Cognitive impairment and World Trade Centre-related exposures

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Abstract | On 11 September 2001 the World Trade Center (WTC) in New York was attacked by terrorists, causing the collapse of multiple buildings including the iconic 110-story 'Twin Towers'. Thousands of people died that day from the collapse of the buildings, fires, falling from the buildings, falling debris, or other related accidents. Survivors of the attacks, those who worked in search and rescue during and after the buildings collapsed, and those working in recovery and clean-up operations were exposed to severe psychological stressors. Concurrently, these 'WTC-affected' individuals breathed and ingested a mixture of organic and particulate neurotoxins and pro-inflammogens generated as a result of the attack and building collapse. Twenty years later, researchers have documented neurocognitive and motor dysfunctions that resemble the typical features of neurodegenerative disease in some WTC responders at midlife. Cortical atrophy, which usually manifests later in life, has also been observed in this population. Evidence indicates that neurocognitive symptoms and corresponding brain atrophy are associated with both physical exposures at the WTC and chronic post-traumatic stress disorder, including regularly re-experiencing traumatic memories of the events while awake or during sleep. Despite these findings, little is understood about the long-term effects of these physical and mental exposures on the brain health of WTC-affected individuals, and the potential for neurocognitive disorders. Here, we review the existing evidence concerning neurological outcomes in WTC-affected individuals, with the aim of contextualizing this research for policymakers, researchers and clinicians and educating WTC-affected individuals and their friends and families. We conclude by providing a rationale and recommendations for monitoring the neurological health of WTC-affected individuals.

On 11 September 2001, terrorists flew jetliners into each of the 110-story Twin Towers located at the World Trade Center (WTC) in New York. The collapse of the WTC and surrounding infrastructures culminated in a dust plume that engulfed the surrounding area ('Ground Zero') and parts of downtown New York City. At Ground Zero, fires fed by jet fuel burned noxious compounds until December 2001[1], emitting clouds of smoke and fumes that permeated the air of New York City. Nearly 3,000 individuals died as a result of the September 11 attacks and hundreds of thousands more were injured[2,3]. First responders — that is, law enforcement, emergency medical and firefighting personnel — were on-site within minutes of the first attack and began evacuating survivors and escorting others to safety. Surviving office employees, area residents, responders and volunteers who engaged in search and recovery and clean-up operations (all hereafter referred to as "WTC-affected individuals"), were exposed to severe psychological stressors, smoke, dust and debris. The thousands of individuals who remained on-site for search and recovery efforts as well as during the clean-up and rebuilding operations that followed were exposed to a toxic mix of contaminants and aerosolized particulate matter (PM) that was expelled from the burning buildings[4].

When efforts shifted from rescue to recovery and clean-up, the types of activities and exposures to inhaled PM also shifted[5]. In the days and weeks that followed the attacks, while lower Manhattan remained engulfed in dust, rescue and recovery workers dug through an inordinate amount of wreckage and rubble in the six-story 'pile', searching for human remains, belongings, and genetic samples for DNA matching and person identification[6]. Thousands of individuals who remained on site for prolonged periods of time were regularly exposed to industrial solvents and environmental toxins[7–10], many of which have been implicated in the pathogenesis of neurodegeneration and/or neuroinflammation[7,11–14]. The physical and psychological challenges endured by these individuals were extraordinary[15]. Since 11 September 2001, researchers have reported that up to 23% of rescue and recovery workers still have WTC-related posttraumatic stress disorder (PTSD)[16,17].

WTC-affected individuals are getting older, but at present, we understand little about how WTC exposures might have promoted the neuroinflammatory and neurodegenerative processes that influence brain ageing. Now, 20 years since the September 11 attacks on the WTC, there are no guidelines in place for research programmes that seek to monitor WTC-affected individuals for signs and symptoms that might be indicative of emerging neurological diseases. In October 2019, the US National Institute for Occupational Safety and Health (NIOSH) convened a meeting to discuss the

emerging evidence of cognitive impairment among WTC responders and to consider the potential for a cognitive screening programme for WTC-affected individuals. The meeting focused on ageing-related declines in cognitive performance and the potential for cognitive impairment among individuals with substantial PM exposures and among those with long-term psychiatric conditions. The meeting was attended by experts in Alzheimer disease and related dementias (ADRD), ageing, environmental exposures and PTSD; research and support staff from NIOSH also attended. The meeting was supported by funding from NIOSH, with no sponsorship from individuals or pharmaceutical companies. In this Perspective, we summarize the evidence concerning neurological outcomes in WTC-affected individuals and present recommendations for future monitoring and research. Overall, we aim to update policymakers, clinicians, researchers, WTC-affected individuals and their friends and family, with strategies outlining the need for an effective cognitive monitoring programme facilitated by ongoing research.

Neurologically active WTC exposures

Understanding the long-term consequences of a severe exposure event such as the September 11 attacks, is likely to require several years, or even decades, of work to accurately identify the relevant exposures, establish their effects, and for expert consensus to be reached. In the case of neurologically active WTC exposures, this process must also account for the heterogeneity in brain resilience and cognitive reserve among WTC-affected individuals, which could modify the risk of cognitive decline[18]. Another challenge facing this research is that the long-term effects of trauma often become 'hidden' as time passes on, as demonstrated by a reduced willingness to talk about one's traumatic experiences and having those memories recede[19]. This process makes it harder to gauge both the level of exposure and the effect that exposure had on responders with trauma. Furthermore, determining the long-term effects of inhaling the mixtures of toxins present at the WTC sites could be challenging, as the types of fine or ultrafine PM that were present at the WTC sites might have been invisible to the individuals present.

Airborne pollutants

Mounting evidence suggests that exposure to air pollutants could cause cognitive impairment and dementia[20]. Indeed, studies in humans have reported that exposure to various airborne contaminants is associated with cognitive dysfunction in children, adults and the elderly[21,22]. Three potential pathways link inhaled airborne PM to neurodegenerative disease (FIG. 1). In the case of the WTC collapse, coarse PM (<10 μm in aerosolized diameter; PM_{10}) was present in the dust cloud, and fine PM (<2.5 μm in aerosolized diameter; $PM_{2.5}$) in settled dust throughout the response period[7]. The dust also included elevated levels of polycyclic aromatic hydrocarbons (PAHs)[7] and detectable levels of metals thought to be neurotoxic[23]. Evidence suggests that $PM_{2.5}$ can be inhaled into the nasal passages and, although coarser $PM_{2.5}$ particles are likely to remain trapped in the lung, finer particles might enter the brain by direct translocation through the cribriform plate or olfactory bulb[24,25]. The 'lung-to-brain' axis could also involve modulation of systemic inflammatory responses such as those mediated by the SOD3 pathway[26]. As PAHs are hydrophobic and can remain in the body for weeks, they could accumulate in the periphery, potentially allowing them to permeate slowly across the lipophilic blood–brain barrier (BBB), and evidence suggests that PAHs can contribute to a variety of brain pathologies[27–32].

