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Kaleidoscope

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How many people with depression are not receiving any treatment, and how many are inappropriately receiving it? Analysis[1] of over 45 000 individuals has tried to better define the scale of the problems, particularly in light of concern about the growth in antidepressant prescribing (though see McCrea *et al* (pp. 421–426, this issue) for a rebuttal to this anxiety). Participants were respondents to the US Medical Expenditure Panel Survey between 2012 and 2013, and they were questioned on depressive symptomatology, sociodemographic characteristics, and any treated illness. Although about 8% screened positive for depression, only about a quarter of these were receiving *any* treatment; conversely, of those *being treated* for depression, just 30% screened positive for the condition. Further exploration showed that factors that increased one's likelihood of appropriately receiving care included: being White, female, better educated, and – in this American sample – having health insurance. Those from Black and minority ethnic groups had a particularly low likelihood of obtaining care. Adding to the gloom in this data-set, when treatment was given, antidepressants were *more* likely to be prescribed to those with the mildest symptoms, despite most data suggesting that antidepressants are least effective in this group.

The strength of the placebo effect in antidepressant trials has been changing, with the average difference between active medication and placebo in trials dropping from 6 to 3 points on the Hamilton Rating Scale for Depression (HRSD) between 1982 and 2008. In the first prospective study to explore causal evidence for *patient expectancy* as a placebo mediator, Rutherford *et al*[2] randomised individuals with major depressive disorder (MDD) to open or placebo-controlled citalopram treatment. After measuring post-randomisation patient expectancy, participants were treated with 8 weeks of either citalopram or placebo. Unsurprisingly, expectancy scores were higher in those in the open group, who knew they were on the active treatment. By the study end-point this group showed a faster improvement in their symptoms: participants with depression who knew they were taking citalopram had, on average, a 6-point HRSD improvement over those also receiving the active drug but who knew they were in the randomised group and thus might be taking placebo. Less than half of antidepressant efficacy trials show medication to be superior to placebo: the authors propose that their findings offer mechanisms for controlling such responses, for example by limiting expectancy through designs with >50% probability of receiving placebo – we refer you to the 'Ten books' selection in this month's *BJPsych* (Moncrieff, pp. 437–439) for an alternative hypothesis.

Suicide prediction is a growing area, and two new papers ask whether the large scale of information contained in electronic health records (EHRs) could assist with this. McCoy *et al*[3] retrospectively analysed about half a million individuals' EHRs, capturing almost one million non-psychiatric hospital discharges over a 9-year period. The use of a general hospital was argued to allow the characterisation of, and generalisability to, a wider patient cohort and number of clinical settings, including those who do not seek or receive psychiatric care. The authors note that about half of those who die by suicide will see their general practitioner in the preceding month, whereas only about a fifth see someone from mental health services. A natural language processing algorithm was used, aggregating words conveying positive or negative emotion in discharge summaries rather than comprehensively evaluating all the records – a process argued to be easily scaled. After adjusting for sociodemographic and clinical features, a positive valence in the discharge summary was associated with a 30% reduction in suicide risk.

Barak-Corren and colleagues[4] also tapped into large sets of EHRs, this time covering 15 years and almost 2 million patients who had three or more in-/out-patient visits. Retrospective analysis of this cohort was used to develop Bayesian models to predict future suicidal behaviour. The model achieved 33–45% sensitivity, 90–95% specificity and early (on average 3–4 years in advance) prediction of patients' future suicidal behaviour. Both papers argue that automated tools may usefully assist in identifying individuals at high risk of self-harm or suicide. Any assistance to risk management must be welcomed, and better than the current lack of such support, though in both cases the actual numbers involved highlight the challenge: in the first study there were 'only' 235 suicides during 2.4 million patient-years of follow-up; in the latter 1.2% met subsequent case definition for suicidal behaviour.

The Turkish author Orhan Pamuk reckons 'Dogs do speak, but only to those who know how to listen'. Despite centuries of effort, this side of our relationship with our canine friends has seemed difficult to test scientifically. Complicating the issue, humans have both word content and prosody to convey a message, while most other animals communicate through tonal sounds. Now work has shown that dogs do have the neural machinery to process human *language* as well as our tone of voice. Writing in *Science*, Andics *et al*[5] propose that dogs can recognise around 1000 words as discriminative stimuli, and they have overlapping brain regions for both human and dog vocal acoustic cues. The research team managed to get dogs in a magnetic resonance imaging scanner to listen to combinations of neutral or praising content words presented in either a neutral or higher-pitched intonation. Comparing the conditions where the intonation suggests praise, but the lexical content is neutral, the right middle ectosylvian gyrus was activated; for lexical content (irrespective of intonation), they found a left-hemispheric bias in cortical activation. They then looked at reward-related regions in the mesolimbic system, finding that both the lexical content *and* congruent praising intonation activate reward pathways. They conclude by suggesting that in non-primate mammals lexical and acoustic information are acquired and represented separately. Further, given the lateralisation effect (which mirrors human speech processing), they suggest that a more ancient neural substrate evolved that provides for binding of acoustic signal properties to environmentally relevant meanings. The neural machinery to separately analyse and integrate word and tonal meanings can evolve in the absence of language. The authors provocatively propose that what makes language uniquely human is therefore not the neural capacity to process words, but the invention of using them. Who's a clever boy!

