explained by the ability of individual animals to keep previous actions in mind as short-term memory patterns.

The researchers performed QTL analysis, and found one genetic region that stood out as different between the various strains of mice; they named this region *Smart1* (short for spontaneous T-maze alternation QTL 1). In particular, animals that had one particular DNA sequence at *Smart1* (dubbed $Smart1^{CAST}$) were especially good at the exploratory task, and those with another ($Smart1^{B6}$) were especially poor.

Having identified this region, Hsiao and colleagues confirmed their findings from the high-throughput behavioural test using a similar but more-complex maze assay designed to test spatial working memory. In this assay, which used fewer animals, mice had to remember which arm of a maze they had visited on a first visit, and choose to visit the other arm to get a reward on a second visit (Fig. 1). Again, $Smart1^{CAST}$ and $Smart1^{B6}$ animals performed better or worse, respectively, than the group as a whole.

Next, Hsiao *et al.* examined gene-expression patterns across several brain regions in these two mouse strains. The most significant differences between the two were in the mediodorsal thalamus, in expression of a gene called *Gpr12* that is located in *Smart1*. This brain region is strongly connected to the prefrontal cortex, which is involved in higher-level cognitive functions such as working memory. The authors found that reducing expression of *Gpr12* led to poorer task performance in $Smart1^{CAST}$ mice, whereas overexpressing the gene improved the performance of $Smart1^{B6}$ animals.

Gpr12 encodes a protein belonging to a family known as orphan receptors, in which no ligand molecule that binds to and activates each receptor has been identified. *Gpr12* probably enhances the activity of mediodorsal thalamus neurons once they are engaged by external inputs (such as those from the prefrontal cortex). Indeed, Hsiao *et al.* found that patterns of neuronal activity in the mediodorsal thalamus became much more in-sync with those in the prefrontal cortex during those parts of the maze test when animals were presumably remembering where they had been on the previous maze run.

Hsiao and colleagues' work provides key evidence to reinforce the conclusions of the 2017 papers[1–3]. Their findings also indicate that coordinated thalamocortical activity patterns depend on the version of *Smart1* present: the more *Gpr12* is expressed from this region, the more thalamocortical coordination occurs and the better the performance of spatial working memory.

The discovery of this role for *Gpr12* could lead to the development of pharmacological agents that boost working-memory performance. However, it would be important to first determine the types of cortical activity pattern that are enhanced by thalamic *Gpr12*. For example, in tasks in which animals have to withhold actions while remembering a task-relevant piece of information[2,7,8], would we see the same type of effect?

It is also intriguing to speculate on what other types of cognitive function could be linked to genetic underpinnings using a QTL approach. The mediodorsal thalamus is known to be involved in switching between tasks[9,10]; could one find a simple and scalable behavioural test that could be used to assess this process and probe its genetic underpinnings?

Finally, to return to the comparison between natural and artificial systems, is the lack of a thalamus-like architecture in most artificial models of intelligence a missed opportunity? On the one hand, artificial recurrent neural networks require no such structure to maintain memory patterns or switch them across tasks. On the other, perhaps incorporating this biological inspiration into artificial-intelligence systems would enable us to expand their computational capabilities, power efficiency or both. It is exciting to think about the many possibilities ahead as we continue to draw biological inspiration from innovative work such as that of Hsiao and colleagues.

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Solar physics

Neutrino detection gets to the core of the Sun

Gabriel D. Orebi Gann

The first detection of neutrinos produced by the Sun's secondary solar-fusion cycle paves the way for a detailed understanding of the structure of the Sun and of the formation of massive stars. **See p.577**

On page 577, the Borexino Collaboration[1] reports results that blast past a milestone in neutrino physics. They have detected solar neutrinos produced by a cycle of nuclear-fusion reactions known as the carbon–nitrogen–oxygen (CNO) cycle. Measurements of these neutrinos have the potential to resolve uncertainties about the composition of the solar core, and offer crucial insights into the formation of heavy stars.

Neutrinos are tiny, subatomic particles. They were first postulated to exist by Wolfgang Pauli in 1930, to account for the energy that was apparently missing during β-decay, a process in which energetic electrons are emitted from an atomic nucleus. The presence of a massless particle that could carry any fraction of the energy from the decay would explain why the spectrum of emitted electron energies is continuous. Pauli's explanation for why neutrinos had never been observed was that they interact incredibly weakly with matter. Subsequent decades of research have yielded a wealth of information about Pauli's 'ghost particle', including the Nobel-prizewinning discovery that neutrinos do, in fact, have a mass[2–4], albeit one so small as to be beyond the reach of current measurements.

Fusion reactions in the Sun produce an astonishing number of neutrinos: roughly 100 billion solar neutrinos pass through each of your thumbnails every second. Because of the weakness of their interactions, they are barely deterred from their path even when they have to pass through the entire body of the Earth: cutting-edge experiments[5] (see also go.nature.com/36sktyj) have struggled to observe a difference in the measured neutrino flux between daytime and night-time, owing to the vanishingly small scale of this effect.

