BJPsych The British Journal of Psychiatry (2019)
214, 379–380. doi: 10.1192/bjp.2019.111

Kaleidoscope

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In the UK, the Mental Health Act has been under the spotlight, not least because of disproportionate numbers of Black and minority ethnic patients being detained. How does UK practice of involuntary detention compare with other countries? Luke Sheridan Rains and colleagues[1] tracked annual incidence detention across time – from 2008 to 2017 – and across 22 countries in Europe and Australasia. They contextualised the data examining legislative frameworks, sociodemographic factors and healthcare characteristics and expenditure. There were enormous variations in median rate of detention: from a high of 282 per 100 000 in Austria to a low of 14.5 in Italy (the UK clocked in at 114.1). The rate of detention has risen faster during this time in the UK than in most other countries, with a cumulative 36% rise from 2008; interestingly, Ireland, Sweden, Finland, Norway and Denmark showed stable or declining rates over this period. The specific legislation did not appear to have an impact on detention rates, but having more inpatient beds, a higher gross domestic product per capita and healthcare spend, more foreign-born individuals in the population and lower rates of poverty led to increasing detention rates. Like good research should, it opens more questions than it answers, and the authors note there are no clear explanations for these variations.

Community treatment orders (CTOs) often evoke strong emotions from clinicians who report good individual successes in breaking the 'revolving door', countered by admission data rebutting this view. Lei *et al*,[2] in a secondary analysis of data from the National Audit of Psychosis, reframe this question asking if CTOs have an impact on *care* received. Their initial findings repeat what others have shown or affirmed: the rate of CTOs varies considerably across organisations, from 1.1% to 20.2% in mental health trusts. However, what lay beneath this was fascinating. Those on CTOs were more likely to have their physical health monitored, including being checked for smoking and substance misuse, have an up-to-date care plan and crisis support contact details, and be offered psychological therapy. Although one can debate causality in who ends up on a CTO; the intriguing aspect is if they are serving as care plan approach augmenters?

No one clarifies theology like Tom Waits: 'don't you know there ain't no devil, there's just God when he's drunk'. The sober gods of the modern major religions are 'moralising gods' (MGs), which is to say, they encourage a virtuous life and discourage (or punish in the afterlife) a life of selfishness. One theory suggests that the religions that honour MGs precede the emergence of large, complex societies; in part, because strangers wanting membership to a larger society have to obey a set of rules (religion) that enforce pro-social and cooperative behaviour. Whitehouse *et al* attempt to test this causal relationship given the current mixed data;[3] studies of Austronesian religions and Scandinavian societies reported that MGs appeared before large societies – in contrast to a study of Eurasian empires that found the opposite. To test these competing temporal relationship hypotheses, they used a database of global history that records data on 414 independent political units over 30 geographical regions from the beginning of the Neolithic period through to the industrial and colonial periods. The first appearance of MGs in the sample was in Egypt around 2800 BC. Further analysis found that measures of social complexity were stronger predictors of the emergence of MGs than linguistic relationships or geographical location. Using 12 regions for which detailed social complexity data was available, they then constructed a time series of social complexity and plotted the time at which MGs appeared in those societies. Consistently, social complexity increased on average in the 1000 years preceding the introduction of MGs and then 'tailed off' after that. In 10 of the 12 regions, the societies reached populations of 1 million within 100 years of the appearance of MGs and in 9 of the 12 regions the appearance of MGs was also chronologically preceded with the appearance of written texts. In a separate analysis of Austronesian and Iceland, consistent with the previous literature, they found that MGs appeared before colonialism suggesting that they were exceptions. In conclusion, they found that doctrinal rituals significantly predate the emergence of MGs by an average of 1100 years and that the rise of social complexity is more about how you worship (ritual), rather than who or what the focus of worship is (god or otherwise).

Depression and psychosis: predicting outcomes. Cuijpers *et al* report on a network meta-analysis of cognitive–behavioural therapy in adults with depression, exploring differences across five delivery formats: individual, group, telephone-administered, guided self-help and unguided self-help.[4] The work took in an impressive 155 trials encompassing over 15 000 individuals; this size and the network methodology contrasts positively with most meta-analyses that only compare two treatment types at a time. The first four methods were significantly more effective (with large effect sizes) than waiting list, care as usual and unguided self-help; however, there were no clear differences between their outcomes. Guided self-help had a higher drop-out rate than individual or group work, and interestingly was considered less acceptable than being on a waiting list. The data are important, not least as it is clearly more cost-effective to provide group and guided interventions; the failure of individual intervention to show superiority runs against the grain of many patients' expectations and therapy requests.

Predictive psychopharmacology often feels just out of reach: the concept makes sense, and we clearly see enormous patient variation to the same drug, but many promising early trials have fallen flat. CYP2D6 is the primary metaboliser of risperidone and aripiprazole to their active metabolites, and Jukic *et al* evaluated the impact genetic variability of the CYP2D6 enzyme has upon clinical responses.[5] They undertook a retrospective analysis of over 2400 genotyped individuals analysing drug metabolism, drug exposure and treatment response at 1 year. Genomic analysis delineated four groups: poor, intermediate, normal and ultra-rapid metabolisers. As one might expect, the rate of metabolism was associated with the concentration of the active moiety of the drug. Poor metabolisers were found to have reduced daily doses of both drugs; both this group and the ultra-rapid cohort were more likely to have risperidone, but not aripiprazole, switched at 1 year – a marker of treatment failure. The authors propose that prospective testing would help individualise more rational mediation care for these two common treatments: specifically, poor and intermediate metabolisers should be initiated on doses up to a third lower than others, and ultra-rapid metabolisers are more likely to benefit from aripiprazole than risperidone.

