NEURALSTEM INC.

“Fast-Acting Synaptic Plasticity Effects of NSI-189 at High Doses”

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MGH CTNI Europe 2018

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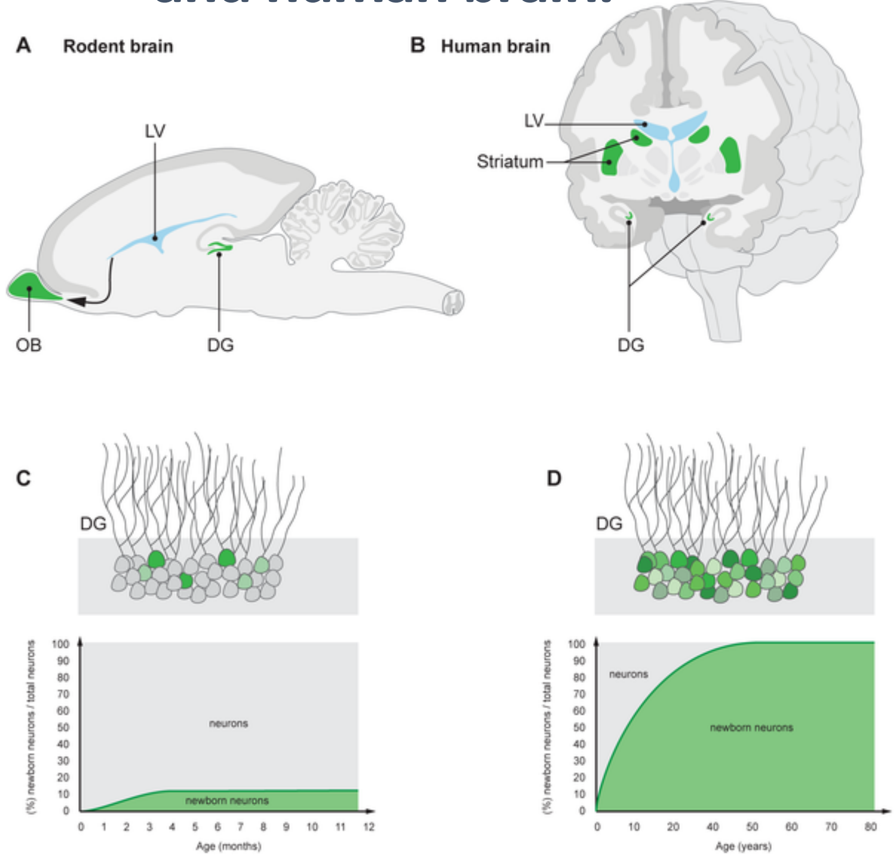
Safe Harbor statements under the Private Securities Litigation Reform Act of 1995: This presentation contains forward-looking statements as defined in Section 27A of the Securities Act of 1933 as amended, and section 21E of the Securities Exchange Act of 1934, as amended. Such forward-looking statements are based upon Neuralstem, Inc.'s management's current expectations, estimates, beliefs, assumptions, and projections about Neuralstem's business and industry. Words such as "anticipates," "expects," "intends," "plans," "predicts," "believes," "seeks," "estimates," "may," "will," "should," "would," "potential," "continue," and variations of these words (or negatives of these words) or similar expressions, are intended to identify forward-looking statements. In addition, any statements that refer to expectations, projections, or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. These forward-looking statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict. Therefore, our actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various risk factors. These risks and uncertainties include the risks associated with the effect of changing economic conditions, trends in the products markets, variations in Neuralstem's cash flow, market acceptance risks, technical development risks and other risk factors detailed in Neuralstem's Securities and Exchange Commission filings. For links to SEC documents please visit the company's Web site: neuralstem.com.

Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this presentation as a result of, among other factors, the factors referenced in the "Risk Factors" section of our Annual Report on Form 10-K for the year ended December 31, 2015 filed with the Securities and Exchange Commission on March 14, 2016, Form 10-Q for the period ended September 30, 2016, an in other reports filed with the SEC. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this presentation, they may not be predictive of results or developments in future periods. Any forward-looking statements that we make in this presentation speak only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this presentation, except as required by law.

Dr. Karl Johe is an employee of Neuralstem, Inc. and holds patents and financial interests in Neuralstem, Inc.

Figure 1. Schematic illustration of adult neurogenesis in the adult rodent and human brain.

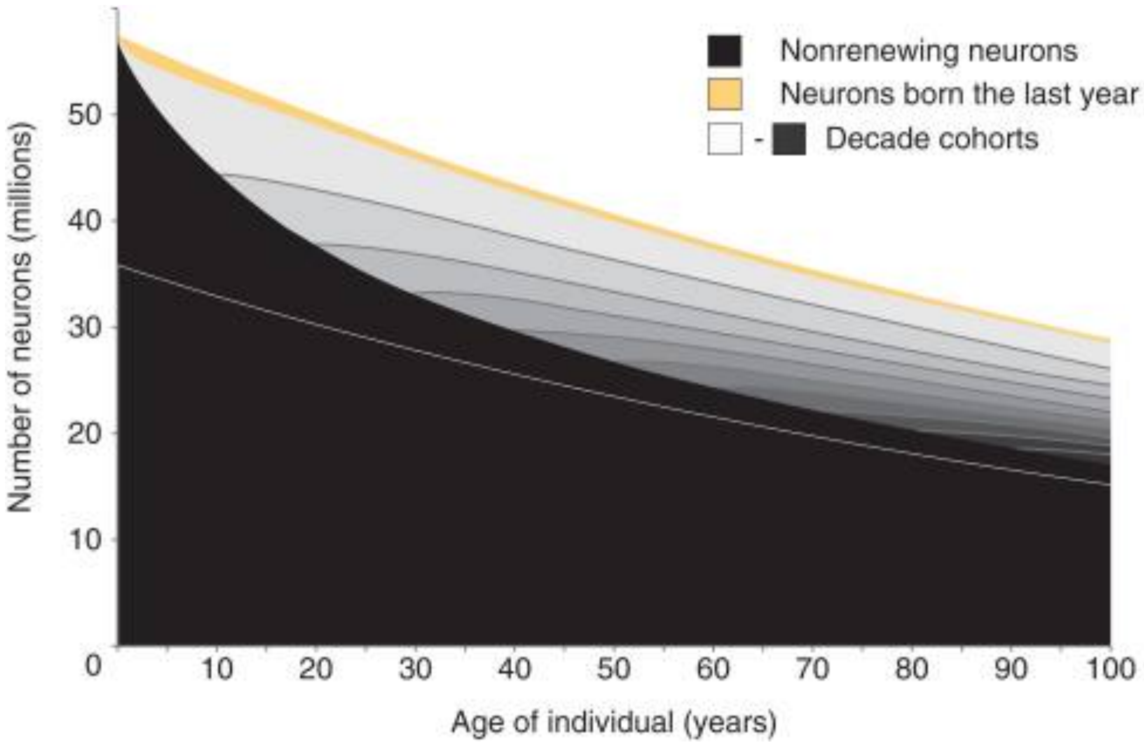


Ernst A, Frisén J (2015) Adult Neurogenesis in Humans- Common and Unique Traits in Mammals. PLOS Biology 13(1): e1002045.

https://doi.org/10.1371/journal.pbio.1002045
http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002045

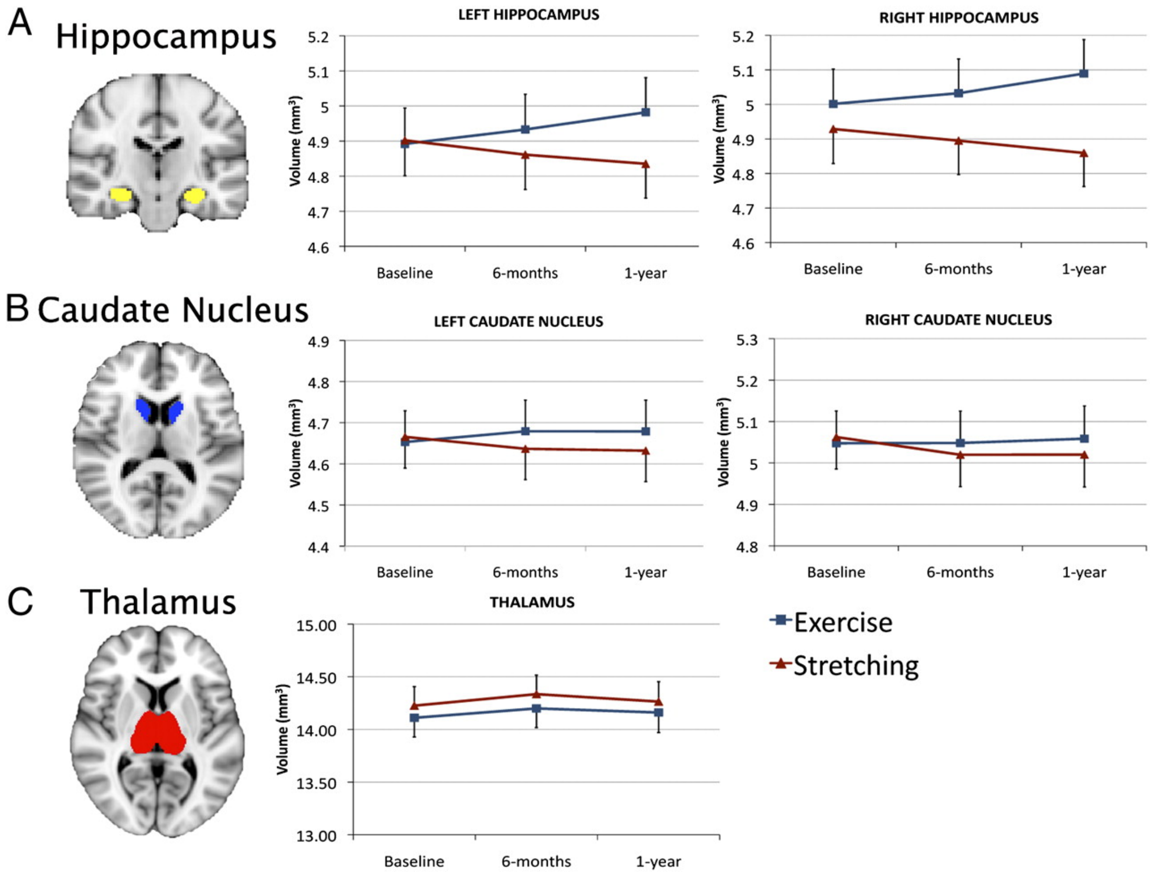
Adult Neurogenesis in Humans

Bergmann O1, Spalding KL1, Frisén J1.



