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Kaleidoscope

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In the UK, increasing contact for the most socially vulnerable is a key inequalities target for integrated care systems, but are outcomes any better for those with greatest need once they do access 'the system'? Vargas Lopes et al[1] tested this in The Netherlands with a national cohort study that mapped out baseline illness, treatment received and mental health outcomes across almost one million Dutch adults. The study is interesting, as most work to date has 'only' shown the inequity in access and not followed up on what happens once care is sought and offered. As one might predict, the poorest quintile had the greatest initial (therapist-measured) illness severity. However, after correcting for severity and individuals' need, those with the lowest incomes received significantly less therapist time than the richest. Further, individuals in the highest income quintile were 17% more likely to have functional improvement than the poorest at treatment end. Of note, the data-set did not capture ethnicity, so this cannot be explored here.

The Dutch model is not very dissimilar to that of the UK, with universal, comprehensive and free healthcare. Society there is generally lauded for being relatively equitable compared to many others in Europe and globally, so one imagines that disappointing as these data are, they are likely to be far worse elsewhere. As well as suffering the greatest problems to begin with, the poorest in society get proportionally less care once in services, and their outcomes are worse: at almost every stage, disadvantage is compounded. There are interesting but potentially tricky policy implications, such as advocating for greater therapy time for those on the lowest incomes. Certainly, getting the most vulnerable and deprived into healthcare remains laudable and necessary; problematically, it looks like it might not be sufficient.

One can reverse this: is the 'acquisition' of a mental health diagnosis or prescribing of psychotropic medication associated with worse subsequent socioeconomic difficulties? The issue is thorny, with lots of confounders, but certainly one could hypothesise that both directly and indirectly these factors might hinder one's life opportunities. However, there have been few large studies on this. Moving from the Dutch to the Danes, Vedel Kessing et al[2] sampled over 1.5 million records from a different large nationwide population register of individuals who were followed up over 23 years between 1996 and 2018. Over three-quarters had received a psychiatric diagnosis or been prescribed psychotropics at some point in their life; about a quarter had a relevant hospital contact. Having a psychiatric diagnosis or prescription was associated with subsequent lower income, increased unemployment and disability benefits, and greater likelihood of being unmarried and living alone. The findings perhaps illustrate what you suspect and see in practice, but it's always good to get the data. As in the first piece, it emphasises that 'finding' those who are most vulnerable is not enough, and that in a biopsychosocial model, the social is normally the most important part.

Antidepressants cause manic switches in individuals with bipolar affective disorders (BPAD), right? It's canonical in psychiatry but actually a complex issue to study robustly. Randomised controlled trials are often underpowered, lack placebo and are of inadequate duration, and strict participant exclusion criteria lead to questionable mapping to real-world populations. Larger naturalistic data-sets compensate for some of this but run into the inevitable challenges of a lack of randomisation and the inability to determine causality. Moving on, some have refined this approach by applying self-controlled designs using within-individual methodologies, so that one can track a person over time and see how their mental health varies when on and off various medications. The problem here is confounding by indication and time-varying factors hindering interpretation of data – all issues we see with varying methodological approaches more generally, each with their strengths and weaknesses. The issue remains critical here with bipolar depression, however; although (hypo)manic episodes define BPAD, the depressive phases account for the large majority of illness burden, and we need the optimal treatment. This is underscored by data suggesting that perhaps half of those with BPAD have received treatment off-license with antidepressants.

Jefsen et al[3] tried to overcome these methodological difficulties using a nationwide health registry (the Danes again), pulling out over 3000 individuals with BPAD. They used the within-individual model but tried to overcome the limitation of time-varying confounding by indication by plotting the incidence of manic and depressive episodes relative to the commencement of an antidepressant, contrasting (hypo)manic episodes before and after this. They found that manic episodes peaked 3 months *before* antidepressant commencement, and depressive episodes were most frequent at the time of their initiation. In other words, these data do not support manic switching but do suggest that time-varying confounding by indication is skewing our interpretation of the existing literature on causality. Perhaps the best way to interpret this is to consider that it's not saying antidepressants cannot or do not cause manic switching, but that most of our trials to date have such methodological issues that, equally, one cannot infer the opposite. It's certainly not the end of the debate, but really emphasises the challenge of doing the research.

