The developing brain in health and disease

Report of a scientific meeting on 19-20 March 2019

The **Academy** *of* **Medical Sciences**

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Executive summary

Human brain development is a complex and dynamic process that is shaped by the continuous interaction between genes and the environment, starting in the embryo and extending through late adolescence, and arguably throughout the lifespan. A better understanding of brain development will shed light not only on the processes underlying cognition and behaviour, but also on the underlying causes of many conditions with neurodevelopmental origins, such as autism and schizophrenia.

There is widespread concern amongst professionals and government agencies in the UK about rising rates of mental health conditions in children and young people, supporting the view that new directions in research and ways of working are needed. There has been significant progress within many areas of neurodevelopmental research in recent years; however, research in the field is often undertaken in silos across a wide range of disciplines. This segregated approach has prevented the full translation of progress in neurodevelopmental research across the breadth of the field to accelerate understanding and clinical benefit.

On 19-20 March, the Academy of Medical Sciences convened a scientific meeting to explore key areas of neurodevelopmental research in a unique forum that promoted discussion and collaboration between disciplines, career stages and sectors. The meeting highlighted the latest advances in neurodevelopmental research through a series of talks, and aimed to identify key research questions that could bring a real impact to the field through targeted discussion sessions. The following key themes emerged at the meeting.

Developing research models
Animal models are an important resource for studying neurodevelopment. However, improved measurement methods, collaboration between teams with expertise in different model systems, and additional validation of models with human data are needed to enhance their utility. More recently, human organoid systems have been developed to study the systems and networks involved in brain development and disease. These approaches are still in their infancy and, to date, methodological issues have prevented their more widespread use. Questions remain regarding the reproducibility of results from organoid-based work in other systems, including humans. Additionally, ethical concerns are likely to be raised as more complex organoids are developed. In future, approaching research questions using a variety of experimental methods – from animal models to longitudinal studies – will be important to validate findings. Further, new computational methods using big data and machine learning will increasingly provide improved mechanistic accounts of developmental and disease trajectories, by integrating different model types to provide deeper insights.

Studies across the lifespan
More research on brain development at a population level across the lifespan is needed. Such research would provide invaluable insights into how risk factors can combine to influence disease trajectories over time. Longitudinal studies will be important in bridging the data gaps between childhood development, adulthood and old age. Improved funding mechanisms will be required to support and incentivise the interdisciplinary collaborations, including working with clinicians in the NHS, and long-term focus that such work requires. Additionally, a central registry of human tissue samples and improved access to human brain tissue in biobanks, especially tissue from children and young adults, are needed. Linking biobank samples to medical records and other datasets would be hugely valuable to progress our understanding of neurodevelopment in health and disease.

Genes and the environment
Progress in our understanding of the genetic and epigenetic variations associated with neurodevelopmental disorders provides an opportunity for improving diagnosis and informed development of more targeted treatments. In addition, further research into environmental exposures and their relationship to genetic factors would enable better understanding of the

causal relationship between environmental risk and neurodevelopmental disorders, improved identification of at-risk groups, and better targeted public health messaging and treatment. New technologies such as smartphones present an opportunity to harness additional types of measures to allow research to be carried out at sufficient scale, to understand how genetic and environmental factors impact on the developing brain over time. Observational studies will need to be supplemented by intervention studies, ideally randomised controlled studies, to confirm causal relationships and inform policy priorities, including early interventions to protect brain development.

Data-driven research

Researchers would benefit from increased data sharing and greater use of existing datasets, especially those in health and education. Improved data collection and standardisation will be required to facilitate data-driven research, although this will need to be balanced against the need to avoid stifling the development of novel techniques. Concerns about privacy and the commercial use of data will also need to be addressed. Increased training provision will be important, as research becomes increasingly data rich and as analytic methods improve. Systematic reviews, meta-analyses and new technologies, such as artificial intelligence, present opportunities to make better use of existing data. The UK is well positioned to establish a biobank of samples collected from children linked to routinely collected health data, such as NHS records, potentially modelled on the NIHR's BioResource centres.

Diversity and interdisciplinarity

Researchers should become more aware of gender differences in the incidence and symptom profiles of neurodevelopmental conditions. Diagnostic tools developed to recognise pathologies primarily in one gender will also need to be updated. Tools that better highlight when studies have a gender bias are needed, as well as experimental designs that represent populations that are ethnically, geographically and socio-economically more diverse. New databases should be designed with protocols that include low tech, simple techniques to allow the inclusion and integration of data sets from low income settings. Academic institutions should do more to encourage interdisciplinary, cross-sectoral collaborations to underpin research on these wider populations.

Greater openness

Greater openness, including publishing so-called negative results, greater transparency of methods and open access publishing, would help to improve the reproducibility of research findings and drive more rapid scientific progress. In addition, researchers need to better engage affected individuals, their families and the public to identify priorities and unmet needs, and to ensure that study designs involving human participants are appropriately tailored. They also have an important role to play in communicating the importance of research for patient and population health, and in encouraging research subjects to participate in research.

The meeting was positively received as providing a unique, independent platform to discuss a wide breadth of subjects, hear the diversity of perspectives shared by attendees, and catalyse connections across the clinical and non-clinical disciplines. This was underlined by participants' enthusiasm to organise a follow-up event of a similar nature in the near future.

Introduction

Brain development begins soon after conception and continues at least through young adulthood. It is shaped by a complex interplay between genes and the environment. Scientific advances that shine new light on these processes can reveal not only the neurological roots of cognition and behaviour, but also of neurodevelopmental conditions. Improved understanding of the causes of these will help accelerate the discovery of new ways to improve the lives of those affected.

There has been significant progress within many areas of neurodevelopmental research in recent years. New experimental techniques are helping to fill the gaps in our knowledge about brain development and the causes of diverse neurodevelopmental conditions, such as autism, attention deficit hyperactivity disorder (ADHD) and schizophrenia, are becoming clearer. However, this progress is slower than it could be because research is often carried out in silos, defined by disciplines (for example, cellular neuroscience, cognitive psychology and psychiatry), or techniques (for instance, neuroimaging, *in vitro* cell studies, and computational neuroscience).

To explore how to address some of these barriers to progress, the Academy of Medical Sciences held a scientific meeting on 19-20 March in Oxford, on the topic of 'The developing brain in health and disease'. The meeting brought together around 100 scientists from a wide range of disciplines and career stages – from early career researchers to global leaders in their fields – as well as other key players, such as funders and publishers. Attendees heard presentations on the latest advances and trends in neurodevelopment research, and discussed how best to drive forward further progress. In organising the meeting, the Academy aimed to foster new, innovative, cross-disciplinary collaborations, and help nurture the next generation of researchers in the field.

This report summarises the key points made over the course of the meeting, including by: the speakers; the early career researchers, who presented 'flash talks'; and participants, who contributed to breakout session discussions on eight important questions about the challenges, opportunities and research priorities relating to brain development and neurodevelopment disorders. The views it presents do not necessarily reflect those of all meeting participants, the Academy of Medical Sciences or its Fellows.

Cutting-edge advances in neurodevelopmental research – summaries of the speakers' presentations

Keynote – The evolution of brain development: mechanisms underlying the human-specific increase in brain size and complexity

Professor Arnold Kriegstein, Director of the Developmental and Stem Cell Biology Program, University of California, San Francisco

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Key messages:
- There is a greater diversity of neural stem cells in humans than in mice.
- Combined comparative analysis in human and non-human primate cell and organoid models reveals human-specific changes during neurogenesis.
- Outer radial glia cells, present in developing human cortex, are implicated in diseases ranging from lissencephaly and cortical dysplasia, to autism and brain tumours.

At the earliest stages of cortical development, the progenitor zones of the embryonic human and mouse brain are similar. However, significant differences emerge rapidly with a huge increase in the size of the human subventricular zone, a region containing neural progenitor cells that divide to produce neurons. Cells responsible for key advanced cognitive functions in humans, are mostly produced in the outer subventricular zone (SVZ), which is not present in rodents.

In 2010, Professor Arnold Kriegstein's group was one of the first to describe a neural stem cell type found in the outer SVZ which they called outer subventricular radial glia-like (oRG) cells. They went on to identify some of their key features: during cell division, for example, they can rapidly 'jump' along their basal fibres over distances of 80-100 microns.[1]

The group has identified genes expressed by both oRGs and ventricular radial glia cells, with which they share many similarities. Around the middle period of human neurogenesis, ventricular radial glia cells give rise to oRGs, which in turn produce and guide the migration of neurons to the upper cortical layers. oRGs are thought to play an important role in producing the higher density and diversity of these key cells in primates.

His group uses cerebral organoids grown in the lab from induced pluripotent stem (iPS) cells to study diseases that originate in early brain development. They have shown that, by about 15 weeks, these contain cells with the gene expression patterns and 'jumping' division behaviour of oRGs.

