Oral Small Molecule Hepatocyte Growth Factor/MET Positive Modulator ATH-1020 Reduces Depression-like Behaviors and Normalizes Pathological EEG Mismatch Negativity in Preclinical Models

Andrée-Anne Berthiaume, PhD, Jewel Johnston, PhD, Robert Taylor, PhD, Kevin Church, PhD
Athira Pharma, Inc. Bothell, WA, USA

ASENT Annual Meeting, February 28–March 3, 2022

Disclosures

- Andrée-Anne Berthiaume, Jewel Johnston, Robert Taylor, and Kevin Church are employees and stockholders of Athira Pharma, Inc.

Neuropsychiatric Disorders: Critical Unmet Need

Depression

3.8%

Of the worldwide population is affected by depression[1]

~280 million

people of all ages suffer from depression, globally[1]

Schizophrenia

~1.2%

of Americans (3.2 million) have the disorder[2]

~24 million

people across the globe have been affected by schizophrenia[3]

20% to 60% of patients with psychiatric disorders—including depression and schizophrenia—experience treatment resistance[4]

New therapeutics with novel MOAs are required to reach these treatment-resistant populations

1. World Health Organization Data Fact Sheet – Depression; 2. https://www.mentalhelp.net/schizophrenia/statistics/;
3. World Health Organization Data Fact Sheet – Schizophrenia; 4. Howes et al. *Mol Psychiatry*. 2021.

HGF/MET Signaling in Neuropsychiatric Disorders

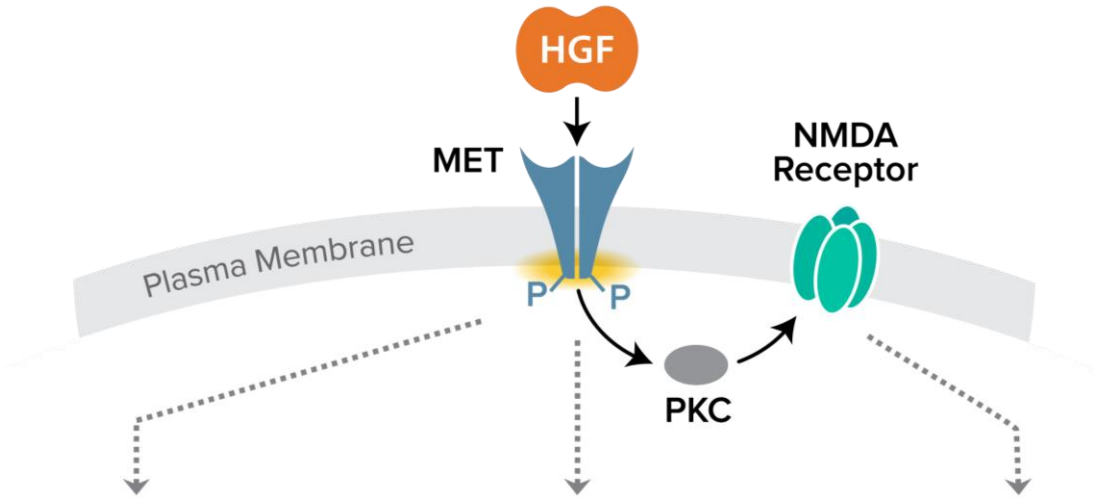
Neuropsychiatric disorders classically involve:

- Neural atrophy and reduced neural plasticity[1–3]
- Increased neuroinflammation and oxidative stress[4]
- Neurotransmitter system dysregulation[5]
- Neurotrophic factor depletion

Human studies show an association between **reduced HGF/MET expression levels and risk of depression and schizophrenia[6–9]**

The HGF/MET system has the potential to alleviate several key components of neuropsychiatric disorders based on its neurotrophic and neuroprotective properties

HGF/MET SIGNALING[10,11]



Neural Network Support	Neuron Health	Neurotransmitter Modulation
Neurogenesis	Regeneration	Synaptic current
Neurite outgrowth	Survival	Synaptic localization
Synaptogenesis	Anti-inflammation	Long-term potentiation

