Introduzione generale; aspetti neurobiologici; update della letteratura scientifica. Le sostanze d'abuso ricreazionali: aspetti neurobiologici, clinici ed epidemiologici

Professor **Fabrizio Schifano**, St George's Medical School, University of London

(Verona, 29 maggio 2006)

Programma delle relazioni

- Cenni storici; la modificazione degli scenari degli stupefacenti nel mondo occidentale negli ultimi 35 anni.
- ‘Droghe’ leggere e pesanti; le droghe sintetiche; le ecodroghe
- Farmacodinamica delle sostanze d’abuso in generale ed approfondimenti in merito alle singole sostanze piu’ presenti sul mercato (THC, MDMA e MDMA-like, eroina, cocaina/crack, alcol, ketamina, amfetamine)
- I consumatori c.d. ‘ricreazionali’: caratteristiche cliniche e sociodemografiche; difficolta’ di aggancio e di mantenimento del rapporto terapeutico
- Il problema della doppia diagnosi, sia dal punto di vista clinico (distinzione in diversi sottogruppi) che psicofarmacologico. Suggerimenti dalla letteratura piu’ recente e possibilita’ di trattamento

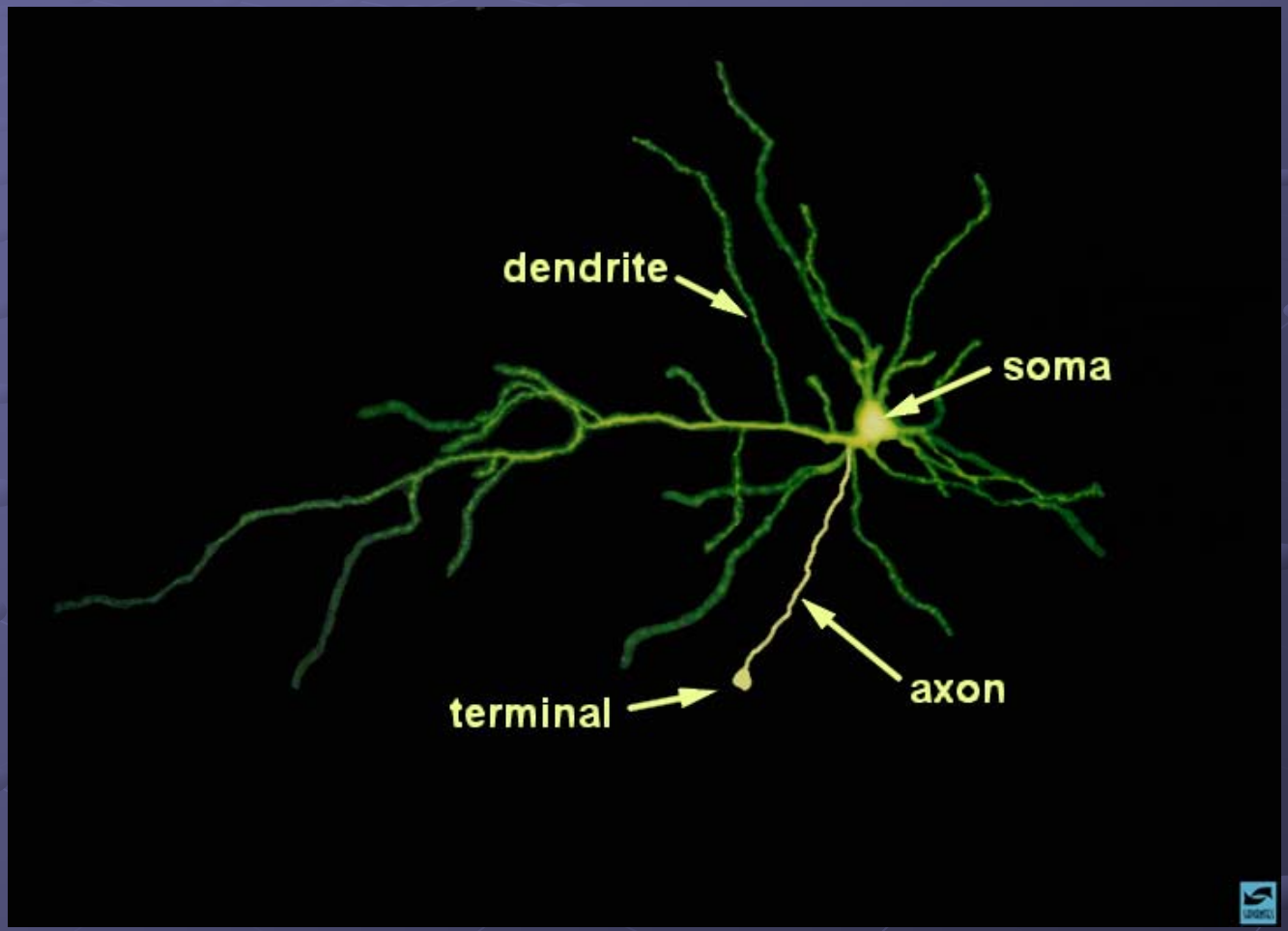
Brief overview of drug abuse history

- 1964-8: probably starts the psychedelic era
- 1968: S Francisco Summer of Love (J Joplin; J Hendrix): MDA, THC, LSD
- 1971-2: heroin finally arrives to Europe
- 1970s: ‘soft’ and ‘hard’ drugs
- 1981, NEJM: 6 AIDS cases first reported
- 1985: HIV positivity is a reality in Europe
- 1987-8: Ibiza
- 1990’s: recreational/polydrug scene
- 2000-….: stimulants; Internet and the ‘novel’ psychedelics

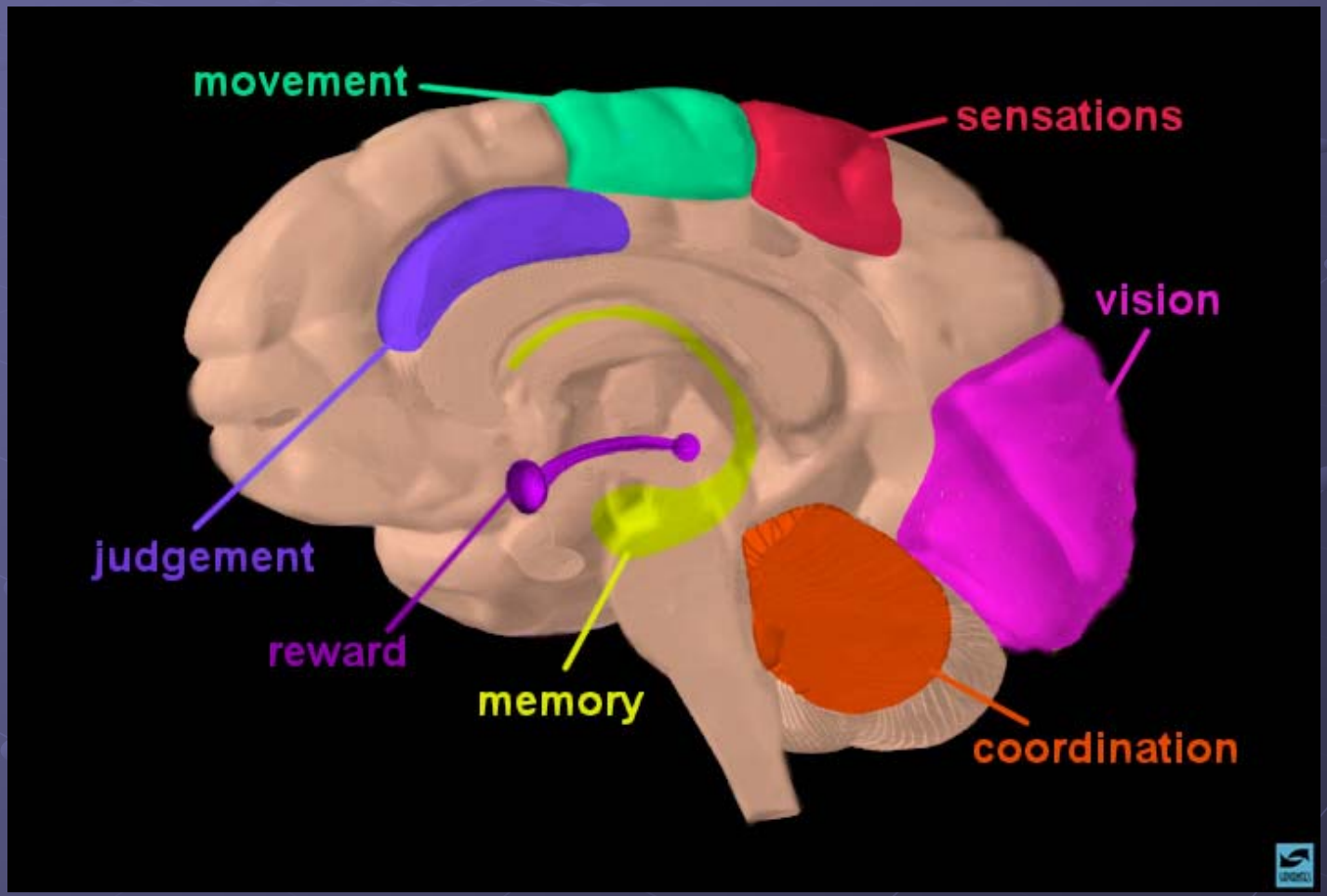
…ma perche’ tutto e’ cambiato?

- the i.v. heroin use is not considered ‘trendy’ any longer
- the newcomers into the illicit drugs market tend to differentiate themselves from the ‘junkies’.
- The uppers’ abuse is frequently observed in the dance scene

