hierarchy demonstrated a biologically sensible organizational structure of the human brain.

We described a previously unidentified parcellation system for the human cortex that reflects shared genetic influences on cortical areal expansion. This system constitutes the first human brain atlas based solely on genetically informative data, which may provide presently undescribed phenotypes that will have greater statistical power for genome-wide genetic association studies in comparison with traditional cortical parcellations. We found evidence for a hierarchical, modular, and bilaterally symmetric genetic architecture. Genetically based lobar regions have been demonstrated across mammalian species (*7*, *8*), and our results are consistent with genetically based regions of human specialization being increasingly differentiated subdivisions of these lobar regions. Our findings may thus be useful for translating results from model organisms into functional and clinical insights about human specializations, so as to understand both order and disorder in the human brain.

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### Supporting Online Material

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# Ecological Context Influences Epidemic Size and Parasite-Driven Evolution


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**The occurrence and magnitude of disease outbreaks can strongly influence host evolution. In particular, when hosts face a resistance-fecundity trade-off, they might evolve increased resistance to infection during larger epidemics but increased susceptibility during smaller ones. We tested this theoretical prediction by using a zooplankton-yeast host-parasite system in which ecological factors determine epidemic size. Lakes with high productivity and low predation pressure had large yeast epidemics; during these outbreaks, hosts became more resistant to infection. However, with low productivity and high predation, epidemics remained small and hosts evolved increased susceptibility. Thus, by modulating disease outbreaks, ecological context (productivity and predation) shaped host evolution during epidemics. Consequently, anthropogenic alteration of productivity and predation might strongly influence both ecological and evolutionary outcomes of disease.**


Parasites can impose strong evolutionary pressure on their hosts during epidemics (*1*, *2*). Parasites often virulently depress survival and/or birth rate of their hosts. As a result, if epidemics become large enough, host populations might evolve resistance to infection because of parasite-mediated directional selection (*1*). Alternatively, if the susceptibility of a host genotype depends on the parasite genotype to which it is exposed, negative frequency-dependent selection can drive cycling of host genotypes through time [that is, "Red Queen dynamics" (*3*, *4*)]. These two ideas about host (co-)evolution during epidemics, evolution of increased resistance and the Red Queen hypothesis, dominate research on evolutionary epidemiology (*1*). However, theory reveals other possibilities, including the evolution of higher susceptibility to infection (*1*, *5*–*8*). Why would hosts evolve greater susceptibility to their virulent parasites during epidemics? When would host populations evolve this way in nature?

The answers to these questions involve trade-offs and ecologically driven variation in disease prevalence. Resistance to virulent parasites can trade off with reproduction; some genotypes have higher fecundity but lower disease resistance, whereas others are less fecund but more resistant. The fittest strategy, then, depends on the net balance between resisting infection and enhancing fecundity. That balance, in turn, depends on ecologically determined disease prevalence. Environments with high resources for hosts (higher productivity) and lower mortality (lower predation) on hosts should fuel large epidemics (*9*–*12*). In these systems, theory predicts that hosts should evolve increased resistance to disease, even though resistant genotypes have lower fecundity. However, when low productivity and/or higher predation constrain epidemic size, populations should become more susceptible because more susceptible genotypes are more fecund.

We test these predictions in a host-parasite system that exhibits the requisite trade-offs and ecologically driven variation in epidemics. Clonal genotypes of the zooplankton grazer *Daphnia dentifera* face a trade-off between fecundity and resistance to infection by a virulent yeast parasite [*Metschnikowia bicuspidata* (*13*)]. Mechanistically, the resistance-fecundity trade-off is driven by variation in feeding rate: Slow feeders consume fewer free-living propagules (spores) of the yeast (conferring higher resistance) but assimilate energy less quickly (yielding fewer offspring). Neither host-parasite genotype specificity nor Red Queen dynamics appear in this system; host resistance does not depend on the parasite genotype to which it is exposed (*14*). This parasite reduces fecundity and survival (*15*). Epidemics erupt commonly in *Daphnia* populations, with maximal infection prevalence sometimes exceeding 60% (*16*, *17*).


