THE WITHDRAWN SUBSIDY

Brain-Derived Neurotrophic Factor and the Trophic Failure of the Synapse in Alzheimer's Disease

The Activity-Dependent Loop · The Amyloid Suppression · The proBDNF Turn
The Val66Met Handle · The Restored Subsidy

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A molecular monograph — companion to Convergent Synaptic Collapse — tracing one neurotrophin from the reproducible fact of its decline to the interventions that restore it, and grading every connection against the one question the fact conceals: cause, or consequence.

"A synapse is not a monument but a subscription — it must be paid, continuously, in the currency of trophic support. Withdraw the payment and the connection does not fall; it fades. Much of what we call the loss of a mind is, at the resolution of a single synapse, an account that stopped being kept."

— ONS Methodology Working Notes, 2026

For those who first saw that the neurotrophin is not a builder of the brain alone but its keeper — and for the patients in whom the keeping is being restored, one vector at a time.

THE ARGUMENT IN BRIEF

The Reproducible Fact

BDNF is reduced in the Alzheimer brain · early, and in proportion to the decline of the mind

The Three Mechanisms of Withdrawal

Amyloid suppresses its synthesis · the precursor turns against the synapse · the activity loop inverts

The Discipline

Every connection graded · cause weighed against consequence · the arrow reversed only where restoration reverses it

The Withdrawn Subsidy ← this volume

This monograph does not settle whether reduced BDNF causes Alzheimer's disease by declaring the neurotrophin protective and its loss catastrophic. It settles what can be settled by naming the reverse-causation null — that low BDNF may be a tombstone of lost neurons rather than a driver of their loss — and by resting the causal weight only on the experiments that reverse the arrow: where BDNF is *restored*, downstream of an unchanged amyloid burden, the synapse and the memory improve.

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Abstract

A synapse is not a structure that is built once and thereafter endures; it is a subscription that must be paid, continuously, in the currency of trophic support. The molecule that carries the largest share of that payment in the adult forebrain is brain-derived neurotrophic factor — BDNF — and this dissertation is an attempt to state, with the honesty the subject demands, exactly what its documented decline in the Alzheimer brain does and does not explain. The observation itself is among the most reproducible in the molecular pathology of the disease: BDNF messenger RNA and protein are reduced in the Alzheimer hippocampus and association cortex, the reduction is present in the earliest clinical stages before frank dementia, and its magnitude tracks the severity of cognitive decline across large autopsy cohorts. Around that firm observation, however, gathers a cloud of interpretive difficulty that the enthusiasm of the field has too often waved away, and it is that difficulty this thesis takes as its central problem.

BDNF is the activity-dependent neurotrophin: it is transcribed and secreted in proportion to neuronal firing, it acts through the receptor tyrosine kinase TrkB to drive the synaptic potentiation and structural maintenance that firing requires, and — because BDNF is itself a target of the CREB-dependent transcription its own signalling activates — it closes a positive-feedback loop in which activity begets trophic support begets the capacity for further activity. This is the molecular substance of *use it or lose it*, and it is also, read the other way, the molecular substance of a vicious cycle. We trace three mechanisms by which Alzheimer's pathology withdraws the subsidy: the transcriptional suppression of specific BDNF promoters by amyloid-β oligomers together with the failure of retrograde TrkB transport; the shift in the balance between the pro-survival mature neurotrophin and its pro-apoptotic precursor, proBDNF, toward $p75^{NTR}$-mediated signalling; and the breaking of the activity–BDNF–CREB loop, which converts a virtuous circle into a descending spiral. We examine the genetic handle the system offers — the Val66Met polymorphism that impairs activity-dependent BDNF secretion and interacts, in the preclinical cohorts, specifically with amyloid burden — and the lifestyle handle it offers, the exercise-induced BDNF that is the leading mechanistic candidate for the protection physical activity confers.

But the heart of this dissertation is a validity ledger built around a single question that the phrase "BDNF is reduced in Alzheimer's disease" conceals: is the withdrawal of the subsidy a *cause* of the neurodegeneration or a *consequence* of it? Fewer neurons, fewer active synapses, and less firing will lower BDNF for reasons that have nothing to do with BDNF being on the causal path — the reverse-causation threat here is not a technicality but the governing difficulty of the entire literature. We grade each connection against it. The strong claims — that BDNF is reduced early, that brain BDNF expression tracks cognitive resilience, that BDNF/TrkB is foundational to the plasticity Alzheimer's destroys — survive. The load-bearing causal claim survives only in the conditional form the interventional evidence licenses: where BDNF has been *restored* — by gene delivery in aged primates and amyloid-bearing rodents, by small-molecule TrkB agonists

— synaptic and cognitive endpoints improve, and it is this class of experiment, not the correlations, that lifts the trophic hypothesis from description to mechanism. What the mapping finally buys is a reframing of the disease's signature failure — synapse loss, the best correlate of dementia — as, in one of its dimensions, a *withdrawn subsidy* rather than a direct poisoning: a trophic bankruptcy that is in principle payable, and whose therapeutic value, like everything else in this disease, is a sharp function of when the payment is resumed.

