Kaleidoscope

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We have experienced a host of extreme natural disasters recently: from severe flooding in Bangladesh to hurricanes Irma and Harvey devastating parts of the Caribbean and USA. How do we mitigate the health consequences of such events? Calling out climate change denial might be a start, but more practically, Shultz & Galea[1] focus on the public health response in the months and years following such incidents. As well as the physical health problems, the psychological sequelae can include the trauma of the event itself, subsequent life hardships, and interruption to mental health services. Data from 2005 Hurricane Katrina showed that 30% of people exposed to the storm developed increased levels of anxiety and mood disorders 30 days after the event, with up to 10% developing post-traumatic stress disorder (PTSD). The authors note how practical restoration of environmental, social and economic facilities provides 'community psychological first aid' that is more effective than the immediate direct psychological support currently being provided to victims of Harvey. The real mental health opportunity, they argue, is through opening up the possibility for more egalitarian and equitable landscaping, accommodation and infrastructure for the most socially vulnerable victims.

Rosellini and colleagues[2] advance the predictive science of PTSD development following a different type of natural disaster: earthquakes. Machine learning was applied to interviews of almost 24 000 Chileans taken 3 months before and after exposure to an 8.8 Richter scale earthquake in 2010. From this, a 67-factor risk tool 'super learner' algorithm was developed that could be used within 1 week of an earthquake occurrence. It had better performance than the individual algorithms, with those in the top 5, 10 and 20% on the basis of the predicted risk accounting for 17.5, 32.2 and 51.4% of probable cases of PTSD.

Tormented, Nietzsche testified that 'the thought of suicide is a powerful comfort: it helps one through many a dreadful night'. Biomarkers predicting transition from such thoughts to acts would be most valuable. Niculescu et al[3] used a longitudinal within-participant design with 293 people with a range of psychiatric disorders to identify a 'top dozen' list, with a wider range of 148 putative blood gene expression biomarkers. They tested these for their predictive ability, and combining this with mental state information identified what they labelled four subtypes of suicidality: high anxiety, low mood, combined, and non-affective (psychotic). Moving beyond universal markers, they sub-analysed by individuals' demographic and clinical factors to produce more personalised and – they propose – precise markers, for example, LHFP being a strong predictor of suicidality in males with depression. They attained area under the curve values of 90% for suicidal ideation and 77% for future hospitalisations when applying these to independent cohorts. Finally, completing this impressive work, the authors start to unpick mechanistic ways through which such biomarkers might affect the biology of suicide, with identified pathways including those linked with neurogenesis and cell death. APOE and IL6 particularly stood out, inferring inflammatory or accelerated aging as common factors; clearly, application to clinical trials targeting interventions is now required.

Donald Hebb was a pioneer.[4] His book *The Organization of Behavior* took in areas as diverse as visual psychophysics, learning for maze navigation, and extrapolated to mental illness in chimpanzees, psychosomatics and psychotherapy. His PhD supervisor turned down a co-author invitation as he didn't think much of it: what might be regarded as an epic fail given its 26 000 or so citations to date. Hebb's most notable contribution was his postulate for associative learning: if cell X synapses with cell Y, then X must fire shortly before Y for the strength of the synapse to be increased. Synaptic long-term potentiation broadly concords with this model so that – after a period of adaptation – the synaptic weight has increased such that in the future, only modest firing of the pre-synaptic neuron X will cause post-synaptic firing Y. Although Hebb never mathematically formalised his postulate for associative learning, it can be formulated trivially as: at some time, the synaptic weight between two neurons, W, is proportional to $R * X * Y$, where R is the learning rate, X is the *pre-synaptic* and Y the *post-synaptic* cell's firing rate. The *rate* of learning R has to account for different behaviours; for example, one learns pretty quickly not to put a hand in a fire (single trial learning, requiring a large R to quickly embed the association between a sensory and effector neuron) whereas it takes months (small R) to acquire motor skills like riding a bike. It implies that R cannot be constant across observed learning behaviours.

In hippocampal CA1, new place-field cells (for spatial navigation) can be formed rapidly by calcium channel-driven excitatory synaptic inputs. CA3 cells provide position-specific input to CA1 cells (i.e. X and Y respectively) but the rate R cannot be constant, as Bittner et al[5] show using intracellular recording of mice CA1 place cells. In CA1 cells a 'ramp' of depolarisation and repolarisation occurs during movements on a treadmill – where the induced 'position' signals the need for the mouse to run faster or slower. This 'hill'-shaped behaviour of CA1 cells suggests that, as pre-synaptic inputs from CA3 signal position on the treadmill, the faster the mouse runs, the wider this 'hill' behaviour will be. However, after CA1 recruitment, the width of this hill did not vary with speed of running. Consequently, the learning rate R has to operate on the order of seconds, and this was found to be true – the 'hill' width in CA1 cells was linearly related to speed of running only during the learning phase. They found that the learning rate R has to follow a variable and asymmetric shape around the peak (mode) of the post-synaptic CA1 cell's depolarisation. This asymmetric, non-Hebbian learning rule enables 'storage' of whole sequences of pre-synaptic events that occur sometime before (and after) the peak activity in the post-synaptic neuron.

