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PERSPECTIVE

The apathy, gait impairment, and executive dysfunction (AGED) triad vascular variant

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Abstract

Apathy, gait disturbances, and executive dysfunction (AGED) often occur together. Although they can arise independently, the presence of one might portend another. This recognition suggests the possible etiology. We focus on the most common, the vascular. We explain the AGED vascular mechanism through the ambibaric brain concept. The brain contains two complementary blood pressure systems: One high in the primitive brain (brainstem, basal ganglia, and thalamus) and a low-pressure system in the *Homo sapiens* brain (cerebral hemispheres). Hypertension inflicts the most damage on the primitive brain. The frontal systems connect to the basal ganglia, then the thalamus and back to the cortex. Many connections converge on the primitive brain where they are damaged by vascular disease. We need methods of determining optimal, individual blood pressures. Although the AGED triad can result from other causes, it should first signal a vascular etiology, the most prevalent, treatable, and preventable one.

KEYWORDS
Executive dysfunction, gait impairment, apathy, prevention, ambibaric brain, hypertension

1 | INTRODUCTION

Apathy, gait impairment, and diminished executive function often occur together, but usually are considered apart. However, an aging phenotype of slow gait, impaired executive function, and depressive symptoms has been described[1] and associated with hypertension and other cardiovascular diseases. In a subset of late life depression patients, this triad was found in 99 of 580 (17%) healthy, nondemented, community-dwelling seniors, aged 70 years or older.[1] Mehta et al. found that relative to younger elderly (65–80 years), apathy becomes more common in old elderly (>80 years).[2] We examined the prevalence of executive dysfunction, gait impairment, and apathy in a clinic-based cohort of community-dwelling older adults free of depression at baseline in the Gait and Brain Study (design and methods have been described in detail elsewhere).[3] Tables 1 and 2 show that apathy, gait impairment, and executive dysfunction were present in 4.3% in the decade 60 to 69 years, 9.1% between 70 and 79 years, and 13.5% in the decade from 80 to 89 years.

The association of executive dysfunction and gait disorders is well established.[1] More recently, it has been shown that hypertension is the main cause of brain small vessel disease that can lead to apathy.[5] Thus the combination of "think slow, walk slow, and feel slow" could be conveyed as apathy, gait impairment, and executive dysfunction (the AGED triad).

Although the exact mechanisms relating hypertension to these three impairments are not fully known, their co-occurrence can be explained by an evolutionary interpretation of the cerebral circulation—the ambibaric brain.[6] The most primitive brains consist of a tube with an enlarged end—the brain. They are supplied by a basal artery giving off short, perpendicular end arteries. This pattern is preserved in humans in the brainstem, the basal ganglia, and the thalamus—the primitive brain. The pressure from the basal arterial

trunk must be stepped down to capillary pressure over a relatively short segment. If a person develops hypertension, the penetrating arteries have to contract harder to maintain a constant blood supply. This often results in hypertrophy of the muscular layer and at times hyalinosis and microaneurysms, with a propensity for occlusions, causing lacunar infarcts or ruptures resulting in intracerebral hemorrhages.

The human (*Homo sapiens*) brain is characterized by the massive expansion of the hemispheres, largely supplied by long branching arteries giving off arterioles penetrating the hemispheres. The long arteries allow for a gradual stepping down of the arterial blood pressure to capillary pressure. Consequently, the human brain effectively has two complementary pressure systems. A high one in the primitive brain and a low one in the *Homo sapiens* brain. Modeling suggests that when the blood pressure in the arm is 115/75, it is 113/73 in the primitive brain and 58/36 in parietal branches of the *Homo sapiens* brain.[7]

The brunt of hypertension damage occurs in the primitive brain. Already in middle age, hypertension is associated with white matter disruption and executive dysfunction that often occurs together with gait impairment and depression.[8,9]

The architecture of all the frontal systems is similar: A part of the frontal cortex connects to the basal ganglia, that project to the thalamus, that in turn connects back to the originating frontal cortex.

