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Kaleidoscope

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We have previously discussed[1] good mental health being more than the absence of illness; how different are the *determinants* of mental well-being and ill health in children? Patalay and Fitzsimons[2] evaluated individual, family, social and wider environmental factors in over 12 000 children aged 11 from the representative UK Millennium Cohort Study. Although there were some instances of factor overlap, they found that the correlates of children's well-being and mental ill health were largely distinct. For mental *ill health*, much of the variance was predicted by problematic peer relationships, arguing with parents, parent and child physical health, cognitive ability and perceived socio-economic status (SES). For mental *well-being*, most variance was predicted by social relationships and school connectedness, home environment and perceived SES.

Interestingly, girls had more symptoms and less well-being than boys, which is counter to typical gender findings in adults. Ethnicity was not associated with well-being, but those from Black and minority ethnic backgrounds had fewer symptoms than White peers. Perhaps counterintuitively, whilst those from wealthier backgrounds had fewer symptoms, they also demonstrated *less* well-being. Much work and effort is rightfully expended by researchers and clinicians trying to find and ameliorate problematic factors that are causing, or may cause, distress in children; less work has explored those factors that might make them flourish and, in time, become happy adults.

Antidepressant axioms or shibboleths: (1) they are not particularly effective in children, and (2) responses are typically binary, and not dose-dependent. Depression is one of the most common mental health conditions seen in children and adolescents, though it has been argued to be underdiagnosed and undertreated due to somewhat undifferentiated symptom profiles. The role of antidepressants has always been controversial; they are not recommended as a first-line intervention, yet antidepressant prescribing in this population is increasing. A meta-analysis in the *Lancet*[3] compared 14 antidepressants in over 5000 individuals across 34 trials. A strength of the network analysis model was that it allowed the generation of treatment hierarchies across drugs that had not been directly compared. Comparing the risk–benefit profile in the acute management of major depressive disorders, there was no clear advantage for medication, with only fluoxetine significantly more effective than placebo. There was also a strong finding of increased suicidality in those given venlafaxine. The findings do not preclude prescribing medication, especially in individuals with more severe symptoms or those failing to respond to talking therapies, but they do add to the note for caution.

In adult populations, there has been much debate about antidepressant dose–response curves and the likelihood of an individual responding to higher doses if they fail to respond at lower ones. The issue clearly matters: while guidelines may vary on their advice, it's common clinical practice for patients to be 'worked up' to higher doses. Following earlier research showing that the single-item 'depressed mood' component of the Hamilton Rating Scale for Depression (HRSD) was most sensitive to medication change, Hieronymus *et al*[4] undertook a patient-level mega-analysis of 11 randomised controlled trials, exploring dose-dependent changes to this single item (rather than the summed total HRSD). In the three drugs tested – citalopram, paroxetine and sertraline – doses at or below the lower end of the therapeutic range were superior to placebo but inferior to higher doses. However, the effects plateaued at paroxetine 20 mg, citalopram 40 mg and sertraline 100 mg, with no further gains seen above these doses. So, one axiom reaffirmed, one shibboleth exposed?

Some intellectual disabilities are due to so-called RASopathies; better understanding of how they lead to cognitive impairment might open up novel therapeutics. The neurodevelopmental class that includes Noonan syndrome, neurofibromatosis and Costello syndrome affects about 1 in 1000 individuals, and is defined by germline mutations in the Ras-ERK signalling pathway that manifest with a common range of cardiac, cutaneous, craniofacial and intellectual changes. Papale *et al*[5] characterised a brain-specific mouse model of severe forms of RASopathies – those linked to *KRAS* mutations. There was an upregulation of ERK signalling that selectively enhanced synaptogenesis in GABAergic interneurons, and the subsequent mouse deficits paralleled those seen in humans. This intracellular change, which only occurred during an early postnatal period, led to permanent increases in inhibitory tone across the brain, constraining synaptic transmission and hippocampal plasticity throughout life. In adult mice, behavioural deficits could be temporarily reversed through GABA inhibition but, perhaps most crucially, treatment with Ras-ERK inhibitors during the critical developmental stage prevented development of the condition. The potential for future interventions in humans is obvious, though the technical and ethical hurdles will be enormous.

A psychosis risk calculator? Between a fifth and a third of those with prodromal symptoms 'convert' within 2 years, but could we better personalise a risk profile for a given individual? This idea is not new in physical health where we have stratified charts for cardiovascular disease for example, but it is novel in mental health. We have well-validated and sensitive epidemiological risk factors, but specificity has been a problem, with most people with these at-risk factors not converting to psychotic illness. As part of the second phase of the North American Prodrome Longitudinal Study (NAPLS-2), Cannon *et al*[6] have created such a risk tool, having followed up almost 600 high-risk participants over several years. Clinical, demographic, neurocognitive and psychosocial factors were evaluated, and factors predicting conversion to a psychotic illness were high levels of unusual thought content and suspiciousness, greater decline in social functioning, lower verbal learning and memory performance, slower speed of processing and younger age at baseline. Factors that did *not* predict transition were: stressful life events, trauma and a family history of schizophrenia. External validation by the same team[7] on an independent high-risk clinical sample confirmed that the calculator had good discrimination. The authors propose that the NAPLS-2 calculator offers a meaningful step towards personalised treatment of early psychotic disorders. An online version is free to use, although psychometric data are required to complete all aspects: http://riskcalc.org:3838/napls/

Some have described the result of the European referendum as 'turkeys voting for Christmas'. The association of birds with Christmas may offer an insight into the neural substrate of conceptual knowledge in humans. Recent findings have demonstrated 'grid cell' representations of *spatial* relationships in the hippocampi: for example, when rats navigate in space, assemblies of cells fire depending on the orientation of the movement, suggesting they have an orientation preference. Similarly, in virtual reality

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navigation in humans, the BOLD signal in the hippocampus fluctuates in a manner that suggests a six-way (hexagonal) symmetrical grid cell representation. Little, however, is known about *non-spatial information* and its representation: might this follow a similar organisational pattern?

