Brain imaging in recreational users of MDMA/psychedelics

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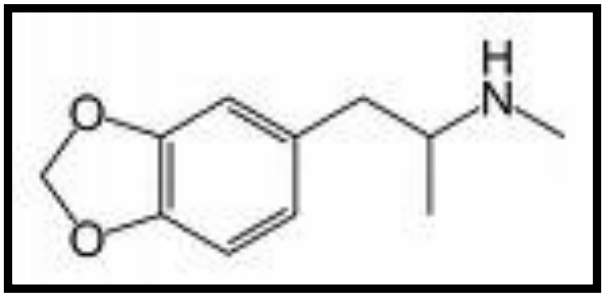
Ecstasy and hallucinogens; measurement of *in vivo* serotonergic brain markers

Proportion of 16 to 59 year olds in UK reporting use of MDMA and hallucinogens during the last year (British Crime Survey 2009):

- MDMA: 1.8%
- Hallucinogens: 0.6%

MDMA: Neurocognitive deficits in humans and neurotoxicity in animals.
(reviews: Baggott 2001, Kalechstein 2007)

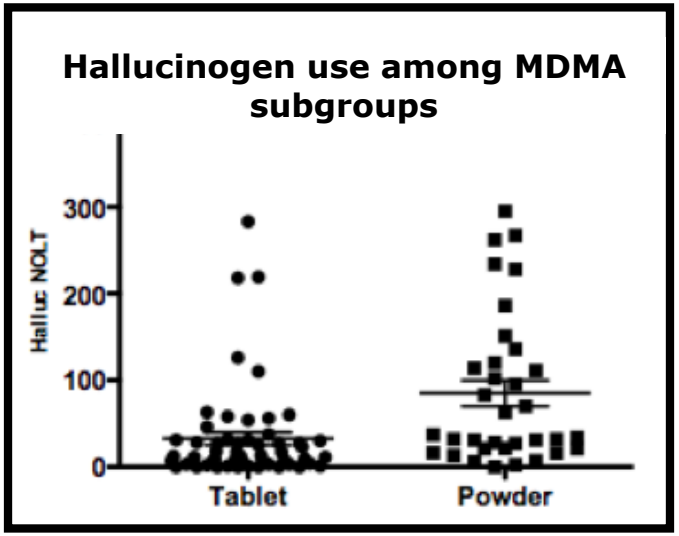


Ecstasy = MDMA = 3,4methylenedioxymethamphetamine

Two distinct MDMA cultures (data from study in 98 drug users, submitted for publication):

- A "high-risk MDMA user style" associated with heavier MDMA use, use at parties, bingeing, tablet preference, and psychostimulant co-administration,

- And "a hallucinogen user style" associated with lighter MDMA use, less bingeing, powder preference, and increased substance experimentation.



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Young adult Danish recreational drug users (n=98);

Btw 18 and 35 years old, report of lifetime history of at least 15 illicit drug experiences (excluding cannabis) and use of MDMA or hallucinogens (at least once) within the past 12 months

•About half of MDMA users had combined MDMA with a hallucinogen at some point during their life, most commonly LSD or psilocybin,
- which is in line with a lifetime prevalence of LSD and MDMA co-administration among MDMA users of 30% reported in a UK study (Winstock 2001).

•Eleven participants stated that MDMA and hallucinogens enhanced each other. Such enhancing effects were also reported by polydrug users in the UK, where 65% of LSD users had used LSD to 'improve the effects' of MDMA and 21% of MDMA users had used MDMA to 'improve the effects' of LSD (Boys 2001).

Co-administration patterns

Substance co-administration at last recalled administration of each substance

	Any	Alcohol	Cannabis	Amphet.	MDMA	Cocaine	Other
Cannabis (98)	62 (52-71)	52 (42-62)	xxx	5 (2-12)	7 (3-14)	3 (1-9)	22 (15-32)
Amphetamines (93)	90 (82-95)	84 (75-91)	35 (27-46)	xxx	13 (7-21)	10 (5-18)	25 (17-34)
MDMA (93)	92 (85-97)	77 (68-85)	49 (40-59)	23 (15-32)	xxx	17 (11-26)	39 (29-49)
Cocaine (91)	97 (90-99)	87 (78-92)	40 (30-50)	13 (8-22)	14 (8-23)	xxx	21 (14-30)
Psilocybin (86)	69 (58-77)	44 (34-55)	44 (34-55)	10 (5-19)	9 (5-18)	2 (0-9)	24 (17-35)
Inhalants (77)	75 (65-84)	53 (42-64)	23 (15-34)	6 (2-15)	13 (7-22)	4 (1-11)	30 (21-41)
LSD (67)	90 (80-95)	63 (51-73)	46 (35-58)	10 (5-20)	16 (9-27)	6 (2-15)	40 (29-52)
Opiods (60)	60 (47-71)	38 (27-51)	33 (23-46)	5 (1-14)	7 (2-16)	3 (0-12)	8 (3-18)
Benzodiazepines	81 (68-89)	47 (35-60)	35 (24-48)	23 (14-35)	14 (7-26)	9 (3-19)	18 (10-30)
GHB (49)	65 (51-77)	35 (23-49)	33 (21-47)	12 (5-25)	6 (1-17)	8 (3-20)	14 (7-27)
Ketamine (49)	82 (68-90)	59 (45-72)	43 (30-57)	12 (5-25)	12 (5-25)	10 (4-22)	39 (26-53)

Co-administration patterns

•The average MDMA dose used at the last recalled administration event was 185 mg (95% CI: 153-216 mg).

•At the last recalled MDMA administration, the simultaneous use of MDMA and either one of the following substances: alcohol, cannabis, amphetamines, cocaine, psilocybin, LSD, or GHB, had no significant effect on MDMA dose.

•Only 8% of the MDMA users did not combine MDMA with another substance (except tobacco) at the last MDMA use.
This group used an average dose of 178 mg (95% CI: 86-270 mg) MDMA at the last recalled event, which was not significantly different from MDMA doses administered when combining with any of the seven substances mentioned above

Co-administration patterns;

•Alcohol was most often used interspersed with rather than before or after MDMA administration ($p < 0.001$)

•Similarly alcohol was most often used in an interspersed pattern when combined with LSD or psilocybin ($p < 0.001$)

•Cannabis was also most frequently used in an interspersed manner when combined with MDMA ($p < 0.001$), LSD ($p < 0.05$), or psilocybin ($p < 0.001$)

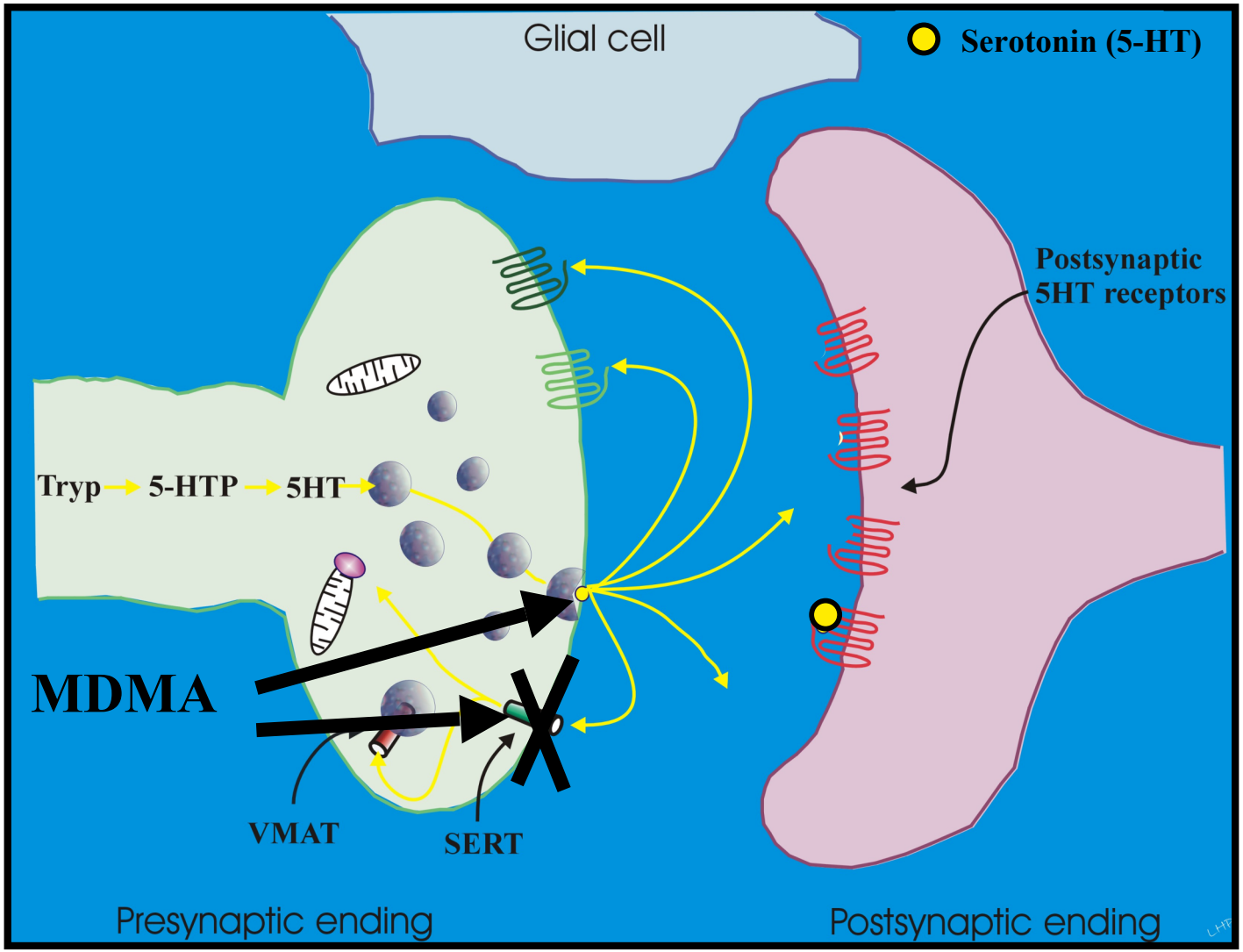
•In addition, 41% administered cannabis *after* taking MDMA, while only 7% used cannabis before MDMA.

