Project Committee on Translational Imaging in Safety Assessment

William Slikker, Jr., Ph.D., ATS
National Center for Toxicological Research
Food and Drug Administration
Jefferson, Arkansas

The views presented do not necessarily reflect those of the FDA

NCTR Mission

- **NCTR conducts peer-reviewed research and develops new scientific tools for FDA to improve public health.**
- **This research produces innovative tools to solve anticipated complex toxicological and other health problems, thus enhancing the science of regulatory decision making.**
- **NCTR provides multidisciplinary training and fosters national and international collaborations with scientists from government, academia, and industry.**

Perspectives on the HESI Imaging Committee

- HESI Committee offers opportunity to pool technical, financial, and human resources; Value added by sharing best practices and experience;
- This type of consensus building essential to moving the field of imaging for safety assessment to a greater level of acceptance, development of standards and common practice;
- Open discussion between government (research and regulatory) scientists with drug development scientists in industry offers the opportunity to assess the practical potential for imaging to improve safety evaluation;
- Significant interest and involvement from numerous pharma companies, CROs, government agencies and academic labs speaks to the unmet needs and opportunities in this area.

When should we use Imaging?

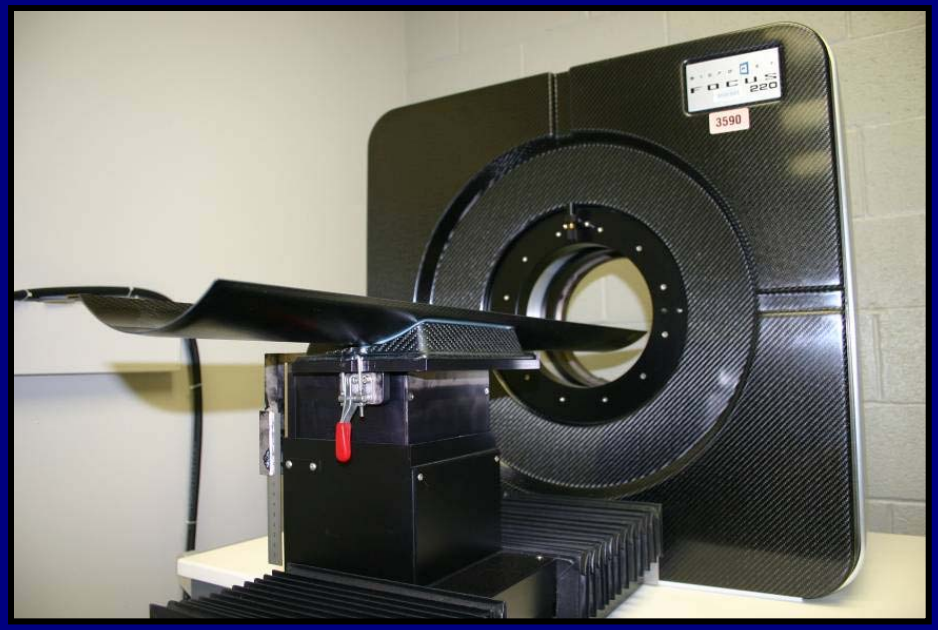
- Need physiological, functional and anatomical data (simultaneously)
- Desire a Noninvasive approach
- Require a Longitudinal design
- Want animal and cost savings

DIFFERENT MODALITIES/ DIFFERENT INFORMATION

ANATOMY	PHYSIOLOGY	METABOLISM	MOLECULAR	FUNCTIONAL
X-ray	USG	MRSI	PET	fPET
MRI	MRSI	PET	MRI	fMRI
CT	SPECT			OI
USG	PET			IR
	IR			

MRI = Magnetic Resonance Imaging; CT = Computed Tomography; USG = ultrasonography; MRSI = Magnetic Resonance Spetroscopic Imaging; PET = Positron Emission Tomography; SPECT = Single-Photon Emission Computed Tomography; IR = infrared; fPET = functional PET; fMRI = functional MRI; OI = optical imaging