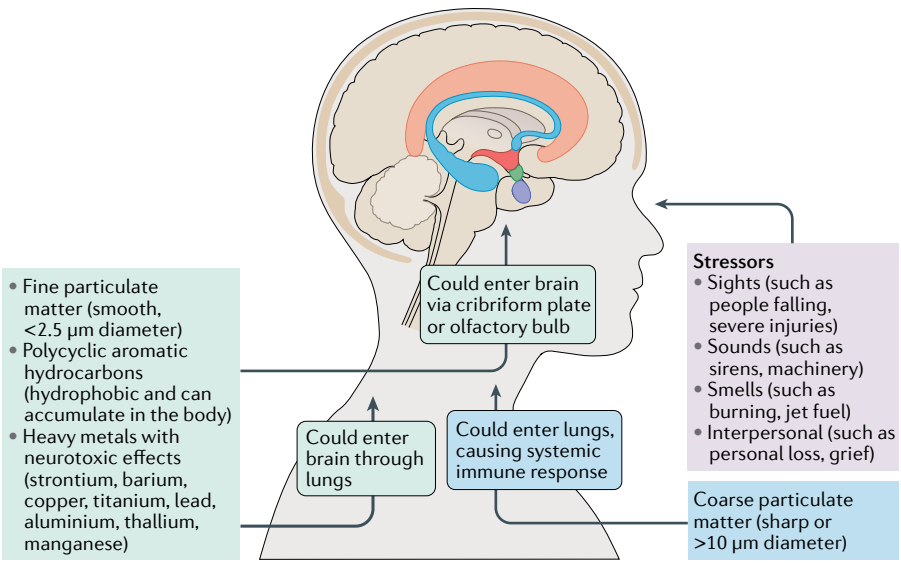

Fig. 1 | **WTC-related exposures and their potential routes to the brain.** Here we highlight the potential for WTC-related exposures to influence the risk of neurodegenerative disease in three different ways. First, by causing a severe and chronic stress response (purple box). Second, through inhalation or ingestion of coarse particulate matter, which induces a systemic immune response (blue box). Third, by entrance of neurotoxic materials directly into the brain, either through the olfactory centres or by passing from the lungs through the blood into the brain (green box).

Post-traumatic stress disorder

One result of the events related to 11 September 2001 was that, more than a decade after the attacks, a substantial percentage of WTC responders had PTSD, resulting from exposure to a large array of stressful experiences[33] (FIG. 1). PTSD is a relatively common outcome of stressful exposures, and can be chronic and heterogeneous. PTSD is characterized emotional and behavioral reactivity including distinct symptom clusters such as avoidance, hyperarousal, emotional numbing and chronic re-experiencing of exposure-related memories[16]. These symptoms are known to cause functional alterations, including changes in nutritional intake and illicit substance usage, often coupled with sedentary behaviour[34]. Although one-third of trauma-exposed individuals maintain a stable trajectory of mental health following exposure[35], an important subset of individuals experience chronic PTSD or report subsyndromal levels of symptoms that can still cause distress and be difficult to manage[36–39]. The neurobiological underpinnings of PTSD risk and determinants of resilience in the aftermath of exposure are complex and multifactorial; however, a considerable number of studies have demonstrated an important association between elevated stress and impaired brain health[40–43].

Putative neurobiological mechanisms

Inhaled PM. A growing body of evidence links exposure to PM with cognitive decline[20] (FIG. 2) and has resulted in the

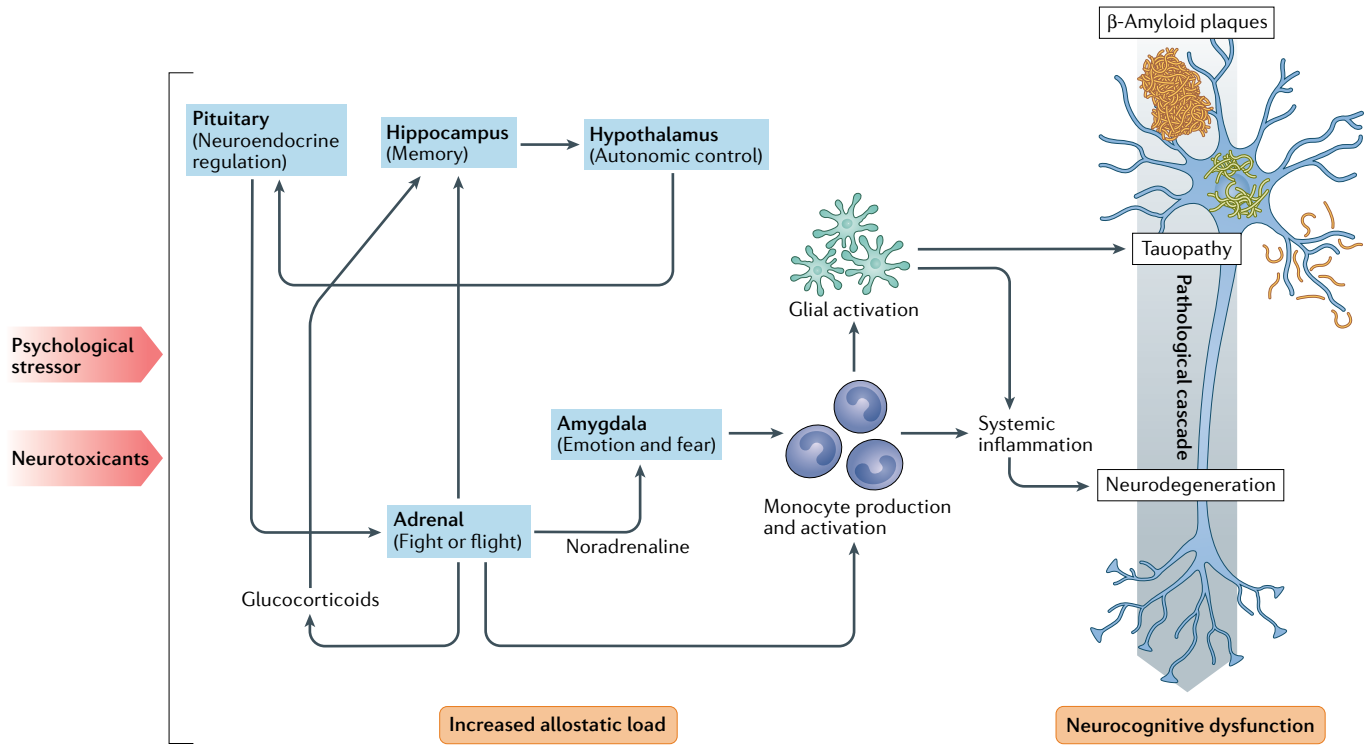

Fig. 2 | **Theoretical mechanisms linking exposure to WTC activities and cognitive symptoms.** Here we illustrate theoretical links between WTC-related exposures, internalized stressors and systemic responses, including chronic activation of the hypothalamic–pituitary–adrenal axis response owing to stress exposures. These exposures are thought to influence monocyte activation, and potentially modulate microglial activation, feeding in to the neurodegenerative amyloid pathological cascade. Arrows indicate the direction of influence, but do not necessarily denote an increase in neuronal activity associated with exposure.

inclusion of inhaled airborne PM in a list of avoidable dementia risk factors published in 2020[44]. In large studies with older Americans, greater exposure to $PM_{2.5}$ and PAH was associated with a greater prevalence of working memory deficits and disorientation[45–47]. In a post-mortem study published in 2017, chronic $PM_{2.5}$ inhalation was associated with white matter glial apoptosis, BBB disruption (possibly mediated by age or by the presence of apolipoprotein E (APOE) 4), oxidative stress, vascular compromise of the BBB and neuroinflammation in children, young adults and canines[48]. The same study also identified evidence of oligomeric and fibrillar amyloid-β (Aβ) accumulation, tauopathy and neurodegeneration in individuals exposed to high levels of $PM_{2.5}$. Other evidence from humans and animal models indicates that lifetime exposure to $PM_{2.5}$ is associated with both brain atrophy and disruption of white-matter connectivity[49]. Data from an in vitro study indicate that PAHs could modulate aggregation of Aβ by the formation of micelle-like Aβ–PAH co-aggregates, which might activate pro-aggregation pathways[50]. The results of a CSF-based study identified an association between $PM_{2.5}$ exposure and biomarkers of cerebrovascular injury in individuals with mild cognitive impairment (MCI) and Alzheimer disease (AD)[51]. Regardless of the mechanism, evidence from rodent models indicates that the brain's response to PM is neuroinflammatory and likely to involve glial activation[52] and accumulation of Aβ peptides[53] in a feedforward cycle.

