

## Kaleidoscope

Derek K. Tracy, Dan W. Joyce,  
Sukhwinder S. Shergill**Quitting smoking isn't easy, even with the advent of e-cigarettes.**

The NHS Stop Smoking Services (SSSs) were established in 2000, and have shown superior results to nicotine replacement alone, but are characterised by low, and dropping, attendance rates. Beneath the highlight figure of a halving of UK smoking prevalence over the past 40 years lies a direct £6 billion cost to the NHS and 80 000 deaths each year, as well as recent concern that clinical commissioning groups are not renewing service funding.<sup>1</sup> Given that the 'health belief model' is based upon a trigger changing behaviour, what will encourage attendance at SSSs, especially with evidence that smokers underestimate their own personal risk? Gilbert *et al*<sup>2</sup> randomised over 4000 smokers across almost 100 general practices to receive either a standard generic advertisement of the SSS clinic, or an individually tailored risk letter and invitation to a no-commitment introductory SSS session. The hosting general practitioners (GPs) and SSS advisors were masked to the allocation. The personalised letter more than doubled the odds of attending the SSS, showing that a more proactive approach can help engagement. Interestingly, the intervention was more effective with men, who are typically less likely to attend and set quit dates.

Craving and physiological reactivity in addiction are, in part, conditioned responses to learned cues. Extinction training, with extended, unreinforced cue exposure, has been shown to reduce these, though in practice, effectiveness has been disappointing. Retrieval extinction is a modification that strategically delivers the technique during a reconsolidation window when retrieved memories appear more amenable to alteration, updating the initial memory with information that is incongruent with the cue. Geroth and colleagues<sup>3</sup> randomised 168 smokers to either smoking-related or non-smoking-related extinction training, and followed-up craving and smoking behaviours. The directed intervention substantially reduced craving in response to both familiar and novel smoking cues, as well as the number of cigarettes smoked per day, at the follow-up 1 month later.

**Nootropics (including nicotine) enhance cognitive performance, and there's much contemporary interest in such agents.** Wesnes *et al*<sup>4</sup> evaluated the effects of the energy drink Red Bull on 24 healthy volunteers in a randomised double-blind three-way crossover study that also included the sugar-free version and a placebo. A standard 250 mL serving of Red Bull contains 80 mg caffeine, 1000 mg taurine and 27 g glucose; the sugar-free variant is pretty much the same, minus the glucose. Red Bull produced a medium effect-size improvement over both the sugar-free version and the placebo across a wide battery of working and episodic memory tests; although surprisingly not influencing the attentional domain. It would seem that *glucose* is the magic ingredient that gives people wings.

Alfréd Rényi said that 'a mathematician is a device for turning coffee into theorems', and despite Wesnes *et al*'s finding, many of us are acutely grateful for the pro-cognitive aspects of the world's most consumed psychotropic. Most research has focused on high doses, shorter-term effects and a narrow range of cognitive domains, but Wilhelmus and colleagues<sup>5</sup> expand this, looking at more sustained effects of 60 mg caffeine on 82 low-/non-caffeine consuming adults. To orientate you, this is about the amount

contained in a standard single espresso. Compared with placebo, caffeine significantly increased feelings of alertness, contentment and overall mood, with objective test performance showing enhanced attention and alertness across a range of batteries up to 1 hour after consumption, dipping off by about 3 hours. Sadly for us, any impact on hard-core grossly excessive coffee drinkers remains untested at this time. Nootropics are sometimes referred to as 'Professor's little helpers' and there is much debate about the principles and ethics of their use, particularly in schools and universities.

**'The brain wants what the body needs' advise Avery *et al*.**<sup>6</sup> **Alliesthesia is the phenomenon whereby the same stimulus may be perceived as pleasurable or unpleasant depending on one's inner state.** Consider the different sensations a hot mug of coffee or a cold can of Red Bull would have on warm or cold hands; we're confident you can think of your own examples of things that might be either pleasurable or painful, depending on the situation. Interoception describes one's sense of one's body. From food to drink to drugs, our inner perceptions are altered by how satiated we feel, and our behaviours are driven by 'positive alliesthesia', an increase in a stimulus's value as it will move us from an aversive interoceptive state back to a homeostatic one. Reported in *Neuropsychopharmacology*, 17 cigarette smokers rated the pleasantness of pictures of cigarettes when they were nicotine satiated or abstinent, during a neuroimaging paradigm with a visceral interoceptive attention task. As one might predict, abstinent smokers rated images of cigarettes as much more pleasant; they also demonstrated significantly reduced mid-insular, amygdalar, and orbitofrontal activity while attending to their bodies' interoceptive signals. Change within the mid-insula predicted pleasantness ratings, and the authors posit that interoceptive processing here potentiates the motivational salience of reward cues through recruiting hedonic reward circuitry.

**Complex human behaviour presents some of the statistically noisiest environments within which to conduct experiments.** Put simply, noisier experimental conditions lead to higher measurement error, which makes it harder to find a small yet robust result in our statistical analyses and inferences. The logic proceeds that had that error (noise) not been present, the result would have been even more spectacular. In an editorial in *Science*, Loken & Gelman<sup>7</sup> challenge this assumption. They present simple simulated experiments where a dependent variable  $y$  is weakly influenced by an independent variable  $x$  – that is, in reality, there is only a small effect size (correlation). Then, this small correlation is distorted with either a small (ideal conditions: high quality, low noise) or large amount of error (suboptimal conditions: low quality, high noise). With large sample sizes ( $n=3000$ ), the suboptimal high noise conditions resulted in weaker correlations (effect sizes) for  $x$  with  $y$  than in the ideal low noise situation. This fits with our intuition – in large studies, small effects are drowned out in the presence of high noise or measurement error. However, in small ( $n=50$ ) experiments, the suboptimal higher-noise experiments produce correlations that do not differ substantially from the ideal low-noise situation. The take home message: in small sample sizes and high-noise experiments, the assumption that a significant effect would have been all the more impressive had there been lower noise/measurement error does not hold. As Loken & Gelman put it '... when it comes to surprising research findings from small studies, measurement error (or other uncontrolled variation) should not be invoked automatically to suggest that effects are even larger'. The familiar discussion section proposal of 'future work should include larger samples' is clearly not one that holds with subtle effects.