The attacks of 9/11 were era defining, and remain etched deeply in all our memories. Work continues to be produced on the long-term effects on survivors, including biological and cultural-narrative impacts on the children of pregnant survivors. Hansen *et al*[6] take this, literally, even further, crossing the Atlantic to see the impact on the incidence of mental ill-health in Denmark. Using a time-series intervention approach with national registry data across the years 1995 to 2012, they found an immediate 16% increase in trauma and stress-related disorders

following the attacks, which had dissipated by about a year later. There were no parallel surges in any other category of mental illness, and the authors note that this may represent a 'kindling' role of distant stressors sensitising individuals to subsequent traumas. Given that we are living through times of frequent and frightening random attacks, the pathological ripples might be travelling further than we imagined, even to those who vicariously experience them.

Research demonstrating Hebbian learning is like the proverbial bus: nothing happens for a while then a bunch of important findings all come at once. Guzman *et al*[7] report on the micro- and macrostructure of the hippocampal CA3 cell network and show how an artificial neural network model from the same observed biological structure can implement pattern completion. This is important because the CA3 neurons are vital in hippocampal memory storage and retrieval. The ability to store a pattern (roughly, a memory of a stimulus) and then reliably retrieve it in the future – from an incomplete version of the stimulus – is critically dependent on the number of neurons involved and the potentiated synaptic connectivity of the neurons. Using *in vitro* recordings of 15 930 pairs of neurons in slices of mouse hippocampus, they identified 146 synaptic connections. A majority of these synapses were chemical rather than electrically coupled. They then extracted the common local and longer-range synaptic motifs – to find that there was a surprisingly low connectivity rate between neurons and synapses, contrary to the classic models of pattern completion networks which assume massive interconnectivity.

Using these physiological variables, they then constructed an artificial neural network model composed of 330 000 simulated neurons with synaptic connections varying from random to the varying levels of synaptic motif structures obtained from *in vitro* observations. Simulations demonstrated that the capacity *and* their ability to complete patterns depend crucially on the presence of efficient sparse connectivity *but* with both the micro- and macrosynaptic motifs where these synapses had reliable transmission. This is in contrast to the classic assumption in neural network models of dense connectivity, but with noisier transmission that would represent redundancy.

Finally, Troy McClure sighed that 'sweet liquor eases the pain' – he may have been even more cannily accurate than he realised. Only about a quarter of those with alcohol dependency receive any treatment, and the response to pharmacological interventions remains low – anything that could help stratify responders would be welcome. Garbutt and colleagues[8] investigated the associations between a sweet-liking phenotype, the degree of alcohol craving, and response to the opioid-blocking medication naltrexone. The pleasure response to sweet taste activates the brain's opioid system, and humans fall into two stable, heritable, categories: those who like sweet taste (SL), and those who dislike it (SDL). Over the 12-week intervention, 50 mg/day naltrexone did not have a significant impact when compared with placebo in 80 active drinking individuals with alcohol dependency; however, it did for the subgroup with the SL phenotype, an effect that was even more pronounced in those who also had a high craving for alcohol. The authors propose that individuals' SL phenotype – which is relatively simple and inexpensive to assess – and level of craving may thus prove practical tools when deciding whether or not to instigate this intervention. It remains unclear what underpins the SL/SDL effect, though it has been suggested that a preference for sweeter substances may represent a less active opioid system that motivates greater external stimulation. Individuals with the SL phenotype may thus be more vulnerable to the opioid-rewarding actions of alcohol, and more sensitive to its pharmacological blockade. Some food for thought: perhaps reflect upon your response the next time you're asked which type of white wine you'd prefer (or, for College Fellows, sherry, one presumes).

1 Olfson M, Blanco C, Marcus SC. Treatment of adult depression in the United States. *JAMA Intern Med* 29 Aug 2016 (doi:10.1001/jamainternmed.2016.5057).

2 Rutherford BR, Wall MW, Brown PJ, Choo T-H, Wager TD, Peterson BS, et al. Patient expectancy as a mediator of placebo effects in antidepressant clinical trials. *Am J Psychiatry* 9 Sep 2016 (doi: 10.1176/appi.ajp. 2016.16020225).

3 McCoy Jr TH, Castro VM, Roberson AM, Snapper LA, Perlis RH. Improving prediction of suicide and accidental death after discharge from general hospitals with natural language processing. *JAMA Psychiatry* 14 Sep 2016 (doi:10.1001/jamapsychiatry.2016.2172).

4 Barak-Corren Y, Castro VM, Javitt S, Hoffnagle AG, Dai Y, Perlis RH, et al. Predicting suicidal behavior from longitudinal electronic health records. *Am J Psychiatry* 9 Sep 2016 (doi: 10.1176/appi.ajp.2016.16010077).

5 Andics A, Gábor A, Gácsi M, Faragó T, Szabó D, Miklósi Á. Neural mechanisms for lexical processing in dogs. *Science* 2016; **353**: 1030–2.

6 Hansen BT, Østergaard SD, Sønderskov KM, Dinesen PT. Increased incidence rate of trauma- and stressor-related disorders in Denmark after the September 11, 2001, terrorist attacks in the United States. *Am J Epidemiol* 8 Sep 2016 (doi: 10.1093/aje/kww089).

7 Guzman SJ, Schlogl A, Frotscher M, Jonas P. Synaptic mechanisms of pattern completion in the hippocampal CA3 network. *Science* 2016; **353**: 1117–23.

8 Garbutt JC, Kampov-Polevoy AB, Kalla-Juhl LS, Gallop RJ. Association of the sweet-liking phenotype and craving for alcohol with the response to naltrexone treatment in alcohol dependence: a randomized clinical trial. *JAMA Psychiatry*, 14 Sep 2016 (doi: 10.1001/jamapsychiatry.2016.2157).

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