•Among users combining MDMA and amphetamines, 71% reported taking amphetamines *before* MDMA, while only 14% took amphetamines after MDMA ($p < 0.001$).

•A similar pattern of initial use of amphetamines was seen for psilocybin ($p < 0.05$) and for LSD (n.s.).

•When LSD was combined with MDMA, 82% of users administered MDMA *after* LSD ($p < 0.01$).

MDMA and hallucinogens: Effects on serotonergic transmission



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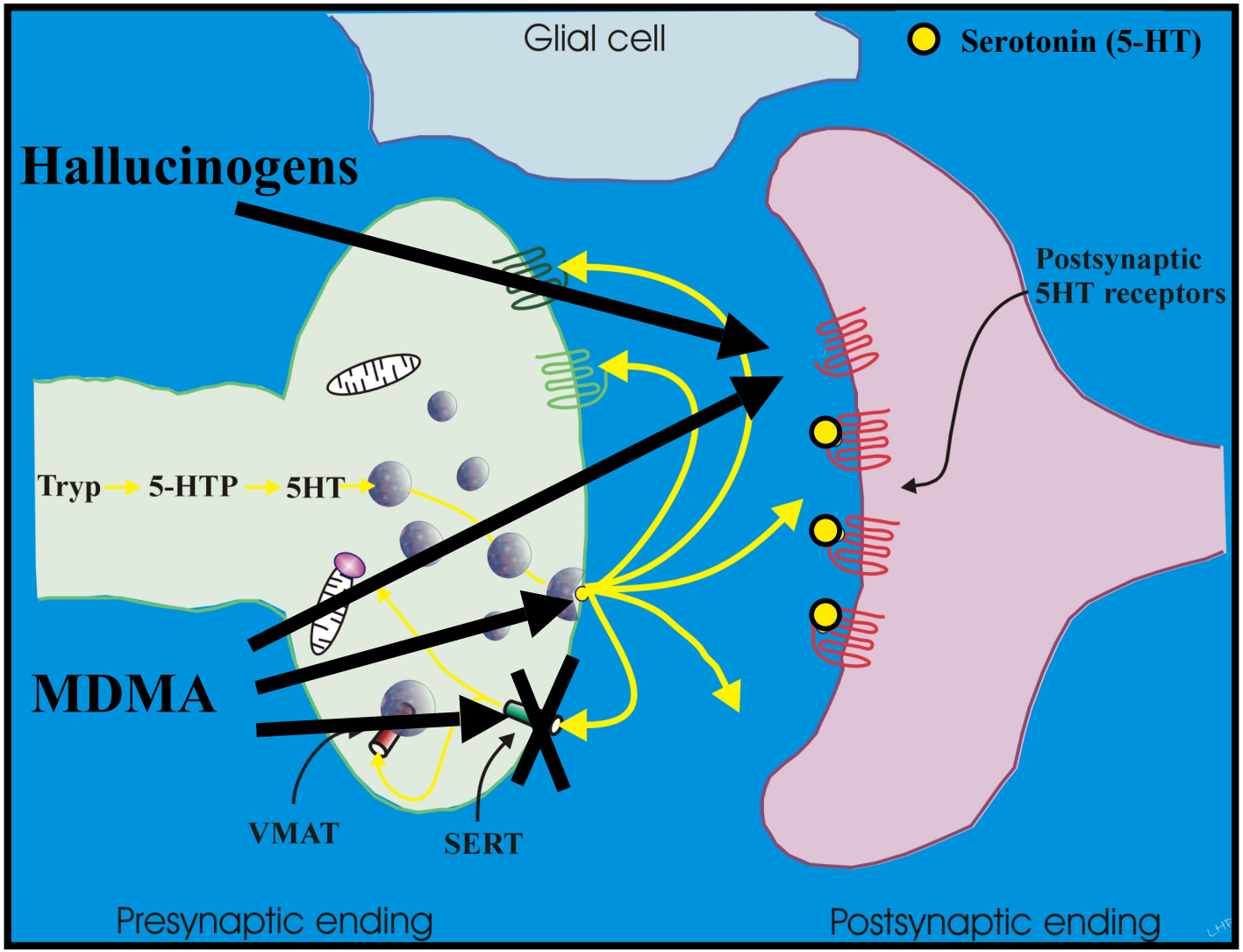
MDMA and hallucinogens: Effects on serotonergic transmission



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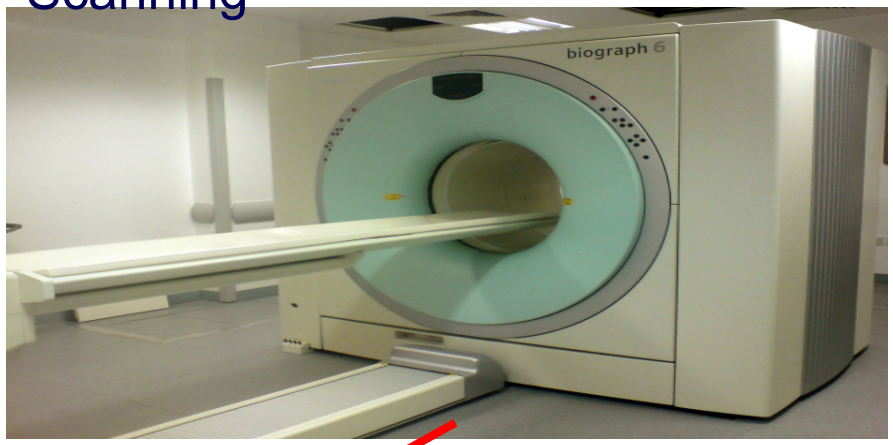
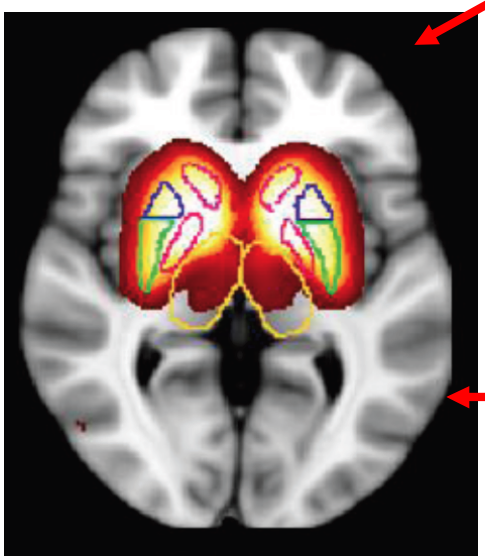
In vivo imaging using positron emission tomography (PET)

