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Kaleidoscope

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Why do serious mental illnesses persist, given the negative evolutionary pressure? These often strike at a young age when individuals are starting families and need maximal resources, and should act to reduce fecundity. Although it is not often highlighted, there are data supporting the association of severe mental illness with increased creativity, artistry and visionary thinking that may benefit society, even if this occurs at a cost to the individual. Are we observing the impact of a delay between the speed of contemporary social change and the ability of the brain to respond to this in an evolutionary time frame? And how might this be investigated in an evolutionary paradigm? Song *et al* examine the *CACNA1C* gene – influencing calcium signalling – that has been repeatedly implicated in the heritability of schizophrenia and bipolar affective disorder.[1] Traditional genetics has explored single-nucleotide polymorphisms (SNPs), but here the authors examined a non-coding aspect – a tandem repeat region involved in regulating the gene's expression. Other hominids (the great apes minus us) have a single homologous 30 base-pair sequence at this point; the 'standard' reference human genome has a tandem repeat of ten 30 base-pair units; however, strikingly, in samples from the 1000 Genomes Project, this was highly polymorphic in size and sequence – from three times to almost four hundred times larger than expected. Such structural variants can be unstable and not easily picked up by typical genotyping and sequencing, which might explain the difference to the modest 'standard' genome. These repeat arrays are big, and appear to be currently confined to *Homo sapiens*, although interestingly other work shows similarities in Neanderthal genomes. This inevitably asks the question as to whether they were causally involved in hominin brain development, but also their influence on individuals' mental health. Sequence variants differed in how they changed gene expression at flanking SNPs, and those with the strongest association with mental illness showed *reduced* enhancer activity. *CACNA1C* encodes the pore-forming subunit of the $Ca_v1.2$ calcium channel. To date, calcium channel targeting drugs have shown mixed therapeutic promise; the findings support potentially refining in whom they might be useful. The study exemplifies the complexity of genetics research – not least the large tracts of repeated sequences in our genome that remain largely unexplored – advancing beyond our knowledge of simple Mendelian variation.

How could serious mental illnesses not exist? The brain is the most sophisticated system in the known universe, and look what happens when you 'helpfully' tinker with the wiring in your children's toys. As with all physical development, there is a pay-off between engineering simplicity versus the gain from complexity; in the case of the brain, rich interconnected hubs (highly connected brain regions with multiple connected branches) and regional hierarchies within the human connectome. Brain diversity offers enormous potential adaptive advantages to individuals and the species, but how far can these be pushed without causing harm? Gollo *et al* looked at the evolutionary tensions of the advantages our sophisticated neural wiring provides versus the costs of any changes to its intricate structure.[2] The human connectome – how hubs link and communicate – has evolved to a relatively stable position, and they speculate what might happen if this was disturbed. They used mathematical modelling to explore multiple randomisations, crucially conserving non-trivial aspects of brain physiology such as its geometry, the total connectivity between hubs and indeed the hubs themselves. The authors found that even small variations very quickly altered brain connectivity, and notably, frontal lobe hubs were especially sensitive to be degraded and disappear. Novel connectomes were produced, and with the most severe changes, a collapsed variant emerged, with the hubs all located deep in the brain, an area that appeared resistant to changes and produced resilient hubs. Extrapolating from this, most standard human variation lives within a relatively narrow phenotypical range – we are ultimately all pretty similar – but it does not take huge variation to produce devastating and highly unstable effects. In particular, they noted how the fragility of hubs in so-altered models had significant similarities to the brain changes and accelerated grey matter reductions seen in schizophrenia. In a linked editorial, Rosalyn Moran notes 'computational psychiatry' as an emerging field that may help better model neuropsychiatric states; a nascent area – akin to the aforementioned complex genetics research – that feels like it is only beginning to show its true promise.[3]

Much has been written on leadership, but research has seldom looked for its neurobiological drivers. Edelson *et al* argue that decisions to lead are grounded in perception of risk, loss, ambiguity and uncertainty.[4] They divided participants into groups of four, with each individual completing a gambling task; reward probability was presented as a partially obscured pie chart, and to introduce ambiguity. In some trials, the gains or losses were completely unambiguous so the researchers could establish participant's disposition to risk aversion. Next, they played the same game, but could lead (take/reject the gamble) or delegate and follow the group's decision. Trials were designated as either 'self' or 'group' with the former being trials where actions only affect the participant and in the latter decisions affect the whole group equally. To simulate real-world group decisions – where each person has different but incomplete information – in the group trials, different parts of the pie chart were obscured for each participant. Therefore, in all trials, the group has more collective knowledge of the risk than any individual.

One hypothesis is that people value the right to make decisions that affect them alone; consistent with this, participants generally tolerated losing complete information (by deferring to the group) when risky decisions only affected them. Similarly, participants often kept control over group decisions rather than deferring to the group (who have more complete information). In neither instance did this correlate with leadership scores. The authors then looked at responsibility aversion, finding a majority defer in group trials with high ambiguity, but there was substantial individual variation. Neither baseline decision-making scores nor willingness to take charge were correlated with leadership: it was, instead, a low 'responsibility aversion', a willingness to persevere and not alter one's actions even when faced with the responsibility for others' welfare, and a confidence in taking such decisions.

