The Weizmann Institute of Science

Brain Stimulation in the Study and Treatment of Addiction

From Animal Models to Humans

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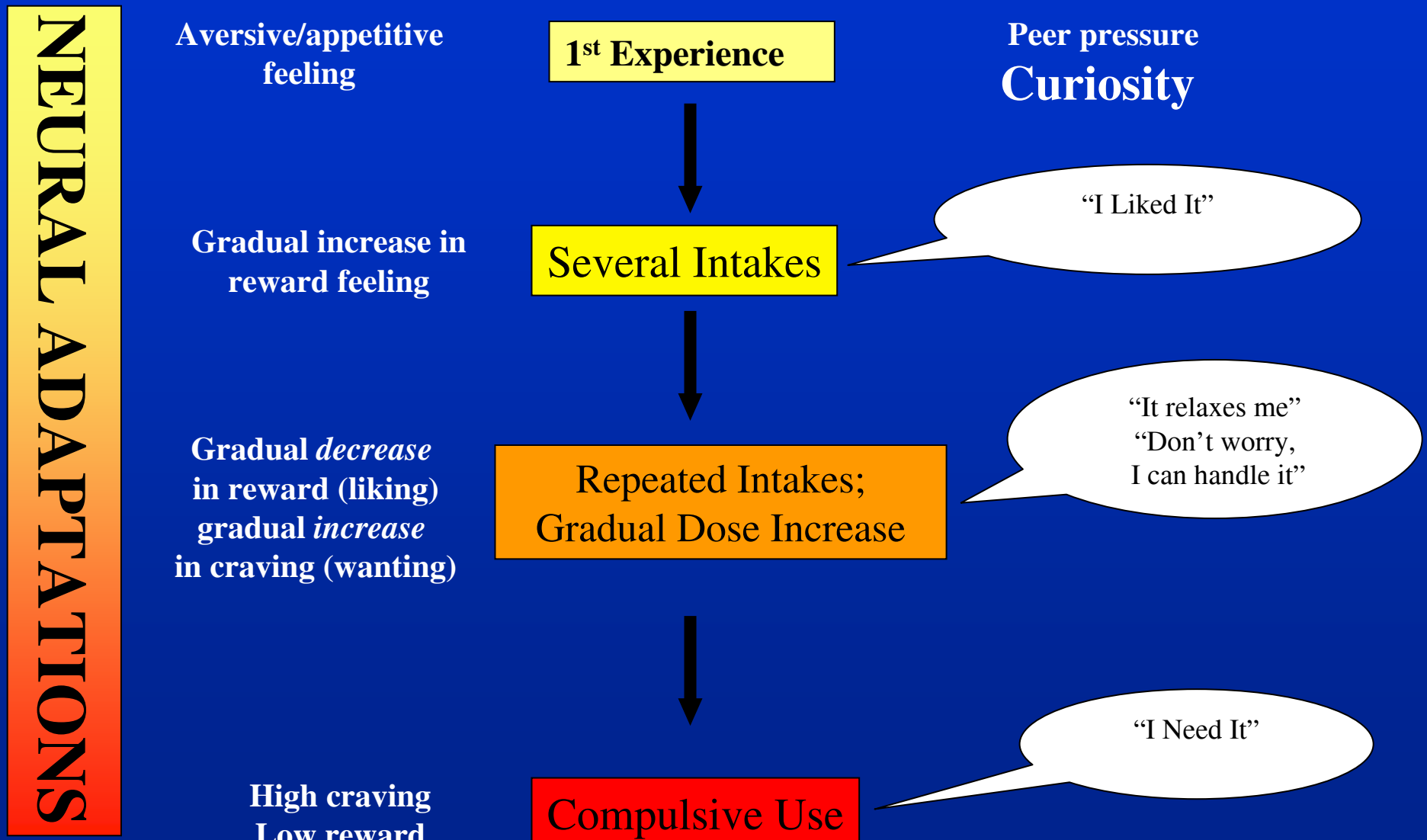
Drug addiction is induced by *repeated exposure*



Basic neuronal adaptations induced by repeated drug use

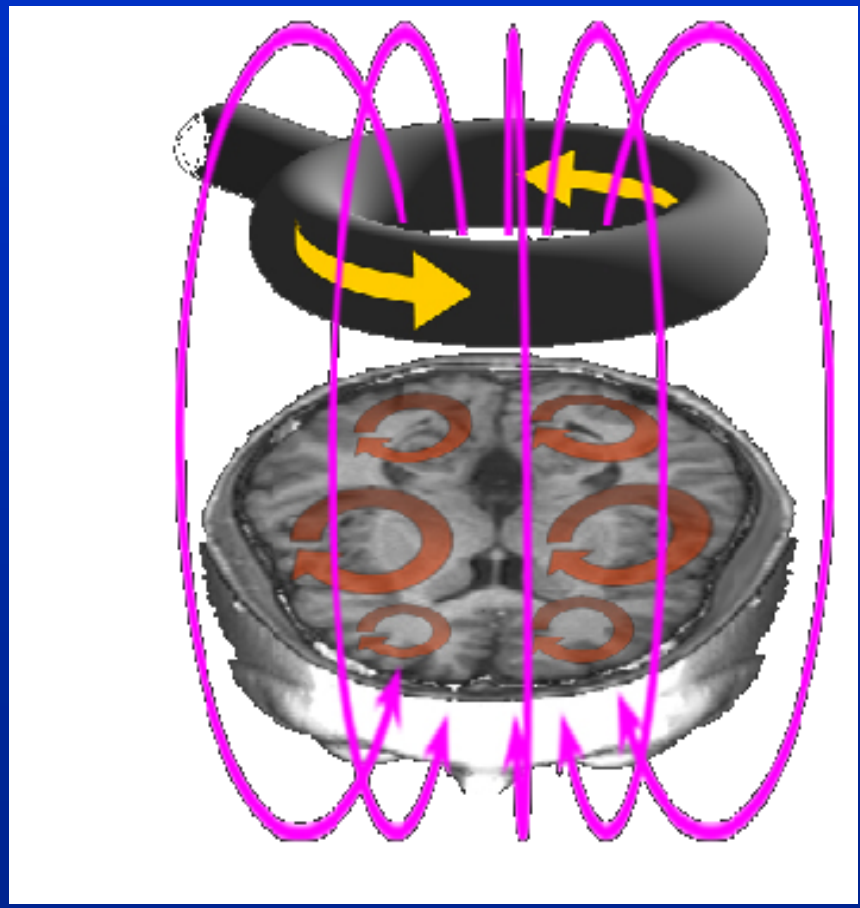
- D1 super-sensitivity.
- D2 autoreceptor sub-sensitivity.
- Tyrosine Hydroxilase upregulation.
- Glutamate receptors upregulation in the VTA.
- Glutamate receptors downregulation in the NAc.
- LTD-like effect in the glutamatergic afferents towards the NAc.
- LTP-like effect in the glutamatergic afferents towards the VTA.
- Low basal release and activity of dopamine.
- Increased dopamine and glutamate transmission in response to drugs, stress and drug-associated cues.

- Various desensitization processes (e.g. downregulation of opioid receptors induced by repeated heroin use).

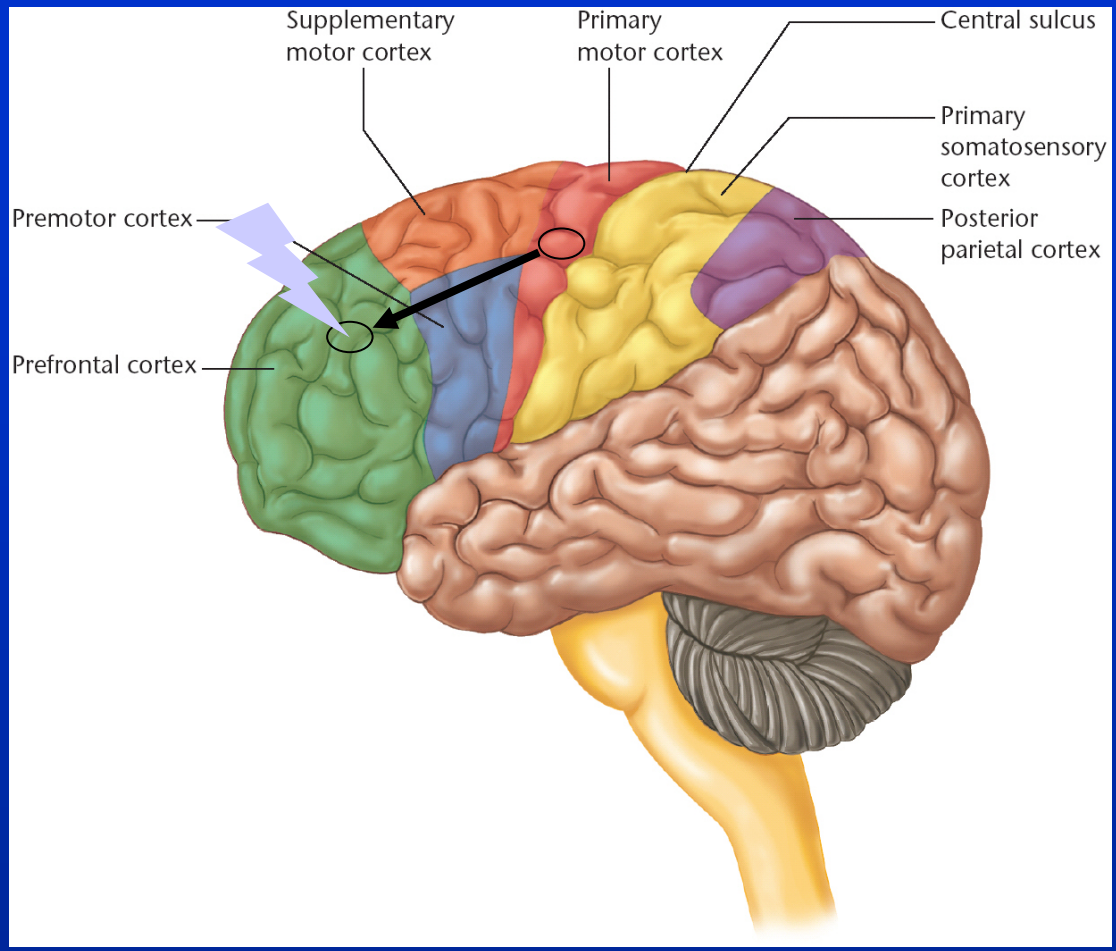
- **Transcranial magnetic stimulation studies show that repeated drug use induce changes in <u>neuronal excitability</u>**

Transcranial Magnetic Stimulation
Basic Principles

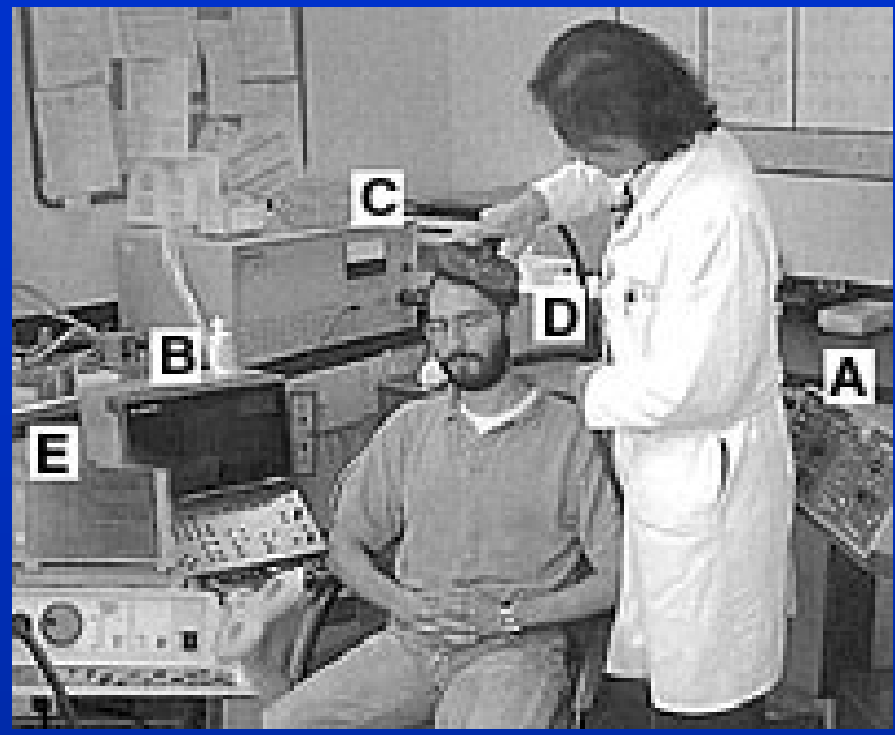
- **Electric field applied over neuronal tissue has been used for many decades of research to induce axonal depolarization.**
- **Earlier, Michael Faraday (1831) established the relationship between electrical currents and magnetic fields.**
- **Rapidly changing electrical currents induce rapidly changing magnetic fields that can produce an effective local electric field and thereby axonal depolarization.**
- **In TMS, capacitors are rapidly discharged into an electric coil to produce an effective magnetic field pulse.**



- Indeed, it is possible to induce motor activation when placing the coil over the primary motor cortex, or visual effects when placed over the occipital cortex.
- Even acute cognitive interference when repetitive TMS is applied over the prefrontal cortex.
- It is possible to measure motor-evoked responses or EEG alterations.



Overall, these studies show reduced cortical excitability in cocaine and nicotine addicts.
(*Feil and Zangen., Neuroscience and Biobehavioral Reviews 2010*)



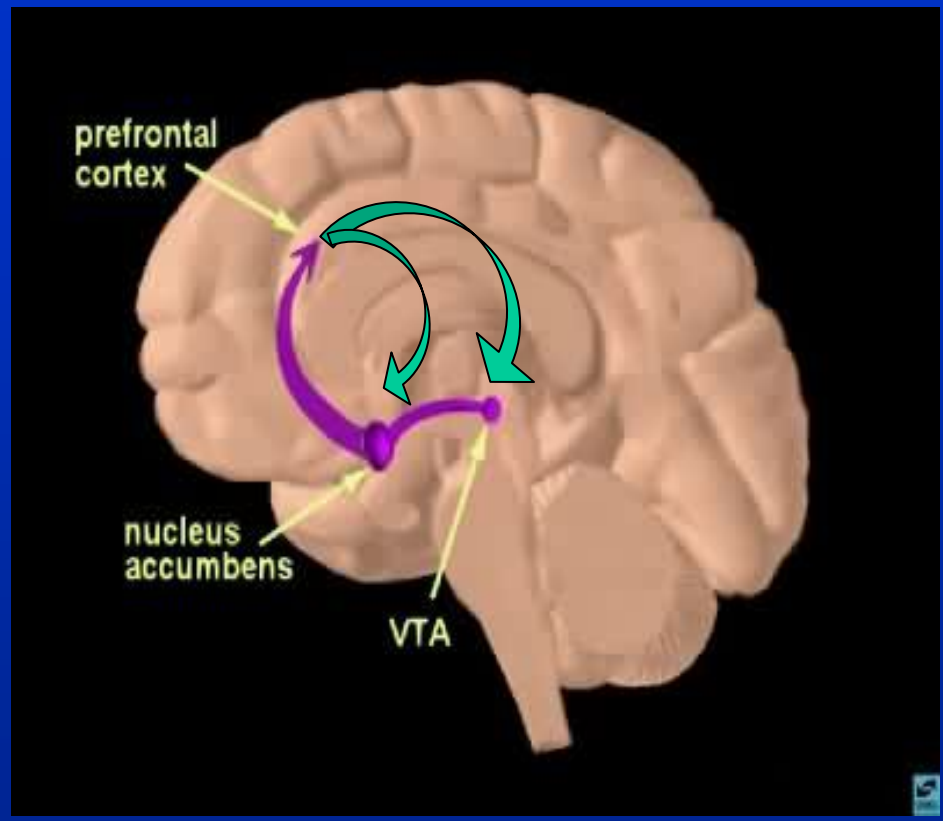
Repeated TMS (rTMS) sessions can induce *long-lasting* effects: High frequency rTMS can increase excitability / produces LTP-like effects, induce DA release and alterations in markers for neuroplasticity (e.g. Zeimann 2004; Hyodo and Zangen., 2002).

Can such effects on neuroplasticity induce therapeutic effect in addiction ?

Where should we interfere?

Addiction involves long-lasting alterations in the Brain Reward System

- Brain centers and pathways that are activated by natural and artificial rewards.
- Electrical stimulation of these centers generate a positive reward.
- Different types of rewards induce dopamine release in the nucleus accumbens.
- Cues that predict reward induce dopamine release in the NAc.
- "Hijacked" by drugs of abuse.



Ventral tegmental area (VTA), Nucleus Accumbens (NAS) Prefrontal Cortex.

Why would repeated electrical stimulation of reward-related brain regions affect addictive behaviors?