In 2017, Professor Kriegstein grew brain organoids from samples taken from patients with Miller Dieker Syndrome, a severe form of lissencephaly, a rare genetic brain disorder characterised by parts of the outer surface of the brain appearing smooth. The study identified abnormalities in oRG cell division in the Miller Dieker cases, suggesting they play roles in cortical folding and brain expansion.[2]

Professor Kriegstein identified the presence of oRG-like cells in samples from patients with glioblastoma multiforme, a highly aggressive glial cell brain tumour. A gene called PTPRZ1 is highly expressed in both foetal oRGs and oRG-like cells in glioblastomas. Glioblastomas implanted into mice missing the PTPRZ1 gene grow very slowly, or fail to spread and grow at all.[3] Tests of PTPRZ1-enriched and PTPRZ1-depleted tumour cells in brain organoids have produced further evidence that these oRG-like cells may be important in glioblastoma formation.

Gene sequencing and gene co-expression network analysis has revealed how genes that regulate the LIFR/STAT3 cell signalling pathway, which is involved in cell differentiation and proliferation, are selectively enriched in oRG cells during development of the cerebral cortex. Adding leukemia inhibitory factor (LIF) to organoids has enabled the development of organoids with an increased number of oRGs, which more closely mimics physiological brain development, thereby increasing their utility for research.

oRGS also show heightened activity in mTOR signalling during brain development. Disruption of this pathway has been implicated in autism, tuberous sclerosis and macrocephaly. Further work has highlighted how abnormal 'balloon cells' involved in a brain birth defect called focal cortical dysplasia express genes that regulate mTOR signalling, suggesting oRGs are involved in the condition.

Comparing brain development in humans with that of chimpanzees, humans' closest relative, could help identify important human-specific features. To circumvent the difficulties in obtaining foetal tissue from chimpanzees, Professor Kriegstein's group has created chimpanzee brain organoids. This allowed the identification of genes expressed solely in oRGs in human brain organoids compared to chimpanzee brain organoids, including, for example, enriched mTOR signalling. This discovery could have important implications for efforts to study conditions where mTOR signalling is disrupted in mouse and non-human primate-based models.

The impact of early fate decisions on forebrain size and organisation: from zebrafish to human culture and back

Professor Corinne Houart, Deputy Director of the Centre for Developmental Neurobiology, King's College London

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Key messages:
- The anterior neural border (ANB) signalling centre is conserved from fish to mouse.
- The timing of ANB induction influences the size of the telencephalon and its complexity.

Scientists seeking to understand when human brains become uniquely human have studied the processes that control the size and timing of development of the telencephalon, which includes the basal ganglia, cerebral cortex and hippocampus. Despite the widespread view that vertebrates are very similar in early development, the telencephalic field is already larger in a mouse than in a fish as early as the appearance of the neural plate, the structure that forms the early basis of the neural system. Professor Houart's research has explored how its relative size is controlled, and whether the amount of space it occupies in the early stages of development influences the size and complexity of the later telencephalon.

Over the last 10-15 years, researchers have used zebrafish to investigate the steps that lead to the allocation of territory inside the neural plate. Two signalling centres made up of groups of cells which secrete proteins that act on neighbouring cells, located at the anterior neural border (ANB) and the midbrain-hindbrain boundary (MHB) of the neural plate, are crucial to this process.

Less is known about the early stages of neural development in the mouse. Experiments on mouse embryos suggest there is a neural cell population that acts as an ANB. Professor Houart's group found that anterior ectoderm tissue transplanted from mice into zebrafish, whose ANBs had been removed, triggered the formation of telencephalic features, thereby showing that the mouse has a functionally equivalent ANB population.

The ANB and the MHB develop at the same time in zebrafish, whereas the ANB appears before the MHB in mice.

Professor Houart found that transplanting an ANB into the fish at an earlier stage of brain development led to the development of a larger telencephalon. These zebrafish formed bigger neural plate telencephalic fields, and had bigger embryonic and adult telencephalons containing sets of neurons that do not normally occur.

In ongoing work, Professor Houart is comparing mouse and human neural plate using tissue and neural plate in culture, derived from iPS cells, to learn more about early human brain development. Her work suggests the ANB plays a key role in the development of larger telencephalons, and therefore in the development of more complex brains.

Cellular plasticity in the development of the cerebral cortex

Professor Oscar Marin, Director of the MRC Centre for Neurodevelopmental Disorders and Centre for Developmental Neurobiology, King's College London

Key message:
- The number of interneurons in the mature brain is dependent on pyramidal cell activity levels. This is mediated through the regulation of PTEN protein in interneurons.

The cerebral cortex contains two main types of neurons:
- Pyramidal cells, which have a characteristic shape, are primarily excitatory and have wider connections within the brain.
- Interneurons, which have diverse morphologies, only local connections and are primarily inhibitory.

Strikingly, they occur in a conserved ratio of around 4:1 in different mammals with different sized brains.

Research in Professor Marin's laboratory has shown that two distinct and consecutive waves of apoptosis, or programmed cell death, for pyramidal and interneuron cells occur in mice in the days immediately following birth. Experimental interventions that increased or depressed pyramidal cell activity between five and 10 days after birth led to the mature cortex having correspondingly greater or smaller numbers of interneurons, respectively.

Bax and Bak proteins play a key role in apoptosis in pyramidal cells. However, mice in which Bax and Bak are deleted from pyramidal cells not only develop a cortex with more pyramidal cells than normal, but also more interneurons.

Professor Marin's group has shown that the number of interneurons in the mature brain depends on pyramidal cell numbers or their activity, and that this is mediated through the expression of the PTEN protein.[4] PTEN gene mutations are commonly found in people with autism spectrum disorders (ASD) who also have macrocephaly.

Professor Marin's group is also investigating what happens when a brain has too many pyramidal cells and interneurons, when the critical period for interneuron cell death in humans is, whether this period particularly sensitive to environmental insults, and whether PTEN mutations prevent apoptosis in the human brain.

Human brain development is often portrayed as a series of consecutive steps. However, Professor Marin's research supports an alternative model of networked and interrelated steps. This suggests that changes during development can lead to cascading defects due to the brain's normal homeostatic mechanism.

Selected poster flash talks – session 1

Dr Katherine Long, postdoctoral researcher, Max Planck Institute of Molecular Cell Biology and Genetics

- Adding extracellular matrix (ECM) proteins HAPLN1, lumican and collagen I, to human foetal neocortex tissue cultures was shown to induce folding in the cortical plate. This suggests the ECM plays an important role in cortical folding during human development.

Daniel Cromb, PhD student, King's College London

- Previous research has linked IGFBP7 gene variants to cerebral grey matter in babies born prematurely. In a study involving 185 pre-term infants, Cromb and colleagues confirmed this finding, and found the genetic variation to be associated with measures of cognition and motor ability at 20 months of age.

Dr Carla Silva, postdoctoral researcher, GIGA Neurosciences, University of Liège

- The CCP1 protein was shown to be the primary regulator of pauses observed in the migration of interneurons during development. Pause duration during migration regulates the number of interneurons reaching the cerebral cortex. This brain structure is able to scale-up the generation of projection neurons when supernumerary interneurons migrate towards cortical regions due to pause duration defects.

Dr Berta Terre, Postdoctoral researcher, The Francis Crick Institute

- Neural stem and progenitor cells (NPCs) have longer proliferative phases in humans compared to other mammals. Dr Terre is studying the expression of the MYCN gene in distinct NPC populations, characterising its role in extended NPC proliferation and seeking to identify human-specific mechanisms that regulate MYCN expression in NPCs.

Dr Michael Bloomfield, Excellence Fellow, University College London

- Dr Bloomfield's systematic review of how stress and trauma in childhood can affect the dopamine system in adulthood identified wide-ranging and long-term changes in dopaminergic function that could help explain how such experiences during development can increase the risk of mental health problems later in life.

Clarissa Catale, PhD student, Sapienza University of Rome

- In a preclinical model, we demonstrated that a brief exposure to an adverse social environment in early "critical" age induces permanent alteration in the structure and functionality of local circuits in the brain. This may denote pathological mechanisms underlying early life, stress-induced susceptibility to develop psychopathologies.

Alexandra Lautarescu, PhD student, King's College London

- A study of infants born prematurely found an association between prenatal stress in mothers and changes in the microstructure of the *uncinate fasciculus*, a white matter tract that connects limbic regions to the frontal lobe, in their offspring. This could explain behavioural and emotional problems

The synaptic origins of brain complexity

Professor Seth Grant FMedSci FRSE, Professor of Molecular Neuroscience, University of Edinburgh

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Key message:
- Behaviours are represented in maps of synapse diversity, rather than circuits of connected neurons. Synapse diversity changes across the lifespan.

Only relatively recently have scientists demonstrated that there are over 1,000 different proteins in the post-synaptic terminal. Mutations in these are involved in over 130 brain conditions. These proteins are assembled in complexes and super-complexes, which make up different types of synapses.

