

Kaleidoscope

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Women are not just small men. Last year, Caroline Criado Perez alerted the public to the very real dangers of male-centred bias in her bestselling book *Invisible Women: Exposing Data Bias in a World Designed for Men*. She laid bare that the male-as-default trope has deadly consequences: women are more likely to die in a car crash because the safety systems were designed for men's larger bodies and longer legs, and in medicine women are more likely to be misdiagnosed and have more negative side-effects of treatment than men. In their *Nature Neuroscience* piece,¹ Rebecca Shansky and Anne Murphy zoom into the way this plays out in the preclinical neuroscience community and propose a way forward for real change and better translational research. Although there has been some progress over the past decade, single-sex animals studies are the norm, so much so that they are rarely justified, though when they are it is often by citing misconceptions.² Despite this neglect of female subjects, extraordinary examples of fundamental sex differences continue to mount across behavioural, cellular and systems neuroscience that make this continued practice indefensible. For example, in male rats, studies of chronic stress paradigms used to inform post-traumatic stress disorder and depression research found structural and synaptic plasticity responses within key areas of the brain that accord with clinical neuroimaging studies. In females, the results were diametrically opposite, questioning our assumptions about the 'fundamental' brain responses to stress, and leading to a sigh of relief that therapeutic developments did not lead to treatment that exacerbated symptoms in women.

Recognising the way that this bias leads to disparate health outcomes for women, an attempt has been made by Canadian, European and American funding bodies to ensure that grant applications include both sexes in design and analysis. However these 'sex as a biological variable' mandates are not enforceable as currently designed and have shown little influence beyond the culture signal. Even so, they are but one piece of the puzzle. True change will require systemic overhaul, as male-only research simplifies the sex factor and investigators do not have to deal with any potential sex differences. Shansky and Murphy lay out the ways funders, editors, peer-reviewers and publishers will have to change to counter the traditional tropes.

'Microdosing' – taking regular very-low-dose psychedelics to improve well-being and cognitive functioning – is a recognised phenomenon, particularly valued in creative industries in California. It typically involves consuming about 10% of the standard recreational dose of LSD or psilocybin (magic mushrooms) a few times a week. At this dosing, the hallucinations and more profound alterations of consciousness that are associated with recreational use do not occur. This is something inherently difficult to study, but Szigeti et al³ report on a novel 'citizen science' methodology. A cohort of 191 individuals who consume psychedelics in this way were enrolled in a 4 week trial where they received online instruction on how to incorporate placebo control into their dosing without clinical support. This involved participants preparing two sets of non-transparent capsules: they filled half with their psychedelic microdose substance of personal choice, and half with nothing (placebo). These were placed in weekly sets (two doses per week) inside envelopes marked with

non-human-readable QR codes that could be scanned to the research team. A semi-random drawing process of the envelopes allowed participants to be divided into three groups for the 4 week trial period: group 1 had only placebo; group 2 had 2 weeks of placebo and 2 weeks of microdosing; and group 3 had 4 weeks of microdosing. Follow-up of participants was continued up to week 9. All individuals showed enhancement in their well-being and life satisfaction across the trial period; there were no differences over time among the different groups – between those taking placebo and those consuming the active drug. Some modest acute variation was found, but it could be explained by participants breaking the blinding. These data suggest that microdosing does not have any effect on your well-being or creativity, but thinking you are microdosing does. A very interesting trial design for a complex area, not least given the ongoing interest in therapeutic uses of psychedelics, notably psychedelic-assisted psychotherapy.

Outcomes in psychoses are notoriously heterogeneous; predictors of this are surprisingly understudied for such an important area. Further, such work often clumps individuals rather crudely and without clear scientific validity. The 'classic' method is that if no episode lasts for 6 months or more, the pattern is considered 'episodic'; and if no remission lasts 6 months or more it is 'continuous'; with the slightly rag-bag 'neither' category for everyone else. Morgan et al⁴ used the AESOP-10 study data to see if they could better map groups of individuals with varying trajectories over time, and then track these back to baseline characteristics and the aforementioned illness episode categories. AESOP-10 is a prospective 10 year follow-up study of over 500 individuals from their first episode of psychosis, with well-delineated sociodemographic and clinical profiles. Their modelling again found considerable variability but nevertheless produced four major pathways: remitting–improving with less frequent and shorter illness periods over time (58.5%); late decline (5.6%); late improvement (5.4%); and persistent, characterised by long periods of symptoms throughout most of the follow-up (30.6%). The first group is heartening, not least as 60% of them attained recovery, and these data are somewhat more optimistic than those from other studies. However, that last group of persisting symptoms is clearly a particular concern, where many met 'treatment resistant' criteria. Factors associated with worse outcomes were male gender, Black Caribbean ethnicity, lower IQ and education at baseline, greater socioeconomic disadvantage, a non-affective psychosis and a longer initial duration of untreated symptoms. The authors argue that the 'classic' descriptors noted at the start – especially the 'neither' group – are inadequate and crude, misclassifying outcomes and potentially misleading the 'hunt for biomarkers'. This is particularly relevant given the observed pattern for many of briefer episodes separated by longer periods in between – offering some positive hope for patients.

