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Bypassing the Blood-Brain Barrier: A Dual-Axis Framework for Parkinson's Disease Utilizing Glymphatic-Lymphatic Clearance and In Situ Chaperone Synthesis

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Abstract

Parkinson's disease (PD) is characterized neuropathologically by loss of dopaminergic neurons in the substantia nigra pars compacta and by aggregation of misfolded alpha-synuclein into Lewy bodies and Lewy neurites, which is proposed to propagate in a prion-like manner following a stereotyped, stage-dependent pattern described by Braak staging. Because any circulating agent intended to act within the central nervous system (CNS) must cross the blood-brain barrier, this review proposes active craniospinal tensioning (ACT), a mechanical, non-pharmacological route to disease modification acting on cerebrospinal fluid (CSF) and cerebral venous pressure dynamics. ACT combines two concurrent mechanisms converging on a single venous-side target within Monro-Kellie/Queckenstedt pressure continuity: suboccipital venous occlusion-rebound, proposed to raise and release craniospinal CSF pressure to accelerate venous-side glymphatic efflux, and dural pull-recoil, a reverse Queckenstedt effect in which spinal elongation is proposed to generate a CSF-side pressure gradient with a coupled venous component. The proposed disease-modifying route is clearance of transiting extracellular alpha-synuclein from the perivascular and interstitial space before it templates a neighboring cell. The claim is scoped to the CNS phase of PD, excluding peripheral vagal or olfactory transport, with its most direct anatomical rationale at the dorsal motor nucleus of the vagus (DMV), one of the two earliest CNS sites of Lewy pathology in Braak staging and adjacent to ACT's craniocervical site of action, where ACT is proposed to act on onward extracellular spread rather than on arrival.

A secondary, hypothesis-generating axis, cerebral venous preconditioning (CVPC), proposes that the same cycle produces venule- and capillary-wall strain sufficient to activate heat shock factor 1 (HSF-1) within the neurovascular unit, beginning at the vessel wall, independent of oxygen tension, with a possible contribution from hypoxia-inducible factor 1-alpha (HIF-1 α) left open; the mechanical route alone is proposed as sufficient. Validation is staged, with diffusion tensor image analysis along the perivascular space (DTI-ALPS) and neuromelanin-sensitive magnetic resonance imaging with quantitative susceptibility mapping (QSM) of the substantia nigra as dual falsification endpoints over at least two years, and any disease-modification claim deferred to a randomized, delayed-start trial. This framework is entirely theoretical, requires clinical validation, and extends a dual-axis template already applied to Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS).

Categories: Neurology, Preventive Medicine, Medical Physics

Keywords: active craniospinal tensioning (act), alpha-synuclein, cerebral venous preconditioning (cvpc), diffusion tensor image analysis along the perivascular space (dti-alps), dural pull-recoil, glymphatic-lymphatic clearance, heat shock factor 1 (hsf-1), parkinson's disease (pd), quantitative susceptibility mapping (qsm), suboccipital venous occlusion-rebound

Introduction And Background

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD) [1] and, per the Global Burden of Disease study, the fastest-growing neurological disease by prevalence, disability, and mortality [2], affecting 2%-3% of the population above age 65 [1]. No therapy has yet been shown to slow or halt the underlying disease process, and patients accrue progressive motor, non-motor, and cognitive disability [3]. The disease process is already well advanced by the time of diagnosis: an estimated 40%-60% of dopaminergic neurons in the substantia nigra pars compacta are lost before the cardinal motor features of bradykinesia, rigidity, and rest tremor appear [4]. Non-motor symptoms, including rapid eye movement sleep behavior disorder (RBD), hyposmia, and autonomic dysfunction, frequently precede the motor diagnosis by five to 10 years for hyposmia and potentially more than a decade for RBD and constipation [4].

This review has three aims. First, it summarizes current understanding of how PD progresses and the status of disease-modifying therapy, none of which has yet been shown to modify that progression. Second, it evaluates whether active craniospinal tensioning (ACT), a non-pharmacological maneuver described in the

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author's prior work, could plausibly act on any part of that progression, distinguishing the established physiology on which it draws from its proposed and untested application to PD. Third, it outlines a preliminary research pathway by which that proposal could be tested and falsified. ACT has not been studied in PD, and every claim about its effect in this disease is hypothetical.

Like other non-motor features, sleep disturbance shows a prodromal pattern: in a population-based cohort, poor sleep quality and short sleep duration were associated with increased risk of parkinsonism and PD only within the first two years of follow-up, and their deterioration preceded diagnosis [5]. A contributory role is not excluded [5], since sleep supports glymphatic clearance of interstitial solutes [6]. In adults monitored by lumbar catheter, one night of sleep deprivation increased cerebrospinal fluid (CSF) tau by 51.5% and CSF alpha-synuclein by 36.4%, whereas neurofilament light chain (NfL) was unchanged [7]. The authors attributed this rise to activity-dependent release rather than reduced clearance [7], so these findings bear on the extracellular protein load available for propagation; this relationship is revisited as an exploratory measure in the "Methodological Framework and Priorities for Clinical Validation" section.

PD pathogenesis is contested across a wider range of proposed mechanisms than that of either of the proteinopathies previously addressed in this series, AD [8] and amyotrophic lateral sclerosis (ALS) [9], and this framework's claim should be read within that landscape, not as a stand-alone account. Mitochondrial complex I dysfunction, oxidative stress, and lysosomal-autophagic failure implicated by GBA1 and LRRK2 variants are each independently supported as contributing mechanisms [3]. None is addressed here, since each is an intracellular or subcellular process with no extracellular or perivascular transit step for a CSF-directed intervention to act upon. Iron accumulation in the substantia nigra [10] and microglia-driven neuroinflammation [3] occupy an intermediate position, plausibly downstream of, or parallel to, the extracellular alpha-synuclein burden that this framework targets, such that mechanical clearance could, in principle, attenuate their triggering signal, though this is not established and is not assumed here. The mechanism this framework does engage is the remaining thread: prion-like, cell-to-cell propagation of misfolded alpha-synuclein [3,11] through the extracellular and perivascular space, the same load-bearing process this series' ALS predecessor targeted for TAR DNA-binding protein 43 and superoxide dismutase 1 [9], and it is to this thread alone that the following sections apply.

