THE BRIDGE

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What does a CAMHS MDT need to know about the genetics of psychiatric disorder?

Identifying imaging biomarkers in the neonatal brain

Plus
Research digests from JCPP and CAMH

Editorial

The Bridge Editor, Dr Juliette Kennedy

Welcome to this Neuroscience themed edition of The Bridge.

The Royal College of Psychiatrists is currently promoting the neurosciences in its curriculum, for training Psychiatrists of the future. One of the many reasons for this is to develop more "Parity of Esteem" between physical and mental health conditions, by highlighting the research evidence that links genetics and a range of neuroscientific findings, to the psychiatric disorders we see in young people.

I attended the third RCPsych Gatsby/Wellcome Neuroscience Conference in the spring of this year and two of the speakers kindly agreed to write for The Bridge. Prof Sir Mike Owen's team (Doherty and Eyre) have written for us their view on "What does a CAMHS MDT need to know about the genetics of psychiatric disorder?". Professor John Quinn and his team (Quinn and Bubb) have written a piece describing the importance of "A Mother's touch" in the development of the baby's brain. These are very readable summaries on the emerging field in genetics, epigenetics and development and also how neuroscience might help us in future clinical practice.

Prof Thomas et al's Annual Research Review into the link between neuroscience and learning is also summarised here. They describe how neuroscience and the psychology of learning might fit together and the importance of "Brain Health" in the classroom. Schmidt et al's study examines the link between EEG tracing, salivary cortisol and anxiety in children, and is summarised here. In 2018, Dafnis Batalle et al. compiled an Annual Research Review where they evaluated the current status of neuroimaging research in neonates and paediatrics to determine the origins of neuropsychiatric and neurodevelopmental disorders.

Genetics and the neurosciences is a rapidly developing field that can feel complex and difficult to understand for non specialists. In the future, workers in CAMHS services may need support in developing skills in genetic understanding, communicating with young people and their families about genetic risk and resilience, and in offering potential future therapeutics, all underpinned by genetic and other neuroscientific understanding. I do hope you find this edition helpful.

A mother's touch: a key player in fine tuning the function of our genome

By John P Quinn & Vivien J Bubb

Professor John Quinn and Dr Vivien Bubb are both in the Department of Molecular & Clinical Pharmacology at the University of Liverpool. Their work is focussed on mechanisms that cause cellular dysfunction in the nervous system. Professor Quinn has a PhD in Virology from the University of Glasgow and is currently the Chair of Neurobiology at the University of Liverpool. Dr Bubb obtained her PhD in Experimental Pathology from the University of Georgetown and is currently a research fellow.

There is debate as to the importance of genetics in determining our behaviour. This debate has become enshrined perhaps due to the early focus of genetics on searching for DNA variation in our genome (termed a polymorphism) that affected protein structure, the hypothesis being that such a protein variant would not be working optimally in our body throughout our life. However, the vast number of polymorphisms discovered to date correlating with behavioural or psychiatric conditions are not in the DNA encoding for protein, but rather in that part of our genome that determines how much, for how long, or in which cells a protein is made. Our environment (chemical, psychological and physiological) regulates the function of these regulatory domains. This has led to the Gene x Environment model (GxE), in which it is proposed that regulatory domains in our genome sense the signalling changes resulting from variation in the environment, which then triggers these domains to modulate the levels of proteins produced: many of these proteins in the brain will be neurotransmitters[1]. The resulting changes in the complement of proteins in the brain will alter the neurochemistry and thus behaviour. The DNA polymorphisms in these regulatory domains determines in part the strength of response to our environment giving us each our 'unique' neurochemistry. Much of this GxE interplay can be considered a response to normal life experiences. These mechanisms have been well characterised in rodent models and subsequently extrapolated to human studies.

A key time for the brain to be affected by the environment is during foetal and/or early childhood development. The role of the mother in supplying the chemicals (placental exchange/early nutrition) and psychological support (touch/stroking) has been demonstrated to modulate behaviour. As our neurons are developing and forming neuronal interactions (hard wiring) in the foetus, infant and young child, any environmental challenge could be argued to have profound effects on behaviour not only in the short term, such as in conduct disorder, but also later in life for a range of behavioural conditions, for example schizophrenia. Indeed, a developmental origin for many psychiatric conditions has been postulated. It is clear that directing support for mother and child would be key to promoting lifelong wellbeing and good mental health.