Depression and psychosis: new treatments. Ketamine continues to tease as a putative rapid-acting antidepressant but frustrate as many results show the effects to be all too temporary, typically gone within a week. Some repeated dosing regimens over a week or two have shown promise, but again symptoms tend to recur shortly after cessation. Phillips *et al* report on an interesting study design to test a

longer-term dosing regimen.[6] First, 41 individuals with treatment-resistant depression undertook an initial double-blind randomised crossover comparison of single infusion ketamine and midazolam (as an active placebo control). Ketamine showed a significantly greater reduction in depressive symptoms at the primary 24 h end-point. They then proceeded to receive an open-label course of six ketamine infusions over a 2-week period. The results showed a cumulative effect, doubling the antidepressant response rate to almost 60% (23% in remission), with a median of three such infusions required to attain this. Participants who has at least a 50% improvement in Montgomery–Åsberg Depression Rating Scale scores ($n = 23$) then continued with weekly maintenance infusions over the following 4 weeks, with participants showing no deterioration in symptoms during that time. An emerging longer-term ketamine strategy is emerging, although the acceptability of this has yet to be tested.

Intravenous sodium nitroprusside (SNP) has shown some promise in early work as a rapid-acting adjunctive treatment in schizophrenia. Any putative mechanism of action remains unclear: *N*-methyl-D-aspartate (NMDA) hypofunction has been shown in psychosis, and SNP releases intracellular nitric oxide, mimicking an effect seen when NMDA receptors are activated; equally, the antihypertensive actions of SNP might therapeutically increase cerebral blood flow. Brown *et al* expand upon the pilot work to a multicentre double-blinded acute treatment in just over 50 participants with refractory psychosis already on a standard antipsychotic.[7] They were randomised to one of three groups, each of which had two 2-week phases: SNP followed by SNP; placebo then SNP; and SNP followed by placebo. The active treatment was infused at a rate of 0.5 μg/kg/min for 4 h. No significant differences were seen across the groups; although it was well tolerated, SNP does not appear to have any therapeutic value as an adjunctive intervention in patients with refractory psychosis.

Our internal state modulates decision-making: for example, when we are thirsty, we prioritise actions to obtain fluid. In computational theories of goal-directed behaviour, a classic approach models pairings of states with available actions. Importantly, learning a policy for knowing which action is optimal for a given state is governed by switching between exploring (trying different, possibly suboptimal, actions) and exploitation (sticking with a recognised optimal action). It seems reasonable that consistent, repeatable patterns of activity distributed over populations of neurons would 'code' for internal state – in addition to representing internal models for the state of the environment. Gründemann *et al* note that neuronal activity of these state representations has remained elusive – and explore the basal amygdala in mice, which is a locus for both affective, social and homeostatic signals, with functional connections to motor networks.[8] Each mouse had a head-mounted microscope that could image calcium-dependent activity of neurons in the basal amygdala during a series of ecologically valid tasks. They were able to classify patterns of population activity that clearly distinguished between the mouse being in the corner or the centre of the open space. Using a fear-conditioning paradigm, they were able to show that the corner-cell firing patterns were independent of the anxiety level of the mouse. The interpretation of centre-versus-corner behaviours in open-field experiments was that exploring the centre of an open field is anxiety-inducing and giving mice anxiolytic medication increases centre-exploration. In these experiments, they showed that two discrete neuron ensembles activated in the centre and corner of open fields behaved similarly in open/closed maze arms. Further, these populations correlated with transitions between centre/corner and open/closed regions, and persisted during conditioning paradigms that induced fear–anxiety freezing behaviour. Rather than just signalling the anxiety of the animal, these 'neural signatures' predicted transition to and from 'exploratory' (uncomfortably, but potentially rewarding) and 'exploiting' ('safe', anxiety free) behaviours.

Finally, it is always easy to tell the baddie or goodie in a movie, right? The scar across the face, the evil grin, stroking a cat and laughing maniacally…old tropes, but we are all susceptible to rapidly categorising people. (Incidentally, we recommend wasting an hour on the endlessly amusing TV trope website: https://tvtropes.org/) Afdile *et al* take us to the movies with a neuroimaging study testing how we implicitly evaluate 'in' and 'out' group characteristics not visible on the face – in this instance exploring sexual orientation.[9] Participants (all men) were scanned while shown the film's main protagonist before and after the screening, the content of which was about some of his life as a gay man; this exposition only becoming clear midway through the movie. Participants who self-identified as gay ($n = 14$) showed significantly greater regional cortical activation on the final character viewing than those who identified as straight ($n = 15$): key regions were in the medial prefrontal cortex, frontal pole, anterior cingulate cortex, right temporoparietal junction and bilateral superior frontal gyrus. The regions are linked with social perception, self-referential thinking, empathy, theory of mind and in-group perception. The authors argue the strength of their work is a more naturalistic approach to how we relate to others than most neuroimaging paradigms that just show various 'face shots' in different emotional states ('happy', 'angry', 'sad'). As for the Kaleidoscope team, independent testing showed similar self-identification brain changes for us when seeing movie images of Marty McFly, Robert Downey Jr and Danny Ocean – a masked design ensured anonymity.

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https://doi.org/10.1192/bjp.2019.111 Published online by Cambridge University Press