Bio-Imaging at NCTR/FDA



MicroPET

23 cm bore

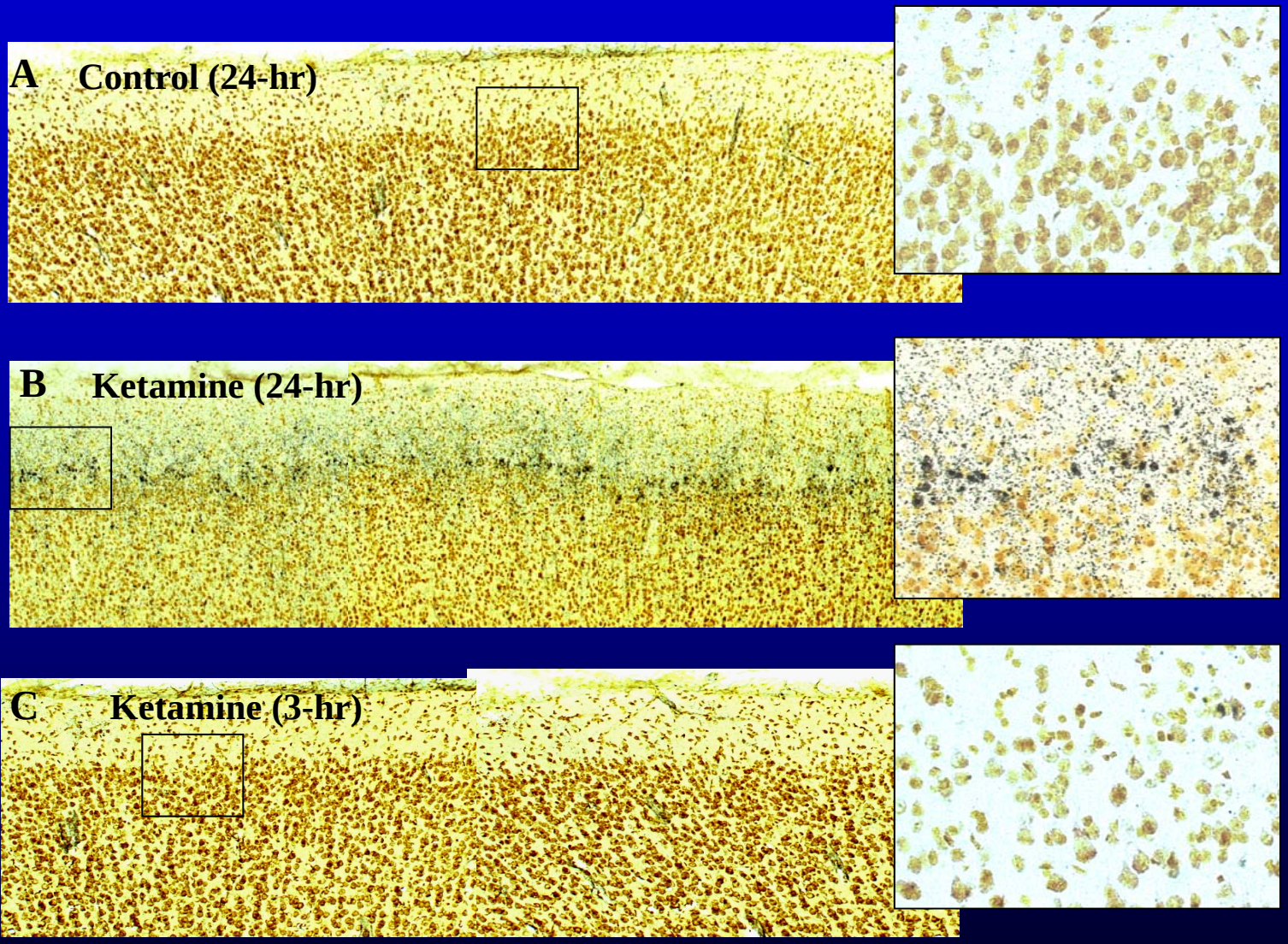
Biospec MRI

7 Tesla, 30 cm bore

Pediatric Anesthetics

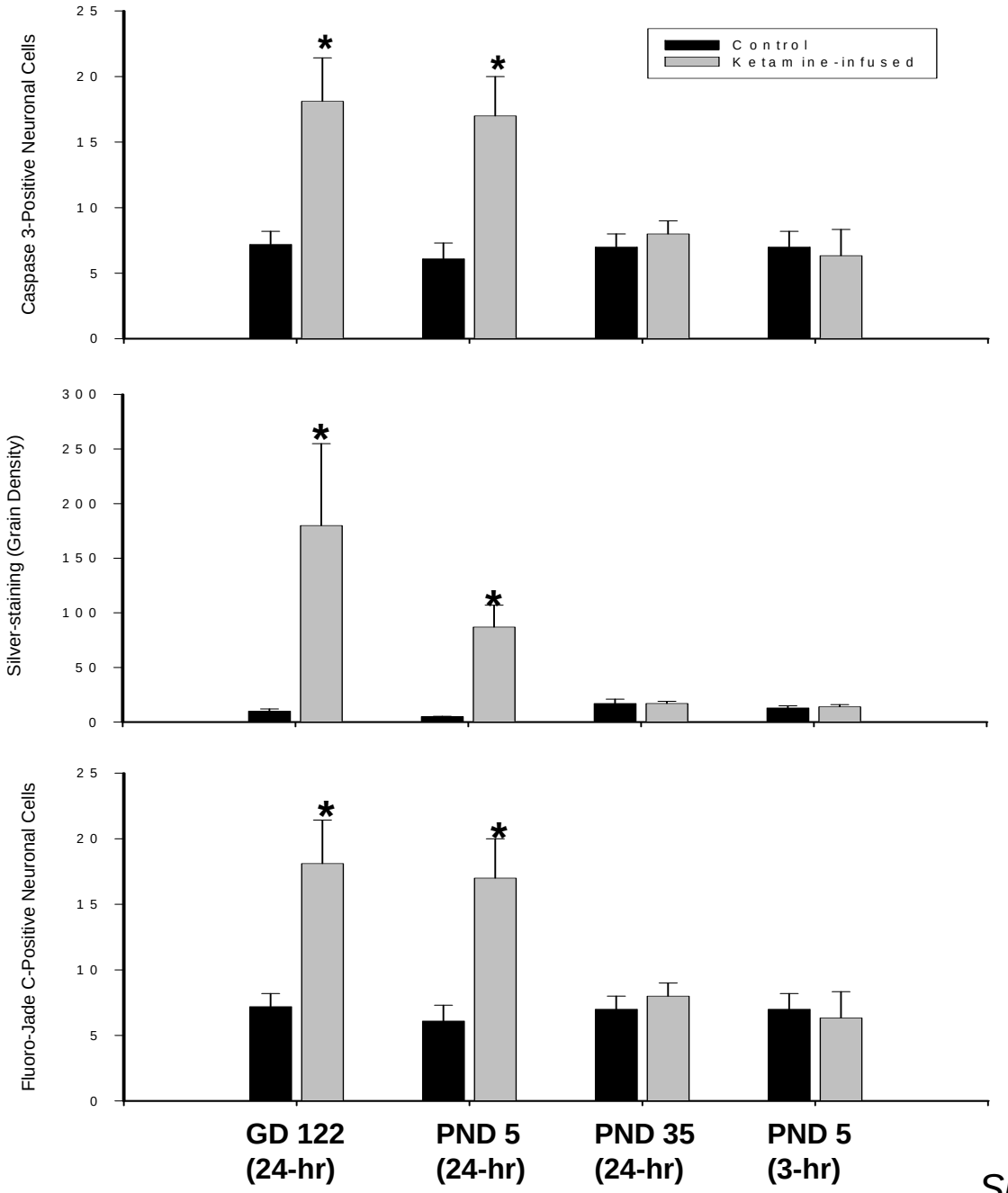
- Ketamine, a non-competitive NMDA receptor antagonist, has been used as a general pediatric anesthetic for surgical procedures in infants.

