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Notes from the Editor

As you already know, I am sure, this is our 10th anniversary year, and we are celebrating with not only the trainee event that we had on March 13th, which was a great success, but also other events and articles. We have some reflections from the trainee event from Tom Carpenter who was the principal organiser. We also have a fabulous 10th anniversary conference booked for **November 6th** at the RCPsych, with some of the biggest names in Evolutionary Psychiatry. Randolph Nesse is coming over from the States and Martin Brune from Germany to speak with us.

In this letter we also have a book review by Annie Swanepoel "The Nature of Nurture: rethinking why and how childhood adversity shapes development" by Jay Belsky.

Lastly in this letter we have two more essays from the essay prize-winners and we also have some feedback on the trainee event.

EPSIG Ireland

The Evolution & Psychiatry Special Interest Group (EPSIG) in Ireland continues to grow, with Gurjot Brar recently appointed as Chair. Current efforts focus on a series of projects in medical education, alongside Henry O'Connell's ongoing delivery of evolutionary psychiatry tutorials to medical students throughout the year. Their meetings are well attended, free to attend online for all and feature a keynote talk by an evolutionist 2-3 times a year.

A proposal for a symposium at the College of Psychiatrists of Ireland winter 2026 meeting has been submitted and U.K. colleagues are very welcome to attend. Annie Swanepoel's symposium on ADHD at the winter 2023 conference was very successful and led to some heuristic research on the day, in terms of knowledge and attitudes to evolutionary explanations in ADHD which has now been published in the Irish Journal of Psychological Medicine.

We wish to draw the attention of readers to a new Substack article published by Gurjot Brar termed "Mismatch Reduction Therapy" found on https://epsig.substack.com/

Future Events

8th International EPSIG Symposium - In-Person - 6th November 2026 - Royal College

Confirmed speakers: Randolph Nesse, Martin Brune, Anne-Laure Le Cunff, Penny Spikins, Laurence Hurst, Paul Keedwell (Session chairs: Agnes Ayton, Annie Swanepoel & Paul St John-Smith). This will be followed by post-conference dinner. Details for registration/booking will be announced in due course.

Collaboration with EP section at WPA

WPA EP Section webinar Program:

1. 26 March 6pm Alfonso Troisi, Emeritus Prof, University of Rome
2. 30 April 6pm, Dr Gul Deniz Salali, UCL, London
3. 28 May 6pm, Dr Iain Campbell, Edinburgh University
4. 25 June 6pm, Prof Samir Okasha, University of Bristol
5. 30 July 6pm, Jay Belsky, Emeritus Prof University of California, Davis

Details of titles and FREE registration links can be found on: https://www.wpanet.org/section-page/evolutionary-psychiatry/

The 4th EPSIG Resident Doctor Engagement Day

By Dr Tom Carpenter

EPSIG (Evolutionary Psychiatry Special Interest Group) held its 4th annual Resident Doctor Engagement Day in March 2026. Around 30 attendees gathered at RCPsych headquarters in London, including psychiatry trainees from across the country, invited speakers, and members of the EPSIG executive committee. It was a well-attended and energetic day that reflected the growing interest in evolutionary approaches to mental health among trainees.

This year's programme centred on the theme of psychosis. Speakers looked at how evolutionary thinking can offer a different perspective on psychotic experiences — including questions such as why psychosis persists in human populations, what its potential adaptive roots might be, and how this kind of framework can be useful for clinicians. The talks fitted together well, giving attendees some practical ideas to take back into their training and clinical work. The day was chaired by Dr Tom Carpenter, with Dr Riadh Abed, Dr Paul St. John-Smith and Dr Reem Abed also in attendance from the EPSIG executive committee, and Dr Riya Gosrani and Dr Benjamin Griffin from the EPSIG trainee shadow executive committee.

The atmosphere throughout the day was friendly and open. Trainees engaged actively in question-and-answer sessions and kept conversations going over the breaks. As with previous Engagement Days, there was a genuine sense of flat hierarchy — a space where trainees at all stages could explore ideas alongside more experienced colleagues.The engagement didn't end when the day finished -- several participants have since joined the EPSIG Resident Doctor WhatsApp group and expressed an interest in getting involved with research activities. These are exactly the kinds of connections these events are designed to encourage — giving trainees who are interested in evolutionary psychiatry a route into getting more actively involved.

