

# **Pain & Pain Medication interactions with cognition**

**Monique Cherrier, Ph.D.  
University of Washington**



# Definition of Pain

- “an unpleasant sensation associated with a specific part of the body”
- Produced by processes that either damage or are capable of damaging the tissues  
“noxious” detected by nociceptors
- Nociceptors only respond to noxious stimuli
- Periphery-spinal cord-thalamus-cortex

# Transmission & Modulation of pain signal

- Spinal cord- transmission using glutamate (both NMDA & Non-NMDA receptors) and substance P
- Ascending modulation- these signals can be inhibited via mu-opioid receptors
- Descending modulation- norepinephrine (NE) and serotonin (5-HT) act at the site of the dorsal horn to modulate ascending signal (e.g. stress)

# Opioid site of action

- Activate the opioid receptors in the midbrain and turn on descending systems
- Activate opioid receptors in the second order pain transmission cells
- Activate terminals of C-fibers in the spinal cord preventing the release of pain neurotransmitters
- Activate opioid receptors in the periphery to inhibit the activation of the nociceptors

# Pain Assessment

Please rate your pain by marking the one number that best Describes your pain at its WORST in the past week

**0 1 2 3 4 5 6 7 8 9 10**

No  
Pain

Pain as bad  
As you can imagine

# Common Clinical Conditions

- Cancer
- Hospice
- Chronic back pain
- Post surgery
- Osteo-arthritis & degenerative joint disease
- Vascular
- Headaches
- Fibromyalgia
- NSAIDs
- Acetometaphine
- Opioids
  - methadone
- Amitriptyline
- ~~Cox-2 inhibitors~~

# Chronic Pain

- Typically inflammatory or neuropathic and characterized by enhanced perception of pain to a nociceptive stimulus (hyperalgesia) and novel perception of a normally innocuous stimulus as painful
- Spinal cord becomes primed
- Hindbrain facilitates descending activation for hypersensitivity

# Bio-behavioral interaction

## Physical:

Inactivity  
Increased pain sensitivity  
Fatigue  
Co-morbid medical conditions  
medications

## Behavioral:

Attempts to control pain (e.g. alcohol)  
Pain/activity avoidance-deconditioning

Person with chronic pain

## Emotional:

depression  
anxiety  
Low stress tolerance

## Social:

Loss of social support  
Isolation & loneliness  
Changes in interpersonal interaction

# Common memory complaints by patients with chronic pain

- Flaws referring to books and films
  - Forgetfulness
  - Handling of everyday things (prospective)
  - Flaws about conversations
- 
- Regression analysis indicated that depression (35%), anxiety (6%) and rumination (2%) were best predictors of complaints

Munoz et al., (2005)

# Attention, Pain & Stress

- Healthy controls vs chronic low back pain
- Cold pressor test with monitoring of low back and arm tension, blood pressure
- Randomly assigned to:
  - Sensory focus, distraction, suppression, control
- Stress: mental arithmetic
- Recovery

- Greatest lower paraspinal (LP) increases were in the suppression group
- The CLBP group demonstrated a further increase of LP during the stress condition this did not occur for the controls
- Weakness or pathology in the LP muscles may leave this system vulnerable to stress reactivity
  - Cycle of chronic low level activation of muscle groups through repetitive tasks in stressful jobs – greater exhaustion and mental tension after work which prevents recuperation

# Persistent pain produces stress like alterations in hippocampal neurogenesis and gene expression

- Rats- given acute or chronic inflammatory stimulus to hind paw (pain) or acute or chronic immobilization (stress)
- Chronic pain and immobilization both decreased BrdU stained cells in the hippocampus
- Decreased BDNF and Nk-1 receptor mRNA levels

(Duric, et al., 2006)

# NP Performance Chronic Low Back Pain

Measure	Pain-Free	CLBP	P value
	N=160	N=163	
RBANS- Im. Mem	103	98	.002
RBANS- Visuosp.	96	95	
RBANS – Lang.	102	99	.004
RBANS- Attent.	105	105	
RBANS- Del. Mem	97	94	.04
Trails B (T score)	53	50	
Grooved Pegboard	45	42	.04
NART-VIQ	98	98	

(Weiner et al., Pain Medicine, 2006)

# Relationship of Mood & Pain & Cognition

- Weiner et al. (2006 ) sample found NP scores correlated with physical performance and pain intensity
- Karp et al. (2006) N=56 (mean age 71 years)
  - Pain severity was associated with greater impairment on number letter switching ( $r=-.42$ )
  - This remained sig. After controlling for depression, sleep, medical co-morbidity, opioid use & education

# Subjective Assessment of Drug Effect

- OAC (0-4)
- Flushing
- Skin Itchy
- Sweating
- Numb
- Dry mouth
- Carefree
- Vomiting
- OCEC (0-10)
- High
- Floating
- Lightheaded
- Confused
- Pleasant/unpleasant thoughts or sensations
- Drunk

