

Hypothesis

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Hypothesis

Proposing A Novel Glutamatergic Regimen as a Missing Link in ADHD Treatment

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is now viewed less as a single catecholamine deficit and more as a timing error in the dialogue between dopamine (DA) and glutamate. Although psychostimulants offer robust symptom relief, many adults continue to report executive dysfunction and "brain fog." This article explores whether the oral "Cheung Glutamatergic Regimen"—originally designed to replicate ketamine-like neuroplasticity—could close that therapeutic gap. After summarising evidence on disrupted DA–glutamate coupling in ADHD, the paper outlines two stimulant-specific adaptations of the Cheung protocol: (a) methylphenidate paired with piracetam, and (b) amphetamine combined with dextromethorphan and piracetam. The discussion concludes with pharmacokinetic cautions surrounding CYP2D6 inhibition and suggestions for future research.

Keywords: ADHD; NMDA; AMPA; cognitive; neuroplasticity; glutamatergic

Introduction

Standard ADHD pharmacotherapy has long centred on boosting synaptic DA and norepinephrine. Over the past decade, however, converging data indicate that symptoms also reflect a mis-paced exchange between DA and glutamatergic circuits in the prefrontal cortex [1,2]. Stimulants normalise this interaction to a degree, yet residual cognitive complaints are common. Ketamine research offers a clue: mood and cognition can improve rapidly once synapses shift from an "NMDA-dominant" to an "AMPA-dominant" state [3].

Ngo Cheung recently proposed a four-component, all-oral stack—dextromethorphan (DXM), a CYP2D6 inhibitor, piracetam, and L-glutamine—that aims to mimic ketamine's full plasticity cascade [3]. The present paper considers whether that framework, with stimulant-specific adjustments, might target the lingering deficits in adults with ADHD.

Dopamine–Glutamate Coupling in ADHD

In the healthy prefrontal cortex (PFC), DA modulates excitatory drive by steering AMPA and NMDA receptor function. Activation of D1 receptors recruits protein kinase A, prompting GluA1-containing AMPA receptors to insert into the postsynaptic membrane—a prerequisite for long-term potentiation [4]. D2 signalling plays the foil, constraining over-excitation [5].

Evidence of Mis-timed Signalling Animal work supports the notion of a coupling error. Spontaneously hypertensive rats (SHR), commonly utilized as a model for ADHD, exhibit increased AMPA-dependent norepinephrine release while demonstrating diminished NMDA-mediated calcium influx [6,7]. The human DRD4 7-repeat allele diminishes NMDA receptor activity in prefrontal cortex neurons at the genetic level [8]. In summary, these results show that ADHD is a condition in which DA does not align NMDA and AMPA throughput, which makes network plasticity less effective.

Why AMPA Enhancement and NMDA Modulation Are Important

An expanding corpus of research on rapid-acting antidepressants indicates that sustained symptom alleviation occurs subsequent to a pronounced shift towards AMPA signaling, alongside a transient reduction of NMDA noise [3,9]. In rodent studies, the inhibition of AMPA receptors negates the behavioral advantages of ketamine, while positive AMPA modulators replicate these effects [10].

Memantine, an uncompetitive NMDA antagonist, already shows promise in ADHD [11]. These observations imply that a therapy combining modest NMDA antagonism with AMPA potentiation could accelerate synaptic repair in ADHD, especially for patients whose stimulant response is incomplete.