Planning is already under way for the 5th Resident Doctor Engagement Day, which has been booked for 19 March 2027. Early discussions point towards a translational theme, looking at how evolutionary ideas can be applied in everyday clinical practice. There are also plans to introduce a poster session, giving trainees the chance to present their own work and ideas in evolutionary psychiatry.

There are numerous opportunities for trainees to get involved — anyone with an interest is encouraged to contact Dr Tom Carpenter - emails can be forwarded by sigs@rcpsych.ac.uk.

Charles Darwin RCPsych EPSIG Prize 2026

Do you want to be invited to speak at an international conference?

If you are a Psychiatry core or specialty trainee, medical student or non-consultant grade psychiatrist in the UK, you are eligible to enter this Essay Competition. Two winners will be invited to speak for 10 minutes each at the in-person EPSIG International Symposium on **6th November 2026** at the RCPsych in London.

The essay submissions must be the applicant's own intellectual contribution. Originality will be valued.

Medical students, foundation doctors and staff grade doctors are all eligible to apply in their own categories with the prizes as below:

What you can win:

Invitation to give a 10-min oral presentation at the EPSIG International conference held in person on **6th November 2026** for the psychiatry core and specialty trainee winners only.

- £100 pound prize money for the winner each of five categories (medical student, foundation doctor, core trainee, specialty trainee, staff-grade doctor)
- Certificate for the runner-up in each of the above five categories
- Winners will have their essay printed in the EPSIG Newsletter that is distributed to all EPSIG members (currently over 3000 psychiatrists and other professionals worldwide)

What you need to do:

Write a 1500 to 2000-word essay (excluding references) relevant to Evolutionary Psychiatry. The essay should be supported by a review of relevant literature and must be your own intellectual work.

The title is: ***"How an evolutionary perspective can improve our understanding of … (anything to do with psychiatry)"***.

You may want to visit the EPSIG YouTube channel at Youtube.com/EPSIGUK, listen to the 'Evolving Psychiatry' podcast (on all major platforms), or read our published newsletters at epsig.org for inspiration and information.

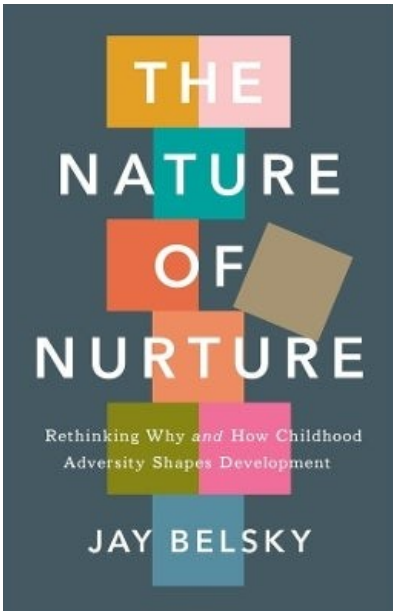
Email your submission to sigs@rcpsych.ac.uk with "Entry for EPSIG Essay prize" as title by 1st September 2026.

What we will do:

Entries will be judged by a panel of three EPSIG Executive Committee members. Criteria for judging will include clarity of expression, understanding of the evolutionary literature and evidence, critical thinking and the overall ability to convey enthusiasm and originality. The committee reserves the right not to award the prize if no entry reaching the agreed minimum standard is received. Winners and highly commended other entrants will be informed by 15th October 2026.

Book Review

The Nature of Nurture: Rethinking why and how childhood adversity shapes development, by Jay Belsky



I first came across Jay Belsky when reading his chapter in the Handbook of Attachment that was published in 1999, the same year that my first son was born. I read the Handbook from cover to cover, and it was Belsky's chapter that stood out for me – because it didn't just address what happened during development but also considered why this might be so. Much later, when I trained in psychiatry in the UK, I again found that I was learning a lot about what happened, but nothing about why this is the case. I was therefore delighted to discover Evolutionary Psychiatry, which broadened my horizons and helped it all make sense.

Belsky's newest book "The nature of nurture", published in 2026, is a tour de force of the evolutionary informed developmental perspective. He reviews not just his own work, but also that of his colleagues. He states that he does not write for the general public and this book is indeed for people who already have some background knowledge and interest in the "evodevo" topic. For those that do, as I would hope would include all psychiatrists and not just child and adolescent psychiatrists, this is an important and insightful read.

For me, the book consolidated disparate bits of knowledge that I had and showed again how we are so much more complex than we give ourselves credit for. Belsky shows elegantly how concepts like fast and slow life history, and orchid/dandelion differential susceptibility are not simple dichotomies but spectra in their own right. Furthermore, there is no possible way of disentangling what is genetic and what is environmental, as these are so interlinked as to make the question irrelevant.