Professor Grant's group last year published the first single-synapse resolution molecular maps of the mouse brain.[5] Each of more than 300 regions and 800 sub-regions has a specific signature of synaptic subtypes, defined by different proteins as well as variations in synapse sizes, shapes and protein co-localisation.
Comparisons of different parts of the brain shows that the distribution of different synapse subtypes can be traced back to early neural patterning events.[6] There is a high degree of correlation between the synaptic composition of different areas of the brain and their levels of connectivity.

Synapses with different proteomes generate different post-synaptic patterns of activity, which change continuously according to their inputs. Information can be said to be written into the nervous system in the proteome of synapses. Professor Grant's research suggests that behaviours are represented in synapse diversity maps, rather than by circuits of connected neurons, as has been more traditionally believed.

Gene expression levels change with lifespan in a characteristic way. Changes in gene expression trajectories peak at the age of 26 for men and 27.5 for women.[7] The genes involved are highly enriched in post-synaptic proteomes, showing the young adult brain undergoes a major synaptic reorganisation.

Professor Grant's group has identified characteristic patterns of distribution of synapse subtypes in different brain regions over the lifespan, and greater levels of similarity of types of synapses between areas of the brain during old age than in young adult life.

These techniques could help identify synapses that are either vulnerable or resilient to specific protein mutations. Professor Grant's group is working to produce a map of synapse distribution in the human brain. If diseases cause synaptome reprogramming in characteristic ways, synaptome mapping could drive important advances in brain disease research.

The role of glial cells in synaptic development and maturation

Associate Professor Nicola Allen, Hearst Foundation Development Chair, Salk Institute for Biological Studies

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Key message:
- Astrocytes release glypican 4 and chordin-like 1 (CHRDL1) to regulate the formation and maturation of neuronal synapses.

Glial cells make up over half of the cells in the human brain, and of these most glial cells are astrocytes. Amongst other roles, astrocytes guide neuron and axon positioning, and regulate the timing of synapse formation in the developing brain.

Astrocytes also facilitate synaptic signal transmission. One of the ways they do this is by releasing molecules that regulate the levels of the AMPA glutamate receptors that neurons use to receive messages at synapses.

Professor Allen's group discovered that astrocytes release a protein called glypican 4 to increase surface levels of the GluA1

AMPA glutamate receptor and induce immature synapse formation.[8] As synapses mature in the developing cortex, there is increased recruitment of the GluA2 AMPA receptor subtype to the part of the neuron that receives signals from neighbouring neurons.

Professor Allen found that a sub-set of astrocytes release a protein called chordin-like 1 (CHRDL1) to trigger an increase in synaptic recruitment of GluA2 AMPA receptors. Professor Allen's group found CHRDL1 is expressed mainly in upper cortical layer astrocytes, and that its expression peaks when synapse maturation is occurring. Mice in the early postnatal phase missing the CHRDL1 gene had a reduction of synaptic levels of GluA2 AMPA receptors and enhanced plasticity in the development of the visual system.[9]

Other researchers have demonstrated that mutations in the CHRDL1 gene causes an eye disorder called X-linked megalocornea, and links have been made between up-regulation of CHRDL1 and both schizophrenia and bipolar disorder. The secretion of CHRDL1 by astrocytes is therefore believed to play a key role in synapse maturation during brain development by triggering increased GluA2 AMPA receptor recruitment.

To understand how the brain develops or goes wrong in developmental disorders, it is important to consider how glial cells interact with neurons, how they change over time, and how this impacts development.

Keynote – Big science approaches to the study of developing brain: how to best harness existing opportunities?

Dr Susan Weiss, Director of the Division of Extramural Research, National Institute on Drug Abuse, US National Institutes of Health (NIH)

Key messages:
- The ABCD study presents a unique opportunity to learn about the effects of adolescent experiences on brain development and behaviour.
- ABCD researchers are releasing data rapidly to encourage other scientists to make use of it, and providing resources to help those without backgrounds in statistics to so do.

The Adolescent Brain Cognitive Development (ABCD) study is a longitudinal study into factors that affect development and functional outcomes from the age of 9-10-years-old to early adulthood. Researchers at 21 sites across the US have recruited 11,878 children, including 2,104 from multiple births.

The study's scope includes the roles of: genetic and environment factors; physical activity; music and arts; screen time; sleep; sports and other injuries; the onset and progression of mental disorders; the effects of alcohol, marijuana, nicotine and caffeine and other substances on health and development.

New technologies and scientific advances mean researchers are better placed than ever to gain insights from the data ABCD is generating. Developments in non-invasive neuro-imaging make it easier to study the developing brain, while advances in big data informatics facilitate the use and sharing of the data collected. Meanwhile, laws on the availability of alcohol, marijuana, and tobacco, and the drug-use landscape, are changing rapidly in the US.

Some, mainly descriptive data from the first 4,500 subjects, at the ages of nine or 10, have been released. These data show, for example, that the more educated the parents, the greater the likelihood that their children take part in arts, music and sports, with the exception of American football, possibly because of concerns about it causing traumatic brain injuries. Initial findings include 8% of participants reporting symptoms of ADHD, around 5.5% showing signs of Oppositional Defiant Disorder, and some 6% having had some form of suicidal ideation. A modified version of a psychosis proneness questionnaire showed that those with a family history of psychosis were more likely to, for example, feel that they might have magical or telepathic powers, and to be distressed by such feelings. They also performed worse on tests of neuro-cognitive functions known to be affected in schizophrenia. If these measures are replicated, they could provide ways to identify those at risk and intervene earlier than currently.

Selected poster flash talks – session 2

Dr Harriet Cullen, Postdoctoral researcher, King's College London

- Genetic likelihood scores for Autism Spectrum Disorder (ASD) were calculated for a group of 139 preterm infants based on genetic variants identified as associated with ASD in a recent genome-wide association study. MRI scans showed increased genetic likelihood for ASD is associated with smaller lentiform nucleus volume in preterm infants, but no significant variation in the caudate nucleus, sub-thalamic nucleus or thalamus.

Dr Emily Brookes, Postdoctoral researcher, University College London

- The BDNF gene is down regulated in Rett syndrome. BDNF was shown to move away from the nuclear periphery during neuronal development and form a loop with another part of the genome, which appears to enhance its transcription. Disruption of this process may be important in Rett syndrome.

Anna Gui, PhD student, Birkbeck College, University of London

- Electroencephalography (EEG) recordings showed infants with emerging autism exhibited atypical neural responses when looking at faces. Patterns of transient semi-stable periods of brain activity called electrical microstates were linked with later social skills in infants with an older sibling with autism.

Dr Susanna Mierau, Lecturer, University of Cambridge

- Loss-of-function mutations in the MECP2 gene cause Rett syndrome and some cases of autism. Cultures of wild-type and Mecp2-deficient mouse cortical neurons develop spontaneous network activity. Machine learning is being used to identify when network dynamics emerge and how this is disrupted by Mecp2 deficiency.

Dr Heather Kitt, NIHR Clinical Academic Fellow, University of Liverpool

- A pilot study involving 100 babies was carried out to assess ways to identify neuro-developmental disorders earlier in low resource settings. The Malawi Developmental Assessment tool (MDAT) picked up fine motors problems; however, a more effective, yet still affordable, screening tool could be developed by adding parts of gold standard assessments used in developed settings.

Dr Patricia Garcez, Lecturer, Federal University of Rio de Janeiro

- Mouse model experiments show that maternal protein malnutrition is a co-factor in congenital Zika syndrome. Tests showed it suppresses the immune system, increases Zika virus load, allows Zika to cross the placenta to infect the developing brain, resulting in microcephaly in newborns.

Dr Joanne Doherty, PhD student, Cardiff University
- Magnetoencephalography was carried out on children with 22q11.2 deletion syndrome and unaffected siblings. The condition, which is associated with multiple developmental and psychiatric disorders, was linked to reductions in resting state brain connectivity. The size of the reductions was linked to the degree of anxiety and social communication problems of affected children.

Initial findings on screen time suggest that different types of screen time have different associations with both brain structure and behaviour.[10] Those engaging in certain types of screen time reported less physical activity and greater sleep disturbances and family conflict, yet those with greater social media activity had more physical activity, better sleep and less conflict within the family. There were also gender effects. The subject is important in relation to mental health, but research findings are often over-simplified when discussed more widely.

Study leaders are keen that ABCD data are used as a resource by the whole scientific community. Alongside the release of data on the first 4,500 participants in 2018, more than 9,000 images from brain scans have been made publicly available. The study's Data Analysis and Exploration Portal is designed to help those without experience in handling large and complex datasets or with limited statistics experience to use the information generated by the study. This open science approach represents a culture shift that is already bearing fruit: at the time of the meeting, seven studies had been published citing ABCD data, four by non-ABCD scientists.

