

# Effects of Opioids on Cognition and Psychomotor Performance

What Test(s) Should Be Considered for a Standardized Abuse Liability Assessment Battery?

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# Outline of Presentation

- Why test?
- What are some tests that have been used to assess opioid effects on performance?
  - Some results from opioid ALA studies with some of the tests
- Preliminary recommendations

# In ALA, why test for cognitive and/or psychomotor impairment?

*British Journal of Addiction* (1991) 86, 1595-1600

## **Performance and physiological measures in abuse liability evaluation**

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### **Abstract**

*Abuse liability testing involves an evaluation of the likelihood of drug self-use and also an evaluation of the harmful effects of drug use. This paper reviews the rationale and utility of examining performance and physiological measures in clinical abuse liability evaluation. It is concluded that there are three important reasons to employ such measures in abuse liability studies: (1) to serve as a reference point to allow for between drug and across measure comparisons; (2) to directly quantify dose-response functions on multiple dimensions of drug effect and thus evaluate the overall profile of effects; and (3) to provide information on the likelihood that drug use will produce harmful effects. The review illustrates each of these purposes and briefly summarizes conclusions from previous studies employing performance and physiological measures in the abuse liability evaluation of sedatives, stimulants, and opioids.*

## In ALA, why test for cognitive and/or psychomotor impairment?

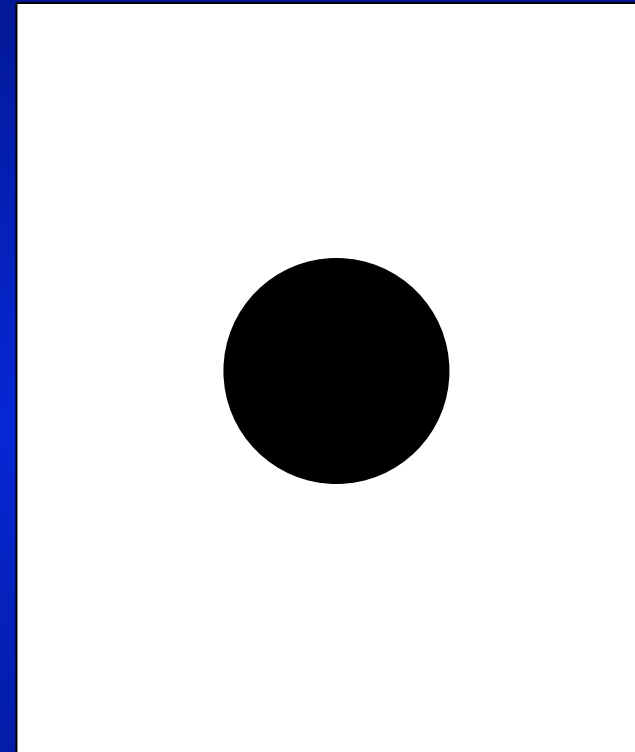
- To directly quantify dose-response functions on multiple measures of drug effect and thus evaluate the overall profile of effects
  - *To provide a more complete characterization of the psychoactive effects of the drug*
- To provide information on the likelihood that drug use will produce harmful effects
  - *Does the drug possess behavioral toxicity, and if so, to what degree?*

# Different ways cognitive and psychomotor performance are measured

- Psychophysical and perceptual processes
  - Critical flicker fusion
  - Maddox Wing Test
- Simple motor performance and reaction time
  - Eye hand coordination
  - Simple reaction time
- Information processing
  - Digit Symbol Substitution Test
  - Logical reasoning
  - Continuous Performance Test
- Complex performance
  - Multiple tasks (divided attention)
- Memory
  - Immediate and delayed recall of words or pictures
  - Two-back task
  - Meta-memory

# Psychophysical, perceptual processes

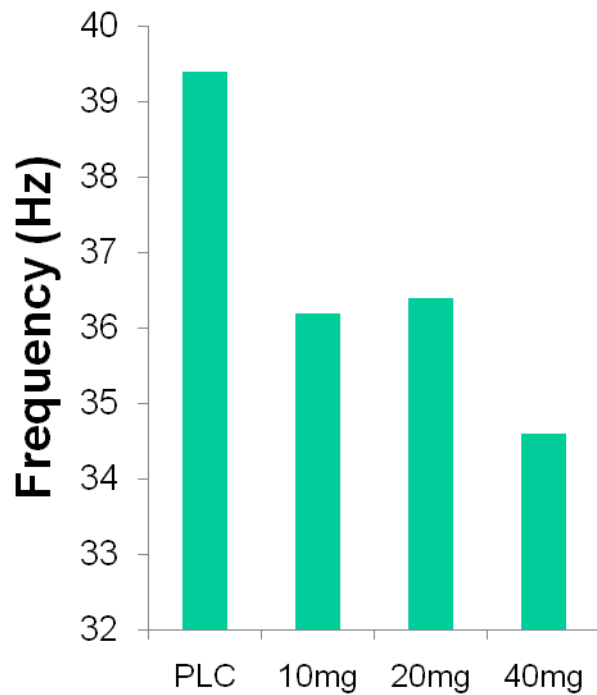
## Critical flicker fusion



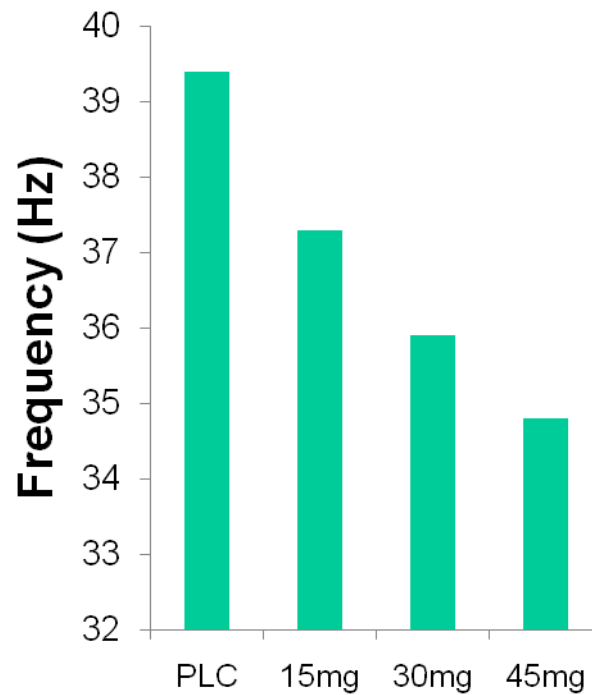
- A measure of alertness/sedation.
- At onset of task rapidly flickering light stimulus appears to be fused and as flicker rate is decreased, person eventually detects that.

