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Kaleidoscope

Derek K. Tracy, Dan W. Joyce, Dawn
N. Albertson, Sukhwinder S. Shergill

There is little in mental health as controversial as electroconvulsive therapy (ECT). *One Flew Over the Cuckoo's Nest* has a lot to answer for, but equally one can understand public caution about a technique involving anaesthesia and induced seizures. The lack of sham-controlled randomised controlled trials (RCTs) has long been a criticism of the technique, but Chittaranjan Andrade hits back in a provocative editorial saying such criticisms cannot go unanswered if they are deterring people from receiving care.[1] Somewhat tongue-in-cheek he notes that we also lack good RCTs to conclude that parachutes work, but they remain very much in use and astonishingly popular among folk who jump out of airplanes. Further, there are large, modern, well-designed RCTs that demonstrate superiority of bilateral and high-dose unilateral ECT to low-dose unilateral ECT, and brief pulse compared with ultra-brief pulse ECT. Such an active placebo is a scientifically valid replacement. Finally, Dr Andrade argues that ECT use over 80 years with application to the most unwell patients, many of whom have been catatonic, would have shown clearly if it was not working in individuals who had been refractory to other interventions. He contrasts its continuance with the disappearance of (Nobel Prize awarded 'discoveries' of) leucotomies and malaria therapy.

Of course, we still need to determine *how* ECT works. Two recent neuroimaging studies have looked at these issues. Takamiya et al scanned 30 patients with late-life depression before, and a week after, a course of right unilateral ECT.[2] Widespread bilateral regional volume expansion was seen, most notably in the right medial temporal lobe. Post-ECT increases in grey matter volume have been consistently reported before now, but the inducing mechanisms have not been clear. What was different with this work was the use of deformation-based morphometry, which does not rely on tissue segmentation and can model volume and shape changes whatever the tissue type. Further, correlating these changes with the electrical field and cumulative seizure duration, the authors found that volume changes could not be explained by electrical stimulation itself, and were in fact related to the cumulative duration of the seizures. Exactly which physiological factors contribute to the growth – from neurogenesis through dendritic and synaptic growth to changes in capillaries and glial cells – remains uncertain. Gybl et al also found post-ECT increased brain volumes in 22 patients who were severely depressed, but here enlargement in left and right dentate gyri – part of the hippocampi – were associated with *worsened* verbal memory.[3] By 6-month follow-up, the volume increases had returned towards normal with correlated improvement in these side-effects. It feels counter-intuitive that enlargement of a memory centre should produce this, but we are reminded that it is not size that counts, and aberrant neurogenesis, other neuroplastic processes or vasogenic oedema and various inflammatory processes might be impairing functioning. These are two papers demonstrating that ECT changes neural volumes but emphasising that this can be a positive or negative thing, depending upon the regions involved.

'Dopamine as the wind of the psychotic fire', Laruelle & Abi-Dargham memorably wrote,[4] but its mechanistic underpinnings driving hallucinations have remained elusive – there is no dopamine in sensory cortices. The inability to directly interrogate hallucinations within animal translational studies has hampered treatment advances in psychosis. A recent *Science* article appears to have cracked it, developing a computational responsible circuitry model of hallucinations.[5] The authors created a sensory detection task that works across species, training humans and mice to listen for a particular tone within white noise and then recording their confidence in its detection. In mice, self-report of hallucinations came in the form of choice selection and then the duration they were willing to wait for a potential reward, which acted as a measure of their confidence. The human vulnerability to these false perceptions was associated with their self-reported tendency to experience spontaneous hallucinations. Within animals, numbers of confident *false* perceptions increased with both the administration of ketamine and raised expectations of hearing the signal – two manipulations known to increase hallucinations in people. Based on these data they produced a model founded on belief updating that explains these false perceptions as the result of expectations outweighing the current sensory information, hypothesising that striatal dopamine must be responsible for encoding one of these decision variables. They were able to tease apart reward expectations, grounded within the ventral striatum, from sensory expectations, by optogenetically increasing dopamine within the striatal tail and seeing a corresponding increase in the hallucinations seen in mice – an effect that was reversed with the administration of haloperidol. Not only does this work create the first direct translational model of a cardinal symptom of psychotic disorders, it puts forward hallucinations as a dopamine-induced bias in the mental computation between prior expectations and current information input. Giving both a method and mechanism, the potential and future directions of their cross-species computational psychiatry approach is perhaps the shot in the arm neurobiological research in psychosis has needed.

Every child has asked why do we need to sleep? There have been arguments it is providing time for the body to self-repair, but this is surprisingly under-explored. It is certainly pretty universal across species, so one imagines it must have an important origin. There are *in vitro* data showing it facilitates clearance of metabolic waste such as amyloid-β and tau. Writing in *Brain*, Eide et al undertook – remarkably – the first *in vivo* study in humans to test this more fully.[6] One cohort of participants had a night's total sleep deprivation before being allowed to sleep, and they were compared with a matched group who slept freely throughout. All were initially given an intrathecal subarachnoid injection of a highly hydrophilic cerebral tracer, gadobutrol, which distributes freely within the brain and can act as a surrogate marker for excreted water-soluble metabolites (including the aforementioned amyloid-β and tau). This was then measured across 85 brain regions before and after their napping. The single night of sleep deprivation impaired tracer clearance across most brain regions, including the cerebral cortex, white matter and limbic structures. This was not compensated for by the subsequent night's rest. It remains less clear exactly how such molecules are cleared, and the authors note recent debate about the recently described vertebrate paravascular glymphatic system in this regard (which is analogous to the lymphatic system, which is very limited in the central nervous system). The data are also interesting in that chronic sleep deprivation has been established as a significant risk factor for Alzheimer's disease and other forms of neurodegeneration. Conversely, sleep disturbances are common in dementias, something ordinarily attributed to loss of sleep-regulating brain regions, but which these data suggest might be because of a build-up of toxic waste products. Of course, our mums told us this in answer to our childhood questions: they were right, as they always are – sleep is vital for brain health and you do *not* catch up on lost sleep.

