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Kaleidoscope

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Life expectancy in England is related to income (and in London, it can be mapped by a resident's nearest tube station[1]). The arrival of a new government offers the opportunity to review the impact of earlier policies designed to reduce health inequality. A new report from the King's Fund[2] has updated Michael Marmot's 2010 publication, *Fair Society, Healthy Lives,* and using a wider range of determinants of lifestyle and health, has found that income-related inequalities in life expectancy have improved since that report. Department of Health policies in the 2000s appear to have contributed to this, although reductions in child and pensioner poverty and improvements in employment and social housing have also impacted positively. Nevertheless, unemployment, housing deprivation, and binge drinking remain key factors in lowering life expectancy. The King's Fund report argues that a more nuanced and integrated policy response for the NHS and other public services will be required by the new government to continue to reduce inequality, but recognises that implementation in an era of austerity poses challenges, particularly for the most vulnerable.

Advocating for greater patient involvement in care, the American Institute of Medicine has produced a framework[3] to establish standards for psychosocial interventions specifically in mental health. It identifies that there is a 'quality chasm' in the 'gap between what is known and what is commonly practiced', with a dearth of access, training, quality measurement, and synthesised coordination of evidence-based psychosocial interventions. A central tenet of this work is the need for service users with their unique perspectives, knowledge and goals, to drive an iterative cycle of informed and meaningful care. Better evaluation of such interventions is critical to systematically appraise their quality, with a view to longer-term service developments and wider implementation. A more patient-centred approach has explored the effectiveness of solution-focused approaches to initiate change in individuals with psychosis. DIALOG+ is a structured computer-mediated tool to appraise patients' concerns and explore potential appropriate solutions. Priebe *et al*[4] undertook a pragmatic cluster randomised controlled trial in community teams, comparing monthly DIALOG+ use with an active control (patients completed the same ratings, but independently and without discussion with professionals) over half a year (total $n = 179$). Those receiving the targeted intervention had better subjective quality of life, and both fewer unmet needs and clinical symptoms at all time points up to 1 year. Interestingly, however, they did not report greater treatment satisfaction, mental well-being or self-efficacy. Implementation of DIALOG+ is not expensive, and indeed the group receiving this had lower care costs. There is an inherent appeal to such formalising of joint-working, both enabling those we try to help to set the agenda, and applying some structured goal-based work to our routine clinic appointments. It is particularly heartening to see these data emerging to support such practice as evidence-based and meaningful.

Commonalities across cultures may help to identify the core features of a disorder. Psychoses are noted for considerable heterogeneity in clinical expression within and across different ethnic groups. Gong *et al*[5] used neuroimaging in 126 individuals with first-episode schizophrenia, and age-, gender- and ethnicity-matched healthy controls from four distinct groups: White Caucasian, African–Caribbean, Japanese and Chinese. There were significant relative reductions in the right anterior insula grey matter in all patient groups, despite variation in their clinical presentations and exposure to antipsychotic medication. The authors label this a 'neuroanatomical signature of schizophrenia', though they note the involvement of the right anterior insula in affective and anxiety disorders. The region has rich connections with the prefrontal and temporal cortices, the thalamus and amygdala, and is implicated in self-awareness and emotional regulation. Such pan-diagnostic changes might fit with a continuum model of many mental health conditions, though it may raise future specificity challenges if enhanced to have a predictive biomarker role.

Synaptic plasticity is vital for brain growth and normal functioning. Now a paper in *Science* has demonstrated[6] that there is a critical early postnatal period for ensuring appropriate plasticity throughout life. After cell proliferation and migration organise the macrostructure of the brain, environmental and sensory stressors leave an 'imprint' via microstructural synaptic plasticity mechanisms, for example long-term potentiation (LTP) or depression (LTD). In the early postnatal period, the *DISC1* gene on chromosome 1q interacts with Lis1 and Nudel signalling molecules as neurons proliferate and migrate in cortex. Later, in adulthood, this neurodevelopmental phase ends and further plasticity is only available via LTP and LTD, with *DISC1* still being expressed post-synaptically in the cortical neurons. The novel work from Cardiff University showed that cortical plasticity in the somatosensory cortex of mice could be disrupted by manipulating *DISC1* expression after neurogenesis and proliferation are complete (which in mice is around day 7), but before the adult mode of LTP/LTD plasticity take over. Subsequently, early developmental LTD was unchanged, but these mice lost the late-adolescent facility for LTP. It appears that cortical reorganisation, at least in the somatosensory cortices of mice, depends on LTD until early adolescence, when LTP 'takes over', and that very early life *DISC1* expression is essential. *DISC1* abnormalities have been identified in schizophrenia, depression and bipolar disorder – illnesses that commonly appear in late adolescence. The authors propose that the rodent-induced changes may model the underlying cognitive deficits associated with *DISC1* mutations, and help explain why psychiatric symptomatology often first manifests in late adolescence.

