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Brain diseases in changing climate

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Abstract

Climate change is one of the biggest and most urgent challenges for the 21st century. Rising average temperatures and ocean levels, altered precipitation patterns and increased occurrence of extreme weather events affect not only the global landscape and ecosystem, but also human health. Multiple environmental factors influence the onset and severity of human diseases and changing climate may have a great impact on these factors. Climate shifts disrupt the quantity and quality of water, increase environmental pollution, change the distribution of pathogens and severely impacts food production – all of which are important regarding public health. This paper focuses on brain health and provides an overview of climate change impacts on risk factors specific to brain diseases and disorders. We also discuss emerging hazards in brain health due to mitigation and adaptation strategies in response to climate changes.

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1. Climate change as a brain health concern.

There is a consensus in the science community that climate change is a major scientific and medical challenge for the 21st century (WHO, 2018). Jointly with other global environmental changes: ozone layer depletion, soil degradation, pollution, and urbanization, changing climate creates an undeniable threat to our planet and human health (Paris Agreement, 2015). Three major components define climate change – global warming, changes in precipitation patterns and increased occurrence in extreme weather events. Global warming is a result of the increasing concentration of greenhouse gases (CO_2, CH_4, N_2O). Current average concentrations of atmospheric CO_2 levels – above 400 parts per million (ppm) (IPCC, 2018) – have climbed from 280 ppm in the pre-industrial times, and are predicted to reach 1000 ppm by the end of this century (Kiehl, 2011). The global mean surface temperature for 2018 amounts approximately 1°C above the pre-industrial levels and is predicted to rise 2–4°C more by 2100 (IPCC, 2018). Changes in precipitation include increased rainfall at higher latitudes and decreased at lower latitudes (IPCC, 2018). Increased frequency and greater intensity of extreme weather events, heat waves, droughts, hurricanes, tropical storms or floods, occur worldwide (IPCC, 2018). In consequence, sea levels continue to rise (3–4 mm/year with significant local variation) and the oceans are becoming more acidic. Wildfires and land degradation are more frequent and promote the release of environmental contaminants as well as alterations of the farming systems. The changing weather throughout the globe may severely affect biological systems, causing the extinction of some animal species, or promoting the expansion of others (IPCC, 2018). Climate change-related economic collapses, forced migrations, armed conflicts, and other social disruptions impose additional threat (Burrows and Kinney, 2016; Mach et al., 2019). Some groups are particularly vulnerable to the changing climate – primarily populations from low- and middle-income countries, with poor health and safety regulations, lack of infrastructure and environmental protection (Daoud et al., 2016; Hallegatte and Rozenberg, 2017). Geographically, coastal and marine regions are more susceptible to damaging impacts of changing climate and natural disasters (Lu et al., 2018). Urban areas (Misslin et al., 2016; Zhang et al., 2019), and areas close to industrial plants (Azuma et al., 2014) are also more likely to be affected.

In light of the overwhelming evidence and broad scientific consensus of a changing climate, associated altered exposures to risk factors may affect human health, and thus also make it a public health concern (Kinney, 2018; Veenema et al., 2017). As numerous environmental factors are playing a role in the onset and severity of human diseases, understanding the modulatory effect of climate change is a priority. In this paper, we focus particularly on brain health. We provide an overview of the climate change impact on risk factors with implications for brain diseases, principally exposure to pathogens and hazardous pollutants, malnutrition, physical and psychological stress (Figure 1). We also discuss risks due to mitigation and adaptation activities in response to the changing climate.

2. Climate change-affected risk factors in brain disease.

2.1. Infectious diseases.

2.1.1. Vector-borne and zoonotic diseases.—Good examples of risks mediated by ecosystem changes are shifts in infectious diseases, particularly vector-borne and zoonotic diseases (VBZDs). The VBZDs ecology is complex and dependent upon multiple factors, including location, altitude, ecosystem, host, vector, weather and the climate. The VBZDs outbreaks are rising worldwide (e.g. avian influenza H5N1) and there is a strong evidence that the changing climate contributes to it (Canavan, 2019). Climate influences the occurrence, incubation period, survival, distribution, and transmission of pathogens and vectors. Changes in temperature, humidity or precipitation affect the VBZDs through host-vector interactions and through ecosystem changes. Climate shifts can also affect the epidemiological dynamics of the disease transmission indirectly, by changing social and cultural behaviors, as well as the economy (Caminade et al., 2019). Climate change is believed to promote the expansion of many tropical disease vectors in warming Europe (Semenza and Suk, 2018) and Northern America (Caminade et al., 2014). On the other hand, certain VBZDs may decrease in particular (warmer) regions, as habitats become less suitable for a host or vector survival and disease transmission (Cizauskas et al., 2017; Lafferty and Mordecai, 2016). The impact of climate change on various VBZDs transmission and epidemiology has been extensively studied and reviewed (Asad and Carpenter, 2018; Caminade et al., 2019; Campbell-Lendrum et al., 2015; Ebi and Nealon, 2016; Lafferty and Mordecai, 2016; Purse et al., 2017; Semenza and Suk, 2018). Herein, we focus on scenarios which contribute to climate-induced changes in geographic distribution and epidemiology of the VBZDs affecting the central nervous system (CNS). The pathogens may target the brain specifically, e.g. Japanese encephalitis and neuroborreliosis, or neurological outcomes may be secondary to the general infection, such as in malaria or yellow fever.

