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Addictive Brain

28th International Congress of the Medical Women´s International Association

Münster, 30th of July, 2010

Dr. Jana Wrase-Post

3 relapse models

1. stress induced relapse
2. re-exposure to the previously experienced drug (priming)
3. drug-cue induced relapse

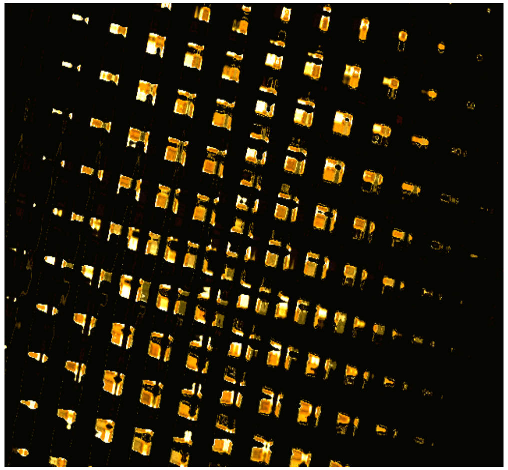
(Shaham, et al., 2000, Shalev et al., 2002, Weiss et al., 2000, Spanagel et al., 2008)

FMRI

Cue-reactivity

Experimentel Design

+



+

Block with 3 alcohol cues
(each picture 6.6 sec)

19.8 sec

ca. 10 – 20 sec

Block with 3 abstract cues
(each picture 6.6 sec)

19.8 sec

ca. 10 – 20 sec

Block with 3 affektive neutral cues
(each picture 6.6 sec)

19.8 sec

Reward System

dorsale Striatum | **anterior Cingulate (ACC)**

ventrale Striatum | **Orbitofrontale Cortex (OFC)** | **Amygdala**

Cocaine Seeking Habits Depend upon Dopamine-Dependent Serial Connectivity Linking the Ventral with the Dorsal Striatum

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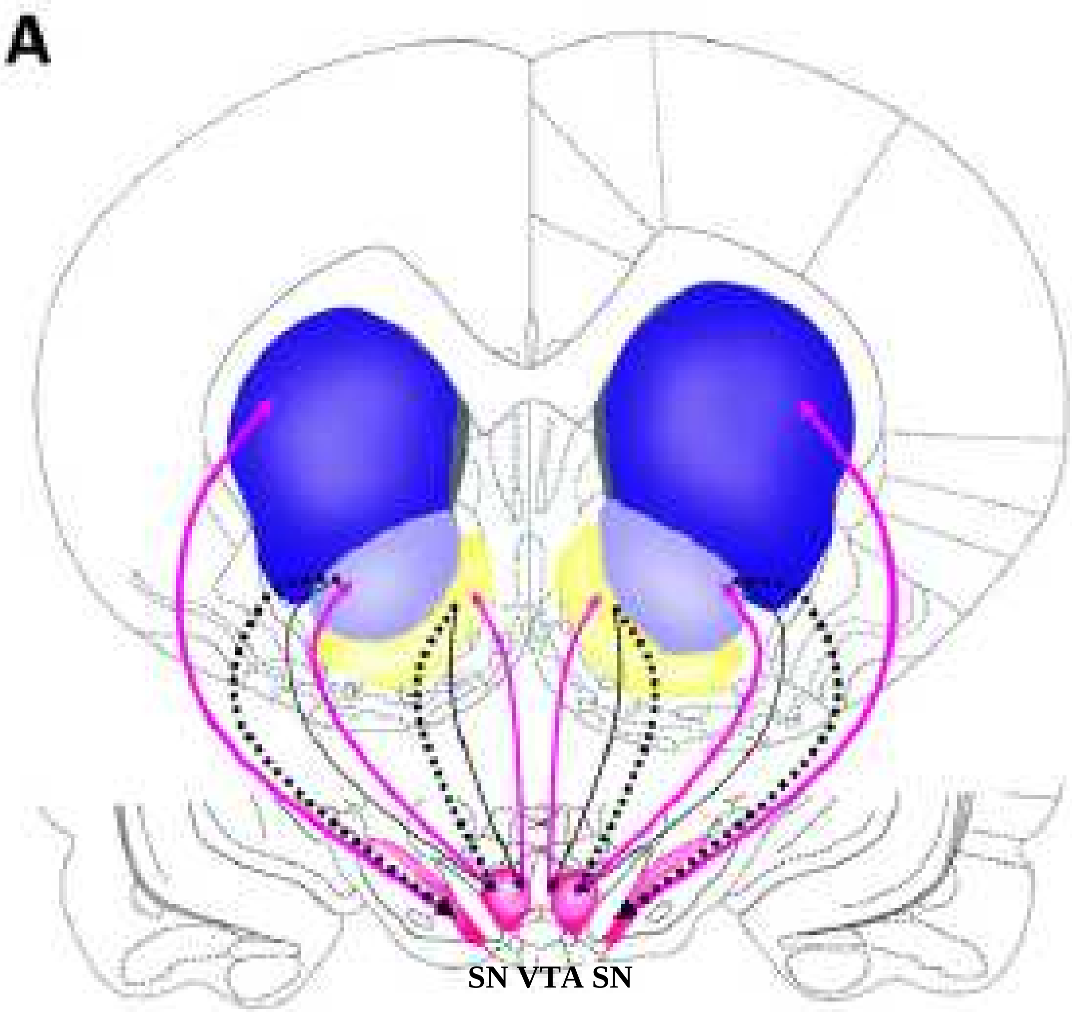

dorsale Striatum: stimulus-response learning (habit learning)

↑

ventrale Striatum: NAc core: classical conditioning

↑

ventrales Striatum: NAc shell: operant conditioning

Belin & Everitt, 2008; Neuron

DA Project

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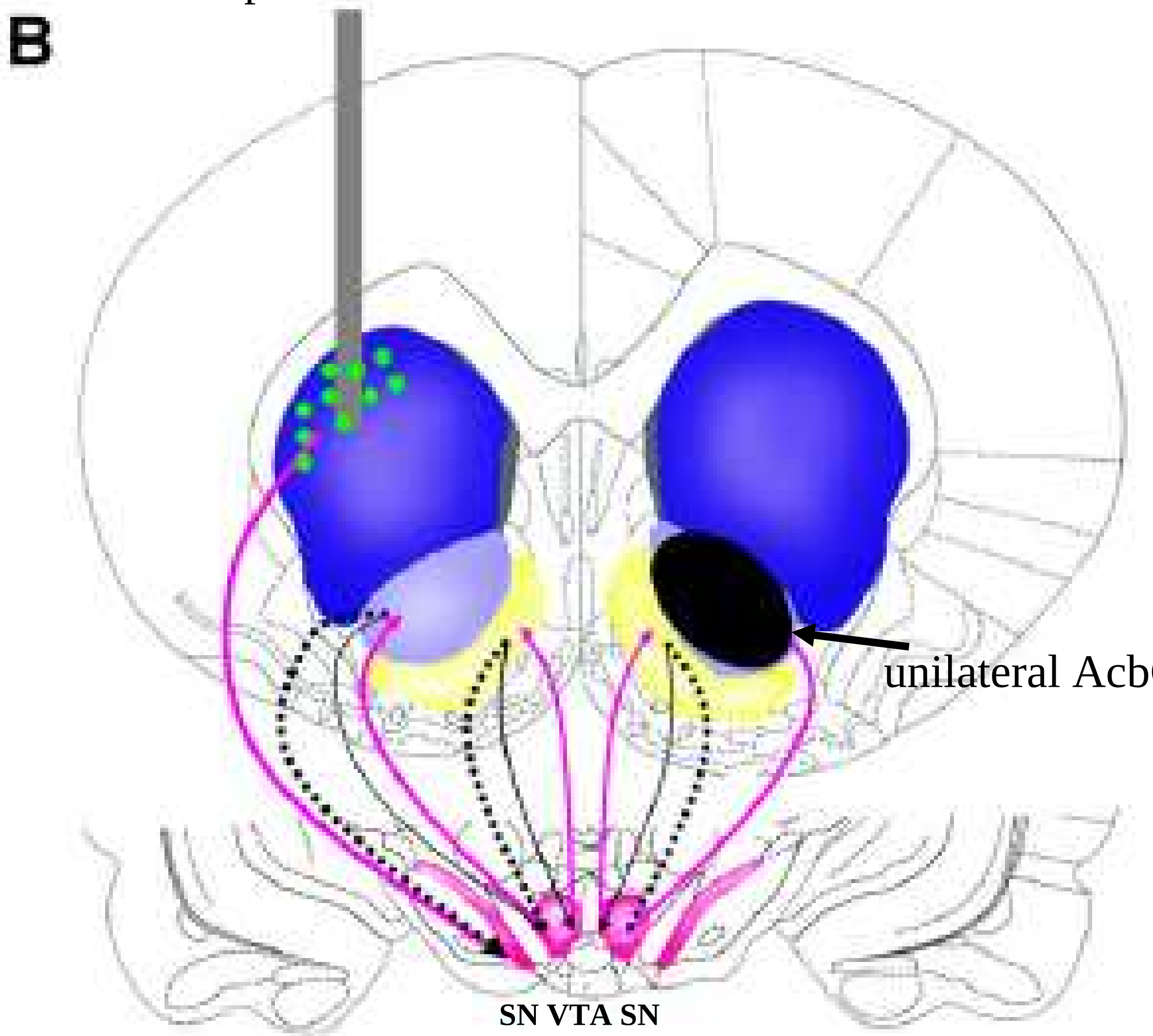

- lesion of NAc core and infusion of a dopamine receptor antagonist into the contralateral dorsolateral Striatum leads to
- disconnection,
- selectively decreasing drug-seeking Behavior

Belin & Everitt, 2008

Cue-induced Activation

- **Cocaine**

  Nac, OFC, ACC, Amygdala, dorsale Striatum

  (Kilts et al., 2004, 2001; Bonson et al., 2002; Wexler et al., 2001; Garavan et al., 2000, Childress et al., 1999; Wang et al., 1999; Maas et al., 1998; Grant et al., 1996)

- **Alcohol**

  Nac, OFC, ACC, Amygdala, dorsale Striatum

  (Gruesser et al., 2004; Tapert et al., 2004, 2003; Myrick et al., 2004; Wrase et al., 2002; Braus et al., 2001; Schneider et al., 2001; George et al., 2001; Modell & Mountz, 1995)

- **Heroin**

  OFC, ACC

  (Daglish et al., 2003, 2001; Soelch et al., 2001; Sell et al., 2000)