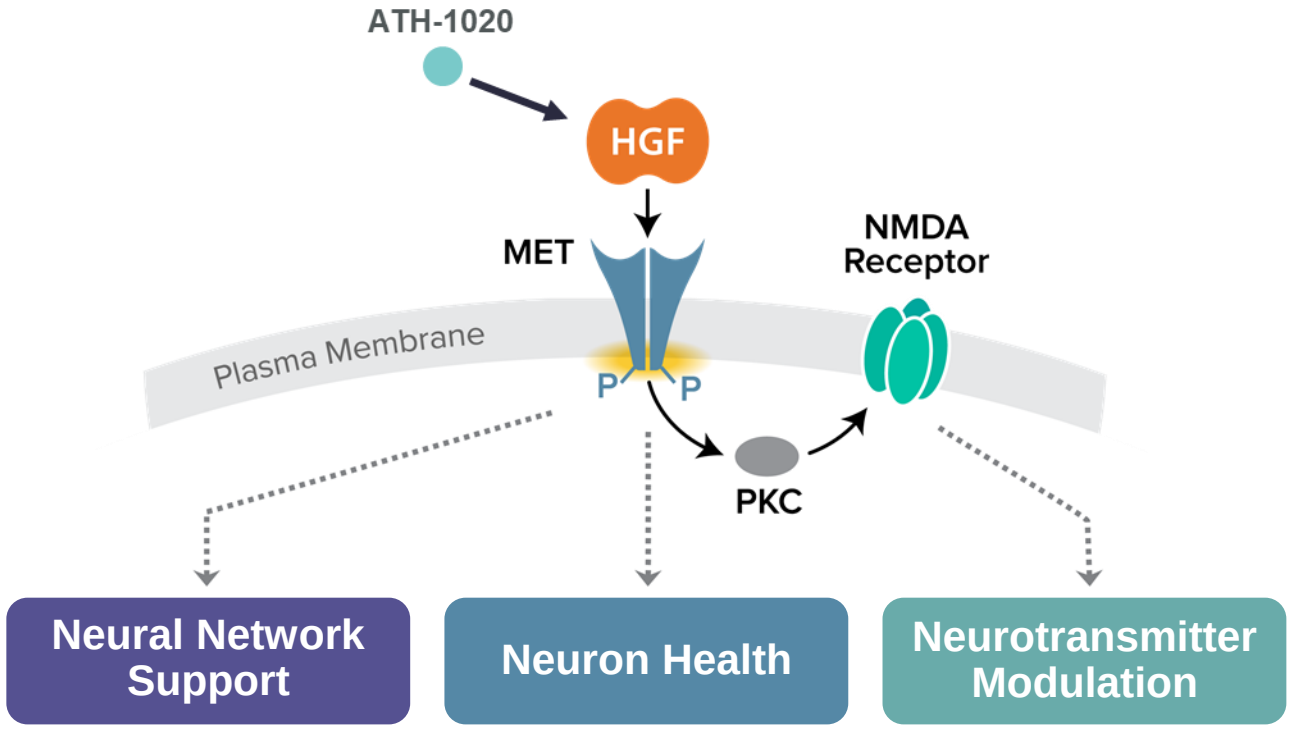
HGF, hepatocyte growth factor; NMDA, N-methyl D-aspartate; PKC, protein kinase C.

1. Autry et al. *Pharmacol Rev*. 2012; 2. Duman and Li. *Philos Trans R Soc Lond B Biol Sci*. 2012; 3. Levy et al. *Psychopharmacology (Berl.)* 2018; 4. Salim. *Curr Neuropharmacol*. 2014; 5. Najjar et al. *J Neuroinflammation*. 2013; 6. Russo. *Proteomics Insights*. 2010; 7. Ciuculete et al. *Epigenetics*. 2020; 8. Russo. *Biomarker Insights*. 2010; 9. Burdick et al. *Am J Psychiatry*. 2010; 10. Desole et al. *Front Cell Dev Biol.* 2021; 11. Hou and Zhang. *Front Cell Neurosci.* 2017.

Objective

Characterize a small molecule capable of augmenting the neurotrophic HGF/MET signaling pathway for the potential treatment of neuropsychiatric conditions

- ATH-1020 was identified as a novel orally bioavailable small molecule that can cross the blood-brain barrier
- ATH-1020 is currently under development for neuropsychiatric conditions



HGF, hepatocyte growth factor; NMDA, N-methyl D-aspartate; PKC, protein kinase C.

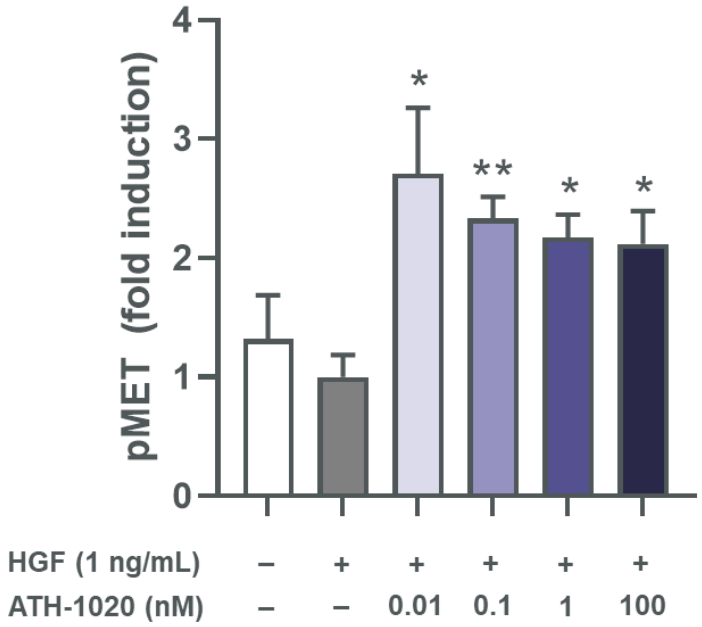
Part 1: Assessing the In Vitro Effects of ATH-1020