- It is one of the most commonly used agents for mild sedation in pediatric emergency departments, endoscopy suites, catheterization laboratories, radiology suites and intensive care units.

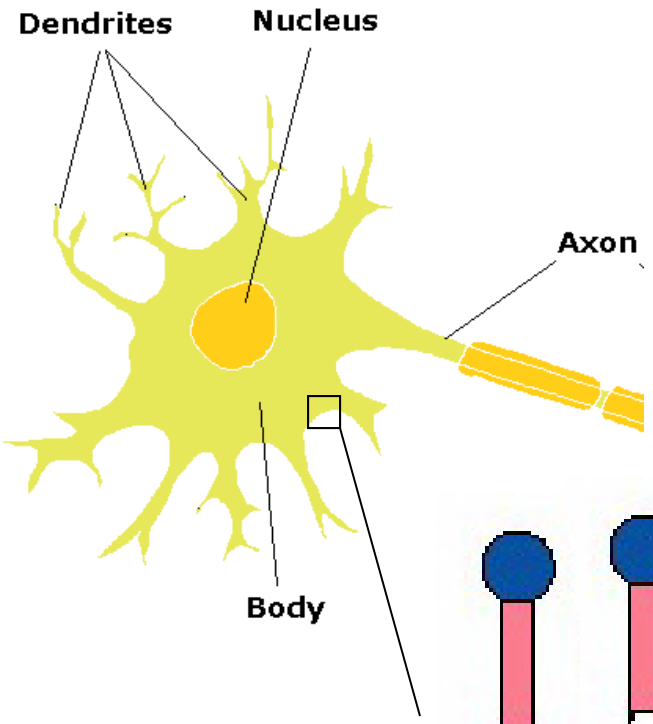


Slikker et al., 2007

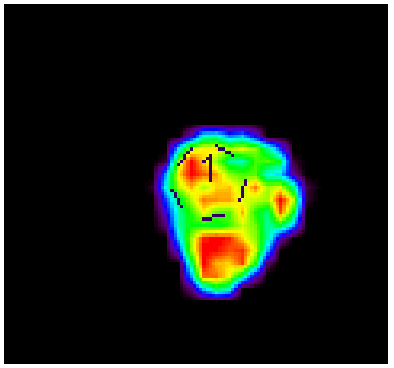
Effects of Ketamine-induced anesthesia on the frontal cortex of the developing monkey