Reading this book has given me renewed respect and a feeling of awe for life, and how we continue to survive. There are no easy answers, and we all just muddle through – as we have done for millennia.

However, I do agree with Belsky on one very important easy answer, that has not been made clearly enough elsewhere. Children suffering is reason enough to intervene and to try to prevent it. There should not be the need to prove the long-term economic consequences of child maltreatment to justify early intervention.

Highly recommended!

Dr Annie Swanepoel

EPSIG Essay Competition 2025—Prize Runner-Ups

How an evolutionary perspective can improve our understanding of paraphilia

Matthew Hastings, Higher Resident

The process of evolution has produced a bewilderingly complex variety of life on our planet. While this can be thought of as due to a process of the fittest genes surviving, it is through sexual reproduction that successful genes are transferred from one generation to another. Sexual reproduction and associated behaviours are therefore critical to the entire evolutionary process honing our species, and others, to be organisms suited to their environments. These behaviours naturally follow predictable patterns to facilitate sexual reproduction, however there are a multitude of human sexual behaviours and preferences that deviate from normal reproductive sex that do not necessarily aid the exchange of gametes, the raising of offspring, and the continued survival of the species. Such deviant behaviour could be viewed as 'anti-evolutionary,' but certain sexual fetishes do exist and have been observed as established patterns of human behaviour for thousands of years. Some of the more extreme of these behaviours are known to psychiatrists as paraphilias, persistent sexual interests in atypical objects, situations, fantasies, urges, or behaviours that can cause distress or impairment. Adopting an evolutionary perspective to their role in human behaviour can better aid the clinician in understanding how these behaviours have developed, and how best to destigmatise and help affected individuals by framing them as conditions resulting from developmental mismatches rather than specific moral failings.

Paraphilia

When considering sexual behaviour it is important not to apply a moralistic stance and while this essay may refer to certain 'deviancies' it is only in relation to biological principles and should not be inferred as the author passing any form of judgement.

Paraphilias in particular are only referred to as such when the sexual practice is so distressing as to cause individuals to seek psychiatric assistance;[1] there are a plethora of non-reproductive sexual practices that confer consensual pleasure to their practitioners who do no not feel the requirement to seek help in modifying their behaviours.[2] Additionally, there are also a number of sexual practices that are widely condemned by many human societies as being 'unnatural' that are commonplace in the animal kingdom such as incest and rape. These are sexual practices that do aid in the transmission of genes across generations and are relied upon by many species as valid reproductive strategies that have been selected for over time.

A relatively small number of individuals display sexual behaviour which is considered disordered and paraphilic.[3] Traditional psychiatric approaches have largely treated paraphilias as pathological aberrations requiring medical intervention. The DSM-5 distinguishes between paraphilias, being atypical sexual interests, and paraphilic disorders when these interests cause distress or harm. According to ICD11 diagnostic criteria these disorders are characterised by persisting and intense sexual arousal manifested as thoughts, urges, and behaviours of a sexual nature with a focus on others who are unable or unwilling to consent, or that cause marked distress. Although this is a landscape that has very much changed with time and evolving cultural norms the following conditions are currently considered paraphilic disorders:[4]

- Exhibitionistic Disorder
- Voyeuristic Disorder
- Paedophilic Disorder
- Coercive Sexual Sadism Disorder
- Frotteuristic Disorder
- Other Paraphilic Disorder Involving Non-Consenting Individuals

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The purpose of sexual reproduction

Sex is the expression of a basic biological drive present in all animals, however in humans, sexual behaviour appears to be far more complicated. It is associated with complex social behaviour, including emotional expression, emotional bonding, and even as part of recreational activity.[5] It is advantageous for the success of offspring if both parents are present and involved in their care, and this is better achieved where the parents are well bonded with a harmonious relationship; in this way sex plays a pivotal role in human monogamy and development. Buss summarised the Human Reproductive tasks in eight points:[6]

1. To compete with members of one's own sex to attract mates
2. To select a mate possessing the greatest reproductive value available
3. To achieve conception
4. To retain one's mate once selected
5. To form reciprocal alliances
6. To build coalitions and participate in cooperative groups
7. To ensure the survival and reproductive success of offspring
8. To invest in kin other than offspring

That there are established strategies for human reproduction raises the question: How can an evolutionary theory which emphasizes reproductive success and adaptive behaviour explain sexual interests that appear maladaptive or even harmful?

