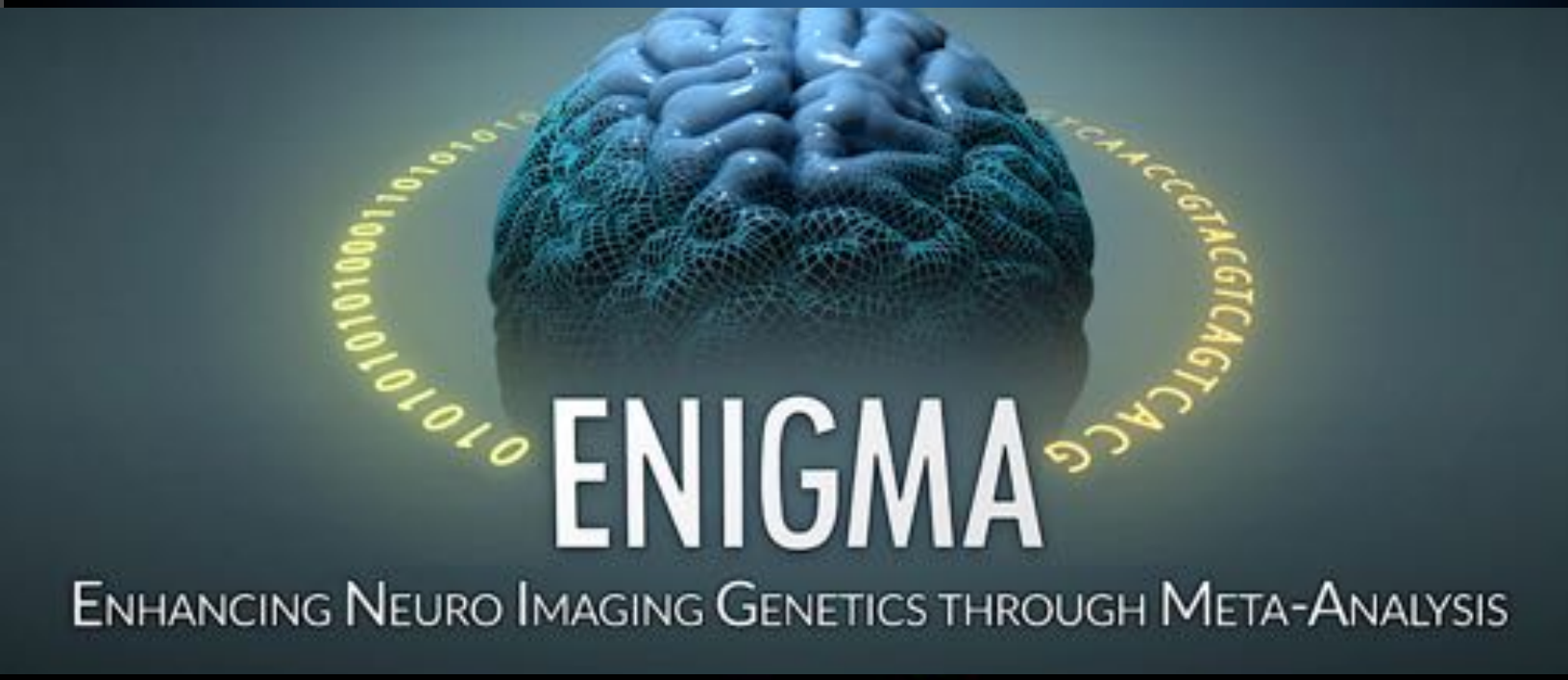


The ENIGMA Center for Worldwide Medicine, Imaging and Genomics unites the worldwide brain imaging and genomics communities to solve biomedical problems that no one group could answer alone. We are a consortium of 185 institutions in 33 countries of the world that combines the data, talents and infrastructure of over 300 scientists working on genome-wide, neuroimaging and clinical data in more than 31,000 subjects.

The 2015 **Organization for Human Brain Mapping (OHBM)** meeting features 15 ENIGMA studies, including large-scale investigations of schizophrenia, bipolar disorder, major depressive disorder, ADHD, HIV, brain lateralization, brain plasticity, and brain development across the human lifespan. ENIGMA researchers also develope new methods for 'big data' analysis (ENIGMA-Connectome and ENIGMA-Shape) and investigate functional enrichment between ENIGMA results and other genome-wide association studies on schizophrenia, multiple sclerosis and epilepsy.

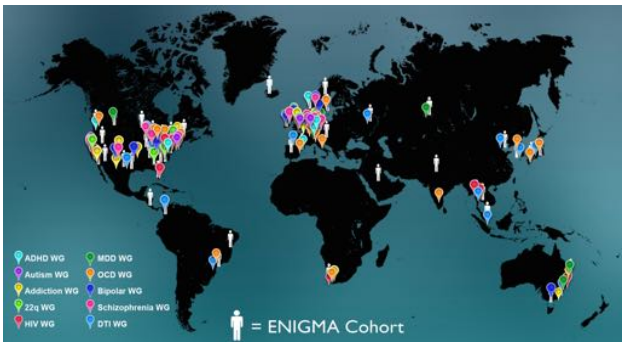
Learn more online: **enigma.ini.usc.edu**

Contents

What is **ENIGMA**?

Enhancing Neuro Imaging Genetics through Meta-Analysis

In 2009, the ENIGMA consortium was launched to bring together researchers – and their genomic and imaging data – to understand brain function and disease. Just six years later, the consortium has grown to include over 300 researchers at 185 institutions. Together we analyze genome-wide, neuroimaging and clinical data from more than 31,000 subjects worldwide. Using this unprecedented amount of data, we study ten major brain diseases, including schizophrenia, bipolar disorder, major depression, ADHD and autism. We look for genes associated with these diseases, examine differences in how the brain responds to different drugs, and trace how different parts of the brain are connected to one another in people with and without brain disease.



ENIGMA's Worldwide Reach - Scientists from 33 Countries Participate. The ENIGMA alliance studies brain scans and DNA at over 185 sites around the world. They created working groups to pool and compare data from many neuroimaging centers to understand brain differences in disorders including bipolar disorder, major depressive disorder (MDD), addiction schizophrenia, and others. The result is a data pool with tens of thousands of subjects. The institutions involved in the working groups are shown on this map from December 2014.

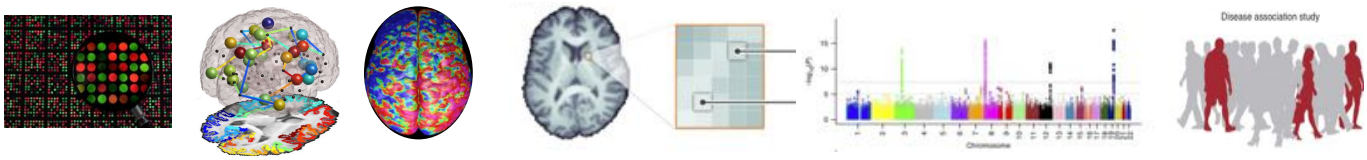
The beauty of ENIGMA is that the results are achieved without shipping data around the world. Instead, collaborative groups are formed within the consortium to tackle their own research questions. We develop and distribute algorithms to others in the consortium, creating a unique opportunity to conduct meta-analysis across multiple centers around the globe. "Using software we send out, projects with tens of thousands of data points get off the ground quickly," says Paul Thompson, PhD, professor at the University of Southern California. Dr. Thompson is co-founder of the ENIGMA consortium and PI for the BD2K-funded *Enigma Center for Worldwide Medicine, Imaging and Genomics*. The center's work lies squarely in developing analytical and statistical tools for big data and is funded as 20 sub-awards to researchers around the globe. "Data is nothing without people," Thompson says.

Professor Paul Thompson
Center Director, ENIGMA

ENIGMA researchers develop and refine algorithms to analyze brain maps, clinical measures and signals, and statistically relate these measures to genomic, environmental, epidemiological, and clinical outcome data. "There are some alliances you can form that make it easier to everybody to do science," Thompson says. "We hope to see discoveries on a scale that hasn't been possible."

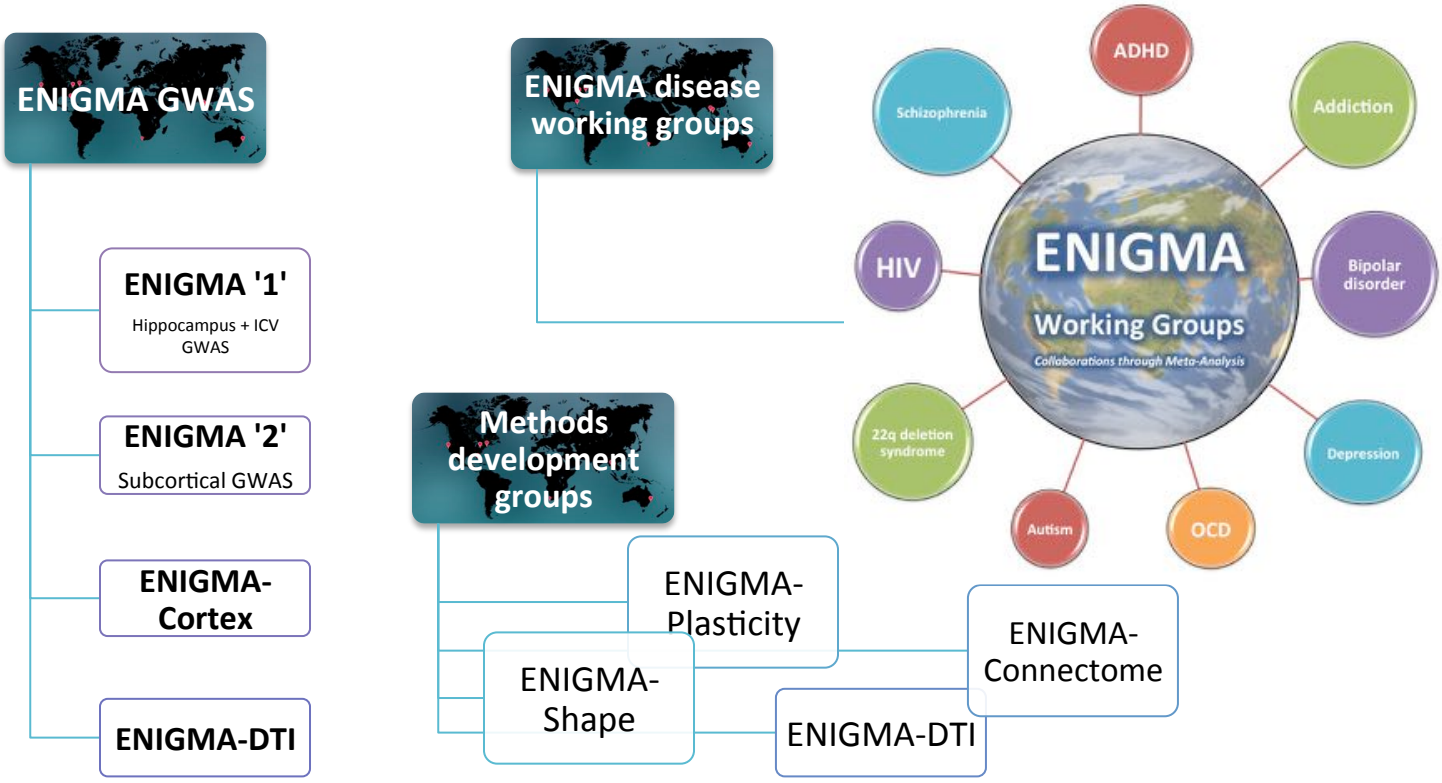
ENIGMA was recognized by the *New York Times* (April 2012), which reported that ENIGMA is transforming medical science by creating a worldwide community and "gives us a power we have not had". The consortium's work is published in high-impact scientific journals including *Nature* and *Nature Genetics* and consortium members have presented scores of abstracts on their work at international scientific conferences. Appended to this brochure, you will find the 16 abstracts on ENIGMA projects, which will be presented at the 2015 meeting of the Organization for Human Brain Mapping.

How does **ENIGMA** work?



- Genotyping chips can now test for over 1,000,000 genetic variants in the human genome.
- Advances in magnetic resonance imaging (MRI) allow scientists to examine the living human brain in unprecedented detail: probing for changes in the volume, shape and connectivity of brain structures.
- **ENIGMA operates at the intersection of genetics and MRI.**
- Experts from 185 institutions conduct state-of-the-art analysis on genotype data and MR images, screening the human genome for genetic variants that may predispose to changes in brain structure.
- This unprecedented collaboration advances distributed computation on US and non-US infrastructure, uniting multidisciplinary talents and data to tackle 10 major brain diseases: schizophrenia, bipolar disorder, major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), autism, 22q deletion syndrome, HIV and addiction.

There are over 20 ongoing ENIGMA projects. Our flagship project, ***ENIGMA GWAS,*** is now in its third phase. We are now probing for genetic variants associated with differences in cortical, subcortical, intracranial and total brain volumes. Other ENIGMA working groups focus on specific neurological and psychiatric diseases, including schizophrenia, bipolar disorder, MDD, ADHD, OCD, autism, 22q deletion syndrome, HIV and addiction. ENIGMA also collaborates with other major international consortia, including the Psychiatric Genomics Consortium (PGC), Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE) and the International League Against Epilepsy (ILAE). Our experts in neuroimaging and statistical genetics are now developing new techniques for large-scale data analysis, including diffusion tensor imaging (DTI) and connectomics.



Most Recent Nature Paper

Dr. Derrek Hibar

Dr. Sarah Medland

LETTER

doi:10.1038/nature14101

Common genetic variants influence human subcortical brain structures

A list of authors and their affiliations appears at the end of the paper

The highly complex structure of the human brain is strongly shaped by genetic influences[1]. Subcortical brain regions form circuits with cortical areas to coordinate movement[2], learning, memory[3] and motivation[4], and altered circuits can lead to abnormal behaviour and disease[5]. To investigate how common genetic variants affect the structure of these brain regions, here we conduct genome-wide association studies of the volumes of seven subcortical regions and the intracranial volume derived from magnetic resonance images of 30,717 individuals from 50 cohorts. We identify five novel genetic variants influencing the volumes of the putamen and caudate nucleus. We also find stronger evidence for three loci with previously established influences on hippocampal volume[6] and intracranial volume[7]. These variants show specific volumetric effects on brain structures rather than global effects across structures. The strongest effects were found for the putamen, where a novel intergenic locus with replicable influence on volume (rs945270; $P = 1.08 \times 10^{-33}$; 0.52% variance explained) showed evidence of altering the expression of the *KTN1* gene in both brain and blood tissue. Variants influencing putamen volume clustered near developmental genes that regulate apoptosis, axon guidance and vesicle transport. Identification of these genetic variants provides insight into the causes of variability in human brain development, and may help to determine mechanisms of neuropsychiatric dysfunction.

At the individual level, genetic variations exist linking influences on brain structures and functions associated with behaviour and predisposition to disease. Within the context of the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium, we conducted a collaborative large-scale genetic analysis of magnetic resonance imaging (MRI) scans to identify genetic variants that influence brain structure. Here, we focus on volumetric measures derived from a measure of basal ganglia (caudate, putamen, pallidum, amygdala, hippocampus and thalamus). To ensure data homogeneity within the ENIGMA consortium, we designed and implemented standardized protocols for image analysis, quality assessment, genetic imputation (to 1000 Genomes reference, version 1) and association (Extended Data Fig. 1 and Methods).

After establishing that the volumes extracted using our protocols were substantially heritable in a large sample of twins ($P < 1 \times 10^{-5}$; see Methods and Extended Data Fig. 1a), with similar distributions to previous studies[8], we sought to identify common genetic variants contributing to volume differences by meta-analysing site-level genome-wide association study (GWAS) data in a discovery sample of 11,171 subjects of European ancestry (Extended Data Fig. 2). Population stratification was controlled for by including, as covariates, four population components derived from standardized multidimensional scaling analyses of genome-wide genotype data conducted in each site (see Methods). Site-level GWAS results and distributions were visually inspected to check for statistical inflation and patterns indicating technical artifacts (see Methods).

Meta-analysis of the discovery sample identified six genome-wide significant loci after correcting for the number of variants and traits analysed ($P < 7.2 \times 10^{-9}$; see Methods) as associated with the ICV, two associated with hippocampal volume, and three with putamen volume. Another four loci showed suggestive associations ($P < 1 \times 10^{-7}$) with putamen volume (one locus), amygdala volume (two loci), and caudate volume (one locus) (Table 1, Fig. 1 and Supplementary Table 1). Quantile–quantile plots showed no evidence of population stratification or cryptic relatedness (Extended Data Fig. 4a). We subsequently attempted to replicate the variants with independent data from 17,546 individuals

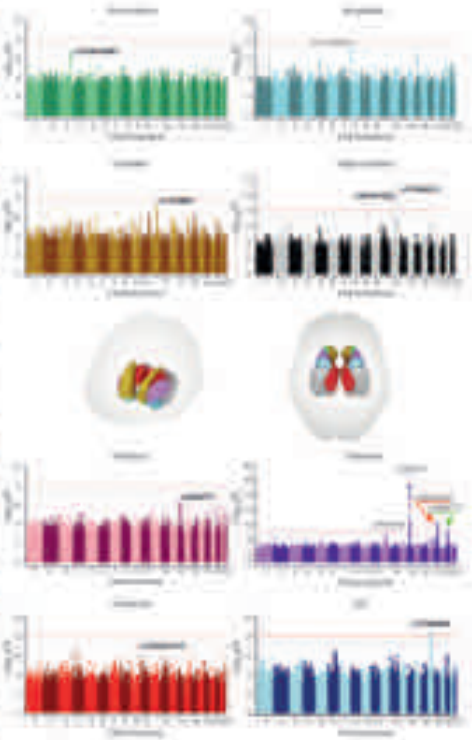


Figure 1 | Common genetic variants associated with subcortical volumes and the ICV. Manhattan plots coloured with a scheme that matches the corresponding structure (shown for each subcortical volume studied). Genome-wide significance is shown for the common threshold of $P = 5 \times 10^{-8}$ (grey dotted line) and also for the multiple-comparisons-corrected threshold of $P = 7.2 \times 10^{-9}$ (red dotted line). The most significant SNP within an associated locus is labelled.