I. The Synapse's Standing Order

A subscription, not a monument

The intuition that the brain's connections are permanent structures — laid down in development, refined in youth, and thereafter simply *there* — is one of the most durable errors in the popular understanding of the nervous system, and it is an error that the study of Alzheimer's disease is peculiarly well placed to correct. A cortical synapse is a standing order on a trophic account. Its receptor complement, its cytoskeletal scaffold, the dendritic spine that houses it, and the presynaptic terminal that addresses it are all in continuous turnover, disassembled and rebuilt on timescales of hours to days, and the difference between a synapse that persists and one that is pruned is not a difference of original construction but of ongoing subsidy. Withdraw the subsidy and the synapse does not fail catastrophically; it fades — first in its capacity to potentiate, then in the stability of its spine, then in its very existence — and it is precisely this graded, quiet fading, rather than any abrupt lesion, that the synaptic pathology of Alzheimer's disease most resembles. Synapse loss is the strongest structural correlate of cognitive decline in the disease, stronger than plaque count and stronger than tangle burden, and any theory of the disease that cannot say why synapses are lost has left its central fact unexplained.

This dissertation proposes that a large part of the answer is a failure of trophic maintenance, and that the molecule at the centre of that failure is brain-derived neurotrophic factor. The proposal is not that BDNF is *the* cause of Alzheimer's disease — it is not, and the discipline of this thesis is largely a discipline of not saying so — but that the withdrawal of BDNF-mediated trophic support is one of the mechanisms by which the disease's upstream lesions, amyloid and tau, are converted into their downstream signature, the disappearing synapse. Between the plaque and the empty spine there is a trophic economy, and BDNF is its principal currency.

The claim, and the danger built into it

Stated baldly, the trophic hypothesis is seductive to the point of being suspicious. BDNF supports neuronal survival, promotes synaptic growth and potentiation, sustains adult hippocampal neurogenesis, and is reduced in the Alzheimer brain — a tidy syllogism in which a good molecule is lost and bad things follow. Precisely because the story is so clean, it is the kind of story a responsible synthesis should distrust. The danger is not that the individual facts are wrong; each of them, taken alone, is well supported. The danger is that they can be assembled into a causal narrative that the evidence does not license, and that the most important interpretive question — whether reduced BDNF drives the degeneration or merely records it — can be smuggled past the reader on the strength of the narrative's elegance. This thesis therefore carries its central doubt on its face rather than in a footnote: the cause-or-consequence problem is introduced here, in the first section, returned to in every mechanistic section, and given a section of its own, the validity ledger, whose function is to be the argument's conscience. The reader is asked to hold every mechanistic claim that follows against the possibility that it has the arrow backwards.

II. What BDNF Is

The neurotrophin and its two receptors

BDNF is a member of the neurotrophin family — the small, secreted, dimeric growth factors that also include nerve growth factor, neurotrophin-3, and neurotrophin-4/5 — and within that family it is the one most abundantly expressed in the adult forebrain and most intimately tied to the plasticity of the mature cortex and hippocampus. It is synthesised as a precursor, proBDNF, which is proteolytically cleaved — intracellularly by furin and proconvertases, and extracellularly by plasmin and matrix metalloproteinases — to yield the mature neurotrophin, mBDNF. This precursor-to-mature processing is not a mere manufacturing detail. The two forms are functionally opposed. Mature BDNF is the pro-survival, pro-potentiation ligand: it binds the receptor tyrosine kinase TrkB (the product of the *NTRK2* gene) with high affinity and initiates the growth-and-maintenance signalling for which BDNF is famous. The precursor, proBDNF, binds preferentially to a different receptor entirely — the p75 neurotrophin receptor, $p75^{NTR}$, in complex with the co-receptor sortilin — and this receptor, when engaged by proBDNF, drives signalling of the opposite valence: growth-cone collapse, long-term synaptic depression, and, in sufficient measure, apoptosis. A single gene, through the regulation of a single cleavage, thus commands both an accelerator and a brake.

The activity-dependent loop

The property of BDNF that makes it central to this thesis, and that distinguishes it from a merely constitutive trophic factor, is that its expression and secretion are *activity-dependent*. Neuronal depolarisation opens voltage-gated calcium channels; the resulting calcium influx activates CaMK and, through it, the transcription factor CREB, which binds the calcium-responsive promoters of the *BDNF* gene and drives its transcription. The BDNF thus made is packaged into dense-core vesicles and secreted in a regulated, activity-dependent fashion, concentrated at active synapses. There it engages TrkB and initiates a signalling cascade — through phospholipase C-γ, through phosphatidylinositol-3-kinase and Akt, and through the Ras–ERK mitogen-activated kinase pathway — that converges once again on CREB. Because CREB drives *BDNF* transcription, and because BDNF activity drives CREB, the system is a positive-feedback loop: activity produces trophic support, trophic support sustains the machinery of activity, and the loop, running forward, is the molecular embodiment of Hebbian maintenance — the biochemical reason that used circuits are preserved and unused ones are surrendered. It is worth naming this loop precisely, because its virtue and its vulnerability are the same structure. A positive-feedback loop that can climb can also fall, and a great deal of what follows is the story of this loop running in reverse.

The gene with many doors

One further structural fact of the *BDNF* gene matters for the Alzheimer story, because it is the point at which amyloid does some of its most specific damage. The gene is not transcribed from a single promoter. In humans it comprises multiple 5′ non-coding exons, each with its own promoter, all splicing onto a common protein-coding 3′ exon — so that the identical BDNF protein can be produced under the control of at least eight distinct regulatory regions, differentially responsive to activity, to calcium, to methylation, and to the transcriptional machinery of different cell compartments. This architecture means that BDNF expression can be selectively suppressed at particular promoters while others are spared, and it is exactly such promoter-selective suppression — of the activity-dependent transcripts in particular — that the amyloid literature reports. The many doors of the gene are not redundancy; they are a set of independently attackable targets, and the disease attacks some and not others.

