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Kaleidoscope

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What triggers violence? We face the uncomfortable contemporary backdrop of public acts of mass violence, often with the media questioning the perpetrators' mental health. It is well recognised that there are *relatively* greater rates of violence in those with psychotic illness – with comorbid substance misuse being a major risk modifier – but the *absolute* rates remain low. Seena Fazel's team evaluated 65 000 individuals with psychoses and 3 million unaffected controls on the Swedish Nationwide Register[1] using a within-individual design to demonstrate that greatest risk occurred in the period following *exposure to violence* – however, there were no significant differences in relative risks between those with psychosis and healthy controls. There were also links to violence in the week immediately following unintentional injuries, self-harm and substance intoxication. Parental bereavement was the main diagnostic differentiator, leading to higher rates of subsequent violent criminality in those with psychosis; the authors propose that family support may thus be particularly protective against violence in this cohort. Although there was little to differentiate those with psychosis from the general population, a key point remains that significant triggers *do* contribute to subsequent violent crime in the short term, and may provide dynamic risk management opportunities for clinicians. It also reiterates the fact that most people with mental ill health do not commit violent acts, and that most violence is perpetrated by those without mental illness.

Locked doors are, literally, part of the furniture in mental healthcare. How useful are they in achieving their core objectives of reducing absconding and suicide? The question sounds so obvious it's remarkable to consider that it has never previously been adequately assessed. In a 15-year naturalistic observational study, Huber and colleagues[2] examined almost 350 000 admissions to 21 German in-patient units of various types: locked, partly locked, open, day clinic etc. Not only were suicide attempts and absconding *not* higher on units with open door policies, but they had *decreased* rates of such events. How can these counter-intuitive findings be explained? Could confinement in a locked ward instil a desire to leave, and might a more therapeutic unlocked open environment encourage engagement? Could this arise as a consequence of an admission selection bias to the different wards? The German model requires that all participating hospitals accept all catchment area patients, regardless of risk profile, suggesting an absence of an admission bias. Noteworthy from a UK perspective, they have about twice the bed capacity per thousand patients that we do. In some European countries, individuals detained under relevant legislation are more commonly treated on unlocked wards, a concept that seems almost alien to current UK practice where even 'informal' patients are typically on locked units. To date, decisions on estates' designs have been led by expert opinion rather than data: is it time for evidence to supplant culture?

How can we use neuroscience to predict risk and lethality of future suicidal behaviour? Cross-sectional data have shown associations between lower midbrain serotonin transporter binding and greater *rates* of attempted suicide, and higher raphe nuclei serotonin$_{1A}$ binding with greater *lethality* and suicidal intent. Oquendo *et al*[3] use these putative biomarkers in the first such prospective observational study of 100 patients with well-characterised major depressive disorders. Positron emission Tomography (PET) found that greater raphe nuclei serotonin$_{1A}$ binding potential – in other words, serotonin system hypo-function – predicted higher suicidal ideation and more lethal such behaviour over the 2-year follow-up period. The authors propose that the effect might be mediated through reductions in serotonergic activity impacting upon mood and decision-making. There is obvious appeal to biomarkers of future suicide risk, but the practicalities of this in terms of cost, sensitivity and specificity mean it won't translate to practice in this current form, regardless of whether hospital doors are open or locked.

'The depressions' is a proposed umbrella term for a phenotype with many underlying and interacting causal pathways (it's also the name of an obscure 1970s punk outfit from Brighton, but they have no further part in this story). Such a model may also help explain the considerable variation in response to interventions commonly seen and there has been a significant recent growth in the wider evaluation of putative factors – think vitamin D. *Metabolomics* is the study of metabolic intermediaries: writing in the *American Journal of Psychiatry*, Pan *et al*[4] assayed neurometabolic functioning in 33 young individuals with refractory depression and found cerebrospinal fluid (CSF) metabolite abnormalities in 21 (and none of the matched controls). Folate deficiency was most common (present in 12/33), and one had low CSF tetrahydrobiopterin (a critical cofactor in monoamine synthesis): replacement therapy with folinic acid (a vitamer of folic acid) and sapropterin (a tetrahydrobiopterin analogue) respectively led to improved symptoms in all affected. We are increasingly comfortable with a spectrum model for mental ill health – though this study was not designed to test whether the abnormalities were causative or sequelae of refractory depression – and our investigative and treatment repertoire may need to grow to match this.

We like research that challenges consensus: separate Kaleidoscope columns recently reported that antidepressants were inferior to mindfulness in relapse prevention, and also had a limited role to play in depressed children. We also like balance. The challenges of waiting times and insufficient psychology resources are familiar ones, so what about alternatives to the ubiquitous cognitive–behavioural therapy (CBT)? The COBRA trial[5] randomised over 400 participants with major depressive disorder (MDD) – stratified by illness severity and antidepressant use – to either behavioural activation from a junior mental health worker with no professional training in psychological therapies, or CBT from a psychologist. The intervention was open label, but assessors were masked, and at the 18-month time point, behavioural activation was non-inferior to CBT. This is the first such high-quality fully powered non-inferiority trial. Cost-effectiveness may remain an issue for the National Health Service for longer than we hoped, as progress on the promised post-Brexit investment of £350 million per week appears to have gone curiously off the radar; so this simpler-to-implement intervention that can be delivered by more junior staff may be good news – until that is resolved.

