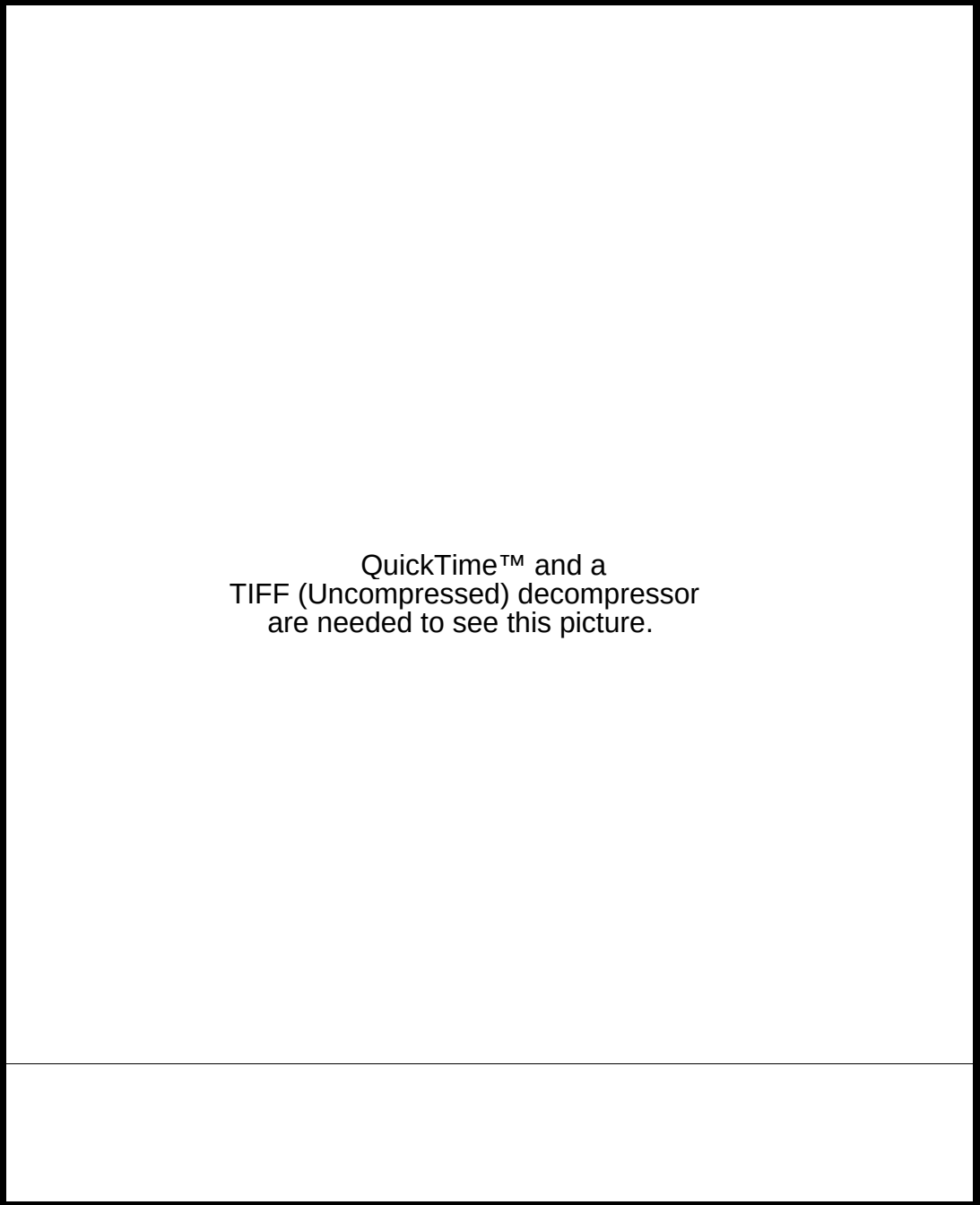
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Methamphetamine: A Good Drug Gone Bad

Carl L. Hart, Ph.D.

Division on Substance Abuse, New York State Psychiatric Institute,

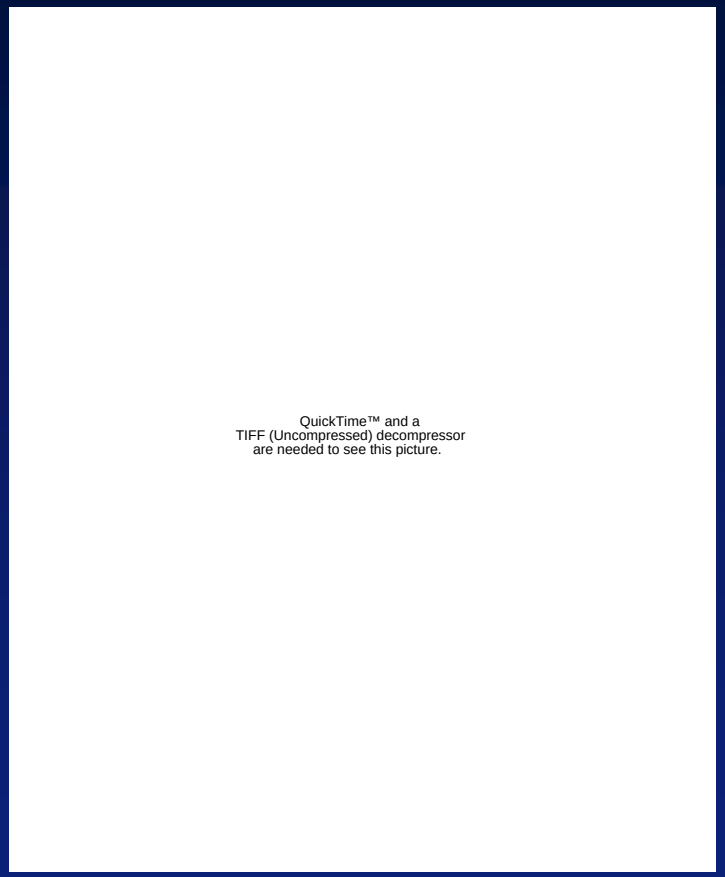
Department of Psychology, Columbia University, and

Department of Psychiatry, College of Physicians & Surgeons of Columbia University

