Conversely, they found that extracts of cortex from those affected by Alzheimer's had reduced REST-inducing activity compared with age-matched controls.

REST is a target of the Wnt–β-catenin signalling pathway[8]. Lu *et al.* showed that REST can be induced by Wnt-3a and Wnt-7a (two proteins from the Wnt family), and that a Wnt-receptor antagonist partially inhibits REST induction. These results suggest that stress can increase Wnt signalling, which, in turn, induces REST expression. It remains to be determined whether Wnt is elevated in only some parts of the brain to influence REST — the authors report evidence of Wnt signalling in the hippocampus and the frontal cortex, but not in the cerebellum, for example. The question of whether the observed changes in Wnt signalling originate from neurons or from other cells in the brain also deserves further investigation.

Lu and colleagues went on to show that loss of nuclear REST is associated with a substantial increase in the expression of genes implicated in apoptosis and Alzheimer's pathology in both the least severe (Alzheimer's disease 1, AD1) and most severe (AD2) forms of the disease. Unexpectedly, however, they observed that another set of genes targeted by REST — those involved in synaptic transmission and other functions of neural junctions — initially show increased expression in AD1, but then reduced levels in AD2. It is plausible that the increased expression of these genes in AD1 is a compensatory mechanism to maintain neuronal homeostasis. Further analysis of gene expression in specific subtypes of neural cells should help to clarify precisely how the observed gene-expression patterns arise.

The authors' observations also raise the question of why gene-expression profiles differ in AD1 and AD2. Further characterization of the environment of the affected genes' chromatin (the DNA–protein complex in which genetic material is organized) and of the binding of other transcription factors in the genes' regulatory regions in the brains of the young, the aged, and those with AD1 or AD2, should provide greater insight into this matter.

Excitingly, this study provides the first detailed investigation of molecular markers in the brain that differentiate between populations of the young, the aged and those with Alzheimer's. Furthermore, by showing that ageing in the brain might be associated with the activation of a specific stress-response program, it implies that sustained maintenance of this program confers protection from neurodegeneration. Indeed, all the healthy centenarians studied in the research showed uniformly high levels of REST.

Could therapeutically stimulating nuclear REST activity in the brain prevent Alzheimer's and other degenerative diseases? On the basis of Lu and co-workers' results, one strategy would be to activate Wnt signalling in aged individuals. However, such activation is also implicated in the development of various cancers[9], and so this approach would probably require careful targeting of Wnt activation in the brain. Alternative strategies include finding either Wnt-independent REST activators or small molecules that prevent the export of REST from the nucleus. A deeper understanding of the molecular mechanisms that govern REST activation in the ageing brain will be crucial for such efforts to be successful. ■

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LOW-TEMPERATURE PHYSICS

Chaos in the cold

A marriage between theory and experiment has shown that ultracold erbium atoms trapped with laser light and subjected to a magnetic field undergo collisions that are characterized by quantum chaos. SEE LETTER P.475

PAUL S. JULIENNE

The use of magnetic fields to manipulate the interactions of ultracold atoms at temperatures below one microkelvin has allowed the experimental and theoretical study of a plethora of exotic phenomena in quantum physics[1]. The report by Frisch *et al.*[2] on page 475 of this issue adds an entirely new twist to this work. Until now, such research has mainly used simple atoms that have relatively simple interactions. Frisch and colleagues worked instead with a complex atomic species, erbium, and combined theory and experiment to demonstrate the signature of quantum chaos in the collisions between two erbium atoms. The results offer the prospect of exploring new avenues of ultracold physics and chemistry using complex atomic and molecular species.

In their study, Frisch *et al.* used a tightly focused laser to trap samples of around 100,000 erbium (Er) atoms in their lowest-energy quantum state at a temperature of about 400 nanokelvins. The samples consisted either of bosonic isotopes (^{168}Er or ^{166}Er), which have integer spin, or of a fermionic one (^{167}Er), which has half-integer spin. They tuned an applied magnetic field to a fixed value between 0 and 7 millitesla and counted the number of atoms remaining after holding them in the trap for 400 milliseconds. The authors found that the number of atoms left in the trap depended strongly on the particular value of the magnetic field selected. Such atom losses are well known in cold-atom physics, and are used to locate features known as Feshbach resonances, which occur when the total (nearly zero) energy of two colliding atoms matches the magnetically tunable energy of a bound diatomic molecular state (Er_2). Tabulating the magnetic-field values at which losses exist pinpoints the 'positions' of the resonances, from which the dynamics of the underlying collisions can be probed.

Frisch *et al.* found that the number of resonances in their system is surprisingly large, much larger than obtained with alkali-metal species such as lithium, rubidium or

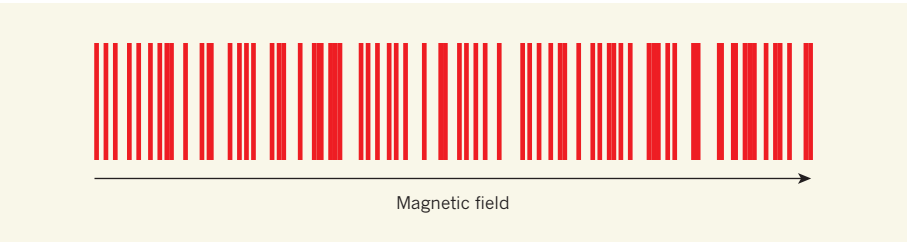

Figure 1 | A barcode of resonances. The lines mark the different values of an applied magnetic field at which erbium atoms from a trapped sample studied by Frisch *et al.*[2] show increased loss from the trap. The distribution of spacing between adjacent lines, which locate features known as Feshbach resonances, indicates that collisions between two atoms have quantum chaotic behaviour.

caesium (Cs). They provide theoretical models that connect this behaviour with chaotic quantum dynamics of the collisions. Because alkali-metal atoms such as Cs have a simple atomic structure (they have zero electronic orbital angular momentum), the resonances of colliding Cs atoms are spaced relatively far apart as a function of increasing magnetic field, and are characterized by simple quantum numbers. By contrast, an Er atom has a complex atomic structure that gives it a total electronic orbital angular momentum of five. Therefore, colliding Er atoms have many more resonances than their Cs analogues, and they are 'mixed' — that is, they are no longer described by simple quantum numbers.

