Does early androgen exposure contribute to autistic traits?

EEG data might help identify children at risk for social anxiety
Welcome to the March 2021 issue of The Bridge!

This issue includes an excellent article on mood disorders in autistic young people, written by experts Dr Emily Jackson, Dr Eleanor Smith, and Dr Aditya Sharma. The authors thoughtfully discuss the overlap between these conditions, challenges in identifying their co-occurrence, and adaptations needed for interventions. They use an evidence-based approach to inform best practice, and highlight the importance of recognising and addressing comorbid mood disorders to improve affected autistic young people’s quality of life.

In The Bridge this month, we also feature fascinating research, recently published in The Journal of Child Psychology and Psychiatry (JCPP) and Child and Adolescent Mental Health (CAMH). This research covers a wide range of developmental, emotional, and behavioural conditions experienced by young people, and uses innovative approaches to better understand the course of illness, neurobiology, risks, and effectiveness of interventions. I hope you enjoy reading!

Updates to The Bridge

There are exciting changes ahead for The Bridge, as we’re planning updates to help us better share the latest clinically relevant child and adolescent mental health (CAMH) research, best practice, and policy, with a focus on accessibility for busy CAMH professionals. As part of these updates, we’re changing to publish quarterly; and we’ll be back in the Summer with our next issue in our new format. I’m keen that we continue to improve so that The Bridge is as useful as possible for our readers. Please do email me at TheBridge@acamh.org with any feedback or suggestions. I’d really like to hear from you!
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The autism community identified mental health as their top research priority in 2016. Autistic children and adolescents are more likely than their general population counterparts to have psychiatric disorders. For bipolar disorder, rates of 7% are seen in autistic children and adolescents versus 1% in their general population peers. Rates for depression are also increased ranging from 0.9% - 29% compared to 2.1% in the general population.

Are there differences in the way mood disorders present in autistic children and adolescents?

ASD impacts on how mood disorders present which can make the diagnosis more challenging. One of the difficulties is the common assumption that ASD is the cause of symptoms, a phenomenon known as diagnostic overshadowing. Knowledge of each individual's euthymic profile and baseline functional ability are essential to allow clinicians to notice changes necessary to diagnose mood disorders. For example, social isolation can be a feature at baseline in ASD but if it is increased or a new feature, depression should be considered. Furthermore, ASD may impact an individual’s ability to describe emotions such as irritability, elation, guilt or worthlessness.

Behavioural changes associated with depression in ASD include a rise in aggressive and self-injurious behaviours and the emergence of gloomy content in art and writing. Increased agitation and loss of temper have also been identified, as well as classical depression symptoms such as changes in sleep, appetite, and concentration.

Behavioural changes associated with mania in autistic children and adolescents can include irritability, increase in goal-directed behaviour, distractibility, increased risk-taking, psychomotor agitation, decreased need for sleep, increased stereotypic behaviour and increased obsession.
If a child’s developmental progress slows, plateaus or regresses, then an explanation should be sought. It is vital that healthcare professionals maintain a high index of suspicion for mood disorders in context of episodic change in functioning e.g. changes in self-care or degree of communication. Remembering mania may present as an apparent improvement from baseline due to features such as over talkativeness.

**Adapting approach to assessment and intervention**

Approaches that can be helpful include adding structure to sessions, keeping to time and taking a collateral history. Collateral history is even more important for this population as there is evidence that autistic children and adolescents will under report symptoms compared to their caregivers. When examining mental state, remember that ASD can impact affect, which can be restricted at baseline.

It is crucial to check comprehension and experience of concepts like guilt, hopelessness and self-esteem. This avoids enquiring for symptoms that may not be in that individual’s repertoire as the level of understanding will differ between individuals.

Seemingly small changes can be very significant in ASD so always enquire for changes in circumstances e.g. change in routine, caregivers, etc. Such change in circumstances can be a factor in precipitating a depressive episode and have been associated with increased risk of suicide in autistic children and adolescents.