- **Repeated drug use induce long-lasting neuroadaptations in reward circuitries, including changes in synaptic strength and neural excitability. Some of these neuroadaptations are thought to mediate cue-induced drug seeking (Kalivas et al., 2009).**

- **Electrical stimulation of sites in the mesocorticolimbic pathway causes dopaminergic and glutamatergic elevations in the NAc and VTA** (e.g. *You et al., 2001*), **both mediated partly via glutamatergic innervations that originate in the PFC.**
- **Therefore, repeated stimulation of reward-related sites may either sensitize or desensitize responses to drugs of abuse or drug-associated cues.**

- **For example: Several studies showed that expression of GluR1 in the VTA is increased by repeated exposure to cocaine** *(e.g. Lu et al., 2003),* **while repeated hypothalamic ICSS downregulates GluR1 levels in the VTA** *(Carlezon et al., 2001).*

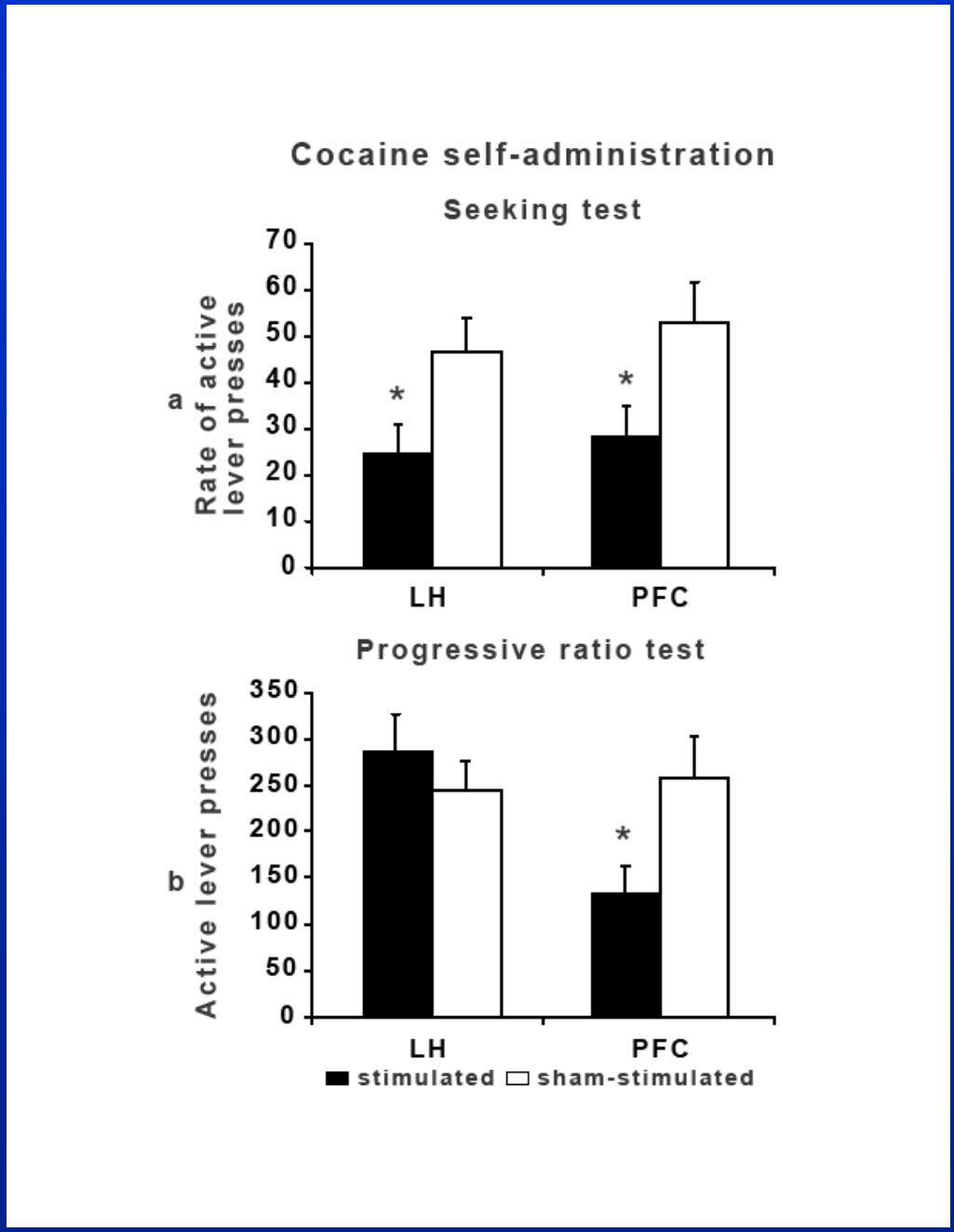
- **We hypothesized that repeated intracranial electrical stimulation (ICES) of reward-related brain areas in rats pretreated with cocaine would hyperactivate the reward system and alter drug-induced neuroadaptations. Therefore, such approach could reduce cocaine reinforcement, seeking, and intake.**
- **We have also began to characterize the effects of repeated ICES on cocaine – induced neuroadaptations by measuring the expression of glutamate receptor subunits within reward-related brain sites.**

(Levy et al., JN 27:14179-89, 2007)

Experimental Procedures

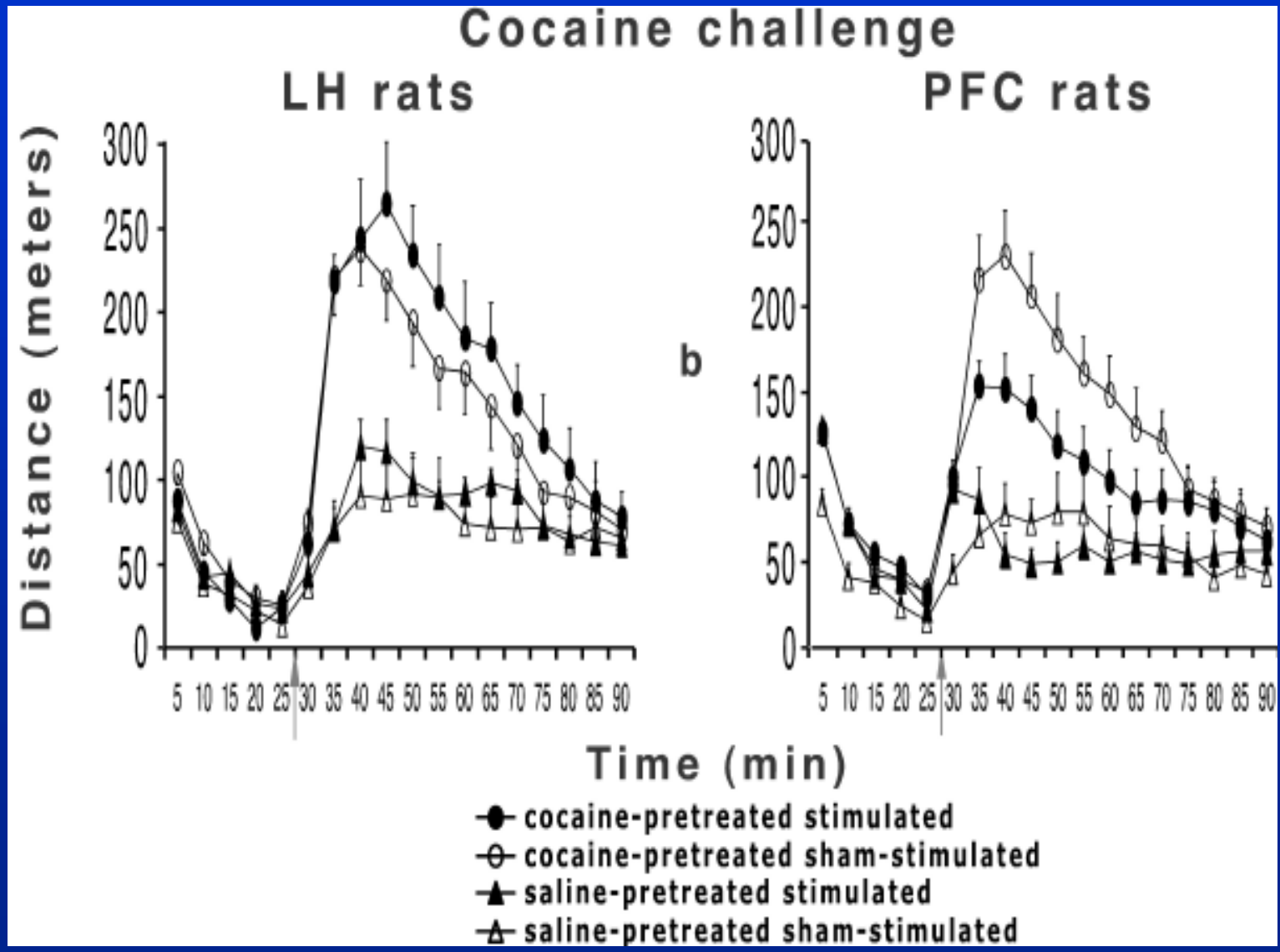
Cocaine Self-administration:

ICES: High frequency stimulation (100Hz or 20Hz), 30min/day for 10 consecutive days. Stimulation was applied at their home cages using ICSS parameters (intensity and pattern)



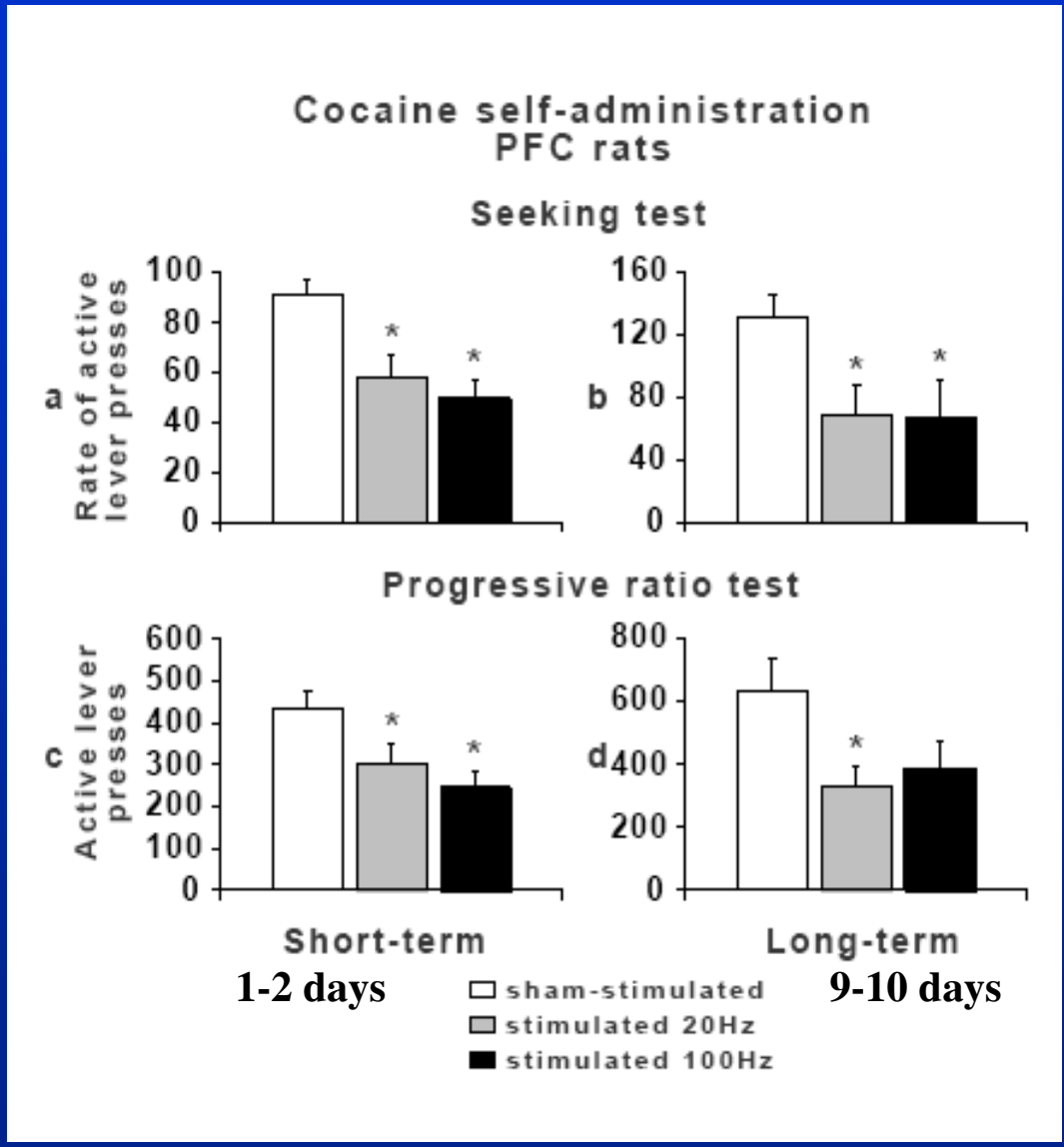
(Levy et al., JN 27:14179-89, 2007)

Psychomotor Sensitization



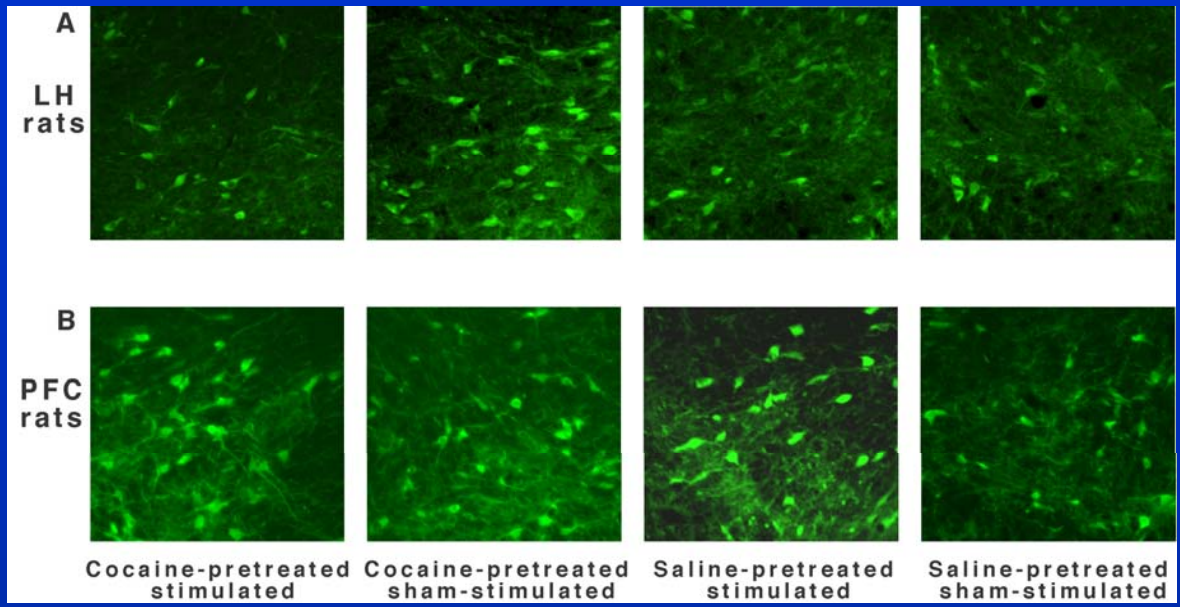
(Levy et al., JN 27:14179-89, 2007)

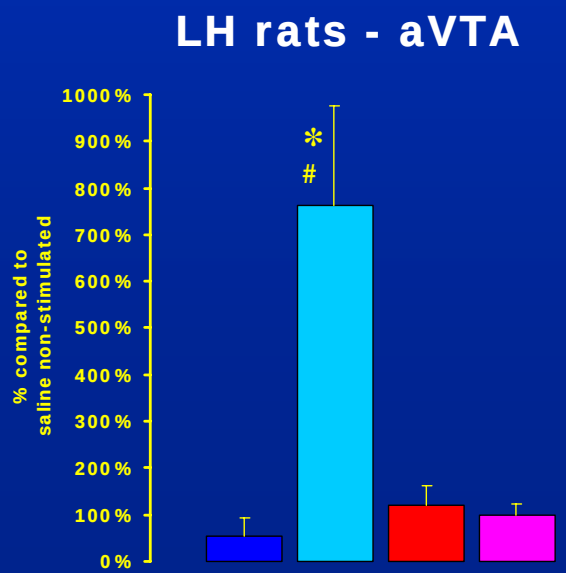
Long-term effect of repeated stimulation

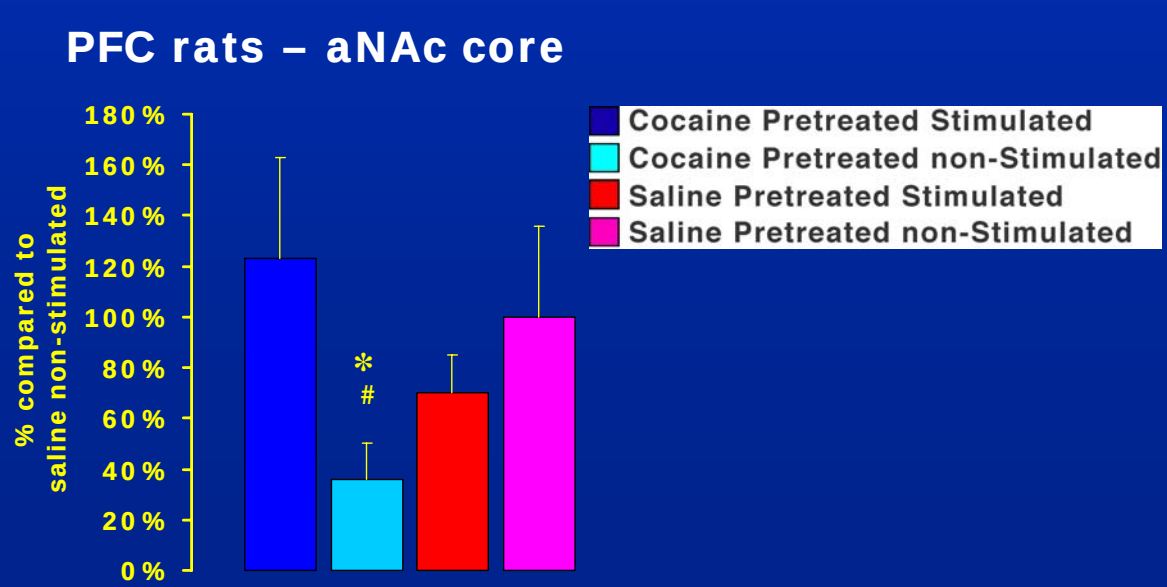


(Levy et al., JN 27:14179-89, 2007)

GluR1 in the VTA and NAc







(Levy et al., JN 27:14179-89, 2007)

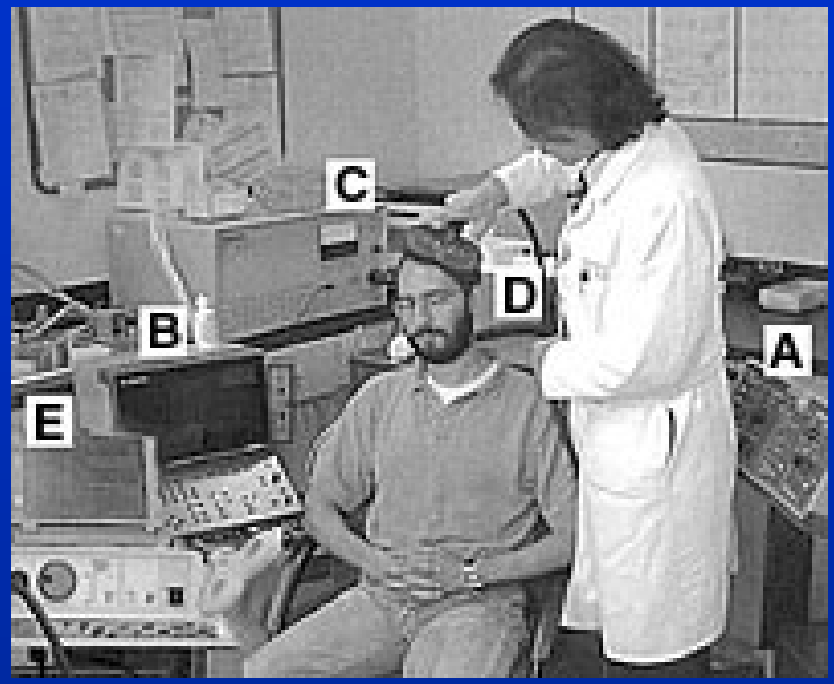
Interim Summary 1

- Repeated ICES of the LH decreases drug-seeking, but not cocaine reinforcement.
- Repeated ICES of the PFC decreases seeking behavior and cocaine reinforcement.
- No effect on natural reward consumption (did not present the data).
- The ICES effects are partly associated with normalization of glutamatergic neural-adaptations in sub-regions of the VTA and NAc.

