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Kaleidoscope

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Covid has made us increasingly familiar with using digital technologies, from work team meetings to social and clinical interactions; where might the novel tech opportunities lie? Social anxiety disorders (SAD) can limit individuals' abilities to leave home and might be a prime target for virtual work. Nordh et al[1] report on a trial of 103 young people with SAD who were randomised to receive either internet-delivered cognitive–behavioural therapy (iCBT) or an active intervention of therapist-guided supportive therapy (iSUPPORT). iCBT included a psychoeducational component, social skills training, focus shifting from internal to external attention, reduction of safety behaviours and avoidance, and relapse prevention planning. Conversely, iSUPPORT included psychoeducation and information on healthy habits and interpersonal relationships, as well as therapist encouragement to generate strategies, but without key CBT components such as exposure. iCBT showed significant superiority in reducing symptoms, including secondary outcome measures such as functional impairment and school productivity, at the 3 month post-intervention point. This is the first such trial of iCBT for SAD using an active comparator, strengthening the results by removing the confounder of non-specific aspects of therapist care; the active intervention was also cost-effective when compared with iSUPPORT. This low-intensity treatment requires only modest therapist input and might target the estimated 90% of individuals with SAD whose symptom profile is less severe and who currently do not receive any intervention at all, as well as those often on long waiting lists for face-to-face therapy.

Digital technologies also offer novel opportunities for individuals with paranoia: as a very broad generalisation, we might recognise that for some they might reduce anxieties about social engagements with clinicians, while equally appreciating that others might have concerns about the technology itself. Garety et al[2] tested 'SloMo', an eight-session digitally supported reasoning intervention, in 361 individuals with psychotic illness randomised to receive this or treatment as usual. The authors state that SloMo adopts an interventionalist-causal approach to enhancing CBT for psychosis by 'targeting reasoning processes considered causal in psychosis'. The technology uses a blended approach that includes a mobile app as well as face-to-face work. At the 12 week point, those receiving SloMo showed greater reductions in paranoia, belief flexibility and observer-rated persecutory delusions. However, there were no significant changes in jumping to conclusions or worry-mediated paranoia, and total scores on the primary measure, the Green et al Paranoid Thought Scale, were similar in both groups at week 24. These two studies in quite different groups show promise using virtual technologies that are proving increasingly acceptable and offer scale-up opportunities that might counter the resource limitation of clinician time.

How much might responses to alcohol in early life predict later difficulties? It's an interesting and largely untested question: one might anecdotally contemplate one's peers' varying interactions with drinking alcohol when young and project them on to later life behaviour. King et al[3] examined 190 young adult drinkers given an initial alcohol challenge (0.8 g/kg of alcohol compared with placebo in a randomised, double-blinded manner), which was replicated 5 and then 10 years later. They reported on their degree of stimulation, sedation and hedonic reward – how much they liked how they were feeling, and how much they would like more of the same beverage. Subsequent alcohol drinking behaviour and any alcohol use disorder (AUD) symptoms were mapped across time. At the study's end-point, just over a fifth of participants met criteria for an AUD, and they were significantly more likely to have reported more alcohol-related stimulation, liking and desiring the alcohol challenge. Interestingly, sensitivity to alcohol stimulation and desire increased with time in those who would develop an AUD, and there was no loss in hedonic intensity over time in this group. The findings potentially open public health educational and intervention opportunities in younger groups before problems emerge.

Less than 10% of those with AUD are estimated to receive any treatment, and existing pharmacotherapies have modest evidence bases: work continues to try to find new interventions. The neuroimmune modulator ibudilast, which selectively inhibits phosphodiesterases 3, 4, 10 and 11, as well as migration inhibitory factor, has shown some early promise. How this might alter behaviour has been unclear, although there is a 'neuroimmune hypothesis of alcohol addiction' that invokes increased expression of pro-inflammatory markers and cellular death. Grodin et al[4] tested both effectiveness and mechanism of ibudilast action in a double-blinded randomised controlled trial of 52 individuals with AUD, who received either ibudilast or placebo over a 2 week period. Those on the active treatment had 45% reduced odds of heavy drinking during this period, as measured by a daily diary. However, it had no effect on the number of non-drinking days or the mood of participants. Interestingly, neuroimaging data showed that ibudilast reduced alcohol-cue-elicited activation in the ventral striatum, and that this attenuation was correlated with altered behaviour. The greater the ibudilast-induced reduction in striatal activity in response to alcohol cues, the less participants drank. The inference is a biobehavioural reduction in rewarding responses to alcohol cues, which in turn decreases the amount consumed. These data add to the positive literature on ibudilast and offer a mechanistic explanation as to how it might work in the brain.

