**Supplementary Materials**

**Table 1: Summary of Neurotrophic Factors and Their Functions in Cognitive Health**

|  |  |  |  |
| --- | --- | --- | --- |
| Neurotrophin | Primary Receptor | Key Functions | Relevance to AD |
| BDNF | TrkB | Synaptic plasticity, LTP, dendritic spine formation | Reduced in the AD brain; correlates with cognitive decline |
| NGF | TrkA | Cholinergic neuron support, basal forebrain maintenance | Critical for the cholinergic system affected early in AD |
| IGF-1 | IGF-1R | Neurogenesis, metabolic support, Aβ clearance | Decreased signaling in aging and AD |
| NT-3 | TrkC | Neuronal survival, synaptic maturation | Supports neuronal populations vulnerable in AD |
| NT-4/5 | TrkB | Similar to BDNF, neuronal survival | Potential compensatory mechanism |

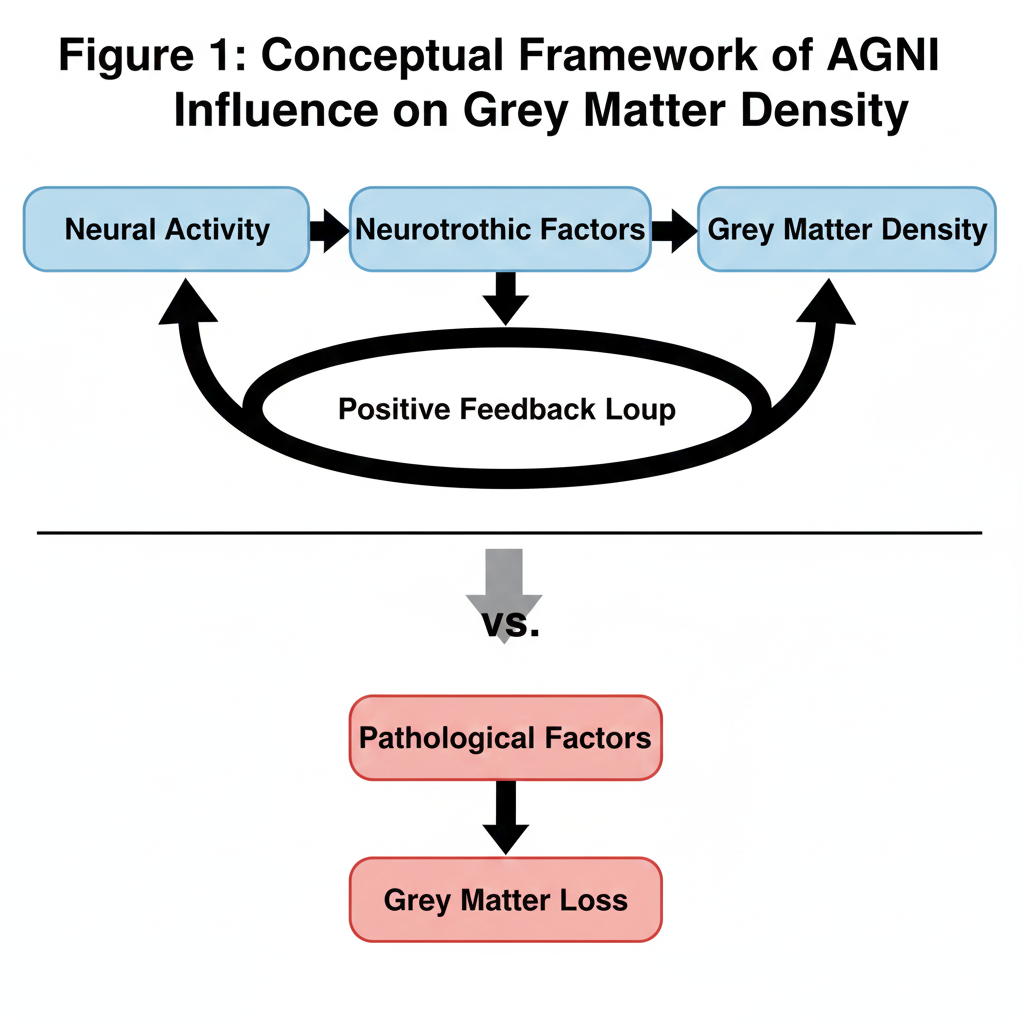
**Table 2: AGNI Components and Their Measurable Indicators**

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| --- | --- | --- | --- |
| AGNI Component | Frequency/Mechanism | Measurement Method | Clinical Significance |
| Gamma Oscillations | 30-100 Hz (peak 40 Hz) | EEG, MEG, LFP | Reduced in AD; correlates with cognition |
| Theta Oscillations | 4-8 Hz | EEG, intracranial recordings | Memory encoding; hippocampal integrity |
| Homeostatic Plasticity | Synaptic scaling | Ex vivo recordings, molecular markers | Network stability; compensation failure |
| STDP | Millisecond spike timing | Multi-electrode arrays, modeling | Learning mechanisms: synaptic refinement |
| Slow-Wave Activity | 0.5-4 Hz | Sleep EEG, intracranial | Memory consolidation; metabolic clearance |