Always debated, especially for those who dip their toes in twitter's hot springs: talking therapies for psychosis, medication in borderline personality disorder. The COMMAND trial explored the mediators of outcome following cognitive therapy for command hallucinations (CTCH).[5] Such symptoms occur in about half with psychosis, and about 50% of the time the voices demand dangerous acts; however, the determinants of what leads individuals to act upon them have been unclear. CTCH looks to reduce the perceived power differential between the voice and the person hearing it, exploring actual lack of control over the commands, the real 'omnipotence' of the voice, and the ability of the voice to follow-through on any threats. A total of 197 individuals were randomised to receive either this intervention or treatment as usual. The active intervention halved acting on threats through the 18-month follow-

up, and perceived 'voice omnipotence' was the best predictor of this rather than overall psychosis severity. Interestingly, childhood trauma, depression and past self-harm were also predictive of acting on commands. The last factor reminds us that although often seen as a herald of increased risk to others, in most instances where harm occurs from commanding hallucinations, it is to the individual experiencing them. The findings also offer up practical aspects for clinicians: assessing the perceived power of a voice in comparison with the hearer. So, one–nil to talking therapies?

Guidelines for pharmacological management of borderline personality disorder do not recommend anything beyond short-term medication. Yet, clinicians and many patients will advocate for their use on an individualised basis, and wider data show medication prescribed in almost nine out of ten such patients in secondary care, the majority on a long-term basis. Lamotrigine is not uncommon in such circumstances: it feels a reasoned pharmacological neuroscientific fit, linking with broad concepts of an overlapping spectrum with bipolar affective disorder and the principle of mood stabilisation. Although there has been some evidence to support this approach, closer scrutiny shows that to be relatively weak so Crawford *et al*'s large trial in the *American Journal of Psychiatry* is to be welcomed.[6] In total, 276 individuals with borderline personality disorder (those with concomitant bipolar affective disorder or psychosis were excluded) were randomised to receive either 400 mg/day lamotrigine or placebo, and were followed up for a year. The results showed no difference between the groups, and although overall adherence rates were relatively low, the conclusion is stark: lamotrigine is not clinically effective in borderline personality disorder. However, both groups did show clinical improvement over the year: the impact of 'just' seeing your patients should never be forgotten. Two–nil to talking therapies?

How best to change doctors' non-evidence based prescribing practice? Certainly, just pointing out national or other guidelines does not seem effective, so Sacarny *et al* report on an alternative method – benchmarking practice against peers.[7] Across 2 years, they targeted the highest-volume non-psychiatry prescribers of quetiapine in older and disabled adults; atypical antipsychotics are very commonly prescribed in these cohorts despite the well-recognised risks of harm. The study captured 5055 doctors in total, or about 5% of all such quetiapine prescribers in the USA. They randomised them to either receive a placebo letter or three peer-comparison letters noting their habits compared with their peers. About half of this American sample were defined as either 'general practitioners' or in 'family medicine', and, roughly, the other half was in 'internal medicine'. The low-cost intervention worked, with just over 11% reduction in quetiapine-days; the findings persisted over 2 years, and there was no evidence of substituting for another antipsychotic.

The US's opioid crisis is well recognised; differentiating it from the UK is the far higher rate of individuals on prescribed medication. Doctor *et al* describe how before the introduction of modified-release opiates in the 1990s, long-term repeat opiate prescriptions were rare.[8] In light of this, they conducted a randomised trial where a group of physicians received a letter from a coroner when one of their patients likely died from controlled drug prescriptions that informed them both of the death (including details of the patient) and re-iterated prescribing guidelines alongside statistics on opiate-related deaths. By linking coroner-investigate deaths to a controlled-substance prescriptions database, they randomised two groups: 82 deaths linked to 388 prescribers (for the letter-based intervention group) and 85 deaths linked to 438 prescribers (for the control group, with no intervention). For both groups, each prescriber's average daily milligram morphine equivalent (MME) prescribing was calculated for the 3 months before a death and between 1 and 4 months after. If sending a letter to the prescriber affected prescribing practice, then one would expect a reduction in MME in the intervention arm, but not the control arm. In the 3 months prior to a death, both control and intervention groups had similar averaged daily MMEs of 72.5. During follow-up, in the intervention group, the daily average MME dropped to 65.7 but the control group MME remained at the same level. Two interesting demonstrations of the psychological power of even indirect peer-pressure.

Finally, 'sarcasm is the lowest form of wit, but the highest form of intelligence'. What about cynicism? It's the negative belief that self-interest drives human behaviour. Cynicism is associated with worse health outcomes and poorer psychological well-being. Nevertheless, in the world of cynicism research (imagine asking a question at their conferences), there is the construct of the 'cynical genius illusion', namely that those who are cynical about things are actually rather bright. Picture that person you work with – you know who we mean – who is condescendingly lording it over everything: they quite fancy themselves, don't they, 'just sayin' it like it is'. Stavrova & Ehlebracht reviewed the perceptions of the general public in several studies, which covered several hundred thousand people, and the actual performance of cynics on cognitive testing.[9] Overall most people believe the stereotype, that cynics are smarter than average. However, when such people were formally tested, they actually tend to do *worse* than average. Turning this around, competent adults tended to only have cynical viewpoints when it was warranted by a given social situation; less competent individuals were more likely to be cynical across the board. It actually seems that cynicism is a coping strategy by the cognitively *less* gifted to avoid being duped by others. So just smile back knowingly when next sneered at.

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