THE NMDA RECEPTOR MODULATOR NYX-458 RESULTS IN LONG-LASTING IMPROVEMENT IN SEVERAL COGNITIVE DOMAINS IN A PRIMATE MODEL OF PARKINSON'S DISEASE COGNITIVE IMPAIRMENT

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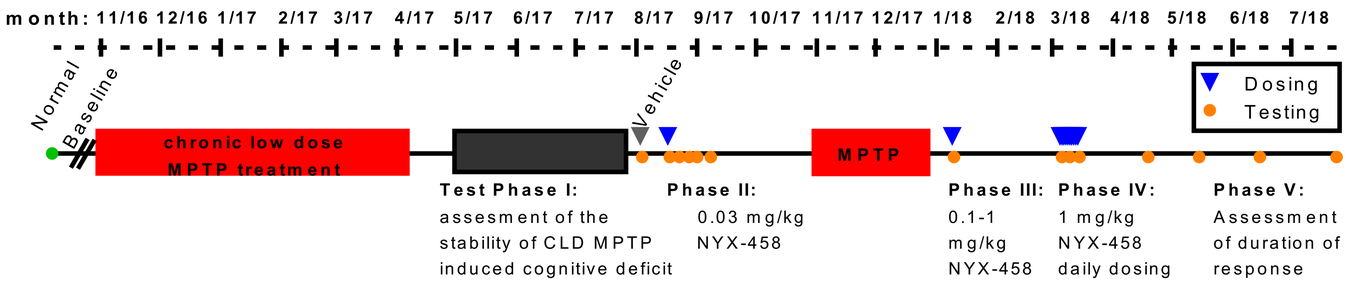
INTRODUCTION: NYX-458 is an orally available N-methyl-D-aspartate receptor (NMDAR) modulator with a favorable safety and PK profile (see poster #521). NYX-458 enhances long-term potentiation and facilitates synaptic plasticity processes in the brain resulting in cognitive enhancement in several rodent models. In Parkinson's disease (PD), dopaminergic cell loss leads to NMDAR dysregulation, dysfunctional synaptic plasticity, and cognitive deficits. As such, NMDAR modulation with NYX-458 could be an effective approach to treating PD cognitive impairment (PD-CI). NYX-458 was evaluated in a chronic low-dose MPTP non-human primate (NHP) model of PD-CI. NHPs were assessed for performance in the variable delayed response (VDR; attention and working memory) and simple discrimination reversal (SDR; cognitive flexibility) tasks after acute and chronic dosing of NYX-458.

Experimental Timeline:

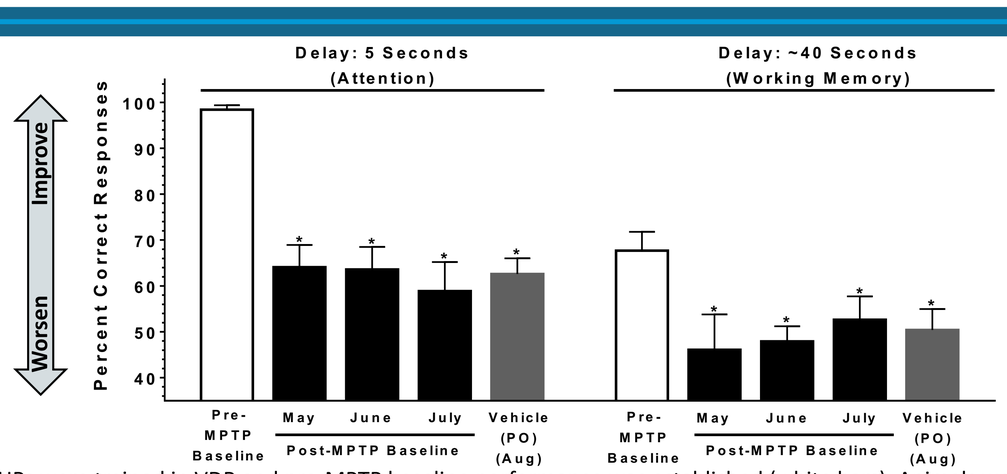


METHODS: NHPs were trained to perform VDR and SDR tasks. MPTP was then administered until stable cognitive deficits were induced (Phases I). NHPs were assessed for cognitive improvement following treatment with NYX-458 (0.03 mg/kg, PO, Phase II). Additional MPTP was administered to induce further cognitive deficit and effect of NYX-458 (0.1-1.0 mg/kg; Phase III) in re-establishing cognitive improvement was assessed. Finally, NYX-458 was assessed after 10 daily doses (1 mg/kg, PO; Phase IV) and after drug was withdrawn to examine duration of response (Phase V).