The physicist Ernest Rutherford said 'If your experiment needs statistics, you ought to have done a better experiment'. Two recent papers challenge the old master, looking at novel ways to utilise large data-sets. Google and a team from Stanford University have collaborated[7] to produce a computing model they claim will facilitate future drug discovery. A recognised critical problem with current drug trials is that they usually involve reporting on relatively small clinical cohorts, taking many years and billions of pounds, and often come with a high failure rate. The large background (and usually unpublished) data-points that trials hold typically have low predictive power – despite their relative size – owing to the complexity of interacting physiological systems and the challenges of low experimental drug hit-finding, even when these processes are automated. There is, the authors argue, a need to standardise, release, and combine disparate information sources, using massively multitask neural architecture to produce deep-learning frameworks. They tested this hypothesis with a large collection of data-sets that contained almost 40 million

measurements for more than 200 targets, and showed that multi-task networks trained on this attained significant enhancement over baseline machine learning – improving as more data were added – which showed some transferability to non-tested tasks.

Large data-sets are also a recognised source of spurious 'discoveries'. You have a hypothesis, design an experiment, and propose necessary statistical tests; after months (or years) of collection you begin analysing but quickly realise the data cannot be tested using the planned ANOVA or regressions. Analysis outside this *a priori* plan raises difficulties common to exploratory analyses, of multiple comparisons and risk of false findings. So how might one adapt such analyses in a principled and rigorous way? One method is the idea of randomly dividing collected experimental data into a 'training' set – used to explore the data and develop models – and then validating these models on a 'holdout' set. Before analysis begins, the holdout set is secured to a data 'vault' which is only made available once the statistical model developed on the training set is confirmed. But what happens if the statistics do not work on the holdout data or over-fit because of inclusion of too many model parameters? Dwork *et al*[8] propose a novel solution to reusing a holdout set by applying *differential privacy*. In analysing large databases (e.g. clinical or financial) where individuals' privacy must be preserved, differential privacy is a probabilistic method of revealing the result of a database query (e.g. what is the mean income of people living in a geographical area) in a way that guarantees the data cannot be de-anonymised, or that queries across multiple data sources cannot be used to infer the identity of individuals. By applying this method to the holdout data-set, one can sequentially test statistics on holdout data in a reusable way that preserves statistical validity and avoids over-fitting because information about the individual data items is never 'leaked' to the analyst.

Finally, *nosce te ipsum*, or know thyself, is an aphorism attributed to Socrates; this function may be associated with activity of the medial prefrontal cortex (mPFC) which has been linked with social cognition. Further refinement has been possible through the observation that delineating information about others is focused more on the dorsal aspect and self-referential thinking in the more ventral region of the prefrontal cortex. Bergström and colleagues[9] advance this with a sophisticated neuroimaging paradigm designed to unpick types of information recollection. Participants were asked to recollect whether they had previously conveyed information to themselves or others, or whether someone else had done this. The dorsal mPFC activated when participants retrieved social information about themselves or others – regardless of whether this was an idea (conceptual) or an action (agentic) – while the ventral mPFC only activated during *conceptual, self-referential* recollections, suggesting that it has a specific role in retrieving memories related to what one thinks about oneself, rather than what one has done.

The social influence of others is seldom more important than during adolescence, profoundly impacting on developing self-concept and actions as a coherent sense of self emerges. An fMRI study[10] found that influence from both parents and peers, tested through portrayal of their (actual) attitudes, activated the adolescents' aforementioned mPFC, as well as other regions involved in mentalisation (the right and left temporoparietal junctions), reward (the ventromedial PFC) and self-control (the right ventrolateral PFC). Interestingly, the same brain regions were equally activated by the two diametric teen forces of peers and parents, though – perhaps counterintuitively – behavioural data demonstrated that they changed their attitudes significantly more to come in line with those of their parents. These cognitive processes of mentalisation, reward, and self-control appear critical for adolescents to evaluate others' perspectives, and to either shift attitudes to match, or to (metaphorically or literally) stand up against those with whom they disagree. Or, to update the Socratic maxim with a 2015 adolescent's makeover, 'Haters gonna hate'.

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