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Kaleidoscope

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We open with some major and significant randomised controlled trials exploring interventions in resource-poor societies. Two papers by the same team writing in the *Lancet* explore the use of non-specialist 'lay counsellor' health workers to deliver brief psychological interventions for excessive alcohol consumption and depression in India. Male harmful drinkers in ten primary health centres were randomised to receive either enhanced usual care (EUC), or EUC and Counselling for Alcohol Problems (CAP).[1] The active intervention produced significantly greater remission and abstinence rates, with an incremental cost per additional remission of $217. A Healthy Activity Program (HAP) for moderately to severely depressed men and women was evaluated in a different cohort,[2] with a parallel design of EUC compared with EUC plus therapy. Once again, the active intervention produced significant improvements, with reductions in depression symptomatology and remission, as well as decreased illness consequences such as days out of work and intimate partner violence. Both interventions were reported to be acceptable to patients and practical for delivery in primary care settings.

Not to be outdone, *JAMA* has two studies of its own. Rahman *et al*[3] tested a multicomponent behavioural intervention delivered by lay health workers in primary care settings to adults in a conflict-affected area of Pakistan. The approach was transdiagnostic, focusing on individuals with psychological distress rather than any diagnosis per se. Five, weekly, 90-minute individual sessions that included problem-solving, behavioural activation, strengthening social support, and stress management were shown to produce clinically significant reductions in anxiety and depression at 3 months compared with EUC. Rounding this all off, Chibanda *et al*[4] took a lay-delivered culturally adapted psychological intervention, the 'friendship bench' of six sessions of individual problem-solving and six sessions of peer support, to primary care patients in Zimbabwe with symptoms of common mental disorders. Once again, the results were impressive against EUC at 6 months. The findings are consistent and compelling across the board: these lay-delivered interventions work and they are cost-effective. Practical implementation is a very different beast, but they could be feasibly scaled up; 75% of the burden of mental illness falls on lower-income countries, and there is an enormous gulf between service provision and need.

Development of post-traumatic stress disorder (PTSD) depends on various factors, including individual predisposition, prior exposure to trauma, and incident type. The lifetime prevalence for PTSD is between about 1.3 and 8.8%, but most studies evaluating the impact of different types of trauma experience have had small sample sizes. Liu *et al*[5] address this, assessing 29 trauma experience types in a large epidemiological survey ($n = 34\,676$) from the World Health Organization that covered 20 countries. Their findings confirm that trauma type very clearly matters: the odds ratios of developing PTSD were elevated for traumatic experiences involving sexual violence (2.7; 95% CI 2.0–3.8) and witnessing atrocities (4.2; 95% CI 1.3–7.9). A history of violent traumatic experience (but not other types of traumatic experience) increased vulnerability to later-life PTSD. The data showed an unexpectedly low prevalence after natural disasters; this is interpreted as suggesting that earlier, smaller, disaster-focused studies, with much higher PTSD rates, may have suffered from a sampling bias and overrepresented highly traumatised survivors. Fascinatingly, past participation in sectarian violence was associated with enhanced *resilience* to the development of PTSD. The authors suggest that this is more likely to be an effect of selection bias rather than a causal relationship: a so-called 'healthy warrior effect' has previously been posited to explain the lower prevalence of PTSD also typically seen among police and emergency service workers.

Confucius anticipated metamemory research: 'True wisdom is knowing what you don't know'. *Metamemory* is a type of metacognition involving self-monitoring and evaluation of our own memories; we have an ability to reflect on our own memory, and report confidence in a retrieval of a particular recollection. The brain structures and neural mechanisms underpinning this have been unknown. Writing in *Science*, Miyamoto *et al*[6] designed an experiment to evaluate monkeys' confidence in remembering past experiences. The macaque monkeys were scanned performing a yes/no memory recognition test with three phases: first, they were presented 4 picture cues in an ordered sequence (1 to 4). Then, in the 'choice' phase, the monkey was trained to select a cue picture (1 of the 4 presented pictures in the sequence, referred to as OLD1, OLD2, OLD3 or OLD4), or indicate 'NEW' if the cue picture was not in the preceding sequence. Finally, in the 'bet' (or wager) phase, they could opt for a high 'bet' (reflecting high confidence) or low bet (conversely low confidence). The monkeys showed classic U-shaped recall performance: if the cue picture was in positions OLD1 and OLD4 in the sequence, they were more often recalled correctly than if the cue was from intermediate OLD2 and OLD3 positions. Further, the monkey response times for recent (OLD4) cues were on the whole faster, leading Miyamoto *et al* to conclude separate and different representational stores for recent (OLD4) versus remote items (OLD1, 2 and 3) in the sequence. High bets were correlated with correct performance on the choice/recognition phase, suggesting that indeed, monkeys gambled higher rewards when they were more confident.

The functional magnetic resonance imaging (fMRI) results could then be parsed for areas differentially activated by high confidence (metamemory) modulated by remote and recent (OLD1 *v.* OLD4) cue positions: for the recent OLD4 item, the supplementary eye fields (SEF) were most active; for items OLD1, 2 and 3, the anterior posterior supraprincipal dimple (aPSPD) was more active. Then, using functional connectivity analyses, they identified that activity in the inferior parietal lobule (IPL) correlated with the aPSPD and similarly, activity in the superior parietal lobule (SPL) correlated with the SEF. Lesions induced by microinjections of the $GABA_A$ receptor agonist muscimol (but not saline) in the aPSPD and SEF affected confidence (but not recognition) performance differentially for recent OLD4 recognition, but not OLD1, 2 and 3 locations: namely, impairing metamemory, but not memory itself. The authors propose that this provides evidence that the SEF is a confidence assessment stream for recent memory, while the aPSPD provides a parallel function for remote memory.