(Levy et al., JN 27:14179-89, 2007)

Transcranial Magnetic Stimulation (TMS)

- Potential application in humans



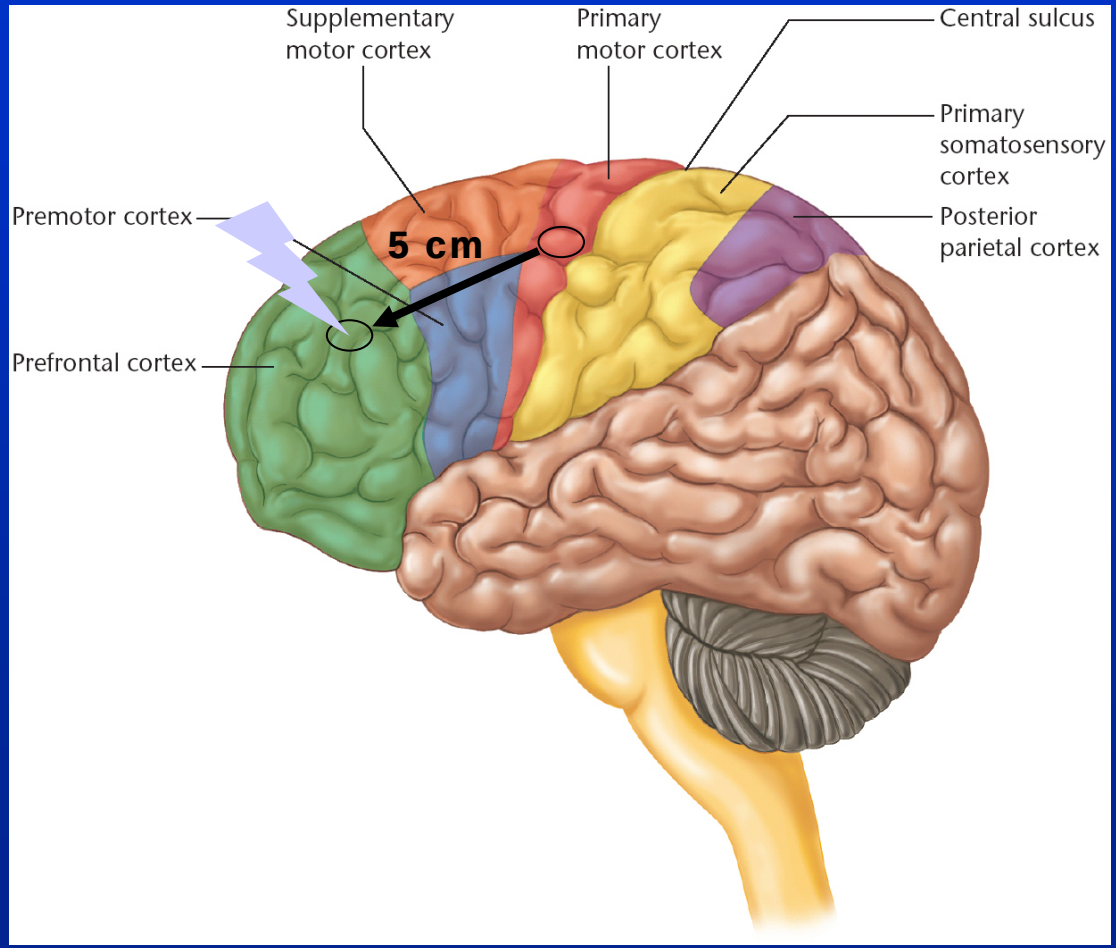
- Repeated stimulation of the PFC using TMS may become a novel treatment strategy for various addictions in humans. It is also used to measure alterations in cortical excitability in addicts.

10 Days of rTMS Treatment over the PFC

- 10 Hz
- 5 sec each train
- 50 pulses/train
- 100 msec ISI
- 15 sec ITI
- 20 trains/day
- 100% of motor threshold

<u>4 Groups:</u>

- Sham Stim Neutral Pics
- Sham Stim Smoke Pics
- Real Stim Neutral Pics
- Real Stim Smoke Pics



(Amiaz et al., Addiction, 2009)

Pictures

Smoke

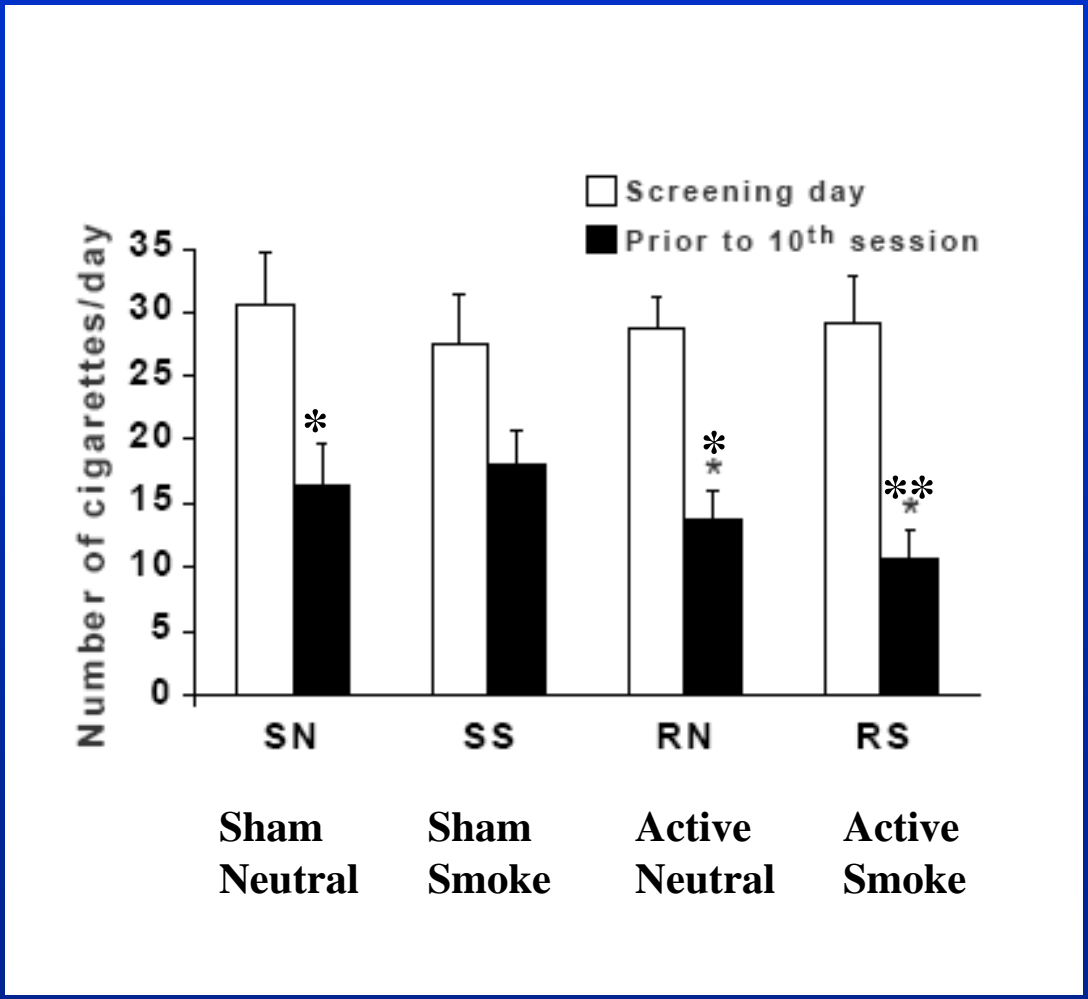



Neutral



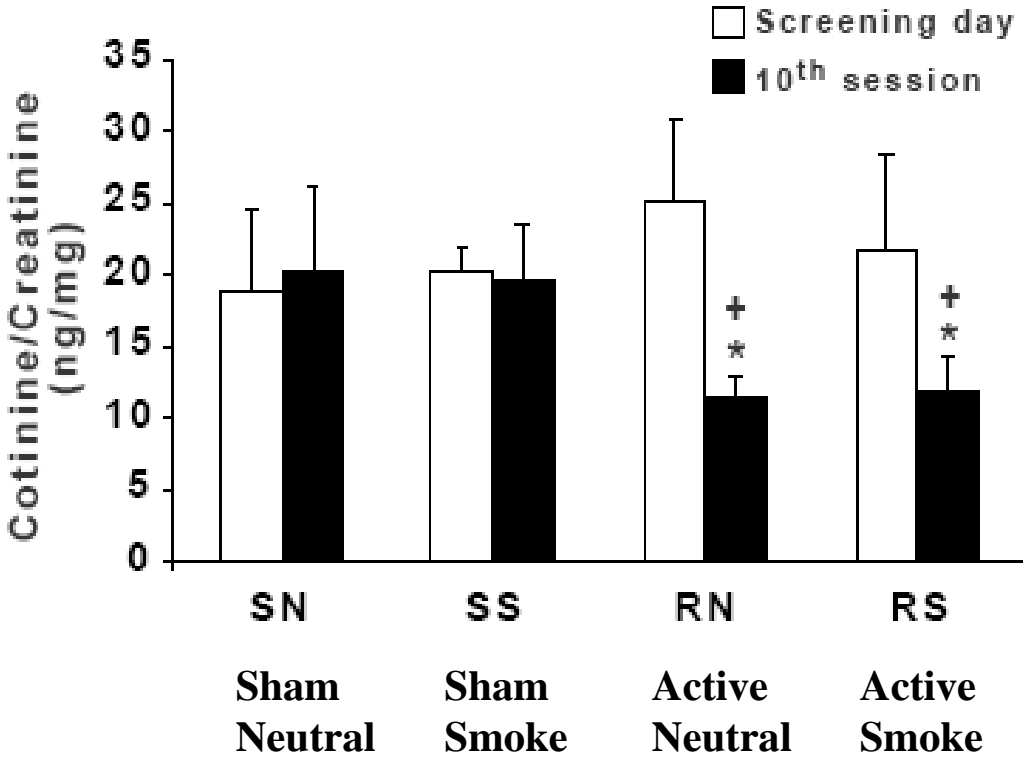

(Amiaz et al., Addiction, 2009)

Number of cigarettes smoked per day (Self-Report)



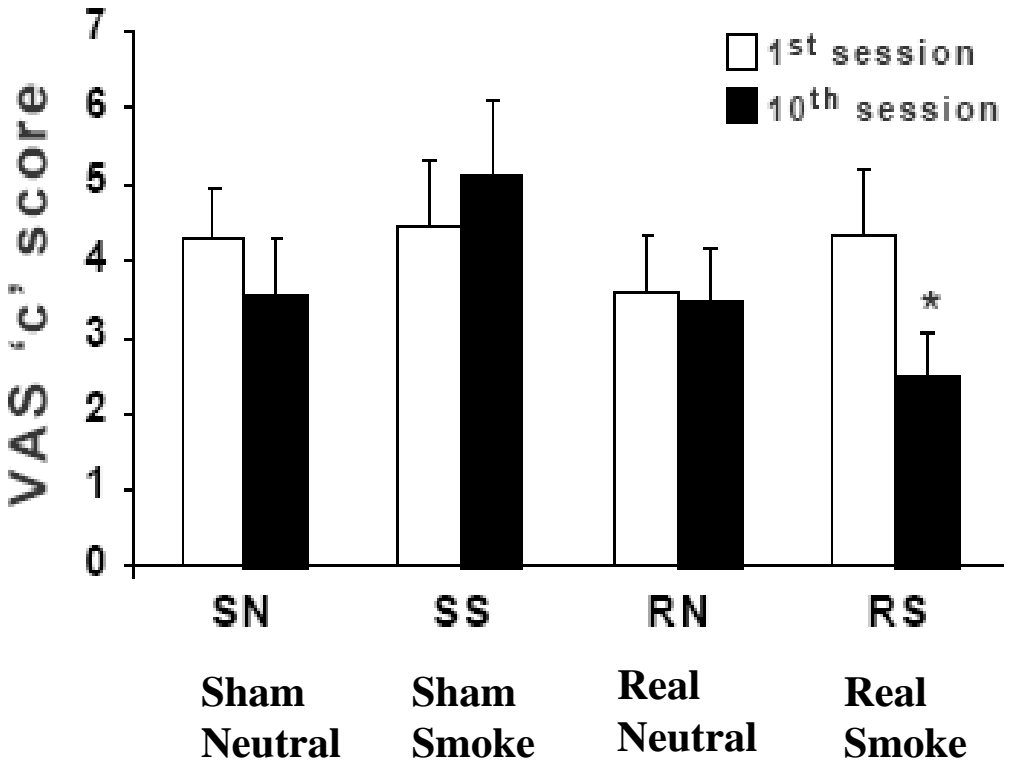
(Amiaz et al., Addiction, 2009)

Cotinine/Creatinin in Urine



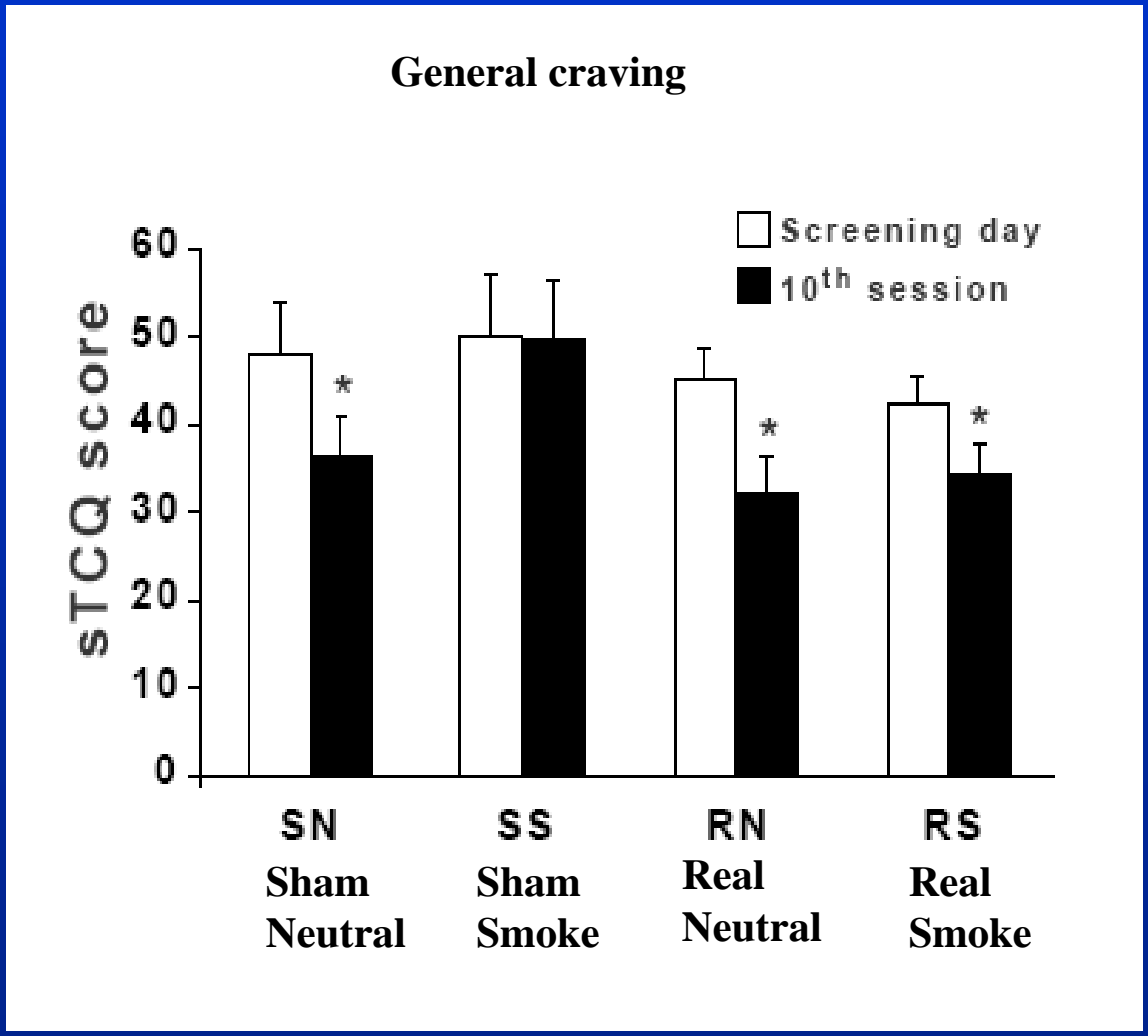
(Amiaz et al., Addiction, 2009)

Cue-induced Craving (VAS)



