

Astrocyte❖❖❖Microglia Coordination Shift Across Ten Axes ❖❖❖ NEUROMETABOLICA WP v0.2 (EN)

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Astrocyte-Microglia Coordination Shift Across Ten Axes

A theoretical synthesis model of dementia genesis with a phenomenological-systems-theoretical framing

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Abstract

Background. The amyloid cascade hypothesis has structured Alzheimer research for three decades, but its explanatory power for the clinical heterogeneity of age-related dementias is limited. Validation studies of the 2024 Alzheimer's Association criteria showed that only about one third of diagnosed cases follow the classical amyloid-cascade ordering. In parallel, the evidence for numerous modifiable risk factors with mechanisms of their own has been consolidating.

Objective. An integrated theoretical model is presented that understands this heterogeneity as the endpoint of a multi-axis coordination shift. The central claim is that clinical dementia in the AD-typical and mixed sense most probably represents a coordination shift of the astrocyte-microglia dyad across several of ten defined biologically and socially grounded axes, amplified by polypharmacological burden. Manifestation as a clinical diagnosis is a threshold-setting within a continuous space of variability.

Methods. Narrative review of approximately 110 peer-reviewed sources from the years 2010-2025, combined with theoretical model-building. Phenomenological-systems-theoretical framing via the Free Energy Principle (Friston), second-order cybernetics (Foerster, Maturana) and dimensional psychiatry (RDoC, HiTOP).

Model. Ten axes with a spectrum matrix across three vulnerability dimensions (congenital-catastrophic, acquired-progressive, subclinical-age-related): protein folding, nitrogen, energy/insulin, glycation, glymphatic, sleep architecture, cardiovascular, inflammation, life course/social/psychodynamic, lipid metabolism. Polypharmacological burden acts as a systemic multiplier. ApoE-ε4 functions as a modifier chiefly via the lipid-metabolism axis, secondarily via protein folding, glymphatic, vascular and inflammation. The astrocyte-microglia dyad couples all axes and manifests coordination shifts in at least four documented mode shifts: A1 polarization, astrocytic urea cycle, AQP4 depolarization and lipid-droplet accumulation. An eleventh theoretical component — stochasticity of manifestation

— explains heterogeneous manifestation under comparable axis burden via life-event contingency, microvascular stochasticity, socio-emotional buffering capacity and neuronal reserve variability.

Phenomenological framing. The language of the model deliberately distinguishes between *coordination shift* and *defect*. This distinction is not cosmetic: it makes the theory compatible with the Free-Energy-Principle tradition, with second-order cybernetics and with dimensional-transdiagnostic research programs. Clinical suffering, care dependency and the burden on relatives are in no way relativized by it.

Implications. Anti-A β monotherapy is only modestly effective clinically because other axes remain untouched; in ApoE4/4 carriers the ARIA risk is additionally elevated. Multi-axis diagnostics and multimodal intervention (FINGER line, genotype-stratified) are the rational consequence. A salutogenic reading — not “why does the system fail?” but “what maintains coordination under chronic burden?” — is proposed as a complementary research strand. Dementia has a social stratification that is structurally mediated, without replacing the biological mechanisms.

Falsification. Twenty-one operationalizable falsification points are formulated; of these, F9 (convergence biomarker panel), F14 (deprescribing RCT), F18 (APOE2 gene therapy, Phase 1/2 ongoing), F20 (TREM2 agonists — first test AL002/INVOKE-2 already negative) and F21 (salutogenic profiles in cognitively intact older people with a risk constellation) are especially directly testable.

Status of the work. Theoretical synthesis paper, not an empirical primary study. It generates hypotheses, not treatment guidelines.

Keywords: Alzheimer’s disease; astrocytes; microglia; apolipoprotein E; glymphatic system; polypharmacology; coordination model; dimensional psychiatry; free energy principle; salutogenesis; theoretical synthesis; neuroinflammation; lipid metabolism

1. Introduction

1.1 State of research

Dementia disorders affect approximately 55 million people worldwide; the World Health Organization projects a rise to 78 million by 2030 and 139 million by 2050 (WHO 2021; ADI 2024). Alzheimer’s disease (AD) is the most common form, followed by vascular dementia, mixed forms, Lewy body dementia and frontotemporal dementias. Mixed pathology — the coexistence of AD-typical and vascular changes — is the rule in 30–40 % of late dementia cases (Schneider et al. 2007; Toledo et al. 2013).

The amyloid cascade hypothesis (Hardy & Higgins 1992; Hardy & Selkoe 2002) has produced considerable heuristic achievements and led to the development of several A β -targeted therapeutics, including lecanemab and donanemab. In recent years, however, indications of a limited explanatory power of the pure amyloid reading have accumulated:

- **Heterogeneous pathology ordering.** A validation study of the 2024 Alzheimer’s Association criteria reported that only about one third of AD cases diagnosed this way follow the classical amyloid-cascade ordering (Mendes et

al. 2025).

- **Modest clinical efficacy of anti-A β therapy.** Lecanemab and donanemab slow cognitive decline by approximately 27–35 % relative to placebo, with non-trivial ARIA risk in ApoE4/4 carriers (van Dyck et al. 2023; Sims et al. 2023).
- **Growing list of modifiable risk factors.** The 2024 Lancet Commission identifies 14 modifiable risk factors that theoretically render about 45 % of dementia cases preventable or delayable (Livingston et al. 2024).
- **Mechanistic deepening along parallel lines.** The glymphatic system (Iliff et al. 2012; Nedergaard & Goldman 2020), astrocytic activation of the urea cycle under A β stress (Ju et al. 2022), ApoE4-mediated lipid dysregulation in microglia (Haney et al. 2024) and the microbiome–brain axis (Chandra et al. 2024) are underrepresented in the pure amyloid reading.

1.2 Gap and contribution

The findings noted above are each well studied in the literature, but rarely connected within an integrated theoretical framework. The present contribution proposes such a framework: a coordination model that understands clinical heterogeneity as the endpoint of a multi-axis coordination shift, with the astrocyte–microglia dyad as the central cellular reference complex.

Relative to an earlier form of this model (WP v0.1, withheld), the present version introduces three structural extensions:

- **Coordination language instead of defect language.** Mechanisms are described as mode shifts, not as forms of failure. This shift is explicitly compatible with Friston’s Free Energy Principle (FEP) and with second-order cybernetics (Foerster, Maturana).
- **Stochasticity of manifestation as its own component.** An eleventh theoretical component explains why comparable axis burden nonetheless results in heterogeneous manifestation.
- **Threshold operationalization of the diagnosis.** The binary dementia diagnosis is framed as a culturally-clinically operationalized threshold within a continuous space of variability — compatible with the RDoC and HiTOP tradition of dimensional psychiatry.

The model is not intended as a competitor to the amyloid hypothesis but as its embedding. It specifies in which subgroups A β is a primary cause (familial AD, about 1 % of all cases; a subgroup of sporadic cases, about one third) and in which A β is an indicator and amplifier of an already ongoing coordination shift (the majority).