Increased activation in the dorsal striatum

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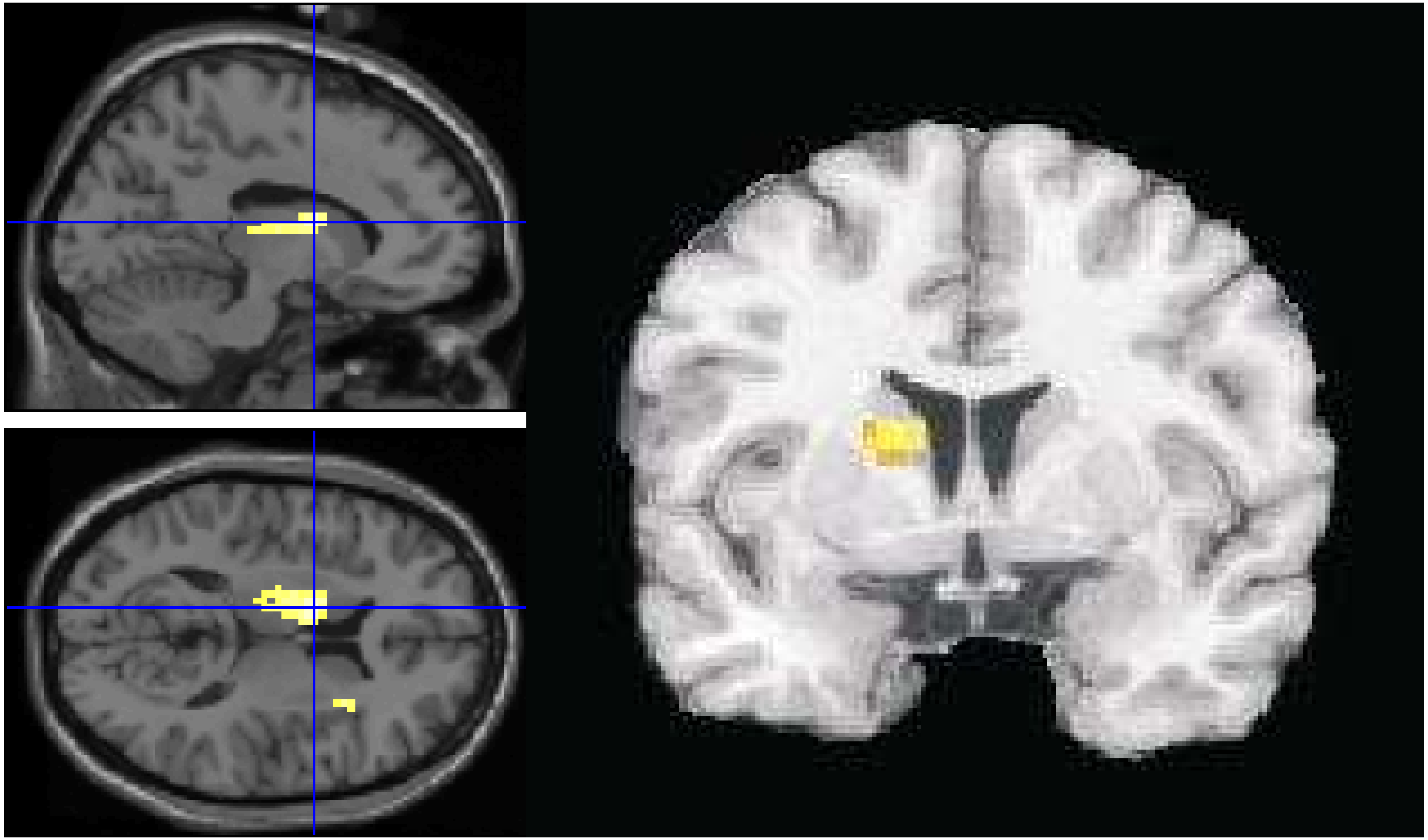
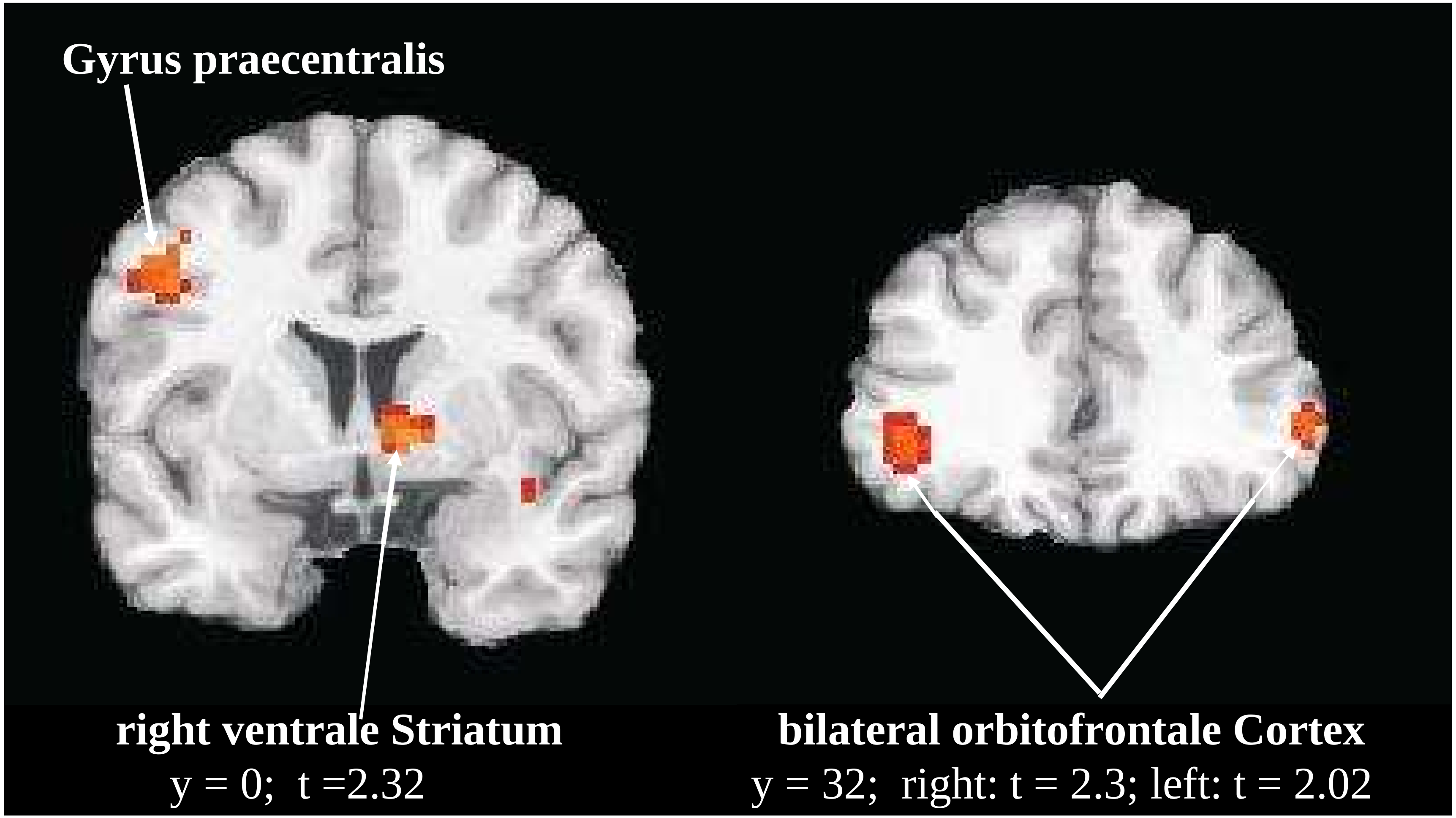
51 alcoholics (17 femals, 34 mals) > 52 healthy controls (20 femals; 32 males)



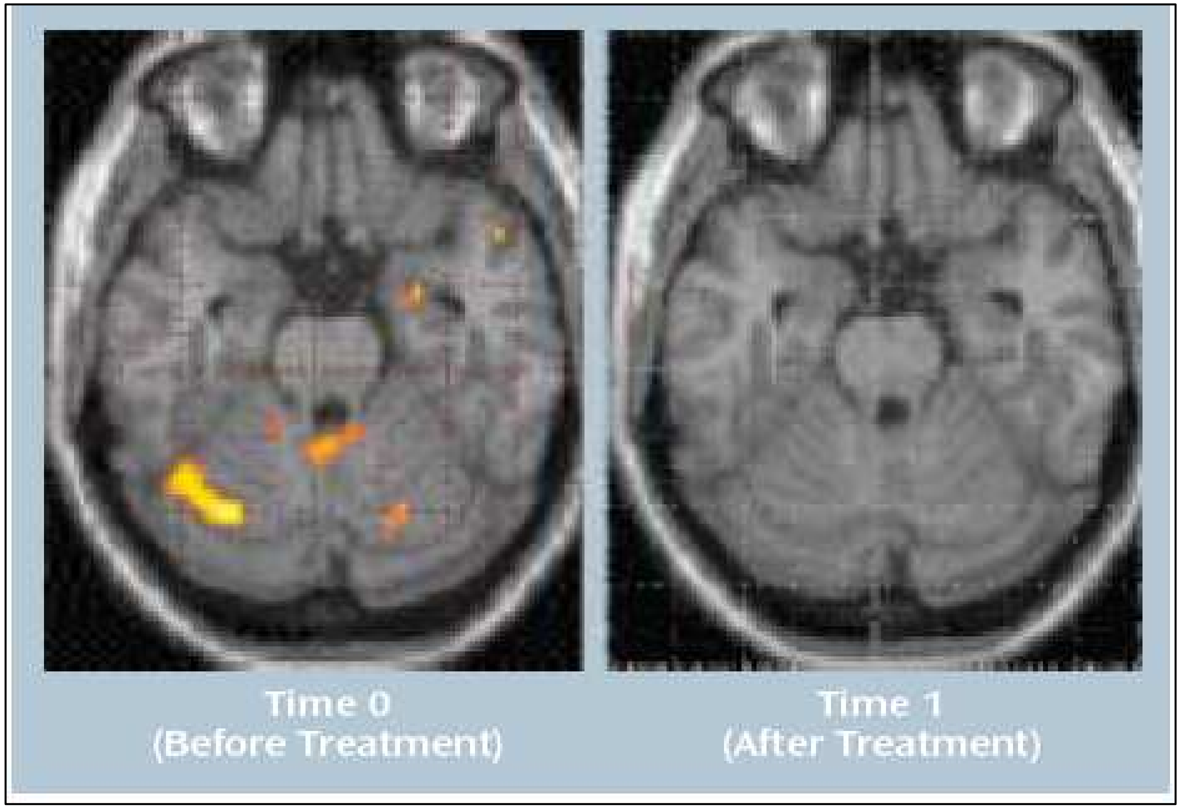
Wrase et al., in prep

Relapse

relapse > abstinent Patients



Amygdala Activation Before and After Treatment



10 abstinent alcohol depenent patients were olfactorely stimulated by ethanol before and after a 3week treatment consisting of 15 h goupttherapy and 150mg/d doxepin.