I'm re-reading Kerouac's 'On the Road' at the moment, and it's made me wistful about the minimum we need to survive; a recent paper tests what's essential for a 'minimal cell'. A minimal cell is one with only genes essential for life, and engineering such a cell allows testing of the impact of various evolutionary pressures. In a study published in *Nature*, Moger-Reischer et al[4] took a stripped-down *Mycoplasma mycoides* bacterium, with just 493 genes, and compared this with the non-stripped-down version (already with a fairly sparse 901 genes) from which it was engineered. (The original strip-down was described in a landmark paper by Craig Venter's team in 2016[5]). In theory, the slimmed version has no room for error, and any mutations have a considerable risk of being terminal, yet mutations are an unavoidable part of life and reproduction, so what would happen? The cut-down led to an initial drop in fitness (growth rate and competitiveness) of over 50%, but this was all regained within 2000 generations (think 40,000 human years). Mutational rates were actually as rapid as those in the non-minimal comparator, and the cell essentially recovered all the fitness it had lost from the stripping-down, but via different mutational paths. What was particularly fascinating was seeing changes in the size of the two cell types: the non-minimal one grew larger, whereas the minimal one did not, but it was the same gene mutation that affected this in both cells. There was a context-dependent aspect: when it was beneficial for the cell's survival that it grew, the gene enabled this; when it was not, it kept it small. Natural selection acts very rapidly on even the simplest of organisms. This work has more than theoretical interest: understanding how organisms overcome evolutionary constraints has implications for medicine in terms of understanding pathogens, as well as the field of synthetic biology and indeed contemplation of the origin of life itself. Much

commentary on this paper has inevitably invoked the famous line from *Jurassic Park*: 'Life finds a way'.

Early identification of Alzheimer's disease, or its precursors, promises tempting therapeutic targets. We know that the illness starts many years before it's clinically manifest. Genome-wide association and translational studies demonstrate that it is far more complex than tau and amyloid and is influenced by systemic factors outside the brain. However, finding reliable and valid markers remains a challenge. Walker et al[6] looked for peripheral biomarkers in 10,000 middle-aged adults (45–60 years old), who were followed up for 25 years, during which time each participant had at least six blood tests, and about a fifth of the sample ultimately developed Alzheimer's disease. They used a large-scale proteomics platform to look for any associations of almost 5000 plasma proteins with subsequent occurrence of the neurodegenerative illness. Thirty-two were initially identified, and these had roles in synaptic functioning, immunity, the organisation of the extracellular matrix and proteostasis. The last of these is particularly interesting, as such regulation helps prevent protein clumping, as occurs with amyloid and tau in Alzheimer's disease. Helpfully, the research team then replicated this in two independent populations, finding over a third to be associated with cerebrospinal fluid biomarkers of Alzheimer's disease, neurodegeneration or brain inflammation. Further network analysis determined a 'protein signature' associated with dementia risk 20 years before illness occurrence. The authors conclude by presenting what they propose as a prioritised set of candidate markers for Alzheimer's disease and putative molecular drivers of disease, and, critically, ones that present in mid-life. Of themselves, these are not sufficient to predict Alzheimer's disease, but in the future they might meaningfully be combined with other health and family factors to do so.

Finally, Ed Sheeran sang 'I'm in love with the shape of you, we push and pull like a magnet do'[7], possibly auguring a *Nature* neuroimaging paper on how the physical geometry of your brain may affect function. Growth in brain size is the dominant feature of our hominin species (for those paying attention to the August Kaleidoscope[8] on the possible cultural innovations of small-brained *Homo naledi*, the reviews are back, and they are *not* kind[9]), but the dominant contemporary paradigm centres instead on the functional connectome underpinning complex human neuronal dynamics. Challenging this, Pang et al[10] analysed functional magnetic resonance imaging data from a range of conditions across 10,000 brain maps, contrasting the influence of our familiar walnut-shaped outer surface with the inner webbed connectome. In essence, we're familiar with the fact that neurons communicate via white matter tracts that can connect to quite distal regions, and much work in recent years has tried to map this out – the connectome. But neurons can also communicate more locally, with waves spreading across surface regions.

The team, which was led by physicists, applied pre-existing theoretical mathematical models that relate to wave-spreading in any number of physical conditions, from banging a drum to geological seismic activity. Why should the brain be any different, they ask? (It's always good to have those from outside one's field ask such fundamental questions: they also teach us new things, here the idea of 'eigenmodes', the spatial patterns of the natural, resonant modes of a system). And, indeed, they showed that contrary to the connectome model, it is the brain's geometry – the very gyri and sulci sculpted within your skull – that is fundamental and a more parsimonious model for cortical and subcortical activity and dynamics, both at rest and when engaging in an activity. As ever, this is not the end of the debate, and the connectome clearly has ongoing importance. Keeping to a musical theme, the authors write 'spatiotemporal patterns of neuronal dynamics emerge from excitations of the brain's structural eigenmodes, much like the harmonics of a plucked violin string arise from vibrations of its own resonant modes'. However, I choose to give the last words back to Sheeran: 'Every day discovering something brand new, I'm in love with the shape of you'.

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