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Kaleidoscope

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Science depends on peer review of new research papers and grant applications, but how much value is added by this process? The journal *Environmental Microbiology* once published[1] a list of their favourite reviewer comments, which included 'The revised version is, on the whole, worse than the original' and 'Is there a chance you could send me any good papers, at least once in a while?' A study published in *Science*,[2] one presumes itself peer-reviewed, presents some impressive big data statistics on this very topic, examining the outcomes of 137 215 research grants in terms of the number of publications, resulting citations, and patent applications. Taking data from the American National Institute of Health between 1980 and 2008, they ranked all studies based on the quality judgement of the peer-review panel, and modelled the effect of this alongside covariates such as institution prestige, and the qualifications, career stage, and grant-winning history of the principal applicants. The results are stark: a one standard deviation drop in peer-reviewers' assessment of the quality of a grant application was associated with approximately 14% fewer publications and an 18% decrease in citations. Even when controlling for publication record, ethnicity, applicants' qualifications and the institution prestige, the same trend persisted: the better the peer-review judgement, the better the outcomes across the number of citations, publications and patent generation. Does this matter? Yes it does; in an age of increasing academic competition and reduced funding, it suggests that big ideas, not big names, matter most.

Environmental stressors have well-established but complex links with mental ill health; recent studies have now better elucidated the underlying factors in racial discrimination and lower educational attainment. Taking a nationally representative sample ($n = 5191$) of African and African–Caribbean Americans, Rodriguez-Seijas *et al*[3] determined that perceived racial discrimination was positively associated with all examined forms of psychopathology and substance use disorders. However, almost all of these associations (substance use disorders being a notable exception) were significantly mediated by so-called transdiagnostic factors. Achenback & Edelbrock first conceptualised[4] transdiagnostic factors, exploring dimensional factors associated with problematic childhood behaviour; later work has refined this into two major latent dimensional phenotypes of internalising (with common factors linking the development, maintenance and comorbidity of affective and anxiety disorders) and externalising (linking substance misuse, impulsivity and antisocial disorders). These have been demonstrated to have genetic underpinnings that are stable cross-culturally and longitudinally, and associated with longer-term clinical outcomes. The authors suggest that the pathways linking discrimination to mental ill health are not directly caused by the stress of perceived racism, but are indirectly mediated by these personality phenotypes. Rodriguez-Seijas and colleagues argue that it is critical to understand this transdiagnostic variance as a parsimonious and important concept for the development of comorbidity, providing a more fruitful target than simpler diagnostic categories.

Schopenhauer considered that 'great intellectual gifts mean an activity pre-eminently nervous in its character, and consequently a very high degree of susceptibility to pain in every form'; he was wrong. The evidence base weighs heavily in favour of poor educational attainment being linked with a greater risk of major depressive disorder (MDD). This association clearly has complex potential pathways: a lack of education leading to MDD through various socioeconomic channels; depression hindering educational attainment; and genetically linked personality or cognitive factors impacting on both. With regard to this last factor, pleiotropy is the phenomenon wherein a single gene affects multiple phenotypic traits, and now a study[5] of almost 10 000 individuals with MDD and 15 000 controls has tested for a genetic correlation between educational attainment and MDD. The work confirmed previous findings of an association between educational attainment and MDD but, crucially, this was not due to any measurable pleiotropic genetic effects. The findings are important as they suggest that non-genetic factors such as socioeconomic status are primary in this relationship. More work is needed to determine causality; for example, does lower economic status cause MDD or higher status protect against it; and what are the relative contributions of related factors such as lifestyle, health, and stress management? If better understood, these might be amenable to preventive intervention, whether on an individual or public health level.

Childhood adversity is linked with the development of psychotic disorders, but how specific is this association? Adversity encompasses a wide variety of potential insults, from neglect through bullying to physical and sexual abuse, and from commercial exploitation to natural and war-related traumas; all have associations with poorer emotional and social functioning and a range of psychological disorders. A recent meta-analysis[6] specifically tested the link in those reporting childhood adversity with the development and course of psychosis, and yielded an approximately two-fold increase in the persistence of psychotic phenomena (weighted odds ratio of 1.76 (95% CI 1.19–2.32)). The authors noted the surprisingly small evidence base for such an important area (only 20 prospective studies over 23 years, with most relying on retrospective recall of adversity), and the heterogeneity and lack of definition consensus within the trauma literature.