To explain the nature of their measured resonance spectrum (Fig. 1), as well as that calculated by their model, Frisch *et al.* borrowed a tool known as random matrix theory from earlier work in nuclear and other fields of physics. By assuming that the various interactions of their system are described by the parameters of this theory, they could reproduce the average spacing between successive resonances. They found that the distribution of spacing for ^{168}Er or ^{166}Er bosons was much closer to one that corresponds to chaotic dynamics, known as a Wigner–Dyson distribution, than to the Poissonian distribution that characterizes regular, non-chaotic dynamics. The ^{167}Er fermions, which also have nuclear spin, showed an even denser set of resonances than the bosonic isotopes, but the authors have not yet analysed this set in detail because of its greater complexity. A study that was reported[3] this year measured similarly dense sets of resonances in systems of cold bosonic and fermionic isotopes of dysprosium (Dy).

Why are these results significant? Let us consider what is special about cold collisions. Because cold atoms move slowly, on average more than 10,000 times more slowly than atoms at room temperature, the Heisenberg uncertainty principle ensures that the uncertainty in their position is large. The colliding atoms no longer behave like particles, but take on wave-like character, with a wavelength that is inversely proportional to their velocity. These wavelengths can become large, one micrometre or more, much larger than the sub-nanometre length of a chemical bond. In this case, collisions become simple and are characterized by a parameter known as the scattering length.

Part of the power and beauty of cold-atom physics is that the scattering length can be made to take on any value by tuning a magnetic field close to a Feshbach resonance[1]. Its value controls the two-body, few-body and many-body physics of ultracold quantum matter. Thus, controlling the field makes the system dance to our tune. Previously, the Feshbach resonances used for such control have been isolated resonances that vary with the field and the atomic kinetic energy in a simple and well-understood way. Now, cold-atom researchers have to figure out how to understand the scattering length associated with a dense set of chaotic resonances such as that observed by Frisch and colleagues. The variation with field and kinetic energy will be more complex than previously encountered. The same is true of the atom-loss processes that are associated with such resonances and that determine the lifetime of a cold atomic system.

Another reason for working with Er is that its magnetic dipole moment is seven times larger than that of alkali-metal atoms. The dipole moment for Dy is even larger. Such large dipole moments, which result in a long-range interaction between pairs of dipoles, could enable the realization of some of the rich variety of phenomena predicted for an ensemble of cold dipoles[4,5]. It will now be necessary to understand the interplay between the dense set of resonances and the long-range dipolar interactions.

Finally, cold molecules — which have rotational, vibrational and other internal degrees of freedom — are expected to have much denser resonance spectra than Er or Dy atoms. Work is also being done to make systems of cold polar molecules, which can have much stronger dipolar interactions than atoms and exhibit a larger range of dipolar phenomena. Therefore, Frisch and colleagues' study is but a prelude to the interesting work that is to come on cold molecular systems, the resonances of which may have quite long lifetimes[6]. We can anticipate that the considerable body of work carried out on the internal relaxation and chemical reactions of excited molecular complexes[7,8] will come into play when chaos turns up at the heart of cold molecular collisions. ■

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OSTEOARTHRITIS

The zinc link

Increased influx of zinc into chondrocytes — the cells that make up cartilage — has been found to activate matrix-degrading enzymes that cause the destruction of cartilage in osteoarthritis.

VIRGINIA BYERS KRAUS

The classic wound-healing response consists of a cascade of events that can be arbitrarily divided into four phases: blood clotting and bleeding cessation; inflammation; cellular proliferation; and wound remodelling with scar-tissue formation[1]. Osteoarthritis, the most prevalent and recalcitrant form of arthritis, has been proposed to be the result of a chronic wound-healing response in joints[2]. Articular cartilage, which is the tissue that lines joint surfaces, has no blood vessels, so wound healing at these sites begins with the inflammatory phase. This phase is characterized by an extensive auto-debridement response, in which dead or damaged tissue is removed. Writing in *Cell*, Kim *et al.*[3] provide compelling data that help to unravel the mechanistic details of this 'clean-up' phase, how it can progress to osteoarthritis, and the role of zinc in this process.

Second only to iron in trace-element abundance in the human body, and well known as a component of wound-healing salves, zinc has long been implicated in wound healing through promoting auto-debridement, anti-infective activity and the re-formation of skin[4]. Now, however, Kim *et al.* show that zinc has a deleterious effect on cartilage through its ability to upregulate enzymes responsible for cartilage degradation in a process that bears a striking resemblance to auto-debridement during wound healing.

The authors found that expression of the zinc-transporting protein ZIP8 increased *in vitro* in chondrocytes — the cells that make up cartilage — in response to IL-1β, an inflammatory cell-signalling molecule that is a key mediator of osteoarthritis. Overexpression of ZIP8 in chondrocytes led to increased levels of intracellular zinc and of zinc-dependent metalloprotease matrix-degrading enzymes that have been implicated in osteoarthritis, including MMP3, MMP9, MMP12, MMP13 and ADAMTS5. These metalloproteases are key mediators of the auto-debridement phase of wound healing: they regulate inflammation;