Unravelling the enigma surrounding brain structure and function

Professor Paul Thompson is the Director of ENIGMA – a project that seeks to understand the brain through extensive collaboration. Below, he discusses the project’s progress, specific areas of focus and some of its most surprising findings to date.

Welcome back to International Innovation! It is a pleasure to speak with you again about the ENIGMA project. How has ENIGMA – the largest brain imaging study in the world – evolved since we last spoke?

Thank you! Since last year, we have combed through over 50,000 people’s brain scans and DNA to work out how brain diseases affect us, how they emerge and spread, and what resists them. We are doing this work in 35 countries, to compile the most detailed picture ever of the brain across the world. Take ENIGMA’s studies of depression, bipolar illness and schizophrenia, for example. By looking at brain scans from over 20,000 people, we see how depression strikes the hippocampus (the brain’s learning and memory system); people who are depressed have a physical loss of tissue in the brain’s learning centres, as well as in parts of the brain involved in motivation and reward. The changes are greatest in people who have been ill the longest, so early treatment is crucial.

ENIGMA’s group studying post-traumatic stress disorder (PTSD) also sees differences in the brains of combat veterans and in survivors of childhood trauma and traumatic brain injury. We are discovering what promotes recovery from trauma, and if the same things work in different countries. ENIGMA’s groups studying epilepsy, Parkinson’s disease and stroke recovery can quickly compare notes – and share new leads – with our groups studying anorexia, addiction, obsessive compulsive disorder, HIV, autism and ADHD. For some of these diseases, ENIGMA has published the largest ever studies this year. They show remarkable consistencies in how these illnesses affect the brain worldwide, and offer some clues on how to resist them.

Clearly, ENIGMA covers a lot of ground. However, there is one area that I would like to turn your attention to – healthy ageing. Why is ENIGMA keen to investigate this area in regards to brain research?

Whether or not we suffer from depression or have a loved one affected by a brain disease, one thing is certain: we are all ageing. The brain ages like the rest of the body – it grows rapidly in childhood and then declines. We all differ in how our brain ages – partly due to genetics, our diet, our family environment and friends, what we do with our brain, and how we spend our time. So we are all keen to know what protects our brain from ageing and what we can do about it.

Most studies to date have only involved a few hundred people, making it hard to tease apart what matters most, or even if some factors matter at all. So you may see in the news that dietary supplements – such as omega-3, or folic acid – might protect the brain, or that even mild levels of alcohol harm the brain. But is this true? And is it true for everyone, or just some people or in some situations? ENIGMA’s data from 35 countries examine tens of thousands of people, making it easier to disentangle how different factors affect the brain, versus all the other things that happen to us in our life.

What have you found to be the most surprising elements of ENIGMA’s results to date?

It was absolutely stunning to me that we could see the effects on the brain of single letter spelling differences in our DNA. We all vary in our genetic code, so in ENIGMA we decided to launch an effort across 250 institutions worldwide who had been collecting brain scans and DNA from large numbers of people. We hit upon 30 hotspots in our DNA that predict brain structure, and some affect our risk for disease – we’re finding more all the time. As so many things affect our brain – our environment, education and our diet. It was truly stunning to me that in every population of the world we could see these DNA differences that predicted brain measures. It is the most extraordinary finding I have seen in 25 years as a scientist.

What benefits does having such a wide network and large pool of project participants offer both to the project and to the results it delivers?

The greatest benefit of a worldwide alliance is speed and efficiency. Obviously, if you and I were to ask the government, or a wealthy donor, to collect 50,000 brain scans at US $500 per scan, it would cost over $25 million and take about 10 years. It would probably be shouted down or people would give up. But people had been collecting brain scans and DNA all over the world, they just weren’t studying them together in a global study. That is what ENIGMA achieved. So, we didn’t have to buy all the computers and infrastructure to analyse them – just as you can use the internet without having to pay for all the computers that store the data, or the people who generated all the data.

The second benefit is the sheer collective brilliance of people around the world in cracking a scientific problem. When ENIGMA published its first study, we got an email from a famous Russian geneticist in Dagestan who said, “I think I know what the gene does that you discovered”. Dr Kazima Bulayeva, a geneticist and medical doctor, had been studying ethnic isolates in Chechnya and Dagestan for decades; she found the same...
gene as we did, implicating the gene in mental illness for the first time, a gene that ENIGMA found has the greatest effect on the size of the brain’s memory system. Bulayeva and I became good friends and we now collaborate with people across Russia, including in Siberia, and, on related questions with people across Asia and in Thailand and Cambodia, as well as Korea, China and Japan.

It gives you pride and faith in humanity to see people from cultures so diverse jointly cracking the enigmas of the human mind. It is like chess or mathematics. There is no monopoly on good ideas, but a collective interest, and we can all take part.

Finally, how would you like to see the project evolve in the future?