Supported by DA03476 and DA19559

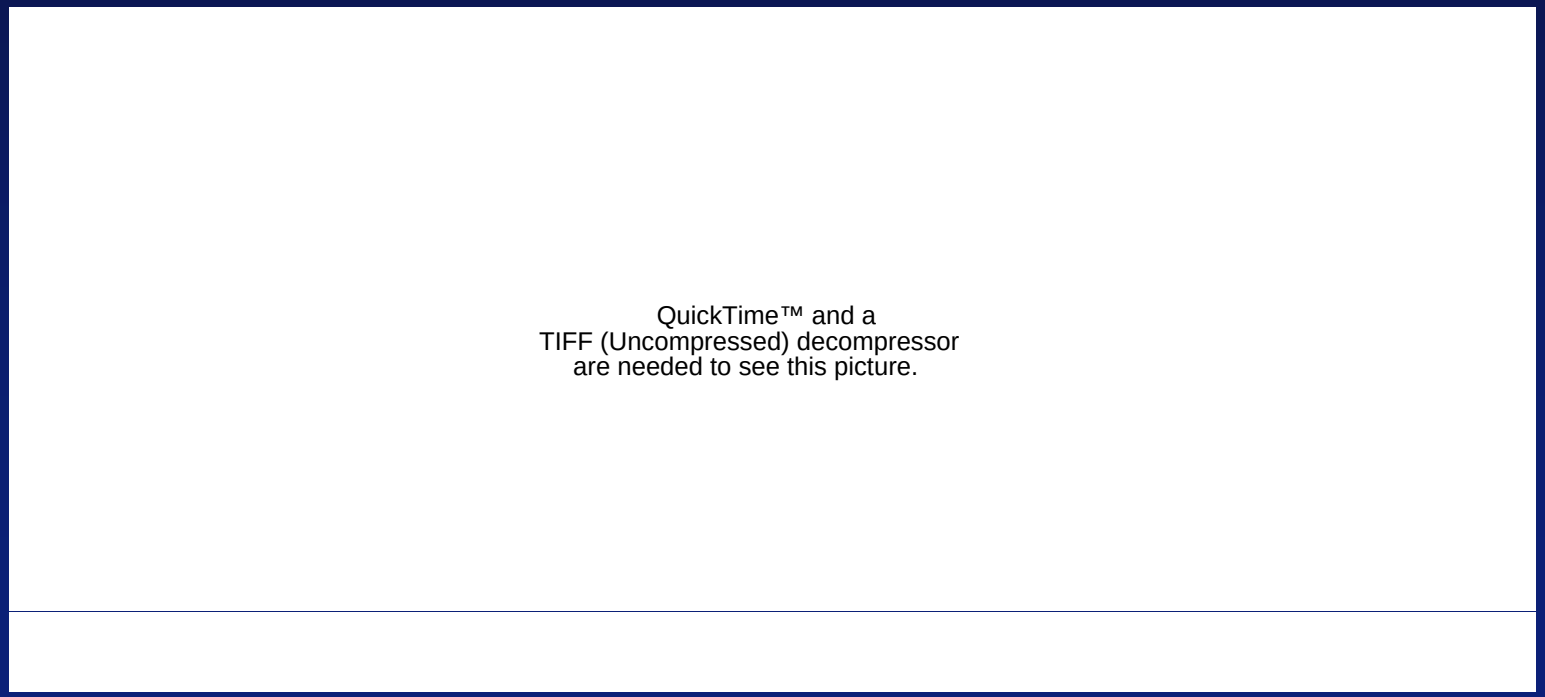
Brief History

- Amphetamines
  - Introduced in the early 1930s
  - Multiple uses including
    - Nasal and bronchial dilator
    - Narcolepsy
    - Depression
    - Parkinson's disease
    - Alcohol dependence
    - Obesity



Amphetamines

- ***d*-Amphetamine**
- **Methamphetamine (MA)**
- **3,4-Methylenedioxymethamphetamine (MDMA = Ecstasy)**



Current Sanctioned Uses

- Methamphetamine (MA)
  - Attention-deficit hyperactivity disorder (ADHD)
  - Obesity
- *d*-Amphetamine (Adderall)
  - ADHD
  - Narcolepsy
  - Military use (off-label)
  - Adjunctive antidepressant (off-label)
- 3,4-Methylenedioxymethamphetamine (MDMA)
  - PTSD and anxiety associate with cancer (under investigation)
  - No approved medical use

Recent Concerns

- **America's Most Dangerous Drug?**
  - » **Newsweek cover story, 8-8-05**
- **MA use associated with:**
  - **Tooth decay**
  - **Cognitive impairments**
  - **Psychological disorders**
  - **Unsightly appearance**

PAYING A PRICE FOR PLEASURE

Stronger and cheaper than cocaine, meth can lure users into a horrifying spiral of addiction.

CRASH, BURN, REPEAT ...

THERESA BAKER, 2001

THERESA, AGE 42, AFTER 5½ YEARS OF METH USE

YOUR BODY ON METH

SKIN SORES: ... METH MOUTH: ...

YOUR BRAIN ON METH

LONG-TERM LOSSES

LIMBIC SYSTEM: ...

HIPPOCAMPUS: ...

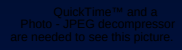
10% LOSS

8% LOSS

Substance Abuse Services, which now sees more women with addictions to meth than to alcohol.

A lot of people never saw the meth epidemic coming. Unlike crack cocaine, which erupted in the nation's urban centers in the 1980s and quickly gained the attention of media and government, meth took hold in rural ... does not have the same hold on policymakers that crack did 20 years ago. I think that's one of the things that has helped the epidemic build in severity, kind of under the radar," says Jack Riley of RAND Corp., the Santa Monica, Calif., think tank. Methamphetamine isn't a new drug, though it has become more powerful as the ingredients and the cooking techniques have evolved. It was first synthesized by a Japanese chemist in 1893, ... in World War II to keep them alert and motivated; kamikaze pilots were said to have taken high doses of the stuff before their missions. In the 1950s, it was commonly prescribed as a ... give housewives a boost. The federal government criminalized the drug in 1970 for most uses (it's still legally available in low doses for the treatment of attention-deficit disorder and narcolepsy), but by then it was illegally being manufactured and distributed by motorcycle gangs in the West. In the early '90s, Mexican trafficking organizations began taking over production, setting up "superlabs" in the California countryside that were able to crank out 50 pounds of meth or more in a weekend. To put

46 NEWSWEEK AUGUST 8, 2005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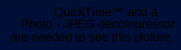
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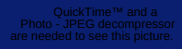
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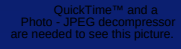
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Shift Work Studies Design

Day	1	2	3	4	5	6	7	8	9	10	11	12
MA	Pbo	Pbo	Pbo	off	5	5	5	Pbo	10	10	10	off
Shift	D	D	D	off	N	N	N	N	N	N	N	off

Day	13	14	15	16	17	18	19	20	21	22	23
MA	10	10	10	Pbo	5	5	5	off	Pbo	Pbo	Pbo
Shift	D	D	D	D	D	D	D	off	N	N	N

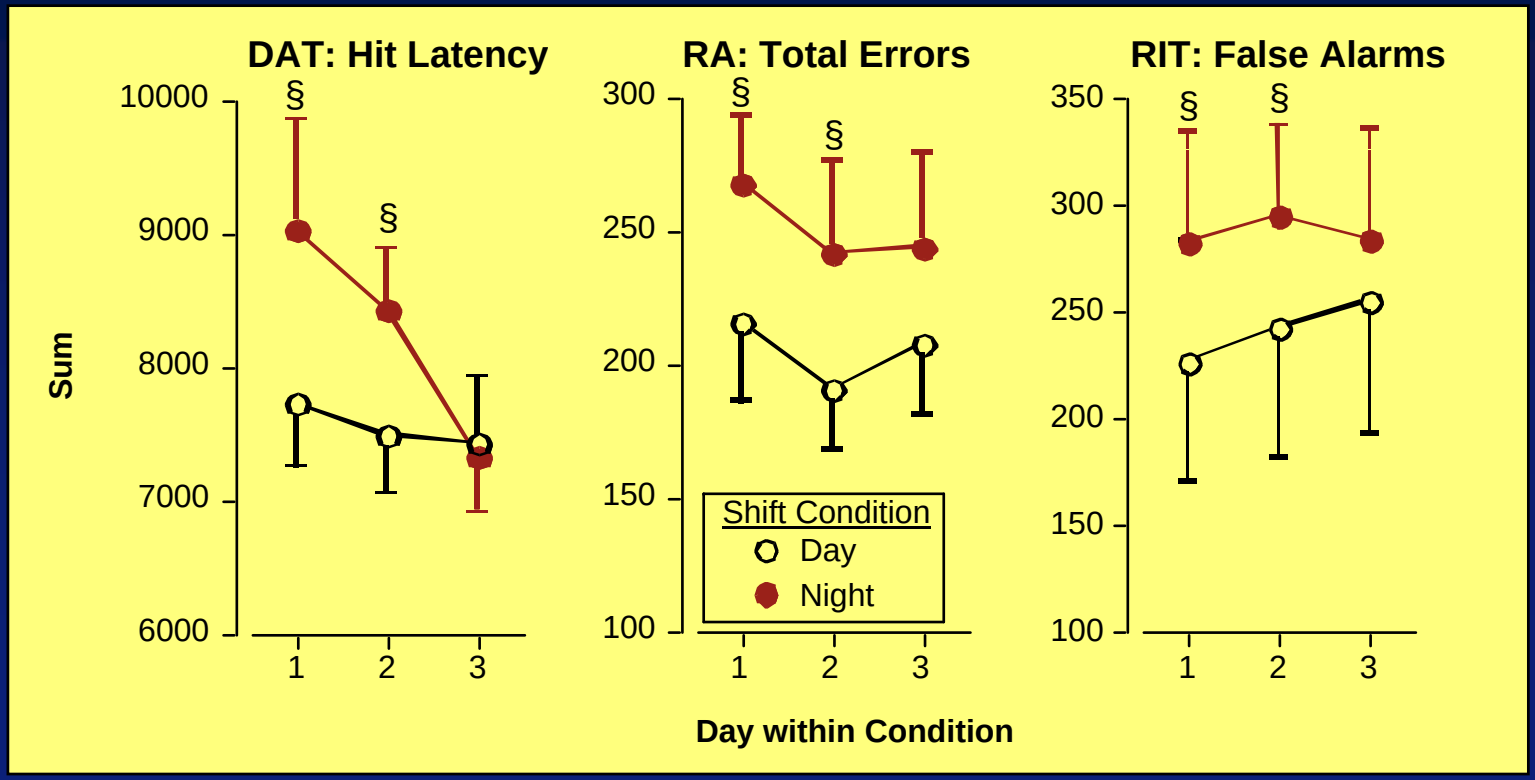
D = shift began at 0815; N = shift began at 0015

