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Kaleidoscope

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Deprivation in early life is associated with childhood psychiatric disorders, but the developmental trajectories of these are not well understood. An intriguing study by Sonuga-Barke *et al*[1] followed up long-term outcomes (to ages 22–25) of children who had suffered severe deprivation, from birth until 4 years of age, in Romanian institutions before being adopted into the UK. Their plight, including partial starvation and a lack of human contact and care under Ceaușescu's regime has been well reported, as has the fact that many showed a remarkable and rapid improvement in developmental delays upon reaching the UK. Through childhood, those who had spent less than 6 months in such an environment suffered comparatively low levels of psychiatric symptoms, similar to their British counterparts. However, despite well-resourced and loving care from their adoptive UK families, children who had spent more than 6 months in this deprivation had persistently greater rates of autism spectrum disorder (ASD), disinhibited social behaviour, and inattention and hyperactivity symptoms that persisted into adulthood. Although childhood cognitive impairment in this more vulnerable group returned to normal levels by later life, they had lower educational attainments and higher rates of unemployment and increased use of mental health services. The authors praise the resilience of the children, noting how a fifth of those who spent more than 6 months in deprived care still remained problem-free at all points: it also underlines how this was not the case for the other 80% of them. In seemingly introspective political times, it reminds us to look outwards.

Bigger is not always better; larger brain size is associated with developing ASD during childhood, but the timing of any brain changes and their relationship to the emergence of signs and symptoms has been less clear. Having a non-invasive, longitudinal measure of brain volume may help predict ASD in children with a significant familial risk. Hazlett *et al*[2] studied 106 high- and 42 low-familial-risk infants using magnetic resonance imaging (MRI) to show how early hyperexpansion of cortical surface area at ages 6–12 months precedes brain volume increases seen in children aged 12 and 24 months who went on to be diagnosed with ASD at 24 months. MRI scans of 15 infants with high risk and diagnosed with ASD aged 24 months (HR-ASD), 91 with high risk but *no* ASD (HR-neg) and 42 low-risk (LR) infants were acquired at 6, 12 and 24 months. The cortical surface area growth rate measurements of the HR-ASD group were significantly higher in the first 12 months of life compared with both the HR-neg and LR groups; this effect disappeared at 24 months. In terms of total brain volume, there was no difference between groups in the first year of life but the HR-ASD group (compared with HR-neg and LR) had higher total brain volumes at 12–24 months. There was no similar pattern observed in measurements of cortical thickness. It appears that cortical surface area expansion in the first year of life *precedes* change in total brain volume observed in the second year. Further, using only the data from HR-ASD (n = 34) and HR-neg (n = 145), a deep-learning classifier was developed, where intracranial volume, cortical thickness, cortical surface area (at 6 and 12 months) alongside gender were used to predict a diagnosis of ASD at 24 months. The classifier achieved 88% sensitivity and 95% specificity (positive and negative predictive values of 81% and 97% respectively). The predictor variables most utilised (11 of the top 12 variables) by the classifier turned out to be cortical surface area, and half of these were variables that referred to measurements at 6 months.

Recognising the depressions as a spectrum phenomenon is one thing; utilisation of this information is another. Highly differing responses to antidepressants are often heralded as evidence of varying underlying biopsychosocial pathogenesis, and the limitations of aggregated clinical scale scores are recognised, but what can we do with this information? Chekroud and colleagues[3] took symptom data (Hamilton Rating Scale for Depression and Quick Inventory of Depressive Symptomatology – Self-Report scales) from nine clinical trials (total $N = 7221$) including STAR*D to cluster depressive symptoms, identifying three robust groups: 'core emotional', 'sleep' and 'atypical' (primarily psychomotor changes and hypersomnia). Using mixed-effects regression analysis, treatment response trajectories of these clusters were mapped. Overall, antidepressants were more effective for emotional symptoms rather than sleep or atypical ones, but there were interesting differences between medications that were often bigger than the difference between active interventions and placebo. For example, high-dose duloxetine was significantly superior to escitalopram in treating core emotional symptoms, and the authors propose patients' symptom clusters may aid drug selection.

Following on from this, there has been much hope and effort invested in pharmacogenetics, predictive response to treatment, and personalised prescribing. The Major Depressive Disorder Working Group of the Psychiatric Genomic Consortium report[4] on polygenic risk scores used to estimate multi-allelic contribution to medication effects and the overlap between major depressive disorder and schizophrenia. STAR*D data were again utilised, this time combined with six other study cohorts. No significant predictor of antidepressant efficacy was obtained. Although data from over 6000 patients were utilised, the authors argue that larger or more homogeneous samples will be necessary if polygenic predictors of response to antidepressants are to be found.

Neurofeedback training has been suggested to be a valuable tool in moderating cortical hyperarousal, with positive reports in moderating attention-deficit hyperactivity disorder, epilepsy and insomnia. However, the research underpinnings are not robust, and hype is no substitute for robust study design. In these disorders, training aims specifically to increase 12–15 Hz sensorimotor cortex rhythms associated with relaxation and inhibition of motor activity, offering an instrumental conditioning approach to reward achievement of a desired electroencephalography pattern. Writing in *Brain*, Schabus *et al*[5] examine neurofeedback in insomnia, with a double-blind design wherein half the participants had placebo-feedback training – in other words, sham. Both the real- and placebo-neurofeedback patients showed equal subjective improvements in sleep, and there were no objective electroencephalographic measurement changes after 12 sessions, inferring no alteration to underpinning sleep neural architecture. The authors further stratified participants into those with 'true' and 'misperceived' insomnia (the latter having subjective but no objective sleep problems), with no impact on the findings. Any accrued benefits appear to be from non-specific confounders such as trust, and receiving care and empathy. The findings highlight the importance of good trial design, and the use of appropriate control conditions if neurofeedback therapy is to last the distance.