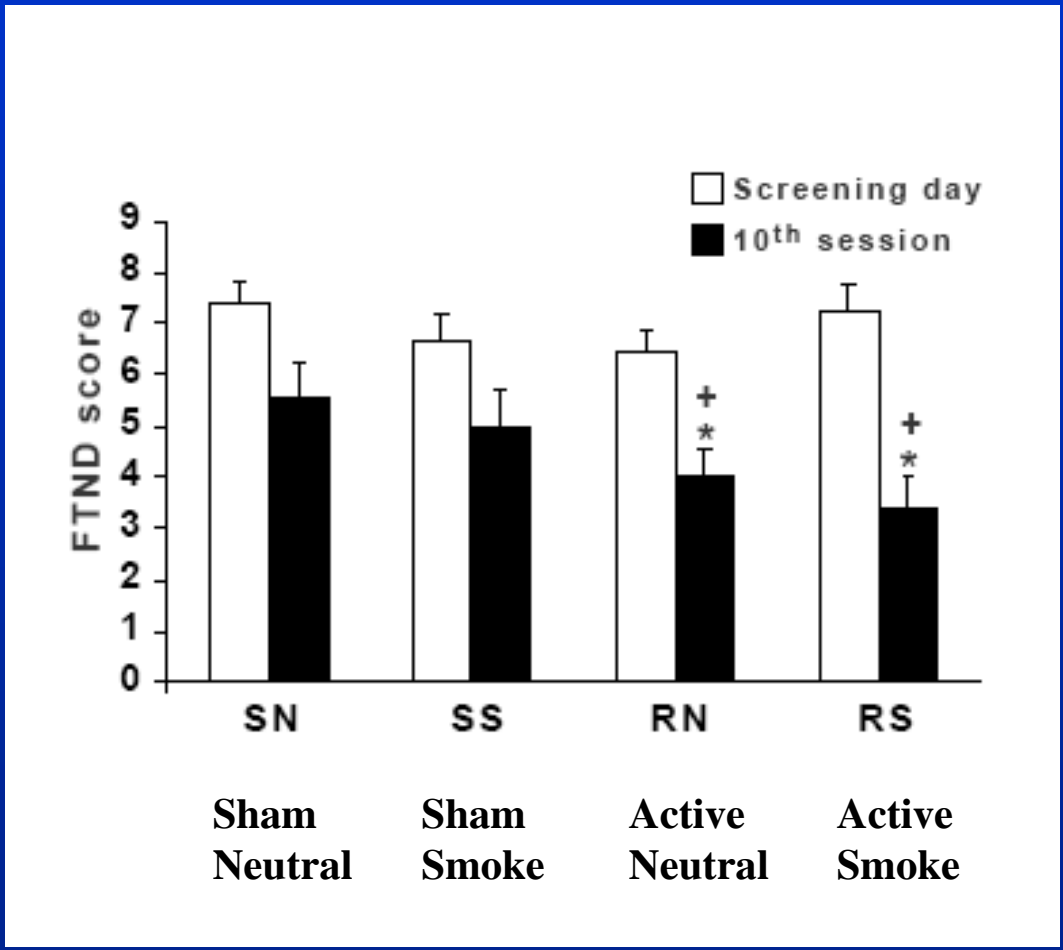
(Amiaz et al., Addiction, 2009)

Tobacco Craving Questionnaire (TCQ)



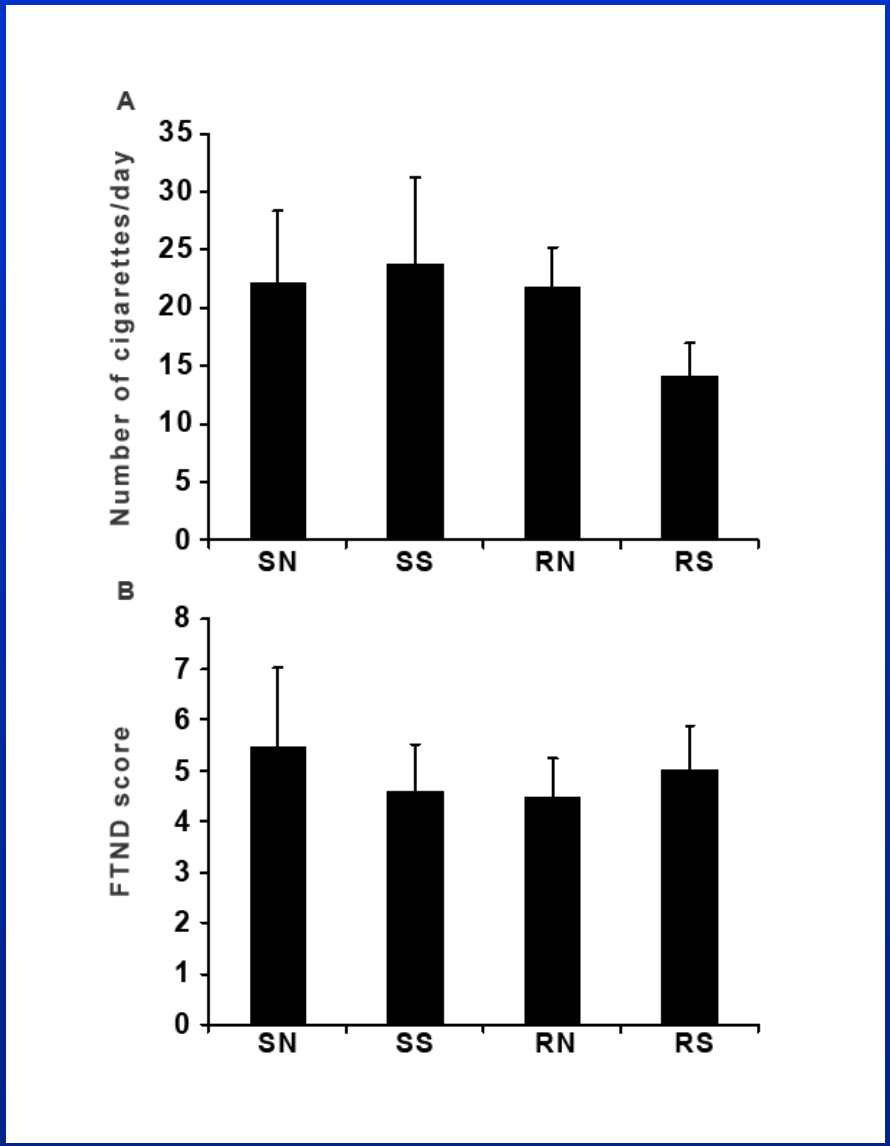
(Amiaz et al., Addiction, 2009)

Fagerström Test for Nicotine Dependence (FTND)



(Amiaz et al., Addiction, 2009)

Follow-Up: 6 months later (phone interview)



(Amiaz et al., Addiction, 2009)

Interim Summary 2

Multiple rTMS sessions of the PFC

- Reduces cigarette consumption.
- Reduces cue-induced craving when stimulation is applied while the memory trace is 'active'.

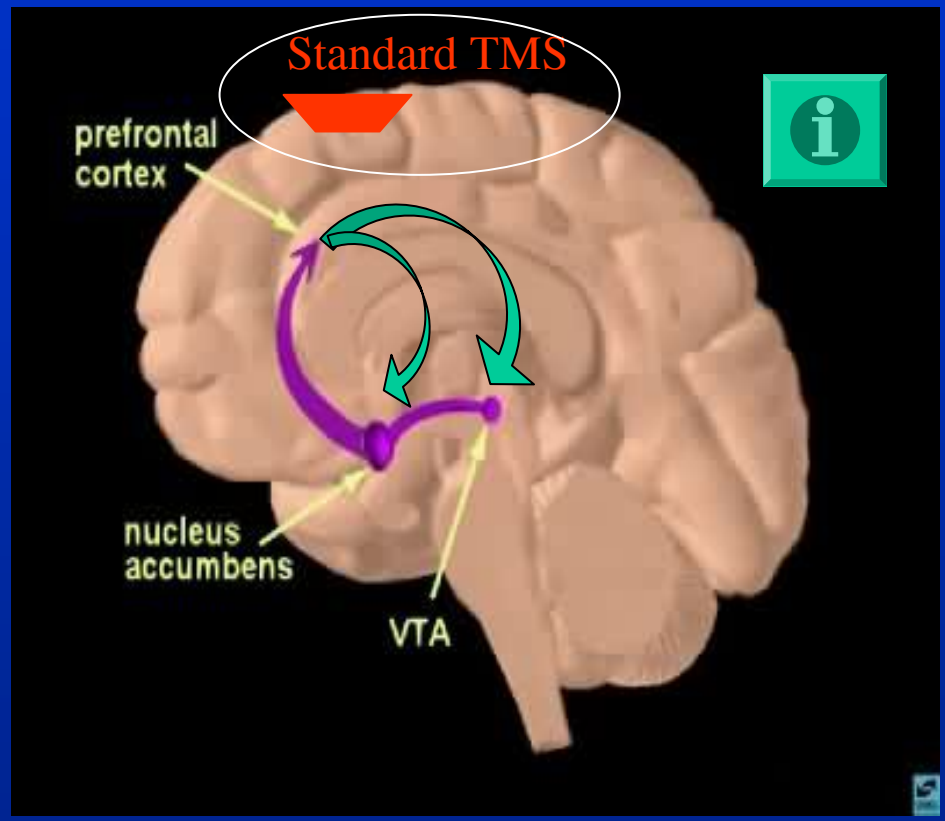
Limitations:

- Only partial effects; Does not induce full quitting.

Where should we interfere?

Addiction involves long-lasting alterations in the Brain Reward System

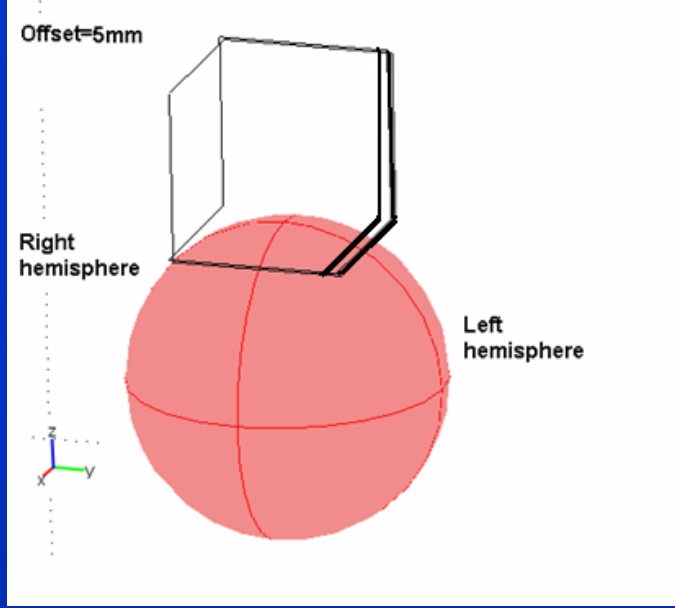
- Brain centers and pathways that are activated by natural and artificial rewards.
- Electrical stimulation of these centers generate a positive reward.
- Different types of rewards induce dopamine release in the nucleus accumbens.
- Cues that predict reward induce dopamine release in the NAc.
- "Hijacked" by drugs of abuse.



Ventral tegmental area (VTA), Nucleus Accumbens (NAS) Prefrontal Cortex.

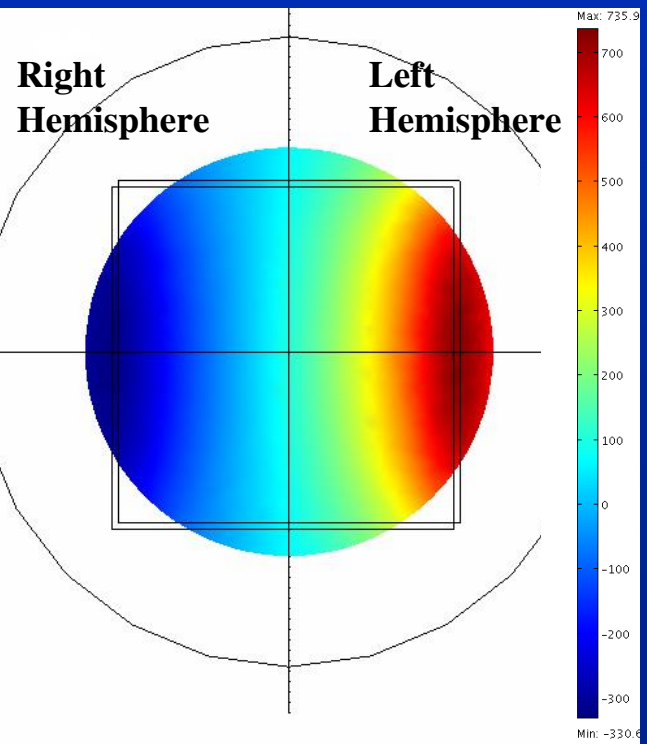
Deep TMS

Computerized **simulations** of electric field **induced by** various coil shapes



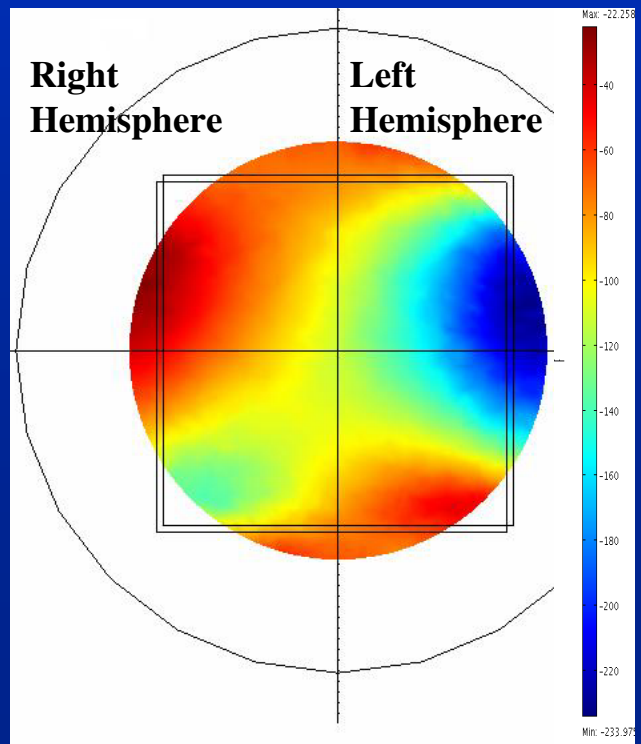
$$E_A = -\frac{\partial A}{\partial t}$$

Induced field:



$$E_\Phi = -\nabla\Phi$$

Electrostatic field:



Total field:

$$E = E_A + E_\Phi$$

=> The electrostatic charge induced by non-tangential coil elements plays a *critical* role.

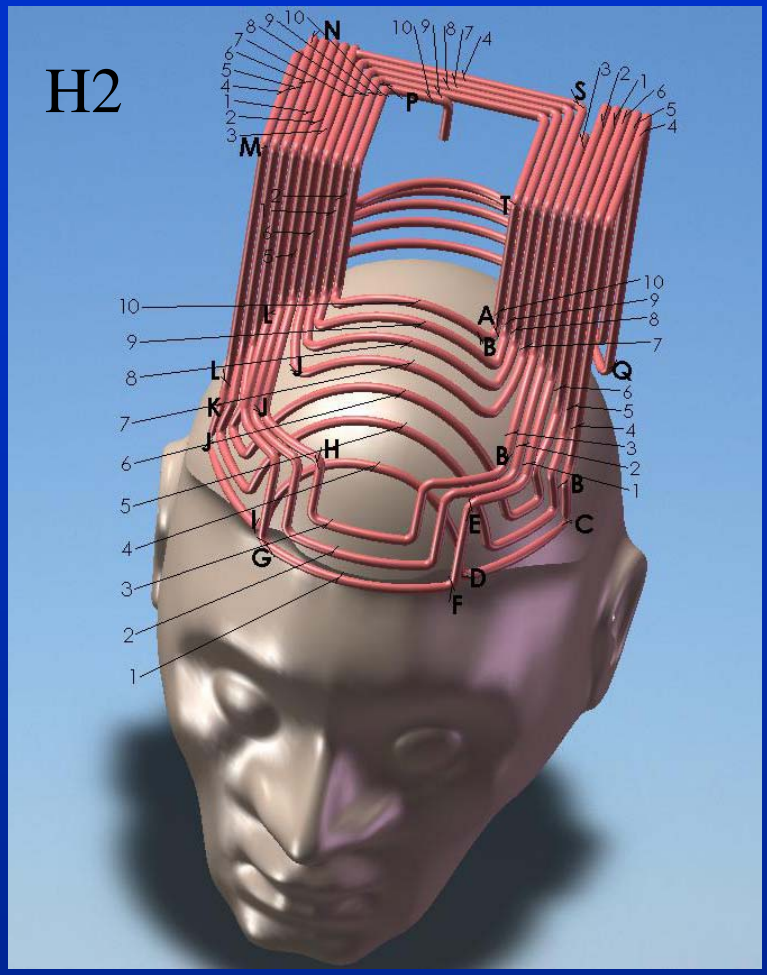
Fundamental principles based on computerized calculations and confirmed by phantom brain measurements:

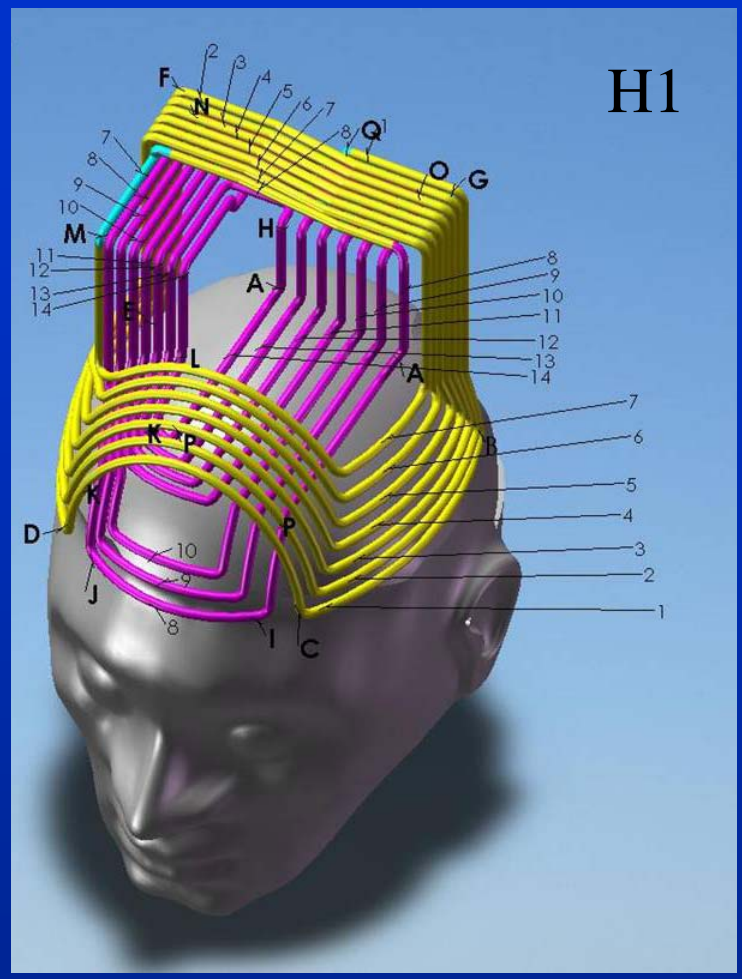
- It is possible to induce summation of fields in depth by spreading several elements of a coil around a theoretical meeting point, as long as the return elements of the circuit (that produce cancellation) are placed far enough from the deep target.