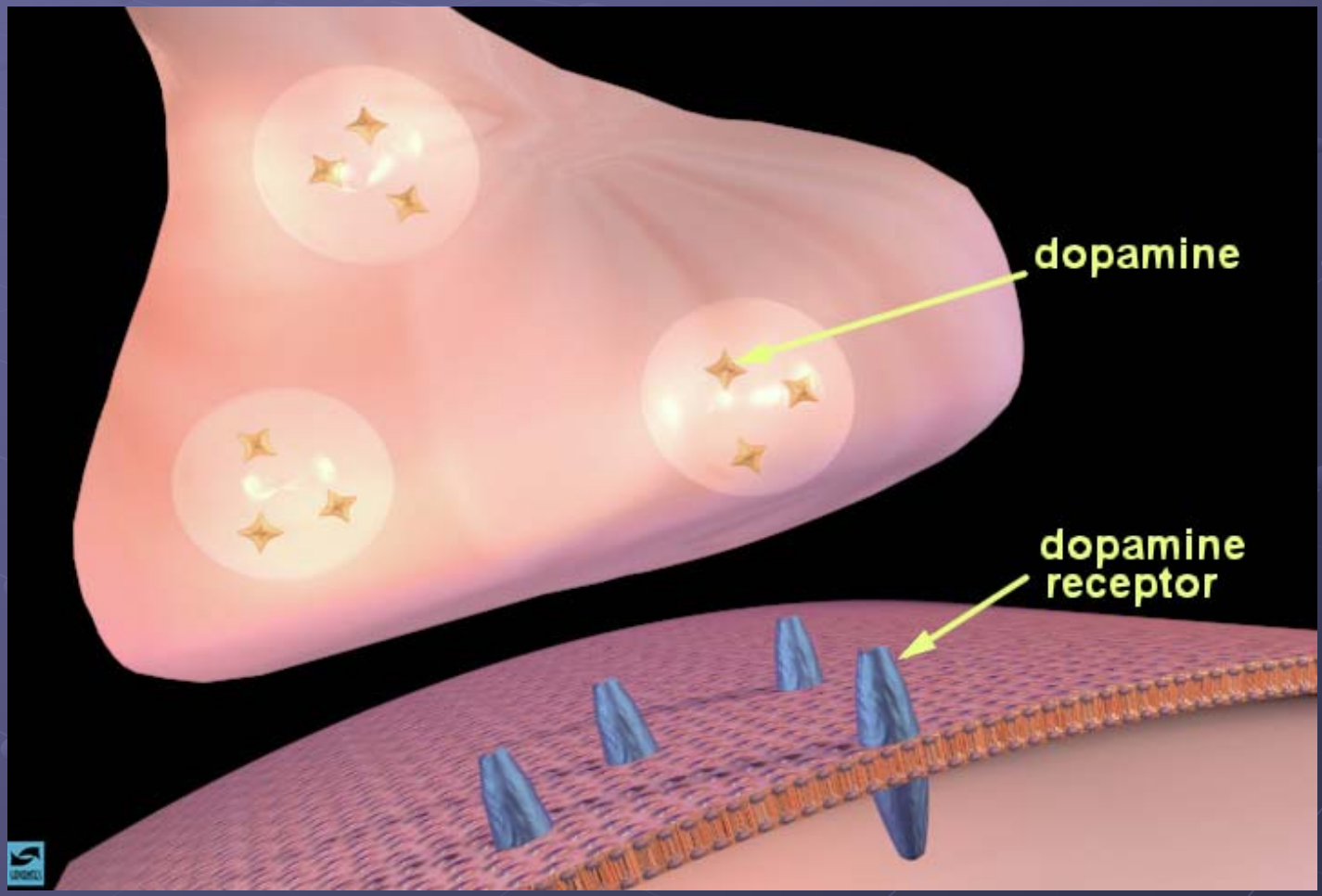
The neuronal structure



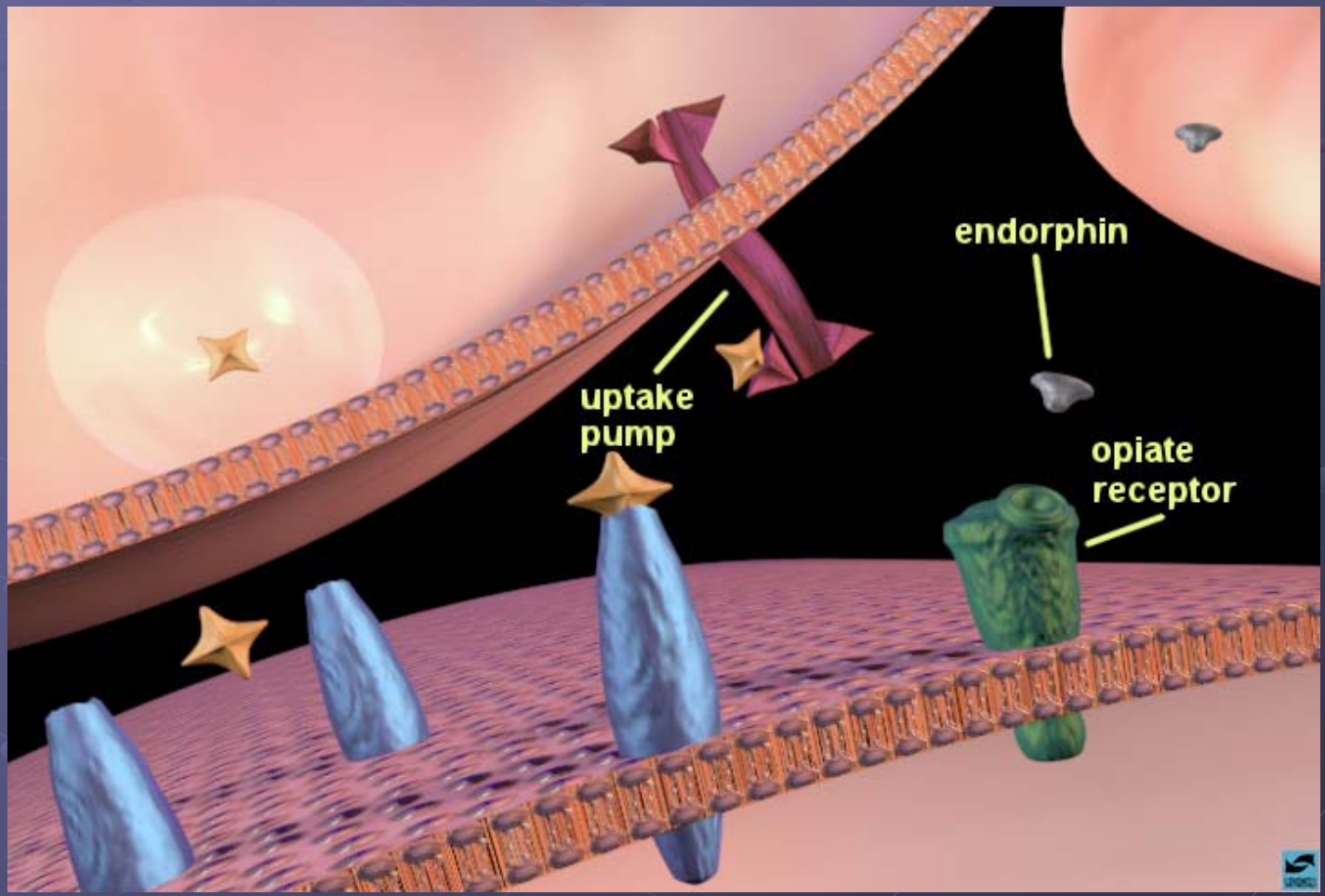
Brain regions



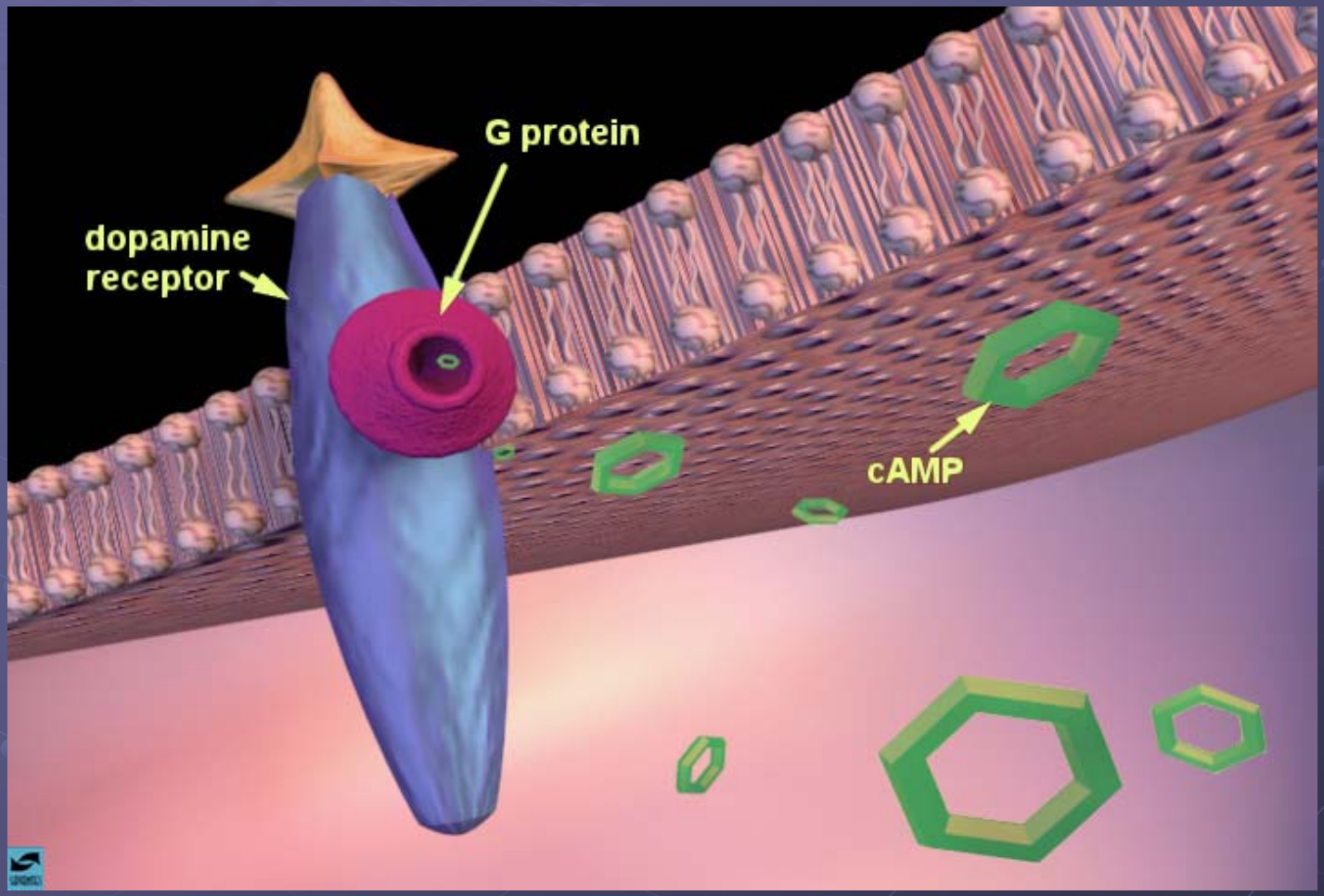
The synapse trasmission



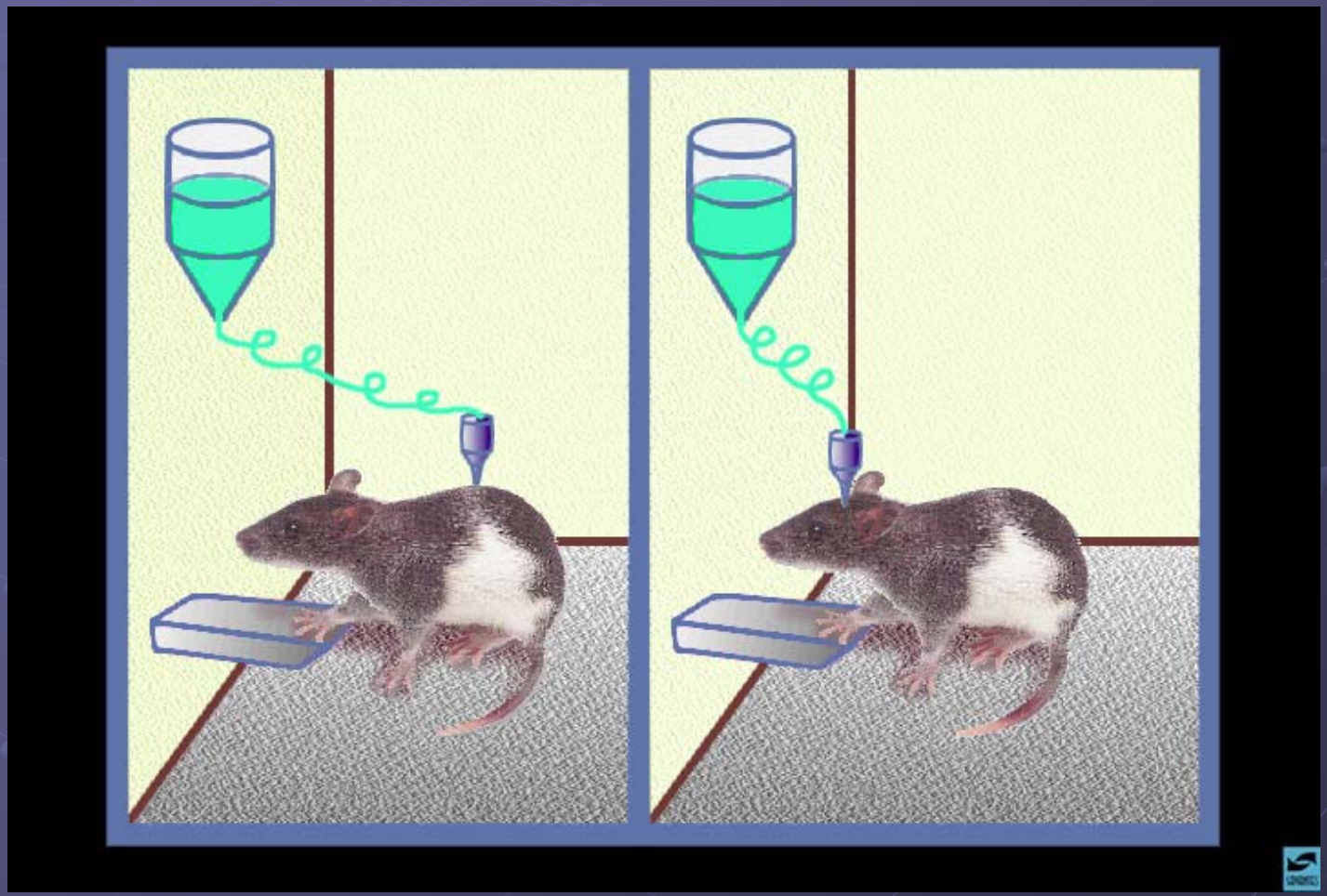
DA neurotransmission



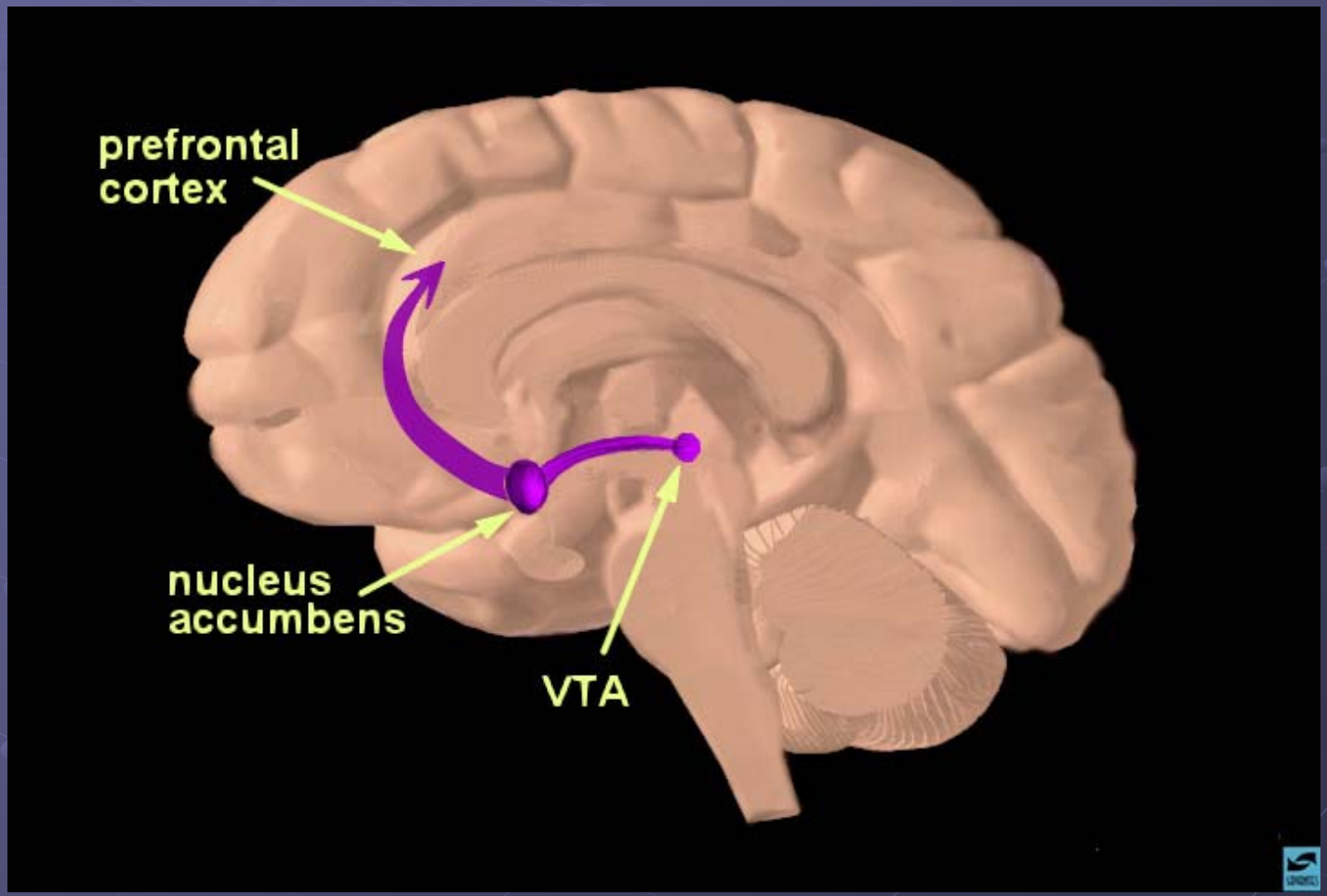
Dopamine and the production of cyclic AMP