One explanation for the common association of AGED could be that most of the relevant brain networks are damaged, because they go through the primitive brain. A common cause is hypertension that can lead to infarcts and hemorrhages. These might be preceded by damage to the pericytes controlling capillary blood flow (Figure 1).

Executive functions are mainly subserved by brain networks arising in the lateral prefrontal cortex; gait control by the prefrontal–striatal networks;[10] and apathy, through damage to connections of the anterior cingulate, with the ventral striatum.[11]

RESEARCH IN CONTEXT

1. **Systematic review**: Apathy, a gait impairment, and executive dysfunction (AGED) commonly occur jointly in the elderly, sometimes masked by the generic description of "late life depression." The recognition of the triad is clinically useful because it often results from hypertension, which is treatable and preventable.
2. **Interpretation**: When the AGED triad occurs with hypertension, it becomes important to realize that blood pressure in the brain is not uniform and treatment needs to be customized. Studies suggest the desirability of lower systolic blood pressure targets, as low as 120 mmHg. Although on average this could be advisable, patients with limited cerebral blood flow autoregulation might be harmed.
3. **Future directions**: Given the high prevalence of hypertension, co-morbidities, and polypharmacy among the elderly, developing non-invasive methods of assessing autoregulation becomes imperative, so that the optimal blood pressure for each individual can be prescribed. This could be one of the highest priorities in personalized medicine.

2 | DISCUSSION

Although hypertension is a common culprit, the AGED triad can also result from other causes such as neurodegeneration, notably in frontotemporal dementias, Parkinson's disease, or brain trauma. However, in these conditions it is usually preceded or overshadowed by other symptoms such as behavioral disorders in frontotemporal dementia, slowing and masking in Parkinson's disease, and memory impairment or emotion dysregulation in head trauma.

The importance of the thinking of an AGED triad stems from the fact that the presence of one component should raise awareness of the risk of developing another and point to an underlying treatable cause, such as hypertension. A number of studies suggest the benefits of intensive blood pressure reduction.[12–15] Treating hypertension is one way to prevent small vessel disease and the subsequent cognitive impairment in executive function.[15] Mechanistically, this supports the potential that hypertension treatment may also prevent or delay gait decline and apathy and prevent the AGED triad. The SPRINT Trial[13] results even suggested lowering blood pressure targets to 120 mmHg. However, fluctuations of blood pressure and acute hypotension can harm the brain.

All clinical trials are selective and exclude patients who might have complicating conditions, such as diabetes, that may impair cerebral blood flow autoregulation. Consequently, if the new recommendations are to be applied widely, we need to know the individual brain autoregulatory capacity. This becomes particularly important in patients with multimorbidities and those taking multiple drugs. Multiple medical conditions lead to multiple drugs being prescribed, some with unintended consequences. Decongestants and nonsteroidal anti-inflammatory drugs can increase blood pressure and sleeping pills can decrease blood pressure. Therefore, one of the greatest needs of personalized medicine is to develop non-invasive techniques to assess cerebral blood flow autoregulation, so that the optimal level of blood pressure for the brain could be individualized. For instance, a phenotype of dual-decliners, older adults who experience concurrent decline in gait speed and cognition (mainly memory and executive functions), has been associated with a higher risk to progress to dementia, as hypertension is a main risk factor associated with this phenotype.[16,17] Early recognition of those experiencing the dual decline in gait speed and cognition can point to those older adults at higher risk of dementia who might benefit the most from a carefully personalized intensive hypertension treatment.

