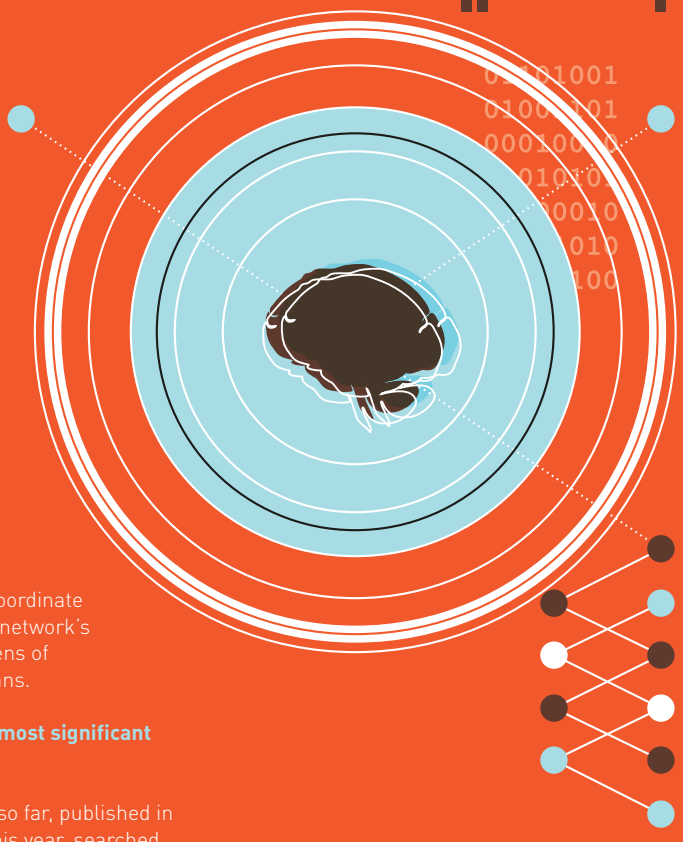
The big picture

Professor Paul Thompson, and **Drs Derrek Hibar** and **Neda Jahanshad** discuss the significant progress being made by taking a global-scale 'big data' approach to understanding brain function and the underlying causes of neuropathogenesis



Can you begin by introducing the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) project, including its participants and overarching aims?

PT: ENIGMA is the largest brain imaging study in the world. It combines the talents and expertise of over 300 scientists from 185 institutions in 33 countries to explore unknowns about the human brain. We study questions such as: 'What factors help or harm the brain?', 'How do the major diseases and psychiatric conditions affect the brain?', and 'Which medications are best?'.

Why has elucidating the links between genotype and phenotype in neurological and psychiatric disorders historically been so difficult?

PT: Even healthy people differ dramatically from each other in brain structure and function; just as faces and personalities are different, each individual's brain circuits are wired together differently, develop at different rates and function in contrasting ways. Our experiences and genes affect the brain – and so do drugs and alcohol, diet, some of the medications we might take, and certain infectious diseases and toxins. With all of these factors at play, it's a huge challenge to disentangle those that help our brains stay healthy from those that promote disease risk.

How does ENIGMA manage big data and ensure efficient coordination between the numerous scientists involved, spread as they are across different institutions and countries?

NJ: ENIGMA is organised into 30 or so working groups that tackle different questions about the brain or study different diseases. Fortunately, these groups are led by the world's top experts in the diseases we study, as well as big data specialists who coordinate the work and help the network's members to analyse tens of thousands of brain scans.

What have been your most significant findings to date?

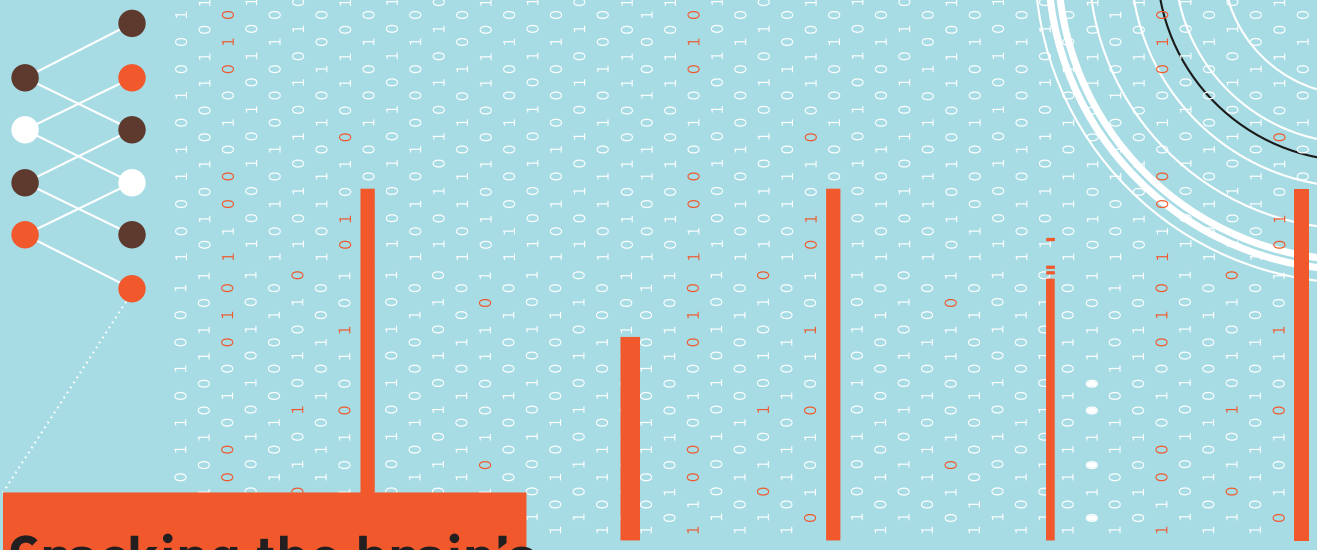
DH: Our largest study so far, published in *Nature* in January of this year, searched through the DNA and brain scans of over 30,000 people and found common genetic variants at the single nucleotide level that affect the size of key structures in the brain. If you think about it, it is absolutely incredible that these same genes affect the brain in the same way in a diverse range of individuals living in over 33 countries worldwide, and a collective effort found them. Now we are trying to determine if these genes affect our risk for disease and, if so, how to counteract their effects.