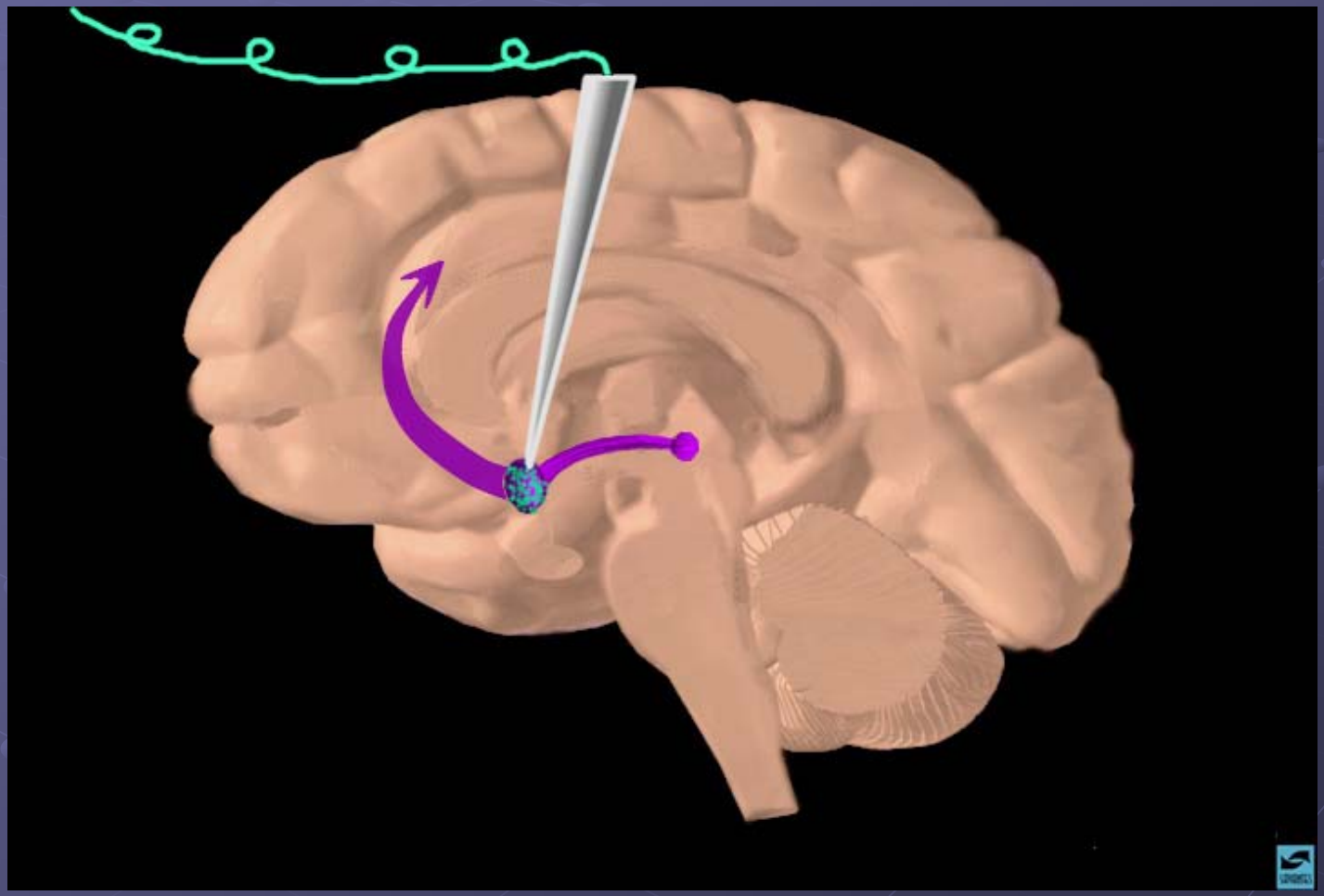
Reward: drug self-administration



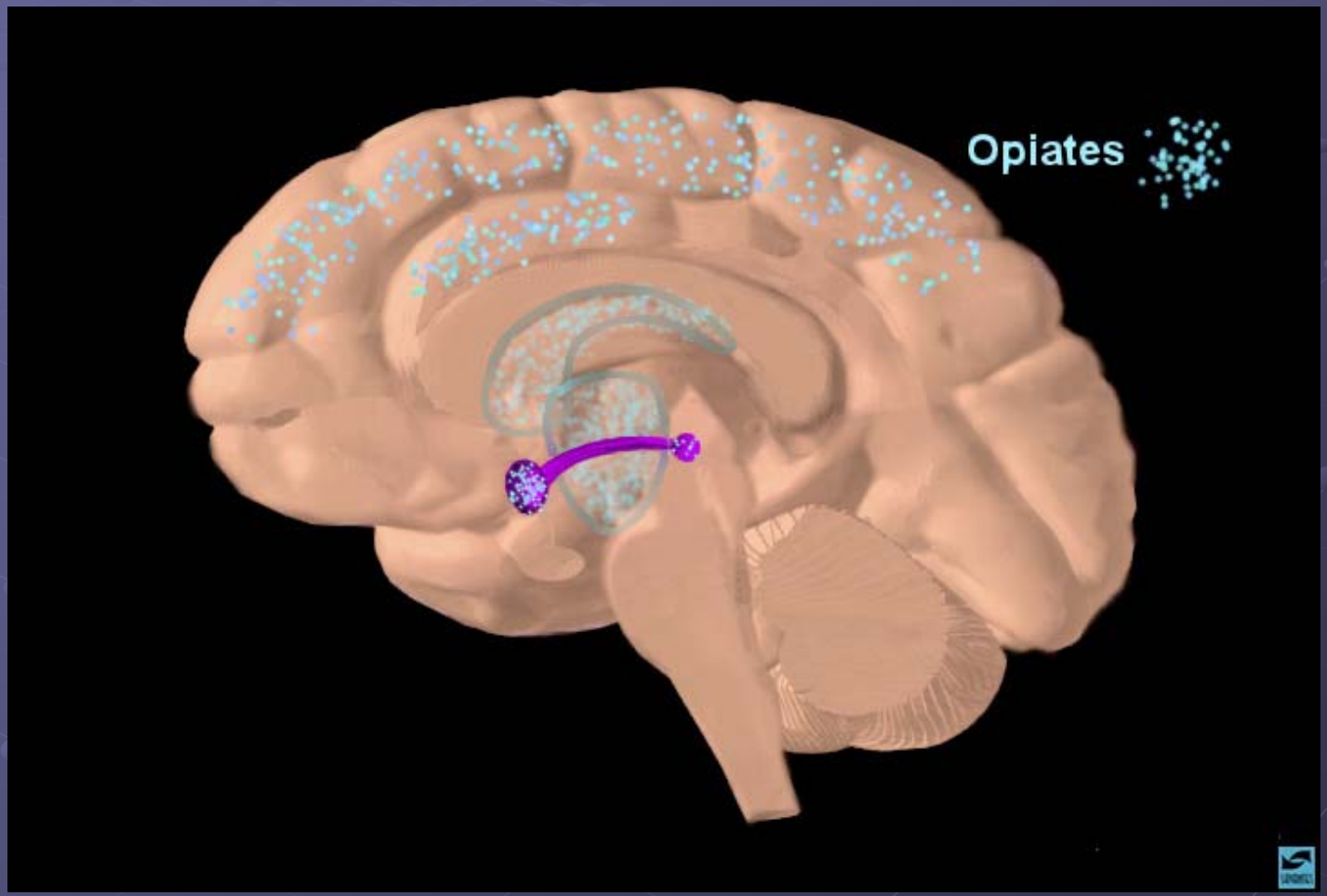
The reward pathway



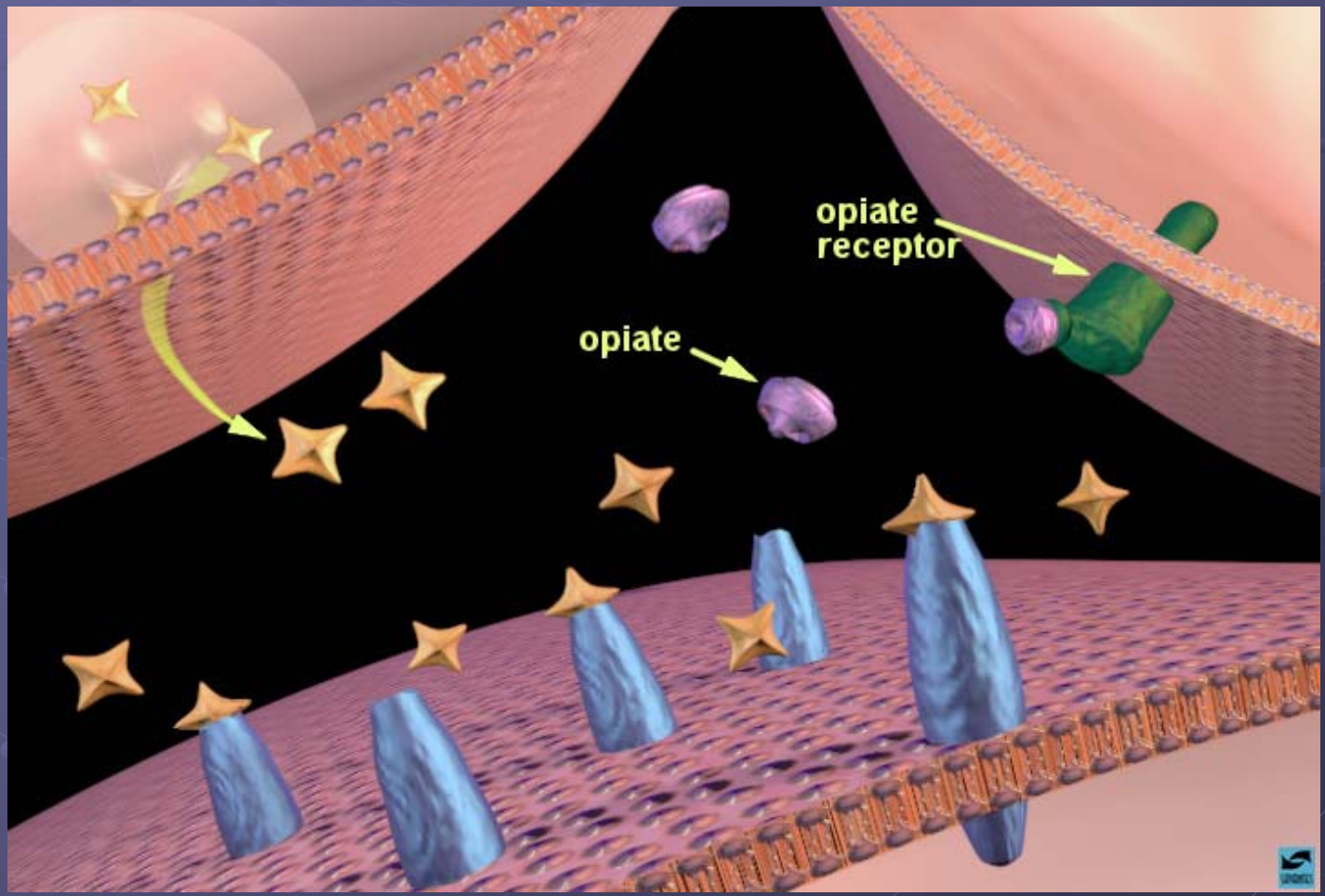
Injection of a drug in the nucleus accumbens



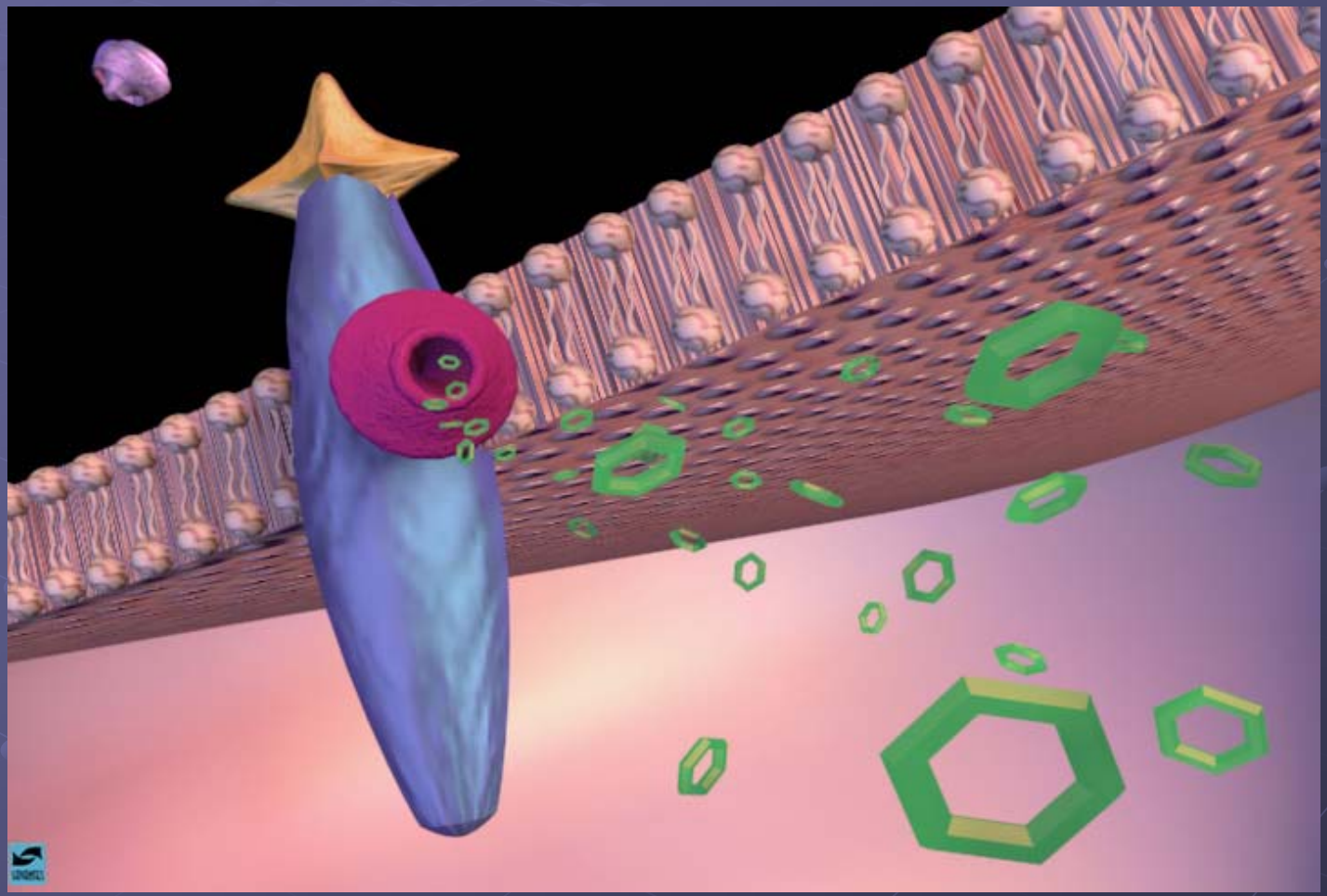
Localization of opiate binding sites



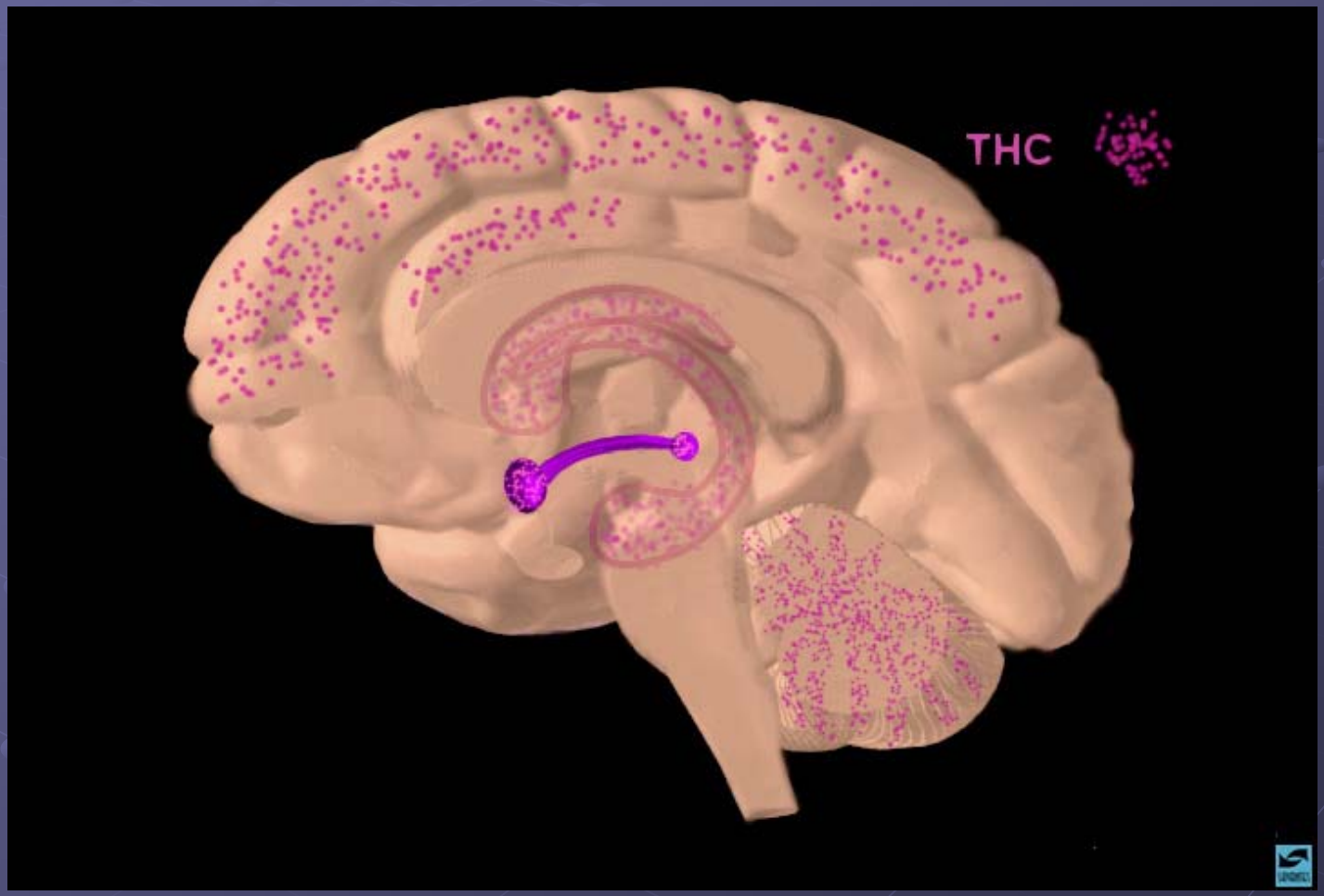
Opiates binding to opiate receptors in the nucleus accumbens: increased dopamine release



