

## **Messing about with the brain:**

### **A response to commentaries on ‘Depression: why electricity and drugs are not the answer’.**

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We thank all authors for the six commentaries on ‘Depression: Why Drugs and Electricity are not the Answer’ (Read & Moncrieff, 2022). We are sorry we cannot address all their points in the space available.

Pariante quotes from Hippocrates: *‘from the brain and from the brain only arise our pleasures, joys, laughter and jests as well as our sorrows, pains, grieves and tears’* (Hippocrates goes on to suggest that madness arises from excessive ‘moistness’ of the brain). This biological reductionism is a contentious position that is central, with varying subtly, to the commentaries by Aftab et al., Meechan et al., Pariante, and Goldberg and Nasrallah, exemplified by the latter’s description of depression as a ‘potentially fatal brain syndrome’.

### **Depression and Antidepressants**

We all share the natural inclination to try to help someone who is suffering, but messing about with the brain, using interventions whose effects we do not fully understand, and that have unproven benefits and well-established harms, is not consistent with the Hippocratic oath (a more valuable contribution).

Aftab et al. do not like ‘binaries’ but the fact is we make distinctions in life. For most people it is self-evident that using drugs to treat diseases of the body is different from using them to modify unwanted emotions or behaviour.

While a fuller rebuttal to the reductionist position has been given elsewhere (Moncrieff 2020a; Moncrieff, 2020b), we agree that depression is ‘not one thing’.

Although we are biological organisms with a large brain providing the capacity for rational thought and complex feelings, this does not mean we can understand human thought, emotion and behaviour in terms of the brain.

In exceptional cases low mood is a consequence of somatic factors - such as an illness like hypothyroidism, or various drugs. Yet, contrary to Goldberg & Nasrallah's assertions, there is no good evidence that 'regular' depression, however severe, originates from biological deficiencies. The largest genetic database study ever conducted showed no association between any candidate gene and depression, or any interaction between such genes and adverse life events (Border et al, 2019). A systematic review and meta-analysis found no evidence that any proposed biomarker, including neuroimaging findings, neurotrophic factors, neurotransmitters or hormones reliably predicted the onset or maintenance of depression (Kennis et al., 2020). We suggest, therefore, that depression, even when severe, is not correctly thought of as an unwanted biological state or disease, but as one of the emotional reactions that we humans manifest as a consequence of our sophisticated evaluation of our circumstances and history. It is important that we distinguish these situations (Moncrieff, 2020a). On the one hand there is an impersonal biological process or disease, that needs to be treated (if possible); on the other, a fellow human being who needs understanding and support.

It is true that most medical treatments do not address the 'underlying biological dysfunctions,' yet they still act on the physiological mechanisms that produce symptoms (e.g. painkillers acting on pain pathways) . Since no such mechanisms have been established for depression, the 'outcome-centred model' Aftab et al. describe amounts to giving brain-modifying chemicals without knowing what they are doing, simply because they change depression rating scales by a couple of points more than placebo. The ever-changing conjectures about how these foreign chemicals might

actually be benefiting the brain (rather than harming it as we might plausibly expect) are not reassuring.

Pariante cites others who, recognising the inconsequential differences between antidepressants and placebo, proclaim that the measures are inadequate. While measuring depression as if it was a piece of string is clearly absurd (as Timimi points out), using the single depression item of the Hamilton scale is no more valid. In the cited study, the difference between antidepressants and placebo on this item was between one point, the criteria for which is ‘These feeling states indicated only on questioning’, and two points, defined as ‘These feeling states spontaneously reported verbally’. It is not obvious that having to be asked if one feels sad or indicates a less severe state than volunteering this information spontaneously. It is also subject to publication bias since it is not the primary outcome.

Goldberg and Nasrallah consider that response rates provide evidence of the effects of antidepressants, but these derivative categorical measures have been shown to artificially inflate effects (Kirsch & Moncrieff, 2000).

### **Electroconvulsive Therapy**

Meehan et al. assert that Electroconvulsive Therapy (ECT) is highly effective, ignoring the fact that all 11 sham-ECT studies (average study size 37) were grossly flawed (Read & Bentall, 2010; Read, Kirsch & McGrath, 2019). Five found no difference between ECT and ‘sham ECT’ during treatment. None found evidence that ECT outperforms placebo beyond the treatment period, or that it saves lives as often claimed by ECT advocates.

Most of the arguments of Meehan et al. have been rebutted in a paper (Read, 2022) identifying the many ‘errors, misrepresentations, omissions, inconsistencies and logical flaws’ in their previous attempt to dismiss these inconvenient truths, and the evidence

that ECT causes memory loss, brain damage, cardiovascular events and, rarely, death.

We have space here for only a few.

Repeatedly trying to undermine the two systematic reviews (Read & Bentall, 2010; Read et al., 2019) that demonstrate the absence of robust evidence in favour of ECT, by wrongly calling them ‘narrative reviews’, is dishonest.