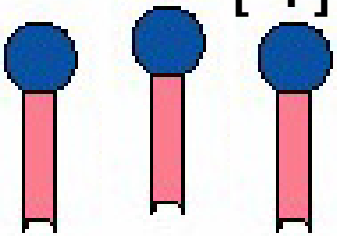
Slikker et al., 2007



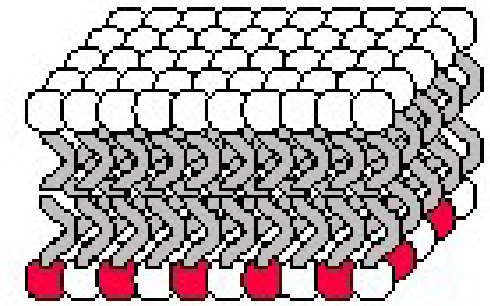
microPET images from a ketamine-treated rat using the specific tracer [^{18}F]-Annexin V



[^{18}F]-Annexin V



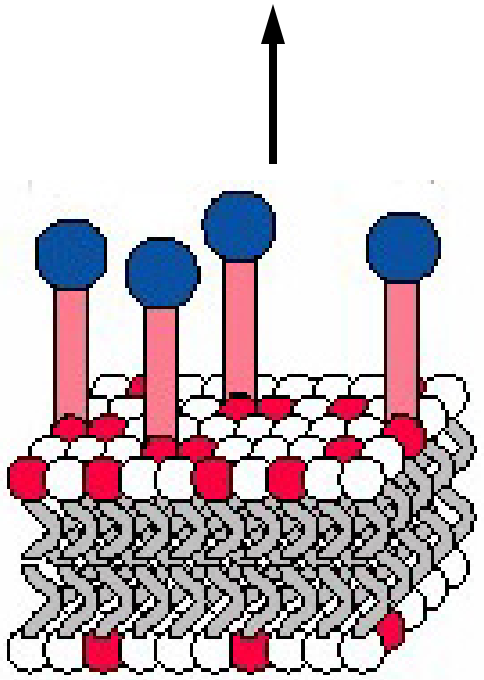
Plasma membrane



Cytoplasm

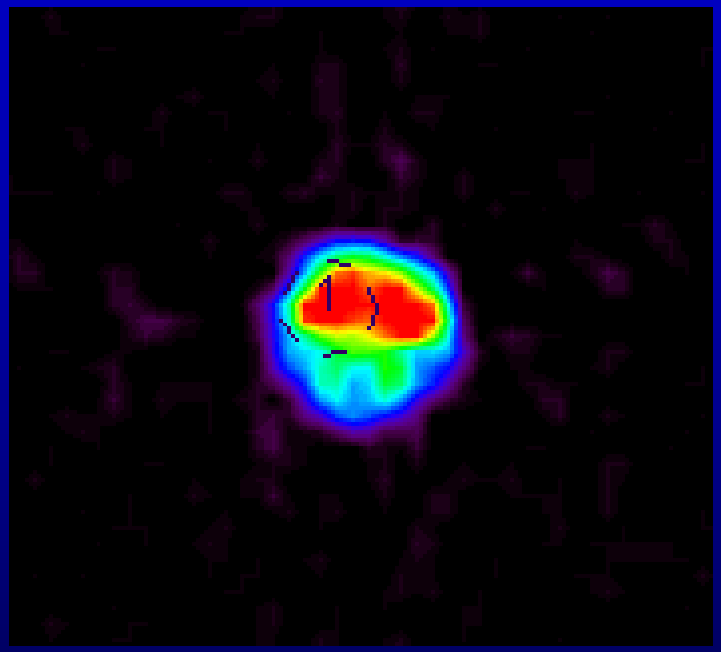
Apoptosis

Externalization of phosphatidylserine



Dorsal

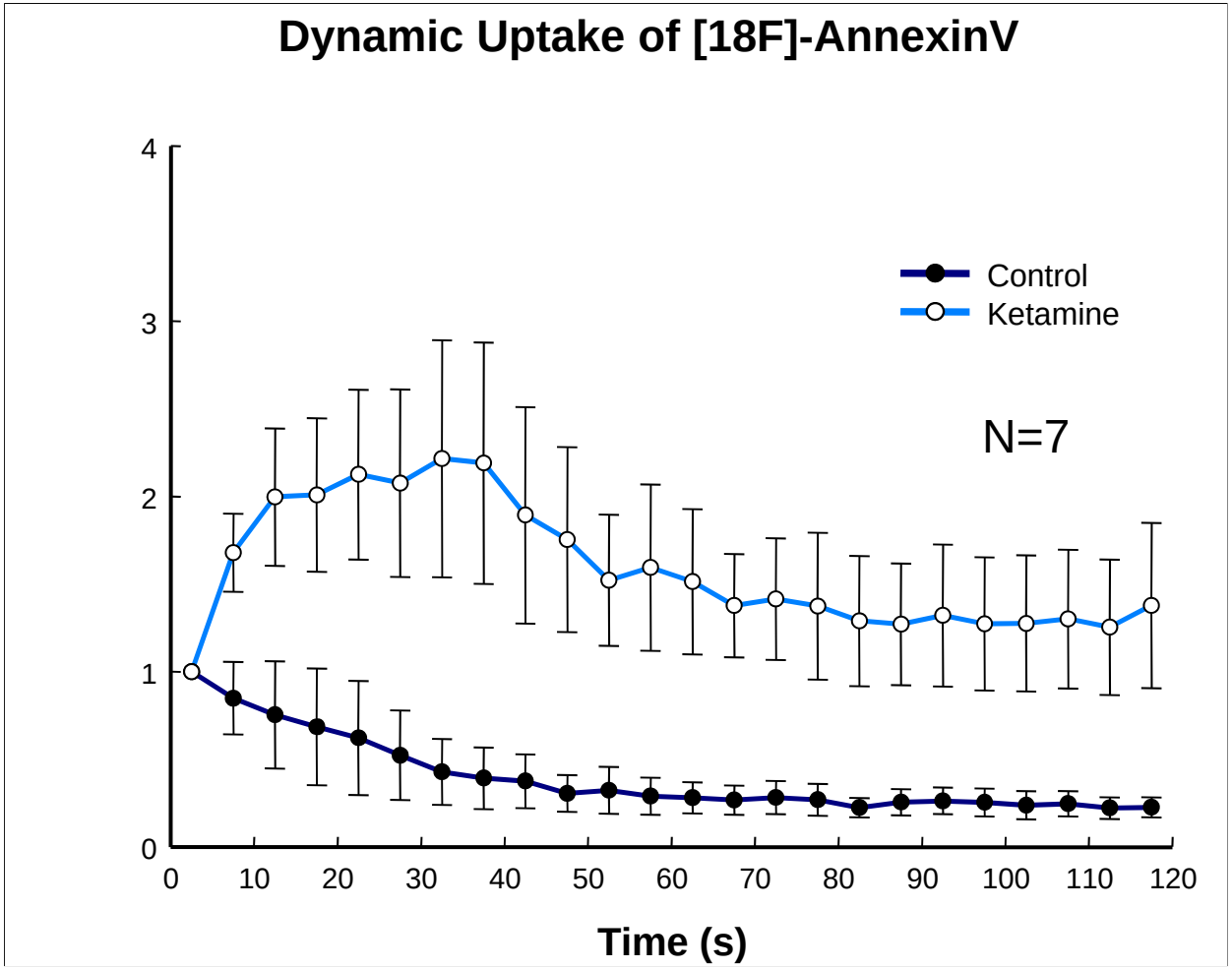
Left



Right

Ventral

Drs. Xuan Zhang (NCTR), Marc Berridge (UAMS), Tucker Patterson, Glenn Newport, Cheng Wang and Merle Paule (NCTR)



