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Kaleidoscope

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The utility of psychoanalytic psychotherapy remains contentious, with questions around the lack of robust research and a persistent but wearing refrain that it is ill-suited to randomised controlled trials. It is heartening to see positive data[1] from the Tavistock Adult Depression Study (TADS), the first fully randomised controlled trial of long-term psychoanalytic psychotherapy (LTPP). A total of 129 participants with refractory depression were randomised to treatment as usual (TAU) or TAU and 18 months (60 sessions) of manualised LTPP, and regularly assessed up to 42 months. The LTPP group showed significant benefits, with the greatest differences evident at the 42-month follow-up (where one-third were in partial remission compared with 4% in the control group). A 'sleeper' effect has previously been posited to underlie some of LTPP's benefits, and this work would lend support to this concept, though perhaps unsurprisingly in this cohort with refractory illness, the full-remission rates remained stubbornly low. Challenges for LTPP research remain the inability to mask participants to treatment condition, and expectations potentially changing with intervention type, as well as the problematic confounder of the considerable hours of patient–therapist contact. Nevertheless, this study confirms that robust research into LTPP can be undertaken, and reinforces the value of longer-term follow-up.

The direct burden of mental ill-health grew by over 40% between 1990 and 2010, a figure not including excess mortality or socioeconomic effects (globally, an estimated US$8.5 trillion in 2010); so where should we be investing? Patel and colleagues[2] review the key messages of the 3rd edition of the World Bank's *Disease Control Priorities* (DCP-3) and note crucial population-, community- and healthcare-level intervention priorities, particularly in low- and middle-income countries. They argue that legislative measures should focus on restricting access to means of self-harm and reducing alcohol demand, while local interventions should target parenting programmes in infancy, and schools life-skills training to engender emotional and social competencies. The proposed health-level initiatives were broken into three domains: self-management, with a focus on web-based interventions for depression and anxiety; non-specialist primary care psychological and pharmacological outreach work; and specialist services for more complex and refractory cases. Costs for low- and middle-income countries are estimated at US$3–4 per head of population, which could be met if governments increased the $<1\%$ of development assistance typically channelled into such fields, and several successful programmes from different countries are discussed as prototype exemplars.

The ROAMER international consortium[3] considered the issue from the perspective of a high-income country – where funding still lags considerably behind societal costs of illness – identifying mental health research priorities for Europe. This expert group, which had service-user representation, pinned down six strategic priorities for the next decade, with the aim of closing this gap: research into mental health promotion and illness prevention, particularly in younger individuals; focus on causal mechanisms of ill-health development across the lifespan; developing shared international multidisciplinary research networks and databases; implementing better interventions through new scientific and technological advances; empowering service users and reducing stigma; and establishing systems that address sociocultural and economic contexts. Both DCP-3 and ROAMER are welcomed roadmaps in identifying future challenges and providing a logical structure for current and planned research and development; however, their success, or otherwise, will depend upon others following them. Mental ill-health is the largest – and growing – contributor to society's illness burden, exacerbated by an ageing population. Inaction is not an option, and there are novel technologies and infrastructures that can now facilitate such work. On a positive note, the authors identify evidence[4] that investment into basic and clinical neurosciences does reap widespread personal, societal and economic reward.

Anxiety disorders demonstrate a considerable heritability, though identifying candidate genes has been hindered by phenotypic diversity, underpowered studies, and ancestry-specific effects. There are few robust gene associations, with a sizeable difficulty engendered by the high level of comorbidity between conditions (panic disorder and agoraphobia having particularly strong connections). Now a meta-analysis[5] of case–control association studies involving 23 variants in 20 susceptibility genes has described significant associations for three common gene variants in 'pure' panic disorder. This was only true for studies with samples of European ancestry, although the authors note this might be due to lower numbers and thus reduced power to detect significance in other populations. The genes have associations with amygdala and hippocampal volumes and monoamine pathways, though interestingly there were null findings for most serotonergic variants.

There are considerable environmental influences in the genesis of anxiety disorders: parenting practices such as modelling of anxiety and overprotection or excessive control have been shown to be significant contributors. Ginsburg *et al*[6] assessed the utility of a family-based intervention to prevent the onset of anxiety disorders in children of anxious parents. A total of 136 families – each with one parent with a DSM-IV anxiety disorder and one child (aged 6–13) without one – were randomised to either the intervention or an information-monitoring control condition, and assessed over 1 year. The incidence of child anxiety was 31% in the control group, and significantly less (5%) in the family intervention – a 'Coping and Promoting Strength' programme grounded in cognitive–behavioural therapy. Effects were similar for boys and girls, and across the age ranges tested. The results are promising, and fit with the aforementioned DCP-3 and ROAMER principles of preventive mental healthcare, although the prevalence of anxiety disorders, and this study's number needed to treat (NNT) of about 4, raise obvious challenges regarding implementation. A good example, perhaps, of where treatment costs need to be counterbalanced by modelling predicted future socioeconomic losses arising from a failure to intervene.

