BRAIN
ESSAY

Climate change and the brain

Did you find it challenging to work during recent heatwaves? What might have been the contemporaneous experience of people with neuropsychiatric diseases? We urgently need to understand the multilayered consequences of global warming on the brain.

The astonishing achievements of the human brain are perhaps even more poignant to those with, or caring for, diseases of the brain. The pandemic is a contemporary example of the power of the brain: its ingenuity led to effective vaccines; its activity enabled the design of population-level responses to the pandemic and allowed their dissemination; and human brain engagement enabled the vast majority of people to act upon common sense and governmental regulations. At the individual level, the human brain is self-evidently critical to our everyday lives and the daily workings of societies. Historically, these same attributes have been crucial for the formation of civilizations and their survival in the face of existential challenges.[1] A crude measure of the value of the brain is that the cost of brain disorders in Europe alone in 2010 was estimated at €798 billion, a third of Europe's total health burden.[2]

For the brain to fulfil its roles requires particular conditions, for example: its development must follow designated trajectories; it must have nutrients and be supported within narrow ranges of physical parameters, such as temperature; it must receive inputs and generate outputs. When these conditions are not met, brain function may be compromised, for example through hypoxia, poisoning (alcohol, drugs), temperature extremes beyond its compensatory capacity, disrupted sleep, psychological trauma and disease. Disordered brain function can reduce the ability of the affected individual to respond to external challenges. Resilience may be compromised acutely or chronically: people with brain diseases may be less able to cope with change.

Disordered brain function has well established consequences and costs. Neurological diseases alone, globally, are the leading causes of disability-adjusted life years and second leading causes of deaths. Mortality within a year after diagnosis is considerably higher in people with a brain disorder than in the general population: deaths associated with a neurological condition are 35% more likely to be premature.[3]

In contrast, acute large-scale environmental challenges to humans with direct consequences for brain function have so far not been common. One such circumstance is during heatwaves. Though studies of their consequences related specifically to brain dysfunction are few, heatwaves undoubtedly impact health, especially in the less resilient.[4] Nonetheless, heatwaves and other environmental challenges have been part of the world within which humans have evolved. Homeothermic humans have thermoregulatory systems, some aspects of which have been externalized, involving clothing, heating, movement and dwellings. But both internal and external thermoregulation have limits.[5] Given sufficiently adverse combinations of circumstances, people still freeze to death in cold snaps or die in heatwaves: for example, excess mortality due to the 2003 heatwave in Europe was over 20 000.

Providing the brain with the necessary working environment is a complex task. In a heatwave, people have to be able to know that the environmental temperature needs them to act, and be able to respond accordingly. If it is too hot, they may need to move to a cooler location, seek shade, drink more, divest clothing, open windows, alter settings of environmental systems, and not exert themselves. Intrinsic thermoregulatory responses, such as sweating, have to be functional. When these responses fail, the temperature of the brain and its host body may rise to levels that further compromise brain function, and can eventually lead to death from heat itself, in which process brain dysfunction plays a central role.[6]

When the function of the brain itself is compromised, its ability to respond to environmental challenge may decline. For example, diseases of the brain may impair the ability to detect dangerous temperatures or their accompaniments, may affect the thought and action needed to activate countermeasures, and may even lead to paradoxical responses, such as wandering out into the heat. Some medications used to treat brain or other conditions may compromise intrinsic thermoregulation. Furthermore, when the dysfunctional brain is then exposed to temperatures and other environmental conditions it has not taken steps to mitigate, its own intrinsic programmes may not achieve compensation or, potentially, even be damaging.

Climate change is here. Even if human greenhouse gas emissions ceased tomorrow, further rises in global temperatures are inevitable because of the long-lasting greenhouse gases already in the atmosphere. The pervasive concerns around global warming are becoming more apparent daily as more research is undertaken. Climate change will lead to more frequent and more intense environmental challenges. Heatwaves alone will become more severe and more frequent. The pace and scope of anthropogenic damage to the planetary climate will have effects for all life.

The shared experience of many is that working during recent heatwaves is hard. Amongst those who are likely to experience the most severe outcomes from climate change will be people with neuropsychiatric diseases, whose ability to adapt and mitigate

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is already reduced. But these are threshold effects. People with neurological (and other) diseases are just probably more likely to be affected first. Subjected to circumstances that overwhelm compensation, anyone could suffer the brain results of extreme temperature—it is just a question of how hard an individual has to be physiologically challenged. Furthermore, the psychological effects of climate change, including those resulting from an acceptance of its inevitability, such as climate anxiety, and those driven by actual experience, such as post-traumatic stress disorder, may magnify vulnerabilities from brain disease.

The consequences of climate change are complicated and daunting to grasp. The situation is not unlike changing one nucleotide in the whole genome (e.g. in the gene *SCN1A*) and then trying to fully comprehend the resulting condition (i.e. Dravet syndrome, the pathophysiology of which we cannot fully explain). The likelihood is that some aspects of climate change will do both: change the whole world and change the operational milieu of each individual brain.

