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What doesn't kill you makes you dumber

Strengthening the link between infectious disease, intelligence and personality

Philip Hunter

The idea that infectious disease during childhood affects the developing brain to impact intelligence has been around for decades. Recent evidence from more rigorous studies, which have controlled carefully for other factors such as nutrition and education, has strengthened the case. If these new epidemiological and molecular studies really do confirm a clear link between childhood infection and intelligence, the consequences for health policy and development assistance could be profound. The results could mandate an increased focus not only on eradicating or controlling infectious diseases, but also on reducing their impact on children in the absence of cures or vaccines.

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Yet, even in the light of new evidence, it is hard to unravel causes from effects, and the debate continues over which diseases are most responsible, along with the precise physiological and molecular mechanisms involved. There is no shortage of theories to explain why infectious disease seems to have so profound an effect on intelligence, and, as a result, on the intellectual and economic performance of whole nations or regions. The stage is set for more studies to drill down into neurological and cognitive mechanisms: to explain why the prevalence of infectious disease is a reliable predictor of intelligence at the population level; to differentiate between the impact of various pathogens; and to identify the evolutionary rationale of these links. There is also mounting evidence that some parasites can alter their host's personality through mechanisms evolved to modify their host's behaviour to their own advantage, which could explain environmental risk factors for mental disorders, such as schizophrenia.

After a few intermittent references earlier last century, the US economist Andrew Kamarck made the first attempt to link infectious disease with a nation's performance during the 1970s [1]. Kamarck identified the interplay of three factors—temperature, humidity and infectious diseases—on the economic performance of nations through their impact on vitality and intellectual attainment.

Somewhat surprisingly, both economists and biologists neglected Kamarck's findings that link infectious disease and either intelligence or performance at a population level for another three decades. Eventually, Christopher Eppig and colleagues at the University of New Mexico in Albuquerque, USA, published a seminal paper in 2010, which reported a strong correlation between the prevalence of infectious disease in a country and intelligence as measured by supposedly culturally independent IQ tests [2]. In the past, other environmental factors, such as average temperature, have been shown to affect intelligence, but in Eppig's study, infectious disease seems to trump these. The country with the highest average IQ of all, Singapore, is hot and humid, but has the world's lowest rates of infectious disease largely because of excellent healthcare.

The Eppig study also offers a plausible explanation for the so-called Flynn Effect, named after the political scientist James Flynn who described and promoted the apparent sustained and significant increase in average intelligence in many developed nations during the past half-century or more [3]. "Our research suggests that infectious disease may be the most important factor influencing IQ," Eppig confirmed. "Infectious disease has the strongest correlation with average IQ, and the largest independent contribution when other factors are controlled." The researchers found that the correlation between average IQ and infectious disease at the cross-national level is between –0.76 and –0.82; 0 would equate to no correlation and –1 would be total correlation. The results indicate a high degree of correlation, and, just as importantly, the study determined that the probability of this correlation having occurred by chance was incredibly low.

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The intelligence scores were largely taken from an earlier study conducted by UK psychologist Richard Lynn and Finnish political scientist Jaan Mikk, which analysed IQ scores from 113 countries [4], and the data on infectious diseases were provided by the World Health Organization. Given that both sets of data were openly available, it was easy for other groups to perform their own analyses to either corroborate or refute Eppig's findings. Chris Hassall and colleagues at Carleton University in Ottawa, Canada, have done just such a follow up to identify or eliminate any statistical artefacts that might

weaken or cast doubt on the findings [5]. One of the significant possible artefacts for which Hassall controlled is a phenomenon known as autocorrelation, which is the tendency for two sets of data to seem to be linked just because they have similar spatial patterns of variation. "Having reanalysed the data, I am fairly convinced that there is a strong correlation between the health impacts of parasites and IQ," Hassall confirmed. In fact, Eppig himself suggested that Hassall's results were stronger than his own. "They found that, when controlling for spatial autocorrelation, infectious disease was an even better predictor of average national IQ than our own analysis had found," he commented.

