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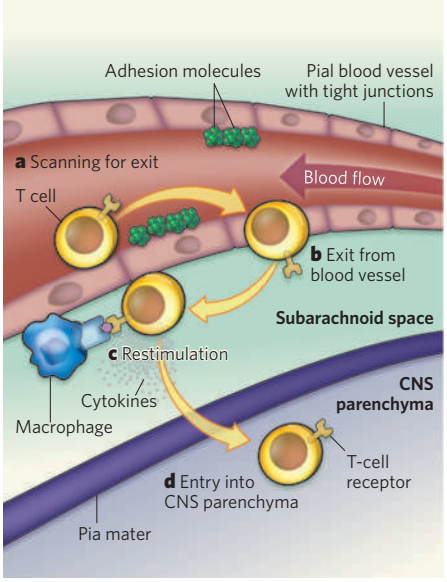

Figure 2 | The second wave. Bartholomäus and colleagues[5] use two-photon imaging to visualize the accumulation of T cells in the CNS after activation of the blood–brain barrier. T cells roll along, and then adhere to, the inner wall of activated cerebral blood vessels (expressing adhesion molecules) that lie next to the pia mater — the inner membrane lining the surface of the brain and spinal cord. **a**, T cells crawl along the vessel wall, mainly against the direction of blood flow, presumably in search of a suitable exit site. **b**, After crossing into the subarachnoid space, these cells move along the outer wall of the blood vessel, where they come into contact with local resident macrophages, which present them with specific antigen. **c**, Antigen recognition results in T-cell restimulation and production of abundant cytokines. **d**, T cells then detach from the blood-vessel surface and enter the CNS parenchyma, where they cause tissue damage.

patrolling the subarachnoid space, where crucial restimulation of T cells takes place[10,11] after their initial encounter with antigen in the periphery. In the case of EAE, Reboldi and colleagues[4] conclude that inflammatory cells invade the CNS in two waves. The first wave is through the choroid plexus, leading to T-cell restimulation by antigen in the subarachnoid space, early CNS inflammation and stimulation of the blood–brain-barrier vasculature (Fig. 1)[12]. Activation of the blood–brain barrier then initiates the second wave: a large-scale inflammatory-cell invasion of the CNS parenchyma, with resulting motor weakness[4,13].

Bartholomäus *et al.*[5] provide a dramatic account of the initial moments of this second wave of CNS inflammatory-cell entry. They study an adoptive-transfer model of EAE in which rats are injected with activated anti-myelin T cells, developing signs of the disease three to four days later. Intravenous injection of activated T cells stimulates the cerebral blood vessels, enabling T cells to bind[14], and obviating the need for the first wave of T-cell entry across the choroid plexus. Bartholomäus *et al.* use sophisticated two-photon imaging to visualize labelled T cells as they move along and exit the blood–brain barrier's pial vessels on the surface of the spinal cord.

The authors witness a fantastic exhibition of lymphocyte gymnastics (see the movies in Supplementary Information to ref. 5). Disease-causing T cells first adhere to the inner walls of the pial vessels and then crawl in continuous contact with activated endothelial cells, most often in the opposite direction to the blood flow. Crawling allows these cells to identify vascular exit sites[15] (Fig. 2a). After crossing the blood-vessel wall (Fig. 2b), the lymphocytes move along the outer surface of the vessel, encountering an array of antigens displayed by antigen-presenting cells, including macrophages. If the T cell recognizes a specific antigen, it remains in prolonged contact with the antigen-presenting cell and produces abundant growth or inflammatory factors (cytokines) (Fig. 2c). Last, the cells detach from the outer surface of the blood vessel and enter the spinal cord, travelling most often alongside penetrating vessels (Fig. 2d). In the spinal cord, they initiate tissue injury. Bartholomäus *et al.* additionally show that activated T cells that are reactive to non-brain antigens also accumulate in, and crawl along, the inner walls of spinal-cord vessels. This finding shows that reaction against CNS antigens is not required for intravascular crawling, which seemed relatively selective for spinal-cord vessels in the authors' studies. However, extravascular restimulation with antigen is required for lymphocyte entry into the CNS parenchyma.