SUV=total radioactivity in ROI x body weight / injection dose

Zhang et al., 2009

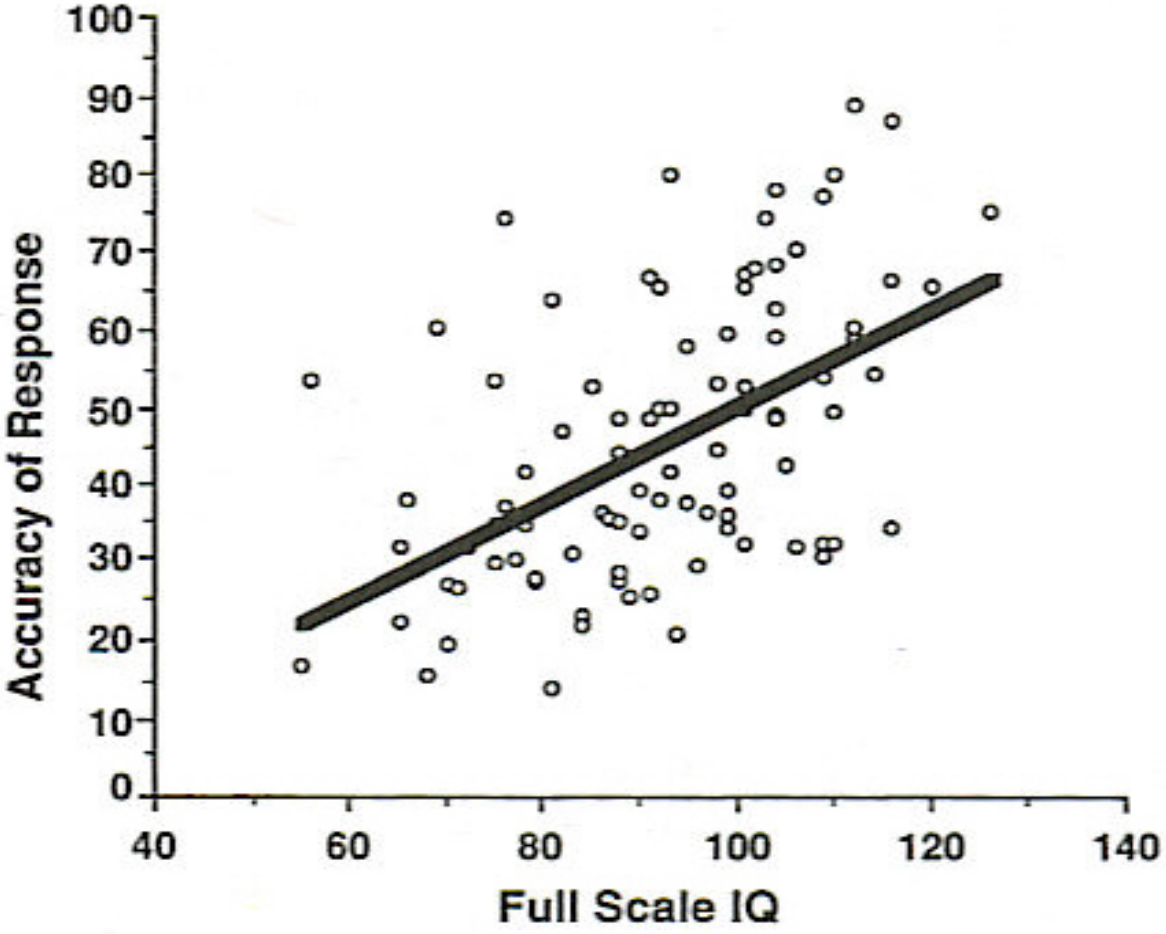
MicroPET Ligands and Targets

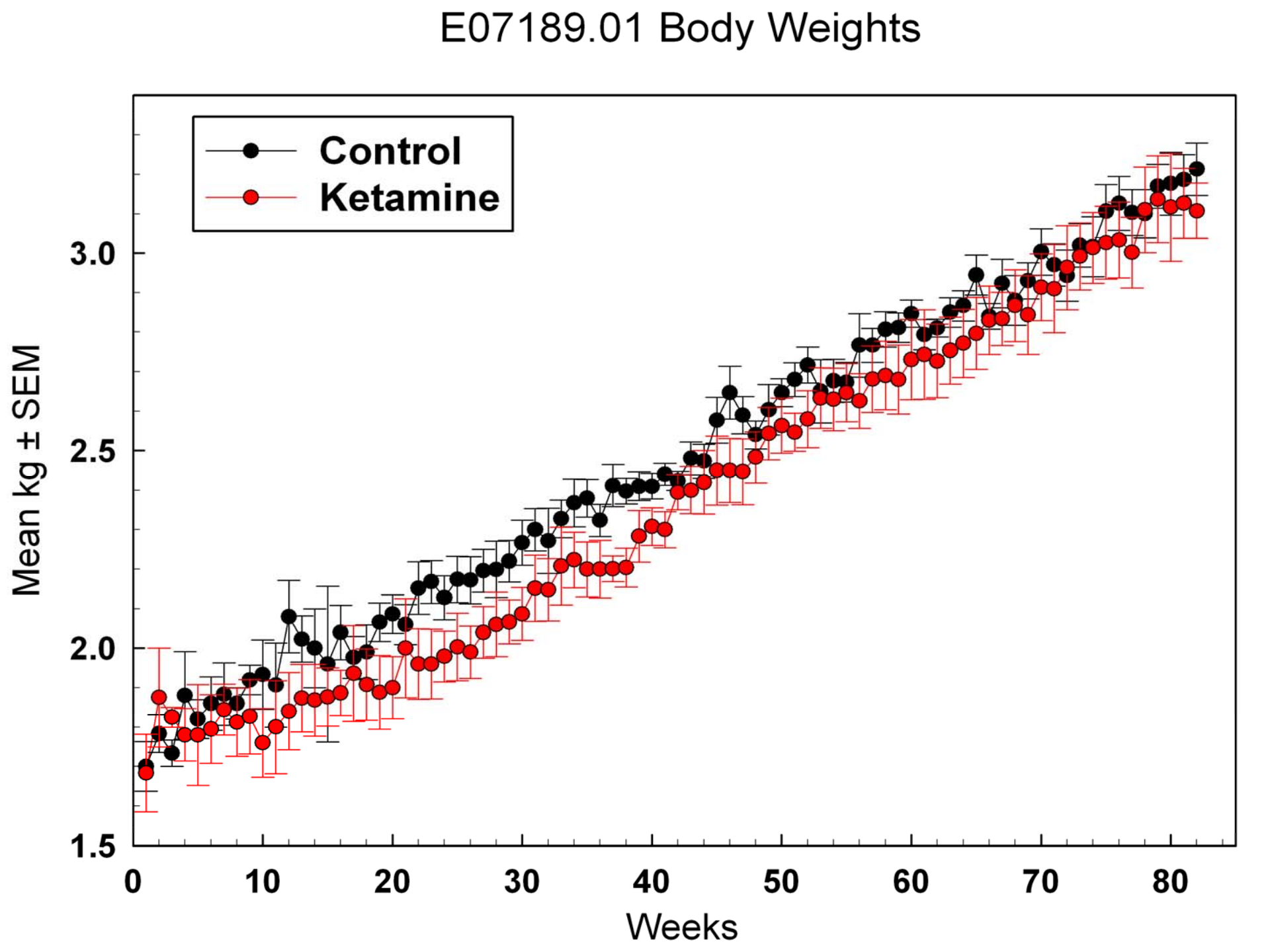
- [^{18}F]-Annexin V: externalized phosphatidylserine (PS) on the extracellular side of the plasma membrane of apoptotic cells
- [^{18}F]-DFNSH: intracellular accumulation in apoptotic cells
- [^{18}F]-AV 45: Aß plaques (amyloid)
- [^{18}F]-FEPPA: peripheral benzodiazepine receptor