Meanwhile, Eppig has published another study analysing the correlation between disease and intelligence within a single country [6]. He chose the USA because there is good data available for individual states, with sufficient variation across the country as a whole to provide the necessary range of data. This study was conducted partly in response to criticism of the first one on the grounds that national differences in culture and education might not have been fully filtered out. By studying just one country with a significant degree of cultural and educational harmony, Eppig hoped to provide an even more convincing case for the link between infectious disease and IQ.

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According to Michael Woodley, who has been studying the link between infectious disease and intelligence at the University of Surrey, UK, the correlation found in the US study is not as strong, but is still significant. "They found a weaker set of relationships, but infectious disease was still a potent predictor of cross state variance in IQ," Woodley said, but added that these studies beg the question of cause and effect. "The question is, have they found evidence that infectious disease has a causal influence on IQ, or is it the case that cross national patterns of IQ affect disease ecology?" he explained. The suggestion is that intelligence itself can affect the prevalence of disease. "My cautious take is that it's a bit of both."

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Hassall conceded that his and the other studies have only identified a correlation between infectious disease and intelligence, albeit a strong one, and not a causal link. But he added that there were plausible underlying physiological explanations for the link, although as yet there is no definitive proof for any.

"We can only speculate about the possible causal links," agreed Joachim Kurtz, a group leader whose lab works on animal evolutionary ecology at the Westfälische Wilhelms–Universität Münster in Germany. "There are at least two non-exclusive possibilities: firstly, given that the brain needs a lot of energy, the energetic costs of parasitic infection and immune defense may provide a mechanistic explanation for the correlation […] a second, slightly frightening and more direct possibility is that parasite manipulation might make hosts stupid."

The first possibility could be caused by the need to reroute energy from the brain to repair tissue damaged by parasites, or by energy lost through malnutrition as a result of diarrhoea, vomiting, or diminished absorption through the digestive tract. It could also result from the parasite accessing cellular or macromolecular resources at the expense of the developing brain, or by the energy cost of maintaining a heightened immune response. All these factors might decrease the energy and nutrients available to the developing brain and cause reduced cognitive capability.

The second possibility cited by Kurtz might involve direct damage to, or alteration of, neurological mechanisms, perhaps deliberately engineered by the parasite for its advantage. The case of rabies is an extreme example of an infection in which the parasite, a virus infecting nerve cells and causing acute encephalitis, changes its host's behaviour to increase the chance of its spreading, in this case causing the host to bite others and spread the virus through saliva.

But there is growing evidence that parasites causing chronic infections can alter behaviour in more subtle ways to increase the chance of transmission. Kurtz cited the case of the protozoa *Toxoplasma gondii*, referring to a recent paper by Czech parasitologist Jaroslav Flegr from Charles University, Prague, which found that infection can trigger various psychiatric and neurological diseases, including schizophrenia, in people with genetic predispositions [7].

"Dozens of studies published in the past 20 years clearly show that toxoplasmosis is responsible for a large number of cases of schizophrenia," Flegr noted. "Recent results, some of them published by our group, show that toxoplasmosis-associated schizophrenia has more severe clinical symptoms than other kinds of schizophrenia." Such symptoms were associated with noticeable changes in brain morphology and included impaired reaction times as well as personality changes, Flegr added. Together, these changes were found to increase the risk not just of suicide but also accidental injury or death [8,9]. Adding these factors together, Flegr estimated that latent toxoplasmosis is indirectly responsible for more than one million deaths per year, which would make it the world's second most dangerous protozoan parasite after malaria, albeit indirectly killing its victims.