PMC full text:
Cold Spring Harb Perspect Biol. 2015 Jul; 7(7): a018994.
doi: 10.1101/cshperspect.a018994

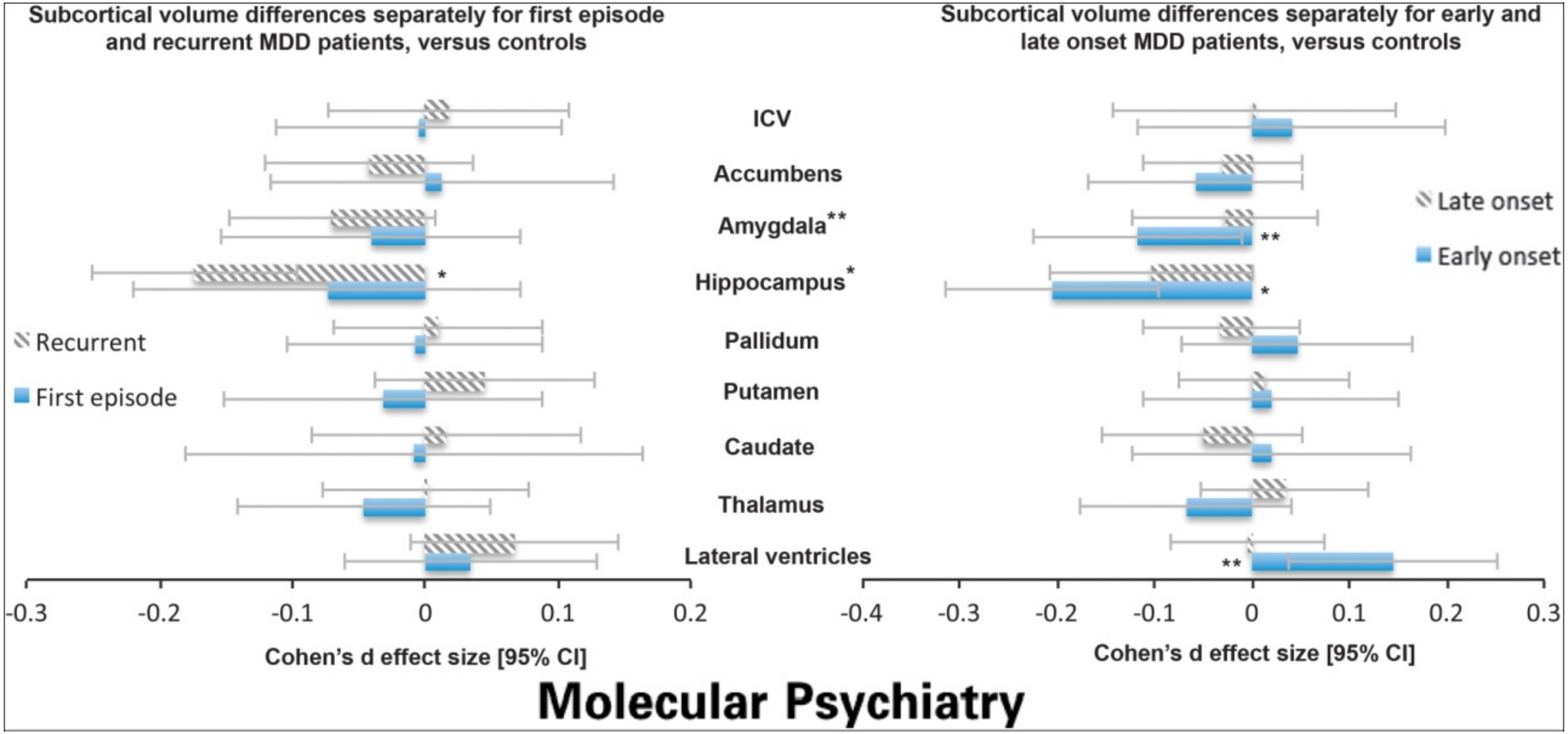
(A) Example of hippocampus segmentation and graphs demonstrating an increase in hippocampus volume for the aerobic exercise group and a decrease in volume for the stretching control group.



Kirk I. Erickson et al. PNAS 2011;108:7:3017-3022

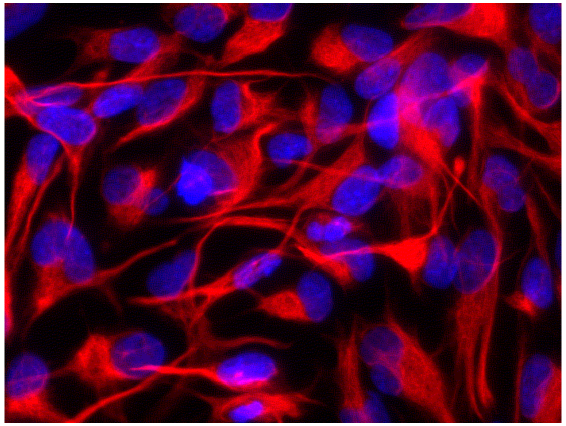
PNAS

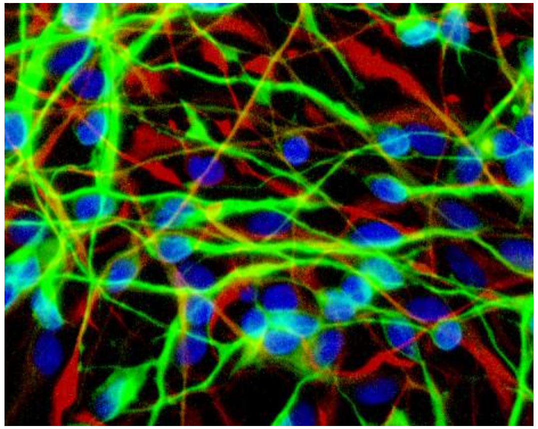
Subcortical brain alterations in major depressive disorder: meta-analysis of 1728 MDD vs. 7199 Controls

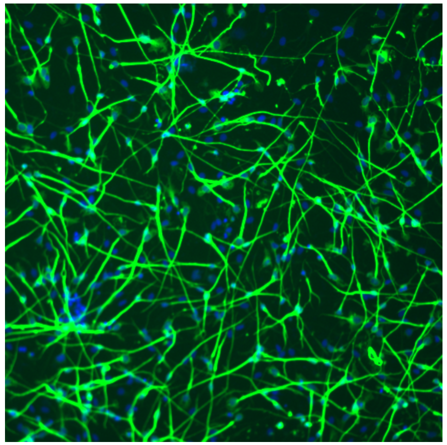


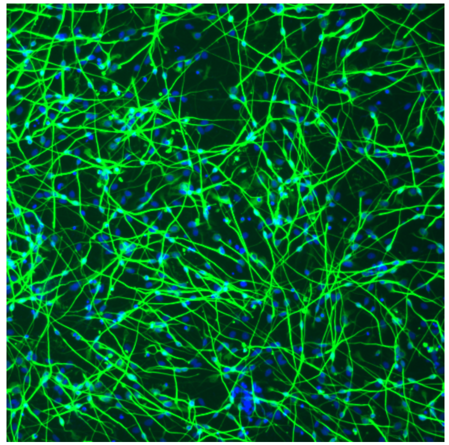
Molecular Psychiatry (2016) **21**, 806-812;doi:10.1038/mp.2015.69