Schneider et al., 2001 AJP

monetary reward cues

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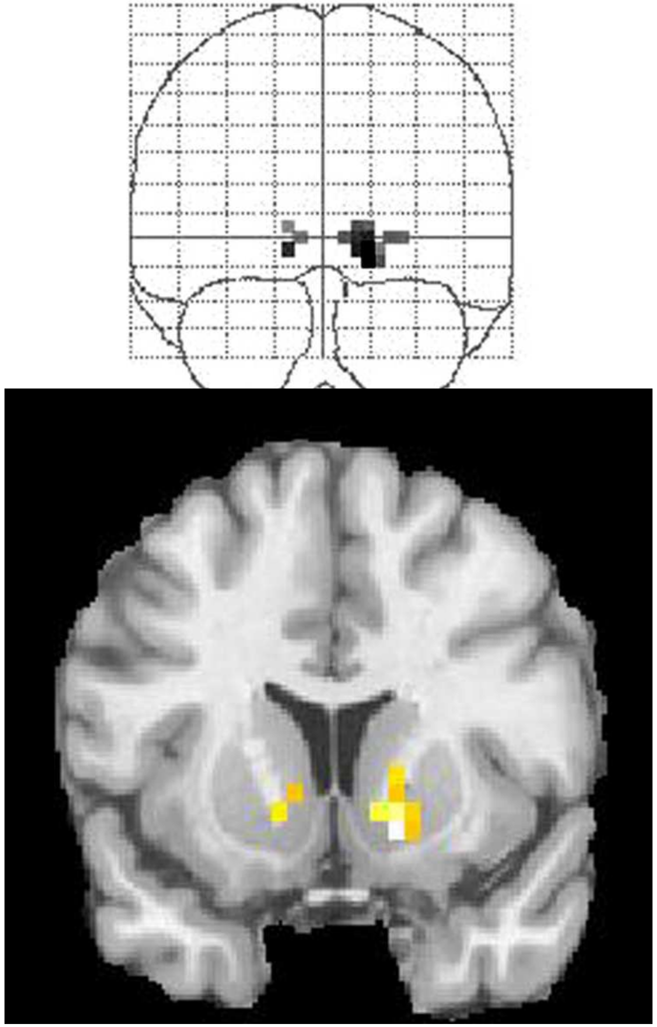
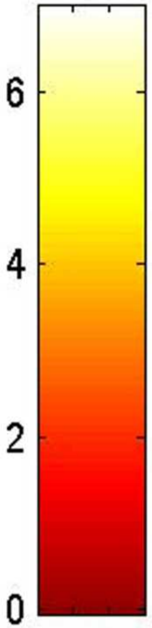
16 healthy male controls



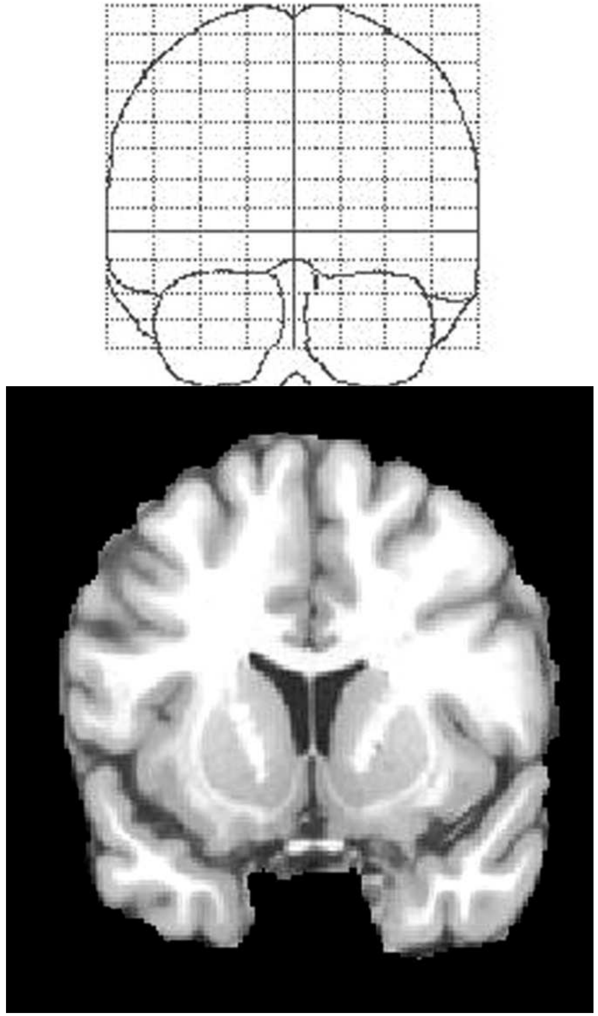
Stronger activity for anticipation of monetary gain vs. no gain



p = 0.001, k=3

Wrase et al., 2007; Neuroimage

16 alcoholdependent, abstinent, male patients



Reduced activity for other reinforcers

• Garavan et al., 2000: increased activity for dorsal striatum & ACC for **cocaine** video > sex video

• Martin-Soelch et al., 2001: reduced activity in the striatum in **smokers** compared to non-smoker for monetary and nonmonetary reinforcement

• Goldstein et al., 2007: reduced activitiy in DLPFC, OFC, Thalamus for monetary reward in **cocaine** addicts

Protective Factor

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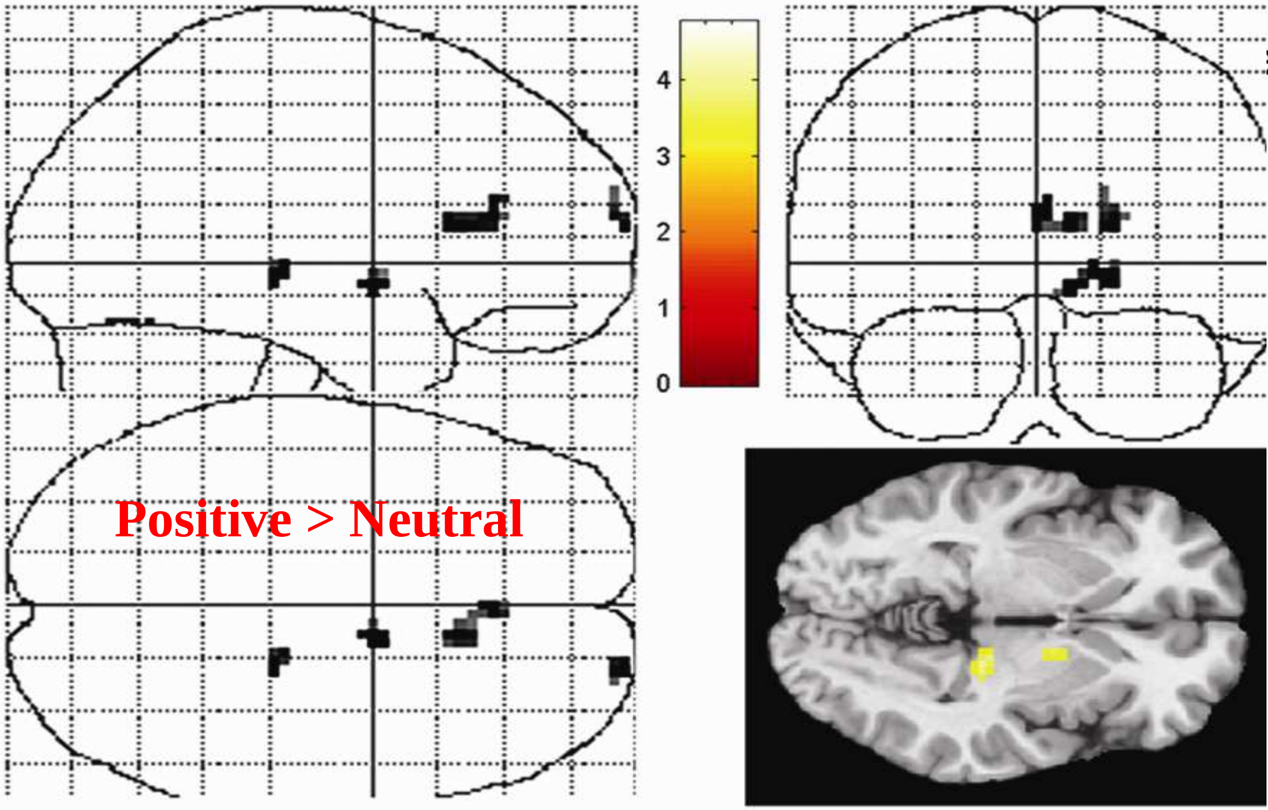
alcoho
750 n



ıutral cue
750 ms

Heinz, Wrase et al., 2007

Conclusion - fMRI

- Increased activation for dug-associated cues
- correlates with Relapse
- reduced activation for non-drug associated cues
- can be influenced by treatment.

Emotional Gender differences in brain activation

Erotic pictures: (Karama et al., 2002; Hamann et al., 2004; Salloum et al., 2004)

Positive and negative pictures (Domes et al., 2010, Wrase et al., 2003)

Sad faces (Lee et al., 2002, Schneider et al., 2000, Derntl et al., 2010)

Antizipation of pain: (Butler et al., 2005)

Hunger (Del Prigi et al., 2002, Smeets et al., 2006, Cornier et al., 2010)

Smell pheromones Savic et al., 2001, Garcia-Falgueras et al., 2006)

Chokolate taste: (Smeets et al., 2004, 2006)

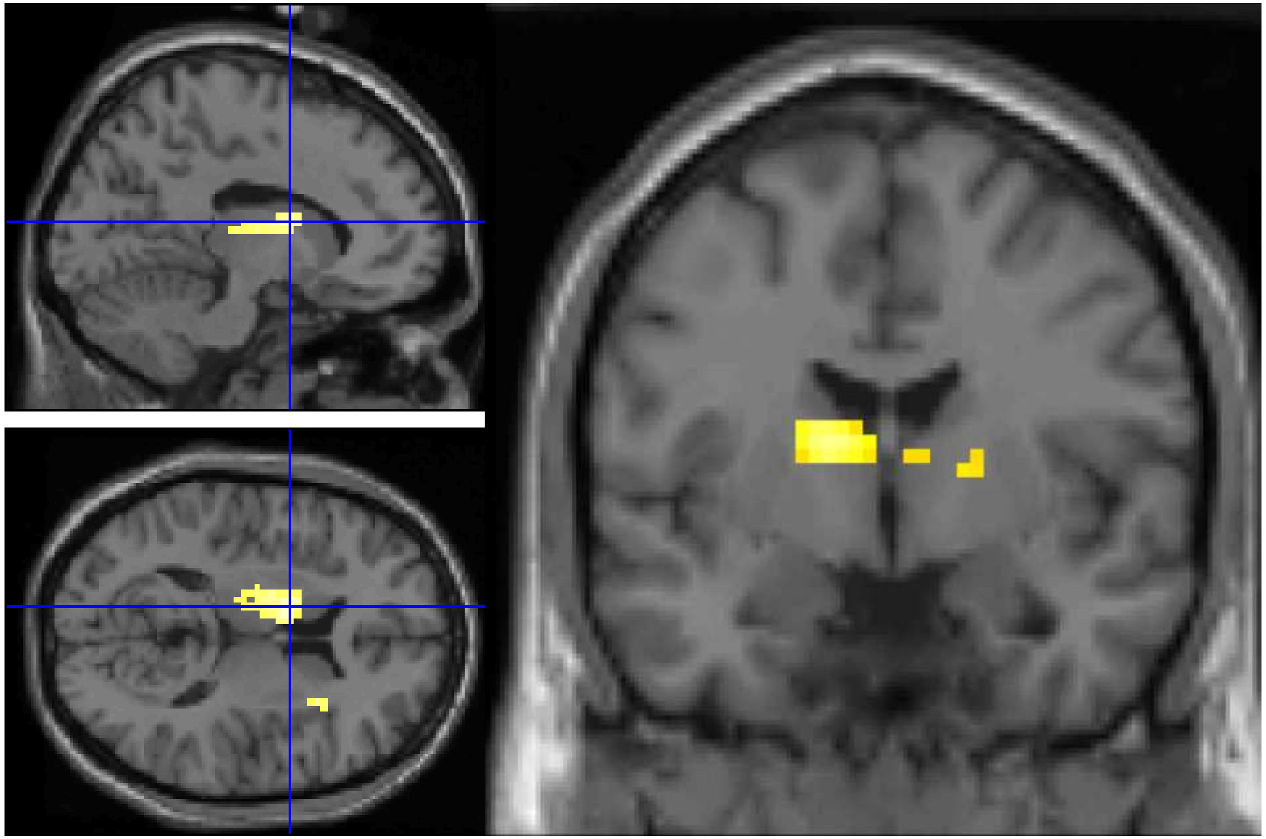
Music: (Nardo et al., 2004)

Humor: Cartoons (Azim et al., 2005)

Reappraisal of negative emotions (Domes et al., 2010)

Empathy (Derntl et al., 2010)

