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Kaleidoscope

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'Compared with treatment as usual (TAU), the active intervention showed…': well what is TAU? It is clearly seen as a control state in research, but does 'usual' care vary from clinical team to team, and across trial protocols? It might include elements ranging from no treatment, through primary to secondary care input, to work with specialised services. These are all evidently quite different, so does this matter and how might it have an impact on results? Cuijpers and colleagues, carried out a meta-analysis of control groups across randomised trials of psychotherapy for adult depression.[1] In total 140 studies were included, incorporating over 15 000 participants. They found TAU was delivered in primary care in 24.3% of studies, 'general medical care' in 25.7%, specialised mental health in 18.6%, perinatal care in 14.3%, and for 17.1% it meant no treatment at all. Interestingly, considering such variable settings, they discovered no significant differences in outcome from psychological therapy across these major categories of TAU, but there was considerable heterogeneity within all TAU groups. There was also notable geographical variation, with effects of psychotherapy being greater in non-Western countries. The authors consider that although this might mean psychological interventions might be 'better' in such cohorts, another interpretation is the size difference is the result of TAU being weaker, with participants not getting the active treatment – and more likely to be receiving no treatment. Undoubtedly all control conditions in a research design pose their own challenges: from waiting list, through psychological placebo (commonly non-directive counselling) to medication placebo. It is evident that TAU is no different, and the authors caution that the 'usual' might be quite variable, and as such should be regarded as a heterogeneous condition in psychotherapy research.

From TAU to the psychological intervention itself: what is actually *happening* in cognitive–behavioural therapy (CBT)? A new Wellcome Trust mental health funding initiative notes the lack of data on how and which specific elements contribute most to the effectiveness of psychological therapies such as CBT.[2] One approach to answering this is provided by Ewbank et al who obtained data from over 17 000 patients receiving internet-enabled CBT (over 90 000 session transcripts in total).[3] They applied a deep learning model to categorise therapist comments into one or more of 24 categories. They demonstrated that increased numbers of key session features, notably 'change methods', were associated with greater odds of reliable clinical improvement. Conversely, greater use of non-therapy related content was linked to reduced odds of improvement and worsened patient engagement. Most research on CBT compares it with the aforementioned TAU (usually showing significant superiority) with global group results that presume intervention integrity; the authors note how perhaps as little as 3.5% of psychotherapy randomised controlled trials adequately assay this. This study advances things in two notable ways. First, it opens up a relatively novel method of researching psychotherapy – deep learning – and second, crucially, it demonstrates the key ingredients of that therapy are doing what they are supposed to, rather than more generic elements such as therapeutic alliance. It now remains to be seen whether these artificial intelligence approaches can be used to clarify which specific elements of the CBT process are most effective in different individuals and problem types, while retaining 'personalised medicine'.

Impaired hippocampal neurogenesis has been implicated as forming an integral part in the pathology of several mental illnesses, including psychosis. Does this also offer a potential target for future therapy? Gobshtis et al report on a transplantation study in rodents using a ketamine-induced model of psychosis.[4] They transplanted bone marrow-derived mesenchymal stem cells; these are multipotent cells that can differentiate into several lineages including those promoting endogenous neurogenesis, and have been shown to have immunomodulatory properties. After being transplanted into the rodents' ventricles on a single occasion they observed that they were successfully engrafted and able to survive for up to 3 months post-transplant. There were increases in hippocampal neurogenesis, reaching normal levels, at both 2-week and 3-month test points relative to non-treated animals. At the behavioural level, this was associated with improvements in social novelty preference and prepulse inhibition. The authors highlight the interesting finding that these behavioural improvements were initially correlated to *FGF2* gene expression, a key proneurogenic gene that promotes cell proliferation and differentiation; but by the 3-month assay such levels had returned to those seen in the controls. At this latter point, behavioural changes were primarily correlated with the notch ligand DLL1, which has been linked to neural stem cell self-renewal. Another finding of note was that short-term treatment with clozapine was only effective during treatment, with results tapering off once it was discontinued; in contrast to the transplantation that seemed to offer a longer-lasting 'fix'. Interestingly, the effects also seemed protective against age-related decline in neurogenesis seen in control rodents (and humans), and the authors speculate that bone marrow-derived mesenchymal stem cells might be protective against normal deterioration seen in cognitive functioning. Naturally, this raises the inevitable hashtag #JustSaysInMice, and interesting questions both around the translational potential to humans, but also speaks to the acceptability and secondary effects of such treatment.