III. The Reproducible Fact

Reduced in the Alzheimer brain

Among the molecular findings in Alzheimer's disease, the reduction of BDNF is one of the least contested. The original observation is now more than three decades old: Phillips and colleagues, in 1991, reported that BDNF messenger RNA is decreased in the hippocampus of individuals with Alzheimer's disease, and the finding has since been replicated at the level of both transcript and protein, in hippocampus and in temporal, frontal, and parietal association cortex, by independent groups using independent methods. Connor and colleagues confirmed the protein reduction and localised it; Ferrer and colleagues documented reduced BDNF alongside altered expression of its receptor TrkB; Hock and colleagues described a region-specific neurotrophin imbalance in which BDNF falls while, in some territories, nerve growth factor is relatively preserved or raised — an imbalance, not a uniform trophic collapse. The reduction is regionally patterned in a way that respects the disease's own topography, falling most in the hippocampal and neocortical territories that bear the brunt of the pathology and sparing regions the disease spares. A molecular change that is reproducible across three decades, multiple laboratories, several brain regions, and both of its measurable products has earned the right to be treated as a fact about the disease rather than an artefact of any one study.

Early, not only late

The single most important refinement of that fact, for the argument of this thesis, is temporal. If BDNF fell only in end-stage disease, in brains hollowed by decades of neuronal loss, the reduction would be most naturally read as a tombstone — a marker of the neurons that are gone. But the reduction is present *early*. Peng and colleagues, examining tissue from subjects across the clinical spectrum, found that both proBDNF and mature BDNF are already decreased in the preclinical and prodromal stages — in individuals with mild cognitive impairment, and even in cognitively intact individuals whose brains bear early Alzheimer pathology — before the frank neuronal depletion of established dementia. The decline of BDNF is therefore not merely a late reading of accumulated loss; it is an early feature, present at a stage when there is still a great deal of tissue to protect. This does not, by itself, establish causation — an early consequence is still a consequence — but it removes the simplest deflationary reading, the one in which low BDNF is nothing but the arithmetic of missing cells, and it places the trophic failure at a point in the disease's course early enough for it to matter.

Tracking the decline of the mind

The third layer of the observation connects the molecule to the phenotype that ultimately concerns us. Buchman and colleagues, working within the Rush Memory and Aging Project — a large longitudinal cohort with annual cognitive testing and brain donation — showed that higher brain BDNF gene expression, measured at autopsy, is associated with a slower rate of cognitive decline over the years preceding death, and that this association is independent of, and additive to, the burden of plaques and tangles. Higher BDNF did not mean less pathology; it meant that a given burden of pathology exacted a smaller cognitive toll. In the language of the resilience literature, brain BDNF behaves like a reserve factor: it does not prevent the lesions, it buffers their consequences. On the periphery, the Framingham Heart Study found that higher serum BDNF was associated with a lower subsequent risk of dementia, a prospective association pointing in the same direction, though — as Section VIII will insist — peripheral BDNF is a far more treacherous measurement than brain BDNF, and this convergence should be weighted accordingly. Taken together, these cohorts establish the observation in its strongest defensible form: BDNF is reduced in the Alzheimer brain, the reduction begins early, and the amount of BDNF a brain retains predicts how well its owner's mind withstands a given load of pathology.

IV. Tracing the Mechanism I How Amyloid Withdraws the Subsidy

Suppression at the promoter

The first mechanistic question is whether Alzheimer's pathology actively withdraws the trophic subsidy or merely coincides with its withdrawal, and the amyloid literature supplies the most direct answer available. Amyloid-β does not simply accompany low BDNF; it *causes* low BDNF, and it does so with a specificity that argues for a real regulatory relationship rather than a bystander effect. Garzon and Fahnestock showed that oligomeric amyloid-β decreases basal BDNF messenger RNA in human neurons through the selective downregulation of particular BDNF transcripts — the activity-dependent transcripts driven from specific promoters — rather than a uniform silencing of the gene. This is a fingerprint, not a smudge: an agent that suppressed BDNF only as a secondary consequence of killing neurons would not preferentially silence one promoter class over another. The promoter selectivity implicates a signalling pathway — amyloid oligomers interfering with the CREB-dependent, calcium-responsive transcription that governs precisely those exons — and it locates the lesion upstream of neuronal death, in the regulation of a living cell's trophic output. Amyloid, on this evidence, reaches into the transcriptional machinery of the surviving neuron and turns down the promoter that activity would otherwise turn up.

The broken CREB node

The convergence of the amyloid literature and the BDNF literature on CREB is not a coincidence of vocabulary; it is a shared node. Amyloid-β oligomers impair CREB phosphorylation and CREB-dependent transcription through several routes — disruption of calcium homeostasis, activation of phosphatases such as calcineurin, and interference with the very TrkB signalling that would normally sustain CREB activity. Because CREB is both the driver of activity-dependent BDNF transcription and the downstream effector of TrkB signalling, an amyloid lesion at CREB strikes the activity–BDNF–CREB loop at its hinge. The consequence is not the loss of a single molecule but the opening of the loop: less CREB activity yields less BDNF, less BDNF yields less TrkB signalling, less TrkB signalling yields still less CREB activity. Amyloid does not merely lower BDNF once; it lowers the system's capacity to restore its own BDNF, which is the difference between a debt and a bankruptcy.

