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Kaleidoscope

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Breaking down mind–body dualism is the theme this month. We know that physical ill health goes hand in glove with mental illness, but chronic physical health problems are too often underestimated. Tian et al[1] used large international biobanks to compare over 85 000 individuals with defined mental illnesses with a similar number of healthy controls. They contrasted a range of health scores across seven body systems – metabolic, hepatic, immune, pulmonary, renal, cardiovascular and musculoskeletal – as well as looking at overall neuroimaged brain health. Poor physical health – particularly metabolic, hepatic and immunological – was evident and shared across those with schizophrenia, bipolar affective disorder, depression and anxiety. Despite this, chronic physical abnormalities were commonly not diagnosed even years after assessment. Interestingly, such differences were more marked than brain changes compared with healthy controls, although variations in white and grey matter were better able to distinguish the various psychiatric conditions. We inadequately identify and manage physical problems in contemporary mental healthcare. This includes through diagnostic overshadowing and fundamental failures in professionals' training and psychiatric services' expectations of care pathways. From screening, through examination and investigation, to accessing care and future preventive work, we need to do better.

Reversing the idea, a paper in the *Lancet*[2] explores a cognitive approach to managing chronic, disabling back pain. Globally, low back pain trumps even depression in terms of years lived with disability: the article notes that its societal costs are greater than those of cancer and diabetes combined. Analgesics typically have limited impact and too often come with a range of unwelcome side-effects. Cognitive–functional therapy (CFT) is an evidenced intervention, teaching patients self-management by targeting pain-related thoughts, emotions and behaviours. Distinct from cognitive–behavioural therapy, it directly addresses pain-inducing activities such as protective muscle guarding and movement avoidance, with a physiotherapist-supported individualised 'clinical reasoning' approach that explores both movements and patients' narratives around these. However, to date, trials have lacked the necessary study size and cost-effectiveness, elements that are redressed in this work. Kent et al compared CFT, with or without movement sensor biofeedback, with usual care in just under 500 patients with this condition. Biofeedback enhances experiential learning through improving individuals' understanding of the effects of normal and corrective movements. Both active interventions produced large, clinically relevant improvements in terms of reducing pain-driven limitation of activity, with similar effect sizes sustained to 1-year follow-up. The improvements were greater and longer lasting than those achieved by most other existing interventions for back pain, although it is not clear why the addition of biofeedback did not further enhance outcomes when added to CFT. As well as being effective in improving quality of life, providing this care was far less expensive compared with alternatives in terms of direct and indirect costs and productivity losses. CFT would appear to offer a low-cost and low-risk yet high-value care pathway that could be delivered in primary care settings.

We're all familiar with Penfield's iconic physiology textbook homunculus that shows a distorted Gollum-esque body mapped to a coronal primary motor cortex; time to check whether it's still accurate. A magisterial paper in *Nature* says 'no', with important implications. As well as using tens of thousands of publicly available neuroimaged data-sets, Gordon et al[3] utilised precision and high-resolution functional magnetic resonance imaging (fMRI) to show cortical interruptions to the canonical concentric somatotopic effector mapping via three cortically thinner regions. These 'inter-effector regions' were strongly connected to each other and to a cingulo-opercular network that is an essential component of broader physiological control and action. The neuroimaging was cross-species and neurodevelopmental, undertaken on macaque monkeys as well as human children at different developmental stages from newborn through infancy to childhood. During evoked motor tasks, these inter-effector areas did not have body region specificity but helped to coordinate action planning of limb and axial body movements, as well as integrating with internal organs such as the adrenal medulla. Data showed that the inter-effector regions were evident by 11 months in human infants and reached adult levels by age 9 years. The authors redefine the M1 motor cortex as having two parallel, contrasting, yet interleaved movement systems: one comprises the more traditionally established effector-specific regions controlling fine movements such as those of the foot and hand; the other, named the somatocognitive action network, or SCAN, integrates broader body movements and goals and helps to control the organism as a whole, including a role in autonomic functioning. The SCAN is relatively bigger in humans than in other primates, which the authors propose is related to our necessarily greater need for complex species-specific actions such as coordination of breathing while talking and integrating hand, eye and body movements in tool use – including physiological and arousal processes such as increased heart rate. They conclude: 'The finding that action and body control are melded in a common circuit could help explain why mind and body states so often interact'.