# Fusion-to-Flicker

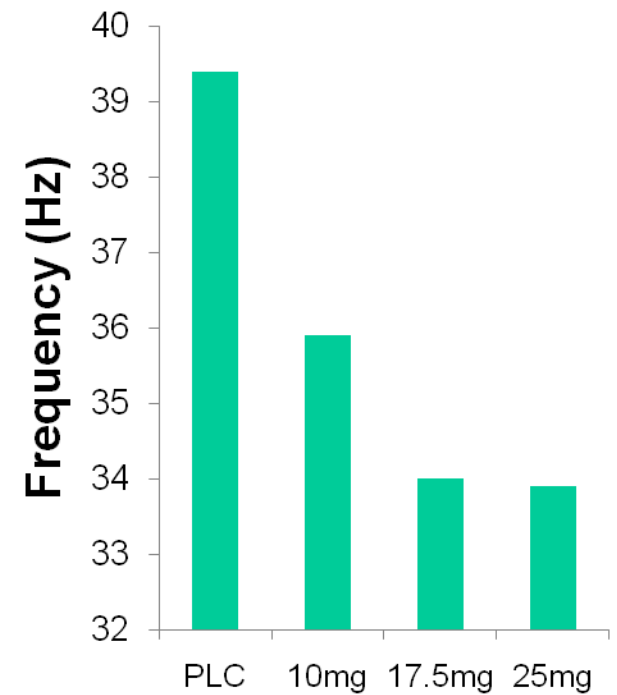
## OXYCODONE



## HYDROCODONE



## HYDROMORPHONE



# Maddox Wing Test

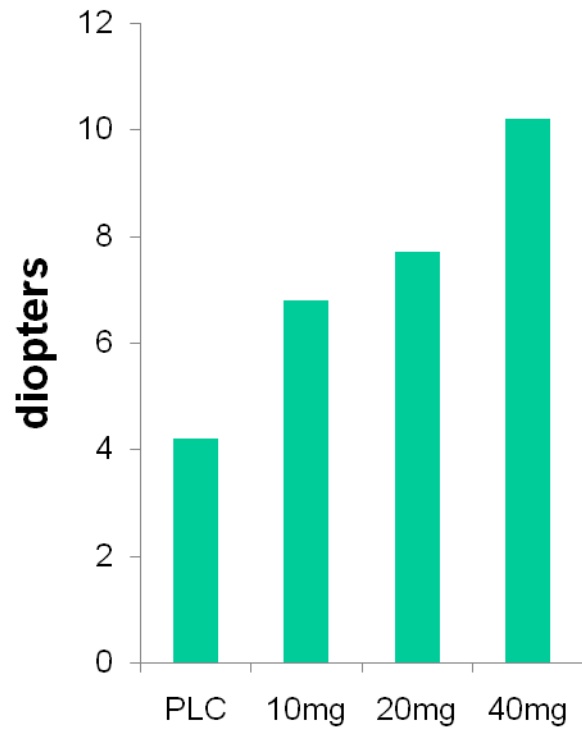


- A perceptual test
- Opioids relax muscles around eyeballs, which results in them diverging outwards (walleyed)
- Phenomenon is “exophoria,” measured in prism diopters