Signalling and transport, not only synthesis

Suppression of synthesis is only the first of amyloid's trophic insults; the second is the corruption of BDNF's action even where the molecule is still made. TrkB signalling is impaired in the amyloid-laden neuron at multiple points: surface expression and dimerisation of the receptor are reduced, and the balance between the full-length signalling receptor, TrkB-FL, and its truncated dominant-negative isoform, TrkB-T1, shifts toward the truncated form, so that a larger fraction of available BDNF is captured by a receptor that cannot transduce it. Ferrer and colleagues' early observation of altered TrkB expression in the Alzheimer brain finds its mechanistic meaning here. Compounding this, BDNF's trophic action on the neurons of the basal forebrain and cortex depends on *retrograde transport*: BDNF secreted at the synapse is internalised with its receptor and carried back along the axon to the cell body, where its survival signal is delivered. Poon and colleagues demonstrated that amyloid-β impairs this axonal retrograde transport of BDNF, so that even BDNF successfully secreted and bound may fail to deliver its message to the soma. The subsidy is thus withdrawn at three points along its path — it is transcribed less, transduced less, and transported less — and each of these is a lesion in a living neuron, upstream of that neuron's death.

V. Tracing the Mechanism II The proBDNF Turn

The balance and the shift

The second mechanism turns on the opposition, introduced in Section II, between the mature neurotrophin and its precursor. In the healthy adult brain the balance is tilted toward mature BDNF and pro-survival TrkB signalling; proBDNF is present but processed efficiently, and the $p75^{NTR}$-mediated brake it commands is held in reserve, deployed for the pruning and depression that plasticity legitimately requires. Lu and colleagues framed this opposition as the "yin and yang" of neurotrophin action, and the metaphor is apt precisely because the two arms are not independent quantities but a *ratio*, and it is the ratio, not either absolute level, that determines the net signal a neuron receives. Woo and colleagues showed that proBDNF, acting through $p75^{NTR}$, facilitates hippocampal long-term depression — the weakening of synapses — which places the precursor squarely on the side opposite to the potentiation that mature BDNF drives. In Alzheimer's disease the evidence suggests this ratio shifts adversely: the proteolytic processing that converts precursor to mature form is impaired in the diseased brain, and the plasmin and matrix-metalloproteinase systems that perform extracellular cleavage are themselves dysregulated by the disease, so that a larger fraction of the total neurotrophin remains as, or is presented as, the pro-apoptotic precursor. The subsidy is not merely reduced in amount; its composition curdles.

From weakened synapse to lost neuron

The functional consequence of the proBDNF turn scales with its severity. At a modest shift, the effect is the tilting of the plasticity balance toward depression and pruning: synapses that mature BDNF would have maintained are instead marked for weakening by proBDNF–$p75^{NTR}$ signalling, and the graded fading of synaptic strength that the disease exhibits acquires a molecular driver on the *loss* side of the ledger to match the failure of support on the maintenance side. At a more severe shift, $p75^{NTR}$ signalling passes from synaptic depression into frank pro-apoptotic signalling, engaging the JNK cascade and the death machinery that $p75^{NTR}$ can command in a vulnerable neuron. The precursor thus offers a mechanism by which the trophic system does not merely fall silent but is actively turned against the synapse and, ultimately, the cell — a mechanism in which the very molecule that ought to maintain the connection is, in its unprocessed form and through the wrong receptor, an instrument of its dismantling. It should be said plainly that the direct human evidence for a pathogenic proBDNF/mBDNF shift in Alzheimer's disease is thinner than the evidence for the simple reduction of total BDNF, and this claim will be graded accordingly; but the mechanism is coherent, it is grounded in established neurotrophin biology, and it converts the trophic hypothesis from a story purely of subtraction into one that also has a term for active harm.

VI. Tracing the Mechanism III The Broken Loop

The virtuous circle inverted

The third mechanism is not a new lesion but the systems-level consequence of the first two, and it is the one that gives the trophic hypothesis its temporal shape. The activity–BDNF–CREB loop of Section II is a positive-feedback system, and positive-feedback systems have two stable modes: a climbing mode, in which each turn amplifies the next upward, and a falling mode, in which each turn amplifies the next downward. The healthy brain lives in the climbing mode — activity sustains BDNF, BDNF sustains the capacity for activity — and the achievement of the disease, in this dimension, is to flip the loop into its falling mode. Amyloid suppresses BDNF transcription and impairs CREB (Section IV); the resulting deficit of trophic support weakens synapses and reduces the neuronal activity that would drive BDNF transcription; the reduced activity lowers BDNF further; and the loop descends. Once inverted, the loop no longer requires the continuous presence of its original trigger to keep falling — it is self-sustaining in its decline, which is why the trophic deficit can outrun and outlast the amyloid burden that initiated it, and why interventions aimed only at the initiating lesion may leave the descending loop turning. A broken virtuous circle is not a static deficit; it is an engine with the sign reversed.

