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Kaleidoscope

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Seafood: it's argued to be good for brain health, though there are niggling worries about all the neurotoxic mercury it contains. So what's the best current evidence? Morris and colleagues[1] undertook post-mortem brain analyses of several hundred research participants, having measured their seafood intake for almost 5 years prior to death. Seafood has high levels of long-chain n-3 fatty acids linked with normal neuronal functioning, and consumption was significantly correlated with less Alzheimer disease pathology indexed by plaque density and neurofibrillary tangle distribution; however, these benefits were only seen in *APOE ε4* carriers. Greater consumption of α-linolenic acid, the plant-based shorter-chain n-3 fatty acid, was associated with a reduced risk of cerebral infarcts regardless of *APOE* status and, interestingly, fish oil supplementation had no effect. And the mercury? Brain levels were positively correlated with seafood intake, but without any significant increase in brain pathology. So, the advice would appear to be keep enjoying your seafood, though only some of us might be deriving benefits for our brains.

Grey matter loss and reduced synaptic connections are highly reproducible findings in schizophrenia, though it has proven complex to determine their cause. Genome-wide association studies of schizophrenia have shown there to be a very strong association with variations in the major histocompatibility complex (MHC) locus; however, this region of chromosome 6 – which covers millions of base pairs – is best known for its role in immune responses, and any functional mechanistic relationships with psychoses have been unclear. In a paper in *Nature*, Sekar and colleagues[2] advance our understanding through evaluation of the MHC genes for complement component 4 (C4). They determined that neuronally expressed C4 proteins localised to synapses, dendrites and axons before being secreted, and mediated synapse elimination. Phagocytic microglia are the principal source of neuronal complement receptors as part of their role in the immune system, and offer a mechanism through which C4-secreting cellular regions could be pruned. Crucially, the authors found that the structurally diverse alleles of C4 genes expressed varying levels of the proteins C4A and C4B in the brain, and it was C4A that was considerably more associated with schizophrenia development. These important findings provide a rational link between the MHC, the immune system, and the aberrant synapse formation and brain changes seen in psychosis.

We still lack effective interventions for the negative and cognitive symptoms evident in psychotic illness. Cariprazine is a novel antipsychotic recently licensed in the USA, which is a partial dopamine agonist with a high affinity for D_2 and, preferentially and uniquely among drugs in this class, D_3 receptors that are thought to have particular roles in cognition, reward processing and affective state. Rodent work[3] has now shown that it reverses subchronic phencyclidine (PCP) induced cognitive deficits in a dose-dependent manner. Experience of past animal model pharmacological work on cognitive deficits teaches us caution – in this study risperidone also reversed some of the deficits, but in humans any such gains from that medication are very modest at best – and there's many a slip 'twixt rodent and man.

We treat suicidality by proxy: with management of any underlying mental health condition, or increased observation. But what if we could acutely reduce such thoughts? Ketamine has attracted attention owing to its rapid effect on depressed mood and suicidal thinking, but it has numerous problems as an intervention. Yovell *et al*[4] took a novel approach, exploring low doses of the opioid partial agonist buprenorphine in severely suicidal patients. The principle is that mental pain – a symptom more associated with suicidality than even low mood or hopelessness – is modulated by an endogenous opioid separation–distress system. The results were encouraging, with significant reductions in suicidal ideation at 2 and 4 weeks compared with placebo; concurrent use of an antidepressant or the presence of an emotionally unstable personality disorder did not alter the response. Further work is needed and, as with ketamine, concern exists about dependency, but the potential life-saving gains in helping sustain individuals through periods of intense despair are self-evident.

The opioid system may also have a broader role in social attachment and bonding. In a cross-over double-blind randomised controlled trial, Inagaki *et al*[5] administered healthy volunteers with the opioid antagonist naltrexone and placebo for 4 days each, and measured feelings of social connection. In both laboratory settings and daily functioning, participants noted significantly less sense of social connection on the antagonist, which was not accounted for by general changes to emotional state. This complex system would appear to neurochemically support the psychosocial construct of human bonding, but whether it can be safely and effectively pharmacologically manipulated for the *benefit* of social inclusion is a question some way off answering. However, the findings do raise the interesting and unexplored issue of whether an adverse impact on social bonding underlies some of the failure of naltrexone in treating opioid dependency.