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Large epidemics depress host density (*16*), and host populations evolve rapidly during epidemics (*14*, *18*, *19*). Epidemics can grow larger in lakes with high nutrient concentrations [an index of productivity (*20*)]. In contrast, vertebrate predation depresses yeast epidemics, particularly because fishes selectively cull infected *Daphnia* (*15*, *21*). Overall, we hypothesized that lakes with higher productivity and/or lower fish predation should have larger epidemics that should select for greater disease resistance in hosts. Conversely, lakes with lower productivity and/or higher predation should have smaller epidemics and hosts might evolve increased susceptibility.

To quantify epidemic size, we monitored epidemics and indices of productivity and predation in weekly sampling visits to seven lakes located in Greene and Sullivan Counties, Indiana. We estimated infection prevalence visually on live hosts by using established survey methods (*15*, *16*, *21*). To calculate epidemic size, we integrated the area under the time series of infection prevalence for each lake. This measure correlates strongly with maximum infection prevalence ($r$ = 0.89, $P$ = 0.008). We also estimated two indices of productivity, total phosphorus (P) and total nitrogen (N), by using standard methods [colorimetric assays and ultraviolet spectrophotometry, respectively (*22*)]. On the basis of ratios of nitrogen: phosphorus measured, productivity in these lakes is likely colimited or even nitrogen-limited (*23*, *24*). Mean length of uninfected adult hosts provided an index of predation pressure; smaller mean length indicates greater fish predation (*25*, *26*).

To characterize host evolution during epidemics, we conducted infection assays for each lake population. To establish isofemale lines, we randomly isolated individual hosts at two time points: in late July before epidemics began (preepidemic) and in mid-November as epidemics waned but before hosts produced sexual females (postepidemic). We used those lines (9 to 21 per lake per period, mean of 15.4) to estimate mean infection risk of host populations (*13*, *14*, *18*) [also supporting online material (SOM)]. Here, infection risk reflects the product of spore uptake and infectivity of the spores once consumed (i.e., per-spore susceptibility). We refer to higher infection risk as "higher susceptibility" and lower infection risk as "higher resistance." All assays were performed by using a single isolate of the yeast, because *Metschnikowia* collected from different lakes and years do not vary in relevant epidemiological parameters (*14*). We then analyzed infection data for each lake with a logistic regression model built with binomial errors and a logit

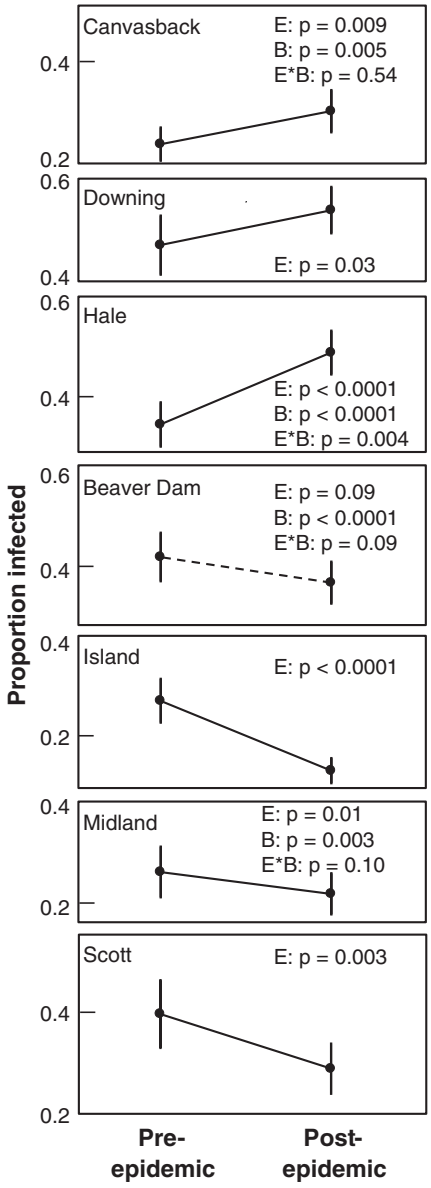


**Fig. 1.** Change in infection risk of seven populations of a zooplankton host (*D. dentifera*) during epidemics of a virulent yeast parasite (*M. bicuspidata*). Proportion infected from pre- and postepidemic lines are shown (means of clonal lines ± SE). E indicates the comparison of the pre- and postepidemic time periods; when applicable, B denotes time blocking, and E*B represents their interaction. The populations in Canvasback, Downing, and Hale Lakes became significantly more susceptible during their epidemics, whereas those in Island, Midland, and Scott Lakes became significantly more resistant. There was no significant change in Beaver Dam Lake (hence the dashed line connecting the two means).