Tau, transport, and the compounding of the fall

Tau pathology compounds the descent along the loop's structural axis. Because BDNF's action depends on retrograde axonal transport, and because tau pathology is fundamentally a disorder of the axonal microtubule cytoskeleton on which that transport runs, the tangle-bearing neuron suffers a transport failure that strikes the trophic system at the same point amyloid does — the delivery of BDNF's survival signal from synapse to soma. The two great proteinopathies of the disease thus converge on the trophic subsidy from opposite directions: amyloid principally suppresses its synthesis and corrupts its receptor, tau principally severs its delivery, and the neuron caught between them is simultaneously making less BDNF, transducing it less well, and transporting what remains less reliably. The loop's inversion is, in this light, overdetermined — driven from the transcriptional end by amyloid and from the transport end by tau — which accounts for the robustness of the BDNF reduction across cases with differing balances of the two pathologies, and which warns that a therapy addressing only one arm may find the loop still descending along the other.

VII. The Genetic Handle — Val66Met

A common variant in the secretion machinery

If the trophic system were merely a passive downstream reporter of upstream pathology, it would offer no independent genetic handle on the disease. It offers one. A common single-nucleotide polymorphism in the *BDNF* gene, rs6265, produces a valine-to-methionine substitution at codon 66 in the prodomain of the protein — the Val66Met variant — carried by a substantial minority of the population. Egan and colleagues, in a foundational study, showed that the Met allele impairs the activity-dependent secretion of BDNF: the variant protein is trafficked less efficiently into the regulated secretory pathway and to dendrites, so that Met carriers release less BDNF specifically in response to neuronal activity, while constitutive secretion is relatively spared. The variant thus strikes at exactly the property this thesis has placed at the centre of BDNF's function — its activity-dependence — and it does so at the level of the germline, present from birth, independent of and upstream of any Alzheimer pathology. In their original work, Met carriage was associated with poorer episodic memory and with measurable differences in hippocampal function, establishing that the variant has cognitive consequences in the healthy brain before any question of disease arises.

The interaction that matters

The relevance of Val66Met to Alzheimer's disease has a complicated evidential history, and honesty requires acknowledging it: studies asking whether Met carriage is a straightforward risk factor for the disease have returned inconsistent results, and meta-analyses of the simple association are, at best, weakly positive and heterogeneous. The variant is not a Mendelian cause and it is not a clean risk allele. The more informative finding is not of a main effect but of an *interaction*. Lim and colleagues, working in the preclinical cohorts of the Australian Imaging, Biomarkers and Lifestyle study, found that among cognitively normal older adults, the Met allele accelerated cognitive decline and hippocampal atrophy *specifically in those with elevated amyloid burden* — that Met carriage was relatively inconsequential in amyloid-negative individuals but became a significant liability once amyloid was present. This gene-by-pathology interaction is more than a statistical curiosity; it is a prediction of the trophic hypothesis realised in human data. If Alzheimer's disease injures the brain in part by withdrawing the activity-dependent BDNF subsidy, then a germline variant that *independently* lowers activity-dependent BDNF secretion should not much matter in a healthy brain — where the subsidy, though reduced, suffices — but should compound the injury precisely when the disease is also withdrawing it. The variant and the pathology strike the same mechanism, and their effects multiply. That the interaction is amyloid-conditional is exactly the shape the trophic model predicts, and it is the strongest human genetic evidence that the BDNF system is not merely a passive reporter but a modifier on the causal path.

VIII. The Cause-or-Consequence Problem A Validity Ledger

The governing difficulty, named

Every preceding section has been written under the shadow of one question, and this section brings it into the light. The sentence "BDNF is reduced in Alzheimer's disease" is true, reproducible, and — read naively — profoundly ambiguous, because it is compatible with two opposite causal structures. In the first, reduced BDNF is a *driver*: the withdrawal of trophic support weakens and eliminates synapses that would otherwise have survived, and low BDNF is a cause of the degeneration. In the second, reduced BDNF is a *tombstone*: neurons and synapses are lost for reasons entirely independent of BDNF — amyloid toxicity, tau, whatever the primary insult may be — and because BDNF is made by neurons and secreted at active synapses, fewer neurons and fewer active synapses yield less BDNF as a matter of simple arithmetic, with BDNF nowhere on the causal path. Reverse causation is not, here, one worry among many; it is *the* worry, the null hypothesis against which the entire trophic literature must define itself, and any honest ledger of the connections must grade each one by how well it survives it.

Strong connections

BDNF is reduced in the Alzheimer brain, early and reproducibly. This is not in serious doubt. The observation spans three decades, multiple laboratories, several regions, both transcript and protein, and — crucially — the early clinical stages (Phillips; Connor; Ferrer; Hock; Peng). *Residual doubt:* none as to the fact; the doubt is entirely about its interpretation, which is the business of the rows below. *Settling question:* not applicable — the observation itself is secure.

Brain BDNF expression tracks cognitive resilience independently of pathology. Buchman and colleagues' longitudinal cohort result — that higher brain BDNF predicts slower cognitive decline over and above plaque and tangle burden — is strong evidence that BDNF sits on the pathway from pathology to *cognitive outcome*, not merely alongside it. *Residual doubt:* an autopsy measurement of BDNF is a single endpoint reading; it cannot by itself distinguish "more BDNF protected the mind" from "a mind declining for other reasons dragged BDNF down with it." *Settling experiment:* the interventional restorations below, which break the correlational tie.

BDNF/TrkB signalling is foundational to the synaptic plasticity Alzheimer's destroys. This is basic neuroscience, established independently of the disease, and it is what makes

the trophic hypothesis mechanistically eligible in the first place. *Residual doubt:* none as to the physiology; the inferential leap is to the disease, addressed elsewhere.