Evolutionary explanations for paraphilic disorders

Clearly, there are no simple explanations for why any individual displays certain sexual preferences as human sexual behaviour is linked to neurohormonal development that begins in utero and continues throughout development involving complex interactions between different neurochemical systems.[7-8] Evidence suggests that brain development plays a role in sexual orientation with over/under-development of certain key areas such as the pre-optic anterior nucleus which controls mounting behaviour in male mammals, or the anterior nucleus which has a role in precipitating receptiveness of females to male mounting behaviour.[2] Furthermore, conditioning mechanisms play a role at key developmental milestones as associations between stimuli and sexual arousal become established and are reinforced.[8] While there are certain stimuli that humans are likely predisposed to finding arousing, it is not possible to predict how the system will eventually be utilised. A complex tapestry of biological and psychological mechanisms exist to guide human sexuality and in general this is advantageous to the survival of the species as on the whole it encourages reproduction. One compelling phylogenic explanation for paraphilia is that they have emerged accidentally as maladaptive byproducts of an overall adaptive mechanism. Possessing a 'sweet tooth' was at one time adaptive for our ancestors in detecting energy-rich foods, however in environments filled with readily available brightly coloured bags of processed sugar the adaptation can now contribute to making us less fit; so too can our innate sexual psychology generate interests that were never directly selected for but emerge from systems that were.

Consider the male sexual psychology that prioritizes visual stimuli, novelty-seeking, and variety more so than females.[2] These traits likely enhanced reproductive success in ancestral environments by motivating males to pursue multiple mating opportunities, yet in modern environments, these same psychological tendencies might manifest as fetishistic attractions to visual stimuli such as clothing, body parts, inanimate objects, or as compulsive seeking of novel sexual experiences.

The paraphilias are thus an unexpected byproduct of a normal adaptive process. This perspective suggests that paraphilias might emerge from the same psychological mechanisms that normally help us form strong preferences and motivations but are perhaps applied to targets that happened to be present during critical developmental periods.

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Sexual Dimorphism of Paraphilia

One of the most striking features of paraphilias is their overwhelming male predominance. Across virtually all paraphilic categories, males outnumber females by ratios that can exceed 20:1.[1,9] This profound sex difference demands evolutionary explanation.

Males and females have faced different reproductive challenges throughout human evolution. For males, reproductive success has typically been more variable and more dependent on competition with other males and successful courtship of females. This has led to the evolution of male sexual psychology characterized by greater risk-taking, higher sex drive, more focus on visual cues, and greater interest in sexual variety.[2]

These evolved sex differences in sexual psychology may explain why males are more prone to developing paraphilias. The same psychological mechanisms that made males effective competitors in the mating-market such as intense sexual motivation, strong conditioning to sexual cues, willingness to take risks for sexual opportunities, may also make them more vulnerable to developing atypical sexual interests when these mechanisms go awry during their nascent development.

This is in contrast to female reproductive strategies that have generally depended more on choosing high-quality partners and securing resources for offspring. This may have resulted in a female sexual psychology that tends to be more contextual, relationship-focused, and less driven by visual stimuli; ultimately, these are characteristics that may be protective against the development of paraphilia.

Origins of paedophilic disorder

Paedophilia is a challenging disorder to manage in the psychiatric context to say nothing of the difficulty it represents to wider society. As it can be defined as persistent sexual attraction to prepubescent children, the condition appears fundamentally maladaptive since children cannot reproduce.[10] However, recent genetic research supports an hereditary nature to paedophilia with studies having identified specific polymorphisms, including variations in the COMT gene (Val158Met), that appear more frequently in paedophilic individuals.[1] The persistence of these genetic variants across generations could suggest that they confer some unknown advantage in certain contexts that make these genes more likely to reproduce.

One hypothesis for this could be that some males who are unable to compete successfully in the adult sexual marketplace may redirect their mating efforts toward less discerning or more vulnerable targets. In this way a low-quality male could secure, or groom, a mate who they will eventually be able to reproduce with. From this perspective, paedophilia could represent a maladaptive response to the failure of normal courtship strategies whereby individuals pursue alternatives that require less social competence or competitiveness. Children are less able evaluate potential mates, or unfortunately resist coercive advances, and therefore present easier targets for those who cannot succeed in age-appropriate relationships. In fact, it is often the case that paedophiles exhibit characteristics associated with poor mating prospects such as lower intelligence, poor social skills, and higher rates of mental health problems.[10] These traits would have likely reduced success in competition for adult mates on the 'open market,' thereby potentially driving alternative strategies.