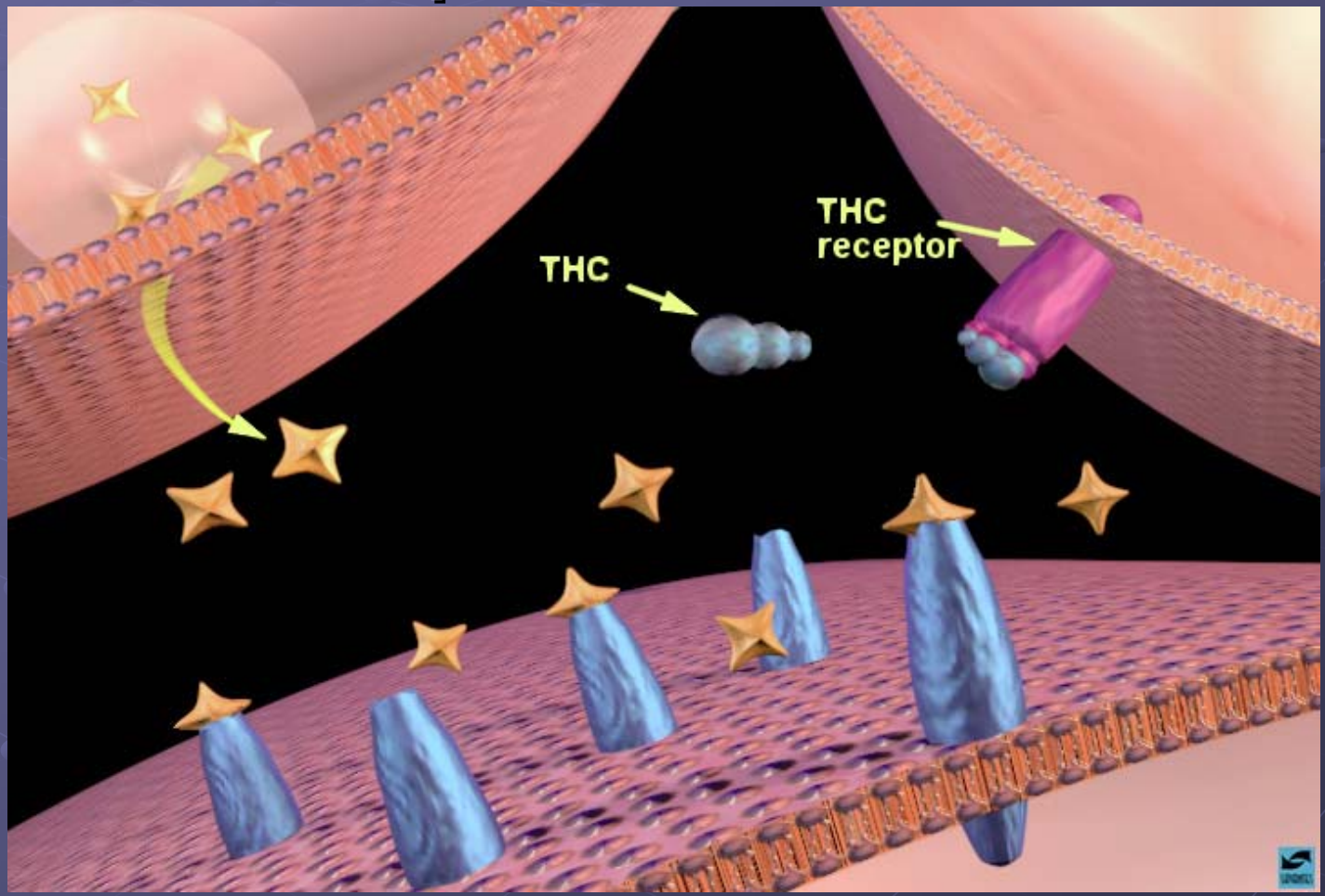
Increased cAMP produced in post-synaptic cell



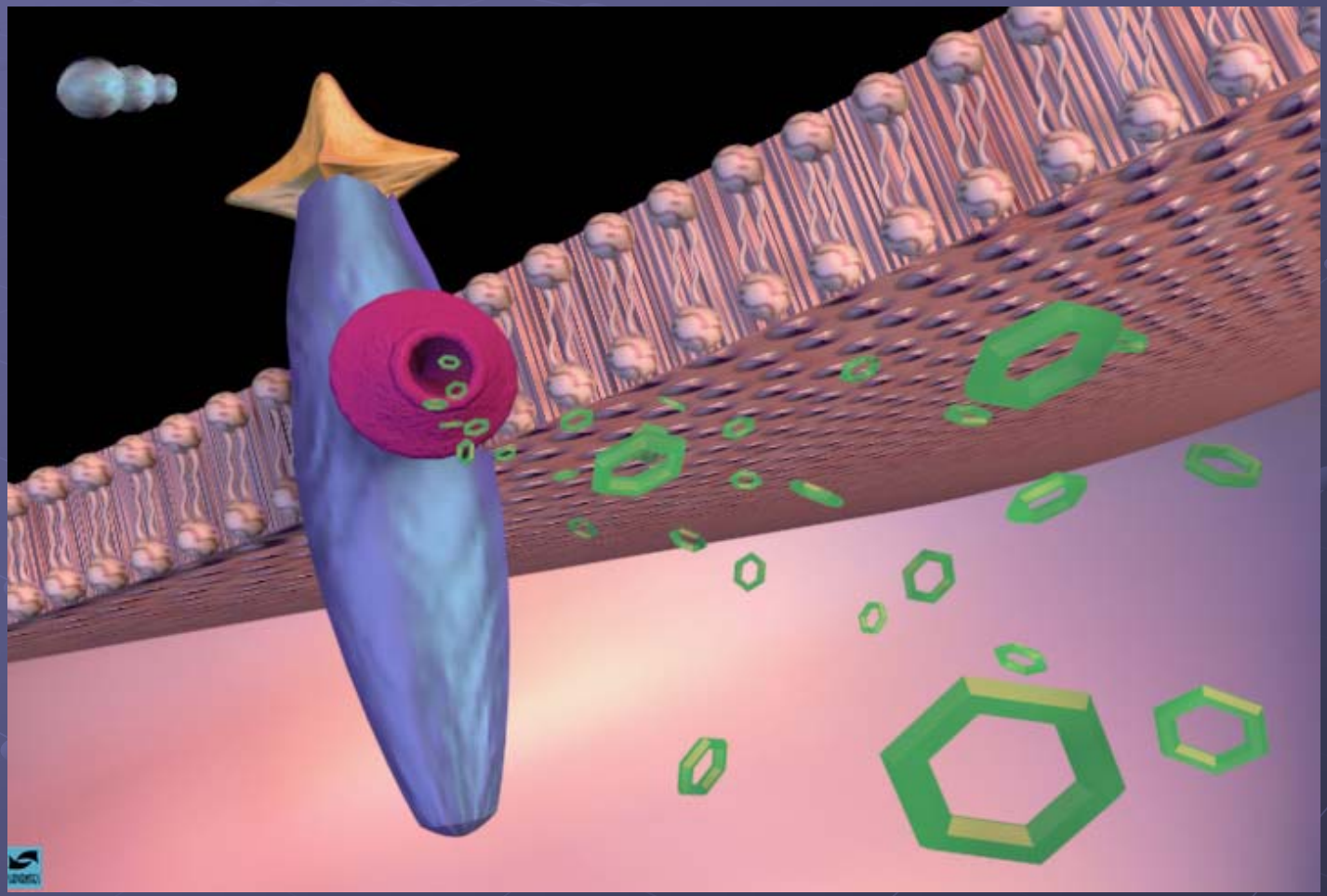
Localization of THC binding sites



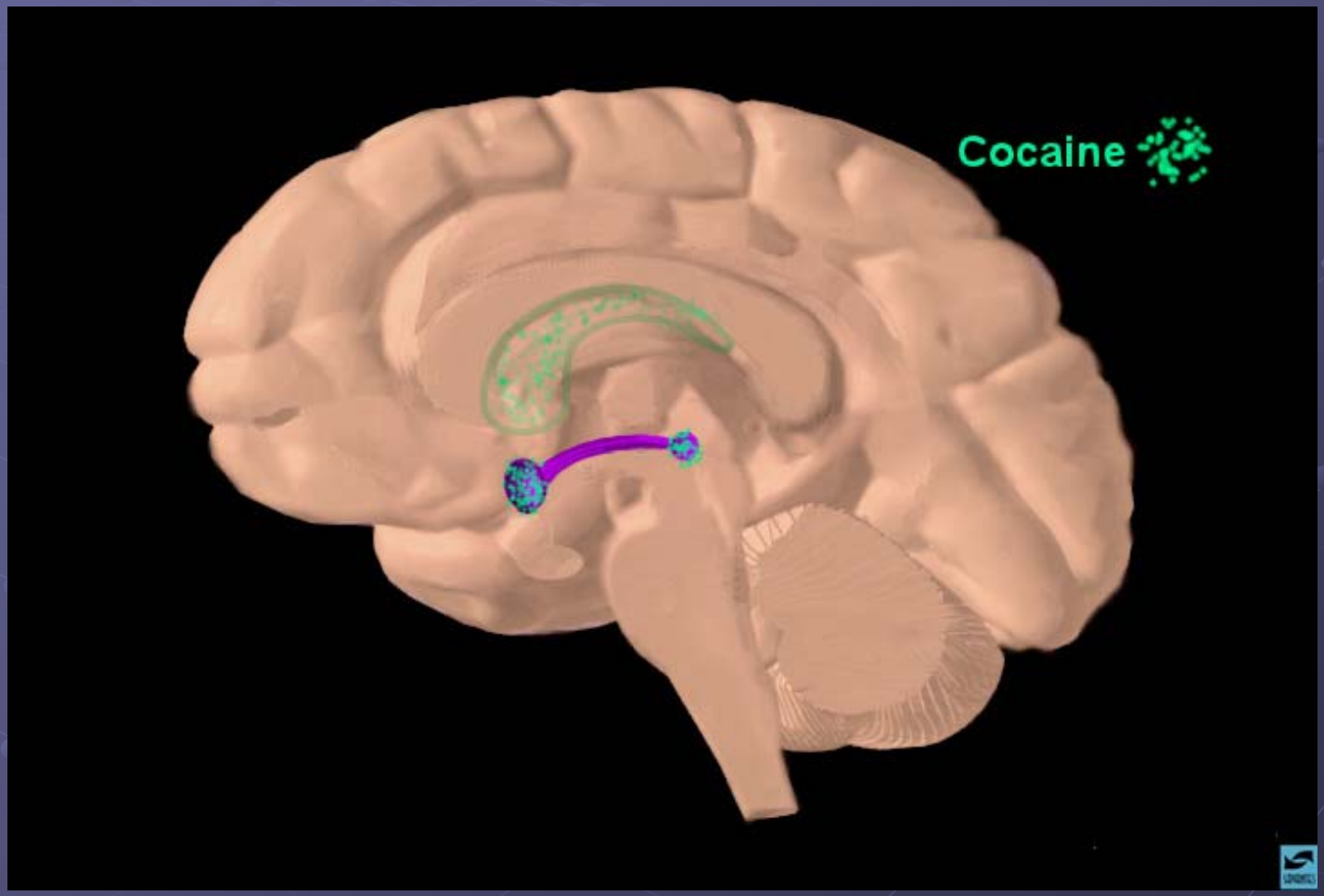
THC binding to THC receptors in the nucleus accumbens: increased dopamine release



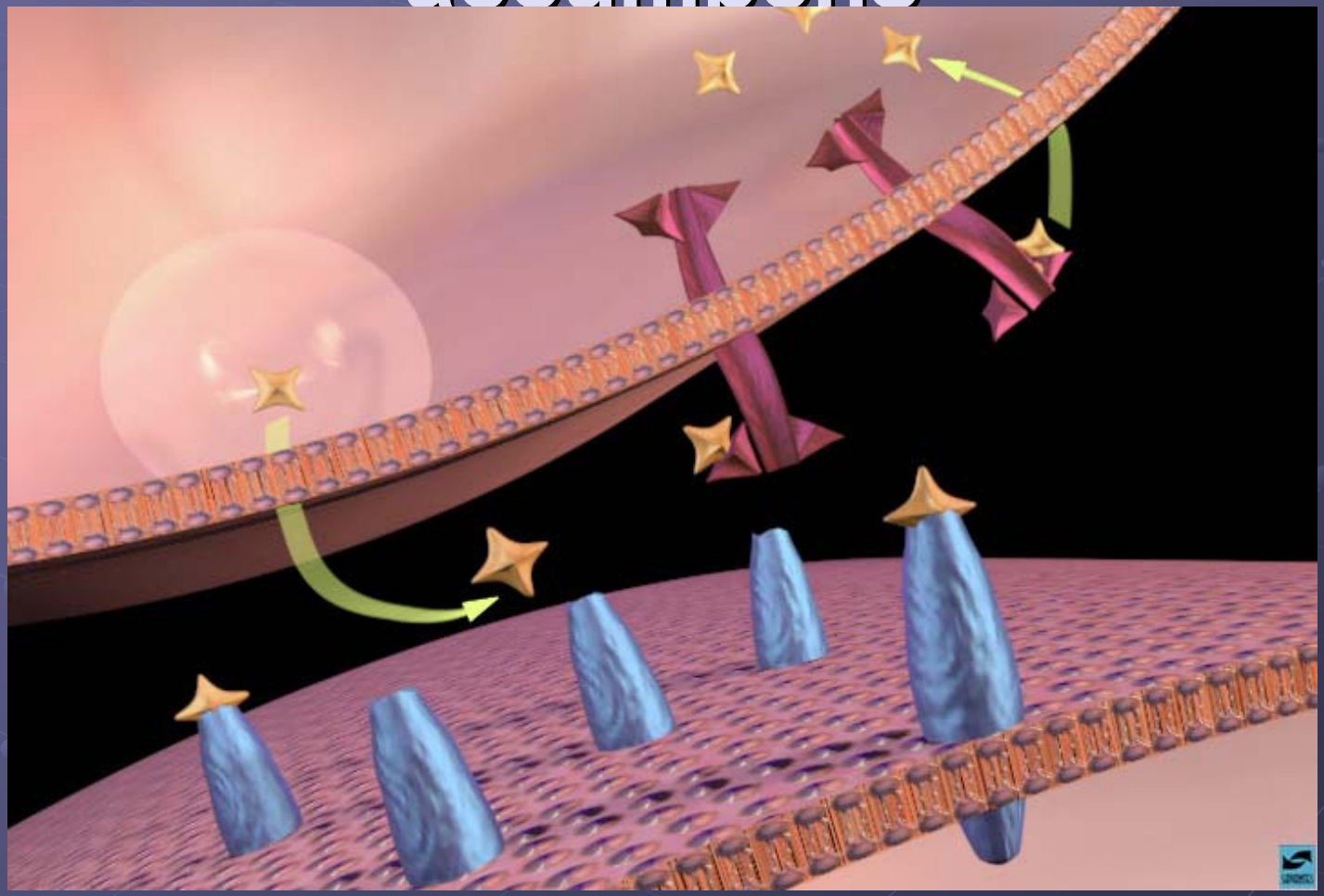
Increased cAMP produced in post-synaptic cell