Daniel Goleman, the author of *Emotional Intelligence*, stated that a prerequisite to empathy is simply paying attention to the person in pain. Similarly, Aristotle wrote 'to perceive is to suffer' and in the domain of pain neuroscience, it turns out they may both have been fairly accurate. The discovery of mirror neuron systems showed how certain populations of neurons implicated in executing a given action also light up when the organism witnesses another performing that action. Thus, witnessing the pain experienced by another activates areas of cortex involved in primary, first-person pain – notably, the anterior insula and anterior midcingulate cortex (aMCC). This is taken to demonstrate that empathy for others' suffering relies on partial, subthreshold activation to represent the other agent's internal state. The anterior insula and aMCC are dense in opioid

receptors and implicated in the motivational–affective component of pain perception. If a 'mirror pain' system subserves empathy, one would reasonably predict that empathy for pain would be reduced as a function of blockade of these receptors. However, what about placebo analgesia? Rütgen *et al*[6] used a novel approach to explore empathy and pain perception: first, the 102 participants were given placebo analgesia and then they either received electrical stimulation or witnessed another person being made to experience pain (to test empathy). Participants' responses were diminished with placebo for both first-person pain and 'empathic' responses to others' pain. A functional magnetic resonance imaging (fMRI) version demonstrated reduced activation of the anterior insula and aMCC in both empathy and direct first-person experienced pain. If this correspondence depends crucially on the anterior insula and aMCC, then it should be possible to demonstrate the reverse phenomenon. The experiment was repeated, but participants were treated with naltrexone (an opiate receptor *antagonist*) after placebo analgesia, and showed that the reduced empathy and perception of pain effects were reversed. Empathy, it would appear, truly is grounded in self-pain.

Regarding sugar, Homer Simpson proclaimed 'I want it all: the terrifying lows, the dizzying highs, the creamy middles', sagely foreseeing contemporary health debates.[8] While the physical sequelae of excess sugar intake – such as obesity and diabetes – are well established, there is less evidence on the impact on brain functioning, although rat models have shown that an intermittent sucrose intake model produces brain changes similar to those seen from amphetamine use. Sharpe and colleagues[9] tested daily exposure to sucrose on rodents, and found that it led to a long-term deficit in learning about food cues. The deficit was dependent upon midbrain dopaminergic prediction-error signalling; lateral-ventricular infusions of the orexigenic stomach-secreted peptide hormone ghrelin produced a similar response – suggesting it mediates this process – and it was reversed by the D_2 agonist quinpirole. The authors propose a model wherein the expectation of intermittent sucrose outside of normal feeding patterns produces large bursts of ghrelin that alter dopaminergic activity. The work is the first to link D_2 receptor alterations with the intake of hedonic foods and aberrant learning about food-cue relationships. The data support the hypothesis that excess sugar leads to brain changes that promote and perpetuate inappropriate food consumption.

Food intake is clearly a complex process, further modulated by experience and environment. Much work has focused on the hypothalamus, particularly its arcuate nucleus, but Kanoski & Grill[10] in an expert review of the role of the hippocampus demonstrate that it has a crucial integrative role in appetitive and ingestive behaviour. Through episodic meal-related memories and conditional associative learning between food stimuli and post-ingestive states, the hippocampus strongly supports cognitive and mnemonic processing in the prefrontal cortex. The hippocampus further integrates external (olfactory, visuospatial and gustatory) and internal (gastrointestinal interoceptive) cues, and has receptors for peripherally driven endocrine signals of physiological energy status that reduce (leptin and small-intestine secreted GLP-1) and increase (ghrelin) food intake. The neuroendocrine elements are considered to be potential therapies in obesity, with a particular current interest in ghrelin.

Finally, Benjamin Franklin reckoned 'Tell me and I forget. Teach me and I remember. Involve me and I learn'. It is the nature of the involvement during social interactions that Hackel *et al*[11] suggest leads to the ability to learn both from immediate reward (i.e. instrumental learning) and by extrapolating from and inferentially using trait information from across social contexts. They cite the example of a colleague at work who offers their resources in abundance: through immediate reinforcement learning we learn they have high utility or value – they give you stuff when you ask for it. One might then infer a high-order property (i.e. traits we assign to that person) generalising to other contexts; for example, they might be expected to bring generous gifts or good wine to dinner parties. Such a higher order of inference learning has traditionally been less explored in reinforcement learning paradigms, though the authors note its importance in social decision making.

In their experiment, 31 participants played games involving four humans and four 'slot machines'. In a 'training phase', certain humans or slot machines paid out more money during interactions, and feedback to the participant included the amount paid by the human (or slot machine) and an indication of the proportion of the total available; the former indicates the reward value of the person/slot machine and the latter their generosity traits. How was this generosity and reward weighted in subsequent decisions? Participants generally relied more on prior generosity (rather than reward) to make decisions in this second phase of the experiment, even when the reward/generosity trade-off was biased towards immediate reward in the training phase. Further, they demonstrated in the fMRI version of the task that the ventral striatum encoded the prediction error for generosity (i.e. trait information) independently of reward – the traditionally assumed role of the ventral striatum. So, people naturally demonstrate preference for generosity, a trait representation, that can dominate over immediate reward – perhaps an important invariant property of humans that health ministers might take heed of in future contract negotiations.

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