**Antipsychotic use for treating psychoses and the behavioural problems evident in Alzheimer's disease are common but contentious, exacerbated by the lack of high-quality neuropharmacological data to inform practice.** It's a central tenet of schizophrenia research that binding to 60–80% of post-synaptic mesolimbic dopamine receptors is necessary, but it is not clear how well this translates to other populations. Writing in *Brain*, Reeves *et al*<sup>8</sup> investigated the relationship between D<sub>2</sub>/D<sub>3</sub> receptor occupancy and amisulpride (which is highly selective for those receptors) blood concentrations in older people with Alzheimer's disease. Clinical antipsychotic effects were attained at a threshold concentration of 20 ng/mL, corresponding to D<sub>2</sub>/D<sub>3</sub> central occupancies of 43% (caudate), 25% (putamen) and 43% (thalamus), far lower than those necessary in schizophrenia. Where extrapyramidal side-effects occurred, they were at a threshold of 60 ng/mL and respective D<sub>2</sub>/D<sub>3</sub> occupancies of 61, 49 and 69%. The authors note that, as with schizophrenia, there is a therapeutic window for optimal treatment of psychoses in Alzheimer's disease. Importantly, these can be attained in this population at very low amisulpride doses due to binding occupancies higher than might be expected for given serum concentrations. Changes to the blood–brain barrier are implicated, but whether age or illness factors primarily produce this has yet to be elucidated.

Mary Anne Evans (better known under her male pen-name, George Eliot) stated 'You may try but you can never imagine what it is to have a man's form of genius in you, and to suffer the slavery of being a girl'. It is uncontroversial that gender stereotypes motivate male and female choices of career and academic pursuits, but less is known about when these culturally inherited and harmful stereotypes begin to affect choices or influence children's perception of gender abilities. Bian *et al*<sup>9</sup> studied children aged between 5 and 7 in four experiments designed to establish how early in development the children's perception of 'brilliance' is differentiated between males and females. First, they were given a gender-neutral narrative describing someone as 'really, really smart' and then shown pictures of four unfamiliar adults (two men and two women) and asked to identify which of the people the story described. Then, they were shown pairs of same or different gendered people, and asked to pick which person in each pair was 'really, really smart'. Finally, they were shown puzzles where they had to match objects (such as a hammer) or attributes (being smart) to pictures of unfamiliar men and women.

The responses were averaged to arrive at a boy and girl group 'brilliance score' across each age (5, 6 and 7 years). The authors simultaneously collected the children's estimates of 'niceness' for the same stimuli in each task, and the images of adults were controlled for attractiveness and professional dress. Aged 5, boys and girls did not differ in averaged 'niceness' or 'brilliance' estimates for male/female identities; however, by 6, there was clear differentiation, with boys more likely to endorse male identities as brilliant (but less nice), and girls more likely to endorse female identities as nice but less brilliant, with results persisting at age 7. In another experiment, they showed children paired pictures of boys and girls and were asked to estimate who got better school grades. Consistent with reality, the girls were more likely to estimate that girls attain higher school grades but this did not correlate with their estimates on brilliance, suggesting perception of ability is not rooted in knowledge of which gender performs best at school. Finally, in terms of influencing boys' and girls' choices of activities, a similar design presented children with

two novel games – one labelled as for children who are 'really, really, smart' (brilliance) and another for children who try 'really, really, hard' (effort). Girls were less interested than boys in the games labelled as 'for brilliant children', but there was no difference in preference between boys and girls for games labelled as requiring effort. The authors finish with '... a sobering conclusion: many children assimilate the idea that brilliance is a male quality at a young age'.

**Finally, risking further perpetuating gender stereotypes we have identified an early hot contender for one of this year's Ig Nobel Prizes (<http://www.improbable.com/ig/>).** In a click-bait title that ensnared one of us, Chiou and colleagues<sup>10</sup> propose that 'sexy women can tempt men down the road of immorality', but we'll let you make your own mind up if you concur with the inference of who's to blame. Ferrari *et al*<sup>11</sup> test the links between aesthetic and moral valuation, noting that attractive individuals are typically conferred with more positive social and interpersonal traits than unattractive ones. The *beauty-is-good* evaluation heuristic emerges early in childhood development, and it has been discussed since antiquity. In Ferrari *et al*'s experiment, participants were primed with an adjective describing desirable, undesirable or neutral aesthetic qualities before being presented with a series of faces whose trustworthiness they had to evaluate. Two brain regions have been implicated in aesthetic and moral valuation, and the authors tested their varying roles by applying transcranial magnetic stimulation (TMS) to each of them between priming and face-presentation. Their results suggest a causal role for the dorsomedial prefrontal cortex – a core region for social cognition – in mediating the link between aesthetic and moral valuation; linking beauty and the beast.

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- 11 Ferrari C, Nadal M, Schiavi S, Vecchi T, Cela-Conde C, Cattaneo Z. The dorsomedial prefrontal cortex mediates the interaction between moral and aesthetic valuation: a TMS study on the *Beauty-is-Good* stereotype. *Soc Cogn Affect Neurosci* 1 Feb 2017 (<https://doi.org/10.1093/scan/nsx002>).