Scanning



Cyclotron

Chemistry



Blood Labs

Clinical area

Recruiting and Screening

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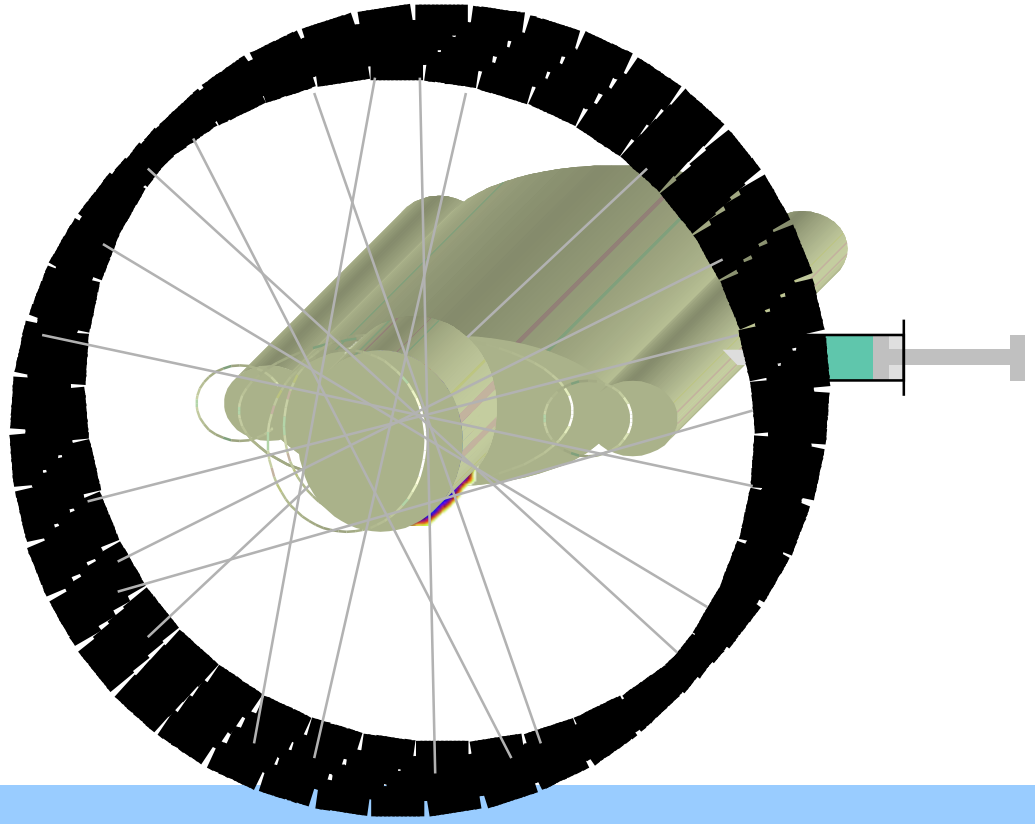
Brain imaging using Positron Emission Tomography (PET)

- Thousands of detectors arranged around patient
- Count many (100s of) millions of coincidences to determine radionuclide distribution



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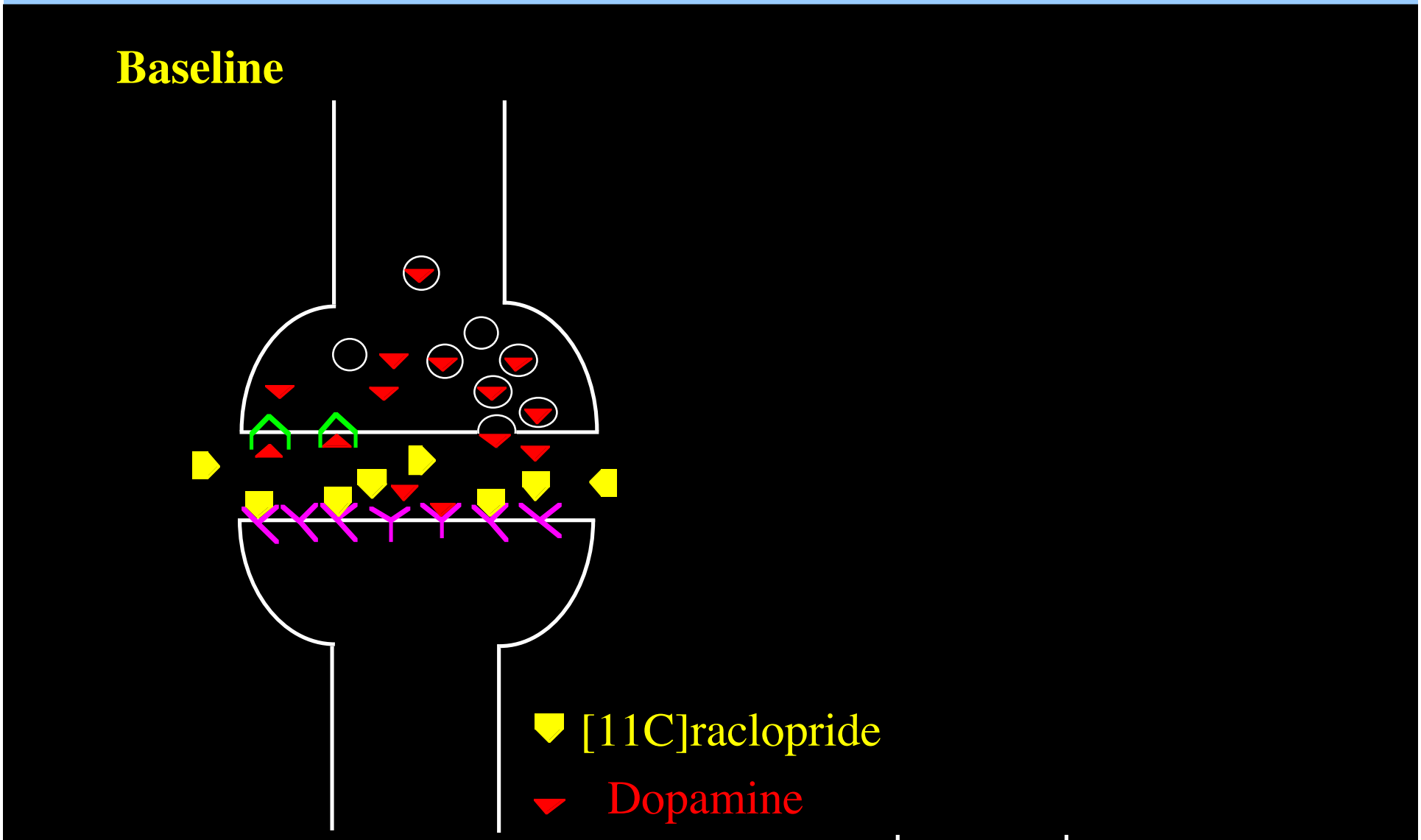
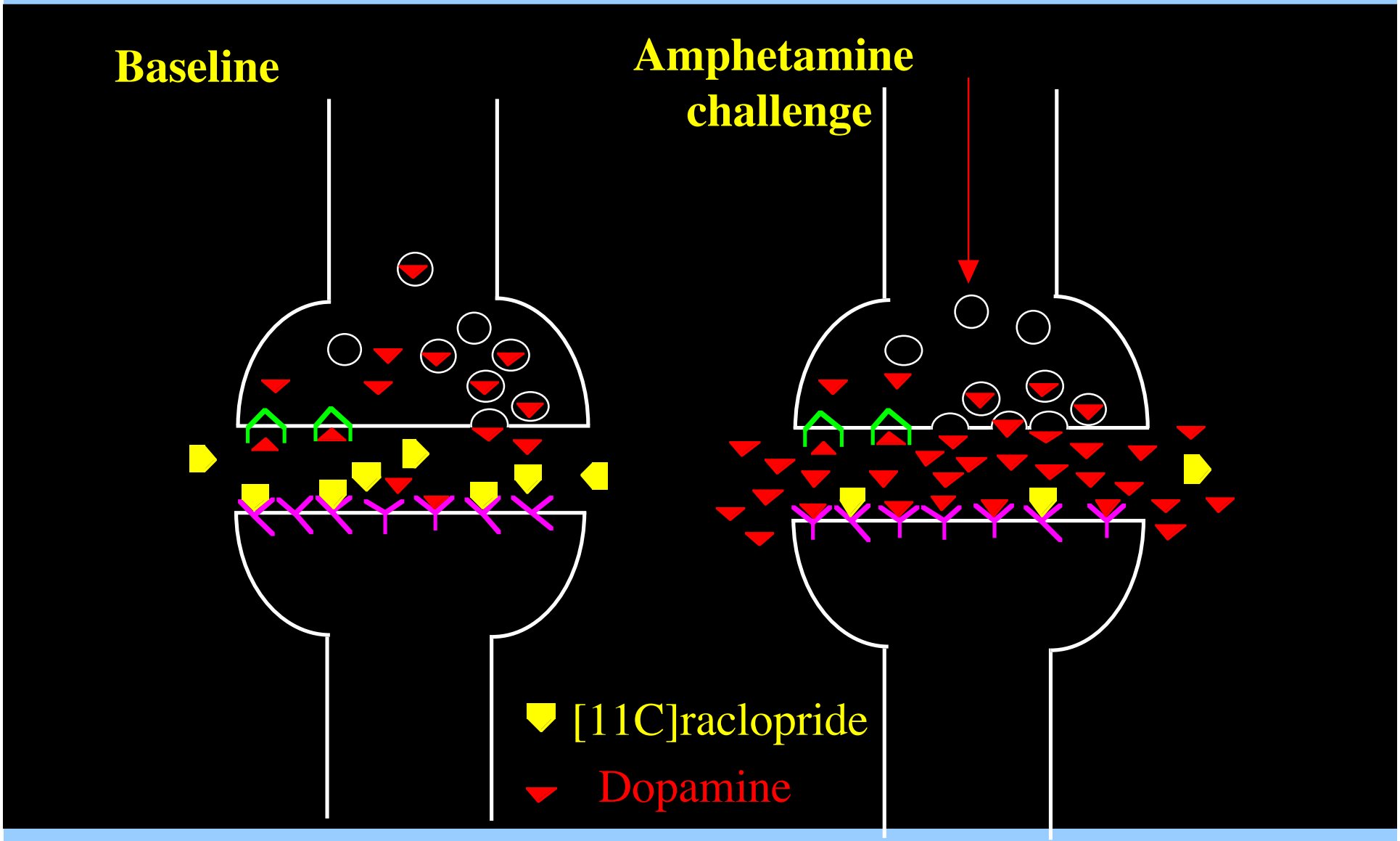
DA neurotransmission



DA neurotransmission



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Aims of PET study

Aims of the study:

- Within a sample of users of MDMA/hallucinogen to assess drug induced ”toxicity” to the serotonergic system.....