Dosing Times: D – 0915; N – 0115

Performance and Shift-work

Performance disrupted during night shift work

Question: Effects of methamphetamine?

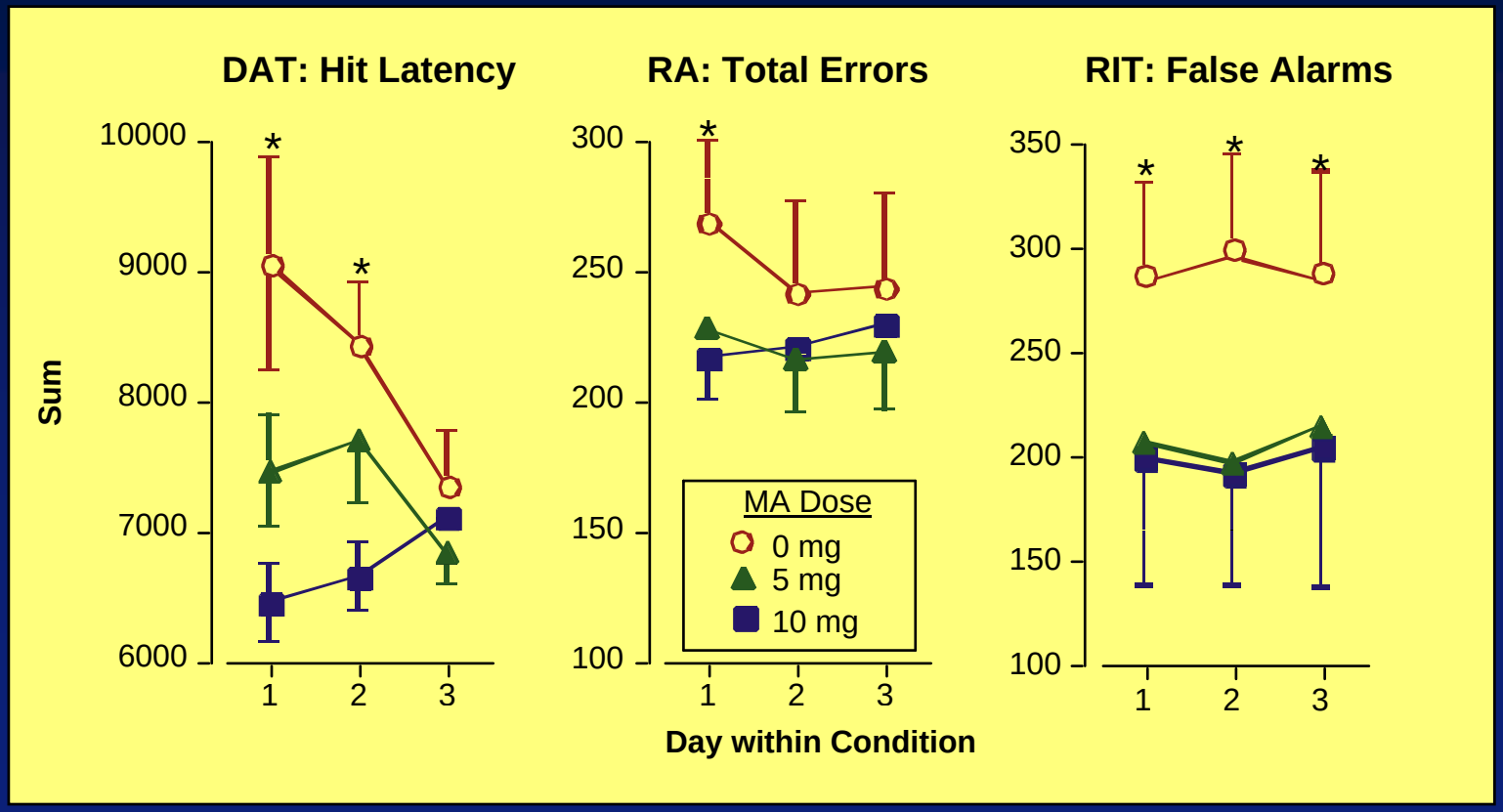


Hart et al. 2003, *Psychopharmacology* 169, 42-51

Effects of Methamphetamine

Low oral doses of methamphetamine attenuated night shift-related disruptions in infrequent users

Question: Is abuse liability greater under conditions engendering poor performance and fatigue?



Hart et al. 2003, *Psychopharmacology* 169, 42-51

Shift Work and MA Self-administration

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
0115	*	*	*	*							*	*	*	*					
0915	*	*	*	*		*	*	*	*		*	*	*	*		*	*	*	*
1715						*	*	*	*							*	*	*	*
Shift	N	N	N	N	off	D	D	D	D	off	N	N	N	N	off	D	D	D	D