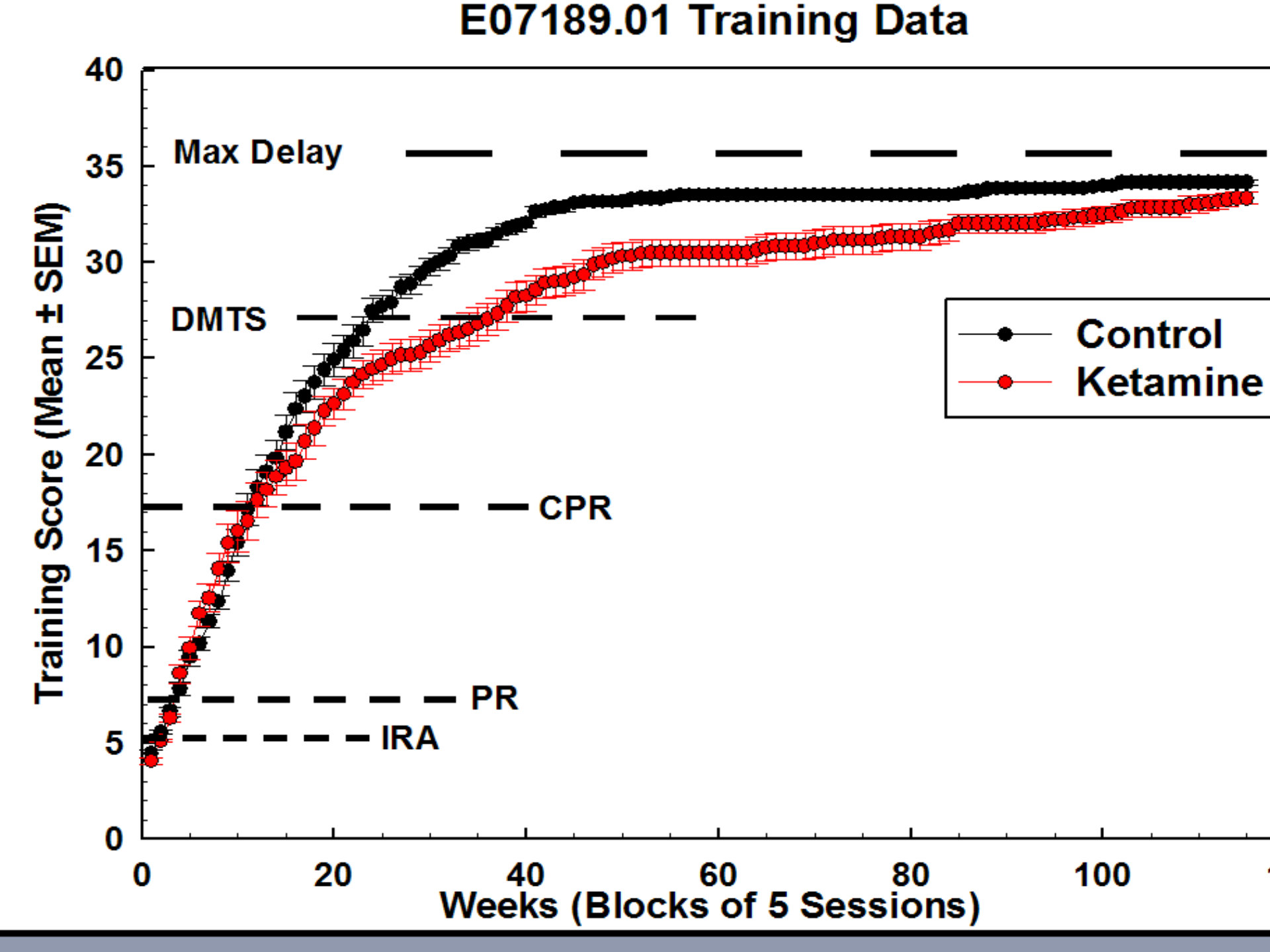
National Center for Toxicological Research (NCTR) Operant Test Battery (OTB) Assessments