Athira PHARMA

Positive Modulation of HGF/MET Signaling by ATH-1020 In Vitro

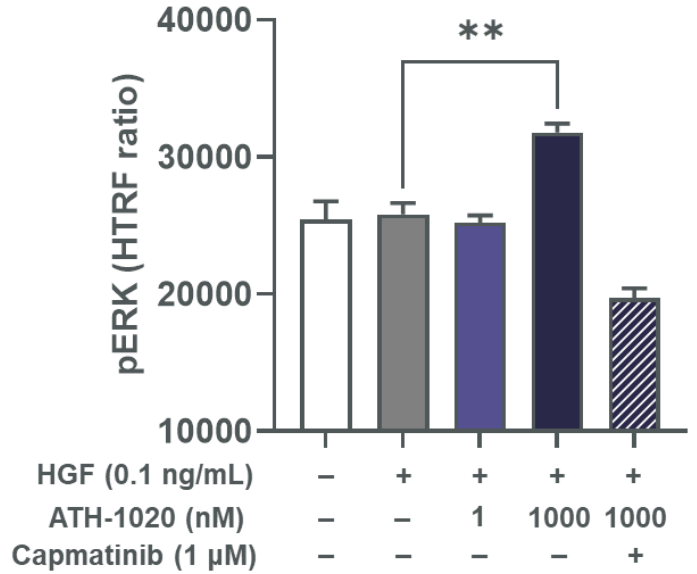
ATH-1020 enhancement of the HGF/MET pathway was assessed in HEK293 cells

- Phosphorylated MET (pMET) was evaluated via ELISA



ATH-1020 + HGF treatment leads to a significant enhancement of MET phosphorylation

- Phosphorylated ERK (pERK) was evaluated via HTRF

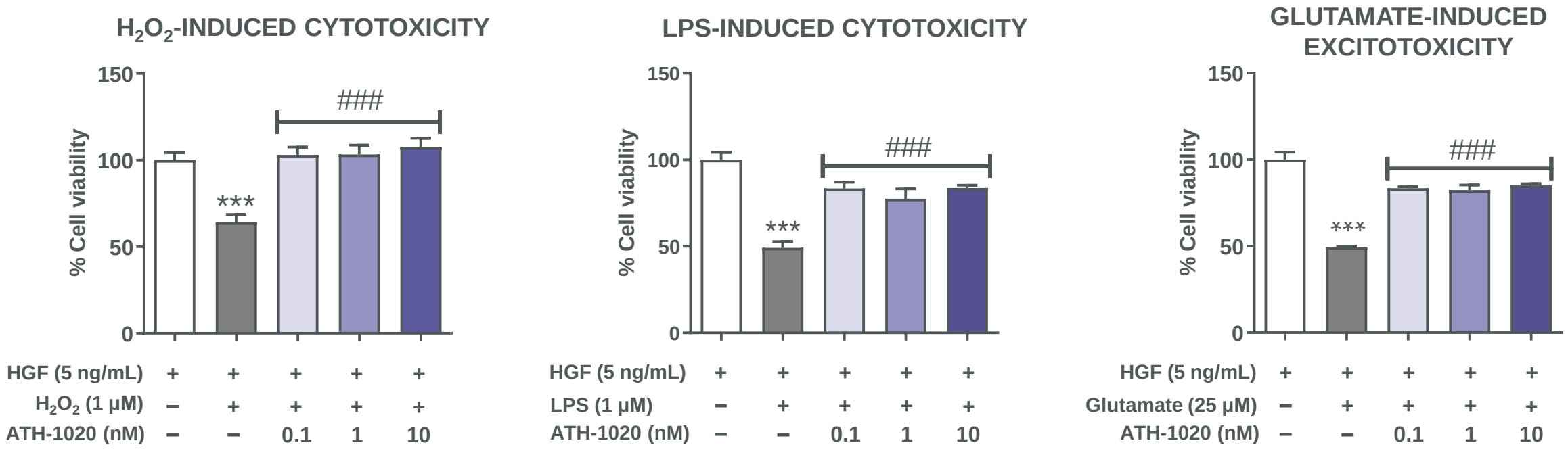


ATH-1020 + HGF treatment leads to increased ERK phosphorylation, the effects of which are downstream of MET activation

Data for each group are mean ± SEM. Statistical significance was determined by Student's t-test for the pMET assay and 1-way ANOVA with Tukey's multiple comparison post-test for the pERK assay. *P<0.05; **P<0.01.
ELISA, enzyme-linked immunosorbent assay; HGF, hepatocyte growth factor; HTRF, homogenous time resolved fluorescence.

