

Kaleidoscope

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Clearly, each patient brings unique issues to therapy, but there has been almost no research on allocating therapists based on complementing these. It's an interesting omission when we consider that the therapeutic relationship is an important factor, and no one would propose that every clinician is equally skilled in all areas. Constantino et al¹ tackle this in a trial of 218 patients randomised in a double-blinded manner to strength-matched or assignment-as-usual psychotherapy from a pool of 48 therapists. Therapists' strengths were pre-determined across a dozen 'problem domains' of the Treatment Outcome Package, assayed using 15 or more historically treated cases. This led to a rating for every therapist of effective, neutral or ineffective in each domain. There were then several 'match levels' for participants in the good-fit therapist group: these went from therapists being effective on the three greatest need domains and not ineffective in any others, to being not effective in the need domains but also not ineffective elsewhere.

It might not surprise you that those with therapists with skills better matched to needs showed significantly better outcomes in terms of reduced symptoms, functional impairment, global distress and domain-specific problems, and there were no adverse outcomes. Perhaps the bigger question is why this has previously been so unstudied. The Kaleidoscope team's anecdotal experiences in the National Health Service have been that teams often try to allocate a therapist based on perceptions of patient need and therapist strengths, although this is usually following an informal discussion without explicit measurement; however, lack of resources usually leads to most cases being allocated in a 'taxi-rank' order. In the UK in recent years we have got better at measuring patient outcomes in therapy. Does it perhaps make us anxious as clinicians to have our strengths – and, moreover, our weaknesses – so empirically measured? If it improves lives, as this work indicates, perhaps it is time to put aside any such personal concerns, given the opportunity to enhance care and outcomes at no additional cost. Previous work has shown that 'above average' therapists can attain outcomes twice those of 'below average' therapists: it might well be that the skills of some in the latter group are just not being appropriately used. Of note in this work, all therapists treated participants in the matched and unmatched groups, and there was no manipulation of the therapy itself, so it was less a case of 'good' and 'bad' therapists but of outcomes being optimised when 'need' and 'skill' were aligned. We talk about precision psychiatry in terms of targeted medications; perhaps we might think along similar lines for psychotherapy. For a reflective clinician, this will also provide better insight into one's strengths and areas for further development.

In May, the *New York Times* ran the headline 'The Psychedelic Revolution Is Coming. Psychiatry May Never Be the Same'. It referred to a paper by Mitchell et al² that reports on a multi-site, randomised and double-blinded Phase 3 study combining a manualised psychotherapy with either placebo or 3,4-methylenedioxymethamphetamine (MDMA) for chronic post-traumatic stress disorder (PTSD). The primary end-point was the CAPS-5 (a blinded clinician-rated PTSD symptomatology scale) total severity score from baseline to 18 weeks later. Participants, with a mean duration of illness of around 13 to 15 years, were given MDMA or placebo at weeks 1, 5 and 9 alongside an integrative psychotherapy. On the primary outcome, the MDMA group had a mean change in

CAPS-5 score of –24.4 versus –13.9 in the placebo group; there were no group differences for suicidality, self-harm or cardiac events. A mixed model repeated measures analysis and commercially available statistics software were used, but unfortunately no details of the linear model (e.g. code or a description of the model) were provided beyond describing how individual participants were considered as random effects, and treatment (MDMA, placebo), baseline CAPS score, dissociative subtype (of PTSD) and study site were fixed effects. The primary efficacy result (beyond effect size estimates with confidence intervals and *P*-values) is presented in the form of a graph with the baseline and three interventional time points on the abscissa, and the MDMA and placebo groups' least-squares (model) estimated mean CAPS-5 scores as the ordinate. Uncertainty is shown as a ribbon representing the standard error of the mean. Finally, the data are described as being used under licence from and available on request to the sponsor (MAPS Public Benefit Corporation).

At face value, a study of 90 people with chronic PTSD demonstrated that MDMA and therapy were more efficacious than therapy alone. What is interesting is how the study was presented to the wider world; press releases, including the *New York Times* coverage, were hyperbolic. One would think that such argument should be unambiguously described with access to the data for an interested reader. The claim of 'highly statistically significant' is presumably made on the basis of the reported very small *P*-values (of the order of 0.001) for the effect size between MDMA and placebo. However, it is also noted that people with the difficult-to-treat dissociative subtype of PTSD benefited more from MDMA; further circumspection may be warranted given the small numbers of six and 14 people in the MDMA and placebo groups, respectively.