1.3 Structure

Section 2 describes the methodology of the synthesis and its phenomenological–systems-theoretical framing. Section 3 presents the ten axes of the model. Section 4 develops the astrocyte–microglia dyad as reference complex. Section 5 describes four documented coordination manifestations. Section 6 introduces the stochasticity of manifestation as the eleventh component. Section 7 operationalizes the threshold-setting of the clinical diagnosis. Section 8 presents four clinical phenotypes with an ApoE-stratified reading. Section 9 makes the social stratification of the biomedical model explicit. Section 10 reinterprets the amyloid hypothesis in light of the model. Section 11 proposes a salutogenic reading as a complementary research strand. Section 12 lists 21 operationalizable falsification points. Section 13 discusses limitations, Section 14 situates the model in relation to alternative models. Section 15 draws conclusions.

2. Methods

2.1 Type of study

This is a **theoretical synthesis paper** on the basis of a narrative review. It is not a systematic meta-analysis, not an RCT, not an empirical primary study. The format is established in the medical-theoretical literature (de la Torre 2002 on the CATCH hypothesis; Hardy & Higgins 1992 on the amyloid cascade hypothesis; Livingston et al. 2017 on the Lancet Commission risk-factor list).

2.2 Data sources

The synthesis rests on approximately 110 peer-reviewed sources from the years 2010–2025, with an emphasis on 2017–2025 for current mechanism studies and 2020–2024 for therapy and risk-factor reviews. Search via PubMed, Web of Science and Scopus on the ten defined axes as well as on astrocytes, microglia, ApoE, the microbiome–brain axis and polypharmacology. Additionally, systems-theoretical and phenomenological sources (Friston, Foerster, Maturana, Husserl, Merleau-Ponty, Plessner, Kitwood).

2.3 Selection criteria

- Original studies on mechanistic findings, preferably with preclinical and clinical validation.
- Systematic reviews and meta-analyses for evaluating effect sizes.
- Umbrella reviews where available (Belessiotis-Richards et al. 2025 for pharmacology; Penninkilampi 2018 for social isolation).
- High-ranking consensus documents (Lancet Commission 2017, 2020, 2024).
- Conceptual sources from systems theory and phenomenology for Sections 2.5 and 7.

2.4 Theoretical model-building

The model-building follows four principles:

- **Multi-axis architecture** with clearly defined and mutually demarcated axes.
- **Spectrum logic** across three vulnerability dimensions per axis.
- **Cellular reference principle**: search for a cell system that is directly coupled to all identified axes and in which the coordination shift becomes physiologically manifest.
- **Phenomenological-systems-theoretical framing**: mechanisms are understood as mode shifts, not as forms of defect.

2.5 Phenomenological-systems-theoretical framing

Three theoretical traditions frame the language of the model:

Free Energy Principle / Active Inference (Friston, since 2010). Living systems — from bacteria to the brain — minimize, via Bayesian inference, the prediction error between internal models (priors) and sensory data (likelihood). In this theory, cognitive phenomena are derivable from the precision-weighting of priors and likelihood. Pathologies are understood not as deficits but as mis-configurations of the precision distribution (Friston 2010; Friston et al. 2017). An application to

dementia lies in the hypothesis that the system’s Bayesian-updating capacity is configured differently under axis burden — priors are possibly weighted more strongly (confabulation), or the sensory input is under-integrated (disorientation).

Second-order cybernetics (Foerster, Maturana). Living systems are understood as self-organizing, self-referential entities (Maturana & Varela 1980; Foerster 2003). “Defect” is not the right language in this tradition; the system operates in a different mode of self-coordination. This reading is not anti-realism — it changes the ontological description, not the clinical reality.

Dimensional psychiatry (RDoC, HiTOP). The NIMH Research Domain Criteria (Cuthbert & Insel 2013) and the Hierarchical Taxonomy of Psychopathology (Kotov et al. 2017) replace categorical-symptomatic diagnostics with dimensional, transdiagnostic readings. Symptoms are mapped onto constructs that are continuously distributed in the general population. In this tradition, dementia is understood not as “the other side of the healthy” but as a specific point in a high-dimensional space of cognitive variability.

This framing allows a consistently coherent model language: what appears as “failure” in the defect picture is described as a coordination shift.

2.6 Falsification discipline

The model is explicitly formulated as falsifiable. Section 12 lists 21 operationalizable hypotheses whose refutation would modify or discard the model.

2.7 Limits of the methodology

- Narrative reviews are subject to selection bias relative to systematic reviews.
- Theoretical model-building is hypothesis-generating, not hypothesis-testing.
- Source selection is essentially English-language dominated; non-English research (especially from Asia) is possibly underrepresented.
- The phenomenological framing is conceptual, not empirically validated. It is offered as a choice of language, not as a proven ontology.

3. The Ten-Axis Coordination Model

3.1 Overview

The model defines ten biologically and socially grounded axes plus a multiplier cross-axis:

#	Axis	Core characteristic
1	Protein folding	Aβ, tau aggregation propensity
2	Nitrogen metabolism	Urea cycle, ammonia detoxification, liver-brain axis
3	Energy/insulin signaling	Brain insulin resistance, glucose hypometabolism
4	Glycation/AGEs	Non-enzymatic modification, RAGE signaling
5	Glymphatic	AQP4-mediated perivascular clearance
6	Sleep architecture	NREM/REM, SWS, BMAL1/CLOCK genetics
7	Cardiovascular and blood flow	AF, HFrEF/HFpEF, hypertension, hypoperfusion
8	Inflammation	Microglia (DAM, NLRP3), A1/A2

		astrocytes, crosstalk
9	Life course, social, psychodynamic	Education, isolation, trauma, possibly psychodynamic factors
10	Lipid metabolism	Cholesterol transport, membrane lipids, sphingolipids, ApoE lipidation

Multiplier cross-axis: Polypharmacological burden (anticholinergic, sedating and other centrally acting substances).

3.2 Spectrum matrix

Each axis has a vulnerability spectrum across three dimensions:

Axis	Congenital-catastrophic	Acquired-progressive	Subclinical-age-related
1. Protein folding	Familial AD (PSEN1/2, APP)	Repetitive TBI	Age-related A β accumulation
2. Nitrogen	Urea-cycle disorders (UCDs)	Cirrhosis, NAFLD/NASH	Subclinical liver fibrosis
3. Energy/insulin	Congenital hyperinsulinemia, MELAS	T2DM, metabolic syndrome	Hippocampal hypometabolism
4. Glycation/AGEs	Glyoxalase defects	Chronic hyperglycemia, renal insufficiency	AGE accumulation
5. Glymphatic	AQP4 polymorphisms	Hypertension, vascular stiffness	AQP4 depolarization
6. Sleep architecture	FFI, narcolepsy	Sleep apnea, shift work	SWS decline
7. Cardiovascular	Cardiomyopathies	AF, HFrEF/HFpEF, hypertension	Vascular stiffness, microbleeds
8. Inflammation	TREM2 (R47H), CD33 polymorphisms	Chronic infections, autoimmunity	Inflammaging, NLRP3 activation
9. Life course/social	Early trauma, low SES	Depression, PTSD, isolation	Loneliness, loss of meaning
10. Lipid metabolism	Familial hypercholesterolemia, Niemann-Pick C, Smith-Lemli-Opitz	High LDL, dyslipidemia, NAFLD-related	Membrane-lipid and glial-cholesterol changes

3.3 Axis evidence in detail

Axis 1 — Protein folding. The classical AD histopathology with A β plaques and neurofibrillary tangles (Braak stages; Braak & Braak 1991) remains central. Familial AD mutations in PSEN1, PSEN2 and APP show that A β overproduction is sufficient for AD pathology (Goate et al. 1991; Sherrington et al. 1995). In the majority of sporadic cases the ordering of A β accumulation, tau pathology and clinical symptomatology is heterogeneous (Mendes et al. 2025).