Neuroprotective Effects of ATH-1020 in Rat Primary Cortical Neurons

Neuroprotective effects of ATH-1020 were assessed in vitro in rat primary cortical neurons using a Cell Titer-Glo cell-viability assay



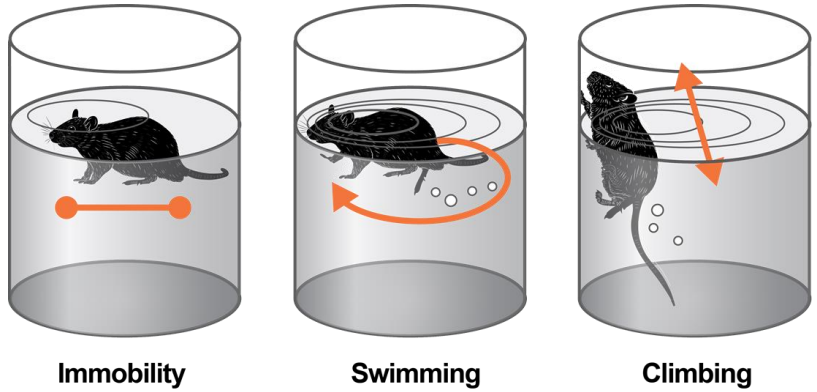
ATH-1020 + HGF treatment leads to increased neuron viability in the presence of neurotoxic insults

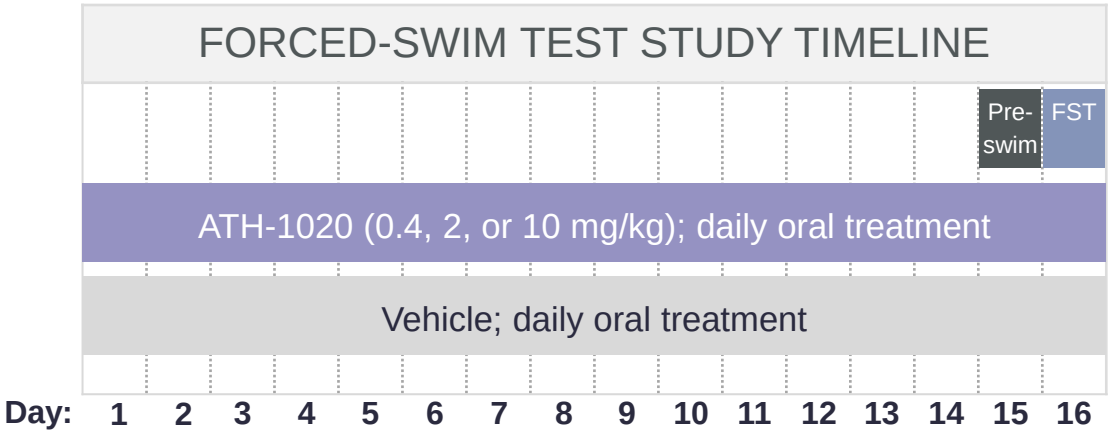
Data for each group are mean ± SEM. Statistical significance was determined by 1-way ANOVA with Tukey's multiple comparison post-test. ****P*<0.001 compared with HGF control; ### *P*<0.001 compared with HGF + insult control.
HGF, hepatocyte growth factor; LPS, lipopolysaccharide.

Part 2: Assessing the In Vivo Effects of ATH-1020

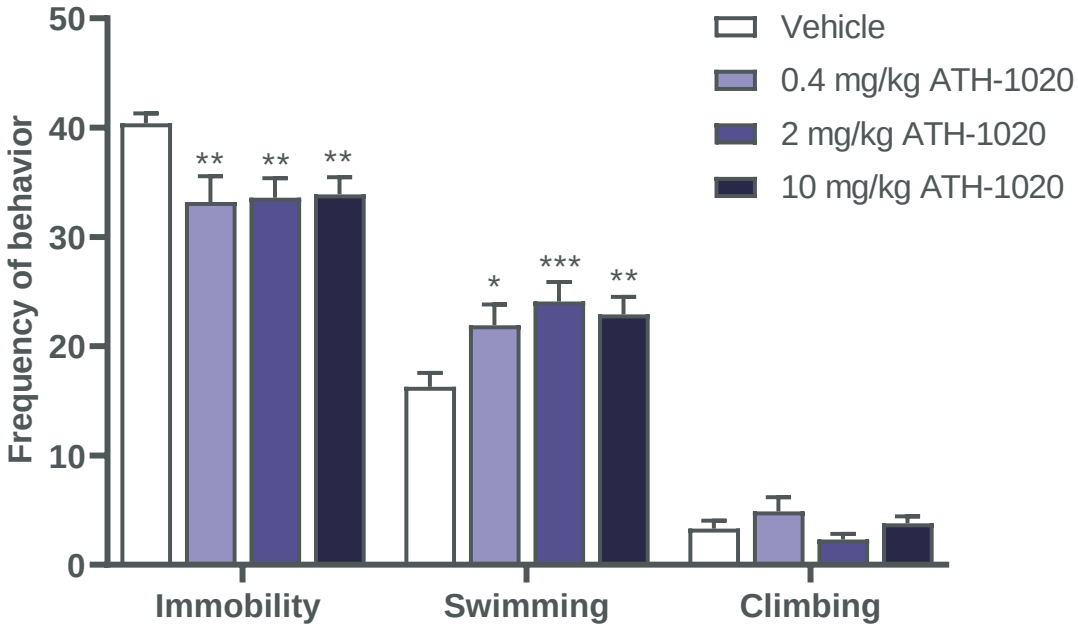
The Effect of ATH-1020 Treatment on a Rodent Model of Depression-Related Behavior