Aedes spp. mosquito is an example of a widespread tropical disease vector currently on a rise (Caminade et al., 2014). This is the major host for infectious arboviruses causing Dengue, Zika, Chikungunya, West Nile, and Yellow Fever (Kleinschmidt-DeMasters and Beckham, 2015). Mosquitoes reproduce and feed more frequently in higher temperatures (Carrington et al., 2013; Yang and Sarfaty, 2016), and with increasing global temperatures, the distribution of the *Aedes spp*. has drastically increased over the past few decades. Future predictions indicate further growth in Europe and North America, but local reductions in Southeast Asia and West Africa (Ebi and Nealon, 2016; Ryan et al., 2019). Dengue is currently the fastest spreading tropical infection in the world (Messina et al., 2019; Stanaway et al., 2016), exhibiting certain neurological outcomes in up to 20% of cases, mostly encephalitis and encephalopathy (Li et al., 2017). Both dengue virus and its vector *(Aedes spp.)* are sensitive to changing climate condition, as reviewed in (Ebi and Nealon, 2016; Li et al., 2018). Chikungunya occasionally affects the brain (Mehta et al., 2018) and its epidemiology is closely tied with weather patterns and climate change, as reviewed in (Meason and Paterson, 2014; Tjaden et al., 2017). Yellow fever can also lead to fatal encephalitis associated with acute inflammation and widespread neuronal damage (Almeida Bentes et al., 2019). West Nile virus is an important emerging neurotropic virus responsible for severe encephalitis outbreaks in humans and horses worldwide (Suen et al., 2014) – this

neuroinvasive infection is a serious threat particularly to infants, elderly and immunocompromised populations (Kleinschmidt-DeMasters and Beckham, 2015). Zika virus has attracted considerable attention recently for its potential to cause microcephaly, cortical thinning and blindness during early development, while meningoencephalitis and Guillain-Barre syndrome in adults (Araujo et al., 2016; Russo and Beltrao-Braga, 2017). The effect of climate changes on the dynamically changing Zika epidemiology has been recently recognized and discussed (Asad and Carpenter, 2018; Depoux et al., 2018). Japanese encephalitis virus belongs to arboviruses transmitted by *Aedes spp.*, but its primary host is another mosquito type, *Culex spp.* inhabiting Southeast Asia and the Western Pacific. The virus causes a severe infection of the brain, with about 68,000 symptomatic cases and 17,000 deaths per year (WHO). Weather conditions, particularly floods, were associated with an increased number of disease cases in China (Zhang et al., 2016).

Anopheles mosquitos transmit a protozoan parasite *Plasmodium falciparum* – the major cause of malaria in humans. This tropical infection kills approximately (approx.) one million people per year, mostly due to coma – cerebral malaria (CM). Survivors of the CM exhibit severe neurological deficits like epilepsy, cognitive impairment, and behavioral disorders, such as attencion deficit, hyperactivity and aggressive behavior, particularly common in young individuals (Hora et al., 2016; Postels and Birbeck, 2013). The impact of changing climate has been addressed in numerous recent studies and findings suggest a significant effect on malaria distribution and epidemiology (Boyce et al., 2016; Caminade et al., 2014; Dasgupta, 2018; Eikenberry and Gumel, 2018; Ivanescu et al., 2016; Leedale et al., 2016; Onyango et al., 2016).

In addition to mosquitos, other vectors transmitting neurological diseases are affected by climate and weather. Geographic distribution of *Ixodes Ricinus*, a species of hard tick that transmits several important brain diseases in Europe and North Africa is influenced by climate change (Alkishe et al., 2017; Jore et al., 2014; Ostfeld and Brunner, 2015). Transmission by the tick lyme neuroborreliosis is caused by bacteria *Borrelia burgdorferi*, and manifests as lymphocytic meningoradiculitis (Bannwarth syndrome) (Garkowski et al., 2017). Tick-borne encephalitis (TBE) is a serious neuroinfection caused by a flavivirus. The disease is seasonal, dependent on the host-seeking activity of nymphs, and increased risk of the TBE has been linked to increasing temperatures (Daniel et al., 2018). Changing climate has been suggested to affect transmission and epidemiology of many other VBZDs exhibiting neurological outcomes: cerebrospinal bacterial meningitis (Codjoe and Nabie, 2014), tuberculosis (Sergi et al., 2019), syphilis (Marinho de Souza et al., 2019), cerebral schistosomiasis (McCreesh et al., 2015; Yang and Bergquist, 2018; Zhu et al., 2017), leishmaniasis (Azimi et al., 2017; Mendes et al., 2016; Purse et al., 2017; Ready, 2008), Chagas disease (Carmona-Castro et al., 2018; Garza et al., 2014), strongyloidiasis (Beknazarova et al., 2016; McMahon et al., 2012), toxoplasmosis (Yan et al., 2016), neurocysticercosis caused by soil-transmitted helminthiases (Weaver et al., 2010), and neurological diseases associated with rabies (Hayes and Piaggio, 2018), or human immunodeficiency virus (HIV) infections (Low et al., 2019).

2.1.2. Water-borne diseases.—Water-borne diseases (WBDs) are infectious diseases caused by a wide variety of pathogens transmitted through water and exhibiting strong

dependence on climate and meteorological conditions, such as heavy rainfall, flooding, and other extreme events promoting the pathogen transmission (Levy et al., 2018; Levy et al., 2016; Walker, 2018). The WBDs are often related to food consumption due to a tight association of food and water. Infections are mostly gastrointestinal (diarrheal), although the pathogens may affect other systems, including the brain. Several previously mentioned VBZDs are also WBDs (e.g. malaria, dengue schistosomiasis, toxoplasmosis), but other infectious diseases associated with water exposure may lead to neurological damage.