TABLE 1 AGED triad prevalence and baseline characteristics in the Gait and Brain Study

	Full cohort Mean ± SD or n,%; min–max N = 370	AGED triad– Mean ± SD or n,%; min–max N = 341	AGED triad+ Mean ± SD or n,%; min–max N = 29	Eta-squared	*P* value
Age in years	72.1 ± 6.7; 59–92	71.8 ± 6.6; 59–92	75.6 ± 7; 60–89	.023	.004
Women n,%	270, 58	201, 58	15, 51	<.001	.45
Number of years of education	14.6 ± 3.1; 6–25	14.8 ± 3.1; 6–25	12.9 ± 2.7; 6–19	.024	.003
Body mass index (kg/cm^2)	28 ± 5.4; 17.8–51.5	28 ± 5.5; 17.8–51.5	28.2 ± 4.1; 23.2–40.8	<.001	.858
MMSE (range 0–30)	27.5 ± 2.2; 18–30	27.6 ± 2.1; 18–30	26.5 ± 2.9; 18–30	.018	.009
MoCA (range 0–30)	24.5 ± 3.5; 12–30	24.7 ± 3.4; 12–30	22.5 ± 3.4; 16–29	.029	.001
GDS (range 0–15)	2.4 ± 2.6; 0–13	2.1 ± 2.5; 0–13	5.4 ± 2.5; 3–12	.111	<.001
Trail Making Test A (seconds)	39.3 ± 15.4; 9–110	38.1 ± 14.7; 9–110	53.9 ± 16.3; 26–99.12	.077	<.001
Trail Making Test B (seconds)	118.1 ± 169.9; 9–300	111.8 ± 174.1; 9–300	191.9 ± 76.6; 127–444.2	.016	.015
Digit span Forward (range 0–16)	10 ± 2.2; 5–16	10 ± 2.2; 5–16	9.6 ± 2.2; 6–16	.003	.333
Digit span Backward (range 0–14)	6.2 ± 2; 1–13	6.3 ± 2.1; 1–13	5.3 ± 1.8; 2–10	.016	.015
RAVLT immediate recall (range 0–15)	7 ± 3.9; 0–15	7.1 ± 3.9; 0–15	5.3 ± 3.2; 0–11	.015	.018
PASE	117.4 ± 59.6; 5–415.2	120 ± 59.8; 5–415.2	86.1 ± 48.5; 25–196.8	.023	.003
SPPB (range 0–12)	9.7 ± 2.1; 2–17	9.9 ± 2; 3–17	7.4 ± 2.6; 2–12	.093	<.001
Total number of medications taken	6.9 ± 4.3; 0–24	6.7 ± 4.3; 0–24	8.6 ± 4.2; 0–17	.014	.024
Lawton–Brody IADL score	7.8 ± 0.6; 2–8	7.8 ± 0.5; 2–8	7.2 ± 1.4; 3–8	.062	<.001
Frailty score (range 0–5)[a]	1.1 ± 1.1; 0–4	1 ± 1; 0–4	2.7 ± 0.9; 1–4	.132	<.001
Grip strength[b] (kg/N)	26.5 ± 10.4; 1–88.6	26.7 ± 10.5; 6.3–88.6	23.5 ± 9.4; 1–44.3	.006	.187
Number of falls in past year	0.6 ± 1.3; 0–12	0.5 ± 1; 0–6	1.9 ± 2.9; 0–12	.074	<.001
Number of falls in past 6 months	0.4 ± 1; 0–12	0.3 ± 0.6; 0–3	1.7 ± 2.7; 0–12	.136	<.001
Usual gait speed (cm/s)	113.9 ± 22.6; 32.28–179	115.9 ± 21.4; 49.12–179	90.7 ± 23.8; 32.28–144.3	.091	<.001
Counting gait speed (cm/s)	108.8 ± 26.1; 22.43–186.5	111 ± 25.1; 37.5–186.5	82.7 ± 23.8; 22.43–131.0	.085	<.001
Naming animals gait speed (cm/s)	100.9 ± 27.3; 28.05–172.8	102.9 ± 26.7; 41.24–172.8	77.1 ± 24.2; 28.05–118.9	.063	<.001
Serial 7 s gait speed (cm/s)	97 ± 27.3; 21.72–180.0	99.1 ± 26.6; 31.92–180.08	73.3 ± 24.7; 21.72–125.7	.065	<.001

Note: AGED triad is defined as (1) having slow gait speed - < 1 m/s-; apathy by scoring ≥2 in the GDS-3A scale[4] and having executive dysfunction and the highest quartile in TMT B.