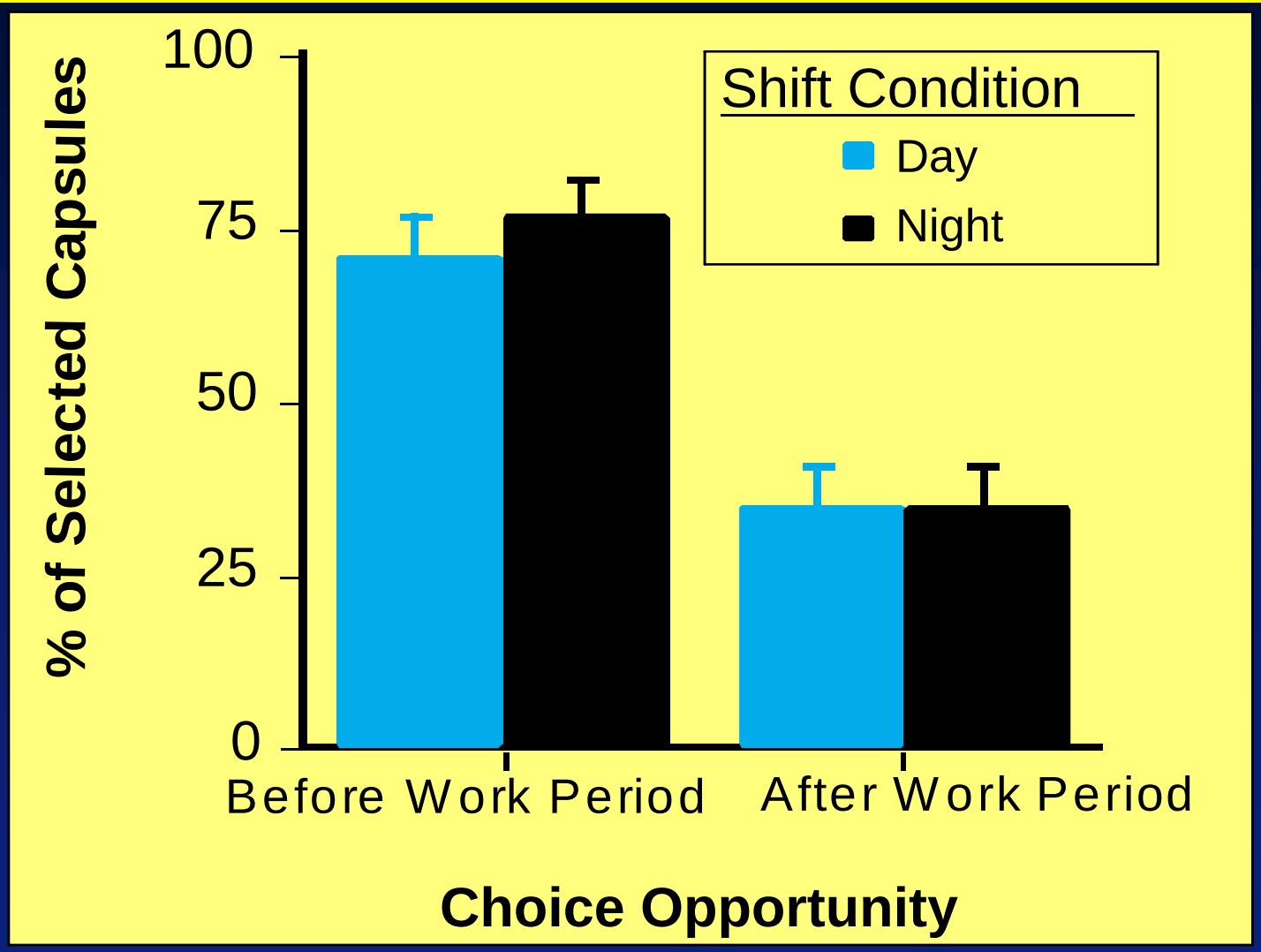
N = Night shift

D = Day shift

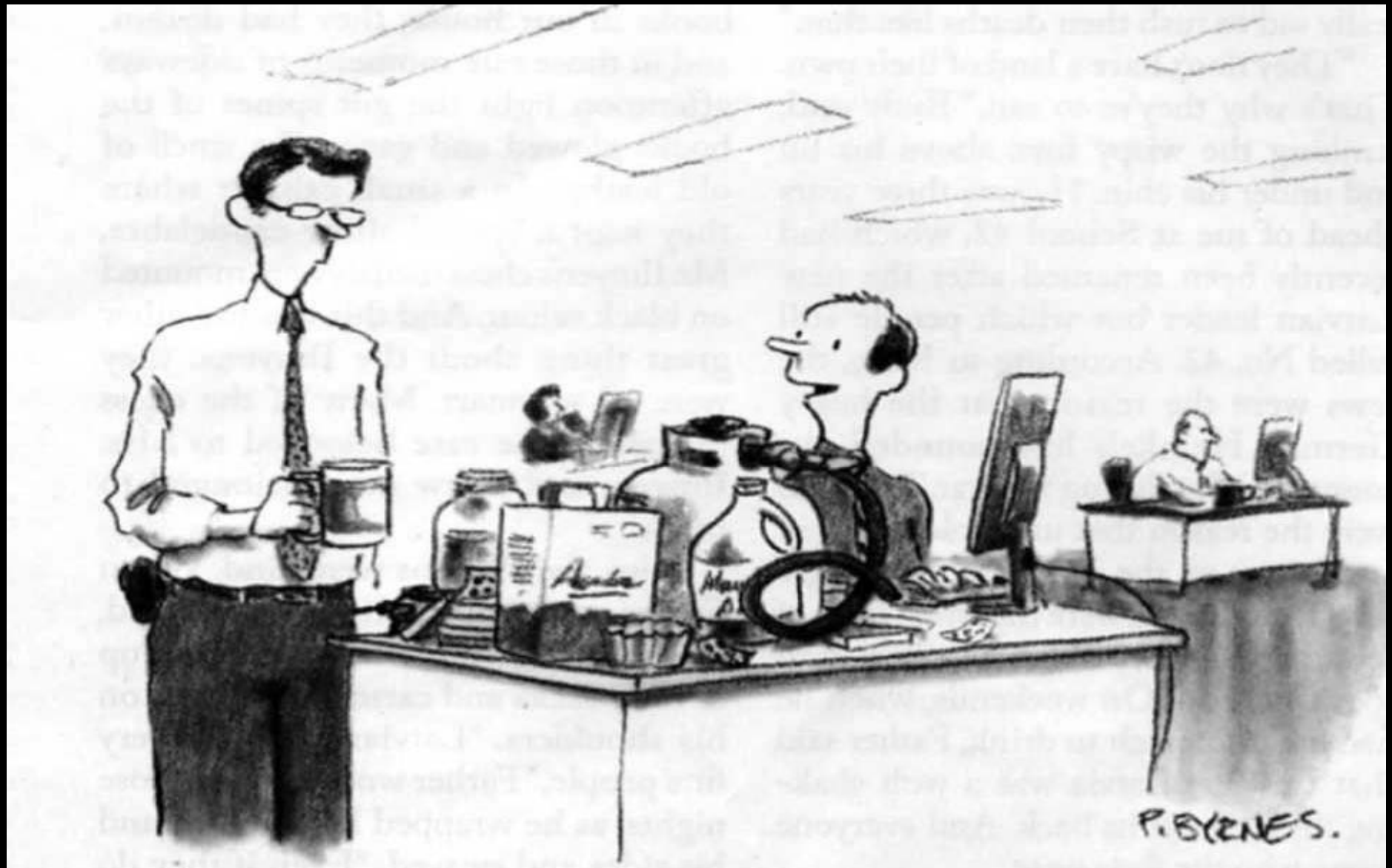
* = MA Choice (10mg vs. $1 voucher)

= No choice

Methamphetamine Self-administration



Kirkpatrick et al. (2009) *Psychopharmacology 203: 771-80*



"Meth doesn't upset my stomach the way coffee does."