Nucleus caudatus



Men versus Women: Alcohol > controlpictures Patients > Controls

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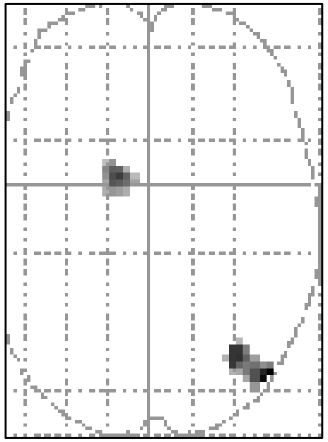
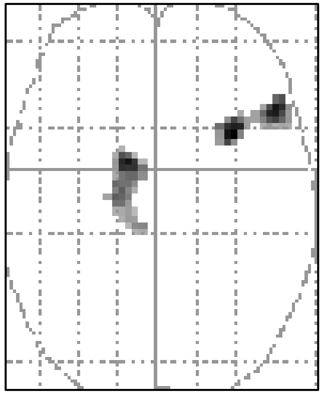
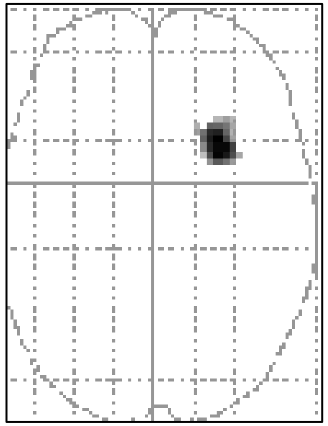
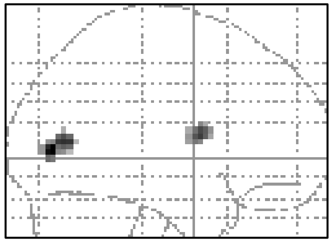
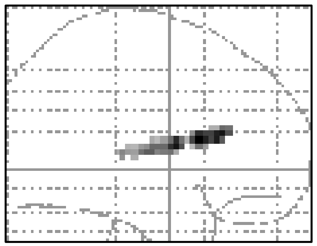
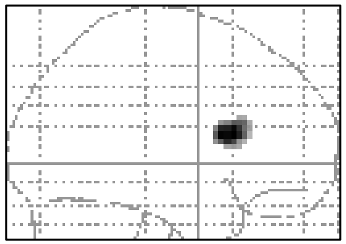
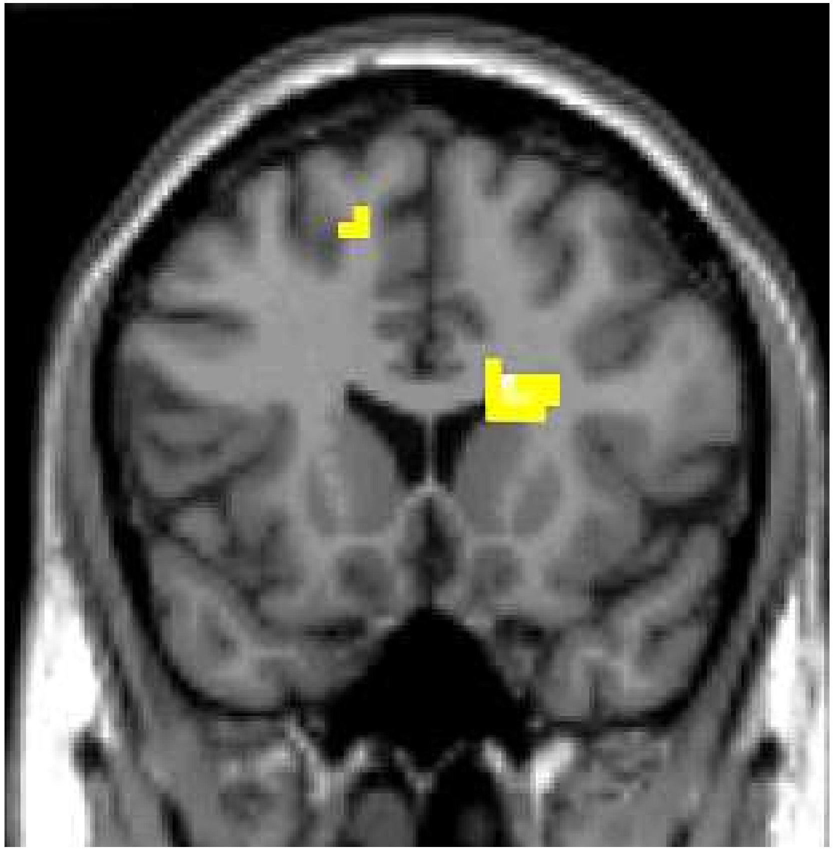
men | **whole sample** | **women**

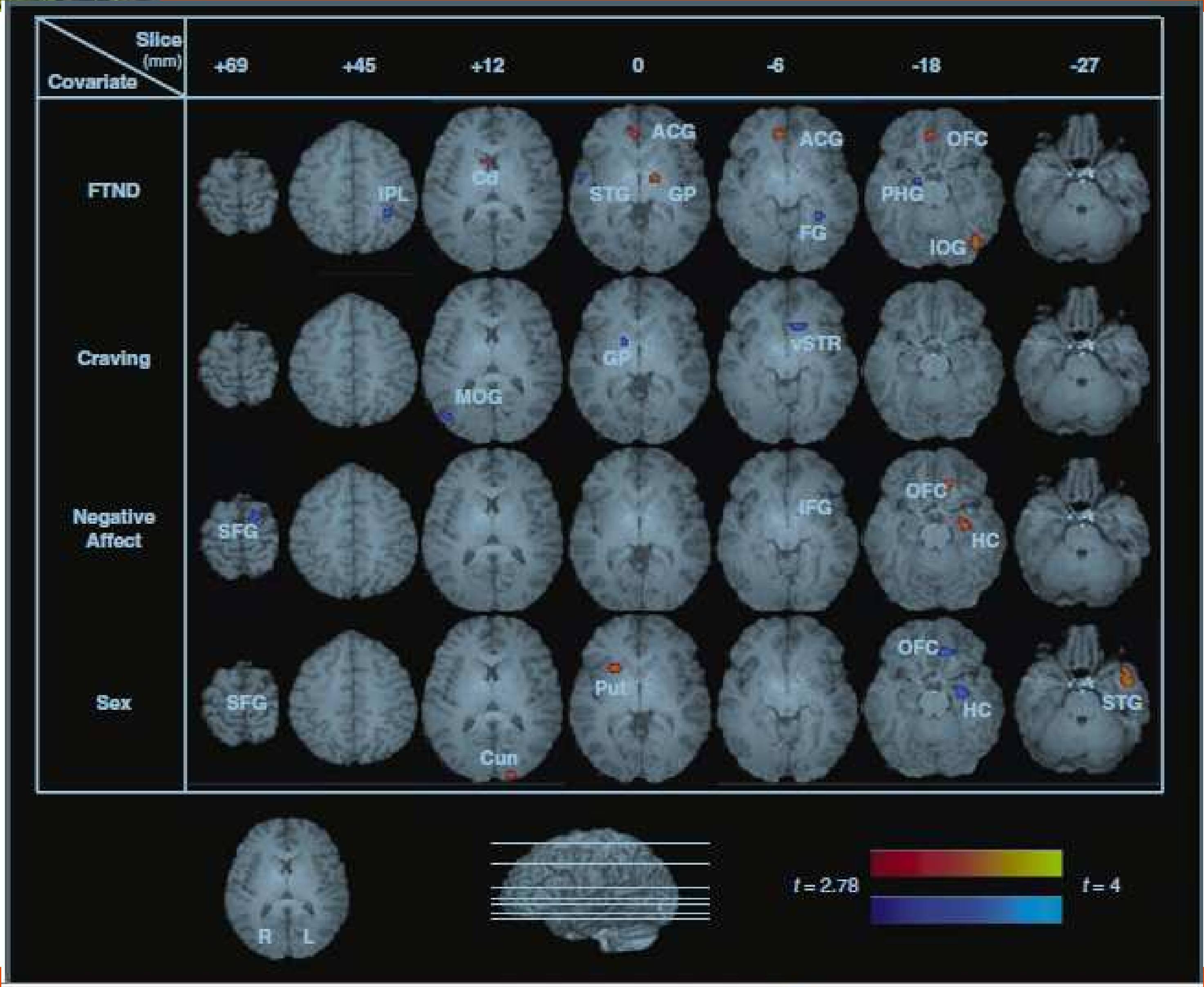







Alcohol > Controlpictures

alcoholdependent women > alcoholdependent men



Smoking cues



McClernon et al., 2008

23 women > 7 men

Differences in brain activation during gambling

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(b) *Game > Control Contrast*									
Males > Females									
Frontal	Left	Orbitofrontal cortex, gyrus rectus	11	−34	34	−10	3.69	0.001	115
	Right	Orbitofrontal cortex	10	18	44	−7	3.72	0.001	375
Sub-lobar	Right	Nucleus accumbens		8	9	−10	2.70	0.007	17
		Amygdala	38	30	−3	−22	2.76	0.006	29
Females > Males									
n/a									

Hoeft et al., März 2008

Conclusion II:

- Gender differences in brain activation towards drug associated cues needs to be considered

