

Kaleidoscope

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The Global Burden of Disease (GBD) is the most comprehensive global epidemiological study, and the analyses of the 2015 data have recently been published (thelancet.com/gbd). This is a rich data-set including observation on the general increase in global life expectancy, with the gains due to significant improvement in HIV outcomes balanced against the significant war-related decreases in male life expectancy in Syria. Interestingly, the age-standardised mortality rate for mental and substance use disorders dropped by over 12% between 2005 and 2015, though with considerable variations between conditions and countries, and the authors further note the difficulty in accurately attributing and coding excess deaths – for example, the years of life known to be indirectly lost to schizophrenia. Total deaths due to self-harm and interpersonal violence did not change much during this period.

As health was found to be improving globally, the ageing population is increasing the numbers of years lived with disability (YLD) and with functional health loss. Consistent with many other conditions, most psychiatric disorders showed an increase in YLD over the past decade: depressive disorders are now the third leading cause worldwide – after lower-back and neck pain, and sense organ diseases – while anxiety disorders were 9th and schizophrenia 12th. The report notes that cost-effective interventions are able to reduce their burden, including in low- and middle-income countries, and that this endorses statements by the World Health Organization and World Bank to make mental health a global development priority. Perhaps fitting with this, data on disability-adjusted life years (DALYs) were relatively stable for most mental health conditions (the growth in disability from substance misuse and eating disorders being notable exceptions) despite the greater YLDs.

To the far end of the lifespan, and Tom Waits said ‘When I was younger, I wanted to be older. Now I am older, I am not quite so sure’, and it turns out that fear of the reaper may be justified by a hard limit on longevity. Theoretical gerontologists like Aubrey de Grey remain convinced that technology will make ageing history, but Dong *et al*¹ note that even as medicine has advanced and average life expectancy increased, there has been a surprising asymptote on the upper limit of years attainable. Maximum reported age at death (MRAD) data from Sweden was 101 in 1860, and by the 1990s this was 108 years. Using the international database of longevity, they show a curious effect, whereby the MRAD increased at a rate of 0.15 years every year between 1970 and 1995; then, around 1997 – when the world’s oldest person Jeanne Calment died aged 122 – the rate became negative, with a decrease of 0.28 years for each year from 1997 to the late 2000s. Overall, this yields a plateau of MRAD at 114.9. Given that people living to ages over 100 are rare events, the authors then analysed data on a series of highest reported age at death (HRAD): all series showed the same pattern, climbing from 1970 to a peak in the late 1990s and then declining. Their analyses suggest that our perception of increased lifespan arises from gains made in certain decades, notably life expectancy has improved for those in the 70–90 year bracket, but eventually, we reach a hard limit of around 114 years.

Neuroendocrine links with depression are accepted, so is there an association with the oral contraceptive pill (OCP)? Boys and girls have about equal rates of depression before puberty, but thereafter female prevalence is about double that of men, and oestrogen and progesterone are often linked with biological explanations for this difference. Using a national Danish register, Skovlund *et al*² followed up over one million females aged 15–34 without evidence of a pre-existing depressive disorder, and found that hormonal contraception was associated with a significant risk of subsequent diagnosis of depression, particularly in adolescents. Eighty per cent of the Danish female population will use oral contraception at some point and the sample was highly representative. While the authors found no influence of sexual activity on the results, the design precluded determining causality. Nevertheless, it raises obvious concern about potential adverse effects of the OCP. As progestin is the main agent in combined and most single-hormone contraceptives, the findings particularly support a progesterone aetiological model of depression.

Postpartum psychosis is relatively common, impacting up to 1 in every 500 deliveries, and can be enormously debilitating. However, while neuroendocrine processes are obvious potential culprits – with especially notable rapid postnatal decreases in oestrogen levels – the molecular pathophysiology has been poorly understood, in part owing to a lack of a valid animal model. Steroid sulfatase (STS) converts sulphated steroids to precursors for oestrogens and androgens, and maternal deficiency of this enzyme has been implicated in postpartum psychosis. Humby *et al*³ update us with a rodent model study that first acutely inhibited STS in new mouse mothers, leading to behavioural abnormalities that were ameliorated by ziprasidone. Further evaluation of this implicated a substrate of 17 genes, one of which – *Nov/Ccn3* – was differentially expressed by those mice given the antipsychotic. The protein associated with *Nov/Ccn3* regulates axonal outgrowth and is highly expressed in the cortex and limbic system. It appears to have a role modulating intracellular calcium signalling, dysfunction of which is known to occur in bipolar and psychotic disorders, and interestingly its expression is inhibited by oestrogen. The authors call for evaluation of variation in these genes and their physiological correlates in human females.