ENIGMA Schizophrenia Working Group Brain Volume Comparison between 2,028 Cases and 2,540 Controls

Dr. Jessica Turner

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Introduction

The nature of brain structural abnormalities in schizophrenia is not conclusively determined. We analyzed brain magnetic resonance imaging scans from individuals with schizophrenia and healthy volunteers, assessed at 15 centers worldwide, using standardized methods. We ranked brain abnormalities by effect size, and examined sources of effect size heterogeneity across samples.

Methods

We pooled, via prospective meta-analysis, subcortical brain volumes computed from magnetic resonance imaging (MRI) brain scans of 2,028 patients and 2,540 controls. The mean age across samples for controls was 31 years (52% male) and for patients 34 years (69% male). Scans were analyzed using standardized image analysis [FreeSurfer (Fischl 2012; Fischl, et al. 2002)], quality assurance (outlier detection based on inter quartile range of 1.5 standard deviations along with visual inspection of segmentations), and statistical methods. Bilateral accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus as well as ventricular volume and total intracranial volume (ICV) were measured. The meta-analysis estimated group contrast effect sizes, controlling for age, sex, and intracranial volume (ICV). Meta-regression analyses identified effect size moderators. Statistical analyses employed the R linear model function lm to generate group contrasts, and R package metafor version 1.9-1 (Viechtbauer 2010) to perform random-effects meta-analyses and meta-regression analyses.

Results

Compared to healthy controls, patients with schizophrenia had smaller hippocampus (Cohen's d=-0.46), amygdala (=-0.31), thalamus (d=-0.31), accumbens (d=-0.25), and intracranial volumes (d=-0.12) and larger pallidum (d=0.21) and lateral ventricle volumes (d=0.37). Putamen and pallidum volume exacerbations were positively associated with duration of illness; hippocampal deficits scaled with the proportion of non-medicated patients in each cohort.

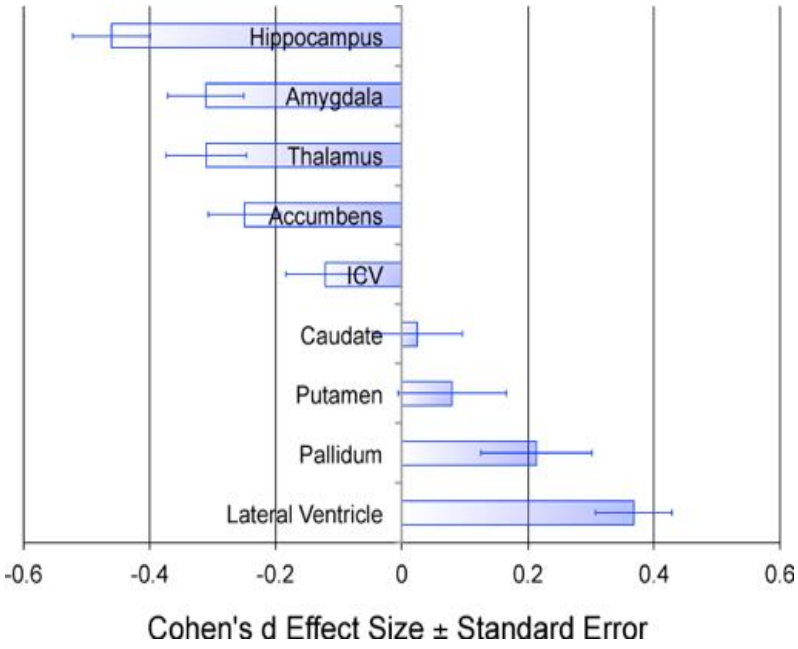

Figure 1. Effect sizes for regional brain volume differences between schizophrenia patients and healthy controls

Conclusion

This prospective meta-analysis of brain imaging data by the ENIGMA Schizophrenia Working Group shows a pattern of subcortical abnormalities in schizophrenia. The pattern is consistent with the largest retrospective meta-analysis of structural brain abnormalities in schizophrenia (Haijma, et al. 2012). Individuals with schizophrenia showed significantly smaller hippocampus, amgydala, thalamus, accumbens, and intracranial volumes and significantly larger pallidum and lateral ventricle volumes. Largest effect sizes were observed for the hippocampus and the lateral ventricles. We demonstrate successful prospective meta-analysis of structural brain imaging data. We are now applying similar methods to cortical surface thickness and surface area measures in a consortium that has grown to 23 centers worldwide.

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White Matter Differences in Schizophrenia: Meta-analytic findings from ENIGMA-SZ DTI

Dr. Sinead Kelly

Kelly S*[1], Jahanshad N*[1], Agartz I[8], Andreassen O[8], Fatouros-Bergman H[9], Brouwer R[5], Cahn W[5], Calhoun V[16], Cannon D[2], Castrillón G[24], Chiapponi C[14], Corvin A[3], Doan N.T[8], Ehrlich S[21], Crespo-Facorro B[23], Flyckt L[9], Fukunaga M[18], Glahn D[7], Gollub R[4], Gur R[11], Tordesillas-Gutierrez D[18], Hashimoto R[19], Hatton S[20], Hibar D[21], Hickie I[22], Horáček J[23], Lopez Jaramillo C[24], Jönsson E[25], Kahn R[26], Kubicki M[27], Knöchel C[28], Oertel-Knöchel V[29], Kikinis Z[30], Langen C[31], Lagopoulos J[32], Lyall A[30], Magnotta V[33], Mandl R[26], McDonald C[8], Melicher T[34], Newell D[30], Pasternak O[35], Piras F[36], Pearlson G[37], Hulshoff Pol H[6], Roalf D[38], Roiz-Santiañez R[39], De Rossi P[10], Rotenberg D[40], Satterthwaite T[41], Spalletta G[42], Spaniel F[43], Stäblein M[44], Tønnessen S[3], Vanegas A[24], Vargas C[24], Voineskos A[45], Westlye L[46], White T[47], Zhao J[48], Thompson P[49], Turner J[50], Donohoe G[51], The ENIGMA-Schizophrenia DTI working group

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Introduction:

Abnormalities of brain white matter (WM) structure have been characterized in schizophrenia (SZ), with consistent findings of altered fractional anisotropy (FA) particularly in frontal, temporal and inter-hemispheric connections (1). Ongoing efforts in ENIGMA-DTI (http://enigma.ini.usc.edu/ongoing/dti-working-group/) have supported the value of large-scale collaborations for meta-analysis, which combine data across independent samples using harmonized analytical techniques (2). This can increase statistical power and result in more robust estimates of effect sizes. The goal of the ENIGMA-SZ DTI working group is to identify robust disruptions in FA of select WM regions of interest (ROIs) for SZ patients worldwide. This will help to identify neuroimaging biomarkers to advance diagnostics and study treatments for the disorder.

Methods:

The ENIGMA-SZ DTI group currently comprises samples from 16 studies around the world, including the United States, Canada, Colombia, Ireland, Spain, Germany, the Netherlands, Norway, Sweden, Czech Republic, Italy, Japan and Australia. No individual imaging or clinical data were shared across institutions for this analysis. The current meta-analysis included 1234 healthy controls and 879 patients from 12 of the 16 sites; across all samples, the average age was 35 years for controls and 36 years for patients. Fifty-six percent of controls were male while 67% of patients were male.

Preprocessing of the DWI images and creation of the FA maps were carried out at each site. The ENIGMA-DTI protocols detailed here: http://enigma.ini.usc.edu/protocols/dti-protocols/ were run on the FA maps. Briefly, these protocols were developed to harmonize data across multiple sites; these include registration of the individual subject FA maps to the ENIGMA-DTI FA template and projection of voxels onto the ENIGMA-DTI template skeleton. Twenty-five bilateral (or mid-sagittal) WM regions of interest (ROIs) were then extracted from the skeletonized images and the average FA within each ROI was determined. We evaluated FA differences between SZ cases and controls at each site by calculating the Cohen's d effect size estimates for diagnosis of SZ at each of the 25 ROIs. Age, sex, their interaction, as well as age squared and its interaction with sex, were used as covariates. Two distinct image acquisition protocols were used at one site. In this case, each protocol was analyzed separately.

Results:

A random effects meta-analysis was conducted on the combined results. The maximal effect size was found for FA of the body of the corpus callosum (BCC) (d=-0.34; SE=0.074, p=5.2x10-6), the corpus callosum (CC) (d=-0.31,

SE=0.076, p=5.6x10-5) and the genu of the corpus callosum (GCC) (d=-0.28, SE=0.060, p=2.3x10-6), all of which were significantly reduced in patients applying a Bonferroni corrected threshold of p < 0.002 (0.05/25). The next largest effect size was for the anterior *corona radiata* (ACR) (d=-0.28, SE=0.067, $p=3.9x10^{-5}$), followed by the fornix (FX) (d=-0.26, SE=0.057, $p=7.9x10^{-6}$), and finally the fornix/*stria terminalis* (FX/ST) (d=-0.21, SE=0.051, p=7.0x10-5) (see Figure 1).

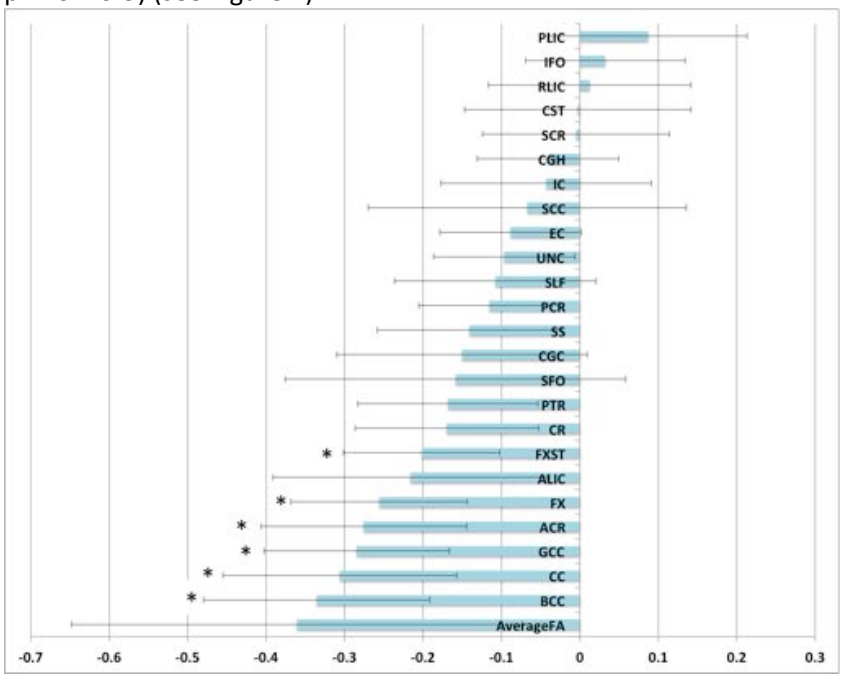

Figure 1. Cohen's *d* effect sizes, after meta-analysis, for FA differences between SZ patients and healthy controls, including age and sex covariates. Error bars represent 95% confidence interval, **P*-value < 0.002 (corrected).

Conclusions:

In the largest meta-analysis of DTI measures in schizophrenia to date, using harmonized protocols, we found the most robust differences between cases and controls in regions of the CC, specifically the BCC and the GCC. Differences in white matter microstructure of these CC regions are in line with the schizophrenia literature (1, 3, 4). Significant effects were also observed in the ACR and FX, which have also been previously reported (5, 6, 7). However, the fornix is reported to be one of the least heritable structures using ENIGMA-DTI protocols (2) likely because the structure can be difficult to delineate on gross DTI voxels due to its small size. Future meta-analyses of these data will study factors that may modulate these effects, including education and IQ, and clinical covariates, including medication, duration of illness, and symptom severity.

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Cortical thickness and surface area differences in bipolar disorder subtypes.

Dr. Derrek Hibar

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Dr. Ole Andreassen

Introduction:

Considerable uncertainty exists about the most powerful biomarkers of the pathophysiology and progression of bipolar disorder (BD; Phillips and Swartz, 2014). We formed the ENIGMA Bipolar Disorder Working Group to identify robust biomarkers of BD, quantify differences in subtype diagnosis, and better understand medication effects and other sources of heterogeneity. Here we present our preliminary work examining differences in BD subtypes in cortical thickness and surface area across the entire brain.

Methods:

High-resolution structural MRI data from 8 sites worldwide were included, from 694 BD type-1 (BDI), 204 BD type-2 patients (BDII), and 1,187 healthy controls (HC). We performed pairwise comparisons of cortical thickness and surface area within 68 bilateral ROIs, obtained using FreeSurfer (Fischl et al., 2002), between BDI, BDII and HC. We used a mixed-effect modeling approach in R with scanner included as a random effect to control for site differences. We controlled for age and sex as fixed effects for thickness analyses, and age, sex, age*age, age*age*sex, and age*sex for surface area analyses. Significance was calculated based on a binary fixed-effect representing differences in diagnosis. We declare any cortical differences significant if they exceed a BH-FDR level of $q<0.05$.

Results:

We found a broad bilateral pattern of significant cortical thinning in BDI compared to HC, consisting of 40 ROIs in lateral frontal, temporal, and inferior parietal brain regions (tabulate results in Figure 1). Surface area was significantly lower in BDI compared to HC in the superior parietal ROI (Cohen's d = -0.229; P-value = 3.60×10^{-5}). There were no significant differences in thickness or surface area when comparing BDII to BDI and HC.

Discussion:

Brain regions showing the most evidence for differences in bipolar disorder were found in frontal and parietal regions of the cortex. The left *pars triangularis* (PTr) showed the most evidence of thinning in BD1 cases when compared to controls (Cohen's d = -0.295; P-value = 9.89×10^{-10}). The ventrolateral prefrontal cortex (VLPFC) where the PTr resides is involved in emotional response regulation, motor inhibition, and together with the parietal cortex spatial attention (Lawrence et al., 2004). Each of these

functions is disrupted in bipolar disorder, but disrupted functional networks have not always been linked to structural changes. Here we provide evidence of cortical thinning across the brain with major thinning in frontal and parietal regions in the largest sample to examine structural MRI in bipolar disorder to date. Further, the direction of effects in BDII was similar to BDI but with lower magnitudes, so BDII may share a similar pathophysiology as BDI but with a weaker impact on the brain. We plan to include additional research groups and clinical variables of interest in future analyses.

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Structural Brain Alterations in Major Depression: findings from the ENIGMA Major Depressive Disorder Working Group

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Background:

Patterns of structural brain alterations in Major Depressive Disorder (MDD) remain unresolved, partly due to low power of individual neuroimaging studies, disease heterogeneity and complex interactions between clinical characteristics and brain morphology. Therefore, we initiated the ENIGMA-MDD Working Group to identify robust imaging markers of MDD using coordinated standardized image processing and statistical analysis protocols. Here, we investigated subcortical volume alterations in MDD in the largest sample to date using an individual participant data (IPD) based meta-analysis approach.

Methods:

Structural T1-weighted MRI scans from 1,808 MDD patients and 7,223 controls from 15 research samples worldwide were analyzed locally using FreeSurfer. Segmentations of subcortical regions, lateral ventricles and total intracranial volumes were visually inspected for accuracy and compared between patients and controls using regression models controlling for age, sex, and intracranial volume. Each local site followed standardized protocols designed to facilitate harmonized image analysis across multiple sites. Separate stratified analyses assessing effects of age of onset, stage of illness (first versus recurrent episode patients), and symptom severity were performed. Results were combined in random-effects meta-analysis models. Meta-regression analyses were used to test whether the mean age of each sample, field strength of MR images, FreeSurfer version, % of patients acutely depressed, % of patients taking antidepressants, and % of patients taking antipsychotics explained a significant proportion of the variance in effect sizes across sites in the meta-analysis. Results were considered significant if they exceeded a Bonferroni corrected P-value threshold ($P=0.05/9$ regions$=5.6\times10^{-3}$).

Results:
Relative to controls, patients had significantly lower hippocampal volumes (Cohen's d=-0.14) – an effect driven by recurrent MDD patients (d=-0.17). Age of onset ≤21 was associated with a smaller hippocampus (d=-0.20) and a trend towards smaller amygdala (d=-0.11) and larger lateral ventricles (d=0.12). Symptom severity did not show detectable associations with regional brain volumes. Sample characteristics including mean age, proportion of antidepressant users and proportion of remitted patients did not moderate brain volume alterations. Samples with a higher proportion of antipsychotic medication users showed larger caudate volumes in MDD patients compared to controls.

Conclusions:
Results of this first initiative of the ENIGMA-MDD working group clearly indicate a key role of the hippocampus in the pathophysiology of MDD. Hippocampal volumes were robustly reduced, particularly in recurrent patients and patients with an age of onset of MDD ≤ 21. Consistent brain differences in other subcortical regions in MDD were less evident. Our findings suggest that the hippocampus is a prime target region for future research to unravel the pathophysiology of MDD and improve treatment. The important next step within our consortium will be to examine cortical brain alterations associated with MDD. We are now applying similar methods to cortical surface thickness and surface area measures.

Subcortical volumes across the life span in ADHD: an ENIGMA collaboration

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Dr. Barbara Franke

Introduction

Neuroimaging studies show structural alterations of various brain regions in children and adults diagnosed with ADHD. In part due to inconsistencies in published results, it remains unclear, however, how these differences develop across the lifespan, and whether effects are brain-wide or localized to particular neurological structures and pathways. To clarify brain changes across the lifespan in a large worldwide sample, an ADHD Working Group was formed within the ENIGMA consortium (http://enigma.ini.usc.edu/).

Methods

Within the ENIGMA-ADHD Working Group cohorts from around the world analyzed MRI scans using fully automated and validated neuroimaging segmentation software (FSL FIRST or FreeSurfer), for which protocols are available on our website. Volumetric summaries of subcortical regions were pooled together and shared across the consortium. Meta- and Mega-analysis for the case-control volume differences of hippocampus, nucleus accumbens, amygdala, caudate nucleus, putamen, pallidum, and thalamus were carried out.