PTSD. Evidence from animal models indicates that repeated exposure to severe stressors is associated with an increase in CSF levels of Aβ[54] and that this increase is likely to be mediated by an overactivation of microglia[55]. Chronic PTSD has also been associated with immunological changes, including neuroinflammation (animal models)[56], neuro-immunological dysregulation (humans and animal models)[57], and changes to microglia and monocyte gene expression and activation (humans and animal models)[58,59]. Converging lines of evidence suggest that chronic PTSD can cause hippocampal atrophy[60], alterations to amygdala structure[61], and dysregulation of rhythmicity in neuroendocrine and circadian systems that can result in abnormal sleep hygiene[62,63]. These changes are also associated with AD.

Chronic PTSD also activates the 'fight-or-flight response' through negative inhibition of the hypothalamic–pituitary–adrenal (HPA) axis by cortisol[64], thereby diminishing the brain's ability to cope with other stressors[65] and sustaining the chronic stress response, which is associated with increased Aβ aggregation and hastening of tau hyperphosphorylation[66] and propagation[67]. Therefore, chronic PTSD might amplify the effects of WTC-related neurotoxic exposures and initiate a cycle of proteinopathy and neuroinflammation (FIG. 2), resulting in neuropathological markers indicative of AD but in regions or topographies that are rarely affected by typical AD pathology[65].

Findings in WTC-affected individuals

Cognitive impairment

To investigate the hypothesis that WTC-related exposures increase the risk of neurodegenerative disease, the WTC Health Program on Long Island, New York, USA, began monitoring cognition in WTC responders who had no history of traumatic brain injury, and participated in rescue and recovery work following the September 11 terrorist attacks. The individuals in this WTC responder cohort are unusual in

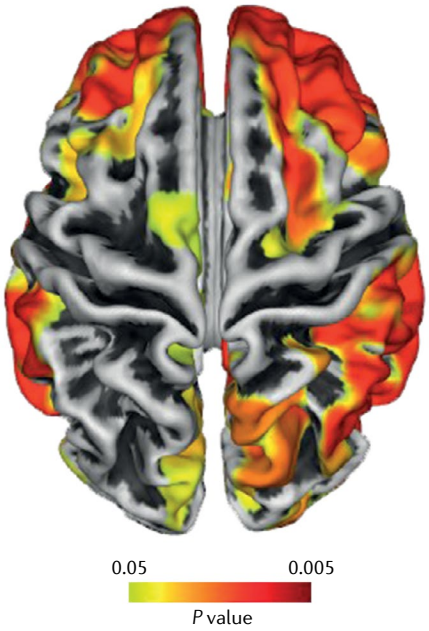

Fig. 3 | **Cortical atrophy in cognitively impaired WTC responders.** Comparison of cortical thickness between cognitively impaired WTC responders ($n = 51$) and cognitively unimpaired ($N = 48$) WTC responders. A yellow-to-red colour scale is used to indicate the statistical significance of the decrease in cortical thickness in the cognitively impaired group. The grey sections show areas where no differences between cognitively impaired and unimpaired responders were identified. Adapted from REF.[72].

several crucial ways. First, they have higher levels of education (>95% have high school diplomas, and >60% have college degrees) than the general population and other WTC-affected populations[68]. Second, the cohort had a mean age of 38 years on 11 September 2001 and 54 years when research on cognitive ageing in WTC-affected individuals began, meaning that the cohort is relatively young when compared with individuals who are typically affected by cognitive impairment such as that caused by AD, the symptoms of which are usually reported after the age of 65 years[69].

Nevertheless, of WTC responders at midlife, 17.8% were cognitively impaired at baseline, and an additional 14.2% developed MCI over the course of 2.5 years[70]. Participants with re-experiencing symptoms consistent with PTSD were at higher risk of developing MCI than participants without re-experiencing symptoms[68]. Indeed, the incidence rate of cognitive impairment in this WTC-responder subpopulation was more than two-fold higher than the incidence rate estimated from a search of population databases for individuals aged > 70 years in the general population.

Detailed neuropsychological information was also collected from the cohort, revealing that cognitive impairment was associated with changes to memory as a locus of cognitive dysfunction[71], a result that was replicated in a separate study of WTC Responders with cognitive impairment[72]. A deep learning approach was applied to longitudinal detailed neuropsychological information from this cohort. WTC responders that the protocol determined to be at high risk of cortical atrophy had higher WTC exposures, more severe PTSD symptomatology, and were at higher risk of MCI, dementia, and death[73]. Crucially, there was a moderation effect, whereby responders with prolonged exposure to the WTC site and possessing the *APOE ε4* allele were at greater risk of developing MCI than responders with a similar duration of exposure and not possessing the *APOE ε4* allele. A large number of WTC responders (11%) self-reported functional limitations[74–76] that seemed to be indicative of psychiatric comorbidities[75].

Data from this cohort of WTC responders do not reliably indicate a difference in risk of meeting diagnostic criteria for MCI between men and women, or among different ethnicities[77–79]. Consistent with cognitive reserve theory[18], evidence indicates that WTC responders with a higher level of education have a lower risk of meeting diagnostic criteria for MCI[77]. However, associations between education and incidence of diagnosis of MCI were sometimes explained by differences in the degree and nature of WTC-related exposures.

Physical impairment

In addition to the cognitive impairment discussed above, research in the same cohort of WTC responders indicates that the presence of WTC-related PTSD was associated with lower grip strength[80] and physical functional limitations[81]. PTSD in WTC responders was also associated with worse physical functioning and cognitive impairment[82]. Studies in other populations have identified physical functional limitations — including slowed walking, slowed chair-rise speed, and lower hand grip strength — as indicators of reduced body strength that are associated with increased disability and mortality[83–85]. Physical functional limitations have also been associated with depressive symptoms[86,87] and cognitive impairment[88,89]. Therefore, physical functional limitations might serve as an important clinical biomarker for non-cognitive dysfunction in WTC-affected individuals.