Primary amebic meningoencephalitis (PAM) is a rare, but extremely fatal infection of the brain caused by *Naegleria fowleri*, known as the “brain-eating amoeba”, commonly found in warm freshwater. Infection usually occurs during recreational water activities, but exposure from drinking water has also been recorded (Cope et al., 2015). The clinical presentation of PAM is often indistinguishable from bacterial meningitis (headache, fever, nausea, and vomiting), thus the diagnosis is difficult and rarely on time – only 27% of cases are diagnosed before death due to the cerebral edema, and mortality rate is above 97% (Capewell et al., 2015). In the last decade, notable changes have been documented regarding PAM epidemiology. Secondary to increased temperatures, first PAM cases have been reported in the northern U.S. (Cope and Ali, 2016; Kemble et al., 2012). Increased incidence of hepatitis A virus (HAV) infection depends greatly on water-related extreme weather events (Gao et al., 2016; Gullon et al., 2017; Hu et al., 2004; Morand et al., 2013). The infection usually manifests as fatigue or jaundice, but sporadically the CNS impairment occurs (Alehan et al., 2004; Hegazi et al., 2011; Lee et al., 2011). Moreover, several bacterial infections producing neurological symptoms and transmitted by water have been affected by the changing global climate, e.g.: leptospirosis (Lau et al., 2010), shigellosis (Cheng et al., 2017; Liu et al., 2017; Song et al., 2018; Zhang et al., 2017), campylobacteriosis (Allard et al., 2011; Rosenberg et al., 2018; Soneja et al., 2016), salmonellosis (Lake, 2017; Wang et al., 2018; Welch et al., 2019), infections of *Escherichia coli* (Hellberg and Chu, 2016; Iqbal et al., 2019; Philipsborn et al., 2016), or *Staphylococcus aureus* (Hellberg and Chu, 2016).

2.2. Environmental neurotoxins.

Multiple environmental contaminants have a neurotoxic effect on the brain. Heavy metals such as mercury (Hg) (Farina and Aschner, 2017; Pletz et al., 2016), arsenic (As) (Escudero-Lourdes, 2016; Tolins et al., 2014), manganese (Mn) (Peres et al., 2016) and lead (Pb) (Andrade et al., 2017; Caito and Aschner, 2015; Singh et al., 2018), pesticides (Burke et al., 2017; Cassereau et al., 2017), persistent organic pollutants (POPs) (Costa et al., 2014; Winneke, 2011), endocrine disruptive chemicals (EDCs) (Ghassabian and Trasande, 2018; Pomara et al., 2015; Weiss, 2012), or biotoxins (Grant et al., 2010) – all have been associated with the development of neurological outcomes in humans. Their occurrence in the environment is due to natural or anthropogenic sources, and accumulation and recycling are subjected to climate and weather changes. How present and future climate shifts alter the transport, transfer, deposition, and fate of various environmental pollutants has been extensively reviewed elsewhere (Kallenborn et al., 2012; Macdonald et al., 2005; Noyes et al., 2009; Schiedek et al., 2007; Van Oostdam et al., 2005). Herein, we discuss the major

concepts regarding climate impact on the circulation of environmental neurotoxins in the air and water.

The weather has a strong influence on the distribution and concentrations of air contaminants, and the changing climate likely accelerates air pollution, especially in urbanized areas. Extreme weather conditions, as well as increased temperature and humidity, promote the formation of particulate matter (PM) and changes in ozone (O_3) levels (Doherty et al., 2017; Kinney, 2018). On the other hand, increased temperatures and locally decreased precipitation are projected to increase the frequency and expansion of wildfires during which the PM and other pollutants (Hg, As, Pb) are released into the environment (Cascio, 2018; Kinney, 2018; Liu et al., 2016). A growing body of epidemiological and modeling evidence suggests that global warming coupled with O3 and PM exposures will exacerbate the prevalence and severity of human disease and mortality (Noyes et al., 2009). While positive association between air pollution exposure and prevalence of neurological diseases is well established (Block and Calderon-Garciduenas, 2009; Costa et al., 2017; Lee et al., 2017; Myhre et al., 2018; Sram et al., 2017; Sunyer and Dadvand, 2019), the potentiating effect of climate change is still poorly studied. Lee et al. (2018) showed that increased air levels of PM, NO_2, O_3, and CO, enhanced the risk of migraine in Korean population (Seoul) and particles' effects were significantly stronger on high-temperature days (Lee et al., 2018).

Intensified precipitation and extreme weather events may cause an overflow of contaminated land, which can lead to remobilization of contaminants from sediments and pollution of freshwater. Additionally, the increased temperature may enhance the volatility of contaminants from soils and water. Rising sea and ocean levels have been shown to intensify As release from contaminated coastal soils (LeMonte et al., 2017). Snow and ice melt release and remobilize sequestered pollutants – in Antarctic soil and permafrost are considered a sink for environmental contaminants, especially heavy metals and POPs, which once released, may disturb their ecological balance (Potapowicz et al., 2019). Climate change-driven oxygen limitation (hypoxia) may also alter neurotoxin deposition – hypoxic episodes reduced solid-phase manganese dioxide (MnO_2) accumulated in the marine sediments causing a substantial increase of bioavailable Mn^{2+} concentrations in the water (Schiedek et al., 2007). Climate change may also influence how environmental contaminants accumulate in the aquatic organisms, enhancing toxicity in them and in humans who depend on seafood in diet. As discussed in (Kennedy and Walsh, 1997; Noyes et al., 2009; Schiedek et al., 2007; Van Oostdam et al., 2005), higher temperatures facilitate the bioavailability, uptake, biomagnifications, transport, degradation, volatilization, remobilization and metabolism of toxic chemicals. For instance, ocean warming intensifies methylation of mercury and subsequent uptake of methylmercury (MeHg) in fish and marine mammals by 3–5% for each 10°C rise in water temperature (Booth and Zeller, 2005). In turn, the amplification of food web bioaccumulation of MeHg and other emerging pollutants under climate change has been proposed (Alava et al., 2018; Taylor et al., 2019). Higher temperatures also facilitate the metabolism of aquatic species. In the light of reduced O_2 concentration, the higher rate of water inflow into the body is needed to extract enough O_2 – this may also increase the exposure to the dissolved pollutants. Bioavailability of contaminants is affected by salinity (McLusky et al., 1986) and acidification (low pH) (Riba et al., 2004), and climate-dependent changes in acidification may enhance bioaccumulation

