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induce a mixed pattern of cell death pathways (ferroptosis, apoptosis, necroptosis…), raising questions about the specificity of the molecular mechanism of ferroptosis. Should these different types of cell death truly be viewed in isolation? Although the initiators, mediators, and regulators of ferroptosis are being discovered, its final executors remain elusive (Table 1). One hypothesis is that PLOOH may be the executor of ferroptosis, but there is no direct quantification of the threshold of PLOOH required to trigger cell death *in vitro* or *in vivo*. Several alternative hypotheses are being proposed. First, some unknown pore-forming proteins may interact with the lipid bilayer, thereby compromising the integrity of the membrane. Such proteins would act similarly to gasdermin D and mixed lineage kinase domain like pseudokinase, which cause plasma membrane permeabilization in pyroptosis and necroptosis, respectively. Second, ferroptosis is accompanied by overactivation of autophagy and lysosomes. The release of lysosomal hydrolases might directly cause the plasma membrane to rupture, in which case ferroptosis would be a type of lysosomal cell death. Third, an imbalanced phospholipid asymmetry might perturb membrane structure and function, leading to ferroptosis. This process then would possibly be regulated by phospholipid flippases, such as P4-ATPases.

As a lytic form of cell death, ferroptosis-mediated inflammation is implicated in the pathogenesis of various diseases. However, it still lacks unique markers to evaluate and distinguish the immune response to ferroptotic and non-ferroptotic cell death. It is likely that human diseases are coupled to the simultaneous deregulation of several cell-death modalities, calling for combined interventions on several pathways.

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Genetic rescue restores long-term viability of an isolated population of adders (*Vipera berus*)

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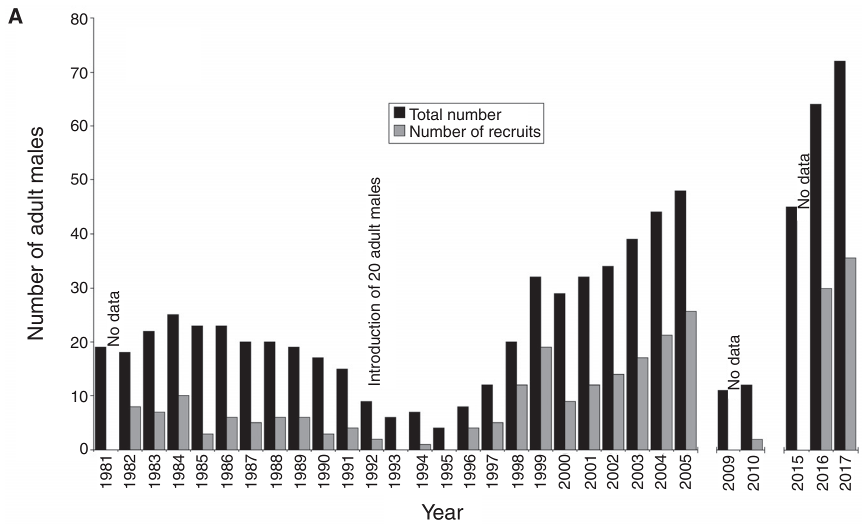
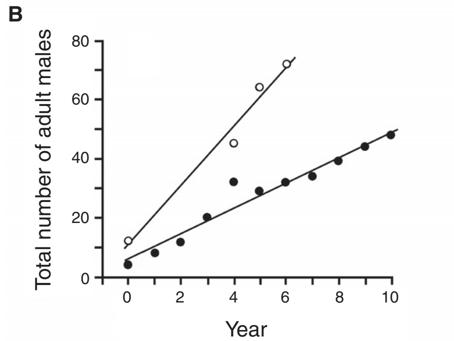
Climate change is regarded as a major threat to global biodiversity [1]. However, another key driver of declines in biodiversity during the last century has been, and still is, the devastating impact of anthropogenic habitat destruction [2]. Human degradation of natural habitats has resulted in large, formerly homogeneous areas becoming exceedingly isolated and fragmented, resulting in reduced genetic diversity and a concomitant increased vulnerability to pathogens [3] and increased risk of inbreeding [4]. In order to restore genetic diversity in small isolated or fragmented populations, genetic rescue — that is, an intervention in which unrelated individuals are brought into a population, leading to introduction of novel alleles — has been shown to reduce the deleterious effects of inbreeding [4,5].