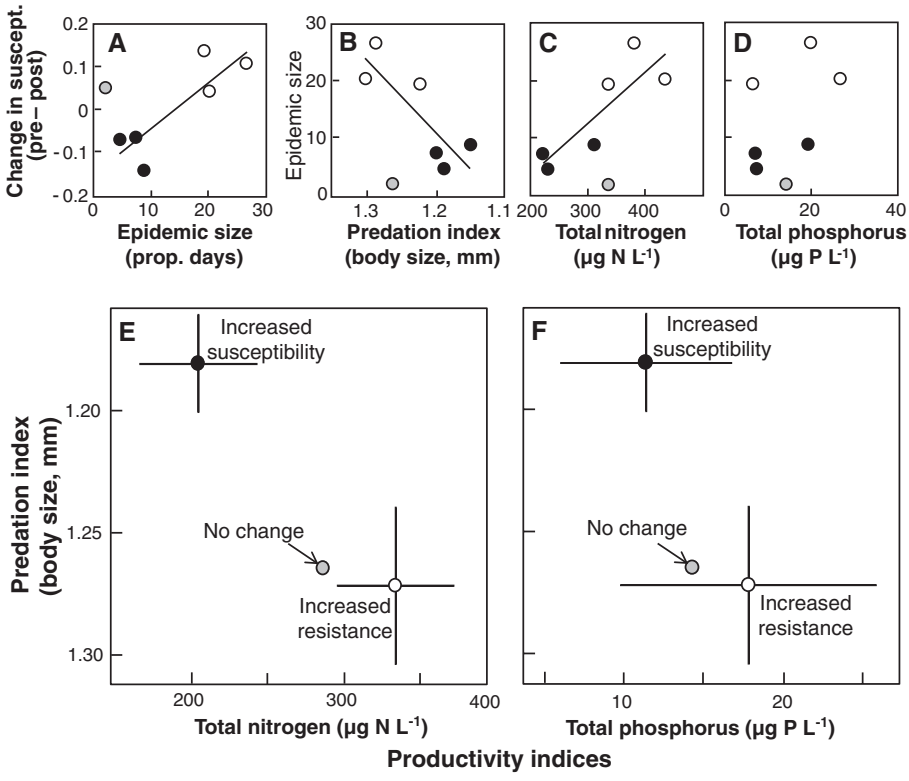


**Fig. 2.** Relationships between epidemic size, predation, productivity, and evolutionary outcomes. Top panels show links with epidemic size (quantified as the area under the infection prevalence curve through time). (**A**) Epidemic size versus change in mean susceptibility (mean proportion infected of postepidemic genotypes subtracted from mean of preepidemic genotypes). (**B** to **D**) Epidemic size is on the *y* axis, plotted versus (B) predation intensity (where smaller body size indicates higher predation) or productivity as indexed by (C) total nitrogen and (D) total phosphorus. Open symbols denote lake populations that evolved increased resistance (as shown in Fig. 1), black symbols indicate increased susceptibility, and gray symbols indicate no significant evolutionary change. (**E** and **F**) Evolutionary outcomes mapped onto predation-productivity space. Note that the *y* axis scales with increasing predation intensity, so small body size (high predation) is at the top. Points in (E) and (F) are lake means (±1 SE).

link function (Proc Genmod, SAS 9.1, SAS Institute Incorporated, Cary, North Carolina). When the infection assays were run over two time blocks, the model also included a block effect and a time-by-block interaction.

The infection assays showed a significant evolutionary response of hosts to epidemics in six of seven lake populations. In three lakes (Island, Midland, and Scott Lakes), host populations became significantly more resistant during epidemics (Fig. 1). However, in three other populations (Canvasback, Downing, and Hale Lakes), hosts became significantly more susceptible to infection. The hosts in the seventh lake, Beaver Dam, did not show a significant change in susceptibility but trended toward increased resistance.