The Kaleidoscope team respects a data-set with robust numbers that sharpens our epidemiological knowledge of mental disorders. Solmi et al³ systematically reviewed and meta-analysed 192 relevant studies incorporating over 700 000 individuals with a diagnosed mental illness. The proportions of people who had received their diagnosis by the ages of 14, 18 and 25 years were 34.6%, 48.4% and 62.5%, respectively; the peak age was just 14 and a half. There were considerable variations among different conditions, and although a detailed description is beyond the scope of our synopsis, several figures stood out. Neurodevelopmental and anxiety/fear-related disorders had a peak age of onset of just 5.5 years of age; 'only' 34.5% of mood disorders and 47.8% of psychotic disorders had begun by the age of 25; whereas bipolar affective disorder had a median age of onset of 33 years. Interestingly, there were few age differences secondary to sex, although there was a trend of slightly earlier onset in men for substance use, affective, and psychotic disorders. The studies, which were globally representative, showed no clear geographical differences, although there may have been inadequate power to determine country-specific variations. The authors note that we are already aware of most of the risk and protective factors for these conditions and suggest that we can now better target schools with age-relevant mental health psychoeducational material. These data are really stark in reminding us how early in life many people are afflicted by mental health problems. They align with the longstanding call to frontload mental health service provision for younger people.

Although we don't often bring you technical reports, a recent paper looks poised to give a boost to the scientific study of social behaviour. Optogenetics allows for the manipulation of specific groups of neurons, engineered to become responsive to light. Light bursts of defined intensity, duration and frequency can be delivered via implanted optical fibres, providing exceptional control in the study of behaviour of freely moving animals.

However, the kit required to make this work is cumbersome and has probably affected some, if not all, of the behavioural data gathered to date. The physical structures necessary to provide light and power require head or back mounting, creating tethered wiring and the appearance of miniature top hats and backpacks on animals, and calling into question how natural a behaviour can be observed. There are internal limitations as well – the mountings restrict the stimulation to pre-programmed patterns and only allow for one or two probes to be placed at a fixed distance. In short, it's good – but the folks at Northwestern University have made it so much better. In *Nature Neuroscience*,⁴ they describe a small, flexible, wireless device that is fully contained beneath the skin and derives power remotely. Functionality is increased too, with real-time programming capabilities across multiple independent implanted light sources. These allow for not only more naturalistic behaviour of animals but also more complexity and control within a single animal and across several during social behaviour. As a proof of principle, the researchers targeted dopamine neurons within the ventral tegmental area and in real time conditioned a place preference, followed by boosting social engagement in freely moving animals. Finally, they tested the theory that generating synchrony of neuronal activity within the medial prefrontal cortex would drive socialisation within a group of animals – something that only the unique characteristics of their optogenetics set-up would allow. Mice experiencing synchronicity spent more time socialising and engaging in classic social behaviours including grooming and sniffing. Social dyads could be created by giving two animals in a group identical synchronised stimulation patterns and could be broken when their neurons were synchronised to different frequencies, confirming the hypothesis and setting us up for the further exploration of complex social interactions. The ability to utilise existing manufacturing processes means there is great potential for reasonable cost and a significant expansion of this approach in behavioural neuroscience.

Finally, we are always in awe at the brain's remarkable abilities to reorganise and were very struck by a fascinating recent case report⁵ of a woman born without a left temporal lobe. The 'normal' functions of this region include high-level language processing, in conjunction with the ipsilateral frontal lobe. However, the individual in question in this case, a highly educated woman with an advanced professional degree, had perfect linguistic skill (and was cognitively at the 98th percentile) – the only potential deficit being her self-report of being a 'terrible speller'. Indeed, she had studied and mastered a second language to a high degree of proficiency as an adult. She only incidentally learned she had lost her temporal lobe at the age of 25 when having a magnetic resonance imaging scan as part of routine investigations for depression. The authors of the paper wanted to evaluate how this woman's brain had compensated. It was expected that her right

temporal lobe would take on the roles that normally occur in the (now missing) left side. However, would the left frontal region have continued to develop independently as a language centre, or does that require a functioning ipsilateral temporal lobe? They found a complete absence of left frontal language activity, with this having shifted to the right side. A single hemisphere appears adequate for a language system, and the temporal lobe delivering this appears necessary to slave the relevant ipsilateral frontal cortex. Language areas in the temporal and frontal lobes do not develop independently but together iteratively. The data also demonstrated that this individual's left frontal lobe functioned perfectly well in tests for higher-level cognitive functioning. It remains unclear what her left-sided regions that might otherwise have been allocated to linguistic processing now 'do', but it would seem likely that these have similarly been repurposed. It seems difficult to imagine that the loss of an entire lobe can occur without major functional deficits. Timing is clearly critical, and agenesis from fetal development meant there was time and scope for the remaining neurons to differentially connect and compensate. There are of course caveats to what one can generalise from a single individual: medical science has very much moved away from 'case studies', and we recognise the dangers of unintentionally sensationalising or appearing voyeuristic at another's expense (we'd further add that the paper is currently a pre-print and has not gone through peer-review). However, the study is remarkable in showing how plastic the brain can be and in helping to clarify the (relatively poorly understood) ontogenetic emergence of language processing. It also resonates with more contemporary thinking of 'networks' of function, away from the notion of 'modular blocks' with inevitable and very specific roles.

References

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