Discovery of Neurogenic Drugs
Based on Human Hippocampal Neurogenesis *in vitro*

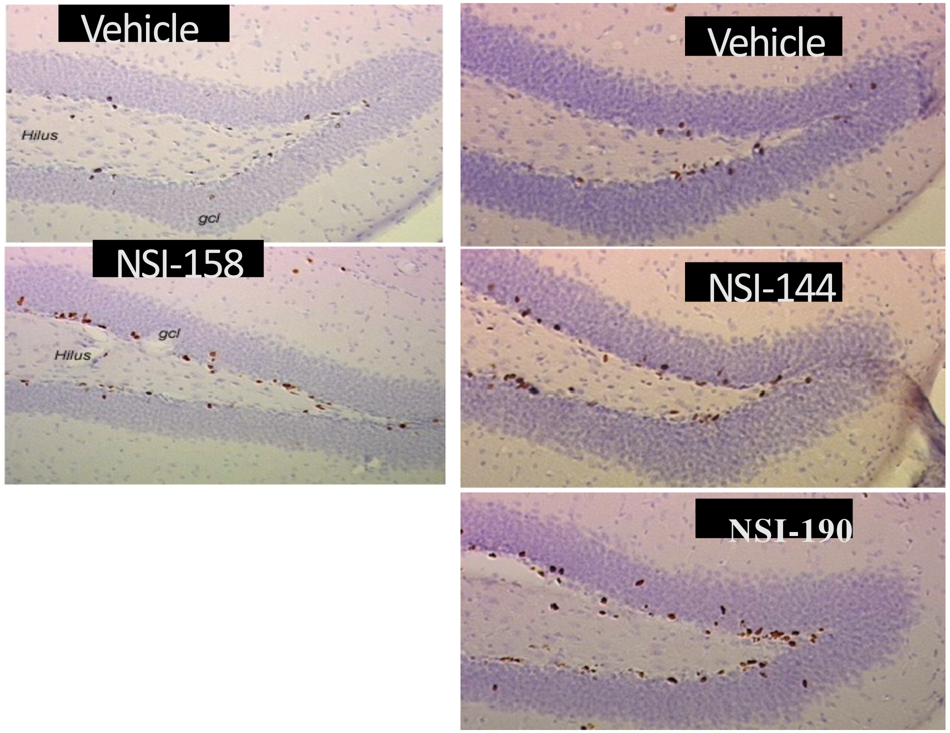

Day 0

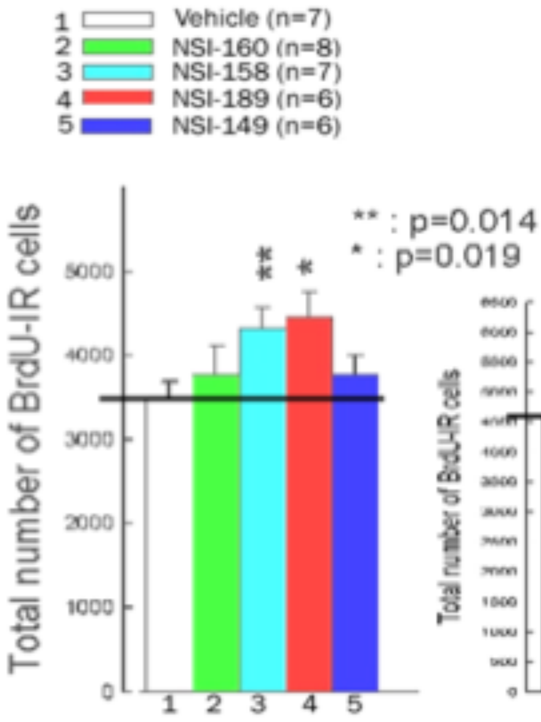

Day 7

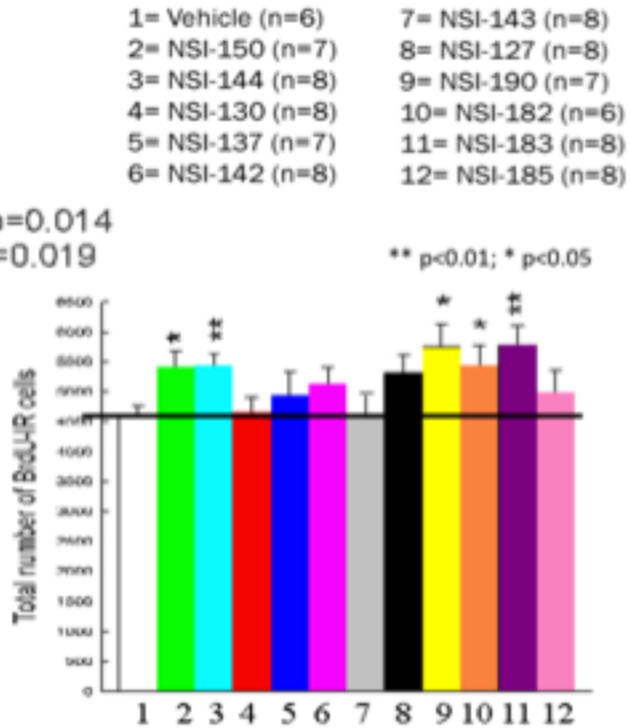

Vehicle Control


NSI-106

Neurogenesis in Healthy Adult Mouse by NSI Compounds (10 mg/kg po)

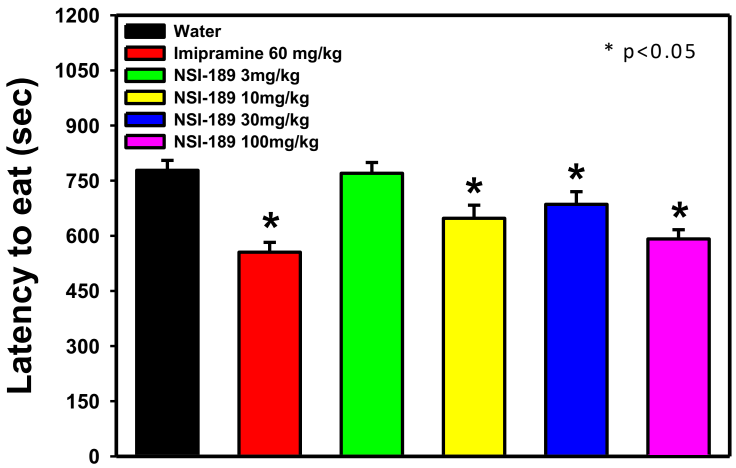


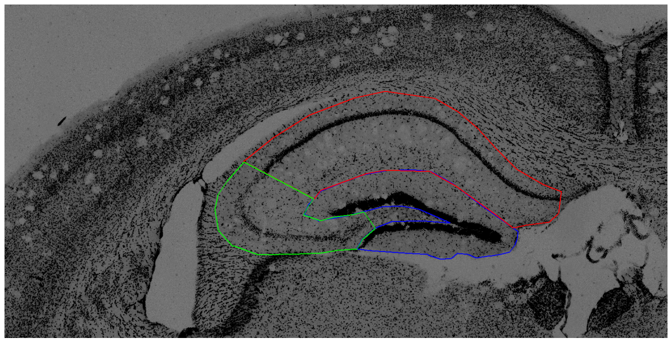


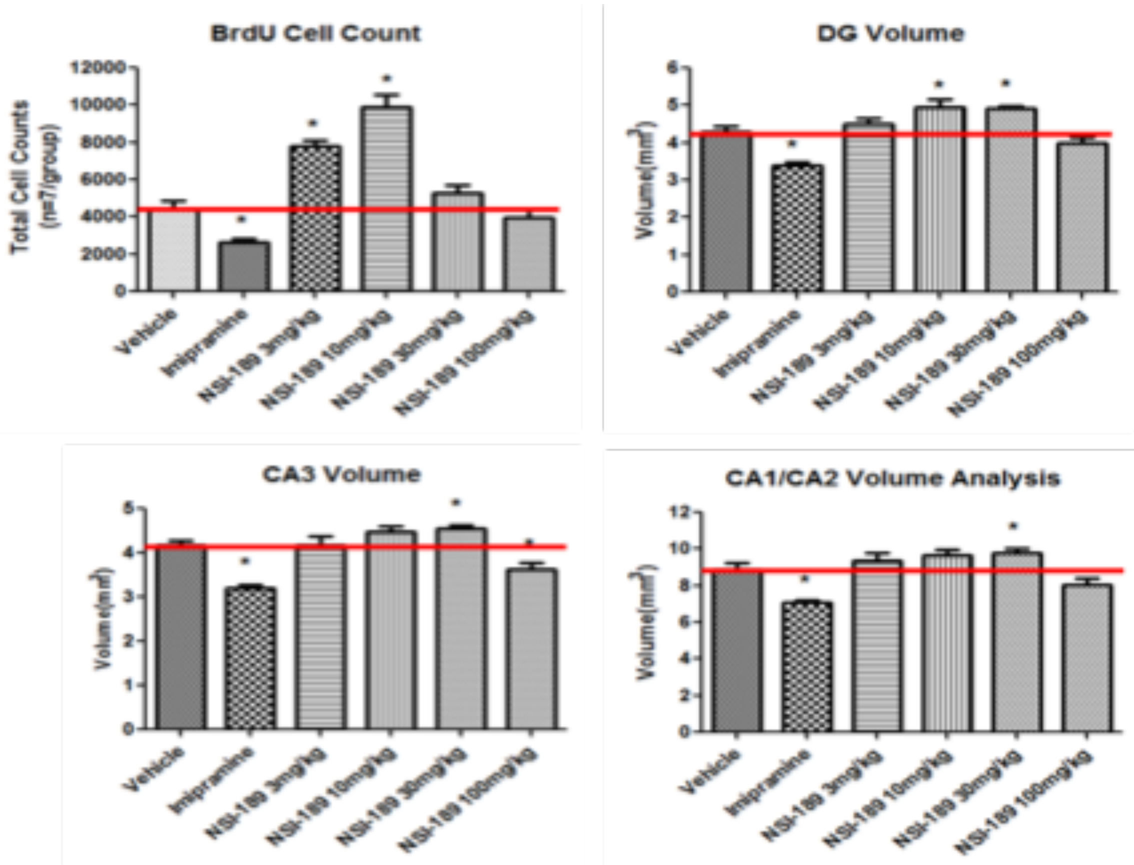


*Conducted by Cerep & NeuroDetective Inc.