Axis 2 — Nitrogen. The liver-brain axis is well established clinically via hepatic encephalopathy (HE) (Vilstrup et al. 2014). Silvey, Bajaj et al. (2024) showed, in a cohort of 68,807 dementia patients without known cirrhosis, that a portion of this group has undiagnosed cirrhosis with potentially treatable hepatic encephalopathy — clinically difficult to distinguish from incipient AD. Ju et al. (2022 *Cell Metabolism*) showed that astrocytes activate the full urea cycle under A β stress — a metabolic capacity previously understood as hepatically localized. Astrocytic production of putrescine, GABA and H₂O₂ acts to impair memory.

Axis 3 — Energy/insulin signaling. The diabetes-type-3 hypothesis (de la Monte & Wands 2008) posits AD as a selective cerebral insulin resistance. Arnold et al. (2018) and others have refined the concept: brain insulin resistance is measurable (PET hypometabolism in temporo-parietal regions before clinical manifestation) and correlates with cognitive decline even in non-diabetic individuals. T2DM increases AD risk by roughly 1.5- to 2-fold (Cheng et al. 2012). [T2 2026-09-29: refined from “doubles” to the range supported in meta-analyses]

Axis 4 — Glycation/AGEs. Sasaki et al. (1998) and Vitek et al. (1994) demonstrated advanced glycation end products (AGEs) in A β plaques and neurofibrillary tangles. Wei et al. (2015) showed that D-ribose — not primarily glucose — is the most potent glyicator among the monosaccharides and induces tau hyperphosphorylation via CaMKII. Skin autofluorescence (Mooldijk et al. 2024) correlates in the Rotterdam Study with dementia incidence (HR 1.21 per standard deviation, 95 % CI 1.01-1.46; n = 2922, 123 dementia cases), independently of age and other tested confounders.

Axis 5 — Glymphatic. Iliff et al. (2012) described the glymphatic system as an AQP4-mediated perivascular clearance mechanism. Xie et al. (2013) showed that A β clearance occurs mainly during sleep. Nedergaard & Goldman (2020) integrated the findings into a unified model. AQP4 polymorphisms modify AD risk (Burfeind et al. 2017). An age-dependent decline of paravascular/glymphatic clearance is described (Kress et al. 2014).

Axis 6 — Sleep architecture. Slow-wave sleep (SWS, NREM stage 3) is the sleep-architectural phase with the highest glymphatic pump activity. SWS declines with age; chronic sleep deficits and sleep apnea (Yaffe et al. 2011) correlate with dementia risk. The rare fatal familial insomnia (PRNP mutations) demonstrates that severe sleep disturbance alone is sufficient for neurodegenerative dementia. A genetic overlap between sleep traits and dementia risk is described (shared genetic risk factors, *Front Genet* 2022, PMID 35656316).

Axis 7 — Cardiovascular and blood flow. De la Torre coined the CATCH hypothesis (Critically Attained Threshold of Cerebral Hypoperfusion; first formulation *Neurobiol Aging* 2000) and developed it in the works cited here (2002, 2012); chronic cerebral hypoperfusion below a critical threshold leads to a neuronal energy crisis and AD pathology. Atrial fibrillation increases dementia risk independently of clinical strokes (de Bruijn et al. 2015; Bunch et al. 2010; Saglietto et al. 2025). Heart failure with reduced and with preserved ejection fraction (HFrEF, HFpEF) both increase dementia risk (Jefferson et al. 2010; Cannon et al. 2017).

Axis 8 — Inflammation. Heneka et al. (2013) showed that NLRP3 inflammasome activation in microglia is central to AD pathology. Venegas et al. (2017) described microglia-derived ASC specks as cross-seeding factors for A β plaques. Liddel et al. (2017) identified A1-reactive astrocytes, which are induced by microglial C1q + TNF + IL-1 α and are neurotoxic. Keren-Shaul et al. (2017) characterized disease-associated microglia (DAM) via scRNA-seq. TREM2 (R47H variant) increases AD risk approximately threefold (Guerreiro et al. 2013).

Axis 9 — Life course, social, psychodynamic. The Lancet Commission (Livingston et al. 2017, 2020, 2024) lists 14 modifiable risk factors. Stern (2012) developed the cognitive-reserve hypothesis. Penninkilampi et al. (2018) and Lara et al. (2019) showed elevated dementia risk from social isolation (HR 1.5-2.0). Yaffe et al. (2010) demonstrated PTSD as a dementia risk factor. Pseudodementia (Wells 1979; Brodaty & Connors 2020) is at least partly reversible.

Axis 10 — Lipid metabolism. The 2024 Lancet inclusion of high LDL as a modifiable risk factor (Livingston et al. 2024) marks the growing awareness of the independent role of lipid metabolism. Haney et al. (2024) showed that APOE4/4 microglia develop ACSL1-positive lipid-droplet-accumulating phenotypes (LDAM) that induce neuronal tau phosphorylation. Blanchard et al. (2022) demonstrated ApoE4-mediated demyelination via the LXR β /ABCA1 pathway in oligodendrocytes. Sienski et al. (2021) showed a disrupted intracellular lipid homeostasis in ApoE4

iPSC astrocytes with accumulation of unsaturated triglycerides and lipid droplets, reversible by choline supplementation. Statins are slightly protective in umbrella reviews (Belessiotis-Richards et al. 2025) with moderate certainty.

3.4 Polypharmacological multiplier cross-axis

Pieper et al. (2020) and Mur et al. (2021) showed, in meta-analyses, a 20–46 % increase in dementia risk under anticholinergic exposure, dose- and time-dependent. Poonawalla et al. (2023) reported a stepwise increase from 15 to 77 dementia cases per 1000 person-years with rising anticholinergic polypharmacy (0 vs. 4+ agents). The 2025 umbrella review (Belessiotis-Richards et al.) confirmed moderate certainty for anticholinergic risk elevation. Benzodiazepines show weaker evidence (very low certainty), possibly confounded by reverse causation. Protective classes: antihypertensives, statins, SGLT2 inhibitors, GLP-1 RAs (moderate certainty); lithium (low certainty).

4. The Astrocyte-Microglia Dyad as Reference Complex

4.1 Rationale for the dyad reading

Astrocytes and microglia form a coupled cell system whose crosstalk is central to the manifestation of the coordination shift:

- (a) **Both cell types are directly coupled to most axes.** Astrocytes couple with all ten axes. Microglia are central primarily to axes 1 (phagocytosis), 8 (inflammation) and 10 (lipid droplets), and involved in several others.
- (b) **Microglia regulate astrocyte polarization.** Liddelow et al. (2017) showed that activated microglia secrete C1q, TNF and IL-1α, thereby converting astrocytes into an A1-reactive, neurotoxic phenotype. A2 astrocytes (induced by ischemia) are rather protective.
- (c) **Astrocytes regulate the microglial spectrum.** Astrocytic secretion of TGF-β, IL-33 and other factors modulates microglial activity (Cekanaviciute et al. 2014; Vainchtein et al. 2018). The crosstalk is bidirectional.
- (d) **ApoE is produced by both cell types.** Sienski et al. (2021) showed astrocytic ApoE4 dysregulation; Haney et al. (2024) microglial ApoE4 dysregulation.
- (e) **Crosstalk configurations hit the system, not one cell type.** ApoE4 shifts LGALS3-mediated microglia-astrocyte crosstalk; microglial ApoE4 knockout reactivates LGALS3 signaling and astrocytic plaque phagocytosis (García-Revilla et al. 2022, *Cell Death Dis* 13:628, PMID 35859075).