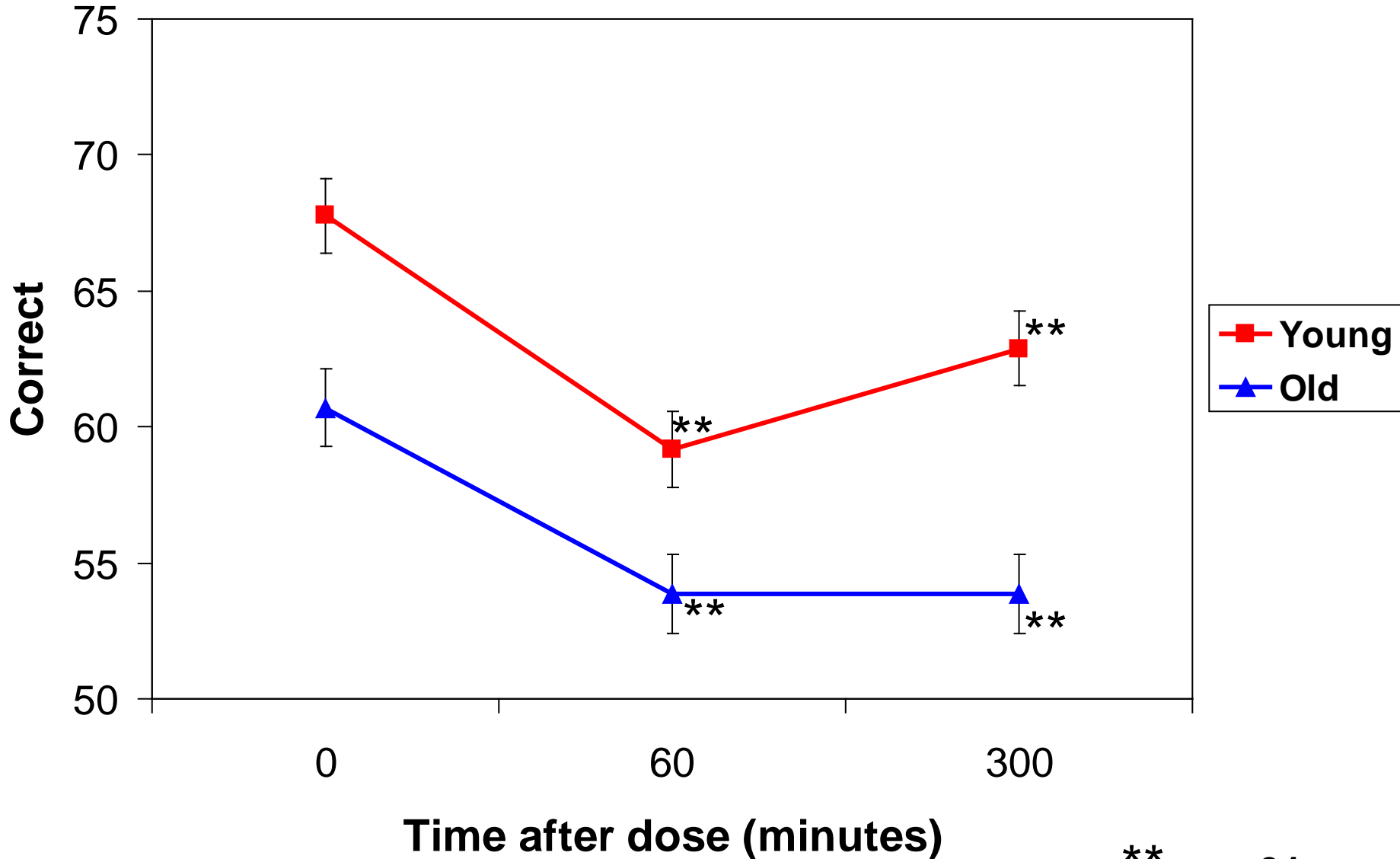
# Relationship of Subjective vs Objective Cognitive Performance While Taking Opioids

- Correlation between subjective reports of cognitive impairment and poor performance on neurocognitive tests (Sjogren, 2000)
- No correlation between subjective reports of cognition and actual performance (Cull, 1996; Klepstand, 2002)

# Opioid effects in young adults

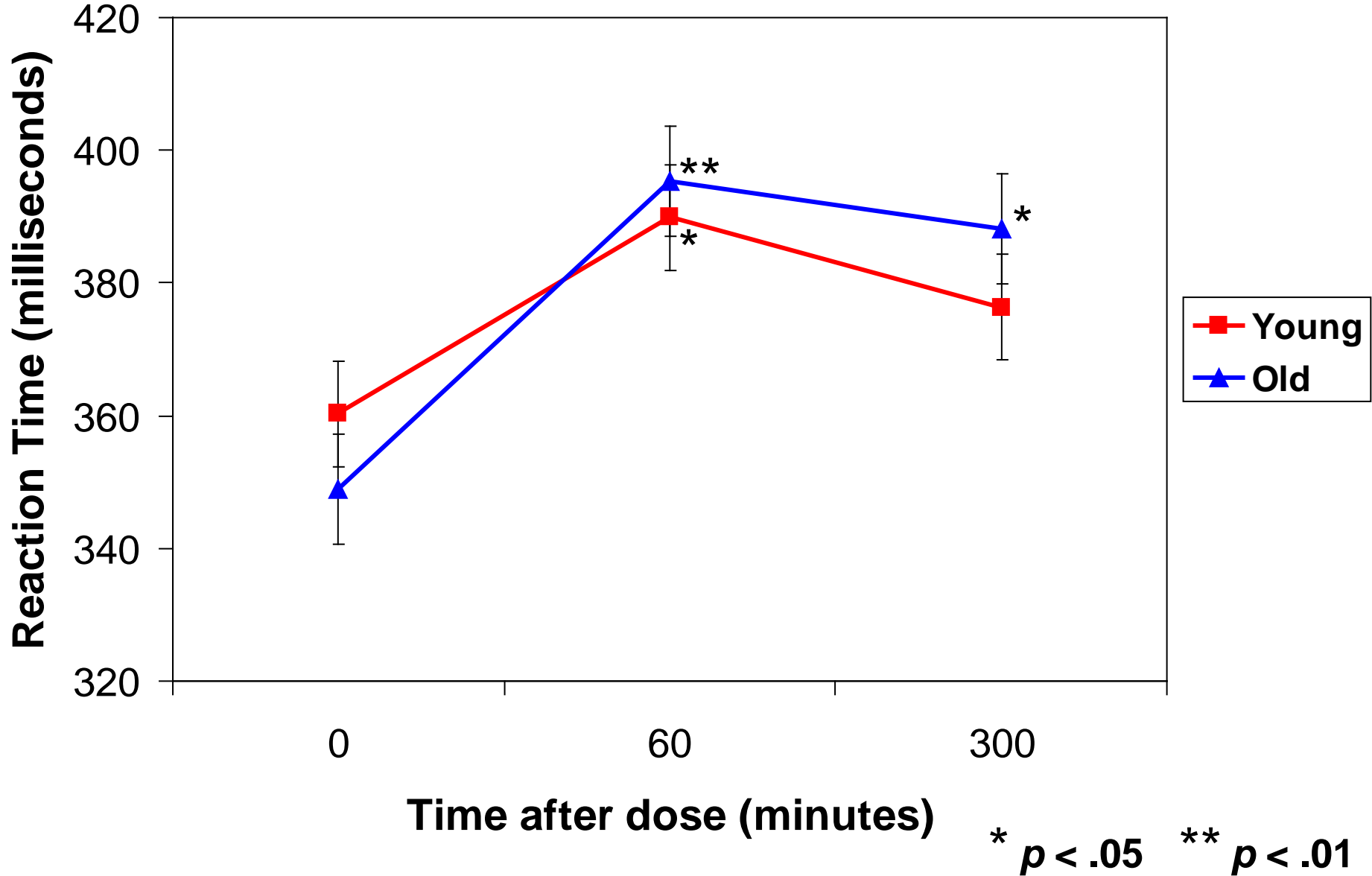
- Single dose IV opioid in young adults- no to minimal cognitive effects (Hill, 2000; Zacny, 1994,1997,1998)
- Oral opioids (e.g. morphine, codeine) have minimal effects on cognition in young adults (Hanks, 1995; Walker, 1998; O'Neill, 2000)
- Cumulative IV doses do demonstrate decreased RT, logical reasoning, concentration, information processing (Walker, 1999)