At the center of this propagation thread is a proteotoxic process: progressive intraneuronal aggregation of misfolded alpha-synuclein into Lewy bodies and Lewy neurites, accompanied by loss of dopaminergic neurons in the substantia nigra pars compacta [3]. Alpha-synuclein aggregates behave in a prion-like manner, templating conformational change in native protein and propagating along interconnected neural networks via cell-to-cell transmission rather than remaining confined to the neuron of origin [12]. Braak's staging model proposed a stereotyped caudo-rostral course, originating in the dorsal motor nucleus of the vagus (DMV) and/or olfactory bulb before ascending through the brainstem, midbrain, and cortex [13]. A refinement distinguishes two subtypes by site of origin [14,15]: body-first PD, in which alpha-synuclein originates in the enteric nervous system and reaches the DMV via retrograde axonal transport along the vagus nerve, consistent with gut-to-brainstem spread in animal models following gastrointestinal inoculation and its prevention by truncal vagotomy [16]; and brain-first PD, in which pathology arises intracranially, rostral to the substantia nigra, without an obligatory peripheral or vagal entry step. A meaningful minority of cases in neuropathological series lack DMV involvement, and many do not follow the classical Braak sequence, consistent with this dual-origin revision [3,17]. This templated propagation is the process this framework's primary intervention targets: removing suspended misfolded alpha-synuclein from the extracellular and perivascular space before it templates a neighboring cell offers a plausible route to slowing disease spread within the central nervous system (CNS), independent of the target cell's own biochemical stress-response capacity.

This same propagation model sets an explicit boundary for a mechanical, CSF/perivascular intervention. The body-first route from the enteric nervous system to the DMV travels via retrograde transport along the vagus nerve's intra-axonal compartment, a peripheral nerve trunk, rather than the CSF or the perivascular space, which any glymphatic-directed mechanism could plausibly influence. No mechanism here acts on this pre-CNS, vagal-axonal phase; the claim begins only once alpha-synuclein pathology has entered the CNS proper, at or after the DMV. This scopes the framework to the CNS phase of body-first PD and to brain-first PD from its outset, leaving the peripheral induction and ascent phase, whether vagal or olfactory, and any prevention claim resting on it, outside its reach.

Current pharmacological options remain overwhelmingly symptomatic: levodopa and dopamine agonists address the dopaminergic deficit but do not modify the underlying proteinopathy or its spread [3]. Efforts to deliver disease-modifying biologics illustrate the barrier constraint facing CNS-targeted therapeutics generally: glial cell line-derived neurotrophic factor (GDNF), a candidate neurorestorative protein, cannot cross the blood-brain barrier (BBB) and has required delivery by direct intraputamen infusion via implanted catheters accessed through a skull-mounted port, bypassing rather than crossing the barrier [18]. Despite achieving putamen-wide coverage, a randomized trial of intraputamenal GDNF did not meet its primary motor endpoint [18], underscoring that circumventing the BBB invasively does not by itself guarantee benefit.

Current PD-specific disease-modification efforts illustrate a related gap between engaging a molecular

target and changing clinical progression. Prasinezumab, a monoclonal antibody targeting aggregated alpha-synuclein, missed its primary endpoint in the Phase 2 PASADENA trial [19] and then narrowly missed significance for its primary endpoint of time to confirmed motor progression (hazard ratio 0.84, 95% confidence interval 0.69-1.01) in the larger Phase 2b PADOVA trial (n = 586) [20], with a more pronounced effect in the prespecified levodopa-treated subgroup (74.2% of participants) and exploratory magnetic resonance imaging (MRI) evidence of reduced nigral iron accumulation; on the strength of these signals it has advanced to the Phase 3 PARAISO trial (NCT07174310) [20]. No disease-modifying PD therapy, whether directed at alpha-synuclein or at a genetically implicated target such as LRRK2, has yet proven effective in a Phase 3 trial or received regulatory approval [3,20].

Evidence of glymphatic involvement in PD is substantial and growing: diffusion tensor image analysis along the perivascular space (DTI-ALPS) [21], the same non-invasive proxy proposed in the companion frameworks, shows reduced indices in PD versus controls across a large literature, with a recent meta-analysis of 21 studies (1,678 patients, 1,088 controls) finding a significant, moderate-effect-size reduction that was greater with longer disease duration and with higher Hoehn and Yahr stage, the latter association reaching significance only among patients at early stages [22]. Reduced DTI-ALPS indices have also been reported in prodromal populations, including isolated RBD [23], and impaired meningeal lymphatic drainage has been separately demonstrated in idiopathic PD by dynamic contrast-enhanced MRI [24], together consistent with glymphatic dysfunction as an early feature rather than a late epiphenomenon. Experimental work links this clearance pathway to alpha-synuclein pathology directly: in A53T transgenic mice, blocking meningeal lymphatic drainage by deep cervical lymph node ligation worsened glymphatic dysfunction and increased alpha-synuclein accumulation, dopaminergic neuron loss, and motor deficits, and aquaporin-4 deletion slowed clearance of injected alpha-synuclein from the substantia nigra [25]. No human study has yet shown that improving glymphatic function reduces alpha-synuclein propagation or alters clinical outcomes in PD, and this remains a central untested premise of the present framework.

The paragraphs above summarize PD pathophysiology and the status of disease-modifying therapy as currently understood in the field; the remainder of this Introduction turns from established disease biology to the hypothesis this framework proposes, and readers should treat this as the point where established findings give way to this paper's own proposal.

The mechanisms of ACT are developed in full in the companion AD and ALS frameworks [8,9] and are summarized only briefly here. Its macro-fluidic axis, suboccipital venous occlusion-rebound and dural pull-recoil, is proposed to act on Monro-Kellie/Queckenstedt pressure continuity to accelerate the passive venous-side efflux of the glymphatic system; its secondary micro-biochemical axis, cerebral venous preconditioning (CVPC), proposes heat shock factor 1 (HSF-1) activation within the neurovascular unit, beginning at the vessel wall, with a hypoxia-inducible factor 1-alpha (HIF-1 α) contribution left open. ACT refers to the maneuver, whether self-administered (ACT-SA) or operator-driven (ACT-OD) [26], which are proposed to be mechanically equivalent. This review extends that template to PD with two disease-specific considerations: the intracellular predominance of Lewy pathology, and the anatomical proximity of the DMV to ACT's craniocervical site of action.