Results

The working group comprises 23 international sites including 1544 cases and 1729 controls. This pooled sample has an age-range of 4-63 years and includes 66% males. Our case-control meta-analysis showed subtle but significantly smaller volumes for the amygdala (Cohen's *d*: 0.15, *p*=0.004), caudate nucleus (*d*: 0.11, *p*=0.004), and putamen (*d*: 0.11, *p*=0.003) for cases compared to controls. The results of the mega-analysis showed similar effect sizes, with greater significance (lower p-values). The differences in amygdala volume between cases and controls differed as a function of age.

Conclusions

Brain structure differences related to ADHD across the lifespan remain largely unexplored. As large, well-powered longitudinal studies are still scarce, the ENIGMA-ADHD Working Group, with a large cross-sectional sample across six decades of the lifespan, is beginning to address this gap.

The ENIGMA-HIV working group: Association of CD4 with subcortical volume in HIV-positive adults


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Introduction:
Human immunodeficiency virus (HIV) enters the brain early in infection, initiating a cascade of inflammatory chemokines and cytokines, which promote neuronal loss (Kaul et al. 2001, Mattson et al. 2005) and subsequent cognitive impairment (Ances et al. 2010). In addition higher viral load and lower CD4 counts have been observed in the striatum and other frontal-subcortical regions (Archibald et al. 2004). As existing data are limited on the profile and consistency of brain changes across cohorts, pooled imaging data may lead to a greater power and ability to understand the biological signature of HIV in the brain. Therefore this working group (http://enigma.ini.usc.edu/ongoing/enigma-HIV-working-group/) has begun to pool imaging data from sites worldwide to investigate associations of subcortical integrity with immunological markers such as CD4.

Methods:
For this study imaging data acquired from adult HIV+ patients scanned at Brown University (N=82) and other sites from the HIV Neuroimaging Consortium (N=182) in the US, as well as patients from the University of Cape Town (N=177) in South Africa were combined to examine associations of CD4 counts with subcortical volume. The protocol for multi-site analysis is further detailed elsewhere (Thompson et al. 2014). In summary, subcortical volumes were parcellated with Freesurfer V5.1 at CHPC, Rosebank, Cape Town. A regression analysis was performed with CD4 counts and subcortical parcellations using the ENIGMA pipeline. After the within-site analysis, an inverse-weighted meta-analysis was performed.

Results:
The multi-site meta-analysis found positive associations of CD4 counts with volumes of the bilateral thalamus ($p = .0008$), right putamen ($p = .001$), bilateral pallidum ($p = .001$), bilateral hippocampus ($p = .03$), bilateral amygdala ($p = .02$), right accumbens ($p = .04$) and total intracranial volume ($p = .002$). For the site analysis, there was a) a significant positive association of CD4 with right amygdala volume ($p = .03$) at Brown University, b) significant associations of CD4 with bilateral thalamus ($p = .02$), right putamen ($p = .01$), bilateral pallidum ($p = .01$), left hippocampus ($p = .008$), and total intracranial volume ($p = .005$) for the other HIVNC sites, and c) positive associations of CD4 and subcortical volume for the bilateral pallidum ($p = .03$) and right accumbens ($p = .02$) at the University of Cape Town.

Conclusions:
This meta-analysis demonstrates the feasibility and utility of pooling data across multiple sites to investigate the relationship between imaging data and immunological indices such as CD4. Neuronal loss in subcortical regions has previously been associated with lower nadir CD4 counts (Thompson et al. 2005) and the current data indicate that this relationship holds even in limbic regions such as the hippocampus and amygdala. Future multi-site studies will study the interaction of HIV clade, other immunological markers and antiretroviral treatment with subcortical and cortical brain measures.

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Subcortical brain volumes across the lifespan based on 10,722 people aged 2 to 92

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Background: Brain structure volumes change throughout life, with different trajectories for different structures. The Lifespan Working group was set up as part of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium (Thompson et al., 2014) to study brain changes over the human lifespan harnessing the power of large-scale multimodal datasets. This initiative aims to overcome limitations of previous research associated with small sample sizes, restricted age ranges within individual samples and wide methodological differences in delineation of brain structures. Here we focused on subcortical areas, vital for cognitive and emotional adaptation to daily life, across the lifespan (Grossberg, 2009). These regions play a role in the development of cognitive and affective dysfunctions (Fredo et al., 2014) and are implicated in numerous psychiatric (Bose et al., 2009) and degenerative brain disorders (Driscoll et al., 2009).

Methods: The ENIGMA Lifespan working group brings together structural MRI brain scans from 35 sites worldwide, from 10 different countries. All images were processed using the automated and validated segmentation package FreeSurfer (Fischl et al., 2002). With validated protocols, we measured the volumes of the following subcortical structures: the thalamus, medial temporal regions (hippocampus, amygdala) and striatum (caudate, putamen, pallidum, nucleus accumbens) in T1-weighted MR images from 10,722 healthy individuals (age range 2-92 years; 90 cohorts). We also measured the volume of the left and right lateral ventricles. We conducted fractional polynomial regression analyses to examine volumetric changes across the lifespan adjusted for intracranial volume and sex. We also examined confounding effects of cohort and scanner field strength.

Results: The volume of all subcortical structures, excluding the ventricles, peaked in the second decade of life and declined thereafter. Striatal structures reached their peak volume first, between the age of 10-14 years; the nucleus accumbens declined nonlinearly with age (Figure 1) while age-related volume reduction was approximately linear and most pronounced for the pallidum (Figure 2A).
The volume of the thalamus (Figure 2B) and medial temporal structures peaked between 15 and 19 years of age; the hippocampal volume changed the least with age, with a prolonged plateau period from the 2nd to the end of the 5th decade (Figure 3A).
The lateral ventricles enlarged with age (Figure 3B). Patterns were similar for men and women. Site and scanner type accounted for less than 3% of the variance.
Conclusions: This is the largest study to date to relate age to subcortical brain volumes across the human lifespan. Our results provide robust information about the volumetric trajectories of subcortical regions and their normal range in healthy individuals and provide a platform to explore biological and environmental factors influencing brain development and aging.

Figure 1. Regression models based on fractional polynomials functions of age on nucleus accumbens volumes for men and females.

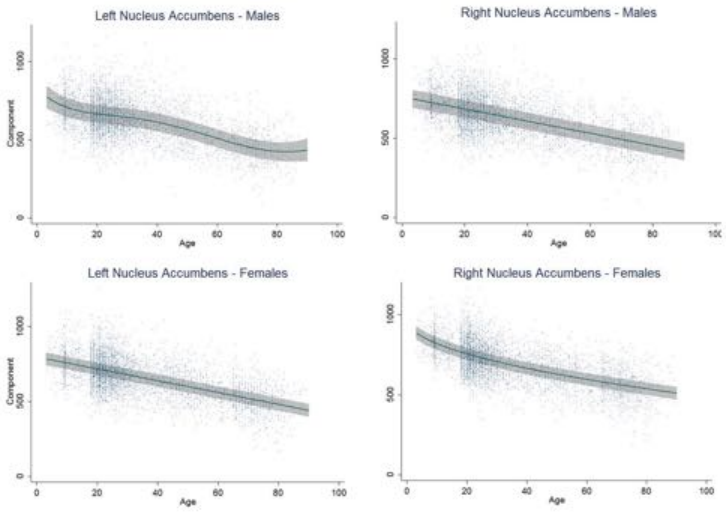


Figure 2. Regression models based on fractional polynomials functions of age on pallidum and thalamus volumes.

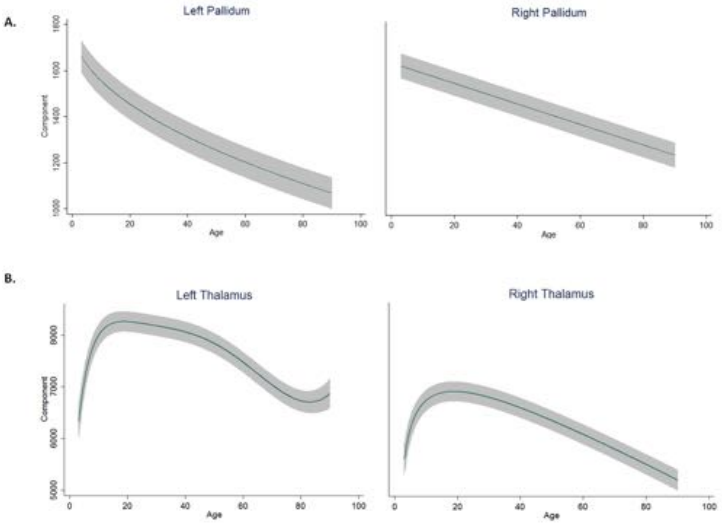
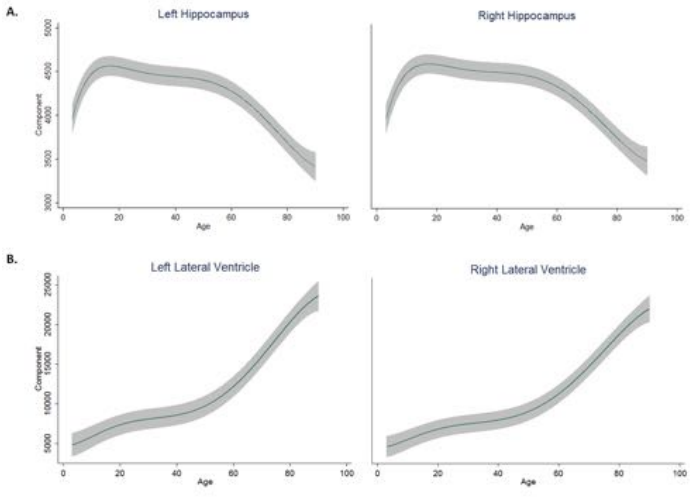


Figure 3. Regression models based on fractional polynomials functions of age on hippocampal and lateral ventricle volumes.



Conclusions: This is the largest study to date to relate age to subcortical brain volumes across the human lifespan. Our results provide robust information about the volumetric trajectories of subcortical regions and their normal range in healthy individuals and provide a platform to explore biological and environmental factors influencing brain development and aging.

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Dr. Tulio Guadalupe

Sex and handedness effects on human subcortical and hippocampal asymmetries meta-analyzed in 5101 individuals aged 14 to 90

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Introduction:

In humans, CNS lateralization is found at the anatomical, cognitive and behavioural levels (Herve et al., 2013). Cognitive functions including language are strongly lateralized in human brains (Mazoyer et al., 2014), while departures from normal patterns of lateralization are often related to psychopathology (Oertel-Knochel et al., 2013).
Although lateralization is important, its developmental and genetic mechanisms are virtually unknown. Structural lateralization of perisylvian regions are visible from the second trimester of gestation (Hill et al., 2010), and the degree of lateralization is related to sex, and steroid hormone biology (Guadalupe et al., 2015). A possible developmental origin of such overt cortical asymmetries may be found in the subcortical structures. Some of these structures show subtle lateralizations which, when altered, have also been related to brain disorders (Csernansky et al., 2004). Subtle subcortical asymmetries may be involved in the early development of lateralized brain networks, as precursors of broader brain asymmetries later on, as in the zebrafish (Concha et al., 2009).
To study subtle, human subcortical asymmetries, and ultimately permit genetic association studies using population variation, large datasets and meta-analyses are required. Here we present the first analysis by the ENIGMA-Lateralization working group, whose goal is collaborative genetic analysis of human brain lateralization. We pooled data on subcortical structures from 6 datasets, to relate their asymmetries to sex and handedness.

Methods:

We analyzed 6 datasets from the ENIGMA consortium (Thompson et al., 2014), the *Brain Imaging Genetics study* (BIG; split by scanner field strength), the *Brain imaging of lateralization study at Groupe d'Imagerie Neurofonctionnelle* (BIL & GIN), the healthy controls from the *Searching for Endophenotypes of Bipolar Disorders Study* (BP), a subset of twin-singletons from *the Queensland Twin Imaging Study* (QTIM), the second follow-up of *the Study of Health in Pomerania* (SHIP-2) and the UK subset of *the Epilepsy Genetics* (EPIGEN) consortium. This resulted in a combined sample of 5101 subjects (Table 1). Handedness status (by self-report) was available for 3 datasets (BIG, BIL & GIN, and SHIP-2).

Table 1: Available sample sizes and corresponding age distributions

	N		Age in years		N-handedness	
	males	females	range	mean	left	right
BIG (1.5T)	733	728	18-80	28.87	67	1205
BIG (3T)	579	729	18-52	23.27	56	1150
BIL & GIN	221	232	18-49	25.90	205	248
BP (controls)	42	45	22-65	42.99	----	----
QTIM	169	423	16-30	22.28	----	----
SHIP-2	538	572	30-90	55.69	57	1053
EPIGEN-UK	35	55	14-64	35.63	----	----

Analyses

Volumes for total brain (TBV) and 7 subcortical structures were estimated by FreeSurfer v5.3, on T1-weighted MRI scans. We calculated an index of volumetric asymmetry (AI: (L-R)/(L+R)) for each structure (see Table 2). We tested whether volumetric asymmetry showed a mean directional bias (Table 2). Covariate effects of age and TBV on the AI's were removed by linear regression before testing for mean differences related to either sex or handedness. Meta-analysis followed the "sample-size" approach as described in (Willer et al., 2010). Prior to meta-analysis, all analyses and test statistics were generated at each participating site following a single analytic pipeline implemented in R.

Results:

Table 2 shows the mean AI's that differed significantly from zero ($p < 0.001$). Table 3 shows the results for the sex differences in AI and meta-analysis, which revealed significant sexual dimorphisms in AI of the thalamus and globus pallidus ($p < 0.001$). The tests for handedness effects on AI did not yield any significant results.

Table 2: Mean volumetric asymmetries (AI) for the seven structures at each site, split by sex. Highlighted in bold are the mean AI's that differed significantly from zero ($p < 0.001$).

Asymmetry Index (L-R)/(L+R)		BIG (1.5T)		BIG (3T)		BIL & GIN		BP (controls)		QTIM		SHIP-2		EPIGEN-UK	
		mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	Mean	sd
Thalamus	**Males**	**0.053**	**0.030**	**0.055**	**0.031**	**-0.01**	**0.023**	**-0.021**	**0.023**	**0.01**	**0.023**	**-0.021**	**0.025**	0.013	0.031
	females	**0.060**	**0.029**	**0.054**	**0.030**	**-0.016**	**0.022**	**-0.013**	**0.025**	**0.013**	**0.022**	**-0.009**	**0.024**	0.01	0.033
Caudate N.	**Males**	**-0.016**	**0.026**	**-0.004**	**0.024**	**-0.041**	**0.025**	**-0.013**	**0.022**	**-0.009**	**0.028**	**-0.008**	**0.022**	0.017	0.046
	females	**-0.007**	**0.024**	0.000	0.022	**-0.043**	**0.022**	-0.008	0.016	**-0.011**	**0.033**	**-0.006**	**0.022**	**0.019**	**0.034**
Putamen	**Males**	**0.016**	**0.033**	**0.022**	**0.029**	**0.035**	**0.02**	**0.019**	**0.023**	**-0.017**	**0.028**	**0.018**	**0.023**	-0.083	0.226
	females	**0.019**	**0.034**	**0.021**	**0.026**	**0.037**	**0.019**	**0.02**	**0.023**	**-0.016**	**0.034**	**0.017**	**0.023**	-0.065	0.244
Pallidum	**Males**	**-0.009**	**0.056**	**-0.018**	**0.065**	**0.012**	**0.033**	**0.049**	**0.043**	**-0.008**	**0.037**	**0.051**	**0.04**	0.038	0.087
	females	**-0.026**	**0.057**	**-0.023**	**0.054**	0.000	0.03	**0.051**	**0.042**	**-0.008**	**0.039**	**0.046**	**0.038**	**0.051**	**0.06**
Hippocampus	**Males**	-0.001	0.030	-0.003	0.027	0.000	0.039	-0.007	0.033	**-0.015**	**0.057**	**-0.014**	**0.027**	0.075	0.166
	females	-0.002	0.025	**-0.005**	**0.026**	-0.001	0.031	-0.012	0.03	**-0.011**	**0.052**	**-0.012**	**0.025**	0.056	0.151
Amygdala	**Males**	**-0.013**	**0.047**	0.000	0.042	**-0.048**	**0.056**	-0.014	0.041	0.017	0.174	**-0.028**	**0.038**	**-0.189**	**0.284**
	females	**-0.012**	**0.044**	0.001	0.046	**-0.041**	**0.057**	-0.013	0.036	0.015	0.187	**-0.024**	**0.036**	**-0.142**	**0.27**
N. accumbens	**Males**	**-0.009**	**0.078**	**-0.067**	**0.071**	**0.044**	**0.075**	0.022	0.072	**0.103**	**0.133**	**0.057**	**0.065**	**-0.081**	**0.164**
	females	**-0.046**	**0.074**	**-0.083**	**0.076**	**0.074**	**0.075**	0.003	0.068	**0.101**	**0.17**	**0.055**	**0.066**	**-0.091**	**0.14**

Conclusions:

Consistent with prior reports, the caudate nucleus showed the most consistency in mean rightward asymmetry across samples and sexes (Figure 1). We also detected for the first time subtle sexual dimorphisms in most subcortical lateralizations, driven primarily by the BIG datasets. Sex effects on subcortical lateralizations were largely independent of overall brain size differences between the sexes. The detection of a biological factor affecting subcortical lateralizations further motivates genetic studies of these lateralizations. The subtlety of these effects underscores the advantages of such meta-analytic collaborations as ENIGMA-Lateralization, to boost statistical power.