The connections that break reverse causation

The reverse-causation null predicts one thing above all: that BDNF is a passive readout, so that *supplying* BDNF to a brain losing it for other reasons should change nothing. The interventional literature falsifies that prediction, and this is the evidential fulcrum of the whole thesis.

Restoring BDNF improves outcomes in animal models. Nagahara, Tuszynski, and colleagues delivered BDNF, by gene transfer and by protein infusion, to the entorhinal cortex of amyloid-bearing transgenic mice and to aged and lesioned non-human primates, and reported improvement of synaptic markers, restoration of gene expression patterns, and rescue of learning and memory — without a reduction in amyloid plaque load. That last clause is decisive: BDNF improved function *downstream* of an unchanged amyloid burden, which is exactly what a causal trophic factor, and not a passive tombstone, should do. *Residual doubt:* these are model systems, and the gap between a transgenic mouse or a lesioned primate and a human Alzheimer brain is real and has swallowed many therapies. *Settling experiment:* the human gene-therapy trial now underway (Section XI).

Small-molecule TrkB agonists reproduce the benefit through the receptor. Independent groups have shown that TrkB agonists — 7,8-dihydroxyflavone prominent among them (Jang and colleagues) — improve synaptic and cognitive endpoints in amyloid models (Devi and Ohno), engaging the same receptor BDNF uses. That the benefit can be obtained by activating the *receptor* directly, bypassing the ligand entirely, strengthens the causal reading: it is TrkB signalling, not merely the BDNF molecule as a correlate, that is doing the work. *Residual doubt:* pharmacological agonists have off-target actions, and the field has debated the specificity and even the direct TrkB-agonism of some of these compounds; the conclusion rests on the convergence of gene delivery, protein delivery, and small molecules, no one of which is decisive alone.

Moderate connections

Amyloid-β suppresses BDNF transcription with promoter selectivity. Mechanistically evidenced in neuronal systems (Garzon and Fahnestock), and the selectivity argues against a pure bystander effect. *Residual doubt:* most directly shown in culture and models; the quantitative contribution of this pathway to the BDNF deficit measured in human brain, relative to the simple loss of BDNF-producing cells, is not established. *Settling experiment:* promoter-resolved BDNF transcript quantification in human tissue, correlated with regional amyloid load and neuronal density, to partition transcriptional suppression from cell loss.

The Val66Met × amyloid interaction places BDNF on the causal path. The amyloid-conditional acceleration of decline in Met carriers (Lim and colleagues, AIBL) is a genetic

argument that survives reverse causation, because the germline variant cannot be a consequence of the disease. *Residual doubt:* the main-effect association of Val66Met with Alzheimer's is inconsistent across studies, and the interaction findings, though replicated in preclinical cohorts, are drawn from specific populations and endpoints and warrant broader confirmation. *Settling experiment:* pre-registered replication of the amyloid-conditional interaction across independent, well-powered preclinical cohorts.

Weaker or frankly proposed connections

The pathogenic proBDNF/mBDNF shift. The neurotrophin biology is solid and the mechanism is coherent, but the direct human evidence that an adverse precursor-to-mature ratio drives Alzheimer synaptic loss is thin, and disentangling a genuine processing defect from the general proteostatic disarray of the diseased brain is difficult. *Grade: coherent hypothesis.*

Peripheral (serum/plasma) BDNF as a biomarker. This is the weakest link in the chain and deserves an unflattering word. Circulating BDNF is overwhelmingly platelet-derived, its relationship to brain BDNF is uncertain, it is confounded by age, sex, activity, diurnal rhythm, and assay platform, and the literature is frankly contradictory — some studies report reduced serum BDNF in advanced disease, others report a paradoxical early increase (Laske and colleagues), and the prospective Framingham association, though real, coexists with this heterogeneity. *Grade: unreliable as a stand-alone biomarker; usable only in aggregate and with heavy caveat.*

The two errors the ledger exists to prevent

Two failure modes would discredit the trophic hypothesis, and naming them is part of resisting them. The first is *tombstone credulity* — reading every reduction of BDNF as a cause when it may be a consequence of cell loss; the ledger guards against it by resting the causal weight not on the correlations but on the restoration experiments, which are the only class of evidence that reverses the arrow. The second is *peripheral overreach* — treating a serum BDNF value as a window onto the brain when it is mostly a window onto platelets; the ledger guards against it by grading peripheral BDNF as unreliable and refusing to let it carry any load the brain and interventional data do not independently support. What survives both guards is a hypothesis that is causal but conditional: reduced brain BDNF/TrkB signalling is on the path from pathology to synaptic and cognitive failure, the interventional evidence shows that supplying it helps downstream of unchanged amyloid, and everything else in the trophic story is graded below that anchor.

IX. The Trophic Reserve Why "Use It or Lose It" Has a Molecule

Exercise, enrichment, and the raised subsidy

The trophic hypothesis makes a prediction that reaches outside the clinic and into the ordinary determinants of brain health: if BDNF is the activity-dependent subsidy that maintains synapses, then interventions that raise BDNF should protect the aging brain, and the intervention that most robustly raises BDNF is physical exercise. Aerobic exercise increases BDNF expression in the hippocampus across a large animal literature, and in humans Erickson and colleagues showed that an exercise programme increased hippocampal volume and improved memory in older adults, with circulating BDNF tracking the change — a result widely, if not conclusively, interpreted as BDNF-mediated. Environmental enrichment and cognitive engagement raise BDNF by the same activity-dependent route. This furnishes the trophic hypothesis with a mechanistic account of two of the best-established modifiable protections against dementia — physical activity and cognitive engagement — and it supplies the missing molecule for the folk wisdom of *use it or lose it*: the used circuit is subsidised, through activity-dependent BDNF, and the unused one is not. Choi and colleagues sharpened the causal claim in a mouse model, showing that the cognitive benefit of exercise could be mimicked by combining the induction of adult neurogenesis with elevated BDNF, and — tellingly — that neurogenesis *without* BDNF was insufficient: the trophic factor was a necessary term in the protective effect, not a passive correlate of it.