- ...by measurements of SERT and 5-HT_{2A} receptor binding using selective PET radioligands.

- To dissociate the effect of MDMA and hallucinogens on these two serotonergic markers.

Methods: Study design

24 MDMA and/or hallucinogen users and 21 non-using controls included.

Exclusion criteria both groups:
- Not 18-35 years old
- Prior or present use of psychoactive medication
- Neurological or psychiatric disorder other than substance abuse or dependence
- Pregnancy, metal devices, claustrophobia

Inclusion criteria for controls:
- No experience with stimulants other than alcohol, nicotine, and cannabis (max x 15)

Inclusion criteria for drug users:
- 10 or more lifetime exposures to MDMA and/or hallucinogens.
- ***Use within last 6 months***
- ***No use within 10 days*** before the scanning

All subjects investigated with:

- Schedules for Clinical Assessment in Neuropsychiatry
- Time Line Follow Back (Drugs)
- Customary Drinking and Drug Use Record

- Hair and urine samples
- Blood screen

- 11C-DASB- and 18F-altanserin-PET
- 3 Tesla MRI

- Different symptom and personality questionnaires
- Neuropsychological tests

Hallucinogens used

Name of hallucinogen	Number of participants who have ever used the substance
Psilocybin (O-Phosphoryl-4-hydroxy-N,N-dimethyltryptamine)	19
LSD (Lysergic acid diethylamide)	18
2-CB (2,5-Dimethoxy-4-bromophenethylamine)	15
2-CI (2,5-Dimethoxy-4-iodophenethylamine)	11
DMT (Dimethyltryptamine)	11
Salvia divinorum	8
2-CE (2,5-dimethoxy-4-ethylphenethylamine)	5
LSA (d-lysergamide = ergine)	5
Mescaline (3,4,5-Trimethoxyphenethylamine)	4
DOB (2,5-Dimethoxy-4-bromoamphetamine)	3
DIPT (Diisopropyltryptamine)	3
AMT (α-Methyltryptamine)	3
TMA-2 (1-(2,4,5-Trimethoxyphenyl-propan-2-amine, 2,4,5-Trimethoxyamphetamine)	3
Ayahuasca	3
2-CT-4 (2,5-Dimethoxy-4-isopropylthiophenethylamine)	2
2-CT-7 (2,5-Dimethoxy-4-n-propylthiophenethylamine)	2

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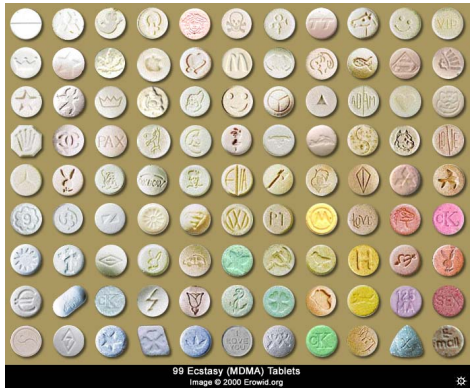
Content of ecstasy pills

Denmark 2006:

- 89% of "e-pills" contained MDMA alone.
- 8% of pills contained MDMA + another stimulant (amphetamine ++).
- 7% of pills contained piperazines (mCPP, TFMPP, MeOPP ++).

(*Oct-Dec 2006, Danish National Board of Health*)



Current "e-pill" status:

- Content of pills varies a lot !
- Many pills seized over the last 2-3 years have not contained MDMA at all.
- Some batches still contain high levels of MDMA.
- More and more piperazines (TFMPP combined with BZP is popular).
- More and more MDMA as powder and crystals.

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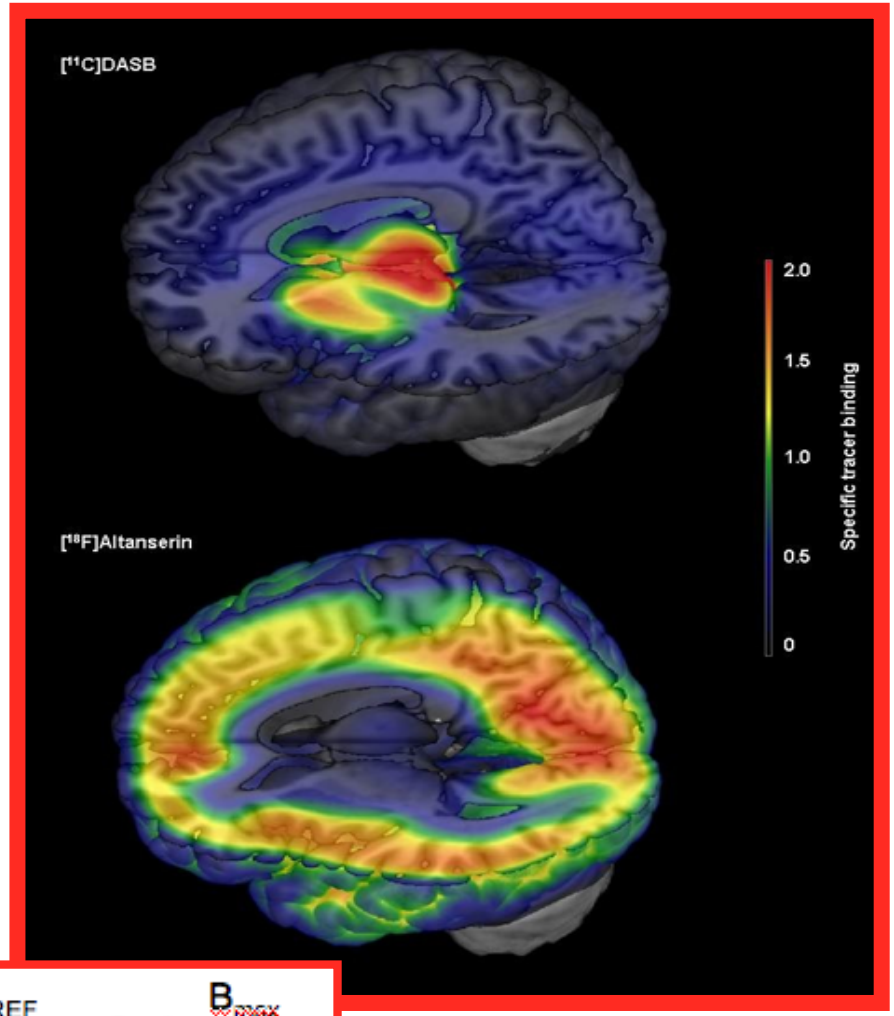
Methods: Imaging of SERT and 5-HT_{2A}

[^{11}C]DASB-PET:

- 90 minutes dynamic acquisition after bolus injection
- 36 frames
- MRTM2 (Ichise 2003)
- k_2' fixed generated from striatal data using MRTM
- Outcome measure: BP_{nd}



[^{18}F]altanserin-PET:

- Steady-state method
- Bolus plus constant infusion, Pinborg et al (2003))
- Oucome measure:

$$BP_p = \frac{C_{ROI}-C_{REF}}{C_{PLASMA}} = f_p * \frac{B_{max}}{K_d}$$

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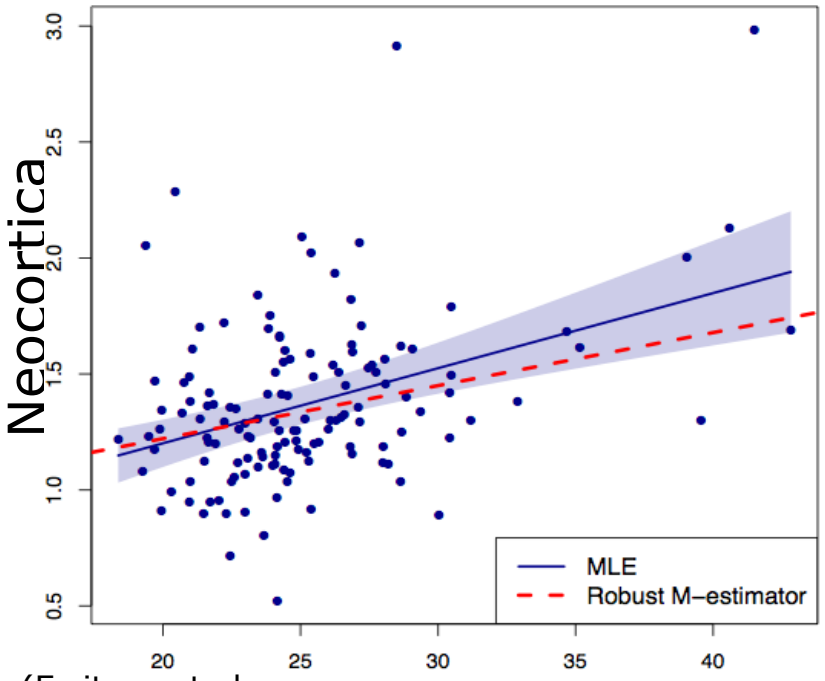
Resultater: Kliniske parametre