- Non-tangential components of any coil shape would decrease efficacy and facilitate the rate of electric field reduction as a function of distance.

Zangen et al., 2005

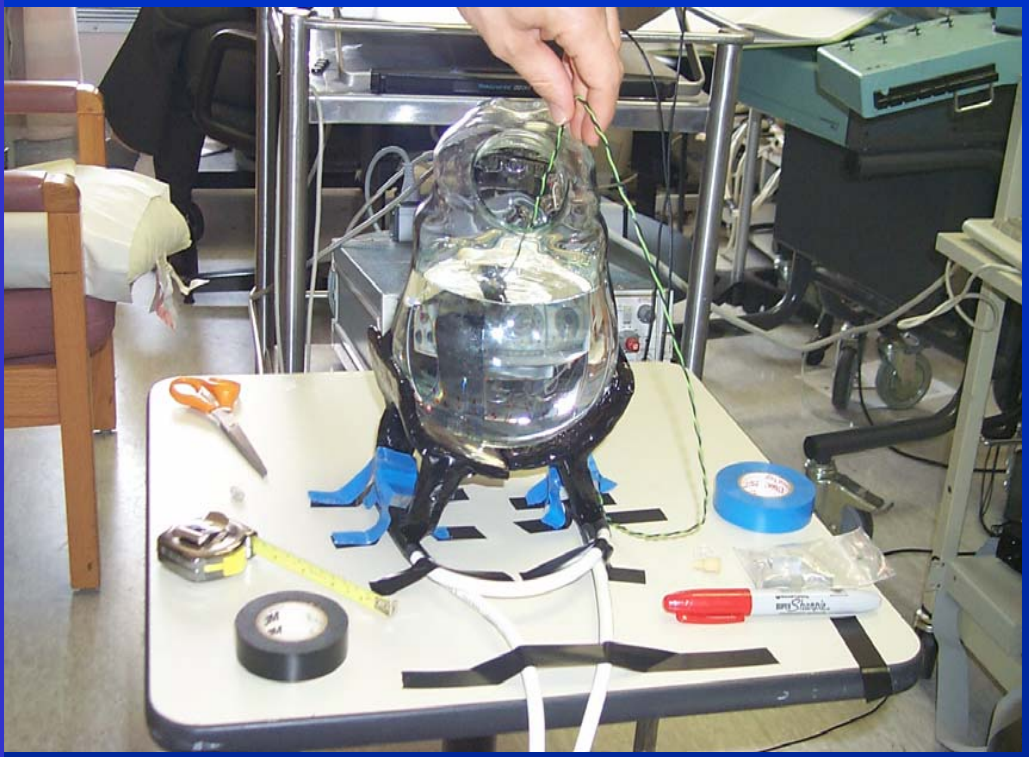
Different versions of the H-Coil



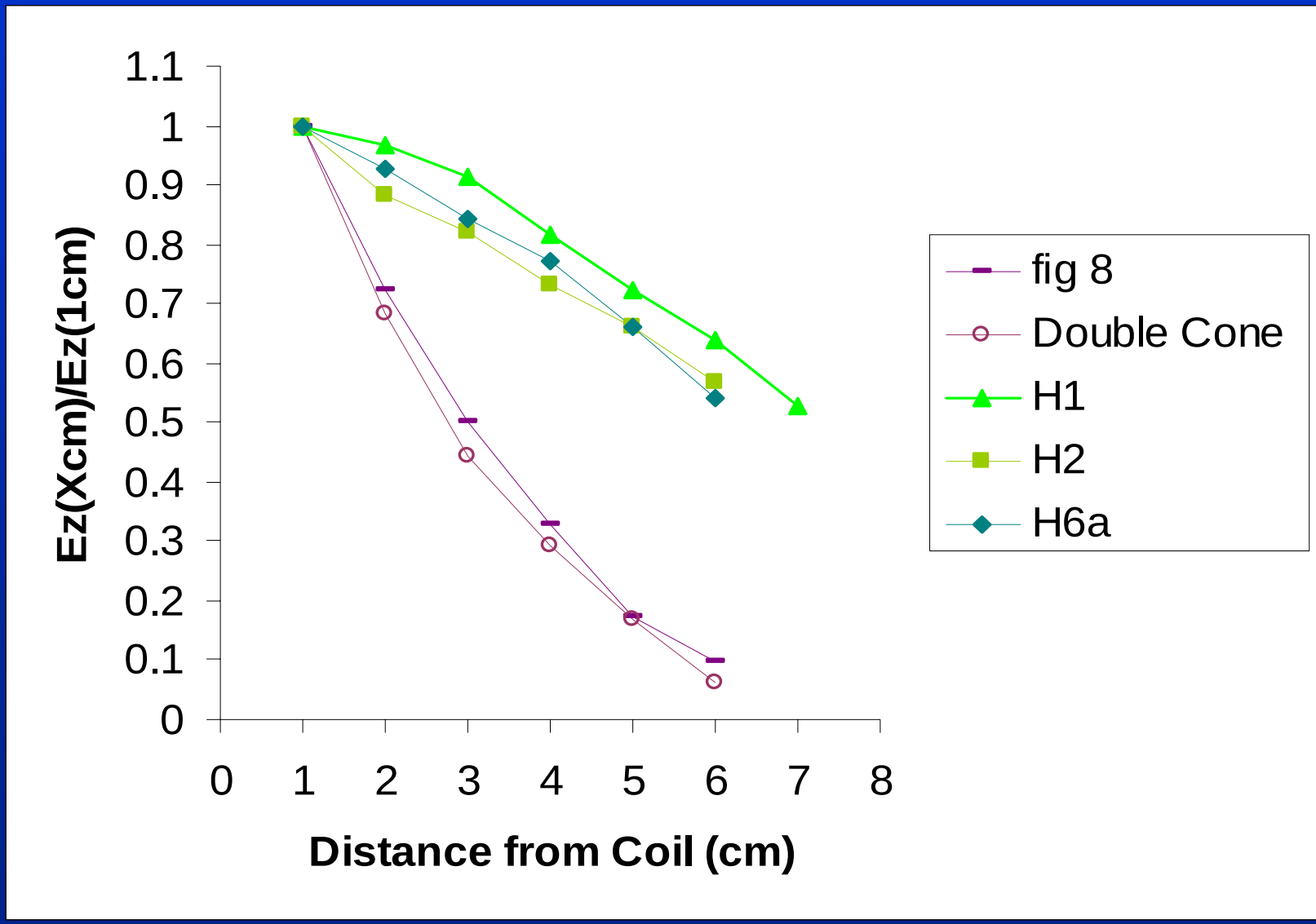


<u>Considerations</u>: Target in depth, directions of axons to be stimulated, *<u>decreasing facial pain</u>* and other risks or side effects.

Phantom Brain Measurements

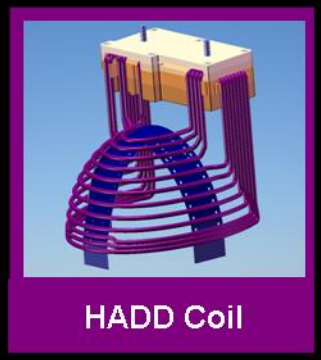


Rate of reduction in the electric field induced by various coils



Zangen et al., 2005; Roth et al., 2007, 2009

Electric Field Distribution at 120% MT


HADD Coil

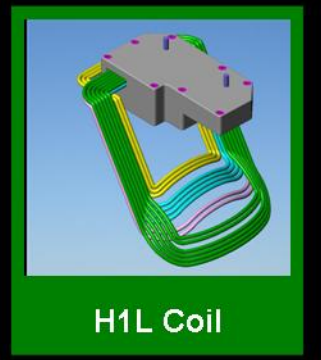
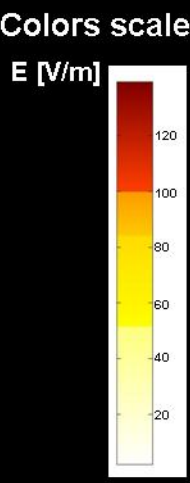
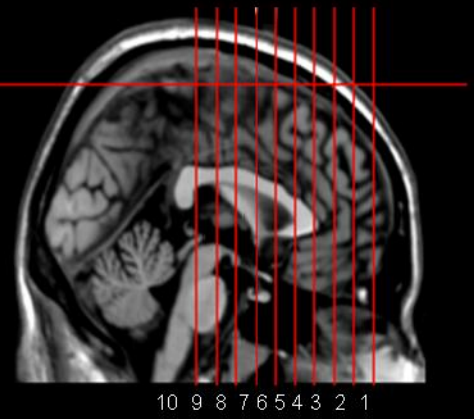
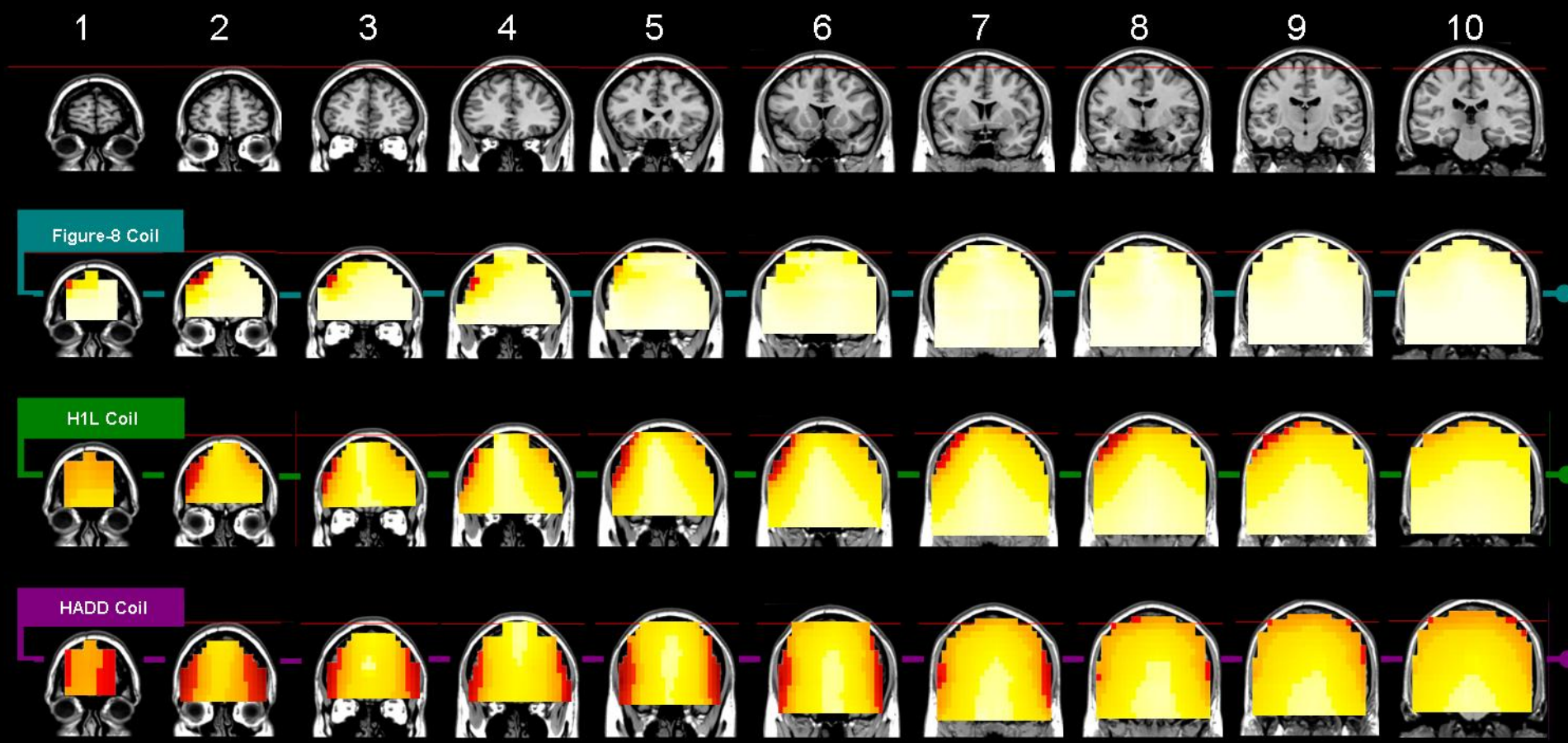