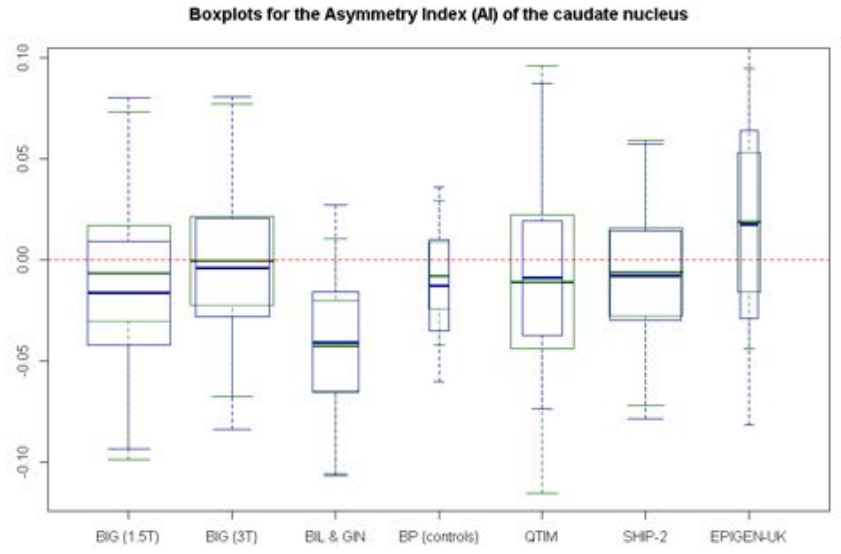

Figure 1: Boxplot of asymmetry indexes for the caudate nucleus at each site, for females (green) and males (blue) separately. Positive values denote a larger left volume compared to the right. The horizontal dotted line represents the point of perfect symmetry. The different widths of the boxes are directly proportional to the square root of their sample sizes

Genetic influences on longitudinal changes in subcortical volumes: Results of the ENIGMA Plasticity working group


Dr. Rachel Brouwer

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Dr. Hilleke Hulshoff Pol

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Background: The brain changes throughout life, from early development to old age. In particular, subcortical volumes follow a nonlinear pattern with age[1-4] and have been shown to be heritable throughout the lifespan[5-6]. However, surprisingly little is known about genetic influences on the changes in subcortical volumes. Establishing heritability of subcortical brain plasticity will be a first step in identifying genetic pathways for brain development and ageing in health and disease. Here, we address the issue of generalizability and robustness of longitudinal heritability across ages.

Methods: We present first findings from four longitudinal twin cohorts (Table 1). In each cohort, changes in subcortical volumes were estimated from longitudinal Magnetic Resonance Imaging data using either the FreeSurfer pipeline or the FSL package. For each subcortical volume, change rates per year were computed. Heritability was estimated using structural equation modeling implemented in the OpenMx package in R for each cohort separately.

Table 1: Demographic characteristics

	Number of subjects with longitudinal data	MZ/DZ pairs	Sex (M/F)	Age at baseline (years)	Scan interval (years)
BrainSCALE	127	25/27	69/58	9.2 (0.1)	2.9 (0.2)
Utwins1	160	36/37	95/55	29.7 (7.8)	5.3 (0.7)
VETSA	331	75/53	331/0	56.3 (2.6)	5.5 (0.5)
OATS	198	58/41	68/130	70.3 (4.6)	2.3 (0.7)

Results: There is a significant heritable component to change in subcortical structures in these four twin cohorts. Individual variation in the change in hippocampus volume showed 28% heritability until age 55, which increased up to 78% in subjects aged over 70. Overall, change rates for subcortical structures showed a pattern of increasing heritability with age (Figure 1).

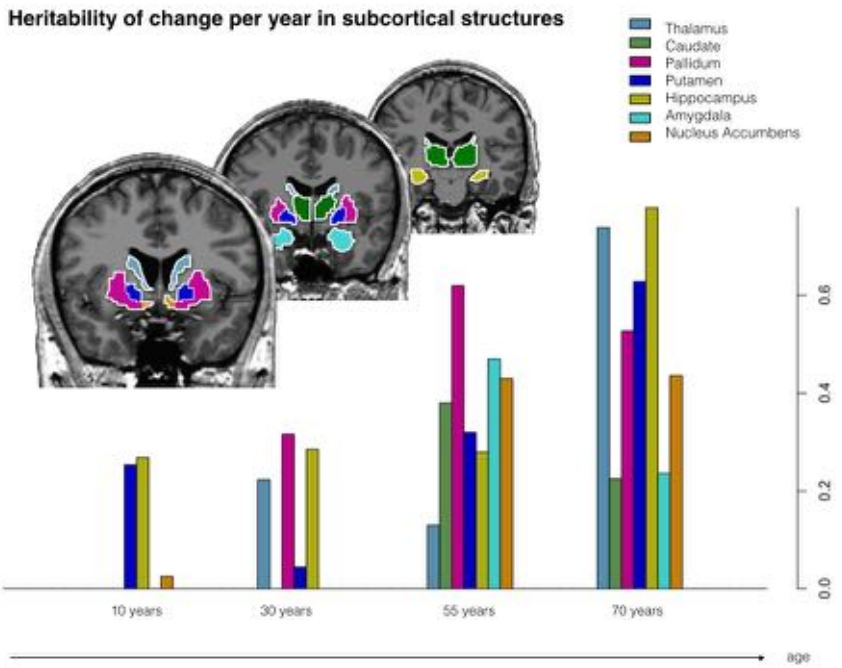

Figure 1: Heritability of change in subcortical structures throughout the lifespan

Conclusion: We find significant heritability for subcortical brain plasticity. Heritability of the change in subcortical volumes seems to increase with age. The volume change of the hippocampus, arguably one of the most plastic brain structures, was heritable throughout the lifespan. It must be noted that at this point we cannot rule out cohort effects (biological and/or protocol related effects). Some of the sources of cohort effects may be modeled using independent estimates of change (e.g. Dima et al., 2015) or ruled out by investigating the genetic and environmental variance components. Recently, genetic variants implicated in subcortical brain volumes have been found through the ENIGMA consortium (Hibar et al., 2015). In the next step, we will search for genes implicated in subcortical brain plasticity.

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Meta-analyzing genome-wide associations with white matter microstructure

Drs. Neda Jahanshad, Peter Kochunov & David Glahn

Jahanshad N, Kochunov P, Armstrong N, Bastin M, Bearden C, Brouwer R, Cannon D, Caseras X, Corvin A, Costa Rica Colombia Bipolar Consortium, Crespo-Facorro B, Deary I, den Braber A, de Zubicaray G, Donohoe G, Fears S, Franke B, Fullerton J, Hariri A, Hashimoto R, Hellard SL, Hibar D, Hulshoff Pol H, Kang S, Kelly S, Knickmeyer R, Knodt A, Lam Zhan Yang S, Lemaitre H, Mandl R, Martin N, McDonald C, McIntosh A, McMahon K, Mitchell P, Nichols T, Nyberg L, Roberts G, Sachdev P, Schumann G, Sprooten E, Stein E, Szeszko P, Tansey K, Tordesillas-Gutierrez D, van Hulzen K, van't Ent D, Wardlaw J,Wen W, Yang Y, Zwiers M, ADNI, Wright M, Håberg AK, Thompson P, Glahn D – the ENIGMA-DTI group.

Introduction:

Diffusion weighted MRI has exponentially expanded our understanding of the brain's structure and organization. Damage or abnormalities in white matter microstructure are found in a variety of neurological, psychiatric, and behavioral disorders suggesting disruptions in brain connectivity may play an active role in disease pathogenesis. Understanding factors that affect the development of brain connections is crucial. Many imaging studies suggest that brain structure is under strong genetic control. Based on recent efforts of the ENIGMA-DTI working group (http://enigma.ini.usc.edu/ongoing/dti-working-group/), the degree of genetic influence over WM microstructure measures obtained is comparable across thousands of subjects and across many cohorts worldwide. This opens the doors to discover specific genetic variants and loci that may shape white matter microstructure as defined through diffusion imaging.

Methods:

As part of the ENIGMA-DTI worldwide consortium effort, standardized diffusion phenotype extraction protocols were developed to ensure reliable extraction of measures across multiple datasets as well as cross population heritability (Jahanshad et al., 2013; Kochunov et al., 2014). In total, 24 reliable bilateral regions of interest (ROIs) were extracted from skeletonized fractional anisotropy (FA) maps as well as an overall measure of average FA. Quality control protocols were developed to visualize single subject images and to check the overall cohort distribution for normality. Standardized genetic imputation was used to map individual genetic files to the 1000 Genomes Project reference data. Genome-wide analysis scripts and protocols were developed and distributed. All protocols may be found online: http://enigma.ini.usc.edu/protocols/dti-protocols/. Briefly, a genome wide association was performed for every region's average FA. Covariates include age, sex, and their linear and nonlinear interactions (with age^2). GWAS analyses were performed using modified versions of on healthy participants only, patients only, and both patients and controls while covarying for disease status. Merlin's fastAssoc was used for twins and family-based studies to account for the reduced degrees of freedom in family studies (Both found here: http://www.sph.umich.edu/csg/abecasis/).

A preliminary fixed-effects inverse-variance weighted GWAS meta-analysis of the overall average FA in 1604 healthy individuals from three cohorts is presented here.

Results:
To date, 35 cohorts from North and South America, Europe, Asia and Australia have joined the effort, with the goal of contributing over 13,500 diffusion weighted scans from individuals aged 2-98.

Approximately 1/3 of the sample includes psychiatric patients diagnosed with schizophrenia, bipolar disorder, depression, Alzheimer's disease, Parkinson's disease, and other disorders. Sites were able to reliable extract phenotypic measures and identify poor quality scans or outliers, if any, through rigorous quality control. Three sites with completed phenotyping and genotyping uploaded summary measures of the GWAS results, without sharing any individual metrics. In a preliminary meta-analysis of healthy individuals from three sites (N=1604 from Europe, North America, and Australia), no genome-wide significant findings ($p < 5x10^{-8}$) were detected so far for Average FA.

Conclusions:
While our preliminary analysis showed no genome-wide significant findings, as expected in a cohort of this size, some loci were suggestively significant ($p < 5x10^{-6}$). However, the sample size is expected to increase ten-fold, and the potential for ENIGMA-DTI and meta-analysis of white matter imaging traits to discover specific genetic modulators of brain integrity and connectivity remains extremely promising.

ENIGMA Voxelwise Meta Analysis for Multi-Site Brain Mapping

Jahanshad N, Hibar DP, Faskowitz J, Medland SE, McMahon KL, de Zubicaray GL, Martin NG, Wright MG, Thompson PM

Introduction:

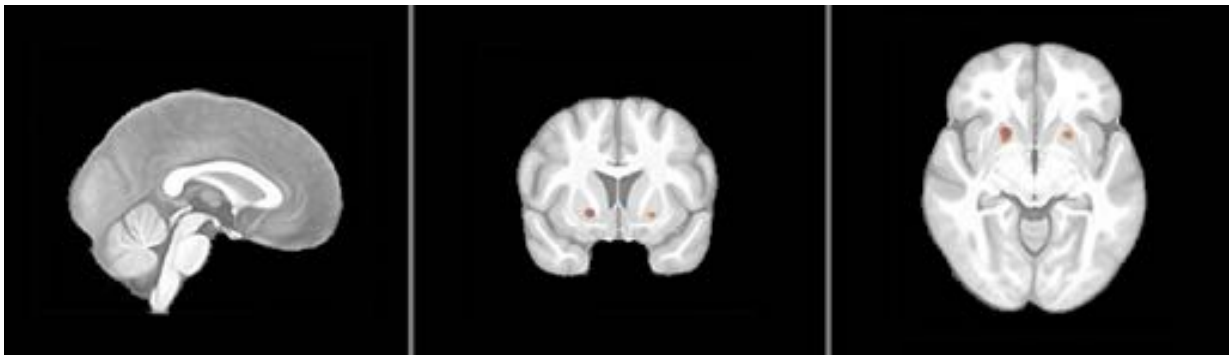
The quest to identify factors that affect the human brain has been accelerated by global alliances such as the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium (http://enigma.ini.usc.edu). ENIGMA has shown that segmentation of brain MRI is reliable enough to detect consistent effects on intracranial and subcortical volumes of single-nucleotide changes in the genome across more than 30,000 individuals in about 50 cohorts worldwide. ENIGMA has pooled brain MRI data from over 30,000 subjects, but has focused so far on simple regional measures of brain volume and fiber integrity, in a vast distributed computation. The power of such studies is unprecedented in brain imaging - discovering variants in the human genome that explain as little as 0.5-1% of the variance in brain measures (Hibar et al., Nature, 2015). Even so, this global effort could be extended to statistical brain maps that detect subtle effects throughout the brain. Regional volumetric measures offer only a limited view of the information available in MRI; voxel-based analyses, which include voxel-based or tensor-based morphometry (VBM and TBM) can yield statistical parametric maps of effects on the brain without the need for prior hypotheses or segmentation of brain regions. If we could show how to detect the volumetric findings of ENIGMA by using voxel-based mapping, subtle effects on many other brain mapping signals could be identified in samples beyond those imaginable today.

Methods:

Two very different cohorts were used in this study. We analyzed structural brain MRI data from the Queensland Twin Imaging Study (QTIM; N=870; mean age 23.1 +/- 2.9 yrs; 534 women; 501 families) and the Alzheimer's Disease NeuroImaging Initiative (ADNI2; N=597; mean age 73.0 +/- 7.2 years; 270 women). A minimal deformation template was created from 32 healthy individuals of each cohort. A multi-channel approach was used to create the template, with 3 fidelity terms driving the alignment: 1 channel being the cortical ribbon, a second being the segmented subcortical structures, and a 3rd being the full skull-stripped T1-weighted brain image intensity. The recent publication from the ENIGMA Consortium performed meta-analysis of genome-wide association scans of the volumes of 7 subcortical structures (Hibar 2015), using the power of around 30,000 individuals from over 50 sites. The most significant association was found to be a SNP associated with the volume of the putamen (rs945270-C/G; $p=1.08x10^{-33}$; N=28,275). In both QTIM and ADNI2 datasets, the number of minor alleles carried at that SNP was regressed against tensor-based morphometry data (Jacobian determinants) on a voxelwise level. Age and sex (and their linear and nonlinear combinations) were used as covariates. In ADNI2, we also covaried for Alzheimer's diagnosis and cognitive impairment (for those with AD or MCI). Kinship was included in the statistical model for QTIM. The Beta and Standard error maps of the regressions were then warped to a common template space. An inverse variance-weighted meta-analysis was then performed at each voxel, to meta-analyze the aggregate effect size for the association of the genetic variant on regional brain volumes. The false discovery rate method was used to account for the multiple comparisons, across the entire image.

Results:

Neither ADNI2 nor QTIM on its own showed voxelwise associations with the ENIGMA-2 top hit. However, after mapping the results to the same space, a meta-analysis of the two cohorts showed remarkable significance -- specifically localized to the putamen only. The lowest *p*-value obtained across the full map was 4.9 x 10^-8 and the FDR-corrected threshold was p=1.3x10^-5.



Conclusions:

Unbiased brain mapping approaches such as voxelwise tensor-based morphometry (TBM) can assess local volumetric differences in large cohorts; when pooling data across templates and sites, these methods can be extremely powerful for finding genome-wide significant genetic variants that affect the brain.

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Towards an ENIGMA connectome atlas: comparing connection prevalence across sites

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Introduction

Brain function depends on efficient information processing in a complex network of anatomically segregated brain regions and their interconnecting white matter pathways, known as the macroscale human connectome [1]. Studies of the connectome have increased rapidly in number in recent years, providing new insights on topics such as healthy brain development and ageing, and brain alterations in neurological and psychiatric disorders. An important step to further expand these insights lies in integration of information from the connectome and its etymological ancestor: the genome [2]. Worldwide collaborative efforts, such as ENIGMA [3], promote this integration through large-scale analyses of neuroimaging and genetic data across different institutes, posing questions about the inter-site consistency of connectome data. Here, we address this topic by examining the prevalence of reconstructed anatomical connections across subjects and sites, paving the way for the formation of a 'connectome atlas'.

Methods

Analyses were performed on reconstructed anatomical brain networks from healthy adults, acquired by three different sites participating in the ENIGMA consortium: the University of Southern California (USC; 39 subjects from ADNI-2 [4]), the Technical University Munich (TUM; 42 subjects) and the University Medical Center Utrecht (UMCU; 46 subjects). Brain networks were reconstructed based on T1- and diffusion-weighted magnetic resonance images using FreeSurfer and custom developed connectome reconstruction software, charting the presence and absence of connections between 82 cortical and subcortical brain regions [5,6].

For each site independently, connectivity information from individual subjects was combined into a single 'prevalence' matrix, listing for every pair of brain regions the fraction of subjects in which those brain regions were found to be connected [7,8]. Based on these prevalence matrices, three different aspects of connectome variability were investigated. First, variation in presence and absence of connections between subjects from the same site was examined by plotting the frequency distribution of all prevalence values in the site's matrix. Second, between-site overlap of group-level connectivity – obtained by thresholding the prevalence matrices [8] – was tested. And third, within-site variability patterns were compared by correlating the prevalence matrices.

Results

In line with prior reports [8], the prevalence distribution of each of the sites was approximately 'U-shaped', with most possible connections (on average 65%) being either consistently absent (prevalence < 0.1, 53%) or consistently present (prevalence > 0.9, 12%) across subjects (**Figure 1**). This relatively high inter-subject consistency was also expressed between sites, as evidenced by a strong overlap *O* between the group-averaged connectivity matrices (mean $O = 90\%$, **Figure 2**). Statistical assessment using matrix randomization showed that the observed overlap scores were highly significant (all satisfying $p < 0.001$). Correlation analysis of the prevalence matrices revealed strong and significant correlations between the variability patterns observed at each site (mean $r = 0.90$, all $p < 10^{-6}$, **Figure 3**).

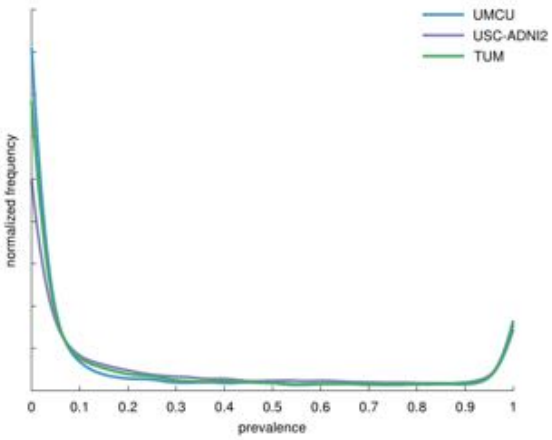

Figure 1. Distributions of genomic prevalence

Figure 2. Group averaged connectivity matrices.