Review

Literature search methodology

This is a narrative, hypothesis-generating review rather than a systematic review. No PRISMA flow diagram was generated, and the process below is reported for transparency rather than as a claim of systematic completeness. Because the physical and biochemical basis for ACT and CVPC has already been searched and developed in the companion ALS framework [9], searches here targeted PD-specific literature. PubMed/MEDLINE was searched through October 2026, without a lower date bound, so that foundational staging literature (e.g., Braak et al. [13]) could be included alongside recent glymphatic and biomarker findings, supplemented by reference-list snowballing and targeted searches for individual claims. Trial status not yet reported in the peer-reviewed literature was confirmed from ClinicalTrials.gov registry entries.

Search terms were combined using AND/OR Boolean operators across six queries: ("Parkinson's disease" OR "PD") AND ("glymphatic" OR "perivascular clearance" OR "DTI-ALPS"); ("alpha-synuclein" OR "Lewy body" OR "Lewy pathology") AND ("prion-like" OR propagation OR "cell-to-cell transmission"); ("blood-brain barrier") AND ("Parkinson" OR "GDNF" OR "intraputaminial"); ("Braak staging" OR "body-first" OR "brain-first") AND Parkinson; ("REM sleep behavior disorder" OR "meningeal lymphatic" OR "isolated RBD") AND (Parkinson OR prodromal OR phenoconversion); and ("HSF1" OR "HSF-1" OR "heat shock protein 70" OR "GLT-1" OR "EAAT2") AND ("Parkinson" OR "dopaminergic neuron" OR "alpha-synuclein"). These six queries returned 672, 1,467, 3,617, 237, 2,411, and 300 records, respectively. Because several queries returned thousands of records, results were not screened exhaustively; the queries were used to map each topic, and sources were selected for direct relevance to the specific claims made, with priority given to recent meta-analyses, comprehensive reviews, and trial reports. The prasinezumab trials (PASADENA, PADOVA, PARAISO) were retrieved by searching the agent and trial names directly, and general PD pathogenesis background is drawn from a recent comprehensive review [3] rather than an independent query. In total, 43

references are cited. No quantitative evidence synthesis, meta-analysis, or meta-regression was planned or performed; the reviewed literature is synthesized narratively.

Inclusion criteria were peer-reviewed, English-language original research articles, randomized controlled trials, meta-analyses, and review articles addressing (a) PD epidemiology, pathogenesis, staging, or pharmacotherapy, including disease-modifying therapy trials; (b) PD-specific glymphatic-lymphatic fluid dynamics or biomarker evidence; (c) HSF-1/heat shock protein 70 (HSP70)-mediated dopaminergic neuroprotection or astrocytic transporter biology in PD models; and (d) prior ACT/CVPC technical reports and companion frameworks by the author, included as the source of the proposed mechanism rather than as independent evidence for it. Human trials, imaging cohorts, and animal models were included deliberately, since each supports a different claim, and the level of evidence behind each claim is identified in Tables 1-2. Exclusion criteria were non-peer-reviewed sources other than the ClinicalTrials.gov registry entries noted above, unreviewed preprints, non-English-language articles, conference abstracts without full-text availability, and sources without direct mechanistic relevance to either axis. A single reviewer (the author) conducted source selection and reference-list snowballing, without a second independent screener or a formal risk-of-bias or quality-appraisal tool; this non-exhaustive, claim-directed selection carries a risk of selection bias, consistent with the manuscript's status as a narrative rather than a systematic review.

Anatomical/disease stage	Evidence tier	Rationale
DMV/brainstem-stage pathology	Evidenced to suggestive	Established venous-compression physiology (Monro-Kellie/Queckenstedt) [27], reviewed in the companion ALS framework [9], combined with the DMV's direct spatial proximity to ACT's craniocervical site of action; not sampled by DTI-ALPS, whose periventricular measurement cannot confirm effect at this site [21]
Rostral cortical-stage and olfactory bulb pathology	Suggestive to extrapolated	Rests on the same intracranial reach argument for both macro-fluidic mechanisms, whole-brain for occlusion-rebound and craniospinal for dural pull-recoil, used in the companion ALS framework [9], without PD-specific spatial proximity
Pre-CNS peripheral phase (vagal or olfactory entry)	Excluded	Intra-axonal transport along the vagus [14-16] or olfactory nerve [3, 13] lies outside the CSF and perivascular space; addressed neither by suboccipital compression nor dural elongation

TABLE 1: Evidence tiering for the proposed relevance of ACT-mediated mechanical clearance across PD's anatomical and disease stages

ACT, active craniospinal tensioning; ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; DMV, dorsal motor nucleus of the vagus; DTI-ALPS, diffusion tensor image analysis along the perivascular space; PD, Parkinson's disease

Component	Established evidence	Proposed/unverified application
Monro-Kellie/Queckenstedt coupling	Established physiology, directly confirmed by MRI [27]; reviewed in Chen [9]	Application of this coupling to ACT in PD has not been measured
Craniocervical venous anatomy	Anatomical continuity of the craniocervical venous network is established (primary sources reviewed in Chen [9])	Anatomical inference from DMV proximity to actual clearance benefit at that site is unverified
Glymphatic influx/efflux asymmetry	Arterial-driven influx and comparatively passive perivenous efflux are established [6]	Whether ACT accelerates venous-side efflux specifically has not been tested
DTI-ALPS reduction in PD	Reduced indices on this indirect proxy [21] across a substantial meta-analytic literature, including prodromal populations [22,23], alongside independently demonstrated meningeal lymphatic impairment [24]	Whether ACT changes DTI-ALPS indices, and whether any change reflects effect at the DMV specifically (given fixed periventricular sampling), has not been tested
Transiting extracellular alpha-synuclein pool	Alpha-synuclein is released from donor neurons, including within extracellular vesicles, is detectable in CSF, and is taken up by recipient cells [3,12]	Whether this transiting fraction represents a meaningful proportion of total pathological burden, and how accessible vesicle-packaged protein is to bulk fluid clearance, is not established
Mechanical strain as an HSF-1 trigger	Mechanical/hemodynamic strain activates HSF-1 in vascular tissue, demonstrated in arterial smooth muscle (primary studies reviewed in Chen [9])	Whether venous-side wall strain, or the local parenchymal deformation it produces, activates HSF-1 specifically in dopaminergic neurons or astrocytes, a cross-vessel-type and cross-cell-type extension, has not been tested
HSF-1/HSP70 neuroprotection once induced	HSP70 protects against alpha-synuclein toxicity and PD-related cell death in model systems [28-30], and pharmacological HSF-1 activation protects nigrostriatal neurons in vivo [31], with endogenous HSP70 contributing to this protection [32,33]	Contingent on the trigger row above, the protective consequence is established in models, and the open question is whether CVPC produces the induction

TABLE 2: Established physiology versus this framework's proposed, unverified application of that physiology to ACT in PD

ACT, active craniospinal tensioning; CSF, cerebrospinal fluid; CVPC, cerebral venous preconditioning; DMV, dorsal motor nucleus of the vagus; DTI-ALPS, diffusion tensor image analysis along the perivascular space; HSF-1, heat shock factor 1; HSP70, heat shock protein 70; MRI, magnetic resonance imaging; PD, Parkinson's disease

No primary studies of ACT or CVPC as applied to PD exist in the literature, and this framework’s theoretical status is addressed in the "Limitations" section.