of some toxic metals, as found with clams (Lopez et al., 2010). Moreover, higher temperatures and lower salinity alter the aquatic species' ability to cope with toxic stress (Heugens et al., 2001; Velasco et al., 2018).

The rise of precipitation, surface water temperature and nutrient loading accelerate growth of harmful algal blooms (e.g. *Pseudonitzschia spp.*, blue-green cyanobacteria and dinoflagellates), which are increasing in frequency, intensity, and duration globally (Chapra et al., 2017; Goldstein et al., 2008; Huisman et al., 2018; Paerl, 2018). They produce neurotoxins – microcystin, saxitoxin, brevetoxin or domoic acid (Chernoff et al., 2017; Grant et al., 2010; Porojan et al., 2016), which accumulate in fish and other seafood increasing the risk of adverse shellfish poisonings, affecting the brain and other organs in humans (Grant et al., 2010; Watkins et al., 2008). The neurological effects include amnesia, epilepsy, parkinsonian- and dementia-like symptoms which may be severe, chronic, and even lethal (Ramsdell and Gulland, 2014; Wang, 2008); some biotoxins may cross the mammalian placenta and accumulate in the amniotic fluid disturbing neurodevelopment (Costa et al., 2010; Ramsdell and Zabka, 2008). Although the most frequent human exposure is *via* consumption of contaminated seafood, the poisoning also occurs through drinking water, consumption of plants irrigated with biotoxin-contaminated water, or swimming in polluted recreational waters.

2.3. Food contamination and malnutrition.

The quantity and nutritional quality of agricultural production depend on soil quality, sunlight, CO_2, temperature, and water availability. Thus, due to increasing temperatures and water-dependent extreme weather events, changing climate will likely affect seasonal food availability, food contamination, or increased consumption of toxin in the diet (Myers et al., 2017). Increasing temperatures enhance soil erosion which facilitates pesticide run-off and pollution, and endorses the need for artificial fertilizers. Changing climate will likely promote weeds growth, the survival of some pests and diseases affecting plant and livestock, thus more herbicides, pesticides, insecticides, and other chemicals will be required, contributing to the even greater contamination of the environment, and subsequently the food (Boxall et al., 2009; Myers et al., 2017). Food is also an important vector of some infectious diseases affecting the brain, like previously mentioned toxoplasmosis (see 2.1.1.), shigellosis, campylobacteriosis, infections caused by *Escherichia coli, Staphylococcus aureus* or HAV (see 2.1.2.). The hot and humid climate is favorable for the growth of mycotoxin-producing fungal molds, thus weather and climate shifts may enhance contamination of food and environment (Paterson and Lima, 2011). Some mycotoxins exhibit severe neurotoxic effects, e.g. fumonisin B1 (Domijan, 2012), lolitrems, paspalitrems (Kozak et al., 2019; Plumlee and Galey, 1994), and several brain diseases have been linked to mycotoxins exposure (Bonnet et al., 2012; French et al., 2019; Ratnaseelan et al., 2018; Terciolo et al., 2018).

Future prognosis indicates that crop production will change and shift geographically, leaving some regions unsuitable for conventional farming. Climate change is likely to increase the area, frequency, and duration of extreme droughts. This will lead to changes in crop yield, higher food prices and consequently lower affordability, reduced calorie availability, and

growing malnutrition in vulnerable populations from developing countries (Myers et al., 2017; Squire and Ryan, 2017). Malnutrition, particularly in early life, profoundly influences neurodevelopment, alters neurocognitive performances and cause severe neurological disorders, as reviewed in (Mattei and Pietrobelli, 2019). Moreover, it has been shown that the burden of conventional neurodevelopmental toxins (e.g. Pb) is exacerbated by malnutrition (Guerrant et al., 2008).

2.4. Brain (patho)physiology.

The brain is at the forefront of animals' interactions with the environment, thus changing climate may have a direct effect on the CNS development and performance, thereby affecting behavior. From animal studies emerges that temperature modulates brain development – changing temperature can alter gene expression (Pallotta et al., 2017), neuronal structure, brain organization (Amiel et al., 2017; Groh et al., 2004), and learning ability (Dayananda and Webb, 2017; Wang et al., 2007). The thermal environment can influence neurogenesis in adult brain (Ramirez et al., 1997). Other abiotic conditions are shown to impair neural function in animals – lowering barometric pressure aggravates depression-like behaviors in rats (Kanekar et al., 2015; Mizoguchi et al., 2011) and induces neuronal activation in the superior vestibular nucleus in mice, linked to the generation of meteoropathy (Sato et al., 2019).

