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Kaleidoscope

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Different clinical, behavioural and neuropathological patterns are seen in the dementias; our ability to subtype them has remained somewhat crude, but their secrets are beginning to unravel. Frontotemporal dementias are particularly heterogeneous, with behavioural, semantic variant primary progressive aphasia and non-fluent variety primary progressive aphasia types. Pathological protein folding and aggregation are common post-mortem findings, but there is considerable variation and they have typically limited correlation with clinical presentation. Neuroinflammation is another putative marker, and Bevan-Jones et al looked at differences in these three clinical groupings, comparing them with matched controls.[1] *In vivo* positron emission tomography (PET) explored activated microglia (via ^{11}C-PK-11195), a broad neuroinflammatory marker, and a radioligand marker (^{18}F-AV-1451) for non-amyloid-β protein aggregation. There was widespread uptake of both ligands across all groups, but the latter marker was significantly increased in temporal regions in semantic variant primary progressive aphasia. Semantic variant primary progressive aphasia and behavioural frontotemporal dementias also showed variation in spatial binding across the temporal and frontotemporal cortices. Post-mortem studies confirmed these findings and distinct patterns of neuroinflammation appear to map onto clinical variants. The data confirm the importance of inflammation in frontotemporal dementias, which co-occurs with pathological protein aggregation in symptomatic phases of illness, but might be an earlier marker in those who are asymptomatic. The question arises as to whether, with time, such investigations might facilitate more accurate diagnoses, and indeed offer tailored therapeutic targets for novel treatments.

Tetreault et al deconstruct Alzheimer's disease, observing that group-level neuroimaging data show strong associations between regional atrophy and diagnosis, progression and symptomatology, but that this is lost at an individual level where there can be considerable clinical and neuroanatomical variability.[2] This hinders our understanding of the condition and the development of biomarkers able to track illness progression in individual patients. The authors report on a novel technique, 'atrophy network mapping', which tests single-participants neuroimaging in Alzheimer's disease localising to syndrome- and symptom-specific brain networks. They compared the individual scans of those with Alzheimer's disease with those of healthy controls – notably no more than 42% of patients had atrophy at any given location – and then determined, via a large (n = 1000) normative connectome, the regions functionally networked to that individual's area of atrophy. Fascinatingly, all patients, despite the aforementioned variations, had atrophy functionally connected to the same regions in the mesial temporal lobe, precuneus cortex and angular gyrus; results replicated in two independent data-sets. This atrophy network mapping was then used to determine symptom-specific networks, and was able to define these for impaired memory and delusions. The findings provide a potential means to localise symptoms to brain networks, and thereafter how this relates to behaviour in Alzheimer's disease in a given individual.

Empathic sharing of witnessed pain is thought to be at the root of our reluctance to inflict harm, something altered in antisocial psychiatric disorders. Within rats, observing another's pain activates emotional mirror neurons in the anterior cingulate cortex (ACC), a representation of emotional contagion. Hernandez-Lallement and colleagues employed a classic behavioural paradigm to examine this vicarious emotion and its role in active harm aversion.[3] In a dual chamber apparatus, rats were trained to press one of two bars for a sucrose pellet, and then placed into the neighbouring compartment to experience unpleasant footshock. These rats were then returned to their original space while another rat was placed in the adjacent room. When 'no harm' was paired with lever choice, all animals pressed away freely enjoying the reward, but when then their bar choice was paired with witnessing their compatriot's footshock pain, animals shifted away from the shocking lever, even though it meant they also got no sweets. While there was a range of variability, overall there was no difference between the actions of male and female rats, and familiarity with the victim made no difference in their choice to avoid causing harm, which happened most often after just one shock. Contingency to their action was key for eliciting this effect, as witnessing random shocks created similar levels of distress in the victims, but not the witness. However, this choice was influenced by the amount of personal gain available. Although rats reduced their harming actions when one or two pellets was the reward, a three-pellet offer was too good to refuse showing a cost limit to the behaviour. Bilateral injection of the gamma-aminobutyric acid type A agonist muscimol into the ACC prior to learning prevented the harm reduction, in alignment with its proposed role in vicarious emotion. In other words, deactivation of the ACC gets rid of this harm aversion. Of course, motivation cannot be accurately ascertained in this paradigm. It may be that witnessing pain is sufficiently aversive that it generates the selfish desire to avoid it, even at a cost. Or it could be true altruism: regardless of gender and how well they know the other, they do not want them harmed – unless the price is right.

No one likes making a physical effort: in ecologically valid settings, this can easily be tested in a domestic gathering of two people when someone suggests unloading the dishwasher. Cognitive effort and motivation are harder to measure (and disentangle from attention, cognitive control and working memory), yet everyone experiences it, and it can also be a core negative feature of psychiatric disorders. Westbrook et al describe a novel application of the n-back task – used to study working memory – with administration of the stimulant methylphenidate (a dopamine and noradrenaline reuptake blocker) and sulpiride (a selective D_2 antagonist).[4] They aimed to show that striatal dopamine alters people's sensitivity to the benefit/cost ratio of cognitive effort either by endogenous level (of dopamine synthesis capacity) or pharmacological manipulation. Fifty participants completed an easy versus hard n-back task. In the easy n-back condition, participants had to indicate when the current stimulus matched that shown to them at $n = 1$ or $n = 2$ trials previously. The hard condition ($n = 3,4$) is more difficult and effortful. Participants were asked to quantify how much money they would require to complete the n-back tasks (the subjective value) and predictably, they found that this correlated as a lower subjective value with increasing n. Using PET of the caudate nucleus, a higher willingness to expend effort was found in participants with higher dopamine synthesis capacity. When low-dose sulpiride and methylphenidate were administered, people with low (but not high) dopamine synthesis capacity increased their subjective values. The authors suggest this is because at low doses, sulpiride blocks presynaptic dopamine autoreceptors, so, like methylphenidate, increases extracellular dopamine levels. Next, they tried to tease apart whether endogenous dopamine synthesis and its pharmacological manipulation affected the participants' evaluation of the benefits or costs of action. Using a psychometric model of choice in the presence of different benefit/cost ratios, they showed that participants were more influenced by benefit if they had high dopamine synthesis capacity and were on methylphenidate (and were more likely to select high-effort choices) and the influence of costs were attenuated by sulpiride. The conclusions Westbrook