The macro-fluidic axis

Mechanical Clearance as a Primary Route to Blocking Prion-Like Propagation

The physical basis for mechanical clearance via suboccipital venous occlusion-rebound and dural pull-recoil, grounded in the Monro-Kellie doctrine and the Queckenstedt test, is developed in full in the companion ALS framework [9] and is not re-derived here. Independently, jugular venous compression in healthy volunteers reduces jugular outflow without altering cranial arterial inflow and increases caudally directed CSF velocity in the cerebral aqueduct [27]. The mechanism is threshold-dependent: the applied force must be sufficient both to occlude the suboccipital venous plexus and to bring the dural sac to full tension. The 60%-70% body-weight load specified in the ACT-OD technical report [26] is proposed to be sufficient to reach both thresholds, although neither threshold has been quantified and whether this load achieves occlusion and full tensioning in vivo has not been confirmed.

The target of this clearance is the same in PD as in ALS [9]. In both diseases, the misfolded protein accumulates predominantly within cells, in PD as Lewy bodies and Lewy neurites, while prion-like spread requires a transit step through the extracellular or perivascular space: alpha-synuclein aggregates are released from donor neurons, including within extracellular vesicles, are detectable as small oligomeric species in CSF, and are taken up by recipient cells [3,12]. Accordingly, mechanical clearance is proposed to act on this transiting extracellular fraction, not on the intracellular Lewy burden, which no CSF-directed mechanism can reach. As in ALS [9], the proportion of total pathological burden this fraction represents is

not established, and vesicle-packaged protein may be less accessible to bulk fluid clearance than freely suspended protein.

The safety consideration raised by deliberately provoking transient venous congestion, developed in the ALS framework [9], applies with added weight in PD, where autonomic dysfunction, including orthostatic hypotension, and postural instability are common [1]; the supervised delivery this implies is specified in the "Methodological Framework and Priorities for Clinical Validation" section below.

Anatomical Reach in PD

The anatomical reach of both mechanisms, whole-brain for occlusion-rebound via the shared craniocervical venous outflow bottleneck and craniospinal for dural pull-recoil via the CSF-filled perivascular spaces present throughout the brain and spinal cord, is unchanged from the companion ALS framework [9]. What is PD-specific is how this reach relates to the disease's proposed points of origin.

The DMV, one of the two earliest proposed CNS sites of Lewy pathology in the classical Braak sequence, alongside the olfactory bulb, and the earliest in the body-first subtype [13–15], sits in the dorsal medulla close to the craniocervical junction, where both mechanisms are proposed to converge. The bulbar lower motor neuron pools addressed in the ALS framework occupy the same medullary region [9], so this proximity is not itself unique to PD; what distinguishes PD is that the structure nearest ACT's site of action is proposed as a site of disease origin rather than one of several affected pools, which suggests that the mechanism may be relevant to PD's earliest CNS-phase pathology and not only its later, more rostral stages. This is a motivating rationale, not evidence of effect: DTI-ALPS, the framework's proposed primary endpoint, samples periventricular white matter rather than brainstem tissue by methodological necessity, and as an indirect measure cannot itself confirm activity at the DMV or craniocervical junction [21]; any inference from a periventricular signal to brainstem-level clearance assumes that supratentorial and brainstem regions respond similarly, which is uncharacterized.

The second proposed entry route, via the olfactory system [3], is treated in the same way as the vagal route. The peripheral step, in which pathology is proposed to travel from the nasal epithelium along the olfactory nerve's intra-axonal compartment, lies outside the CSF and perivascular space and is beyond the framework's reach. Once pathology is established in the olfactory bulb, however, it is intracranial and falls within the reach of both macro-fluidic mechanisms: the whole-brain reach proposed for occlusion-rebound and the craniospinal reach proposed for dural pull-recoil, which together are proposed to agitate and remove transiting alpha-synuclein. Like the rostral cortex, the olfactory bulb lacks the DMV's direct proximity to the craniocervical junction. The framework's claim, therefore, covers the CNS phase of PD regardless of entry route, with its most direct anatomical rationale at the DMV and brainstem, and excludes only the peripheral steps through which pathology first reaches the CNS.

Given this heterogeneity across PD subtypes and Braak stages, an evidence-tiering approach offers a more defensible framing than a single, undifferentiated claim (Table 1), reflecting anatomical proximity to ACT's site of action rather than independent confirmation of efficacy at any tier.

The micro-biochemical axis

A Secondary, Mechanotransductive, and Hypoxic Route to In Situ Chaperone Synthesis

CVPC proposes that the same occlusion-rebound cycle activates HSF-1 within the neurovascular unit, beginning at the vessel wall, through mechanical wall strain, with a HIF-1 α contribution left open. Its trigger and candidate site of action are developed in the companion ALS framework [9] and are not re-derived here; what differs in PD is the cell population the induced response would need to reach.

Candidate Targets in PD

In ALS, the case for a non-neuronal route rests on motor neurons' documented high threshold for HSF-1 activation, such that protection would have to arise from the non-neuronal components of the neurovascular unit, such as astrocytes, pericytes, and endothelial cells, rather than from the motor neurons themselves [9]. Dopaminergic neurons of the substantia nigra pars compacta present a different picture. HSP70 prevents alpha-synuclein-induced dopaminergic neuron loss in a *Drosophila* model [28], reduces alpha-synuclein aggregation and toxicity in cell culture [29], and, applied as a cell-permeable recombinant protein, protects neurons and astrocytes against rotenone-induced cell death, as well as fibroblasts from patients carrying PINK1 or LRRK2 mutations [30]. Pharmacological HSF-1 activation with the heat shock protein 90 inhibitor geldanamycin protects the nigrostriatal dopaminergic system in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, with increased striatal nuclear HSF-1 and HSF-1 binding at heat shock elements in the HSP70 promoter [31], demonstrating the nuclear translocation-to-promoter-binding step in vivo within the nigrostriatal system, though in striatal tissue rather than in dopaminergic cell bodies specifically. Loss-of-function evidence indicates that endogenous HSP70 contributes to this protection: HSP70.1 knockout mice show worsened MPTP-induced dopaminergic degeneration and motor

impairment [32], and microRNA-mediated downregulation of HSP70 increases alpha-synuclein aggregation in alpha-synuclein-overexpressing human SH-SY5Y neuroblastoma cells [33]. No activation deficit comparable to that of motor neurons has been reported for dopaminergic neurons in the literature reviewed here, so if CVPC-induced activation reaches these neurons directly, protection would not require an intermediary cell type.