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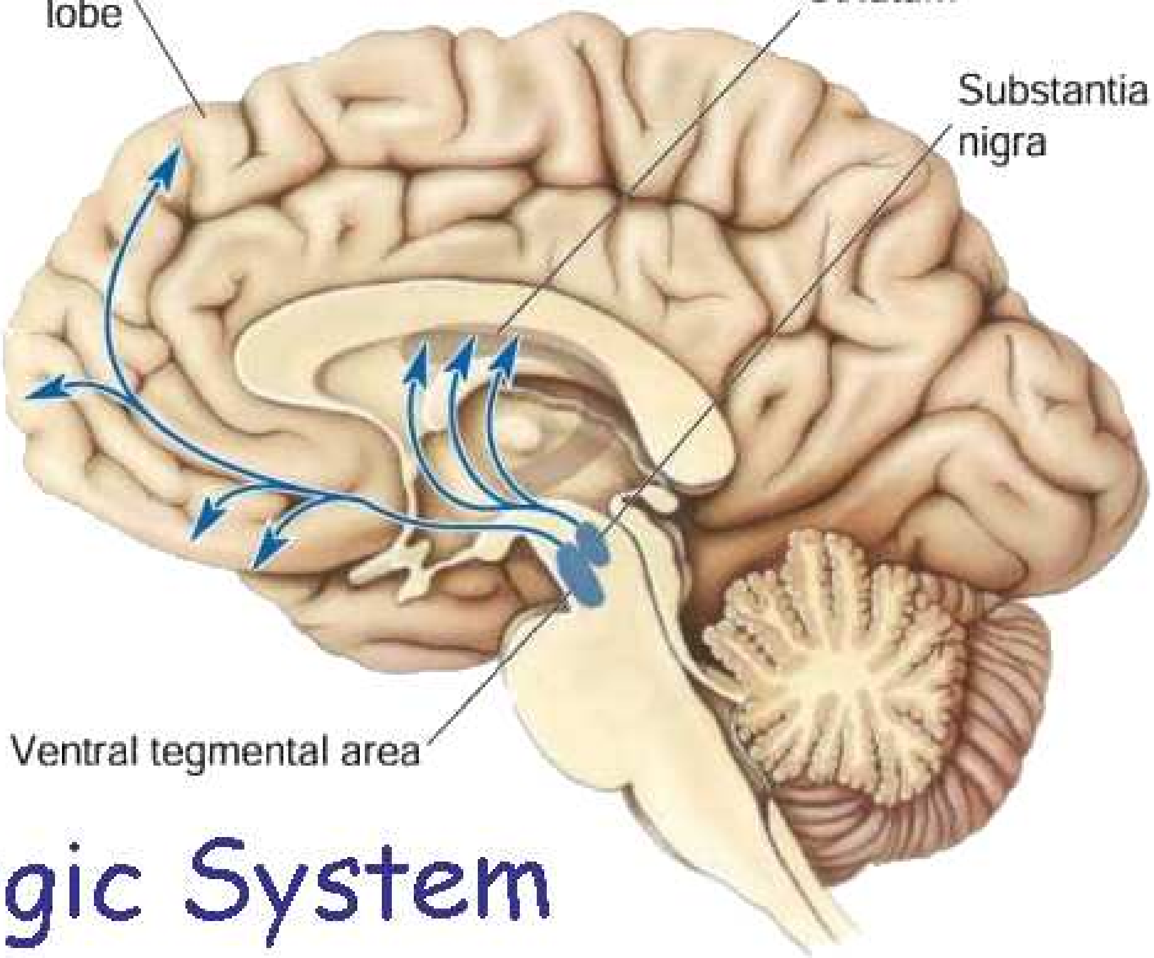
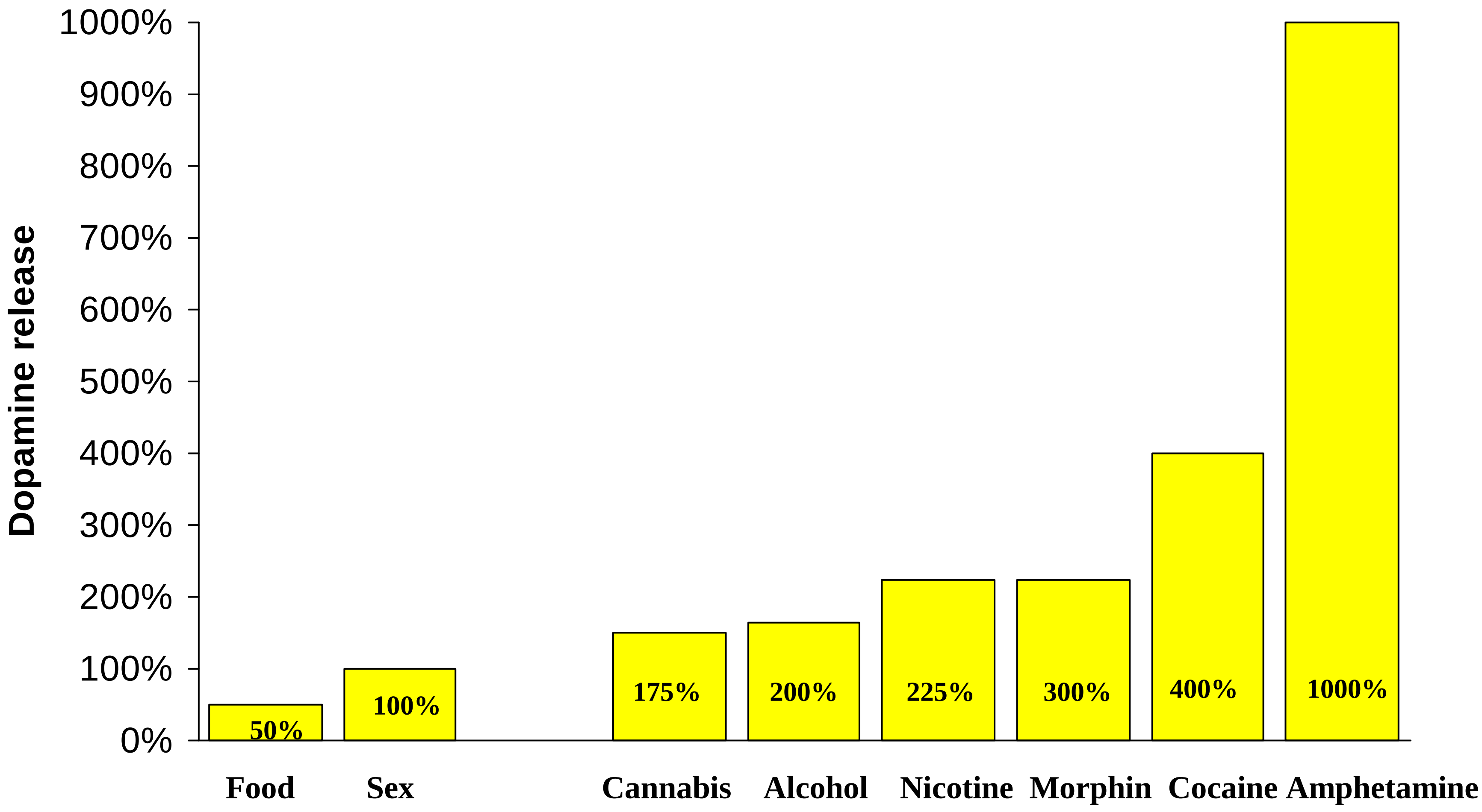
Dopamine (DA) released from the ventral tegmental area

Reward, reinforcement, working memory



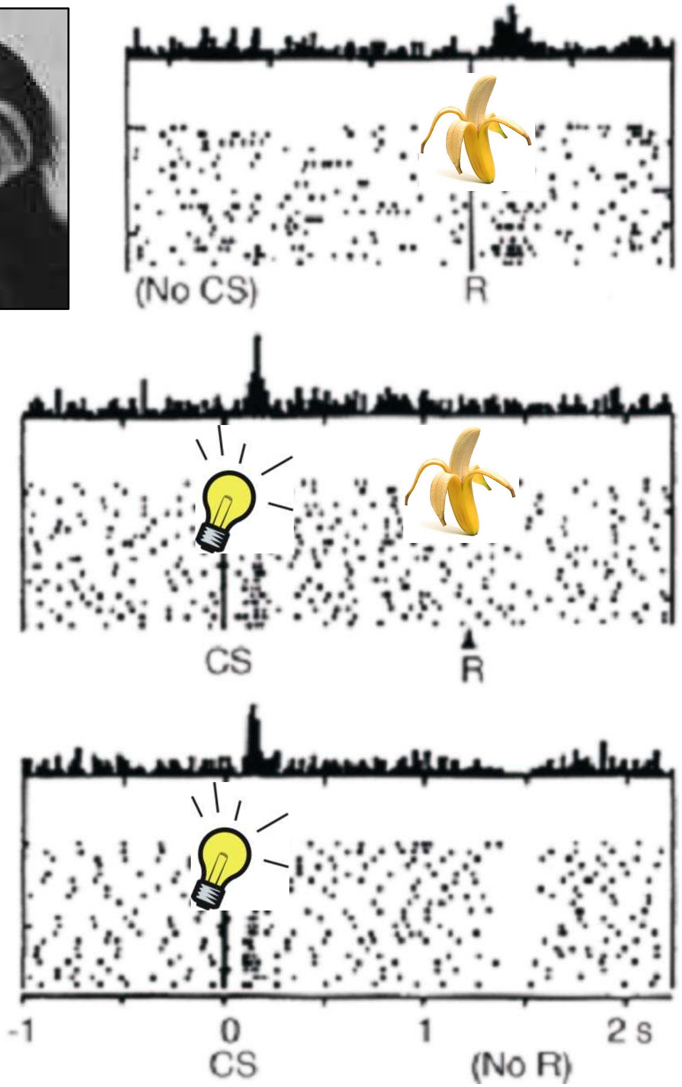
Dopaminergic System

Dopamine and drugs



(Wise, 2000)

Dopamin



Keine Vorhersage
Auftreten von unerwarteter Belohnung (R)

Vorhersage (CS)
Auftreten von erwarteter Belohnung (R)

Vorhersage (CS)
Ausbleiben von erwarteter Belohnung

Schultz et al., 1997 Science

Additional spines due to cocaine

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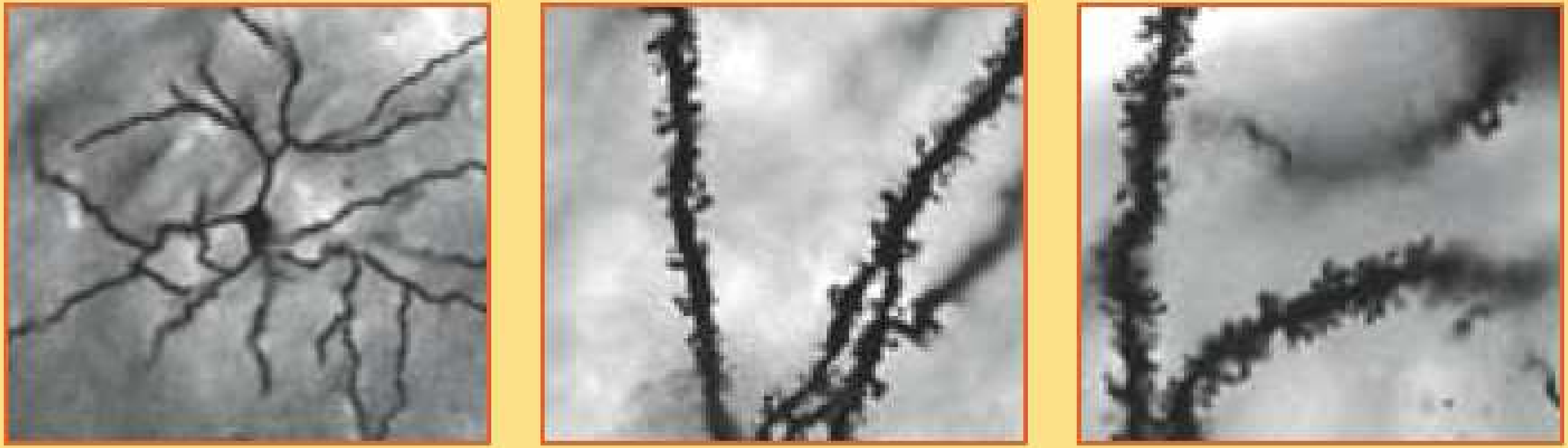

MICROGRAPHS of nucleus accumbens neurons in animals exposed to nonaddictive drugs display dendritic branches with normal numbers of signal-receiving projections called spines (*left* and *center*). But those who become addicted to cocaine sprout additional spines on the branches, which consequently look bushier (*right*). Presumably, such remodeling makes neurons more sensitive to signals from the VTA and elsewhere and thus contributes to drug sensitivity. Recent findings suggest that delta FosB plays a part in spine growth.