Reserve, resilience, and the honest limit

Placed against the resilience finding of Section III — that brains richer in BDNF withstand a given pathology better — the exercise literature suggests a unified reading in which BDNF is a substrate of cognitive reserve: a quantity that can be raised, prospectively, by how a life is lived, and that determines how much pathology a brain can absorb before the mind fails. This is an attractive and, in its broad strokes, well-supported picture, and it is also one where the discipline of the validity ledger must be reapplied, because the human causal chain has an unmeasured link. We can raise BDNF with exercise; we can show that higher BDNF tracks better outcomes; but the step that exercise protects cognition *because* it raises BDNF — the *because* — is inferred in humans, not demonstrated, since the BDNF step in an exercising person's brain cannot be directly measured and the peripheral surrogate is unreliable. The animal evidence (Choi) supplies the missing *because* in model systems, and the human evidence supplies the endpoints; the bridge between them is a reasonable inference rather than a proven mechanism, and it is graded here as such. The trophic reserve is the trophic hypothesis at its most hopeful and its most practically consequential, and precisely for that reason it is where overstatement is most tempting and most to be resisted.

X. Falsifiable Predictions

A synthesis earns its keep by exposing itself to refutation, and the trophic hypothesis, because it makes claims about mechanism, timing, and intervention, generates predictions sharp enough to be wrong.

On timing of the deficit. If reduced BDNF is on the causal path and not merely a tombstone, promoter-resolved BDNF transcription — corrected for neuronal density — will be found reduced in surviving neurons of early-stage brains, ahead of and out of proportion to cell loss. If, instead, per-neuron BDNF output proves normal and the tissue deficit is fully explained by the arithmetic of missing cells, the causal reading is falsified and the tombstone reading vindicated.

On the interventional arrow. If BDNF/TrkB signalling is causal, restoring it — by gene delivery or a validated TrkB agonist — will improve synaptic and cognitive endpoints in humans *downstream of unchanged amyloid and tau*, as it does in animals. A restoration that changes biomarkers of trophic signalling but leaves cognition untouched, at any disease stage, would sharply constrain the hypothesis.

On stage-dependence. The trophic hypothesis inherits the temporal architecture's signature claim: the benefit of restoring the subsidy will depend on when it is restored. Restoration will help most while synapses are stressed but present and neurons still alive to respond, and will help progressively less once the synapses it would maintain are already gone. A BDNF therapy that helps equally regardless of stage — or, conversely, only in end-stage disease — would falsify the stage-dependence.

On the Val66Met interaction. The amyloid-conditional liability of the Met allele will replicate in independent preclinical cohorts, and Met carriers will prove differentially *less* responsive to BDNF-secretion-dependent interventions (such as exercise) and differentially *more* responsive to interventions that bypass secretion (such as direct TrkB agonism). A flat response profile across genotypes would argue that the variant's mechanism has been misread.

On the peripheral surrogate. If — and only if — a brain-derived, platelet-corrected fraction of circulating BDNF can be isolated, it will track brain BDNF and cognitive trajectory far better than total serum BDNF, which will remain a poor and contradictory marker. Continued failure of even a corrected peripheral measure to track the brain would confirm that the periphery is the wrong window and should be abandoned as a biomarker source.

XI. Therapeutic Implications — Restoring the Subsidy

The delivery problem and its answers

The therapeutic promise of the trophic hypothesis has been evident for thirty years, and so has the reason it has been so hard to realise: BDNF is a large, labile protein that does not cross the blood–brain barrier, diffuses poorly, has a short half-life, and — delivered indiscriminately — can provoke aberrant sprouting and pain through peripheral neurotrophin receptors. The history of BDNF therapeutics is largely a history of the delivery problem, and the contemporary strategies are best understood as three distinct answers to it. The first is *gene delivery*: viral-vector expression of BDNF placed stereotactically in the vulnerable cortex, so that the protein is manufactured in situ and continuously. Nagahara, Tuszynski, and colleagues' preclinical programme — efficacy in amyloid mice and in aged and lesioned primates, downstream of unchanged plaque burden — provided the rationale, and that rationale has advanced to an AAV-BDNF gene-therapy trial in humans with early Alzheimer's disease and mild cognitive impairment, the most direct test the trophic hypothesis has ever received. The second answer is the *small-molecule TrkB agonist* — 7,8-dihydroxyflavone and related compounds — which sidesteps the delivery problem entirely by activating the receptor with a brain-penetrant small molecule rather than delivering the ligand; the preclinical efficacy is real, the debate over specificity and mechanism is unresolved, and the class remains promising rather than proven. The third answer is *indirect elevation*: exercise and the several approved drugs (certain antidepressants, fingolimod, and others) reported to raise BDNF, whose appeal is safety and availability and whose limitation is that they raise BDNF modestly and non-specifically, and — for the exercise arm — depend on the very activity-dependent secretion that Val66Met and advanced disease impair.