The astrocyte-mediated route emphasized in the companion ALS framework [9] remains available as a second, non-exclusive pathway, and in PD, astrocytes may be the more direct recipients of CVPC's mechanical trigger. Astrocytes ensheath nigral dopaminergic neurons and their adjacent microvessels, so their endfeet are the first parenchymal structures deformed when venules and, to a lesser extent, capillaries engorge during occlusion and recoil on release. Because the parenchyma is mechanically soft and microvascular density is high, this cycle of strain and release is proposed to arise locally around each engorged vessel and to be distributed throughout the tissue, rather than to depend on the accompanying rise in intracranial pressure, which, applied uniformly, deforms cells little, and to be greatest at occlusion onset and release, before intracranial and venous pressures equilibrate. Consistent with a change in the parenchyma's mechanical state, jugular venous compression increases brain tissue stiffness on magnetic resonance elastography in healthy volunteers, to a degree that depends on how much venous outflow is diverted through collateral pathways [27]. Loss of astrocytic support function is itself proposed to contribute to dopaminergic neuron vulnerability: upregulation by ceftriaxone of the astrocytic glutamate transporter 1 (GLT-1), known in humans as excitatory amino acid transporter 2 (EAAT2), protects dopaminergic neurons and improves motor and cognitive outcomes in toxin-lesion PD models [34,35], although ceftriaxone also acts through other mechanisms, so these studies do not isolate the transporter effect [36]. On this route, CVPC would protect dopaminergic neurons indirectly by preserving the support function of the astrocytes surrounding them. Whether this strain-and-release cycle activates HSF-1 and induces HSP70 in dopaminergic neurons, astrocytes, both, or neither has not been tested, and neither has whether the deformation produced by transient occlusion is sufficient to do so; because everyday straining and coughing also raise cerebral venous pressure transiently, any such effect would depend on magnitude, duration, or repetition beyond these ordinary fluctuations, which has not been characterized. This axis therefore remains a secondary, hypothesis-generating extension that neither strengthens nor weakens the primary macro-fluidic claim.

Precedent and Contrast: Prior Pharmacological Evidence

In contrast to ALS, where ceftriaxone and arimoclomol both reached completed human trials whose null or inconclusive results neither support nor undermine CVPC's proposed mechanism [9], no human trial results have been reported for either agent in PD. Ceftriaxone's PD evidence remains confined to rodent MPTP and 6-hydroxydopamine models [34,35] and in vitro studies (reviewed in [36]); a Phase 2 trial in PD dementia (NCT03413384) is listed as completed in March 2026, with results not yet reported. Arimoclomol, a co-inducer of the HSF-1-mediated heat shock response, showed benefit in a Phase 2/3 trial in Niemann-Pick disease type C [37] but has not been trialed in PD. CVPC's relevance to PD therefore lacks even the negative-trial precedent available to the ALS framework, consistent with treating this axis as secondary and hypothesis-generating rather than load-bearing.

Synergy at the neurovascular unit

The two axes are hypothesized to follow the biphasic timeline developed in the companion frameworks [8,9]. In the Synchronous Phase, suboccipital venous occlusion-rebound and dural pull-recoil occur together within the same several-second maneuver. Because PD's CNS-phase pathology is predominantly intracranial, the cranial configuration of the ALS framework applies [9]: dural pull-recoil is proposed to agitate transiting alpha-synuclein in the perivascular and interstitial space, and both mechanisms are proposed to converge on venous-side efflux throughout the intracranial compartment, including the DMV and brainstem. In the Metachronous Phase, hours later, HSF-1 activation in dopaminergic neurons, astrocytes, or both, if it occurs, would add incremental protection; the framework's central claim does not depend on it.

Established evidence versus proposed framework

The evidentiary basis for this framework is uneven, and should be read as such (Table 2). No component, macro-fluidic or micro-biochemical, has been directly measured in the context of ACT or in PD; every claim connecting established physiology to ACT's proposed effect is therefore inferential rather than demonstrated.

Limitations

Limitations shared across this series are addressed in the companion ALS framework [9]: the narrative review format, the incomplete establishment of prion-like templating as a driver of human disease progression, the absence of direct measurement of any component of ACT's mechanism, and the lack of a non-invasive method to confirm suboccipital venous plexus occlusion in vivo. The limitations below are those that PD's biology and anatomy modify or add.

First, the classical Braak sequence on which this framework's DMV-proximal rationale depends does not describe all cases, as noted in the "Introduction" [3,17]. Should regional network vulnerability or independent multifocal onset prove to be a larger driver of PD progression than staged, templated spread, the anatomical rationale linking ACT's craniocervical site of action to PD's earliest pathology would be correspondingly weakened, regardless of whether ACT achieves its proposed clearance effect.

Second, neither imaging endpoint proposed in the "Methodological Framework and Priorities for Clinical Validation" section samples the anatomical site on which this framework's rationale depends most heavily. DTI-ALPS, the proposed primary endpoint, samples periventricular white matter at the level of the lateral ventricle bodies by fixed methodological necessity, and as an indirect diffusivity measure, it cannot directly confirm clearance activity even at that site, let alone at the DMV or craniocervical junction [21]. The inference from a periventricular signal to brainstem-level effect rests on an unverified assumption of near-uniform glymphatic responsiveness between supratentorial and brainstem regions. The proposed secondary endpoint, neuromelanin-sensitive MRI and quantitative susceptibility mapping (QSM) of the substantia nigra, samples the site where PD progression is measurable rather than the site where the mechanism is argued to act most directly. Both endpoints therefore test for a downstream consequence at a distance from the proposed site of action.