The HEALthy Brain Child Development (HBCD) study is another large, multi-site longitudinal research project, which, like ABCD, is led by the NIH. Currently in the planning stage, it will study brain, cognitive, behavioural, social and emotional development beginning at birth and will include a focus on the impact of the US opioid epidemic. Researchers anticipate that studying pregnant mothers and newborns will present significant technical and ethical challenges. Large-scale longitudinal studies, like ABCD and HBCD, present unique opportunities to learn about how early events and experiences along with genetics affect brain development, behaviour and a wide variety of outcomes.

Keynote – The influence of the environment on the developing brain: A perspective from adult mental illness

Professor Peter Jones FMedSci, Deputy Head of the School of Clinical Medicine, University of Cambridge and Director, NIHR Collaboration for Leadership in Applied Health Research & Care East of England

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Key messages:
- Multiple environmental factors have major impacts on the risks of developing psychiatric disorders.
- Inflammation is a possible mediator of environmental impacts on psychiatric disorder risk.
- Research on mindfulness training for students provides an example of how a positive intervention can mitigate a negative environmental effect on mental health.

The term 'environment' can mean different things with reference to psychiatric disorders, including the environmental cues people use to make predictions, the broader external physical environment, and the brain's micro-environment. An individual's brain also plays a role in generating their environment through perception and the creation of meaning.

The contribution of genetics to the manifestation of schizophrenia has long been debated. However, a recent study into the incidence of new cases of schizophrenia in 17 settings in six European countries and one in Brazil, found large variations in incidence even after adjusting for confounding factors.[11] This suggests environmental factors most likely during childhood and adolescence – such as economic deprivation, migration, social disconnection, population density and drug use – play an important role in the onset of the disorder. Another recent study found as many as one in five new cases of schizophrenia might be attributable to the use of cannabis.

While the onset of schizophrenia typically occurs during the post-puberty period, and the second and third decades of life, the prenatal period, infancy and childhood are important in the establishment of risk factors. A birth cohort study carried out in Finland, for example, found those who only learnt to stand unsupported at 11 or 12 months of age or later were more likely to develop schizophrenia than those who did so by nine or 10 months.[12]

Multiple studies have found an association between those with higher childhood and adolescent IQ, and lower risk of diagnosis with schizophrenia later in life.[13] Bacterial and viral infections early in life have also been linked to greater risk of developing the condition in adulthood, as have recalled traumas such as emotional, physical and sexual abuse.[14, 15]

Inflammation has been proposed as a possible mediator of environmental impacts on the brain. People with psychotic disorders like schizophrenia die earlier than average, often of cardiovascular disease, which has its own inflammatory mechanisms. Psychotic and affective disorders themselves are pro-inflammatory. One study found nine-year-olds with elevated levels of the inflammatory marker interleukin-6 were more likely to develop psychotic disorders and depression at age 18.[16] There is also evidence of links between childhood trauma and later elevation of inflammatory markers, including interleukin-6.

In a randomised controlled study, Professor Jones showed that an eight-week mindfulness course early in the academic year could reduce stress levels in undergraduate students at exam time: those who received mindfulness training were less distressed when doing their exams than controls, suggesting it had improved their resilience.[17] While there is ample evidence that factors like drug use, economic deprivation and infections can increase the risks of mental illness, Professor Jones's work on mindfulness demonstrates environments can also be altered in ways that can improve mental health.

Keynote – Neurodevelopmental disorders: Integrative genomics reveal the developmental origins of neuropsychiatric conditions

Professor Daniel Geschwind, Director of the Center for Autism Research and Treatment (CART), Senior Associate Dean and Associate Vice Chancellor of Precision Health, University of California, Los Angeles

Key messages:
- Transcriptional networks can be used to identify the molecular pathology of neuropsychiatric disorders, inform disease modelling, and identify when and where risk genes are acting.
- Autism risk genes are highly expressed during early foetal brain development during the peak of neurogenesis, and are linked to transcriptional regulation and synaptic development.
- Genomics provides a foundation for interrogating the relevance of in vitro systems.

Autism is clinically and genetically heterogeneous, and often overlaps with other neurodevelopment disorders. It forms part of a continuum of normal variation in various dimensions, including language, social behaviour and repetitive-restrictive behaviour.

There is no single 'autism gene' responsible for the disorder; rather, large effect mutations and small effect common single nucleotide polymorphisms (SNPs) can disrupt neurodevelopment, which increase the risks of ASD. Genetic tests can identify almost 20% of mutations that are currently known to contribute to ASD. But genetic risk is heterogeneous; it is predicted that there are hundreds of rare genetic mutations that increase the risk of ASD, none of which account for more than 1% of cases. Many traits are the result of the combined effects of more than one mutation, and in some cases single mutations can influence more than one trait. This complex genetic background presents significant challenges for neurobiology and a mechanistic understanding of the pathophysiology.

Gene network analysis can help characterise the molecular pathology of neuropsychiatric disorders and provide a quantitative phenotype for cross-disorder comparisons. It can also inform disease modelling, reveal when and where risk genes are acting, and identify disease mechanisms.

Professor Geschwind's group used transcriptomic analysis to identify discrete modules of co-expressed genes associated with autism. Two thirds of cases showed up-regulation of microglia and astrocyte genes, and down-regulation of neuronal genes involved in vesicle transport and synaptic signalling.[18] The causal genes predominantly affected the neuronal component. Microglial up-regulation has been shown to be specific to ASD. Subsequent studies using other techniques have confirmed there is a shared molecular neuropathology for more than half of ASD cases.[19]

Professor Geschwind's group also used transcriptomic analysis as a quantitative molecular phenotype tool, in cases of autism, schizophrenia, bipolar disorder, depression, and alcoholism matched with controls. Significant gene expression overlap between ASD and both schizophrenia and bipolar disorder were shown. The degree of shared transcriptional

dysregulation between conditions was related to genetic correlations, suggesting a significant causal genetic component.[20] Professor Geschwind showed how it is possible to use other experimental paradigms at the microscopic and macroscopic levels, such as human functional magnetic resonance imaging (fMRI) resting-state datasets and brain gene expression datasets, to begin to understand what these altered patterns of gene expression might mean, suggesting that they are related to activity dependent gene expression programs.[21] This suggests that in future it will be possible to employ similar techniques to make links between gene expression patterns associated with disorders and the specific functions they represent.

Another recent study led by Professor Geschwind's group deployed RNA sequencing to brain tissue samples from more than 2,000 people, to highlight the transcriptional networks involved in schizophrenia, bipolar disorder and ASD in more detail, and to highlight the molecular pathways and cell types involved. Changes at the transcript isoform level, as opposed to the gene level, showed the greatest effect sizes and disease specificity. Together with genome-wide association studies, this research will facilitate the discovery of candidate risk genes.[22] Differences in gene networks involved in synaptic development, regulating gene expression, and the way cells, including neurons, package their DNA into the nucleus, were observed in autism. The risk genes were most highly expressed during the embryonic period around the time of synaptic development, and in the early postnatal period.

While associations between gene mutations and brain disorders have been identified, it can be difficult to place these mutations in functional networks with regard to how the brain develops. Better understanding of regulatory networks during neural cell lineage specification and cortical development is needed for this and for understanding how non-coding variation impacts brain development. Professor Geschwind's group developed a 3D map highlighting how gene regulation occurs via chromosome folding that brings regulatory regions into contact with target genes in a tissue-specific manner, and used this to identify multiple candidate risk genes for schizophrenia.[23] In a companion study, common genetic variants associated with educational attainment, intracranial volume and neuropsychiatric disease risks were found to be enriched within regulatory elements involved in cortical neurogenesis, showing the importance of the process for adult human cognitive function.[24] A genome-wide association study based on Danish health registries showed that the loci responsible for non-disease specific liability across major psychiatric disorders were driven by gene regulation during foetal neurodevelopment, again highlighting early development as a key window of vulnerability.[25]

Increasingly promising in vitro tools are being developed to model the effects of mutations in cell contexts. Gene networks can be used to validate them, by providing unbiased comparisons between these in vitro models and in vivo development. Professor Geschwind hopes in future to be able to identify brain disease mechanisms through a process of reverse engineering from large-scale genetic perturbation data via validation in model systems.

Studying human brain development and disease with stem cells

Professor Rick Livesey, Chair of Stem Cell Biology, UCL Great Ormond Street Institute of Child Health

Key message:
- Defects in neuronal cellular waste disposal systems that can be seen in early development are causes, not consequences, of the amyloid beta accumulation seen Alzheimer's disease.

While most Alzheimer's disease cases are sporadic, and have both multiple genetic and environmental causes, around 2% are familial or entirely genetic. The genes involved in familial Alzheimer's disease are expressed during development; however, pathology is not seen until patients are in their twenties. This delay offers important insights into the relationship between brain development and disease.

