field-based estimates of carbon losses in logging concessions in Borneo[8] were as much as six times lower than those derived from satellite data.

Such discrepancies could be caused by a mismatch between the areas studied using the two methods, by incomplete removal of plantation areas from the satellite data or by methodological biases. A validation strategy that includes site-specific field data could be helpful for understanding and reducing the discrepancies. Geo-referenced information on carbon stocks in secondary, old-growth and logged forests is increasingly available from meta-analyses and studies of networks of forest plots[4,6,9,10]. We suggest that a validation procedure that involves more integration of satellite- and ground-based data is necessary, and would increase the chances that estimates of carbon uptake made with Heinrich and colleagues' approach will be used by policymakers.

The uptake of carbon that occurs during regrowth of degraded and secondary forests is considered to be one of the foremost ways in which climate change can be mitigated naturally. However, this process is under pressure. Forest degradation is often a precursor of deforestation[11], and many secondary forests are cleared within one or two decades[12]. Moreover, the contribution of regrowth to forest carbon stocks is small in regions in which degradation is an integral part of the current land use, for example in forestry concessions[10] or areas where shifting cultivation — a rotational agricultural system in which plots are farmed on a temporary basis — is practised.

But there is another crucial point to keep in mind: carbon uptake by regrowing forests cannot fully offset the losses incurred by the high rates at which tropical forests are being degraded and converted to agricultural land, pasture and mines[13] — as Heinrich and colleagues' study confirms. Substantially reducing tropical deforestation would therefore contribute much more to climate-change mitigation than would forest regrowth. Avoiding deforestation, particularly that of old-growth forests, should thus be a high priority for policymakers — not only to increase carbon storage, but also to protect the rich biodiversity of these ecosystems.

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The authors declare no competing interests.

Neuroscience

How loss of social status affects the brain

Alexander Z. Harris & Nancy Padilla-Coreano

Dominant mice that are forced to unexpectedly give way to subordinates in a rigged test lose social status and miss opportunities for pleasure. These effects are due to changes in a neuronal circuit that involves the brain's 'anti-reward' centre.

Loss of social status is a risk factor for a person developing depression[1]. This propensity seems to be evolutionarily conserved, because subordination leads to traits associated with depression — such as social avoidance and decreased motivation — in several species[2–4]. However, the biological underpinnings of the phenomenon have remained unknown. Writing in *Cell*, Fan *et al.*[5] unveil a mechanism for how the loss of social status changes pleasure-seeking and coping behaviours in mice.

In 2011, the group that performed the current study demonstrated that position in the social hierarchy determines which mouse will defer when two are placed in a narrow tube, with room to pass only when one retreats out of the tube[6]. In the current work, Fan and colleagues blocked the exit behind the subordinate mouse — this rigged the competition so that the dominant mouse was forced to back down and lose (Fig. 1).

After just four days of repeated loss to a subordinate, the formerly top-ranked mouse behaved submissively in competitions for resources, suggesting a lowering of their social rank. They were also more passive than control mice (which walked through a tube without an opponent) when placed in a stressful environment, indicating a change in coping style. Unlike control mice, they showed little preference for sweetened water — a sign that their ability to process pleasure was impaired. These outcomes did not emerge when the top-ranked mouse lost to a higher-ranked mouse from a different cage, suggesting that it was