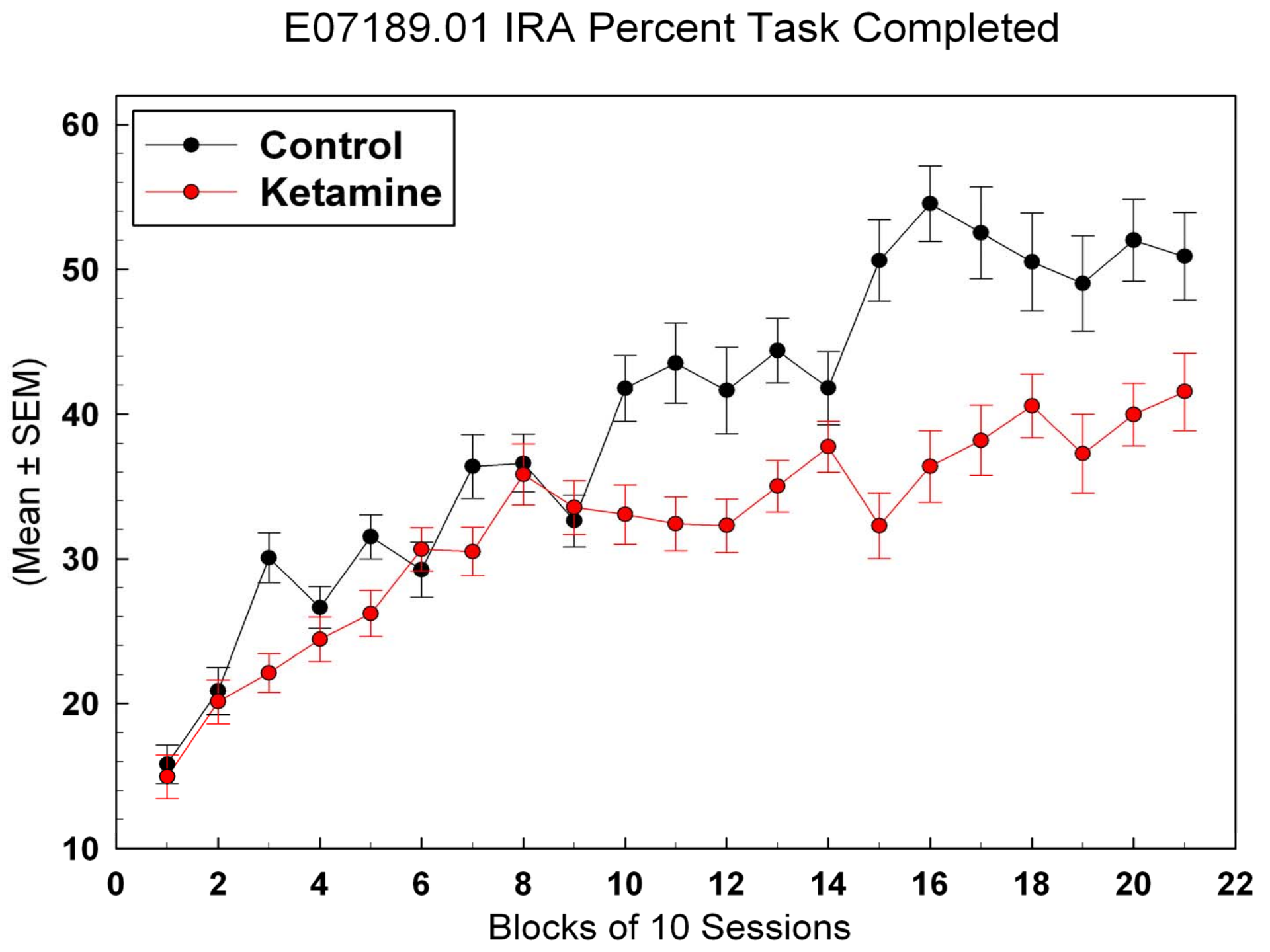
- Motivation
- Color and Position Discrimination
- Learning
- Short-term Memory

Learning Task




E07189.01 Body Weights
Control
Ketamine
Mean kg ± SEM
3.0
2.5
2.0
1.5
0
10
20
30
40
50
60
70
80
Weeks


E07189.01 Training Data
Training Score (Mean ± SEM)
Weeks (Blocks of 5 Sessions)
Max Delay
DMTS
CPR
PR
IRA
Control
Ketamine
0
5
10
15
20
25
30
35
40
0
20
40
60
80
100


E07189.01 IRA Percent Task Completed
Control
Ketamine
(Mean ± SEM)
Blocks of 10 Sessions
60
50
40
30
20
10
0
2
4
6
8
10
12
14
16
18
20
22

Applications of Imaging to Toxicology and Risk Assessment

- Multiparametric analysis (analysis of same animal over time)
- Unique information – anatomy, physiology, genetics, metabolism, function (animal model validation)
- Quantitative measures – PK/PD, volumetric analysis, gene expression
- Preclinical to clinical – animal to human
- Biomarkers – translational surrogate markers

Acknowledgements

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