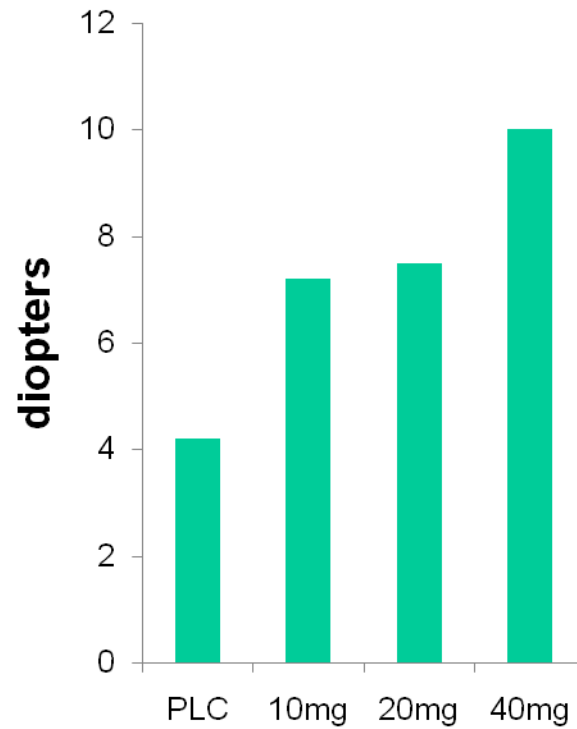


# Maddox Wing Test

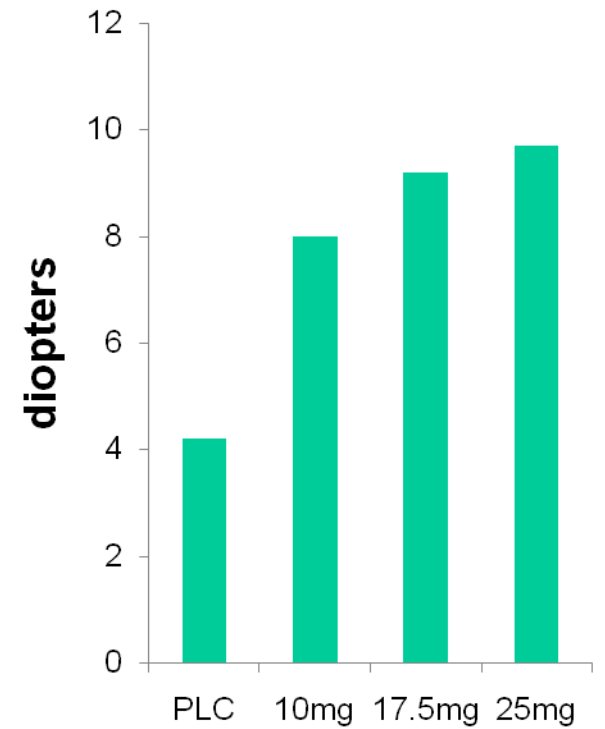
## OXYCODONE



## HYDROCODONE

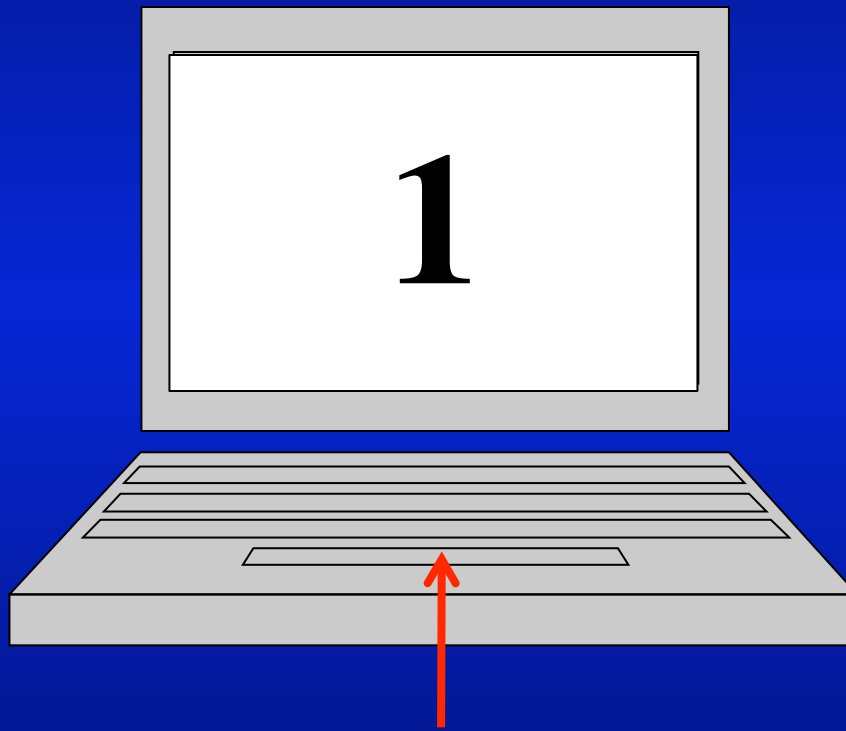


## HYDROMORPHONE



# Simple motor performance & RT

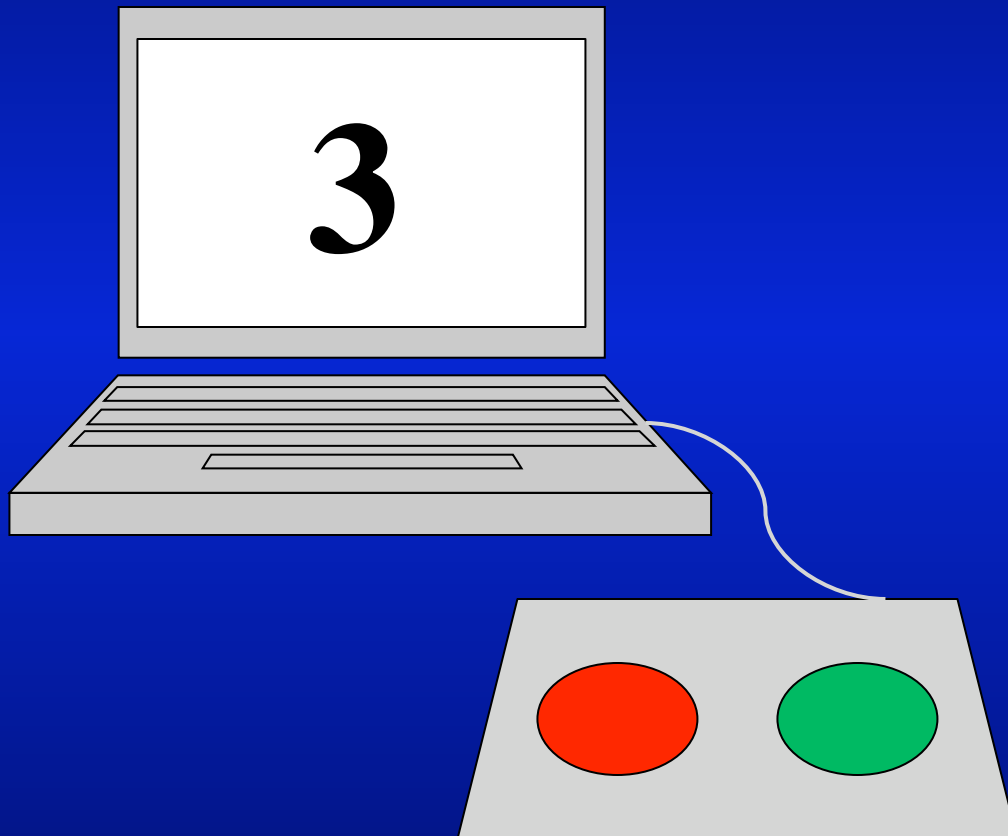
*visual reaction time test*



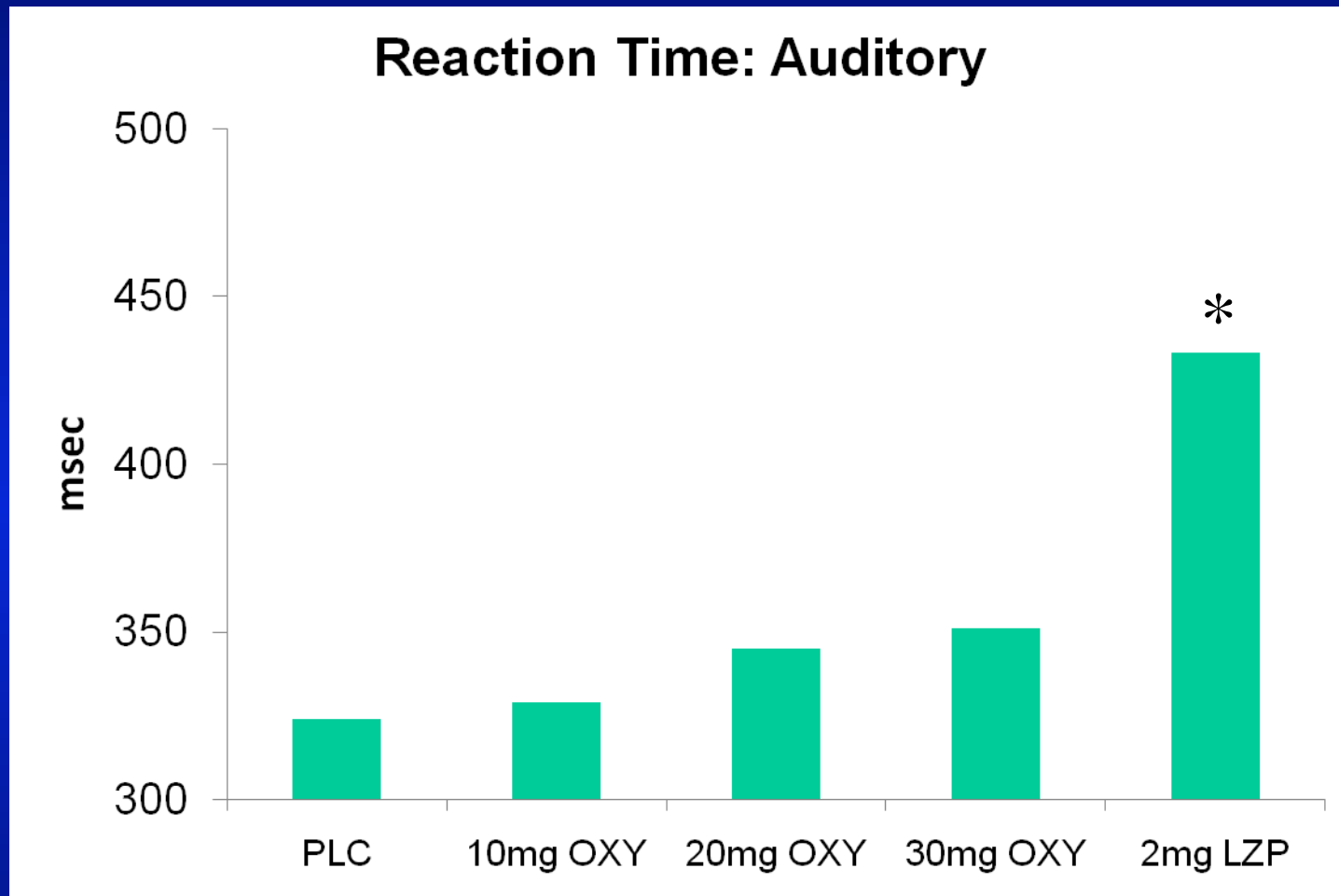
Space bar

- Subjects asked to press the space bar as soon as number 1 appears on the screen