As anticipated by theory (SOM), these evolutionary trajectories correlated with ecologically driven variation in epidemic size. Among the six lake populations showing a significant evolutionary response, change in mean susceptibility correlated strongly with epidemic size (Pearson correlation: $r = 0.86$, $P = 0.030$, $n = 6$; Fig. 2A). Further, in those six lakes, epidemics were larger at lower predation intensity (larger size of hosts; Pearson correlation: $r = 0.86$, $P = 0.029$, $n = 6$; Fig. 2B) and where total nitrogen was higher (Pearson correlation: $r = 0.83$, $P = 0.040$, $n = 6$; Fig. 2C); the trend was similarly directed, but not significant, for total phosphorus (Pearson correlation: $r = 0.50$, $P = 0.3$, $n = 6$; Fig. 2D). Overall, hosts became more susceptible to the yeast in lower productivity lakes with higher vertebrate predation but evolved toward decreased susceptibility in more productive lakes with lower vertebrate predation (Fig. 2, E and F; $t$ tests for differences between two groups; results for body size, $t_4 = 3.19$ and $P = 0.033$; nitrogen, $t_4 = 3.18$ and $P = 0.034$; phosphorus, $t_4 = 0.88$ and $P = 0.43$). Thus, ecological gradients, through their effects on epidemic size, influenced evolutionary outcomes of hosts during outbreaks of a virulent parasite. These qualitative predictions also arose from a general, trait-based epidemiological model built for similar epidemiology and parameterized for our particular system (SOM).

These results show that hosts can evolve enhanced susceptibility to their virulent parasites during epidemics [also see (*27*) for a similar but unreplicated occurrence]. A combination of observations, experiments, and modeling all suggest causation for this initially counterintuitive finding. When ecological factors promote large epidemics, hosts should evolve to become more resistant to infection. However, resistance-fecundity trade-offs can prompt host populations to evolve increased susceptibility when ecology constrains epidemic size. Overall, we demonstrated that ecological context influences epidemic size, which, in turn, determines evolutionary responses of hosts to epidemics. This suggests that alteration of predation pressure on hosts and productivity of ecosystems may influence the ecology and evolution of host-parasite interactions.


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**Supporting Online Material**

www.sciencemag.org/cgi/content/full/335/6076/1636/DC1
Materials and Methods
Fig. S1
Tables S1 and S2
References (*28*–*32*)


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# Rapamycin-Induced Insulin Resistance Is Mediated by mTORC2 Loss and Uncoupled from Longevity


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Rapamycin, an inhibitor of mechanistic target of rapamycin complex 1 (mTORC1), extends the life spans of yeast, flies, and mice. Calorie restriction, which increases life span and insulin sensitivity, is proposed to function by inhibition of mTORC1, yet paradoxically, chronic administration of rapamycin substantially impairs glucose tolerance and insulin action. We demonstrate that rapamycin disrupted a second mTOR complex, mTORC2, in vivo and that mTORC2 was required for the insulin-mediated suppression of hepatic gluconeogenesis. Further, decreased mTORC1 signaling was sufficient to extend life span independently from changes in glucose homeostasis, as female mice heterozygous for both mTOR and mLST8 exhibited decreased mTORC1 activity and extended life span but had normal glucose tolerance and insulin sensitivity. Thus, mTORC2 disruption is an important mediator of the effects of rapamycin in vivo.


Age-related diseases—including cancer, neurodegenerative disorders, cardiovascular disease, type II diabetes, and many others—are the major contributors to morbidity and mortality in Western society. The high frequency of these diseases in the elderly limits the benefit that can be obtained by targeting them individually (*1*). However, targeting the aging process directly may offer a way to delay the incidence of many age-related diseases simultaneously. To date, the only molecule that appears to influence the intrinsic rate of aging in mammals, as evidenced by a robust extension of maximum life span, is rapamycin, an inhibitor of mechanistic (previously referred to as mammalian) target of rapamycin complex 1 (mTORC1) (*2*, *3*).

mTOR is a kinase that integrates inputs from many nutrients and growth factors. mTOR is found in two distinct protein complexes: mTORC1, which regulates numerous cellular processes related to