The varied symptoms of mood disorders highlight the importance of being aware of differentials to avoid misdiagnosis and inappropriate medication. For example psychomotor agitation driven by mania could be misinterpreted as hyperactivity in context of Attention Deficit Hyperactivity Disorder. Subsequent treatment with methylphenidate may further increase the risk of mania in children and adolescents in the first three months if not on a mood stabiliser. Similarly mistaking the impact of mania on frequency of repetitive behaviours as obsessive compulsive disorder may lead to use of selective serotonin reuptake inhibitors (SSRIs) which in turn may exacerbate mania.

There are few validated instruments both to screen for and measure severity of mood disorders in autistic children and adolescents, which may contribute to the variation in prevalence statistics. Where interviews are used, few studies modify these for an autistic sample and there is little data on the impact of using adapted interviews. It is also notable that many studies investigating mood disorder exclude autistic individuals.

**References:**

Psychological therapies such as Cognitive Behavioural Therapy and relapse prevention work can be used for children and adolescents but these may need to be adjusted to take the person’s ASD into account.7

**Key points**

- Mental health clinicians have a vital role in considering mood disorders as a differential when autistic young people present with a change in behaviour.

- At interview: ask caregivers for a collateral history, use accessible language when enquiring for symptoms relating to mood, enquire for change of circumstances and stressors, leave more time for the interview and ensure good time-keeping.

- Refer when needed: bipolar disorder and depression in autistic children and adolescents should only be diagnosed by clinicians experienced in making these diagnoses for this population.

- Remember that recognising mood disorders positively impacts quality of life and functionality with prompt diagnosis and treatment.10

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**References (continued):**


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**Dr Emily Jackson**

Dr Emily Jackson is a CT1 psychiatry trainee at Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust. She graduated from Queen’s University of Belfast in 2016 in Northern Ireland before returning to the North East of England. She has interests in child mental health, psychosis and bipolar disorder.

**Dr Eleanor Smith**

Dr Eleanor Smith is a Consultant Child and Adolescent Psychiatrist with Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust and an Associate Clinical Lecturer at Newcastle University. She is the Consultant Psychiatrist for the Complex Neurodevelopmental Disorders Service, a specialist Autism Spectrum Disorder Clinical Academic Team.

**Dr Adi Sharma**

Dr Adi Sharma is a Clinical Senior Lecturer and Hon Consultant in child and adolescent psychiatry at Newcastle University (Translational and Clinical Research Institute) and Cumbria, Northumberland Tyne and Wear NHS Foundation. After medical and psychiatry training in India he moved to the United Kingdom in 2002 to pursue further clinical research training and was awarded a PhD in 2013 by Newcastle University. His clinical academic interests include the identification of factors (including psychiatric comorbidities) that impact on and improve psychosocial outcomes in early onset (<25 years) mood disorders across the world.
Between 10 and 20% of teenagers have a chronic illness: an ongoing health condition that lasts at least 3 months, and for which a cure is unlikely. Research suggests that teenagers with chronic illnesses are more likely to also have low mood and develop depression than their healthy peers. Some affected teenagers are offered cognitive behaviour therapy (CBT) for depression; however, the approach may require adaptations as the relationship between the chronic illness symptoms and depression is complex, and certain symptoms of chronic illness (e.g. fatigue) can make accessing CBT difficult.

Earlier this year, researchers at the University of Bath performed a scoping review of all studies that have reported on CBT for depression in teenagers with chronic illnesses. Alice Morey and Maria Loades identified 12 studies that included various chronic illnesses (such as diabetes, inflammatory bowel disease and polycystic ovary syndrome) and analysed what adaptations had been made to CBT for depression when used in this context.
They identified two main ways in which CBT for depression was adapted for teenagers who have a chronic illness. First, the delivery of CBT was more flexible, as evidenced by: some telephone rather than face-to-face appointments to reduce travel burden; shorter sessions to accommodate for symptoms like fatigue; additional parental involvement to help implement the CBT strategies and to understand the family’s narrative about the chronic illness; and CBT session scheduling to coincide with other hospital appointments for convenience.

Second, the content of CBT was expanded in several ways to incorporate the chronic illness context. For example, psychoeducation included a focus on the links between thoughts, feelings, behaviour, and chronic illness symptoms. Unhelpful illness-related thoughts, as well as more general negative thoughts, were addressed, while stress management, skills building, and behavioural activation included a focus on chronic illness management. Others allowed time for working with the teenager to improve their communication about the chronic illness with their parents and healthcare professionals.