Effect in Chronic Novelty Suppressed Feeding Model of Depression: Increased HI Neurogenesis and Volume (10-30mg/kg po)

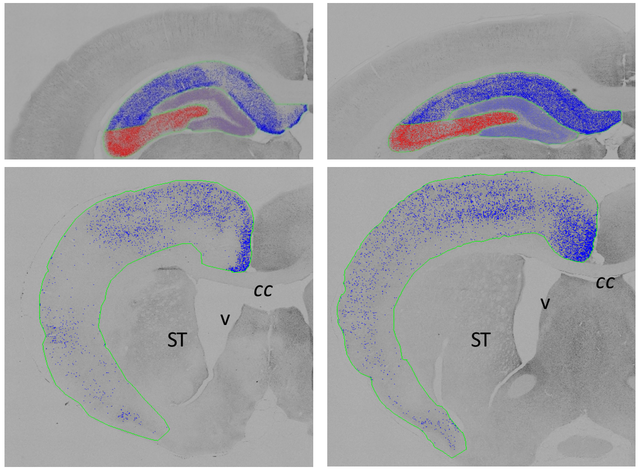




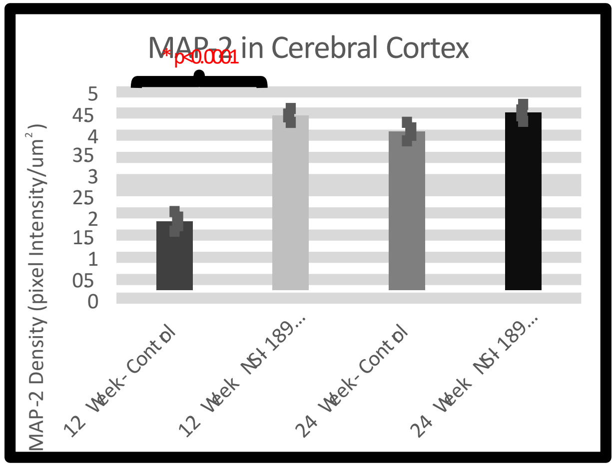


Synaptic Remodeling during Recovery from Ischemic Stroke Brain (30mg/kg po)

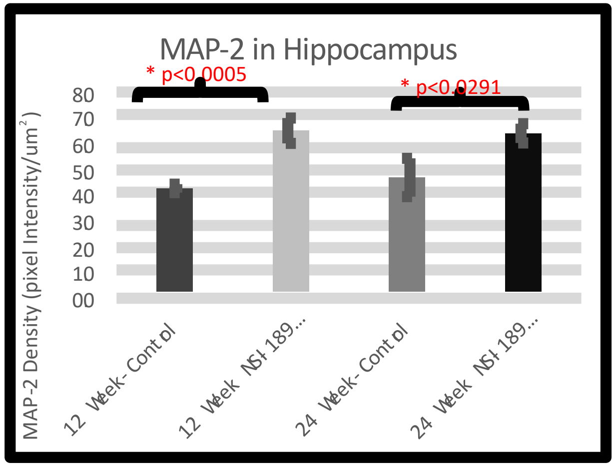
	12 Weeks Vehicle	**12 Weeks NSI-189**
MAP-2ab Staining in Hippocampus		
MAP-2ab Staining in Cerebral Cortex		



A. MAP-2 in Cerebral cortex

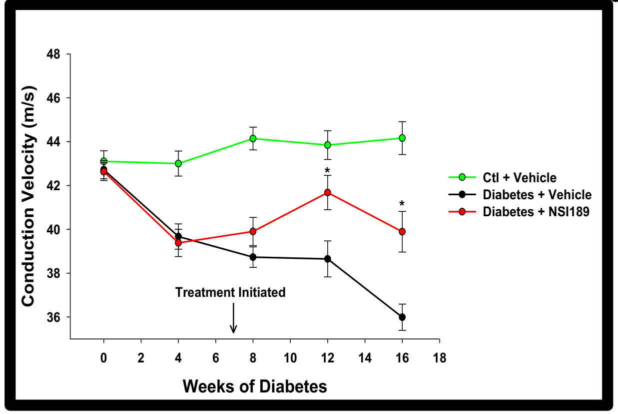


B. MAP-2 in Hippocampus

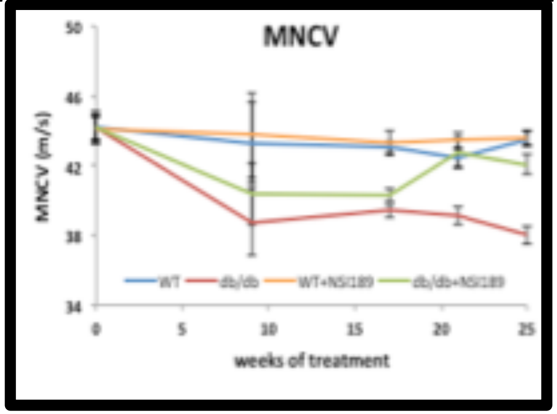


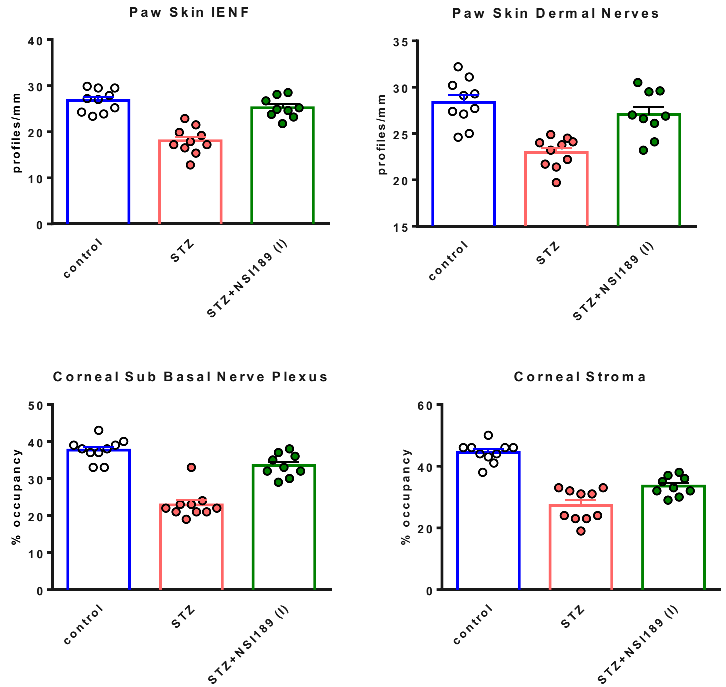
Motor Nerve Conduction Velocity in Type 1 and Type 2 Diabetic Models (10-30mg/kg po)

Type 1 Diabetes Model—Intervention Study

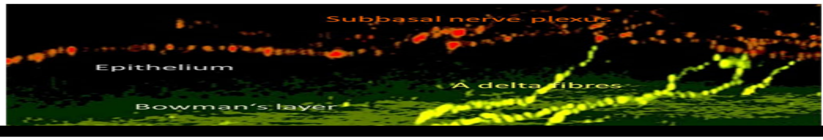


Type 2 Diabetes Model—Prevention Study





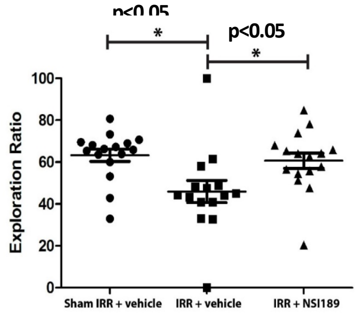
Number of PGP 9.5-stained profiles in the epidermis (intra-epidermal nerve fibers: IENF)



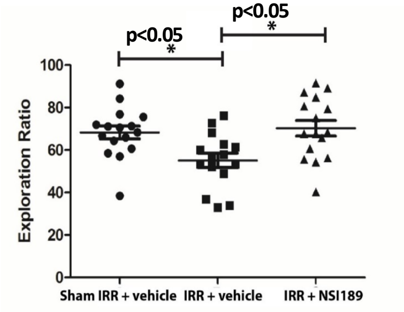
3D reconstruction of nerve structure in the mouse cornea: A delta fibers (yellow) penetrating the Bowman's layer and spreading into the sub-basal nerve plexus (red)

Amelioration of Cognitive Deficits in Radiation-Induced Brain Injury Model (30mg/kg po)

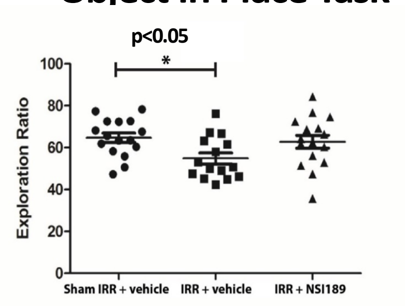
Spatial Cognitive Impairment
Novel Place Recognition Task



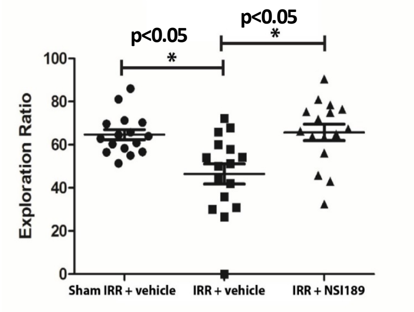
Episodic Memory
Novel Object Recognition Task



