of non-neuronal brain cell called astrocytes into neurons[16], a solution that holds great potential if it can be achieved in individuals with Parkinson's disease.

The authors also found that, despite losing the ability to perform their most important task – releasing dopamine – the axons of the substantia nigra dopamine neurons in the MCI-Park mice remain intact for an unexpectedly long time. These observations suggest that there might be a considerable window during which axonal degeneration could be prevented in the surviving substantia nigra neurons. By demonstrating a severe decrease in the function of these dopamine neurons before the loss of the actual neurons, this work also calls into question the widely taught principle that most dopamine neurons are dead by the time the disease symptoms begin. Instead, it supports evidence from post-mortem investigations that many of these neurons in people with symptoms of Parkinson's disease might still be living[17] and salvageable using future disease-modifying therapies.

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Particle physics

Electrons show the need for improved neutrino models

Noemi Rocco

Experiments on electrons interacting with atomic nuclei have shown that the models used to measure neutrino oscillations – and thereby possibly to understand the formation of the Universe – are less accurate than we thought. **See p.566**

Neutrinos are among the most elusive particles in the Universe – they can pass through sophisticated particle detectors without leaving a trace. And yet precise measurement of neutrinos is one of the highest priorities in particle physics, because it will provide crucial information about the Universe and how it was formed. It might also explain why the Universe seems to be mostly made of matter, even though the Big Bang should have created just as much antimatter. To obtain such measurements, experiments rely on theoretical models that predict how neutrinos interact with the nuclei of atoms. On page 566, Khachatryan *et al.*[1] (members of the CLAS and e4v collaborations) report evidence that these models are not as accurate as expected – suggesting that analysis of current and future experiments designed to characterize the properties of neutrinos might need to be rethought.

Neutrinos are difficult to detect because they interact weakly with the matter around them: unlike electrons, they have zero electric charge, so they don't experience a force when placed in an electromagnetic field; and because they are also very light, their mass cannot be measured directly. On the rare occasions when neutrinos do interact with their surroundings, they can produce particles known as charged leptons – either an electron, or one of two other particles known as muons and tau leptons, all of which have negative electric charge. The type of lepton produced depends on a property known as flavour, and so there are three flavours of neutrino: electron, muon and tau.

Around two decades ago, scientists realized that neutrinos change flavour as they move through space[2,3]. These changes are known as neutrino oscillations, and they can occur only because each flavour is a mixture – a quantum superposition – of three states that have different masses. This means that the oscillations can exist only if neutrinos have non-zero mass. But the idea that neutrinos have non-zero mass is inconsistent with the standard

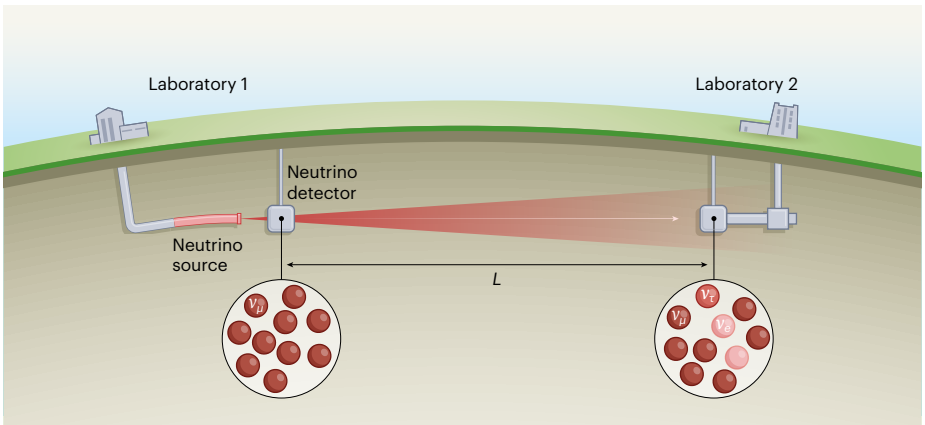

Figure 1 | An experiment to detect neutrino oscillations. There are three flavours (types) of neutrino – electron, muon and tau, denoted respectively ν_e, ν_μ and ν_τ – and neutrinos undergo oscillations in flavour as they move through space. The probability that neutrinos of one flavour that are produced at a source turn into neutrinos of another flavour depends on the energy of the neutrino beam and on properties known as the oscillation parameters. These parameters are estimated by measuring the energy distribution of the neutrino beam at a detector close to the source and at one a distance L away (where L is typically thousands of kilometres). Khachatryan *et al.*[1] showed that the models used to infer these energies fail to properly describe an analogous experiment on electrons, calling the accuracy of these models into question.

model of particle physics, the accepted model for describing the subatomic Universe. The discovery therefore marked a pivotal moment in the search for physics beyond this model.