Neuroimaging

In vivo neuroimaging work has reported heightened amygdala reactivity[90] and evidence of amygdala and hippocampal atrophy[91] in individuals who were within 1.5 miles of the WTC site on 11 September 2001 compared with individuals who were living >200 miles away. Furthering this work, a study of white-matter health showed evidence of changes to connectivity in WTC responders with diagnosis of MCI when compared to cognitively unimpaired WTC responders[78]. Additional results from that study showed that exposure duration and PTSD symptoms were both associated with increased glial activation as measured using PET[92]. In another study, a two-by-two design was used to examine differences in regional brain volume among WTC responders with and without dementia and with and without PTSD[93]. WTC responders with dementia had reduced cortical thickness when compared with cognitively unimpaired WTC responders across 21 of 34 regions clustered over the frontal, temporal and parietal lobes of the brain (FIG. 3). Further analyses in this study clarified that hippocampal atrophy was evident in WTC responders with dementia across six hippocampal subfields, with focal changes in the presubiculum, but that hippocampal and cortical atrophy were only evident in PTSD when accompanied by cognitive impairment. Comparisons to normative control data[94] indicated (FIG. 4) that, although cognitively unimpaired WTC responders had cortices that were generally larger than the normative data, both cognitively impaired and unimpaired WTC responders had evidence of atrophy in the entorhinal cortices, the fusiform gyri, and throughout the temporal lobes[72]. In follow-up analyses, deep learning applied to MRI data was able to accurately classify participants as either cognitively impaired or cognitively unimpaired with an accuracy of 90%[95]. Overall, these brain volume changes are consistent with the changes that occur in AD (TABLE 1), although other diseases can cause similar changes.

Markers of ageing

Additional studies in WTC-affected populations have identified changes in cellular mechanisms consistent with more rapid ageing; for example, decays in pulmonary functioning were identified by comparing pre-exposure and post-exposure data from WTC responders[96]. Other findings include elevated plasma C-reactive protein[97] and increased allostatic load[98], and differences in gene expression[58] in WTC responders

with PTSD compared with those without PTSD. Lower pulmonary function in WTC responders was associated with shortened telomere length[99]. More specifically, PTSD in WTC responders was associated with changes in the expression of genes, including *FKBP5*[100], within monocytes. We hypothesize that these changes might result in the transcriptome-wide changes in pathways linked to monocyte gene expression that were observed in single-cell analyses[58]. Researchers also identified changes in plasma levels of several proteins, including neurocan and brevican, that were associated with both PTSD and MCI[101]. The same study found PTSD-related MCI to be more severe than PTSD alone in terms of proteomic markers of systemic dysfunction[101].

A comprehensive research agenda

Ageing-related diseases that involve cognitive impairment are often characterized by an insidious onset period, which is frequently decades long. This is important in the context of WTC-related exposures, as it provides a potential window for research and therapeutic intervention. The most recent National Institute on Ageing and Alzheimer's Association (NIA-AA) AD Research Framework considers AD as a diagnosis based solely on biomarkers of pathology, with MCI and AD dementia being clinical consequences that can be heterogeneous in terms of symptoms and might not always be present[102]. This terminology replaces the previous one — which included preclinical AD, MCI due to AD (prodromal AD) and AD[103,104] — and therefore forms the basis for the overall proposed nosological structure (TABLE 1). AD can be preceded or accompanied by neuropsychiatric symptoms, depressive symptoms and/or mood disorders[105], in addition to changes in gait, motor and other physical functions[106,107]. ADRD are the most common causes of ageing-related cognitive impairment worldwide[108] and cerebrovascular disease is the second-most common cause of cognitive impairment in most ageing populations[109]. The symptoms of this vascular cognitive impairment and dementia (VCID) often mimic those of AD dementia[108], making the differential diagnosis of cognitive impairment difficult in the absence of neuroimaging-based and biofluid-based biomarkers.

Both AD and VCID contribute to the dementia seen in other ageing-related neurodegenerative conditions, for example, Parkinson disease (PD)[110]. At the same time, evidence indicates that some rarer neurodegenerative conditions might be less rare in their milder forms than originally believed. For example, dementia with Lewy bodies (DLB) may cause symptoms consistent with AD owing to the presence of amyloidosis and tauopathy, which are often comorbid among those with DLB[111]. Other relevant neurodegenerative conditions include chronic traumatic encephalopathy, which has emerged as a clinical phenotype among individuals with repeated head injuries, and a number of novel disease states, including limbic age-related TAR DNA-binding-protein-43 encephalopathy (LATE), primary age-related tauopathy (PART)[112], and suspected non-AD pathophysiology (SNAP)[113]. Although these definitions are useful, neurodegenerative diseases are often mixed in aetiology and

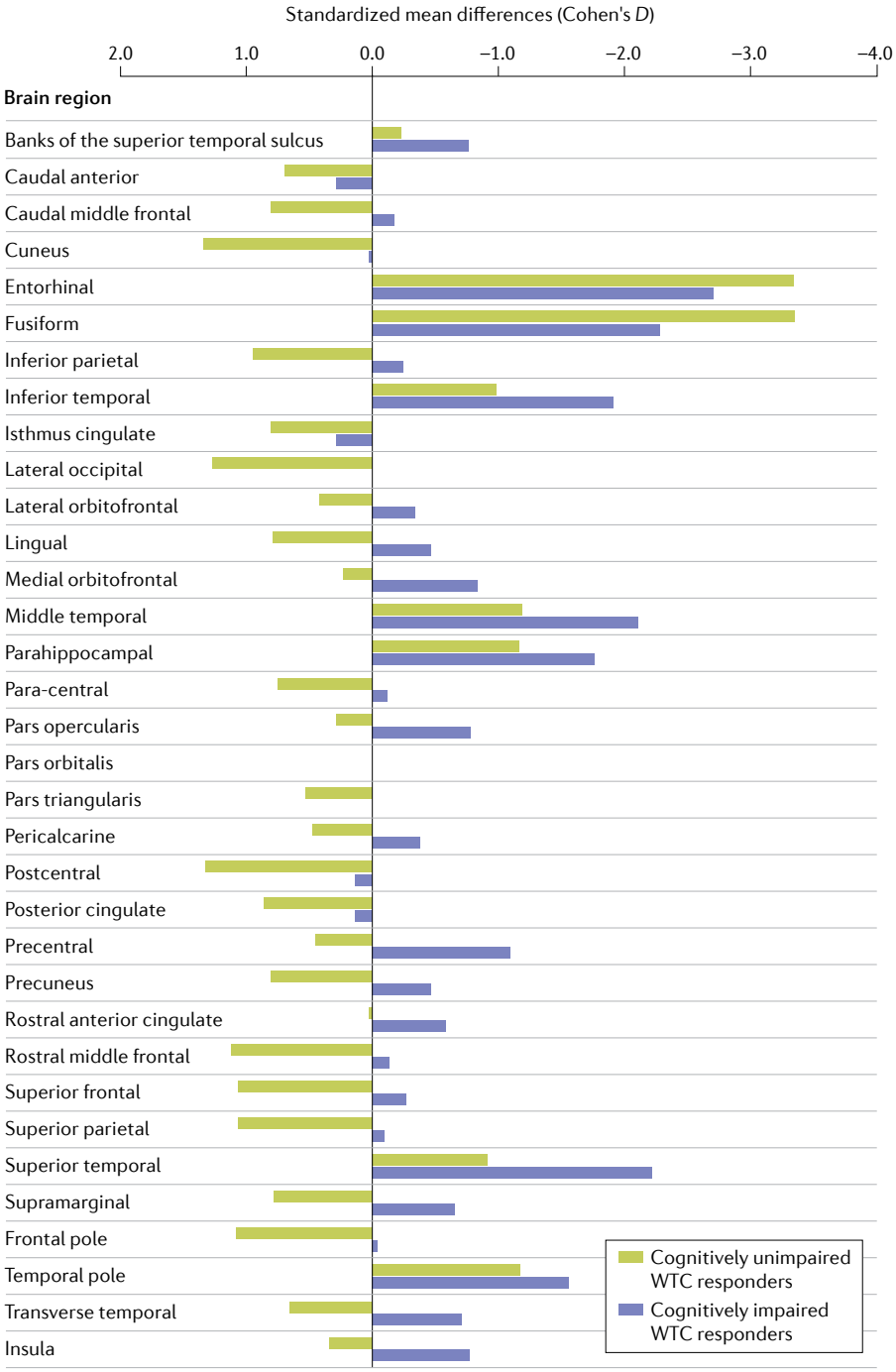

Fig. 4 | **WTC responder cortical thickness change from normative data.** Changes in cortical thickness in cognitively impaired and cognitively unimpaired WTC responders when compared with an independent dataset[95] from non-WTC exposed cognitively unimpaired individuals. Effect size is indicated by Cohen's *D* values. Data from REF.[73].