In Constantinescu *et al*'s recent paper in *Science*[8], a conceptual 'navigation' task was designed, wherein humans learned to associated pictures of birds with Christmas symbols. Participants were shown bird stimuli that varied in the length of the neck and legs (essentially, along a single spatial dimension) and trained to choose Christmas symbols depending on the appearance of the bird characterised by its neck:leg ratio. So, there was a two-dimensional (2D) plane with neck length on one axis and leg length on the other, with associated Christmas symbols plotted at different neck/leg length coordinates. In the scanning phase of the experiment, participants watched a video of a bird 'morphing' with its legs and neck increasing/shrinking in a particular ratio. They were then instructed to imagine the outcome of the video continuing to morph with the same proportions and, for the imagined end point of the morphing process, select the correct Christmas symbol they had been trained on earlier. Using this method, the imagined morphing formed a trajectory in the plane of neck/leg lengths which 'arrived' at a coordinate in the 2D plane of a specific Christmas symbol. By varying this trajectory (e.g. an angle through the space of leg/neck lengths) and recording the accuracy of participants' choosing of the correct Christmas symbol, the experimenters could determine how different brain regions respond to different trajectories in this abstract, conceptual space.

Participants with greater accuracy showed more directional modulation (i.e. the angle of the trajectory in the 2D conceptual space of neck/leg length and Christmas symbols) of the fMRI BOLD signal in the ventral aspect of the medial prefrontal cortex, with correlated activity in the entorhinal cortex suggesting multiple areas were responding with the same 'conceptual' trajectory preference. To test the hexagonal nature of this conceptual grid representation, the authors reanalysed the data using 4-, 5-, 7- and 8-fold symmetry, but only found statistically significant effects in the 6-fold (hexagonal) symmetry case. The findings support the concept that the brain organises *concepts* into a mental map that can be navigated in a similar way to *spatial* ones through relational codes laid out in a hexagonal grid-like pattern.

A feared consequence of Brexit is that UK-based scientists will lose out, and become unwelcome partners, on European grant applications. Science is evermore based on both international and interdisciplinary collaboration; beyond politics, how do such factors affect grant applications? Writing in *Nature*, Bromham *et al*[9] analysed Australian data on research council funding to look for associations with an index of discipline diversity/collaboration and the success achieved in finding funding. They took 18 476 project proposals submitted over 5 consecutive years (2010–2014) – with an annual success rate of 15–20% – and developed a metric called interdisciplinary distance (IDD) to quantify the degree of collaboration between scientific fields for a given project. IDD ranged from 0 (a single field of study) to 1 (representing the most diversity), and there was a linear, negative association between it and the probability of being recommended for funding, such that the more interdisciplinary the application, the less likely it would be funded. This effect was preserved when controlling for year of application, number of applicants, prestige of the university and primary research field.

The authors postulate that grant panels are often organised in scientific or subject-specific groups, reducing the confidence they have in robustly assessing the quality in different strands of such proposals. For psychiatric research, a higher IDD impacts the chances of funding success much harder than for psychology and cognitive science. The physicist Hannes Alfven said 'Scientists tend to resist interdisciplinary inquiries into their own territory. In many instances, such parochialism is founded on the fear that intrusion from other disciplines would compete unfairly for limited financial resources and thus diminish their own opportunity for research'. His cynicism appears to have been well founded, though removing others from different disciplines feels even more unpalatable than usual in this current climate of political introversion.

Finally, we've all been stumped by a smart (or smarmy) student asking us to explain the phenomenological difference between a hallucination and a dream. It's an old question: John Keats pondered 'was it a vision, or a waking dream? Fled is that music: do I wake or sleep?' In contemporary neuroscience, the construct of clear consciousness is not a binary one, and functions such as sensory discrimination, perceptual awareness and attention persist – albeit at differing levels – during REM sleep. Waters *et al*[10] update us, noting Hughlings Jackson's original scientific model of shared sensory discharges, to show that they do indeed overlap in terms of subjective descriptions and some underlying brain mechanisms (as do hypnagogic and hypnopompic phenomena that occur in about 70% of the population). However, some critical differences remain. Sleep perceptions are immersive, whereas hallucinations form discrete overlays on true perceptions, and sleep-based phenomena only utilise a subset of the neural networks involved in hallucinations. In particular, during REM sleep, connections between higher-order areas (e.g. the prefrontal and association regions) and unimodal sensory areas are broken, manifesting in the continuous, often fantastical elements so uniquely characteristic of the oneiric state. Current understanding would suggest that most hallucinations are not due to REM processes intruding into waking consciousness. In Richard Linklater's 2001 film *Waking Life*, the protagonist challenges us that we cannot distinguish our dreams from our real existence: philosophical debates may continue, but we now have a detailed paper to commend to precocious students.

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