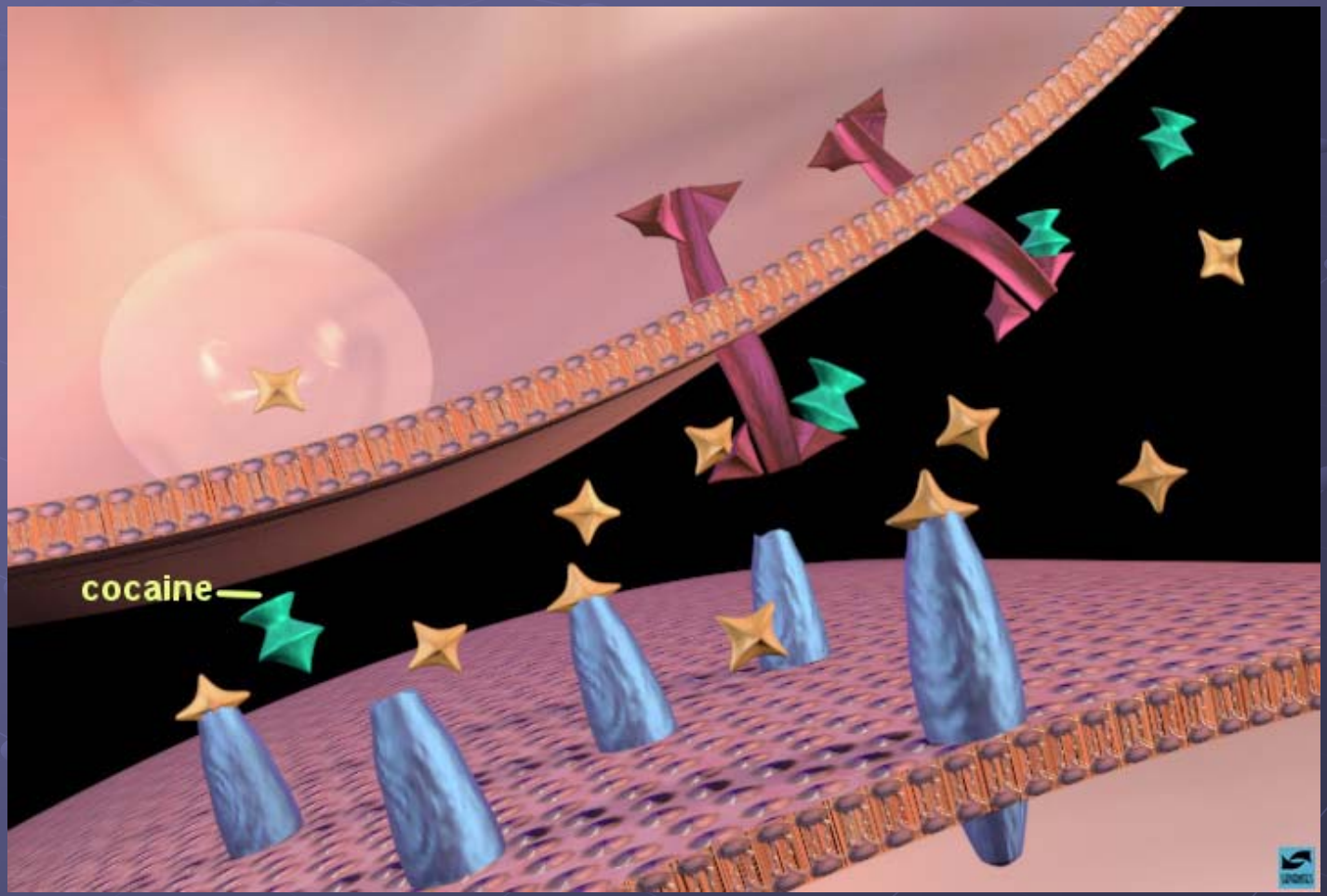
Localization of cocaine ‘binding’ sites



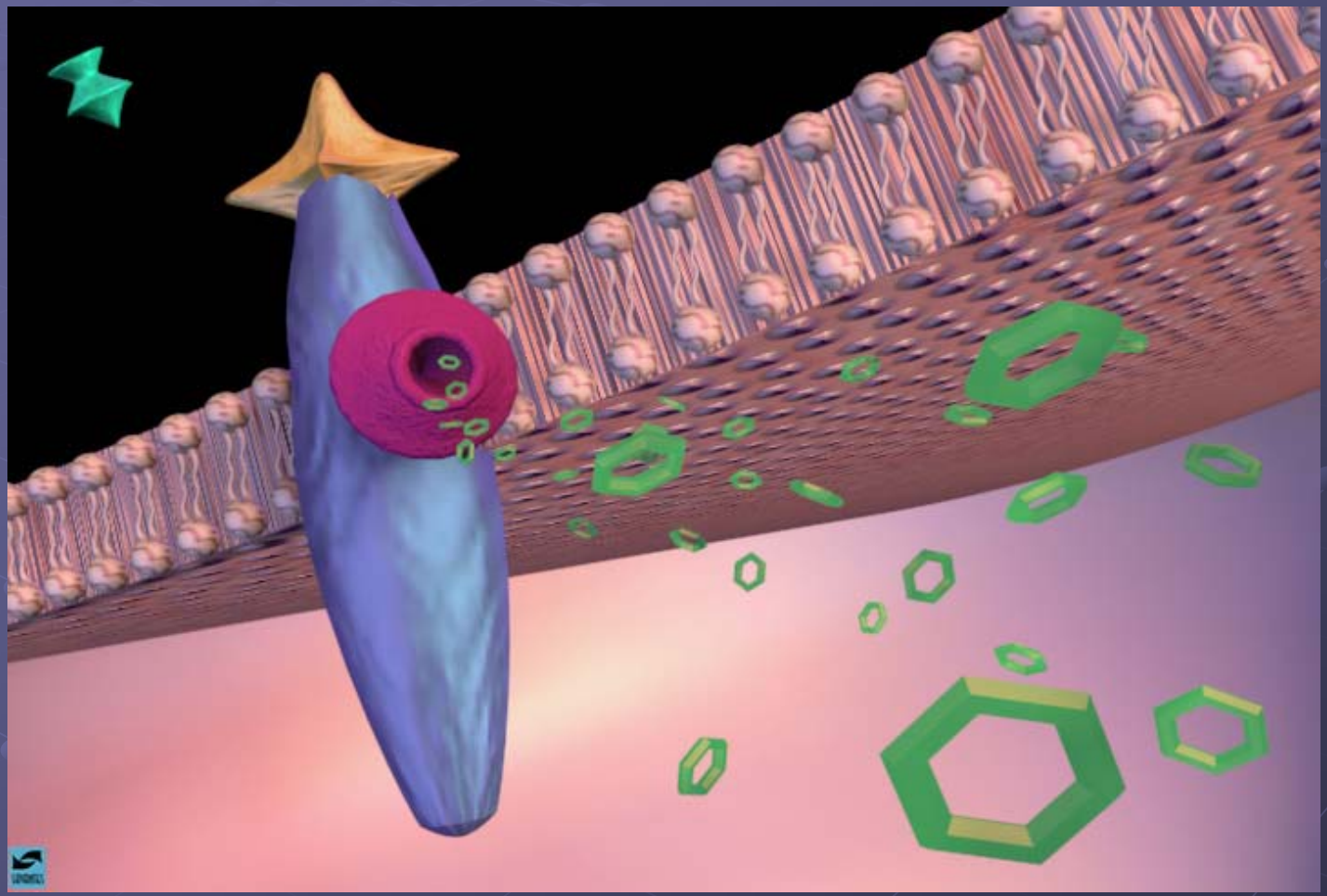
Dopamine binding to receptors and uptake pumps in the nucleus accumbens



Cocaine binding to uptake pumps; inhibition of dopamine uptake



Increased cAMP produced in post-synaptic cell



I neurotrasmettitori, la loro funzione e le sostanze d'abuso

Fig. 12-2 THE RELATIONSHIP BETWEEN NEUROTRANSMITTERS, THEIR FUNCTIONS, STREET DRUGS, MENTAL ILLNESS, AND PSYCHOTROPIC MEDICATIONS.

COLUMN 1 Neurotransmitter	COLUMN 2 Some Major Functions	COLUMN 3 Street Drugs Which Disrupt the Neurotransmitter	COLUMN 4 Associated Mental Illnesses	COLUMN 5 Medications Used to Re-balance Neurotransmitters
Serotonin	Mood stability, appetite, sleep-control, sexual-activity aggression, self-esteem.	Alcohol, nicotine, amphetamine, Cocaine, PCP, LSD, MDMA (ecstasy)	Anxiety, depression Manic depression Obsessive/compulsive disorder	Buspirone, tricyclic antidepressant, lithium, MAO inhibitors, sertraline, tryptophan, fluoxetine, chlomipramine
Dopamine	Muscle tone/control, motor behaviour, energy, reward mechanism, attention span, pleasure, emotional stability.	Cocaine, nicotine, PCP amphetamine, caffeine, LSD, Ritalin, marijuana, alcohol, opiates.	Schizophrenia Parkinson's disease	Lithium, MAO inhibitors, Phenothiazine, antipsychotics, thiazine antipsychotics, tyrosine, taurine.
Norepinephrine and epinephrine	Energy, motivation, eating, attention span, pleasure muscle tone, stimulation heart rate, blood pressure, dilation of bronchi assertiveness, alertness, confidence	Cocaine, nicotine, amphetamine, caffeine, all stimulants, PCP, marijuana	Depression, manic depression, anxiety, and panic disorders, narcolepsy, sleep problems, attention deficit disorder	Tricyclic antidepressants, Lithium, MAO inhibitors, phenothiazine, antipsychotics, prescription amphetamines, Ritalin, clonidine, barbiturates, Benzodiazepines, beta blockers, tyrosine, d,lphenylalanine
Endorphin, Enkephalin	Pain control, reward mechanism, Stress control (physical and emotional)	Heroin, other opiates, PCP, marijuana, alcohol, anabolic steroids	Schizophrenia, depression	Methadone, LAAM, naltrezone, buprenorphine, dilphenylalanine
GABA (gamma aminobutyric acid)	Inhibitor of many neurotransmitters, muscle relaxant, control of aggression, arousal	Alcohol, marijuana, barbiturates, PCP, benzodiazepines	Anxiety and sleep disorders	Benzodiazepines, glutamine
Acetylcholine	Memory, learning, muscular reflexes, aggression, attention, blood pressure, heart rate, sexual behaviour, mental acuity, sleep, muscle control	Marijuana, nicotine, alcohol, Cocaine, PCP, amphetamine, LSD	Alzheimer's disease schizophrenia, tremors	Phenothiazine antipsychotics, anti Parkinson agents lecitin, choline
Cortisone, corticotropin	Immune system, healing, stress	Heoin, anabolic steroids, cocaine	Schizophrenia, depression, insomnia, anxiety	Corticosteroids (Prednisone, cortisone), ACTH
Histamine	Regulator of emotional behaviour, sleep, inflammation of tissues, stomach acid secretion, allergic response	Antihistamines, opiates	Depressive Illness	Antihistamines, tricyclic antidepressants

La storia di uno psiconauta

"THE HISTORY OF A PSYCHONAUT"

Richmond Community Drug and Alcohol Team

Richmond Healthcare Hamlet

La storia di uno psiconauta

History and details of drug use

- **Alcohol:** 1st intoxication at the age of 4 (sic!) Use/misuse still continues.
- **THC:** began the use at the age of 9½ and still continues (20 joints a day).

La storia di uno psiconauta

Benzodiazepines:

- began the use at the age of 11; in the past,he went up to 100 mg daily. At the moment, he's been prescribed with 35 mg daily.

Barbiturates:

- he was taking unspecified amount of these compounds in the past

La storia di uno psiconauta

- **Opiates:**

Morphine: began the use at the age of 11, and continued up to a few years ago (he was using up to 600 mg I.v. daily), when he began the use of:

Dihydrocodeine: at the moment he is using 7 tablets daily (210mg);

Heoin: began the uase at the age of 12; regular use was up to 1 year ago (he still uses it from time to time)

He tried also: Hydromorphone HC1
(Dialaudid)
Mepheridine
(Pethidine; Demerol)

Methadone: prescribed with it up to 10 years ago (he was taking up to 250-300 mg daily).

La storia di uno psiconauta

Kava-Kava: occasional and recreational use (when abroad)

MDMA: no more than 30 tablets lifetime.

MDA: he like more than MDMA; he manufactured the pills by himself.

Ketamine: roughly 10 occasions of use.

PCP: he manufactured it by himself on an odd and irregular basis.

La storia di uno psiconauta

LSD:

began its use at the age of 11; stopped a few years ago.

Mescaline:

he gave it up to a few years ago, after many years of regular use.

Magic Mushrooms:

recreational and occasional use.

DMT:

he manufactured it by himself.

Yage; Ayahuasca:

Occasional and recreational use.

Ibogaine:

Occasional and recreational use.

La storia di uno psiconauta

SUMMARY

Uppers: Cocaine; Amphetamines; Cathinones

Downers: Benzodiazepines✓; Opiates✓; Alcohol✓
Barbiturates; Kava-Kava

All Arounders: LSD; Mescaline; DMT; Yage; Ayahuasca
PCP; Ketamine; MDMA; MDA; THC✓;
Ibogaine.

(✓ current use).

XTC/MDMA synthesis

Erowid Online Texts : PiHKAL #109 MDMA

http://www.erowid.org/library/books_online/pihkal/pihkal109.shtml

A CHEMICAL LOVE STORY

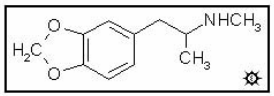
ALEXANDER & ANN SHULGIN

hosted by erowid.org

BACK MAIN INDEX TiHKAL FORWARD

#109 MDMA

MDM; ADAM; ECSTASY; 3,4-METHYLENEDIOXY-N-METHYLAMPHETAMINE



[3D .jpg image]
[3D .mol structure]

SYNTHESIS: (from MDA) A solution of 6.55 g of 3,4-methylenedioxyamphetamine (MDA) as the free base and 2.8 mL formic acid in 150 mL benzene was held at reflux under a Dean Stark trap until no further H2O was generated (about 20 h was sufficient, and 1.4 mL H2O was collected). Removal of the solvent gave an 8.8 g of an amber oil which was dissolved in 100 mL CH2Cl2, washed first with dilute HCl, then with dilute NaOH, and finally once again with dilute acid. The solvent was removed under vacuum giving 7.7 g of an amber oil that, on standing, formed crystals of N-formyl-3,4-methylenedioxyamphetamine. An alternate process for the synthesis of this amide involved holding at reflux for 16 h a solution of 10 g of MDA as the free base in 20 mL fresh ethyl formate. Removal of the volatiles yielded an oil that set up to white crystals, weighing 7.8 g.

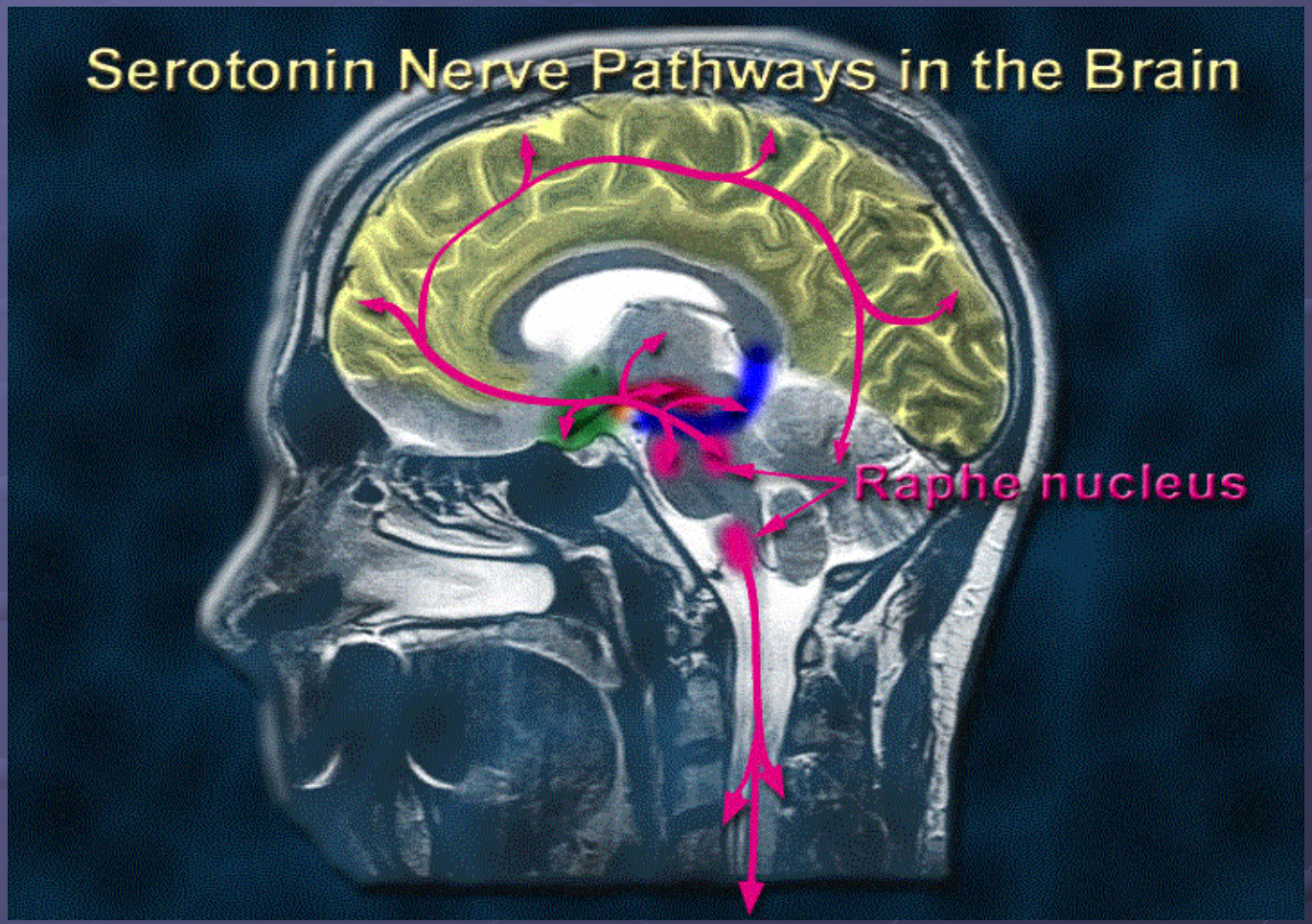
A solution of 7.7 g N-formyl-3,4-methylenedioxyamphetamine in 25 mL anhydrous THF was added dropwise to a well stirred and refluxing solution of 7.4 g LAH in 600 mL anhydrous THF under an inert atmosphere. The reaction mixture was held at reflux for 4 days. After being brought to room temperature, the excess hydride was destroyed with 7.4 mL H2O in an equal volume of THF, followed by 7.4 mL of 15% NaOH and then another 22 mL H2O. The solids were removed by filtration, and the filter cake washed with additional THF. The combined filtrate and washes were stripped of solvent under vacuum, and the residue dissolved in 200 mL CH2Cl2. This solution was extracted with 3x100 mL dilute HCl, and these extracts pooled and made basic with 25% NaOH. Extraction with 3x75 mL CH2Cl2 removed the product, and the pooled extracts were stripped of solvent under vacuum. There was obtained 6.5 g of a nearly white residue which was distilled at 100-110 ° C at 0.4 mm/Hg to give 5.0 g of a colorless oil. This was dissolved in 25 mL IPA, neutralized with concentrated HCl, followed by the addition of sufficient anhydrous Et2O to produce a lasting turbidity. On continued stirring, there was the deposition of fine white crystals of 3,4-methylenedioxy-N-methylamphetamine hydrochloride (MDMA) which were removed by filtration, washed with Et2O, and air dried, giving a final weight of 4.8 g.