Given this long-term nature of psychoses for many, there are valid concerns about harms from long-term treatment with antipsychotics. Most randomised controlled trials only cover a 2 year follow-up. As part of the long-term Chicago study, Harrow et al⁵ followed up 139 patients over a 20 year period to investigate associations between medication use and clinical outcomes. Consistent with the study by Morgan et al, most participants had further episodes of psychosis subsequent to their initial one, but after the first 2 years those not on antipsychotics had better outcomes in terms of having fewer relapses and hospital admissions than those maintained on medication. This is both interesting and potentially alarming – suggesting that treatment might make people worse. The supersensitivity hypothesis is a putative explanation – long-term dopamine blockade adversely alters synaptic physiology. It is always good to have more long-term data, but the paper also

highlights the challenge of determining causality. People who take more paracetamol over longer periods of time have worse histories of headache; those who stop taking the medication usually have fewer in the long term. No one would argue that paracetamol causes headaches, because the causality is the other way around: we need to have more and longer treatment in those who are not doing so well. This is ‘confounding by indication’; the authors argue they got around this by measuring prognostic factors at the start of the 20 year period, though one might counter that the reliability of these can be challenged. The study does show that some people can do well off medication, which takes us back to the Morgan et al study and the challenges of trying to prospectively determine who these people might be. Only a prospective randomised controlled trial can truly unpick this, but that creates enormous ethical challenges for long-term work in debilitating conditions. It also reaffirms being judicious in prescribing, and working with the individual in front of you.

Antipsychotics really only tackle positive symptoms, but cognitive and negative ones are more predictive of quality of life: we need novel interventions. Fleischhacker et al⁶ report on a double-blind randomised placebo-controlled study of a novel glycine transport inhibitor, BI 425809. Glutamate dysfunction has been a strongly replicated finding in psychoses, including cognitive dysfunction, but the ubiquity of glutamatergic neurotransmission across the brain makes it very complex to modify pharmacologically. Glycine offers nuance, as it is a co-agonist at glutamatergic NMDA neurons. Inhibiting the glycine transporter, as BI 425809 does, would thus enhance glycine levels and increase signalling (think selective serotonin reuptake inhibitors and serotonin levels). Over 500 patients aged 18–50 years, with cognitive scores on average two standard deviations below the normative mean, from across 81 centres in 11 countries were randomised to receive either 2 mg, 5 mg or 25 mg of BI 425809, or placebo (in a 1:1:1:1 manner), in addition to their stable oral antipsychotics. Six dose-response models were designed to allow multiple comparisons (with all blinded to which one the patient was on), and cognition was measured using the MATRICS battery across 12 weeks. Five of the six dose-response models showed significant superiority to placebo at week 12, with maximum gain in the higher dosing range. The drug was relatively well managed in all. These are really interesting phase 2 results: the past teaches us caution about getting too optimistic too early – bitopertin was a similar glycine inhibitor that demonstrated positive results in phase 2 studies but was yet not effective in phase 3 studies. It is not hyperbole to state that enhancing cognitive performance would be a game-changer in the management of psychoses.

Finally, in modern parlance, an ‘echo chamber’ is a situation where beliefs become reinforced among a limited or closed group of people with similar beliefs. The term has been widely applied to social media, enabled by people ‘sharing’ links or material to self-selected groups, and following like-minded influencers or sub-community groups. Analyses have shown that fake news propagates faster than ‘real’ news on Twitter,⁷ but there have been few comparative studies across different platforms such as Facebook, Reddit and Twitter, where mechanisms for sharing information

differ. Cinelli et al⁸ analysed these platforms, adding ‘Gab’, a Twitter-a-like that attracts right-wing adherents, some of whom have been banned by the other platforms (think QAnon). For a given social media user, the ‘leaning’ or polarisation of the content they produced was averaged and its political leaning ascertained (‘left’, ‘centrist’ or ‘right’). This was repeated for groups of connected people. Then, homophily (the tendency of individuals to associate with other similar people) was measured by identifying arcs between users, supplemented by homophily ‘networks’ and ‘neighbourhoods’, examining the average ‘leaning’ of nearby people on ‘hot’ topics: abortion rights, vaccines, politics and all topics on Gab. Facebook exhibited the most marked polarity (on vaccines) compared with Twitter (for abortion). Reddit communities and Gab (overall) showed less polarity but rather only one collective neighbourhood (suggesting that users join these social media platforms almost exclusively because of their preferred ‘leaning’ – left-leaning on Reddit and right-leaning on Gab). By analysing information flows in the networks on each platform, they show that on Twitter and Facebook, users are more likely to receive information propagated by users with similar leanings. By contrast, on Reddit and Gab, users were less likely to be exposed to information propagated by people with similar leanings, plausibly because these platforms are self-selecting for polarised views in the first place (the users are more homogenous and the platforms themselves may be a ‘giant echo chamber’). Finally, what about the role of content-promoting algorithms? Unlike Facebook and Twitter, Reddit allows users to ‘tweak’ the content-feed algorithm. The researchers compared consumption of similar news content over Facebook and Reddit and found that the segregation of users was higher on the Facebook platform. The bottom line: there’s a lot of reinforcing of that echo chamber online. We’re delighted to have you on Team Kaleidoscope and suggest you stick to our column and webinar for all the news you need.

References

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