Overall, the findings from this review indicate that chronic illness might present unique practical barriers to adolescents engaging in CBT for depression. Therapists may need to adapt both the delivery and content of CBT to best help teenagers with chronic illnesses to address depression symptoms.

**Referring to:**

**References:**

**Glossary:**
**Cognitive-behavioural therapy:** a form of talking therapy that encourages patients to adapt the way they think and behave to improve the way they feel. CBT is based on the concept that thoughts, behaviour and feelings are interconnected. CBT tends to focus on current problems and finds practical ways to change negative patterns, in order to develop more helpful strategies of addressing these problems.
Earlier this year, Margaret Snowling and Charles Hulme at the University of Oxford compiled an Annual Research Review for the Journal of Child Psychology and Psychiatry on reading disorders. Their review provides a timely update on their earlier review published in 2012, offering a perspective on how expert understanding of children’s reading disorders has changed since this time. We asked the researchers to summarise their key findings:

“Perhaps the clearest change we identified was the critical importance of oral language”, say Snowling and Hulme. “Since 2012, it has become abundantly clear that early difficulties in oral language development (typically occurring before school entry) presage later problems in learning to read. Furthermore, language difficulties seem to have important causal influence on the later development of both decoding (reading aloud) and comprehension skills”. Another theme Snowling and Hulme identified was the very high rate of comorbidity between reading disorders and other cognitive disorders – particularly language disorders and mathematics disorders.

The researchers explain that reading disorders can be broadly split into problems in learning to decode print (usually referred to as dyslexia) and problems in learning to comprehend what can be decoded (usually referred to as reading comprehension impairment). “These two forms of reading problem seem to arise from different forms of language difficulty and require different forms of treatment”, explain the researchers. “Fortunately, evidence suggests that both of these forms of reading disorder can be ameliorated by suitable specialist teaching.”

Snowling and Hulme outline several of the evidence-based interventions for decoding. These interventions typically promote word reading by integrating training in phonological awareness with reading practice using books. They also highlight the evidence-based interventions for reading comprehension. These interventions are generally language based and promote comprehension through vocabulary instruction, oral narrative and reading comprehension strategies. Research over the coming years now needs to focus on resolving issues surrounding the implementation of such interventions if they are to be more successfully embedded in practice, as well as the timing and frequency of reading interventions for at risk children.

Referring to:

References:
Progressive cortical thinning might identify children at risk of developing psychotic spectrum symptoms

By Dr. Jessica Edwards

Offspring of patients with schizophrenia or bipolar disorder have an increased risk of developing these conditions. However, our capacity to predict the long-term outcomes of these at-risk individuals is limited. Now, researchers in Spain have investigated whether longitudinal changes in brain structure differ in individuals at high familial risk who develop psychotic spectrum symptoms, compared to those who do not and to low-risk controls.

“Our early observations suggested that at baseline, offspring of patients with schizophrenia exhibit subtle reductions in cortical volume compared to offspring of patients with bipolar disorder and to low-risk controls”, explains lead author Gisela Sugranyes. “Here, we wanted to see if this reduction changes over time, and if so, how such structural brain changes correlate with the symptom trajectory”.

The team recruited 79 offspring (aged 6-17 years) of patients with schizophrenia or bipolar disorder (high-risk), and 49 low-risk controls. They then performed clinical, cognitive and neuro-imaging assessments at baseline and at 2 and 4-year follow-up. They found that 20 of the high-risk offspring developed psychotic spectrum symptoms during the follow-up period; 5 of the low-risk individuals developed these symptoms and were excluded from the imaging analyses. Over the follow-up period, the high-risk individuals who developed psychotic spectrum symptoms showed a greater level of cortical thinning in the occipital lobe, compared to both high-risk participants who did not develop these symptoms and low-risk controls. Additionally, these individuals had a smaller total brain surface area and grey matter volume at baseline than both comparison groups.