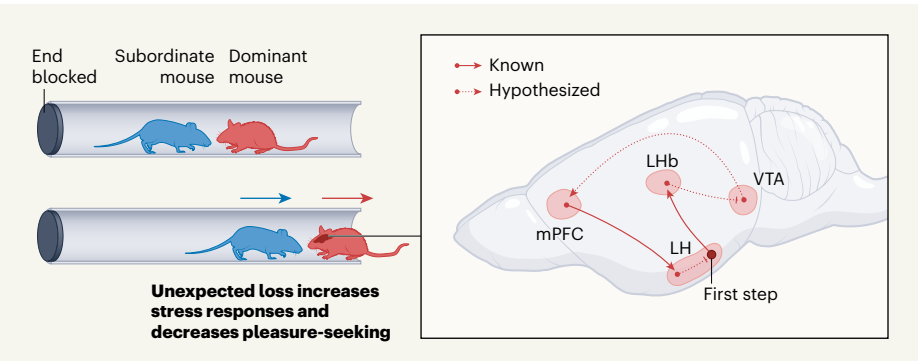

Figure 1 | A neural circuit underlying the effects of social-status loss. When mice of different social ranks are placed in a narrow tube, the subordinate mouse typically defers, retreating to let the dominant mouse past. Fan *et al.*[5] blocked the end of the tube behind the subordinate mouse, so that the dominant mouse had to defer. Repeated unexpected losses by the dominant mouse led to increased stress responses and decreased pleasure-seeking behaviour. The authors find that these behaviours are related to increased activity in the brain's lateral hypothalamus (LH), which signals to the lateral habenula (LHb) — the brain's 'anti-reward centre' (first step marked for navigation). This, in turn, decreases activity in the medial prefrontal cortex (mPFC), perhaps by inhibiting the release of dopamine from the ventral tegmental area (VTA). Signalling from the mPFC to the LH generates a feedforward loop that exacerbates the behaviours.

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From the archive

Examining Saturn's rings, and Charles Darwin shares observations about place recognition by horses and cats.

50 years ago

A radar scan ... has produced the surprising suggestion that Saturn's rings may be composed of chunks of solid rock, and not of dust, gas or ice particles, as widely believed. The scan ... produced much stronger signals from the rings than expected. The echoes suggest that the material in the rings has rough, jagged edges, and that the chunks are probably at least a metre across.

From *Nature* 16 March 1973

150 years ago

As several persons seem interested in Mr. Wallace's suggestion that animals find their way home by recognising the odour of the places which they have passed whilst shut up, you may perhaps think the following little fact worth giving. Many years ago I was on a mail-coach, and as soon as we came to a public-house, the coachman pulled up for the fraction of a second. He did so when we came to a second public-house, and I then asked him the reason. He pointed to the off-hand wheeler, and said that she had been long completely blind, and she would stop at every place on the road at which she had before stopped. He had found by experience that less time was wasted by pulling up his team than by trying to drive her past the place, for she was contented with a momentary stop. After this I watched her, and it was evident that she knew exactly, before the coachman began to pull up the other horses, every public-house on the road ... I think there can be little doubt that this mare recognised all these houses by her sense of smell. With respect to cats, so many cases have been recorded of their returning from a considerable distance to their homes, after having been carried away shut up in baskets, that I can hardly disbelieve them ... Now, as far as I have observed, cats do not possess a very acute sense of smell, and they seem to discover their prey by eyesight and by hearing.

Charles Darwin

From *Nature* 13 March 1873

the unexpected nature of the loss that caused the changes.

Which neuronal circuits could mediate this change? A brain region called the medial prefrontal cortex (mPFC) encodes social status in various species[7–9], and manipulating the activity of neurons that project from the mPFC to the brain's hypothalamus can alter winning behaviour and social status in mice[8]. Neurons in the lateral hypothalamus, in turn, project to a region called the lateral habenula (LHb), and Fan *et al.* found that inhibiting this circuit prevented the negative behavioural outcomes of the forced-loss experiment.

The LHb is known as the anti-reward centre, because it responds to aversive stimuli and to outcomes that are less rewarding than expected[10]. Fan *et al.* found that losing to a subordinate (but not a high-ranking mouse) activated LHb neurons. LHb neurons inhibit dopamine-releasing neurons in a region called the ventral tegmental area (VTA), which is involved in reward processing[10]. Thus, inhibition of dopamine neurons probably contributed to the reduced preference for sweetened water observed by Fan and colleagues in mice that lost social status. However, more work is needed to confirm this possibility. Moreover, because pleasure-seeking is a complex process that includes motivation, enjoyment and forming accurate expectations, future studies should determine which aspects of pleasure are disrupted by loss of social status.

In addition, the authors showed that activation of LHb neurons led to inhibition of neurons in the mPFC. LHb neurons do not make direct contact with the mPFC, but the authors hypothesized that the VTA acts as a node between these two regions. Together, the findings indicate that a loop circuit between the mPFC, the hypothalamus and the LHb regulates downward social mobility and the depression-like behaviours that can subsequently emerge.