Nitrous oxide, well accepted for use in medicine and dentistry ('laughing gas'), has also been shown to relieve depression symptoms upon administration for 24 h. However, the dosing tested to date (a 50/50 combination with oxygen) generates nausea in a subset of people, limiting its potential use. A recent *Science Translational Medicine* article reports on a phase 2 trial investigating variation in dose and effectiveness across a longer duration, using a within-subject design. Each participant experienced three randomised dosing treatments separated by a month: 50% nitrous oxide/50% oxygen, 25% nitrous oxide/75% oxygen and pure oxygen. Study participants all had severe treatment-resistant major depression with a median of 17.5 years of major depressive disorder and 4.5 unsuccessful antidepressant drug treatments. Both doses of nitrous oxide significantly alleviated depression symptoms compared with the control for a 2 week duration, with no difference in efficacy between them. However, there were significantly more adverse effects seen at the highest dose, with the 25% nitrous oxide/75% oxygen combination being effective and well tolerated. After full study completion, 85% of participants had improved enough to warrant a change in their depressive symptom category (from severe to moderate, for example), while 55% reduced their Hamilton Rating Scale for Depression score by 50% or more, and 40% were judged to be in remission. Although this was a small study, the results are promising and somewhat on par with those for ketamine in treatment-resistant individuals. However, nitrous oxide has practical advantages over ketamine. As it is a volatile gas, the anaesthetic aspects of the drug clear quickly, allowing for less observation and hold time after treatment, and the ability to drive oneself home. A study directly comparing the two will be one to watch.

The ability to reproduce or replicate an experiment and its results is the foundation of the scientific method. By this process, an initial hypothesis and the evidence supporting it are tested by independent teams. The 'replication crisis' is well documented, and even some of the leading commentators on replication crises are themselves being criticised. But so what? One could posit that replication crises are merely noise created by 'self-appointed data police' rather than a tangible harm to science (for a description of this new lexicon, see https://absolutelymaybe.plos.org/2016/09/29/flying-flak-and-avoiding-ad-hominem-response/). One way to measure the impact of failed replication is to examine the history of citations for studies – a crude marker, but one that at least exposes the penetrance of a paper on the subsequent body of literature – and Serra-Garcia and Gneezy[5] tested this with papers in psychology, economics and general science journals (e.g. *Nature* and *Science*). They collected citation metrics for studies subjected to three large replication projects. A paper's findings were considered 'replicated' if (a) the original paper described a specific hypothesis test (i.e. reported a significant null-hypothesis test with P-value <0.05 in a two-sided test with a specific direction of effect), and (b) the same effect direction and null-hypothesis test was obtained in the replication studies. In the three replication projects, 39% of psychology, 61% of economics and 62% of general science experiments were successfully replicated.

For each replicated and non-replicated study, Google Scholar citation counts from the date of publication (until the end of 2019) were collected, as well as impact factors for the journals in which citations were found. They queried whether papers that were replicated were cited more or less often than those that were not. Papers with successful replications were cited on average 153 times *less* often than those without. Citation counts appear to favour or inflate the impact of what could be argued to be false-positive findings (given that they did not replicate independently). Interestingly, this effect was most pronounced for papers in the most prestigious journals, *Science* and *Nature*. Serra-Garcia and Gneezy then assessed the impact of replicable and non-replicable studies; to do this, they defined any paper that cited one of the studies in the three replication projects as a 'citing paper', collected how often 'citing papers' were subsequently cited and determined whether these 'citing papers' appeared in high-impact-factor journals. Papers that cited non-replicating studies were themselves cited on average 25.6 times compared with 23.7 times for those citing non-replicated studies. There was no appreciable difference between the impact factors of journals publishing these 'citing papers'. Finally, the authors note that a mere 12% of citations of a paper that failed replication actually describe this non-replicability finding. Overall, it seems that publishing a result that does not stand up to scrutiny doesn't substantially harm the impact of the original work, at least as measured by citations.

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