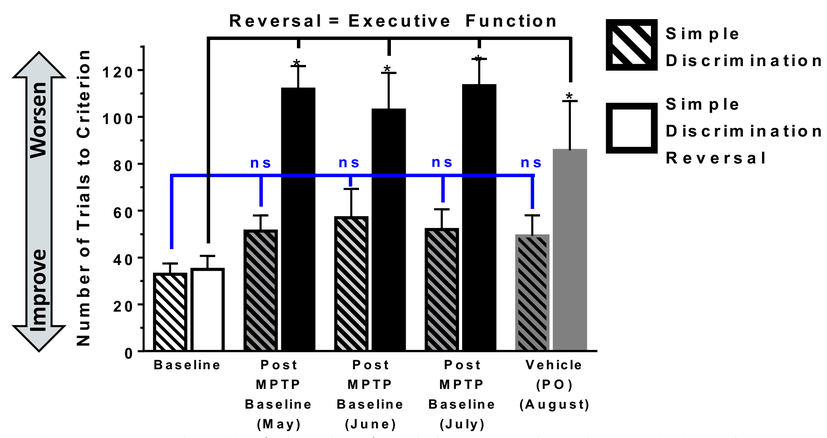
Variable Delayed Response (VDR)

Simple Discrimination Reversal (SDR)

Phase I: Chronic low-dose MPTP in the NHP results in stable cognitive deficits akin to that seen in Parkinson's cognitive impairment

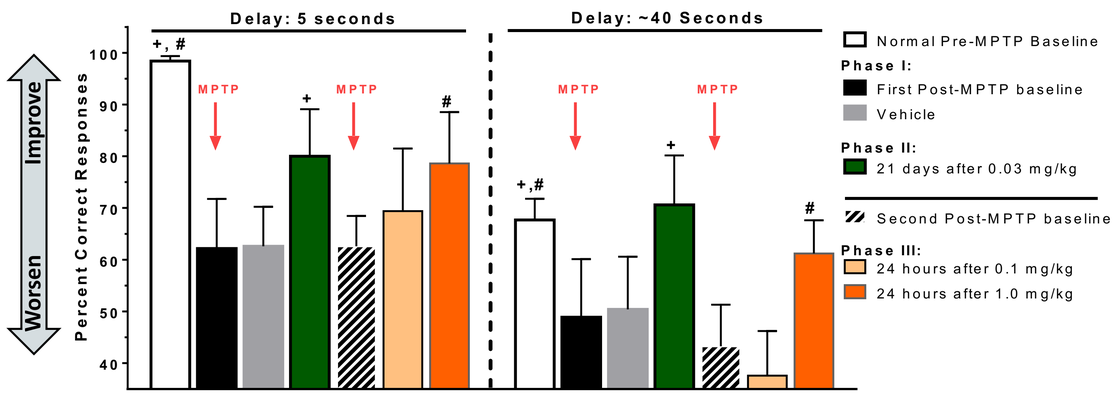


Phase I VDR: NHPs were trained in VDR and pre-MPTP baseline performance was established (white bars). Animals were given low-dose MPTP until cognitive deficits apparent. MPTP dosing was stopped and animals continued testing over 3 months to confirm stable deficits in VDR performance (black bars). Animals were orally dosed with vehicle to confirm no effect on performance (grey bars). *p<0.05, compared to pre-MPTP baseline.

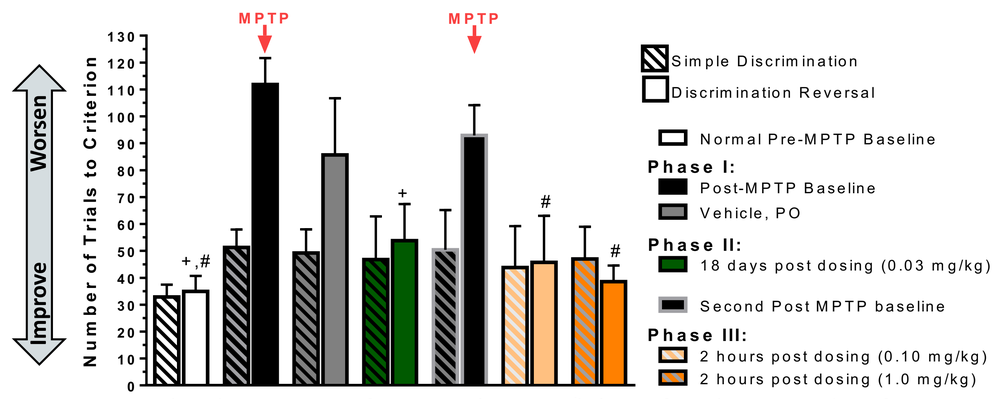


Phase I SDR: NHPs were trained in SDR (white bars) and then given low-dose MPTP until cognitive deficits apparent. MPTP dosing was stopped and cognitive performance evaluated over 3 months (black bars). Animals were then given vehicle (grey bars). *p<0.05, compared to pre-MPTP baseline.

