BJPsych The British Journal of Psychiatry (2022)
221, 771–772. doi: 10.1192/bjp.2022.161

Kaleidoscope

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Sexual violence is a significant trauma for anyone, but its frequency and impact on mental health of adolescents have not been well mapped. This might at first seem a little surprising, but much of the existing work has been on broader adverse childhood experiences at a younger age, or sexual and intimate partner violence in university populations. The work that does exist on mid-adolescence often comes from populations that have suffered assault, hindering generalisability of findings, or cross-sectional work that limits findings to associations rather than causes. Writing in *Lancet Psychiatry*, Bentivegna and Patalay[1] took data from the nationally representative longitudinal UK Millennium Cohort Study of children born between 2000 and 2002. They explored the occurrence of sexual violence – whether a sexual assault or unwelcome sexual approach – in the previous year in 5000 girls and approximately the same number of boys, all of whom were aged 17. Over a fifth of the young women reported such an experience in the previous year, including 5.3% who had experienced a frank sexual assault. The rates were lower in young men, but still 5.4% had experienced some form of sexual violence in the prior year. Sexual violence created distress in both sexes, including increasing rates of self-harm and suicide attempts. When various confounders were redressed, the authors estimated that perhaps a fifth of serious mental health problems in young women and a tenth of those in young men were likely to be directly caused by sexual violence. As well as the clear need to support those who have suffered such violence, this raises the obvious target, and challenge, of preventive work. Vulnerable individuals – including where there are histories of intergenerational and intimate partner violence – and their families, schools and local communities are all appropriate avenues to explore. Given that there are evidence-based interventions and educational programmes available, the outstanding question is how prepared our local services are for safe, trauma-informed disclosure and support.

Though nearly a century beyond Lashley's attempts to find the physical locations of memories in the brain, our efforts to fully elucidate the engram continues. Of particular interest to mental health is the physical nature of emotionally charged memories. Whereas the hippocampus processes multiple aspects of contextual memory, the ventral hippocampus relays emotions and their valence to downstream targets. The Ramirez laboratory at Boston University used optogenetics to articulate[2] what happens in the ventral CA1 (vCA1) region at the cellular and molecular levels when emotional experiences are processed in a rat model. Using Fos-based transgenic rats, a dual cFos tagging strategy and immunohistochemistry, positive and negative engrams were differentiated at multiple time points within the same subject. The initial positive memories were made by exposing the male rats to a female, whereas the negative memory was allied to a foot shock. Anatomical visualisation of the results revealed that the cells associated with the pleasant memory were located in the posterior sections of the vCA1, whereas aversive engrams were largely in the anterior sections, with an intermingling in the medial space. Ninety minutes after the last behavioural experience, they found that a different positive or negative experience (sweetened condensed milk or restraint stress, respectively) recruited activation of previously labelled cells of a similar valence, creating a Venn diagram of localisation for emotionally relevant cells in the vCA1.

Despite the different locations and associations with distinct emotional information, the cells showed no differences across several physiological measures including firing frequency, adaptation rate and spike rate. However, there were observed differences in where these cells projected within emotional processing areas. Although both types of cells projected to the medial basolateral amygdala and prefrontal cortex, unique projection patterns from the positively and negatively tagged cells were seen throughout the network. The cells also demonstrated unique patterns of gene expression, showing little overlap, leading the authors to conclude that these are transcriptionally distinct subpopulations, a result that was echoed by the DNA methylation patterns. Perhaps most relevant, using a conditioned place-preference paradigm, they confirmed that stimulating the unique projection terminals of the positively and negatively tagged cells drove place preference and avoidance, respectively. Interestingly, this was amenable to change, with artificial stimulation of the positive projection terminals during fear conditioning able to neutralise the conditioned avoidance. Although the overall findings of distinct locations, projections and molecular signatures of emotionally valiant information from the vCA1 are exciting on their own, the behavioural data are particularly intriguing. Not only could we potentially differentiate positive and negative memories in the hippocampus, we could target them to neutralise the types of negative memories that affect a person's mental state. Although direct neuronal stimulation is not viable in a human population, the work lends credence to the potential benefits of memory manipulation in a clinical setting. Whether this is through directed recall, non-invasive stimulation or pharmacological means remains to be seen, but this paper offers a unique theoretical foundation for intervention.

Associations between patterns of daily activity and mental state are well established, but there are fewer data focused on older adults in relation to depressive symptoms and cognitive performance. In particular, disruption to diurnal patterns is sometimes presumed to be an inevitable part of aging. However, data do not support this cliché, indicating instead that such disruption is often linked to illness, including depression and dementia. Prior data have shown that 'fragmentation' of activity, namely greater disruption within periods of rest and activity, and 'robustness', or the conformity of this to a 24 h model, were predictive of depression. Smagula et al[3] add to this, with cross-sectional accelerometer and mental health data on 1800 Americans (57% female) over the age of 65, weighted to represent about 32 million older adults. Four subgroups emerged: early rising/robust patterns (38%); shorter activity duration/less 'modelable' (33%); shorter active periods/very weak (10%); and later activity offset/very weak (20%). To elaborate on these a little further: the first and largest group typically had activity start before 07.00 h, with a 15 h active period and the most robust activity on all measures. The second group started their day later and finished earlier but still had robust measures of activity. The last two groups had quite disrupted patterns across all measures. In terms of how these groups linked with symptoms: Patient Health Questionnaire-9 depression scores ≥10 occurred in 3.5%, 4.7%, 7.5% and 9.0%, respectively; and progressive mild cognitive impairment scores less than one standard deviation below the mean occurred in 7.2%, 12%, 21% and 18%, respectively. So, there was clear, statistically significant variation associated with the four different activity patterns and, interestingly, the pattern of exact depression symptoms varied among groups. What has been less clear from most previous work is how much diurnal changes contribute to or are a consequence of any mental health condition, and of course there could be bi-directional relationships. These findings open up the potential of testing for this, with putative therapeutic implications: activity can be modified, although this is not

always easy, and this can have feedback loops involving cellular circadian activity. The big question is whether such interventions might effect positive clinical change; being able to identify subcohorts would help to refine such future work.

