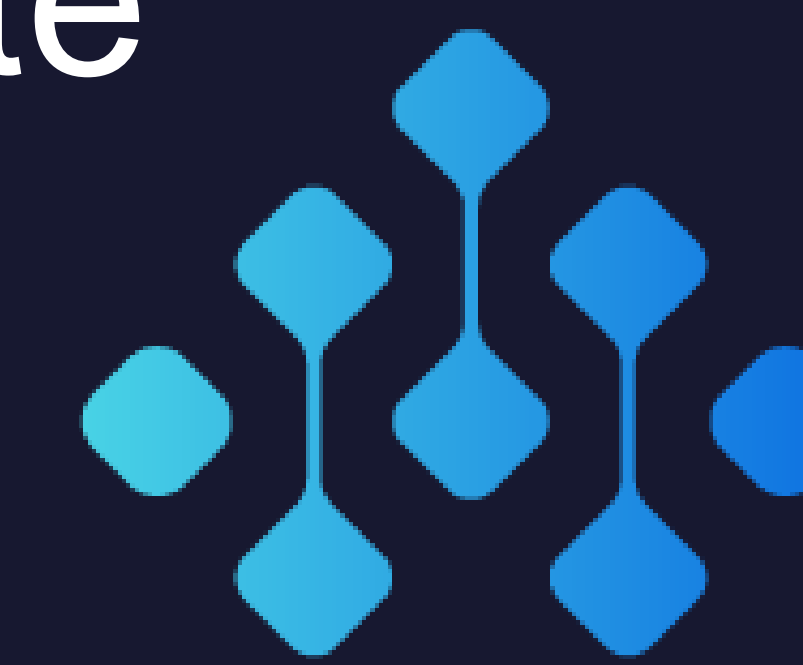


Effects of ATH434, a Clinical-Phase Small Molecule with Moderate Affinity for Iron, in Hemiparkinsonian Macaques

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Alterity
THERAPEUTICS

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INTRODUCTION

ATH434 is a novel brain-penetrant iron-binding small molecule currently in phase 2 clinical trials for Multiple System Atrophy (MSA) based on efficacy in multiple murine parkinsonian models. In Parkinson's disease (PD)¹ and MSA² models, ATH434 reduced disease-related excess substantia nigra (SN) iron and aggregated α -synuclein. ATH434 is postulated to redistribute excess labile cellular iron, facilitating its export. Contrary to high-affinity iron chelators previously tested in PD, ATH434's moderate iron affinity precludes it from interfering with endogenous iron trafficking proteins such as transferrin.

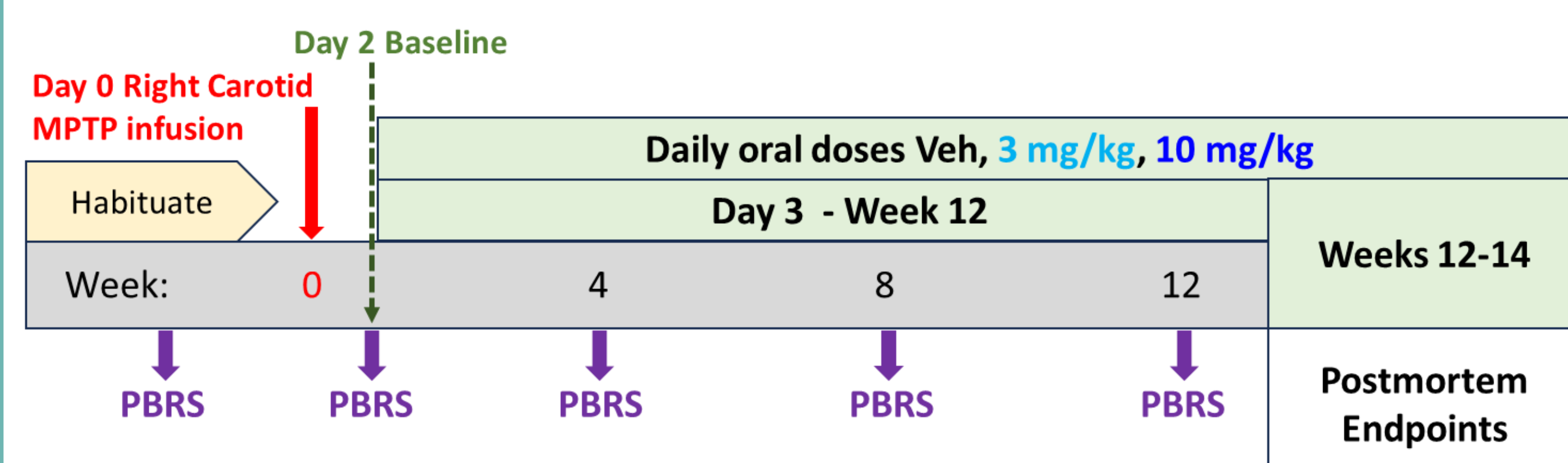
OBJECTIVES

- Determine whether orally-dosed ATH434 improves motor performance in a nonhuman hemiparkinsonian model of PD when administered after symptom onset.
- Relate clinical observations to changes in brain iron, synaptic integrity, and tyrosine hydroxylase positive (TH+) neurons.