Amphetamine caused DA-Disbursement is conditionable

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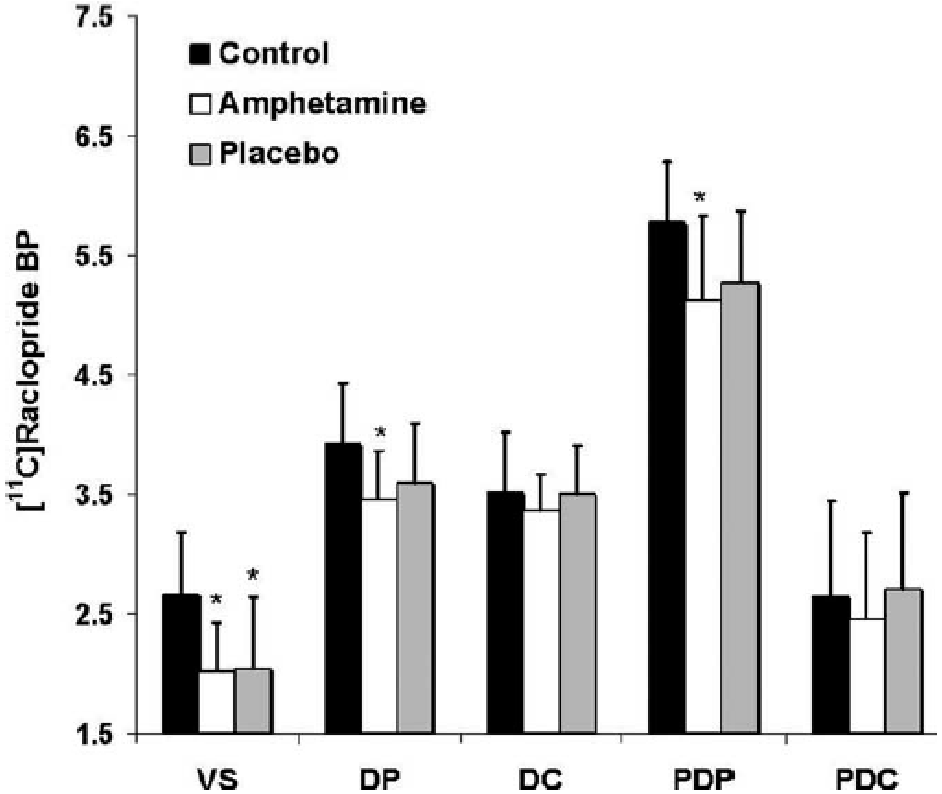
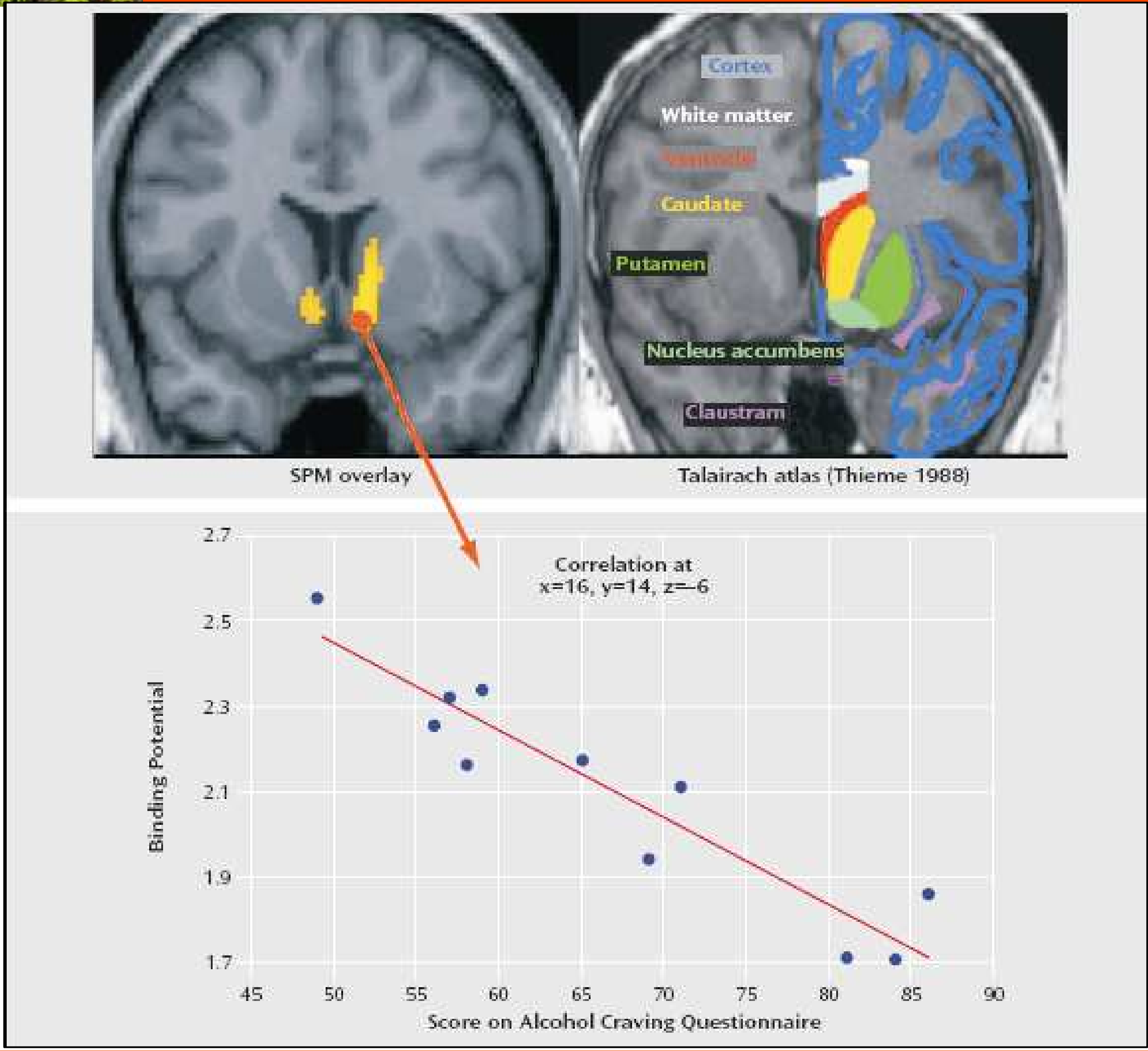


- n = 9 healthy men
- received Dextroamphetamine 0,3 mg/kg PET on three separate occasions every other day in the Scanner (Raclopride)
- after 2 weeks > Placebo
  - ➢ 22% reduction of raclopride in the ventrale Striatum under Dextroamphetamine
  - ➢ 23% reduction of raclopride under Placebo!!!
  - ➢ Amphetamine and contextual cues increase DA-Release almost in the same way

Boileau et al., 2007; JNS

Decrease of D2 receptors



Heinz, et al., 2005, AJP

Negative correlation between D2-receptor availability and cue-induced brain activation

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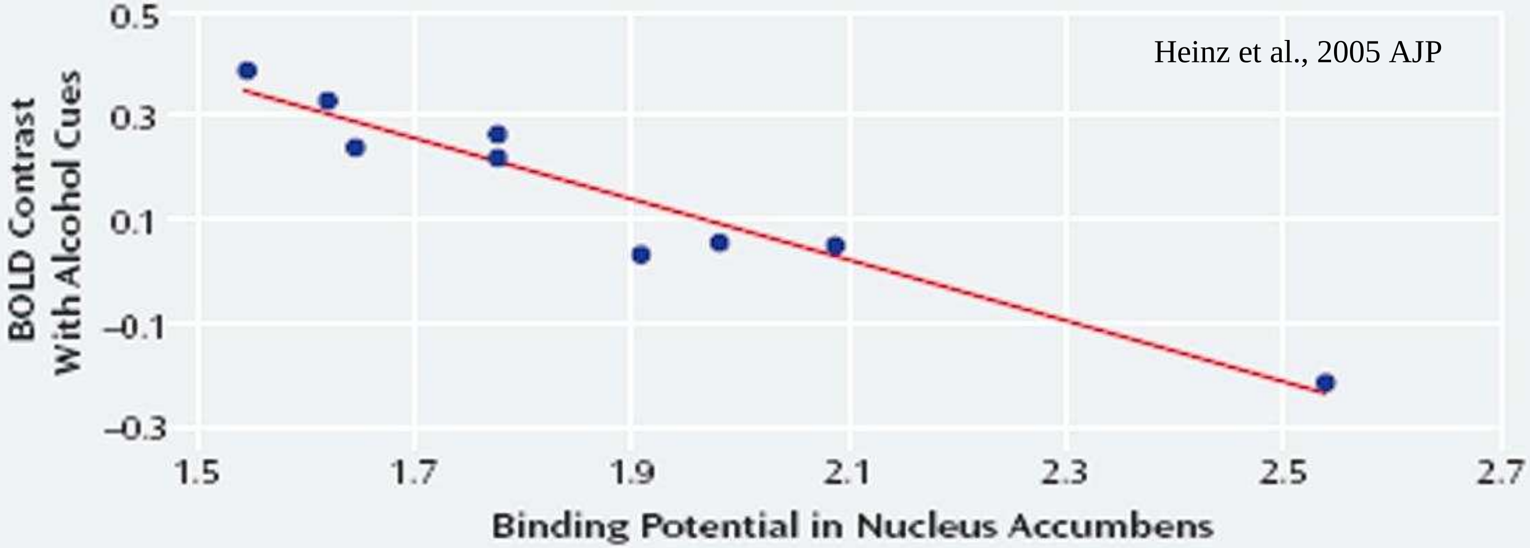
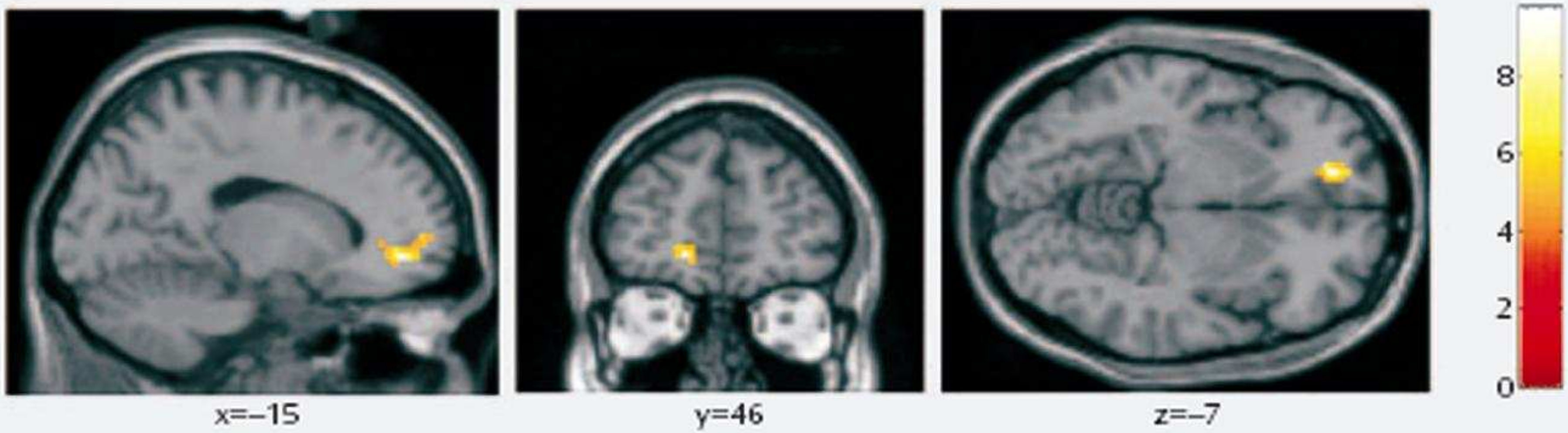
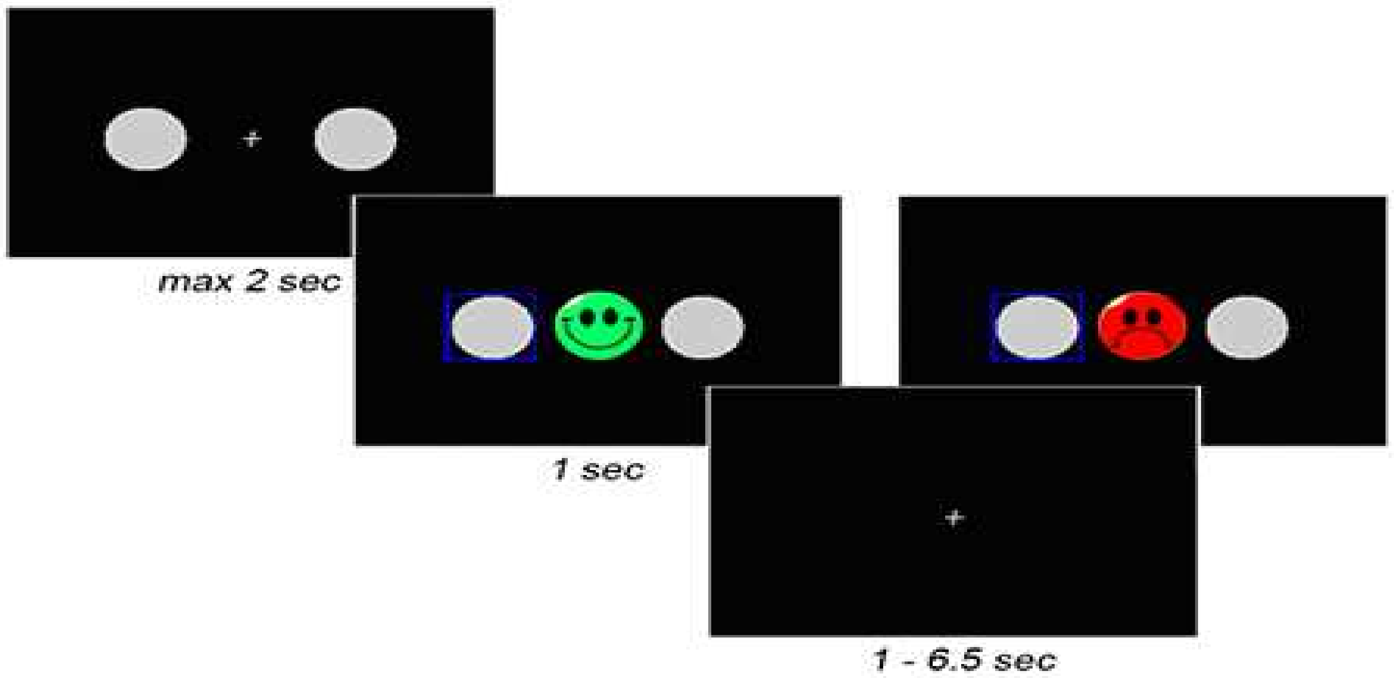