Neutrinos are therefore both challenging to observe and yet able to offer insights into

REF. 1

Figure 1 | The Borexino neutrino detector. The Borexino experiment detects light produced when solar neutrinos scatter off electrons in a large vat of liquid scintillator — a medium that produces light in response to the passage of charged particles. The Borexino Collaboration wrapped the detector in thermal insulation to control temperature variations in the detector. This helped the team to take the highly precise measurements needed to detect solar neutrinos produced by the Sun's secondary solar-fusion cycle[1].

otherwise unreachable regions of the Universe, such as distant supernovae or the interiors of stars. Energy produced in the centre of the Sun in the form of photons takes tens of thousands of years to escape, but a solar neutrino can escape the Sun and reach Earth in just eight minutes. This gives us a unique window into the core of this blazing star.

The Sun is powered by fusion reactions that occur in its core: in the intense heat of this highly pressurized environment, protons fuse together to form helium. This occurs in two distinct cycles of nuclear reactions. The first is called the proton–proton chain (or *pp* chain), and dominates energy production in stars the size of our Sun. The second is the CNO cycle, which accounts for roughly 1% of solar power, but dominates energy production in heavier stars[6].

The first experiment to detect solar neutrinos was carried out using a detector in Homestake Mine, South Dakota. This used measurements of *pp*-chain solar neutrinos to probe the Standard Solar Model (SSM), which describes nuclear fusion in the Sun. The surprising result from this experiment was that only approximately one-third as many neutrinos of the expected type (flavour) were detected[7].

A decades-long campaign of experiments followed, seeking to resolve this 'solar neutrino problem'. Nobel-prizewinning results from the Sudbury Neutrino Observatory in Ontario, Canada, eventually explained the deficit: the neutrinos were changing flavour between their production and detection[3]. The Borexino experiment at the Gran Sasso National Laboratory in Italy followed up this result with a full spectral analysis of neutrinos from many stages of the *pp* chain[8]. This analysis finally allowed the field to come full circle, reopening the possibility of using solar neutrinos as a means of probing the Sun's interior.

The Borexino Collaboration now reports another groundbreaking achievement from its experiment: the first detection of neutrinos from the CNO cycle. This result is a huge leap forward, offering the chance to resolve the mystery of the elemental composition of the Sun's core. In astrophysics, any element heavier than helium is termed a metal. The exact metal content (the metallicity) of a star's core affects the rate of the CNO cycle. This, in turn, influences the temperature and density profile — and thus the evolution — of the star, as well as the opacity of its outer layers.

The metallicity and opacity of the Sun affect the speed of sound waves propagating through its volume. For decades, helioseismological measurements were in agreement with SSM predictions for the speed of sound in the Sun, giving confidence in that model. However, more-recent spectroscopic measurements of solar opacity produced results that were significantly lower than previously thought, leading to discrepancies with the helioseismological data[9]. Precise measurements of CNO-cycle neutrinos offer the only independent handle by which to investigate this difference. Such measurements would also shed further light on stellar evolution.

The chief obstacles to making these measurements are the low energy and flux of CNO neutrinos, and the difficulty of separating the neutrino signal from sources of background signals, such as radioactive-decay processes. The Borexino experiment detects light produced when solar neutrinos scatter off electrons in a large vat of liquid scintillator — a medium that produces light in response to the passage of charged particles. A precise measurement of the energy and time profile of the detected light allows the scintillation caused by solar neutrinos to be differentiated from light resulting from other sources, such as radioactive contamination in the scintillator itself and in surrounding detector components.

The Borexino Collaboration carried out a multi-year purification campaign to ensure unprecedentedly low levels of radioactive contaminants in the scintillator. Even so, minor convection currents caused by temperature variations allowed radioactive contaminants to diffuse from the outer edges of the detector. The researchers mitigated this effect by establishing exquisitely fine control of thermal variations in the detector (Fig. 1), thus allowing them to achieve the extremely challenging

feat of detecting CNO neutrinos. The resulting measurements are not yet precise enough to resolve the question of solar metallicity, but they offer a path towards this objective.

Future experiments will seek to improve on the precision achieved by Borexino, by developing innovative methods to identify and reject background noise caused by radioactive contamination. In the meantime, the Borexino Collaboration's tremendous accomplishment moves us closer to a complete understanding of our Sun, and of the formation of massive stars, and is likely to define the goal in this field for years to come.