Alternatively, another hypothesis for an evolutionary basis of paedophilia could be due to a eugenic male preference for younger, more fertile partners becoming pathologically amplified. Traditionally, males who preferred younger females would have gained some reproductive advantage, as youth correlates with fertility and reproductive potential.[2] However, in some individuals, this preference system may become exaggerated, extending beyond the optimal range into prepubescent ages where no reproductive benefit exists.

An evolutionary perspective of exhibitionistic disorder

Exhibitionistic disorder involves sexual arousal from exposing one's genitals to unsuspecting strangers and typically predominately

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affects males.[1] From an evolutionary perspective, exhibitionism may represent a misapplied version of sexual display behaviours that serve important functions in courtship across many species.

Charles Darwin observed *"in the most distinct classes of the animal kingdom with mammals, birds, reptiles, fishes, insects, and even crustaceans, the differences between the sexes follow almost exactly the same rules; the males are almost always the wooers..."*[2] In fact male sexual displays are ubiquitous in nature, from peacock tail feathers to primate genital presentations. These displays serve to attract mates and assert dominance, representing costly signals of their valuable genetic quality and reproductive fitness.[5] Human males are no different in this regard and clearly engage in the same kind of displaying behaviours such as demonstrations of wealth and high status, as well as demonstrations of physical and mental prowess. It is possible that exhibitionism may emerge when these display mechanisms become misdirected toward inappropriate targets or contexts. Although the exhibitionist experiences sexual arousal from the display itself rather than from successful mate attraction, which suggests a disconnection between the behavioural mechanism and its adaptive function. The preference for non-consenting, scandalised observers may reflect a desire to dominate which is an archetypal male instinct traditionally associated with reproductive success.[2]

Voyeurism and mate assessment

Voyeuristic disorder involves sexual arousal from observing unsuspecting individuals who are undressing, naked, or engaging in sexual activity.[1] As with all paraphilias voyeurism shows a strong male bias, and there is even evidence it is the most common paraphilia in men from one large study, however there are inherent limitations in the collection of such sensitive data where responders may not accurately reflect the true demographic.[9]

In considering this behaviour in terms of how it conveys reproductive success one hypothesis could be that it represents an exaggeration of existing and adaptive cognitive processes and behaviours for assessing the quality of a potential mate. Gathering information regarding potential mates could been advantageous to secure reproduction, and males in particular may benefit from more accurately assessing female fertility and sexual availability, as well as competition from other males. Covert observation would have provided valuable information while minimizing social risks or aggressive responses from sexual competitors.[11]

Modern voyeuristic behaviour may reflect ancient information-gathering strategies applied inappropriately, although as with exhibitionism the sexual arousal component suggests a significant deviation from the normal mate assessment mechanism. In this case the observation process itself becomes the primary source of gratification rather than leading to appropriate courtship behaviours. The age of onset in adolescence aligns with the activation of adult sexual motivations and mate assessment systems. During this critical developmental period, normal mate evaluation mechanisms may become misdirected toward inappropriate targets, leading to persistent voyeuristic patterns in later life.

A problem with this hypothesis is the low preponderance of voyeurism in women, as the assessment of potential mates is traditionally within the female evolutionary purview. Given this proposed evolutionary adaptation is more important and more developed in one sex then it might be expected that that sex be more affected by dysregulated amplification of the system.

Conclusion

Paraphilic disorders are a ripe area for further consideration from the perspective of the evolutionary psychiatrist. While this short exploration of the topic mainly proposed theories that follow pathological expressions of healthy responses that are vulnerable to excess expression and dysregulation, there are likely numerous examples of evolutionary vulnerabilities for paraphilia that are due to the mismatch between our ancestral environments and the modern day. The development of the internet in particular has allowed for a great proliferation in human sexual expression and unfortunately not all of it can be considered healthy.