# Digit Symbol

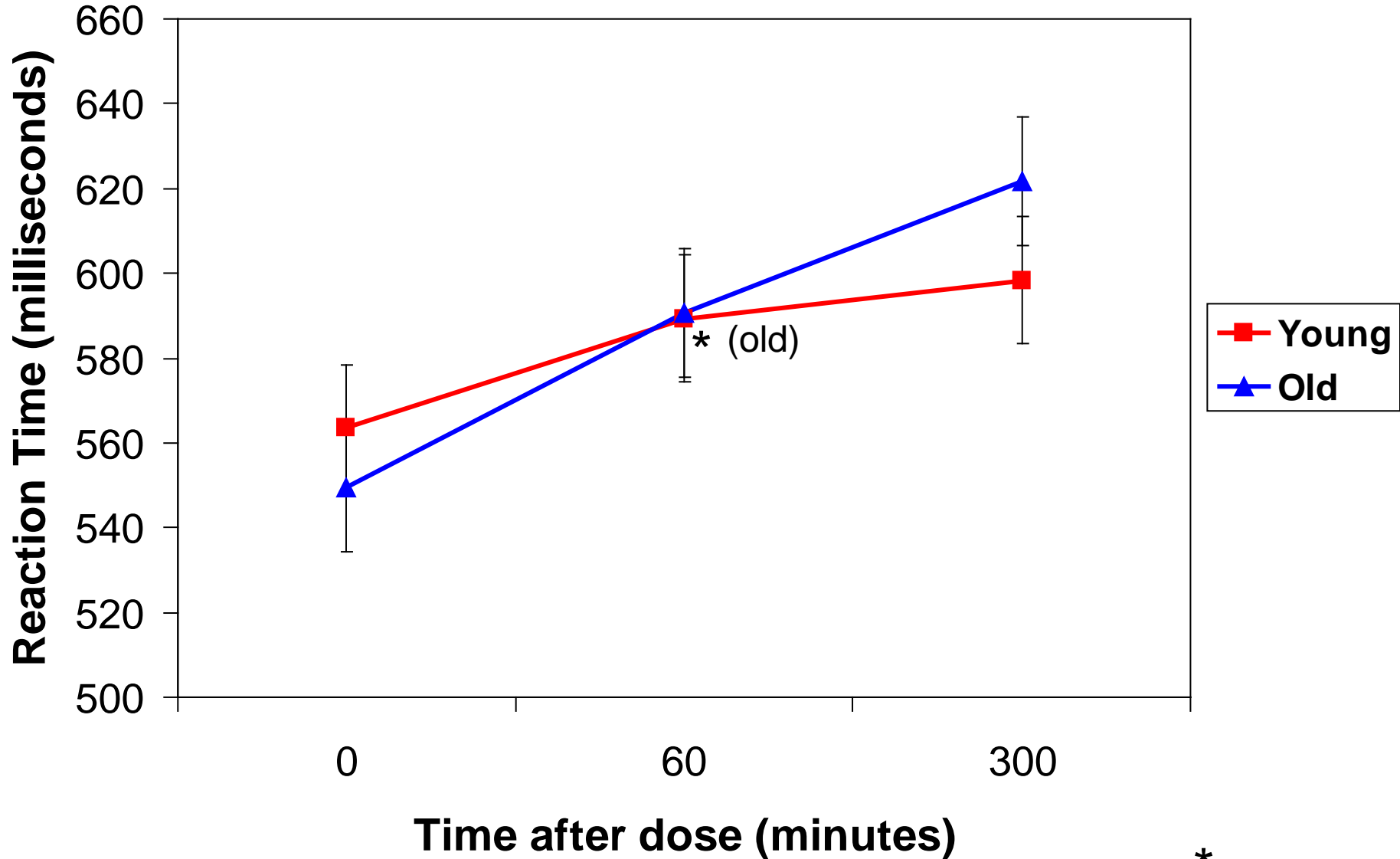


\*\*  $p < .01$

# Simple Reaction Time

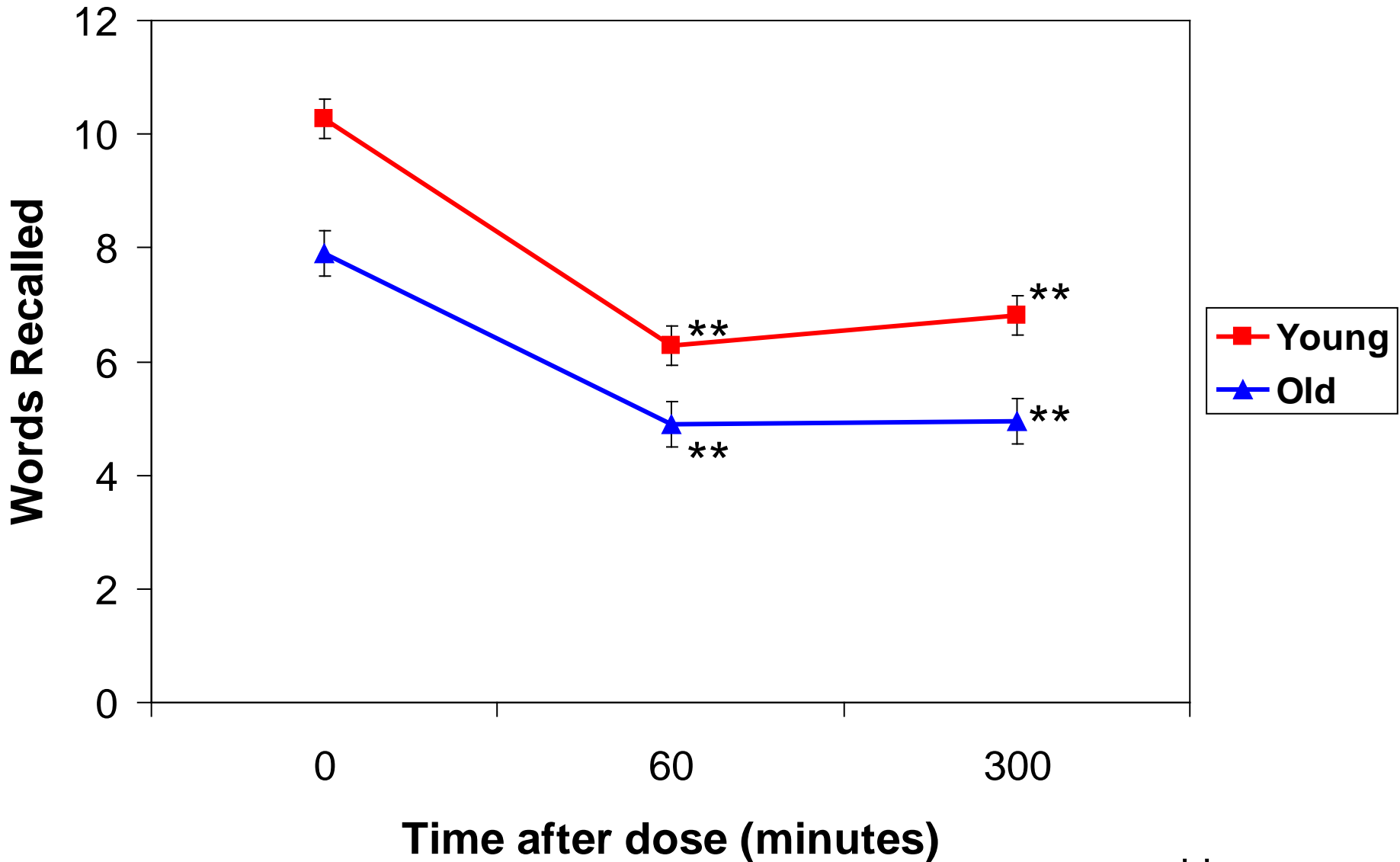


# Choice Reaction Time



\*  $p < .05$

# HVLT - Verbal Memory: Delayed Recall

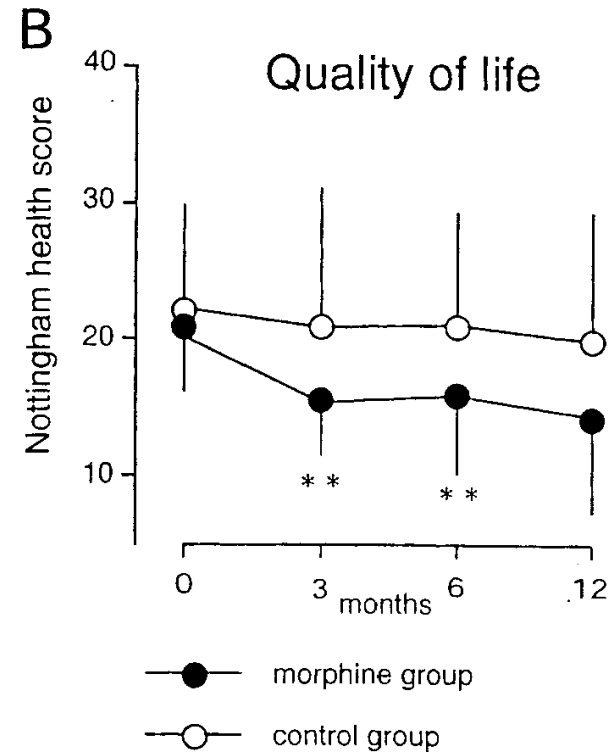
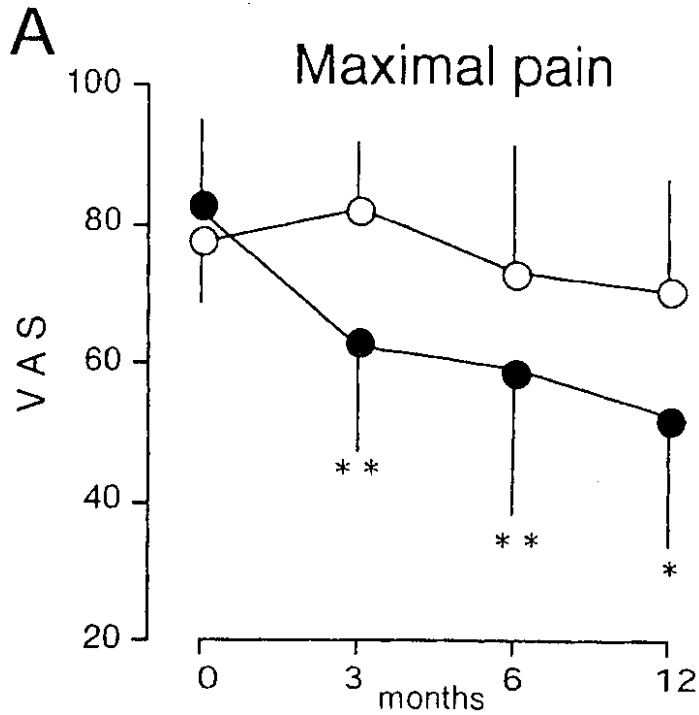


\*\*  $p < .01$