Interim Summary (MA and Shift Work)

	Single Low Oral Doses
Compromised performance	improved
Self-administration	Sensitive to contextual factors e.g. work requirements
Deleterious Effects	Not apparent

Repeated Oral Dosing Design

Day	1	2	3	4	5	6	7	8	9
MA	Pbo	Pbo	Pbo	5	5	5	Pbo	Pbo	Pbo

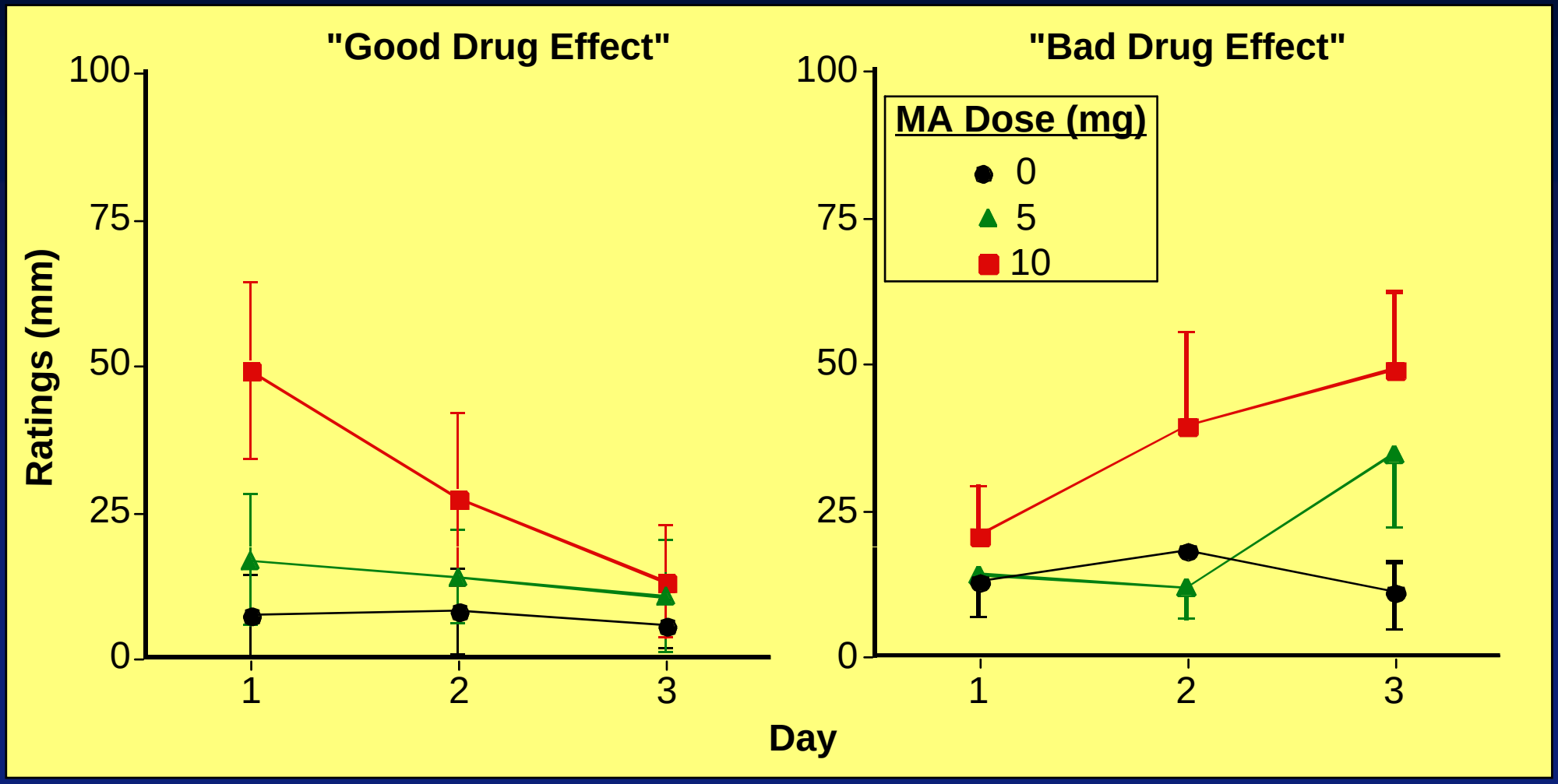
Day	10	11	12	13	14	15
MA	10	10	10	Pbo	Pbo	Pbo

Dosing Times: 1000 and 1800

MA = Methamphetamine

Repeated: Subjective Effects

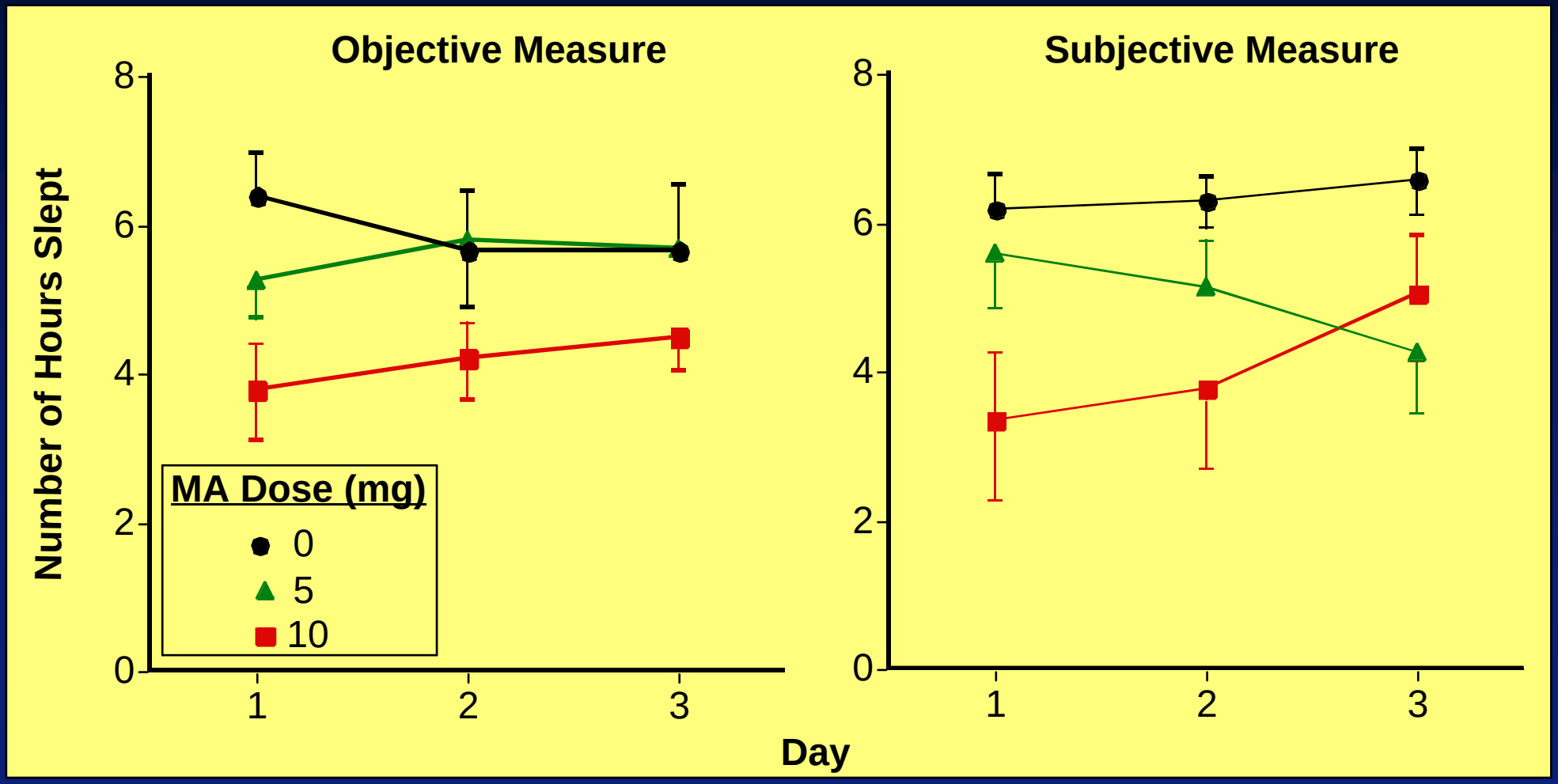
“Positive” subjective effects decreased over time, while “negative” effects increased



Comer et al. 2001, *Psychopharmacology* 155, 397-404

Repeated: Sleep Effects

Largest dose decreased sleep



Comer et al. 2001, *Psychopharmacology* 155, 397-404

Interim Summary (Repeated Dosing)