There is a lot of interest in internet-based therapy for depression: it offers the opportunity to reach large numbers quickly and, of course, it’s cheap; but does it also have the potential to cause harm? Most work to date has been proof-of-concept, and little is known about any adverse effects. This fits with a wider dearth of research on harms from psychological interventions, though a ‘deterioration effect’ as individuals commence therapy is a long-recognised, if understudied, phenomenon. Ebert *et al*⁴ performed a meta-analysis of individual patient data from 18 randomised trials – covering 21 intervention types and about 2000 participants – on internet-based guided self-help for adult depression. Overall, the interventions were associated with clinical benefit, and a reduced risk of deterioration compared with control conditions, but some of the participants receiving active interventions did deteriorate. Notably, in those with lower educational attainment, the risks of deterioration were greater for those receiving the intervention than for those in the control group, although overall this group benefitted from such care. It suggests that educationally lower-achieving individuals might need additional support to understand the material, and to militate against potential increases in perceived lack of self-efficacy and hopelessness.

How do antidepressants work? The debate has moved from acute effects at the serotonin and noradrenaline receptors to

downstream effects on neurogenesis. Hippocampal neurogenesis in the dentate gyrus is a recognised sequela of many antidepressants (and, interestingly enough, of non-pharmacological interventions, including exercise), but how this is induced has remained incompletely understood. Brooker *et al*⁵ have demonstrated in a mouse model that the selective serotonin reuptake inhibitor fluoxetine inhibits the BMP-4 (bone morphogenetic protein) ligand, and increases production of the BMP inhibitor noggin, which reduce levels of BMP with subsequent increases in neurogenesis. Genetic deletion of the type II BMP receptor in neural progenitor Ascl1-expressing cells resulted in new cell birth, implicating binding at these sites as a key mechanism. Neurogenesis was associated with reduced anxiety and depressive behaviours in the mice, and BMP signalling may thus be a novel and important future therapeutic target.

Ketamine's NMDA receptor antagonism has sparked interest in this receptor's role in depression, prompting a search for novel compounds that might produce therapeutic actions without the harms associated with ketamine itself. Sancora *et al*⁶ report on the adjunctive use of the novel NMDA channel blocker lanicemine (AZD6765) in individuals with a history of inadequate response to antidepressants. The multicentre trial recruited just over 300 participants already taking antidepressants who were randomised to additionally receive either 15 intravenous injections of the novel compound (two dosing regimens were tested), or a saline placebo, over 12 weeks. The active medication was well tolerated, but showed no benefit over placebo. The authors note that the placebo group had a very large decrease in symptoms (13 points on the MADRS), and harking back to last month's column⁷ the very invasive nature of i.v. injections may heighten expectations.

Theory of mind is vital to our understanding of the beliefs, desires, and intentions of others – a skill that confers advantage in terms of predicting collaboration and avoiding conflict. Crucially, there is a difference between spotting patterns in stimuli (e.g. merely observing the actions of others) and an understanding of the intentions of others. The philosopher Daniel Dennett summarises this as taking the intentional stance: 'A little practical reasoning from the chosen set of beliefs and desires will in many – but not all – instances yield a decision about what the agent ought to do; that is what you predict the agent will do'.⁸ There remains debate about whether this is a uniquely human cognitive faculty, and Krupenye *et al*⁹ set about testing non-human primates' abilities in theory of mind. Anticipatory gaze – measured using eye tracking – enabled the experimenters to infer the ape's belief about the world; namely, they will gaze at a target which reflects either the state of the world, or their belief about an actor. The experimental stimuli consisted of videos, showing (for example) two haystacks located to the left and right of the scene. Actor A is shown watching actor B hide behind the right haystack. Actor A then goes off behind a closed door (i.e. cannot observe the scene) and actor B then surreptitiously moves back to the left haystack. Actor A then comes back out of the door (apparently, with a big stick if the images in the paper are to be believed) and approaches the centre of the scene. The ape's first eye gaze (to the left or right haystack) is then used as evidence for it having inferred whether actor A knows which haystack to approach (to presumably beat the other actor with the big stick). Of 19 chimpanzees, 14 bonobos and 7 orangutans ($n=40$), 30 gazed to the target that corresponded to actor A's false belief (that actor B remained behind the right haystack) and 10 looked to the left haystack (which reflects the participant ape's knowledge of the actual world rather than A's belief). The authors conclude that this demonstrates theory of mind in non-human primates because they can infer the actor's false beliefs.