# Reaction Time: Choice

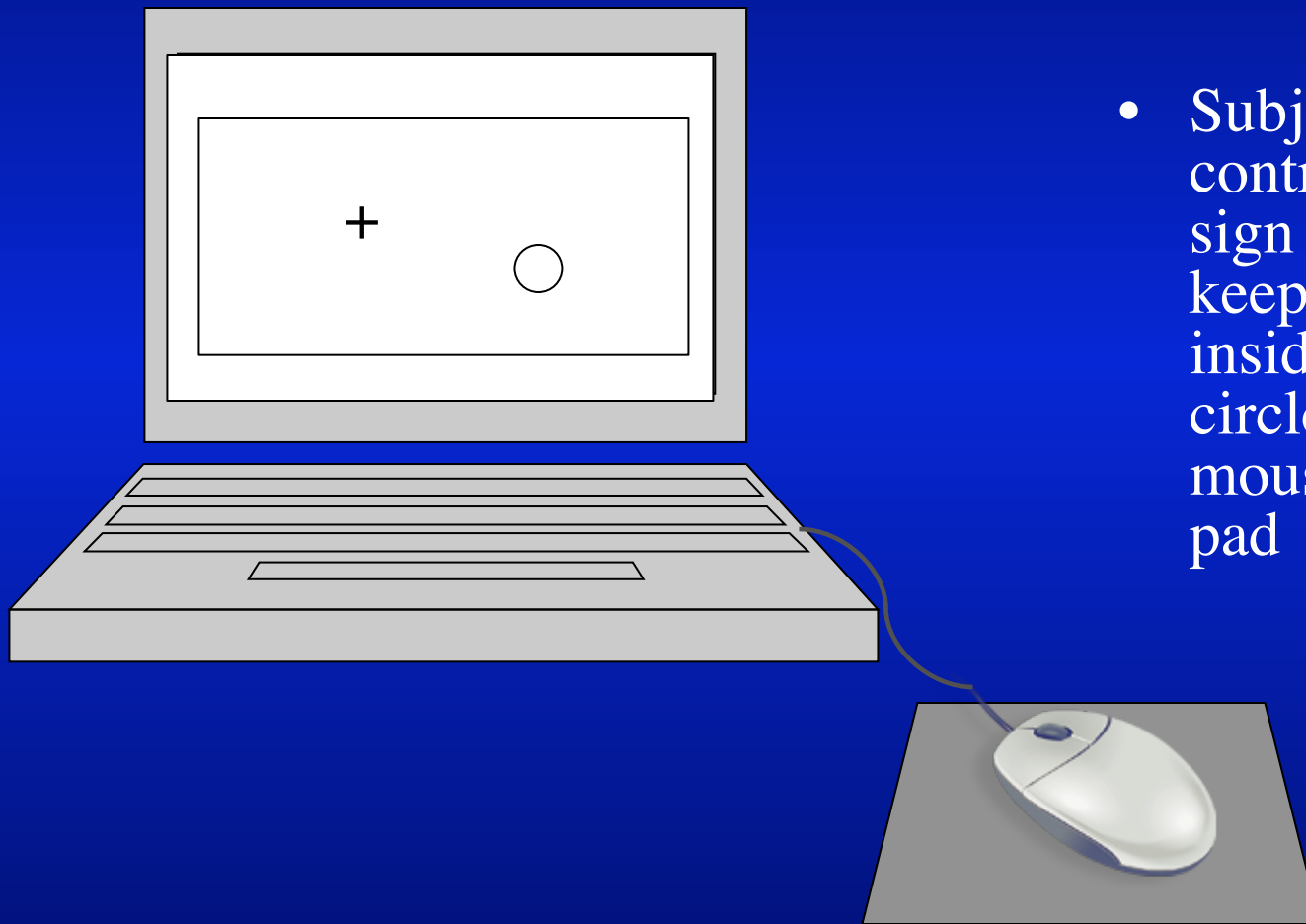


- If number 3 appears on the screen, hit the red button
- If number 6 appears on the screen, hit the green button

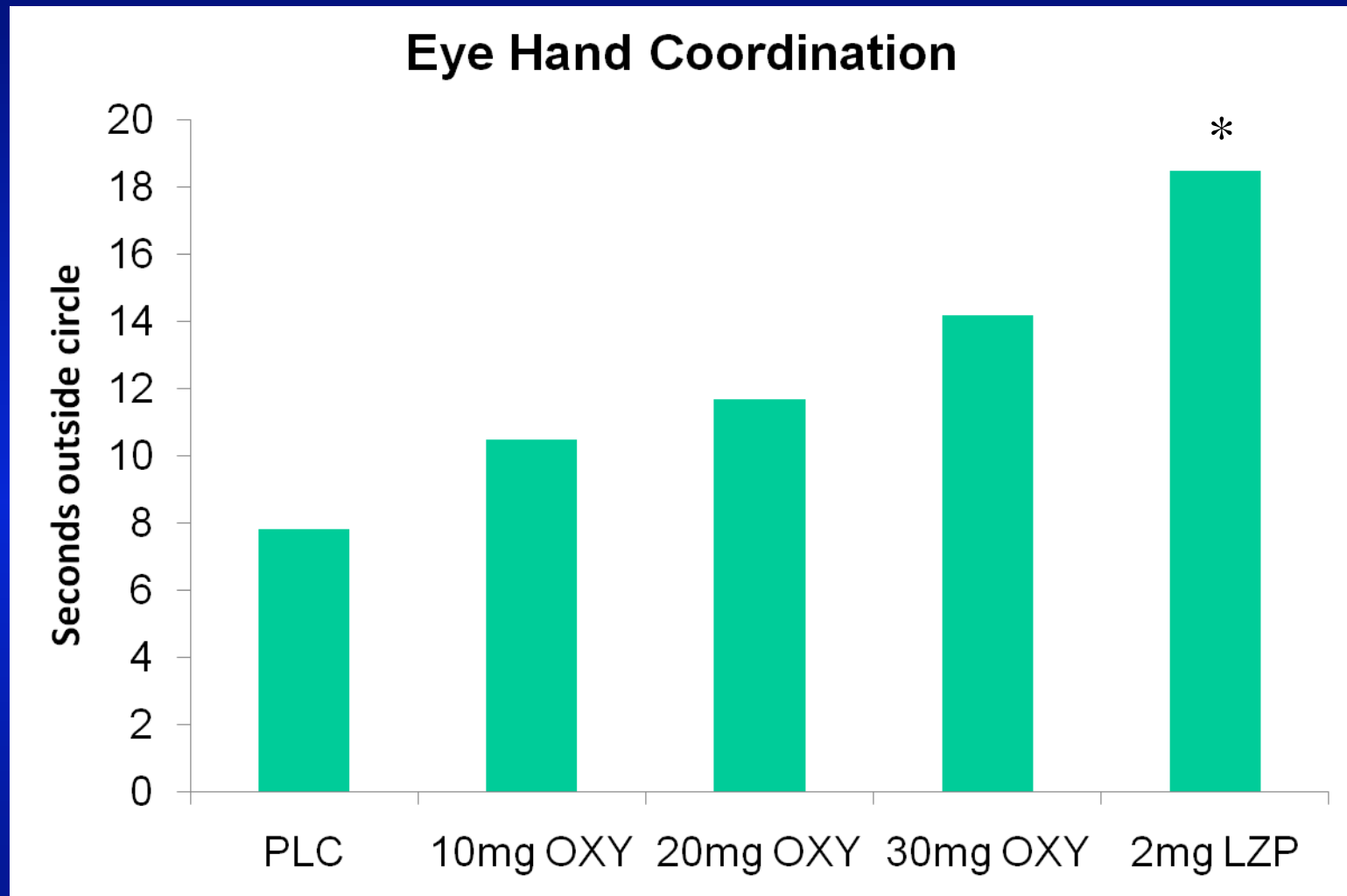


Zacny and Gutierrez, 2003 *Psychopharmacology* 170:242-254

# Eye-hand Coordination Test



- Subject has the control of the plus sign and the task is to keep the plus sign inside of the moving circle by guiding the mouse on the mouse pad