	Repeated Low Oral Doses
Sleep	disrupted
Positive Subjective Effects	decreased over time
Negative Subjective Effects	increased over time

Study Design (i.n. MA)

Week	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
0				Adm			
1	25	R		12	R		
2	0	R		50	R	Out	

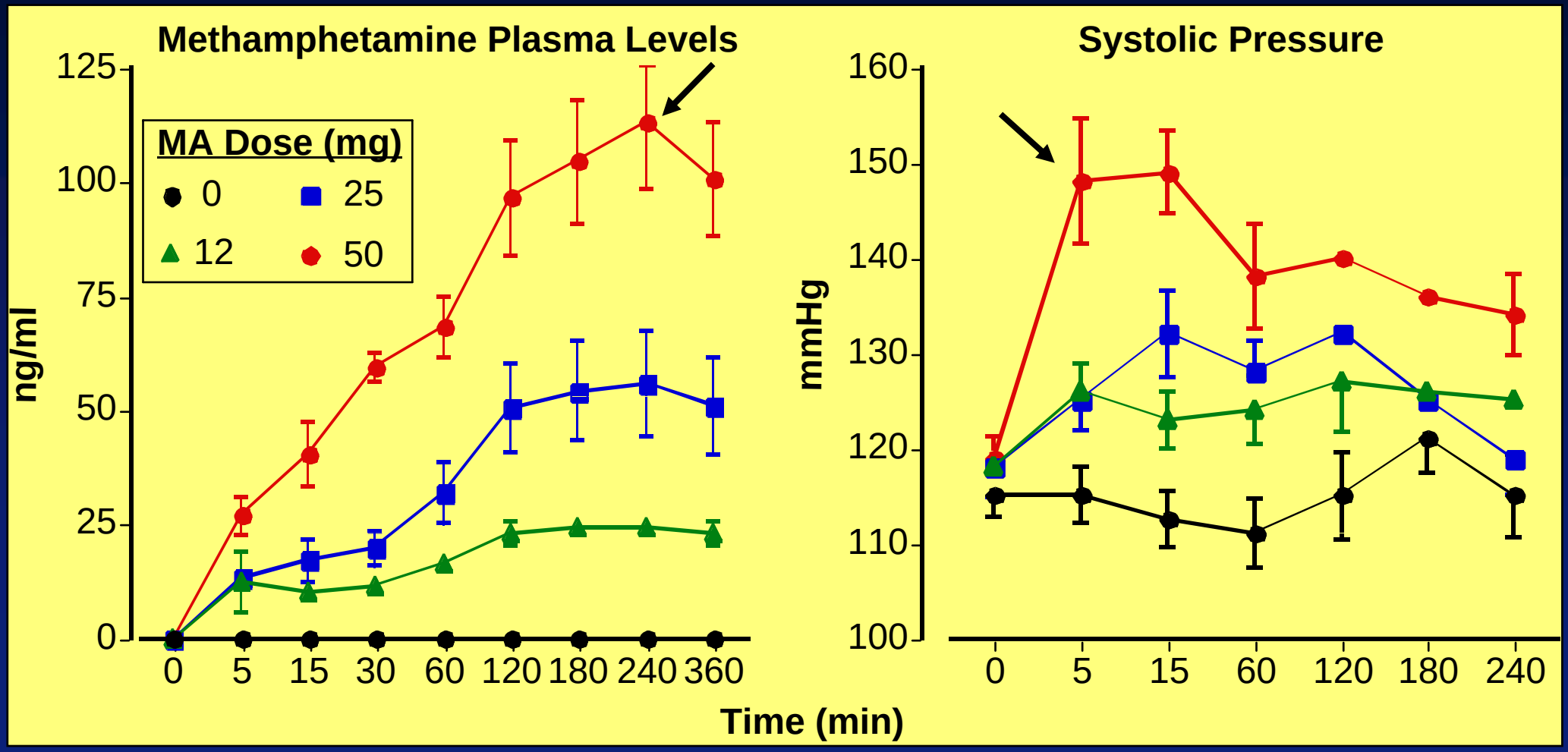
Methamphetamine Doses: 0, 12, 25, 50 mg/70 kg

Adm: Admission

R: Residual effects assessed

Acute: Physiological Effects

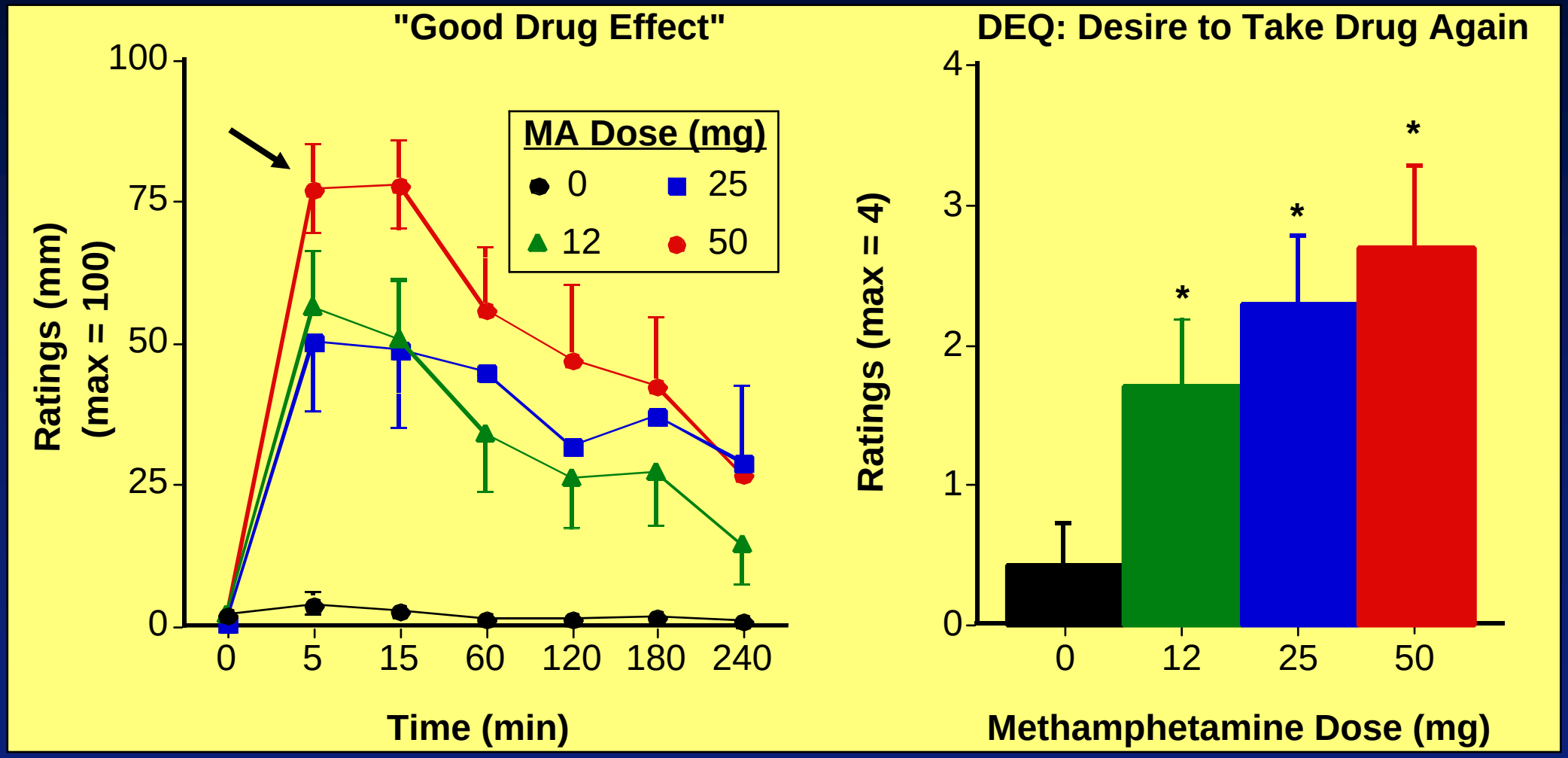
Methamphetamine produced dose-dependent increases in plasma levels & blood pressure