FORCED-SWIM TEST[1]





FORCED-SWIM TEST RESULTS



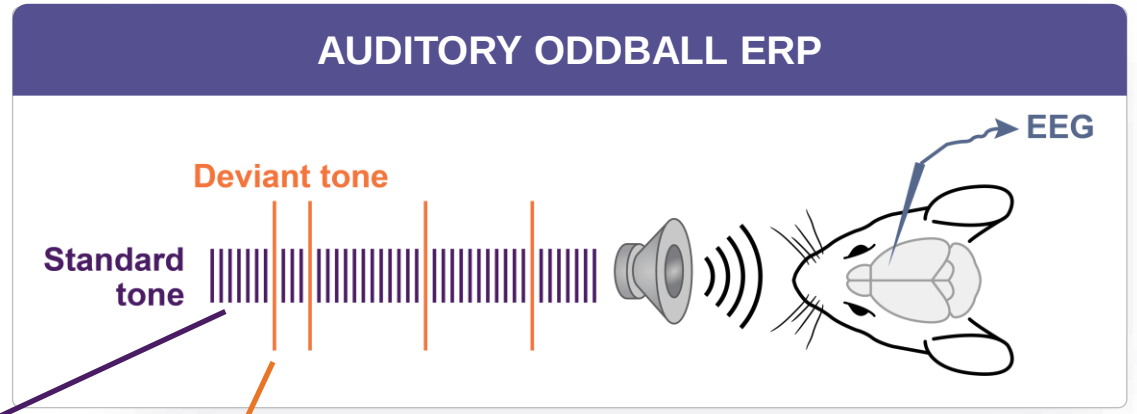
ATH-1020 significantly reduced immobility in the forced-swim test, while increasing swimming behaviors

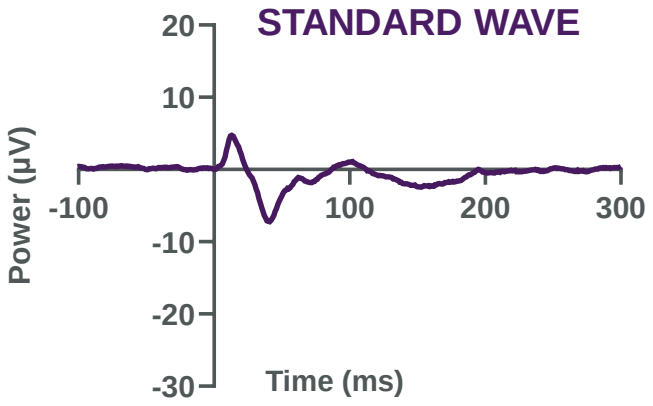
Two-way ANOVA with Dunnett's multiple comparisons vs vehicle were conducted. *P<0.05, **P<0.01, ***P<0.001.
FST, forced-swim test.

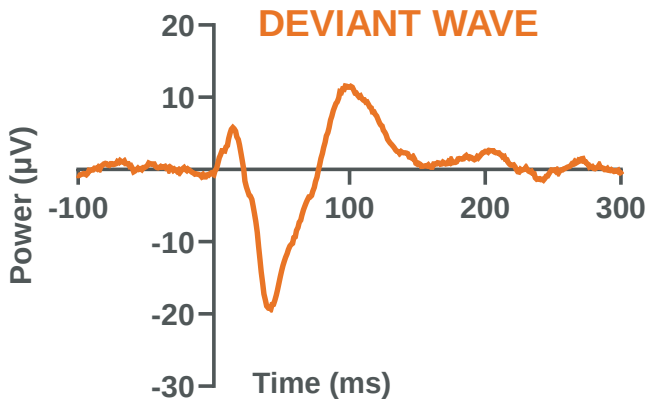
1. Nie et al. IEEE Intl Conference on Automation Sci and Engineering. 2008.