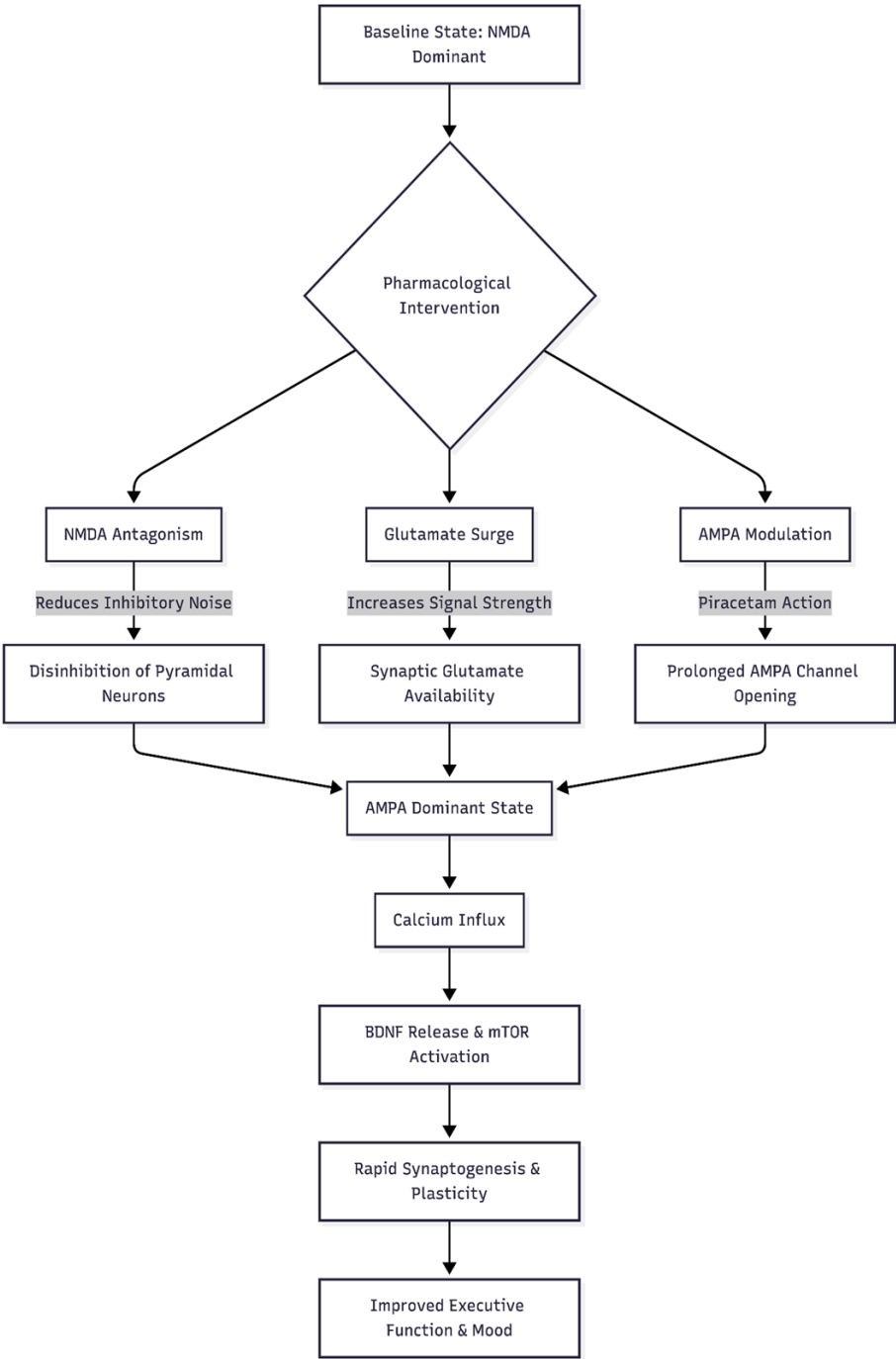


Figure 1. This flowchart demonstrates the theoretical "Cheung Glutamatergic Regimen" mechanism, showing how the different components interact to shift the brain state from NMDA-dominant to AMPA-dominant.

The Original Cheung Glutamatergic Regimen

Cheung's protocol pairs four low-cost agents [3]:

- Dextromethorphan (DXM) – delivers a rapid but short-lived NMDA block.
- A strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine) – prolongs DXM exposure.
- Piracetam – a positive allosteric modulator (PAM) at AMPA receptors, keeping channels open longer.
- L-glutamine – replaces presynaptic glutamate stores and buffers excitotoxic spikes.

The sequence unfolds as follows: NMDA inhibition lowers baseline noise; pyramidal neurons discharge a glutamate pulse; piracetam heightens AMPA throughput; calcium entry releases BDNF and activates mTOR; rapid synaptogenesis follows [12]. In principle, the same cascade might restore PFC network efficiency in ADHD.

Adapting the Regimen for Stimulant Classes

Modification A: Methylphenidate Plus Piracetam (± Glutamine)

Therapeutic doses of methylphenidate (MPH) raise extracellular glutamate in the PFC by roughly 20–40 % through D1-ERK pathways [13]. The increase is transient—plasma clearance occurs within three hours—limiting excitotoxic risk. Hence, MPH itself can supply the "push," rendering high-dose DXM unnecessary.