Shifting gear slightly, we have also learned that our early *Australopithecus* ancestor Lucy – the female hominid skeleton found in Ethiopia in 1974 – may have held the false belief that trees were safe for early bipeds. Kappelman *et al*¹⁰ describe new evidence from examining Lucy's fossilised bones that suggest peri-mortem injuries resulting from a fall from height (they helpfully include a step-by-step diagram of the proposed fall as well as a table of mean velocities and energies resulting from typical tree heights). Compression and hinge fractures in, for example, her right femur are consistent with such a mechanism as are smaller bony injuries in the upper skeleton. Writing in *Nature*, the authors note that as her Pliocene fossil is a key element in the debate about arboreal locomotion in early human evolution, it is ironic that she died falling from a tree. Skeletal findings suggest she put her arms out in an attempt to break the fall, so we can use our theory of mind to infer she at least had some beliefs about physics.

Finally, we trust *BJPsych* readers give short shrift to psychics, but have you ever considered that there might be a pathology – beyond exploitative charlatanism – to their voices? It is, perhaps, an unusual question, but on the basis that some such individuals might not be intentional swindlers, Powers *et al*¹¹ conducted interviews with so-called *clairaudient* psychics – non-help-seeking individuals receiving daily auditory messages (to complete your education on the topic, *clairvoyants* see visions). Malinger tests determined that they were not feigning, and their experiences were phenomenologically similar to a group with diagnosed psychotic disorders. Crucially, the psychics were able to control the onset and offset of the voices, they were not distressed by them, and they had received a positive reception from others about them. The data fit with anthropological work on voice-hearing in shamans, and authors propose that scientists may have much to learn from psychics about the cognitive psychology and neurobiological continuum of voices; we just recommend they don't dial any telephone advice lines that require credit card details.

- Dong X, Milholland B, Vijg J. Evidence for a limit to human lifespan. *Nature* 2016; **358**: 257–9.
- Skovlund CW, Mørch LS, Kessing LV, Lidegaard O. Association of hormonal contraception with depression. *JAMA Psychiatry* 28 Sep 2016 (doi: 10.1001/jamapsychiatry.2016.2387).
- Humby T, Cross ES, Messer L, Guerrero S, Davies W. A pharmacological mouse model suggests a novel risk pathway for postpartum psychosis. *Psychoneuroendocrinology* 2016; **74**: 363–70.
- Ebert DD, Donkin L, Andersson G, Andrews G, Berger T, Carlbring P, et al. Does internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials. *Psychol Med* 2016; **46**: 2679–93.
- Brooker SM, Gobeske KT, Chen J, Peng C-Y, Kessler JA. Hippocampal bone morphogenetic protein signaling mediates behavioral effects of antidepressant treatment. *Mol Psychiatry* 4 Oct 2016 (doi:10.1038/mp.2016.160).
- Sancora G, Johnson M, Khan A, Atkinson S, Riesenberger R, Schronen J, et al. Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and history of inadequate response to antidepressants: a randomized, placebo-controlled study. *Neuropsychopharmacology* 29 Sep 2016 (doi: 10.1038/npp.2016.224).
- Tracy DK, Joyce DW, Shergill S. Kaleidoscope. *Br J Psychiatry* 2016; **209**: 444–5.
- Dennett D. *The Intentional Stance*. MIT Press, 1987: 17.
- Krupenye C, Kano F, Hirata S, Call J, Tomasello M. Great apes anticipate that other individuals will act according to false beliefs. *Science* 2016; **354**: 110–3.
- Kappelman J, Ketcham RA, Pearce S, Todd L, Akins W, Colbert MW, et al. Perimortem fractures in Lucy suggest mortality from fall out of tall tree. *Nature* 2016; **537**: 503–7.
- Powers III AR, Kelley MS, Corlett PR. Varieties of voice-hearing: psychics and the psychosis continuum. *Schizophrenia Bull* 7 Oct 2016 (doi:10.1093/schbul/sbw133).