Meechan et al. attack these reviews because they ‘focus almost exclusively on older sham ECT (sECT) trials, going back to the 1980s’. Is it the reviewers’ fault that ECT advocates have failed to conduct any such studies for nearly forty years? Meechan et al. repeat the old argument that this is because non placebo studies are more ‘ethical’. What other medical researchers argue that it is unethical to find out whether a treatment works because they can’t withhold that treatment in a placebo study because they *believe* it works?

Meechan et al. again irresponsibly minimise mortality rates, memory loss and brain damage. For example, the crucial, prospective Sackeim study demonstrating significant memory loss after six months (Sackeim et al., 2007) is dismissed because it ‘included use of outmoded sine-wave ECT’ rather than the brief pulse method frequently used today. Meechan et al. conveniently omit, however, that Sackeim et al. compared sine wave and brief pulse and found no difference in the amount of damage to either anterograde and retrograde amnesia at six month follow up. Meechan et al. also wrongly describe the reduction in autobiographical memory (retrograde amnesia) after six months as ‘small’. Sackeim et al. reported the scores as ‘markedly below baseline values ( $t(251) = 21.1, p < 0.0001$ )’.

In reporting the Sackeim study we are accused of ‘conflating cognitive test performance with brain damage’. What else should one call dysfunction of an organ caused by about ten electric shocks and convulsions, six months later?

Meechan et al.’s concerns about patient expectancy and about suicide studies have been addressed elsewhere (Read et al., 2019; Read, 2022; Read & Moncrieff, 2022).

Pariante's critique rests solely on quoting a promotional piece from the Chair of the International Society for ECT, which, as usual, cites ECT response rates without acknowledging the necessity of placebo comparisons (Rasmussen, 2009; Read & Bentall, 2010; Read et al., 2019). Goldberg and Nasrallah state only that 'Meta-analyses of ECT for depression indicate large effect sizes', with no mention of the poor quality and bias of those meta-analyses and the studies on which they relied (Read et al., 2019), or of the meta-analysis they reference (UK ECT Review Group, 2003) finding 'limited randomised evidence on the efficacy of ECT in the specific subgroups of patients who are presently most likely to receive it'.

There is just not enough evidence of sustained, worthwhile benefit from ECT or antidepressants to justify exposing people to their many adverse effects. We mess with the brain at our peril.

## References

- Border, R., Johnson, E., Evans, L., Smolen, A., Berley, N., Sullivan, P., & Keller, M. (2019). No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. *American Journal of Psychiatry*, 176(5), 376-387. doi:10.1176/appi.ajp.2018.18070881
- Kennis, M., Gerritsen, L., van Dalen, M., Williams, A., Cuijpers, P., & Bockting, C. (2020). Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis. *Molecular Psychiatry*, 25(2), 321-338. doi:10.1038/s41380-019-0585-z
- Kirsch, I., & Moncrieff, J. (2007). Clinical trials and the response rate illusion. *Contemporary Clinical Trials*, 28, 348-351. doi.org/10.1037/cns0000164
- Moncrieff, J. (2020a). "It was the brain tumor that done it!" Szasz and Wittgenstein on the importance of distinguishing disease from behavior and implications for the nature of mental disorder. *Philosophy, Psychiatry & Psychology*, 27(2), 169-181. doi:10.1353/ppp.0.0023.
- Moncrieff, J. (2020b). Not in our brains: On the complex relationship between biology and behavior. *Philosophy, Psychiatry & Psychology*, 27(3), 321-323. doi:10.1353/ppp.2020.0039.

- Read, J. (2022). Response to yet another defence of ECT despite the absence of robust efficacy and safety evidence. *Epidemiology and Psychiatric Sciences*, 31, e13. doi: S2045796021000846
- Read, J., & Bentall, R. (2010). The effectiveness of electroconvulsive therapy: A literature review. *Epidemiology and Psychiatric Sciences*, 19(4), 333-347. doi:10.1017/s1121189x00000671
- Read, J., Kirsch, I., & McGrath, L. (2019). Electroconvulsive Therapy for depression: A Review of the quality of ECT vs sham ECT trials and meta-analyses. *Ethical Human Psychiatry and Psychology*, 21(2), 64-103. doi.org/10.1891/EHPP-D-19-00014
- Read, J., & Moncrieff, J. (2022). Depression: Why drugs and electricity are not the answer. *Psychological Medicine*, doi.org/10.1017/S0033291721005031
- Rasmussen, K. (2009). Sham ECT studies in depressive illness. *Journal of ECT*, 25(1), 54-59. doi:10.1097/YCT.0b013e3181719b23
- Sackeim, H., Prudic, J., Fuller, R., Keilp, J., Lavori, P., & Olfson, M. (2007). The cognitive effects of ECT in community settings. *Neuropsychopharmacology*, 32(1), 244-254. doi:10.1038/sj.npp.1301180
- UK ECT Review Group. (2003). Efficacy and safety of ECT in depressive disorders. *Lancet*, 361, 799-808. doi.org/10.1016/S0140-6736(03)12705-5