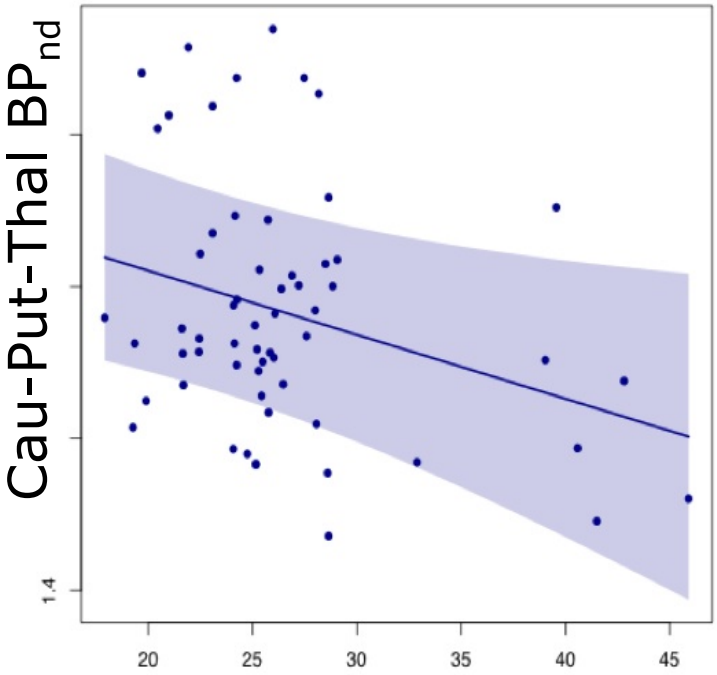
5-HT_{2A} vs BMI
N=136



(Erritzoe et al, 2009)

BMI (kg/m^2)

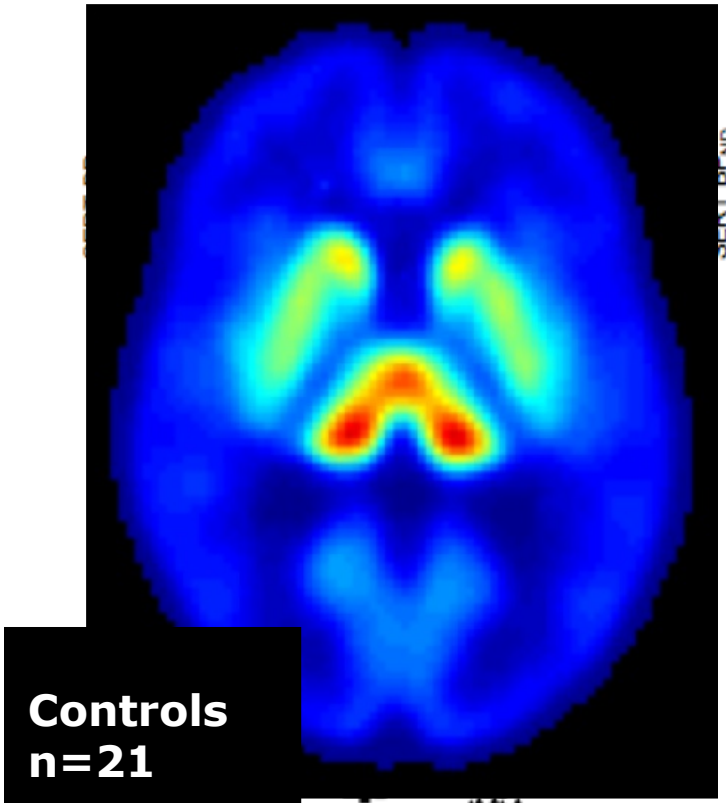
SERT vs BMI
N=60



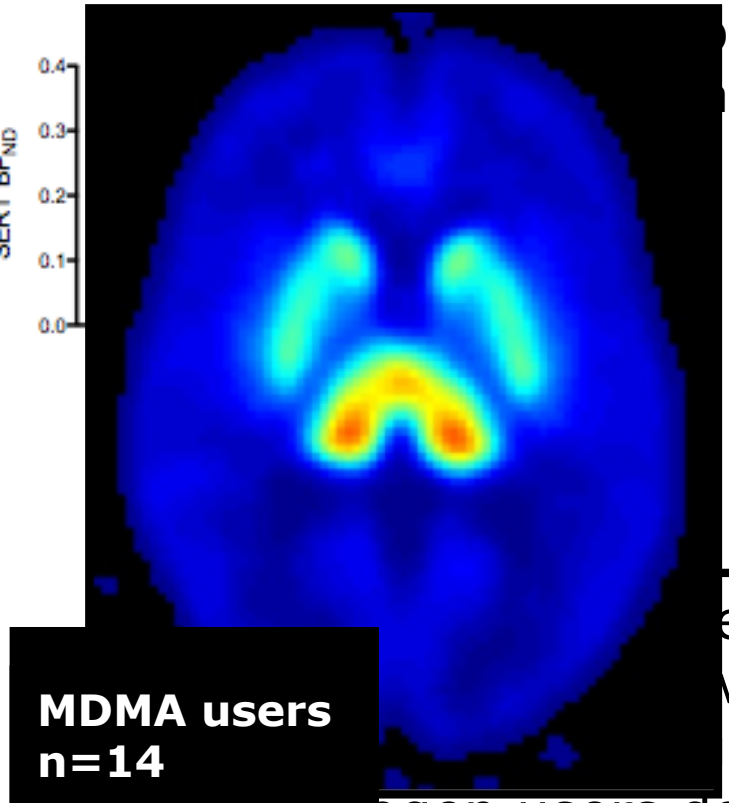
(Erritzoe et al, 2010)

BMI (kg/m^2)

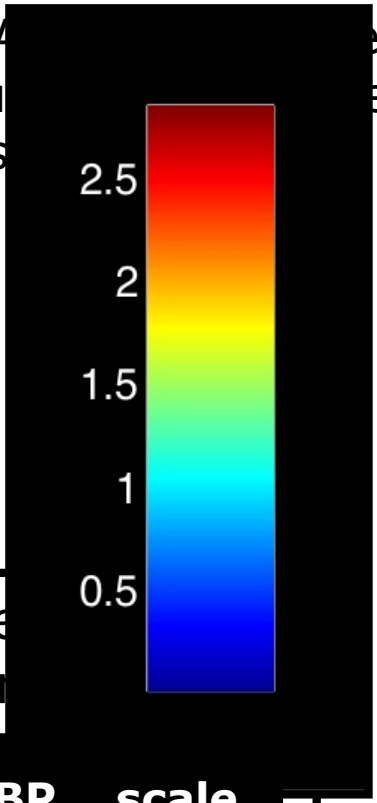
Serotonin Transporter (SERT) binding;
MDMA preferring users, Hallucinogen preferring users, and controls