Climate change-related atmospheric conditions have been also associated with neurological issues in humans. Both increases and decreases in temperature lead to a significant (approx. 20% for 5°C change) increase in the number of migraine reports in German population in 2011–2012 (smartphone app and web form study) (Scheidt et al., 2013). Heat stroke is a life-threatening condition – severe increase in body temperature with central nervous system dysfunction that often includes combativeness, delirium, seizures, and coma. It primarily occurs in immunocompromised individuals during annual heat waves, but exertional heat stroke is observed in young fit individuals performing strenuous physical activity in hot environments (Leon and Bouchama, 2015). When the influence of weather on the incidence of primary spontaneous intracerebral hemorrhage was analyzed, changes in barometric pressure (Garg et al., 2019), the PM and O_3 concentrations (Han et al., 2016), but not temperature, primarily affected the incidence of the condition. The impact of thermal conditions on intracerebral hemorrhage seems to be complex (Luo et al., 2018; Ma et al., 2018). Overall, the topic is little explored, moreover, it is still not clear how environmental conditions affect the core body and brain temperature (Cramer and Jay, 2016; Kiyatkin, 2018; Smith and Johnson, 2016; Szekely and Garai, 2018).

Although direct indications on the effect of climate change on brain (patho)physiology are limited, general understanding of the underlying mechanisms arise from *in vivo* and *in vitro* studies of the impact of heat stress and hyperthermia on brain metabolism. Given the exogenous cause of hyperthermia during current climate change, in this section we intentionally avoided discussion of the observations dealing with endogenous hyperthermia due to impaired brain thermoregulation (Kiyatkin, 2005).

Despite the observation of heat-induced increase in basal metabolic rate in certain brain regions, a significant decrease was observed in human caudate, putamen, insula, and

posterior cingulum neuron metabolism (Nunneley et al., 2002). It is also notable that, even at a relatively stable global cerebral blood flow in environmental hyperthermia, regional (prefrontal cortex, somatosensory areas and limbic system) blood flow tended to decrease, being associated with mood state and cognitive changes (Qian et al., 2014). Heat-induced reduction in cerebral blood flow was also associated with reduced orthostatic tolerance (Crandall and Gonzalez-Alonso, 2010). Certain cerebrovascular effects of endogenous hyperthermia may be also mediated by heat-induced hyperventilation and hypocapnia (Ross et al., 2012) with subsequent respiratory-induced alkalosis (Bain et al., 2015). The latter were shown to reduce cerebral blood flow during passive hyperthermia (Bain et al., 2013). The patterns of cerebral blood flow under environmental hyperthermia also correspond to the observed functional heterogeneity of brain regions (Qian et al., 2013). Particularly, environmental hyperthermia (50 °C) was shown to impair functional connectivity of brain that may underlie alteration of cognitive performance and work behavior (Sun et al., 2013), as well as visual short-term memory (Jiang et al., 2013). Whole body hyperthermia induced long-term learning and memory deficits in rats with mild traumatic brain injury (Titus et al., 2015). Heat stress was also shown to impair blood-brain barrier and blood-cerebrospinal fluid barrier structure leading to an increase in their permeability and brain edema in rats (Sharma et al., 2010). These effects were found to be aggravated by diabetes (Muresanu et al., 2010a) and hypertension (Muresanu et al., 2010b).

Seizures are considered as the most common complications of hyperthermia and heat stroke (Leon and Bouchama, 2015), being at least partially associated with heat-induced activation of transient receptor potential cation channels (TRPV4) and N-methyl-D-aspartate receptors (NMDAR) signaling, as demonstrated in a zebrafish model (Hunt et al., 2012). High temperature exposure was shown to induce hyperthermic seizures along with inflammatory response in rats, that was aggravated by lipopolysaccharides treatment (Eun et al., 2015). Environmental hyperthermia was shown to aggravate adverse effects of brain trauma (Hermstad and Adams, 2010) even in the case of mild brain injury (Sakurai et al., 2012). Body hyperthermia (39°C) had a significant interactive effect with epileptic seizures in inducing neuronal injury in the amygdala and hippocampus (Suchomelova et al., 2015). Hyperthermia (39–40°C) was shown to induce epileptiform discharges in cortical neurons *in vitro* through interference with gamma-aminobutyric acid (GABA) receptor signaling (Wang et al., 2011). Structural changes due to heat-exposure (37–40°C) were observed in neurons and their axons, glia, as well as cerebral vascular endothelium (Sharma and Hoopes, 2003).

The intimate mechanisms of the observed effects of hyperthermia are still to be estimated, although some common pathways have been revealed (Figure 2). Heat stress is considered as an environmental prooxidant factor (Slimen et al., 2014). Heat exposure (44 °C) was shown to induce oxidative stress in brain and Tau pathology in laboratory rodents (Chauderlier et al., 2017), providing an additional link between hyperthermia and neurodegeneration. Correspondingly, high temperature exposure was shown to decrease antioxidant superoxide dismutase (SOD) expression and activity in neuronal HT-22 cells with subsequent cell death (El-Orabi et al., 2011). In addition to oxidative stress, exposure of primary cortical neurons to heat stress resulted in endoplasmic reticulum (ER) stress, inhibiting protective heat shock responses (Liu et al., 2012). These observations are generally in agreement with the indications of tight interplay between ER and oxidative stress in brain pathology (Thornton