4.2 Full coupling map

#	Axis	Astrocyte coupling	Microglia coupling
1	Protein folding	Aβ internalization, lysosomal degradation	Aβ phagocytosis, NLRP3, ASC specks
2	Nitrogen	Glutamine synthetase, urea cycle under stress	Indirect via systemic NH3
3	Energy/insulin	Insulin receptor, GLUT-1, lactate shuttle	DAM glycolysis shift
4	Glycation/AGEs	RAGE expression	RAGE expression
5	Glymphatic	AQP4 on endfeet — central	Indirect via BBB inflammation
6	Sleep	Astrocytic BMAL1/CLOCK	Microglial circadian

			activity
7	Cardiovascular	Endfeet on vessels, BBB, vasomotion	Perivascular microglia, BBB disruption
8	Inflammation	A1/A2 polarization	DAM, NLRP3, TREM2
9	Life course/social	Stress hormones (cortisol), plasticity	Stress-induced microglial priming
10	Lipid metabolism	Cholesterol main producer, ApoE, lipid droplets	LDAM (Haney 2024), TREM2 lipid sensing

4.3 Astrocyte as central reference element

Although the dyad reading refines the one-sided astrocyte focus, the astrocyte remains the element directly coupled to the most axes. Four structural reasons: largest cell quantity (20–40 % of CNS cells); structural ubiquity (endfeet on practically all CNS vessels); metabolic versatility (glutamate recycling, GLUT-1, lactate shuttle, glutamine synthetase, cholesterol synthesis); reactive plasticity (A1/A2 polarization, glymphatic modulation, ApoE secretion). Microglia are understood in the model as the main regulators of reactive astrocyte polarization, as well as a direct manifestation of the lipid and inflammation axes.

5. Four Coordination Manifestations

In the coordination shift of the astrocyte–microglia dyad, at least four documented mode shifts can be distinguished, which are adaptive in acute form and become pathogenic under chronic burden. They are not competitors but different responses to different axis burdens and can coexist.

5.1 A1 polarization of the astrocyte

Activated microglia secrete C1q + TNF + IL-1 α (Liddel et al. 2017). Nearby astrocytes shift into an A1-reactive phenotype: hypertrophic morphology, altered transcription, neurotoxic secretion of a not yet fully characterized factor. A1 astrocytes kill neurons and oligodendrocytes in vitro. In AD, PD, MS and ALS brains they are abundant. A1 polarization is an acutely adaptive response to acute inflammation that persists under chronic inflammation and acts neurodegeneratively.

5.2 Activation of the astrocytic urea cycle

Ju et al. (2022) showed that astrocytes activate the full urea cycle under A β stress — a metabolic capacity previously understood as hepatically specific. The astrocytic production of putrescine, GABA, H₂O₂ and NH₃ leads to memory impairment and has been reproduced in the mouse model. The activation is intended as a detoxification response but is itself memory-impairing.

5.3 Reduced AQP4 polarization and glymphatic mode shift

Glymphatic function requires polarized AQP4 expression on astrocytic endfeet (Iliff et al. 2012). With age, under chronic vascular stiffness and under chronic sleep deficits, AQP4 depolarizes — the site-specific arrangement is modified. The consequence is reduced ISF clearance of A β , tau and other solutes. A regional impairment of paravascular clearance in the aging brain is described (Kress et al. 2014).

5.4 Lipid-droplet accumulation in the dyad

Haney et al. (2024) identified ACSL1-positive, lipid-droplet-accumulating microglia

(LDAM) as a prominent phenotype in ApoE4/4 patients. Fibrillar A β induces ACSL1 expression, triglyceride synthesis and lipid-droplet accumulation in ApoE4 microglia. LDAMs show modified phagocytosis and secrete factors that induce neuronal tau phosphorylation. In parallel, lipid droplets also accumulate in ApoE4 astrocytes (Sienski et al. 2021), with altered glycolysis and altered supply to neurons.

5.5 Positive feedback loop

The four manifestations can mutually reinforce one another:

↓ AQP4 → ↓ A β clearance → ↑ microglial NLRP3 → ↑ A1 astrocytes → ↑ inflammation → ↓ BBB → ↑ TMAO, LPS entry → ↑ microglial priming → ↑ DAM polarization → in ApoE4: ↑ ACSL1/lipid droplets in microglia → ↑ tau phosphorylation → ↑ neuronal loss → ↓ sleep quality → ↓ AQP4 (amplification)

The loop has several entry points and several amplification nodes. This multiplicity explains why clinical dementia is not reversible through mono-intervention.

5.6 Mode reading of the four manifestations

In the phenomenological-systems-theoretical framing (Section 2.5), the four manifestations are understood as mode shifts, not as defects. A1 polarization is a different polarization of the astrocyte under chronic burden; the astrocytic urea cycle is a different metabolic configuration under A β stress; AQP4 depolarization is a different spatial arrangement of the channel; lipid-droplet accumulation is a different lipid handling. The system continues to do its best; in a different configuration. This choice of language is not trivialization — the clinical consequences are real and severe — but ontological refinement.

6. Stochasticity of Manifestation as the Eleventh Theoretical Component

6.1 The heterogeneity gap

The model described in Sections 3–5 explains what must come together for clinical dementia to manifest. It does not sufficiently explain why, under comparable axis burden, the clinical manifestation turns out heterogeneous — why one ApoE4/4 carrier with cardiovascular risk, T2DM, moderate polypharmacology and social burden becomes demented, while another with a similar profile remains cognitively intact until 90.

This heterogeneity is clinically everyday, but under-explained in the model. It is addressed here as an **eleventh theoretical component** — not an axis in the spectrum sense, but a **realization condition** that decides whether a given axis profile becomes clinically manifest or remains compensated.

6.2 Three non-exclusive readings

(a) Hidden variable. There is one or more not-yet-identified factors — a specific gene variant, an epigenetic configuration, an early-childhood environmental exposure — that structure the manifestation. This reading motivates the ongoing search for additional genetic risk loci beyond APOE and TREM2 (Bellenguez et al. 2022).

(b) Non-linear thresholds. The axis burden acts not additively but via non-linear thresholds and critical phase transitions. Just below threshold the system remains compensable; just above it, it tips over. Such thresholds are typical in complex systems (Scheffer et al. 2009 on the theory of critical transitions in complex systems).

(c) Stochastic manifestation. Given comparable axis profiles, additional stochasticity — neuronal variability, contingent life events, microvascular chance — decides whether and how it becomes manifest. In the Friston FEP tradition this can be understood as a “non-deterministic active-inference trajectory”: the system continuously minimizes prediction error, but the specific configuration in which it collapses is not fully determined by initial conditions.

All three readings plausibly act together.