Could you discuss any difficulties or hurdles you have encountered in establishing the ENIGMA network?

PT&NJ&DH: The main hurdle has been obtaining funding, as it's unusual to have a scientific project span more than 30 countries. Much of what ENIGMA does is not funded. We rely on volunteer work from researchers worldwide who believe it is a worthwhile alliance with worthwhile goals. We started ENIGMA in 2009, relying on local resources and goodwill to get the projects going. However, as the network grew, it became harder to follow up the opportunities without support for people to run analyses at different sites across the world. The National Institutes of Health (NIH) funded the ENIGMA Center for Worldwide Medicine, Imaging, and Genomics in 2014, and it was one of 11 National Centers of Excellence in Big Data Computing in the Biomedical Sciences funded last year. This helps us support some developments in ENIGMA, but the project would never be sustainable without the global efforts of all the national and private funding agencies of the participating countries and institutions. Thousands of patients and volunteers offer their time, energy and expertise. We are constantly looking for support from people who want to fund work on specific illnesses, or to help trainees in different countries to get involved.

What do you hope to accomplish over the next six months of the project?

PT&NJ&DH: We'll see the first reports from the ENIGMA groups studying autism, addiction, attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). We also expect to report on factors that affect complex brain traits from diffusion-based magnetic resonance imaging (MRI), including genes that may control the extent to which various parts of the brain communicate with one another. Collaboratively, we are all working hard around the globe to make these discoveries at a rate that would be unimaginable for a single study. We are all excited to see the findings, as they are among the largest-ever imaging studies of these brain disorders. They should not only point to the most important systems of the brain that are disrupted for each disease, but also help determine factors that affect worsening of these illnesses.



Cracking the brain's genetic code

Since 2009, the **Enhancing Neuro Imaging Genetics through Meta-Analysis** project has pooled brain scans and genetic data from over 30,000 individuals. Its aim is to understand the role of genetic and environmental factors within psychiatric and neurological health and disease

ACCORDING TO THE World Health Organization (WHO), mental and substance use disorders are the leading cause of disability worldwide, contributing to 23 per cent of all years lost. Although scientific understanding of these conditions has increased significantly over recent years, much is still unknown about their causes and pathogenesis, particularly on a neurological level. This is especially true of the role played by genetic and environmental factors in shaping brain structure and function and, therefore, psychiatric health and illness.

This is where the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) network steps in. Just as its namesake – Alan Turing's famous code-breaking machine – sought to decipher secret messages sent during World War II, the present-day enigma, in this case, is the complexity of the brain's genetic code, which this collaborative team of scientists aims to crack. To achieve this ambitious goal, ENIGMA must operate at an unprecedented scale; only with extensive imaging and meta-analysis of multiple, diverse cohorts can the subtle patterns necessary for the clarification of how genetics and the environment interact be identified. ENIGMA employs an innovative 'crowdsourcing' structure in which its members contribute their time, expertise, brain scans and genetic data.

AROUND THE WORLD

Leading the project is Paul Thompson, a professor of neurology in the Imaging Genetics Center at the University of Southern California, USA. "The Center is a primary coordinating site for ENIGMA," Thompson elucidates. "Our multidisciplinary team of researchers helps to harmonise the technical protocols for our projects and supports the analysis of DNA and brain scans from all over the world." He is joined at the Center by a crossdisciplinary team of over 35 researchers, including Drs Derrek Hibar and Neda Jahanshad. Across the wider network, ENIGMA's members are divided among more than 30 working groups – each of which focuses on a specific brain disease, question about the brain or methodological development – and further specialise into their own, more targeted subgroups.