It is quite hard to fund ENIGMA as the scientists are in 35 countries. So we are looking for ways to pay for the work. ENIGMA saves money and offers a high yield on the invested time by making use of data already collected. By getting more people to work together, it gives us a source of power that we have never had. The New York Times described ENIGMA as giving brain research a new source of power, while the medical journal, The Lancet, highlighted ENIGMA as a project where “crowdsourcing meets neuroscience”.

In the coming years I’d like to see ENIGMA’s projects on different diseases spin off to become financially sustainable in the long term. We should be able to boost public health by discovering factors that resist brain disease and brain ageing. ENIGMA is just one piece in a global effort tackling brain disease, but the sheer breadth of collaboration in ENIGMA is very unusual in science.

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Saving the brain by stalling its decline

The ENIGMA project is the largest brain imaging study in the world. It brings brain scientists from around the globe together to look at a myriad of brain diseases and to understand the factors that help or harm the brain, including those that keep us healthy as we age.

**THE ENHANCING NEURO** Imaging Genetics through Meta-Analysis (ENIGMA) project is one of the largest scientific initiatives in history. Since it began six years ago, it has brought together over 500 scientists from 35 countries to discover the factors that help or harm the brain. By pooling worldwide experts in fields such as medicine, mathematics and the genome, the project analyses 18 major brain diseases, studying what causes them, what treatments are best, what factors put individuals at risk and what protects us.

*International Innovation* first published an article about ENIGMA in May 2015 and, since then, the project has evolved to the point where the brain scans of over 50,000 people have been analysed. Within the project, there are over 30 active working groups, including the recently established Save the Brain project. The main goals and overarching aims of Save the Brain are to discover the factors that keep the brain healthy as we age. While there is a wealth of evidence regarding what harms the brain – such as brain trauma, concussion, untreated depression and drug and alcohol abuse – very little is known about what helps us.

By analysing brain scans from thousands of people, the researchers hope to build a portfolio of evidence of factors that can help protect the brain as we age. Professor Paul Thompson is the Director of ENIGMA. He is clearly a passionate advocate for what this groundbreaking project seeks to achieve. “Alzheimer’s disease, for example, doubles in prevalence every five years after the age of 60. So if you could delay Alzheimer’s by five years, only half as many people in each age group would have it,” explains Thompson. “So we need to work out what factors delay disease and what factors boost the brain’s ‘reserves’ and offer a greater resilience to brain decline.”

With that in mind, the team working on the Save the Brain project is studying several factors, such as cardiovascular health and diet, stress reduction, hormonal changes, alcohol and drug abuse, and medications and supplements. Each topic facilitates the building up of new information to inform strategies that slow down the brain’s decline.

The investigations have so far uncovered some fascinating discoveries, such as the significant impact cardiovascular health and physical fitness have in delaying dementia. For instance, people who walk for half an hour every day have younger looking brains than those who do not, while the rate of brain loss is even slower for people who exercise more.

According to Thompson, each different activity has different health effects. “High intensity exercise gets oxygen-rich blood into the brain, but milder forms of exercise – even meditation – can reduce stress, which is also a big killer of brain cells,” he explains. “People with high levels of the stress hormone, cortisol, suffer fastest erosion of brain tissue, making it crucial to get those stress levels down.” Thus, exercise and stress reduction are the two biggest ways to save millions of brain cells from dying every year.

**CRACKING THE CODE**

Studies of Alzheimer’s disease over the last 20 years show that a person’s body mass index (BMI) is an excellent predictor of how fast the brain is ageing. Interestingly, BMI has been shown to correlate with a person’s educational level and, though there are obviously other factors at play, people who are more educated tend to have a lower BMI.

This was a major motivation that pushed the team to look into the blood for markers of healthy ageing and investigate the DNA of individuals. Ultimately, this led to 300 scientists from ENIGMA publishing papers using DNA and brain scans in an effort to crack the genetic code of the brain.

They found eight markers in the genome where different people’s genes have a different ‘spelling’ and, on average, people with some of these spelling differences had brains that looked 3-4 years older. By pooling DNA from around the world, ENIGMA has managed to find

Researchers have mapped brain decay caused by methamphetamine use. The damage affected memory, emotion and the reward system.

The project analyses 18 major brain diseases, studying what causes them, what treatments are best, what factors put individuals at risk and what protects us.
ENIGMA

OBJECTIVES

• To create a network of like-minded individuals interested in pushing forward the fields of brain research, imaging and genetics and to share ideas, algorithms, data and information on promising findings or methods

• To discover what keeps the brain healthy as we age and to look for protective factors by analysing brain scans collected all over the world every day

• To replicate promising findings via member collaborations, ensuring consistent and reproducible discoveries

FUNDING

US: National Institutes of Health

Australia: National Health and Medical Research Council

Europe: European Research Council • Seventh Framework Programme (FP7) • Wellcome Trust • Medical Research Council • NHS • Research Councils of Norway and Sweden • German Federal Ministry of Education and Research • French National Agency for Research • Science Foundation Ireland • Netherlands Organisation for Scientific Research • Scottish Mental Health Research Network

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