and are much more difficult to characterize in the case of sporadic neurodegenerative diseases.

The study by Braz et al. raises several questions for future research. It will be important to determine the early circuit defects that occur in humans with the HD mutation, in addition to the structural neurodevelopmental alterations (3). Moreover, it will be crucial to investigate other brain circuits involved in HD (11), because pathological changes in subcortical regions, including the basal ganglia, play a key role in the clinical symptoms. At the molecular level, the cascade of events linking mutant HTT to changes in the synaptic machinery also remains to be explored. One interesting hint comes from the experiments performed by Braz et al. with mice lacking Htt. These mice exhibited neonatal circuit impairments similar to those of the HD mice but did not return to the normal state. The similarity of phenotypes caused by mutant HTT and by lack of HTT suggests that the impairments in HD are at least partially due to insufficient amounts of the normal version of the protein, and not solely to the toxic mutated version. This finding is important, because not all approaches to treat HD by lowering HTT expression distinguish between the mutant and normal forms of the protein (12). The study of Braz et al. reinforces the idea that decreased levels of normal version can be deleterious. HTT has roles in multiple physiological processes, including intracellular trafficking, autophagy, and synaptic transmission (13, 14), which could be disturbed when normal HTT is not present in adequate amounts. The exact nature of the compensatory mechanisms that counteract the early defects and prevent disease onset is another exciting question to be addressed.

The findings by Braz et al. have crucial translational implications, too. Because many HD mutation carriers are not identified until adult age, it will be necessary to determine the duration of the “window of opportunity” for potential interventions that ensure benefit later in life. Is perinatal treatment the ideal option, or would a treatment at a later presymptomatic stage also be sufficient? In addition, a lot of attention is currently focused on HTT-lowering treatments (12). Although these are promising, it is important to keep looking for alternative or complementary options, such as those targeting early synaptic deficits.

REFERENCES AND NOTES

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applying the average $z_{MAR}$ to all taxa comes with some caveats. For instance, the confidence intervals surrounding the estimate of global genetic diversity loss are very wide (ranging from 0 to 100%). This raises some questions as to its broad applicability. For instance, different ecosystems have been affected by human activities to different degrees, and there is a need for a more granular approach to estimating genetic diversity loss. As Exposito-Alonso *et al.* themselves have pointed out, high-altitude ecosystems have only lost 0.3% of their area, whereas highly managed forests have lost a whopping 67% of theirs. Additional variations may also arise from biological differences between species (i.e., ability to disperse, mating systems, geographic ranges), which will, in turn, influence patterns of gene flow across space. Although the authors investigated the potential influence of between-species variation in these traits on $z_{MAR}$ and found no statistically significant associations, their sample size was limited to 20 species and more work in this area is needed for this to be conclusive. The ability to further test the robustness of the global genetic diversity loss calculations should improve as more landscape and genomic data become available.

Despite its potential limitations, this framework for calculating genetic diversity loss as a function of habitat loss holds promise for conservation biologists and policy experts charged with species preservation in the face of rapid environmental change. Further testing of the MAR with empirical and simulated datasets will reveal additional insights into the broad-scale utility of global genetic diversity loss estimates for conservation efforts. In a time when habitat loss and climate change are altering ecosystems faster than scientists can study them, the MAR will be a vital tool for scientists and policy-makers who are attempting to understand the magnitude of past genetic diversity losses and plan for the future. ■

**REFERENCES AND NOTES**

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Exposito-Alonso *et al.* claim that even species whose conservation status is considered “least concern,” such as the willow flycatcher shown here, may have already lost a substantial amount of genetic diversity.

Diversity loss concerning reductions in habitat does not yet exist. Exposito-Alonso *et al.* adopt the mathematical framework of the SAR to demonstrate that the accumulation of genetic variants (i.e., mutations) follows a similar trend as species diversity, with the number of mutations within a species being proportional to the habitat area to the power $z_{MAR}$ The MAR subscript is used by the authors to represent what they call the mutations-area relationship (MAR).

Exposito-Alonso *et al.* evaluated the MAR in the small flowering plant thale cress (*Arabidopsis thaliana*), a model species in plant biology and genetics, and found that their model can accurately predict genetic diversity loss from habitat contractions. Because the power of the MAR lies in its potential to inform genetic diversity loss in species with or without genomic data, the authors expanded their testing dataset. In all, they tested the generality of the MAR using publicly available genomic data from 20 plant and animal species, including humans, several plants, and fruit flies. They found that the critical component of the MAR calculation, $z_{MAR}$, was quite consistent across the 20 species. Thus, this relationship may be applicable for approximating $z_{MAR}$ in species where genomic data is absent.

By combining the average $z_{MAR}$ and estimates of pre–21st century land transformations, Exposito-Alonso *et al.* conclude that an average of 10 to 16% of genetic diversity has been lost globally since the industrial revolution. This number is already greater than 10%, which is the permissible percentage of genetic diversity loss as recommended by biodiversity policy experts for healthy ecosystems moving forward (1, 5). Further, when this model is used to estimate the rate of genetic diversity loss for individual species, it is clear that even species classified as “least concern,” such as the willow flycatcher (*Empidonax traillii*), a North American songbird, have already lost a substantial amount of genetic diversity. Although compelling, indiscriminately...
Estimating global genetic diversity loss
Kristen Ruegg and Sheela Turbek

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