Reversal learning paradigm

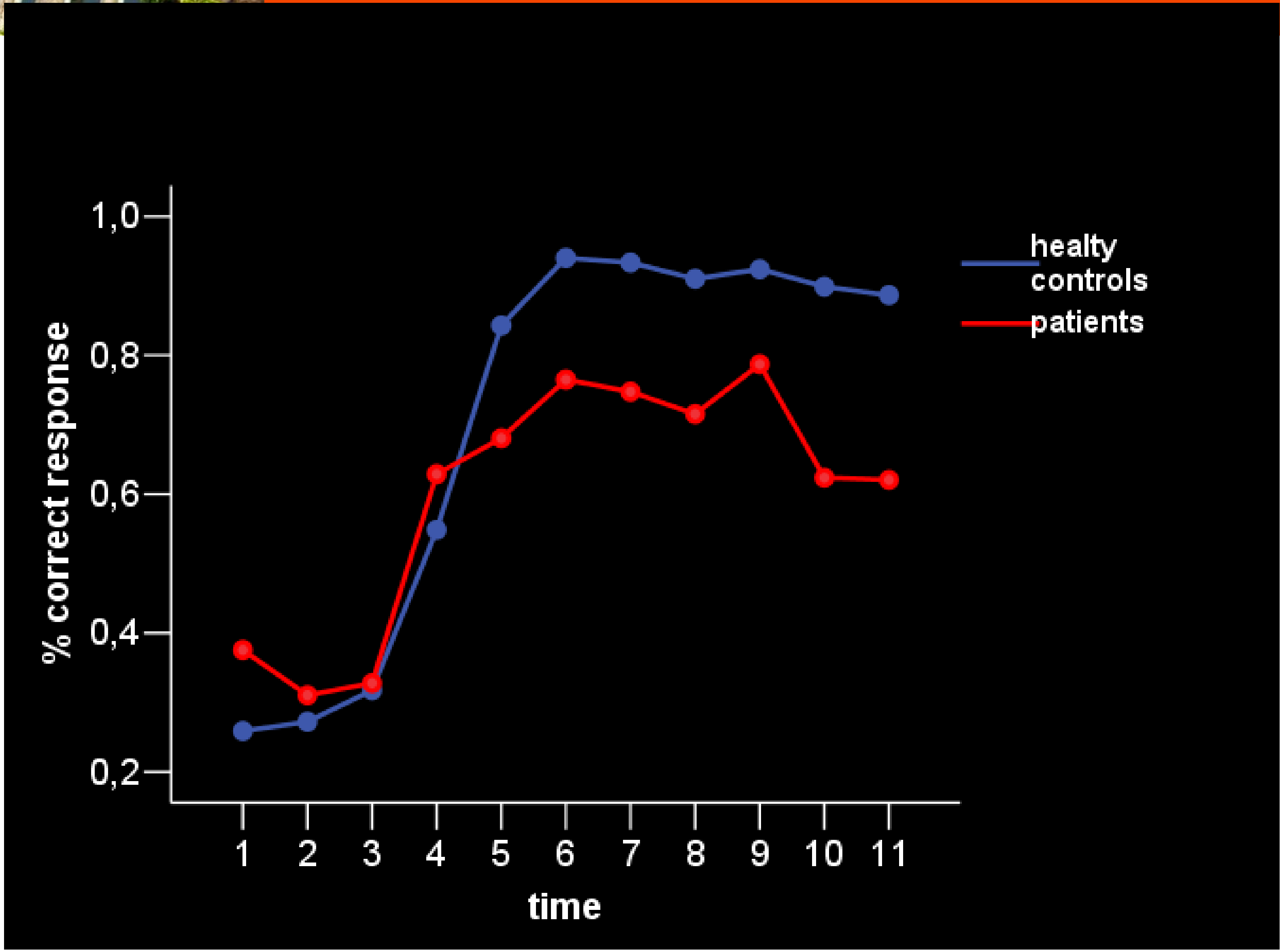


2 runs * 100 trials

6 – 10 conditions per run

Park, …Wrase, 2010

Verringerte Fähigkeit des Umlernens bei alkoholabhängige Patienten



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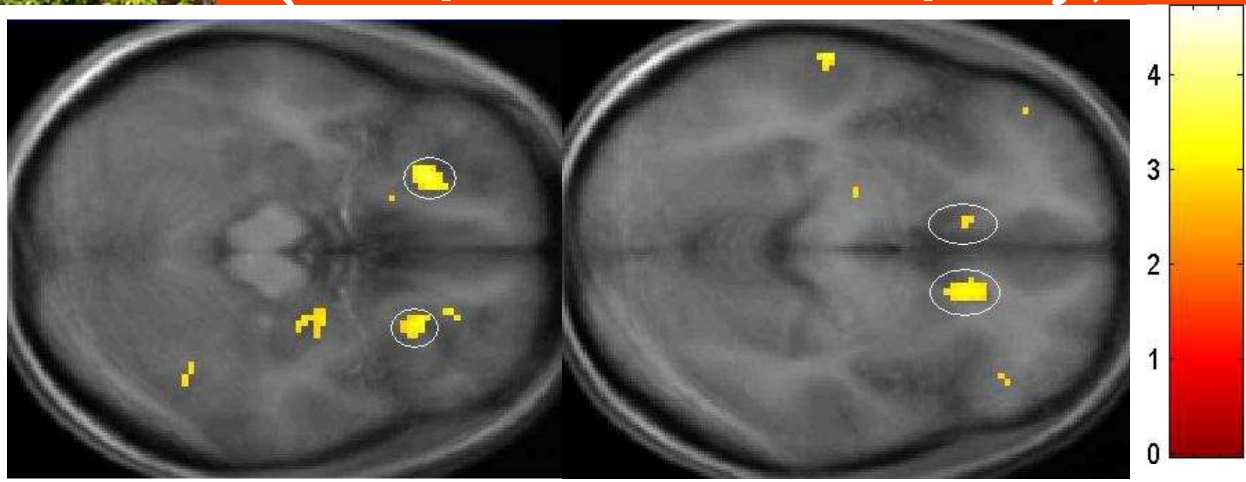
fMRI Analyses
(Loss/switch > Loss/stay) in

P < 0.005



Bilateral Orbitofrontal Cortex

z = -18

Bilateral Caudate Head

z = -6

Alcohol dependent patients show reduced activation during decision adjustment in OFC & Caudate

> Patients are impaired in reward learning

Park, …Wrase, Heinz, 2010 JNS

Dopamine and Relapse

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- Dopamine is critical for acute reward and initiation of addiction

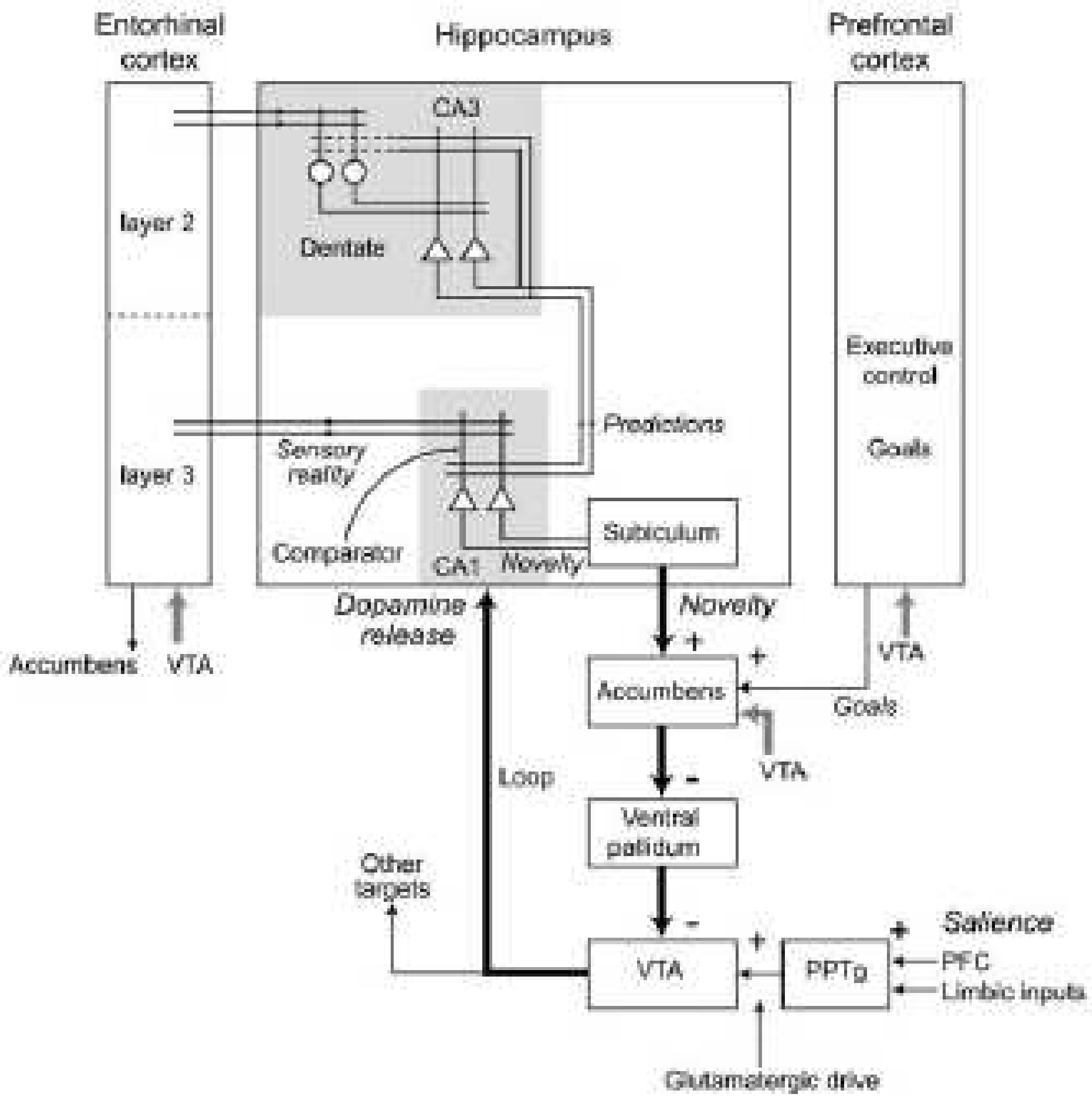
- Maintenance of addiction results primarily from cellular adaptations in anterior cingulate and orbitofrontal glutamatergic projections to the nucleus accumbens.

