# Carphology by A Fo Ben

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## DAMNING WITH FAINT PRAISE

Who knew that despite being first described in 1867, the neural pathways that underpin fainting are poorly understood? The Bezold–Jarisch reflex is a triad of apnoea, bradycardia and hypotension and also syncope. This cardioinhibitory reflex is speculated to be mediated by vagal sensory neurones (VSNs). Researchers used single-cell RNA-sequencing data and HYBRiD (a tissue clearing technique similar to the clarity method) to show VSNs that express neuropeptide Y receptor Y2 (NPY2R) predominately connect the heart ventricular wall to the area postrema within the medulla. Furthermore optogenetic activation of NPY2R VSNs triggers the classic syncope triad causing a mouse to faint, whereas photostimulation revealed a range of phenotypes reflected in clinical syncope, including reduced cardiac output, cerebral hypoperfusion, pupil dilation and eye-roll.

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## DISTRESSED GENES

Tabloid newspapers are infamous for printing misleading headlines that fill the front page, but then printing apologies in microscopic text buried inside days later. It is therefore important that the NEJM reports five boys with Duchenne's muscular dystrophy who had 'strikingly similar suspected unexpected serious adverse reactions' following adeno-associated virus (AAV) gene therapy. These children were enrolled in three separate trials aiming to deliver a shortened yet functional microdystrophin transgene. Symptoms started 3 to 6 weeks after receiving the AAV. All had severe proximal and distal limb weakness sufficient to stop them walking, as well as bulbar and respiratory weakness; three needed transient ventilatory support. All showed myositis, two with myoglobinuria, and three had myocarditis. Interestingly and importantly all five had similar *DMD* mutations – large overlapping deletions between exons 8 and 21. The transgene had introduced significant nonself epitopes, specific to this deletion. Prompt recognition allowed all gene-therapy studies to form a working group and prevent any further harm.

*N Engl J Med*. 2023;388(24): 2294–2296.

## HEADS OR TRIALS?

The open label study of a long-acting subcutaneous compound (risperidone plus TV-46000) met pre-defined endpoints of reducing relapse rates in people with schizophrenia vs oral risperidone. However this is not the study that we needed to see. A head-to-head of depot/long-term antipsychotics for efficacy and a longer term study of adverse effects are needed. For schizophrenia here, also read epilepsy. A randomised controlled trial run over 12 to 18 weeks with the primary end point of halving seizure frequency compared with placebo is no way to look at slowly emerging side effects in the medium to long term (such as metabolic syndrome, bone health); the low number of head-to-head studies in neurology as a whole is a scandal to which we have become accustomed.

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## BOSTON MORTALITY PARTY

Figure 1 adapted from Lancet. 2023;402 (10407):1065–1082.

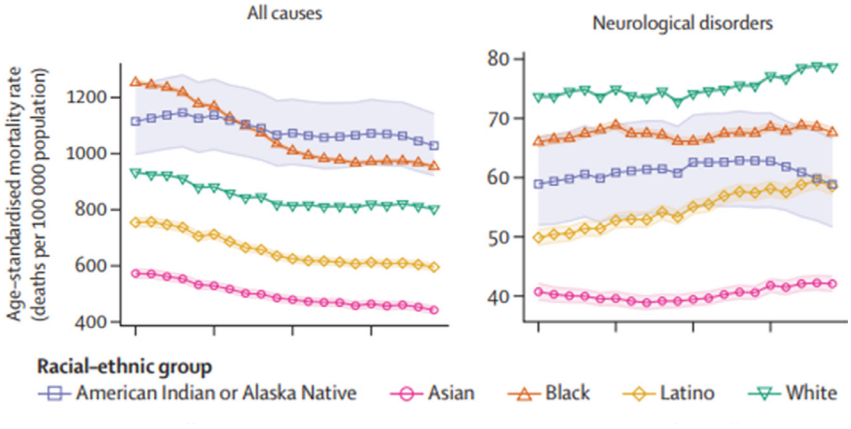


**Figure 1** A systematic review of the cause-specific mortality by county, race, and ethnicity in the USA, 2000–2019 makes for interesting reading. Neurological disorders were within the top five cause of death for all ethnicities except one (American Indian and Alaskan native). Neurological disorders are singular for having the highest estimated mortality among the White population – a trend not seen in any other cause of death.

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