Timing is the therapy

The single most important therapeutic implication is not which agent but when. The trophic hypothesis, married to the temporal architecture, predicts that restoring the subsidy is a maintenance intervention, not a resurrection: it can preserve synapses that are stressed but still present, and it cannot rebuild circuits whose neurons are gone. This predicts a therapeutic window that opens early — in preclinical and prodromal disease, when the trophic deficit is established (Peng) but the tissue it would protect largely survives — and closes as the disease consumes its substrate. It is the same logic that governs every intervention in this disease and the same logic the validity ledger applied to the biology: the value of resuming a withdrawn subsidy is a function of how much remains to be subsidised. This reframes the endpoint for a BDNF trial. The natural expectation — that a trophic factor should reverse established dementia — is the wrong test and has contributed to premature disappointment with neurotrophin therapeutics across neurodegeneration. The right test is preventive maintenance in the early window, measured not by the recovery of lost function but by the slowing of its loss, in a population selected for surviving-but-stressed tissue and, plausibly, stratified by the *BDNF* genotype that determines how the subsidy is best delivered.

XII. Placing BDNF in the Temporal Architecture

The Temporal Architecture of Collapse describes Alzheimer's disease as a stereotyped progression across half a century — a bioenergetic ignition in the brainstem, a homeostatic microglial bridgehead in the hippocampus, and a synaptic disintegration at the perineuronal net — held together by named bridges and unified beneath by the age-dependent failure of homeostatic systems. BDNF does not compete with that architecture; it supplies one of the currencies in which the architecture's final act, the loss of the synapse, is transacted. Where the *Convergent Synaptic Collapse* thesis describes the many roads by which the disease arrives at the disappearing synapse, the trophic hypothesis names the account those roads overdraw: the standing subsidy that maintained the synapse, and whose withdrawal converts each upstream lesion into its downstream signature. The architecture's bridges and BDNF's loop are the same kind of object — self-amplifying couplings that carry the disease forward — and the activity–BDNF–CREB loop, inverted, is a mechanism by which the synaptic phase becomes self-sustaining once entered, independent of the amyloid that lit the fuse.

Read this way, BDNF also threads the architecture's other themes. It is the molecule of the *reserve* the resilience literature keeps invoking, the substrate by which a life's activity is banked against

a later load of pathology, and thus the cell-biological name for why two brains with identical plaque burdens can hold minds decades apart. It is *activity-dependent*, which ties the disease's molecular core to the behavioural determinants — exercise, engagement, sleep, the whole apparatus of *use* — that the epidemiology has long known to matter and the mechanism has struggled to explain. And it carries a *germline handle*, Val66Met, whose amyloid-conditional effect is a clean instance of the gene-by-time interaction the architecture treats as its signature. BDNF is not the architecture's foundation; it is one of the load-bearing currencies in its upper storeys — the trophic subsidy whose slow withdrawal, across every phase, is the price the synapse finally cannot pay.

XIII. Conclusion The Withdrawn Subsidy

We began with a correction of a common error — that the synapse is a monument rather than a subscription — and we end with its consequence for a disease. Alzheimer's disease destroys synapses, and the loss of synapses is the truest structural correlate of the loss of mind; between the disease's upstream lesions and that final loss there is a trophic economy, and brain-derived neurotrophic factor is its principal currency. The withdrawal of that currency is among the most reproducible molecular facts of the disease: BDNF is reduced in the Alzheimer brain, the reduction begins early, and the amount a brain retains predicts how well its owner's mind withstands a given burden of pathology. We have traced three mechanisms of the withdrawal — the amyloid-driven suppression of BDNF transcription and the corruption of its receptor and transport; the shift of the neurotrophin balance toward the pro-apoptotic precursor and its p75 receptor; and the inversion of the activity–BDNF–CREB loop from a virtuous circle into a self-sustaining descent — and we have found the disease's two proteinopathies converging on the trophic subsidy from opposite ends, amyloid throttling its synthesis and tau severing its delivery.

We have graded the connections honestly, because the elegance of the trophic story is exactly the reason to distrust it, and because the sentence at its centre — *BDNF is reduced in Alzheimer's disease* — is compatible with the molecule being a cause or merely a tombstone. The reverse-causation null is the governing difficulty of the field, and the correlations, however consistent, cannot by themselves defeat it. What defeats it is the one class of evidence that reverses the arrow: restoring BDNF, by gene delivery and by receptor agonism, improves synaptic and cognitive outcomes *downstream of an unchanged amyloid burden*, in animals and now under test in humans. That result lifts the trophic hypothesis from description to conditional mechanism — reduced BDNF/TrkB signalling is on the path from pathology to synaptic failure — while the ledger holds the weaker claims, the proBDNF turn and the peripheral biomarker, below that anchor, and grades the exercise-reserve chain as an inference whose human *because* remains to be proven.

What the mapping finally offers is a change in the character of the disease's central failure. Synapse loss, read as a direct poisoning, is a catastrophe to be prevented; read as a withdrawn subsidy, it is in part a bankruptcy to be paid — a trophic deficit that is, in principle, restorable, and whose restoration, like every intervention in this disease, is worth precisely as much as the tissue that remains to receive it. The subsidy was withdrawn slowly, across decades and across every phase of the collapse, and the therapeutic question the trophic hypothesis leaves us is not whether it can be resumed — the biology says it can — but whether it can be resumed early enough, in the narrow window while there is still a synapse standing to be maintained, to matter to the mind that depends on it.

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