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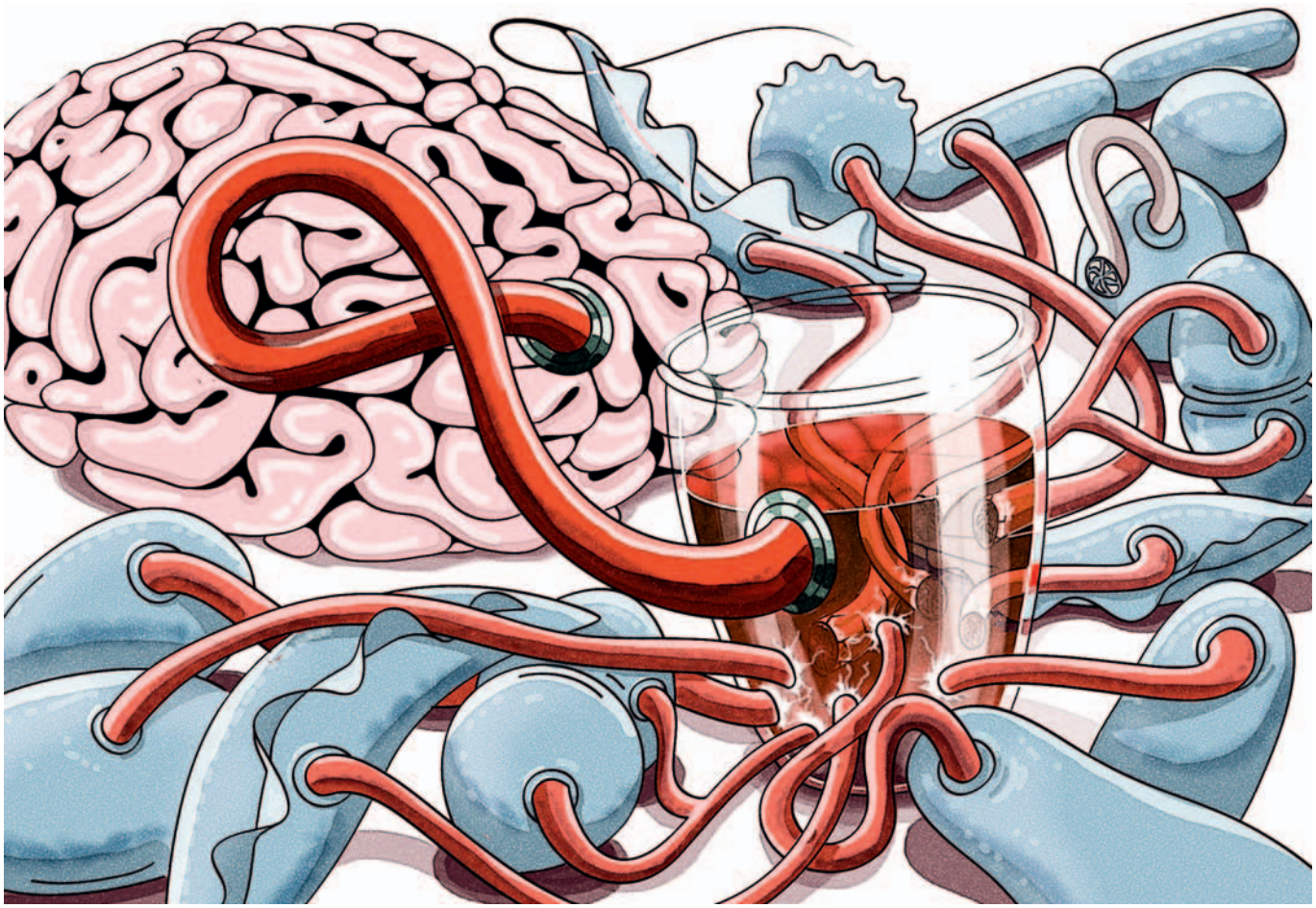
In the case of *T. gondii* the same 'chicken and egg' question arises of whether infection causes the psychiatric disorders, or whether psychiatric disorders make infection more likely. According to Flegr, there is molecular evidence to support the hypothesis that infection causes psychiatric disorders. "It has been known for a long time that toxoplasmosis increases the concentration of dopamine in the infected brain," he said. "In 2009 it was shown that the genome of *Toxoplasma* contains genes for two rate-limiting enzymes for synthesis of dopamine in the brain tissue [10]. Another study then demonstrated that large amounts



of this neurotransmitter are synthesized in cysts of *Toxoplasma* in the brains of infected laboratory animals [11]."