et al draw from their PET, modelling and psychophysical experiments are that (overall) striatal dopamine increases motivation for cognitive effort by driving up the effect of benefits versus costs when making decisions. The findings help explain the mechanism of action of psychostimulants in attention disorders and as nootropics – they seem to work through enhanced motivation, not cognition.

Although the risk of psychosis is known to be disproportionately high in ethnic minority immigrants to Western countries, the causes for this have been difficult to pin down. Using data gathered from 16 centres in six countries (1130 people with first-episode psychosis, 1497 controls), the contributions of social disadvantage, linguistic distance (language distance and fluency in the majority language) and discrimination were investigated.[5] Using multivariate logistic models it was shown that although current socioeconomic status could act as a buffer to some extent, linguistic difference had a significant impact on first-generation immigrants, and social disadvantage was a driver of psychosis across generations for all except white ethnic minority groups. Discrimination was strongly associated with odds of developing a psychotic disorder, but became insignificant after other factors of disenfranchisement were taken into account. The finding of psychosocial disempowerment as a major contributor to excess risk of psychosis is consistent with literature showing a protective effect of living within communities of the same ethnocultural group. Although mechanism was not addressed, having an outsider status has been associated with dopamine sensitisation, a process reactive to environmental influence and directly relevant to alterations seen in psychosis. These findings are the first to speak directly to the drivers of psychosis in immigrant minority ethnic groups and, importantly, hint at the potential impact of public health strategies on intervention and prevention in outcomes for these vulnerable groups. However, too many individuals continue to experience racism in society, and will be very aware of the direct and indirect psychological harms from this: we're not sure these findings will wholly assuage.

The risk factors for suicide include occupation and gender, with physicians having higher rates than the population at large (including more than those in the military), and men greater rates than women. Does gender have an impact on suicide mortality rates (SMRs) within medicine in the same way as the rest of society? *JAMA Psychiatry* published a meta-analysis and systematic review of physician suicide over time, including analysis by gender.[6] Overall, they found that physician suicide has declined since 1980, with male doctors fairing much better than men in the general population (SMR, 0.67). For women doctors, although this too is on the decline overall since the 1980s, the results when compared with women in the general population were reversed with a much higher rate of suicide (SMR, 1.46). How to interpret these data? Several factors are likely interplaying. Compared with the general population, suicide makes up a relatively high proportion of mortality for physicians, likely because of the *decreased* risks from other causes: in other words, doctors' outcomes are better in other health conditions, so the suicide data are relatively worse. However, career-related variables were the greatest physician risk factors; psychiatry and anaesthetics took the top two places, with the review hinting toward workload and training burdens. Explaining the higher relative rates in women medics is challenging. It is notable that in the USA, since 1980 the number of female medical school graduates has doubled to 48%; however, the overall female participation in the wider labour force has only increased by 4%, indicating a swift shift in gender dynamics within medicine not seen generally. A rhetorical question is whether women in medicine have faced greater additional societal or work-based challenges than their male counterparts as their exposure to an inherently stressful job has grown. A practical question is how to fix this.

Finally, the relationship between the media and suicide remains contentious. Kaleidoscope previously reported on a rise in rates in young people following the airing of the Netflix show *13 Reasons Why* that described the suicide of a fictional character.[7] Another common question is whether reports of celebrity suicide, which inevitably attract many column inches, public interest and speculation negatively have an impact on others. This is clearly a methodological challenge to study, but writing in the *BMJ* Niederkrotenthaler et al systematically reviewed and meta-analysed 20 studies that compared time points before and after such events.[8] They found a 13% rise in suicide rates in the period following death (median follow-up was 28 days); when the celebrity's method of death was reported there was a 30% rise in death by the same method. Several things might be happening here: the first is identification with, and loss of, the dead person; the second is a putative 'normalisation of suicide' as a means of coping with distress; and finally, detailing methods might precipitate copying such acts in vulnerable people. The findings clearly matter; for better or worse, we live in a culture where celebrities and their lives have a high profile, and it is not surprising that their deaths are both reported and have a significant impact on many. We think that you will be able to recall some such deaths that have had an impact on you. However, the authors remind us that this is not a new phenomenon, and describe how there was an increase in such acts following the publication of Goethe's tale of unrequited love and suicide *The Sorrows of Young Werther* in 1774.[9] There were some contemporary reports of people being found dead beside copies of the book, and it is sometimes called the 'Werther effect'. This is something inherent in human nature, so 'blaming celebrities' is not the place to start. It also tells us that there are things we can do, and equally, ignoring this is not an option. A first obvious step would appear to be for those working in media to report sensibly, not glorifying deaths or discussing undue detail. Guidelines do exist, including ones drawn up by the World Health Organization, but they are just not always implemented.

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