Across species, when individuals are repeatedly exposed to an inescapable aversive situation, they lose the capacity to escape from other, avoidable aversive situations — a pattern of behaviour known as learned helplessness[11]. It is notable that, after four days of forced loss, formerly dominant mice exert less resistance to losing, suggesting that they are displaying learned helplessness. Activation of the mPFC protects mice from learned helplessness[12], and Fan and colleagues found that such activation also protected animals from the harmful effects of social-status loss. Perhaps, then, the two phenomena are controlled by similar neuronal circuits.

However, this similarity also raises a key limitation of Fan and colleagues' study — it did not include female mice. When rats are given the opportunity to stop an otherwise inescapable aversive stimulus, the mPFC becomes activated in males but not females (thus preventing the development of learned helplessness only in males)[13]. This finding raises the possibility that social-status loss might engage different circuits in male and female mice, with different behavioural outcomes. It will be important to address this gap in future studies.

Tests designed to induce chronic stress in rodents (such as repeated encounters with an aggressor) often lead to decreased social rank[3] and an altered preference for sweetened water[14,15], but the relationship between the stressful experience and reward processing remains unclear. Fan and colleagues' demonstration that status loss affected the neural circuitry underlying pleasure-seeking behaviour suggests that chronic stress causes its effects through similar circuitry. Fighting back during encounters with an aggressor induces dopamine-mediated neuronal activity[16] and predicts resilience against the negative outcomes of chronic stress[17]. This dopamine release might offset LHb-mediated inhibition of dopamine neurons that Fan *et al.* show is induced by subordination.

Perhaps the most promising aspect of Fan and colleagues' study is that, in mice that have lost social status and the desire to seek pleasure, activating the mPFC to ensure the animals win tests once more restores their social status and their preference for sweetened water. This finding has implications for potential future therapies for depression. One type of therapy involves active scheduling of pleasant activities[18], with participants asked to rate how pleasant they expect a given activity to be, engage in the activity and then re-rate its pleasantness. This therapy is thought to work by positively reinforcing behaviours that promote good mood. However, Fan and colleagues' work raises the possibility that this approach actually works by highlighting that the experience was unexpectedly pleasurable. This hypothesis could be tested clinically, and if true, could shift clinical practice towards selecting activities that will prove unexpectedly pleasant, illustrating the potential of brain-circuit studies in mice to guide treatment development.

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The authors declare no competing interests.
This article was published online on 7 March 2023.

Metabolism

Mitochondrial molecule controls inflammation

Taylor A. Poor & Navdeep S. Chandel

Cellular organelles called mitochondria contain their own DNA and RNA. The molecule fumarate has now been found to trigger the release of these nucleic acids into the cytosol, aberrantly activating inflammation. **See p.490 & p.499**

Although mitochondria are often referred to as the powerhouses of the cell, these organelles can also act as signalling hubs that control physiological processes[1]. One such signalling pathway controls inflammation[2]. Now, Zecchini *et al.*[3] (page 499) and Hooftman *et al.*[4] (page 490) report that fumarate (a molecule produced as an intermediate of metabolic processes in mitochondria) triggers the activation of specific inflammation-related pathways. Their findings have implications for cancer and inflammatory diseases.

Viruses that contain double-stranded DNA can be detected in the cell cytosol by the cGAS–STING pathway. By contrast, viral double-stranded RNA in the cytosol is sensed by the RIG-I- and MDA5-dependent mitochondrial antiviral-signalling (RIG-I/MDA5-MAVS) pathway, components of which are anchored to the outer membrane of mitochondria. Both of these pathways lead to the transcription of genes that encode a type of signalling protein called interferon-I (IFN-I), which activates the immune system to mediate antiviral responses.

Notably, mitochondria contain their own circular double-stranded DNA called mtDNA, which is transcribed to mitochondrial RNA (mtRNA) and subsequently translated to produce proteins needed to generate energy-carrying ATP molecules. The release of mtDNA and mtRNA from mitochondria into the cytosol can activate IFN-I-dependent antiviral immunity through the cGAS–STING and RIG-I/MDA5-MAVS pathways[5,6]. This can occur when cells are infected by pathogens such as influenza virus or the bacterium *Mycobacterium tuberculosis*, which can trigger the release of mtDNA. It can also happen during radiation therapy, which generates breaks in mtDNA and so results in the transcription of short mtRNAs that are released into the cytosol.