From all-or-nothing to graded response; there is much still to learn about the functioning of even a single neuron. Writing in *Science*, Gidon et al explored the ex-vivo dendrites of layers 2 and 3 in human cortical pyramidal neurons – something previously done almost exclusively on rodent tissue.[5] The human cortex, at about 3 mm, is unusually thick compared with other species, especially in the aforementioned layers, forming very big, complex dendritic trees. As it is the dendrites that determine axonal output, they can be considered the computational aspect of a neuron, managing multifaceted inputs. Cells were taken from surgically resected slices from individuals with epilepsy, and subjected to dual somatodendritic patch clamp recordings and two-photon imaging that allowed the team to directly investigate the cells' properties. Astonishingly, they discovered an entirely new class of calcium-mediated dendritic action potentials (dCaAPs). These were very different to classical neocortical action potentials of *N*-methyl-D-aspartate spikes and dendritic calcium action potentials that increase with stimulus strength. Here, with dCaAPs they found that their impact on neuronal waveform output was *graded*, and not the all-or-nothing action potential typically described and understood. dCaAP amplitudes were greatest at threshold-level stimuli, and weaker for larger inputs. dCaAPs in dendrites thus allow individual neurons to decode linearly non-separable inputs, a computation the authors note that was previously considered to necessitate multilayered networks. What this means is that cells can compute an 'anticoincident function for multiple input pathways', which effectively limits the strength and number of inputs. A delicate balance of excitation and inhibition is required to generate a dCaAP, which the paper highlights means that counterintuitively, inhibition can actually increase the neuron's excitability. This has never been seen before

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in any neuron of any other species. To contextualise this, it had previously been thought that the dendritic input and axonal output can manage the logical operations of AND and OR. Here the authors demonstrated that a single dendritic compartment of a single neuron in your head can compute the XOR operation or logic gate; that is some seriously cool science.

Callous–unemotional behaviour is a noted risk factor for the development of antisocial behaviour; but what causes the callous–unemotional nature in the first place? Waller et al tested fear responses to social and non-social stimuli, and observed social affiliations in a sample of 620 pre-schoolers at age 3 years.[6] Why examine children's responses to fear? Decreased fearful arousal has been implicated in callous–unemotional behaviour because of a loss of inhibitory processes when faced with threatening cues. Similarly, lowered awareness of, or sensitivity to, fear displayed by peers infers problematic empathy. Social affiliation is the drive to have close relationships, manifesting through reduced physical distance, touch, eye contact, shared gestures and vocalisations. A lack of social affiliation risks loss of development of typical empathic learning. Following on from the initial assessment, the children's callous–unemotional and oppositional and defiant behaviours were monitored over the subsequent 2 years. They found that fearlessness and low social affiliation predicted greater callous–unemotional behaviour, but not the oppositional or defiant types. The authors also tested the impact of parental input, measuring their harshness and warmth levels. Once again there was a divide on how it had an impact on the different behaviours in children: harsh parenting was associated with more callous–unemotional behaviour in fearless children, but more oppositional–defiant behaviour in fearful children. The findings are particularly interesting as they specify a longitudinal relationship between these early life factors, and delineate callous–unemotional as a subgroup distinct from oppositional–defiant disorder. Also, they open up potential intervention strategies for behaviours that can have profound and enduring subsequent emotional, societal and financial costs.

Finally, although we imagine ourselves as rational consumers of information, we all suffer from biases: discounting information that contradicts decisions we have made in the past, and favouring judgements delivered with confidence. Computational modelling and psychological theories suggest we actually lose sensitivity to information that contradicts our previous choices. Kappes and colleagues, assessed the impact of the deliverer's confidence on our appraisals.[7] Participants guessed the prices of houses for sale and placed a wager, which acted as a proxy for confidence. Then, during a function magnetic resonance imaging scan, they went over each decision again with the option to change their bet after hearing whether a supposed partnered participant agreed and what their partner wagered, a proxy for their confidence. As expected, confirmation bias was found with participants making a change to their wager only when their partner agreed with them. From a neural perspective, this could be attributed to only one area: the posterior medial prefrontal cortex, which appears to be involved in post-decision performance monitoring, signalling to adjust our behaviour accordingly. There was a relationship between the partner's indicator of confidence and the signal strength here, but only when the partner agreed. So, this suggests that upon hearing something we disagree with we conceptualise it as invalid, discarding it and we are functionally deaf to the confidence of delivery. It seems intuitive, as evidenced by the public discourse around climate science and politics, but perhaps it is valuable to appreciate this vulnerability in cognition while practising in medicine and psychiatry, especially as it has an impact on both the clinician and patient perspectives. In science, we design and follow protocols to help mitigate our biases, but the tools we use are only as good as those using them.

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