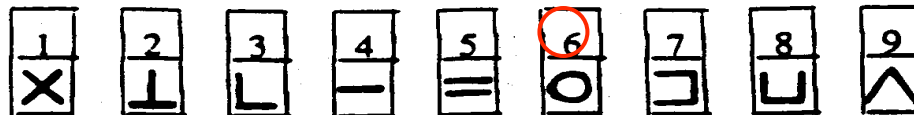


Zacny and Gutierrez, 2003 *Psychopharmacology* 170:242-254

# Digit Symbol Substitution Test (DSST)

University of Chicago Department of Anesthesia and Critical Care	NAME:	
TEST TIME 0 1 3 5 7	DATE:	TIME:

DIGIT  
SYMBOL



8	7	6	2	4	3	9	1	5	3	7	4	6	2	8	9	1	8	5	6	7	2	4	9	3
□	□	=	L	—																				

2	7	6	5	8	9	1	3	4	6	5	7	8	2	1	4	3	9	2	7	5	3	6	2	8

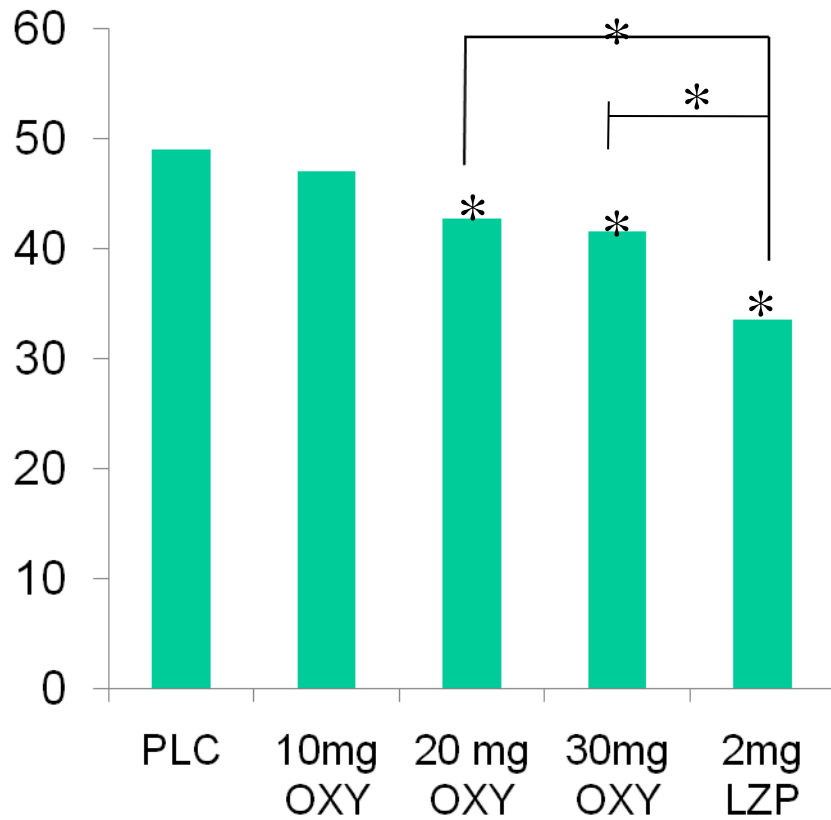
Wrong symbol  
substituted

5						1	2	4	3	7	6	9	1	5	4	3	2	8	7	9	1	5	6	7

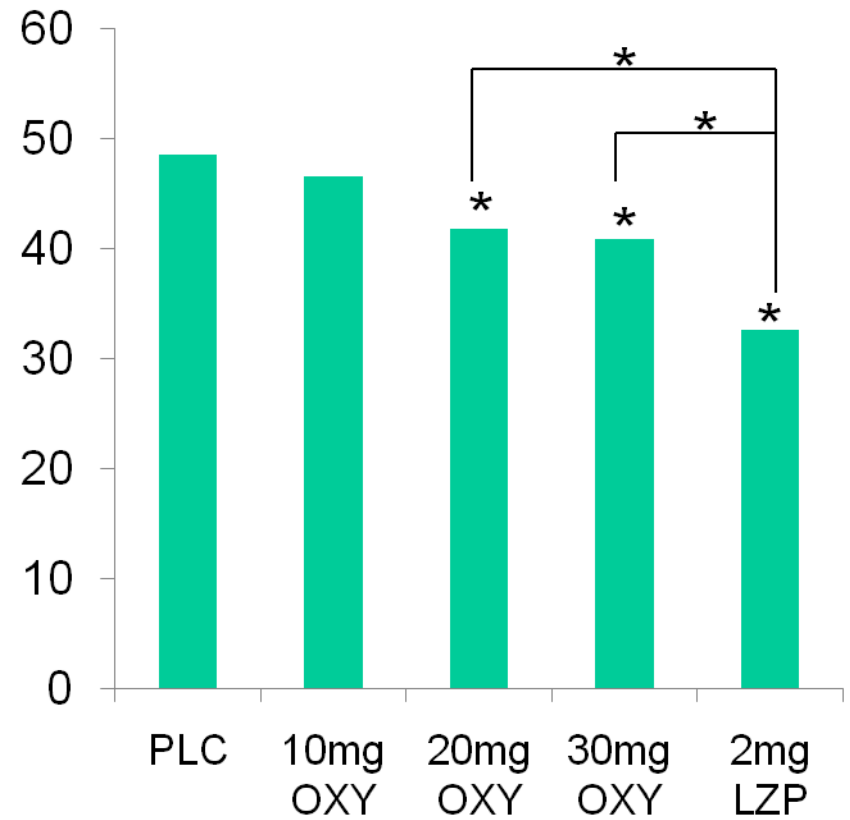
6	5	7	8	2	1	4	3	9	1	8	9	5	4	3	6	7	2	8	1	6	4	7	9	3

Dependent measures: number of symbols drawn, and drawn correctly in 1 minute

### DSST Completed Symbols



### DSST Correct Symbols





## COMPUTER TECHNOLOGY

### An automated version of the digit symbol substitution test (DSST)

DANIEL R. McLEOD, ROLAND R. GRIFFITHS, GEORGE E. BIGELOW,  
and JOHN YINGLING

*Department of Psychiatry and Behavioral Sciences*  
*Johns Hopkins University School of Medicine, Baltimore, Maryland 21205*  
*and Department of Psychiatry, Baltimore City Hospitals, Baltimore, Maryland 21224*

An automated version of the Digit Symbol Substitution Test is described that employs a relatively inexpensive, commercially available microcomputer to present and score the task. Advantages of the automated DSST include: (1) objective scoring of both speed and accuracy of test performance, (2) printed copies of test scores, (3) convenient administration under standardized test conditions, and (4) the capacity for repeated assessment of an individual's performance over time. Task performance data for individual subjects following doses of pentobarbital are presented; these data illustrate both the stability of task performance under constant conditions and the within-subjects sensitivity of task performance to experimental manipulations.