Zecchini *et al.* and Hooftman *et al.* now reveal that fumarate has a role in mtDNA- and mtRNA-dependent inflammation (Fig. 1). Fumarate is converted to malate by the enzyme fumarate hydratase. Both groups observed that pharmacological or genetic inhibition of fumarate hydratase increased the intracellular levels of fumarate, which activated the RIG-I/MDA5-MAVS pathway.

Zecchini and colleagues found that fumarate also activated the cGAS–STING pathway, although Hooftman *et al.* discovered that inhibiting the activity of STING or silencing the expression of cGAS had no effect on inflammation. The reason for this discrepancy is not fully clear. One simple explanation could be that fumarate has different effects in different cell types, because Zecchini *et al.* used kidney cells, whereas Hooftman *et al.* studied immune cells called macrophages.

How could mtRNA or mtDNA escape from the mitochondrion and pass through the organelle's two membranes into the cytosol? Previous work[6] suggests that BAX and BAK proteins generate pores that release mtRNA, although whether this process involves fumarate is unknown. In addition, mitochondria shed small mitochondrial-derived vesicles

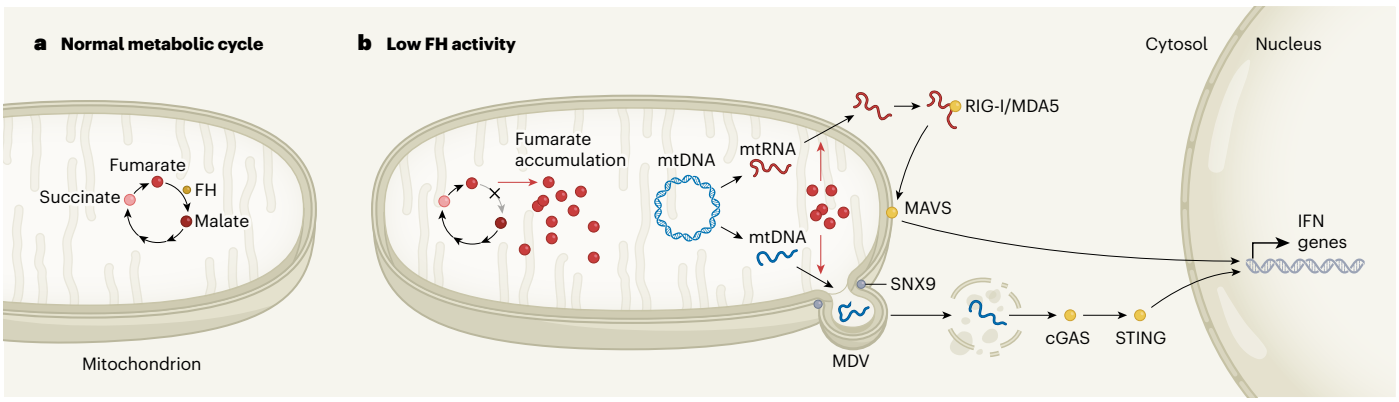

Figure 1 | A role for fumarate in inflammation. a, In organelles called mitochondria, the enzyme fumarate hydratase (FH) converts the molecule fumarate into malate, as part of a normal metabolic cycle. **b**, In some cancers and immune disorders, the activity of FH is reduced, and fumarate accumulates. Two groups[3,4] show that fumarate accumulation leads to the release of nucleic acids from mitochondria. Release of mitochondrial RNA (mtRNA) might involve a change in the electrical potential across the mitochondrial membrane. Mitochondrial DNA (mtDNA) might be released in mitochondrial-derived vesicles (MDVs), which bud off from the membrane in a process that involves the protein SNX9. The released mtRNA and mtDNA activate the RIG-I/MDA5-MAVS and cGAS–STING signalling pathways, respectively. These pathways trigger the transcription of genes that encode type-I interferon (IFN) proteins, which induce inflammation.

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