H1L Coil

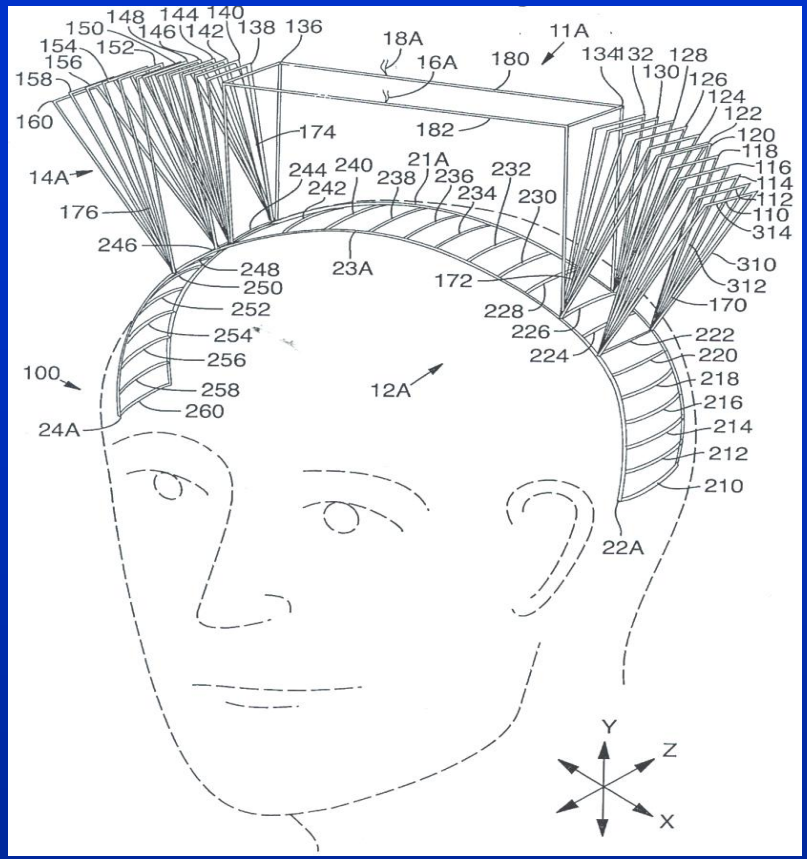

Figure-8 Coil

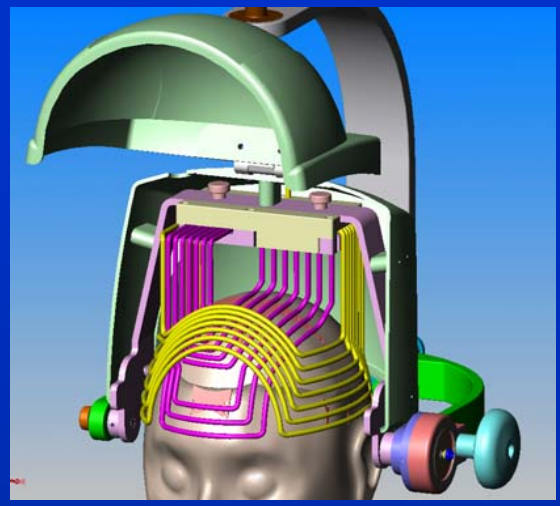


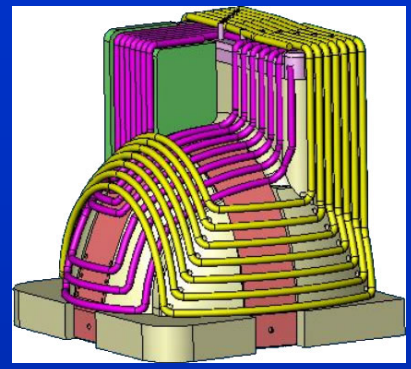




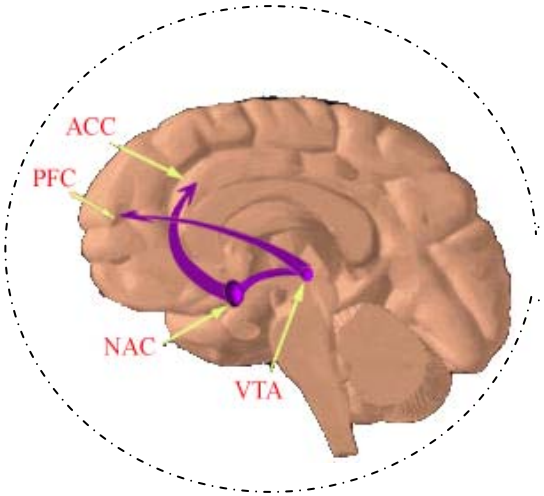
Ongoing Project - Deep TMS

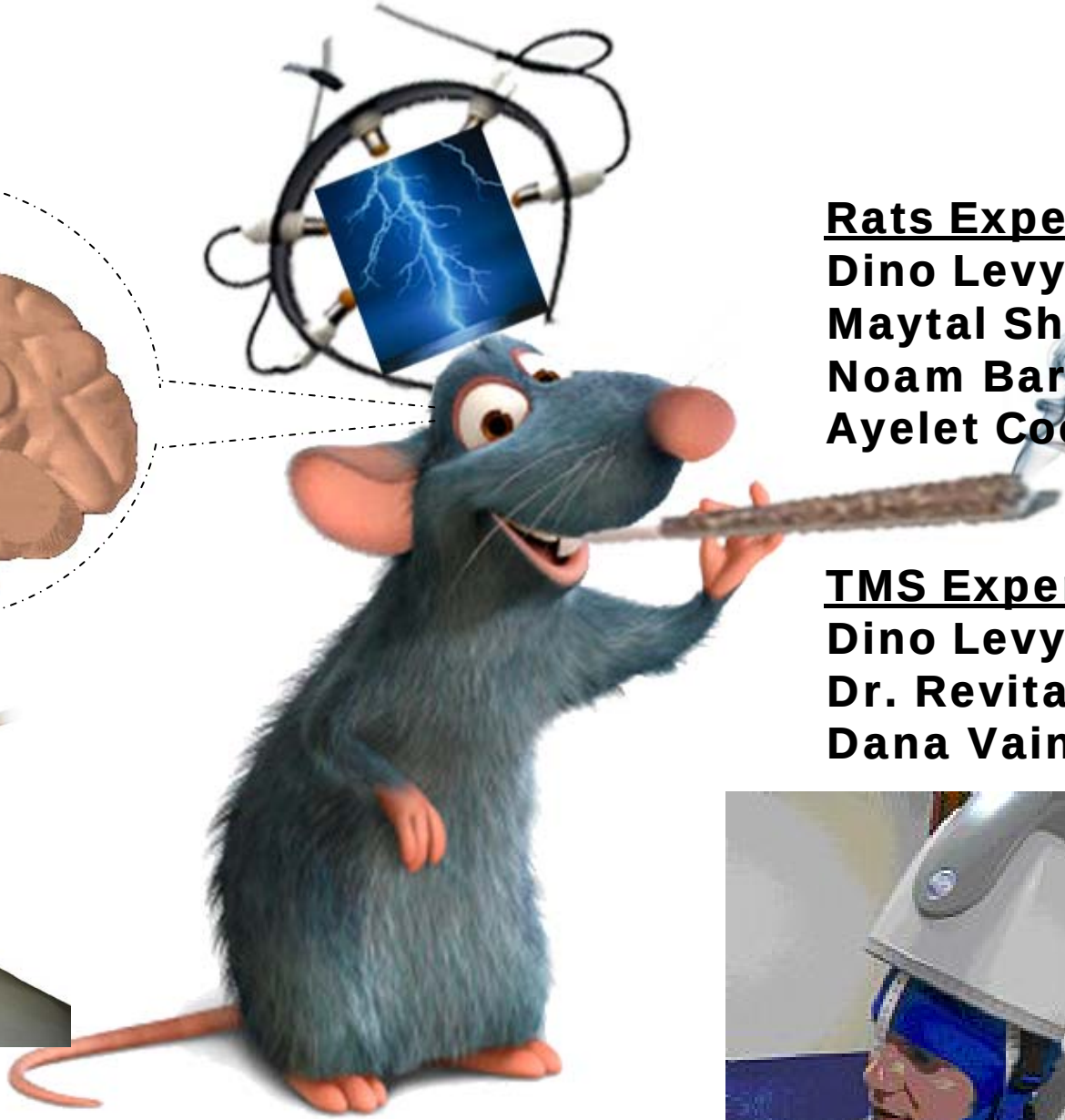






Acknowledgments





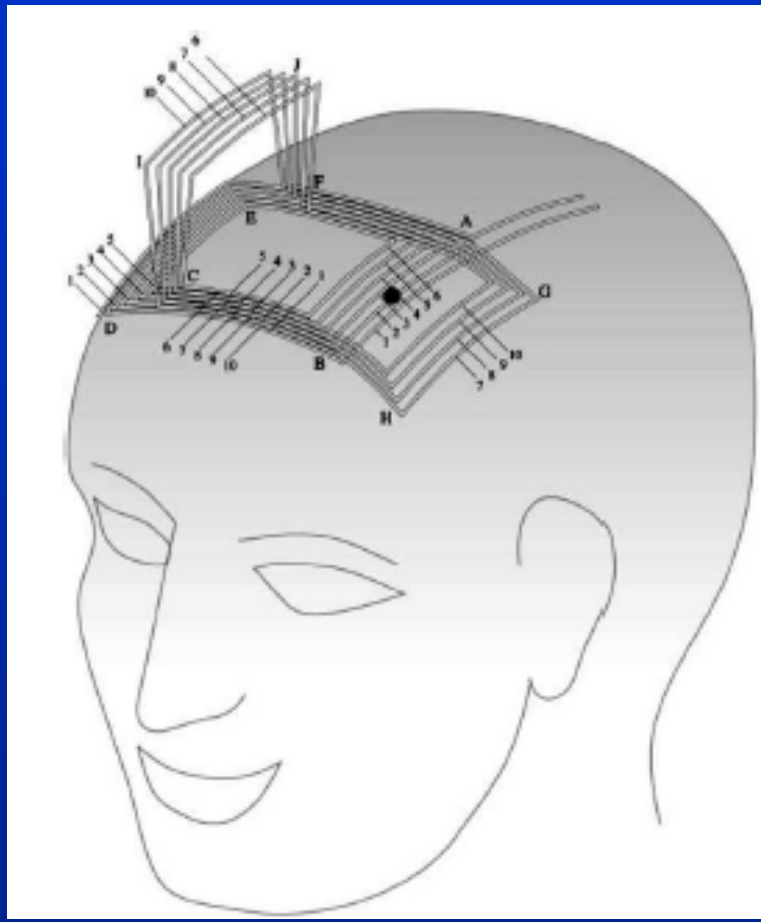
Rats Experiments:
Dino Levy
Maytal Shabat-Simon
Noam Barnea-Ygael
Ayelet Cooper

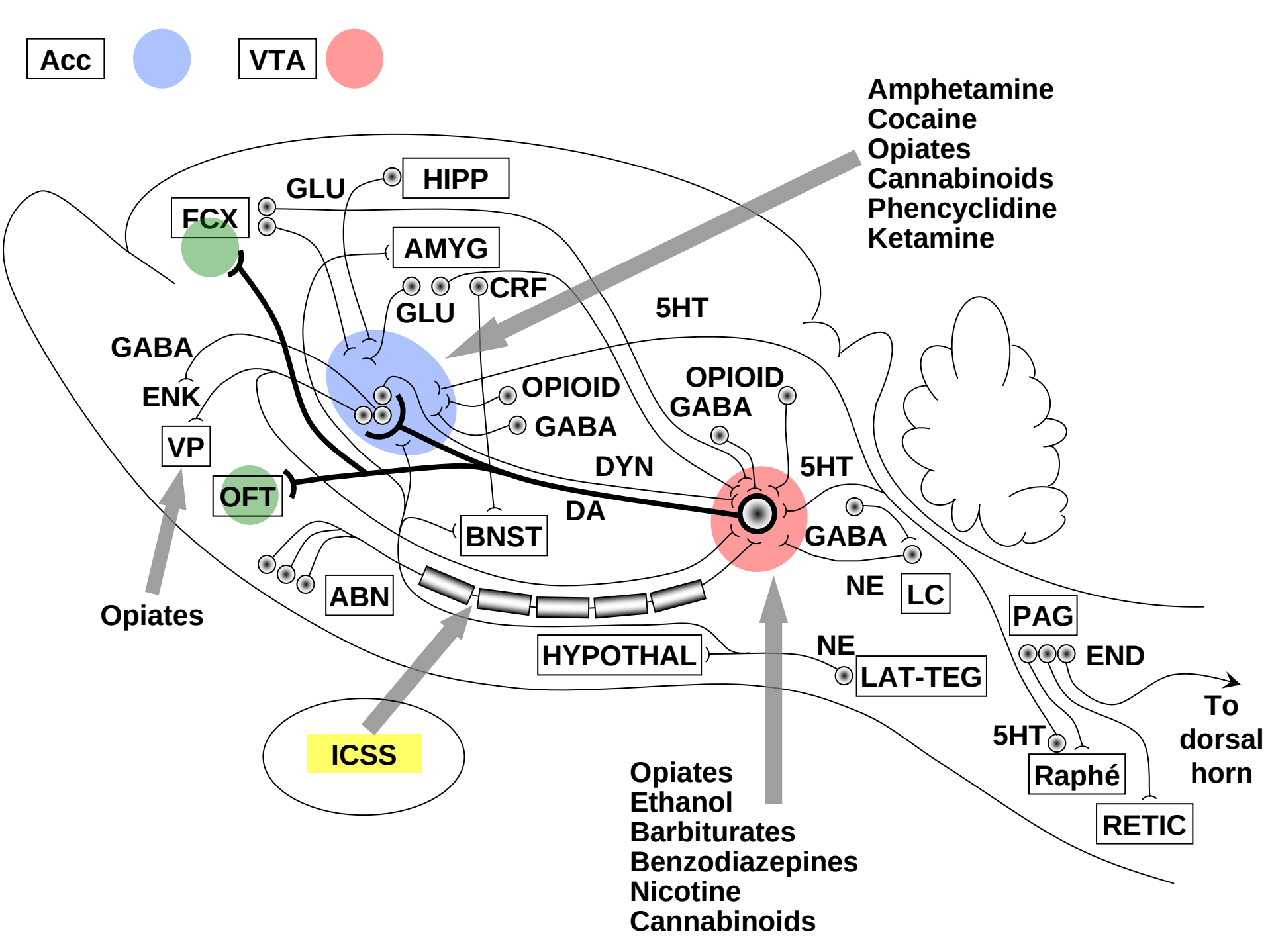
TMS Experiment:
Dino Levy
Dr. Revital Amiaz
Dana Vainiger

Example (described at Zangen et al., 2005):

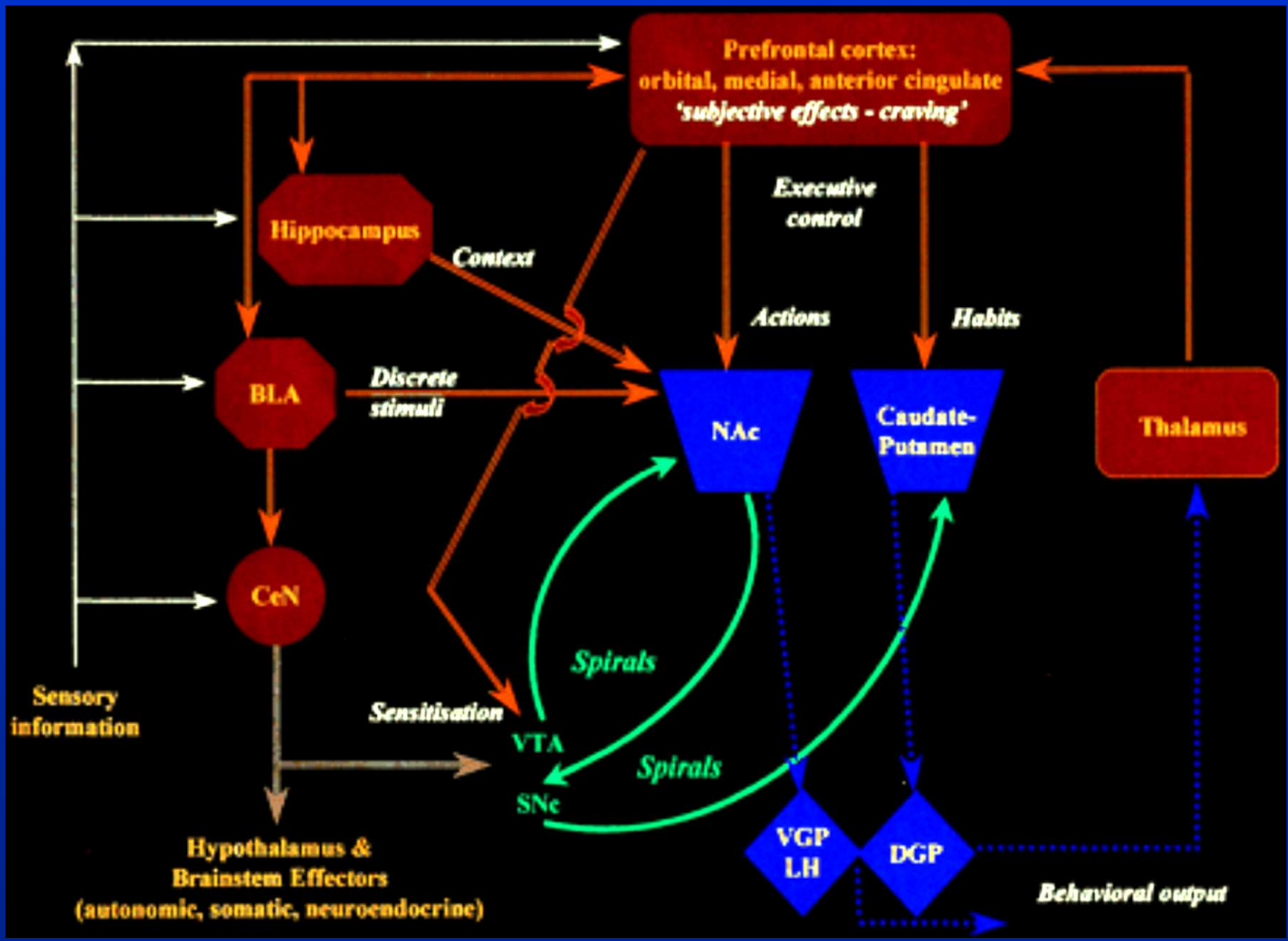
- Summation of electric impulses
- Base complementary to the head
- Minimization of non-tangential coil elements
- Return paths location and non-tangential elements remote from target
- Proper orientation of coil elements- parallel to target bundles

Sketch of an H-Coil



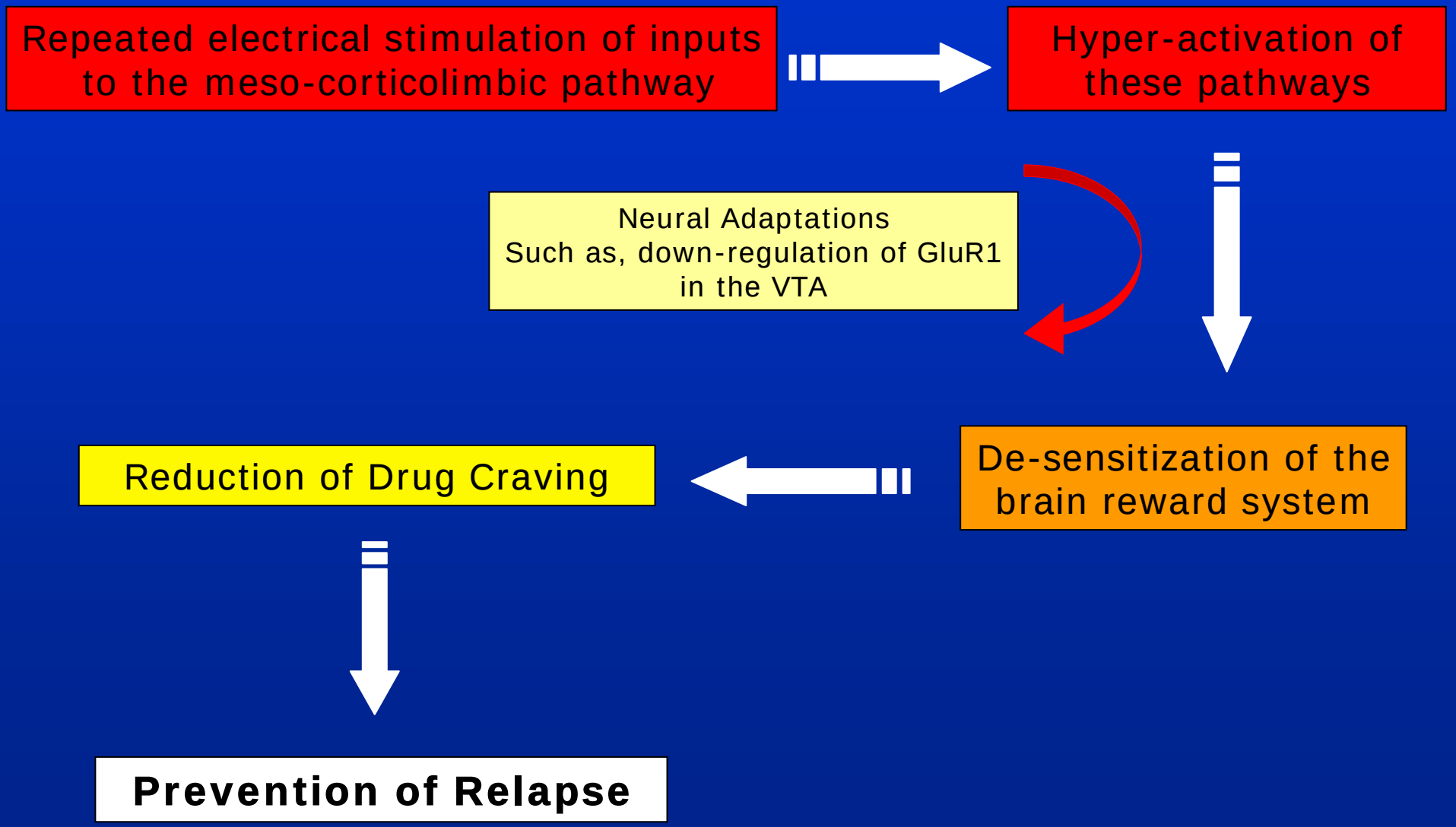

Acc
VTA
Amphetamine
Cocaine
Opiates
Cannabinoids
Phencyclidine
Ketamine
HIPP
GLU
FCX
AMYG
CRF
GLU
5HT
GABA
ENK
VP
OPIOID
GABA
OPIOID
GABA
DYN
5HT
OFT
DA
BNST
GABA
ABN
NE
LC
Opiates
PAG
END
HYPOTHAL
NE
LAT-TEG
To
dorsal
horn
5HT
Raphé
RETIC
ICSS
Opiates
Ethanol
Barbiturates
Benzodiazepines
Nicotine
Cannabinoids

The Reward Circuitry

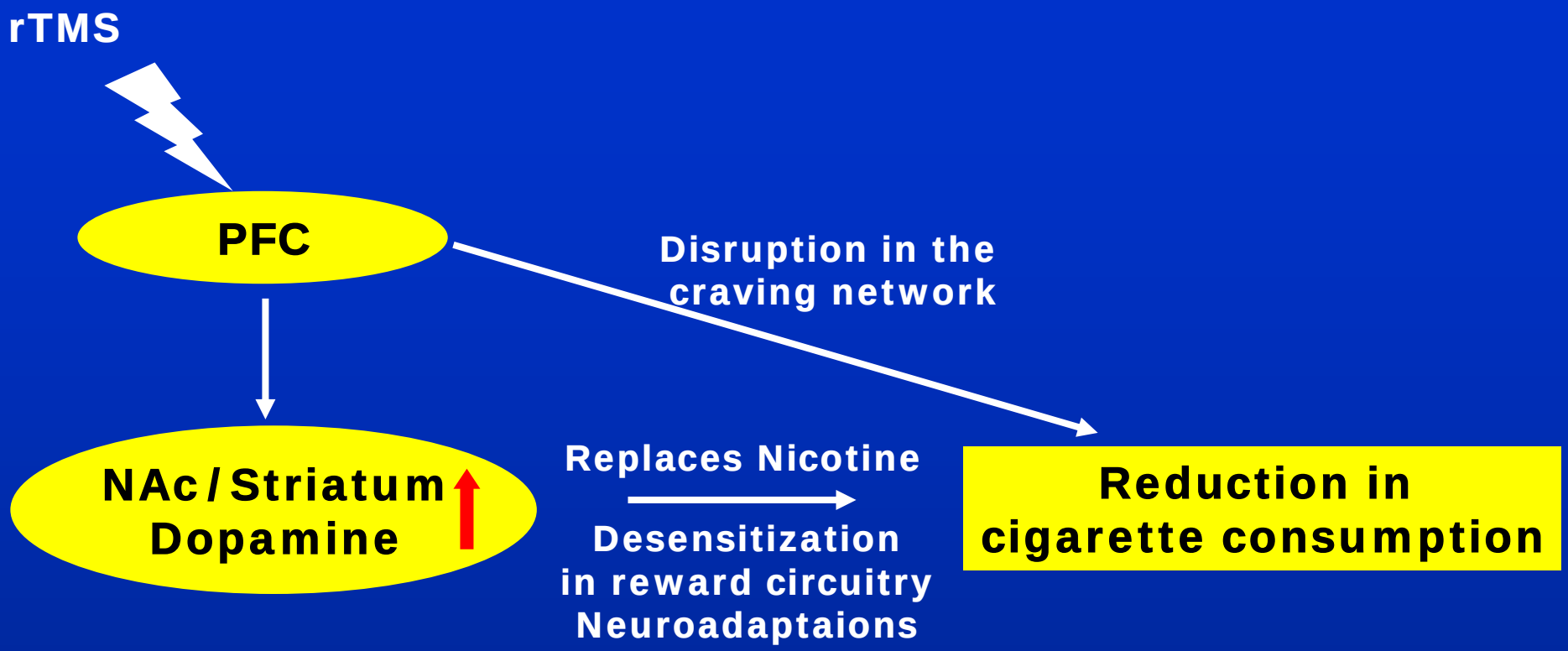


Can we interfere with the alterations induced in the reward circuitry in addiction?