6.3 Four realization conditions

The stochasticity of manifestation can be decomposed into four operationalizable conditions:

- **Life-event contingency.** What actually happens in the individual’s life? Widowhood, retirement, illness of a close person, a move into a care home — such events have different effects on differently pre-burdened axis profiles.
- **Microvascular stochasticity.** Which small vessels bleed or clog, and when? Microbleeds and silent infarcts are statistically distributed, not deterministic.
- **Socio-emotional buffering capacity in the concrete life situation.** Are reliable attachment figures available? How is emotional resonance configured in everyday life?
- **Neuronal reserve variability.** Beyond education reserve (Stern 2012) there are non-education-dependent components of neuronal reserve that let the system compensate — presumably anatomical, presumably plasticity-related, precisely hard to capture.

These conditions do not fit into the spectrum scheme of the ten axes. They act on a different level — not as drivers of the coordination shift, but as conditions of its clinical visibility.

6.4 Consequence for research and clinical practice

Acknowledging stochasticity changes the research and clinical perspective in two directions:

On the research side it suggests that the search for “the decisive factor” may lead not to a single factor but to a distribution problem. Personalized medicine in the dementia field would have to map, beyond axis profiles, also realization conditions.

On the clinical side it suggests that prognoses for individual patients are to be formulated with fundamental caution. Even with a clearly burdened axis profile, the individual course trajectory is not determined. This is not reassurance against real risks, but an ontological clarification.

7. Threshold-Setting as a Methodological Task

7.1 The binary diagnosis within the continuum

The clinical dementia diagnosis is binary — a person is demented or not. This binarity is clinically and institutionally necessary (care levels, legal capacity, care planning), but it is an **operationalization within a continuous space of variability**.

The ten axes are continua with three vulnerability dimensions. The clinical manifestation is a specific configuration in a high-dimensional space. Who is designated “demented” depends on cultural, clinical and institutional thresholds — not on a binary biological fact. The MCI category established in contemporary psychiatry (Petersen 2004) and the concept of subjective cognitive decline (SCD; Jessen et al. 2014) already make this threshold problem implicitly visible.

7.2 Connection to dimensional psychiatry

The NIMH Research Domain Criteria (Cuthbert & Insel 2013) and the HiTOP initiative (Kotov et al. 2017) have already made the step from the categorical to the dimensional model in general psychiatric research. Symptoms are mapped onto constructs that are continuously distributed in the general population. The spectrum reading of schizophrenia (van Os et al. 2009) has shown that psychotic experiences are far more frequent in the general population than clinically diagnosed schizophrenia; the difference is threshold, not category.

In the dementia field, a comparable step is pending. The present model suggests that here too a dimensional-transdiagnostic research framework with continuously distributed axis-burden profiles would be more productive than the purely categorical “AD versus vascular versus mixed” classification, which in practice often seems artificial.

7.3 Consequences for clinical practice and research

- **Diagnostic thresholds are operationalized, not naturally given.** They are the result of cultural, clinical and institutional agreement. They can legitimately be set differently.
- **Cross-cultural comparisons must take thresholds into account.** Differences in dementia prevalence between countries partly reflect differences in threshold operationalization, not only incidence.
- **MCI patients are not “preclinically demented” but “near the threshold”.** This reformulation has clinical consequences for counseling and treatment decisions.
- **Multi-axis burden profiles are more informative than binary diagnoses.** For research purposes, documenting a person’s axis profile would be more informative than the binary diagnosis.

7.4 Limits of the dimensional reading

The dimensional reading is not universally superior. In clinical practice, binary threshold-settings are necessary for institutional care (care allowance, legal capacity, treatment decisions). The position held here is not to abolish binarity but to keep its operationalized character visible.

8. Clinical Phenotypes and ApoE-Stratified Reading

8.1 Four convergence phenotypes

Four heuristic clinical phenotypes can be derived from the model. They are not diagnostic categories but constellations that occur frequently in geriatric and gerontopsychiatric practice.

The polypharmacologically burdened patient. Dominant axes: polypharmacology multiplier, 8 (inflammation), often 9 (socially isolated with high medication need). Mechanism: anticholinergic load → modified cholinergic microglia regulation → modified inflammation → altered A β clearance. Reversibility: high with timely deprescribing.

The cardio-cognitive patient. Dominant axes: 7 (cardiovascular), 5 (glymphatic), 8 (inflammation), 3 (energy). Mechanism: CATCH hypothesis — chronic hypoperfusion → astrocyte energy crisis → reduced AQP4 → A β stagnation → reactive astrogliosis → vascular endothelial modification → microbleeds. Reversibility: medium with consistent risk reduction.

The socio-affectively burdened patient. Dominant axes: 9 (life course/social), 6 (sleep, modified by depression), 8 (stress-induced inflammation). Mechanism: chronic stress → HPA-axis alteration → cortisol → hippocampal atrophy → cognitive symptoms → social reactions amplify isolation. Reversibility: pseudodementia component reversible; primarily neurodegenerative component not.

Mixed types — the normal case. The majority of very old dementia patients combine elements of the three phenotypes. This is not complicating comorbidity but the expected manifestation of a multi-axis coordination shift.

8.2 ApoE-stratified reading

The ApoE genotype distribution in the population modifies the manifestation of the four phenotypes.

ApoE4/4 homozygous (about 2 % of population, about 10–15 % of AD cases): mean disease onset 10–15 years earlier; higher A β load; LDAM accumulation; early demyelination; BBB modification manifest early. Dominant axis: 10 (lipid metabolism), amplified by 5, 7, 8. Interventions with disproportionate plausibility: Mediterranean diet, exercise, blood-pressure control, statins, in future APOE2 gene therapy (LX1001, Phase 1/2, interim data 2024/25). Anti-A β therapy with the highest ARIA risk.

ApoE4 heterozygous (about 25 % of population, about 50 % of AD cases): HR about 3 relative to ϵ 3/ ϵ 3. Heterogeneous course. ApoE4 as amplifier, other axes often co-determining.

ApoE3/3 (about 60 % of population, most frequent AD genotype in late AD): typical course, disease onset 75+. Other axes dominate. General multi-axis prevention per Lancet 2024.

ApoE2 carriers (about 13 % of population): protective, about 40 % reduced risk (Corder et al. 1994). When AD occurs, it is usually late and mild. ApoE2/2 (about 0.5 %) is a valuable study population for protective mechanisms.

8.3 Cross-table phenotype × genotype

	ApoE4/4	ApoE4-het	ApoE3/3	ApoE2 carriers
Polypharmacological	Very high vulnerability	High vulnerability	Vulnerable from 75+	Late, rather mild
Cardio-cognitive	Early manifestation, high ARIA risk	Typical from 70	Typical from 75	Rather low
Socio-affective	Early manifestation,	Typical	Life-course-	Rarely clinically

	depression-amplified		determined	manifest
Mixed types	Rule; early onset	Rule; medium onset	Rule; later onset	Exception

This stratification is heuristic, not diagnostic.

9. Social Stratification of the Biomedical Model

The ten axes are not evenly distributed across the population. Low education, low socioeconomic level, migration under precarious conditions, women in patriarchal structures and ethnic minorities in discriminatory societies statistically accumulate several axis burdens: lower education (axis 9); more frequent depression and trauma (9); higher cardiovascular burden (7); higher diabetes prevalence (3, 4); chronic sleep deprivation from shift work (6); higher polypharmacology load with poorer medical care; higher air pollution in disadvantaged residential areas (8).

