Glossary

First-, second-, third-generation sequencing: Step-wise improved methods for determining the order of nucleotides (sequence) in a target DNA molecule. Initial first-generation sequencing methods could 'read' only about 1000-nucleotide-long sequences. Second-generation sequencing can provide much longer sequences (even entire genomes) by simultaneous generation and subsequent alignment of large numbers of short reads. Third-generation sequencing can produce continuous reads of more than 2 million nucleotides from individual DNA strands.

Repeat expansion disorders: A group of disorders caused by an unstable expansion (increase in number) of short tandem repeats above a disease-specific threshold.

reported by Sun and colleagues in this issue of *Brain*, raises questions with important clinical implications: Does the phenotype of NIID include essential tremor, or can essential tremor be caused by repeat expansions in *NOTCH2NLC*, indicating that it represents a neuropathologically distinct condition? The future will reveal whether Sun and co-authors have uncovered the very first monogenic aetiology of essential tremor.

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Competing interests

The authors report no competing interests.

References

Bahlo M, Bennett MF, Degorski P, Tankard RM, Delatycki MB, Lockhart PJ. Recent advances in the detection of repeat expansions with short-read next-generation sequencing. F1000Res 2018; 7: 736.

Charles P, Camuzat A, Benammar N, Sellal F, Destée A, Bonnet AM, et al. Are interrupted SCA2 CAG repeat expansions responsible for parkinsonism? Neurology 2007; 69: 1970–5.

Cumming SA, Hamilton MJ, Robb Y, Gregory H, McWilliam C, Cooper A, et al. De novo repeat interruptions are associated with reduced somatic instability and mild or absent clinical features in myotonic dystrophy type 1. Eur J Hum Genet 2018; 26: 1635–47.

Ishiura H, Shibata S, Yoshimura J, Suzuki Y, Qu W, Doi K, et al. Noncoding CGG repeat expansions in neuronal intranuclear inclusion disease, oculopharyngodistal myopathy and an overlapping disease. Nat Genet 2019; 51: 1222–32.

Paulson H. Repeat expansion diseases. Handb Clin Neurol 2018; 147: 105–23.

Pešović J, Perić S, Brkušanin M, Brajušković G, Rakočević-Stojanović V, Savić-Pavićević D. Repeat interruptions modify age at onset in myotonic dystrophy type 1 by stabilizing DMPK expansions in somatic cells. Front Genet 2018; 9: 601.

Sone J, Mitsuhashi S, Fujita A, Mizuguchi T, Hamanaka K, Mori K, et al. Long-read sequencing identifies GGC repeat expansions in NOTCH2NLC associated with neuronal intranuclear inclusion disease. Nat Genet 2019; 51: 1215–21.

Sun Q, Xu Q, Tian Y, Hu Z-M, Qin L-X, Yang J-X, et al. Expansion of GGC repeat in human-specific NOTCH2NLC gene is associated with essential tremor. Brain 2020; 143: 222–233.

Tian Y, Wang J-L, Huang W, Zeng S, Jiao B, Liu Z, et al. Expansion of human-specific GGC repeat in neuronal intranuclear inclusion disease-related disorders. Am J Hum Genet 2019; 105: 166–76.

Westenberger A, Reyes CJ, Saranza G, Dobricic V, Hanssen H, Domingo A, et al. A hexanucleotide repeat modifies expressivity of X-linked dystonia parkinsonism. Ann Neurol 2019; 85: 812–22.

Growing evidence links air pollution exposure to risk of Alzheimer's disease and related dementia

This scientific commentary refers to 'Particulate matter and episodic memory decline mediated by early neuroanatomic biomarkers of Alzheimer's disease', by Younan *et al.* (doi: 10.1093/brain/awz348).

Given the ageing of the global population, the number of individuals with Alzheimer's disease and related dementia (ADRD) is expected to double approximately every 20 years, to an estimated 115 million people by 2050 (Prince *et al.*, 2013). As there are no disease-modifying treatments for the most common types of dementia, identification of modifiable risk factors for ADRD is of paramount importance.