Abbreviations: AGED, apathy, gait disturbances, and executive dysfunction; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PASE, Physical Activity Scale for the Elderly; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; SPPB, Short Physical Performance Battery.

[a]Frailty score calculated from five items: weakness, exhaustion, low physical activity, unintentional weight loss of at least 10 lb in 1 year and slow gait.

[b]Grip strength: average of three trials.

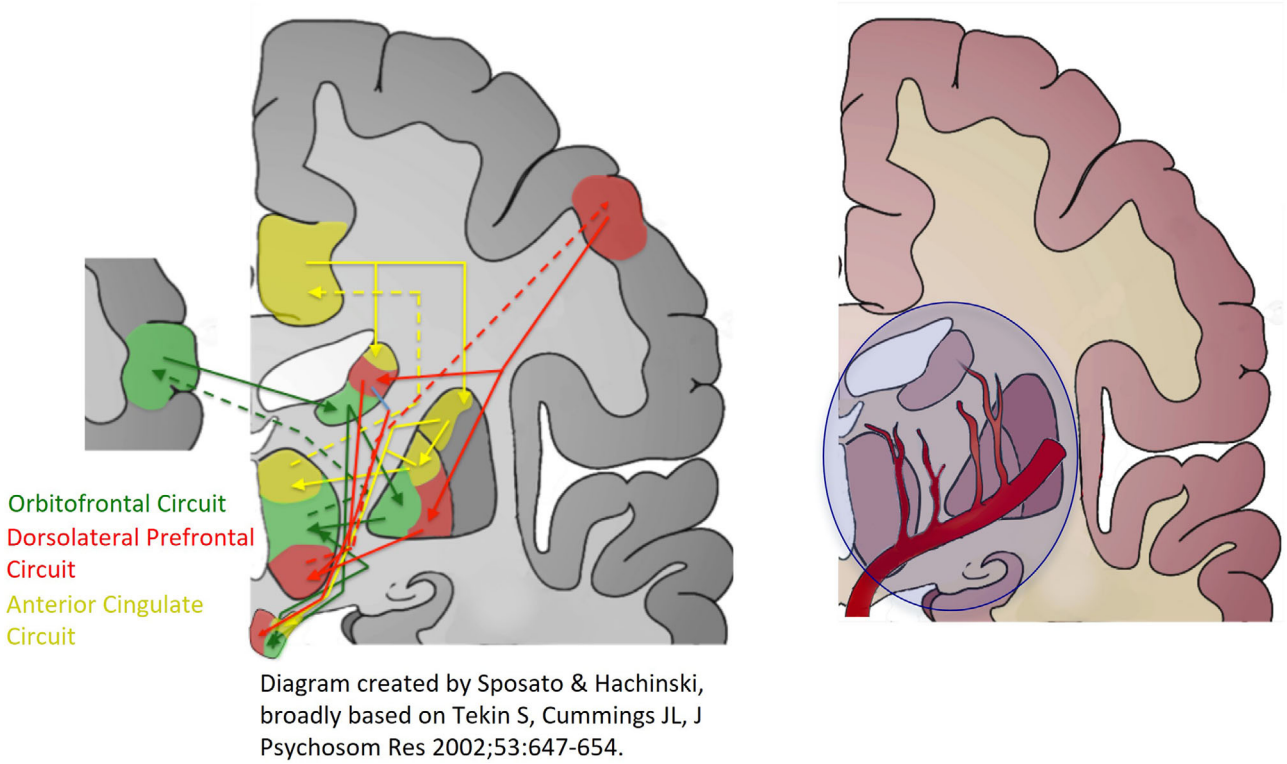

FIGURE 1 High-density circuits subserving of apathy, gait control, and executive function in brain regions prone to hypertension-mediated injury. Solid lines represent efferent pathways and dashed lines afferent pathways

TABLE 2 AGED triad + per age decade prevalence

Age decade range	AGED triad + n,%
60–69 (N = 141)	6, 4.3
70–79 (N = 175)	16, 9.1
80–89 (N = 52)	7, 13.5

Abbreviation: AGED, apathy, gait disturbances, and executive dysfunction.