Kalivas & Volkow, 2005

DA and addiction memory

- DA ensures that long-term plasticity cannot occur unless it is behaviorally advantageous
- without DA late LTP does not occur and early LTP decays wihtin about an hour

Lisman & Grace, 2005



once only administration

- Induction of LTP in dopamine neurons due to:
  - cocaine
  - amphetamine
  - nicotine
  - morphine
  - ethanol

  (Saal et al., 2003, Ungless et al., 2001)

- Induction of LTD on GABAergic synapse in the VTA by Ethanol (Melis et al., 2002)

Conclusion

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- Drugs lead to increased DA-Disruption which is conditonable
- This Conditioning is increased under stress (Piazza et al., 1990)
- Dopaminergic Dysfunction > reduced D2-Receptors
- correlates with Craving,
- and increased cue-induced activation in OFC and ACC
- and reduced activation during rest,
- which reduces the inhibitory control
- and causes loss of control and automatic drug consuming behavior
- and that´s why correlates with relapse

Conclusions for Treatment from imaging data

a) Salience reduction of drug- and drug cues
b) Salience increase of other reinforcers
c) Reduction of stress
d) Reduction of conditioned and automatic behavior
e) Increase of inhibitory and executive prefrontal control

Pharmacological Intervention: *Neuroleptics*

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- Since neuroleptica diminish unspecifically the processing of all reward indicating cues and lead to an overall reduction in motivation – they are not adequate for treatment in addiction

- Cue exposure therapy can help to „unlearn“ automatic relapse inducing behavior

Cue exposure

- extinguishing these cue memories has not proven to be effictive in reducing relapse in either humans (Conklin and Tiffany, 2002) or rats (Crombag and Shaham, 2002)

Why?:

- highly context-dependent nature of extinction.
- When extinction of the drug-associated cue occurs in the treatment facility the conditioned responses to the cue (e.g., increased heart rate; craving) may be reduced, but it is unlikely that these effects will transfer to the drug-taking environment.
- In animal models, extensive extinction training in a non-drug taking context of both the instrumental response and either a discriminative stimulus (SD) or discrete cue (CS+) associated with drug, does not significantly reduce renewal of drug-seeking (Kearns and Weiss, 2007; Crombag and Shaham, 2002; Crombag et al., 2002).
- Cue exposure in the drug-taking environment is less practical, but may be more efficacious than extinction in a rehabilitation facility.
- There is one report of cue exposure in an immersive virtual reality environment, which was more effective in eliciting conditioned responses than traditional slides or videos, and may therefore be a more effective way of achieving effective cue extinction within a rehabilitation setting (Kuntze et al., 2001)

Taylor et al., 2008

Cue-induced relapse prevention

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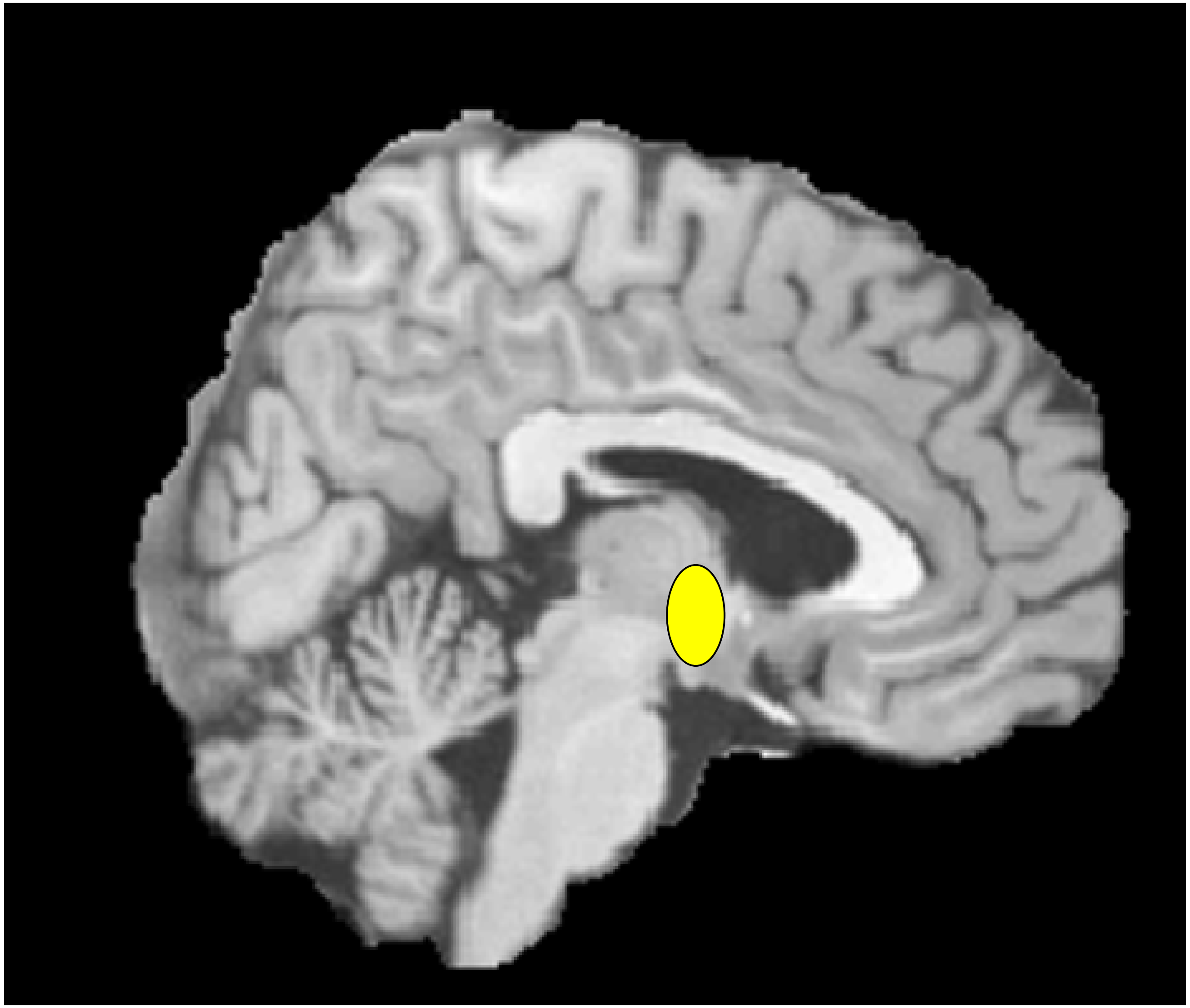
- mechanisms that subserve cue-induced relapse to drug-seeking are associated with drug-induced adaptations in DA/glutamate-regulated signaling cascades
- a promising approach would be to

1) enhance cue extinction learning with agents that are known or predicted to have mnemonic effects,
2) extinguish cues in multiple contexts to reduce the context-dependency of extinction,
3) alter contextual processes that depend on the hippocampus,
4) inhibit reconsolidation, and finally,
5) do a combination of the above

(Taylor et al., 2008; *Neuropharmacology*)

Speculation: Before Psychotherapy



Speculation: After Psychotherapy

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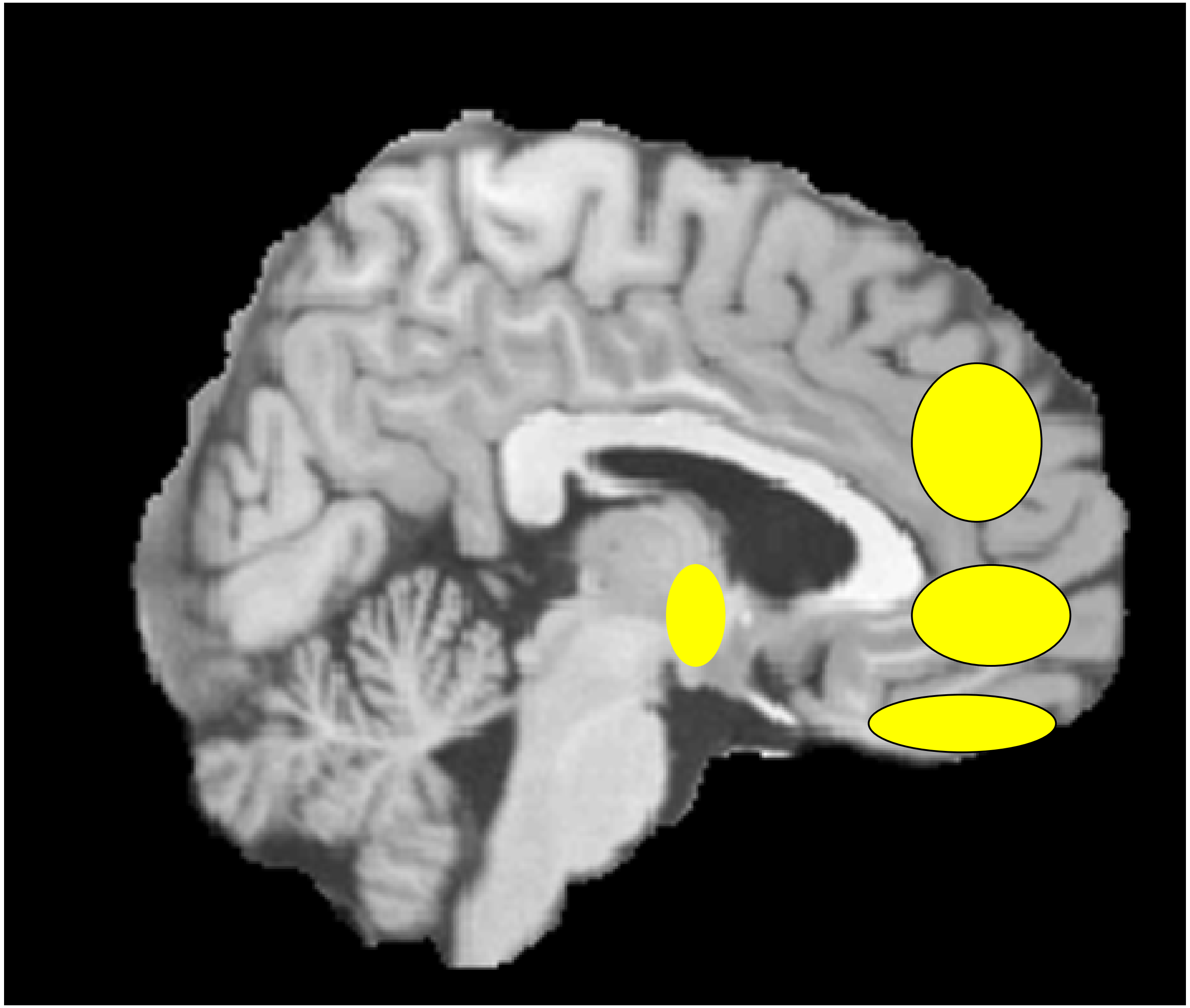

Thank you for your attention and to:

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