Here we report on a study of an isolated, and initially severely inbred, adder (*Vipera berus*) population in southernmost Sweden [4] spanning 37 years (1981 to 2017). In the 26 years after the introduction of 20 novel males in 1992, we observed a rapid increase in genetic diversity and a dramatic increase in offspring viability [4], resulting in enhanced recruitment and concomitant increase in adder numbers (Figure 1A,C,D; supporting our previous findings [6]). This long-term study also revealed that in spite of a population bottleneck (80% reduction of adder numbers in 2009 and 2010), population genetic heterozygosity, a measure of genetic diversity, was higher in 2017 than





C

Year	H_{obs}	H_{exp}
1991–92	0.181	0.170
2005	0.244	0.237
2017	0.243	0.241

D

Year	ΔH	p
1991–92 vs 2005	0.066	<0.0001
1991–92 vs 2017	0.070	<0.0001
2005 vs 2017	-0.004	0.0008

Figure 1. Population demographic and genetic effects of genetic rescue.
(A) Annual number of male adders recorded from 1981 to 2017. (B) Temporal increase in total male adder numbers from 1996 to 2005 (filled circles) and from 2010 to 2017 (open circles). Zero depicts the total number of males recorded 1996 and 2010, respectively. (C) Observed and expected heterozygosity recorded in 1991–1992 (prior to the introduction of the 20 novel males), 2005 (prior to the reduction in adder numbers observed in 2009 and 2010) and in 2017 (after the reduction in observed in 2009 and 2010). (D) Pairwise comparison of heterozygosity.

in 2005 (Figure 1D). Moreover, the annual increase in adder numbers after the bottleneck (2010 to 2017) was higher than that observed prior to the bottleneck (1992 to 2005; $F_1 = 41.7$, $p < 0.0001$; Figure 1B). For logistic reasons common to many field-based studies, we lack treatment replication and a control population (BACI design). Nevertheless, these findings suggest that the benefits of genetic rescue can extend through subsequent periods of population reductions.

Positive long-term effects of genetic rescue on population viability have recently been questioned based on a study of the Isle Royale wolf (*Canis lupus*) population [7]. The genetic rescue of the wolf population was, however, restricted to one male migrating into the population in 1997. Although this male sired numerous litters, the genetic contribution to the population was restricted to alleles from one individual, which most likely underpins the observation that the effect of genetic rescue in the Isle Royale wolf case was short-lived.

In the present study, 20 novel males from two distant populations were introduced in 1992 to the population, which at that time had only 9 males. The introduced males were recorded mating with all reproductive females, who also mated with the resident males. Prior to the introduction of the novel males, the mean proportion of malformed and/or inviable offspring was 31.6% [4]. Female adders mate with multiple males and a higher number of male partners increases offspring viability [8]. The total lack of inviable offspring and the increase in annual recruitment after the introduction of novel males strongly suggest that the enhanced offspring viability was underpinned by intra-uterine sperm selection of optimal male haplotypes, that is, ‘cryptic female choice’ [9].

Both short-term and long-term reduction in population size can cause significant reductions in genetic diversity [10]. Although we do not know exactly what year the population bottleneck observed in 2009 and 2010 was initiated, we find it reasonable to assume that it coincided with the construction of a house and brick wall in 2006 (see Supplemental Information). By 2015 the population number had, however, recovered to that recorded in 2005. This suggests that the bottleneck may have lasted for five to six years, corresponding to a maximum of two adder generations. In spite of this, our findings show that genetic diversity of the population was higher in 2017, after the bottleneck, compared to that recorded in 2005, prior to the bottleneck. Moreover, the population number increased at a faster rate after the bottleneck than it did prior to the bottleneck. In our view, this strongly suggests that the positive effects of the genetic rescue resulted in such a significant increase in population genetic diversity that it enabled the population to overcome the genetic impact of the subsequent bottleneck. This study emphasizes the value of empirical long-term studies of genetic rescue to complement and test the predictions of the rich theoretical frameworks that have been developed in this field.