Third, as in ALS [9], the macro-fluidic axis acts only on the transiting extracellular fraction of a predominantly intracellular protein, and the proportion of the total pathological burden represented by this fraction has not been established. The concern is sharpened in PD by evidence that alpha-synuclein transfer occurs in part within extracellular vesicles [3], which may be less accessible to bulk fluid clearance than freely suspended protein. Should vesicle-mediated or contact-dependent transfer prove to be the dominant route, the macro-fluidic axis's disease-modifying potential would correspondingly be reduced.

Fourth, the closest existing test of targeting extracellular alpha-synuclein has not yet demonstrated clear clinical benefit: prasinezumab, directed against aggregated extracellular alpha-synuclein, failed to meet its primary endpoints in PASADENA and PADOVA [19,20]. This result does not determine whether the extracellular route contributes little to progression or whether systemic antibody delivery achieved insufficient target engagement in the CNS, nor does it test mechanical clearance as proposed here. It nonetheless means that the premise that reducing extracellular alpha-synuclein slows clinical progression remains unconfirmed in humans, a premise on which this framework's primary axis depends.

Fifth, the capacity of dopaminergic neurons and astrocytes to activate HSF-1 and benefit from HSP70 is supported in PD models [28-33], narrowing the uncertainty relative to ALS, in which motor neurons' high activation threshold leaves even this capacity in question [9]. What remains unproven is the trigger. Within vascular tissue, mechanical strain as an HSF-1 activator has been demonstrated in arterial smooth muscle within the vessel wall, and its extension to venous-side strain and to astrocytes or dopaminergic neurons outside the vessel wall has not been tested, as set out in Table 2. Whether the local parenchymal deformation proposed in the "Candidate Targets in PD" section reaches a magnitude sufficient to activate HSF-1 has not been characterized; the hypoxic contribution left open in this framework does not depend on strain magnitude.

Finally, dural pull-recoil depends on achievable spinal elongation, which normal aging may reduce but is not expected to prevent, whereas disease-related structural change, such as ossification of the posterior longitudinal ligament, ankylosing spondylitis, rheumatoid arthritis, or surgical fusion, may substantially limit it in individual patients; whether the axial rigidity and stooped posture frequent in PD [38,39] similarly limit elongation during the maneuver has not been characterized. Suboccipital venous occlusion-rebound, by contrast, targets a craniocervical structure whose compression is largely independent of spinal flexibility [9], so where elongation is limited, pull-recoil's contribution is expected to narrow, but the macro-fluidic axis is not expected to be lost. More generally, ACT is not proposed as universally applicable: pre-existing conditions, whether structural, such as those above, or systemic, such as autonomic dysfunction or craniocervical instability, may limit or preclude its application in individual patients, and the decision to apply it rests with the supervising practitioner. ACT's original purpose as a preventive posture-correction and spinal-decompression maneuver [40] also bears on this: sustained practice begun before structural changes develop is proposed to help preserve the spinal mobility on which pull-recoil depends. Because ACT is proposed as a disease-modifying intervention that slows further propagation rather than reversing pathology or neuronal loss already sustained, its benefit is predicted to be greatest when initiated early, a prediction that motivates restricting the validation pathway below to early-stage and prodromal disease.

Oncologic safety

The oncologic safety considerations developed in the companion ALS framework [9], mechanical loading at the craniocervical junction and spinal cord, and a secondary concern should HSF-1/HSP70 induction occur, apply without modification, since the DMV-proximal target lies within the same region. ACT should be considered contraindicated or used with caution in patients with a known or suspected primary neoplasm anywhere within the CNS, and is intended for practitioner-supervised application.

Methodological framework and priorities for clinical validation

Design Principles, Scope, and Tier 1

The pathway below is a preliminary research proposal intended to make this hypothesis testable, not an established intervention protocol. Its parameters are specified in advance only so that a first study can be interpreted against them. An animal model is not proposed as a preliminary step, for the same reasons detailed in the companion ALS framework [9]. This framework adopts the Tier 1/Tier 2 staged design and dual-endpoint falsification standard established there, with the parameters of each tier fixed in advance rather than revised in response to an initial result.

The validation pathway is restricted to early-stage and prodromal PD. Because ACT is proposed to slow further propagation rather than reverse neuronal loss already sustained, the tissue it could protect is greatest early. The imaging endpoints adopted below have natural-history rates characterized in early disease [10,41]. Their sensitivity later in the disease, when much of the nigral signal they track has already been lost, has not been established. The disease-modification trials against which this pathway is positioned also enrolled early-stage patients [19,20]. ACT in mid-stage or late-stage PD is therefore not proposed for formal validation here. Its application in individual patients rests with the supervising practitioner on a case-by-case basis, and no inference of efficacy is drawn from such use. Throughout the pathway, ACT is proposed as a supplementary adjunct to standard care, not as an alternative to symptomatic therapy, and participants continue their existing treatment.

Tier 1 is disease-nonspecific and follows the companion ALS framework [9]. A result showing no clinically significant adverse vital-sign perturbation, obtained in any population, supports proceeding to PD-specific testing. The acute Tier 1a feasibility sub-study specified there, a small, fixed number of ACT-OD-delivered cycles with pre- and post-maneuver DTI-ALPS comparison, applies here without modification, since DTI-ALPS's sensitivity to a brief mechanical perturbation is a property of the imaging method and the maneuver, not of any single disease's pathology. As in the companion ALS framework [9], a null Tier 1a result is treated as uninformative as to mechanism rather than as evidence against the macro-fluidic axis.

Disease-Specific Tier 1 and Delivery Mode

Disease-specific Tier 1 reconfirmation is nonetheless proposed before Tier 2, given the possibility of PD-related alterations in perivascular architecture or CSF dynamics that a healthy volunteer cohort would not capture. It is performed in patients meeting the Tier 2 eligibility criteria below. Early-stage patients are expected to retain the squat capacity and postural control required by ACT-SA, so ACT-SA with a spotter is the default delivery mode. Participants with orthostatic hypotension or other autonomic findings on enrollment assessment use ACT-OD instead, since an operator-driven device builds supervision into every cycle. The two modes are proposed as mechanically equivalent and are described in detail in [26,40,42]. All sessions are logged for hold duration and presyncopal onset.