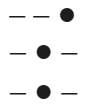
# Computerized Version of the DSST

1	2	3	4	5	6	7	8	9
--●	-●-	-●-	-●-	--●	●--	--●	-●-	●--
-●-	--●	--●	-●-	-●-	●--	--●	●--	-●-
-●-	-●-	--●	--●	--●	-●-	-●-	●--	●--

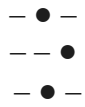
6



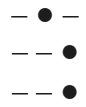
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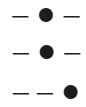
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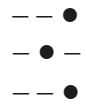
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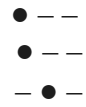
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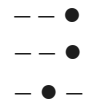
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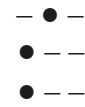
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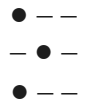
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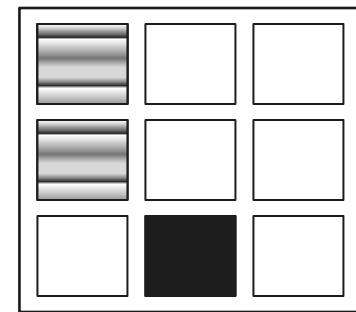
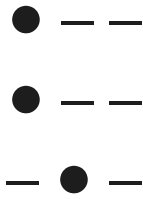
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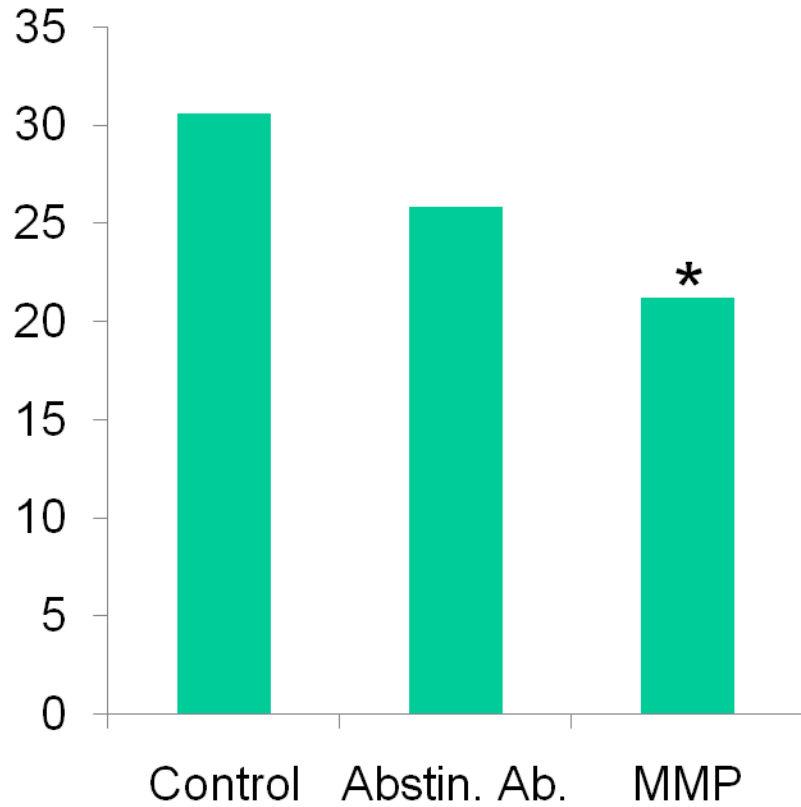
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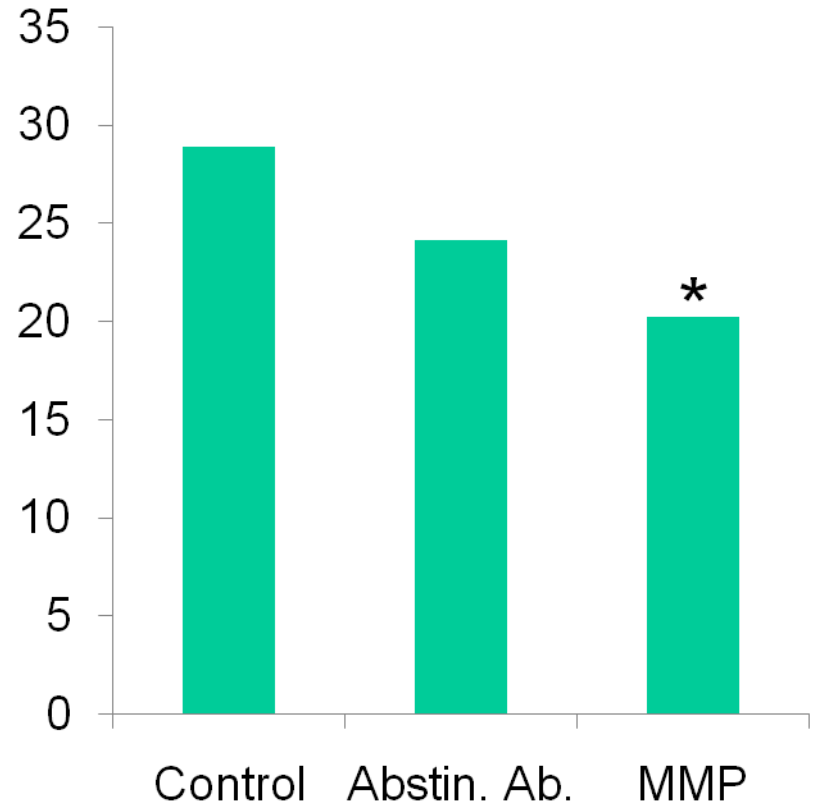
6



### Completed Symbols



### Correct Symbols



# Logical Reasoning Test (Baddeley, 1968)

- One minute computerized test
- TRUE/FALSE statements about juxtaposition of the two letters 'A' and 'B'
- Dependent measures: number of trials done and number of trials done correctly

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Examples:

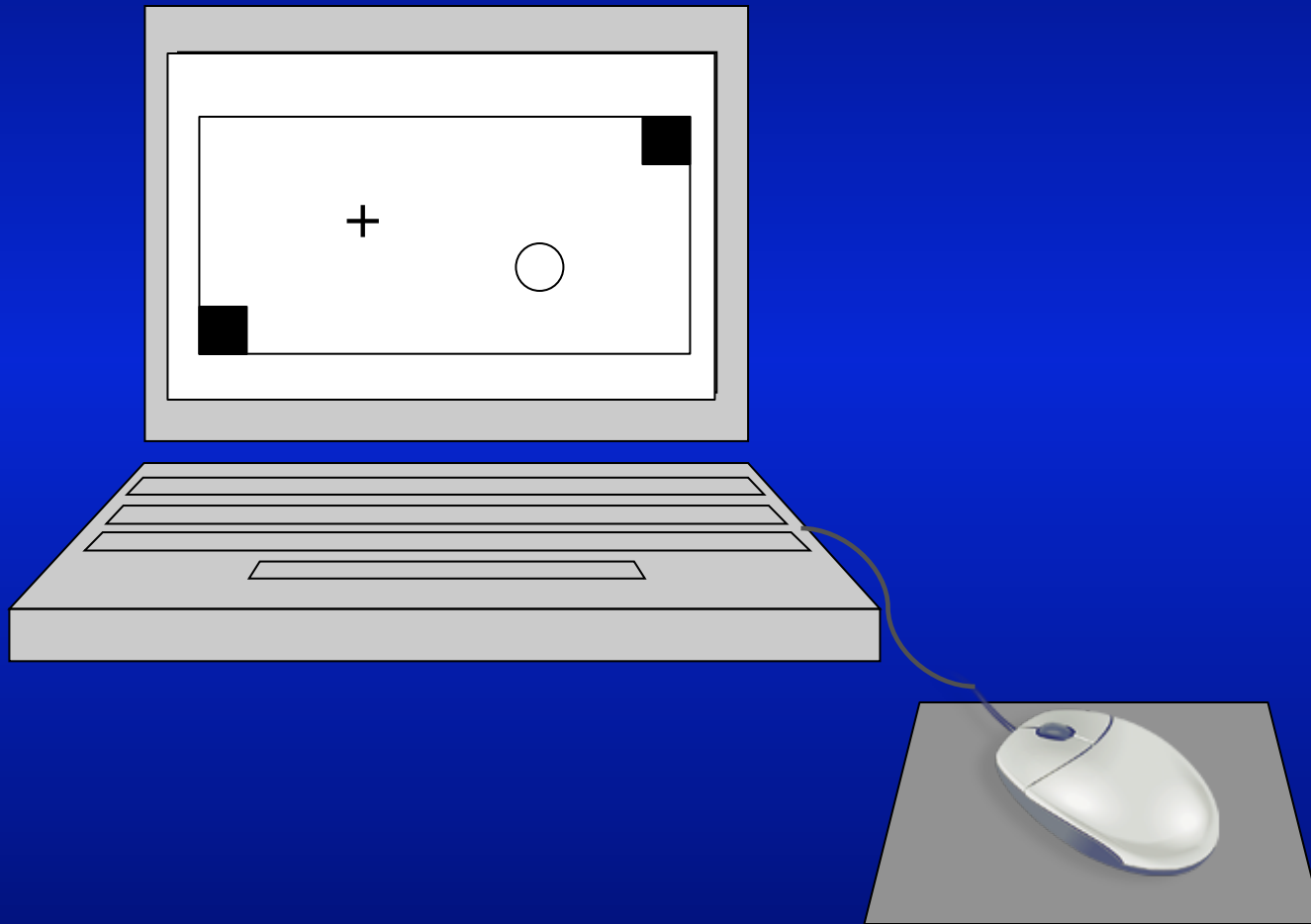
AB

B is preceded by A

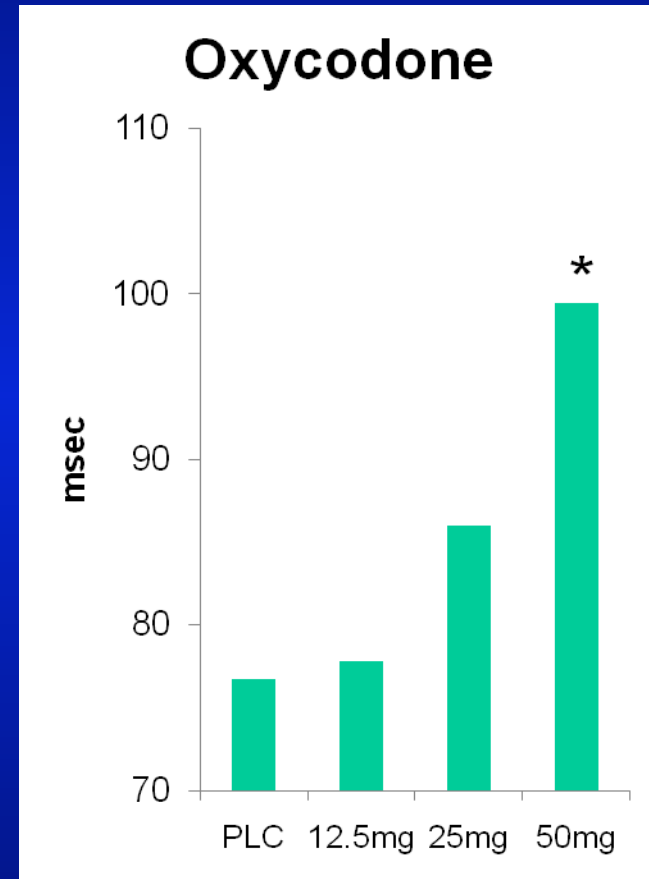
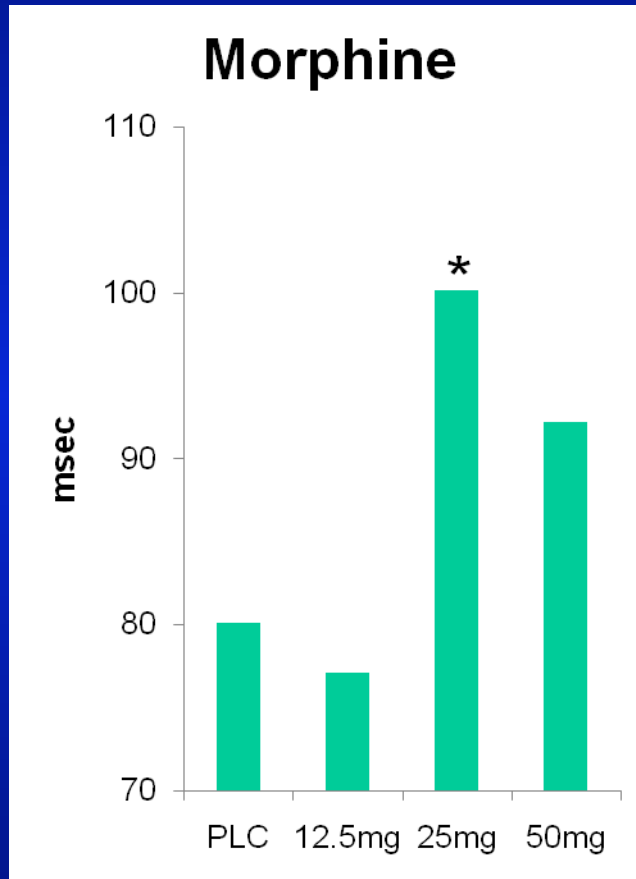
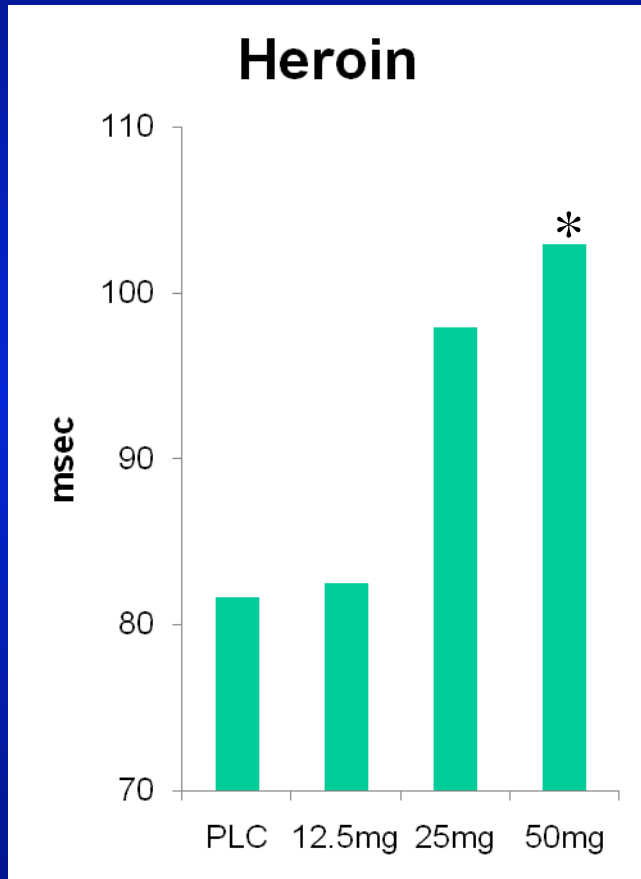
BA