Chiming with issues of methodological concern, the mathematician Blaise Pascal opined that 'People almost invariably arrive at their beliefs not on the basis of proof but on the basis of what they find attractive'. Mogil & Macleod[6]

describe a new kind of research paper, the 'preclinical trial', which aims to increase confidence in multiple single, often small-scale published experiments while allowing exploration of novel ideas in basic science. They focus on animal studies relevant to developing disease therapies, as basic-science researchers are good at formulating novel hypotheses and possess the technical expertise to conduct these studies. However, on the basis of positive finding, they must then spend time and money reproducing the same experiment to increase confidence (i.e. lowering the probability that the result is a false positive). Problematically, this focuses teams on producing one, apparently confident confirmation of their hypothesis and moving to publication: it is then costly for another team to reproduce the experiment wholesale to confirm or refute the result – and there is little incentive to work this hard trying to eventually publish a null result.

Mogil & Macleod suggest that in advance, plans are made between consortia of basic scientists to contribute their data from multiple exploratory studies (e.g. multiple animal experiments) to be submitted for a confirmatory, 'preclinical' analysis. Then, a separate team perform an *a priori* planned analysis of these data using more stringent thresholds for significance ($P<0.01$) with sufficient data from each exploratory experiment. They argue that positive predictive values should be used to guide sample size and necessary significance thresholds (resulting, as it transpires, in a requirement for larger sample sizes in the basic studies). Blinding and randomisation are required – as usual – to prevent bias. They propose that this allows the basic-science teams to focus on generating and testing hypotheses (suggesting that they ignore attempts at hypothesis testing to a defined *P*-value), shifting issues of replicability and testing of false positives to the separate preclinical analysis team. They then propose a culture shift, from publishing one high-impact result from a single basic-science experiment, to a more regarded, higher-impact paper containing the results from the confirmatory analyses.

Borderline personality disorder (BPD) is highly prevalent and can be terribly debilitating. Several psychotherapeutic approaches have been recommended, and Cristea *et al*[7] update us on their efficacy. In the BPD literature, many trials have been carried out by those people who had developed the intervention under evaluation. The authors restricted their meta-analysis to trials with a randomised control intervention, stratifying by whether the interventions were stand-alone or added to existing treatment. In total, 33 studies ($N=2256$) were included, with symptom change, self-harm, and suicide as the defined BPD-relevant outcomes – a useful moment to remind ourselves that suicide is *fifty* times more common in this group than in the general population. Dialectical behaviour therapy and psychodynamic approaches were the only types demonstrated to be more effective than the control interventions, but overall the gains over non-specialist interventions were modest and the literature was marked by considerable publication bias. Interestingly, neither the number of sessions nor duration of treatment was associated with benefits. Nevertheless, where positive gains accrued, they were maintained for an average of about 2 years. The authors argue that greater improvement from more specialist interventions may follow from their highly structured and manualised approach fitting the common desire for consistency in those with BPD.

Our out-going College President has never been shy of being part of a provocative scientific debate: always backing the evidence base, we hasten to add. Writing with colleagues in the *Lancet*,[8] the crucial issue of the effectiveness of post-military-deployment mental health screening and advice about help-seeking are tested. UK Royal Marines and Army personnel returning from Afghanistan were randomised at a platoon level to receive either tailored help-seeking, or general mental health advice. Initial assessments were undertaken 6–12 weeks post-deployment, with follow-up 10–24 months later, utilising a battery of scales for post-traumatic stress disorder, depression, anxiety and alcohol misuse. This is the first randomised controlled trial on the topic, and it incorporated an impressive 10 190 military personnel. Post-deployment screening for mental ill-health based on tailored advice was not effective at reducing illness prevalence or increasing help-seeking. Several countries, notably the USA, have already implemented routine screening. The implications of this study, and the continuing mental health needs of our service personnel, are enormous: between 2001 and 2014 over 220 000 were deployed to Afghanistan or Iraq (almost two-fifths more than once), with 632 deaths and 838 serious injuries.

Finally, the 'mad cat lady' is a recurring cultural trope, and there has been a peculiarly enduring link between (why always female?) cat owners and mental ill-health. There have been concerns about neuropsychiatric sequelae to congenital or early life infection with the parasite *Toxoplasma gondii*, which reproduces exclusively in cats, but can spread to other warm-blooded animals. Infection in humans can result in the formation of cysts in the brain, and it has been linked to the development of schizophrenia and obsessive–compulsive disorder (thus, fascinatingly, providing a logical model for the cat hoarder – like something from a horror movie, the parasite may *make* you collect more cats for it). A team from University College London investigated the psychosis link[9] using prospectively collected UK birth cohort data. There findings were strongly conclusive that cat ownership during pregnancy and exposure to cats in early childhood were *not* associated with psychotic experiences at ages 13 or 18. Good news for feline lovers everywhere, though *T. gondii* infections can be problematic, and guidance remains for pregnant women to avoid handling soiled cat litter. On the basis of these data, it appears that cat owners are just the same as everyone else – an old wives' tail, perhaps.

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