Bartholomäus and colleagues' work[5] is replete with such interesting concepts and findings that its careful perusal will undoubtedly yield many more insights. This coherent molecular close-up of the first steps in CNS autoimmunity brings with it the promise of new therapeutic strategies. ■

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EARTH SCIENCE

Lasting earthquake legacy

Tom Parsons

Earthquakes occur within continental tectonic plates as well as at plate boundaries. Do clusters of such mid-plate events constitute zones of continuing hazard, or are they aftershocks of long-past earthquakes?

Early on the morning of 16 December 1811, an earthquake of about magnitude 7 shook the centre of the United States around a small town on the Mississippi called New Madrid. By 7 February 1812, it had triggered three more shocks of similar magnitude[1]. The earthquakes broke a set of faults along the Arkansas, Missouri and Tennessee state boundaries, apparently reactivating an ancient rift in the interior of a continental tectonic plate[2].

On 31 August 1886, a magnitude-7 shock struck Charleston, South Carolina; low-level activity continues there today. One view of seismic hazard is that large earthquakes will return to New Madrid and Charleston at intervals of about 500 years[3]. With expected ground motions that would be stronger than average[4], that prospect produces estimates of earthquake hazard that rival those at the plate boundaries marked by the San Andreas fault and Cascadia subduction zone[3,4]. The result is two large 'bull's-eyes' on the US National Seismic Hazard Maps (Fig. 1) — which, for example, influence regional building codes and perceptions of public safety.

But what if earthquakes are not always going to return to mid-continental locations such as New Madrid or Charleston? From data on activity at New Madrid and elsewhere in the world, Stein and Liu (page 87 of this issue)[5] identify a global inverse correlation between aftershock duration and tectonic deformation rates. They argue that localized high rates of mid-continental activity, taken to reflect steady-state plate deformation, may instead be very long-lived aftershock sequences.

As first noted by Omori[6] in 1894, and now known as Omori's law, aftershock rates

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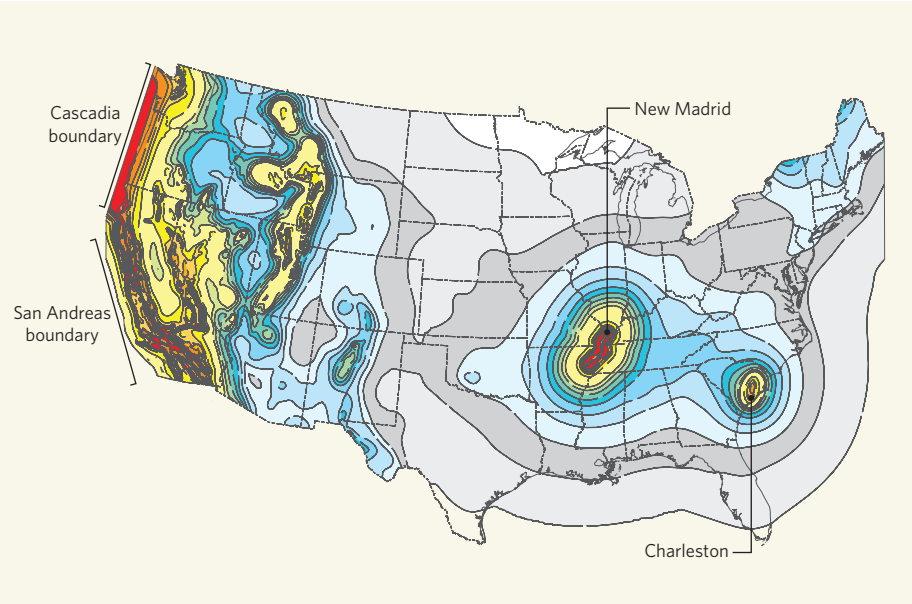

Figure 1 | Probabilistic assessment of seismic hazard in the United States[3]. Warm colours show regions with the highest probability of strong shaking, which tend to be located near, or influenced by, major plate boundaries. Earthquake clustering in mid-continental areas such as New Madrid and Charleston is here interpreted to reflect continuing deformation sufficient to produce frequent large earthquakes. This expectation, combined with the anticipated ground response, produces hazard estimates that rival those for plate-boundary zones on the west coast. Stein and Liu[5], however, suggest that low-level, mid-continental seismic activity can be attributed to a long-lived sequence of aftershocks.

are highest immediately after a mainshock, and then decay as a function of inverse time (Fig. 2). Stein and Liu[5] demonstrate that aftershocks decay very slowly where there is little tectonic deformation, and can persist for hundreds of years. By contrast, aftershock rates at fast-deforming plate boundaries return to the background level within about ten years.