“To have immediate translation to clinical practice, our findings will need to be validated in a large, external sample”, explains Dr Sugranyes. “However, these data do suggest that information that can be obtained from brain MRI scans might help identify high-risk individuals who are likely to develop psychotic spectrum symptoms”. Going forward, the researchers would like to examine whether these findings are also relevant to youth who develop psychotic symptoms during adolescence, regardless of familial risk. Then, we might be well-positioned to stratify familial high-risk individuals according to their risk of progression to disease, and to implement early, tailored interventions.

Referring to:

References:

Preschool vocabulary acquisition is associated with later language and literacy skills. Genetic factors might partially explain this link, but the precise mechanisms are unclear. Thus far, twin-based studies have implicated mechanisms involving genetic amplification or genetic innovation.

In their latest study, an international team of researchers, including first author Ellen Verhoef and lead scientist Beate St Pourcain from the Max Planck Institute (MPI) for Psycholinguistics investigated this problem using genome-wide genetic data from participants of a large UK population-based cohort. Specifically, the scientists evaluated the evidence for an amplification of genetic factors related to early vocabulary versus genetic innovation occurring during development. To do so, they studied expressive and receptive vocabulary skills at 38 months of age and various language- and literacy-related skills, as well as nonverbal intelligence, at age 7 to 13 years in approximately 6,000 unrelated children. They then analyzed genetic relationships between early-childhood expressive and receptive vocabulary, and later language and literacy-related skills.
The researchers found little support for the emergence (i.e. innovation) of novel genetic sources for language, literacy or cognitive ability during mid-childhood or early adolescence. However, they did find evidence to support that genetic factors contributing to early childhood receptive vocabulary were amplified. These genetic factors seemed to explain most of the genetic variance underlying differences in later reading, verbal and nonverbal cognitive skills.

“While individual predictions of a child’s future language and reading abilities using very early vocabulary scores are poor, and this includes genetic predictions, our study clearly highlights that the genetic foundations underlying these early skills play an important role during later life, in particular for literacy and cognitive skills, as observed in a large population-based cohort”, explains St Pourcain. “Thus, our study underlines the need for (1) accurate and detailed assessments of language skills during toddlerhood, which are currently only sparsely available in large-scale cohorts, and (2) an in-depth characterisation of genetic factors contributing to early language development, so that we can better understand the genetic and non-genetic processes contributing to later-life outcomes”.

Referring to:

References:

Glossary:
Genetic amplification: genetic factors are associated with a trait throughout development and increasingly explain that trait as age progresses.
Genetic innovation: genetic factors (that were previously unrelated to a trait) become associated with that trait during development.
Children with behavioural disorders, such as ADHD or conduct disorder, are more likely to experience partnership problems in adulthood, including partner conflict and lower relationship satisfaction. But whether there is an association between commonly observed childhood behaviours and patterns of long-term romantic partnering in adulthood among the general population is unclear. Francis Vergunst and colleagues followed almost 3,000 children across 25 years: they collected teacher-rated behavioural assessments – for inattention, hyperactivity, aggression, opposition, anxiety and prosocial traits – made when children were aged 10 to 12 years, and linked these to their partnering patterns from age 18-35 years based on their relationship status reported in their annual tax returns.

The researchers identified five distinct partnering trajectories: early-partnered, mid-partnered, late-partnered, early-partnered-separated, and delayed-or-unpartnered. "After adjusting for the child’s sex and family background, we found that anxious or inattentive children were more likely to remain unpartnered across early adulthood while those who were aggressive-oppositional were more likely to separate and to spend fewer years partnered", explains Vergunst. "Conversely, prosocial children – those rated by their teachers as being kind, helpful and considerate – showed earlier and more sustained patterns of partnership across early adulthood".

These findings add to growing evidence that children with behavioural problems, even at sub-clinical levels, are more likely to experience social and economic marginalisation as adults, including exclusion from romantic partnership.1-3 "Early screening and monitoring are critical as children found to be at-risk could benefit from evidence-based prevention and support programs", speculates Vergunst. "Those with serious difficulties should be considered for specialist educational and clinical input as indicated by formal assessment. This should improve not just partnering prospects but also a wide range of adverse life outcomes that have been repeatedly linked with early behavioural problems".