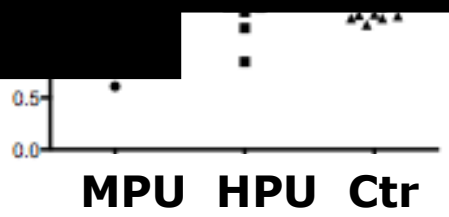
Controls n=21



MDMA users n=14



BP_{ND} scale



ogen users do
from ctr in SERT binding
- No differences in Midbrain

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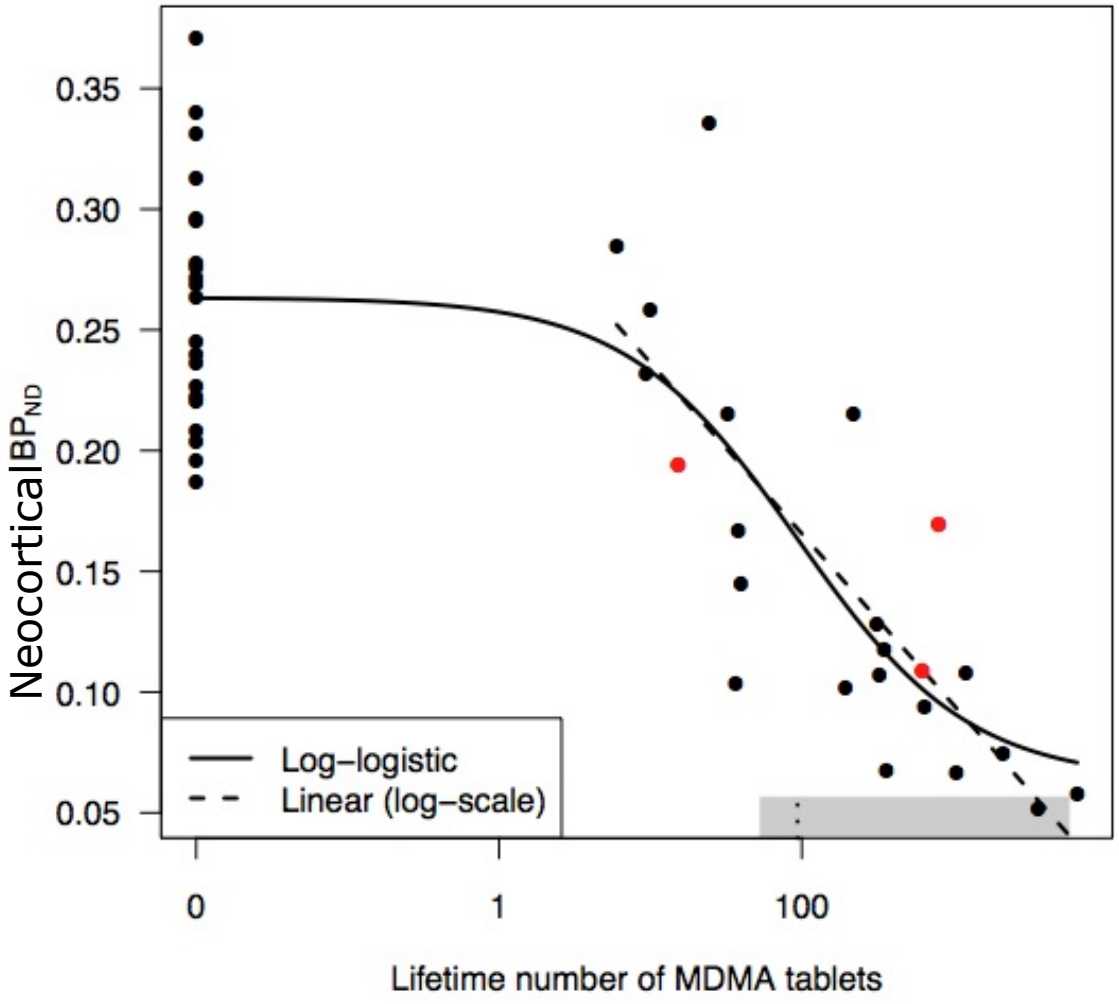
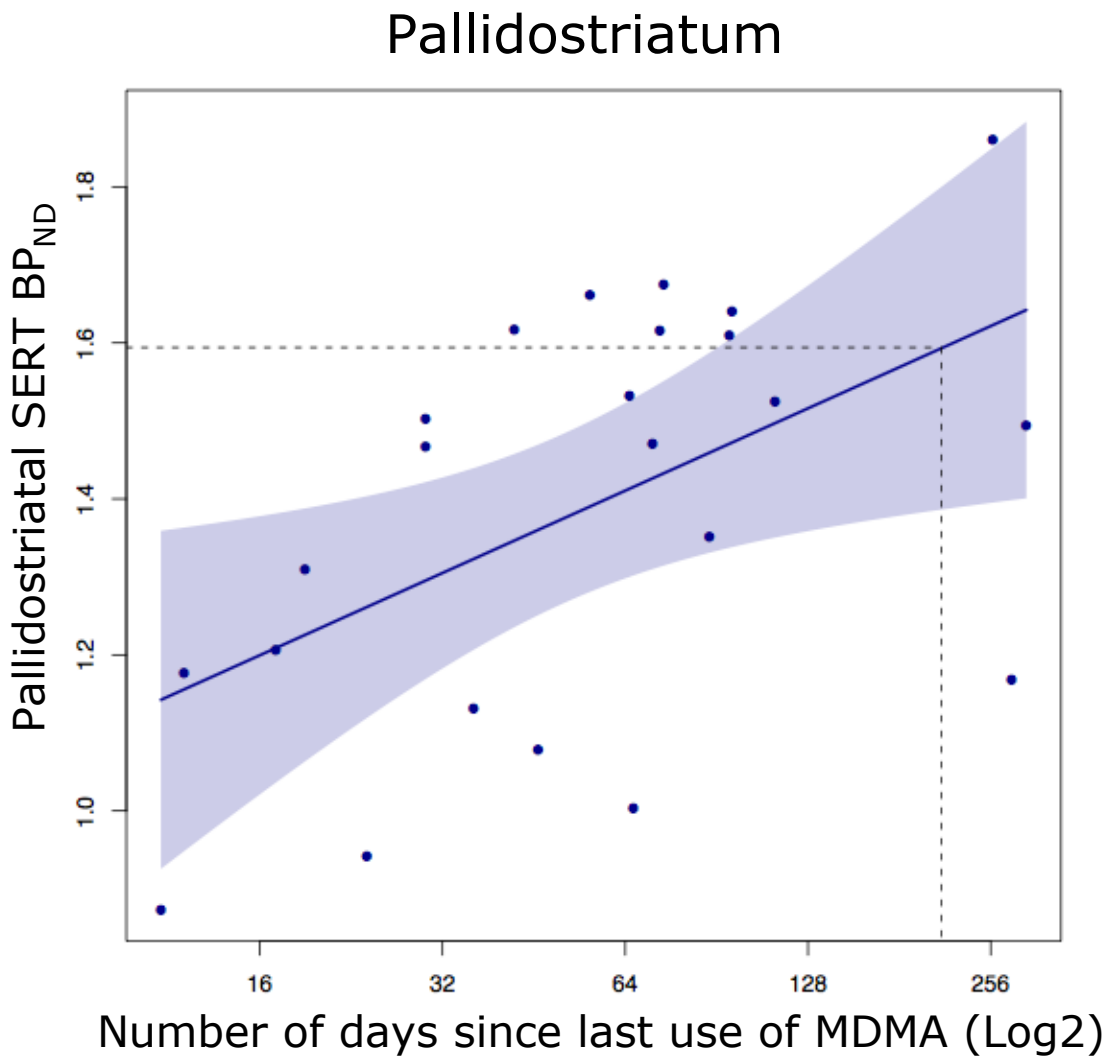
Dose-response: SERT and number of MDMA tablets



- The more MDMA tablets, the lower SERT
- Same in amygdala, thalamus, and pallidostriatum
- No dose-response in midbrain

Results: Recovery of SERT BPnd ?



- The longer since last MDMA use, the more "normal" SERT binding
- ~212 days recovery time in striatum
- Same pattern in amygdala, thalamus, and midbrain
- No reversibility in neocortex

(Analysis performed with correction for lifetime MDMA use)

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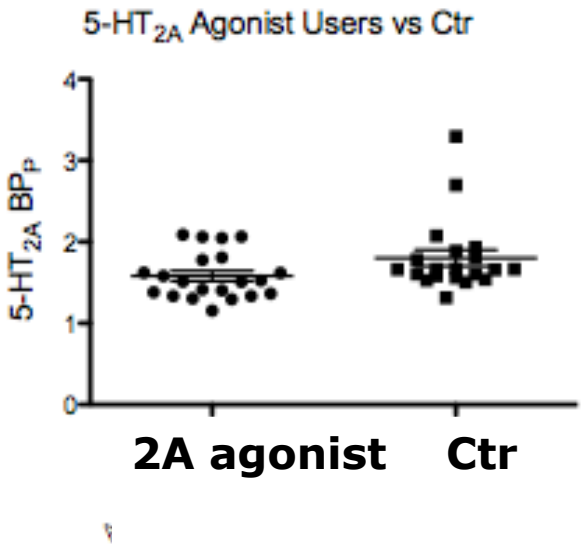
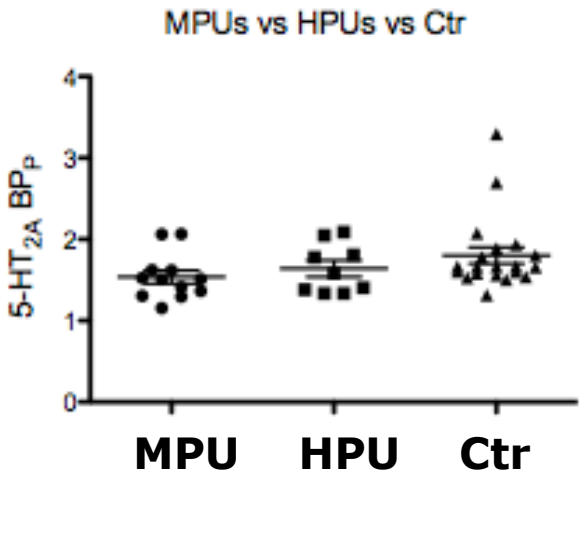
Neocortical 5-HT_{2A} binding; 2A agonist users vs controls

Cortical 5-HT_{2A} binding 10 % decreased among agonist users





P=0.038 (MannWhitney)

P=0.071 (KruskalWallis)

Conclusion from MDMA/Hallucinogen study

Hallucinogen use:

• Unchanged SERT binding; ***no*** *5-HT toxicity in such users?*

MDMA use:

• Decreased global SERT binding; *5-HT toxicity or depletion?*

• Dose-response with SERT; *supports 5-HT toxicity/depletion?*

• Regional reversibility of SERT reduction; *formation of new terminals or recovery after depletion - and what about cortex?*

• No SERT effect after limited MDMA use.

MDMA/Hallucinogen use:

• Slightly decreased cortical 2A binding; *a compensatory mechanism (adaptation to synaptic 5-HT levels / direct agonism) ?*

Mechanism behind MDMA effect on SERT:

• Mediated through pre-synaptic mechanism (- since no SERT effect of hallucinogens) ?