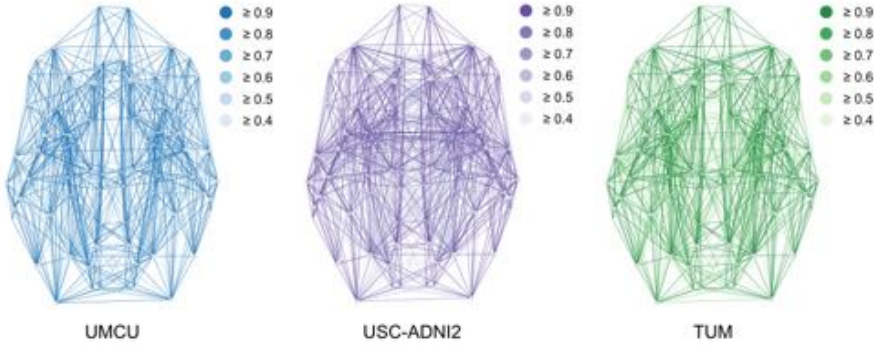

Figure 3. Prevalence of individual white matter connections

Conclusions

Despite numerous sources of variation (e.g., scanner vendor, acquisition protocol, country of residence), the presence or absence of connections in reconstructed macroscale connectomes was highly consistent between sites. It should therefore be feasible to perform large-scale collaborative analyses to integrate connectomics and genomics. The observed overlap in connection prevalence may in particular allow the formation of a worldwide 'connectome atlas', documenting how frequently each connection occurs in diffusion tractography-based connectome reconstructions.

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Meta-Analysis of Subcortical Shape Reveals Differences Between Schizophrenia Patients and Controls.

Dr. Boris Gutman

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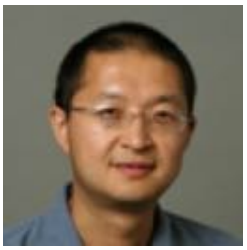

Dr. Lei Wang

Introduction:

The ENIGMA working group on Schizophrenia (SZ) combines efforts and MR datasets to discover subtle disease effects in the brain. Among several analyses, subcortical shape is a promising approach. Importantly, total brain volume alone may not be affected by SZ, but changes in sub-nuclei of the deep subcortical structures may differ before or after psychosis onset. In this situation, a fine-grained shape analysis is more likely to detect disease-related effects than volumetric measurements. Several smaller studies show SZ-related shape differences in specific subcortical structures, particularly the thalamus, caudate and hippocampus [1, 2]. On the other hand, gross volumetric differences have been confirmed in larger studies [3, 4]. Here we apply the recently developed Medial Demons toolkit to analyze shapes of subcortical region boundaries in two schizophrenia datasets.

Methods:

The Medial Demons algorithm parametrically registers surface models of subcortical boundaries. The approach minimizes the mismatch between curvatures and features generated by the medial models of the shape [5] and a pre-computed atlas in the fast spherical demons framework [6]. Surface meshes are mapped to a sphere, minimizing metric distortion [7]. The Demons algorithm then non-linearly warps the spherical parameterization over the atlas to match curvatures. As the demons regularization minimizes metric distortion, the entire pipeline is nearly metric preserving. The final one-to-one mapping between shapes of different subjects preserves curvature and metric properties (Fig. 1).

We applied the Medial Demons algorithm to datasets of people with SZ and controls from two ENIGMA-participating sites: TCD Dublin: 223 Controls, 57 SZ; and NUIG Galway: 80 Controls, 102 SZ, for a subject total of N = 462. Seven subcortical structures were extracted with FreeSurfer 5.1, and meshed following [8]: Thalamus, Caudate, Putamen, Pallidum, Hippocampus, Amygdala, and Nucleus Accumbens. Radial Distance (RD) and Log of Surface Jacobian Determinant (JD) [9] were used as point-wise features. Thus, each subject was represented by two sets of features at roughly 55,000 points representing the entire subcortical boundary set. Standard statistics were computed testing the difference of means at each point for each feature, controlling for age, sex and age*sex. This resulted in two sets of p-values each point for each dataset. Meta-analysis of the two datasets was performed following [10], using the sample size strategy for estimating the overall p-value at each surface point.

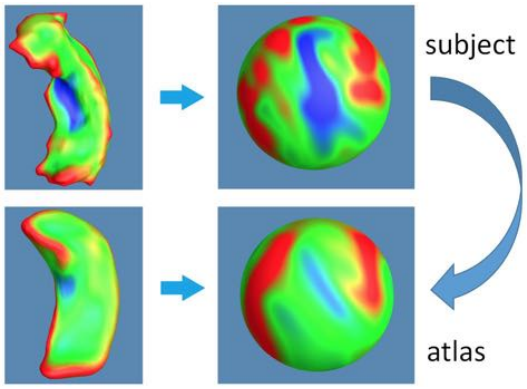

Figure 1. Medial Demons Mapping

Results:

Significant differences between controls and SZ subjects were found in the thalamus, caudate, hippocampus, and the left accumbens. In each case, the direction of the effect indicated reduced sub-regional volume in the SZ cohorts. In the hippocampus, the region of significance (Fig. 2) was largely confined to the posterior section of CA-1. Only JD passed False Discovery Rate (FDR) connection at p = 0.05 in the left accumbens and only the RD feature was significant in the left caudate. The other ROI's either passed FDR for both the Jacobian and RD, or showed no effect using either feature. Critical q's for thresholding the significance maps were as follows (Fig. 3), for JD: Right Hippo q = 0.019, Left Hippo q = 0.017, R Thalamus Q = 0.030, L Thalamus q = 0.036, L Accumbens q = 0.0459, R Caudate q = 0.0038. For RD: R Hippo q = 0.00053, L Hippo q = 0.0037, R Thalamus q = 0.012, L Thalamus q = 0.016, R Caudate q = 0.0061, L Caudate q = 0.004. Treated as a whole, the combined Jacobian and RD over the entire subcortical complex passed FDR at q = 0.0068.

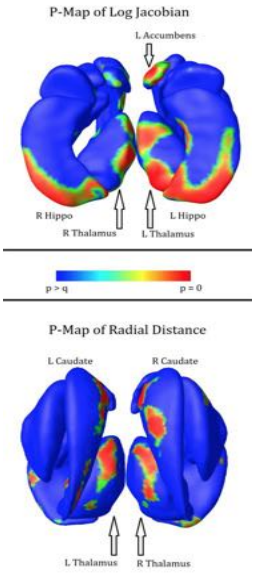

Figure 2. P-maps corresponding to meta-analysis of shape

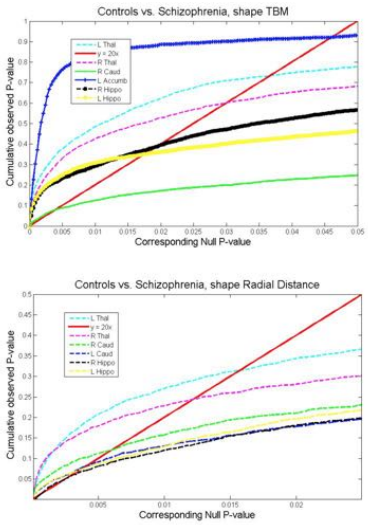

Figure 3. False Discovery Correction

Conclusions

We have presented a meta-analysis of subcortical shape using two complementary shape features. Our meta-analysis shows promise, revealing subtle differences even in a modestly sized sample. In the future, we will combine additional datasets in a more powerful meta-analysis of subcortical shape in schizophrenia.

Evaluating overlap between genetic influences on schizophrenia risk and subcortical brain volumes

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Dr. Jason Stein
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Background:
Many psychiatric disorders are heritable, but their phenotypic heterogeneity and genetic complexity have made it hard to identify specific genetic factors associated with disease risk until recently. The difficulty in identifying genetic risk factors for neuropsychiatric diseases has prompted alternative and complementary approaches for gene discovery. The intermediate phenotype approach posits that genetic search may be higher powered when using more tractable, simpler, and informative phenotypes that have similar genetic architecture to the disease itself. Intermediate phenotypes must satisfy two basic criteria: (1) genetic correlation with disease: the same genetic risk factors that create disease-related changes in the intermediate phenotype also create risk for developing the disease of interest, and (2) higher effect size than disease: the genetic risk factors must have a stronger effect on the intermediate phenotype than on the disease itself. Brain structure traits have been particularly appealing in this framework. Here, we use multiple methods to evaluate the extent of overlap between genetic variations associated with differences in subcortical brain structure volumes (amygdala, caudate nucleus, hippocampus, nucleus accumbens, pallidum, putamen, thalamus) and intracranial volume from the Enhancing NeuroImaging Genetics through Meta-analysis (ENIGMA; discovery sample: 13,171 subjects) with those associated with risk for schizophrenia from the Psychiatric Genomics Consortium (PGC; 36,989 cases and 113,075 controls).

Methods:
Genome-wide association study summary statistics were analyzed from the ENIGMA2 consortium [2], where 7 subcortical phenotypes and intracranial volume were studied. Genome-wide disease association study summary statistics were also analyzed from the Schizophrenia Working Group of the Psychiatric Genomics Consortium [5]. Overlapping samples were excluded from the analysis. Global genetic overlap between brain structures and schizophrenia was evaluated via a two-sided rank-rank hypergeometric overlap test [4] when using 172,652 independent SNPs ($r2 > 0.25$ in 1000 Genomes EUR; MAF > 0.01). Specific genetic variants influencing both risk for differences in brain structure and schizophrenia were evaluated with a conjunction test [3] to assess the effect of each SNP on both difference in brain structure and risk for schizophrenia. Conjunction results were corrected for a downward bias in significance using the relaxed intersection union test [1].

Results:

To evaluate global similarity, we quantified overlap between two SNP association lists ranked by their association statistics. As shown in Figure 1, overlap in the rank-ordered lists between genetic variants influencing any of the eight brain phenotypes and those creating risk for schizophrenia was not statistically significant. In addition, the overlap between genetics of hippocampal volume and thumb whorl structure was used as a negative control and showed similar levels of overlap to brain structure and schizophrenia.

We then used a conjunction test to identify specific genetic variants influencing both changes in brain structure and risk for schizophrenia genome-wide. No SNP demonstrated genome-wide significant association to both schizophrenia and brain structure. Several sub-threshold loci did arise from this analysis including those near *FOXO3*, *DLG2*, and *DCC* genes (Figure 2).

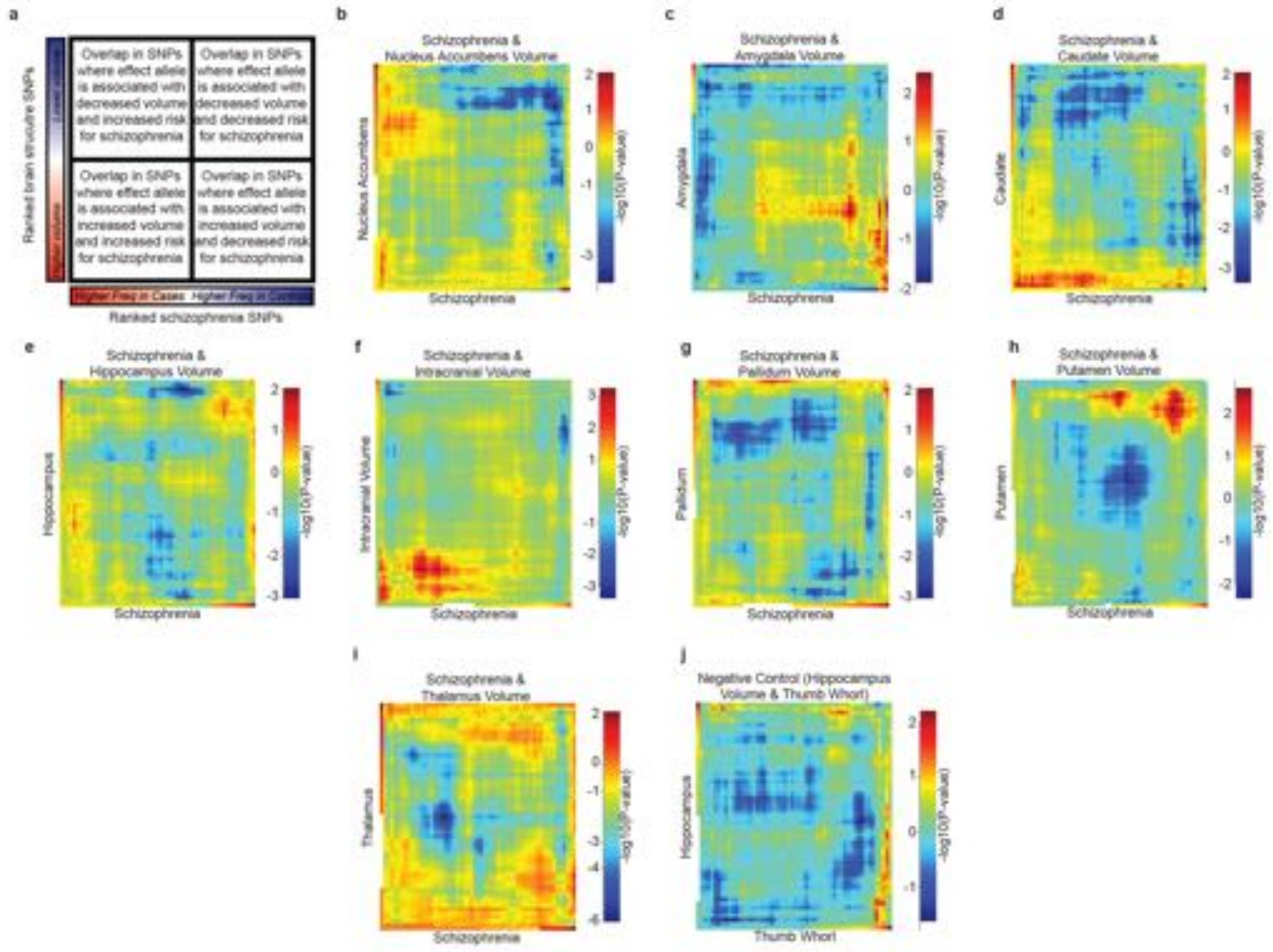

Figure 1: Evaluating the genome-wide overlap between genetic influences on schizophrenia and subcortical volumes. (a) A cartoon describing the output map is shown. (b-i) 172,652 independent SNPs (r2 > 0.25 in 1000 Genomes EUR sample; MAF ≥ 0.01 in both ENIGMA2 and PGC2) present in both the PGC2 and ENIGMA2 studies were selected independent of association to any phenotype. Association results were then ordered based on the significance of their association to the phenotype (–log10(P-value) multiplied by the sign of the effect) and statistical significance was evaluated using the Rank Rank Hypergeometric Overlap test (step-size: 3000 SNPs). (j) The same test for overlap was conducted with a finger whorl phenotype expected to have no overlap with brain structure genetics. Overlap in the rank-ordered lists between genetic variants influencing any of the eight brain phenotypes and those creating risk for schizophrenia was not statistically significant. In addition, the overlap between genetics of hippocampal volume and thumb whorl structure was used as a negative control and showed similar levels of overlap to brain structure and schizophrenia.

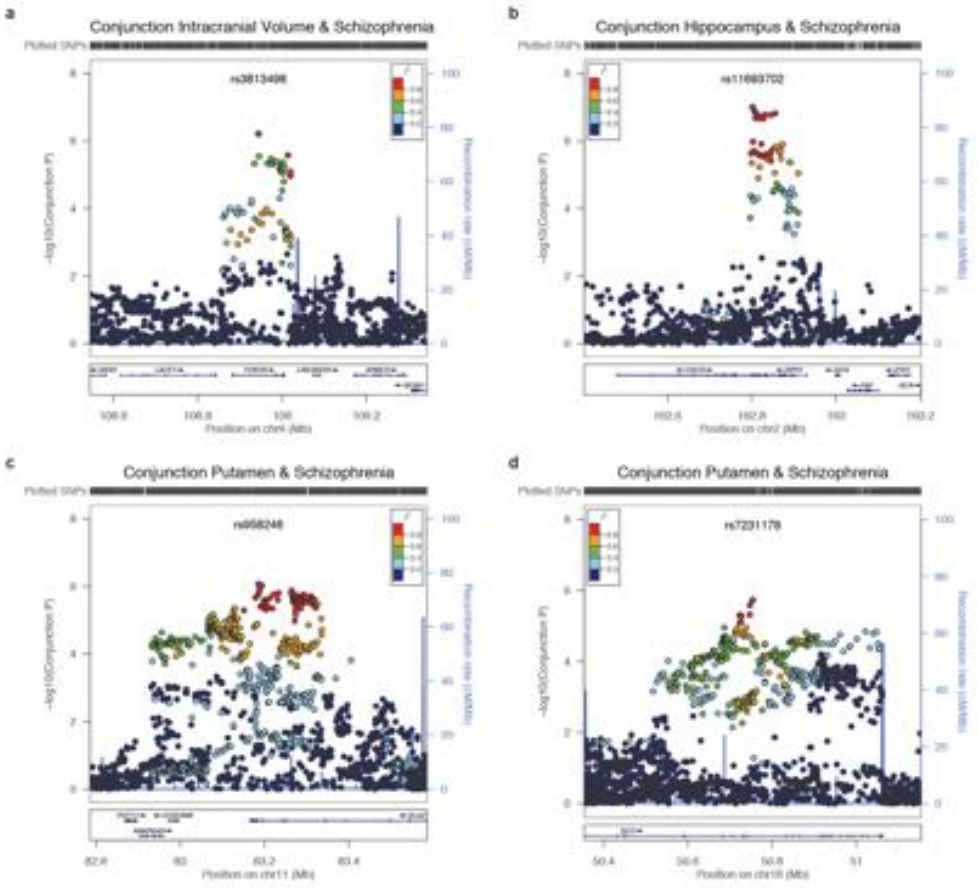

Figure 2: Identifying specific genetic loci which influence both risk for schizophrenia and brain structure. We used a conjunction test to identify specific genetic variants influencing both risk for schizophrenia and changes in brain structure genome-wide. The conjunction test was run genome-wide using 7,510,842 SNPs found in both the ENIGMA2 and PGC2 studies with MAF ≥ 0.01. Conjunction results are then corrected for a downward bias in significance using the relaxed intersection union test. No SNP demonstrated genome-wide significant association to both schizophrenia and brain structure. Several sub-threshold loci did arise from this analysis that bear comment given the possibility that stronger significance may be achieved in future studies. (a) First, the conjunction between intracranial volume and schizophrenia was associated with a locus on chromosome 6 marked by rs381349 where the T allele increases ICV and decreases schizophrenia risk, in the expected direction for a schizophrenia risk factor. This locus is found intronic in the FOXO3 gene known to be involved in neural stem cell proliferation and renewal. (b) Second, the conjunction between hippocampal volume and schizophrenia was associated with a previously mentioned locus on chromosome 2 marked by rs11693702, although in the opposite direction expected for a schizophrenia risk factor (A allele increases schizophrenia risk and increases hippocampal volume). (c,d) Finally, the conjunction between putamen volume and schizophrenia was associated with two interesting loci in the expected direction for schizophrenia risk factors marked by rs958246 (chromosome 11; A allele is associated with increased schizophrenia risk and increased putamen volume) and rs7231178 (chromosome 18; A allele is associated with increased schizophrenia risk and increased putamen volume). These SNPs are found in intronic regions of the DLG2 gene, which encodes a key component of the post-synaptic density, and the DCC gene, a netrin receptor involved in axon guidance.