Referrals for psychiatric assessment of those detained in police custody are common, but this is a considerably underexplored area in the scientific literature. The 43 police forces that cover England and Wales made over 13 million arrests (84% male) over the past 10 years; many of these individuals had mental health needs, and some were appropriately further referred, but what do we know about them? Andrew Forrester and colleagues redress this gap,[7] evaluating the clinical and demographic characteristics of more than 1000 consecutive police custody referrals over an

18-month period to a pilot service in South London. It operated an open-referral system, and ran 12 hours a day, 7 days a week. Those referred had high levels of mental ill-health and substance misuse, self-harm and suicidality, and various vulnerabilities, including intellectual disability. Almost 10% were acutely unwell or required admission to a psychiatric hospital. The findings help confirm what many of us have suspected, but for which we lacked good data: this is a vulnerable and often somewhat ignored or underserved cohort. The study also shows not only that appropriate resources are required, but that a mental health service delivery model can be applied within police custody as an effective tool in assessing those who present there.

We have previously proposed 'the depressions' as a spectral term[8] to cover and explain the varying responses to treatment. We remain shackled by categorical diagnostic systems that cluster syndromes of aetiologically heterogeneous conditions. Depression is an example, with five of nine – or two of three depending on which system one uses – symptoms 'required' for a diagnosis, presenting hundreds of permutations. Writing in *Nature Medicine*, Drysdale *et al*[9] propose that neuroimaging can separate 'depression' into four neurophysiological 'biotypes' with distinct patterns of resting-state functional dysconnectivity between the limbic and frontostriatal networks. Functional magnetic resonance imaging was applied to almost 1200 individuals with depression, and clustering them by fMRI signature allowed the creation of diagnostic classifiers with high sensitivity and specificity for depression subtype in multisite validation and an out-of-sample replication set. Addressing the vital issue of *utility*, the subtypes also predicted response to therapeutic repetitive transcranial magnetic stimulation (rTMS). Time for a trial with antidepressants.

There is a consensus that pruning – where densely connected neural networks are made sparse – is a defining process in the neurodevelopmental trajectory of the brain from infancy through adolescence to adulthood, and there is a debate that errors in this process lead to disorder, for example, in schizophrenia. It is somewhat difficult to provide empirical evidence for this in humans; however, new MRI techniques allow the quantification of macromolecular and lipid tissue volume (MTV) alongside measures of the tissue's lipid and cholesterol composition in cell walls and myelin by proton relaxation times (T1). These are associated with changes to multiple tissue compartments, including increases in cell bodies, dendritic structures, and myelin sheaths. Gomez *et al*[10] propose that pruning would predict lower MTV and longer T1 times, whereas proliferation would predict higher MTV and shorter T1 times, in adults than in children. Using 25 adults (age range 22–28 years) and 22 children (5–12 years), they first used fMRI to localise each participant's posterior and mid-fusiform gyrus (pFus and mFus – areas implicated in face recognition) and the collateral sulcus (CoS – implicated in place recognition). They then obtained MTV and T1 measurements in each participant for these areas and found that T1 measurements were most sensitive. The adults had shorter mean T1 times than children, suggesting proliferation – rather than pruning – in the pFus face-selective areas. Importantly, in adults, the mean T1 in the pFus is lower than in the CoS, but this differentiation is absent in children – suggesting that as neurodevelopment progresses, proliferation affects face (but not place) recognition areas. This maturation interfaces structural and functional changes in the brain: developing brain function requires cortical proliferation as well as pruning.

Finally, there has been a zombie outbreak in New York City. Novel psychoactive substances (inaccurately, but more commonly, labelled 'legal highs') are a growing concern in many branches of medicine, including psychiatry. A subgroup – synthetic cannabis receptor agonists (SCRAs) – modulate the brain's endocannabinoid system. However unlike 'traditional' cannabis, they are typically *full* agonists at cannabinoid receptors (tetrahydrocannabinol – THC – the major psychoactive component of cannabis, being a *partial* agonist) and they lack cannabidiol, an antipsychotic agent found in cannabis. There are data that 'spice', 'black mamba' and 'noids', as they are commonly called, are often very powerful, with growing evidence for significant agitated and psychotic states in some individuals.

In July 2016 there was mass intoxication in one neighbourhood of New York, linked to the novel psychoactive substance 'AK47 24 Karat Gold', catching the media's attention as those intoxicated appeared like 'zombies'. Adams and colleagues[11] analysed samples of the drug and serum and urine samples from some of those affected, determining the novel SCRA AMB-FUBINACA to be responsible. Its potency was consistent with the strong depressant effects clinically and anecdotally reported; the authors cite it as an example of an emerging class of 'ultrapotent' cannabinoids. Part of the problem with legal highs has been the cat-and-mouse rapid introduction of new compounds as older ones were banned; in the UK the Psychoactive Substances Act 2016 was enacted aiming, at least in part, to reduce this. It has closed 'head shops' and moved purchasing back to drug-dealers and online. Any effects on drug consumers' habits or reducing harms have yet to be seen. A major – but currently speculative – anxiety is whether SCRAs will also prove neurodevelopmentally damaging in the longer-term to some younger consumers.

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