Piracetam, the "pull," slows AMPA receptor desensitisation and boosts conductance [14]. Stacking the two may sharpen executive functions and lift motivational tone. L-glutamine can be included for patients under chronic stress whose glutamate reserves are depleted [15].

Dosage sketch: MPH at the individual's established dose; piracetam 600-1200 mg/day in divided doses; optional L-glutamine 500-1000 mg/day.

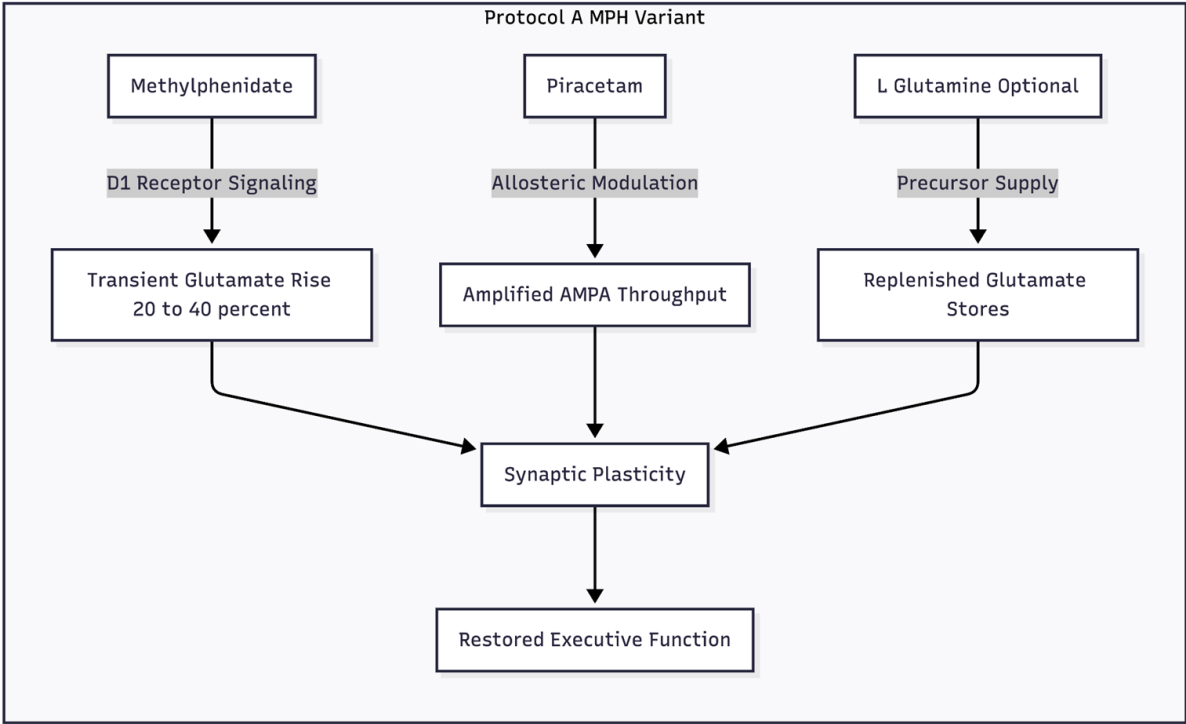


Figure 2. This diagram illustrates the specific adaptation for patients taking Methylphenidate, highlighting why DXM is removed and how the stimulant provides the glutamate "push."

Modification B: Amphetamine + DXM + Piracetam (± Glutamine)

Amphetamines provoke larger, longer glutamate surges—often doubling extracellular levels for 6–12 h [16]. If piracetam were added alone, sustained AMPA opening could tip neurons toward calcium overload. Introducing DXM provides a concurrent NMDA "brake," trimming calcium influx while still permitting AMPA-mediated plasticity.

Dosage sketch: standard amphetamine prescription; DXM 45–60 mg timed-release (no CYP2D6 booster to avoid amphetamine toxicity); piracetam 1,200 mg twice daily; optional L-glutamine as above.