Conclusions:

Using the largest available samples for an analysis of the potential overlap between genetics of subcortical volume and schizophrenia, we do not find strong evidence for overlap. Beyond major disease risk haplotypes, imaging and psychiatric disease traits still require sample sizes of more than 10,000 patients to identify genome-wide significant common variants. We concede that power to detect overlap is still limited with current samples; other brain traits or analyses may empower discovery of variants affecting both traits.

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Genetic pleiotropy between subcortical brain volumes and multiple sclerosis risk variants: A preliminary analysis.

Rinker D[1], Hibar D[1], Jahanshad N[1], The International Multiple Sclerosis Genetics Consortium (IMSGC)[2], The ENIGMA2 Consortium[3], Beecham A[2], Oksenberg J[4], McCauley J[2], Thompson P[1]

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University of Southern California

Introduction:

Multiple common genetic variants are thought to play a role in the pathogenesis of multiple sclerosis (MS), but the overall architecture of genetic risk is not yet determined. Recent genome wide association studies (GWAS) have implicated a number of risk variants across the genome -- including many outside the traditionally implicated MHC and HLA regions. There is also increasing evidence that pleiotropy - defined as a gene variant that affects two or more different traits - exists between common MS risk variants and those associated with risk for other disorders.

Here we used recently developed methods to test for pleiotropy between results of a recently published MS GWAS follow-up (IMSGC, 2013), (n=14,498 MS cases and 24,091 controls), and a recent MRI study which conducted 8 separate GWAS of subcortical volumes (accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, and intracranial volume; n=13,171)(Hibar, 2015). The MS sample comes from a custom ImmunoChip genotyping array that provided the most comprehensive list of MS loci to date. Our goal was to identify and test whether genetic variants associated with variations in brain structure are also associated with risk for developing MS. In doing this, we can identify brain regions that might serve as useful biomarkers of genetic risk for MS and also discover novel risk variants for the disease.

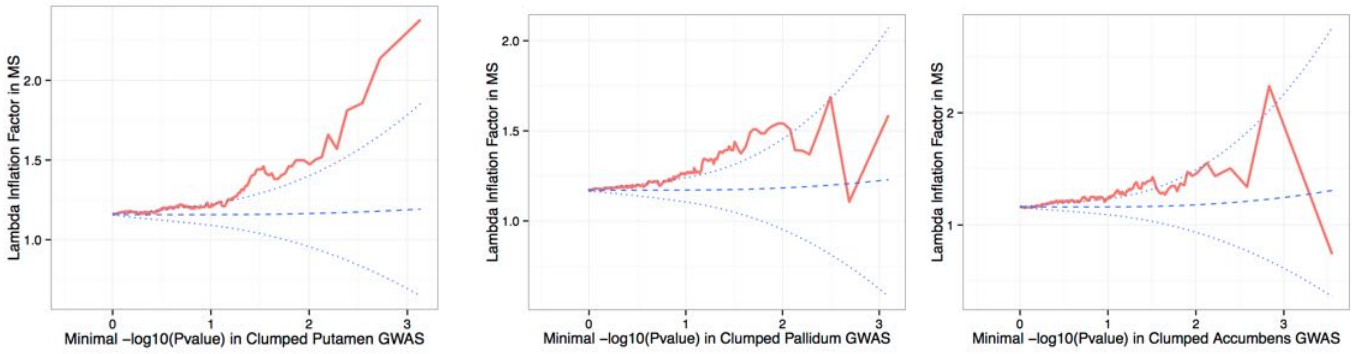
Methods:

Summary statistics from the MS GWAS follow-up were combined with data from a recent GWAS of subcortical volume by the ENIGMA Consortium. In total, 107632 SNPs overlapped between the MS GWAS and ENIGMA studies of subcortical brain volumes. To obtain a set of independent SNPs representing each LD block across the genome, we ran LD clumping in PLINK with the following parameters (--clump --clump-kb 500 --clump-p1 1 --clump-p2 1 -- clump-r2 0.2). After clumping there were 24271independent, overlapping SNPs which we carried forward for analysis. We used Continuous Inflation Analysis (CIA) to examine the statistical overlap between the two datasets. CIA is a threshold-free method to assess global evidence of enrichment between any two pairs of traits. Inflation statistics were calculated using a permutation-based approach and significance was

determined using a FDR threshold of q < 0.05. As a follow up analysis, for any of the structures that we found evidence of significant overlap with MS, we performed pleiotropy-informed conditional FDR whereby we incorporate the results from the GWAS of brain structure as a Bayesian prior to boost power to detect novel MS risk variants. Variants were considered significant if they passed an FDR threshold of q < 0.05.

Results:

Using CIA we found significant evidence of overlap between variants in MS risk genes and the volume of the putamen, pallidum and accumbens (Figures 1, 2, 3, respectively). In follow up analyses of the putamen, pallidum, and accumbens we used pleiotropy-informed conditional FDR and identified 35 novel variants that may be associated with MS risk. Each of these loci are putative novel variants that were previously undetected in the MS GWAS. Among the novel variants we found one exonic snp and a number those discovered have possible links to B-lymphocyte function. Several other variants associated with leukemia and rheumatoid arthritis were found to be pleiotropic with MS.

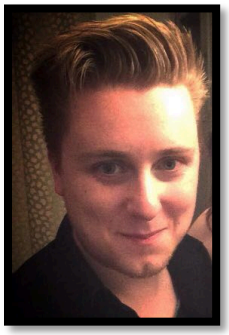


Continuous inflation analysis (CIA) plot of MS enrichment conditioned on brain volume GWAS. Points outside of the 5th and 95th percentile (blue dotted lines) are significantly enriched.

Conclusions:

Our results may indicate overlap between MS-associated genes and those that are associated with regional volumes in several subcortical brain regions. These findings corroborate previous literature that suggests genetic overlap between some disease variants and those associated with differences in brain structure. They also highlight the feasibility of CIA to increase power to detect novel associations when performing genetic enrichment studies. Novel risk variants identified in this study may lead to future hypotheses regarding the complex pathophysiology of MS.

Polygenic contributions of ENIGMA2 hippocampal SNPs in 8,835 epilepsy patients and 29,037 controls.



Dr. Christopher D. Whelan

Whelan CD[1,13], Speed D[2], deKovel C[3], Bradfield J[4], Hongsheng G[5], Leu C[2], ILAE Consortium on Complex Epilepsies[6], Hibar D[1], Stein J[7], Johnson M[8], Sisodiya S[2], Goldstein D[9], Delanty N[10], Medland S[11], Franke B[12], Thompson PM[1], Cavalleri GL[13]

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Dr. Gianpiero L. Cavalleri

Introduction:

Hippocampal sclerosis (HS) is a common feature of focal epilepsy, present in 50-75% of all surgical resections in the disorder. However, the underlying cause of HS is debated. Animal models and post-mortem cell counts suggest that HS can result from recurrent epileptogenesis, but some MRI investigations point to a familial component to HS and concomitant neuronal loss within hippocampal regions. Recently, the second major phase of the Enhancing Neuro Imaging Genetics through Meta-Analysis project (ENIGMA2) identified genome-wide significant signals correlating with hippocampal volume, in a study of 29,037 individuals (Hibar et al., 2015). Preliminary investigations in our laboratory have illustrated isolated patterns of statistical correlation between ENIGMA2 single nucleotide polymorphisms (SNPs) and SNPs from the International League Against Epilepsy's (ILAE) meta-genome-wide analysis of the genetic determinants of complex epilepsies (ILAE, 2014; see Fig. 1). Accordingly, the present study tested the hypothesis that variants predisposing *en masse* to differences in hippocampal volume may, in turn, contribute towards epilepsy predisposition.

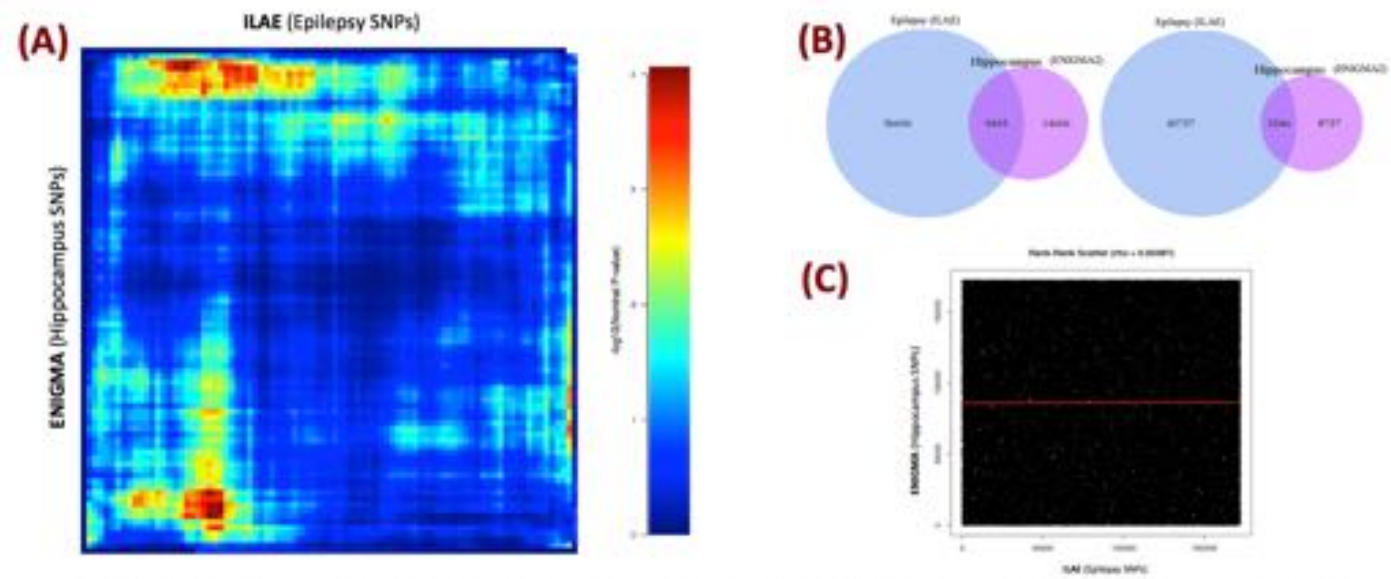


FIGURE 1: (A): A rank-rank hypergeometric overlap (RHHO) heat map depicting an enriched overlap region (red/yellow) between SNPs of medium-to-high signal strength (bottom left) in the ILAE (epilepsy) results and SNPs of high signal strength in the ENIGMA2 (hippocampus) results. **(B)**: Venn Diagram illustrating partial-to-moderate overlap between under-enriched SNPs (i.e. SNPs that correlated significantly less than expected by chance) on the left and partial-to-moderate overlap between over-enriched SNPs (i.e. SNPs that correlated significantly greater than expected by chance) on the right between ILAE and ENIGMA. **(C)**: Rank-rank scatter plot indicating an even spread of overlap between strongly and weakly associated SNPs in ILAE and ENIGMA-hippocampus (no particular clustering pattern can be observed along the diagonal).

Methods:

Three overlapping sets of genetic variants were extracted from our discovery sample (the ENIGMA2 summary statistics) and segregated based on their nominal statistical significance thresholds (p_T): (i) $p_T < 0.01$, (ii) $p_T < 0.05$ and (iii) $p_T < 0.1$. These SNP sets, weighted for local linkage disequilibrium and effect size, were used to generate quantitative risk scores for all patients and healthy controls in our target sample (the ILAE Consortium on Complex Epilepsies). Using a basic logistic regression in R, all risk scores were related to disease state across nine major epilepsy centres, collectively comprising: (i) a phenotypically mixed sample of epilepsy patients (n=8,835), (ii) three epilepsy 'subtypes', including genetic generalized epilepsies (n=2,620), (iii) non-lesional focal epilepsies (n=2,275) and focal epilepsies with HS (n=625) and (iii) an independent sample of healthy controls (n=26,163). Log odds ratios and standard errors from each site were meta-analyzed using the *metafor* R package.

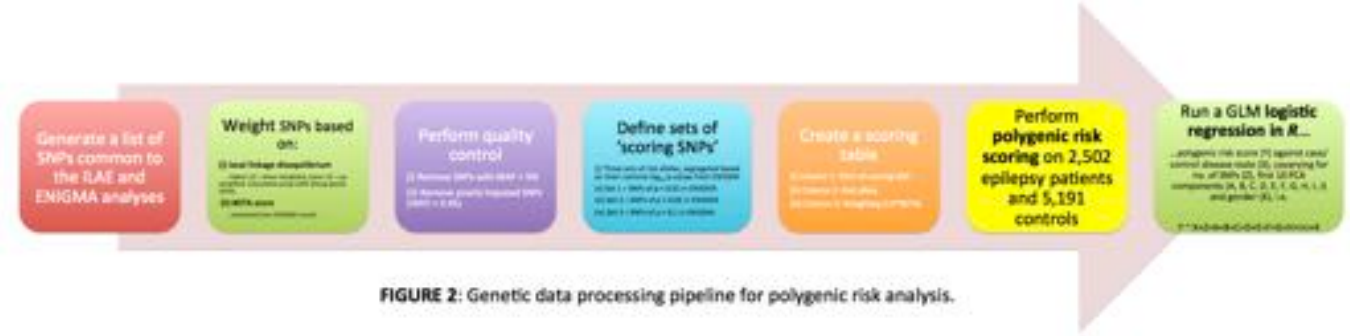


FIGURE 2: Genetic data processing pipeline for polygenic risk analysis.

Results:

We found no significant association between disease state and risk score for (i) the phenotypically-mixed epilepsy sample, (ii) the genetic generalized epilepsy sample or (ii) the non-lesional focal epilepsy sample (p>0.05). A trend towards significance was observed for focal epilepsy patients with evidence of HS on routine MRI examination; however, this smaller group (N=625) may have been under-powered to detect any moderate polygenic effect (p=0.08). Observed polygenic risk scores explained up to 1% of total variance in disease state in our risk model.

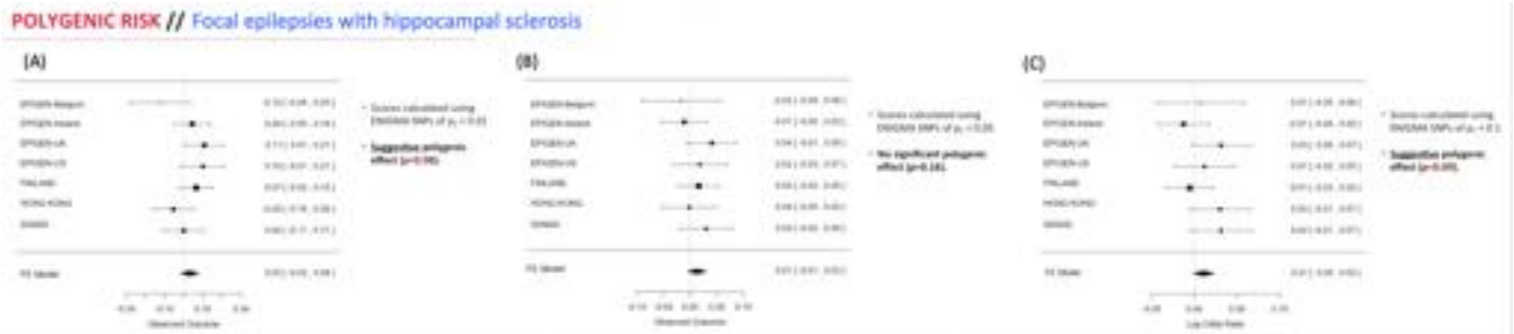


FIGURE 3: Fixed-effect meta-analysis of polygenic risk scores from seven major epilepsy centres (EPIGEN-Belgium, EPIGEN-Ireland, EPIGEN-UK, EPIGEN-US, Finland, Hong Kong and SANAD) on focal epilepsy patients exhibiting mesial temporal sclerosis on routine MRI examination. No significant polygenic effect was observed, although a trend towards significance was observed for scores calculated using ENIGMA2 SNPs of (A) pT<0.01 and (C) pT<0.1.

Conclusions:

Being genetically predisposed to having a smaller hippocampal volume may not be a risk factor for epilepsy; rather, observed HS may be a consequence of recurrent seizure activity in focal forms of the disorder. Further analyses in a larger sample of focal epilepsy patients with confirmed HS are currently ongoing to confirm or reject this position.

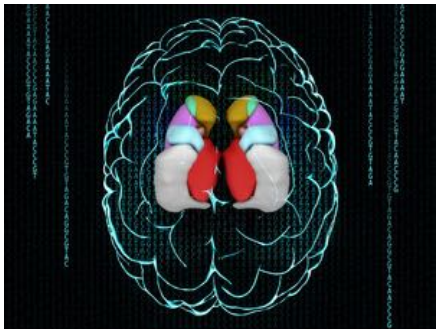
Recent Press on ENIGMA:

Science Magazine

Eight genes that make us brainiacs

ELIZABETH PENNISI / SCIENCE MAGAZINE

The size of key brain structures (colors) are influenced by different genes.