Table 1 | **Symptoms and biomarkers of common neurodegenerative diseases**

Phenotype	Cerebrovascular disease	AD	LATE	Primary age-related tauopathy	CTE	PD	DLB	FTLD	WTC cognitive impairment (evidence to date)
Symptoms									
Episodic memory loss	Present	Present	Present	Present	NC	NC	Present	Present	Present
Executive functional decrements	Present	Present	NC	Present	NC	NC	NC	NC	Present
Visuo-spatial decrements	Present	Present	NC	Present	NC	NC	NC	NC	Present
Resting tremor	NC	NC	NC	NC	NC	Present	NC	NC	Unknown
Physical functioning decrements	NC	Present	NC	NC	NC	Present	NC	NC	Present
Behavioural changes	NC	Present	NC	Present	Present	NC	Present	Present	Unknown
Disorientation	Present	Present	NC	Present	Present	NC	Present	Present	Present
Bioindicators									
White-matter changes	Present	NC	NC	NC	NC	Present	NC	NC	Unknown
Amyloid deposition	NC	Present	NC	Absent	Absent	NC	NC	NC	[Plasma]
Tauopathy	NC	Present	NC	Present	Present	NC	NC	Present	Unknown
Cortical atrophy	NC	Present	NC	Present	NC	NC	NC	Present	Present
Hippocampal atrophy	NC	Present	Present	NC	NC	NC	NC	NC	Present
α-Synuclein pathology	Absent	Absent	Absent	Absent	Absent	Present	Present	Absent	Unknown

In the table, we note when characteristics are common (present) in the condition or are absent, but we do not note when symptoms or bioindicators are sometimes present. For example, individuals diagnosed with DLB often also have evidence of amyloid positivity. Additionally, although evidence of the presence of atrophy might be listed as present, in many cases, including in the analysis of cortical atrophy along with amyloid deposition and tauopathy, the specific pattern of biomarker changes might help to distinguish between diseases. AD, Alzheimer disease; LATE, Limbic age-related TDP-43 encephalopathy; CTE, chronic traumatic encephalopathy; PD, Parkinson disease; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; NC, not common.

the presence of one may hasten the onset of others[114]. These considerations are important when attempting to identify the aetiology of the early-onset cognitive impairment presenting in some WTC responders.

Monitoring

To improve the capacity to identify outcomes more proximally in time to their relevant exposures, prior clinical work in WTC responders has focused on the identification of MCI, preclinical AD, or prodromal AD. These prodromal disorders represent early clinical symptoms that emerge during cognitively impairing diseases and thus indicate possible neurodegenerative disease[115]. However, MCI, preclinical AD and prodromal AD differ in crucial ways. For example, although preclinical AD is now defined as a biological disorder characterized by the presence of AD biomarkers[116] often found in asymptomatic individuals[117], MCI is a clinical syndrome that was originally defined by the presence of isolated memory impairment[118], but is now also thought to present as impairment isolated to other cognitive domains[119]. MCI is often a prodrome for more severe diseases, and individuals with MCI might begin to exhibit non-cognitive symptoms, including worsening depressive symptoms, changes in mood and anxiety as well as changes in physical functioning, biomarkers, cognitive performance and general wellbeing[120–122].

The WTC Health Program is a comprehensive clinic-based monitoring programme; however, the programme is limited to assessments that are performed within research studies and does not actively perform systematic monitoring of cognitive performance or decline across larger populations (BOX 1). There is a growing consensus that the neurocognitive findings in several research studies are identifying a syndrome that raises concerns about the level of risk in WTC-affected individuals, and that improved characterization of cognitive decline and identification of neuropathology that explains the presentation of these effects is needed. Therefore, understanding how and why we observe cognitive impairment at midlife in WTC-affected individuals, and whether it will progress to dementia, is essential. Nevertheless, we should note that, as we have not yet elucidated the underlying neurobiological aetiology for the observed early-onset cognitive impairments in WTC-affected individuals and have not yet examined neuropathology in the brains of WTC-affected individuals, our use of language and nomenclature remain tentative and exploratory.

Consensus is lacking as to whether individuals with normal levels of risk should undergo routine cognitive monitoring for clinical purposes, in part because the negative effects of a diagnosis on individuals and their families could be considerable and, to date, few benefits are expected from such diagnoses[123]. However, the research presented above suggests that some WTC-affected individuals might be considered at high risk of developing MCI and dementia because of their experiences at the WTC. A central benefit of cognitive monitoring might be the ability for individuals and their families to anticipate changes that could occur and to act preventatively where possible[124]. Monitoring could also help patients and their families to understand cognitive and behavioural changes as they emerge. Therefore, we propose a multi-tiered monitoring approach that focuses on the use of cognitive and biomarker tools, and could be used in research to characterize and understand the WTC phenotype (BOXES 2–4).

Cognitive function. Comprehensive neuropsychological assessments are frequently expensive, time-consuming and burdensome to individuals, and can be complicated to analyse; however, an increasing number of alternative approaches are available, including online versions of

Box 1 | **The World Trade Centre Health Program**

The World Trade Centre (WTC) Health Program was established by Congress with the passage of the James Zadroga 9/11 Health and Compensation Act of 2010[212] (the Zadroga Act). Administered by NIOSH, the programme operates a survey-based registry and provides medical monitoring and treatment benefits to WTC-affected individuals with conditions having emerged from exposures to toxins, trauma or adverse conditions resulting from the 11 September 2001 terrorist attacks. To date, the NIOSH-funded clinical monitoring programmes have enrolled 80,146 WTC responders along with 28,349 WTC survivors[213]. Twenty per cent of responders were exposed to the dust cloud and 45% of responders spent ≥60 days working on-site at the WTC, with ≥10% of responders having been diagnosed with WTC-related PTSD. Additionally, the NYC WTC Health Registry enrolled 71,437 individuals who self-identified at enrolment in 2003–2004 as having been exposed to the WTC sites based on occupational or residential exposures[214]. Currently, the WTC Health Program only monitors for cognitive health with an annual monitoring clinic visit, which is not as comprehensive as the cognitive and neuropsychological batteries performed during research visits. As such, many changes in cognition and behaviour could go undocumented, with any cognitive decline detected during the monitoring visit only warranting a referral to the patient to seek further assessment from their primary health physician.

many cognitive screening tools and mobile phone-based cognitive assessments[125]. To characterize the extent to which cognitive dysfunction might manifest clinically, a brief cognitive tool (for example, the Montreal Cognitive Assessment (MoCA)) might be useful if it collects information from a variety of cognitive domains such as attention, concentration, executive function, memory and visuospatial skills. The MoCA was used in all WTC-responder research discussed here because it has a high reported sensitivity and specificity for MCI and dementia (for example, 95% specificity and 96% sensitivity for dementia)[126]. However, evidence suggests that the MoCA is less specific in populations that are less educated and more disadvantaged[126]. Work with WTC responders is now beginning to rely on a validated auditory version of the MoCA that can be administered via videoconferencing services[127].