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Genetics

Neanderthal DNA raises risk of severe COVID

Yang Luo

A genetic analysis reveals that some people who have severe reactions to the SARS-CoV-2 virus inherited certain sections of their DNA from Neanderthals. However, our ancestors can't take all the blame for how someone responds to the virus. **See p.610**

A key part of tackling COVID-19 is understanding why some people experience more-severe symptoms than do others. Earlier this year, a segment of DNA 50,000 nucleotides long (corresponding to 0.002% of the human genome) was found to have a strong association with severe COVID-19 infection and hospitalization[1]. Zeberg and Pääbo[2] report on page 610 that this region is inherited from Neanderthals. Their results not only shed light on one reason that some people are more susceptible to severe disease, but also provide insights into human evolutionary biology.

DNA sequences that are physically close to one other in the genome are often inherited (linked) together. These blocks of DNA, known as haplotypes, therefore contain tightly linked variants — DNA sequences or nucleotides that vary between individuals in a population. For example, the COVID-19 risk haplotype described earlier this year[1] harbours variants across its entire 50,000-nucleotide span that are inherited together more than 98% of the time. Long haplotypes such as this could be a result of positive selection, maintained in our genomes because they contributed to our species' chances of survival and reproductive success. They could also be introduced as a result of interbreeding with archaic hominin species such as the Denisovans and Neanderthals.

Some 1–4% of the modern human genome comes from these ancient relatives[3]. Many of the surviving archaic genes are harmful to modern humans, and are associated with infertility and an increased risk of disease[4]. But a few are beneficial. Examples include the Denisovan-like version of a gene called *EPAS1* that helps modern Tibetans to cope with life at extremely high altitudes[5], a Neanderthal gene that increases our sensitivity to pain[6] and others that help us fend off viruses[7].

To investigate whether the COVID-19 risk haplotype might have been introduced from our ancient relatives, Zeberg and Pääbo compared the region with an online database of archaic genomes from around the world. They found the region to be closely related to that in the genome of a Neanderthal individual that lived in modern-day Croatia around 50,000 years ago, but it was not related to any known Denisovan genomes.

The authors next checked the prevalence of the Neanderthal-derived haplotype in the modern human population. They report that it is rare or completely absent in east Asians and Africans. Among Latin Americans and Europeans, the risk haplotype is maintained at a modest frequency (4% and 8%, respectively). By contrast, the haplotype occurs at a frequency of 30% in individuals who have south Asian ancestry, reaching as high as 37% in those with Bangladeshi heritage (Fig. 1).

The researchers therefore speculate that the Neanderthal-derived haplotype is a substantial contributor to COVID-19 risk in specific groups. Their hypothesis is supported by hospital data[8] from the Office for National Statistics in the United Kingdom, which indicates that individuals of Bangladeshi origin in the country are twice as likely to die from COVID-19 as are members of the general population (although other risk factors will, of course, contribute to these statistics).

Why has this haplotype been retained in some populations? The authors posit that it might be protective against other ancient pathogens, and therefore positively selected for in certain populations around the world[9]. But when individuals are infected with the SARS-CoV-2 coronavirus, the protective immune response mediated by these ancient genes might be overly aggressive, leading

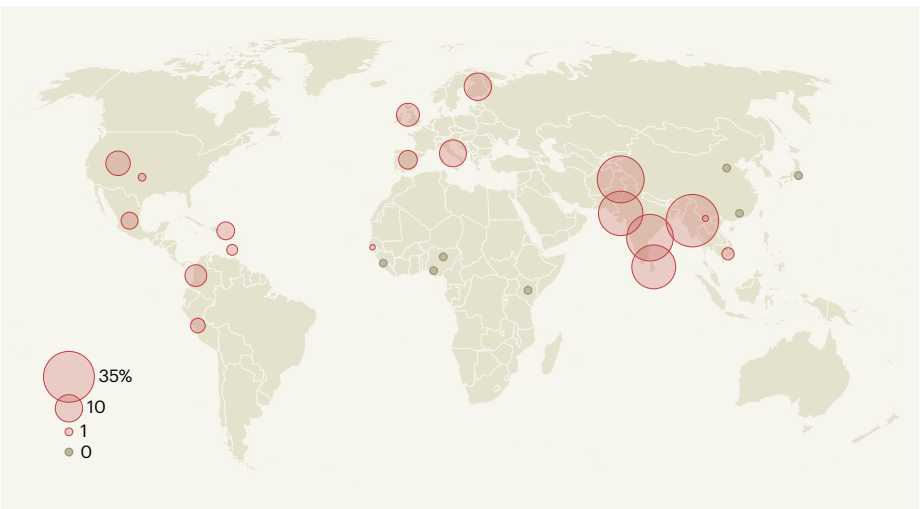

Figure 1 | Uneven global spread of a genetic risk factor for COVID-19. Zeberg and Pääbo[2] report that a long sequence of DNA that is associated with severe COVID-19 infection and hospitalization is derived from Neanderthals. The sequence is unevenly distributed across modern human populations. This map shows the frequency at which the risk factor is found in various populations from around the world. The sequencing data for these populations were gathered by the 1000 Genomes Project[10]. (Adapted from Fig. 3 of ref. 2.)