Potential Treatment for Drug Addiction?

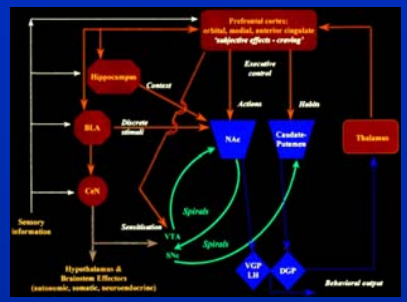


Hypothesis


rTMS
PFC
Disruption in the craving network
NAc/Striatum Dopamine
Replaces Nicotine
Desensitization in reward circuitry Neuroadaptaions
Reduction in cigarette consumption

Hypothesis

Smoking related cues



Activation of Smoking related cues' circuit / memory

rTMS

The circuit is labile for disruption

Blocking of cue-induced craving

- Is the PFC the best site of intervention?
- Can brain stimulation block the association between the ‘cue’ and the drug?
- Relapse prevention?
- Back to the rats and the GluR1…

The Basolateral amygdala (BLA)

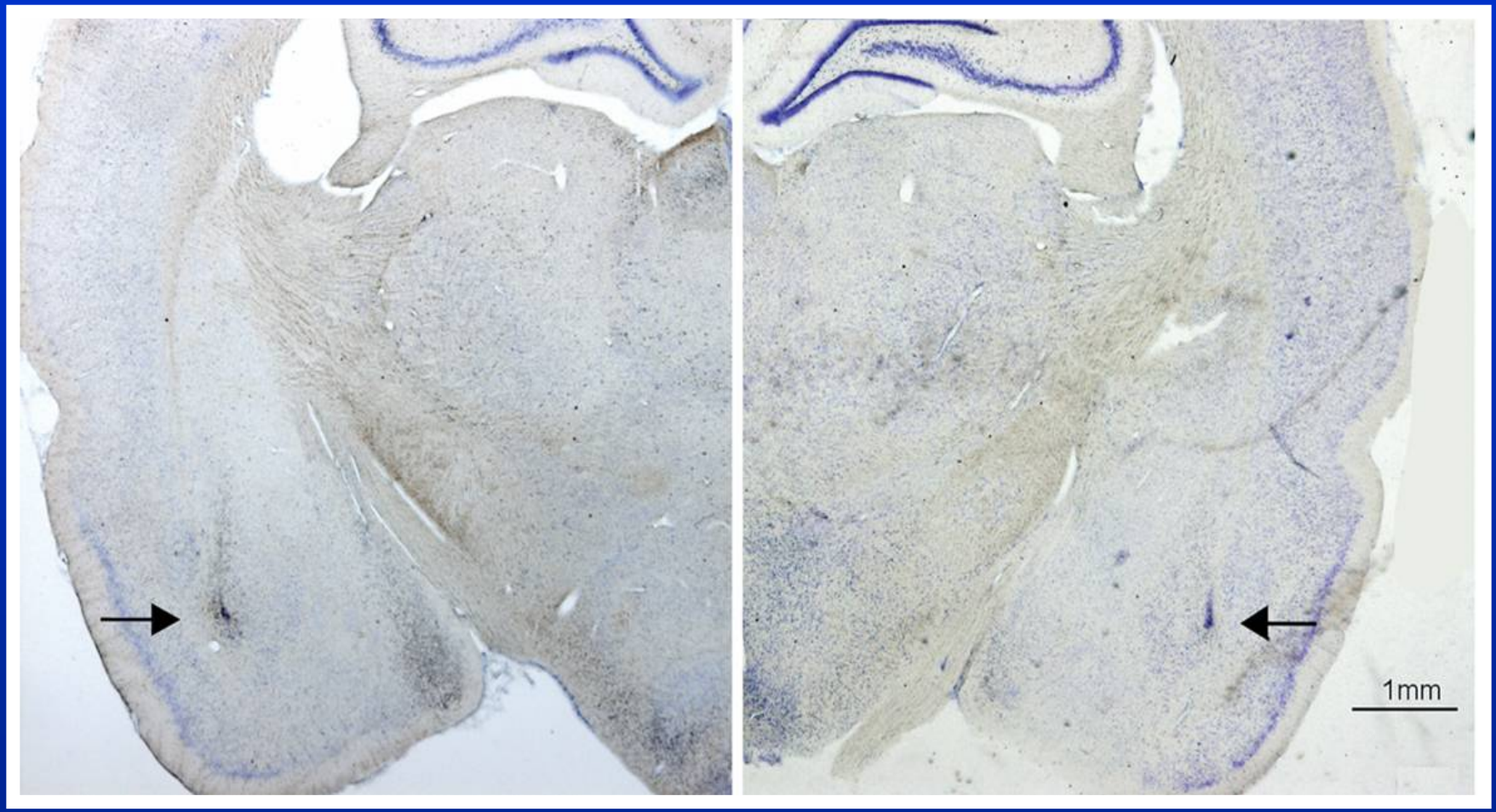
• The BLA has been implicated as a critical component of the neural circuits subserving the acquisition, consolidation and expression of cue-drug associations, which likely drive drug-seeking during relapse.

• Long-lasting vulnerability to cue-induced drug-taking behaviors involve maladaptive neuroadaptations. Notable among these are persistent alterations in glutamatergic synapses in the amygdala (e.g. Lu et al. 2005).

• Low frequency of electrical stimulation of specific brain sites can interfere with local activity and induces long-term depression (LTD) in BLA neurons (Wang and Gean 1999).

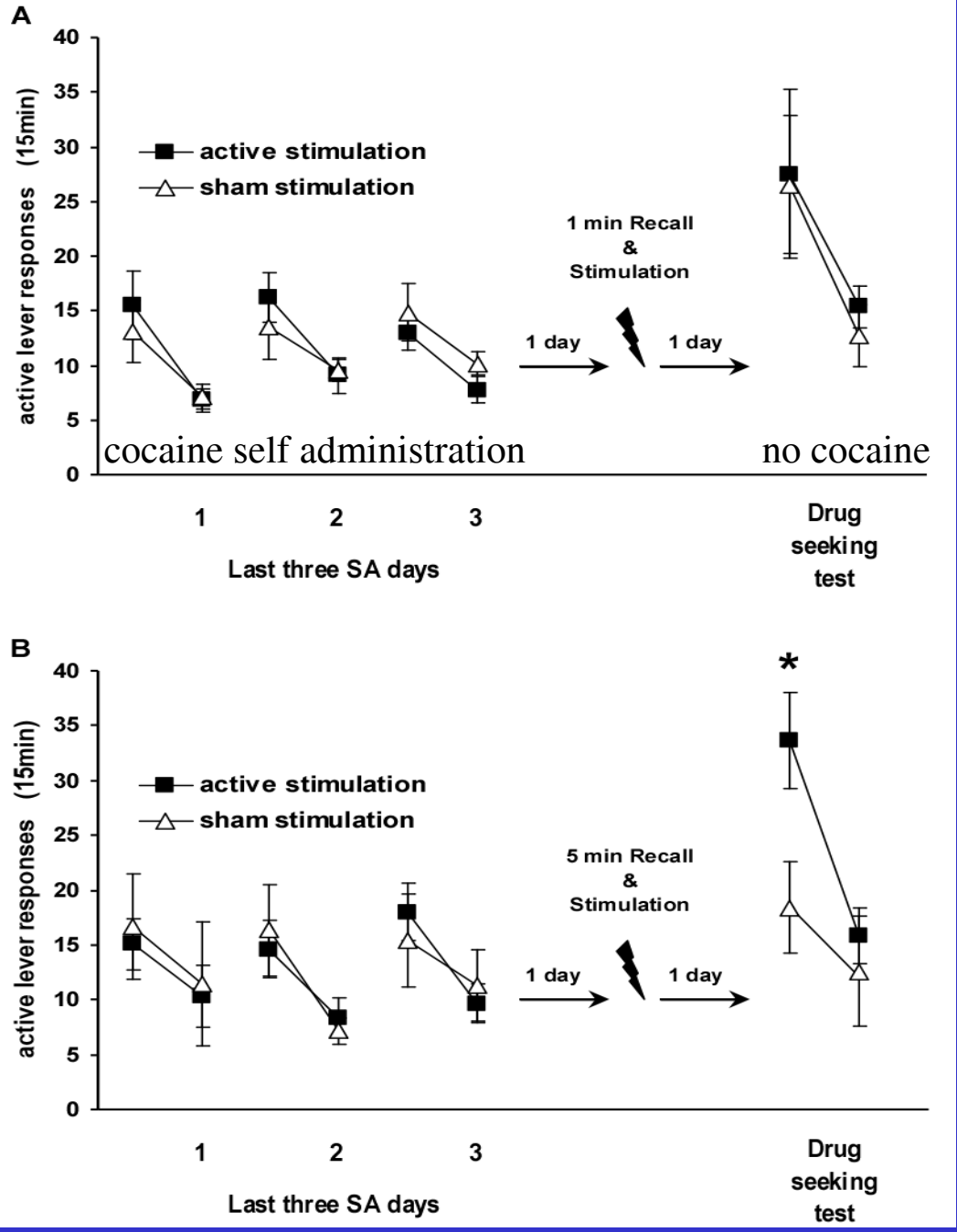
• GluR1 phosphorylation has been shown to play a critical role in synaptic associative learning (Lee *et al.* 2003) and LTD.

Stimulation of the BLA

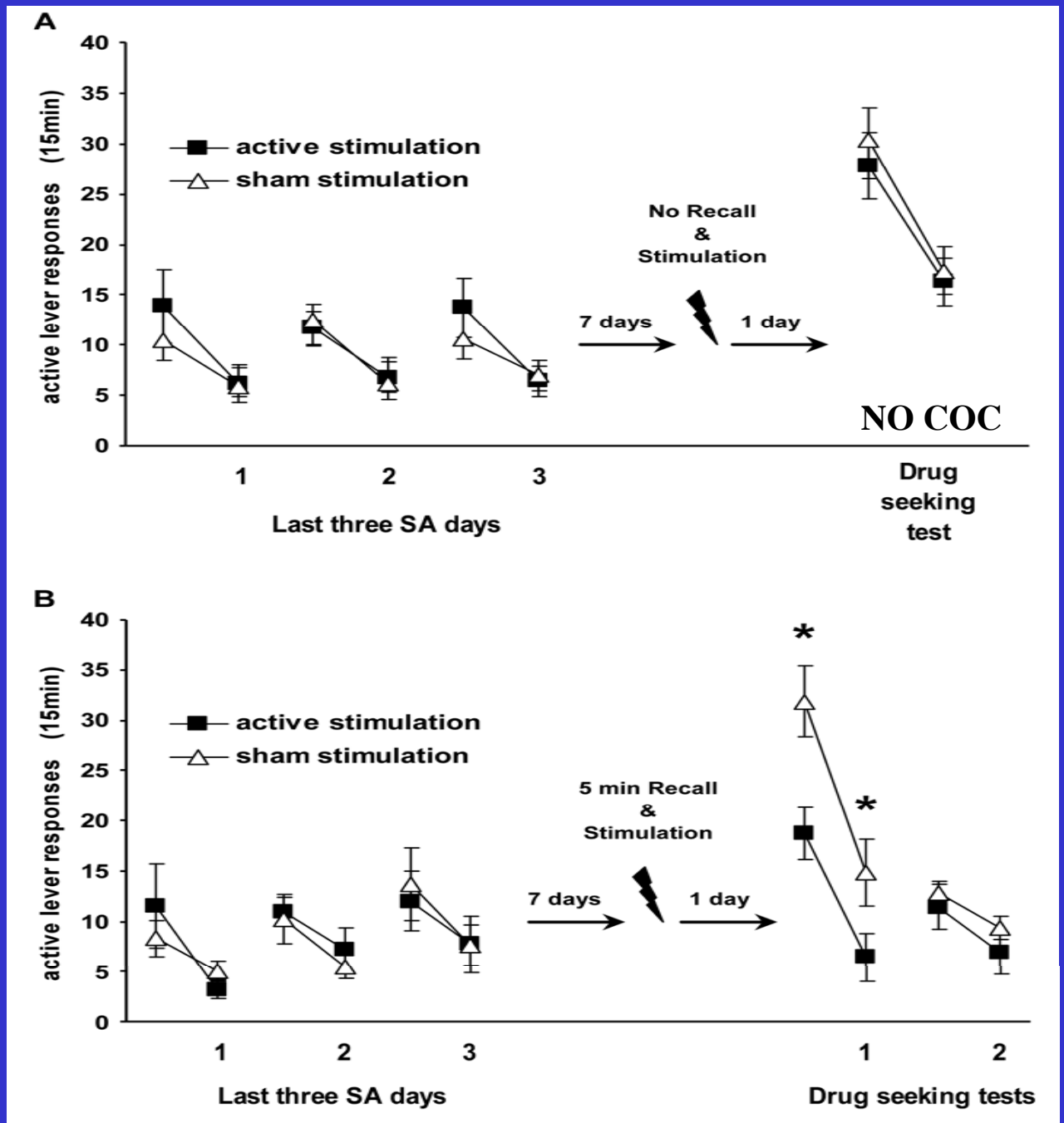


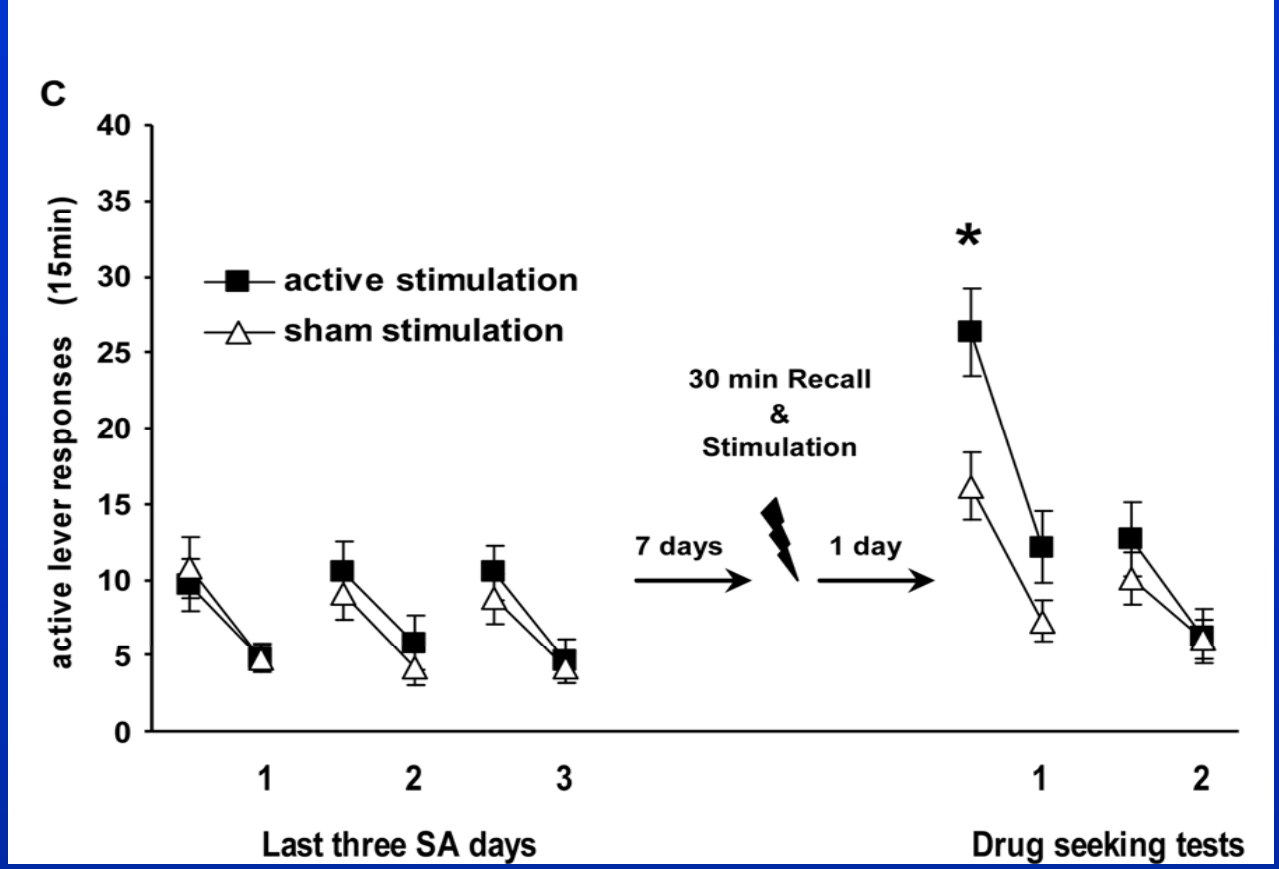
A single 15-min session of low frequency (1Hz) using an LTD protocol