Neutrino oscillations are studied using an approach known as a long-baseline experiment[4], in which neutrinos produced by a particle-accelerator complex are first detected a short distance away, and then at a detector far away (Fig. 1). These experiments are carried out at large facilities such as the forthcoming Deep Underground Neutrino Experiment (DUNE)[4], which will consist of two detectors: one near the source of the neutrino beam at Fermilab in Illinois, and the other 1,300 kilometres away in South Dakota. Long-baseline experiments are also under way at the Hyper-Kamiokande detector in Japan[5].

Current efforts at these facilities include Fermilab's NOvA experiment (https://novaexperiment.fnal.gov) and the T2K experiment (http://t2k-experiment.org) in Japan. Both experiments measure the properties of neutrino oscillations by monitoring how the distribution of neutrino energies changes as the particles propagate (Fig. 1). But these energies cannot be measured directly — instead, they must be reconstructed using information about the charged particles that are produced when the neutrinos interact with a target. In the case of NOvA and T2K, the targets are made of atomic nuclei, because this maximizes the number of interactions.

Khachatryan *et al.* tested the accuracy of the models used in such experiments to reconstruct neutrino energies. To do so, they exploited the observation that the probability of interactions between electrons and nuclei takes a similar mathematical form to the probability of interactions between neutrinos and nuclei, although the strength of the interactions is different. This promising strategy implies that models describing the probabilities of neutrino–nucleus interactions should also apply to those of electron–nucleus interactions, the properties of which are well known. So, using an electron beam with a known energy, Khachatryan *et al.* tested how accurately these models could reconstruct this energy using information about the electron–nucleus interactions.

Most of the events that occur when an electron hits a nuclear target involve the electron interacting with the target's protons and neutrons, collectively known as nucleons, after which a single nucleon is emitted. But other events are possible, including processes in which the electron couples to interacting nucleons, leading to two nucleon emissions. In this case, one of the nucleons hit by the electron is subsequently reabsorbed by the nucleus. The incoming electron can also excite the nucleon it hits, producing pions, which are the particles responsible for holding the nucleus together.

Khachatryan *et al.* used reconstruction models to simulate all these possibilities, and focused only on those with one electron, one proton and zero pions in the final state. Their crucial finding was that most of the energies obtained in this way failed to reconstruct the correct incident energy.

A key novelty of Khachatryan and colleagues' work is the use of semi-exclusive data, which means that one or more of the products of interactions were measured directly rather than inferred — in this case, the scattered electrons and charged particles knocked out from the nucleus. The value of the electron energy used in the authors' experiments is commensurate with that used for the neutrino beams in current and planned oscillation experiments. The results therefore indicate the need for substantial improvement in the accuracy of the way in which neutrino interactions are modelled. They also highlight the power of electron-scattering data in ensuring that these models achieve the level of accuracy needed to fully exploit the future discovery potential of these high-precision experiments.

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Genetics

From genes to health

Yukinori Okada & Qingbo S. Wang

The protein-coding portions of more than 450,000 individuals' genomes have been sequenced, and analysed together with the individuals' health data, revealing rare and common gene variants linked to various health-related traits. **See p.628**

To link genetic variations to human health, we need to collect genetic data and health-related information from as many individuals, and in as much detail, as possible. The principles of such association testing are long-standing[1], and the field of human genomics has expanded in scale and quality in the past few decades. On page 628, Backman *et al.*[2] report a new milestone. They have analysed the protein-coding parts of the genome — called the exome — of more than 450,000 individuals whose health and genetic data have been collected in the UK Biobank, identifying 12.3 million variants that lead to changes in the encoded protein, which are known as coding variants. The authors then tested these variants for associations with 3,994 health-related traits (health phenotypes) and found 8,865 such associations (Fig. 1). This work is on an unprecedented scale in terms of the number of participants and the quantity of genetic and clinical data gathered.

Initial analysis of data from the UK Biobank[3] included genetic information that was limited to common variants already known to occur in a relatively large proportion of individuals (for example, more than 1% of the tested population). However, such variants are probably only the tip of the iceberg of the total variation in the human exome. The use of whole-exome sequencing (WES) technology was the key to obtaining detailed information about exome variation.

In 2016, the Exome Aggregation Consortium[4] presented aggregated WES data for a group of more than 60,000 people, which was later expanded to include exome and genome data from more than 140,000 individuals[5]. These studies provided a systematic quantification of the biological impact of human genetic variants. However, the impact was not linked to specific phenotypes, because the data set lacked detailed clinical information, highlighting the value of the health records of the UK Biobank.

Previous analyses have also combined exome (or even whole-genome) data with detailed phenotypic data. For example, the DiscovEHR collaboration sequenced about 50,000 exomes[6], the Trans-Omics for Precision Medicine Program sequenced almost 54,000 exomes[7], and previous studies using the UK Biobank data analysed nearly 50,000 exomes[8] and more than 280,000 exomes[9]. However, the results of these previous analyses consistently indicated that it would be valuable to expand the sample sizes further. Indeed, Backman and co-workers demonstrate that, by increasing the sample size by less than 10-fold, about 20 times