Our study shows that long-term studies are crucial to allow for a robust documentation of the effects of genetic rescue and, moreover, in order to be successful, large numbers of novel alleles have to be introduced into the focal population.

SUPPLEMENTAL INFORMATION

Supplemental Information includes two figures, experimental procedures, and supplemental references, and can be found with this article online at https://doi.org/10.1016/j.cub.2020.08.059.

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This manuscript is dedicated to Jon Loman, who passed away prior to the last version of

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AUTHOR CONTRIBUTIONS

T.M., J.L. and B.U. designed the research; T.M., J.L., L.A., H.A. and B.U. performed the research; T.M. and A.G. analysed the data; T.M., H.A., A.G. and B.U. wrote the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Events are perceived earlier in peripheral vision

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Visual perception is not instantaneous. It takes a few milliseconds for light to be transduced in photoreceptors and tens of milliseconds more for neuronal spikes to occur at successive levels of the visual hierarchy. Moreover, the latency of responses varies across the visual field and the cortical hierarchy. In peripheral compared to central vision, the impulse response of primates' ganglion cells has a higher peak occurring at shorter latency [1], and yet humans' primary visual cortex is activated later [2]. The diversity of these physiological results makes it difficult to predict when is the perceived present [3], especially when events are presented across the visual field. This question cannot be directly addressed with paradigms traditionally used to investigate perceptual latencies. In particular, response times are not suitable because they are influenced by decisional mechanisms, motor-related processing or compensatory mechanisms [4,5]. Likewise, temporal order judgements between foveal and peripheral stimuli are not suitable because humans overweigh foveal information when making perceptual decisions [6]. Here we explicitly asked participants to estimate *when* a stimulus is perceived within a fixed duration temporal interval, rather than relative to another stimulus presented in its near temporal proximity. We show that the perceived time of a visual event depends on its position in the visual field. We find a large bias to report events earlier when they were presented in the periphery.

Participants first learned the duration of a fixed interval that was used as a temporal frame in the main part of the experiment. A bar representing the hand of a clock (Figure 1A) made a full revolution in 2 seconds. In the main part of the experiment (Figure 1B), the hand of the clock was no longer presented, and participants were asked to attend to the whole duration of the temporal frame. The start and end of the frame were signalled by a change of the fixation point and a brief tone. On each trial, at random times after the frame onset, a pair of clearly visible stimuli were presented briefly (33 ms) on either side of the fixation. At the frame offset, the hand of the clock was presented, and participants adjusted its position to indicate when the event was perceived.

We tested the perceived time for events presented at fixation and ten different eccentricities (from 2 to 18 degrees of visual angle). Events presented at fixation were perceived veridically, but there was a large bias to report events earlier (negative temporal bias) when they were presented in the periphery (Figure 1D). From a trial-by-trial linear mixed-effect analysis, we found that temporal bias — the difference between reported and presented time — was affected by the position of the event in the visual field ($X^2(1) = 23.65$, $p < 0.001$). We also found that temporal bias was affected by presented time ($X^2(1) = 679.5$, $p < 0.001$), showing the presence of a range effect. Importantly, there was no interaction between presented time and eccentricity, indicating a constant range effect irrespective of the eccentricity ($X^2(1) = 0.45$, $p = 0.5$; Figure 1C,D).

Our findings are at odds with previous investigations of the perceived synchrony between centrally and peripherally presented stimuli. In one classical study in particular [7], a peripheral stimulus needed to be presented earlier for it to be perceived simultaneous with a foveal stimulus. However, given the temporal uncertainty of the first stimulus in these experiments, and known biases favouring centrally presented stimuli [6], it is plausible that these previous results were confounded by the time needed to shift attention to a peripheral location.

When attention is diffused across a large area of space, temporal resolution is impaired [8]. Since in our experiment there was no spatial uncertainty about the events' location, the absence of interaction between presented time and eccentricity suggests that the temporal bias in favour of peripheral events is not due to attention.

When the present is perceived is an important and not well understood problem. The most straightforward hypothesis is that the perceived time of a stimulus is related to its processing, and that events are perceived when