Effect of BLS stimulation on drug seeking after 1 day



Effect of BLS stimulation on drug seeking after 1 week




C
active lever responses (15min)
40
35
30
25
20
15
10
5
0
active stimulation
sham stimulation
30 min Recall
&
Stimulation
7 days
1 day
*
1
2
3
1
2
Last three SA days
Drug seeking tests

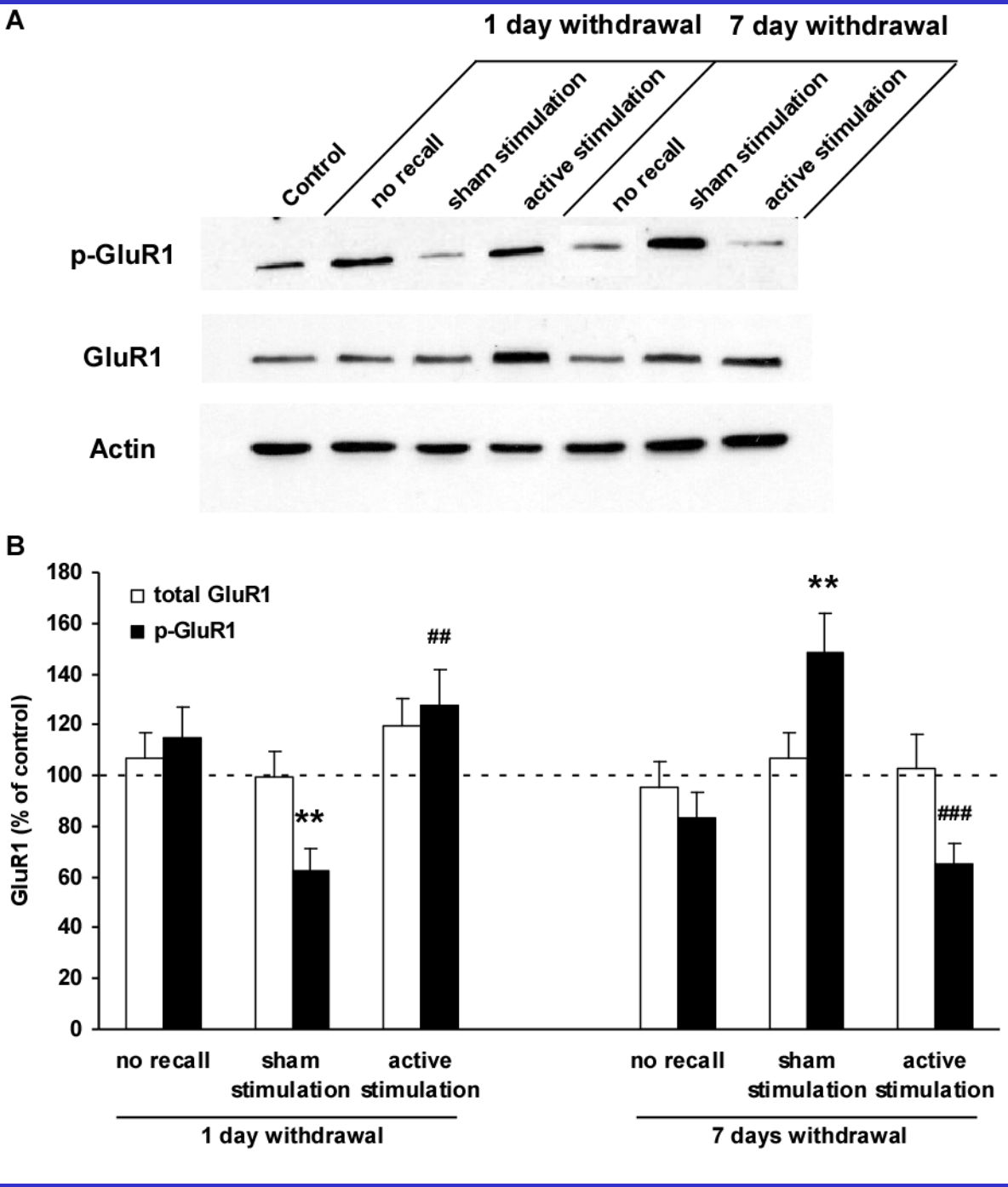
1 day post ICES in the BLA (1 Hz):

- 5min but not 1min of retrieval induced an extinction process, which dominated behavior in the test session.
- ICES of the BLA following 5min but not 1min retrieval disrupted extinction.

One week post ICES (1 Hz):

- 5min retrieval did not initiate extinction.
- ICES of the BLA following 5min retrieval impaired cue induced drug-seeking.

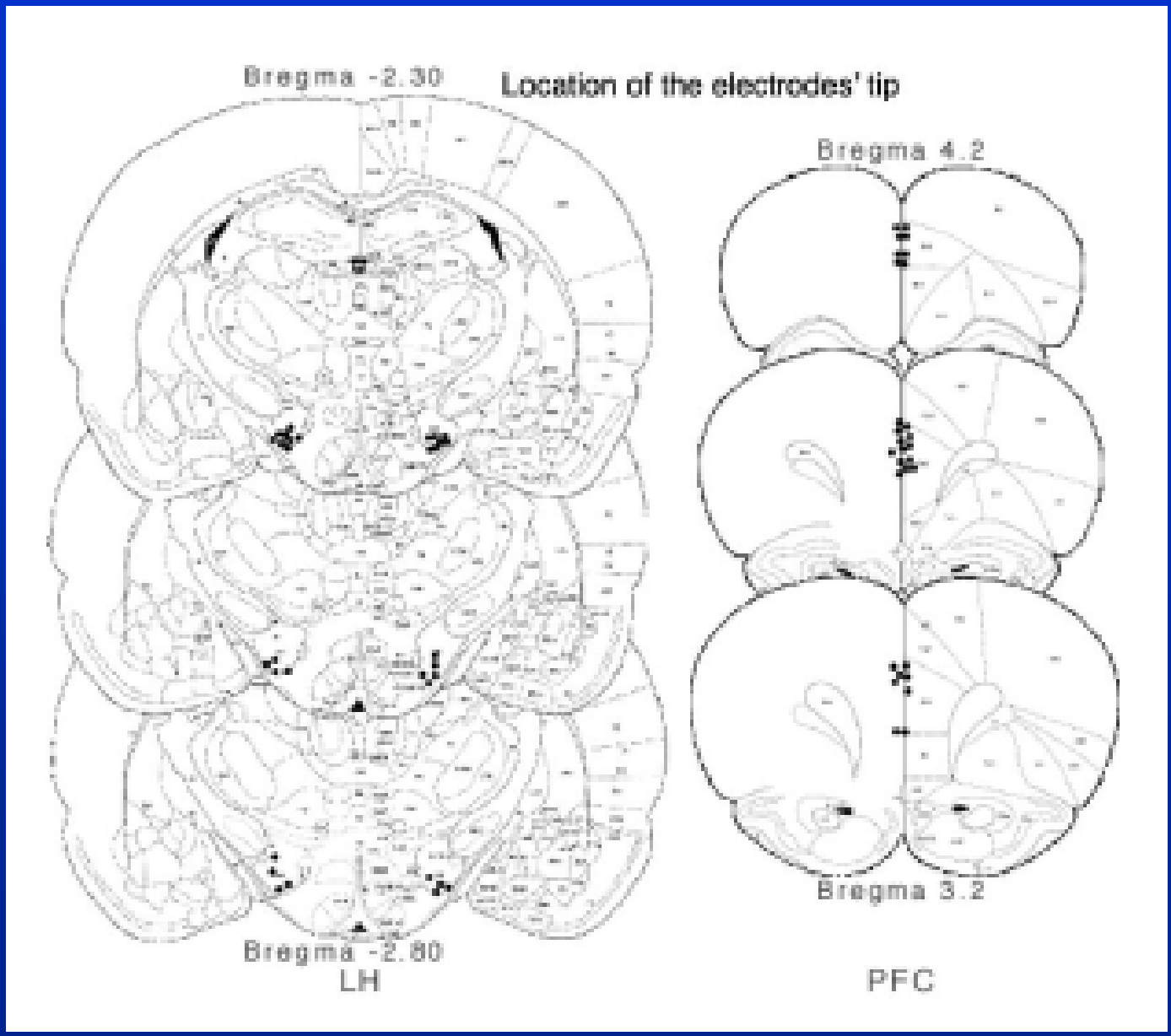
- 30min retrieval initiated extinction.
- ICES of the BLA following 30min retrieval disrupted extinction.


A
1 day withdrawal
7 day withdrawal
Control
no recall
sham stimulation
active stimulation
no recall
sham stimulation
active stimulation
p-GluR1
GluR1
Actin
B
total GluR1
p-GluR1
GluR1 (% of control)
180
160
140
120
100
80
60
40
20
0
##
**
**
###
no recall
sham stimulation
active stimulation
no recall
sham stimulation
active stimulation
1 day withdrawal
7 days withdrawal

- Again, the effects of BLA stimulation were opposite in direction depending on the timing of stimulation.

- The exact same physical intervention (15 min, Hz BLA stimulation at the same intensity) can induce different and even opposite effects depending on timing .

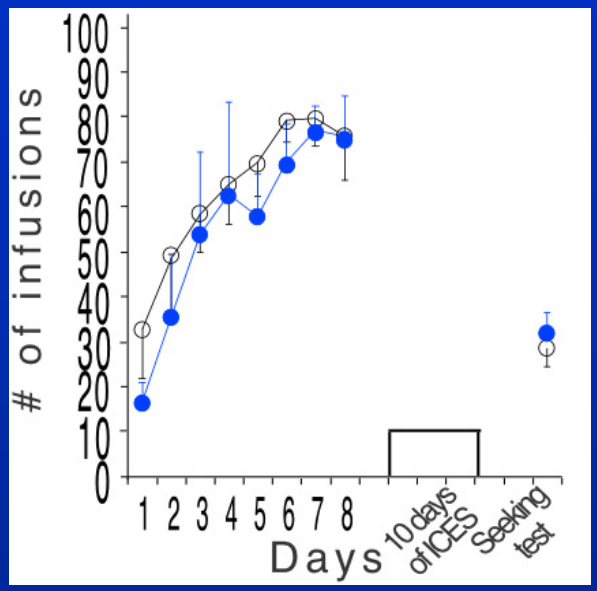
- This timing-dependent effect of stimulation on GluR1 together with the timing-dependent effect of stimulation on behavior suggest that stimulation parameters per se are not the only factors that direct the neurochemical and behavioral outcomes and that neuronal activity in the stimulated region affects the outcome of stimulation.



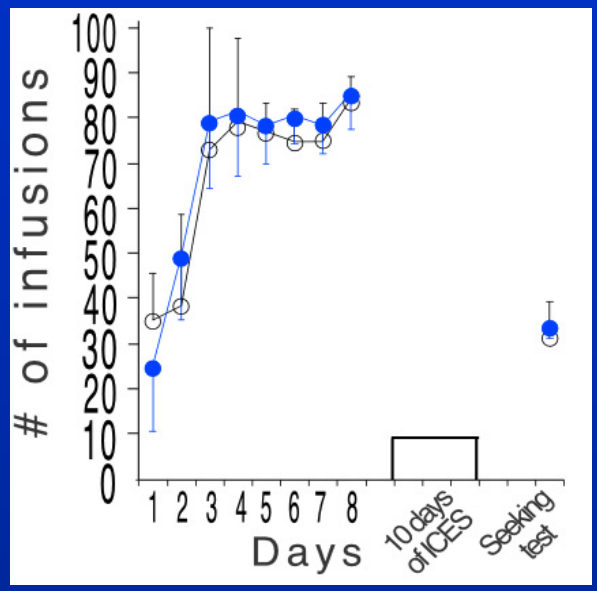
(Levy et al., JN 27:14179-89, 2007)

Effect of ICES on Sucrose Self-Administration – LH & PFC

Acquisition of Self-Administration



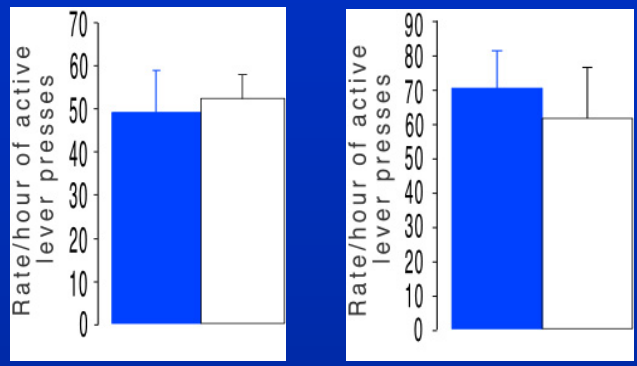
LH



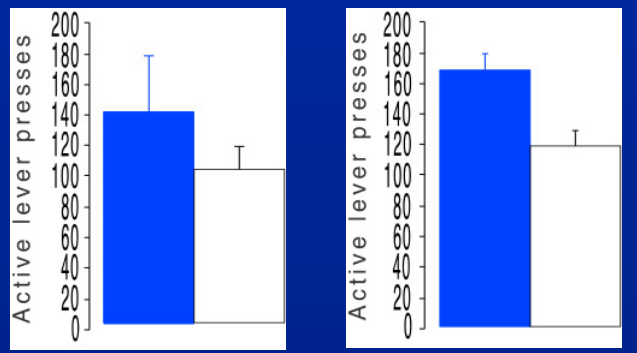
PFC

stimulated non-stimulated

Drug-Seeking Test (No Cocaine)



Progressive Ratio Test

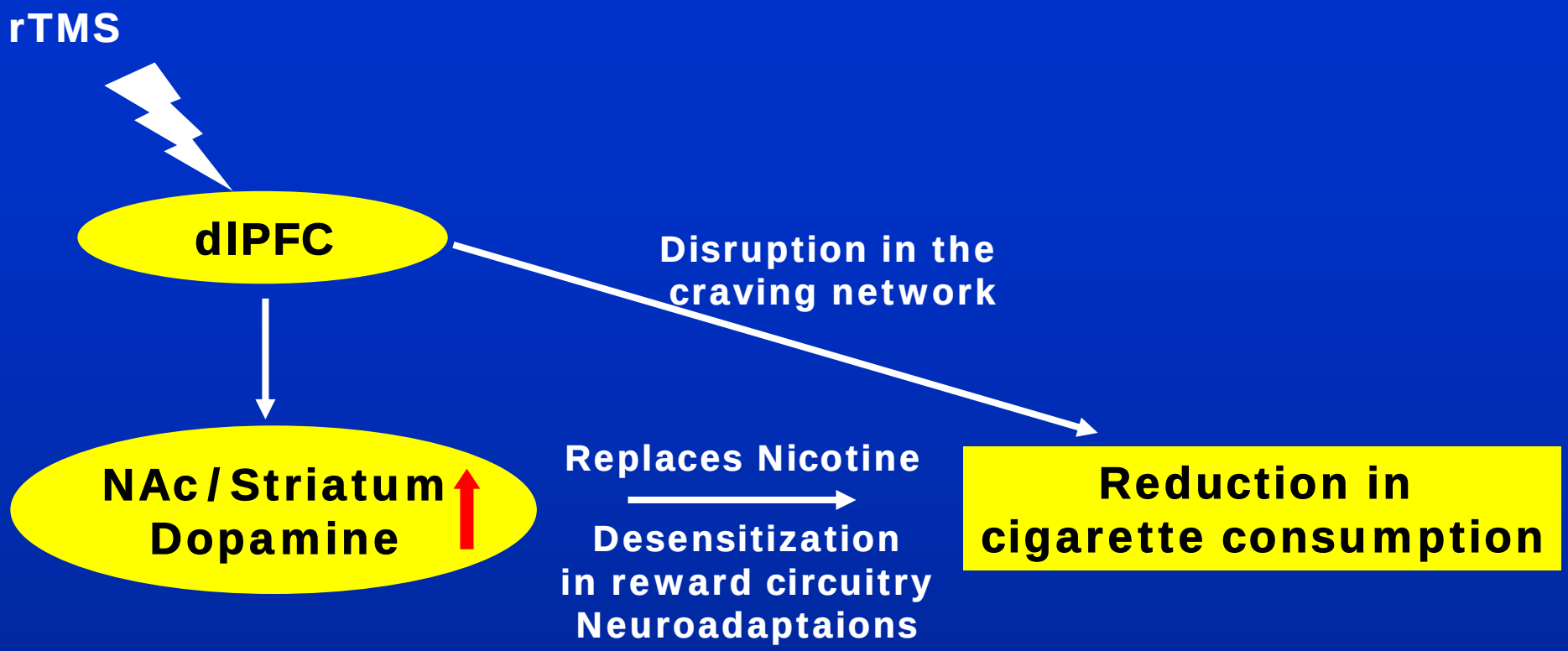


LH PFC

- No effect on sucrose consumption

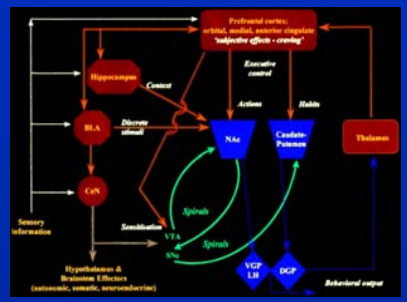
Levy et al., J. Neuroscience (2007)

Hypothesis


rTMS
dlPFC
Disruption in the craving network
NAc/Striatum Dopamine
Replaces Nicotine
Desensitization in reward circuitry Neuroadaptaions
Reduction in cigarette consumption

Hypothesis

Smoking related cues



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