Why do we suffer stress? It might not feel it, but it is adaptive and helpful. It prioritises negotiating a threat, and without it, our ancestors were more likely to end up as lunch for large carnivores. In an expert review in *Biological Psychiatry*, Zhang et al update us on emerging insights, including the key roles of the amygdalae in coordinating physiological and behavioural responses through its complex inputs and long-range outputs.[7] Multimodal sensory inputs are integrated with top–down cortical information and contextual hippocampal memories, all modulated by a range of neurotransmitters, notably serotonin. These output to an impressive array of brain areas and phylogenetically ancient stress responses, including: 'freezing' (a particularly ancient, but not always helpful, outcome) via the prefrontal cortex (PFC); anxiety responses via the nucleus accumbens and hippocampus; motor changes through the basal forebrain; hormonal and autonomic regulation via the hypothalamus and nucleus of the solitary tract respectively; and appetitive and aversive learning through the lateral substantia nigra. A whole suite of options for an animal under pressure; you might not be surprised that with increasing 'sophistication', as we move towards primates, the PFC (especially the medial PFC) and hippocampi becomes ever much more critical in top–down control around contextual fear retrieval, appraisal and renewal. Homeostatic mechanisms mean that stress literally remodels the amygdalae, with circuit-specific alterations in neuronal spine and dendrite growth and density.

In a contemporary world we are more attuned to how stress responses, particularly when chronic, can be problematic. Fitting with real-world experience, early-life adversities can particularly have an impact on amygdalar architecture, and make some individuals more vulnerable to future insult. Rodent optogenetic data have shown how circuitry manipulation can alter anxiety responses; chronic stress paradigms weaken top–down influences leading to neuronal disinhibition and greater emotional disturbances, impaired recognition of novel objects, aggression and learned helplessness. We are reminded *why* antidepressants are prescribed in a range of anxiety and stress-related (such as post-traumatic stress disorder) conditions, with attempts to re-regulate aberrant circuitry, and at a cellular level, cognitive–behavioural therapy is also considered to exert effects through re-regulation of the PFC over the amygdala. These data also help us think about potential translational neuropsychiatric approaches to treatment. The authors propose our growing understanding of the neurobiology offers opportunities including delineation of neural-circuit-defined 'biotypes' of patients and boutiqued future interventions. They put forward the emerging data on real-time functional magnetic resonance imaging neurofeedback training in depression as an early example.

Finally, speed dating is like natural selection but without the romance – or so we have heard. But it might also be a way of studying the evolutionary development of intimate relationships. In an eclectic paper, Arantes et al manage to link the economic growth of the speed-dating industry to the Angry Birds movie franchise and, at the same time, study how participants allocate cognitive resource to the task of finding a mate.[8] They begin by surveying the literature on attractiveness through an evolutionary lens: perceived attractiveness influences automatic cognitive processes that might confer selective reproductive advantage (for example, if one had to efficiently locate a mate). One such automatic cognitive process is the perception of time – when people are engaged in cognitively demanding tasks, they perceive time as longer than the measured elapsed time. So, the researchers sought to examine the effect of perceived attractiveness on the perception of time in a speed-dating experiment. Their hypotheses were derived from parental investment theory: women are more 'investing' – which is to say, when a woman finds a potential partner more physically attractive, she then begins allocating cognitive resource to exploring other factors that make the person a potential suitable mate. This is because mating (for females) is associated with a higher cost in evolutionary terms – pregnancy is a 9-month commitment. The same theory proposes that men do the opposite – once they have decided someone is physically attractive, they pretty much just 'go with it' without expending further cognitive resources (present company excepted, naturally). These assumptions lead the authors to propose the hypothesis that when women find a speed-dating partner attractive, they will invest cognitive resource (which is effortful) and therefore perceive time to be progressing more *slowly*. On the other hand, when men find someone attractive, they will perceive time as moving more quickly because they do not engage more demanding cognitive processes – they want to, ahem, move things on. Their experiment recruited 18 women and 19 men, between the ages of 18 and 27 years of age, who all identified as heterosexual. Prior to the actual speed dates, all participants rated all others' attractiveness (from photos) on a scale from 10 (hot) to 1 (or not). After each of the 173 speed dates participants were asked to give an indication of the duration of the date (1–8 min) and to again rate the attractiveness of each individual date. The actual duration of dates was under experimental control, and ranged from 3 to 6.25 min. The headline result was in keeping with their hypothesis: women generally perceived date-time as longer (than actual time) and this perceived exaggeration of time also correlated with the woman's rating of attractiveness of their date. For men, it was the opposite: the more attractive they rated women they were paired with, the shorter the estimate duration of the speed date. As a postscript, of the 173 speed dates, only 32 resulted in exchange of contact details and 3 intimate relationships were formed (lasting 6 months, but they do not specify if it felt longer or shorter for the couples involved). We feel there is a joke in there somewhere about men, for once, exaggerating about things being shorter than they actually are, but if there is, it does not befit the august *BJPsych*, so we will not look for it.

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