of brain regions allowing for too much or too little impact due to experience, both of which can result in mental disorders. We will be continuing our investigation into this work by examining sex differences in residual variability, and how subject life history may impact these measures.

Thank you very much for visiting my poster.