et al., 2017). Heat-induced mitochondrial dysfunction (irreversible mitochondrial membrane potential ΔΨm depolarization) with subsequent caspase-3 activation and apoptotic signaling was proposed as the potential mechanisms of hyperthermia-induced death of cultured rat neurons (White et al., 2012). Earlier studies revealed increased infarct volume and increased mortality in heat-exposed animals with ischemic stroke (Noor et al., 2003), that may be associated with heat-induced increase in matrix metalloproteinase (MMP-2) activity as well as basal membrane protein degradation and loss (Alam et al., 2011; Meng et al., 2012). Increased excitability of brain seems to play a significant role in heat-induced brain damage. For example, heat stress (38°C) significantly increased brain glutamate and aspartate levels in rats, whereas GABA and glycine concentrations were reduced, thus providing a shift to excitatory neurotransmitters (Sharma, 2006). These findings are in agreement with decreased hippocampal GABAergic synaptic transmission (Qu et al., 2007). Systemic glutamate levels were reduced in rats exposed to mild hyperthermia (37–39°C), whereas further heating (42°C) significantly elevated circulating glutamate concentrations (Zlotnik et al., 2010). Correspondingly, increased NMDAR signaling was also shown to contribute to heat-induced seizures (Morimoto et al., 1995), whereas NMDAR down-regulation had a protective effect in acclimation (Ely et al., 2015). Hyperthermia was shown to cause depolarization and reduced input resistance in parallel with increased synaptic activity of hippocampal pyramidal cells and inhibitory interneurons, being also indicative of higher excitability of the brain (Kim and Connors, 2012). It is expected that impaired calcium Ca^{2+} homeostasis may also contribute to neuronal damage under heat exposure, although the existing data are limited (White et al., 2012). Hyperthemic-dependent Ca^{2+} dysregulation has been shown in pathomechanisms of other systems, like smooth muscles (Burke and Hanani, 2012) and endothelial cells (Li et al., 2015). The latter may be involved in impaired cerebrovascular reactivity at heat stress exposure..

Prolonged heat exposure in mice resulted in a proinflammatory milieu being characterized by increased nuclear factor NF-κβ signaling and increased expression of interleukin IL-1β, tumor necrosis factor (TNF-α), cyclooxygenase-2, and inducible nitric oxide synthase (iNOS) in hippocampus with subsequent decrease in neuronal and synaptic density, and gliosis (Lee et al., 2015). Neuroinflammation was also associated with altered hypothalamic monoamine content and glutamate levels in heat-stressed (42°C) animals (Chauhan et al., 2017). Systemic inflammatory response syndrome is considered as an important pathway in heat stroke (Leon and Helwig, 2010).

Taken together, heat exposure induces complex metabolic changes in brain, resulting in formation of pathogenetic cascades including heat-induced oxidative stress, ER stress, mitochondrial dysfunction, apoptosis, excitotoxicity, neuroinflammation, and impaired brain microcirculation, being all implicated in neurodegeneration and other brain diseases.

2.5. Mental health.

Climate-related environmental changes may profoundly impact psychological well-being and mental health, particularly among those with pre-existing vulnerabilities or living in ecologically sensitive areas. Climate change may affect physical health (heat stress, injury, disease, disruption to food supply), or endorse mental health issues directly, by exposing

people to the psychological trauma. Such trauma can be induced by multiple factors, particularly those related to extreme weather events and natural disasters: personal loss; destroyed environment, landscapes, infrastructure, and communities; decreased food access; depressed economy and impaired financial security; forced migration or social conflicts. Moreover, psychological distress may result from acknowledging climate change as a global environmental threat (Fritze et al., 2008). Depression and anxiety (Mamun et al., 2019), post-traumatic stress disorder (PTSD) (Hanigan et al., 2018; LaJoie et al., 2010; Pietrzak et al., 2012; Schwartz et al., 2017), increased substance use (Rohrbach et al., 2009), and suicide rates (Carleton, 2017; Fountoulakis et al., 2016a; Fountoulakis et al., 2016b; Hanigan et al., 2012) are increasing with changes in climate conditions. For instance, depression symptoms were eight times higher among people in flooded homes (Azuma et al., 2014). Short-term exposure to extreme weather, climate warming, or tropical cyclone was associated with worsened mental health, as concluded from data drawn from nearly 2 million U.S. residents between 2002 and 2012 (Obradovich et al., 2018): shifting from monthly temperatures between 25 °C and 30 °C to >30 °C increased the probability of mental health issues by 0.5% points, 1°C of 5-year warming was associated with a 2% increase in the prevalence of mental health issues, and exposure to Hurricane Katrina was associated with a 4% increase in this metric (Obradovich et al., 2018). PTSD and psychological distress have been observed years after a hurricane, particularly among vulnerable populations (LaJoie et al., 2010; Paxson et al., 2012). For a more comprehensive reading on the climate change impact on human mental health, we recommend recent reviews (Berry et al., 2018; Bourque and Willox, 2014; Burke et al., 2018; Dyregrov et al., 2018; Hayes et al., 2018; Torres and Casey, 2017; Trombley et al., 2017).

3. Mitigation and adaptation to climate change produce additional risk factors for brain diseases.

Emerging health risks related to changing climate can be minimized and avoided *via* effective mitigation and adaptation pathways. One of the major targets of the Paris Agreement is to limit global warming to no more than 2°C above the pre-industrial levels by 2100 (Paris Agreement, 2015). There are many potential paths to reach this goal, although no current strategy can prevent the change in climate that has already occurred (Portier et al., 2010). The major strategy of climate change mitigation aims to reduce global greenhouse emissions, through reduction of energy consumption and the use of fossil fuels, development and expansion of alternative energy sources and energy conservation technologies. Moreover, carbon capture and storage, changes in land use (reforestation) and actions aiming to preserve ecosystems and conserve biodiversity are introduced, as reviewed in (Tong and Ebi, 2019; Woodward, 2019). Climate change is very complex and difficult to predict – it occurs fast and manifests differently in different places. Analogously, the indirect impact and health risks associated with human responses and undertaken actions, due to the scale and speed, are also uncertain and challenging (Carney, 2016). Mitigation and adaptation responses to changing climate will likely disturb the environment and consequently human health – numerous strategies may have both positive and negative effects, most of which are poorly recognized or understood.