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EPSIG Essay Competition 2025—Prize Winner

How an Evolutionary Perspective can improve our understanding of schizophrenia

Isaac Grennan, Medical Student

The evolutionary paradox of schizophrenia

Schizophrenia is a complex mental health disorder consisting of a combination of positive (e.g., hallucinations and delusions), negative (e.g., anhedonia, blunted affect, asociality, and alogia) and cognitive symptoms[1]. These symptoms can cause significant distress and functional impairments in those who suffer from schizophrenia[1]. Indeed, considerable research has demonstrated that schizophrenia substantially reduces the probability of surviving and having offspring, known as 'evolutionary fitness'[2]. Some estimates suggest that the evolutionary fitness is reduced by up to 70% in those with schizophrenia[2,3]. Schizophrenia is also strongly heritable, with numerous alleles being demonstrated to confer a genetic risk[1,4]. Reasoning from first principles, you might expect that these alleles that confer risk for a disorder that vastly reduces evolutionary fitness would be selected against across generations[2]. However, many of these alleles remain relatively common within and across geographically and temporally distributed populations[2]. Indeed, evidence even suggests that several schizophrenia-associated alleles have been evolutionarily selected for across time[2,5]. This contradiction is at the core of the 'evolutionary paradox of schizophrenia'[6]. In this essay, I will explore the evidence for one putative solution to this paradox, the 'cliff-edge hypothesis'[2].

Why might evolution select for disorder?

This problem exists at the core of evolutionary biology: why are certain alleles that seem to reduce evolutionary fitness resistant to negative selection pressures[7]? I will approach this problem first with respect to a well understood disease associated allele, the allele for haemoglobin S[8]. Sickle cell is a recessive blood disorder of the haemoglobin protein which causes red blood cells to sickle in shape, particularly in hypoxic conditions[9]. This can result in a sickle cell vaso-occlusive crisis, causing pain, ischaemic tissue damage and even death[9]. Those with sickle cell disease, therefore, have measurably reduced evolutionary fitness[2]. However, those heterozygous for haemoglobin S (sickle cell trait) have increased resistance to malaria[8]. Sickle cell trait thus increases fitness in environments where malaria is endemic[8]. This creates a tension in natural selection, where the heterozygous genotype is selected for, but the homozygous genotype is selected against[7] (**Fig. 1**). Known as antagonistic pleiotropy, this situation has been proposed to determine the relative prevalence of alleles in a number of recessive disorders, including cystic fibrosis and beta thalassemia[7].

The equilibrium point for the prevalence of such an allele depends on the relative advantage and disadvantage of the heterozygote and homozygote, respectively. Specifically, the greater the advantage conferred by the heterozygous genotype, the more prevalent an allele will be. Conversely, the greater the disadvantage of homozygotes, the smaller the proportion of individuals that will express a certain allele[8]. Interestingly, however, even in extreme examples where the homozygous genotype has a 100% lethality and the heterozygote has a small advantage to fitness (approximately 1%), natural selection would be expected to maintain allele frequency such that roughly 1/10,000 individuals were homozygous rather than removing the mutation from the population[8]. This indicates that even a small relative advantage can be sufficient to result in the maintenance of an allele within the population.

From monogenetic to polygenetic

This framework suggests that schizophrenia -associated polymorphisms might be selected for if they confer an advantage at a moderate 'dose', even if they create a high risk of the disorder at a high 'dose'[2]. Sickle cell is a monogenetic disorder: in this case, the dose response curve between the

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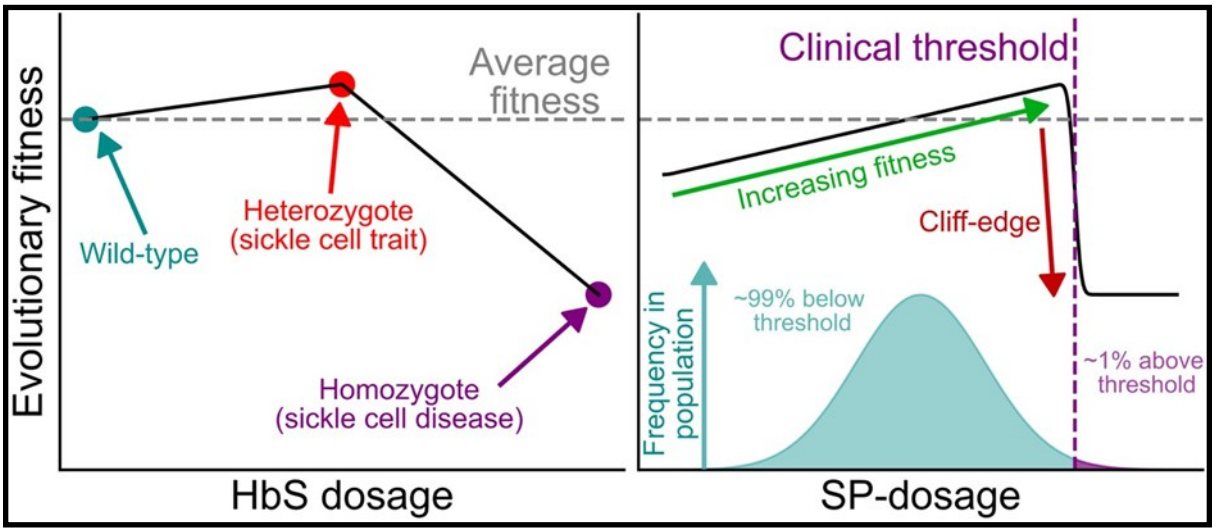