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AD-PS score: Alzheimer's Disease Pattern Similarity score. Using a statistical process, the investigators quantify the extent to which participant structural MRI scans have patterns of grey matter atrophy that resemble those derived from patients known to have Alzheimer's disease dementia.
$PM_{2.5}$: Particulate matter with aerodynamic diameter <2.5 μm. $PM_{2.5}$ exposures have been consistently linked to adverse health outcomes, including cardiovascular disease, respiratory problems, and mortality. As such, $PM_{2.5}$ levels are regulated by many countries around the world, including the USA, where $PM_{2.5}$ standards are part of the National Ambient Air Quality Standards (NAAQS), which specify a maximum amount of particulate matter to be present in outdoor air.

As a class, environmental risk factors for cognitive decline and ADRD have received relatively little attention, despite established neurotoxicity of many pollutants. The exception to this is the small but growing literature suggesting that higher air pollution exposure is associated with worse cognitive performance, faster cognitive decline, and increased risk of cognitive impairment or dementia (Power *et al.*, 2016). Almost all studies to date that examine the association between exposure to air pollution and cognition or dementia suggest a link between the two. However, this literature has met with scepticism, despite evidence that common sources of bias are unlikely to account for the observed associations (Power *et al.*, 2016). Additional evidence linking air pollution to ADRD-related markers of brain pathology is needed both to strengthen the evidence base and to provide insight into the mechanisms by which air pollution exposures may be related to ADRD. In this issue of *Brain*, Younan *et al.* present evidence linking particulate matter (PM) air pollution to late-life cognition and explore whether this association is mediated by changes in brain structure using data from a subset of participants of the Women's Health Initiative (WHI) study (Younan *et al.*, 2020).

Younan *et al.* leverage existing cognitive test score and MRI data from sub-studies of the parent WHI study. Air pollution exposures are highly related to time and space. Based on geocoded participant addresses, the authors estimated exposure to one air pollutant, $PM_{2.5}$, at each eligible participant's residential address in the 3 years prior to their first MRI as a proxy for long-term personal exposures. Use of residential address to assign individual-level exposures is a common choice in air pollution research, in part because regulatory efforts to curb air pollution exposures rely on regulating ambient levels. The authors were then able to link the new $PM_{2.5}$ air pollution estimates to existing cognitive and MRI data in order to test hypotheses about the link between $PM_{2.5}$ exposures and late-life cognitive change. The time of the first MRI is considered 'baseline' for the purposes of this study.

First, the authors consider the association between $PM_{2.5}$ and both baseline performance and longitudinal change in episodic memory, as measured by the California Verbal Learning Test (CVLT). The CVLT measures both verbal learning and verbal memory. Verbal learning is assessed through performance on immediate recall of word lists and yields two measures (CVLT Trials 1–3 and CVLT List B). Verbal memory is assessed through delayed recall of word lists and yields two additional measures (CVLT List A Short-Delay Recall, CVLT List A Long-Delay Recall). The authors also considered a summary measure that was the average of the Trials 1–3, Short-Delay Recall, and Long-Delay Recall scores. Notably, the authors did not find an association between long-term $PM_{2.5}$ exposure and baseline performance on the CVLT using any measure. While $PM_{2.5}$ exposure was associated with greater decline in CVLT-based measures of verbal learning (CVLT Trials 1–3 and CVLT List B), there was no association between $PM_{2.5}$ and change in the CVLT-based measures of verbal memory (CVLT List A Short-Delay Recall and CVLT List A Long-Delay Recall) or the composite score.

Next, the authors used a separate statistical mediation model to examine whether the associations observed between $PM_{2.5}$ and verbal learning (CVLT Trials 1–3 and CVLT List B), were mediated by simultaneous change in a neuroimaging-based marker of ADRD-related brain atrophy, the Alzheimer's Disease Pattern Similarity (AD-PS) score. Using this model, the authors report that individuals with greater exposure to $PM_{2.5}$ have greater change in the AD-PS score and that change in AD-PS score is itself associated with greater cognitive decline in the CVLT-based measures of verbal learning. This was interpreted as evidence that the association between $PM_{2.5}$ and change in verbal learning scores was mediated by increasing grey matter atrophy in selected brain regions. The path through the AD-PS score explained 11% (CVLT Trials 1–3) or 23% (CVLT List B) of the adverse association observed between higher $PM_{2.5}$ and decline on these measures of verbal learning. While the findings were robust to most sensitivity analyses, the authors did not find evidence of mediation using change in total grey matter, rather than change in the AD-PS. These findings suggest that the observed associations between $PM_{2.5}$ exposures and cognitive decline in verbal memory are partially, but not primarily attributable to exposure-related atrophy in specific regions of the brain.