It is illustrative to consider this one disease that primarily affects the brain. Dravet syndrome is the most common (~1/15 000 live births) of the group of rare conditions called the developmental and epileptic encephalopathies. Most cases are due to heterozygous loss-of-function variants in the gene *SCN1A*, that encodes the channel $Na_v1.1$, an exquisitely temperature-sensitive protein key to normal brain function. People with Dravet syndrome typically have drug-resistant seizures that can be provoked by fever and high ambient temperatures, intellectual disability, and multiple comorbidities, including autonomic, gait, sleep, speech and swallowing difficulties; behaviour, appetite and social interactions may be disrupted. People with Dravet syndrome are rarely able to live independently, and have an increased risk of premature mortality, often due to sudden unexpected death in epilepsy.

Amongst the anti-seizure medications regularly used in Dravet syndrome are valproate, clobazam, stiripentol and topiramate. Families of people with Dravet syndrome often relate that those affected cannot properly regulate their own temperatures. Most children with Dravet syndrome live with their families; many adults with Dravet syndrome are in residential care. In the UK at least, most residences, home or care, do not have air conditioning (an option with its own carbon challenges). Even this short description shows how complex this single condition is, and prefigures its multiple levels of potential vulnerability to climate change (Fig. 1).

As a thought experiment, overlay a heatwave onto the life of an adult with Dravet syndrome in residential care. As the outdoor temperature rises, the indoor temperature rises, depending on the fabric and ventilation of the building; night-time temperatures remain elevated, because window opening is limited for the safety of the resident, and further disrupt sleep. Thermoregulatory dysfunction, intellectual disability, treatment including topiramate (which can cause hypohidrosis) and lack of mobility together mean that this person cannot engage effective heat loss mechanisms, both physiological and behavioural, and may not detect or be able to communicate their overheating. Altered brain and body temperature can lead to further abnormalities of the dysfunction of mutant $Na_v1.1$ channels, the basis of Dravet syndrome pathophysiology, and of normal $Na_v1.1$ channels. Possibly for days in a row, the patient cannot sleep properly, cannot say they are uncomfortable, may not have had enough water and will have aggravated decompensation of $Na_v1.1$ function, together resulting in more seizures and worsening comorbidities. An ambulance will be called, but, at least in the heatwave in the UK during July 2022, increased demand meant longer delays, and longer waits outside emergency departments, the enclosed (and hot) back of an ambulance compounding the environmental stress on the patient.[7]

Figure 1 The threat of high temperature in a person with a vulnerable neurological condition. A young person with Dravet syndrome needing to keep cool and well hydrated to avoid seizures being provoked by high ambient temperature during a recent heatwave.

All the individual elements of this imagined scenario have happened, and stringing them together represents, in credible microcosm, the multiplicative dangers of climate change for some people with neurological disease. The scenario could be translated, for example, to people with other channelopathies, myasthenia gravis, demyelinating diseases, spinal cord injury, stroke, dementia or various psychiatric diseases, noting also that various drugs, such as some antidepressant, antipsychotic or mood-stabilizing medications, can disrupt thermoregulation.

Climate change, with its far-zreaching everyday consequences across every aspect of life, demands our immediate attention. Without brains working optimally, we will be less able to tackle, manage or live with whatever extents of climate change we will in the future, or now, experience. We can perhaps anticipate some of the likely results by studying closely the brain in which function is already abnormal. Even if by some improbable grace, the human brain turns out to be resilient to climate change, we still need to observe organizational (e.g. NHS, National Health Service), national and international calls for more sustainable practices because the changing climate will still have terrible effects.

We have an added duty to act, because healthcare and scientific research themselves have disproportionately high carbon footprints, but also because we already know that other elements of healthcare systems are not yet resilient to climate change: rails buckle, roads melt, floods destroy bridges—supply chains fail.

We need to educate ourselves about climate change and raise awareness. More data on the effects of climate change on human health and human disease are required. More research therefore needs to be undertaken, more sustainably. We need to start to reimagine healthcare delivery altered in every aspect by the demands of adaptation and mitigation: we could still learn from the pandemic, rather than squander the progress made by its exigencies. We need to consider how best to raise sustainably the next generation of the neuroscience community. For example, how do we balance the undoubted benefits of conferences with their unarguable carbon cost? We can learn from people with neurological diseases how life can be lived when neurological function is compromised: for example, how to travel when driving is not permitted, or how challenges are met when cognitive, motor or sensory functions are compromised.

Unless we focus on these areas now, we risk an escalating feedback loop of compromised brain function and growing inability to respond. In globally challenging times, 'building back better' should include an intent to improve neurological healthcare and improve sustainability—realizing co-benefits from different ways of doing things. For the person with Dravet syndrome, for example, we could now better inform carers and families about the person's sensitivity to temperature, ensure tailored delivery of heatwave alerts, promote informed usage of cooling measures such as nocturnal room ventilation and daytime shading, ensure sufficient hydration, include consideration of heatwaves in emergency rescue protocols, and for the future, better understand the particular vulnerabilities generated by Dravet syndrome pathophysiology for more informed adaptation. Thus, we could both increase resilience for that person to the dangers from heatwaves, whilst also reducing additional healthcare burdens from heat-related admissions.

Action to meaningfully tackle climate change has to be at governmental and international levels. Political will may be growing; organizational initiatives, such as Greener NHS, are happening,[8] technological advances may also serve well. But in any circumstances, there will be at least uncomfortable changes in the environment. Climate change needs us, as neuroscience professionals, trusted by society, to lead the way, change our practice in an informed manner, raise awareness and perform the necessary research, all together, all now.

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