Finishing this unification, might there really be a shared neural basis for all psychiatric comorbidities – the proposed neuropsychopathological (NP) factor? It feels, surely, too big an ask, but an impressive collaboration writing in *Nature Medicine*[4] lay claim to finding this Grail. Taking a large longitudinal cohort that ran to early adulthood and utilising multitask connectomes, they explored neuroimaging data and internalising (anxiety, depression, eating disorders, etc.) and externalising (attention deficit, autism spectrum, conduct disorder, etc.) symptoms. The NP is reported to be a genetically determined neural phenotype of delayed development of the prefrontal cortex. This transdiagnostic NP primarily targets top-down regulatory circuits, which have been linked with dysfunctional emotional and reward processing more generally. It was found across different developmental time points and associated with poor executive functioning, and was generalisable to the resting state connectome and clinical samples. Interestingly, and against the grain of other work on the topic, there was a hyperconnectivity of this prefrontal circuitry, which can variously be argued to represent compensation for inefficient bottom-up processing or a disruption and delay of normal developmental executive control efficacy through synaptic pruning and stabilisation. What does it all mean in reality? Psychiatric comorbidities are certainly common – the authors highlight data showing that perhaps a quarter of adolescents meet multiple diagnostic criteria – and one can reason about shared biopsychosocial origins or risk factors. If this is taken as a vulnerability factor, there are implications for both preventive work and (particularly early) interventions if it turns out to be a reliable biomarker in clinical practice.

We're at an exciting frontier in genome analyses, with ever-greater computer processing power being able to handle ever-

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bigger data-sets. Cross-species work offers the potential to identify survival-crucial highly conserved and species-specific fast-evolving innovative regions. 'Zoonomia' is the largest mammalian genomic database, and an international collaboration write in *Science*[5] on comparative constraint and innovation across these species. The principle is that anything conserved for long time periods and across multiple species must have been highly selected for and inferentially is critical for life; conversely, fast-evolving species-specific regions might underpin unique elements. Taking data from 240 placental mammalian species, the authors found that at least 332 million bases, or just over 10% of the human genome, were unusually conserved across species, with 4552 of these near-perfectly 'ultraconserved' and identical in 98% of the species. Fascinatingly, of over 100 million significantly constrained single bases, four-fifths were outside protein-coding exons and half had no known functional annotations. In other words, they are being very strongly selected for retention in our shared gene pool across species, but we don't know what they are doing, and many do not appear to be coding for proteins but are presumably regulatory enhancers or promoters. Understanding the genomes of our mammalian cousins is of more than just academic interest. The authors cite the example that if we understood bases associated with the exceptional capacity for cellular recovery seen in hibernating animals, then we would be better placed to translate this to human therapeutics, for example, in mitochondrial disorders.

Size matters, but isn't everything – when it comes to brains at least – and a new preprint[6] asks whether there are smarter approaches to evaluating evolutionary changes in cognitive development. Castillon et al trek back 400 million years – something that always warms the cockles of my evolutionary heart – and suggest that mere brain-scaling is inadequate as a mechanism to explain our species' complexity. A bottlenose dolphin's brain, for example, is larger than yours, though I'd challenge their similar assertion regarding Neanderthals (with more recent data suggesting this was within the error bars of early *sapiens* whose brain size exceeded that of modern humans). They (the paper authors, not Neanderthals) cleverly used multi-modal neuroimaging, notably integrating positron emission tomography/MRI scanning, to allow simultaneous measurement of the cerebral metabolic rate of glucose and the extent of synchronised signalling between brain voxels. This showed that our more recent frontoparietal hominin brain connections are far more energy dependent than the phylogenetically older sensory-motor pathways – needing up to two-thirds more energy per unit volume. It's certainly a proxy measure, but 'energy in' is telling us something about 'work done', and, in the brain, work is information processing. There has been an allometric expansion of hominin brains over time, but those regions that have expanded most have needed relatively more energy, even taking their greater size into account. Histological and transcriptomic data independently confirm upregulation of G-protein-coupled receptors in such regions, with genes coding for molecular signal transduction functioning appearing to be driving much of this demand. Ninety-five per cent of genes overexpressed in these regions are involved in ionotropic (glutamate, GABA) signalling and, notably, in greater metabotropic signalling such as serotonin, dopamine and noradrenaline signalling, which have complex, energy-dependent downstream cellular effects. In other words, the arrangement, density and complexity of neuromodulators are involved in the more complex cognitive processes, including memory processing, and have evolved to make you human.