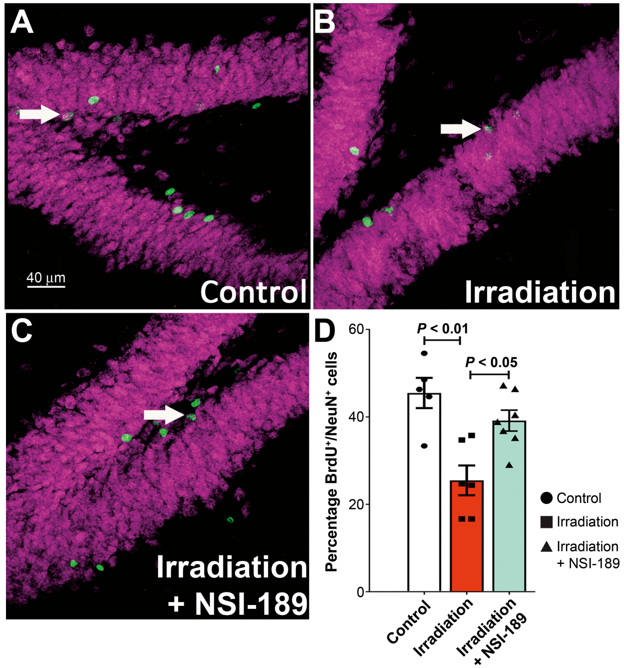
Spatial Memory
Object in Place Task



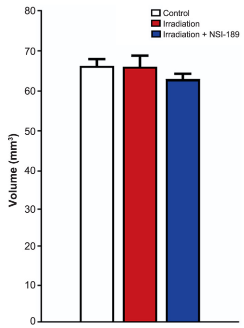
Spatiotemporal Episodic Memory
Temporal Order Task



Neurogenesis



Hippocampal Volume



Barrett et al. (2017) Radiation Research 189(4):345-353. 2018
https://doi.org/10.1667/RR14879.1

Dose Escalation Safety for 28 days in MDD Patients

A Phase 1B, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Escalation Study Evaluating the Effects of NSI-189 Phosphate, a Neurogenic Compound, in Patients with Major Depressive Disorder (MDD)

Maurizio Fava, M.D., Karl Johe, Ph.D., Lev G. Gertsik, MD, Larry Ereshefsky, PharmD, Bettina Hoeppner, Ph.D., Martina Flynn, David Mischoulon, M.D., Ph.D., Gustavo Kinrys, M.D., and Marlene Freeman, M.D.

Phase 1b Study Design

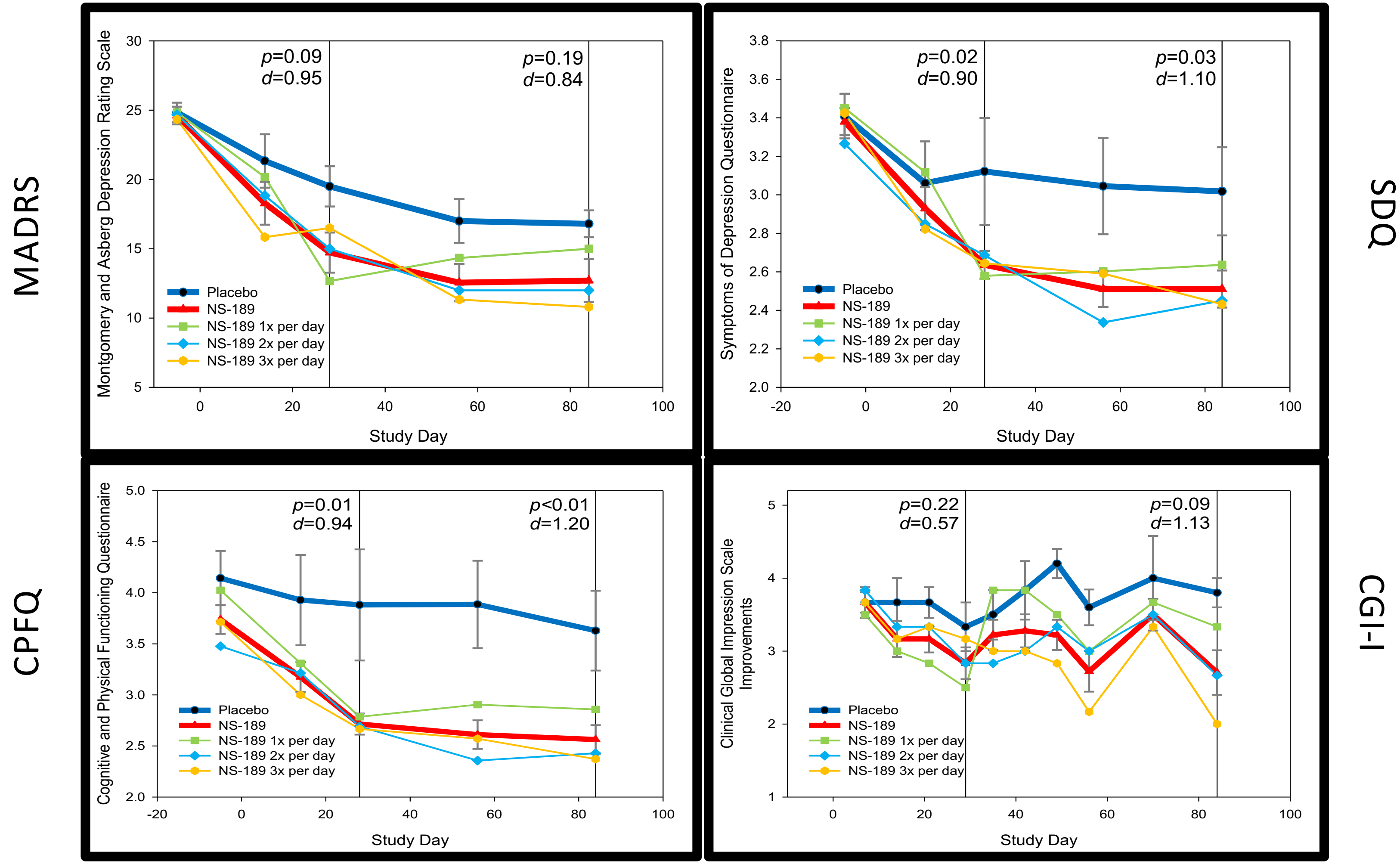
- Double-blind, randomized, placebo-controlled, multiple-dose study with three ascending cohorts (N=24)

Cohort 1	N=8 (6 drug, 2 placebo)	40 mg QD
Cohort 2	N=8 (6 drug, 2 placebo)	40 mg BID
Cohort 3	N=8 (6 drug, 2 placebo)	40 mg TID
Drug Treatment: 28 days	**No-Drug Follow up: 35, 42, 49, 70, 84**	

Participants

- Male or female, 18 to 60 years of age, diagnosed with MDD, recurrent, as per DSM-IV-TR confirmed by SCID-CT
- Patients at screening could be taking an antidepressant medication(s), or have a history of taking antidepressant medication(s) in the past for their depressive disorder
- At least two prior depressive episodes (including current episode)

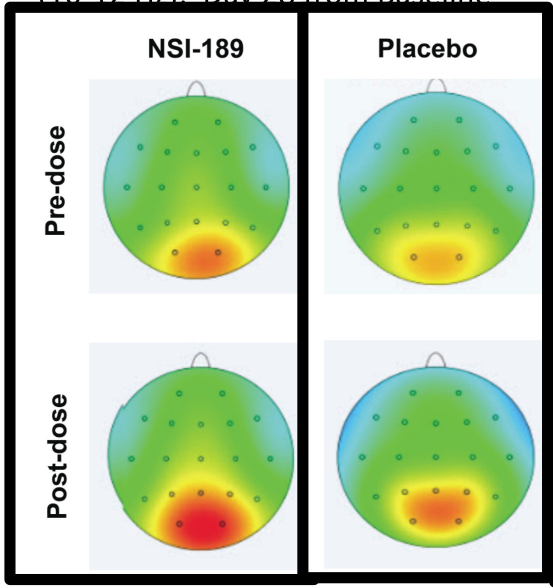
Phase 1b Clinical Outcomes



Biomarker Results

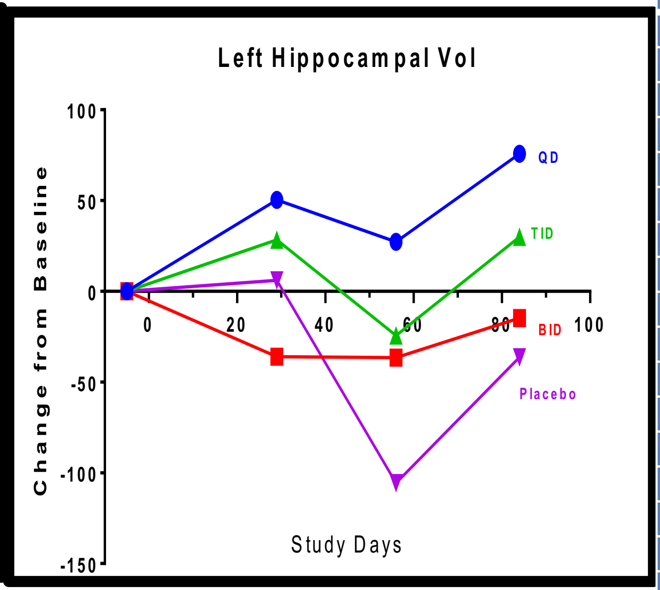
qEEG

Topographs of High Frequency alpha (10-12 Hz): Day 28 from Baseline



Left posterior temporal (T5) (t=2.45, p=0.02)
Left parietal regions (P3) (t=3.31, p=0.004)