Live brain tissue can be very helpful for research, but access is tricky: most people are understandably reluctant to have scientists take bits of brain out of their heads. Human cortical organoids (hCOs) are one way around this: these are self-assembling three-dimensional systems grown from human induced pluripotent stem cells. However, hCOs have limitations, not least that their 'free growth' without sensory input and lack of output to behavioural circuits just doesn't match real-world *in vivo* conditions. How similar are they to 'real' brains? One possibility is to transplant hCOs into an existing brain – ideally at an early, plastic stage of development – to facilitate axonal and synaptic integration. Writing in *Nature*, Revah et al[4] describe their trial of transplantation into the primary somatosensory cortex of early postnatal immunodeficient rats. The choice of the somatosensory cortex allowed both thalamocortical and corticocortical inputs during hCO maturation. They demonstrated the development of mature cell types not otherwise seen in hCOs *in vitro*, which integrated anatomically and functionally in the rat's brains. The authors were able to establish links within this circuitry, modulating rat neuronal activity and subsequent behaviour via the hCO neurons. Not only did this masterly piece of work produce more sophisticated and realistic brain models with which to model both health and pathological functioning, but such grafting into immature animals will facilitate long-term studies. An obvious target will be future transplanting of patient-derived cells to determine circuit-level phenotypes that cannot currently be elucidated.

Finally, who doesn't like a good mHealth app? One recent health secretary (and you'd be forgiven for struggling to remember which one, given the current rate of cabinet churn) was so enamoured with them that they released their own personal app to provide a window into government life for their constituents. It included a feature (not a bug) that requested access to your phone's photo gallery. There were some mysteriously positive (read: sarcastic) five-star reviews, including one user who described life without the app as '… living without it is like watching William Burroughs threatening God with a shotgun while you lick broken glass off the rails of the Berlin U-Bahn'. Anyway, if we want the population to engage with the mHealth app ecosystem to improve their health, a key indicator will be meaningful user engagement; it's no use if people download something and then never really use it. A recent scoping review[5] looked for evidence of randomised controlled trials (RCTs) of mHealth apps and, explicitly, those that examined engagement per protocol. Missing data (from non-engagement) would threaten the validity of conclusions drawn from RCT data, and Lipschitz et al chose depression trials as a focus. Lipschitz et al introduce a five-element framework to examine engagement as follows: (a) what information was given to participants about how to engage with the app and what would constitute adherence to these recommendations; (b) the rate of engagement among those randomised to use the app; (c) app-use metrics including frequency of use; (d) duration of interactions with the app; and (e) the number of participants who completed the intervention. They found 150 eligible full-text articles, of which 22 were within scope of the review's full criteria. Of note, the 22 RCTs targeted depression symptoms, but there was diversity of clinical and non-clinical groups including depression, suicidal ideation, anxiety and bipolar disorder, as well as non-clinical populations such as university students.

The authors found that, on the whole, engagement (over the five domains they defined) was rarely reported; of those 22 RCTs that did report on the single measure of 'used the app at least once', only 64% reported data. When this measure was reported, the number of app-use instances – alongside duration of engagement on each use – was present in only 59% of trials. Consistent with other research, they found that engagement (in the few cases it was reliably reported) dropped substantially as the trial progressed – for example, in one study, just over 80% used the app during the first 8 weeks, and this declined to just over 50% by the end of the trial. Only 50% of trials described the how many participants could be considered to be 'completers' of the intervention – so we can only speculate as to how to draw conclusions about these apps' efficacy or effectiveness – but in the literature available in this review, only six studies provided completion rates data and, of these, completion rates were 50% or lower.

References

1 Bentivegna F, Patalay P. The impact of sexual violence in mid-adolescence on mental health: a UK population-based longitudinal study. *Lancet Psychiatry* 2022; **9**(11): 874–83.

2 Shpokayte M, McKissick O, Guan X, Yuan B, Rahsepar B, Fernandez FR, et al. Hippocampal cells segregate positive and negative engrams. *Commun Biol* 2022; **5**: 1009.

3 Smagula SF, Zhang G, Gujral S, Covassin N, Li J, Taylor WD, et al. Association of 24-hour activity pattern phenotypes with depression symptoms and cognitive performance in aging. *JAMA Psychiatry* 2022; **79**: 1023–31.

4 Revah O, Gore F, Kelley KW, Andersen J, Sakai N, Chen X, et al. Maturation and circuit integration of transplanted human cortical organoids. *Nature* 2022; **610**: 319–26.

5 Lipschitz JM, Van Boxtel R, Torous J, Firth J, Lebovitz JG, Burdick KE, et al. Digital mental health interventions for depression: scoping review of user engagement. *J Med Internet Res* 2022; **24**: e39204.

https://doi.org/10.1192/bjp.2022.161 Published online by Cambridge University Press