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Kaleidoscope

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It cannot have escaped our readers' notice that there has been a public increase in the awareness of the impact of dementia on people's lives: politicians have raised concerns about a dementia 'time bomb' as a greater number of people live to an older age; and even the 2013 G8 summit declared[1] that there was a need for international initiatives to tackle this illness. The inevitable call for more research is underscored by the lack of any new licenced medications for Alzheimer's disease since 2002. There has been much interest in a putative role for statins – which inhibit the HMGCR enzyme, the rate-limiting step in cholesterol production – as retrospective epidemiological data have shown that they can reduce the risk of developing Alzheimer's disease by up to 70%; but, frustratingly, administration of these drugs to those with the illness appears to produce little benefit. Recent data have now shown that the gene encoding this HMGCR enzyme is a potent modifier for the age at onset and rate of conversion from mild cognitive impairment to Alzheimer's disease.[2] Indeed, this work would indicate that its G-negative allele is second only to APOE2 as the most common and important protective genetic variant for spontaneous Alzheimer's disease.

The genetics of Alzheimer's disease are complex: even high-risk loci typically only confer additional risks in the region of a few per cent, and clarifying interactions with other genes is made more difficult by epigenetic changes – the alterations environmental stressors induce to gene regulation and protein synthesis. However, two teams have independently tackled these challenges in epigenome association studies. De Jager *et al*[3] analysed over 700 prospectively collected autopsied brains and found that DNA methylation changes were significantly associated with both presymptomatic accumulation of Alzheimer's disease pathology and illness burden. Fitting with this, work by Lunnon *et al*[4] found that hyper-methylation of the ankyrin 1 gene was associated with entorhinal cortical brain changes, a region that is considered a primary site of disease manifestation. Studies with these large participant numbers will be necessary if epigenetic profiling is to contribute towards an improved mechanistic understanding of this illness, sufficient to influence clinical care through developing novel therapeutic agents, or providing biomarkers for optimising the use of existing medication.

Given that a proactive response is better than a reactive one, how effective might intervention strategies be against the most commonly replicated Alzheimer's disease risk factors of diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational achievement? Data have typically suggested that these account for about half of illness burden but, using relative risks from existing meta-analyses, Norton *et al*[5] calculated that the interdependence of these factors means that a more accurate figure is that about one-third of cases are attributable to modifiable factors. Modelling a causal relationship between factors and appropriate timely interventions to reduce each by 10% (or 20%) per decade, the authors calculated that the illness prevalence could be reduced by 8.3% (or 15%) by 2050: to put this into perspective that would be 8.8 (or 16.2) million fewer cases by this time.

Many medical conditions are complicated by comorbid depression. There is an increasing awareness of the need to treat such depressive episodes, but there is a prevailing contrary view that depression is to be expected with any severe medical illness, and therefore treatment is unlikely to be effective. It is heartening to see the results of the SMaRT Oncology-2 trial of depression in patients with cancer:[6] depression responded to treatment in 62% of patients in the active intervention arm, against 17% of patients receiving care as usual. The specialist treatment arm comprised treatment sessions by a specially trained nurse, supervised by a liaison psychiatrist: 75% of these were treated with an anti-depressant at a minimum effective dose *v*. 48% in the usual care group. Unsurprisingly, the specialist treatment group also reported a greater improvement in other cancer-related symptoms such as pain, fatigue, quality of life and functional ability. It is very clear that proactive treatment approaches benefit not only depression, but also have a concomitant impact on quality of life and physical symptoms. These data provide a call not only for offering optimal mental health treatment as routine in cancer care, but also for patients to actively seek help, and combat the view that depression is an inevitable part of any severe physical illness.

The link between chronic physical ill health, cognition and affective symptoms is exemplified by the experience of pain. In those with chronic pain, the most commonly observed affective symptoms include amotivation, with decreased activity, loss of interest in pleasurable activities and increased fatigability. Schwartz *et al*[7] ask whether there is a common neural mechanism underlying motivation in chronic pain using a mouse model and a progressive ratio operant task. This is an experimental paradigm wherein mice are required to execute more nose-poke behaviours to earn rewards as time progresses: the time at which they 'give up' being taken as an index of motivation. The authors demonstrated that in induced chronic inflammatory and neuropathic pain, the mice showed an approximately 40% drop in the nose-poke behaviours; though performance was unchanged on operant tasks where rewards were easily or consistently obtained without increased effort. Their data suggest that the reduction in motivated behaviour in both chronic pain models is attributable to changes in the nucleus accumbens, where there was evidence of long-term depression (LTD) in medium spiny neurons of the indirect D_2-mediated pathway. The nucleus accumbens is part of the basal forebrain that is implicated in: motivated behaviour; the subjective experience of pain; and part of the ventral striatum network responsible for reinforcement learning, where stimuli become associated with rewards through executing actions in the environment. The molecular basis of this LTD is triggered via galanin-1 receptors: galanin-1 receptor-deficient mice failed to show the same reduction in motivation observed in the control mice after induction of chronic pain. This suggests that preventing galanin-mediated LTD in the nucleus accumbens could prevent the changes in motivation that accompany chronic pain, and this is reinforced by the observation that galanin polymorphisms in patients with chronic pain predict comorbidity.

Finally, it was 37 years ago that the American psychiatrist George L. Engel wrote[8] about the biopsychosocial model that it: 'provides a blueprint for research, a framework for teaching, and a design for action in the real world of health care', and in contemporary psychiatry it has attempted to provide an integrative model for formulating and treating mental illness. However, its overuse has led to the suggestion that it has become vacuous – following the Popperian fiat that a theory that explains everything explains nothing – and a rebuttal to Engel is that 'other less eclectic, less generic and less vague alternatives

exist. Psychiatry would do well to look to them, rather than revisit an outworn label'.[9]

Now a large multidimensional dataset has used neuroimaging, genomics, personality and life experience data to classify 692 adolescents into *current* alcohol users, and to predict *future* alcohol misuse 2 years later.[10] The novelty of the approach lies in combining data from these different domains, given that individually, they are limited in making predictions about drinking behaviour. Using regression analysis specialised for high-dimensional data the authors found that while brain regions associated with emotional regulation (ventromedial and lateral left prefrontal cortex) predicted current binge drinking status, future binge drinking was predicted by brain structures associated with inhibitory control and reward outcome. In terms of relative contributions, the history variables dominated the age-14 classification, whereas brain, history and personality variables contributed more for predicting age-16 binge drinking.

Perhaps 'biopsychosocial' remains eclectic but can move with the times, and is not so vague or generic as to have lost its way or value.

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