World-leading big data specialists contribute their expertise to help the network effectively manage and analyse the enormous amount of data the projects generate. This process is made easier by the fact that ENIGMA has no centralised repository of data; rather, specific measures for the calculation of brain scan and DNA data are agreed upon beforehand, and each working group site is sent the appropriate computer software and algorithms to install onto its existing computer infrastructure, enabling them to run their own analyses. These algorithms are essential to the process, as they enable ENIGMA to circumnavigate the logistical and administrative bureaucracy associated with international data sharing by ensuring that no raw data are ever transferred between any of the ENIGMA research centres. This system also promotes the inclusion of researchers

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ENIGMA employs an innovative 'crowdsourcing' structure in which its members contribute their time, expertise, brain scans and genetic data

Since its establishment in 2009, the project has succeeded in mobilising over **300 scientists** across **185 institutions** in **33 countries**, and analysed biodata from over **30,000 individuals** across the globe.

from low- and middle-income countries, as it removes cost barriers associated with purchasing new equipment. Significantly, such scientists currently comprise around 10 per cent of the ENIGMA network.

TEASING OUT PATTERNS

So far, ENIGMA activity has resulted in publications in a number of high-profile journals, including *NeuroImage*, *Nature Genetics* and *Twin Research and Human Genetics*. However, one recent effort, entitled 'Common genetic variants influence human subcortical brain structures' has attracted particularly high levels of interest following its publication in *Nature* a few months ago. The paper outlines common genetic variants that affect the size of subcortical structures in the brain, identified following a genome-wide association study involving data from over 30,000 individuals. "This work was years in the making and combined data from 185 medical centres around the world with nearly 300 authors contributing to the project," reveals Hibar, who coordinated the research in this area. "Harmonisation of data analysis and troubleshooting were the keys to success for this world-spanning, diverse effort."

This is just one arm of ENIGMA's myriad activities and progress is fast being made in other areas. For example, within the past few months ENIGMA has submitted neuroimaging studies of schizophrenia, bipolar disorder and major depressive disorder for publication – the largest of their kind in the world. "We are only now beginning to show that this type of work is possible, but its ultimate implications are limitless," enthuses Jahanshad. For the time being, the researchers plan to focus their research efforts in this area towards the identification of novel biomarkers and unexploited therapeutic targets.

GAINING MOMENTUM

The ENIGMA consortium is confident that its meta-analyses will continue to produce results of significant scientific and clinical importance. Within the next year there are plans to publish – in addition to the schizophrenia, bipolar disorder and major depressive disorder studies already submitted – the world's largest ever neuroimaging studies of attention deficit hyperactivity disorder (ADHD) and addiction, as well as a report charting age effects on brain volumes, and the results of a genome-wide screen for common genetic variants associated with cortical thickness and surface area. New working groups are also being set up to focus on epilepsy, post-traumatic stress disorder, Parkinson's disease and cancer/chemotherapy treatment.

The speed with which new working groups are emerging is emblematic of the accelerating momentum within ENIGMA. Researchers are attracted to the network's world-spanning structure and are passionate about utilising the big data generated to drive forward discoveries. Hibar is just one such example: "I started off working on ENIGMA as a volunteer during my undergraduate years, and I was so captivated by its promise that I joined the lab and have not left since," he reveals. "I am grateful for having the opportunity to show that team science is possible in the field of neuroimaging genetics."

ENIGMA NETWORK

OBJECTIVES

- To create a network of like-minded individuals interested in pushing forward the field of imaging genetics
- To replicate promising findings via member collaborations, ensuring consistent and reproducible discoveries
- To share ideas, algorithms, data and information on promising findings or methods
- To facilitate training, including hosting workshops and conferences on key methods and emerging directions in imaging genetics

KEY COLLABORATORS

Details about the chairs of the network's working groups can be found here:

www.enigma.ini.usc.edu/about/consortium

FUNDING

ENIGMA is funded by a National Institutes of Health (NIH) U54 grant from the Big Data to Knowledge Program, and by public and private agencies across the European Union, Australia, Asia and 33 countries worldwide.

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PROFESSOR PAUL THOMPSON gained a Master's at the University of Oxford, UK, and his PhD from the University of California, Los Angeles, USA, where he later held a professorship. He moved to his current position at the University of Southern California (USC) in 2013 where, in addition to his research, Thompson is Associate Dean for Research at the Keck USC School of Medicine and Director of the University's Imaging Genetics Center.

DR NEDA JAHANSHAD studied biomedical and electrical engineering at Johns Hopkins University, USA, before moving to the University of California, Los Angeles, where she received her PhD in Biomedical Engineering. She is now Assistant Professor of Neurology at USC's Imaging Genetics Center.

DR DERREK HIBAR obtained his BSc and PhD from the University of California, Los Angeles, USA, and is currently Assistant Professor at USC in the University's Imaging Genetics Center. Hibar coordinates several international efforts within the ENIGMA Consortium focused on the genetics of the brain with extensions to bipolar disorder and major depression.