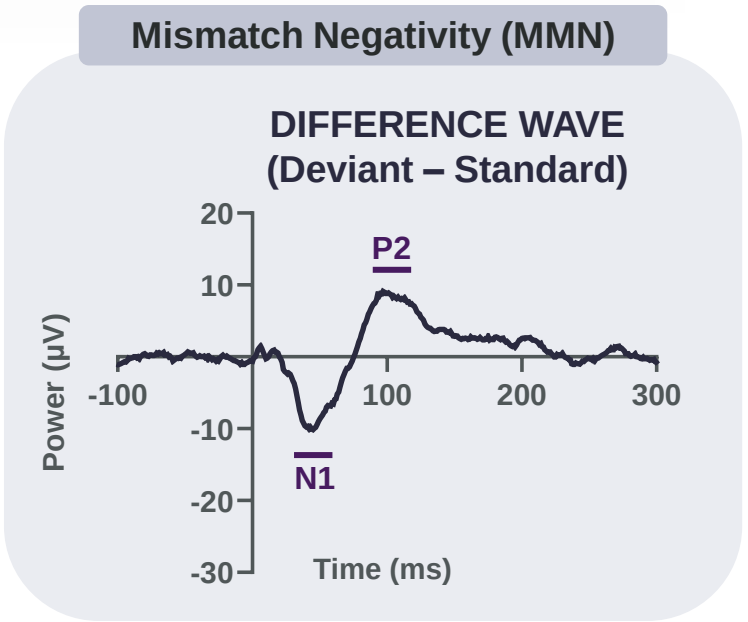
EEG Recordings of Auditory Event-Related Potentials (ERPs)

- Young adult Sprague-Dawley rats had wireless telemetry devices implanted[1]
- ERPs captured during an auditory oddball paradigm[1]
  - Standard tones presented 90% of the time
  - Deviant tones presented 10% of the time









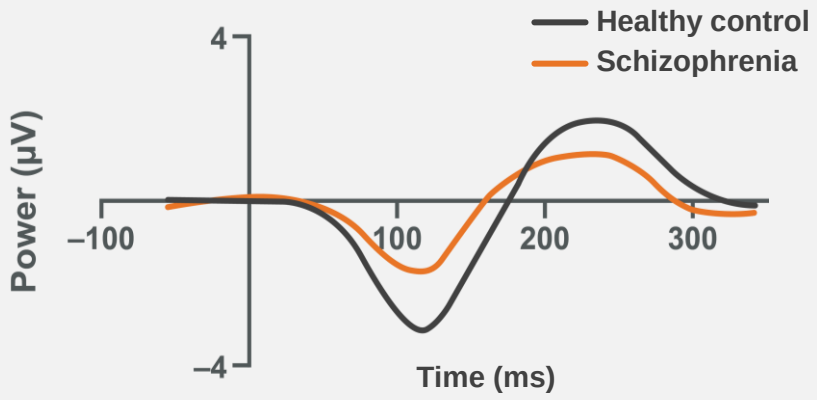
EEG, electroencephalogram; ERP, event-related potentials; MMN, mismatch negativity.

1. Leiser et al. Poster presented at Schizophrenia Intl Research Society. 2019.

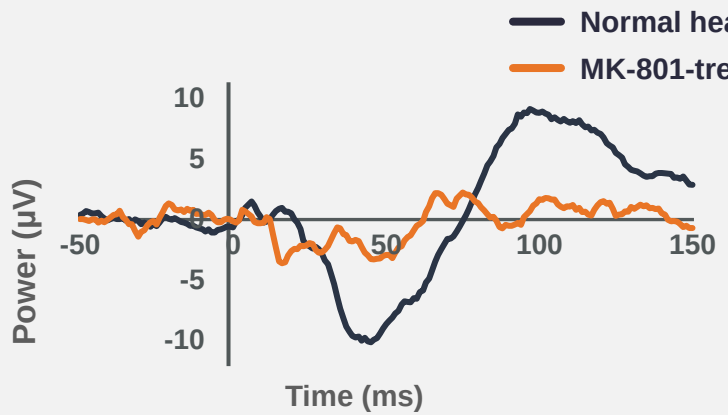
MMN Response Is Translatable From Clinical Schizophrenia to Rodent Models

- A blunted MMN response is a hallmark of clinical schizophrenia[1]
  - Reflects sensory processing deficits on a neural level

Mismatch Negativity in Humans[1]