In the animal kingdom, humans are known for our big brains. But not all brains are created equal, and now we have new clues as to why that is. Researchers have uncovered eight genetic variations that help determine the size of key brain regions. These variants may represent "the genetic essence of humanity," says Stephan Sanders, a geneticist and pediatrician at the University of California, San Francisco, who was not involved in the study.

These results are among the first to come out of the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) collaboration, involving some 300 scientists from 33 countries. They contributed MRI scans of more than 30,000 people, along with genetic and other information, most of which had been collected for other reasons. "This paper represents a herculean effort," Sanders says.

Only by pooling their efforts could the researchers track down subtle genetic influences on brain size that would have eluded discovery in smaller studies. "We were surprised we found anything at all," says Paul Thompson, a neuroscientist at the University of Southern California in Los Angeles. But in the end, "we were able to identify hot points in the genome that help build the brain."

For the analyses, Thompson and his colleagues looked for single-letter (nucleotide base) changes in DNA that correspond to the sizes of key brain regions. One region, the hippocampus, stores memories and helps one learn. Another, called the caudate nucleus, makes it possible to ride a bike, play an instrument, or drive a car without really thinking about it. A third is the putamen, which is involved in running, walking, and moving the body as well as in motivation. The researchers did not try to examine the neocortex, the part of the brain that helps us think and is proportionally much bigger in humans than in other animals. The neocortex has crevices on its surface that look so different from one individual to the next that it's really hard to measure consistently across labs.

There's a strong link between the sizes of many of these parts of the brain and overall cognitive ability, Thompson says. "Having more brain tissue is better." Diseases such as Alzheimer's damage the hippocampus, while Parkinson's, for example, impairs the putamen.

The team discovered eight "letter" differences that can shrink brain tissue by about 1.5%, depending on the letter inherited, Thompson and his colleagues report online today in Nature. Some of the letter variants were inside a gene, while others were near key genes.

The most influential gene pinned down, KTN1, helps tell brain cells where to go in the putamen. Two additional variants in the putamen are associated with genes that can cause colon or immune system cancers and seem to regulate the number of cells in that brain region. The remaining five genes do various things, including inhibit programmed cell death, a natural process that can cause brain regions to shrink if it goes unchecked.

Many of the eight genes are active during brain development and may play a role in neuropsychiatric disorders such as autism and schizophrenia, Sanders says. He hopes ENIGMA researchers will next look to see if there are links between a particular brain region's size and one of these disorders. At this point, a genetic test for these variants won't be much help in the clinic, says Faraneh Vargha-Khadem, a developmental cognitive neuroscientist at University College London who was not involved with the work. To diagnose patients, "you go not by what's inside the brain or what's inside the gene, but by what symptoms the patient is showing," she says. Still, "it's good to know that these structures have genetic variation," she says. "It alerts physicians to the relationship between genes, brain structure, and behavior," a relationship that may one day become useful to clinicians.

Science| DOI: 10.1126/science.aaa6373

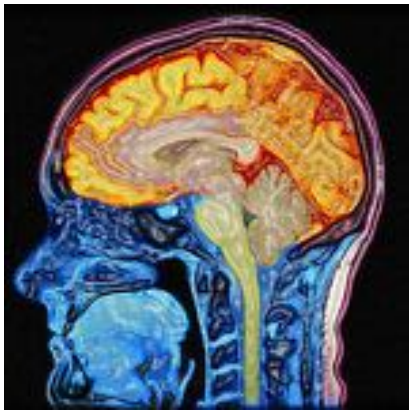
MIT Technology Review

Crowdsourcing Study of 30,000 Images Connects Genes to Brain Size

DNA data and medical images were combined to find genetic links to brain anatomy.

By Antonio Regalado January 21, 2015

The brain remains an enigma to geneticists, but big data strategies could help.



A large network of neuroscientists and doctors that compared over 30,000 brain images with people's DNA says it's found several genes that appear to influence the size of brain structures involved in intelligence and memory, as well as the volume of the brain itself.

Although the medical importance of these clues remains far from clear, the consortium, called Enigma, says its work demonstrates a novel distributed-computing strategy able to sort through vast numbers of MRI scans and DNA test results. "What Enigma is doing is combing through every pixel of every scan and comparing it to every genome," says Paul Thompson, the neuroscientist who organized the research. "This is a roadmap to how you do this."

Thompson, who is head of the Imaging Genetics Center at the University of Southern California, believes Enigma is the largest collaboration ever to combine efforts to study the brain. The new study, published today in the journal Nature, lists 287 authors and 193 institutions. The study involved the analysis of 30,717 brain scans as well as DNA information gathered by researchers in Cambodia, South Africa, the United States, and other countries.

MRI scans are expensive, and analyzing them requires intensive computation. Especially when combined with DNA information, these data are too large to easily move over the Internet, and in some cases privacy rules prevent them from crossing national borders. The consortium says it is solving this problem with a distributed approach in which all the centers are given common algorithms with which to process their images, after which then their findings were weighted and combined.

Large studies linking genes with disease have not paid off well in neuroscience. For some common conditions, like depression, there are no convincing DNA clues at all. Instead of giving up, however, some researchers are instead seeking ways to vastly increase the size of studies. In the case of Enigma, that happened by "crowdsourcing" analysis of existing MRI scans. "There are brain images of many kinds on Alzheimer's, schizophrenia, and autism that people have collected for decades. There is just astronomical data that is siloed," says Thompson.

The big data approach is in vogue. Last year, the National Institutes of Health awarded Enigma and several other centers $32 million as part of a plan by the funding agency to plow more than half a billion into new ways of exploiting biological data over the next seven years. In an interview last month, Mark Guyer, an adviser to the NIH program, called Big Data to Knowledge, says the agency believed data analysis, not collecting data, was now the "bottleneck" to research.

Enigma capitalized on what would be more than $30 million worth of existing brain scans (assuming each cost $1,000), taken of people who ranged in age from age nine to age 96. By comparing the scans to people's DNA, the Enigma researchers say they found eight regions of the genome that influenced either the overall size of the brain, or the volume of its substructures.

The strongest effects were found in the putamen, a part of the brain that influences learning and movements, and which is notably smaller in people with Parkinson's and Huntington's, says Thompson. In a person with two of the gene variants identified, the structure would be 2.8 percent smaller, according to the research.

Despite the scope of the effort, the size of brain structures weren't successfully linked to any psychiatric illness, although Thompson says there are clues pointing in that direction. "It might not be as simple as the gene gives you a smaller putamen and you get these diseases, but the genes are likely to affect how many cells you have, and how they get to the right place," he says. "It's vital to know how it's built."

To critics, the Enigma project embodies the shortcomings of big, mathematics-driven biology, which focuses on data that are easier to feed into computers. Evan Charney, an associate professor at the Duke Institute for Brain Sciences and its public policy school, called the study "depressing" because of how it downplayed life events and environmental influences, like exercise and stress, that also affect the brain's anatomy. "None of this played any role in the authors' analysis," he says.

Thompson says he is convinced that more data, and new mathematical techniques, will eventually lead to substantial breakthroughs in brain science as they have in other domains, like speech processing or the cracking of the WWII-era Nazi cipher after which the consortium is named. He says until recently it was "heresy" to even suggest that gene variants could be linked to what's seen in medical images. "People said you will never see the effects of personal genomes in brain scans," says Thompson.

Los Angeles Times

Genes linked to brain size may help explain some neurological diseases

By MELISSA HEALY

January 21, 2015

- When it comes to brain structures, does size matter? Probably
- Find the genes that influence certain brain structures' volume, and you might uncover how disease takes hold

A consortium of brain and genetic scientists from 30 nations has uncovered a number of genetic variants that appear to influence the volume of certain brain structures. Their findings may help uncover the roots of some neuropsychiatric diseases.

In one of the largest research undertakings of its kind, a team of geneticists and neuroscientists has uncovered a number of genetic variations that influence the size of some key brain structures, including the hippocampus and the putamen. The result may advance understanding of such devastating neurodegenerative diseases as Alzheimer's, Parkinson's and Huntington's.

To link genes and brain structure, a consortium of 290 scientists from 30 different countries conducted scans of the brains and genomes of roughly 31,000 people--"a computationally extraordinary task," according to USC neuroscientist Paul Thompson, one of the effort's leading investigators.

Their findings, reported Wednesday in the journal Nature, identify five novel genetic variants that appear to influence the size of two structures in the brain's basal ganglia--the putamen and caudate nucleus--that help govern the initiation and control of learned movement.

The study also confirmed earlier research locating a site on the genome that affects the brain's overall volume, and another that influences the size of the hippocampus, a key structure in the formation and retrieval of memories.

The findings provide insight "into the causes of variability in human brain development, and may help to determine mechanisms of neuropsychiatric dysfunction," the authors wrote. Such massive collaborations might help uncover the forces that drive normal brain development as well, they wrote.

The work was done by a consortium called the Enhancing Neuro-Imaging Genetics through Meta-Analysis, or ENIGMA. Two-thirds of the 30,717 individuals they studied in their analysis were healthy, and the remaining one-third had a range of neuropsychiatric diseases. The subjects ranged in age from 9 to 97.

"It is truly remarkable that you can see something as subtle as a single letter-change" in the genome's 25,000 protein-coding genes, and link it to variations in the size of a distinct brain region, Thompson said in an interview.

The volume of certain brain structures is likely to be an important measure of those structures' ability to function properly and fight off disease, said Thompson. With aging, for instance, many of the structures found to be influenced by genes lose volume, and that appears to make them vulnerable to disease, he added.

If genes contribute to make one individual's hippocampus smaller than another's, said Thompson, that person's brain might essentially be aging faster and therefore may be more at risk for neuropsychiatric disease.

"If my mental bank account is depleted, am I more at risk?" asked Thompson. "It's not far-fetched" to believe so, he added.

The eight gene sites uncovered were found in populations across a broad geographic range. The genetic variations that influenced brain volume in East Asians were the same those found to do so in Europeans, Africans and Americans.

Huffington Post

Cracking The Brain's Genetic Code

The Huffington Post | By Carolyn Gregoire
Posted: 01/23/2015

An international team of over 300 scientists are taking on an ambitious project to identify eight common genetic mutations that appear to age the brain by three years on average. The team, known as Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) Network, hopes to pave the way for new treatments for Alzheimer's, autism and other neurological disorders.

Led by researchers at the University of Southern California, neuroscientists from more than 190 scientific institutions are bringing together a wealth of data, including brain scans and genetic data from 33 countries around the globe to identify and target genes that either enhance or deteriorate key brain regions.

"The ENIGMA Center's work uses vast datasets as engines of biomedical discovery; it shows how each individual's genetic blueprint shapes the human brain," Dr. Philip Bourne, associate director for data science at the National Institutes of Health, said in a statement. Using MRI data from more than 30,000 people, the researchers screened millions of genome variations to determine which ones affected important brain areas implicated in common neurological disorders. They discovered eight genes that are capable of either eroding or strengthening brain tissue, which may alter the "brain reserve" by two to three percent. In this respect, the genes seem to exert an effect on how resilient our brains are to disease.

"We have some preliminary data that shows the genes driving brain size may affect disease risk," Dr. Paul Thompson, ENIGMA's principal investigator, said in an email to the Huffington Post. "Some affect the memory systems of the brain that decline in Alzheimer's disease. Other genes affect deep brain nuclei that degenerate in Parkinson's and Huntington's disease. If you think of the brain as a mental bank account, we need to know what depletes it and tops it up."

The findings could help to devise future treatments for neurological disorders using pharmacogenomics, which uses an individual's genetic makeup to determine treatment response and created more tailored interventions.

"If an existing treatment were more effective for certain people, or only in certain people, ENIGMA would help to personalize medicine," Thompson explains. "The pain killer codeine, for example, is thought to be less effective in people with certain genetic codes. Imagine if that was true for psychiatric medications too -- it may be, and ENIGMA may offer one way to find out."

The project, which is the largest of its kind, was made possible through a $23 million grant from the National Institutes of Health as part of its Big Data Initiative to improve biomedical data. It's a powerful testament to the kind of impact that global data collection and scientific collaboration can have.

"I love this kind of work -- it pays off financially, as people share resources and skills, and it gives us a power we never had in neuroscience," said Thompson. "It is not just data. It's also people in 33 countries working together to crack the brain's genetic code. Having 300 of the world's greatest minds attack the same problem reminds us of the allied code-breaking effort in World War II."

The findings were published in the journal *Nature*.

Ireland: The Irish Times

Scans and DNA combine to help understand brain development

Three Irish groups participated in major international study

Dick Ahlstrom Wed, Jan 21, 2015, 18:53

NUI Galway professor of psychology Gary Donohoe said the study in terms of numbers was enormous but had to be so in order to succeed.

The study in terms of numbers was enormous but had to be so in order to succeed, said Prof Gary Donohoe, NUI Galway professor of psychology. It involved 30,000 people worldwide in a project called Enigma, Enhancing Neuroimaging Genetics Through Meta-Analysis.

There were almost 300 scientists from 193 institutes including NUIG, Trinity College Dublin and the Royal College of Surgeons in Ireland, Prof Donohoe said.

The project involved taking brain scans of all the participants, making it possible to compare the size of brain structures, he said. The scientists then mapped the DNA of the participants allowing them to match up DNA against the structures, looking for any links between the two.

"We know how the brain forms, the steps in this and the organisation of the brain but there are lots of things we don't know," said Prof Donohoe.

Variations

Small variations in parts of the brain occur and genes in the DNA cause this to happen, but the effects of this are very small.

"In order to test the effect you need thousands and thousands of participants," he said. This included healthy people and ill, those with neurodevelopmental and with mental health problems and also degenerative diseases.

The researchers looked at brain structures involved with memory, movement, learning and motivation.

"We were trying to understand some of the unknown biology that affects neurodevelopment. The more data you have, the more accurate the assessment of the underlying architecture of the brain."

Research

The research was published in the journal Nature. Science Foundation Ireland and theHealth Research Board part-funded the research here.

So far the study has revealed five genetic variants that influence the size of certain brain structures, a real accomplishment given the vast amount of information that must be collected and then analysed by computers and the scientists.

One relates to the hippocampus, a structure linked to memory. The size of the structure has been implicated in Alzheimer's disease and schizophrenia, Prof Donohoe said.

"We will take some of these early results and start to learn more about them, looking in particular at the hippocampus."

Russia: Gazeta

Варианты взрывают мозг

Размер отдельных частей человеческого мозга обусловлен генетическими вариантами

Фотография: iStockphoto
22.01.2015, 08:17 | Владимир Корягин

Найти взаимосвязь между размером отдельных областей человеческого мозга и генетическими вариантами удалось участникам крупнейшего в мире научного консорциума, среди членов которого есть и ученые из России.
В рамках консорциума ENIGMA ученые сравнивают магнитно-резонансные изображения мозга и изучают геномные особенности каждого человека, пытаясь найти генетические причины заболеваний. Это самый крупный на сегодня проект: в нем участвуют 307 ученых из 85 стран, среди которых есть и российские исследователи. Об одном из последних успехов ученых, отмеченном публикацией в журнале Nature, «Газете.Ru» рассказала ведущий автор статьи — профессор Института медицинских исследований Бергхофера Сара Медланд.

«Россия и США не могут долго не общаться»
О сотрудничестве ученых России и США, о проекте по изучению генетической природы болезней мозга человека, реформе Российской академии наук и будущем... →
— Какие задачи ставят перед собой участники консорциума ENIGMA?
— В рамках ENIGMA мы исследуем, как различные генетические варианты влияют на структуру и функционирование мозга, а также пытаемся понять, что является причиной некоторых заболеваний. В рамках консорциума существуют несколько рабочих групп, некоторые из которых, к примеру, занимаются изучением шизофрении, депрессии, биполярного аффективного расстройства.
— Чему посвящена нынешняя статья?
— Нам удалось идентифицировать несколько общих вариантов ДНК, которые влияют на размер отдельных частей мозга.
Примечательно, что одни и те же обнаруженные нами генетические варианты влияют на мозги десятков тысяч людей по всему миру. Некоторые из них связаны с раком, психическими расстройствами и влияют на развитие мозга. Мы очень близки к тому, чтобы понять, как эти гены влияют на организацию живого мозга.
— Удалось ли узнать что-то новое, например, про шизофрению?
— Нет, но одна из областей мозга, которую мы изучали, может быть с ней связана. Это предмет будущих исследований.
Одна из главных задач консорциума ENIGMA — выявление отличий в строении мозга у людей с шизофренией и у тех, кто ей не страдает.

Имплантаты стали ближе
Вживлять имплантаты в спинной и головной мозг стало легче и безопаснее благодаря методике, разработанной при участии российских ученых. →
Если удастся выявить, что какие-то гены влияют на риск развития шизофрении, это поможет нам понять, как же ей противостоять.
— Какие методы применялись вами?
— Поскольку генетические варианты, взятые у отдельных индивидуумов, нам мало чем могут помочь, мы вынуждены работать с колоссальным объемом образцов и информации. В то же время все эти тесты и анализы настолько дорогие, что ни одна исследовательская группа не в силах взять их настолько много, чтобы этого было достаточно для полноценного исследования. Поэтому исследователи из разных стран объединили свои усилия.
Итогом этой работы, вобравшей в себя результаты деятельности множества групп со всего мира, и стала статья в Nature.