We can gain insight into the mechanisms underpinning childhood behaviour and the role of the mother from both rodent and human studies. For example, licking and grooming in rodents could be considered similar to human mother/child bonding activities such as stroking. In both scenarios, these actions are, in part, regulating serotonin pathways, a well-characterised neurotransmitter modulating behaviour not only in children but adults. Levels of serotonin are modulated by polymorphism, in a key regulator of levels of the neurotransmitter, monoamine oxidase A (MAOA), in children this GxE interaction (MAOA genetic variation x maternal stroking) can be correlated with temperamental traits such as anger proneness[2].

In general, variations in a specific regulatory domain can vary from being common, to being present in only a few percent of the population; however, some polymorphisms harbour a larger genetic risk for a behavioural disorder than others. Clearly therefore our own genetic signature will influence how we each respond to a similar challenge; this can be a good thing and gives us in part our individuality. Similarly, the strength of an environmental challenge (good or bad) can affect the same pathways resulting in different levels of neurochemistry. Therefore balancing this combinational effect of genetic signature with environment will be a key parameter in how we mature as adults.

In the short term the GxE interplay allows us to adapt and respond to normal life events, however in response to an inappropriate environment or traumatic stress, the brain will respond by changing how we utilise these normal regulatory mechanisms in the medium to long term, to protect us from sensory damage. One major modulator of long-term change is epigenetic variation. The simplest form of epigenetic modulation is adding or removing chemical groups (methyl groups) to the regulatory DNA to make that DNA more or less accessible to the proteins in the signalling pathways, thus the DNA's response becomes altered to the signalling cues. The conundrum is that these epigenetic changes could remain on the DNA for a long time, even after cessation of the trauma, thus altering behaviour in the long term[3]. However, the more we learn about epigenetics, the more likely it is we will become able to determine the best strategies, to recover our optimal response to environmental challenges after such chemical changes to the genome (it has been shown in many models that epigenetic changes are reversible without damage to the DNA).

As we would all acknowledge, a nurturing environment is beneficial and the simple act of stroking could have a profound effect at the molecular and genetic level on shaping behaviour. Of course, in humans it is unlikely that when a mother (or indeed parent or carer) strokes a baby that this is not the only sensory benefit to the child, it also encompasses eye contact and skin warmth amongst many other factors which could have an effect at the molecular level. All of these could act to alter the activity of our genetic signature, thus affecting our neurochemistry.

Neuroscience is opening up new windows on how parental interactions can shape our biology. One emerging area, which surely is deserving of more research, is how maternal care impacts on the activity, of what the media has termed , 'jumping genes'. These jumping genes, many of which have regulatory domains in them, can copy and paste themselves into new locations in the genome of cells within the brain and a major focus in CNS health is their action in ageing and neurodegeneration. A high profile study in rodents in 2018 demonstrated that jumping gene activity in the brains of littermates can be modified by maternal care[4]. If this finding was replicated in humans it would have significant implications for the long-term development of the baby into adulthood. We know little about the biological or psychological significance of such genome alterations for the individual.

Therefore, biology and genetics research has shown us some of the underlying mechanisms that could be said to support the old adage that we all need a cuddle now and then, and this is possibly never truer than when we are babies and young children. Due to differences in the composition of our genome, some of us may need more cuddles than others to obtain the same neurochemical benefit for good mental health not only as children, but to prime our brains for dealing with life challenges as adults.

Key points:

- Nature and nurture combine to shape the individual and our wellbeing, this is in part by modulating the function of DNA
- The simple act of parental touch and contact can act on the neurochemistry of a child's brain.
- How a child responds to their life events will in part be directed by their own personal genetic signature (DNA variation)
- In many ways this 'nature and nurture' synergy is reflected in the personalised medicine revolution now taking place in so many aspects of health which targets an individual's unique features of their DNA.

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Coupled delta-beta wave activity might predict social anxiety in children

By Dr Jessica Edwards

Oscillations in frontal brain activity can be categorised as slow (delta) or fast (beta) waves that have different functional and behavioural correlates. Recording these waves by electroencephalography (EEG) has shown that coupled delta-wave and beta-wave oscillations might be a correlate of higher neuroendocrine (namely cortisol) activity and social anxiety in adults;[1] whether this is the case in children, however, is unclear. Now, researchers from McMaster University, Canada, have examined whether individual differences in salivary cortisol levels at baseline and parent-reported social anxiety levels are associated with resting, coupled delta–beta frontal wave activity.