There has been even less focus on the *timing* of any such trauma. Alameda *et al*[7] regularly evaluated the clinical functioning of 285 individuals, with varying trauma histories, over 36 months in the early stages of a psychotic illness. A history of sexual and physical abuse (SPA) was elicited in just under a quarter, and was associated with worse social functioning during adolescence (i.e. before the onset of psychosis); however, only *early* SPA (occurring before the age of 11) was associated with long-lasting impairment, and those exposed at a later age showed better outcomes. Interestingly, the impact of SPA appeared to be restricted to social domains, while academic functioning remained similar to that of unaffected peers. A proneness–persistence–impairment model of psychosis posits that many factors can impact the expression of psychotic experiences, and in most cases such phenomena are transitory; however, where they persist, there may be value in timely interventions to attenuate the consequences of childhood trauma.

Every year, the Darwin Awards (http://www.darwinawards.com/) offer up examples – which they label chlorinating the gene pool – of *Homo sapiens* who fail to predict the rewarding and punishing consequences of decisions; Namburi *et al*[8] keenly observe in their paper in *Nature*, 'The ability to differentiate stimuli predicting positive or negative outcomes is crucial for survival'. The basolateral part of the amygdala (BLA) acts as an acquisition locus for sensory integration, motivational stimuli,

and associative areas including the hippocampus – projecting to the amygdala and the nucleus accumbens (NAc) in the ventral striatum. Different (non-overlapping) neuronal populations in the BLA code for positive and aversive outcomes, but how does this lead to the expression of different behaviours over time, for example, when learning which reward-seeking or fear-related actions to execute? BLA projections to the NAc have been shown to be active in reward-related behaviours, whereas the BLA to amygdala projections are associated with expressing conditioned fear responses. Namburi *et al* show strengthening of synaptic weight as an increase in expression of glutamatergic post-synaptic receptors in the BLA-amygdala projecting neurons after fear conditioning, whereas the BLA–NAc projections were strengthened after reward learning. These opposing synaptic changes highlight the neurophysiological basis of discrete pathways for associating behavioural responses for rewarding and aversive valence stimuli. Aberrations of this may underlie aspects of emotional dysregulation in mental ill health.

Heterogeneity is a clinical hallmark of both psychotic and affective disorders, adding fuel to diagnostic debates. Now, work[9] has looked at using neuroimaging biomarkers to differentiate these two major classes. Initially, multivariate pattern classification of structural magnetic resonance imaging (MRI) scans was utilised to identify and cross-validate a differential diagnostic signature of schizophrenia ($n = 158$) from patients with MDD ($n = 104$); major clinical variables such as age at onset and illness stage were then quantified against this; finally, this paradigm was tested in an independent patient cohort including individuals with bipolar disorder ($n = 35$), first-episode psychosis ($n = 23$), and at-risk mental states for psychosis ($n = 89$). In the novel sample, neuroanatomical diagnosis was correct for 72% of those with schizophrenia and 80% of those with MDD; schizophrenia was marked by relative prefronto-temporo-limbic volume reductions and premotor, somatosensory and subcortical increases. The presence of affective symptoms in schizophrenia or psychotic symptoms in depression did not alter accuracy; however, the occurrence of earlier onset and accelerated brain aging in depression promoted misclassification, as the image became more like that of schizophrenia. This work supports the concept of an illness spectrum modified by important individual variables, but the translation to clinical practice remains some steps away.

Pharmacologically, the tool-kit for psychosis may have just grown a little broader, with evaluation[10] of the novel compound brexpiprazole, a partial agonist at serotonin $5HT_{1A}$ and dopamine D_2 receptors, and an antagonist at $5HT_{2A}$ and noradrenaline $\alpha_{1B/2C}$ receptors. This is pharmacodynamically somewhat similar to aripiprazole, though brexpiprazole has lower dopaminergic activity and stronger serotonergic/noradrenergic antagonism than this more established agent, conceptually promising less akathisia, insomnia and nausea. Initial results were promising in a 6-week international 65-site double-blind randomised controlled study of 636 individuals with schizophrenia. Brexpiprazole was significantly superior to placebo at the two higher test doses (PANSS treatment differences −8.72 and −7.64 for 2 mg and 4 mg/day respectively), with akathisia the most common side-effect. There was moderate weight gain on the active treatment, but no significant changes in lipid or glucose levels. The effect sizes and numbers needed to treat fit with existing antipsychotics; a head-to-head medication trial is needed, and questions that remain include longer-term data (not least around side-effects) and whether 'one more D_2 modifier' will add much to real-world clinical practice and patients' lives.