Mismatch Negativity in Rats



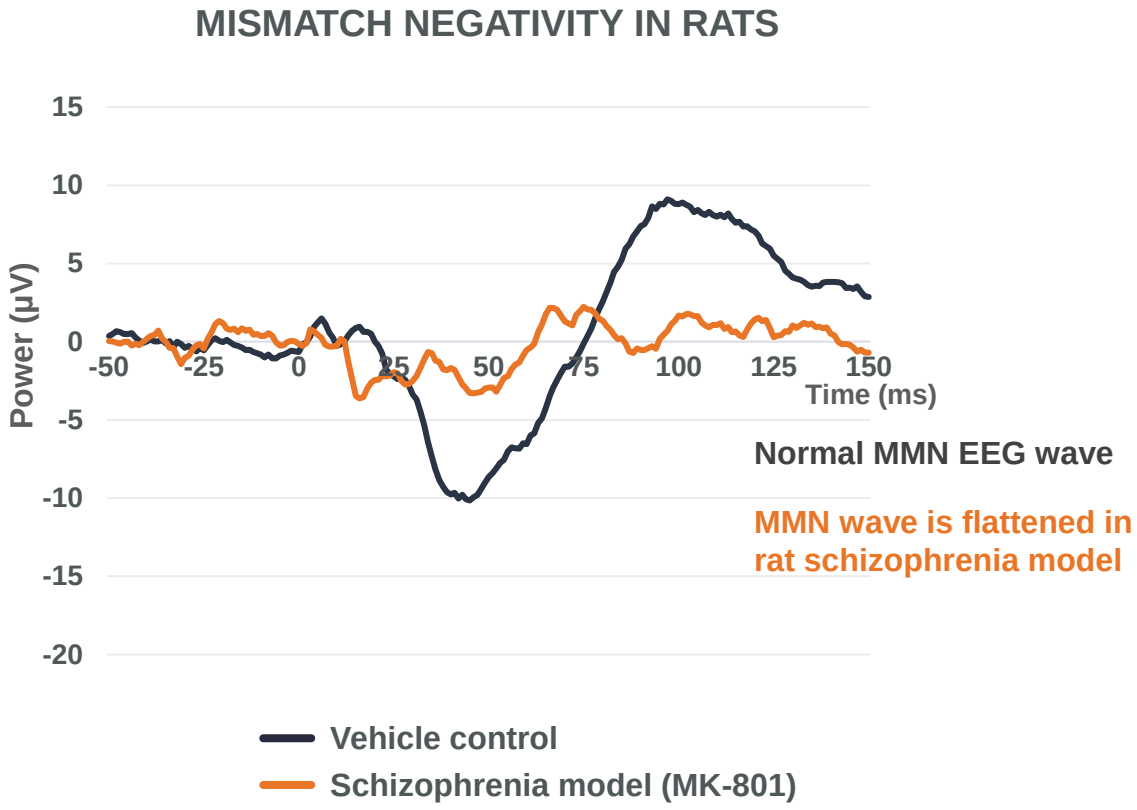
- Schizophrenia can be modeled in rats by treatment with the NMDA receptor antagonist MK-801[2,3]
  - Similar to the drug PCP, which can cause schizophrenia-like symptoms in healthy humans[3]
- The MMN deficit is recapitulated in rodent schizophrenia MK-801 model[2]

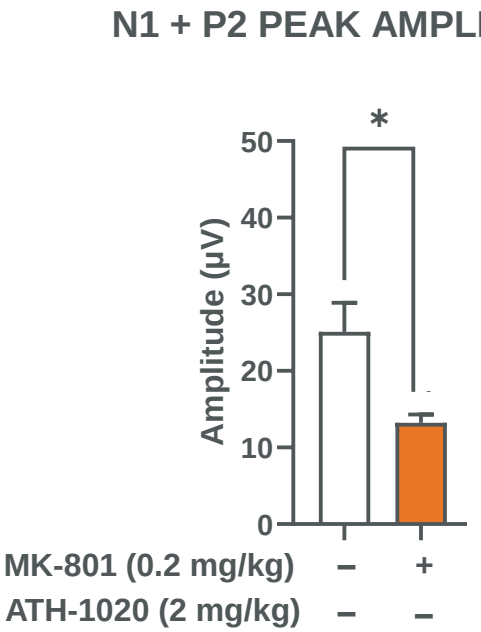
EEG, electroencephalogram; MMN, mismatch negativity; NMDA, n-methyl-D-aspartate; PCP, phencyclidine.

1. Murphy et al. *Front Psychiatry*. 2020. 2. Leiser et al. Schizophrenia Intl Research Society. 2019. 3. Olszewski et al. *Biol Psychiatry*. 2008.

Effect of ATH-1020 Treatment on MMN in a Rat Schizophrenia Model

- Rats were treated with 3 doses of ATH-1020, at 48h, 24h, and 5 min before MK-801 administration
- MK-801 was administered 60 minutes before EEG recordings were captured