# Sustained release opioid

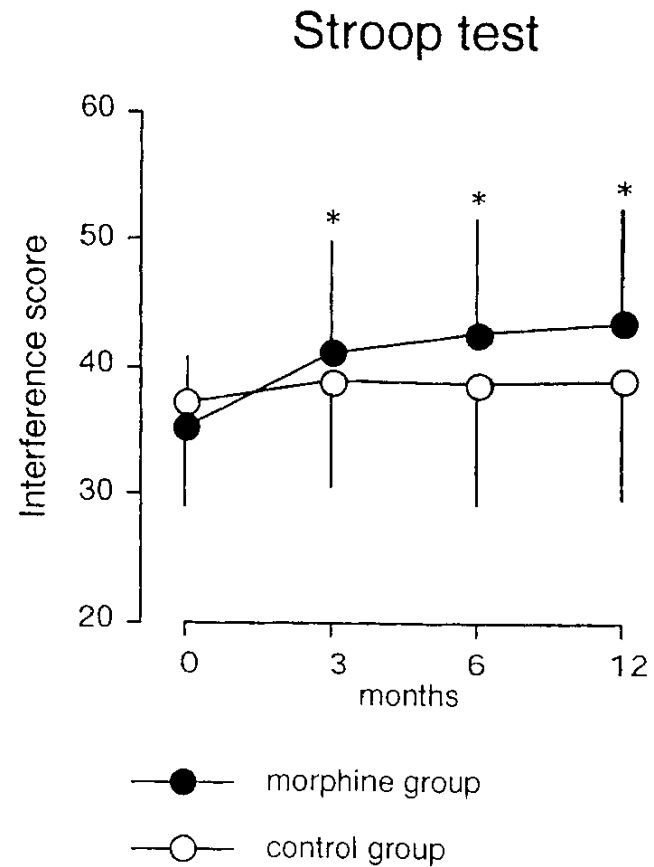
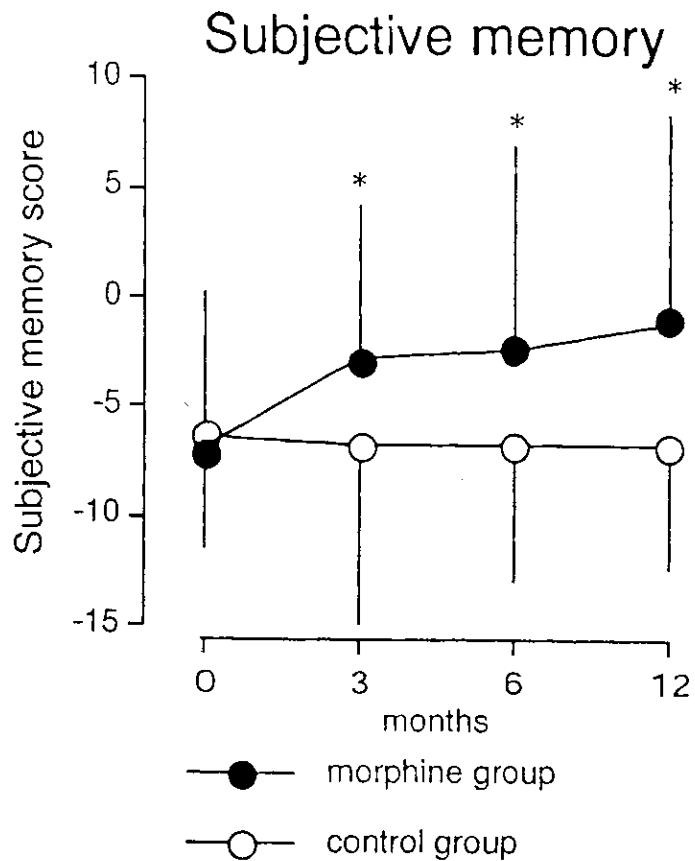
- Patients chronic non-malignant pain N=18
  - Oral sustained release morphine on a low dose and titrated up to efficacy or side effects and maintained on stable dose
- Neuropsychological, QOL & Mood assess.  
At baseline, 3, 6 and 12 months
  - Buschke, Stroop, TMT, WAIS, RT,