Context of SERT-MDMA findings

- These findings concur well with earlier studies in animals as well as in humans where decreased SERT binding has been observed in moderate to heavy, but not in light, MDMA users. Like in the present study, a negative association between SERT binding and the extent of MDMA use has been detected in most of these earlier imaging studies in humans .
- Also in line with our data, several studies support reversibility of the SERT-changes in relation to MDMA use; cerebral SERT binding is reduced in MDMA users with a relatively short abstinence of 24 days , 70 days (women only) and 145 days , but normal in MDMA users with longer abstinence periods: 514 , 885 , and 1000 days. A follow-up study and two independent studies further support the notion that a long-term recovery of SERT availability takes place after termination of MDMA use.
- By extrapolation, we estimate that full recovery of pallidostriatal SERT binding takes place approximately 200 days after the last MDMA dose; this estimate is in accordance with Buchert et al. (2006) who suggest that full recovery takes from several months to a few years. It should be remembered that as a consequence of our study design, this calculation is based on inter- rather than intra-individual data.

Extra thoughts about the cortex in heavy MDMA users

We found: SERT binding unaffected in midbrain but decreased in the heavy MDMA users especially in cortex; with an ant-post gradient (SERT most affected in occipital ctx).

This observation is in accordance with:

1) An early primate study with preserved 5-HT cell bodies but damage to 5-HT terminals; the longer distance (occ ++) from raphe nuclei the more affected terminals (Hatzidimitriou 1999).
2) Three other 11C-DASB-PET studies (McCann 2005, Urban 2012, Kish 2010). (Older studies using other tracers cannot report from cortex)

In addition, 5-HT2A receptor data (from Reneman 2002, Urban 2012, Di Iorio 2011) are in support of serotonergic changes in cortex. All three studies show increased 5-HT2A binding (>< our data). Interpreted as compensatory mechanism secondary to serotonergic depletion/toxicity.

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Extra thoughts about the cortex in heavy MDMA users

- *NO* signs of reversibility in cortical areas using 11C-DASB-PET in any of the 4 studies.

- One other 11C-DASB-PET study conducted in former MDMA users reported no difference btw ex-users and ctrs (Selvaraj 2008). However only frontal - but not from more dorsal cortical regions - SERT data were presented.

  Open question....:
  Is SERT gone due to toxicity to the 5-HT axons/terminals or is SERT ”gone” due to e.g. re-location/downregulation ?

- In cultured transfected cells; SERT re-located from membrane to cytoplasmic fraction following exposure to MDMA !
- We will test how 11C-DASB binds to SERT in different cellular compartments.

Extra thoughts about the cortex in heavy MDMA users

- Another approach to try to understand whether heavy recreational MDMA use is toxic to 5-HT terminals in cortex could be to look for other markers of neuronal damage.

Evidence of neuroinflammation after MDMA exposure in animals:

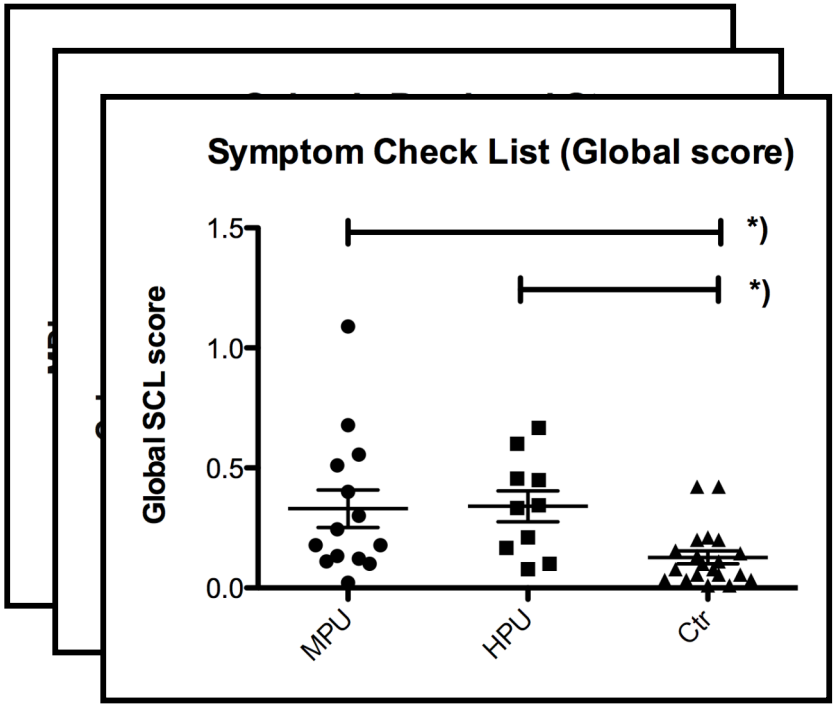
- Microglia activation (increased 3H-PK11195 binding, OX-42 immunostaining, and levels of the cytokine IL-1ß) has been detected.
- Minocycline prevented the MDMA-induced IL-1ß release and microglial activation in the frontal cortex and prevented 5-HT neurotoxicity.

Future study? :

- Combination of microglia activation with PET, MR spectroscopy, MR diffusion imaging - measure cortex of heavy MDMA users.

Symptom measures

- Major Depression Inventory (MDI)
- Cohen's Percieved Stress
- Symptom Check List (SCL 90-R)



No significant associations were detected between severity of symptoms and binding measures or lifetime drug use.

Personality domains and drug profiles

NEO-PI-R; “the big five”:

Neuroticism
Openess
Extraversion,
Agreeableness
Conscientiousness

Personality domains and drug profiles

NEO-PI-R; "the big five":

Neuroticism
Openness
Extraversion,
Agreeableness
Conscientiousness

- Fantasy
- Aesthetics
- Feelings
- Actions
- Ideas
- Values

Griffith et al, 2011:

Significant increases in Openness following single high dose of psilocybin. Remained increased after 14 months in participants who had had mystical experiences during the drug session.

Personality domains and drug profiles

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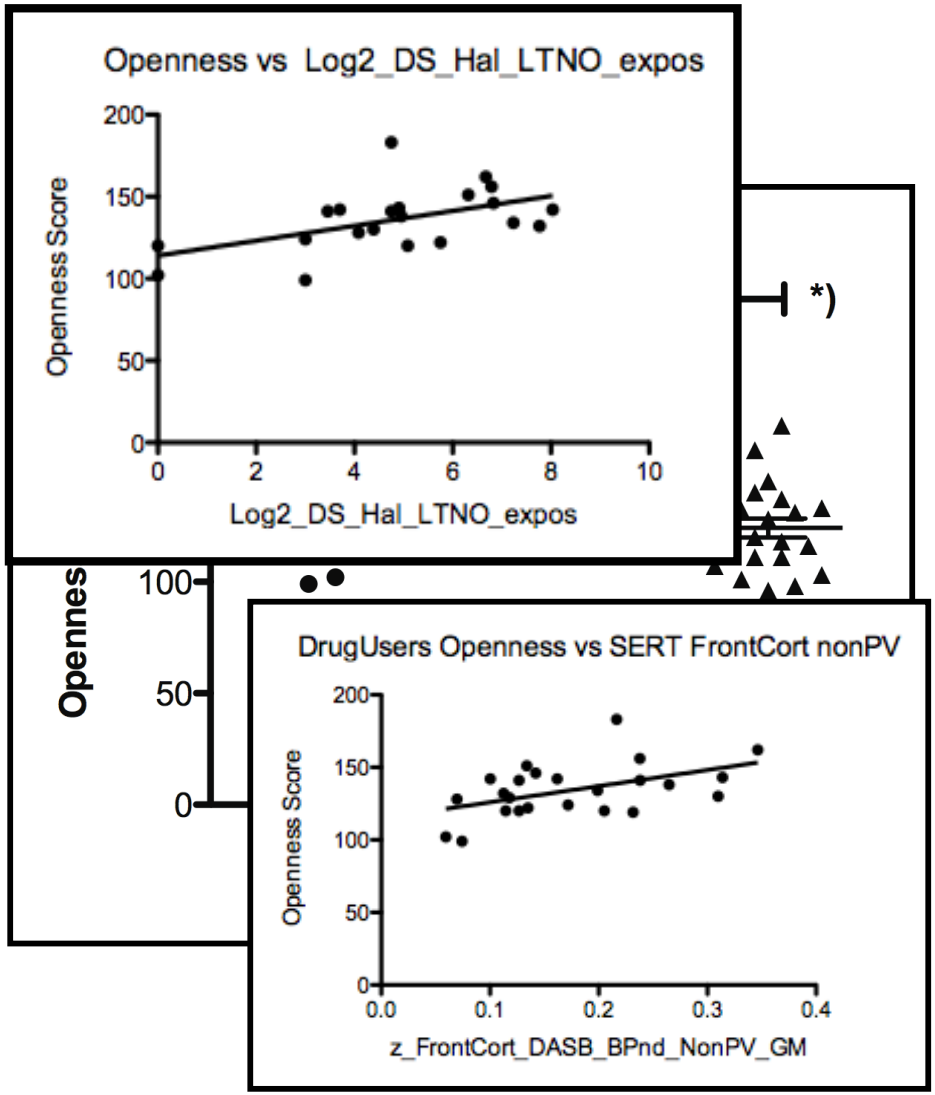