Hart et al. 2008, *Neuropsychopharmacology* 33, 1847-1855

Acute: Positive Subjective Effects

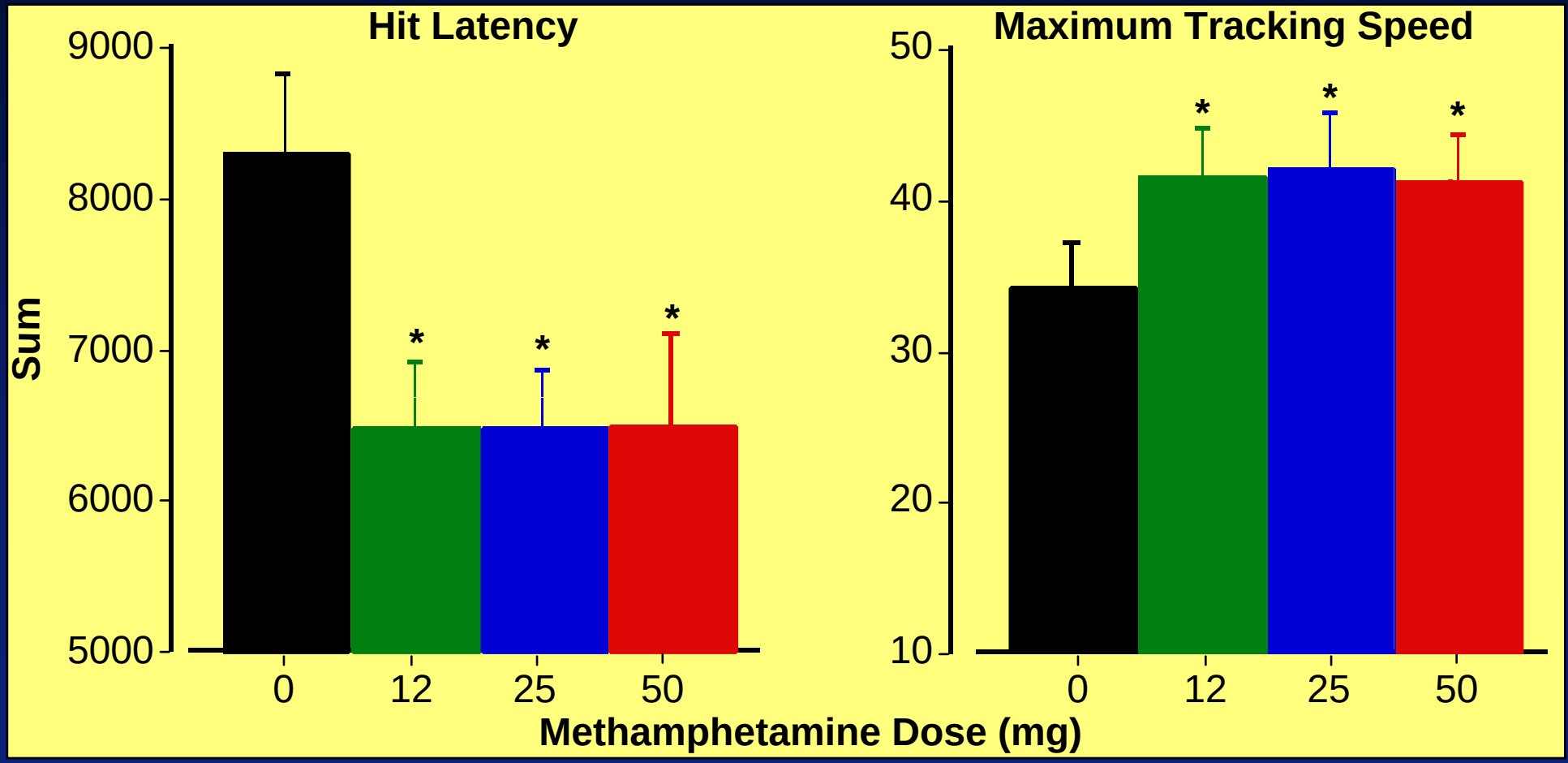
Methamphetamine produced dose-dependent increases in “positive” subjective effects



Hart et al. 2008, *Neuropsychopharmacology* 33, 1847-1855

Acute: Performance Effects - DAT

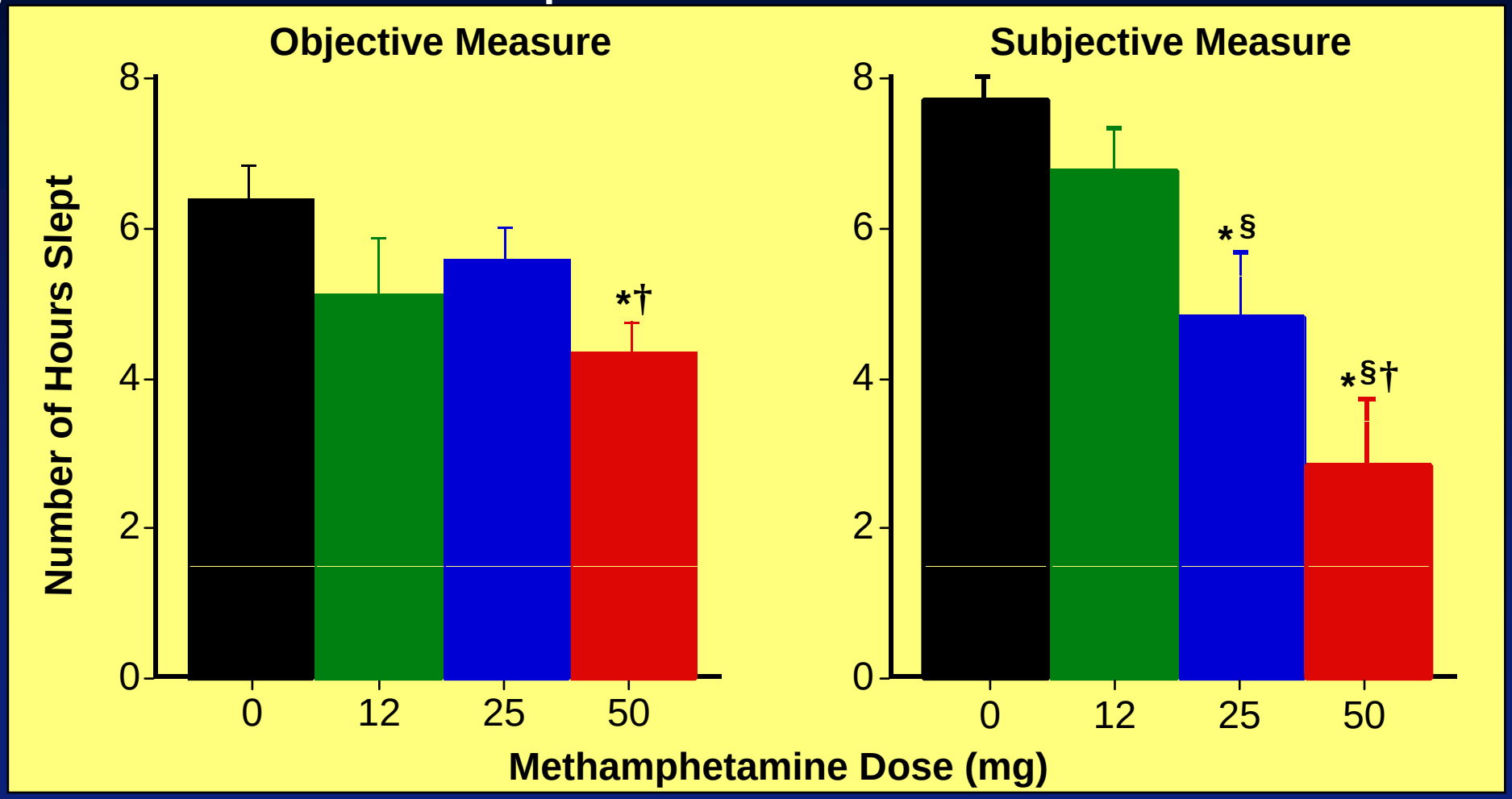
All methamphetamine doses improved RT and sustained attention



