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Kaleidoscope

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Drugs and violence are often observed as bedfellows; both have been associated with psychosis but the nature and timing of their relationships remains unclear. As part of the UK Prisoner Cohort Study, Keers *et al*[1] prospectively followed up 967 prisoners convicted of sexual or violent offences (about a quarter of whom had a psychotic illness) in the community after release. Schizophrenia was associated with greater rates of violence, but the risk was mediated by untreated psychosis or when presenting with persecutory delusions – and no other definable psychopathology. Interestingly, drug-induced psychosis did not increase the risk of violence *per se*, once the substance misuse itself was accounted for. Does treatment have an impact on risk of violence in a population-based sample of patients with psychosis? Fazel *et al*[2] demonstrated reductions in violent crime in patients during the time they were prescribed antipsychotics. Interestingly, the rates of violent crime were also reduced in patients with bipolar disorder who received mood stabilisers. Therefore, in addition to the effects of antipsychotics and mood stabilisers on relapse rates, their potential effects on violence and crime could be used to make decisions about management for these groups of patients. There is a clearer need for the appropriate treatment of prisoners with psychotic illnesses if their risk of violence is to be moderated. Cannabis is one of the most commonly used social drugs worldwide; it increases risk of psychosis, but there has been little to offer pharmacologically to those dependent upon this most prevalent illicit drug, and various trials of mood stabilisers, antidepressants and α2 adrenergic agonists have generally been disappointing. Allsop *et al*[3] evaluated the novel cannabis extract nabiximols, containing cannabidiol – which has been shown to attenuate paranoia and euphoria – and tetrahydrocannabinol, delivered as a buccal spray. The active drug group showed statistically significant benefits in reduced withdrawal irritability, depression and cravings and remained longer in treatment. However, both placebo and drug groups showed reduced cannabis use at follow-up, with placebo being as effective as nabiximols in promoting longer-term cessation.

Predicting depression and the response to treatment of depression are challenging issues. Vitamin D deficiency is common, but does it cause depression? There has been much anecdotal conversation on the topic over the past few years, but seemingly little strong evidence, and a nagging worry that it is a fad or New Age hypothesis – although the prefrontal cortex, hippocampus and amygdala have vitamin D receptors with posited roles in cognition. Milaneschi and colleagues[4] undertook examination of the levels of vitamin D in a large cross-sectional cohort with current or remitted depressive disorders. Lower vitamin D levels were found in those with depression compared with controls. In those who were depressed, 25(OH)D levels were inversely associated with symptom severity, indicating a dose–response gradient, and increased risk of having a depressive disorder at the 2-year follow-up point. These data support the hypothesis that low vitamin D levels are a risk factor for depression, although the study design means that inferences on the directionality of association cannot be made. The next step is assessing the effectiveness of any treatment intervention. McGrath and colleagues[5] assessed potential differences in brain metabolic patterns – measured using fluorodeoxyglucose positron emission tomography (PET) – associated with clinical outcomes in 82 patients with major depressive disorders. After an initial scan, the patients, who were not on any treatment at trial commencement, were randomised to 12 weeks of treatment with either escitalopram or cognitive–behavioural therapy (CBT); those who did not achieve remission were given a second 12-week treatment of escitalopram and CBT. PET data showed greater metabolism in the subcallosal cingulate in participants whose depressive illness was non-responsive to treatment compared with those whose illness remitted. Given that current interventions are often picked on the basis of symptom severity and patient preference, activity within the subcallosal cingulate may represent a candidate biomarker for non-response to first-line treatments, though a current problem in the literature of putative biomarkers is meaningfully synthesising disparate study designs that typically involve small participant numbers.

Recognising and relating to other people is a core social skill; in the psychiatric mental state examination, 'poor rapport' is rarely a sign of good prognosis, and studies confirm that such social dysfunction is a prodromal hallmark of impending first onset psychosis. The case of Henry Molaison (1926–2008), a man whose surgical resection of the anterior hippocampus, entorhinal cortex and amygdalae left him unable to recognise people he had known for years, implicates the medial temporal lobe in social interaction as a kind of recognition device. In the hippocampus, declarative memory is mediated by a feedforward network of processing from entorhinal cortex, through dentate gyrus to CA3, finally arriving at the common hippocampal output at CA1. The anatomically distinct CA2 region lies between CA3 and CA1 but its functional role is relatively unexplored. A recent paper in *Nature*[6] suggests that it has primacy in social recognition; knockout mice with inactivated CA2 neurons that had preserved spatial memory showed no change in anxiety behaviour or response to fearful stimuli when compared with a control mice group. The knockout mice (similarly to the control mice group) still preferred to occupy chambers containing littermates; however, time spent interacting with novel unrelated mice was significantly less than for the control group. In tests of novelty exploration, both the knockout and the control group behaved similarly with novel objects – suggesting that the specific deficit is in interacting with novel species-mates rather than a generalised loss of exploratory behaviours. Sadly, the phenomenology of the internal world of mice remains poorly documented – the paper not once mentioning 'rapport'. Recognition in the visual domain is clearly predicated on accurate perception and interpretation, and how this occurs in the presence of so much potential ambiguity in the human brain remains a challenge. Clearly, visual perception requires the brain to convert the continuous distribution of wavelengths of the visible electromagnetic spectra impinging on the retina into a discrete internal percept. Categorical perception is the discrete end-point of decoding the continuous stream of visual input – and it happens quickly: the ventral visual stream decodes visual stimuli in around 200 milliseconds. But how does the continuous activation of a network of millions of neurons in early visual cortex (V1) result in a decoded percept (a representation) in object recognition centres in inferior temporal cortex? Cichy, Pantazis and Oliva used magnetoencephalography (MEG) and functional magnetic resonance imaging to identify the timing of the mechanisms of distinguishing animate *v.* inanimate objects and then human *v.* non-human objects in a paper in *Nature Neuroscience*.[7] They found that 'signatures' of activity which discriminate

between the 92 images could be extracted at approximately 100 milliseconds after stimulus presentation. Further, coherent time-series signatures emerged for categories of 'animate' (157 ms), 'naturalness' (122 ms), 'human/animal bodies' (170 ms) and human *v.* animal faces (127 ms). It is not clear how robust these patterns of neuronal network activity (at MEG resolutions of milliseconds) can be in resolving analogous ambiguous auditory stimuli and hence their implications for the spontaneous generation of hallucinations – perceptions in the absence of stimuli.

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3 Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, et al. Nabiximols as an agonist replacement therapy during cannabis withdrawal. A randomized clinical trial. *JAMA Psychiatry* 2014; **71**: 281–91.

4 Milaneschi Y, Hoogendijk W, Lips P, Heijboer AC, Schoevers R, van Hemert AM, et al. The association between low vitamin D and depressive disorders. *Mol Psychiatry* 2014; **19**: 444–51.

5 McGrath CL, Kelley ME, Dunlop BW, Holtzheimer III PE, Craighead WE, Mayberg HS. Pretreatment brain states identify likely nonresponse to standard treatments for depression. *Biol Psychiatry* 19 December 2013 (doi: 10.1016/j.biopsych.2013.12.005).

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7 Cichy RM, Pantazis D, Oliva A. Resolving human object recognition in space and time. *Nat Neurosci* 2014; **17**: 455–62.

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