BJPsych The British Journal of Psychiatry (2016)
208, 98–99. doi: 10.1192/bjp.208.1.98

Kaleidoscope

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Why does schizophrenia persist? It is not rare and onset is relatively early in life; one might predict that evolutionary pressures would eliminate this profoundly disabling condition. We have previously noted the good epidemiological evidence to link it to creativity.[1] Now Srinivasan and colleagues[2] have analysed large genome-wide association studies of schizophrenia and a range of other phenotypes (including anthropometric measures) and, through comparison with Neanderthal and primate sequences, calculated a likelihood index of positive selection in humans after divergence from other hominids. Gene loci associated with schizophrenia were found to be significantly more prevalent in genomic regions likely to have undergone recent positive selection in humans. Susceptibility to schizophrenia appears to have arisen as a by-product of our species' unique achievements in language and imaginative thinking. The persistence of schizophrenia is, the authors propose, related to the very process of becoming and being human.

However, we also recognise that there is significant heterogeneity in the presentation of psychotic illness; could the differential response to medication offer a measure of stratification? Antipsychotic medications act as dopamine and serotonin receptor antagonists, and also block the voltage-gated K^+ channel Kv11.1. Heide *et al*[3] considered response to the antipsychotic risperidone in the CATIE cohort, with a particular focus on variants in the gene encoding Kv11.1 and hepatic metaboliser status. They found that risperidone – but not other atypical antipsychotics – caused greater *in vitro* block of the Kv11.1-3.1 isoform of the K^+ channel, and that individuals with this genotype showed a better response to the drug, particularly if they were also one of the 7% with slow metaboliser status. The findings suggest that Kv11.1 channels may have a therapeutic role in antipsychotic action – as well as their better established side-effect of causing cardiac QT prolongation – and offer another small nudge towards predictive pharmacotherapy.

Differential medication response has also long been recognised with lithium. Song *et al*[4] performed a genome-wide association study (GWAS) in a large sample of Swedish and British self-reported and objectively reported bipolar affective disorder lithium responders as well as healthy controls. This identified an intronic single- nucleotide polymorphism of *SESTD1* as a novel risk gene for lithium responsiveness. This encodes a protein involved in the regulation of phospholipids, which have previously been linked with the pathogenesis of bipolar affective disorders.

Mertens *et al*[5] took another approach to the same issue, utilising induced pluripotent stem cells from six patients with manic-type bipolar affective disorder – three lithium responsive and three non-responsive – and four unaffected controls. From these cells they grew populations of hippocampal dentate gyrus granule-like neurons: those from individuals with bipolar affective disorder showed upregulation of cellular calcium signalling, protein kinase A and C signalling pathways and action potential firing systems. They also demonstrated greater sodium channel activation, with lower action potential thresholds and greater evoked potential numbers – all suggestive of a global hyperexcitability. Lithium was applied for 1 week to the bipolar affective disorder patients' dentate gyrus cells: in the lithium *responders*, this significantly reduced sodium/potassium currents and the total number of evoked and spontaneous action potentials, but no such effect was found in the lithium *non-responders*. RNA sequence analysis of the lithium-treated neurons showed that in the non-responsive cells, 40 genes were altered by treatment, whereas in the responder group, 560 genes were affected, suggesting an effect of treatment on gene expression. Further, in lithium-responders, 84 genes are implicated in downregulation of protein kinase pathways, action potential firing and upregulation of the sodium/potassium exchange ATPase gene. Previous findings using a similar technique[6] did not show hyperexcitability of neurons derived from people with schizophrenia – suggesting that the effect of lithium is specific to both genotype and phenotype. It has been argued that lithium responders represent a subtype of bipolar affective disorder; these studies support this concept.

A skit from *The Frost Report* in 1966 showed the impressively tall, bowler-hatted and formally dressed John Cleese standing to the left of a shorter, suited Ronnie Barker; in turn he stood next to the even shorter, casually dressed Ronnie Corbett. Cleese looks down to Barker and states, in dismissive clipped Received Pronunciation, 'I am upper class, so I look down on him'. Barker looks up to Cleese and explains, 'I look up to him, because he is upper class'; he then turns to Corbett and condescends, 'but I look down on him, because he is lower class. I am middle class'. After a long pause, and staring straight ahead, Corbett reports, 'I know my place'. Humans appear to prefer fair distribution of resources, and yet there remains extraordinary disparity between rich and poor: does the *visibility* of wealth differentials in networks of people influence this preference?

Nishi *et al*[7] constructed experiments placing participants into networked groups with on average 17 individuals, including 5 direct neighbours. During each round, participants chose to 'contribute' units of wealth such that each of their connected neighbours would increase their wealth by 100 units, or to 'defect', paying nothing (preserving their wealth) and providing no benefit to their neighbours. At the end of the round, the behaviour of their neighbours was revealed, and a selection of pairs were allowed to sever and/or form ties with their neighbours – new connections were formed only if both participants agreed. These games were then iterated over multiple trials, with wealth increasing and decreasing for each participant. Initial conditions of inequality were tested at different levels. First, a 'no inequalities' condition was established such that all participants had 500 units each to start. Then, a 'rich *v.* poor' system was established such that some participants had more initial units than others, but the mean per capita amount was 500 units, just distributed unevenly. On top of these conditions, an 'invisible *v.* visible' wealth condition was tested. In the former, participants knew only their own wealth and their neighbours' behaviour; in the latter, as well as behaviour of the neighbours, they could see the accumulated wealth of their neighbours.