Hart et al. 2008, *Neuropsychopharmacology* 33, 1847-1855

Residual: Sleep Effects

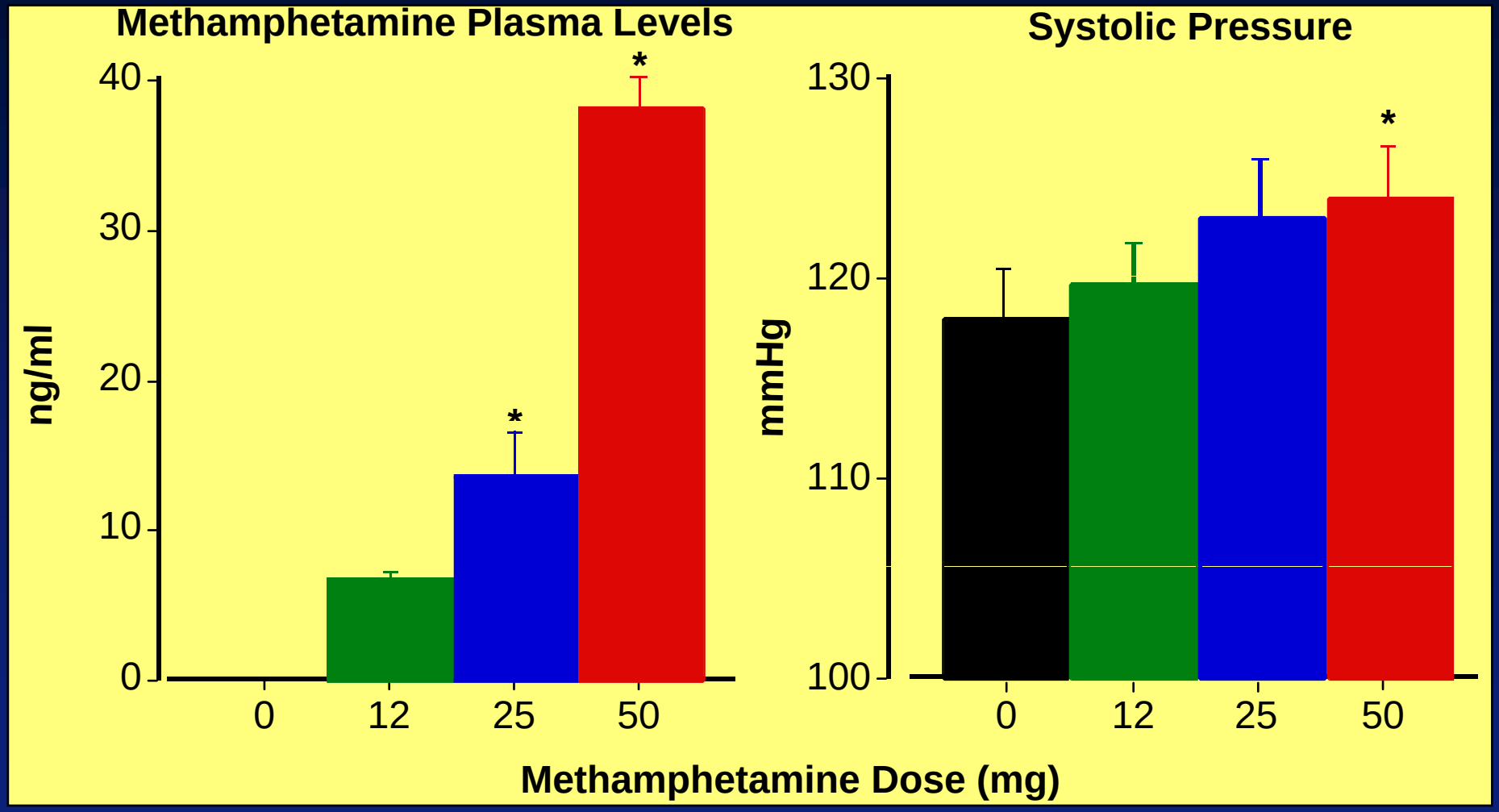
Larger doses decreased total sleep time



Perez et al. 2008, *Drug and Alcohol Dependence* 94, 258-262

Residual: Physiological Effects

Next-day plasma levels and blood pressure increased by larger doses



Perez et al. 2008, *Drug and Alcohol Dependence* 94, 258-262

Interim Summary (i.n. MA)

	Acute Effects	Residual Effects
Sleep		disrupted • subjective sleep more sensitive
Physiological Effects	increased	increased
Positive Subjective Effects	increased	
Negative Subjective Effects	unaltered	unaltered
Cognitive Performance	improved	unaltered

Ongoing Study

- Repeated i.n. MA dosing
  - 3 doses per sessions (2 hr inter-dosing interval) for 3 consecutive days
- Preliminary Findings
  - Sleep dramatically disrupted
  - Inter- and intra-session tolerance to subjective and physiological effects

Take-home Message

- Drugs are not good or bad
  - Every drug has multiple effects
- Drug effects are dose-dependent
  - Route of administration important
- Set and setting important considerations

Prof. Marian Fischman

Oct 13, 1939 - Oct 23, 2001

Reprinted from JAMA @ The Journal of the American Medical Association November 20, 1996 Volume 276

Review

Crack Cocaine and Cocaine Hydrochloride

Are the Differences Myth or Reality?

Dorothy K. Hatsukami, PhD; Marian W. Fischman, PhD

Objective.—To review and discuss the differences and similarities between the use of crack cocaine and cocaine hydrochloride; and to determine how these findings might affect policies on the imprisonment and treatment of cocaine users.

Data Sources.—English-language publications were identified through a computerized search (using MEDLINE) between 1976 and 1996 using the search terms "smoked cocaine," "crack cocaine," "freebase," and "cocaine-base." In addition, manual searches were conducted on references cited in original research articles, reviews, and an annotated bibliography, and on selected journals.

Study Selection.—Only those articles that compared various routes of cocaine administration or types of cocaine (cocaine base or crack cocaine vs cocaine hydrochloride) were examined.

Data Extraction.—Studies were reviewed to obtain information on the composition of the 2 forms of cocaine, and the prevalence, pharmacokinetics and pharmacodynamics, abuse liability, pattern of use, and consequences across the various routes of cocaine administration and forms of cocaine.

half of them using it in the past year. By 1985, the number of those ever using cocaine had increased to 25 million, and the peak of that epidemic was reached, with steadily diminishing numbers over the next 7 years. However, a new epidemic was beginning: crack cocaine, a readily smokable form of cocaine hydrochloride, was being sold in unit doses for $3 to $5 per rock. The availability of a relatively cheap smokable form led to a marked expansion of cocaine use among the poor and ethnic minorities,[2,3] and its use was accompanied by violent crime and devastation of both inner-city areas and families.