METHODS

MPTP Model

- Single right carotid artery injection of MPTP on Day 0
- Parkinson Behavior Rating Scale (PBRS) assessed 5 times: prior to MPTP, Day 2 (pre-dose Baseline), during dosing (Weeks 4, 8, 12)
- Side Specific Motor, General Motor, General Behavior
- \uparrow scores = worse symptoms
- 12 macaques selected for study based on Baseline PBRS
- Daily oral doses of vehicle or ATH434 (3 or 10 mg/kg): Day 3 to Wks 12-14

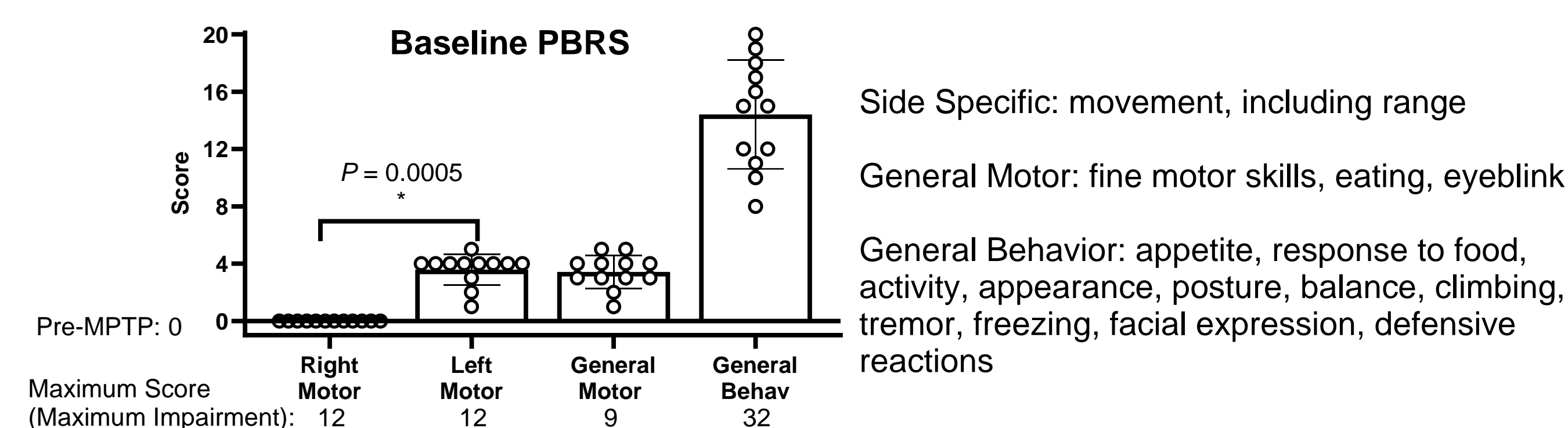


Postmortem endpoints

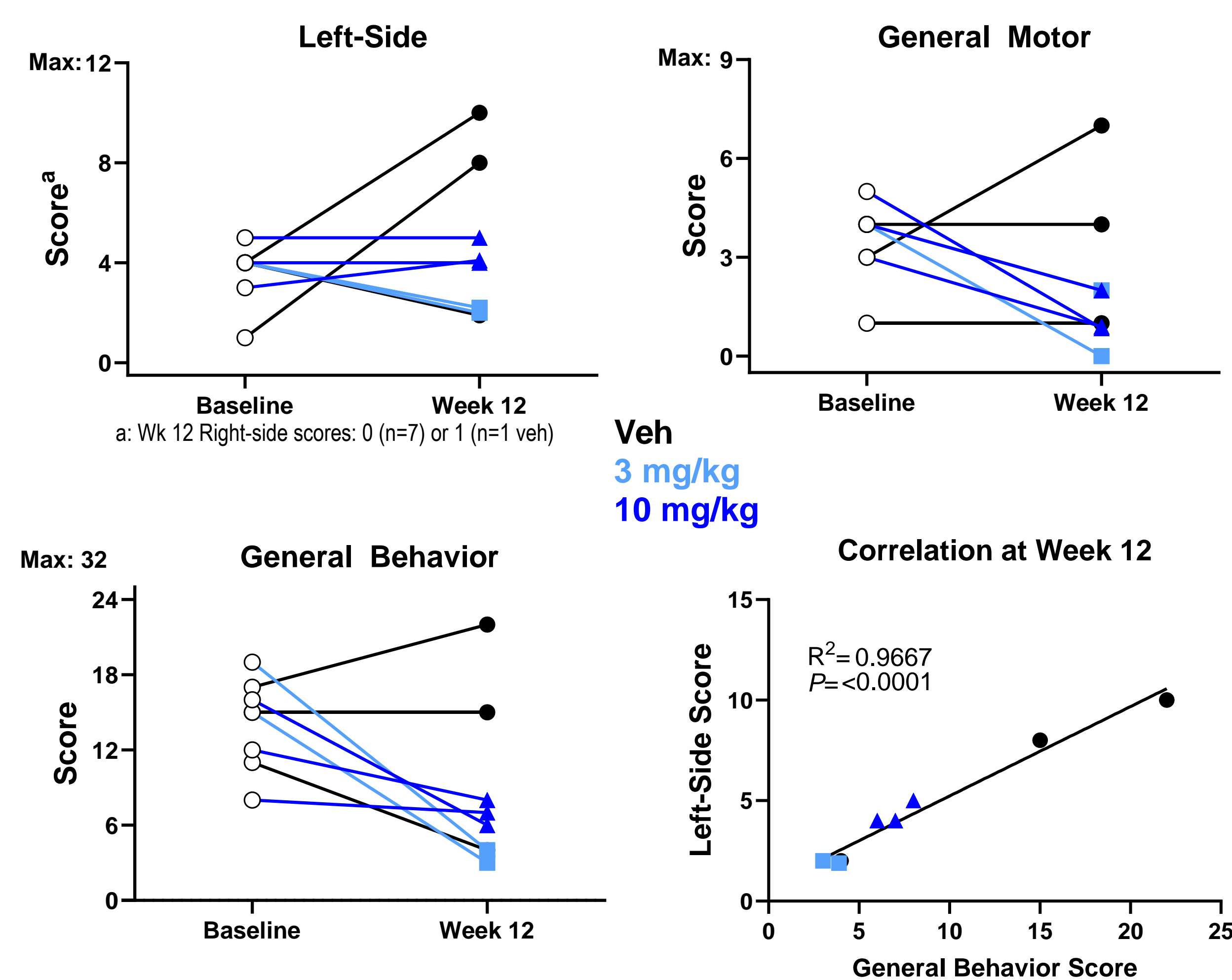
- SN iron (inductively-coupled plasma mass spec.)
- Dopamine transporter (DAT) density (PET)
- TH+ SN neurons (stereology)
- Dorsal striatal synaptophysin (Western Blot)

RESULTS

Hemiparkinsonian Model at Pre-Dose Baseline



ATH434 Improved Motor and Behavior Outcomes



- 8 macaques were evaluable at Week 12.
- ATH434-treated macaques had stable or improving scores from Baseline to Week 12.
- Two of 3 vehicle-treated macaques did not demonstrate improvement.
- Improved general behavior was well-correlated with reduced motor impairment.

References

1. Finkelstein et al (2017) The novel compound PBT434 prevents iron mediated neurodegeneration and alpha-synuclein toxicity in multiple models of Parkinson's disease. *Acta Neuropathol Commun* 5.
2. Heras-Garvin et al (2021) ATH434 Reduces α -Synuclein-Related Neurodegeneration in a Murine Model of Multiple System Atrophy. *Mov Disord* 36:2605-14. Finkelstein et al (2022) The Compound ATH434 Prevents Alpha-Synuclein Toxicity in a Murine Model of Multiple System Atrophy. *J Parkinson's Dis* 12:105-15.