Phase II and III: NYX-458 administration resulted in long-lasting improvement in cognitive performance that was reproduced after further MPTP-induced impairment

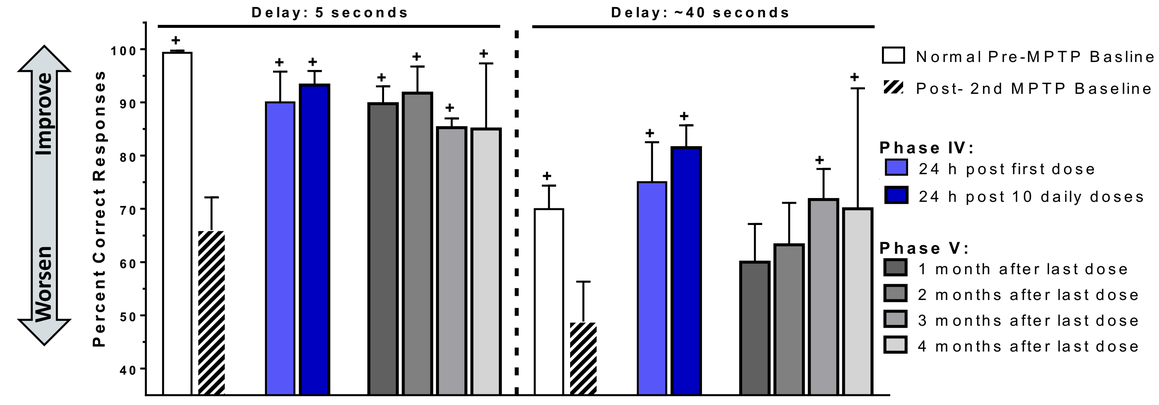


Phase II VDR: A single administration of NYX-458 (0.03 mg/kg) significantly improved performance with both short and long delay lengths for at least 3 weeks post-administration (green bars). **Phase III VDR:** A 2nd round of MPTP resulted in further cognitive deficit (striped black bar). Administration of 0.1 mg/kg NYX-458 had no change on VDR performance (light orange bar) while administration of 1.0 mg/kg resulted in significant improvement (dark orange bar). +p<0.05 vs. initial MPTP baseline; #p<0.05 vs. second MPTP baseline

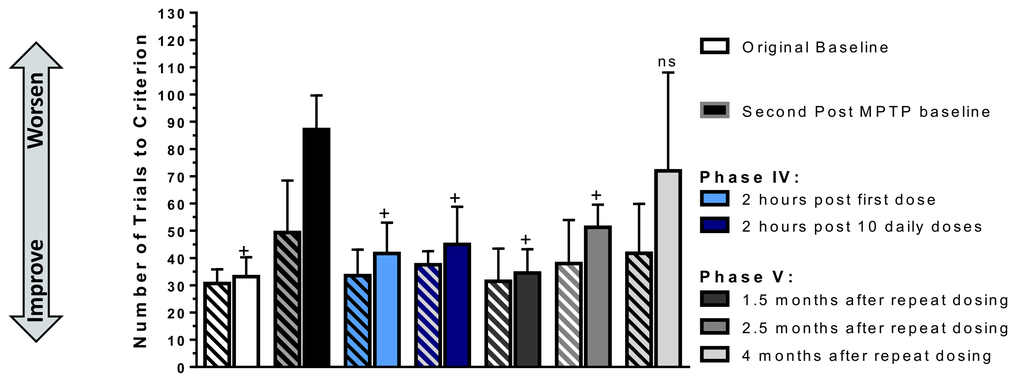


Phase II SDR: A single administration of NYX-458 (0.03 mg/kg) significantly improved performance in discrimination reversal with no effect on simple discrimination (green bars). **Phase III SDR**: A 2nd round of MPTP resulted in further deficit in discrimination reversal (black bar with grey outline). Administration of 0.1 (light orange) or 1.0 (dark orange) mg/kg NYX-458 significantly improved performance in discrimination reversal. +p<0.05 vs. initial MPTP baseline; #p<0.05 vs. second MPTP baseline

Phase IV and V: The effect of NYX-458 on cognitive improvement is maintained with repeat daily administration and is stable for 3 months after drug withdrawal



Phase IV VDR: Animals were administered 10 daily doses of NYX-458 and demonstrated significant improvement in both short and long delay lengths that was maintained through the 10th daily dose (blue bars). **Phase V VDR**: Animals were re-assessed monthly for 4 months after their last administration of NYX-458. Improvement continued for 4 months. +p<0.05 vs. second MPTP baseline



Phase IV SDR: Animals were administered 10 daily doses of NYX-458 and demonstrated significant improvement in discrimination reversal that was maintained through the 10th daily dose (blue bars). **Phase V SDR:** Animals were re-assessed at 1.5, 2.5 and 4 months after their last administration of NYX-458. By 4 months post-administration animal performance was no longer significantly improved. +p<0.05 vs. second MPTP baseline

CONCLUSIONS

- Chronic low-dose MPTP administration in the non-human primate causes deficits in attention, working memory, and executive function similar to that seen in Parkinson's cognitive impairment
- NYX-458 administration results in a robust, long-lasting and reproducible improvement in cognitive performance in MPTP-treated NHPs
- NYX-458 does not exacerbate MPTP-induced motor disturbances or interfere with the anti-Parkinsonian activity of L-dopa in non-human primates with MPTP-induced motor deficits (see poster 521)
- **NYX-458 may be a well-tolerated and effective therapeutic for Parkinson's disease cognitive impairment**

FINANCIAL DISCLOSURES

A. Barth, A. Khan, J. Moskal, and C. Cearley are employees of Aptinyx