Rate-and-state friction theory holds that fault failure depends on competition between initially very slow slip speed (rate) and the evolving duration (state) of a population of contact points in a fault. Stein and Liu's observations confirm a major prediction of that theory — that the aftershock decay period on a fault should depend directly on the rate at which tectonic stress accumulates[7]. Declining aftershock sequences at New Madrid and Charleston, along with little steady-state deformation, would mean that earthquake hazard rates are declining as well.

We have independent methods of assessing whether plate deformation is continuing. On the one hand, palaeoseismology — a kind of forensic seismology that reads geological clues left by prehistoric earthquakes — has been used to interpret quake clusters that occurred around AD 900 and AD 1450 at New Madrid[8]. When combined with the 1811–12 series, the upshot of this analysis was the estimate of a 500-year recurrence interval used for hazard mapping[3]. On the other hand, space geodesy — the use of a space-based reference frame to monitor current crustal movements — reveals present-day deformation rates in the New Madrid zone that are indistinguishable from those of the rest of the continental interior, and that have been interpreted as New Madrid shutting down[9]. Digging deeper into the palaeoseismic record indicates temporal earthquake clusters that are followed by millennia of quiescence[10], a finding that reconciles these contrasting observations if we are now entering a quiet period.

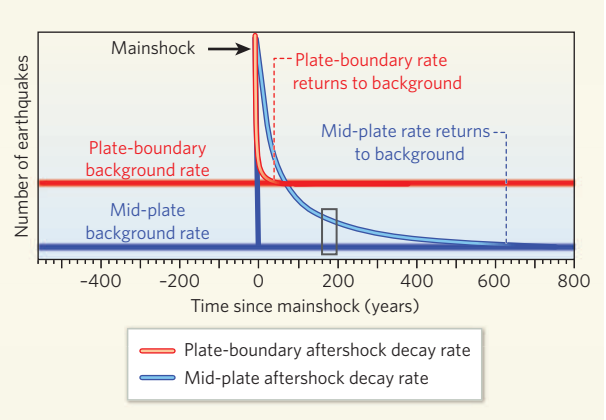

Figure 2 | Comparison of aftershock decay rates from plate-boundary and mid-plate regions. Mainshocks cause temporarily heightened earthquake rates of a duration controlled by the rates of tectonic deformation[5]. The black box shows the modern instrumental observation window on a long-lived decay sequence of mid-plate aftershocks. That window has been open for only about 40 years, illustrating the difficulties in distinguishing aftershocks from the lower, steady-state background rate of earthquake occurrence.

This is where geological time versus human time comes in. Meteorologists have the benefit of having watched hundreds of seasonal cycles to support their weather forecasts. Earthquake forecasters, however, have not yet witnessed a complete seismic cycle in slowly deforming continental interiors anywhere on Earth. The task is akin to predicting a full-year's weather based on watching one week in January. Stein and Liu's study[5] inevitably suffers from this problem; it is difficult to accurately calculate a long aftershock decay trend from a brief observation time. A limited view of earthquake history can actually be dangerous: despite the huge shocks that recently caught many by surprise in Sumatra and in Wenchuan, China, there is still a tendency to place undue emphasis on known past events in hazard assessments when trying to see the future.

A better understanding of mid-continental seismicity, one that avoids excessive influence from events in the recent past, will require that historically unbroken crustal weak points are not overlooked. Fault mapping and palaeoseismology at unconventional locations may be required to find out if places such as New Madrid and Charleston are special. At the same time, we must discriminate between the signals of steady-state deformation and the slowly fading legacy of historical earthquakes.

The large uncertainties arising from our brief glimpse into mid-continental earthquake cycles are unavoidable. Forecasters will thus have to follow multiple possibilities, including those with Omori-law time-decaying hazard estimates, through a logic-tree structure. With that approach, there is the prospect of arriving at a practical solution that properly balances the available resources for earthquake mitigation and the distribution of earthquake-resistant building structures in mid-continental regions. ■

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