For instance, reduction in the use of fossil fuels will likely reduce the release of neurotoxicants such as As, Hg, and other contaminants into the environment (Gustin and Ladwig, 2004; Hu and Cheng, 2016; Ito et al., 2006). But it may also open new routes of human exposure, e.g. due to improper disposal of energy-saving fluorescent light bulbs containing Hg, or heavy metals release associated with manufacturing and disposal of batteries used in electric vehicles (Bronstein et al., 2009; Noyes et al., 2009). Nuclear power plants are potential sources of contamination and they have strong environmental impacts on water availability and quality. Increased reliance on hydroelectric power, which typically requires the construction of dams, may change local VBZDs ecologies and alter diseases transmission (Zhou et al., 2016). Mitigation focused on the preservation of forests and wetlands are also likely to impact VBZDs ecology and transmission.

Adaptation efforts may increase environmental contamination and human exposure to neurotoxic compounds, due to e.g. the increased use of insecticides to cope with transmission of VBZDs vectors or application of (new) pesticides and herbicides in response to changed requirements for food production (Noyes et al., 2009). Interestingly, the indirect consequences of climate change, e.g. shifts in agriculture and resource exploitation may have a more pronounced impact on contaminants presence in the environment, than direct climate change, as shown on the example of POPs (Kallenborn et al., 2012). Capture and storage of water runoff to adapt to drought may provide more suitable breeding habitat for mosquitoes, thereby increasing incidence of VBZDs. Moreover, increased application of biofuels as alternative energy sources or genetically modified organisms, may have a questionable effect on food-borne diseases and human nutrition. Climate change-related, drought-triggered famines may lead to increased consumption of resilient plants such as grass pea, cassava or cycad seeds, containing neurotoxicants which are associated with a high-burden of neurological diseases. Unbalanced grass pea *(Lathyrus sativus)* consumption due to substantial amount of neurotoxic β-N-oxalyl-L-α,β-diaminopropionic acid (ODAP) has been associated with neurolathyrism, a neurodegenerative disease that causes paralysis of the lower body. In normal socio-economic and environmental situations, in which grass pea is part of a balanced diet, neurolathyrism is virtually non-existent (Lambein et al., 2019). Cassava *(Manihot esculenta*, also known as mandioca, yuca) is a root vegetable resistant to poor soil and drought, which is an important staple, particularly among people who live in poverty and remote tropical areas (Gleadow et al., 2016). Unprocessed cassava contains high amounts of neurotoxic cyanogenic glucosides (linamarin and lotaustralin), associated with development of myeloneuropathy and konzo (Kashala-Abotnes et al., 2019). Edible cycads seeds contain multiple neurotoxins (methylazoxymethanol, β-methylamino-l-alanine, β-alanine-l-oxalylamino and cycasin) and their consumption has been associated with the development of neurodegenerative diseases with motor impairment, such as amyotrophic lateral sclerosis or Parkinson's disease (Rivadeneyra-Dominguez and Rodriguez-Landa, 2014). Thus, in the light of such complex climate-environment-human interactions, scrutinized examination of the neurological health risks associated with mitigation and adaptation strategies is needed.

4. Conclusions.

Climate change rapidly and extensively disrupts global ecosystems with yet unknown consequences for human. Rising average temperatures and sea levels, and intensification of extreme weather events impact environmental factors which directly or indirectly affect human health. Moreover, the impact of human responsive actions associated with mitigation and adaptation strategies poses additional hazard through intensification of some health risk factors. Many of them, separate or jointly contribute to increased occurrence of brain diseases. Changing climate conditions promote transmitting of pathogens infecting the brain; intensify environmental pollution increasing risk of exposure to the harmful neurotoxicants; create food contamination and shortage potentially leading to brain-affecting malnutrition and poisoning. Climate-driven natural disasters and their socio-economic consequences have a strong and persistent impact on the mental health of affected populations. Moreover, drastically changing weather conditions may directly disturb brain physiology. Yet scientific evidence is sparse, and more research is needed to recognize and effectively address all these emerging and complex challenges associated with climate change-driven environmental risk factors of neurological diseases.

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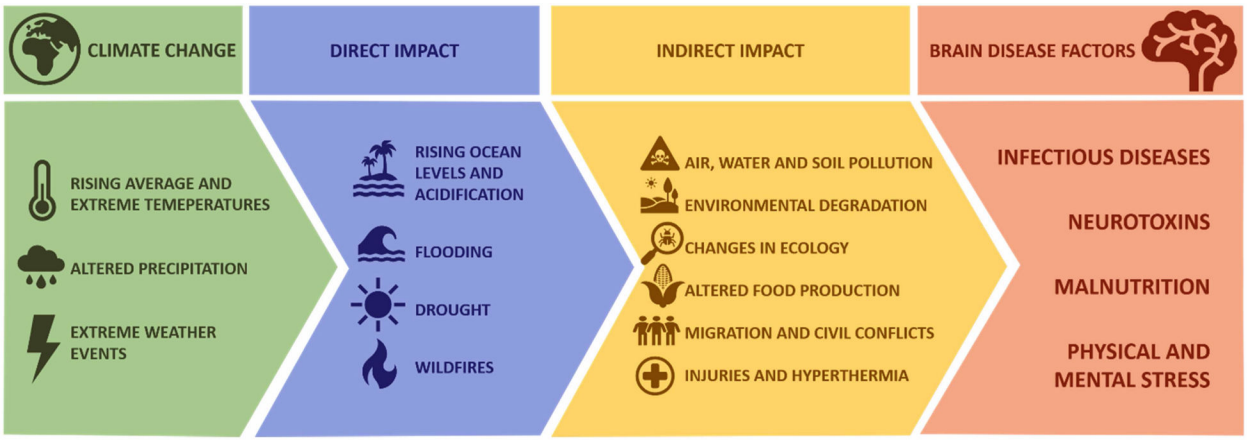

Figure 1.