Finally, how good are you at statistics – honestly? Could be a bit sharper – amirite? In work to make both David Dunning and Justin Kruger proud, Lakhlifi et al[7] ask the smarter question: not how good is healthcare professionals' statistical literacy, but how aware are they of such deficits in the first place? In other words, do you know what you don't know? The authors note that when provided with the relevant information to calculate a positive predictive value, a key measure in determining whether a positive result means a person has a condition or illness, clinicians often confuse this with sensitivity and only get the correct result about 10% of the time. Here's a straightforward example from the paper to perhaps get you sweating a little: in a population of 1000 people, ten have disease X; among those ten, nine will receive a positive test result, whereas 901 of the 990 healthy people will receive a negative result. How do you think you'd do in calculating a positive or negative predictive value for that simplified investigative test? The authors surveyed a little under 1000 medical students and physician residents, testing their skill and confidence on three topics: vaccine efficacy, *P*-value and diagnostic test result interpretation. Further, they asked in each instance how confident the participant was with their result, on a sliding scale from 'I am sure that it is incorrect' to 'I am sure that it is correct'. Overall, those tested didn't do so well on their stats; for example, only half could correctly identify the correct definition of a *P*-value. Moreover, most thought that they did fine, with high confidence, even on incorrect answers. If there's a positive, the authors found a 'metacognitive sensitivity' insofar as, despite their biased levels of confidence, participants knew they were a bit shakier on those they got wrong. Speaking of biases, seeing that they controlled for gender, experience and research activity, I went in expecting a stronger false confidence from cockier young men. You know the type. Or maybe that's just my experience around some choice academic and teaching institutions that shall remain nameless. Interestingly, the authors did not report on gender for this: I choose to stand by my prejudice until corrected by some hard data. Stats matter in medicine, for clinicians as much as academics: you need to be able to interpret the literature through your career. But so does having insight into how well you can do this, and where your gaps are. It makes me think we might all benefit from intermittent repeating stats top-up sessions; that certainly feels more useful than some of my current 'how to correctly lift a cardboard box' mandatory training.

References

1 Tian YE, Di Biase MA, Mosley PE, Lupton MK, Xia Y, Fripp J, et al. Evaluation of brain-body health in individuals with common neuropsychiatric disorders. *JAMA Psychiatry* [Epub ahead of print] 26 Apr 2023. Available from: https://doi.org/10.1001/jamapsychiatry.2023.0791.

2 Kent P, Haines T, O'Sullivan P, Smith A, Campbell A, Schutze R, et al. Cognitive functional therapy with or without movement sensor biofeedback versus usual care for chronic, disabling low back pain (RESTORE): a randomised, controlled, three-arm, parallel group, phase 3, clinical trial. *Lancet* [Epub ahead of print] 2 May 2023. Available from: https://doi.org/10.1016/S0140-6736(23)00441-5.

3 Gordon EM, Chauvin RJ, Van AN, Rajesh A, Nielsen A, Newbold DJ, et al. A somato-cognitive action network alternates with effector regions in motor cortex. *Nature* 2023; **617**(7960): 351–9.

4 Xie C, Xiang S, Shen C, Peng X, Kang J, Li Y, et al. A shared neural basis underlying psychiatric comorbidity. *Nat Med* [Epub ahead of print] 24 Apr 2023. Available from: https://doi.org/10.1038/s41591-023-02317-4.

5 Christmas MJ, Kaplow IM, Genereux DP, Dong MX, Hughes GM, Li X, et al. Evolutionary constraint and innovation across hundreds of placental mammals. *Science* 2023; **380**(6643): eabn3943.

6 Castrillon G, Epp S, Bose A, Fraticelli L, Hechler A, Belenya R, et al. An energy costly architecture of neuromodulators for human brain evolution and cognition. *BioRxiv* [Preprint] 2023. Available from: https://www.biorxiv.org/content/10.1101/2023.04.25.538209v1.

7 Lakhlifi C, Lejeune FX, Rouault M, Khamassi M, Rohaut B. Illusion of knowledge in statistics among clinicians: evaluating the alignment between objective accuracy and subjective confidence, an online survey. *Cogn Res Princ Implic* 2023; **8**(1): 23.

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