MRI



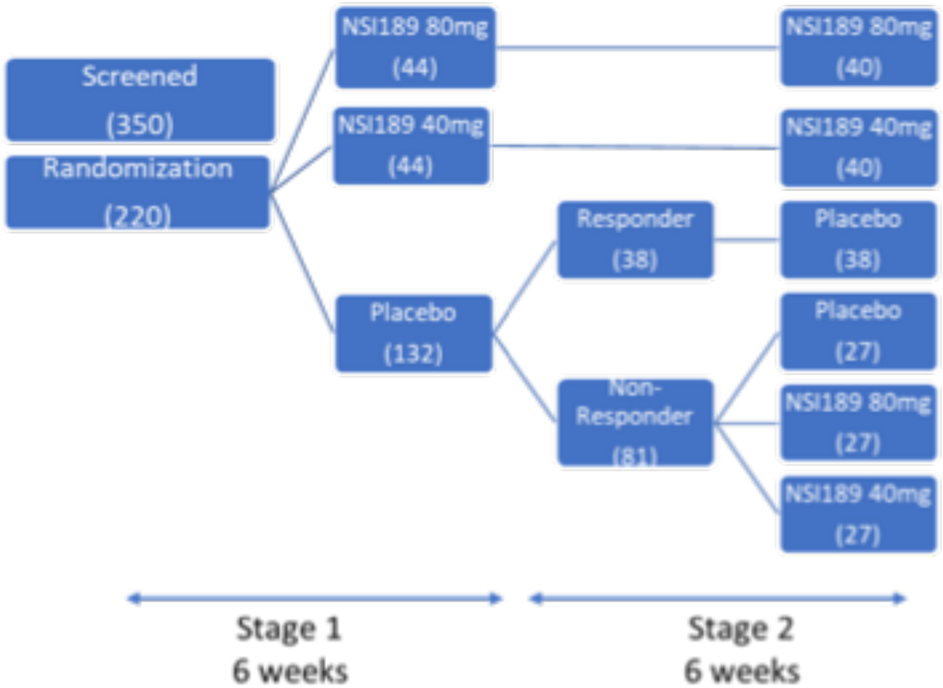
Blood

Pt. ID	Designation	Probablilty
501	PR	1.000
502	R	1.000
504	R	1.000
505	R	1.000
506	R	1.000
508	NR	0.032
602	R	1.000
603	R	0.961
604	PR	1.000
605	PR	1.000
606	PR	0.998
608*	PR*	0.000*
627	R	0.980
701	R	1.000
702	R	0.987
703	R	0.000
705	NR	0.031
706	R	1.000
707	R	0.995

Phase 2a Mono-Therapy of Recurrent MDD

Study Design

Sequential Comparison Parallel Design



Screening period: 14-28 days

Treatment period: 12 wks, Assessments performed weekly

Stat Power: >80% , 2-sided $p \leq 0.05$, d=0.5 (MADRS)

Long-Term follow-up (separate study): 24 weeks to assess durability (open label, all subjects discontinue treatment)

MDD Phase 2a Study Results

Endpoint	Validated/FDA Accepted	40mg stat sig (combined)	Cohen's d (stage 2)	80mg statsig (combined)	Cohen's d (stage 2)
MADRS (Primary)	Yes/Yes	No	0.25	No	0.19
HAMD-17	Yes/Yes	No	0.33	No	0.38
QIDS-SR (patient reported)*	Yes/No	p=0.040 (Stage 2 only)	0.68	No	0.39
SDQ (patient reported)*	Yes/No	p = 0.044	0.64	No	0.20
CPFQ (patient reported)*	Yes/No	p=0.035	0.47	No	0.10
CGI-I	Yes/Yes (2°)	Trend p=0.148	0.58	Trend p=0.081	0.46
CGI-S	Yes/Yes (2°)	Trend p=0.132	0.56	Trend p=0.055	0.66
Cogstate Brief Battery	Yes/No	No	0.2-0.3	No	0.2-0.3
CogScreen-MDD	Yes/Yes (safety only)				
Executive Function*		p=0.048	0.66	Trend p=0.150	0.59
Attention*		P=0.034	0.27	No	0.17
Memory**		p=0.002	1.12	p=0.015	0.69
Working memory*		p=0.020*(Stage 2 only)	0.81	Trend p=0.125	0.51

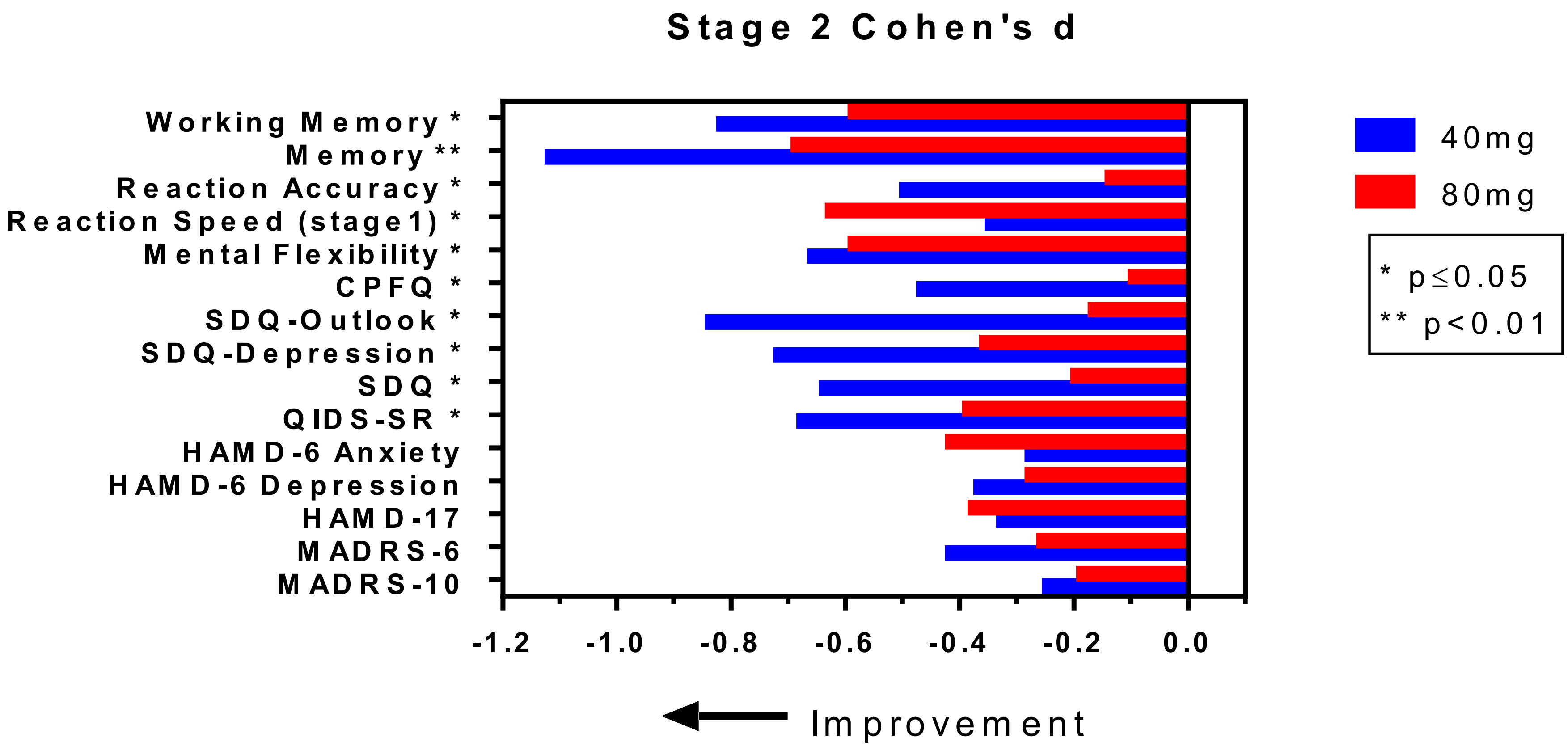
*p<0.05; **p<0.01

CogScreen-MDD Test Findings for NSI-189 v Placebo (Following 6 weeks of Treatment*)

40mg vs. Placebo	80mg vs. Placebo
Simple Attention (SATADRTC); Improved response speed	**Simple Attention** (SATADACC), Improved response accuracy
Complex attention / Executive Function (SATACACC); Improved accuracy	
Memory (SDCDRACC); Improved accuracy	**Memory** (SDCDRACC); Improved accuracy
	Reduced impact of negative feedback on subsequent responses on Working Memory task SATINRTI; Improved response speed

*SCPD design not suitable for evaluating effects of 12 weeks of treatment.

Effect of NSI-189 vs. Placebo on Recurrent MDD



Number of CogScreen-MDD Variables (n=33) Showing Significant ($p < 0.05$) Correlation with Depression Severity