Although global measures, including the MoCA, are an excellent way to screen individuals efficiently and effectively, they are insufficient to confirm a clinical diagnosis of MCI. Therefore, as is typically used in the neurological or cognitive health care setting, a more specialized and detailed instrument is necessary to survey all the domains of cognitive function that might become impaired in WTC-affected individuals. In the WTC responder efforts, one research team used the Cogstate Brief Battery platform to provide cognitive scores in a time-efficient and cost-efficient manner[71,72,78,128,129]. The Cogstate platform is a computer-administered approach that uniformly measures fluid cognition using data and metadata collected during game-like tasks. This approach assesses multiple cognitive domains but is associated with minimal practice effects[130,131]. Recently, a Cogstate profile was found to be highly effective at differentiating between WTC responders with and without cortical atrophy[73]. Our recommendations for research on cognitive symptoms in WTC-affected individuals are summarized in BOX 2.

Motor function. Motor dysfunction could also be monitored in WTC responders, as individuals often experience changes in movement before the onset of manifest, diagnosable neurocognitive disease[106]. Long-term and serial screening exams will be crucial for the successful identification and characterization of patterns of decline across a range of objectively assessed functional symptoms. These symptoms could either be assessed independently or as a part of clinical measures such as the Short Physical Performance Battery (SPPB), which measures walking speed, chair-rise capabilities, balance limitations and grip strength[132]. Indeed, work published in 2020 suggests that mild motor dysfunction, including reduced grip strength and slowed chair-rise speed, are ageing-related functional indicators that precede PTSD-related cognitive impairment in WTC responders but are not implicated in non PTSD-related forms of WTC-cognitive impairment[133]. However, further work is needed to assess fine motor skills in WTC responders.

Neuropsychiatric and other symptoms. Changes to behaviours, and impairment of social functioning and social cognition (in part owing to changes in persona) are important parameters in dementia research. Very little is known about the nature, severity and natural history of dementia in WTC-affected individuals. However, neuropsychiatric symptoms, such as increased anxiety and depression, are common in dementia[134]. These symptoms are extremely important to friends and family, and are often identified by family members because they can cause caregiver stress[135] as well as emotional difficulties[136] and reductions in quality of life[137] among individuals with cognitive impairment and their caregivers. Concurrently, cognitive impairment often results in increased difficulties navigating physical spaces[138], leading to impaired abilities to operate motor vehicles[139] or manage finances[140]. Together, functional limitations such as these can fundamentally change the experience of ageing, thereby warranting close clinical follow-up when monitoring WTC responders

Potential biomarkers. Studies of neurocognitive diseases increasingly rely on imaging and fluid biomarkers as outcomes of interest, in part because they can help to elucidate the mechanisms underlying differences in cognitive outcomes. However, such biomarkers have not yet been thoroughly profiled in WTC-affected individuals. Post-mortem examination will ultimately be a crucial tool for understanding the effect of WTC-related exposures on the brain, and will enable us to establish whether components of WTC dust are present in the brain tissue. However,

Box 2 | **Monitoring cognitive and non-cognitive symptoms**

Goal: to clarify cognitive and non-cognitive changes, including measures of emotional, social and physical function, to identify hallmarks of cognitive impairment in WTC-affected individuals

- Further research using regular neurocognitive screening to establish incidence rates and risk factors for dementia in WTC-affected individuals considered to be at high risk of cognitive impairment
- A secondary tiered research effort incorporating more comprehensive cognitive evaluations to monitor domain-specific functional changes might be useful
- More research is needed to understand when memory loss in WTC responders is accompanied by other cognitive and non-cognitive changes
- Further evaluation of the associations between multi-domain cognitive decline and concomitant motor and behavioural changes should be performed to establish whether these features indicate the presence of a novel WTC-related phenotype

owing to the age range of WTC-affected individuals, neuropathological information does not yet exist for this population. Here, we focus on the neuropathological features that could be studied to further our understanding of cognitive impairment in WTC-affected individuals. Many of these neuropathological changes are features of AD pathology, but we do not yet know whether WTC-related cognitive impairment and/or dementia follow a pathogenesis resembling that of typical sporadic AD. Furthermore, neurodegenerative conditions are often comorbid with one another[141]. The predominant neuropathological information necessary to determine whether WTC-affected individuals with MCI are experiencing early AD or ADRD are discussed in greater depth below.

The neuropathology of AD is characterized by the formation of amyloid plaques (consisting predominantly of Aβ) and intraneuronal propagation of tauopathy throughout the brain[102,142]. Quantification of CSF Aβ levels is a slightly more sensitive approach for the detection of amyloid pathology than amyloid PET neuroimaging[143]. However, an advantage of amyloid PET scans over CSF markers of Aβ levels is that amyloid PET scans provide information about regional distribution of Aβ deposition in the brain. Amyloid PET imaging can be judged positive or negative visually and can also be reliably quantified. The microtubule associated protein tau undergoes aggregation and a range of post-translational modifications including 'hyperphosphorylation' in AD[144]. With tau PET imaging, standardized uptake value ratio (SUVR) images normalized to cerebellar grey matter can be used to determine the extent of 3R and 4R tauopathy in specific brain regions. To detect early changes in AD, studies suggest relying on the location and spread of tau pathology, as tangle pathology can develop before the onset of clinical symptoms[129,144–146]. Tau can also be measured in CSF and is small enough (48–67 kDa, depending on isoform) to pass through the BBB and, therefore, to be found in plasma. Early work suggests that plasma total tau is elevated in clinically diagnosed AD[147], acute traumatic brain injury[148], and other neuropathologies[149–151]. Tau protein phosphorylated at residues 181, 213, or 217 seem to be more specific biomarkers for AD than total tau[152–155]. Plasma markers of amyloid, tau and neurodegeneration have been used to successfully distinguish between WTC responders with and without cognitive impairment[156].

Early AD is often marked by hippocampal and cortical atrophy, and researchers have proposed the identification of cortical thinning, as detected with MRI, in the differential diagnosis of patients with cognitive impairment and AD[157,158]. Cortical thinning has also been observed in WTC responders with possible mild dementia when compared with cognitively unimpaired WTC responders[72]. In addition to cortical volume, several other markers could be used to further investigate neurodegeneration in WTC-affected individuals. First, diffusion tensor MRI is a useful technique for detection of abnormalities in white matter and assessment of structural connectivity of different brain regions[159]. Second, markers of brain glucose metabolism, such as ^{18}F-fluorodeoxyglucose PET, can be used to detect decreased metabolic rate (hypometabolism), which occurs in regions of neurodegeneration[160,161]. Third, the neurofilament light chain is a small (70 kDa) protein that is present in neurons and provides structural support to the microtubule array that transports nutrients and maintains neuronal integrity. The neurofilament light chain is small enough to pass through the BBB and is detectable in plasma and CSF, providing a nonspecific marker of neurodegeneration. Neurofilament light chain levels in plasma are highly correlated with those in CSF[162].