The primary gene mutations involved in familial Alzheimer's disease are in APP, which controls the expression of the amyloid precursor protein, and in PSEN1 and PSEN2, which regulate the processing of APP. Professor Livesey's group generated iPS cell-derived forebrain neurons from patients with mutations in these genes, and observed the production of longer amyloid beta peptide fragments, which are known to accumulate in the brains of people with Alzheimer's disease.[26] He identified pronounced defects in the lysosome and autophagy-based cellular waste disposal systems of early iPS cell-

derived neurons.[27] Inhibiting production of beta-secretase, one of two key enzymes involved in processing amyloid precursor protein, corrected lysosome and autophagy defects in APP, and PSEN1 mutant neurons, as did knocking out the APP gene in neurons with PSEN1 mutations. This suggests these defects in neuronal waste disposal systems, already seen in early development, are primary causes of Alzheimer's disease, not consequences of the characteristic protein accumulation seen in cases of the disease.

Professor Livesey and colleagues have also used single cell RNA sequencing, comparing frontal cortex cell nuclei from cases of early-onset familial Alzheimer's disease with controls. Medical text books generally highlight how the condition affects excitatory neurons, but spares the interneurons which create neural circuits. Professor Livesey's group found that, in fact, Alzheimer's disease also affects inhibitory interneurons. This is important, because around half of people with familial Alzheimer's disease have epilepsy or signs of it, and disruption of the balance between excitatory and inhibitory neurons is thought to be key in epilepsy.

Strategic brain mechanisms for lifelong learning and plasticity

Professor Zoe Kourtzi, Professor of Experimental Psychology and Deputy Head (Research) of the Department of Psychology, University of Cambridge

> *Key message:*
> - The use by the brain of different approaches to cognitive tasks and corresponding different regions, and its ability to re-organise in response to impairment, offers insights into its plasticity.

Humans have an amazing capacity to differentiate similar objects or find similarities between them in complex environments. Professor Kourtzi's group has investigated the role of gamma-aminobutyric acid (GABA) in learning and brain plasticity. She used magnetic resonance spectroscopy to show that learning-dependent changes in visual GABA were linked to improved ability to detect and discriminate between features.[28] Training on a target detection task involved local connectivity and disinhibition of the visual cortex. Training on a feature discrimination task involved inter-cortical interactions relating to suppressive visual processing.

Participants asked to predict which symbols would come next in increasingly complex sequences of symbols, were found to adopt one of two strategies. Those who tried to memorise the whole sequences learnt more slowly than those who sought to maximise their chances by taking more note of symbol frequency and probabilities.[29] These strategies involved different patterns of brain activity. Maximising chances engaged dorsolateral prefrontal, cingulate, sensory–motor regions, and basal ganglia (dorsal caudate, putamen). Memorising, or 'matching', engaged occipitotemporal regions, including the hippocampus, and basal ganglia (ventral caudate).

This shows the brain can use alternative routes to solve the same problem. Professor Kourtzi's group asked patients with mild cognitive impairment due to Alzheimer's disease, characterised by hippocampal dysfunction, to carry out a visual orientation prediction task. These participants were able to improve their performance, with brain imaging showing they were more likely to use frontal-striatal circuits, as opposed to those in the hippocampus in learning to improve their performance on the task, compared to age-matched controls.[30] This underlines how the brain is capable of re-organising to support life-long learning. It also offers insights into the role of brain plasticity in both normal and abnormal development.

The value of cohort and population studies in neurodevelopmental research

Professor Anita Thapar CBE FMedSci FLSW, Professor of Child and Adolescent Psychiatry, Cardiff University

> *Key message:*
> - Longitudinal birth cohorts can capture subjects before disorder onset, provide insights into the developmental origins and progression of disorders, detect changes in risk factor profiles and avoid clinical referral bias.

There is substantial overlap in symptoms and risk factors between child neurodevelopment disorders like ADHD, autism spectrum and learning disorders that typically onset in the early developmental period. There are improvements with age as those affected mature; however, longitudinal studies show many remain affected in adult life.

Around two-thirds of children with ADHD will either still have the disorder or exhibit at least some symptoms of it in adulthood. In a UK cohort, those with ADHD symptoms that persisted into adolescence had higher ADHD genetic risk scores than those who remitted, but did not have higher genetic risk scores for schizophrenia, bipolar disorder or depression.[31] Those with more than one neurodevelopmental disorder in childhood were also more likely to have persistent ADHD.

Schizophrenia typically onsets after adolescence. However, a recent cohort study observed that schizophrenia genetic liability was associated with social development and behaviour problems as early as age four, and cognitive, social communication and language difficulties from age seven.[32] This supports the hypothesis that childhood impairments that precede schizophrenia onset are likely to be early signs of underlying genetic liability.

Depression can present in adolescence or later. Cohort studies suggest that depression behaves differently at different ages. Similar proportions of boys and girls are diagnosed with depression in childhood; however, from middle adolescence onwards females are at greater risk. Treatment response also varies with age.

Genetic studies also suggest differences in aetiology across development. Early-onset depression appears to show greater genetic overlap with schizophrenia and bipolar disorder.[33] Population-cohort studies have also shown schizophrenia genetic risk scores are more strongly associated with emotional problems in childhood to mid-life, while depression genetic risk scores show more consistent associations later.

Longitudinal birth cohorts are invaluable as they can capture individuals before disorder onset, help researchers examine developmental changes and avoid clinical referral bias. Genetics, imaging and cognitive tasks can provide bridges from cohort studies to neuroscience. In future, increased depth of measures is needed in study cohorts, with more harmonisation of measures across childhood and adult life.

References

1. Hansen DV (2010), Neurogenic radial glia in the outer subventricular zone of human neocortex. Nature **464**, 554-561.

2. Bershteyn M (2017), Human iPSC-derived cerebral organoids model cellular features of lissencephaly and reveal prolonged mitosis of outer radial glia. Cell Stem Cell **20(4),** 435-449.

3. Shi Y (2017), Tumour-associated macrophages secrete pleiotrophin to promote PTPRZ1 signalling in glioblastoma stem cells for tumour growth. Nature Communications **8**, 15080.

4. Wong FK (2018), Pyramidal cell regulation of interneuron survival sculpts cortical networks. Nature **557**, 668–673.

5. Zhu F (2018), Architecture of the Mouse Brain Synaptome. Neuron **99(4)**, 781-799.

6. Ibid.

7. Skene NG (2017), A genomic lifespan program that reorganises the young adult brain is targeted in schizophrenia. eLife **6**, e17915

8. Allen NJ (2012), Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors. Nature **486(7403)**, 410-414.

9. Blanco-Suarez E (2018), Astrocyte-Secreted Chordin-like 1 Drives Synapse Maturation and Limits Plasticity by Increasing Synaptic GluA2 AMPA Receptors. Neuron **100(5)**, 1116-1132.

10. Paulus MP, et al. (2019) Screen media activity and brain structure in youth: evidence for diverse structural correlation networks from the ABCD study. NeuroImage **185**, 140-153.

11. Jongsma HE (2018), Treated Incidence of Psychotic Disorders in the Multinational EU-GEI Study. JAMA Psychiatry **75(1)**, 36-46.

12. Isohanni M (2001), Early developmental milestones in adult schizophrenia and other psychoses. A 31-year follow-up of the Northern Finland 1966 Birth Cohort. Schizophrenia Research **52(1-2)**,1-19.

13. Khandaker GM (2011), A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. Schizophrenia Research **132(2-3)**, 220-7.

14. Khandaker GM (2012), Childhood infection and adult schizophrenia: a meta-analysis of population-based studies. Schizophrenia Research **139(1-3)**, 161-8.

15. Varese F (2012), Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophrenia Bulletin **38(4)**,661-71.

16. Khandaker GM (2014), Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatry **1(10)**, 1121-8.

17. Galante J (2017), A mindfulness-based intervention to increase resilience to stress in university students (the Mindful Student Study): a pragmatic randomised controlled trial. Lancet Public Health **3(2)**, e72-e81.

18. Voineagu I (2011), Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature **474(7351)**, 380-4.

19. Parikshak NN (2016), Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. Nature **540(7633)**, 423-427.

20. Gandal MJ (2018), Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science **359(6376)**, 693-697.

21. Wang GZ (2015), Correspondence between Resting-State Activity and Brain Gene Expression. Neuron **88(4)**, 659-66.

22. Gandal MJ (2018), Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science **362(6420)**, eaat8127.

23. Who H (2016), Chromosome conformation elucidates regulatory relationships in developing human brain. Nature **538(7626)**, 523-527.

24. de la Torre-Ubieta L (2018), The Dynamic Landscape of Open Chromatin during Human Cortical Neurogenesis. Cell **172**, 289–304.

25. Spork AJ (2019), A genome-wide association study of shared risk across psychiatric disorders implicates gene regulation during fetal neurodevelopment. Nature Neuroscience **22(3)**, 353-361.

26. Moore S (2015), APP Metabolism Regulates Tau Proteostasis in Human Cerebral Cortex Neurons. Cell Reports **11(5)**, 689–696.

27. Hung OY (2018), Altered γ-Secretase Processing of APP Disrupts Lysosome and Autophagosome Function in Monogenic Alzheimer's Disease. Cell Reports **25(13)**, 3647-3660.

