

Kaleidoscope

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Diagnosing mental illness can be difficult. We are all aware of the flaws of ICD and DSM, but they remain utilitarian, and neuroscience has yet to offer meaningful empirically based alternatives. Attention-deficit hyperactivity disorder (ADHD) is perhaps the emblematic exemplar of both a spectrum disorder and a disorder whose very construct raises heated diagnostic debate. Karalunas *et al*¹ have attempted to refine subtyping of childhood ADHD by combining appraisal of temperament with physiological measurements of cardiorespiratory functioning, functional connectivity magnetic resonance imaging (fcMRI) data, and clinical outcomes in 437 children with a well-characterised illness to produce a novel classification algorithm. They propose that there are three types of ADHD – mild (normative emotion regulation), surgent (extreme levels of positive approach/motivation), and irritable (extreme levels of negative emotionality) – that are stable over time and independent of DSM presentation. The authors argue that multimodal diagnostic criteria – in this instance, incorporating several physical investigations – provide for a superior description over the existing heterogeneous concept of ADHD, and that this sets the stage for better testing of interventions and outcomes. Undoubtedly this is part of a broader, longer-term picture of numerous parallel fields of research contributing to how we will conceptualise and diagnose mental ill health. The grey results with fuzzy boundaries may make us yearn for the imperfect comfort and false certainty of the current categorical systems.

Fitting with this, inflammatory biomarkers have attracted much discussion, although the common finding of dysregulation in mental illness is complicated by debate about causality, sensitivity and specificity. As part of a wider birth cohort study, Khandaker *et al*² sampled the systemic inflammatory markers interleukin-6 (IL-6) and C-reactive protein (CRP) in approximately 4500 9-year-old children, and assessed for psychopathology at age 18. Adjusting for sociodemographic factors, they found that higher IL-6 levels in childhood were associated with the subsequent risk of depression and psychotic experiences in a dose-dependent manner. The pathogenic processes that may link the inflammatory markers and mental illnesses remain unresolved, but early altered immune states might serve as a useful future risk marker. Similarly, the hormone cortisol has complex roles in the regulation of physiological processes including inflammation and stress responses, and hypercortisolaemia has a long-recognised association with depression. Otte *et al*³ administered fludrocortisone and placebo to 24 unmedicated patients with depression and an equal number of controls in a randomised crossover study. Fludrocortisone, which binds to the mineralocorticoid receptors that occur in greatest number in the hippocampus and prefrontal cortex, improved verbal memory and executive functioning, as well as reducing cortisol levels, in both groups. Moving on from the question of biomarkers, this work advances the issue to ask whether neuroendocrine or inflammatory dysregulation could serve as future therapeutic targets.

The ‘moral treatment’ of mental illness that came to the fore in the 19th century, based on humanitarian principles, was a turning point in mental healthcare. Morality itself has been

more difficult to study in an empirical fashion. Indeed, Bertrand Russell observed that ‘[t]he infliction of cruelty with a good conscience is a delight to moralists. That is why they invented Hell’. We were fascinated by Hofman *et al*’s study⁴ in *Science* on the occurrence and impact of moral acts in the real world. A diverse sample of 1252 adults received a text message at five random times between 9am and 5pm on three successive days, inviting them to report if they had witnessed, learned about, or were the target of a moral or immoral act, along with an account of their emotional response. The authors demonstrated a ‘moral licensing’ phenomenon, whereby a person doing a good deed earlier in the day was more likely to undertake an *immoral* act later that day; and ‘moral contagion’, wherein being the benefactor of a positive action made individuals more likely to behave morally. In addition, they found that people identified as religious were no more likely to commit moral acts – though they experienced more gratitude and pride in response to a positive act, and greater guilt, embarrassment and disgust following an immoral one. Greatest happiness was attained when being the benefactor of a good deed; the greatest sense of purpose from undertaking one – and of course we experience both in disseminating this news to our readers.

Deaths attributable to gang activities are dominated by young men. Scientific hypotheses for the use of lethal aggression include evolutionary-adaptive struggles over resources, though the US National Violent Death Reporting System suggests⁵ that only about a quarter of these deaths appear to be precipitated by competition over criminal ‘resources’ such as drugs’ trading. Most gang-related homicides recorded by this system between 2003 and 2008 appeared to be quick, retaliatory acts between gang communities, in open public spaces and usually occurring in afternoons, evenings and at weekends. In their *Nature* paper, Wilson *et al*⁶ provide analysis of lethal aggression in chimpanzee and bonobo populations collected from 18 communities over five decades. Their study tested the competing hypotheses of whether it is human impact on their environment or the aforementioned evolutionary-adaptive resource advantage that explains lethal behaviour – but it is the similarity with human behaviour that is striking. They found that attackers and victims of killings were mostly male (92% and 73% respectively), most were inter-community attacks (66%) in groups where the median ratio of attackers to victims was 8:1. Analysis of these *Pan* species showed that the most important predictors of violence were those related to adaptive strategies – age, sex, community membership and outnumbering the victim.

Finally, there is frequent encouragement to be more ‘mindful’ these days, arguably akin to being ‘reflective’ in earlier times. We were mindful of the common perception that there are gender differences in memory, when reading a neuroimaging meta-analysis by Hill *et al*⁷. While there has been much behavioural work comparing memory functioning in men and women, far less focus has been applied to potential underlying neurophysiological differences. This study of almost 1000 individuals reported considerable areas of overlap between the genders, but there were also differences: females consistently activated more prefrontal and limbic structures, such as the amygdala and hippocampus; males activated a more distributed network that included more spatial processing parietal regions. These results fit with behavioural data, demonstrating that the genders pull upon different cognitive resources and strategies when problem solving. As well as the general interest of these findings, one is reminded of the broader issue of how a large amount of MRI work is undertaken on right-handed males, neuroimaging’s answer to

the man on the Clapham omnibus. Although this is done to remove confounders (namely, being female) – the rationale for which is indeed exemplified by Hill *et al*'s findings – it raises awkward questions about the applicability of existing neuro-imaging findings to the whole population. This thought requires more reflection, mindful that this is best done by a mixed-gender team.

- 1 Karalunas SL, Fair D, Musser ED, Aykes K, Iyer SP, Nigg JT. Subtyping attention-deficit/hyperactivity disorder using temperament dimensions. Toward biologically based nosologic criteria. *JAMA Psychiatry* 2014; **71**: 1015–24.
- 2 Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life. A population-based longitudinal study. *JAMA Psychiatry* 13 August 2014 (doi:10.1001/jamapsychiatry.2014.1332).
- 3 Otte C, Wingenfeld K, Kuehl LK, Kaczmarczyk M, Richter S, Quante A, et al. Mineralocorticoid receptor stimulation improves cognitive function and decreases cortisol secretion in depressed patients and healthy individuals. *Neuropsychopharmacology* 18 July 2014 (doi:10.1038/npp.2014.181).
- 4 Hofmann W, Wisneski DC, Brandt MJ, Skitka LJ. Morality in everyday life. *Science* 2014; **345**: 1340–3.
- 5 Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report; Gang Homicides – Five US Cities, 2003–2008. CDC, 2012 (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6103a2.htm>).
- 6 Wilson ML, Boesch C, Fruth B, Furuichi T, Gilby IC, Hashimoto C, et al. Lethal aggression in Pan is better explained by adaptive strategies than human impacts. *Nature* 2014; **513**: 414–7.
- 7 Hill AC, Laird AR, Robinson JL. Gender differences in working memory networks: a brainmap meta-analysis. *Biol Psychol* 2014; **102**: 18–29.