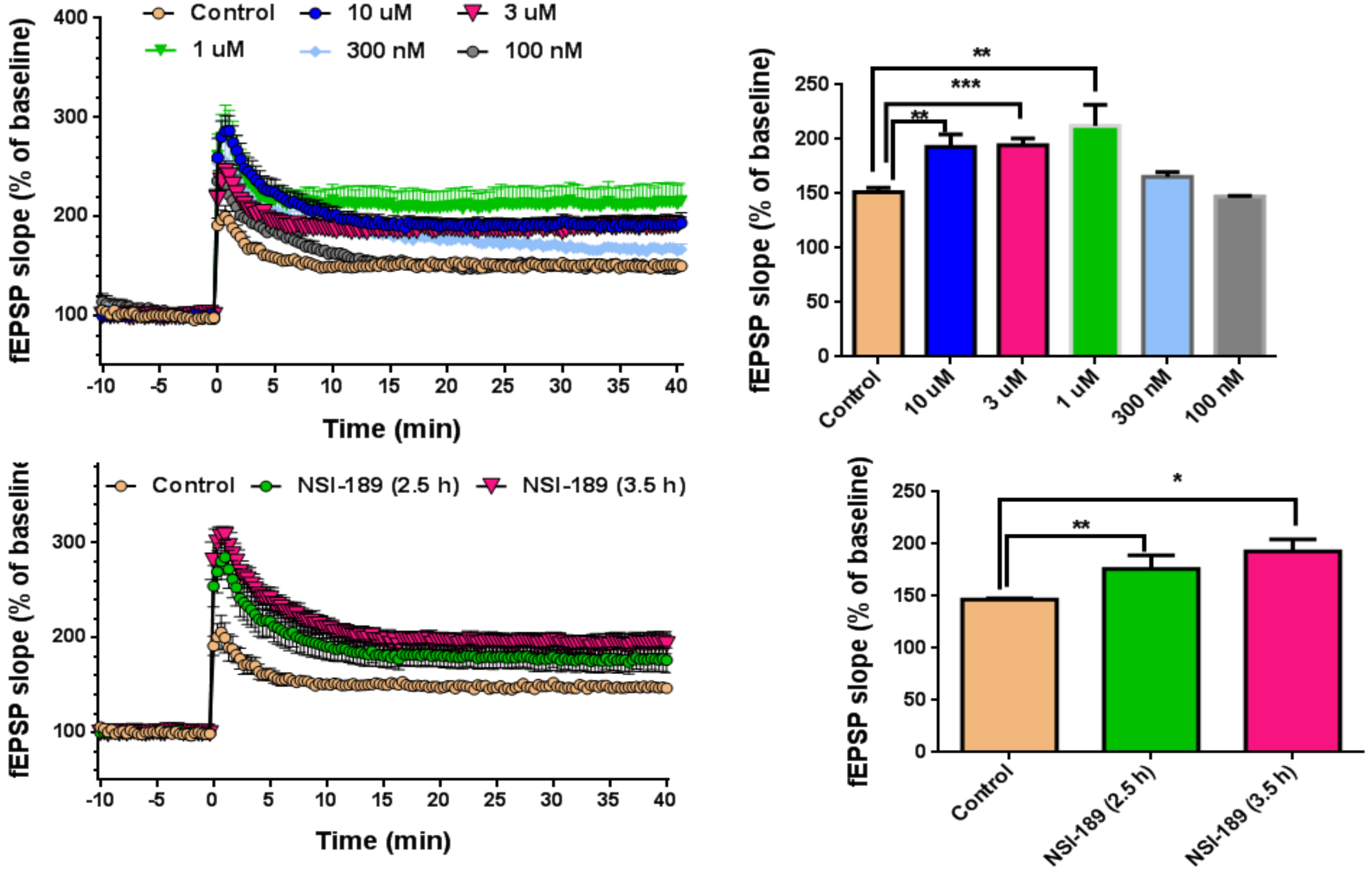
	At Baseline Visit	At 12 –Week Visit
MADRS	4 (11%)	4 (11%)
HAMD-17	5 (14%)	6 (16%)
SDQ	6 (16%)	3 (8%)
CPFQ	**11 (30%)**	5 (14%)

- For 33 variables, 2 variables (5%) are expected by random chance to show correlation at $p<0.05$.
- Findings suggest that performance on CogScreen-MDD has little relationship to clinician-rated depression severity.
- Strongest relationship found is between self-reported cognitive difficulties (CPFQ) and CogScreen-MDD at Baseline.

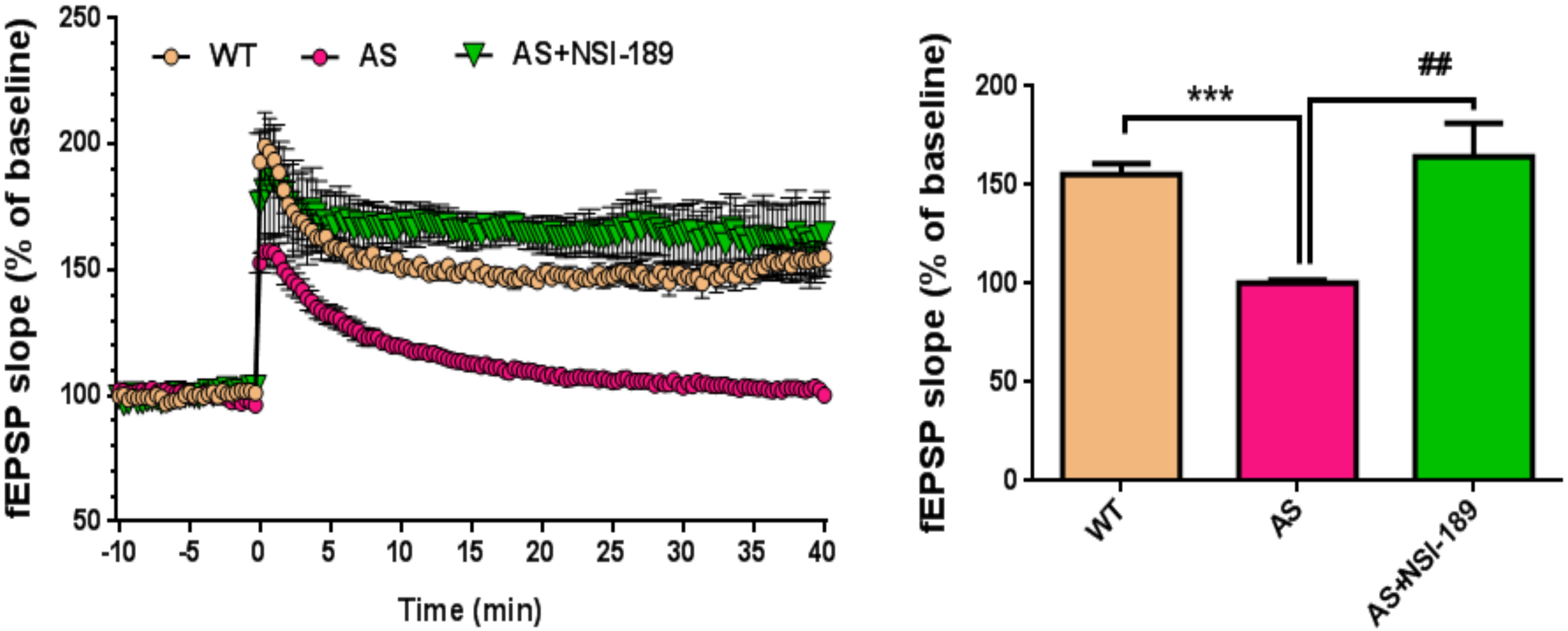
Summary

- NSI-189 (40/80mg) showed significant improvement in cognitive functioning following 6-weeks of treatment.
- CogScreen-MDD measures of processing speed, working memory, executive functioning, and negative feedback, were found to be relatively insensitive to depression severity but were sensitive to treatment with NSI-189.
- Improvements in cognitive functioning appeared to be independent of clinician-rated change in mood.

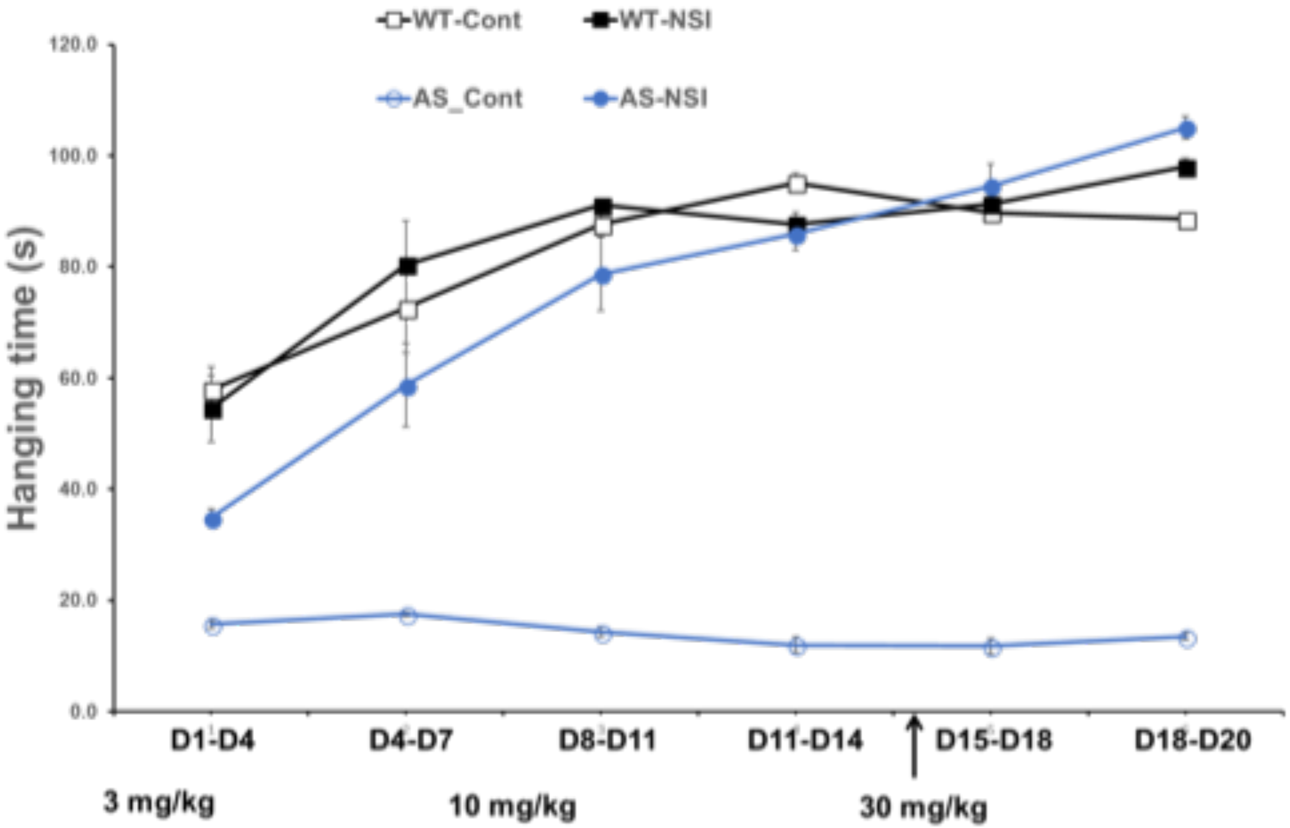
Dose- & Time-dependent Enhancement of LTP Magnitude *in vitro*