Although the AD research framework[102] is a compelling method for characterizing disease using amyloid, tau and neurodegeneration, a large autopsy study consisting of individuals over the age of 50 years reported that only one-third of all-cause dementia cases were attributed to 'pristine' pathological AD, as indicated by Aβ plaques and neurofibrillary tangles, whereas up to seven other neuropathologies, including Lewy bodies and cerebrovascular disease, explained much of the remaining disease[163]. This is of relevance to research efforts attempting to identify the underlying aetiology for the observed early-onset cognitive impairment in WTC responders. Indeed, understanding the contributions of neurodevelopmental factors[164], the presence of protective proteins[165], and cognitive reserve (which could prevent the expression of clinical symptoms despite significant pathology) might help to predict the rate of cognitive decline. *APOE* ε4 is the most potent and prevalent risk factor for late-onset sporadic AD — *APOE* ε4 homozygosity increases AD risk more than tenfold[166]. *APOE* ε4 is associated with breakdown of the BBB, which makes it particularly relevant to WTC-affected individuals who were exposed to PM[167,168]. Our recommendations for research into the neuropathological changes in WTC-affected individuals are summarized in BOX 3.

Potential treatment targets

In 1995, Plassman et al.[169] showed that variation in old-age cognitive performance could be attributed to early life exposures that were carried through to adulthood, findings which have since been replicated[170–173]. Furthermore, research tracking cognitive trajectories from age 43–69 years identified a subtly faster rate of memory decline from midlife to early old age in *APOE ε4* carriers than in non-carriers[174]. These efforts have supported a review of intervention studies and a set of guidelines to help prevent AD, published in 2020[175]. The guidelines include prevention and aggressive treatment of hypertension[176], reduction in obesity at midlife, smoking cessation, physical activity, socialization and treatment of diabetes. Steps have also been made towards improving amyloid clearance[177] and reducing risk of symptom progression in dementia[178]. Exogenous insults can accumulate over time to affect the rapidity of ageing and contribute to the risk of ADRD[179]. WTC-affected individuals were mostly exposed after schooling was completed, but as these individuals continue to age they are at increasing risk of experiencing cognitive impairment despite relatively low smoking rates and high levels of access to healthcare. Therefore, to maximize efficacy, therapeutic interventions for cognitive impairment must

Box 3 | **Neuropathological information**

Goal: to examine markers of neuropathology in WTC-affected individuals with the aim of explaining the aetiology of cognitive impairment, and of improving diagnosis and monitoring

- Biofluid, neuroimaging and post-mortem histopathological markers of neurodegeneration, including cortical and hippocampal atrophy and proteinopathy, should be studied in WTC-affected individuals and compared with those associated with known neurodegenerative conditions
- The degree and nature of cerebrovascular disease burden in WTC-affected individuals should also be determined with the aim of improving our understanding of the aetiology of cognitive impairment in WTC-affected individuals and determining correspondence with existing diagnostic entities

be implemented while sufficient cortical substrate remains. The unique nature of WTC-related exposures might also provide exposure-specific treatment targets. In this section, we discuss physical activity, treatments for persistent re-experiencing of symptoms, and cognitive remediation, all of which provide some promise of mitigating long-term neurological health outcomes in WTC-affected individuals.

Physical activity. A meta-analysis of randomized controlled trials of physical exercise interventions in individuals aged >50 years identified cognitive benefits associated with aerobic, resistance, multimodal and tai chi interventions[180]. These benefits were observed for 45–60-minute exercise interventions of moderate or high intensity regardless of frequency or length. Benefits were observed for attention, executive function, memory and working memory, but not for global cognitive measures. Participants with MCI and cognitively healthy participants benefited from the interventions. Although these meta-analysis findings would seem to support the use of exercise programmes for physically able WTC-affected individuals, most of the 36 studies included in the analysis had small sample sizes, so that unmeasured confounders cannot be ruled out. To address this limitation, a randomized clinical trial followed up participants ($n = 132$) for 24 weeks and found significant improvement in aerobic capacity and executive functioning, an increase in cortical thickness in the left frontal region, and a decrease in body mass index (BMI) in the groups of participants trained in aerobic exercise, but not in the group of participants performing stretching and toning only[181]. A second study examined the effect of physical activity on inflammation and found that exercise was associated with increased levels of interleukin-6 and tumour necrosis factor-α in the serum[182]. It is difficult, however, to achieve reliable adherence to exercise training.

Box 4 | Research in treatment safety and efficacy

Goal: to examine the safety, feasibility and efficacy of interventions to improve cognition in WTC-affected individuals

- We suggest the use of interventions specifically targeted at reducing risk of dementia, including active efforts to aggressively reduce hypertension via pharmaceutical or targeted exercise and nutritional interventions, in older WTC-affected individuals
- We suggest that, given the large burden of cognitive impairment in WTC responders reporting re-experiencing symptoms, efforts should be made to reduce symptoms in this group, for example, by use of cognitive behavioural therapies to address active PTSD symptoms
- We suggest that treatments (such as cognition-oriented training) that focus on the improvement of cognitive performance in relation to everyday functioning could help prevent further decline in WTC-affected individuals with mild cognitive impairment manifesting as slowed processing speed or attentional difficulties
- A key focus of future research should be to establish the safety and feasibility of any proposed interventions in WTC-affected individuals with additional physical and psychological comorbidities

Pharmacological and neurobehavioural treatments for PTSD. Chronic PTSD is a debilitating condition with substantial costs to society, resulting from lost productivity, and treatment efforts to date have been largely ineffective[183,184]. The selective serotonin reuptake inhibitors paroxetine and sertraline are the only FDA-approved pharmacological treatments for PTSD. Evidence indicates that paroxetine ameliorates PTSD symptoms in 60% of treated individuals and sertraline in 30% of treated individuals; yet fewer than 20% achieve full remission[185]. However, more promising evidence has been reported for the use of off-label pharmacotherapies, for example, ketamine[186,187].

PTSD is characterized by central noradrenergic hyperactivity and the α1-adrenoreceptor antagonist prazosin has been tested as a therapeutic intervention for PTSD in seven clinical trials, of which six produced a positive result[188–195]. One of the largest such studies involved a cohort of 67 active-duty soldiers (mean age 29 years, mean rank sergeant (E5)) with combat-related PTSD nightmares and sleep disturbance who were randomized to receive either prazosin or placebo[194]. Prazosin was associated with an improvement in sleep quality, Clinician Administered PTSD Scale (CAPS) nightmare scores, the CAPS distressing dreams score, the Pittsburgh Sleep Quality Index, and total CAPS score[193]. However, a follow-up study of predominantly Vietnam veterans with stable chronic PTSD suggested that the benefits of prazosin treatment are concentrated among individuals with evidence of central noradrenergic hyperactivity[193].

Although evidence indicates that prazosin can specifically reduce re-experiencing of symptoms, clinical practice guidelines strongly recommend cognitive behavioural therapy (CBT) and cognitive processing therapy for the treatment of PTSD because they aim to help patients understand the associations between thoughts, feelings and behaviours associated with trauma, and specifically focus on changing behavioural patterns and thought processes[196]. To achieve this aim, structured sessions are used to help patients reconceptualize traumatic events in a way that diminishes ongoing negative effects in daily life[197–199]. Cognitive therapy, derived from CBT, has the same focus as CBT, but also aims to disrupt disturbing behavioural and thought patterns by altering negative memories of trauma[200,201]. Finally, prolonged exposure is a treatment regimen with a modified CBT approach to teach patients to prevent avoidance when approaching trauma-specific memories, feelings and situations, enabling the patient to no longer associate them with danger[202].