28. Frangou P (2019), Learning to optimize perceptual decisions through suppressive interactions in the human brain. Nature Communications **10**, 474.

29. Wang R (2017), Learning Predictive Statistics: Strategies and Brain Mechanisms. Journal of Neuroscience **37(35)**, 8412-8427.

30. Ludt CDB (2015), Learning temporal statistics for sensory predictions in mild cognitive impairment. Neuropsychologia **75**, 368-380.

31. Riglin L (2016), Association of Genetic Risk Variants With Attention-Deficit/Hyperactivity Disorder Trajectories in the General Population. JAMA Psychiatry **73(12)**, 1285-1292.

32. Riglin L (2017), Schizophrenia risk alleles and neurodevelopmental outcomes in childhood: a population-based cohort study. Lancet Psychiatry **4(1)**, 57-62.

33. Power RA (2017), Genome-wide Association for Major Depression Through Age at Onset Stratification: Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Biology Psychiatry **81(4)**, 325-335.

Neurodevelopmental research: key challenges and future priorities

Building on the speakers' presentations, participants discussed in groups some of the key challenges to research into both normal and pathological brain development, and into potential interventions to improve the lives of those affected by disorders. Each group contained a mix of researchers from across different disciplines and career stages to foster innovative, interdisciplinary thinking on tackling existing challenges and priority areas for future research.

Developing models

Animals

While important insights about brain function have come from experimental models like fish and mouse, animal models sometimes fail to capture complexity of human brain development. Extrapolating results from mice and other animal models to humans can therefore be misleading. More detailed understanding of animal brain development and improved measurement methods are required. Additional work on other species, such as non-human primates, is also needed. Collaboration across teams with expertise in different model systems (as described by Professor Houart in her talk) and additional validation of models with human data offer further ways to address these issues.

Computational methods

There is a need to move beyond simply describing what happens in the brain during development to understanding how brain function changes over time to promote the emergence of cognition. New computational methods and frameworks can provide improved mechanistic accounts of developmental and disease trajectories. Predictive models of development can be used and their validity tested. As these models become more complex and include a greater variety of data, statistical and bioinformatic expertise will become increasingly important and it is likely that progress in the handling of big data and in machine learning will provide major opportunities to drive research forward. Increasingly, successful research teams include members with deep expertise in computational models as well as others with a broad spectrum of skills. It is hoped that, in the future, advanced computational models will be able to integrate a range of different types of data to provide deeper insights. Given the variety of data needing integration, further planning is needed to configure analysis teams so that they can exploit the full potential of big data science to gain insights and support other lines of investigation nationally.

Organoids

Many traditional methods of modelling neurological development and disorders focus on the roles of individual cells, proteins, molecular pathways or genes. Brain organoids have become an increasingly popular way to study brain development. However, the processes involved are complex even in these relatively simple preparations and studying how different elements interact as part of a system is challenging. Fortunately, rapidly improving functional annotation of the genome and the increasing availability of unbiased methods for 'omics analyses provide new tool-kits for assessing the complexity of organoid development. Comparing the phenotypes of organoids from those with disorders with healthy controls can point to genes and pathways that contribute to disorders (as Professor Kriegstein outlined in his talk). They can also provide good models for early development, but current limitations include limited lifespans and connectivity, as well as lack of supportive elements such as vasculature. Care must be taken with the interpretation of findings from research using organoids, as results may not be reproducible in other systems, including in humans. Ethical concerns are increasingly likely to be expressed as more complex organoid models are developed.

Multi-method approaches

It is important to make use of multi-level methods, including molecular, cellular and systems neuroscience, as well as genetics and environmental influences. For example, research in the 1990s demonstrated that neglected children in Romanian orphanages suffered specific cognitive deficits, some of which were easier to recover from later in life, depending to a significant degree on the age at which fostering commenced. The studies provided important new insights; however, little is known about the biological pathways involved in these effects and variations. Researchers can validate their findings by integrating the results of studies that approach the same research question with a variety of experimental methods.

Improved understanding of physiological brain development requires both deep, detailed insights into the function of cells, networks and behaviours, obtained for example in animal models, and the broader framework provided by, for example, cross-species and longitudinal approaches.

The limitations of models

Modelling neurodevelopmental disorders is challenging, and is especially difficult in the case of polygenic conditions. Animal and cellular models often fail to account for disease variability, for example. Experimental models can have different levels of validity at molecular, cellular, connectivity and behavioural levels, and it is therefore important to select those that are most appropriate to the systems under investigation.

Modelling traits or symptoms may often be more appropriate than modelling disorders. One aspect of a particular psychiatric condition may be better modelled in a mouse and another in patient-derived cells, for example. Looking at traits or symptoms across disorders could help researchers select the best models.

Participants suggested that greater progress would be made if researchers focussed on how best to model the processes they are trying to understand, without necessarily relying on the techniques they are familiar with. Convergence of findings across models through, for example, parallel investigations in different organisms, is likely to be more informative than trying to develop perfect models, which rarely exist.

Studies across the lifespan

Measurement across the lifespan

There is a pressing need to study brain development at a population level across the lifespan to enhance our understanding of neurodevelopment in health and disease. Measures used must be relevant and meaningful to the populations being studied. These can change across the lifespan. Such work could address the need to improve understanding of the typical sequence of human neurodevelopment and normal variation.

The varying impact of different types of insult at different points of development needs consideration. The same brain injury can lead to aphasia in adults, but not in children, for example. Researchers also need to consider how risk factors can combine to shape trajectories across time, and take into account the impacts of other aspects of physical health on the brain, rather than looking at the brain in isolation.

Longitudinal studies

Despite being difficult to establish, longitudinal studies are required to bridge data gaps between childhood development, adulthood and old age. It is important that these studies include sensitive, well-validated measures of cognition, and in children and adolescents, measures of academic performance. Undertaking longitudinal research is usually expensive and generally requires large teams. Maintaining contact with participants in long-term studies can also be challenging. The organisational and incentive frameworks in which researchers operate can encourage silos that undermine the interdisciplinary collaboration that such research requires. Funding bodies should develop mechanisms to incentivise studies that span several decades, as the US NIH has done with the ABCD study (see Dr Susan Weiss's talk).

Critical and sensitive periods

There is general agreement among researchers that critical and sensitive periods exist, but more work (of the type described by Professor Marin in his talk) is needed to identify them and understand their underlying mechanisms. It would be beneficial to have more precise and consistent definitions of these periods in human populations and across species. One complication is that these periods appear to occur at different times in different people. Both genetic and environmental

variation can play a role in defining how 'critical' a critical period is, and could potentially influence when these periods occur. There are also practical and ethical issues around studying these periods experimentally in humans.

For mechanistic studies, we need to understand to what extent parallels can be made between different systems and models, such as between the visual systems of mice and humans, where much research has been carried out, to inform research on critical and sensitive periods. Greater brain plasticity during these periods can have different levels of influence on outcomes, depending on the systems involved. The identification of biomarkers of critical periods could help scientists go beyond the description of what goes wrong in pathology to potential interventions at relevant times.

Human brain tissue

A major gap affecting the ability to research the human brain is the difficulty in obtaining good quality brain tissue samples, especially from children and young adults. The establishment of a central registry of details of human tissue samples and improved access to postmortem brain tissue in biobanks would be valuable. There is also a need for more longitudinal research on human tissue at different biological scales. The establishment of baby and juvenile biobanks could help to address the need for improved understanding of normal development and variation. Insufficient research starts at the human level and validates findings using other experimental systems.

Improved access to human brain tissue would improve understanding of:
- The links between brain structure biomarkers and structural changes, and between behaviour and structural change.
- Key developmental times points, their triggers and their link to behavioural change.
- The physiological processes underlying human neurocognitive development and the variables that affect it.

Genes and the environment

Linking genes to neurodevelopmental disorders

More work is needed to connect variations in DNA associated with neurodevelopmental disorders in critical genes and intergenic regions. This will be facilitated by advances in the functional annotation of the genome and will help researchers link genes, biological pathways and processes of interest. Even in those disorders that are are caused by single gene mutations, multiple downstream pathways can be affected. Refining our understanding of these pathways and how they work together to cause or mitigate dysfunction is necessary for improved, more targeted treatments.

When considering interventions, it may be useful to look at circuits or networks that can be influenced in multiple ways, including by multiple genes (as Professor Geschwind outlined in his presentation). Epigenetic effects can vary by cell type, so appropriate tissue and cell types should be used when studying disorder mechanisms. The complex polygenic nature of genetic risk for some human neurodevelopmental disorders, for example autism spectrum disorders, poses challenges for mechanistic research using conventional disease models, which are often limited to studying the effects of disruption of a single gene. New cellular and organoid models can accommodate genetic complexity but have their own limitations. There is a need to link findings using these approaches to systems- and behavioural-level research in animals and humans.

A key question is whether it is always best to treat the underlying mechanisms of the disorder or the symptoms they cause. Some participants emphasised that genetic variation is not pathology. A society without neurological diversity, and its associated genetic diversity, would be a poorer society. People may not want to be 'cured' of their enhanced ability to spot patterns within data and better than average memory skills, for example.