Referring to:


References:


Researchers in the USA have analysed whether the levels of branched-chain amino acids (BCAAs) detectable in maternal plasma and newborn cord blood are associated with the development of attention-deficit hyperactivity disorder (ADHD) later in childhood. Neha Anand and colleagues used data from 626 children involved in the Boston Birth Cohort, which was recruited from a largely urban, low-income, US minority population. Of these participants, 299 had clinically diagnosed ADHD and 327 were neurotypical. The researchers collected maternal and cord blood samples soon after birth, measured BCAAs by liquid chromatography-tandem mass spectrometry, and compared the data between the two groups. They found an association between higher BCAA levels in cord blood (but not in maternal blood) and an increased risk of developing ADHD in childhood. The researchers explained that pending validation, these findings might provide insights into mechanisms that contribute to ADHD development. The findings could also suggest that cord metabolites might be useful early predictive biomarkers for ADHD.

Referring to:
Researchers in Hong Kong and Cambridge have explored the influence of early androgen exposure on autistic traits during childhood. It has been proposed that higher levels of androgens (such as testosterone) during early life might contribute to the development of autistic traits, and that this might explain why autism is more common in males than females. Karson Kung and colleagues collected data from 97 boys and 110 girls from the Cambridge Baby Growth Study. They measured the anogenital distance (AGD) and penile length — two putative biomarkers of early androgen exposure — at birth and at 3 months-of-age. Then they assessed autistic traits via a parent-reported questionnaire when the child reached 9-13 years-of-age. Consistent with previous studies,\(^1\) they found no significant associations between the two androgen exposure biomarkers and autistic traits in boys, girls or both sexes combined. Assuming that AGD and penile length are accurate biomarkers, it seems that early androgen exposure might not explain the sex bias observed in autism.

Does early androgen exposure contribute to autistic traits?

By Dr. Jessica Edwards

Referring to:


References:


Electroencephalography (EEG) is a non-invasive method to monitor the electrical activity of the brain. There are five main broad frequency bands in the EEG power spectrum: alpha, beta, gamma, delta and theta. Data suggest that EEG-derived delta–beta coupling — indicating related activity in the delta and beta frequency bands — might serve as a marker of emotion regulation.1,2

Researchers at The Pennsylvania State University have studied for the first time, the association between delta–beta coupling and childhood risk for anxiety, considering both inter-individual (between-person) and intra-individual (within-person) delta–beta coupling. “We modelled delta–beta coupling as an intra-individual neural process to see whether quickly-changing patterns of delta–beta coupling were associated with social anxiety and temperament”, explains lead author Berenice Anaya. “We wanted to go beyond the group-level correlations of delta–beta coupling usually reported in the literature, and link participants’ own neural patterns to their anxiety scores”.

Anaya et al. recruited 177 children (aged 9-12 years) to their study and collected delta–beta EEG coupling data and parent report of anxiety and behavioural inhibition (BI). They found stronger inter- and intra-individual delta–beta coupling in children with more social anxiety symptoms. However, surprisingly children with high levels of BI showed weaker intra-individual delta–beta coupling compared to those not exhibiting BI.

“We believe our findings have implications for clinical practice, because we show that we can capture variation at the level of the individual, rather than averaged across a group, and that stronger delta–beta coupling is associated with risk for anxiety”, explains Anaya. “Indeed, the strong coupling patterns capture risk even when delta and beta power deviate from an individual’s average levels. This finding further supports the use of delta–beta coupling as a marker for anxiety risk, and it sets the stage for future research to explore developmental trajectories of intra-individual patterns of delta–beta coupling in relation to precursors of anxiety”.

Referring to:

References:

Glossary:
Behavioural inhibition: a temperamental profile characterised by shy, hypervigilant and fearful behaviours in new social situations, which is associated with a higher risk for social anxiety.

Inter-individual delta–beta coupling: the average coupling pattern of each person, compared between participants.