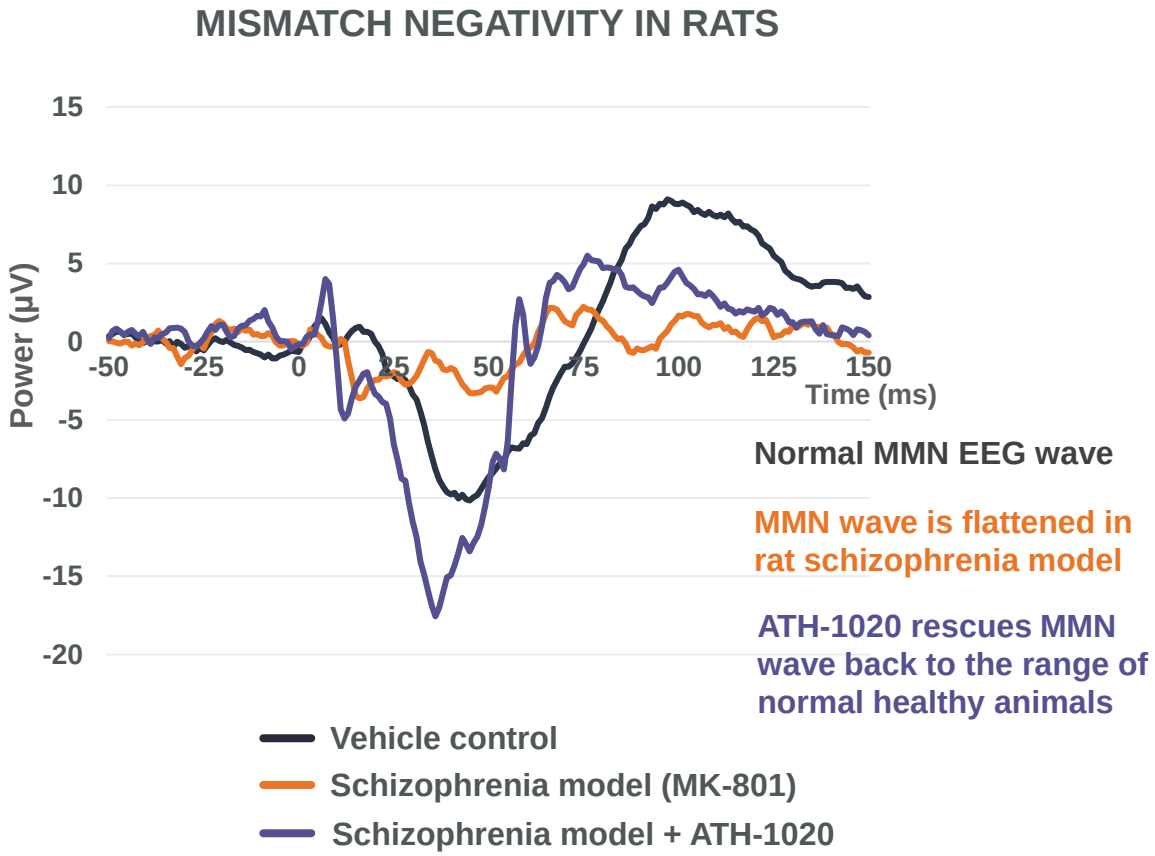


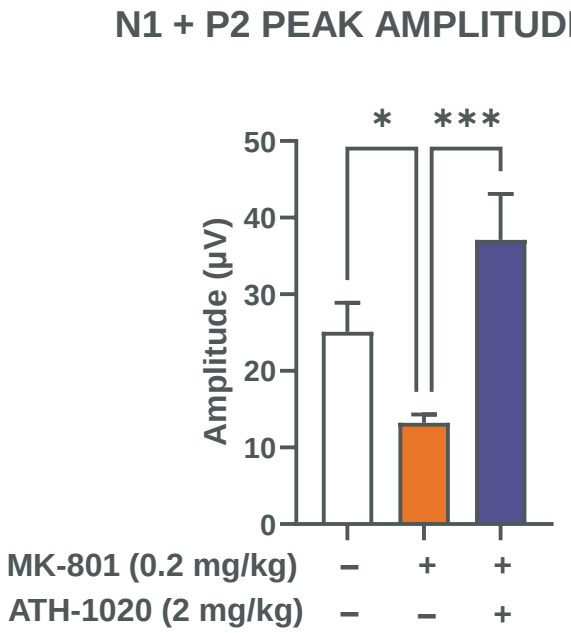


One-way ANOVA with Dunnett's multiple comparisons post-test. *P<0.05, ***P<0.001.
EEG, electroencephalogram; MMN, mismatch negativity

Effect of ATH-1020 Treatment on MMN in a Rat Schizophrenia Model

- Rats were treated with 3 doses of ATH-1020, at 48h, 24h, and 5 min before MK-801 administration
- MK-801 was administered 60 minutes before EEG recordings were captured





ATH-1020 rescues the MMN deficit seen in the rat MK-801 schizophrenia model

One-way ANOVA with Dunnett's multiple comparisons post-test. *P<0.05, ***P<0.001.
EEG, electroencephalogram; MMN, mismatch negativity

Summary of Findings

In vitro findings validate MOA and support ATH-1020 promotion of neuronal survival

- ATH-1020 treatment leads to augmentation of MET phosphorylation and activation of downstream signaling pathways in the presence of HGF
- Pretreatment with ATH-1020 has a protective effect in primary rat cortical neurons when challenged with neurotoxic insults

In vivo findings support the potential of ATH-1020 in two independent rat models

- Depression-related behaviors can be mitigated by treatment with ATH-1020 in the FST rat model
- ATH-1020 rescued the MMN response blunting in the MK-801-induced rat model of schizophrenia

Based on these promising preliminary results, ATH-1020 will continue to be developed for the potential treatment of depression and schizophrenia in clinical populations

Athira PHARMA

FST, forced swim test; MMN, mismatch negativity; MOA, mechanism of action.

Thank You

Athira PHARMA