(Tassain et al., Pain, 2003)



- Pain significantly decreased
- Overall Quality of life improved

(Tassain et al., Pain, 2003)



**Subjective memory rating improved**

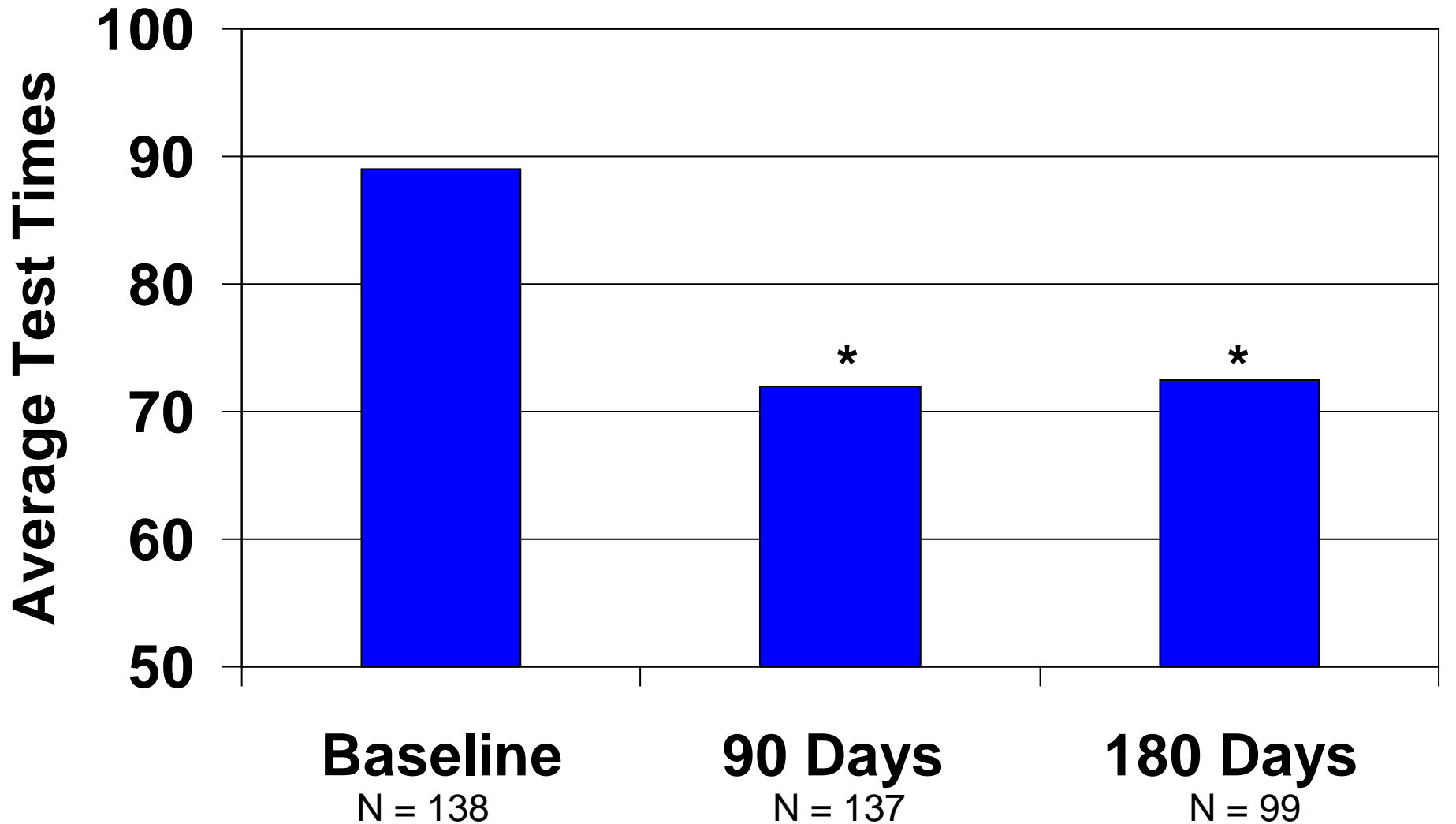
**Objective performance improved: Stroop, Digit symbol**

(Tassain et al., Pain, 2003)

# Long Term Opioid Use

- N= 144 patients with chronic low back pain
- Mean age = 46 years
- Assesses prior to the start of oxycodone with acetometaphine vs transdermal fentanyl and again after 90 and 180 days
- Neuropsych. Tests and mood measures
  - DSST, Trail making test part B
  - BDI, SF-36