They collected EEG recordings from 50 children with a mean age of 7.59 years and collated the data with basal salivary cortisol and social anxiety levels collected at two time points, separated by 1 year. They found that stably high basal salivary cortisol levels and social anxiety across the two time-points, were independently associated with relatively high, correlated delta–beta-wave activity.

The researchers propose that such neural oscillatory patterns may help identify children at risk for stable avoidance and fear-related profiles. They consider that future studies should extend such longitudinal analyses of coupled delta–beta-wave activity, starting from early childhood to better understand the value of coupled delta–beta-wave activity in predicting social and emotional development in children. Furthermore, work is needed to explore the future potential of psychological interventions on these correlations to reduce social anxiety in both adults and children.

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Glossary:

Electroencephalography (EEG): a non-invasive, electrophysiological method to record electrical activity generated by synchronised neurons in the brain.

Cortisol: a glucocorticoid-class steroid hormone made in the adrenal gland and controlled by the hypothalamus, pituitary gland and adrenal gland. Often referred to as the "stress hormone", cortisol is typically released during stress, but also helps regulate blood sugar levels, metabolism and inflammation.

Delta wave: a high-amplitude wave produced in the brain, with a low oscillation frequency of ~0.5-4 hertz. Delta-wave activity is typically associated with stage 3 NREM sleep.

Beta wave: a low-amplitude wave produced in the brain, with a high oscillation frequency of ~12.5-30 hertz. Beta wave activity is typically associated with wakefulness.

Identifying imaging biomarkers in the neonatal brain

By Dr Jessica Edwards

The past decade has seen great improvements in magnetic resonance imaging technologies, such that it is now possible to image the developing brain in utero. In 2018, Dafnis Batalle and colleagues compiled an Annual Research Review for the Journal of Child Psychology and Psychiatry, where they evaluated the current status of neuroimaging research in neonates and paediatrics to determine the origins of neuropsychiatric and neurodevelopmental disorders.

The researchers highlighted some interesting points regarding the effects of preterm birth on neurological, behavioural and cognitive outcomes. Numerous imaging studies have shown that white matter[1] and cortical connectivity abnormalities[2] in preterm babies might be associated with late language development and impaired cognitive performance in children, respectively. They also outlined some of the recent studies that have started to identify putative infant brain markers that might be associated with neurodevelopmental disorders. Most advances have been in autism, where such markers might include cortical surface area expansion[3] and increased extra-axial cerebral spinal fluid volume[4]. Batalle et al. urge caution, however, when translating such neurodevelopmental "risk factors" to a complex pathological phenotype such as autism. Many of the studies to date have focused on at-risk subgroups of children, and it is unclear whether imaging findings can be applied to broader groups. In addition, imaging biomarkers of neurodevelopmental disorders typically have a small effect size and thus much larger, longitudinal cohort studies are needed to derive truly empirical evidence.

Predicting true behavioural or disease outcomes from brain imaging data is clearly a challenge. Batalle et al. are reassured, however, that the expansion of neonatal neuroimaging research over recent years reflects the increased awareness that psychiatric diseases might be better described as disorders of brain development.

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Neuroscientific insight can boost learning: neuro-fact or neuro-fiction?

By Dr Jessica Edwards

Earlier this year, Professor Michael Thomas and colleagues compiled an Annual Research Review for the Journal of Child Psychology and Psychiatry, highlighting the contributions that neuroscience can make to understanding learning and classroom teaching. Here, we summarise their main findings, the current challenges to the field and the future of educational neuroscience.

Educational neuroscience is based on the principle that understanding the neural mechanisms underlying learning may inform classroom teaching practice and policy. Since its inception in the 1990s, however, the concept of educational neuroscience has been the subject of heated debate. While teachers generally seem enthusiastic about the links between the brain and learning mechanisms, understanding does not always align with the science (so-called 'neuromyths'). For example, numerous companies now sell 'brain training' materials that use neuroscience merely as window-dressing. In addition, some in the education and psychology fields are resistant to such an inter-disciplinary approach to understanding learning, seeing neuroscience as reductionist or too remote from the classroom.