The link between genetics and the environment

The accuracy of predicting the risk of developing neurodevelopmental disorders using genetic variation data could be enhanced by considering environmental factors, such as educational attainment and socio-economic status, for example. Genetic data could be used alongside other biomarkers to identify those who are most vulnerable to environmental risks. Cannabis use may pose greater risks for people of certain genetic profiles than for others, for example. This could allow for more targeted public health messages and, potentially, more targeted and effective treatments.

The incorporation of genomic data in epidemiological studies offers opportunities to make causal inferences, especially

when pooled data shows genotype-outcome correlates in multiple individuals. However, the demonstration of causation might also require experimental design in relevant animal or cellular models. Twin studies can also help disentangle genetic and environmental causal factors.

The role of the environment

Examples of environmental factors that impact on the developing brain include parenting styles, nutrition, parental substance use, social stress, socio-economic status, and, more recently, the use of electronic devices. Much of our existing knowledge is based on observational studies, which point to correlations rather than causation. More intervention studies are needed, ideally randomised controlled studies, to establish causal links between the environment and neurodevelopment, and to inform policy priorities. These should not be done at the expense of observational studies, which are also still required to identify potential risk factors for further evaluation. Some environmental factors have their effects prenatally, potentially making addressing secondary post-natal symptoms more practical than seeking to deal with primary symptoms in utero.

In future, more studies should have samples in multiple countries to highlight the impacts of different environmental settings on brain development. A recent example is the EU-Gene Environment Interactions study, which explored factors associated with rates of new cases of schizophrenia in 17 settings in six European countries and one in Brazil (see Professor Peter Jones's talk).

More research is needed to identify early diagnosis methods, based on biomarkers or high-risk behaviours, for example. The investigation of environmental factors should not just focus on negatives, but also seek to identify protective factors. The measures used in many observational studies are based on questionnaires. Such research could be improved through the use of other types of measures. These could include more population data, deeper phenotyping, and data from wearable devices and smartphone apps.

Prevention

Treatments for neurodevelopmental disorders will have greater efficacy if disorders are detected early. Children and adolescents in whom conditions are identified sooner are likely to have better life trajectories than those who are diagnosed later in life. Teachers are not trained in the biological aspects of neurodevelopment and health professions do not generally have training in education. There may be scope for more effective early intervention to protect brain development through addressing this disconnect as well as the current lack of research frameworks and infrastructure that would facilitate working across this border.

Some participants suggested 'prevention' of neurodevelopmental disorders may be seen as stigmatising in some contexts, and suggested 'ameliorating phenotypes' might be better perceived. The input of affected patients and families should be sought to shape the way such discussions are framed. There can also be issues around whether it is appropriate to wait for diagnosis before intervening, or intervening when there is indication of risk.

Data-driven research

Better use of existing data

The additional data required to inform better lifespan research could come through increased data sharing, and greater use of existing health and education datasets. The UK is well positioned to use linkage to national records as proxy to efficiently incorporate outcomes. Access to NHS data can be challenging. Some participants suggested that introducing opting-out of enabling the use of data for research rather than opting-in might help with the volume and diversity of data required for research. Improved understanding of the implications of the EU's General Data Protection Regulation (GDPR) by the research community is also required. Notwithstanding these difficulties, there are tremendous opportunities in the UK to establish a biobank of samples collected from children linked to routinely collected data, such as NHS records, given the existence of the NHS and the investment in big data approaches such as the NIHR BioResource.

Data need to be standardised and methods of data collection improved to maximise the benefits from population and cohort studies. This could be facilitated through early collaborations between those who design studies and those who analyse them, including biologists, mathematicians and computer scientists. Multidisciplinary approaches are required to produce databases that can integrate genomic data, neuroimaging data, social parameters, electronic health records and clinical

information. Integration across disciplines is also needed. Systematic reviews, meta-analyses and new technologies, such as artificial intelligence, present opportunities to make better use of existing data sets.

New data and methods
Access to new databases for researchers should be streamlined subject to appropriate ethical safeguards. They should also be designed for use across global regions, including both high and low resource use settings. Protocols should ideally include both low and high fidelity techniques, to allow the inclusion and integration of data sets from these different settings.

One of the challenges is that the scientific community is learning how to use big data in meaningful ways at the same time as new methodologies for undertaking the studies to generate the data are being developed. Improved training for those in both junior and senior positions will be important as research into brain development becomes more data rich and as analytic methods improve.

Driving forward progress though data-driven approaches may require working with big technology companies to optimise outputs. Public concerns about privacy, data confidentiality and the commercial use of data therefore need to be addressed.[34]

Diversity

Gender
There are numerous examples of gender differences in the incidence and symptom profiles of neurodevelopmental conditions. For example, most neurodevelopmental conditions are more common in males and the average age of onset of schizophrenia is later in women than in men. However, it has been suggested that the greater incidence of autism among males might be partly attributable to under-diagnosis in females. Similar proportions of boys and girls are diagnosed with depression, although females are at greater risk from middle adolescence onwards. Suggested explanations for this include differences in brain development, hormones linked to puberty, post-puberty social environments, emotional expression and awareness, social evaluation, and male-female variations in patterns of gene expression at different ages.

Researchers should become more aware of these differences and other gender-based impacts in their research. Participants highlighted the problem of studies with male-only or primarily male subjects, and suggested there is a need for tools that make it clearer when this is the case. Diagnosis tools developed to recognise pathologies primarily in males also need to be updated to better recognise gender specificities.

Ethnic, geographical and socio-economic diversity
The high proportion of male participants (adults and children) in neurodevelopmental research is not the only sphere in which the field lacks diversity. Participants highlighted the need for experimental designs that represent populations that are ethnically, geographically and socio-economically more diverse. Studies with only narrowly representative participants are limited in their applicability. Having population samples in multiple countries, for example, allows for greater comparison of different environments and provides improved confidence in findings associated with the impacts of environmental factors on brain development (see the EU-Gene Environment Interactions study on the key determinants of schizophrenia highlighted in the section above on 'The role of the environment').

Multidisciplinary collaboration
Research environments still frequently encourage a fragmented approach that can prevent scientists from having a broader overview of the field. Participants repeatedly noted how they generally worked in silos of various types, such as academic disciplines, experimental techniques and developmental periods. When trying to tackle subjects that require an understanding of development across the lifespan or the relevance of critical and sensitive periods for example, information from a wide range of sources, such as genetic studies, biobanks, medical and educational records and big data-based research, is relevant. Recent years have seen a growing emphasis on the need for multidisciplinary and interdisciplinary collaboration. Progress has been made, yet more needs to be done by academic institutions, funding bodies and others to enable this type of approach. The US NIH-led ABCD study of the effects of adolescent experiences on brain development and behaviour (see Dr Susan Weiss's talk) is an example of multidisciplinary good practice.

Working across sectors

Greater collaboration across sectors is also needed. Clinicians can play a vital role in informing research priorities to ensure they address unmet clinical need. Bridging gaps between education and health professionals could provide opportunities for earlier intervention to protect brain development. Further opportunities for those wishing to address neurodevelopmental problems from different perspectives to come together and discuss research opportunities are needed.

Greater openness

More open approaches

The lack of reproducibility of some research findings remains problematic and is exacerbated by the difficulty in publishing so-called 'negative' results. Pre-registration of studies is one potential solution, whereby the introduction, hypotheses, methods and analysis plans are approved by a journal before the experiment is carried out, with a strong guarantee of publication regardless of whether the study's findings are 'positive' or 'negative'. However, it was agreed that neurodevelopmental researchers need to develop further mechanisms to ensure future experimental studies are relevant, valid and reproducible. Participants suggested advances could be made through the adoption of 'open science' approaches and principles. These could include the use of common and transparent methods, common controls and shared materials, data harmonisation and the sharing of information across groups. Working in open and convergent ways can have a range of benefits, including driving more rapid scientific progress, ensuring research is made more accessible to the public and making sure researchers receive the credit they deserve for their work. Working with publishers that emphasise the importance of more open approaches, such as F1000 Research, would help to enhance the reproducibility of research and increase the dissemination of research findings.

The ABCD study provides another example here, with its open and collaborative approach, including the active encouragement of the use of ABCD data by external researchers to advance their work (see Dr Susan Weiss's talk).

Public engagement and involvement

Researchers need to better engage patients and the public in their work to ensure that research is informed by patient priorities and responds to an unmet need, and that study designs involving human participants are appropriately tailored. They also need to explain the benefits of allowing researchers to use patient data in research and help to allay public concerns about privacy and confidentiality. Such engagement activities could include giving talks in schools, creating exhibitions, blogging, presenting research on YouTube and talking to policymakers.