There have been some interesting developments in how the brain is wired to communicate, retain information and learn. In his 1949 book *The Organization of Behavior*, Donald Hebb proposed a simple rule that aims to explain associative learning grounded in the behaviour of populations of neurons and synaptic plasticity. Simply, if a pre-synaptic neuron spikes persistently enough to cause activity in a post-synaptic cell a short time later, an adaptive process strengthens the synaptic 'weight' between them. In the subsequent decades, this simple principle was

bolstered by mathematical formulations that modelled stable long-term potentiation (LTP) and depression (LTD). An important theoretical consequence of Hebbian learning is pattern completion: this is when neurons adapt their synaptic networks so they are effectively 'trained' to reliably respond as an ensemble to a complex stimulus – such as a visual pattern. Later, the same population's activity reflects that of the learned full stimulus when only a smaller subset of the neurons in the assembly are stimulated. For example, if presented with a noise-degraded visual image of a familiar object, we are usually able to recognise it because neural networks in the visual and inferotemporal cortices perform pattern completion with the partial stimulus.

Manipulating individual neurons to show how Hebb's principle actually constructs assemblies of adapted cells has remained technologically difficult. Carillo-Reid *et al*[6] used optogenetic manipulation to literally build a cell assembly in the visual cortices of awake mice. They were able to distinguish distinct (but intermingled) circuits of neurons that respond differentially to either direct photostimulation (photo ensembles) or visual stimuli (visual ensembles). Repeated photostimulation of neurons in photo ensembles ended up recruiting (coactivating) other cells, suggesting a Hebbian mechanism at work. Then, the authors demonstrated pattern completion in the same assemblies by recording the photo-ensemble circuit's response when activating only individual cells. Of note, the visual and photo ensemble networks did not interfere or 'overwrite' each other. Finally, they tested the resilience of these new artificially imprinted photo ensembles, showing that the patterns of circuit activations were preserved after 1 and 2 days. Cortical ensembles may constitute emergent building blocks of cortical function, and the authors propose they have demonstrated Hebb's principle *in vivo* at the single-cell resolution.

Nietzsche said, 'Without forgetting it is quite impossible to live at all' and one challenge of memory research is how – with apparently finite neuronal resources – the brain is able to form new memories without obliterating existing information. In modern neuroscience, memory is discussed as cell assemblies activating and representing 'traces' of the stimulus or event – or 'engrams'. One early and influential theory of memory is the Hopfield network, which is composed of a number of simulated neurons wired together such that the simulated 'synapses' between each neuron have either excitatory or inhibitory connections. Hopfield networks can be shown to robustly learn and recall 138 simulated stimuli for every 1000 neurons in the network. Beyond this limit, there is degradation and interference for recalled 'memories'. Importantly, each simulated neuron participates in the storage of many discrete stimuli such that when two stimuli are sufficiently similar, an overlapping set of neurons participate (become active) in its storage and retrieval.

So, how do real neural networks store and recall new and existing memory? Rashid *et al*[7] examined engram storage and recall in lateral amygdala neurons in mice. Awake mice were exposed to two discrete events separated by intertraining intervals (ITIs) of 1.5, 3, 6, 18 or 24 hours. Both events consisted of one of two distinct auditory stimuli (CS1 and CS2) and Event 2 was always 'CS2 + foot shock' whereas Event 1 stimuli and timing varied. They found that Event 1 memory was stable across all ITIs, whereas Event 2 memory was enhanced if Event 1 was 'CS1 + foot shock' and the ITI was shorter – suggesting coallocation of neurons to engrams if there is similarity between stimuli and they are temporally close. Then they used a group of mice exposed to the Event 1 and Event 2 paradigm separated by either 6 or 24 hours. Using fluorescent *in situ* hybridisation, they labelled neurons for mRNA that is selectively representative of different time periods of preceding neuronal activity (5 and 30–40 minutes respectively). They tested memory for CS1 and then CS2 separated by 25 minutes and after removing the brains of the trained mice, the patterns of labelled neurons showed coallocation of neurons suggestive of a shared representation of the engram for Event 1 and Event 2 but only for mice trained with an ITI of 6 hours. The authors propose that if Event 1 neurons are still excitable after 6 hours, then the Event 2 engram is coallocated to neurons shared with Event 1. If the ITI is longer, then a different population of neurons is recruited to encode Event 2 such that they become disambiguated. Finally, they used direct optogenetic manipulation to test how neurons that 'recognise' the stimulus (i.e. an active engram) inhibit other neurons to prevent recruitment to the same engram. Essentially, there is a time window where an active engram prevents creation of a new engram for sufficiently similar stimuli in a 'winner-take-all' fashion. As time elapsed, at around 24 hours, this mechanism 'released' neurons for recruitment to new engrams. The principles are argued to provide a foundation for understanding how memories are organised within associative networks.

Finally, communication on a larger scale: the childhood game of 'Chinese whispers' was the – perhaps somewhat politically incorrectly titled – way of watching with amusement as messages changed with time. The 'social transmission of information' provides a more scientific nomenclature, but what does the research literature say about the underlying principle of the game? Bebbington *et al*[8] modelled the serial reproduction of information across 92 four-person chains, utilising stories containing various degrees of positive and negative information. They found that negative information preferentially survived transmission, and that ambiguously valenced information became ever more negative as it went from person to person. It perhaps makes sense that as a social species we retain negative information that might be more critical for threat avoidance; more trivially, maybe it explains why the news often feels depressing and filled with stories of despair. It also makes us wearily suspect that all you'll take from this month's column is that violent locked doors need folic acid but not CBT. As, for some of us, the new academic year kicks off, we will test the hypothesis by letting you pass on to relevant colleagues – and watching how the message distorts – new research that shows[9] one's effectiveness as a teacher is based on one's looks, purple monkey dishwasher.

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