In rebuttal to this debate, Thomas et al. propose that a purely psychological approach to education that ignores neuroscience poses a risk to educational practice and learning development. Critically, psychology continues to use theoretical concepts that are at odds with how the brain works. "The brain seems to use specific circuits to support the content of learning, and so when one trains on one task, there is little transfer to very different tasks;[1] additional training on transfer activities (so-called meta-cognitive skills) is needed to apply skills to new situations", explains Thomas. "Psychology, by contrast, continues to use theoretical ideas involving general-purpose computing devices ('working memory', 'attention') and hypothesises that training on certain skills will produce very general benefits". This latter concept, however, has not been sufficiently supported by empirical evidence.[1]

The key message presented by Thomas and colleagues in their review, is that neuroscience can in fact interact with education in two main ways: either through psychology — where an understanding of brain mechanisms helps to improve psychological theories of learning — or directly, through conceptions of brain health (Figure 1, see page 9). In terms of this direct route, they rationalise that although the brain supports the mind, it is also a biological organ with certain metabolic needs (e.g. nutrition, energy supply) and vulnerabilities (e.g. to stress, lack of sleep, environmental pollution).

This direct pathway between neuroscience and education revolves around putting the child in the classroom in the best position to learn. To do so, Thomas et al. explain that educational outcomes need to be thought of in terms of the nested constraints that encompass the individual, the classroom and the school, as well as the family environment and society. Interestingly, the researchers discuss that based on current data,[2] home conditions seem to be more powerful in influencing educational outcomes than what happens in school. This finding suggests that school practices are not always the limiting factor on performance.

The field of educational neuroscience is still somewhat in its infancy, and much more work remains to be done to make evidence-informed decisions about educational practices. "Although learning seems like a simple idea, it is very complex from the point of view of the brain: it involves the interplay of perhaps eight different neural systems", says Thomas. "Understanding what optimises learning through this interplay (for example, via concepts such as spaced learning and retrieval learning) is a huge challenge". In this regard, organisations such as the Educational Endowment Foundation[3] are helping the field to take steps forward. This foundation supports randomised controlled trials (RCTs) of new educational techniques, which with time, are expected to produce an expanding knowledge base of what works and encourage evidence-informed approaches to educational policy making.

Thomas et al. themselves are conducting such RCTs at the Centre for Educational Neuroscience[4], University of London. "We are currently conducting a large-scale RCT to evaluate a new learning activity for maths and science in primary age children, known as UnLocke[5]", says Thomas. "This computer-based activity is based on two neuroscientific insights: (1) that to learn new maths and science concepts, children frequently have to over-ride their previous learning or intuitive knowledge (e.g., learning that -5 is less than -4, having previously learnt that 5 is more than 4; learning that the world is round despite years of experience of playing football on apparently flat playing fields); (2) that this 'overriding

skill', called inhibitory control,[6] can be improved with training, so long as the skill is practiced in the context of the material where it is needed, in this case, counter-intuitive concepts in the age-appropriate maths and science syllabus". The results of the UnLocke study are anticipated shortly.

A critical challenge to overcome in the field now, is to translate neuroscientific findings into useful educational practices. "The field of psychology offers a salutary lesson — despite 125 years of research on learning and memory, there are still practices carried out in the classroom that (with the support of solid empirical evidence) are clearly ineffective;[7] conversely, effective practices have not yet found their way into the classroom", explains Thomas. "Translation needs to be supported by organisational structures that bring together educational practitioners and researchers; medicine offers a good example about how this can be done".

To address this challenge, the researchers hope that the next decade will have a greater focus on the neuroscience of teaching, including the processes underlying teaching skills, and the explicit knowledge teachers need about neuroscience that will help them with their practice. "We also need a greater focus on understanding sources of individual differences in learning ability, be they genetic or environmental (such as socioeconomic status), and then alter teaching to optimise learning for the individual child", says Thomas. "To ensure advances in these areas, teachers themselves will need to become more involved in driving the neuroscience research agenda".

Overall, it is clear that educational neuroscience must be a dialogue that is as much about teachers stimulating research directions and thinking about how new findings may be useful in the classroom as it is about researchers communicating the findings of their cognitive neuroscience studies. "If the example of public health is anything to go by, it may be that large improvements in educational outcomes are possible, but only by combining many small effects, such as sleep, nutrition, stress reduction, optimising engagement, etc.", says Thomas. "The pressing agenda for educational neuroscience over the next decade is to establish the evidence base in all of these areas".

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Key points:

- Interdisciplinary research is the best way to improve learning outcomes in the classroom.
- Teachers understanding learning and the implications it has for their teaching should form the basis of their teaching practice.
- The field of educational neuroscience is intrinsically translational and one of its goals is to engage with policy makers.
- Researchers must not overstate the current state of the basic science and the maturity of translation.
- Simultaneously, researchers should not understate the importance of the science of learning in supporting an evidence-informed approach to policymaking in education.