B follows A

# Divided Attention Test



# Peak Average Hit Latency



*Comer et al. 2008 Neuropsychopharmacology 33:1179-1191*



## Working memory: 2-back test

- 60 consonants sequentially shown on a computer screen
- When consonant is shown that was shown two steps or positions back, respond YES
- When consonant is shown that was not shown two steps back, respond NO

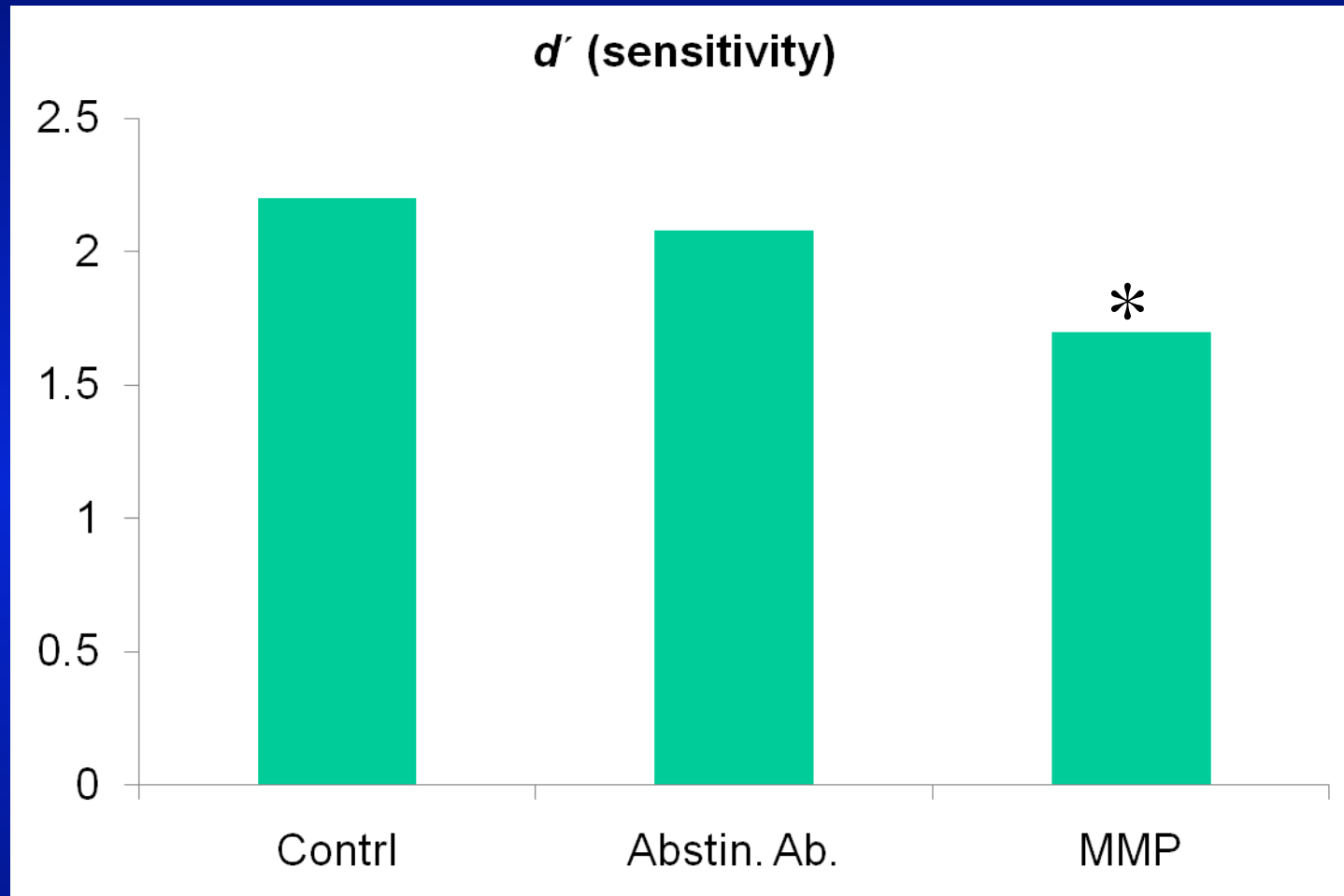
*Cohen et al. 1994 Human Brain Mapp 1:293-304*

# Two-back test

p

YES

NO



## Factors to consider regarding choice of test

- Its sensitivity to opioid effects
  - Simple reaction time not good...
- Its “availability”
  - Some tests are proprietary...not commercially available
  - Some tests are expensive (CANTAB...>\$10,000)
- Its complexity
  - Want to choose a test in which after a suitable practice period, person is at asymptote

# Factors to consider regarding choice of test

- Length of test
  - Cannot be too long because it is a secondary measure of interest
    - Vigilance (sustained attention) tests are probably not good candidates
- Its history of use in opioid ALA
  - If only one lab has used the test, doubtful whether there will be a consensus on other labs willing to adopt the test

# History of Use: DSST

- Opioid studies
  - Hopkins lab (Bigelow/Preston/Strain/Walsh) studies
  - Columbia lab (Comer)
  - U Chicago lab (Zacny)
- Sedative (benzodiazepine) studies
  - Hopkins lab (Griffiths/Roache/Mumford/Evans/Mintzer etc.)
  - U Chicago labs (de Wit, Zacny)
  - U Kentucky labs (Rush, Kelly)
  - Centre for Addiction/U Toronto (Sellers, Busto etc.)

# DSST

- Advantages:
  - Volunteers reach asymptote quickly
  - Impairment has been found in a number of studies with abusers, and non-abusers, in different labs
  - Can administer multiple times within a session
  - A number of labs in the country already use it
  - Can make across-drug class comparisons
- Disadvantages:
  - In some studies with post-addicts, DSST performance was not affected by im opioids (Hopkins lab)

Experimental and Clinical Psychopharmacology  
1995, Vol. 3, No. 4, 432-466

# A Review of the Effects of Opioids on Psychomotor and Cognitive Functioning in Humans

James P. Zacny  
The University of Chicago

The literature on the effects of opioids on psychomotor and cognitive functioning in humans is evaluated. Some studies have examined the acute and chronic effects of various opioids on different

Cognition/psychomotor performance is more likely to be impaired in naïve volunteers than in occasional/habitual users perhaps because of tolerance processes..

If one does detect impairment it is generally reduced speed of doing something, while accuracy is preserved.