# Mean Digit Symbol Substitution Test

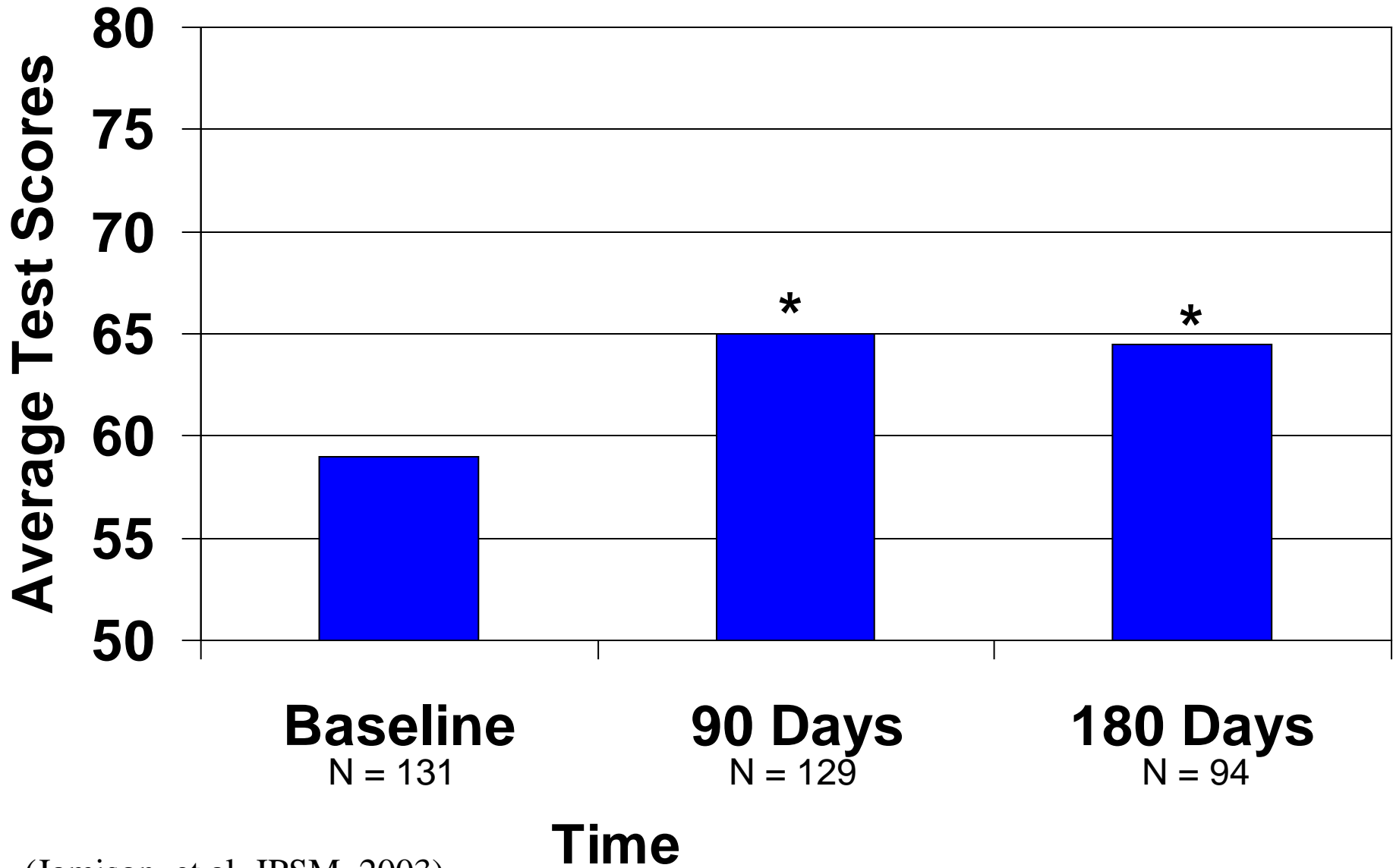


(Jamison, et al. JPSM, 2003)

**Time**

\*  $P < 0.001$ , Change from baseline

# Mean Trail Making Test



(Jamison, et al. JPSM, 2003)

\* P < 0.001, Change from baseline

# Driving Assessment

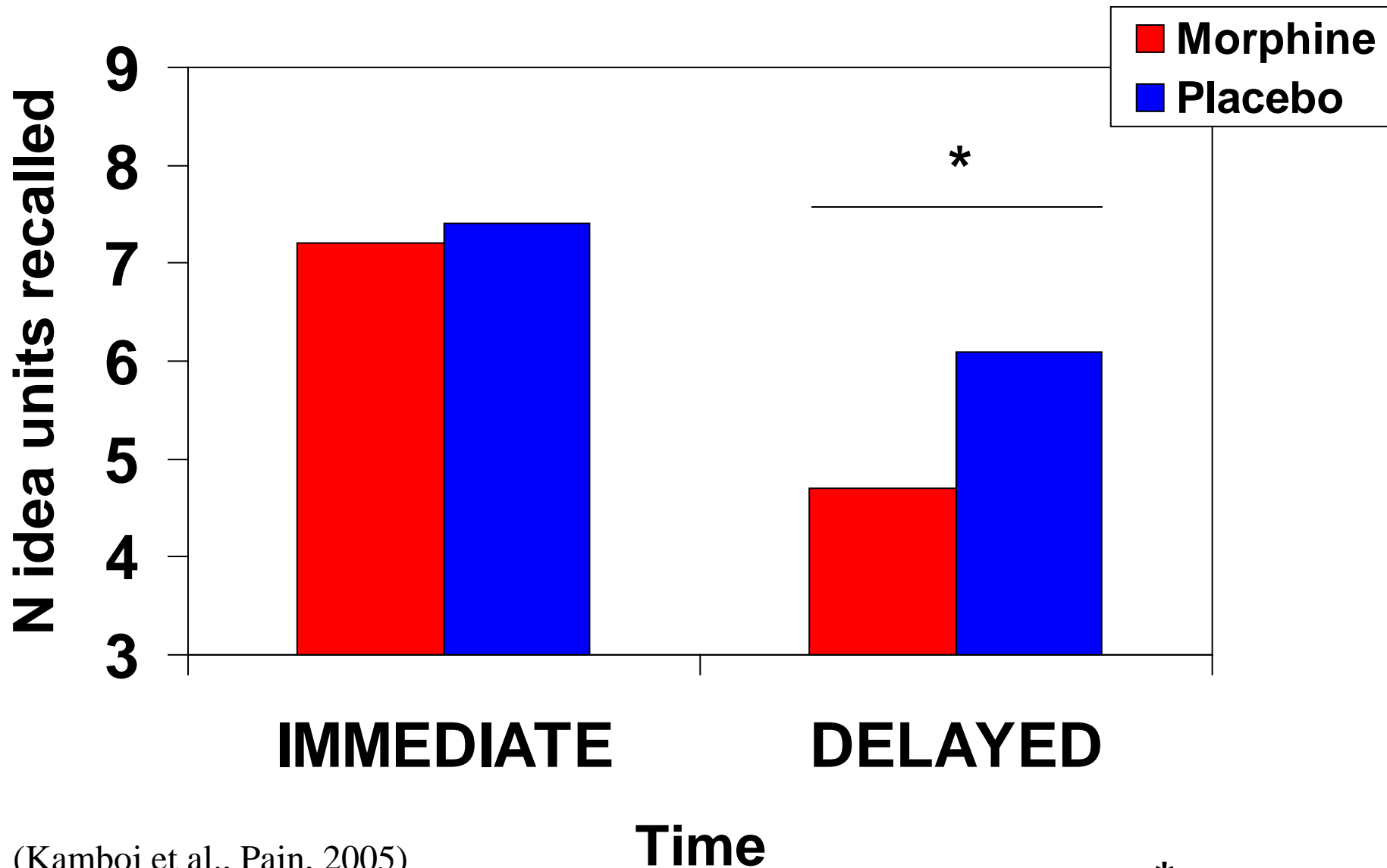
- Studies examining participants with chronic pain on stable doses of various opioids
- No sig. Difference between patients and controls
  - Gaertner et al, Acta Anesh. Scan. (2006) – CRO
  - Sabatowski et al. JPSM (2003) – transdermal fentanyl
  - Menefee et al., Pain, (2004) – transdermal fentanyl- & pts. Improved on visual motor tracking, visual memory and attention
- Sig. Decrements between pts. & controls
  - On two tests out of large battery- a test of continuous-monotonous attention (Schindler et al., Eur. Addit Res., 2004)
  - ? Used participants from drug addiction outpatient clinic on methadone or buprenorphine