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Glossary:

Spaced learning: a learning technique whereby information is repeated multiple times, in short bursts of 15-20 minutes each. Each training session is separated by a 10 minute interval during which the learners do a different task, usually comprising physical activity.

Retrieval learning: formally known as "the testing effect", retrieval practice involves frequent tests or quizzes to bring learnt information out of the memory and into the mind.

Inhibitory control: a cognitive process whereby impulses and habitual or dominant responses are inhibited in order to focus attention on a new task with new goals or requirements.
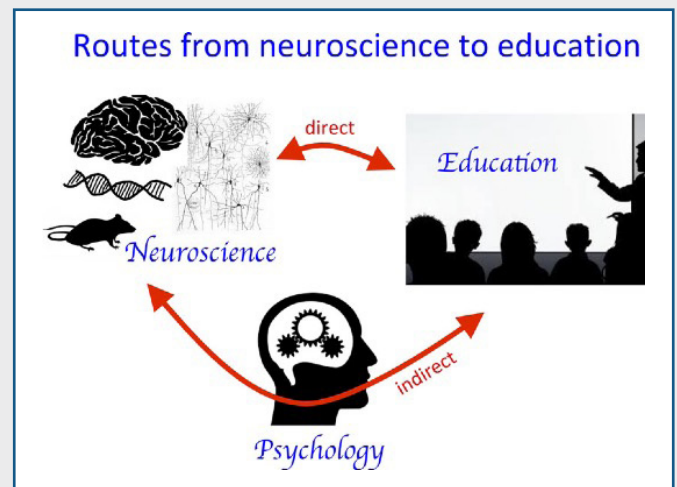

Figure 1. Two pathways linking neuroscience to education. Reproduced with permission from the authors of Thomas, M.S.C. et al. (2019), Annual Research Review: Educational neuroscience: progress and prospects. J Child Psychol. Psychiatr. 60: 477-492. doi: 10.1111/jcpp.12973.

What does a CAMHS MDT need to know about the genetics of psychiatric disorder?

By Joanne Doherty and Olga Eyre

Jo Doherty is a WCAT (Wales Clinical Academic Track) Fellow and CAMHS trainee in South Wales. For her PhD, she used brain imaging to investigate brain structure and function in children with a genetic syndrome associated with high risk of psychopathology (22q11.2 deletion syndrome).

Olga Eyre is also a WCAT Fellow and CAMHS trainee in South Wales. She recently completed her PhD examining links between irritability and depression in children with ADHD and other neurodevelopmental difficulties.

Our knowledge of the genetics of psychiatric disorders has increased rapidly in recent years. This article aims to summarise what has been learnt, focusing on some of the psychiatric disorders commonly seen in CAMHS, before going on to discuss how these findings may be relevant to clinical practice.

Genetics of childhood psychiatric disorders

It has been clear for many years that genes are important in the aetiology of psychiatric disorders. It has been possible to infer this from both twin and family studies. Twin studies have shown heritability ranging from 70-90% for psychiatric disorders such as ADHD, ASD, schizophrenia and bipolar disorder, to around 40-60% for anxiety and depression. Family studies have shown increased risk of disorder in relatives of those affected. For example, children with ADHD are 5-9 times more likely to have a first degree relative with ADHD (Chen et al., 2008, Faraone et al., 2000), while for child and adolescent depression, the risk is 2-4 times higher for those who have a family member with depression (Rice et al., 2002). Interestingly, familial risk extends beyond the disorder diagnosed in the index case, and cross-disorder effects have been reported. For example, relatives of children with ASD are at increased risk of ADHD and vice versa (Miller et al., 2019).

In recent years these genetic epidemiological findings have been augmented by molecular genetic studies. These started with candidate gene studies in which particular genes were selected for investigation because they were thought to be involved in the pathophysiology of the psychiatric disorder in question i.e. based on a priori hypotheses. However, using this approach, it was only possible to study a small number of genetic variants, selected based on unproven hypotheses, with a high risk of false positive results. The variants identified using this approach have had small effects with no real predictive value, and have proven difficult to replicate using more novel approaches.