Finally, scientifically one might be minded to have more optimism for Ireland, following its liberal welcoming of same-sex marriage, and perhaps less for Britain, following its election of a Conservative government. Why? The data suggest that liberals are happier than conservatives[11] (fascinatingly, a recent paper[12] confirms that liberals also drink more lattes; however, extrapolating to any causal relationship between good coffee and happiness must be regarded as speculative for now). But how might such liberal–conservative debates translate to mental health clinicians, our practice, and research? A review[13] of psychological sciences has concluded that the field has lost the political diversity it once had, with data showing that 84% of psychology professors self-identify as liberal, 8% as conservative (with a voting pattern in the USA of 11 : 1 Democrat to Republican). This, the authors argue, leads to an embedding of liberal values into research questions (often through value-inferring biased words such as *deny*, *legitimise*, *rationalise*) and an avoidance of 'unpalatable' topics (e.g. work on stereotypes and prejudicial attitudes). They put forward a criticism that some of this is due to a hostile and discriminatory environment for non-liberal viewpoints, and contend that an empowering of politically dissenting minorities would challenge orthodoxy and improve the quality of everyone's work. It raises the question of our biases and asks: what don't we see? This feels a little bit like Donald Rumsfeld's notorious 'unknown unknowns', but we trust that with regard to this column, you will tell us if we stray either side too far off-centre.

1 Environmental Microbiology. Referees' quotes – 2006. *Environment Microbiol* 2006; **8**: 2233–4.

2 Li D, Agha L. Big names or big ideas: Do peer-review panels select the best science proposals? *Science* 2015; **348**: 434–8.

3 Rodriguez-Seijas C, Stohl M, Hasin DS, Eaton NR. Transdiagnostic factors and mediation of the relationship between perceived racial discrimination and mental disorders. *JAMA Psychiatry* 22 April 2015 (doi:10.1001/jamapsychiatry.2015.0148).

4 Achenbach TM, Edelbrock CS. The classification of child psychopathology: a review and analysis of empirical efforts. *Psychol Bull* 1978; **85**: 1275–1301.

5 Peyrot WJ, Lee SH, Milaneschi Y, Abdellaoui A, Byrne EM, Esko T, et al. The association between lower educational attainment and depression owing to shared genetic effects? Results in ~ 25 000 subjects. *Mol Psychiatry* 2015; **20**: 735–43.

6 Trotta A, Murray RM, Fisher HL. The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. *Psychol Med* 22 April 2015 (doi: 10.1017/S0033291715000574).

7 Alameda L, Ferrari C, Baumann PS, Gholam-Rezaee M, Do KQ, Conus P. Childhood sexual and physical abuse: age at exposure modulates impact on functional outcome in early psychosis patients. *Psychol Med* 24 April 2015 (doi:10.1017/S0033291715000690).

8 Namburi P, Beyeler A, Yorozu S, Calhoon GG, Halbert SA, Wichmann R, et al. A circuit mechanism for differentiating positive and negative associations. *Nature* 2015; **520**: 675–8.

9 Koutsouleris N, Meisenzahl EM, Borgwardt S, Riecher-Rossler A, Frodl T, Kambeitz J, et al. Individualized differential diagnosis of schizophrenia and mood disorders using neuroanatomical biomarkers. *Brain* 2 May 2015 (doi:10.1093/brain/awv111).

10 Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 16 April 2015 doi: 10.1176/appi.ajp.2015.14101275).

11 Tracy DK, Joyce DW, Shergill SS. Kaleidoscope. *Br J Psychiatry* 2015; **206**: 439–40.

12 Macy M, DellaPosta D, Shi Y. Why do liberals drink lattes? *Am J Sociol* 2015; **120**: 1473–511.

13 Duarte JL, Crawford JT, Stern C, Haidt J, Jussim L, Tetlock PE. Political diversity will improve social psychological science. *Behav Brain Sci* 18 July 2014 (doi: 10.1017/S0140525X14000430).

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