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Background for fMRI study in MDMA users

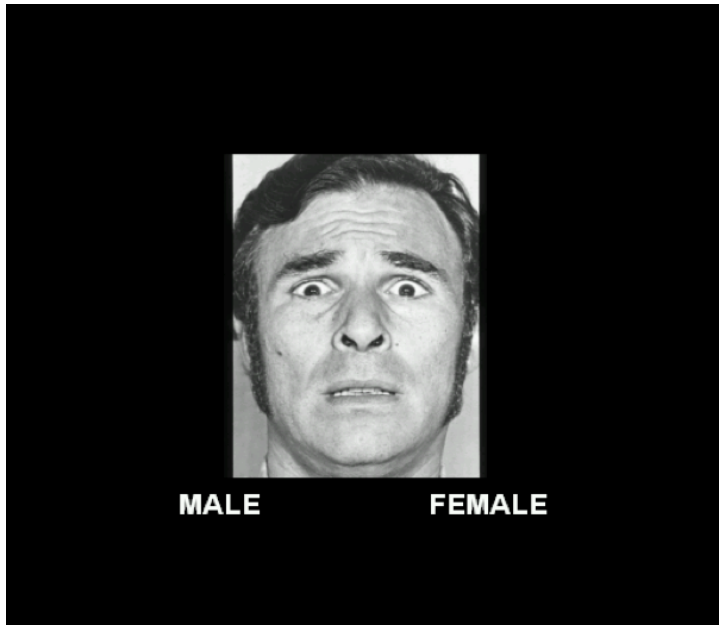
- Increased amygdala activation observed in patients with affective disorder conditions and in healthy control subjects during experimental presentation of fearful facial expressions of emotion (Morris et al 1996), fear conditioning (Morris et al 2001a), and during verbally guided anticipation of shock (Phelps et al 2001).
- Manipulation of brain 5-HT levels in humans is associated with effects on recognition of emotional facial expressions (Attenburrow et al. 2003; Browning et al. 2007; Harmer et al. 2003a; Murphy et al. 2006);
- Decreasing serotonergic function via acute tryptophan depletion increases hemodynamic responses in the amygdala to negative facial expressions in healthy subjects with a family history of depression (van der Veen et al. 2007) and in threat-sensitive subjects (Cools et al. 2005).
- Conversely, enhancing serotonergic function by administering selective serotonin re-uptake inhibitors (SSRIs) leads to a decrease in amygdala activation when processing negative faces (Del-Ben et al. 2005, Anderson et al. 2005).
- Rhodes et al. (2007) has shown a negative correlation between SERT density in left amygdala and left amygdala activity during emotional face processing.
- Furthermore, carriers of the short allele of the SERT promoter polymorphism which is associated with a reduced expression of SERT and a blunting of overall central serotonergic function (Reist 2001) show an increase in amygdala activation when processing aversive faces compared to carriers of the long allele of the SERT promoter (Hariri et al. 2002).
- Heavy recreational MDMA use can be used as model of chronic 5-HT depletion.

Hypotheses

1) MDMA users show more amygdala activity during aversive face processing

2) Amygdala activity during aversive face processing is positively associated with lifetime MDMA use and/or negatively associated with SERT binding

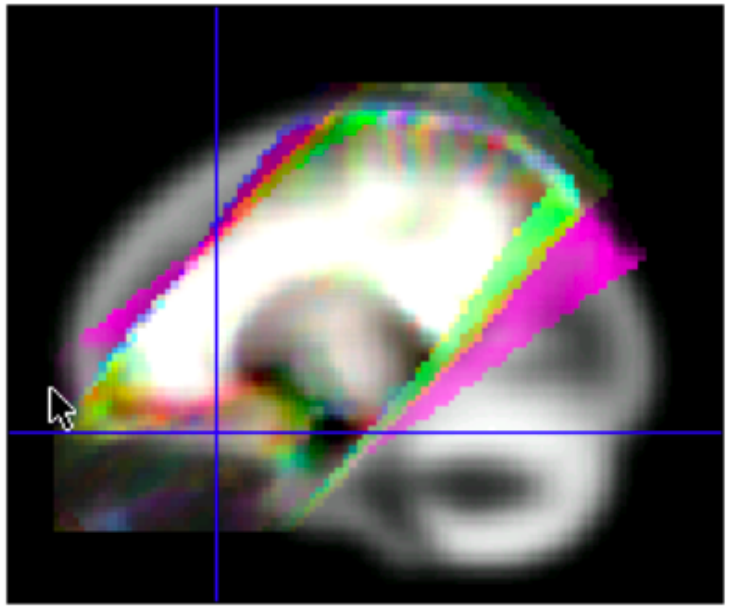
fMRI study in MDMA users



Emotions:

Neutral (A), anger (B), disgust (C), fear (D), and sadness (E)

Design:
ABACADAEABACADAE



Field of view

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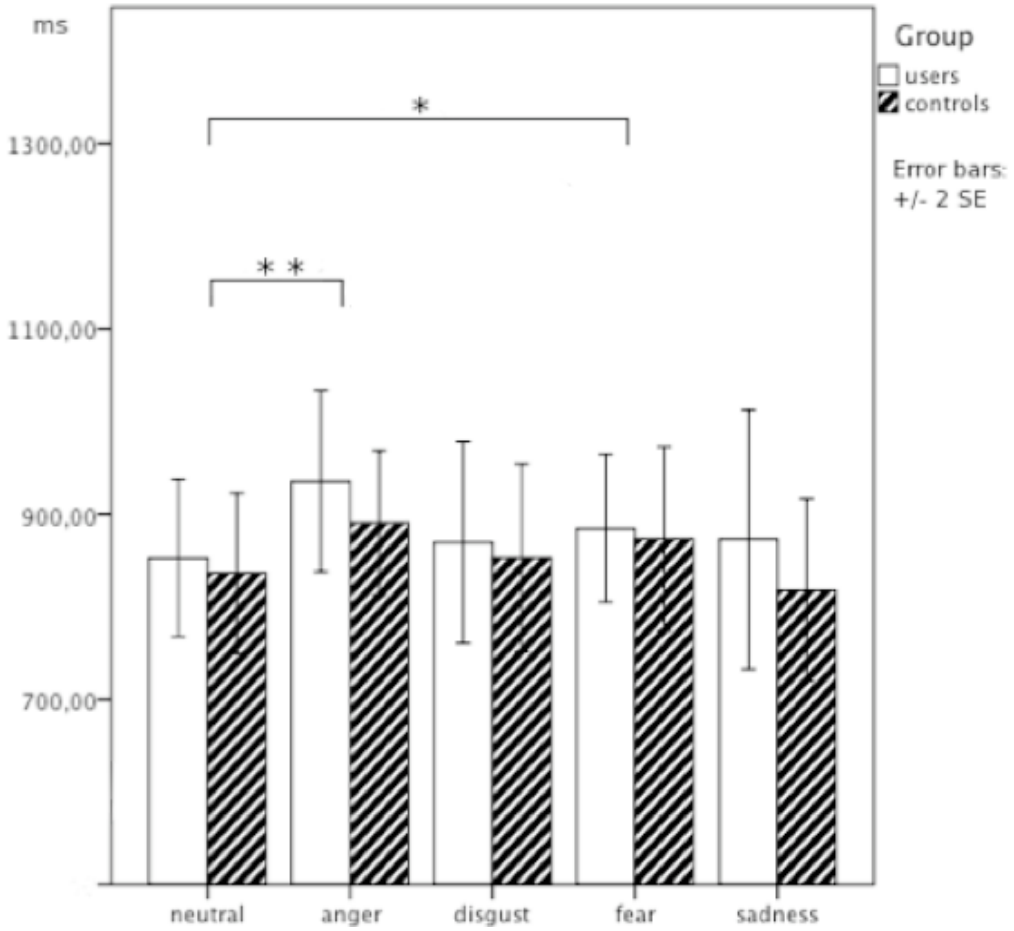
Behavioral result: reaction time



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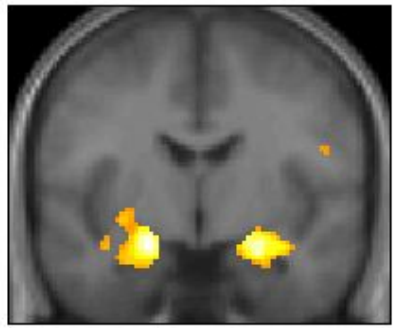
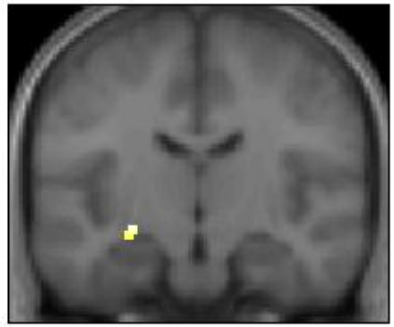
fMRI results

- Main effect of emotional faces on amygdala
- No between group differences in amygdala
- Positive correlation between lifetime MDMA use and activity in left amygdala/hippocampus...(?)..needs further analysis!
- No correlation between SERT binding and amygdala activity





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No conflicts of interest