Figure 1: In the cliff-edge model (analogous to sickle cell disease) with increasing SPdosage there is an initial increase in fitness, followed by a sharp decline. Left: A schematic showing the dose response curve of the number of alleles of HbS and evolutionary fitness. As the 'dosage' of HbS increases from wild-type (0 alleles) to heterozygous (1 allele), fitness increases. However, further increases in HbS 'dosage' from heterozygous to homozygous (2 alleles) lead to a sharp reduction in fitness. **Right:** A schematic showing the dose response curve of schizophrenic-polygenetic risk on evolutionary fitness in the cliff-edge model. Initially, increasing SP-dosage increases fitness, followed by a sudden decline when the clinical threshold for being ultra-high risk for schizophrenia is reached. Also, pictured here is a schematic of the distribution of SP-dosage within the population

genetic expression and fitness is simple[2,8]. That is, one and two haemoglobin S alleles confer a survival advantage and disadvantage, respectively[8]. How does this apply to a complex polygenic disorder such as schizophrenia?

Mitteroecker et al.[2] modelled risk genotypes for schizophrenia as a continuous heritable trait reflecting an individual's overall risk of developing the schizophrenic phenotype. They then went on to postulate a dose-response relationship between an individual's genetic-risk profile and their evolutionary fitness. They argue that as a person's schizophrenic polygenetic dosage (SP-dosage) increases, there is initially increasing fitness[2]. However, at some point as SP-dosage increases, a threshold is crossed after which the individual is at ultra-high risk of schizophrenia and there is a sudden reduction to overall fitness[2]. This threshold would arise at an extreme position of SPdosage such that approximately 1% of the population would go on to develop schizophrenia (**Fig. 1**) (matching the empirically observed prevalence[1,10]). As a result, for the majority of the population, increasing the expression of polygenic risk genes for schizophrenia increases their overall fitness[2]. There is, therefore, a proposed evolutionary trade-off between the reduction in fitness that occurs in a small proportion of the population with SP-dosage above the clinical-threshold and the increasing fitness experienced by the majority of the population[2].

The view from the cliff-edge

The cliff-edge hypothesis provides a theoretical framework by which schizophrenic risk genes may be selected for[2]. However, two empirically testable postulates follow from the cliff-edge hypothesis, which I will discuss below.

Polygenic risk alleles for schizophrenia should be evolutionarily selected for across time. Several schizophrenia risk alleles appear to have increased in prevalence in humans as compared to Neanderthals[2,5], suggesting positive evolutionary

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selection. Equally, changes in methylation in schizophrenia risk genes further support this line of evidence.
Methylation acts to functionally downregulate the expression of genes within DNA[11]. There is reduction in methylation of schizophrenia associated risk alleles in humans as compared to Neanderthals[2,12], again suggesting positive selection.

While evidence supports positive selection in early evolution, negative selection of some risk alleles has been observed in later human evolution[13]. This negative selection seems at odds with the cliff-edge hypothesis. Mitteroecker et al. offer the following explanation[2]: in early evolution, the SP-dosage would have been at a low average level in the human population. As such, the SP-dosage was at a considerable distance from the fitness cliff edge and increases in SP-dosage would generally confer a fitness advantage and thus be selected for. However, as the population approaches a new equilibrium point with higher SP-dosage, the population average will exist closer to the cliff-edge. At this point, evolutionary increases in the SP-dosage run the risk of producing large increases in the proportion of the population that go on to develop schizophrenia with the associated fall in evolutionary fitness. This produces an evolutionary turning point, after which new mutations which further increase SP-dosage will be selected against[2].