Restoration of LTP from Angelman Syndrome mouse *in vitro* (1 microM)

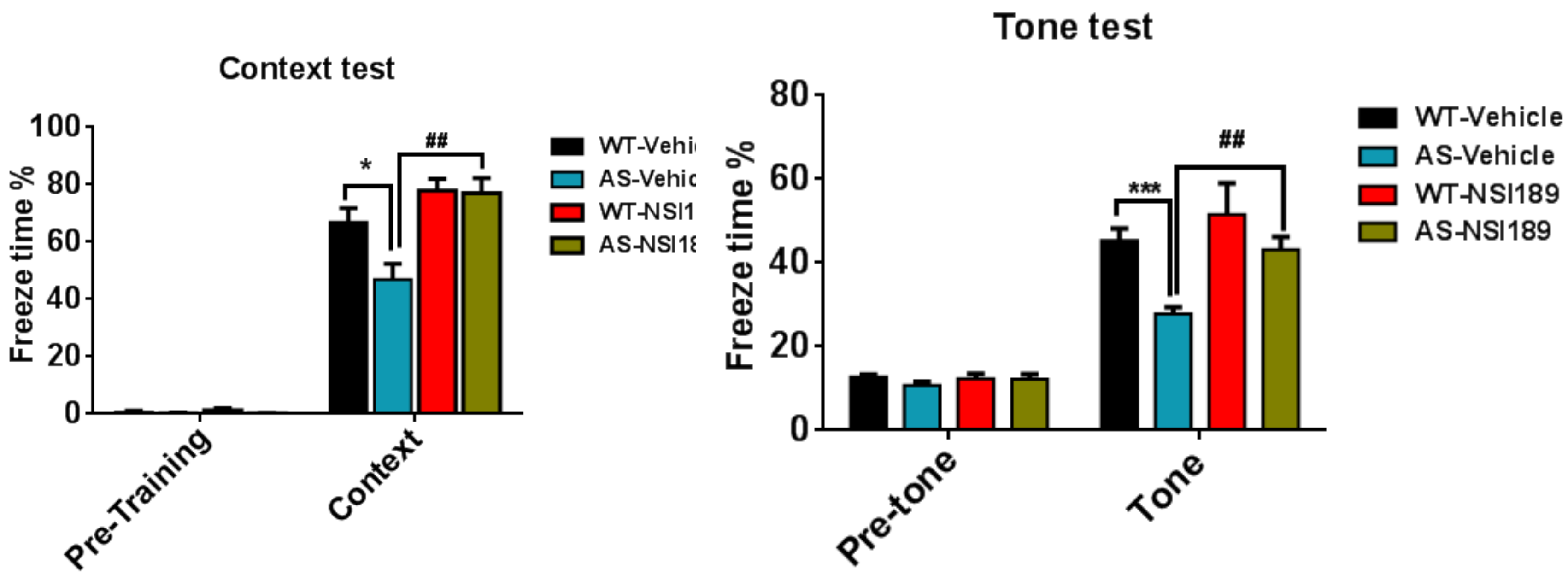


Reversal of Motor Deficit from Angelman Syndrome mouse *in vivo* (30mg/kg i.p.)



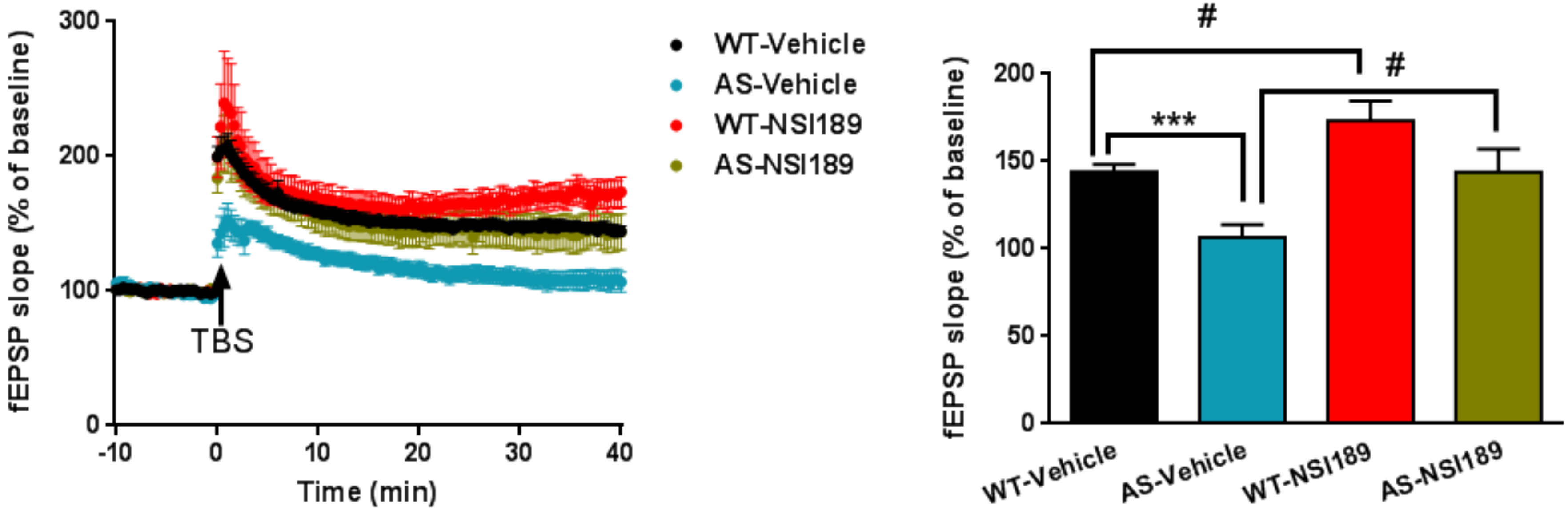
Reversal of Cognitive Deficit from Angelman Syndrome mouse *in vivo* (30mg/kg i.p.)

Fear conditioning test

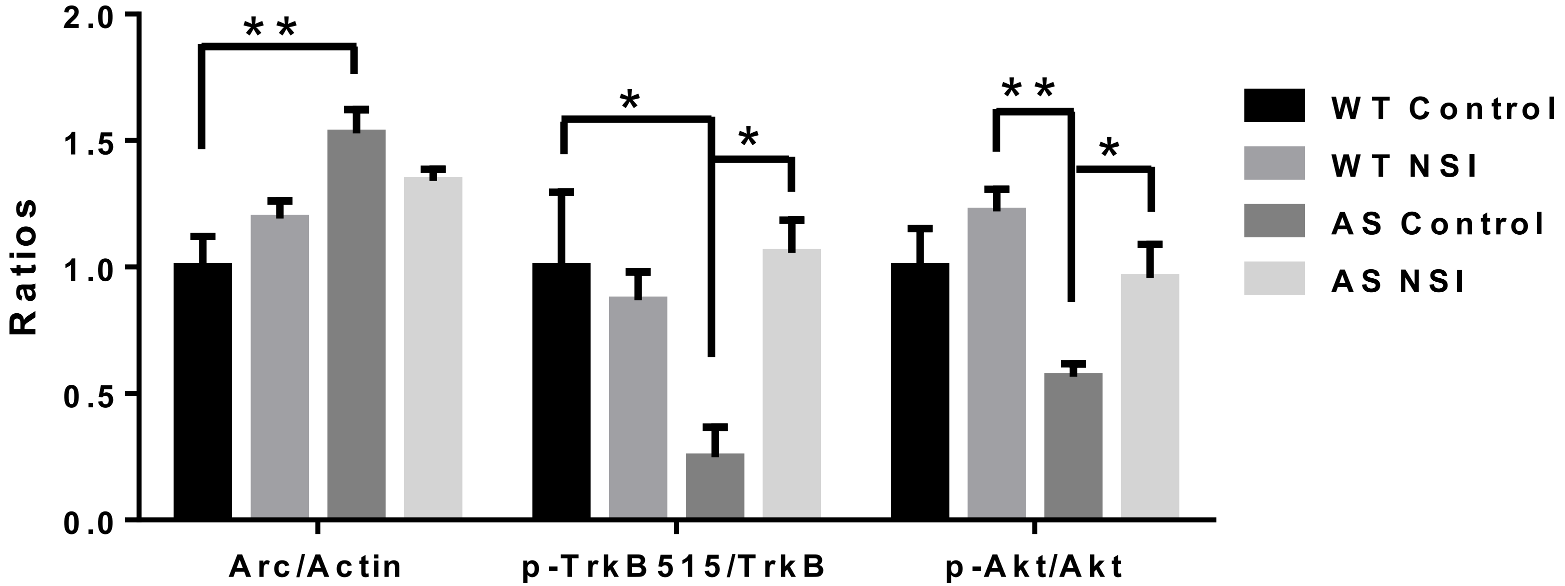


Restoration of LTP from Angelman Syndrome mouse *in vivo* (30mg/kg i.p.)

TBS induced LTP



Normalization of Synaptic Proteins in AS mice hippocampus (30mg/kg i.p.)



Conclusion

- At 1-3 microM in the CNS, NSI-189 induces fast treatment effects by mechanisms enhancing synaptic plasticity
- At 0.1 – 0.3 microM in the CNS: NSI-189 induces and maintains treatment effects chronically by mechanisms enhancing neurogenesis and regeneration