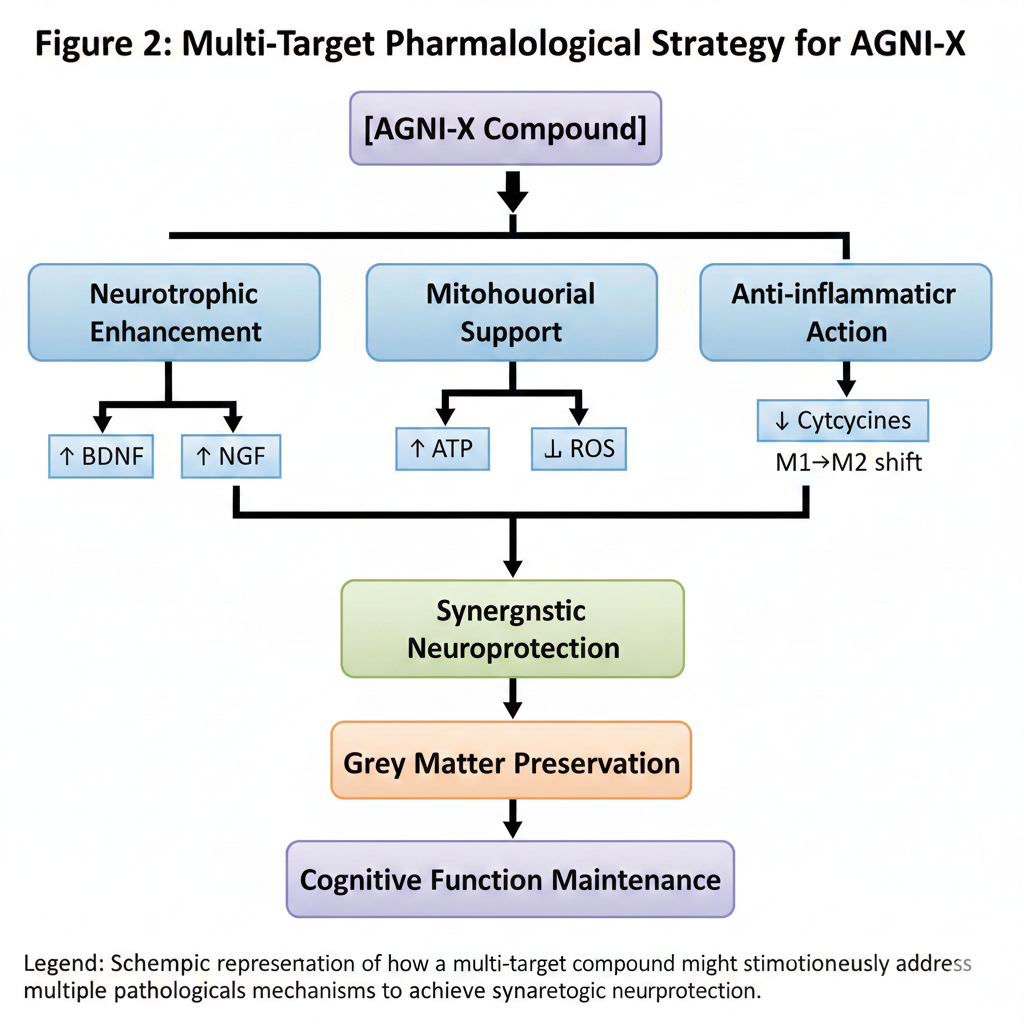
**Table 3: Theoretical Translation Probabilities for AGNI-X Development**

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| --- | --- | --- | --- |
| s | Success Probability | Cumulative Probability | Key Challenges |
| In Vitro Cellular Studies | 10-30% | 10-30% | Target validation, cellular model relevance |
| Animal Model Efficacy | 20-40% | 2-12% | Species differences, model limitations |
| Human Clinical Benefit | 10-20% | 0.2-2.4% | Heterogeneity, outcome measures, and BBB penetration |

**Figure 1: Conceptual Framework of AGNI Influence on Grey Matter Density**

**Legend:** The diagram illustrates the proposed relationship where neural activity stimulates neurotrophic factor production, which enhances grey matter density, creating a positive feedback loop. This constructive cycle competes against pathological factors that drive grey matter loss.

**Figure 2: Multi-Target Pharmacological Strategy for AGNI-X**

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**Legend:** Schematic representation of how a multi-target compound might simultaneously address multiple pathological mechanisms to achieve synergistic neuroprotection.

**Figure 3: Proposed Grey Matter Dynamics Over Time**

Grey Matter Density (G)

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│ Normal Aging

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│ AD Pathology (Untreated)

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│ Hypothetical AGNI-X Intervention

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Youth Middle Age Elderly

**Legend:** Conceptual trajectories of grey matter density across lifespan under three scenarios: normal aging, untreated AD pathology, and hypothetical AGNI-X intervention. The intervention scenario shows attenuated decline compared to untreated AD.