Increased expression of schizophrenia risk genes should be positively correlated with evolutionary fitness in nonschizophrenic individuals.
For the cliff-edge hypothesis to hold, you would expect there to be some empirically measurable advantage in fitness with increasing SP-dosage in non-schizophrenic individuals, presumably at some neuropsychiatric level[2]. However, at the level of cognition, SP-dosage is in fact negatively correlated with general intelligence[14], with deficits in working memory and executive function being particularly implicated[15]. Equally there is some evidence that increased SP-dosage is associated with increased age-driven cognitive decline[16]. As such, if an overall neuropsychiatric advantage is to be conferred, it must be at a level that is poorly captured by standard intelligence testing. Indeed, there is some evidence that in spite of poorer overall general intelligence, that educational performance is positively correlated with SP-dosage[17].

One possible such domain is creativity and divergent thinking where schizophrenic individuals appear to have an advantage[2,18,19]. Indeed, multiple studies have demonstrated a correlation between schizophrenia risk alleles and creativity[19–21]. However, whilst robustly statistically significant, only around 0.4% of the variance in creativity can be explained by SP-dosage[19]. Mitteroecker et al. do argue that only a weak increase in fitness in non-schizophrenic individuals is necessary for positive selection of schizophrenia risk genes[2]. However, it is not clear whether this very small effect at the level of creativity would qualify.

Overall, this mixed evidence at the level of neuropsychiatric features does not provide strong support for a clear selection advantage for schizophrenia risk genes. Does this challenge the foundations of the cliff-edge hypothesis?
Is all polygenetic risk created equal?

Recent research by Bhattacharyya et al. provides insight into this seeming paradox, demonstrating that SP-dosage is not a single, homogenous variable[17]. They identified two groups of schizophrenia -risk conferring single nucleotide polymorphisms (SNPs), *concordant* and *discordant* alleles. *Concordant* alleles, as described above, increase the risk of developing schizophrenia and are associated with a reduction in general intelligence and academic attainment[17]. However, *discordant* alleles, fascinatingly, increased schizophrenia risk but were associated with higher levels of cognitive performance[17]. Bhattacharyya et al. identified 270 loci that harboured *discordant* SNPs[17]. These *discordant* genes tended to be associated with the neurodevelopment of the hindbrain and cerebellum, and synaptic function, whereas *concordant* alleles were associated with neurogenesis[17].

Perhaps, considering SP-dosage as an amalgam of all of the risk conferring alleles, as is commonly used in studies investigating the relationship between SP-dosage and psychometric features, is a fundamental misstep. This analysis will pool the effects of *concordant* and *discordant* alleles into a

(cont.)

single variable. Bhattacharyya et al. found that the number of *concordant* gene loci was approximately 30% greater than the number of *discordant* loci[17]. Therefore, it is possible that when *concordant* and *discordant* alleles are aggregated into SP-dosage that the effects of *concordant* alleles win out, giving the impression of a negative relationship between SP-dosage and cognition in nonschizophrenic individuals[17]. As such, a careful dissection of *concordant* and *discordant* genetic risk may be of considerable benefit to future research.

When does the cliff-edge hypothesis apply?

The requirements of the cliff-edge hypothesis are for the alleles that make up SPdosage to confer a fitness advantage in those with subclinical schizophrenia risk. This property could be well captured by the aggregate sum of *discordant* risk conferring alleles and so may be a more sensitive way to define SP-dosage for the cliff-edge model. Perhaps then this model of evolutionary selection applies only to the *discordant* subset of alleles. How are concordant risk alleles maintained despite reduced fitness across a range of polygenetic doses?

In the case of concordant alleles, while not subject to positive selection by a cliff-edge phenomenon, other explanations from evolutionary biology may apply. For instance, in 'evolutionary mismatch', these alleles may have been selected for by pressures from historical living conditions that do not apply to contemporary life[2,22]. Alternatively, benefits conferred not directly by the individual but at the level of related kin[2,23] or differences in reproductive behaviour[2,24] may also play a role in the evolutionary selection for concordant alleles.

Conclusions

The cliff-edge model provides a theoretically attractive framework to explain how alleles which confer a risk for schizophrenia undergo positive selection pressures[2]. In practice, however, this model can likely only apply to the *discordant* subset of schizophrenic risk genes, which have fundamentally different dose-response properties to *concordant* alleles[17]. Future research relating schizophrenic polygenic dosage to psychometric feature should therefore not consider all risk genes homogenously and should consider a nuanced bi/multivariate approach. It is important to highlight that the cliff-edge model does not prohibit a role for other modes of positive selection pressure in the maintenance of alleles that confer a risk of schizophrenia[22–24]. In fact, here I outline a possible synergistic role of the cliff-edge model with other hypotheses such as evolutionary mismatch, particularly in the case of *concordant* alleles.

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