# Chronic Dosing + PRN use

- N= 14 patients receiving palliative care and taking a CR opioid
- Examined immediate verbal memory at baseline (RBANS) and larger battery of cognitive tests 45 minutes after taking IR opioid or placebo
  - Finger tapping, verbal fluency, elevator counting, digit span, immediate recall RBANS story 2 and delayed recall of 1 and 2, TEA

(Kamboj et al., Pain, 2005)

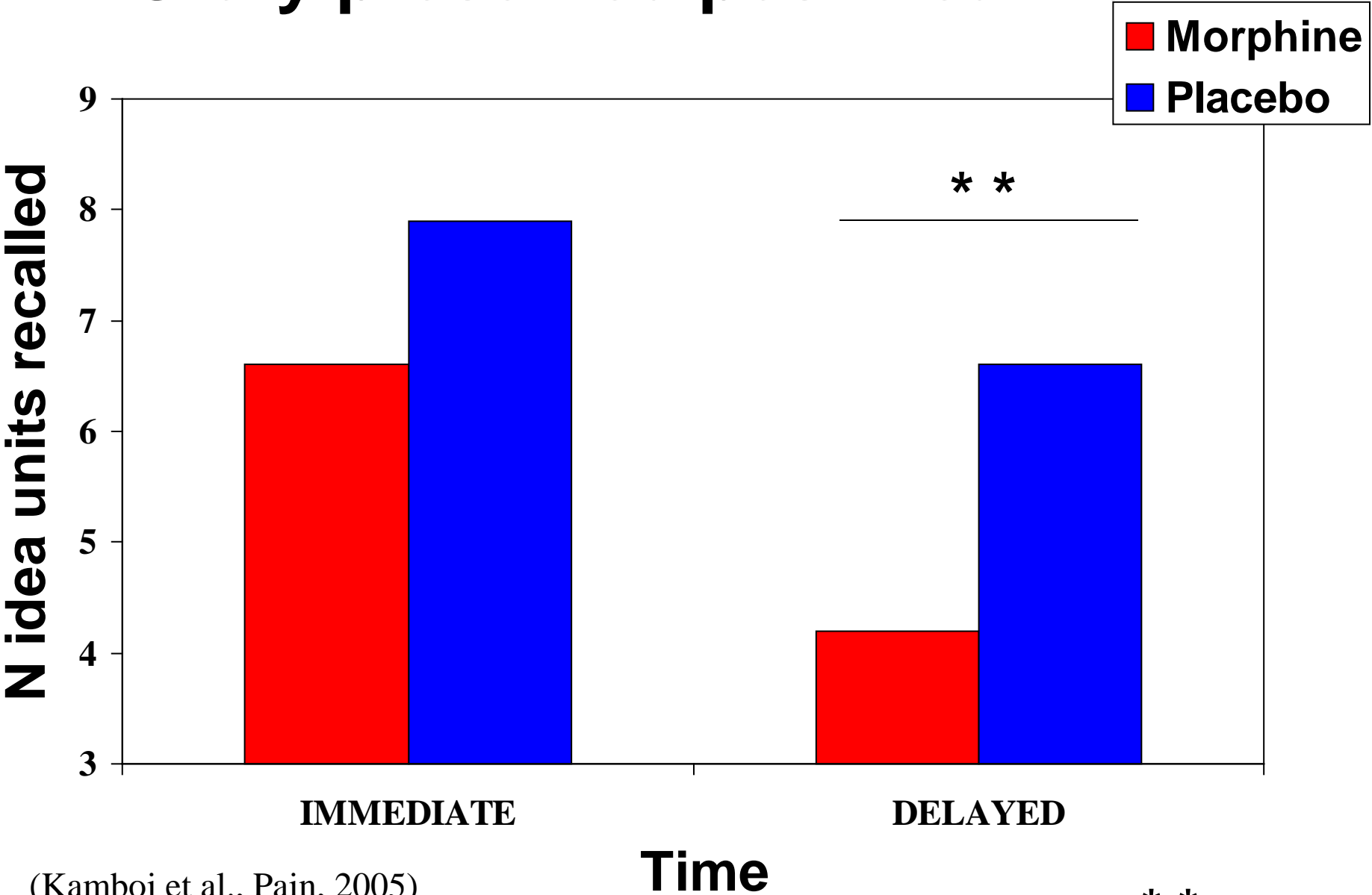
# Story presented pre-treatment



(Kamboj et al., Pain, 2005)

\*  $P = 0.024$

# Story presented post-treatment



(Kamboj et al., Pain, 2005)

\*\*  $P = 0.003$

# Results

- No other significant effects compared to placebo for:
  - Verbal fluency
  - Digit Span and Tests of Everyday Attention
  - Trail Making Test
  - Finger Tapping