Nocebo: the argument that drug trial participants aren't really 'blinded' – as the presence of side-effects is a give-away for being on an active treatment – explaining why antidepressants out-perform placebo. It's a reasonable proposal; how to test this? Hieronymus and colleagues[6] explore, using a patient-level *post hoc* analysis of randomised controlled trials (RCTs) of citalopram or paroxetine. Those on medication did better than those on placebo, but more importantly, their primary analysis compared those on active treatment *without early adverse effects* to those on placebo, and found the medication significantly superior on the depressed mood item of the Hamilton Rating Scale for Depression (HRSD). This, they propose, is inconsistent with the central tenet of the nocebo argument. None of these individuals had any symptoms that might alert them that they were receiving an active treatment; any impact of an inference that they were thus taking placebo should affect both groups equally. Further, evaluating those on active treatment *with* adverse effects, they found no relationship between their severity and clinical response. The findings undermine the core nocebo hypotheses, and the authors ask why, if it were true, it was never previously found with central

stimulants, barbiturates, and opiates prior to the development of antidepressants. However, we suspect this is not the end of the debate.

'Is cognitive behavioral therapy the gold standard for psychotherapy?' is the title of a provocative editorial by Leichsenring & Steinert.[7] They comment on several problems in the existing literature. In a recent meta-analysis using Cochrane criteria only 17% of RCTs of CBT for anxiety and depressive disorders were considered of high quality. It was benchmarked against a waiting-list condition – hardly a strong comparator – 80% of the time in anxiety disorder studies and 44% of depression trials: you may wish to retain the authors' nugget that allocation to waiting list is psychology's version of nocebo. Researcher allegiance has been argued to be inadequately managed, with some studies specifically forbidding the comparison arm from using available coping techniques, leading to what was labelled 'intent-to-fail'. On top of this, effectiveness data are not as strong as one might imagine, the technique performing less well in the more methodologically robust trials, with small to moderate effect sizes over treatment as usual: typical rates of response are about 50% in depression. Indeed, even the central tenet of changing key cognitive processes may be erroneous, and despite its prominence in treatment algorithms, there is limited evidence that CBT is more effective than other psychotherapies. CBT helps many individuals; but, just like all other interventions in mental health, it doesn't work for everyone, and it has considerable limitations.

There has been much coverage of 'dreamers' – children of illegal US immigrants. Now, Hainmueller et al[8] **have examined the effects of a migrant's immigration status on the mental health of their offspring.** Eleven million unauthorised immigrants are parents to 4 million children born in the USA: all face the omnipresent risk of deportation, exposure to parental anxiety and acculturative stress alongside more obvious (and confounding) 'underclass' sociodemographic status. Problematically, a parent's unauthorised immigration status makes survey- and experiment-based approaches difficult because people are naturally disinclined to report their status. Hainmueller et al overcome this by examining data from unauthorised immigrant parents who fall either side of the age cut-off criteria of the DACA (Deferred Action for Childhood Arrivals) policy. DACA defers deportation for 2 years for people with children, grants them access to temporary work and allows the parent access to Emergency Medicaid (EM) cover. Because their children are US citizens, they automatically qualify for 'full' Medicaid, for which claims are electronically recorded and billed. By combining these two sources, parent immigration status and their children's health can be studied. Parents under the age of 31 on 15 June 2012 qualify for DACA-related benefits, and these can be matched with parents who are a few days older and *do not* qualify, providing a quasi-randomised design. Using Oregon's records, 5653 unauthorised immigrant mothers with a total of 8610 children were identified; in an analysis of pre- and post-DACA era children, 7.8% and 3.3% (difference 4.5%, $P = 0.037$) respectively had diagnoses of acute stress, adjustment or anxiety disorders. The authors conducted a number of sensitivity analyses to validate the assumptions of a quasi-randomised methodology; the rates of diagnoses in the pre- and post-DACA measure was not significantly different (suggesting continuity in clinical practice) and factors such as emergency attendance rates did not differ (suggesting that DACA did not change healthcare utilisation behaviours in parents). The authors conclude by suggesting that the protective effects of the DACA policy might be increased by introducing pathways for unauthorised immigrants offering a route to citizenship.

Finally, the past 18 months have seemingly relegated psephology – the study of elections and voting – to the same waste basket that contains astrology and numerology. Population surveys tend to base their predictions on people's degree of agreement with a given candidate or position; and we've all seen how accurate that is, especially among undecided voters who ever more commonly swing elections. Taking this to the brain, cortical N400 event-related potentials have been shown sensitive to semantic violations ('I drink my coffee with milk and socks') and social violations ('Samantha is dancing at the museum'). This has also been shown to work for *individual's* moral values (e.g. getting those with contrary religious beliefs to read the statement 'I think that euthanasia is an acceptable course of action'), and pushing aside media political commentators, Galli et al[9] tested whether this brain signature could thus be used to predict future voting. Before the Brexit referendum, they recorded this in a range of individuals with varying voting intentions while they were discussing their agreement or otherwise with a range of Remain and Leave arguments such as 'free access to healthcare for all EU migrants should be allowed'. N400 readings incongruent with individuals' opinion of the European Union predicted actual voting behaviour in both decided and undecided voters more accurately than explicitly expressed preferences. Given the difficulty in science funding, this approach could be worth pitching to a suitable super-PAC (political-action committee)? Science trumps politics: Make Academia Great Again!

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4   Tracy DK, Joyce DW, Shergill SS. Kaleidoscope. *Br J Psychiatry* 2015; **207**: 465–6.

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7   Leichsenring F, Steinert C. Is cognitive behavioral therapy the gold standard for psychotherapy? The need for plurality in treatment and research. *JAMA Psychiatry* 21 Sep 2017 (https://doi.org/10.1001/jama.2017.13737).

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9   Galli G, Sirota M, Materassi M, Zaninotto F, Terry F. Brain indices of disagreement with one's social values predict EU referendum voting behavior. *Soc Cogn Affect Neurosci* 11 Sep 2017 (https://doi.org/10.1093/scan/nsx105).