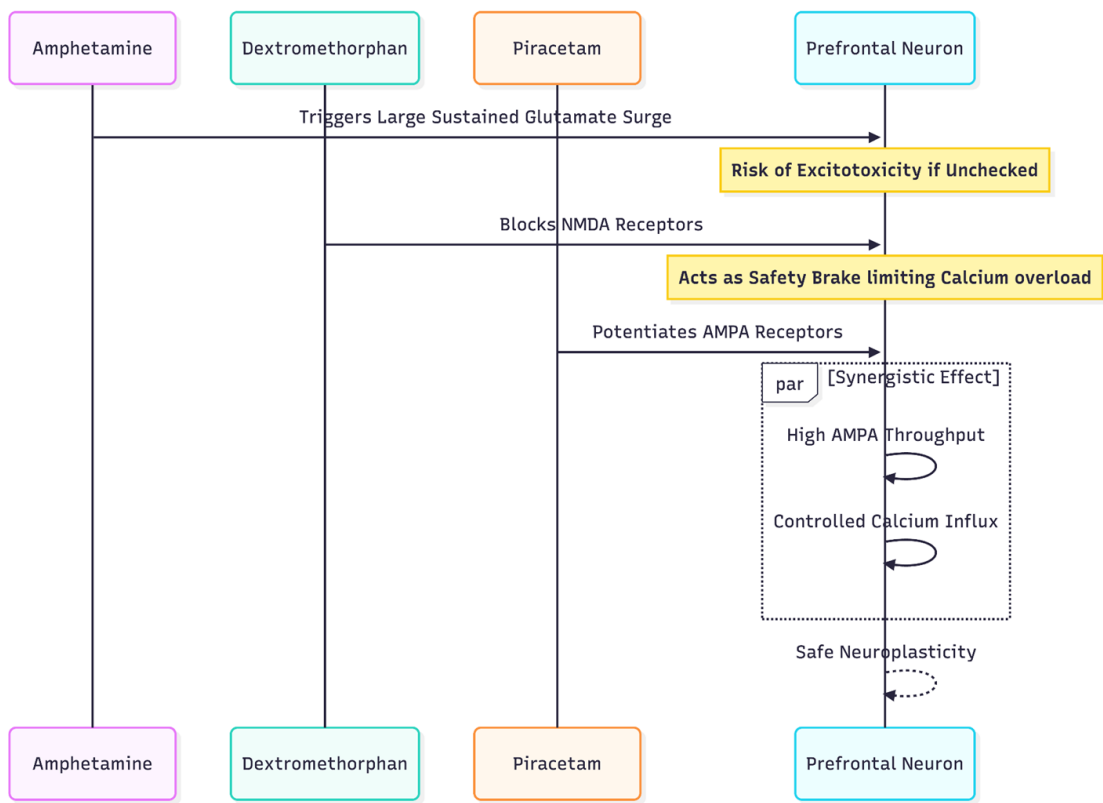


Figure 3. This diagram illustrates the more complex adaptation for Amphetamine users, emphasizing the necessity of adding DXM as a safety brake against excitotoxicity due to the stronger glutamate surge caused by amphetamines.

Pharmacokinetic Caveats: The CYP2D6 Constraint

DXM and many amphetamines share CYP2D6 metabolic pathways. Strong inhibitors such as fluoxetine, paroxetine, or bupropion can elevate blood levels of both drugs, risking hypertension or serotonergic toxicity [17]. Therefore, the MPH-piracetam plan may safely pair with CYP2D6 inhibitors if DXM is omitted. By contrast, the amphetamine-based protocol should avoid additional CYP2D6 blockade unless the patient is considered a CYP2D6 fast metabolizer.

Clinical Evidences

Preliminary case observations endorse the MPH-piracetam combination: one adult with ADHD indicated that the addition of 1,200 mg piracetam to 18 mg MPH reinstated sustained attention and motivation; the benefits dissipated upon withdrawal and re-emerged upon rechallenge [18]. A small controlled trial also found that cognitive scores were better when piracetam was added to stimulant therapy [19]. The next step is to do a lot of testing.

Conclusion

A growing literature frames ADHD as a disorder of DA-guided glutamatergic timing. The Cheung Glutamatergic Regimen offers a mechanistic blueprint—brief NMDA dampening, amplified AMPA drive, and replenished glutamate stores—for correcting that timing. With stimulant-specific adjustments, the protocol could alleviate residual cognitive symptoms while avoiding excitotoxic pitfalls. Prospective trials will determine whether this hypothesis translates into everyday clinical benefit.

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