of contact with the outside world. The effects on their brains, it turned out, were substantial.

Structural MRI performed by neuroscientists at the Max Planck Institute for Human Development before and after the trip showed anatomical changes to the dentate gyrus, a region of the brain that feeds information into the hippocampus and is associated with learning and memory; the crew members’ dentate gyriuses had shrunk by an average of around 7 percent.10 The crew members also had reduced blood levels of brain-derived neurotrophic factor (BDNF), a protein involved in stress regulation and memory, and they performed worse on tests of spatial awareness and attention than they had before they left.

The participants in this study were contending with more than just social isolation during their expedition, making it hard to know whether the observed brain changes are linked to lack of social contact as opposed to circadian disruption or some other aspect of their experience. But researchers studying social isolation and loneliness in the general population are also beginning to document differences in brain structure that could help reveal biological mechanisms at play. (See illustration below.)

Surveys already suggest that many people have felt increasing loneliness since the pandemic began.

While distinguishing between loneliness and social isolation is impossible in animal studies, these kind of manipulative experiments offer a unique insight into effects of isolation on the brain, says Monica Zelikowsky, a neuroscientist at the University of Utah School of Medicine. Mouse work she carried out while a postdoc at Caltech, for example, revealed a previously unknown role for Tac2, a signaling neuropeptide implicated in diverse cognitive functions, in mediating the behavioral effects of isolation.11

The peptide was highly expressed across broad regions of the brain in mice that had been housed alone for several weeks, the team found, and a molecule called Tac2 normally binds to. The findings suggest that Tac2 may be involved in regulating some of the effects of long-term isolation, rather than immediate stress induced by separation from companions, Zelikowsky notes. She adds, however, that there’s still a lot about the neuropeptide the team doesn’t know, including how it may interact with hormones involved in the stress response and whether it functions in the same way in humans.

One area where animal studies and observational research in humans may be starting to align is the link between isolation and inflammation—a response that can have negative effects on cognitive function as well as on other processes throughout the body. For example, more than a decade of animal work has shown increased circulation of inflammatory signaling molecules such as interleukin-6 in isolated mice, and a recent meta-analysis of more than two dozen human-focused papers on the topic noted that studies of people experiencing loneliness consistently reported increased blood concentrations of this same cytokine. The meta-analysis also found that social isolation was primarily linked to higher levels of C-reactive protein (CRP) and fibrinogen, two molecules involved in inflammatory responses in mice and humans.12

Panfoot, a coauthor of one of the studies included in that meta-analysis, says that the picture starting to emerge from this line of research is that social isolation and loneliness have distinct but closely related effects on inflammatory responses. Her study found that social isolation was associated with higher levels of CRP and fibrinogen, while loneliness was associated with lower insulin-like growth factor-1, a molecule that helps inhibit inflammation. “Both isolation and loneliness were linked to inflammation,” she says, “but while social isolation was linked to inflammatory markers themselves, for loneliness it was related to a pathway that involved how much those inflammatory responses are allowed to happen, or are inhibited from happening.”

Like research on any potential health risk, studies of social isolation still struggle to connect the dots between observations and concrete biological outcomes. Human studies can only reveal correlations, and experimental animal research “can show you that pathways can work in principle, but it doesn’t show they operate like that” in practice, says Steptoe. Nevertheless, research so far has helped to flesh out neuroscientists’ understanding of the sorts of factors involved in