This accumulation is structurally mediated, not individual failure. The Lancet Commission (Livingston et al. 2024) documents that marginalized groups develop dementia earlier and show more severe courses. Demographic data show that age-standardized dementia incidence in high-income countries has fallen since the 1990s (better education and vascular risk management), while it is rising in low- and middle-income countries.

What does not follow from this. Dementia is not “only socially caused”. The biological mechanisms of the ten axes are real and causally involved. The social stratification acts mediated via these mechanisms, not parallel to them.

What follows from this. The most effective dementia prevention at the population level is presumably political (education, social, environmental policy) and not primarily pharmacological. At the individual level, multi-axis risk reduction remains rational but depends on structural preconditions.

10. Reinterpretation of the Amyloid Hypothesis

In light of the coordination model, the role of A β can be specified:

In familial AD (about 1 % of all cases): A β is a primary cause. PSEN1/2 or APP mutations lead to A β overproduction; the classical amyloid cascade is valid.

In the majority of sporadic cases: A β is an indicator and amplifier of an already ongoing multi-axis coordination shift. Astrocytes under competing burden deliver reduced A β clearance; microglia lose their phagocytosis efficiency; A β accumulates secondarily.

In a subgroup: A β is nearly an epiphenomenon — other axes dominate the clinical picture.

The AA-2024 validation study (Mendes et al. 2025) is consistent with this reading: only about one third of AA-2024-positive cases follow the classical amyloid-cascade ordering. The remaining two thirds show divergent biological-clinical coupling, which is interpretable in the coordination model as a differing axis profile.

Consequence for therapy. Anti-A β therapies (lecanemab, donanemab) presumably work more strongly in the amyloid-dominated subgroup than in the overall collective. Clinical effect sizes of 27–35 % slowing are consistent, within the

coordination model, with only one axis being addressed. ARIA problems arise especially in ApoE4/4 carriers whose vascular-glymphatic axis (5, 7) is pre-damaged — that is, precisely where A β is not the sole cause.

A multi-axis strategy (see Section 12.3) would presumably be more effective for the majority of patients than any mono-intervention.

11. Salutogenesis as a Complementary Research Strand

The language shift from failure to coordination suggests an inverse research question: not “why does it fail?” but “what maintains coordination under chronic burden?”. This reading connects to Antonovsky’s salutogenesis concept (Antonovsky 1979, 1987), originally developed for stress resilience.

Operationalizably, salutogenesis research for dementia can be formulated thus: What distinguishes ApoE4/4 carriers who remain cognitively intact until 90 (about 40–50 % of this group) from ApoE4/4 carriers who become demented at 60–70? Which coordination strategies of the brain system maintain coherence under chronic axis burden? Which life-conduct structures support which coordination strategies?

This research would be not a replacement but a complement to risk-factor research. It would more systematically address the stochasticity of manifestation discussed in Section 6. In particular, it would operationalize the question of **protective factors beyond the Lancet list**: sense-of-meaning experience, social embeddedness beyond isolation/non-isolation, cognitive-emotional strategies for dealing with age-related changes.

Methodologically, longitudinal studies on “cognitively-intact-remaining very-old people with a risk constellation” would be indicated — a subgroup largely overlooked in current research, because outcome research focuses primarily on dementia cases.

12. Empirical Implications and Falsification Points

The model is formulated as testable. 21 falsification points are operationalized.

12.1 Axis-specific predictions (F1-F8)

- **F1.** Plasma ammonia, BCAA, FIB-4 and glutamine-glutamate ratio correlate with cognitive status in large dementia cohorts (UK Biobank, ADNI, Whitehall II — directly testable).
- **F2.** Metabolic changes (HbA1c variability, FIB-4, AGE accumulation) occur in longitudinal studies before A β -PET positivity.
- **F3.** A subgroup of clinically demented patients without classical A β /tau pathology but with pronounced multi-axis metabolic disturbance can be identified at autopsy.
- **F4.** HE therapies (lactulose, rifaximin) improve cognitive symptoms in MCI patients with subclinical hyperammonemia (RCT-feasible).
- **F5.** Urinary profiles of specific polyamines and organic acids correlate with dementia severity.
- **F6.** The ODC1/putrescine axis (Ju 2022) is reproducibly detectable in post-

mortem brains.

- **F7.** UCD heterozygotes show elevated dementia incidence in old age (register study).
- **F8.** Glutaminolysis markers are reproducible in aging brains.

12.2 Integrated predictions (F9-F13)

- **F9.** An integrated convergence biomarker panel (FIB-4 + HOMA-IR + NH₃ + BCAA + APOE status + Aβ_{42/40} + p-tau-217 + GFAP + NfL + CNS sphingomyelin/ceramide) achieves, in an ML-based classifier, an AUC > 0.8 against clinical dementia diagnosis, higher than Aβ-PET alone.
- **F10.** Aβ pathology is detectable in old cetaceans (scientific strandings).
- **F11.** AQP4 polymorphisms modify dementia risk in UK Biobank and ADNI.
- **F12.** Shift work increases dementia incidence after adjustment for confounders.
- **F13.** Pigeons (*Columba livia*) can be established as a model species for comparative Aβ research.

12.3 Interventional predictions (F14-F20)

- **F14.** Systematic deprescribing of anticholinergic medications in 75+ patients with MCI reduces dementia incidence at 5-year follow-up (RCT design available).
- **F15.** A multimodal intervention acting simultaneously on several axes (sleep + liver + glucose + blood pressure + social + lipid) improves cognitive outcome more strongly than the FINGER standard combination.
- **F16.** CNS lipid biomarkers (plasma sphingomyelin, ceramide, phosphatidylcholine subtypes) correlate with cognitive decline independently of Aβ and vascular risk.
- **F17.** Selective LXR activation reduces AD pathology in preclinical animal models.
- **F18.** APOE2 gene therapy improves the clinical course in ApoE4 homozygotes (LX1001, NCT03634007, Phase 1/2 ongoing; interim data 2024/25: dose- and time-dependent CSF APOE2 increase, reduction of CSF tau biomarkers in over two thirds, no ARIA — efficacy endpoint still open).
- **F19.** TMAO reduction through dietary or pharmacological intervention reduces dementia incidence in risk cohorts.
- **F20.** TREM2 agonists change the clinical course in MCI/mild AD. **First test negative:** the TREM2 agonist AL002 (INVOKE-2, n=381, Phase 2) missed the primary endpoint (CDR-SB) on 2024-11-25 and showed no effect on secondary clinical endpoints, Aβ-PET or AD biomarkers (INVOKE-2, NCT04592874; *Nat Med* 2026, doi:10.1038/s41591-026-04273-1, PMID 41787076); the extension study was discontinued. The point is thereby, in its narrow form (agonistic TREM2 antibodies as monotherapy), provisionally refuted; it remains open for other TREM2 approaches and for the question of whether microglial single-target modulation without simultaneous addressing of further axes is fundamentally insufficient (consistent with the model's multi-axis thesis).

12.4 Salutogenesis prediction (F21, new in WP v0.2)

- **F21.** Axis-burden profiles of older people who remain cognitively intact with a risk constellation (especially ApoE4 carriers over 80 years without MCI) differ from similarly burdened people with dementia by additional salutogenic variables not contained in the previous risk-factor list. These variables presumably comprise sense-of-meaning experience (e.g. Antonovsky's sense of coherence), active social embeddedness (beyond isolation indicators), cognitive-

emotional coping strategies and non-education-dependent neuronal reserve. Operationalizable in longitudinal studies on very-old people with documented risk constellations.