3 | CONCLUSION

The concept of the ambibaric brain (complementary high and low brain blood pressure systems) explains the vascular variant of the AGED triad. Its recognition can point to underlying treatable conditions such as hypertension, and to a cautious management of blood pressure fluctuations, including postural hypotension, in older adults. Future clinical trials assessing the effect of treating hypertension on these neurogeriatric impairments are needed to identify early interventions that prevent disability in these individuals.

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CONFLICTS OF INTEREST

No conflicts of interest have been declared by the authors.

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REFERENCES

1. Hajjar I, Yang F, Sorond F, et al. A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: relationship to blood pressure and other cardiovascular risks. *J Gerontol A Biol Sci Med Sci*. 2009;64(9):994-1001.
2. Mehta M, Whyte E, Lenze E, et al. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *Int J Geriatr Psychiatry*. 2008;23:238-243.
3. Montero-Odasso MM, Barnes B, Speechley M, et al. Disentangling cognitive-frailty: results from the Gait and Brain Study. *J Gerontol A Biol Sci Med Sci*. 2016;71(11):1476-1482.
4. Bertens AS, Moonen JEF, de Waal MWM, et al. Validity of the three apathy items of the Geriatric Depression Scale (GDS-3A) in measuring apathy in older persons. *Int J Geriatr Psychiatry*. 2017;32(4):421-428.
5. Clancy U, Gilmartin D, Jochems ACC, et al. Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis. *Lancet Psychiatry*. 2021;8(3):225-236.
6. Hachinski V, Østergaard L. The ambibaric brain: pathophysiological and clinical implications. *Stroke*. 2021;52(6):e259-e262.

7. Blanco PJ, Müller LO, Spence JD. Blood pressure gradients in cerebral arteries: a clue to pathogenesis of cerebral small vessel disease. *Stroke Vasc Neurol*. 2017;2:108-117.
8. Montero-Odasso M, Hachinski V. Preludes to brain failure: executive dysfunction and gait disturbances. *Neurol Sci*. 2014;35(4):601-604.
9. Patience J, Lai KSP, Russell E, Vasudev A, Montero-Odasso M, Burhan AM. Relationship between mood, thinking, and walking: a systematic review examining depressive symptoms, executive function, and gait. *Am J Geriatr Psychiatry*. 2019;27(12):1375-1383.
10. Annweiler C, Montero-Odasso M. Vascular burden as a substrate for higher-level gait disorders in older adults. A review of brain mapping literature. *Panminerva Med*. 2012;54(3):189-204.
11. Le Heron C, Apps MAJ, Husain M. The anatomy of apathy: a neurocognitive framework for amotivated behaviour. *Neuropsychologia*. 2018;118(Pt B):54-67.
12. ACCORD Study Group; Cushman WC, Evans GW, Byington RP, et al, ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575-1585.
13. Heimark S, Mariampillai JE, Narkiewicz K, Nilsson PM, Kjeldsen SE. Which target blood pressure in Year 2018? Evidence from recent clinical trials. *High Blood Press Cardiovasc Prev*. 2018;25(2):151-158.
14. White WB, Wakefield DB, Moscufo N, et al. Effects of intensive versus standard ambulatory blood pressure control on cerebrovascular outcomes in older people (INFINITY). *Circulation*. 2019;140(20):1626-1635.
15. Palta P, Albert MS, Gottesman RF. Heart health meets cognitive health: evidence on the role of blood pressure. *Lancet Neurol*. 2021;20(10):854-867.
16. Montero-Odasso M, Speechley M, Muir-Hunter SW, et al. Dual decline in gait speed and cognition is associated with future dementia: evidence for a phenotype. Canadian Gait and Cognition Network. *Age Ageing*. 2020;49(6):995-1002.
17. Tian Q, Studenski SA, Montero-Odasso M, Davatzikos C, Resnick SM, Ferrucci L. Cognitive and neuroimaging profiles of older adults with dual decline in memory and gait speed. *Neurobiol Aging*. 2021;97:49-55.

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