Cognitive remediation and training. Cognition-oriented training consists of a non-invasive set of standardized training tasks that focus on the improvement of distinct cognitive processes and abilities such as attention, memory, information processing and problem solving[203,204]. The tasks are used to train individuals with mild or severe dementia and the goal is to retain or improve functioning within a specific cognitive domain, leading to improved performance in domain-associated tasks. This approach works mainly through mechanisms of restorative neuroplasticity (reviewed in REF.[205]). Indeed, studies using cognitive training have identified associations between the

Glossary

Cognitive reserve theory
The theory that individual differences in the cognitive processes or neural networks underlying task performance enable some individuals to cope better with brain damage than other individuals

Healthy worker effect
The tendency for those who are working to be healthier, on average, than those who were unemployed or who do not participate in the workforce, leading to a consistent under-estimation of the impact of occupational exposures

Re-experiencing symptoms
Having sudden and unwanted traumatic memories that intrude into or even seem to replace what is happening in the current moment

receipt of structured training programmes and neural activation in key brain regions among healthy older adults[206] and people with MCI[207,208]. One promising form of cognitive training, called Useful Field of View (UFOV) training, is designed to improve the speed of information processing through practice of visual attention tasks. Results from multiple clinical trials suggest that UFOV training could improve ability to perform instrumental activities of daily living and reduce symptoms of depression and anxiety[209], with one study reporting a UFOV-associated reduction in the risk of dementia over a ten-year follow-up period among initially healthy older adults[210]. However, we cannot focus solely on cognitive impairment and should be aware of the potential for psychiatric symptoms to increase over time in individuals with neurodegenerative disease. These symptoms should be monitored and treated accordingly, as they tend to have an outsized role in patient and caregiver distress. Our recommendations for research into treatment safety and efficacy in the WTC-affected population are listed in BOX 4.

Summary

The research performed thus far has advanced our knowledge of a range of neurological issues in WTC-affected individuals. However, crucial gaps in our understanding highlight the next steps that are required to move this research programme forward (BOXES 2,3 and 4). First, as WTC-affected individuals with cognitive impairment seem to have broad reductions across domains of cognitive performance (including episodic memory and processing speed), we need to carefully compare data on exposure-related neurocognitive symptoms with data on PTSD-related neurocognitive symptoms, to determine whether and how WTC-related neurocognitive impairment fits a known clinical phenotype. Second, neuroimaging, neuropathological, genetic and multi-omic data are needed to elucidate the aetiologies of the cognitive and behavioural symptoms that are central features of clinically diagnosed MCI in WTC-affected populations. Third, we need to examine relevant biofluid-based and neuroimaging-based evidence of proteinopathy and neurodegeneration in WTC-affected individuals to develop the appropriate diagnostic, prognostic and mechanistic paradigms for WTC-related exposures and their symptom–biomarker correlations. For example, the finding that cognitively unimpaired WTC responders have early signs of cortical atrophy points to the need for future work to improve characterization of the earliest indicators of disease to provide responders with access to treatment as early as possible, with the aim of improving long-term outcomes. Last, we need to investigate and validate any potentially prophylactic interventions that are safe and effective for improving functioning in WTC-affected individuals with PTSD, and those who are at risk of developing clinical cognitive impairment.

Limitations

The recommendations made here are based on the only objective evidence available to date, which comes exclusively from studies of WTC responders. Outside the WTC Health Program on Long Island, studies have not examined objective indicators of cognitive impairment in WTC survivors and only subjective data are available on cognitive impairment of employees of the Fire Department of the City of New York[75]. Relying solely on research performed in WTC responders has several limitations. First, residents and other community members present in the affected area encompassed a wide range of ages (from newborns to older individuals), disparate backgrounds, and a broad spectrum of occupations and socioeconomic statuses. In contrast, responders are a uniformly advantaged group with relatively high socioeconomic status. Second, a healthy worker effect is present, given that not every person is eligible to be a police officer or firefighter and that some eligible individuals choose not to volunteer. Third, first responders also receive substantial training and preparation that might have helped them to maintain cognitive reserve[18], whereas other WTC-affected individuals might have lacked this physical and psychological preparation. Fourth, WTC responders hold positions that are often preferred by military personnel, and prior military experience and many aspects of warzone deployment could be associated with lifelong differences in cognitive performance[211]. Last, the studies performed to date and discussed here compared WTC responders to internal controls, which assumes that cognitively unimpaired WTC responders are a good comparison group; however, one of our studies revealed that cognitively unimpaired WTC responders have evidence of cortical atrophy in the temporal lobe when compared to data on age-matched and sex-matched non-WTC-affected individuals[72], potentially highlighting the need for an appropriate control population. A limited focus on Fire Department of the City of New York employees could also be concerning because they were more severely exposed than other WTC-affected populations. These limitations highlight an increasing need to perform research with non-responding WTC survivors and with non-WTC-exposed controls.

Conclusions

The Zadroga Act[7] (BOX 1) authorizes ongoing research activities and manages care for covered WTC-related conditions. To date, WTC health programmes have focused on a number of conditions, including respiratory conditions, gastrointestinal disease, PTSD, depression and cancer, but have not monitored neurological symptoms or diseases in WTC-affected individuals. An increasing number of studies suggest the potential for WTC exposures to affect neurological outcomes. Crucially, those who endured and responded to the attacks on the WTC on 11 September 2001 have highlighted the potential for a novel emerging neurological condition of unknown aetiology or a new manifestation of a known disorder, such as AD. Although the US preventive services task force has suggested that cognitive screening may not always be beneficial in situations where there are not clear benefits, such as in situations where individuals are young and the risk of dementia is low[123]. The consensus developed among experts attending this 2019 US NIOSH meeting was that WTC-affected populations might be at greater risk of cognitive impairment than the general population, probably as a result of experiences on-site at the WTC, and concluded that more research was needed in a number of highlighted areas. We hope that the recommendations presented in this Perspective will help researchers and, if supported, policymakers to consider next steps for monitoring WTC responders as they age.

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Competing interests
The authors declare no competing interests.

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Review criteria
A comprehensive literature review was completed in advance of the 2019 US National Institute for Occupational Safety and Health (NIOSH) meeting using a database of papers published about World Trade Center (WTC) exposures and outcomes maintained by the NIOSH programme. Speakers were invited by two WTC researchers and asked to provide two representative papers of their own work to be briefly discussed during the meeting to educate audience members about their research. In preparation for this Perspective, a scoping literature search was also conducted using PubMed, including articles published in the areas of cognition, ageing, neurobiology, neuroimaging or neurodegeneration in survivor and responder populations affected by WTC attacks from 11 September 2001 to 1 May 2021 (search terms: "World Trade Center" AND (cogniti* OR aging OR neurobiology OR neuroimage* OR neurodegener*). The search resulted in 70 non-overlapping citations; relevant studies were retained and cited in this Perspective and studies specific to the topics of interest in this Perspective were highlighted. Attendees were also asked to discuss the relevance of MCI in this cohort and highlight important aspects that merited further investigation. The meeting was recorded and transcribed. Each presenter was asked to review transcripts for errors and for clarity, and all presenters were asked to review this manuscript for accuracy and to ensure final agreement with these materials. A writing team was tasked with capturing meeting materials and relevant background in this paper, and all authors were provided with opportunities to edit, modify and update sections in the final manuscript.