One particular challenge that was highlighted at the meeting concerned participants dropping out of longitudinal studies over time. Additional ways to encourage them to continue their involvement are required. For example, ABCD subjects receive birthday cards from the research team and are invited to social events linked to the study to encourage continued participation (see Dr Susan Weiss's talk). Participants suggested that taking research to people, rather than expecting them to attend clinics or laboratories to take part, could be another way to encourage greater public involvement while also improving study population diversity.

References

34. https://understandingpatientdata.org.uk/

Conclusion

'The developing brain in health and disease' scientific meeting was deliberately broad in its focus, bringing together scientists at different career stages from a range of clinical and non-clinical disciplines, as well as funders and publishers. The discussions were vibrant and wide-ranging, with the following points and priorities emerging from the conversations:

- Enhanced animal and cellular models of both normal and pathological neurodevelopment are needed, alongside improved efforts to validate them against human research. Despite their current limitations, brain organoids provide an emerging and promising way to model neurological development. Investigating key questions using different experimental models and types of research will help validate findings.
- Improved understanding of normal human development and variation is another important priority area. More longitudinal studies by multidisciplinary teams to study brain development across the lifespan are required.
- Additional work on human tissue and greater access to biobanks are needed, especially those housing samples taken from children and young adult. Linking a national biobank of samples from children with medical records and other data could drive research progress. It would comprise a unique asset to UK research.
- Appropriate cell and tissue types should be used when investigating the mechanisms behind neurodevelopmental disorders. More intervention studies are needed to inform policy priorities. There is also a need for further research on environmental drivers, including drivers of positive development, especially in children and adolescents.
- Better use of existing data and increased data sharing is required. The benefits could be maximised through improved data standardisation and collection. Increased collaboration between those who design and analyse studies is also needed. Computational neuroscientists will continue to be of increasing importance. Researchers at all career levels need improved training on how to harness the potential of AI.
- Researchers should pay greater attention to the way neurodevelopment conditions affect males and females. Populations from different locations, ethnicities and socio-economic backgrounds should be represented in studies. More multidisciplinary collaborations are needed, as are projects that involve partnerships between those in different sectors, such as scientists, clinicians, educationalists and industry representatives.
- Greater openness in research can help address challenges such as reproducibility. Patient and public engagement is important in tailoring research to patients and responding to unmet clinical need, as well as spreading messages about the value of research. Researchers have an important voice in allaying and helping to address ethical considerations, as well as privacy and confidentiality concerns.

The meeting aimed to stimulate the generation of holistic ideas for a greater understanding of normal brain development and neurodevelopmental disorders, in view of laying the foundations for advances that could ultimately lead to improved healthy brain development, cognition and wellbeing. Convening individuals from different research backgrounds to hear about a broad range of cutting-edge research, discuss current challenges, think about solutions and propose future research priorities proved to be an innovative and fruitful approach. The value in the experience was underlined by the widespread enthusiasm for participants to organise a similar multidisciplinary event in the near future.

Annex 1: Steering Group for 'The developing brain in health and disease'

This meeting was developed by (affiliations correct at the time of the meeting):

Professor Sir Michael Owen FMedSci FLSW [co-Chair], Director of MRC Centre for Neuropsychiatric Genetics and Genomics; Director/Clinical Professor, Division of Psychological Medicine and Clinical Neuroscience; and Emeritus Director of the Neuroscience and Mental Health Research Institute, Cardiff University

Professor Kate Storey FRSE FMedSci [co-Chair], Head, Division of Cell and Developmental Biology, and Chair of Neural Development, University of Dundee

Professor Sarah-Jayne Blakemore FBA, Professor of Cognitive Neuroscience and Deputy Director of the UCL Institute of Cognitive Neuroscience, University College London

Dr François Guillemot FMedSci, Head of Division of Molecular Neurobiology, The Francis Crick Institute, and President of the International Society for Developmental Neuroscience

Professor David Rowitch FMedSci, Joint appointment as Professor and Head of Paediatrics, University of Cambridge, and Professor of Pediatrics and Neurological Surgery, UC San Francisco

Professor Barbara Sahakian FBA FMedSci, Professor of Clinical Neuropsychology, University of Cambridge; President of the International Neuroethics Society; and Honorary Clinical Psychologist, Addenbrooke's Hospital, Cambridge

The Academy is grateful for their guidance and input.

Annex 2: Programme for 'The developing brain in health and disease' scientific meeting

19 March 2019 Brain development – From early embryo to adolescence

09:00   Registration

Session 1 – Chaired by Professor Sir Robert Lechler PMedSci, President, Academy of Medical Sciences

09:30   Welcome and Programme outline
Professor Sir Robert Lechler PMedSci, President, Academy of Medical Sciences

09:40   **Keynote - The evolution of brain development – mechanisms underlying the human-specific increase in brain size and complexity**
Professor Arnold Kriegstein, Director of the Developmental and Stem Cell Biology Program, University of California, San Francisco

10:20   Experimental models to study brain development: pros and cons of *in vivo* animal models and *in vitro* human models
Professor Corinne Houart, Deputy Director of the Centre for Developmental Neurobiology, King's College London

10:45   Selected poster 'flash talks'

11:00   **Refreshment break**

Session 2 – Chaired by Professor Sarah-Jayne Blakemore FBA, Deputy Director of the UCL Institute of Cognitive Neuroscience, University College London

11:25   Cellular and synaptic plasticity in the development of the cerebral cortex
Professor Oscar Marin, Director, MRC Centre for Neurodevelopmental Disorders and Centre for Developmental Neurobiology, King's College London

11:50   Closing the gap between genes, brain, cognition and behaviour
Professor Seth Grant FMedSci FRSE, Professor of Molecular Neuroscience, University of Edinburgh

12:15   Periods of increased sensitivity and vulnerability in brain development
Professor Nicola Allen, Hearst Foundation Development Chair, Salk Institute

12:40   Selected poster 'flash talks'

12:55   **Lunch with poster session**

Session 3 – Chaired by Professor David Rowitch FMedSci, Professor and Head of Paediatrics, University of Cambridge

14:25 Breakout sessions (refreshments served)
1. What are the main challenges and opportunities for experimental studies of brain development in animals and cellular models? *What are the key priorities for research?*
2. What are the major gaps in our understanding of normal human brain structural, behavioural and cognitive development? *What are the key priorities for research in human subjects?*
3. How does knowledge of critical and sensitive periods inform research into neurodevelopmental disorders? *What are the key priorities for research?*
4. How can we study development more effectively across the lifespan? *What are the key priorities for research?*

16:45 Feedback from the breakout sessions and panel discussion

17:15 Keynote – Big science approaches to the study of developing brain – how to best harness existing opportunities?
Dr Susan Weiss, Director of the Division of Extramural Research at the National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH)

18:00 Drinks reception

19:00 Dinner

20 March 2019 Neurodevelopmental disorders

Session 4 – Chaired by Professor Kate Storey FMedSci FRSE, Head of the Division of Cell and Developmental Biology, University of Dundee

09:00 Welcome and programme outline

09:10 Keynote – The influence of the environment on the developing brain
Professor Peter Jones FMedSci, Deputy Head of the School of Clinical Medicine, University of Cambridge and Director, NIHR Collaboration for Leadership in Applied Health Research & Care East of England

09:50 Deciphering the aetiology of early development disorders
Professor Matthew State, Chair of the Department of Psychiatry and Director of the Langley Porter Psychiatric Institute and Hospital, University of California, San Francisco

10:15 Refreshment break

Session 5 – Chaired by Dr François Guillemot FMedSci, Head of Division of Molecular Neurobiology, The Francis Crick Institute

10:45   Modelling neurodevelopmental disorders to study pathologic brain development
Professor Rick Livesey, Wellcome Trust Senior Investigator, University of Cambridge

11:10   Brain plasticity and cognition
Professor Zoe Kourtzi, Professor of Experimental Psychology and Deputy Head (Research) of the Department of Psychology, University of Cambridge

11:35   Child neurodevelopmental disorders: using cohorts and population studies.
Professor Anita Thapar CBE FMedSci FLSW, Professor of Child and Adolescent Psychiatry, Cardiff University

12:00   **Lunch with poster session**

Session 6 – Chaired by Professor Sir Mike Owen FLSW FMedSci, Director of the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University

13:15   Breakout sessions (refreshments served)
1. What are the implications of recent genetic findings in neurodevelopmental disorders for research into disease mechanisms and treatment? *What are the new directions for research?*
2. How can we leverage the potential of Big Data from population and cohort studies to understand neurodevelopmental disorders? *What new study designs and databases are needed?*
3. Can we prevent neurodevelopmental disorders? What are the major environmental factors that impact on the developing brain? *What are the new directions for research and policy?*
4. Can we develop valid models of neurodevelopmental disorders? *What should we model and how can we do it?*

15:35   Feedback from the breakout sessions and panel discussion

16:05   **Keynote – Neurodevelopmental disorders: Integrative omics approaches and beyond**
Professor Daniel Geschwind, Director of the Center for Autism Research and Treatment (CART), University of California, Los Angeles

16:45   **Closing remarks**

17:00   **Close**

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