(from 3,4-methylenedioxyphenylacetone) This key intermediate to all of the MD-series can be made from either isosafrole, or from piperonal via 1-(3,4-methylenedioxyphenyl)-2-nitropropene. To a well stirred solution of 34 g of 30% hydrogen peroxide in 150 g 80% formic acid there was added, dropwise, a solution of 32.4 g isosafrole in 120 mL acetone at a rate that kept the reaction mixture from exceeding 40 ° C. This

Epidemiology of ecstasy consumption (Schifano et al, Hum Psychopharmacology Oct 2003)

- Less than 1% have tried it in Finland, 5-6% in Spain and Belgium, 8-9% in Italy, Ireland, Holland and in the **UK.**
- Last year use amongst those in the 16-24 age group in England and Wales was 5%
- Number of 'regular' users in England: 70,486; occasional users: 361,619 (best estimates)
- The **UK** accounts for most of the ecstasy tablets seized in the **EU**

5-HT; from the dorsal raphe nucleus to…..



XTC: neurotoxicity issues

- Animals: effects of acute and/or long term administration of MDMA are highly selective, exclusively damaging brain 5-HT neurons; some brain regions show evidence of complete recovery but others remain denervated up to 7 years after treatment with MDMA
- The ‘pruning’ effect
- Humans: still not clear if the 5-HT damage at the neuronal level is permanent or partially reversible.

XTC: neuroimaging evidence

- MDMA users who are currently abstinent show a decrease in serotonin transporter availability with PET.
- A SPECT study of the 5-HT transporter density in sub groups of MDMA users including those who were abstinent for more than one year showed that heavy use of MDMA was associated with neurotoxic effects particularly in women, although female ex-users showed reversible changes.
- The degree of psychopathology and 5-HT alterations are best predicted by the number of MDMA tablets consumed. A PET study showed impaired glucose metabolism in MDMA users and showed that younger users were more vulnerable to its toxic effects.
- Heavy MDMA users show significant reduction in binding ratios in women but not in men

XTC: neuroimaging evidence

- fMRI in MDMA heavy long term abstinent users and moderate users: in comparison with non-users, heavy users had weaker blood oxygenation level dependent (BOLD) responses than moderate users and controls in frontal and temporal areas, suggesting altered brain functions associated with prior MDMA use.
- Studies using the MRS showed reduced N-acetyl aspartate/ creatine ratios of frontal cortex of users correlated with the degree of MDMA exposure in those abstinent for 12 weeks indicating neural injury.
- All in all, these studies indicate a long term and persistent toxicity of MDMA on cognitive function, some of which appear to be gender specific.

Psychopathological issues

- In XTC consumers: inverse correlation between serotonergic function levels on one side and aggression, novelty seeking and impulsivity scores on the other side
- long-term psychiatric disturbances (which are the possible untoward sequelae of the long-term use of ecstasy): depression, psychotic disturbances, bulimic disorders, impulse control disorders, panic attacks and social phobias have all been described
- Cognitive performances are significantly reduced in the MDMA-using subjects with respect to well-matched controls and memory recall is compromised even in previous consumers who are now drug-free.

XTC medical consequences

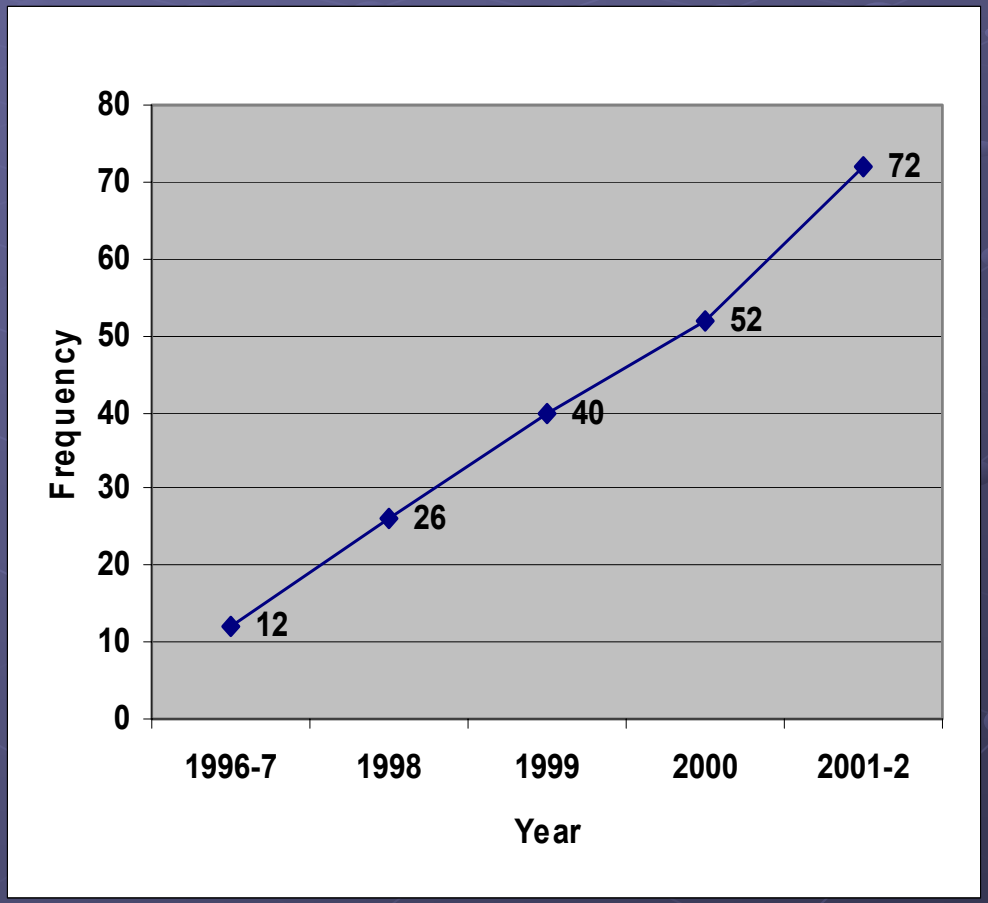
- convulsions, thrombocytopoenia, CID
- toxic acute hepatitis (idiosyncratic response to MDMA; Henry et al. 1992).
- Bizarre behaviours (consequence of the post-MDMA central 5-HT decrease; Schifano 1995). Webb et al (2003) analyzed the causes of all deaths which occurred in England and Wales in the year 2000 and found that stimulants, including MDMA, particularly featured in traumatic accidents.
- The existence of an underlying natural disease acts as a contributory factor for the induction of a potentially fatal condition (i.e.: arrhythmias, Dowling et al. 1987).

National Programme on Substance Abuse Deaths (np-SAD)

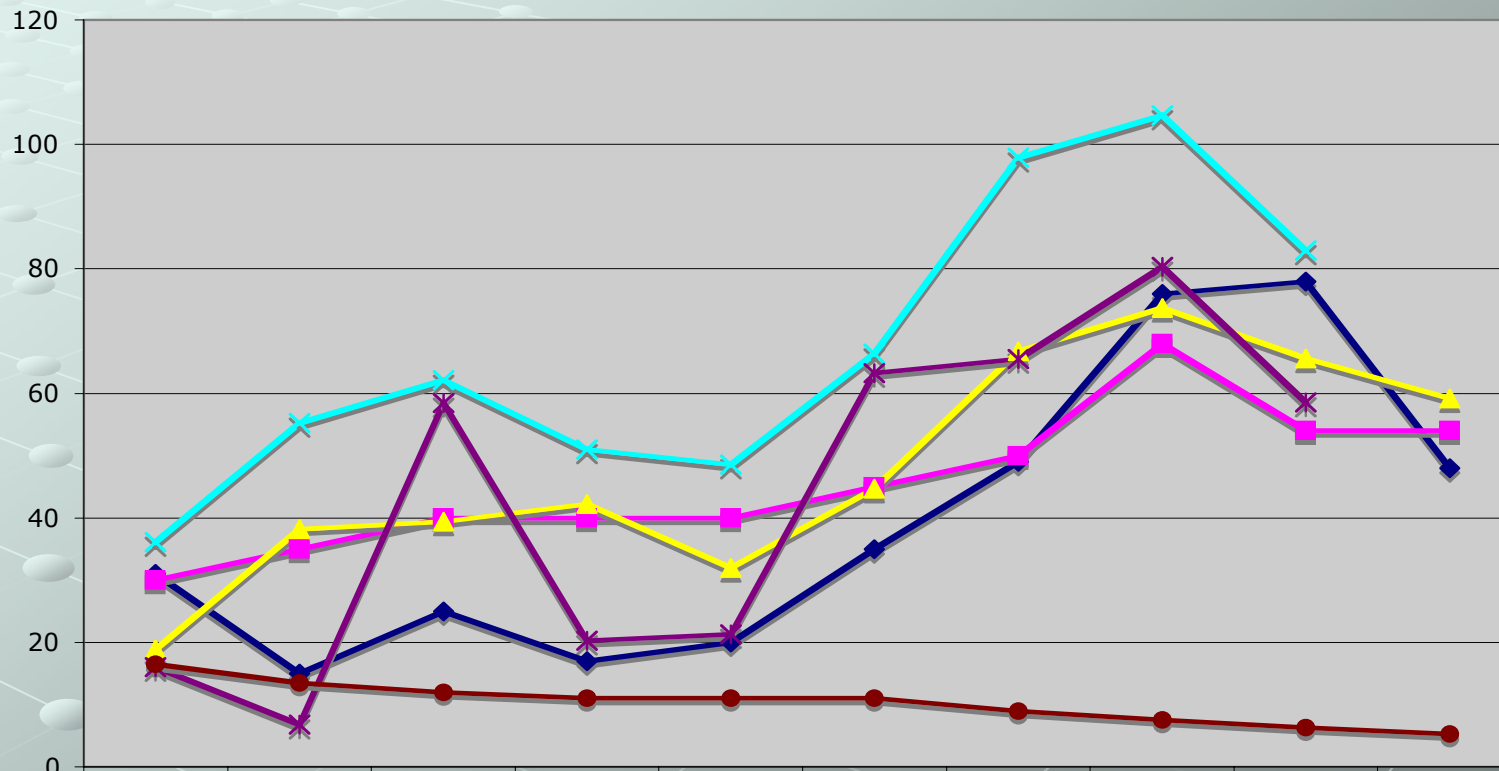
- established in 1997
- collects all of the information pertaining to drug related deaths from the UK coroners' and procurators' fiscal jurisdictions.
- For np-SAD database, cases must meet one or more of the following criteria: presence of one or more psychoactive substances directly implicated in death; history of dependence or abuse of psychoactive drugs; presence of controlled drugs at necroscopic examination. The response rate from the coroners in England and Wales has recently approached 90%.
- Funded by th DoH

Death rates from ecstasy (MDMA, MDA) and polydrug use in England and Wales 1996-2002

(Schifano et al, Hum Psychopharmacology, 2003; Schifano et al, BMJ 2003; Schifano, Psychopharmacology 2004)



Ecstasy in the UK, 1994-2003 (Schifano et al, J Psychopharmacology, May 2006)



	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Death mentions	31	15	25	17	20	35	49	76	78	48
BCS (%) x10	30	35	40	40	40	45	50	68	54	54
Offenders (100s)	18.810	38.210	39.370	42.210	31.960	44.700	66.700	73.700	65.600	59.200
No. seizures (100s)	36.140	55.210	62.160	50.980	48.500	66.370	97.840	104.600	83.000	
Doses seized (100,000s)	15.982	6.775	58.480	20.290	21.273	63.296	65.500	80.300	58.520	
Price (£)	16.5	13.5	12	11	11	11	9	7.5	6.33	5.3

Increase in XTC-related deaths; why?

- *A consistent decrease in ecstasy prices over the years.*
- *The variability of ecstasy tablets' content; non linear pharmacokinetics of MDMA*
- *The media attention*
- increase in ecstasy fatalities in the second part of the '90s seems related, at least in the UK, to a more general *increase of stimulant-related fatalities.*

XTC lethal dosage

- LD50 in mice: 80-115 mg/kg (Steele et al. 1994).
- small animal species require higher dosages of drug to achieve equivalent drug effects
- An average ecstasy tablet in the UK has been reported to contain 60-69 mg of MDMA (Cole et al. 2002).
- With the ingestion of some 20 – 30 tablets, the equivalent of the LD50 dose described in small animals can be achieved (Schifano, Psychopharmacol-Berl, 2003).
- Up to 40-50 ecstasy tablets have been described as the maximum dosage taken on a single occasion (Henry et al. 1992; Parrott 2001)
- individuals whose serotonin levels are chronically low will be attracted by higher dosages/5-HT ‘boost’
- a reverse tolerance/sensitisation phenomenon can occur in experienced stimulant users

XTC deaths' issues

- The risk of 'overdosing' with ecstasy seems somewhat unpredictable
- Further research should better describe, in large scale samples, the clinical implications of ecstasy misuse in the context of a polydrug intoxication
- The possible individual genetic vulnerability to ecstasy deaths should be more accurately described

The serotonin syndrome

- All develop a (mild-degree, in most cases) serotonin syndrome after acute drug intake.
- Signs and symptoms: enhanced physical activity; sweating; incoordination; mental confusion; trismus; jaw clenching; agitation; hyperreflexia; hyperthermia; shivering; rhabdomyolisis; metabolic acidosis; myoclonus; tremor and nistagmus (Ener, 2003)
- Direct consequence of the MDMA-induced 5-HT1-like and 5-HT2 receptor stimulation, which results in a marked increase of central serotonin levels (Liechti and Vollenweider 2001).
- Some of the MDMA acute effects (tachycardia; overarousal; hypertension) may well be due to the more general NA/DA stimulation
- 5-HT release is intensified by parallel use of DAergic (cocaine and amphetamines) compounds.

MDMA: metabolic and genetic issues

- Metabolism of the derivative methamphetamines has been assigned to CYP2D6.
- The major metabolic pathway involves demethylenation, whilst an alternative pathway is initiated by N-dealkylation.
- CYP2D6 gene: substantial ethnic diversity. Four categories of activity have been characterised; ultrarapid metaboliser (UM), extensive metaboliser (EM), intermediate metaboliser (IM) and poor metaboliser (PM) (Ball, 2003). Most of the genetic variants are inactive and approximately 5 to 10% of Caucasians are classified as poor metabolisers, whilst 1 to 7% of Caucasians are ultrarapid metabolisers
- genetic variation at CYP2D6 is a candidate research area for severe toxic reactions including fatalities

Pharmacokinetics and pharmacogenetics

- MDMA secondary metabolic pathway: the COMT enzyme is involved in the transformation of HHMA (the main MDMA metabolite) to HMMA (Helmlin et al. 1996; Maurer et al. 2000; Segura et al. 2001).
- HMMA may stimulate the release of the anti-diuretic hormone vasopressin so that an excessive water retention, coupled with hyponatraemia, can be observed (Fallon et al. 2002; Forsling et al. 2002). Young women may be at greater risk (Budisavljevic et al. 2003; Parr et al. 1997).
- range of COMT activity (due to genetic polymorphism) may explain some of the inter-individual differences in vasopressin secretion after MDMA consumption.

Heavy use, psychopathology, genetics

- More problematic (i.e those who show higher levels of psychopathology after the beginning of stimulants' use with respect to controls) users may have a decreased metabolic ability. As a consequence, they will achieve higher blood levels of the index stimulant compound, which in turn will result in higher neurotoxicity/psychopathology levels.

- But also: ecstasy increase mainly the CNS levels of both DA and 5-HT. Heavier users might have given the preference to these specific compounds because of their innate decreased ability to synthesise sufficient levels of DA and/or 5-HT.