Kaleidoscope has a pharmacology focus this month. In the previous *BJPsych*, preconceptions on electroconvulsive therapy were shaken,[6] with methodologically robust data showing it was not associated with lasting cognitive impairment, but was linked with cortical thickening. This month, Tiihonen and colleagues[7] address a similar issue over mortality associated with long-term antipsychotic and antidepressant use in schizophrenia. It is a peculiarity that there is so little high-quality data for such a hotly debated issue. Using a Swedish nationwide database of over 20 000 individuals, they found that moderate- and high-dose antipsychotic and antidepressant use were associated with a 15–40% *reduction* in overall mortality compared with no use of these medications. The study could not determine causality: those not on medication might have many relevant clinical differences, including both milder and more severe presentations, medication administration might be a proxy for other forms of clinical monitoring and input, and antidepressant medications have anti-coagulant and anti-inflammatory properties that could be therapeutic in cardiovascular disease. The story was not all positive however, as the long-term use of high-dose benzodiazepines was associated with a 70% increase in mortality in this cohort; as with drug benefits, the broad explanations of direct iatrogenic effects and an altered clinical profile are likely to be relevant. We remain cognisant of the many types of iatrogenic effects, but this is an area where evidence is crucial.

Metacognition is thinking about thought: does this matter in mental health? Davis *et al*[8] evaluated metacognitive ability and its impact on functioning in war veterans with post-traumatic stress disorder (PTSD). Individual factors are critical in terms of development of, or resilience against, the onset of PTSD after the occurrence of a traumatic event, though these are currently

poorly understood. However, metacognitive ability is an obvious potential target as it may index an individual's core self-concept and ability to contextualise traumatic events. The authors evaluated trauma-related cognitions about the self (including self-blame) and the world; clinical symptomatology; and broader metacognitive ability. A younger age and greater depressive symptoms were associated with more negative cognitions, while low levels of self-reflectivity and high cognitive self-consciousness were related to self-blame, even after controlling for other clinical and demographic factors. The cross-sectional design did not allow causality to be tested, but the study opens up the potential for integrative therapeutic interventions addressing patients' sense of mastery and recognition of their mental states.

Nietzsche wrote that: 'For those who need consolation no means of consolation is so effective as the assertion that in their case no consolation is possible'. Prairie voles, unlike other members of their genus, are monogamous and show high levels of affiliative behaviour, including dual parenting of pups; they are therefore a popular experimental animal model because of these apparent similarities to humans (except, perhaps, German nihilist philosophers). Meadow voles, in contrast, are promiscuous breeders with no formal social structure and only one parent cares for the pups. Burkett *et al*[9] describe an experiment on 'consolation behaviours' in prairie voles (where they comfort other distressed voles), behaviour presumed dependent upon a form of empathy. They hypothesised that this would be contingent on intact neural structures and chemical features found to underpin similar behaviours in humans, who, along with the great apes, are the only other animals to demonstrate empathy. Assigning the prairie voles to either 'observer' or 'demonstrator' roles (the former seeing a distressed prairie vole after the latter has been isolated and subjected to foot shocks), they found that observers were quick to initiate and provided longer consolation grooming behaviours than control meadow voles.

In the shocked-demonstrator condition – when the observer and demonstrator prairie voles were separated by a clear barrier after the shock condition, thereby *preventing* consolation grooming – plasma cortisol was high and was correlated in both animals, suggesting physiological state matching (i.e. a precursor to empathy). Further, when oxytocin antagonists were injected into the cerebral ventricles of demonstrators, and then grooming was tested in the shocked-demonstrator condition, the grooming behaviour was extinguished in the shocked condition. This suggests that oxytocin has a unique role in behaviours driven by *observed distress* in others, rather than simply separation. To localise the neural structures involved, direct injection of oxytocin receptor antagonist to the anterior cingulate (but not the adjacent prelimbic cortex or nucleus accumbens shell) replicated the effect.

Finally, to the Study of Maternal and Child Kissing (SMACK) working group's evaluation[10] of maternal comfort provided through kissing of minor injuries. This showed that this universal practice led to no improvement on the Toddler Discomfort Index (TDI) at 5 minutes post-injury *v.* sham kissing and no intervention. The author notes that 'the lack of efficacy of maternal kisses compared with "sham" kisses suggests that, despite being advocated by doctors and endorsed by virtually all mothers, there is no scientific justification to the practice'. There was no Nietzschean arm to the study where parents simply advised their children that there was no consolation to be had. SMACK warned that the effectively useless intervention of 'kissing boo-boos' might even delay the administration of efficacious treatments 'such as BacBe-Gone® antibacterial ointment and Steri-Aids® self-adhesive bandages'. The authors (who disclose that their work was sponsored by P&J, who manufacture these antibacterial agents) conclude by recommending a moratorium on the practice.

The article is a satirical piece (and there is no 'P&J'). A commentary by Chawla[11] explains that the 'real' author behind the SMACK working group was Mark Tonelli from the University of Washington Medical Centre, who wanted to emphasise interpersonal and patient-centred factors that are often ignored when interpreting systematic evidence from randomised controlled trials and applying them to clinical practice. Kaleidoscope urges all parents to continue comforting their children through kisses, and perhaps keeping them away from works by Nietzsche.

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