# Driving Assessment Caveats

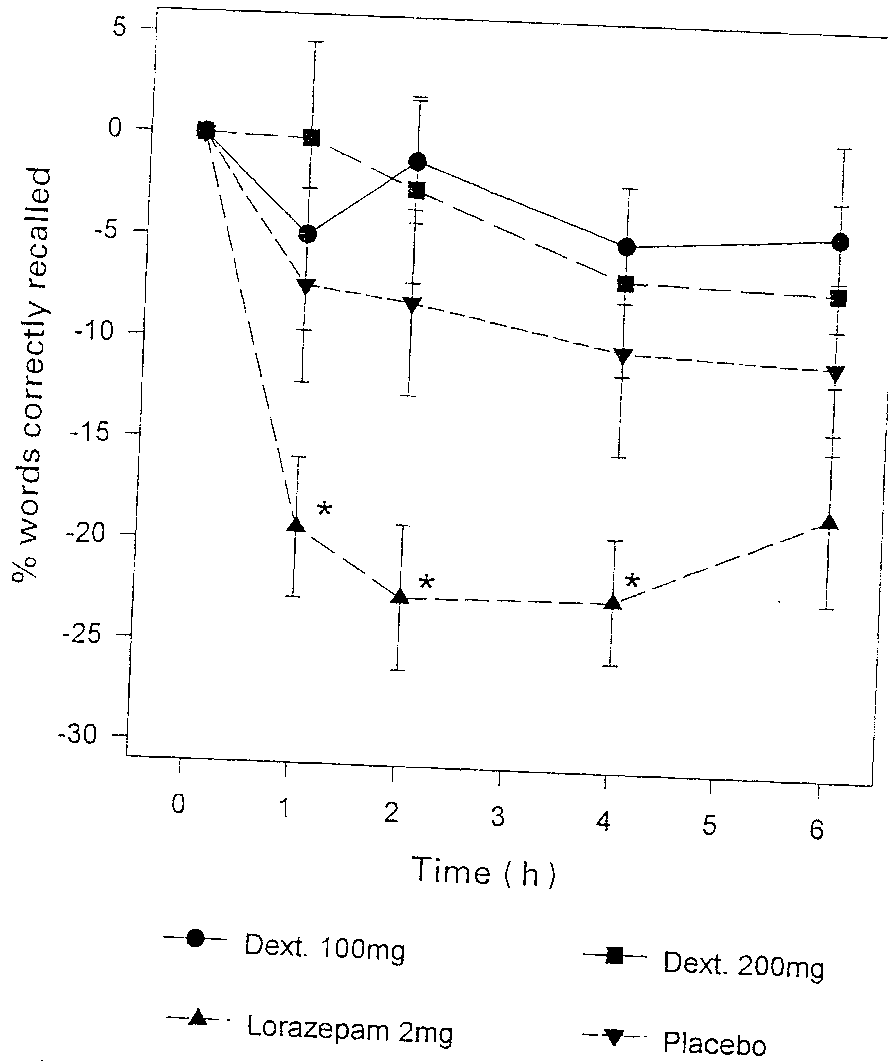
- Other factors may interfere with optimum driving ability
  - Age
  - Risk taking/ impulsive/daring behavior
  - Previous driving record & defensive driving behaviors
  - Alcohol history
- Driving test may not be the best measure of driving performance

# Additional Medication Cautions

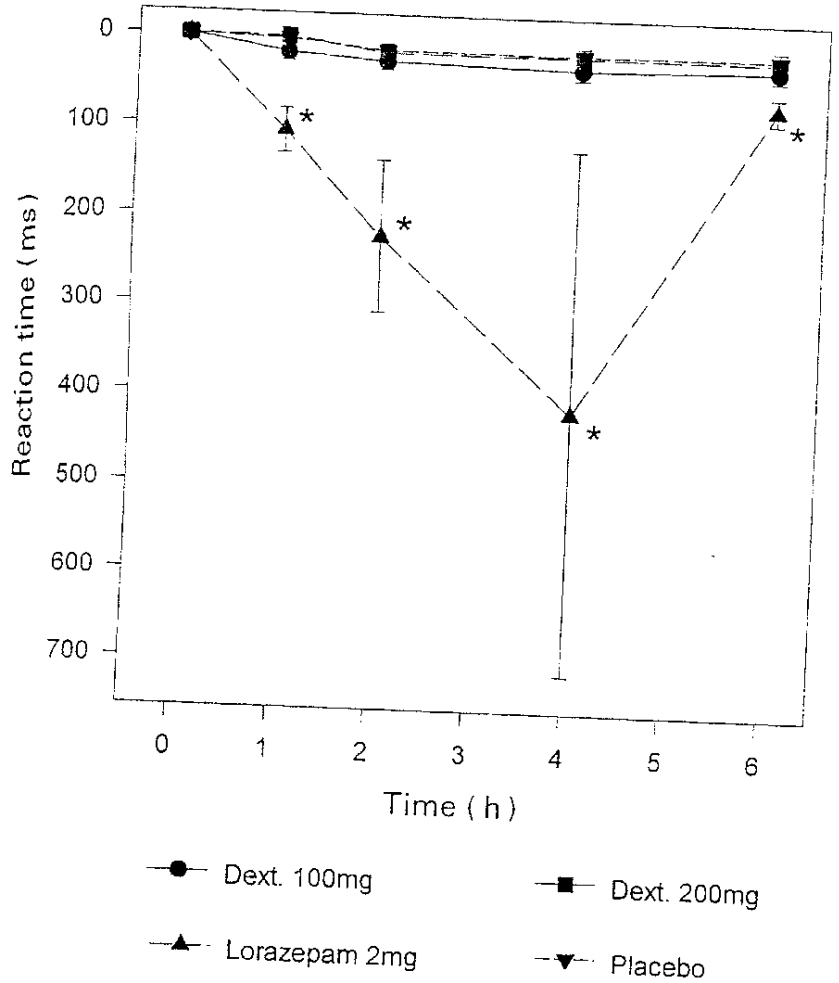
- Other medications and conditions can cause impairments in cognition and driving abilities
  - Sleep apnea
  - Vascular conditions and heart medications
  - Sleep deprivation
  - Other medications and medical conditions- cancer, benzodiazepines, asthma- allergy medications

# Opioids vs Benzodiazepines

- Four way cross over experiment
  - 100mg, 200mg dextropropoxyphene
  - 2mg lorazepam
  - Placebo
- Battery of cognitive tests –computerized CDR
  - Word recall, RT, picture recognition, scanning, vigilance
- Testing at baseline, 1, 2, 4, and 6 hours post drug



A plot of the means (SEM) for the percentage of words correctly recalled



A plot of the means (SEM) for reaction time

## Lorazepam –significant decline in word recall and reaction time

# Summary & Recommendations

- Pain and chronic pain can have adverse effects on cognition
  - May be modulated by mood, health & motivation
- Pain medications may have adverse effects on cognition
  - Immediate release, IV, dose escalation or PRN immediate release on top of SR, modulated by other factors such as age, health status

# Summary and Recommendations

- Individuals who are on stable doses of sustained release opioids
  - Demonstrate minimal or no adverse effects of medication
  - May be considered safe to drive- with caveats
- Other medications and medical conditions and mood states may have a greater impact on cognitive functioning
- There can be a disconnect or lack of association between subjective sense of cognitive abilities and actual performance

# Summary and Recommendations

- Be cautious about performing tasks during peak drug effects when increasing opioid dose or taking a prn dose for breakthrough pain
- Rely upon memory aids
- Wait until peak drug levels have started to decline for cognitively demanding tasks