The XTC-like drugs

- **MDA** (‘love drug’, the parental compound of MDMA)
- **MDEA** (‘Eve’, which has effects similar to those of MDMA)
- **MBDB** (‘TNT’)
- **2-CB** (‘nexus’)
- **BOD** (allegedly providing yourself with ‘…16 hours of inner strength, good mood and contentedness’)
- **DOB** (reported to be 33 times more powerful than MDMA itself; effects would last for up to 24 hours)
- **4-MTA** (‘flatliners’; likely to be the result of the work of some researchers who were looking for new serotonergic agents)
- **2C-T-7** (‘Blue Mystique’; created by A Shulgin and also one of his personal favourites). There is a complete series of 2C-T compounds (which includes **2Ci**, **2C-T-2** etc), either been synthesized already or just theorised

The 2C-T compounds

- 2C-T-7 is the most famous of a group of 24 compounds
- 2C-T compounds have structural and pharmacodynamic properties similar to other phenethylamine hallucinogens (mescaline, MDMA, PMA, 2C-B) and to indoleamine hallucinogens (LSD, psilocybin)

PKD & Blade Runner Nexus and Rachael

The latest generation of replicants (*Nexus*-6) are virtually indistinguishable from humans. While replicants can outperform humans physically and even mentally, they possess two **achilles heels**: a programmed four-year lifespan and ***the inability to show empathy***. This latter weakness forms the basis for discriminating them from humans via a Voight-Kampff (VK) *test of empathic responses* to carefully worded questions and statements

Rachael: Her primary natural attribution is the spider, Deckard's knowledge of which proves to Rachael that she is a replicant. The spider is the Great Mother in her aspects and the genetrix who spins the web of life from out of her own substance. Rachael can certainly be considered the weaver of Deckard's fate. As the Great Mother, Rachael is also ***Eve***.

What are other names for 4-bromo-2,5-dimethoxyphenethylamine?

Nexus	**2C-B**
Bromo	Toonies
Performax	2's
Spectrum	Synergy
Venus	Eve
Erox	Zenith
Cloud Nine	Utopia
Cee-Beetje	Afterburner Bromo
BDMPEA	MTF

2C-B

Synthesized by A Shulgin (California) in the early ’70s

Distribution of the hallucinogen 2C-B has been sporadic since it became a Schedule I drug in 1995.

Since 1999, however, seizures of this drug have increased.

Practical info on 2C-B; Nexus

•can be ingested orally in its pill and capsule forms or "snorted" in its powder form. Users report that 2C-B's effects are more intense when it is snorted.
•Some users consume 2C-B in combination with other illicit drugs including MDMA (called a "party pack") and LSD (referred to as a "banana split").
•2C-B produces euphoria and increased visual, auditory, olfactory, and tactile sensations.
•Doses of 20 to 30 milligrams result in very overt hallucinations. Even higher doses will produce extremely frightful, LSD-type hallucinations and morbid delusions.
•Proponents of its use consider the drug to be both a psychedelic and an "entactogen" ("touching within"). At low doses, users report feeling "in touch with themselves and their emotions" and often report erotic sensations

Stimulants' deaths: the np-SAD findings (Ghodse, Schifano et al 2003; 2004)

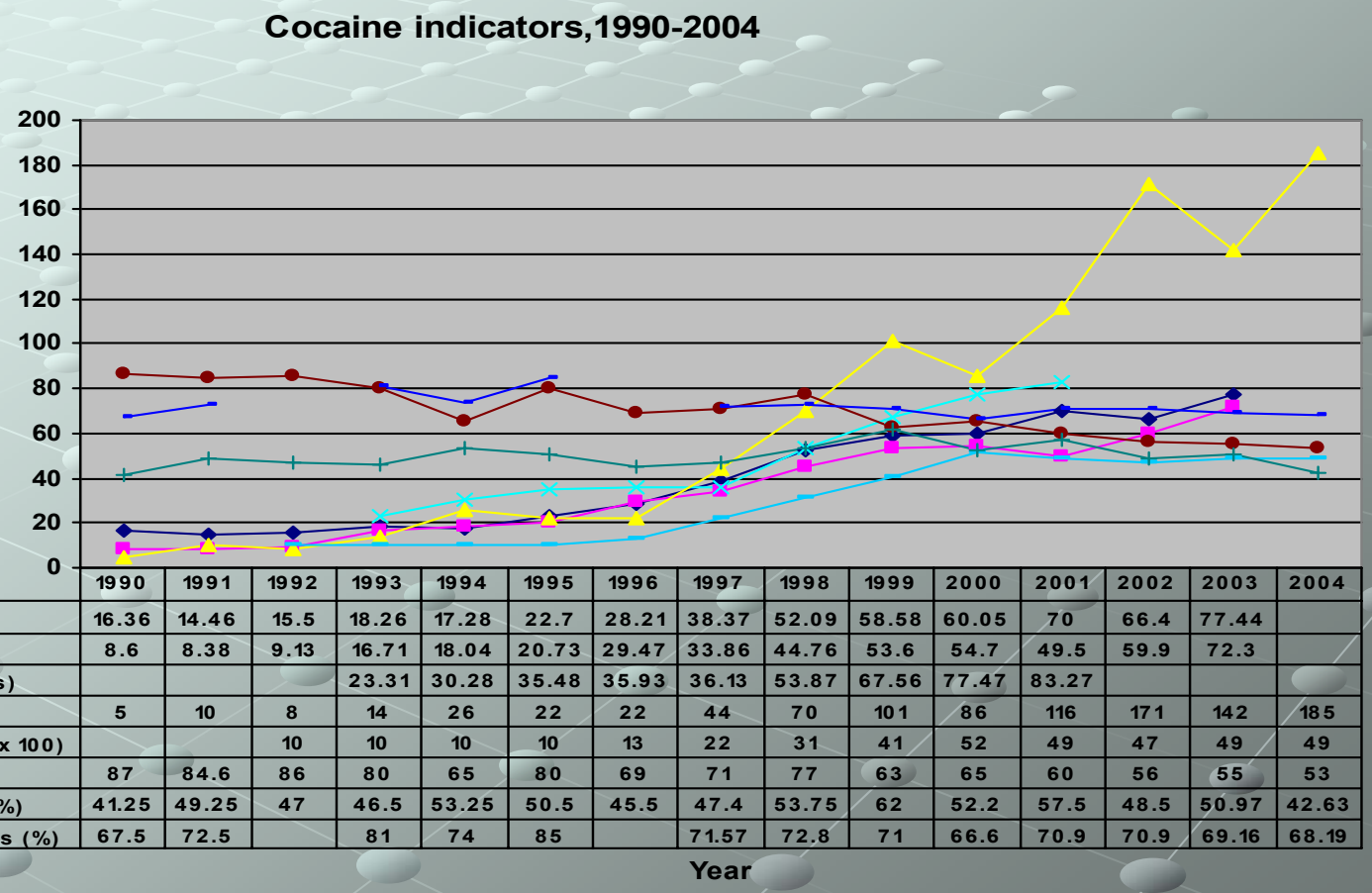
- In England and Wales, an upward trend (+ 98%) in cocaine related deaths reported by coroners in Jan-June 2003 with respect to the previous year was observed

- Amphetamines: +60% (2002 vs 2001)

Cocaine deaths double in one year……..
Sunday May 23, 2004

15 years of cocaine in the UK

(Schifano and Corkery, 2006)



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
No of seizures (100s)	16.36	14.46	15.5	18.26	17.28	22.7	28.21	38.37	52.09	58.58	60.05	70	66.4	77.44	
No FG & caut (100s)	8.6	8.38	9.13	16.71	18.04	20.73	29.47	33.86	44.76	53.6	54.7	49.5	59.9	72.3	
RDMD episodes (100s)				23.31	30.28	35.48	35.93	36.13	53.87	67.56	77.47	83.27			
Deaths (UK)	5	10	8	14	26	22	22	44	70	101	86	116	171	142	185
BCS last year use (% x 100)			10	10	10	10	13	22	31	41	52	49	47	49	49
Price (£/gram)	87	84.6	86	80	65	80	69	71	77	63	65	60	56	55	53
Mean purity - police (%)	41.25	49.25	47	46.5	53.25	50.5	45.5	47.4	53.75	62	52.2	57.5	48.5	50.97	42.63
Mean purity - Customs (%)	67.5	72.5		81	74	85		71.57	72.8	71	66.6	70.9	70.9	69.16	68.19

Cocaine: the clinical picture

- **Binge**
- **Crash**: begins 15-30 minutes after the binge and lasts for a period of 9 hours-4 days. It is characterised by dysphoria and by different levels of craving.
- **Withdrawal properly called**: lasts approximately for 1–10 weeks; craving, anxiety and dysphoria levels are very high; considerable relapse risk.
- **Extinction phase**: both behaviour and mood level are gradually going back to normality. However, environmental stimuli can trigger sudden peaks of craving. Indefinite duration.

Cocaine: the available formulations

- The cocaine powder (hydrochloride) can be snorted; low bioavailability levels. It can be injected as well but…..
- ….can't be smoked (because it decomposes at high temperatures). The alkaloid part is freed from the base through the use of ether. The result of this process is known as 'free-basing'…..
- …and another form of 'free-basing' is called 'crack'. The HCl powder is heated with baking soda and water. Pure cocaine crystals are obtained. Both a quicker and a stronger 'high' and a shorter duration of action are reported.
- I.V. use of crack: use of citric acid

Smokable methamphetamines; "Crystal meth"

- **An extremely powerful stimulant.**
- **Causes an intense high that includes increased energy, talkativeness, and excitement**
- **Users are very unpredictable and can easily turn from euphoric to violent.**
- **Post-high low can lead to dependence**

Crystal meth possible psychopathological consequences

- **Anxiety, depression and insomnia**
- **Inability to function socially**
- **Paranoid thoughts; hallucinations; psychotic behaviour**
- **Homicidal and suicidal thoughts**

Newest designer drugs

- of the new benzyl or phenyl piperazine type (eg, BZP, MDBP, mCPP, TFMPP, MeOPP)
- of the pyrrolidinophenone type (eg, PPP, MOPPP, MDPPP, MPPP, MPHP) have gained popularity and notoriety as rave drugs.
- These drugs produce feelings of euphoria and energy and a desire to socialize.
- knowledge of the metabolism is a prerequisite for toxicologic risk assessment. Polymorphically expressed CYP2D6 is the major enzyme catalyzing the major metabolic steps of the studied piperazine- and pyrrolidinophenone-derived designer drugs.

DMT-like drugs

- Schedules of controlled substances: placement of alpha-methyltryptamine (AMT) and 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT) into schedule I of the Controlled Substances Act (Sept 2004)

- One 4th-position tryptamine that deserves consideration and investigation is the N,N-diethyl cousin of psilocin/psilocybin called 4-hydroxy-DET (see entry #16 in *TIHKAL*) or more commonly referred to as **CZ-74** in the scientific literature.

Polypharmacy use

- alcohol is taken with ecstasy at the beginning of the night to get a stronger/better high (MDMA, whilst in the presence of alcohol, shows more significant physiopathological effects. Other options: pre-party packages containing SSRIs; moclobemide
- Cocaine, amphetamines and/or additional ecstasy tablets are taken to maintain arousal and a state of alertness (the MDMA entactogenic effects fade away in 2 – 4 hours).
- Finally, opiates and/or high (i.e. sedatives) dosages of alcohol are taken in the last part of the night to calm down before going home since the untoward after-effects of ecstasy (namely: irritability and restlessness) persist well beyond the end of the empathogenic and entactogenic pleasurable effects.

La doppia diagnosi

QUATTRO DIVERSE TIPOLOGIE DI DOPPIA DIAGNOSI

- paziente psichiatrico che inizia uso di sostanze
- slatentizzazione di fenomeni psicopatologici da parte delle sostanze stesse
- condizione psichiatrica temporanea (tossica)
- consumo cronico di sostanze che determina l'inizio di una patologia psichiatrica persistente

La doppia diagnosi

"QUARREL TRA SPDC E SERT"

- SPDC: prima l'uovo e poi la gallina, al Sert la pensano in maniera contraria
- nei Sert si pretende la "guarigione", non nel SPDC
- pazienti maschi preferiscono l'etichetta di tossicodipendenti, non cosi per le femmine
- nel SPDC si usano psicotropi, i Sert tendono a non prescriverli
- nel SPDC vi è più attenzione all'""holding", nei Sert viene data maggiore enfasi all'autonomia personale

La doppia diagnosi

- nel Sert:ottica di confronto con i pazienti

  nel SPDC: supporto dei pazienti
- nei Sert: possibilità di anonimato dei pazienti

  nel SPDC: anonimato non possibile e tendenza alla collaborazione con altri servizi.
- Sert (e CT): talora ci lavorano non professionisti (non così nel SPDC)
- Sert più orientati in senso "spirituale"
- Sert (e CT): talora permettono che si "tocchi il fondo"
- Formazione/informazione dei pazienti: più importante nei Sert.

I disturbi di personalita', l'impulsivita' e l'abuso di sostanze

Drugs of abuse: imbalance of neurotransmitters; impulsivity/violence

Reasons:

- *Direct* (drugs pharmacologically inducing increase of impulsivity levels)
- *Indirect* (impulsivity/violence occurring in order to attain drugs)
- However, intoxication, neurotoxic and withdrawal effects are often being confused

Psychological dimensions

Anxiety / Depression / Impulsivity:

A cluster linked to 5-HT decrease?

Psychological dimensions

SEROTONIN - TESTOSTERONE

- **5-HT decrease: increase of IMPULSIVITY**
- **TESTOSTERONE increase: increase of AGGRESSION**
- Impulsivity tends to correlate with anxiety and depression (serotonin)
- Primary psychopaths: little stress (low cortisol levels; high testosterone levels)

Drugs of abuse and aggression

- Drugs of abuse have a significant impact on the stress responsive hypothalamic-pituitary-adrenal (HPA) axis.
- Both cocaine and nandrolone decanoate have an impact on the endogenous opioid system (EOS) and the dopaminergic system. Each of these systems has also been implicated in the mediation of aggressive behaviours

Drugs of abuse and aggression

- Alcohol is clearly the drug with the most evidence to support a direct intoxication-violence relationship.
- GABA, 5-HT, DA involvement
- Increases violence (drunkenness and disorderly;
- football riots…)
- Type II alcoholics are impulsive and aggressive

Alcohol

- alcohol negatively affects cognitive performance and has a differential effect on the descending versus the ascending limb of the BAC curve
- Not to be overlooked the impact of a family history of alcoholism and a family history of violence on the development of childhood behavioural problems and adult problems with drugs, alcohol, and violence

GABA receptor, alcohol, benzodiazepines

- Usually, a GABA stimulation suppresses aggression
- High dosages of positive allosteric modulators of GABAA receptors (alcohol, benzodiazepines, and many neurosteroids) generally shift from heightening aggressive behaviour to being sedative and anti-aggressive
- GABAA receptor:heteropentameric protein constituted by various subunits; the subunit composition differentially affects the sedative vs anxiolytic actions of benzodiazepines
- Possible interest of targeting alpha subunits of the GABAA receptor

Benzodiazepines

- Diazepam selectively impair ability to recognise expressions of both anger and fear but not other emotional expressions
- Flumazenil completely reverses midazolam-induced paradoxical reactions

Flunitrazepam (Rohypnol)

- At higher doses, the drug can cause lack of muscle control and loss of consciousness. Other adverse effects include confusion and occasional aggression
- In psychiatrically vulnerable subjects (i.e., with high scores on boredom susceptibility and verbal aggression) this poses a serious hazard: flunitrazepam abusers become cold-blooded, ruthless and violent, and do not remember their violence.