Direct and indirect consequences of global climate change contribute to increased occurrence of risk factors in brain disease.

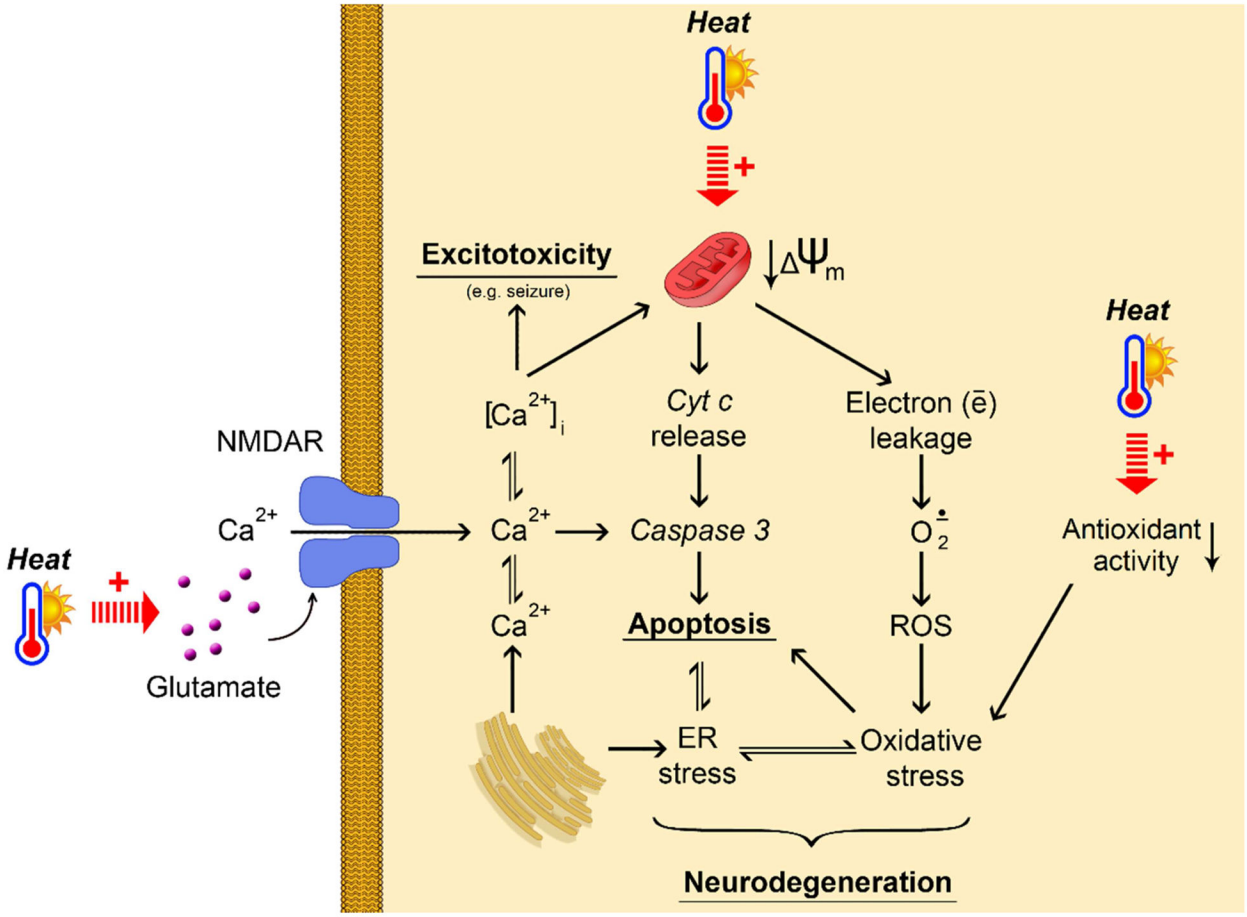

Figure 2.

Hypothetical mechanisms of the impact of heat exposure on brain (patho)physiology. Heat exposure results in mitochondrial dysfunction decreased mitochondrial membrane potential ($\downarrow\Delta\psi_m$) causing increased electron leakage. The latter is associated with increased superoxide ($O_2^{\cdot-}$) generation and further increase in reactive oxygen species (ROS) production resulting in oxidative stress together with decreased antioxidant enzymes activity. Both oxidative stress and heat exposure impair endoplasmic reticulum (ER) functioning ultimately leading to ER stress. Increased cytochrome c (Cyt c) release due to mitochondrial dysfunction induces caspase-3 activation and apoptotic signaling. The latter is aggravated by oxidative and ER stress. Hypothetically, a tight interplay between mitochondrial dysfunction, apoptosis, oxidative stress and ER stress may underlie heat-induced neurodegeneration. The overall effect of heat exposure is also associated with increased brain glutamate levels, although the particular mechanisms are unclear. Elevated glutamate levels induce NMDA receptor signaling causing intracellular Ca^{2+} flux. Taken together with Ca^{2+} release from ER, glutamate-induced Ca^{2+} uptake results in increasing intracellural calcium levels ($[Ca^{2+}]i$) levels, leading to excitotoxicity and seizures. Moreover, increased $[Ca^{2+}]i$ levels aggravate apoptotic signaling through caspase-3 activation.