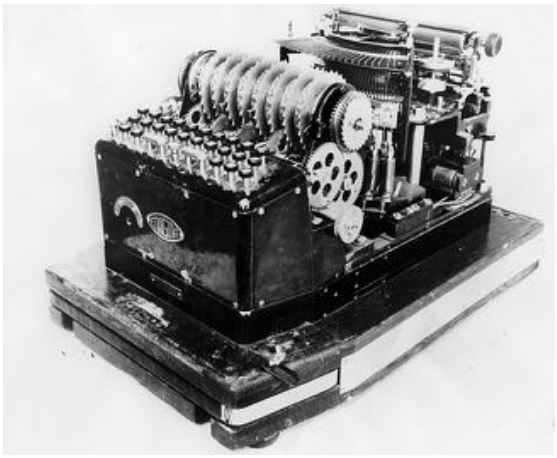
Как человек стал алкоголиком
Историю взаимоотношений человека с алкоголем проследили ученые. Оказалось, эффективно расщеплять этиловый спирт научились еще наши далекие предки... →
— Вам помогали российские ученые?
— Да, с нами работала российский генетик Казима Булаева. Она изучает влияние генетических вариантов на генетических изолятов Дагестана. Ей удалось выяснить, что, возможно, существует связь между генами, оказывающими воздействие на определенные области мозга и связанными с психическими заболеваниями.
— Часто ли вы сотрудничаете с учеными из России?
— Да, у нас есть несколько проектов, которые мы реализуем вместе с рядом лабораторий из новосибирского Академгородка и некоторыми московскими больницами. Кроме того, у нас есть партнеры в Сколковском институте науки и технологий. А в рамках последней конференции Startup Village нам представилась возможность рассказать о работе консорциума ENIGMA перед большой аудиторией.

Italy: Alzheimer Riese

ENIGMA: decifrare il codice genetico del cervello per trovare cura all'Alzheimer

Giovedì 22 Gennaio 2015 09:06 | Scritto da Redazione

L'alleanza di ricerca globale ENIGMA, analizzando oltre 30.000 scansioni cerebrali, ha trovato 8 mutazioni genetiche comuni che portano all'invecchiamento cerebrale, aprendo la possibilità un giorno di svelare i misteri dell'Alzheimer, dell'autismo e degli altri disturbi neurologici.



La macchina per criptare i messaggi Enigma H29 usata dalla Wehrmacht tedesca dopo il 1929. (Fonte: cryptomuseum.com)

Ricercatori della University of Southern California (USC) hanno guidato un consorzio globale di 190 istituzioni, la più grande collaborazione esistita fino ad ora, che ha identificato 8 mutazioni genetiche comuni che sembrano invecchiare il cervello in media di tre anni. La scoperta potrebbe portare a terapie e interventi mirati per l'Alzheimer, l'autismo e le altre malattie neurologiche.

Un team internazionale di circa 300 scienziati, chiamato rete Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) ha messo insieme scansioni cerebrali e dati genetici da tutto il mondo per individuare i geni che aumentano o distruggono delle aree cerebrali chiave in persone provenienti da 33 paesi. Questo è il primo studio di alto profilo realizzato da quando i National Institutes of Health (NIH) hanno lanciato i loro centri di eccellenza «Big Data to Knowledge» (BD2K) nel 2014. La ricerca è stata pubblicata Mercoledì 21 gennaio sulla rivista Nature a controllo dei pari.

"Gli scienziati di ENIGMA analizzano le scansioni cerebrali e i genomi in tutto il mondo per trovare i fattori che aiutano o danneggiano il cervello; questa raccolta e ricchezza di dati ci dà la forza di violare il codice genetico del cervello", ha detto Paul Thompson, PhD, professore alla Keck School of Medicine dell'USC e ricercatore principale di ENIGMA. "Il nostro team globale ha scoperto otto geni che possono erodere o potenziare il tessuto cerebrale delle persone di tutto il mondo. Ogni cambiamento in questi geni sembra modificare il «conto in banca del cervello», la riserva cognitiva, del 2 o 3 per cento. La scoperta guiderà la ricerca per trovare trattamenti medici più personalizzati per Alzheimer, autismo, depressione e altri disturbi".

Lo studio potrebbe aiutare a identificare le persone che avrebbero i maggiori benefici da nuovi farmaci destinati a salvare le cellule cerebrali, ma è necessaria più ricerca per determinare se le mutazioni genetiche sono implicate nella malattia.

Nelle immagini di risonanza magnetica (MRI) di 30.717 individui, i ricercatori di ENIGMA hanno esaminato milioni di "differenze di ortografia" nel codice genetico, per vedere quali di esse influenzano la dimensione di parti chiave del cervello. L'analisi MRI si è concentrata sui dati genetici di 7 aree del cervello che coordinano il movimento, l'apprendimento, la memoria e la motivazione. Il gruppo ha identificato otto varianti genetiche associate alla diminuzione del volume cerebrale, molte delle quali si trovano in più di un quinto della popolazione mondiale. I portatori di una di quelle 8 mutazioni avevano, in media, regioni cerebrali più piccole rispetto a quelle del cervello senza mutazione di coetanei; alcuni dei geni sono implicati nel cancro e nelle malattie mentali.

In ottobre 2014 i NIH hanno investito quasi 32 milioni di dollari nella Big Data Initiative, creando 12 centri di ricerca negli Stati membri per migliorare l'utilizzo dei dati biomedici. I due centri di eccellenza BD2K della USC, tra cui ENIGMA, hanno ricevuto 23 milioni dollari per 4 anni di studio. "Il lavoro del centro ENIGMA usa vasti insiemi di dati come motori per le scoperte biomediche; esso dimostra come il modello genetico di ogni individuo dà forma al cervello umano", ha detto Philip Bourne, PhD, direttore associato per la scienza dei dati ai NIH. "Questa alleanza 'Big Data' mostra cosa prevede di raggiungere il programma BD2K con i nostri 12 centri di eccellenza per il calcolo Big Data".

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Hanno collaborato Derrek P. Hibar, Neda Jahanshad e Arthur Toga della USC. ENIGMA è finanziato in parte dai NIH e da enti pubblici e privati di tutto il mondo.

Australia: ABC

Gene sweep finds variants that make your brain unique

Thursday, 22 January 2015 Marc Llewellyn
ABC

The research offers insight into why different sub-cortical areas of the brain are larger in some people than others (iStockphoto: janulla)

Brain power A large international study has identified variations in the human genome that influence the size of structures deep within the brain.

The research offers an insight into why different sub-cortical areas of the brain are larger in some people than others, and could throw light on why some people develop conditions such as schizophrenia, Alzheimer's disease and Tourette's syndrome.

"Many neuropsychiatric diseases and conditions, like depression and schizophrenia have effects on the regions we've studied, says study co-author Dr Sarah Medland from Brisbane's QIMR Berghofer Medical Research Institute.

"Improving our understanding of how these structures develop and how they function might help us work out where changes of those structures are coming from in those diseases," says Medland.

The meta-analysis using data from 193 institutions from around the globe (which together form a consortium called ENIGMA) appears in the latest edition of Nature.

The data was derived from genetic studies and MRI scans from more than 30,000 people.

"Each of the research groups involved in the study ran the same sequence of analyses on the data they had collected. We've combined the results of these analyses generating one of the largest imaging genetics studies to date," says Medland.

Seven structures

The research concentrated on seven structures within the brain that play important roles in everyday behaviours such as learning and memory.

It also looked at a measure of overall brain size.

"We wanted to see if we could find some of the genetic variants that influence how those structures form in the general population," says Medland.

"Once we've got a better understanding of what a normally developing brain looks like, we hope it will be easier to identify how diseases might influence these areas."

One of the areas of the brain the research looked at was the putamen, which is involved in body movements and learning. The research identified several genetic variants that influenced the size of this structure.

Others were shown to influence the overall size of brain and the hippocampus, a structure associated with spatial navigation and memory.

Genetic variants were also identified that appeared to influence the size of the amygdala (associated with memory, emotion and decision-making), and the caudate nucleus (linked to both voluntary movement and learning as well as memory, sleep, emotions and language).

Medland says the study demonstrates that a collaborative analysis of genetic and imaging data can identify relationships between genetic variants and human brain development and dysfunction.

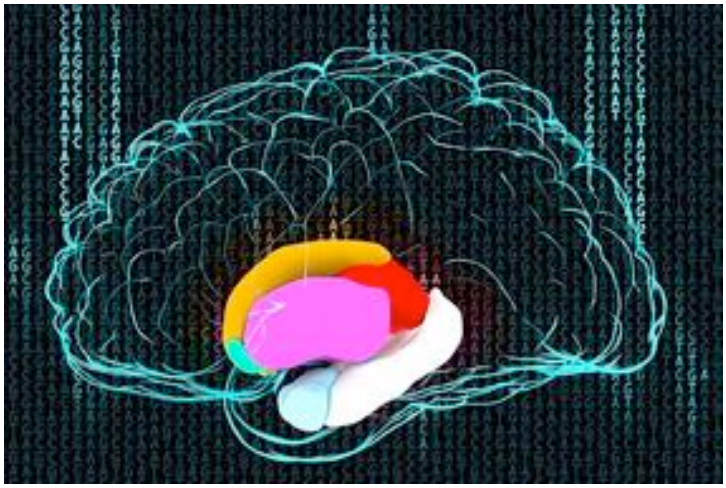
"Research of this kind is prohibitively expensive for one institution to do, and none of this work would be possible without all of the input from scientists and participants from around the world."

Spain: Agencia Sinc

Descubren variaciones genéticas asociadas a cambios en el cerebro de miles de personas

Un estudio del consorcio internacional Enigma, con participación española, revela cómo afectan cambios en el genoma sobre la estructura cerebral. Los resultados son útiles para conocer qué procesos genéticos hay debajo de las enfermedades neuropsiquiátricas.

SINC | | 21 enero 2015 19:00



Un grupo internacional de investigadores ha descrito cómo influyen diversas variantes genéticas en la estructura del cerebro. El objetivo fue descubrir si dichas variaciones comunes (SNPs) en el genoma humano modifican el volumen de partes del cerebro determinantes para la memoria o el comportamiento, y que están relacionadas con enfermedades mentales.

En el trabajo, publicado esta semana en la revista Nature, participa el grupo de investigación en psiquiatría del Hospital Universitario Marqués de Valdecilla de Santander, con el experto en neuroimagen Roberto M. Roiz Santiañez como único representante español.

"La enorme complejidad de la estructura y organización del cerebro humano está determinada por influencias genéticas y por factores ambientales (ejercicio físico, alimentación, edad, uso de drogas…)", explica a Sinc, Roiz Santiañez.

La enorme complejidad de la estructura y organización del cerebro humano está determinada por influencias genéticas y por factores ambientales

Para investigar cómo las variantes genéticas comunes afectan la estructura de estas regiones del cerebro, los científicos combinaron datos de resonancia magnética cerebral y de análisis genéticos (GWAS) de más de 30.000 individuos y encontraron que muchas de estas variantes parecen ejercer sus efectos a través de los procesos de desarrollo conocidos.

Los resultados revelan la existencia de cinco variantes genéticas que influyen significativamente en el volumen de estructuras cerebrales subcorticales (putamen y núcleo caudado, que juntas forman el núcleo estriado, que actúa como entrada de información).

Además, se ha replicado el hallazgo de otras tres variantes genéticas asociadas al volumen del hipocampo –una región clave implicada en el aprendizaje y la memoria, conocida por estar asociada con la esquizofrenia– y al volumen intracraneal.

"Estas variantes muestran un efecto concreto sobre el volumen de determinadas estructuras cercanas a genes que condicionan el desarrollo cerebral durante el embarazo y primeros meses de vida", añade el autor español. "Por lo tanto, su identificación puede ayudar a entender los mecanismos que participan en enfermedades".

Logros a través de la colaboración

El nuevo trabajo ha sido posible gracias a la creación de un consorcio internacional de investigación, ENIGMA, que desarrolla estudios colaborativos de imagen cerebral y genéticos que, analizando a miles de pacientes, puedan demostrar efectos imposibles de poner en evidencia en grupos aislados.

Mapa de los participantes en el estudio ENIGMA, que combina escáneres cerebrales y datos genéticos de 33 países. / Paul Thompson

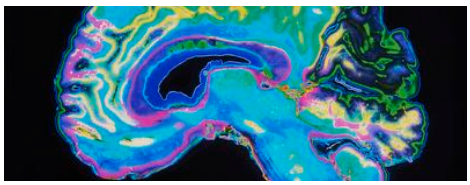
Así, según señala a Sinc Paul Thompson, uno de los autores principales e investigador en la Universidad de Southern California (EE UU), "sorprendentemente se encontró que estas mismas variantes genéticas afectan al cerebro de decenas de miles de personas en 33 países de todo el mundo".

Algunas de estas variantes están dentro, o cerca de, los genes implicados en el cáncer, las enfermedades mentales y el desarrollo. "Esto demuestra que tenemos diferencias individuales en nuestro ADN que parecen afectar el tamaño de las regiones del cerebro", concluye.

Referencia bibliográfica:
Common genetic variants influence human subcortical brain structures. Nature, 21 de enero de 2015. DOI: 10.1038/nature14101

Mexico: Conacyt Prensa

Investigador mexicano coordina metaanálisis de estudio genómico internacional



Por Antonio Trejo
México, DF. 21 de enero de 2015 (Agencia Informativa Conacyt).- Un ambicioso estudio genómico que involucra la participación de más de 300 científicos de todo el mundo, agrupados en el consorcio Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA), ha identificado la relación entre variantes genéticas comunes y el tamaño de diversas estructuras subcorticales del cerebro humano.

El científico mexicano Miguel E. Rentería, becario posdoctoral en el Instituto de Investigaciones Médicas QIMR Berghofer, en Brisbane, Australia, fue responsable de liderar parte de este esfuerzo internacional, al diseñar los protocolos de análisis genético que aplicaron los diferentes grupos participantes en el proyecto, coordinar la comunicación entre los grupos de investigadores, así como llevar a cabo parte del metaanálisis y estudios secundarios, cuyos resultados han sido consignados en la revista especializada Nature.

"En 2010 inicié mis estudios de doctorado en el Instituto de Investigaciones Médicas QIMR Berghofer, aquí en Australia. Fue entonces cuando me involucré en las primeras fases del proyecto ENIGMA, que combina el análisis de imágenes cerebrales de resonancia magnética y datos genómicos. Después surgió la oportunidad de ser uno de los analistas principales durante la segunda fase del proyecto", explicó el investigador en entrevista telefónica para la Agencia Informativa Conacyt.
Las tomografías por resonancia magnética (TRM) estructural de más de 30 mil voluntarios, unidas a su información genética que aportaron institutos y laboratorios de todo el mundo, fueron analizadas por los científicos participantes en el proyecto, liderados principalmente por grupos de investigadores en Australia, Estados Unidos y Holanda.
"En esta etapa, que concluyó en 2014, analizamos el volumen intracraneal y siete regiones subcorticales: hipocampo, amígdala, globo pálido, tálamo, núcleo caudado, putamen y núcleo accumbens. Descubrimos ocho asociaciones genéticas.La muestra –poco más de 30 mil individuos– fue lo suficientemente grande y nos permitió demostrar la relación entre la variación genética y la forma en la que esta influye en el volumen del encéfalo", explicó.
Con la genética, ahora los investigadores podrán explicar entre el siete y el 15 por ciento de las diferencias en tamaño cerebral entre una persona y otra. "En esta etapa del estudio identificamos también algunos mecanismos específicos –ligados a la variación genética y volumen de las estructuras cerebrales– que contribuyen a la muerte celular programada, direccionamiento de axones y transporte vesicular", agregó el doctor Rentería, quien también es miembro del Sistema Nacional de Investigadores (SNI) y becario posdoctoral del Consejo Nacional de Ciencia y Tecnología (Conacyt).
En el largo plazo, los resultados podrían ser útiles para el desarrollo de nuevos métodos de diagnóstico y prevención, o para tratamientos farmacológicos de enfermedades como esquizofrenia, trastorno bipolar, depresión, alzhéimer y demencia. De hecho, el consorcio ENIGMA ya está organizado en varios grupos de interés que abordan enfermedades en particular.

Invitación a México
Desde 2010, los líderes de ENIGMA invitaron a laboratorios e institutos del todo el mundo a participar en el proyecto, con análisis de imágenes por resonancia magnética y datos genómicos de sus voluntarios sanos o pacientes.
A pesar del carácter incluyente y democrático del proyecto científico, el doctor Rentería lamenta que la gran mayoría de los individuos incluidos en el estudio hayan sido de ascendencia Europea, y que la participación de instituciones mexicanas –y del resto de América Latina- fue nula. "Yo creo que la limitante fue que en nuestro país todavía no es común que los laboratorios combinen la neuroimagen con la genómica", dijo. "Sin embargo, en ENIGMA 2 incluimos una muestra de mexicanos-americanos de San Antonio, Texas. La mitad de las asociaciones reportadas replicaron en la muestra con ancestría mexicana".
Para las siguientes fases de ENIGMA, el investigador mexicano reiteró la invitación: "Si algún centro de investigación o laboratorio desea participar aportando imágenes cerebrales, aun cuando no tenga datos genómicos, puede hacerlo. El primer paso es registrase en elsitio en internet del proyecto ENIGMA o contactar directamente a este servidor".
Es importante mencionar que la identidad de los pacientes permanece bajo resguardo del laboratorio que originalmente procesó las imágenes y datos genómicos. "Nosotros solo trabajamos con metadatos, el protocolo de investigación no permite ni necesita los datos personales de los pacientes, asociados a las imágenes cerebrales y datos genómicos", explicó.
Finalmente, el especialista resaltó que el enorme esfuerzo personal que ha aportado al proyecto ENIGMA se suma al talento de un gran equipo de científicos con los que trabaja, no solo en el Instituto de Investigaciones Médicas QIMR Berghofer, sino alrededor del mundo.
"Este es un gran trabajo de equipo. Tengo que reconocer de forma particular el trabajo y apoyo de mis colegas Derrek P. Hibar, Jason L. Stein y el profesor Paul M. Thompson en Los Ángeles, y a mis supervisores aquí en Australia: Sarah E. Medland, Margaret J. Wright, y el profesor Nicholas G. Martin. Pero en especial, reconocer a todos los grupos del consorcio ENIGMA, que han hecho una gran labor".

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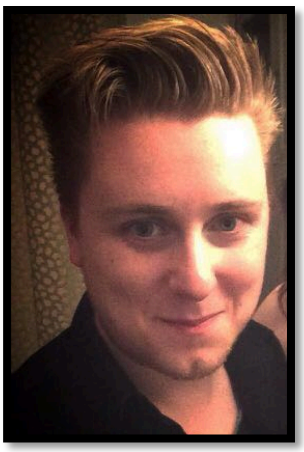

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