THC

- Cannabis reduces likelihood of violence during intoxication, but mounting evidence associates withdrawal with aggressivity.
- The word “Assassino” derives from Hashish.
- Does it calm down? (“Love & Peace” of the 70’s)
- THC and Psychosis

Anabolic steroids

- Rhoid rage’
- AAS use may serve as a "gateway" to opioid abuse

Date rape drugs

- Dating violence is perpetrated by both males and females and occurs frequently within heterosexual dating relationships
- Alcohol, flunitrazepam, ketamine, and GHB have been used to facilitate sexual assault

Ketamine, Special K

- Ketamine is a dissociative anaesthetic used primarily in veterinary practice. It may be injected, swallowed, snorted, or smoked
- Like phencyclidine, ketamine interacts with the N-methyl-D-aspartate channel. Analgesic effects occur at lower doses and amnestic effects at higher doses. Toxic effects include confusion and hostility

GHB; Liquid XTC

- GHB, a naturally occurring fatty acid derivative of gamma-aminobutyric acid, was introduced as a dietary supplement. Increasing doses progressively produce amnesia, drowsiness, dizziness, euphoria, seizures, coma, and death

The Psychonaut 2002 EU project

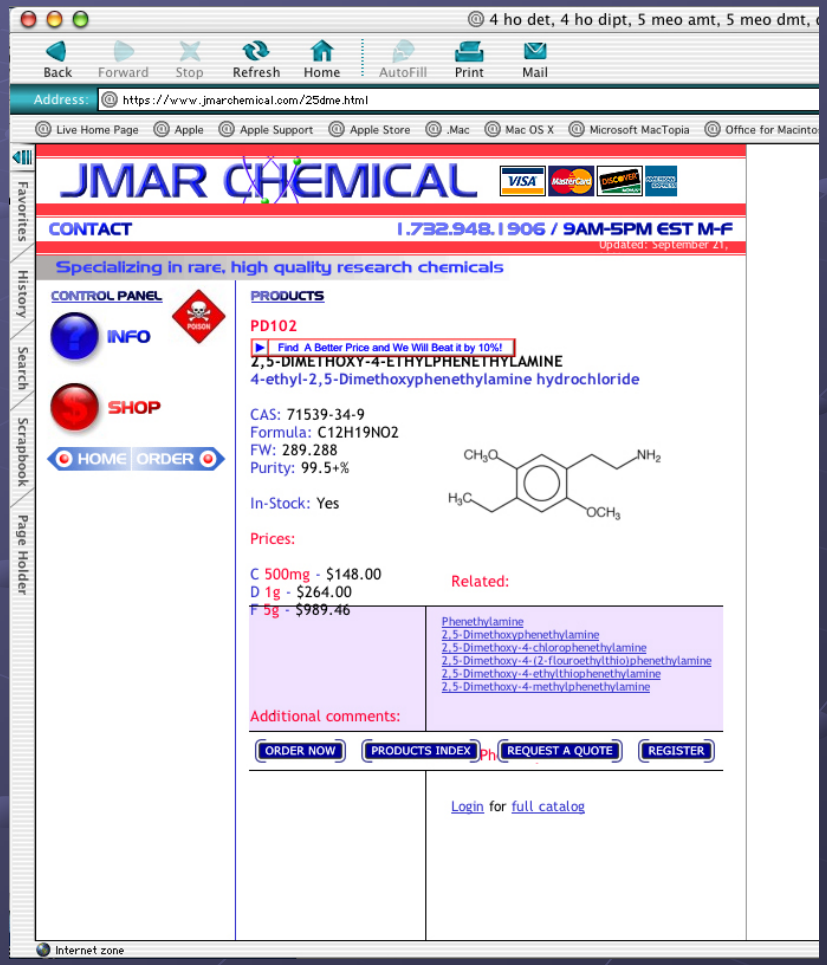
(Schifano et al, Neuropsychopharmacol Biol Psychiatry, in press)

(http://www.psychonaut2002.org)

…Let's buy some

Blue Mystique

(Schifano et al, J Psychopharmacology, in press)



Internet map (2004)

Background

- The Internet offers the best and quickest way to realise any exchange of news, trends and money and its popularity is especially on the increase in the “dot-com” generation (Wood, 2001)
- The only scientific literature quoted in the websites is Pihkal (Shulgin and Shulgin, 1991), that remains the principal source on how to synthesise 2C-T-7 and related compounds

Background

- An exhaustive web mapping on drug-related issues can provide significant and updated information on new drugs, new trends and modification of drug scenarios
- The web might be of huge interest for the practising clinician; in fact, the technical knowledge on new products entering the market is hardly obtained through reference books and scientific journals

Psychonaut 2002 background

Funded by grant of the European Commission, Public Health Directorate

England, Italy, Germany, Portugal, Spain, France, Finland, Denmark, Scotland

Headed by: Division of Mental Health, Addictive Behaviour, St George's, University of London, UK (Dr F. Schifano)

Psychonaut 2002 aims

1. To develop a reliable methodology to search and assess for information online
2. To foster **collection** and **analysis** of **data** from web pages related to recreational/illicit substances
3. To provide professionals with easily accessible assessment of 'drugs on the Internet' through a new protected **WEBSITE**
4. To identify emerging trends that can be addressed for prevention and immediate intervention
5. To start an '**EARLY WARNING SYSTEM**' at the European, national and regional level

Psychonaut 2002 methods

FOUR STAGES

- Google and AltaVista: Search by key word
- Links from the most interesting sites
- Chat rooms: on-line participant observation

PILOT STUDIES

EACH PARTNER ASSESSED

- A specific substance in English
  (i.e.: St George's: Ecstasy/MDMA)
- ALL substances in their home language
  (7 languages: Danish, Finnish, French, German, Italian, Portuguese and Spanish)

Psychonaut 2002 Sampling

KEYWORD SEARCH RESULTS (first 1,000):

- First 100 sites in English
- Proportional sampling: 5% of the remaining 900 sites
- First 10 sites in other languages
- Coding directly on the *Psychonaut 2002* website http://www.psychonaut2002.org

Psychonaut 2002 questions

RE: ADVOCATING DRUGS

- How many sites do promote the use of drugs ?
- Are they really easy to be accessed?
- Are they well developed?
- How do they compare with the ant drug sites?
- Info on novel drugs?
- Useful info for professionals?

RE: SELLING AND BUYING DRUGS

- How many sites do sell drugs?
- How often are these sites visited?
- Types of drugs sold?
- Distribution of drugs?
- Restricted access?

Assessed substances

- Cannabis
- Herbs, plants (psychoactive plants, ecological drugs)
- Precursors to illicit drugs (manufacturing drugs)
- Amphetamines
- Heroin, opiates
- Other stimulants, inhalants, solvents
- Ecstasy (MDMA)
- Cocaine
- Prescription drugs
- Tobacco
- “Dance” drugs (Ketamine, LSD, GHB)

Methods

- To address these issues, a number of pilot studies were initially run in using several search engines between those available and two were chosen for their importance, reliability and popularity: Google™ and AltaVista™.

- To overcome the problem of the ever changing and expanding nature of Internet and search engines, on the week starting on June 23rd 2003 each of the 11 research partner carried out a “snapshot” of the available websites with contents related to the different classes of psychoactive drugs, including misuse compounds, identified with selected key word(s).

Methods (2)

- Each of the participating centre was given the “core” task of assessing the online information available in English related to a specific group of compounds and was required to investigate in its own language all of the remaining other groups of compounds as well.

- As a result, assessment of the information available was carried out in 8 languages. Although in most instances over 100,000 web pages URLs (addresses) may be reported as a result of a query, both Google™ and AltaVista™, in common with other engines, are designed for displaying only up to the first 1,000 pages searched (Schifano et al, 2003).

Results

- Number of websites found by Google™ and AltaVista™ running a search for the different groups of psychoactive compounds : 3,104
- The snapshot produced a total of almost 5,000 websites, of whose about 3,000 were in English. Survey data of sampled websites included website position towards drugs' use and possibility of purchasing psychoactive drugs

Examples of psychoactive compounds allegedly offered for sale on the web

- **Opioid analgesics:** buprenorphine; butorphanol; codeine; dextropropoxyphene; hydromorphone; levorphanol; meperidine; methadone; morphine; nalbuphine; opium injection; oxycodone; oxymorphone; pentazocine; propoxyphene; codeine

- **Hallucinogenic tryptamines and phenethylamines:** DMT (dimethyltryptamine); 4 OH-DET ("CZ-74") (N,N-diethyl-4-hydroxytryptamine); 4 OH-DIPT (4-hydroxy-N,N-diisopropyltryptamine); 5-MeO-AMT (5-methoxyalpha-methyltryptamine); 5-MeO-DMT (5-methoxydimethyltryptamine); DPT (N,N-dipropyltryptamine); 4-acetoxy-DIPT (4-acethoxydiisopropyltryptamine); 2C-I (2,5-dimethoxy-4-iodophenethylamine); 2C-T-2 (2,5-dimethoxy-4-ethylthiophenethylamine); 2C-T-7 (2, 5-dimethoxy-4-(n)-propylthiophenethylamine)

Results

- Harm reduction and pro drugs websites showed lower ranking levels than governmental, anti drugs and prevention websites
- Information which is of possible concern for at-risk and vulnerable users is the one which is more readily and promptly accessible on the web

Psychoactive compounds for sale on the web (Schifano et al, Progr Neuro-Psychopharmacol Biol Psychiatry June 2006)

- **Plants, herbs, mixtures:** Salvia divinorum, Lophophora williamsii ("Peyote"); Trichocereus pachanoi ("San Pedro"); Banisteriopsis caapi and Psychotria viridis ("Ayahuasca")

- **Others:** Anabolic steroids; phentermine; phendimetrazine, barbiturates; sildenafil; dextromethorphan

Prescriptions drugs

- There is a multitude of web sites providing information, advice and purchasing possibilities for a wide range of prescription drugs. These can be classified in:

- ***"legitimate" online pharmacies*** looking to provide an online version of the services normally provided on the High Street. These sites require the customer to have a prescription from their own doctor, and will often refuse to supply potentially abusable drugs, such as opioids, tranquillisers, or drugs such as Ritalin.

- ***"lifestyle" pharmacies*** selling "lifestyle" prescription drugs. Such "lifestyle" drugs include *Propecia* for baldness, *Phentermine* and similar for obesity, *Viagra* for impotence, and *Zyban* for nicotine dependencies. These sites often provide their customers with a "prescription" based upon online self-reported symptom checklists. A majority of these sites are based in the US and are aimed at US customers, although some will ship internationally.

- ***"no prescription required" pharmacies*** that are willing to provide any form of prescription drug, shipping internationally (even though in most countries this is illegal), and without an independent medical prescription being written.

Online pharmacies

Further results

- Online data of more concern (including description of ecstasy-type hallucinogenic drugs' purchase modalities), were found here to be the most readily and promptly accessible online. This is an intriguing issue, since it has been suggested that most consumers of recreational drugs (i.e.: MDMA; "ecstasy") access the Internet to obtain information.

Novel psychoactive compounds on the web

- “... I plan on getting some 2c-e...also, what amount did you take?..”
- “…2C-P is the biz I hear..”

Internet and drugs considerations

(Schifano et al, J Psychopharmacology, November 2005; Schifano et al, Progr Neuropsychopharmacol Biol Psychiatry, June 2006)

- The Internet offers the best and quickest way to realise any exchange of news, trends and money and its popularity is especially on the increase in the “dot-com” generation

- Those who meet the prerequisites of literacy, Internet access and credit card ownership and who are most likely to come from the socio-economically privileged sections of society may possibly comprise the group of “expert drug users”/”psychonauts”

Major values and main limitations of the study

10. One of the major values of this study is that information available online was assessed in 8 languages. Taken together, five of these languages (English, Spanish, Italian, German, French) are used by about 80% of those who access Google

- One of the major limitations of the project was given by the use of a fixed set of key words during the “snapshot”. Use of trained softwares (e.g. metacrawlers) and assessment of newsgroups/chatrooms/bulletin boards could possibly have improved the coverage of this study. On the other hand, we aimed at carrying out here an analysis of that information which is immediately available to the average user.

The 16-countries, Psychonaut Early Warning System, EU application

(deadline for presentation: 19th May, 2006)

- An exhaustive web mapping on drug-related issues can provide significant and updated information on new drugs, new trends and modification of drug scenarios
- The web might be of huge interest for the practising clinician

Project 1st step

- monitoring of the web and identification of putative novel misusing compounds/novel combinations
- online queries will be formulated, with the help of search engines and scanning softwares, in **14 EU languages**, with a selection of different keywords. To carry out further Psychonaut EWS exercises on selected compounds, a purposeful website sampling technique will be used.

The 16-countries, Psychonaut Early Warning System, EU application; 2nd step

- Once a putative novel psychoactive compound/combination of compounds will be identified, the scientific literature will be first thoroughly searched
- When related law enforcement data (i.e.: seizures; deaths; arrests for possession; drug related offences) will not be available at all, a few ‘key informants’ (clinicians involved in the Psychonaut EWS network; ravers; club attenders; Community Drug Treatment clients; web surveys respondents etc) will be approached.
- Key informants will act as ‘sentinel networks’
- Finally, a clinical pharmacological/toxicological risk assessment for each identified compound will be carried out.

The 16-countries, Psychonaut Early Warning System, EU application; 3rd step

- the processed information will be posted on the Psychonaut EWS website

- access will be restricted to identified health agencies: A&E departments; Drug Treatment Centres; National Poison Centres within the EU.

Future scenarios

- it is not possible to know whether substance use and misuse will **increase or decrease** over the **next twenty years**.

- Examples of indicators that make future levels of drug use unclear include:

  - Female use is not as high as male use
  - Rural use is lower than use in the cities
  - People are taking drugs earlier in their lives
  - People are continuing to use drugs later in life.

- Whatever the ultimate levels the **harms caused** by the use of 'recreational' drugs **will continue** to have a significant negative impact on society in terms of crime, public health and effects on the economy.

Future scenarios

- Many of the 'recreational' drugs of today will be those that society will continue to use in the next 20 years.
- This includes tobacco and alcohol as well as illicit drugs such as amphetamines, (ecstasy), ecstasy-like drugs, cocaine, heroin and cannabis.
- But there are also likely to be new synthetic 'recreational' substances.

Novel drugs' sources

- new learnings about neuroscience – we now know of more than 60 chemicals that have a role in the operation of the brain
- databases of small molecules that have the potential to have an effect on the brain
- substances developed for clinical use
- illicit laboratories.

Future, novel, drugs' combinations

- We are likely to see **novel drugs combined in new ways** as users gain a better understanding of the effects of combinations of drugs.
- The upper increases energy and alertness, but this could be accompanied with anxiety and the downer is a relaxant.
- A recent example from Iceland: abolition of licensing times led to bars staying open all night – and to drinkers taking a stimulant drug so that they can stay awake longer to drink alcohol.

The future; role of the genomics' knowledge

Over the next 20 years, genomics may provide individuals with:

- a better understanding of the effect that a 'recreational' drug will have on them
- information on an individual's risk of addiction to a range of 'recreational' drugs.

New drug tests

They could allow:

individuals: to monitor the amount of a drug in their system in real time and its probable effect on their behaviour and performance

clinicians: to identify in a timely and precise way the different novel compounds; either syntetic or herbal

The future: pharmacokinetic considerations

- The way that drugs are taken has a significant effect on the user. Any device that opens the way for the active ingredients to get to the brain quickly will produce a faster 'hit' and a bigger 'high'. But it will also increase the potential for addiction and poses a risk of death.
- Example: the hypodermic syringe brought benefits to healthcare but also had a profound effect on the way drugs were taken.
- There are a number of new and developing technologies that could be used to deliver drugs in new ways. Examples include patches, vaporisers, depot injection and direct neural stimulation.

Future producers of so-called 'recreational' drugs

- Pharmaceutical companies may find that the drugs they develop for mental health are inappropriately used for 'recreational' purposes. This has happened with heroin, amphetamines and methylphenidate.
- Advances in technology such as the growing availability of information online, may increase the capabilities of illicit producers and make it easier for them to develop novel 'recreational' drugs in smaller quantities.
- This may make it more difficult to discover where illicit drugs are being manufactured, possibly from common raw materials

Going backward in the future: the ecological drugs

- plant drugs compete with chemicals.
- morphine and cocaine: earliest examples of the transition of plant to manufactured medicine.
- khat illustrates how a lack of technological innovation can impede the wider diffusion of a substance.

Going backward in the future: the ecological drugs

- Literally hundreds of products are available.
- morphine and cocaine: earliest examples of the transition of plant to manufactured medicine.
- Khat illustrates how a lack of technological innovation can impede the wider diffusion of a substance.

Conclusions (1)

- The **pharmacodynamics** of illicit drugs is very **complex**; too many gaps in knowledge. Different brain structures and different neurotransmitters are involved in the different stages of the addiction process
- **tailoring treatment** to subgroups of patients based on **genotype** may improve responses (Kosten et al, 2002)
- **Illicit drugs**' effects are **highly rewarding**; with a 100% bioavailability (ie: crack cocaine) their addictive liability reaches the highest levels known for a drug

Conclusions (2)

- Take into account both the bio-psychosocial model and the role of Self-Help groups (i.e.: NA, CA, AA etc)
- **In the long run, the psychopathological consequences are the norm, and NOT the exception**