12.5 Prioritization

From a resource perspective, the following points are especially urgent:

- **F9** (convergence biomarker panel): directly implementable in data terms with existing cohort data, theoretically central.
 - **F14** (deprescribing RCT): clinically highly relevant, RCT methodology established, resource-light.
 - **F18**: an industry-funded trial is running (LX1001, Phase 1/2), interim data 2024/25 positive at the biomarker level, efficacy analysis pending. **F20**: the first test (AL002/INVOKE-2) was already negative at the efficacy endpoint (2024); the point is provisionally refuted in its narrow form (see 12.3).
 - **F19**: methodologically challenging, but relevant for public-health statements.
 - **F21** (salutogenesis): methodologically demanding, but conceptually innovative and complementary to risk-factor research.
-

13. Limitations and Reservations

The model has clear limits, made explicit here:

1. **Not all dementia forms fit.** Prion dementias (CJD, FFI), severe familial AD forms and some FTD subtypes are monogenetic and do not follow the coordination scheme. Lewy body dementia has α -synuclein pathology, which appears only indirectly in the model. The model makes no universal claim.
2. **A β is not “irrelevant”.** A β remains an important biomarker and, in a subgroup, a driver. The model specifies the role rather than arguing it away.
3. **The astrocyte is not “the solution”.** Reference-complex status does not mean that therapies must be primarily astrocyte-targeted. The most effective interventions are axis-specific and act secondarily on astrocytic function.
4. **No immediate clinical application.** The model is a theoretical synthesis, not a treatment guideline. It generates hypotheses, not therapy recommendations.
5. **No pharmacological advertising.** Mentions of GLP-1 agonists, spermidine, rapamycin, lithium, TREM2 agonists or APOE2 gene therapy are referenced as mechanistically or empirically relevant, not as recommendations.
6. **Genetic vulnerability is not destiny.** Even ApoE4/4 homozygotes remain cognitively intact into old age in 40–50 % of cases. Lifestyle modification has real effects.
7. **Social stratification is not a complete explanation.** The structural reading in Section 9 makes statistical gradients visible; it does not absolve the individual of responsibility for life conduct.
8. **The 10th axis, lipid metabolism, is a modeling decision, not an ontology.** Other modelers could embed lipid effects in axes 7 or 8. The decision made here rests on the clarity of the ApoE data; it is not compulsory.

9. **The astrocyte-microglia dyad is a simplification.** Oligodendrocytes (myelination), pericytes (BBB integrity), endothelial cells, T cells (adaptive immunity) are involved. The dyad is singled out because it directly couples the most axes; it is not the only relevant cell system.
 10. **The phenomenological-systems-theoretical framing is a choice of language, not an ontology.** It is offered because it is more consistent with Friston-FEP, Foerster/Maturana and RDoC/HiTOP than the defect language. It is not “the truth about dementia”. Clinical suffering remains real and severe.
 11. **No anti-psychiatry appropriation.** The coordination reading does not play diagnostic and therapeutic practice against the phenomenology of the disease. Foucault, Laing and Szasz formulated important institutional critiques; the position held here is not identical with them.
 12. **No romanticism.** Tom Kitwood and others developed person-centered care; that is important. A romanticizing variant (“spiritual journey”, “expansion of consciousness”) is not held here. Dementia is a serious disease.
 13. **Stochasticity of manifestation is an acknowledgment of complexity, not a renunciation of explanation.** Section 6 concedes that the model does not fully explain the heterogeneity of manifestation. This is a limitation, not a merit.
 14. **The psychodynamic reading remains speculative.** In predecessor material collections (v0.6 §3.5) a psychodynamic co-reading (dementia as a second-order defense formation, Hinze 1987, Le Gouès 1991) was hinted at. It is not central here because it is not empirically supported to the same degree as the biomedical axes.
 15. **Falsifiability.** If empirical findings show that clinical dementia frequently occurs without axis convergence — that is, that mono-axis courses are the rule — the model would need to be revised. Section 12 lists 21 such touchstones.
-

14. Discussion: Relationship to Alternative Models

Relationship to the amyloid cascade hypothesis. The coordination model is not intended as a competitor. It embeds the amyloid hypothesis: in familial AD and in a subgroup of sporadic cases A β is a primary cause; in the majority it is an indicator and amplifier. The heterogeneity of ordering that became visible in the AA-2024 validation study becomes an expected property rather than an anomaly.

Relationship to the vascular hypothesis. The CATCH hypothesis (de la Torre) is retained as axis 7 and specified through coupling to glymphatic (5), inflammation (8) and energy (3). AD and vascular dementia are not separate entities but endpoints of a multi-axis coordination shift.

Relationship to the diabetes-type-3 hypothesis. De la Monte & Wands’ hypothesis is integrated as axis 3, specified through the glycation axis (4) and the cardiovascular axis (7).

Relationship to the infection hypothesis. Itzhaki et al. (1997) and others have posited infectious pathogens as triggers of AD. The model treats infections as an inflammation entry channel (axis 8) — relevant for a subgroup, not universally pathogenic.

Relationship to the inflammation hypothesis. Heneka et al. (2015) formulated neuroinflammation as a central mechanism. The model retains inflammation as axis 8 with a central position (NLRP3, A1 astrocytes, DAM) but specifies the position — inflammation is not the sole cause, but one of ten axes whose coupling with the astrocyte-microglia dyad is especially dense.

Relationship to the Lancet Commission risk-factor list. The 14 Lancet factors are fully compatible with the model; almost every one can be assigned to one or more axes. The model complements the list through an underlying cellular reference principle, the explicit polypharmacology multiplier axis, the glymphatic and nitrogen axes, and the salutogenic reading.

Relationship to the Free Energy Principle. The model is conceptually connectable to Friston's FEP. An application of FEP to dementia is pending but implicitly laid out — the four coordination manifestations can be understood as changes in the precision distribution of the Bayesian-updating system.

What the coordination model contributes. Four specific contributions: integration of ten parallel research lines within one theoretical framework; clinical phenotyping with ApoE stratification; falsification operationalization with 21 testable points; a phenomenological-systems-theoretical framing that makes the model consistent with Friston, Foerster/Maturana and RDoC/HiTOP.

15. Conclusion

Clinical dementia in the AD-typical and mixed sense is most probably a coordination shift of the astrocyte-microglia dyad across several of ten biologically and socially grounded axes, amplified by polypharmacological multiplication. ApoE-ε4 acts as a systemic modifier, primarily via the lipid-metabolism axis. Clinical manifestation typically occurs when three or more axes slip simultaneously into the acquired or subclinical range. The heterogeneous manifestation under comparable axis burden is explained via four realization conditions: life-event contingency, microvascular stochasticity, socio-emotional buffering capacity and neuronal reserve variability.

Anti-Aβ mono-therapies are only modestly effective clinically because other axes remain untouched. Multi-axis diagnostics and multimodal intervention (FINGER line, genotype-stratified) are the rational consequence. A salutogenic reading — what maintains coordination under chronic burden? — is proposed as a complementary research strand.

The binary dementia diagnosis is a threshold-setting within a continuous space of variability. It is clinically and institutionally necessary, but its operationalized character remains visible in the model. Dementia has a social stratification that is structurally mediated, without replacing the biological mechanisms.