More recent studies have looked across the whole genome for variants associated with psychiatric disorders without any a priori hypotheses about the genes or chromosomal regions involved. This hypothesis-free, genome-wide (genomic) approach has successfully identified genetic variants associated with a number of psychiatric disorders. The findings include both common genetic variants involving small

changes in the DNA sequence, e.g. Single Nucleotide Polymorphisms (SNPs), and rare variants involving large structural DNA changes, e.g. Copy Number Variants (CNVs). Genome-wide association studies (GWAS) compare hundreds of thousands of common genetic variants (present in >1% of the population) between patients and controls and suggest that these common variants are relevant in psychiatric disorders. Large scale international collaborations which have included many thousands of cases and controls have resulted in the identification of > 100 genetic loci for schizophrenia (Pardiñas et al., 2018) and depression (Howard et al., 2019), around 30 for bipolar disorder (Stahl et al., 2019), 12 for ADHD (Demontis et al., 2019) and 5 for ASD (Grove et al., 2019). As sample size and power increases, further loci are likely to be identified. Individually, these variants exert only very small effects, but it is possible to derive composite genetic risks scores, based on the findings from GWAS. Studies of 'polygenic risk scores' find an additive effect of common variants, i.e. people with higher polygenic risk scores are at increased risk of having a psychiatric disorder or traits of a psychiatric disorder. However, polygenic risk scores are only weakly predictive and so cannot be used either diagnostically or prognostically in the clinical setting. They also show overlap across disorders, for example, ADHD polygenic risk scores are associated with depressive symptoms (Brikell et al., 2018).

While most individual common variants exert only small effects on the risk of psychiatric disorders, a number of rare structural variants have been found to be more highly-penetrant (Kirov, 2015). These Copy Number Variants (CNVs) result from the deletion or duplication of large segments of DNA, resulting in too many or too few copies of one, or in most cases, several, genes. CNVs have been found to be associated with several psychiatric disorders, e.g. ASD (Sanders et al., 2015), ADHD (Thapar, 2018), schizophrenia (O'Donovan & Owen, 2016) bipolar disorder (Green et al., 2016) and depression (Kendall et al., 2019), as well as cognitive impairment (Kirov, 2015). A number of genetic regions seem to be particularly susceptible to these rearrangements and to be associated with psychopathology. These include region 11.2 on chromosome 22, which can be deleted or duplicated. 22q11.2 deletions are associated with very high rates of ADHD and anxiety disorders (~35%) in childhood and adolescence, and schizophrenia (~30%) in adulthood (Schneider et al., 2014).

Overall, findings from genome-wide genetic studies provide clear evidence that psychiatric disorders are complex and polygenic, with both common and rare genetic risk factors. These studies also echo clinical experience and the findings from genetic epidemiological studies, suggesting overlap between disorders and a continuum of psychopathology. New technology such as whole exome and whole genome sequencing will provide novel insights into other risk variants that have thus far been undetectable using GWAS. The next step will be to understand how genetic risk factors alter biology as this could lead to better diagnosis and treatment. Understanding how genes and the environment interact is another important research area, not least because this will be relevant for interventions, particularly if environmental risk factors are potentially modifiable.

How are genetic findings relevant to clinical practice?

The aim of much of the research into the genetics of psychiatric disorders has been to better understand, the underlying biology of these conditions, in order to improve diagnosis and treatment. While new diagnostic tests and medications remain some way off, current knowledge about the genetic basis of psychiatric disorders can help young people and their families to understand their illness better, and also help to alleviate the sense of shame or guilt that often accompanies a diagnosis (Curtis, Adlington, & Bhui, 2019). While for the majority of CAMHS cases, genetic testing will not be appropriate, there are people in whom genetic testing could be beneficial. For example, children with intellectual disability and neurodevelopmental disorders may benefit from testing for structural variants as the diagnostic yield in such cases is relatively high (Bass & Skuse, 2018). Similarly, where there is clinical suspicion of a structural variant (e.g. due to physical and psychiatric manifestations known to be associated with a genetic syndrome), identification of a CNV could help health professionals to counsel families about physical and psychiatric risks, monitor and treat symptoms if they present, identify other family members who may wish to be tested and plan future care. Whether receiving a genetic diagnosis reduces or increases stigma experienced by patients has been the topic of some debate, however, recognising a biological basis for psychiatric disorders will help psychiatry to gain parity of esteem with other branches of medicine which will ultimately lead to improved patient care.

Key Points:

- Psychiatric disorders are complex and polygenic.
- Both common and rare genetic variants play a role in the aetiology of psychiatric disorders.
- There is evidence of genetic overlap across psychiatric disorders.
- Although genetic testing cannot be used for diagnostic purposes, understanding that psychiatric disorders have a genetic component can be helpful for young people and their families.

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