The practitioner screening specified in the companion ALS framework [9] for autonomic dysfunction, arrhythmia, and uncontrolled hypertension applies unchanged, including its provision that a screened condition requires supervising-practitioner assessment before enrollment rather than serving as grounds for exclusion. Two conditions are also named here. Known or suspected craniocervical instability, as in rheumatoid arthritis, is treated as an exclusion criterion, since longitudinal distraction may stress compromised craniocervical ligaments. Known glaucoma or ocular hypertension instead requires supervising-practitioner assessment before enrollment, since intraocular pressure follows venous pressure and may rise transiently during the hold, an effect that has not been characterized. Participants whom the practitioner judges unable to tolerate the fixed parameters are not enrolled, so that practitioner judgment governs eligibility while the tested protocol remains fixed. The two limitations qualifying any direct physiological confirmation stage, the suboccipital venous plexus's inaccessibility to targeted ultrasound and the inability to attribute a downstream change to suboccipital venous occlusion-rebound versus dural pull-recoil in isolation, are the same as in the companion ALS framework [9] and are not restated here.

Proposed Study Parameters

Because ACT as applied to PD has never been directly tested, the parameters below are fixed rather than left open to iterative adjustment, for the same reasons of falsifiability established in the companion ALS framework [9]. The applied load for ACT-SA follows prior technical reports [26,40,42], and for ACT-OD it is set to the participant's full lift-off from the seated position, corresponding to the 60%-70% body-weight range established in the ACT-OD technical report [26]. Hold duration is defined by a physiological endpoint rather than by time: each session consists of a single hold maintained until presyncopal onset, typically reached at approximately five seconds, with 10 seconds as the absolute maximum permitted in the ALS framework [9], a ceiling the endpoint-defined hold is not expected to reach. Presyncopal onset is defined as the participant's first perception of lightheadedness, tinnitus, visual dimming, or impending faintness, at which point the hold is released immediately, by the participant in ACT-SA or by the operator on the participant's signal in ACT-OD, with the participant remaining seated until symptoms have fully resolved;

no attempt is made to intensify these symptoms. Presyncopal onset serves as a practical, tolerability-based endpoint rather than a validated marker that suboccipital occlusion has occurred [9]. The absence of presyncopal onset within 10 seconds is treated as a signal to pause and reassess rather than as grounds to increase load. The hold duration reached in each session is recorded, both to document protocol fidelity and as a potential dose variable. In participants with orthostatic hypotension, presyncopal onset may instead reflect a fall in systemic arterial pressure from reduced venous return to the heart during suspension, rather than cerebral venous outflow occlusion; hold duration is therefore interpreted alongside orthostatic status.

Session frequency is fixed at three times daily, the upper end of the range in prior technical reports [26,40,42], rather than the three- to five-times-daily frequency adopted for ALS, whose short, fatal prognosis justified a less conservative baseline [9]; PD's decade-plus course and the frequency of orthostatic hypotension [1] warrant no departure from the original range. Investigators may adopt different parameters if they are specified before enrollment and reported, in which case results test a modified protocol. These parameters are informed by the author's sustained personal practice since 2017, in which holds of approximately five seconds reliably produced presyncope and holds approaching 10 seconds produced poorly tolerated presyncope; this evidence is anecdotal, single-subject, and non-PD-specific, and does not establish safety or efficacy at a population level.

Stooped posture is common in PD [38], and its more severe form, camptocormia, occurs in 3%-18% of patients and is associated with increased falls, back pain, and reduced quality of life; existing treatments show inconsistent benefit, and dopamine agonists can paradoxically worsen the deformity [39]. ACT was originally developed as a posture-correction and spinal-decompression maneuver [40], with the mechanisms addressed in this framework proposed as an additional, mechanistically distinct effect rather than its original rationale. PD's high prevalence of axial postural impairment accordingly gives patients a plausible symptomatic incentive, independent of this framework's disease-modifying hypothesis, to sustain the frequent practice Tier 2 requires. Any perceived postural or back-pain benefit is not evidence toward, and should not be conflated with, the clearance-based mechanism this framework's endpoints are designed to test.

Tier 2: Endpoints, Duration, and Falsification

Only following a positive PD-specific Tier 1 result is Tier 2 proposed: sustained ACT practice at the fixed parameters above, with repeat imaging against baseline, in early-stage patients defined as Hoehn and Yahr stages 1-2, within three years of diagnosis, and untreated or on stable symptomatic monotherapy, approximating the early-stage populations of PASADENA and PADOVA [19,20]. Changes to symptomatic therapy during the study are recorded. Although the DMV and adjacent brainstem structures sit closer to ACT's craniocervical site of action than to DTI-ALPS's periventricular sampling region, DTI-ALPS is retained as the primary endpoint for consistency across this series, alongside a PD-specific, clearance-independent secondary endpoint: neuromelanin-sensitive MRI and QSM of the substantia nigra pars compacta, analogous to plasma NfL in the ALS framework's Tier 2 [9], with the posteroventral substantia nigra prespecified as the QSM target region. This is adopted over a plasma or CSF alpha-synuclein seed amplification assay or dopamine transporter single-photon emission computed tomography (DAT-SPECT) because it is the biomarker the field's most advanced disease-modifying candidate already uses: PADOVA reported a numerically smaller decline in nigral neuromelanin signal and significantly less iron accumulation on MRI as exploratory evidence of pathobiological effect [20]. Because neuromelanin-sensitive MRI and QSM are structural sequences, they can be acquired during the same scan session as DTI-ALPS, reducing the burden compared with separate DAT-SPECT or lumbar puncture visits. The same sessions can also be read for white matter hyperintensities and cerebral microbleeds as safety measures of small-vessel injury, at no additional scan time.

Tier 2 in PD extends its observation period to at least two years, rather than the three- to six-month interval used in the ALS framework, a departure justified by PD's decade-plus course rather than by a change to the falsification standard. This minimum follows from the intervals over which the two imaging endpoints have been characterized against healthy controls, which differ. Neuromelanin signal in the substantia nigra pars compacta declines measurably over an approximately two-year follow-up in early PD relative to healthy controls [41]. Posteroventral nigral susceptibility on QSM was characterized over a four-year follow-up in which the annual rate of increase in PD differed significantly from that in healthy controls, with susceptibility rising by 9.2% over that period; at baseline, it correlated inversely with nigral neuromelanin content, and posteroventral R2*, the transverse relaxation rate sensitive to iron, correlated inversely with striatal dopamine transporter binding [10]. A two-year minimum is accordingly proposed, rather than an optimum, with the QSM endpoint interpreted against a natural-history rate established over a longer interval and a longer observation period preferable where feasible. This differs from recent PD disease-modification trials, such as PASADENA and PADOVA, whose clinical primary endpoints, based on the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), required 52 to at least 76 weeks because motor scores change slowly and variably in early disease [19,20]. Tier 2's duration is instead set by the interval over which its imaging biomarker trajectories have been established.