The model is presented as a theoretical synthesis — not an RCT, not primary empirics, but a systematized theory with 21 clearly formulated testable predictions. Its value will prove itself in the empirical testability of these predictions.

The phenomenological-systems-theoretical framing is a choice of language, not an ontology. It is offered because it keeps the model compatible with established research traditions (Friston-FEP, Foerster/Maturana, RDoC/HiTOP) and avoids the ontological foreshortenings inherent in the previous defect language. Clinical

suffering, care dependency and the burden on relatives are in no way relativized by this choice of language. Convergence failure is now called a coordination shift; the pain it brings remains the same.

The most effective dementia prevention at the population level is presumably political (education, social, environmental policy) and not primarily pharmacological. At the individual level, multi-axis risk reduction remains the rational strategy — dependent on structural preconditions that the model cannot itself create. The salutogenic question — what maintains coherence under chronic burden? — deserves research funding of its own.

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(NOTE reference verification — T1 COMPLETE (2026-09-28): all 97 references checked and sourced. 71 GREEN, 10 books/reports hand-checked, 8 misattributed corrected, 8 unlocatable replaced with real, verified substitute sources (Hauglund→Kress/Illiff 2014, Wang→Front Genet 2022, Peng→Arnold 2018, Münch→Vitek 1994, Bunch 2019→2010, Wong→Cannon 2017, Yan→Galectin-3 review 2022, Sekita→Brodaty 2020). No entry without a verifiable source. The author lists of the two previously PMID-identified substitute sources (#13 Chen/Wang/Huang/Jia; #40 García-Revilla et al.) were completed on 2026-09-29 from the primary sources. Newly added (2026-09-29): #98 to update the F20 trial status (AL002/INVOKE-2, negative result). F18/F20 trial statuses updated against ClinicalTrials.gov/primary publications. T2 (does the source carry the claim) completed at the load-bearing points (2026-09-29, see T2 statement-check). Publication target: syntagma-science (platform-centred); strand FORSCHUNG/NEUROMETABOLICA, identifier slug neurometabolica-wp; English full translation delivered. Released — upload by author. See T1 verification protocol.)

Appendix A: Cross-reference to predecessor works

Version	Stage	Content	Integrated into WP v0.2 section
v0.1	Material collection	Metabolic axes	\$3.3 axes 1, 2
v0.2	Material collection	UCDs, cancer, diabetes type 3	\$3.3 axes 2, 3
v0.3	Material collection	Sleep, glymphatic, USWS	\$3.3 axes 5, 6
v0.5	Synthesis	First six-axis synthesis	\$4 (deepened)
v0.6	Material collection	Pharma, cardio, social/psychodynamic	\$3.3 axes 7, 8, 9; \$3.4
v0.7	Synthesis	Nine-axis full synthesis	\$3, \$4, \$8, \$10
v0.8	Material collection	Microglia, microbiome, ApoE-ε4	\$4, \$5, \$3.3 axis 10
v0.9	Synthesis	Ten-axis synthesis, dyad, ApoE stratification	\$3, \$4, \$8
v0.10	Material collection	Coordination, continuum, stochasticity	\$2.5, \$5.6, \$6, \$7, \$11
WP v0.1	(withheld)	Earlier form	not published
WP v0.2	Threshold A	Theoretical Synthesis Paper	—

Appendix B: What changed relative to WP v0.1

WP v0.1 was prepared after v0.9, then recognized as incomplete through a voice-memo input of 2026-05-27 and withheld. The phenomenological-systems-theoretical lens worked out in v0.10 was missing. WP v0.2 differs from WP v0.1 in five points:

1. **Title.** “Convergence failure” → “coordination shift”.
2. **Model language throughout.** “Failure” replaced by “mode shift” where appropriate. Four manifestations formulated explicitly as a mode reading (\$5.6).
3. **New Section 2.5.** Phenomenological-systems-theoretical framing (Friston, Foerster/Maturana, RDoC/HiTOP) as a methodological section.
4. **New Section 6.** Stochasticity of manifestation as the eleventh theoretical component.

5. **New Section 7.** Threshold-setting as a methodological task (interface with dimensional psychiatry).
 6. **New Section 11.** Salutogenic reading as a complementary research strand.
 7. **Falsification point F21** on salutogenesis research added.
 8. **Limitations expanded** with points on the phenomenological framing (points 10, 11, 12, 13).
-

Appendix C: Short glossary

- **A1/A2 astrocytes:** Reactive astrocyte modes (Liddelow 2017). A1 induced by activated microglia, neurotoxic. A2 induced by ischemia, rather protective.
 - **ACSL1:** Acyl-CoA synthetase long-chain 1. Marker for lipid-droplet-accumulating microglia in ApoE4 (Haney 2024).
 - **AGEs:** Advanced glycation end products.
 - **Active inference:** Friston tradition: living systems minimize prediction error via Bayesian updating and action adaptation.
 - **AQP4:** Aquaporin-4. Water channel on astrocytic endfeet, central to glymphatic function.
 - **ARIA:** Amyloid-related imaging abnormalities.
 - **DAM:** Disease-associated microglia.
 - **CATCH:** Critically Attained Threshold of Cerebral Hypoperfusion.
 - **FEP:** Free Energy Principle (Friston).
 - **FINGER:** Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability.
 - **HiTOP:** Hierarchical Taxonomy of Psychopathology.
 - **Coordination shift:** Mode shift of a cellular or physiological system under burden; a non-defect-oriented choice of language.
 - **LDAM:** Lipid-droplet-accumulating microglia.
 - **NLRP3:** Inflammasome complex.
 - **RDoC:** Research Domain Criteria (NIMH).
 - **Salutogenesis:** Antonovsky concept; the question of health-maintaining factors.
 - **SCFA:** Short-chain fatty acids.
 - **Stochasticity of manifestation:** eleventh theoretical component; realization conditions that decide whether an axis profile becomes clinically manifest.
 - **TMAO:** Trimethylamine-N-oxide.
 - **TREM2:** Triggering Receptor Expressed on Myeloid cells 2.
-

Appendix D: Self-audit (WORKSHOP LINE v1.3)

- A4 trace separation: FORSCH only. ✓
- A5 session audit (2026-05-27): WP v0.2 distills v0.1–v0.10, all the same strand NEUROMETABOLICA. ✓
- B5 source obligation: ~97 core references 1979–2025, peer-reviewed dominated. ✓
- B13 anti-conspiratorial: §9 structural, not conspiracy-theoretical. ✓
- Threshold: A (in content). ✓ Released for syntagma-science (upload by author) — T1 complete (97/97 sourced, 2026-09-28), T2 load-bearing points (2026-09-29), F18/F20 trial statuses updated, English full translation delivered. Identifier: slug

neurometabolica-wp.

- Naming: NEUROMETABOLICA retained. ✓
- C20 cross-reference index: Appendix A. ✓
- Objectivity rule v1.3: end-check passed. ✓
- Naturalistic fallacy blocked on both sides: §9, §13 points 6, 7, 10, 11, 12. ✓
- Closure function: §15. ✓
- Tom's voice-memo input of 2026-05-27 cleanly documented as phenomenological stimulus (Acknowledgements; v0.10 as cross-reference). ✓

*Working Paper v0.2 (English translation), Threshold A, strand
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6747 · forschung@tschueller.com · CC BY 4.0 · privately funded, independent ·
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(upload by author). In case of doubt, the German master is authoritative.*