This study must be interpreted within the context of its limitations. While the focus on episodic memory is justified, this study cannot provide insight into whether $PM_{2.5}$ may affect other areas of cognition or whether

any effects of $PM_{2.5}$ on other domains in cognition are mediated by similar changes in the brain. The participants included in the sample were healthier and generally of higher socioeconomic status than the overall WHI sub-study population with available cognitive or MRI data. Similarly, those who returned for a second MRI were healthier and of higher socioeconomic status than those who did not. In addition, the participants were all female, and the vast majority were white and well-educated. Whether and how these factors affect the validity and generalizability of the findings is unclear. Another potential limitation is that the authors use $PM_{2.5}$ exposures over the 3 years prior to the first MRI as their estimate of exposure; this may not represent the relevant window of exposure. Finally, other air pollutants may also exert independent effects on ADRD and related outcomes.

Overall, the Younan *et al.* study is consistent with the broader literature linking $PM_{2.5}$ air pollution exposures to worse late-life cognitive outcomes. However, the current body of literature considering neuroimaging outcomes is both sparse and heterogeneous. These differences may be related to differences in study design. While the evidence suggesting mediation by progression of brain atrophy in selected areas of the brain is novel, it relies on demonstrating an association between $PM_{2.5}$ exposures and atrophy of selected brain areas. A prior study using a summary measure for volumes of structures known to atrophy in Alzheimer's disease failed to show associations between $PM_{2.5}$ exposure and this summary measure (Power *et al.*, 2018). To the contrary, the current study and a second study using the same WHI MRI data demonstrate associations between $PM_{2.5}$ exposures and grey matter structures based on methods using a voxel-wide analysis (Casanova *et al.*, 2016; Younan *et al.* 2020). In addition, most of the prior studies assessing the link between air pollution and neuroimaging markers of brain pathology considered data from a single MRI, whereas Younan *et al.* considered change across two MRI scans. Further work is needed to replicate the mediation results observed here and to examine whether these study design differences account for the heterogeneous findings.

Within the context of the existing literature, the Younan *et al.* paper in this issue of *Brain* provides additional support for the hypothesis that higher exposure to $PM_{2.5}$ is related to increased risk of ADRD and related outcomes, and suggests that this is mediated by observable changes to the grey matter. However, the implications of this investigation and the growing body of similar work on air pollution and late-life cognitive health go beyond whether air pollution is a modifiable risk factor for ADRD and related outcomes. As a class, environmental exposures represent an understudied set of potential risk factors for neurological conditions. Further consideration of the impact of an expanded set of exposures on the brain is warranted.

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Competing interests

The author reports no competing interests.

References

Casanova R, Wang X, Reyes J, Akita Y, Serre ML, Vizuete W, et al. A voxel-based morphometry study reveals local brain structural alterations associated with ambient fine particles in older women. Front Hum Neurosci 2016; 10: 495.

Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: a systematic review of epidemiologic research. Neurotoxicology 2016; 56: 235–253.

Power MC, Lamichhane AP, Liao D, Xu X, Jack CR, Gottesman RF, et al. The association of long-term exposure to particulate matter air pollution with brain MRI findings: the ARIC study. Environ Health Perspect 2018; 126: 027009.

Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013; 9: 63–75.e62.

Younan D, Petkus A, Widaman K, Wang X, Casanova R, Espeland M, et al. Particulate matter and episodic memory decline mediated by early neuroanatomic biomarkers of Alzheimer's disease. Brain 2020; 143: 289–302.

Does early cognitive decline require the presence of both tau and amyloid-β?

This scientific commentary refers to 'Amyloid and tau imaging biomarkers explain cognitive decline from late middle-age', by Betthauser *et al.* (doi: 10.1093/brain/awz378).

In vivo biomarkers of tau and amyloid-β pathology have become essential tools in research into preclinical Alzheimer's disease, as accumulation of both proteins begins many years before clinical symptoms emerge. In recent years, the first PET imaging probes sensitive to tau aggregates, such as ^{18}F-flortaucipir (^{18}F-AV-1451), have been studied intensively in cohorts of cognitively