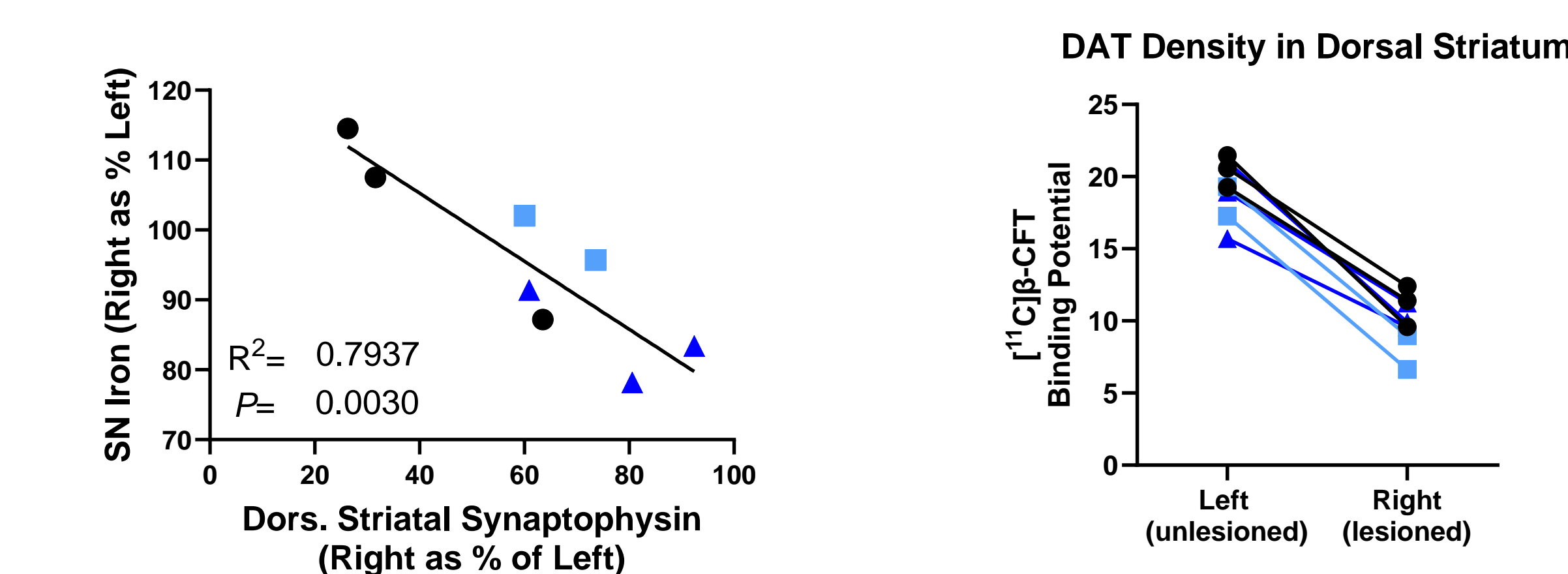
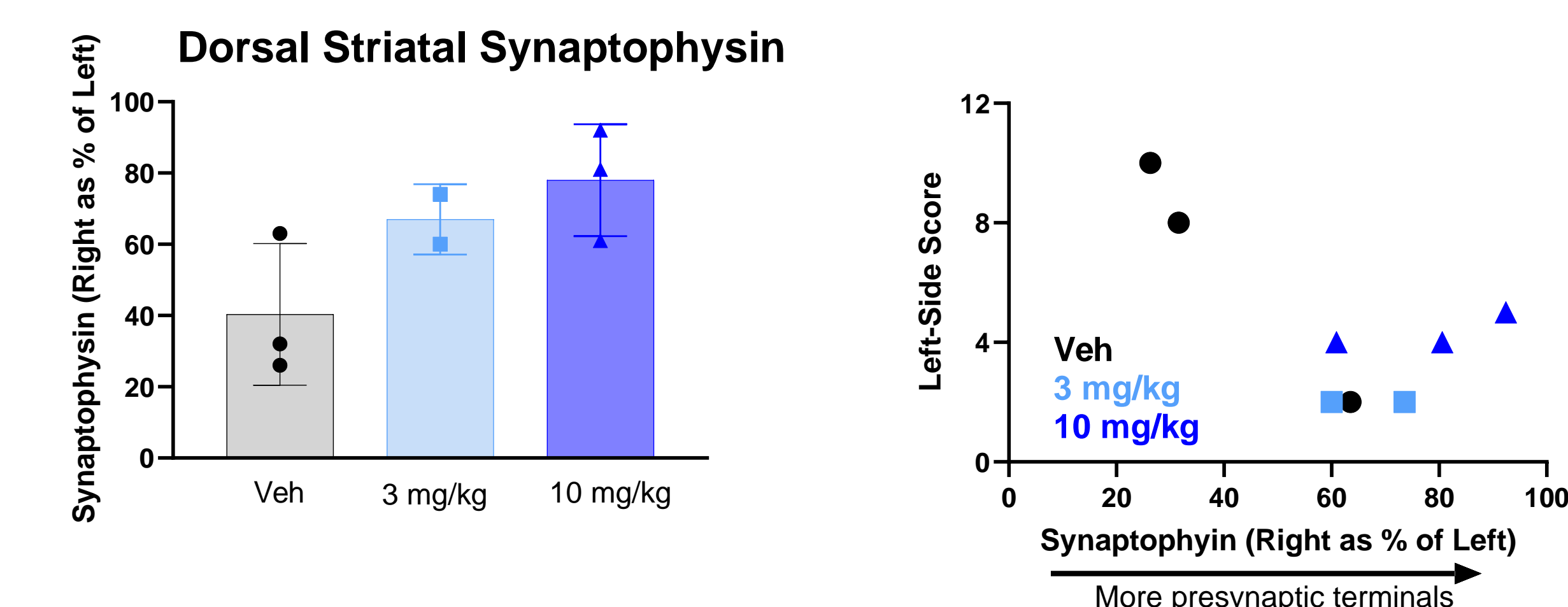
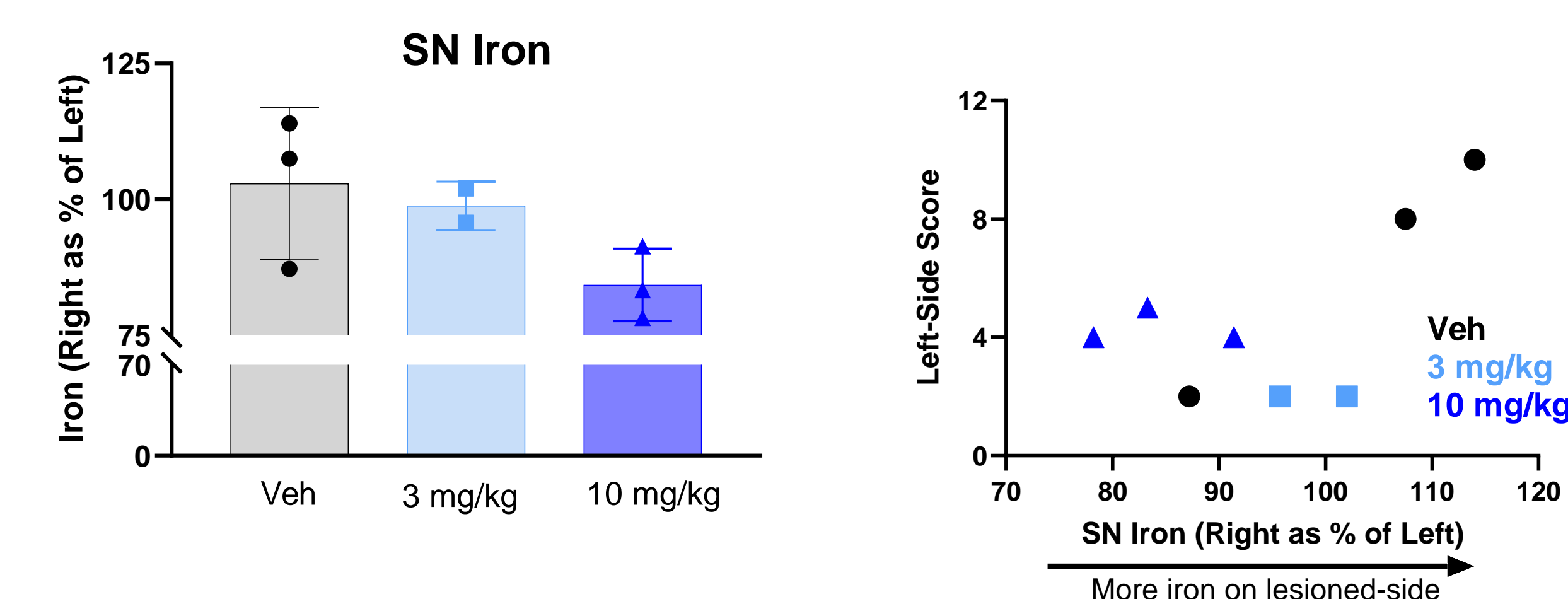
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RESULTS

ATH434 Reduced Iron and Increased Synaptophysin



TH+ SN Neurons (Right as % of Left, Mean \pm SD):
Veh: 52 \pm 16; 3 mg/kg: 77 \pm 26; 35 \pm 16

- ATH434-treated macaques had lower right SN iron and greater right dorsal striatal synaptophysin.
- Lesion size by PET and surviving TH+ SN neurons did not differ with ATH434.

CONCLUSION

- ATH434 treatment led to lower right SN iron and improved motor and general behavior scores in this primate model of PD.
- Favorable parkinsonian outcomes were associated with lower SN iron and higher striatal synaptophysin, suggesting functional neurite or synaptic recovery.
- These results support further investigation of ATH434 for the treatment of PD.