A positive result requires favorable change at both endpoints; consistent with the dual-endpoint standard in

the companion ALS framework [9], a decline in DTI-ALPS or a neuromelanin/QSM trajectory at or beyond the published natural-history rate, either alone, is sufficient to falsify the claim. Because Tier 2 compares each participant against baseline and published natural-history rates rather than a concurrent control, a positive result would establish biological activity, not disease modification, since favorable change relative to historical data may also arise from regression to the mean, differences in scanners or protocols between studies, or selection of motivated participants. Imaging should follow a harmonized acquisition protocol on the same scanner across visits, and a concurrent control group is preferable even at this stage where feasible. Sample size, the statistical analysis plan, and the thresholds defining favorable and unfavorable change should be prespecified with independent statistical input before enrollment, and any efficacy study should include clinically meaningful outcomes alongside the imaging endpoints. A positive Tier 2 result would therefore be confirmed in a randomized, delayed-start trial before any disease-modification claim is made: if an early-start group retains its advantage after a later-start group begins ACT, the difference cannot be explained by a symptomatic or placebo effect, and all participants eventually receive the intervention. MDS-UPDRS Part III may be included as an exploratory clinical measure, but should not substitute for imaging endpoints, given the potential for confounding by concurrent dopaminergic therapy. Sleep measures (Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale) may also be included as exploratory measures, extending the bidirectional sleep-glymphatic relationship noted in the "Introduction." These instruments capture subjective quality and daytime restfulness distinct from sleep duration, but this framework cannot distinguish whether any observed change reflects a consequence of improved clearance, a contributor to it, or an unrelated effect, so no directional claim is made or tested. Disease duration, orthostatic hypotension status, delivery mode, and any structural spinal condition limiting elongation are recorded as stratification variables.

Tier 3 and the Boundary of the Pathway

A positive Tier 2 result would motivate a third stage not proposed for ALS: extension into a prodromal, biomarker-defined at-risk population, such as individuals with isolated RBD, hyposmia, or GBA1/LRRK2 variant carrier status [4,43], in which reduced DTI-ALPS indices have already been reported independently of any intervention, at least in isolated RBD [23]. Tier 3 retains the hold, frequency, and delivery-mode rules of Tier 2. Endpoint sensitivity, however, cannot be assumed to carry over. In the same cohort that established the QSM trajectory adopted for Tier 2, nigral iron in isolated RBD was only mildly and non-significantly elevated at baseline, and no longitudinal change was detected over follow-up, although the isolated RBD arm declined to 11 participants by the third visit [10], consistent with slow iron accumulation during the prodromal phase. The nigral secondary endpoint may therefore lack the sensitivity in a prodromal cohort that it has in diagnosed disease, and a Tier 3 design would need to establish an appropriate progression measure for that population rather than inherit Tier 2's progression measure. This extension addresses the distinct, stronger claim that sustained practice could delay or prevent phenoconversion to clinical PD; as an efficacy study, it should be conducted with a concurrent control group and should not be undertaken before a positive Tier 2 result in diagnosed disease.

One exception to this sequence is proposed. Isolated RBD combines frequent phenoconversion to a synucleinopathy [4,23] with the absence of any established disease-modifying or preventive therapy [3], so that, once Tier 1 safety is established, the balance of risk favors early feasibility testing in this population. A feasibility cohort in isolated RBD may therefore begin in parallel with Tier 2, measuring only tolerability, adherence, and retention, with no efficacy claim, and continue into long-term phenoconversion follow-up, so that retention data and accumulated follow-up are available when Tier 2 reads out. This staged pathway does not address, and cannot be extended to address, the peripheral vagal or olfactory intra-axonal transport phases proposed for PD's two entry routes; no tier tests alpha-synuclein propagation before CNS entry, and none is expected to affect it.

Long-Term Safety

Because ACT is proposed for sustained practice, including by largely healthy prodromal individuals, its safety over years to decades cannot be established within any single tier. Participants who continue ACT after their study period would remain in structured long-term follow-up with standardized adverse-event reporting, including repeat review of the MRI small-vessel measures, so that multi-year exposure data accumulate beyond the trial periods. The author's sustained personal practice, noted above, is consistent with long-term tolerability, but remains anecdotal and does not substitute for this follow-up.

Conclusions

PD is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta and by aggregation of misfolded alpha-synuclein, which is proposed to propagate in a prion-like manner along interconnected neural pathways, and no disease-modifying therapy has yet proven effective in a Phase 3 trial. This framework proposes ACT, delivering suboccipital venous occlusion-rebound and dural pull-recoil concurrently, as a mechanical, non-pharmacological route to disease modification that requires no molecule to cross the BBB. Its primary axis is the clearance of transiting extracellular alpha-synuclein from the perivascular and interstitial space before it templates neighboring cells. Its anatomical rationale is most direct at the DMV and brainstem, adjacent to ACT's craniocervical site of action, and it excludes the

peripheral vagal and olfactory phases that precede CNS entry. A secondary, hypothesis-generating axis, CVPC, proposes that the same cycle activates HSF-1 to protect dopaminergic neurons, either directly or via astrocytes. This axis is neither required by the primary claim nor a substitute for it.

This framework is entirely theoretical: no component has been directly measured, and no clinical data yet exist for ACT as applied to PD. It is offered as a falsifiable hypothesis. Tier 2 requires concordant favorable change on both DTI-ALPS and neuromelanin/QSM MRI over at least two years in early-stage disease, and unfavorable change on either is sufficient to falsify the claim. A positive result would be confirmed in a randomized, delayed-start trial before any disease-modification claim is made, and efficacy testing in prodromal populations is contingent on a positive Tier 2 result. Because ACT is proposed to slow further propagation rather than reverse established neuronal loss, its benefit is predicted to be greatest with early initiation. Its origin as a low-cost posture-correction and spinal-decompression maneuver makes it suitable for sustained use should validation succeed. The same dual-axis logic will be applied to Huntington's disease, spinocerebellar ataxia, and fatal familial insomnia in forthcoming companion papers as separate hypotheses. ACT is proposed as a supplementary, practitioner-supervised adjunct under investigation, not a replacement for standard care.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Huan-Wei Chen

Acquisition, analysis, or interpretation of data: Huan-Wei Chen

Drafting of the manuscript: Huan-Wei Chen

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