There was significantly higher wealth inequality at the end of the games when neighbour wealth was visible compared with the invisible wealth conditions: knowing one's neighbours' income made the social network behave more selfishly. In terms of social networking behaviours, they found that visibility of wealth reduced cooperation (pay *v.* defect) and also reduced the appeal of social connection with others (the making or breaking of connections with neighbours). One prescient result was found in the initial inequality experiment: defectors who were rich compared with their neighbours continued to defect and not change behaviour as the experiment progressed. Poorer participants were more likely to behave cooperatively, essentially investing in the neighbourhood wealth. As this process unfolded, the rich got richer (compared with neighbours) while a pocket of poorer participants nearby continued contributing and getting relatively poorer. Visible

inequality breeds more inequality, and reduces cooperation and social connectivity; as Marx observed, 'While the miser is merely a capitalist gone mad, the capitalist is a rational miser'.

Are diagnoses of autism spectrum disorders (ASDs) really increasing, and what does that mean? Mental health is unique in the way that changing diagnostic rates are challenged, feeding into public and professional debates about 'medical models' (whatever that actually means), shifting diagnostic criteria, and a so-called 'reporting drift' of a greater cultural emphasis on social and communicative skills. There is also a counter-argument, that there has been a true rise in the incidence, potentially driven by environmental factors and later-life parenthood. Russel and colleagues[8] explored the numbers using a cross-cohort comparison of over 20 000 British 7-year-old children assessed in either 1998/9 or 2007/8. They found that the more recent cohort had significantly increased risk ratios (1.55 and 1.61 respectively) of being diagnosed with either ASD (incidence of 1.68%) or behavioural traits associated with ASD (6.86%). They propose that this is a reflection of us doing a better job, assisted by greater parent and teacher awareness, in recognising real difficulties. It has been argued that there has been a more recent levelling off in diagnostic rates, and it will be interesting to compare these figures with future data-sets.

Adult attention-deficit hyperactivity disorder (ADHD) faces similar debates, and we have particular challenges in providing good evidence-based care. NICE advocates medication as the first-line intervention, and current guidelines[9] state that there is insufficient evidence to support psychological therapy. COMPAS, the first multimodal, multicentre randomised clinical trial[10] of non-pharmacological treatments in adult ADHD, allocated 419 out-patients aged 18–58 to cognitive–behavioural group psychotherapy or non-specific individual clinical management counselling, and methylphenidate or placebo. The psychological intervention was weekly for 12 weeks and thereafter monthly for a further 9 sessions, with the medication arm continuing for the same 1-year time frame. Against hypothesis, the highly structured group intervention performed no better than individual clinical management, although both groups showed significant improvement over base-line. Both were enhanced by methylphenidate; however, overall the mean differences between all groups were relatively small. The strength of this work over the (limited) previous studies on the effectiveness of psychological work is the tightly controlled medication *v*. placebo arm, and the longer-term follow-up. The findings do support psychological interventions in this group, but suggest that more easily implementable individual counselling is also effective. Nascent services for this population are developing nationally; these data might help with rational service planning.

Women with bipolar affective disorder have a higher relative risk of postpartum relapse than those with any other psychiatric condition. Although there are many studies on the topic, variations in reporting mean that it can be hard for clinicians to provide accurate information to patients to help guide care; for example, there appears to be a distinct subgroup of women with solely post-partum psychotic episodes. A systematic review and meta-analysis[11] has tried to tease apart these factors. This found an overall postpartum relapse risk of 35%, but it is the subanalyses that are perhaps more interesting. Women with a history of bipolar affective disorder had a 37% chance of relapse (and a 17% chance of a severe postpartum episode requiring hospital admission), compared with 31% of those with a history solely of postpartum psychosis. Although we are rightfully mindful of the potential teratogenicity of mood stabilisers, conversations must consider that the relapse rates in bipolar disorder were 66% in those who were medication-free during pregnancy, compared with 23% for those on prophylactic treatment. Other risk factors have been described in the literature, including parity, a positive family history, and obstetric complications; however, they are generally under-studied and were unsuitable for meta-analytic inclusion in this work.

Finally, Brian Clough once casually remarked 'Frank Sinatra, he met me once'. We are motivated to maintain a positive view of ourselves, and resist challenges to perceived self-confidence through self-affirmation about our competencies and values. Cascio and colleagues[12] explored the neural mechanisms underpinning this, and demonstrated that regions involved in self-reflection (medial prefrontal cortex (mPFC) and posterior cingulate cortex) and valuation (ventral striatum and ventromedial PFC) were preferentially activated by affirmation and reflecting on future-oriented core values; such thinking also predicted increased receptivity to a subsequent set of health messages designed to reduce sedentary behaviour. Self-affirmation decreases stress, increases well-being, and facilitates positive change: try it now.

Unfortunately others often don't share our competencies (or modesty), and we all have to put up with those close to us making us cringe (vicarious embarrassment is the technical term, to save your blushes). Neuroimaging work[13] looked at neural responses to witnessing threats to either a friend's or a stranger's social integrity. Regions involved in aversive affect (the anterior insula and anterior cingulate cortex) and aforementioned self-reflection (mPFC) were activated in both instances. However, the former were more active when witnessing friends being challenged, along with the precuneus, which is associated with self-related thoughts. The closer others are to us, the more we feel what they feel: the good, the bad, and the ugly.

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https://doi.org/10.1192/bjp.208.1.98 Published online by Cambridge University Press