There has been growing evidence that such disruption in dopamine production does increase the risk of developing schizophrenia [12]. Flegr speculated that this manipulation of the host's neurotransmitter production, primarily an increase in dopamine combined with a decrease in serotonin, has its roots in animal evolution. "At least some of the changes are most probably results of manipulative activity of the parasite aimed at increasing efficiency of transmission from an intermediate animal to definitive host by predation," he explained. "Some are probably just side effects of chronic disease."

Although infection by *T. gondii* is particularly common in Africa and South America, Flegr noted that it also has a high incidence in cooler and drier regions, being associated with the consumption of raw vegetables and raw meat. The latter factor perhaps explains its high prevalence in France and Germany, where 40–50% of the population are infected, compared with less than 20% in the UK and USA. These are large figures nonetheless, so the recent findings highlight the urgency of further research to understand the genetic risk factors that predispose infected individuals to neurological illness.

When it comes to the less clearly defined issue of intelligence, researchers are just beginning to identify candidate genes in the host. Among the best known is microcephalin, a gene known to regulate brain size, but the precise role of which in intelligence has yet to be explained. However Heiner Rindermann from the Institute of Psychology at Chemnitz, Germany, has found evidence that high levels of microcephalin within a population seem to be associated with low levels of disease and higher intelligence [13]. "Microcephalin does not predict IQ at the individual level, but it does at ecological scales," Rindermann said. The reason the operation of microcephalin can only be seen at the population level, he explained, is that it does not provide any physiological protection against disease but does make people more sensitive to dirt and more likely to indulge in hygienic behaviour, which affects all people in the vicinity.

"The role of infectious disease burdens as the principal mediator of this ecological relationship suggests that populations exhibiting high levels of microcephalin were better able to cope with historical disease burdens," Rindermann reasoned. "We believe that microcephalin might have encoded for disgust sensitivity, hence more sensitive populations transitioning out of the hunter-gatherer mode of subsistence and into the agrarian one could have carried on growing such that the frequency of IQ-enhancing mutations could have increased via runaway gene-culture co-evolution."

This three-way link between microcephalin, disease and intelligence remains speculative, but the overall association between infectious parasites and broad cognitive behaviour is increasingly well

established. It is not yet clear, though, which diseases are the main culprits, with a few exceptions such as *T. gondii* for psychotic disorders. Differentiating between the different pathogens is one of the main targets for research in the field, according to Eppig. "We have not done empirical work on this question yet, although we have a project in the works, but our hypothesis predicts that the infections that cause the greatest amount of energy to be diverted away from the brain will have the largest detrimental effect," he said. "This means that long-term, chronic, infections are more likely to have a greater detrimental effect on the brain than short-term infections. In particular, we predict that parasites causing diarrheal diseases, malaria and tuberculosis, to name a few, will have the largest effect."

However, Woodley commented there is evidence that sexually transmitted diseases rather than diseases of the intestinal or respiratory tracts have the largest impact on intelligence. But these diseases are often chronic, although Woodley suggested that the correlation could simply result from people with higher IQs being less likely to catch them.

All this research paints an increasingly detailed picture of how infectious diseases and the development of intelligence are linked; but there is clearly much more to be done to unravel the underlying mechanisms. The evidence already accumulated indicates that continuing efforts to eradicate disease in the developing world should be increased. However, as Hassall pointed out, the societal case for doing that stands on its own and does not need to be associated with intelligence.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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