Intra-individual delta–beta coupling: the time-dependent coupling pattern that a person shows when delta and beta power deviate from usual states and are higher or lower relative to their own average.
Adolescents who identify as a sexual minority (e.g., gay/lesbian, bisexual) are at an increased risk for suicidality compared to their heterosexual counterparts. Until now, inherent limitations in study design has meant that the extent of this association has been unclear. Now, Lauren O’Reilly and colleagues have used data from the Child and Adolescent Twin Study in Sweden to determine the magnitude of the association between sexual orientation and adolescent suicide attempt (SA) and self-harm (SH) after considering the role of shared genetic and environmental factors and childhood psychopathology. O’Reilly et al. used a co-twin control design, where they compared each twin to their co-twin who differed on their sexual orientation status. By doing this, they were able to estimate the extent by which sexual orientation is associated with SA and SH after accounting for all the genetic and environmental factors that make twins similar. They ultimately found that sexual orientation minority youth were around 50% more likely to attempt suicide or SH than heterosexual youth. These findings may support the minority stress hypothesis, which proposes that experiences of prejudice, discrimination, and internalised homophobia among sexual minority youth is related to poor mental health outcomes.

“We believe that the implications of these results are two-fold”, explains O’Reilly. “First, they highlight the necessity of improved screening, assessment, and interventions for suicidality in LGBTQ youth in various settings (health care, school, etc.); and second, they put a spotlight on the importance of future research to examine factors that may specifically explain the relationship between sexual orientation and SA/SH such as gender nonconformity, victimization, and poor social support, using methodological approaches such as the co-twin control design, that compare family members”.

Further work is now necessary to determine whether these findings can be generalised to other countries. If these data do indeed support the minority stress hypothesis, then a stronger association between sexual minority status and SA/SH in countries with less cultural and legislative support for LGBTQ individuals would be expected.

References:
Is frontoamygdalar connectivity in the resting brain linked with externalising behaviours during development?

By Dr. Jessica Edwards

Externalising problems tend to vary over the course of development, but often peak in late adolescence. Data suggest that the frontoamygdalar brain circuitry (involved in emotion regulation) might have an important role in mediating externalising behaviour. Indeed, studies involving clinical samples and using task-based approaches have found decreased frontoamygdalar functional connectivity in those exhibiting externalising behaviours.

Less is known about how the frontoamygdalar circuitry functions when the brain is at rest and how resting-state functional connectivity might be associated with externalising behaviour during development in the general population. Researchers in the Netherlands and the USA have started to address this knowledge gap, asking whether externalising behaviour is associated with amygdala-anterior cingulate cortex (ACC) or amygdala-orbitofrontal cortex (OFC) functional connectivity across adolescence and young adulthood in the brain at rest.
Thijssen et al. recruited 111 participants aged 11-23 years old from the general population. Each participant underwent a resting-state fMRI scan every 2 years for up to 6 years. They found that externalising behaviour was associated with increased amygdala-ACC and amygdala-OFC functional connectivity over the course of adolescence and young adulthood. However, they did not find evidence for differential developmental trajectories of amygdala-ACC or amygdala-OFC functional connectivity for different levels of externalising behaviour; both low and high externalisers showed the same pattern of stable or increasing amygdala-ACC and amygdala-OFC co-activation over the study period. For amygdala-ACC functional connectivity, the association with externalising behaviour was mostly explained by the level of externalising behaviour at the start of the study rather than a change in externalising behaviour over time. Meanwhile, the association between externalising behaviour and amygdala-OFC functional connectivity seemed to be driven by within-person changes in externalising behaviour over time.

“These results contrast with task-based fMRI studies, but align with other resting-state functional MRI studies in suggesting that individuals showing higher levels of externalising behaviour show increased frontoamygdalar functional connectivity, perhaps indicating a more vigilant state for neural networks important for emotional processing and control when the brain is at rest”, explains Thijssen. “The differential findings for amygdala-ACC and amygdala-OFC functional connectivity emphasises the differential role of these networks in emotional processing. They also highlight the need to investigate changes in brain function and behaviour using longitudinal data”.

An important limitation of this study is the composition of the study sample. The participants mostly comprised white participants from middle to upper-middle socioeconomic groups. Moreover, only few participants showed clinical levels of externalising behaviour. The researchers hope that future studies that involve larger and more varied samples will shed further light on the neuro-developmental trajectories of externalising behaviour.

Referring to:

References:

Glossary:
Externalising problems: maladaptive behaviours which are directed externally towards the environment, such as aggressive or rule-breaking behaviours.