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Blood Pressure's Role in Alzheimer's Disease Pathology

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What is known about BP and AD?

An expanding body of research is revealing complex relationships between elevated blood pressure (BP), cognition, and Alzheimer's disease (AD). BP is a well-established risk factor for cerebrovascular disease and brain atrophy. Mounting evidence indicates that high BP increases late-life dementia risk[1]; however, the associations with cognitive impairment and dementia are less consistent for late-life than for midlife BP measures. More recently, PET imaging research has linked higher late-life BP with greater extent of *in vivo* β-amyloid deposition[2]. Corroborating evidence from autopsy studies demonstrate that excess pulsatile pressure is associated with β-amyloid and tau neuropathology[3,4]. The existing literature coalesces to: 1) implicate elevated BP in the age-related expression of AD pathology; 2) underscore the critical importance of better defining the peripheral vascular contributions to AD pathology[1], beyond hypertension; and 3) posit BP control as a potential common target for AD and agerelated cognitive decline. The importance of vascular pathology to AD is highlighted by recent estimates that 25% of AD cases are β-amyloid negative[5], and an estimated 50% of AD cases display 'mixed' vascular and AD pathology[6].

What does the article by Roussotte et al.[7] add?

New research in this issue by Roussotte et al.[7] adds to knowledge regarding the relationship between BP and *in vivo* AD pathology measures. The authors tested whether systolic and diastolic BP were associated with global cognition in 101 middle-aged and older adults without dementia. A statistically significant association was detected between diastolic BP, but not systolic BP, and cognition. Individuals with higher diastolic BP also had significantly greater levels of FDDNP radioligand binding indicating greater burden of β-amyloid plaques *and* tau neurofibrillary tangles. Mediation analysis found that FDDNP binding *statistically* mediated the association of diastolic BP and global cognition by accounting for about 30% of the association. These findings advance current literature by: (1) demonstrating statistical mediation in a highly relevant and conceptually plausible causal model (linking BP to cognition via AD pathology), and (2) using the FDDNP ligand, which binds not only to β-amyloid, but also to tau.

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Caveats and limitations of the work by Roussotte et al.[7]

As the authors recognize, the cross-sectional, observational study design prohibits inferring temporal relations and residual confounding may be an issue. The study was unable to test whether BP *independently* predicted *changes* in cognition by *influencing future* β-amyloid accumulation; previous longitudinal studies have not observed this association.[8] Further, FDDNP binding was the only mediator of the diastolic BP-global cognition relationship examined; it would be valuable to evaluate whether cerebrovascular pathology was an additional mediator (e.g., white matter disease, lacunar infarction, cerebral microbleeds). In addition, FDDNP is a non-selective ligand that binds to the β-sheet structure of both β-amyloid and neurofibrillary tangles; while these data provocatively suggest the potential relevance of BP to tau binding, they provide no indication of the relative presence of β-amyloid and neurofibrillary tangles in this sample or the inherent affinity of the ligand for each form of AD pathology. Thus, this work sets the stage, but has not directly implicated BP with *in vivo* tau accumulation; such a finding could substantively refine current conceptual frameworks regarding the vascular contributors to AD.

The study's sample may also not be generally representative of older adults. Rates of antihypertensive use (20%) were low for the age group (39-87 years with equal distribution above and below 64 years of age), and ApoE-e4+ prevalence (45%) was high. It is also unclear whether the observed associations were similar in mid-life and later life sample sub-strata.

Is elevated diastolic or systolic BP the problem, or what lies beneath?

These results intensify the debate regarding whether excess systolic BP or diastolic BP is more detrimental to brain health, and implicate AD pathology burden as a whole, and not just β- amyloid. The findings suggest that cardiovascular conditions leading to diastolic dysfunction (e.g. heart failure and arterial stiffening) may provide novel details of the relationship between vascular disease, AD pathology and cognition. That said, it is important to note that the observed associations were in a similar direction for both BP indexes (but were stronger and statistically significant for diastolic BP).

BP is a complex phenotype that tends to increase with age, yet BP alone may not adequately represent the underlying mechanisms connecting peripheral hemodynamics to increased AD risk. Aging epidemiology studies underscore the need to consider not only the form of BP implicated, but also the stage of life at which BP is measured as well as the extent of arterial stiffness underlying BP. It has been proposed that mid-life hypertension and elevated BP may represent the cumulative burden of hypertension on the brain. The observed physiologic declines in diastolic and systolic BP in late-life[9,10] may obscure studies of late-life BP and brain health. While not measured in this study, the arterial stiffness underlying BP monotonically increases with age and contributes to the risk for both hypertension and dementia.[6] Recent research has shown that arterial stiffness is associated with cognition, evidence of cerebrovascular damage, and β-amyloid deposition, independent of late-life BP[2]. Arterial stiffness provides a physiologic link between hypertension and structural abnormalities in the brain. Stiff arteries transmit excessive pulsatile flow to the brain. This

process may damage the microvasculature and inhibit the perivascular clearance of soluble β-amyloid from the brain[2].

What are the implications of this work?

The inherent complexities of the mechanisms linking BP to brain health are only beginning to emerge. To further establish that BP is a causal factor in AD, future longitudinal research is needed to assess the trajectories of BP, *in vivo* AD pathology and cognition over time. The current work now sets up the field to initiate longitudinal follow-up studies incorporating Aβ and tau-specific PET measures along with MRI markers of neurodegeneration and cerebrovascular disease. Future work may benefit from considering the impact of including these other known pathologic hallmarks of dementia in causal and statistical mediation models of BP and cognition.

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