# Ist risikoarmer Kokainkonsum möglich?

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# Addictive potential of cocaine

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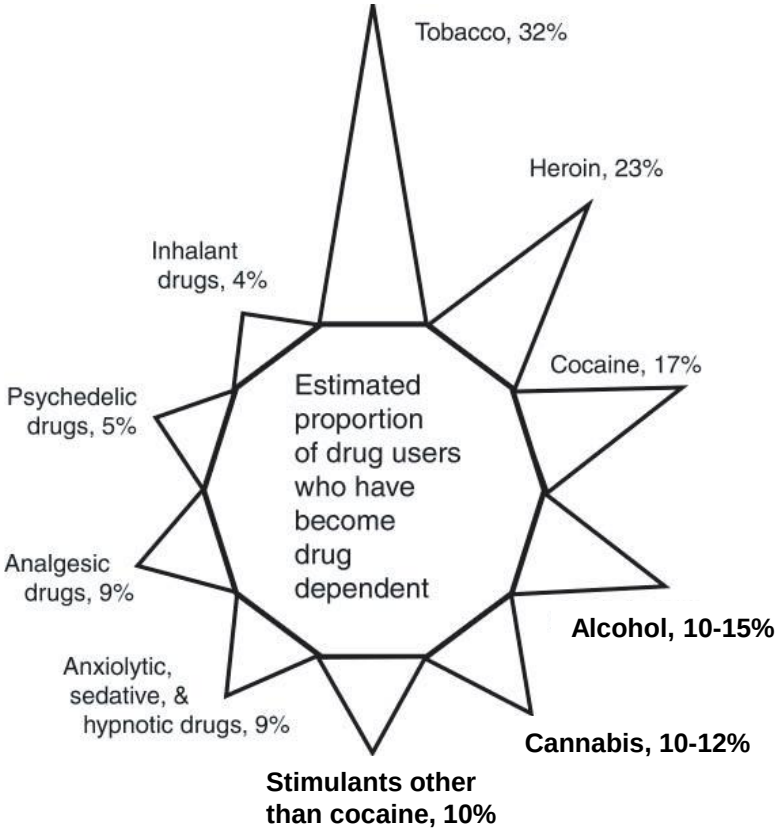
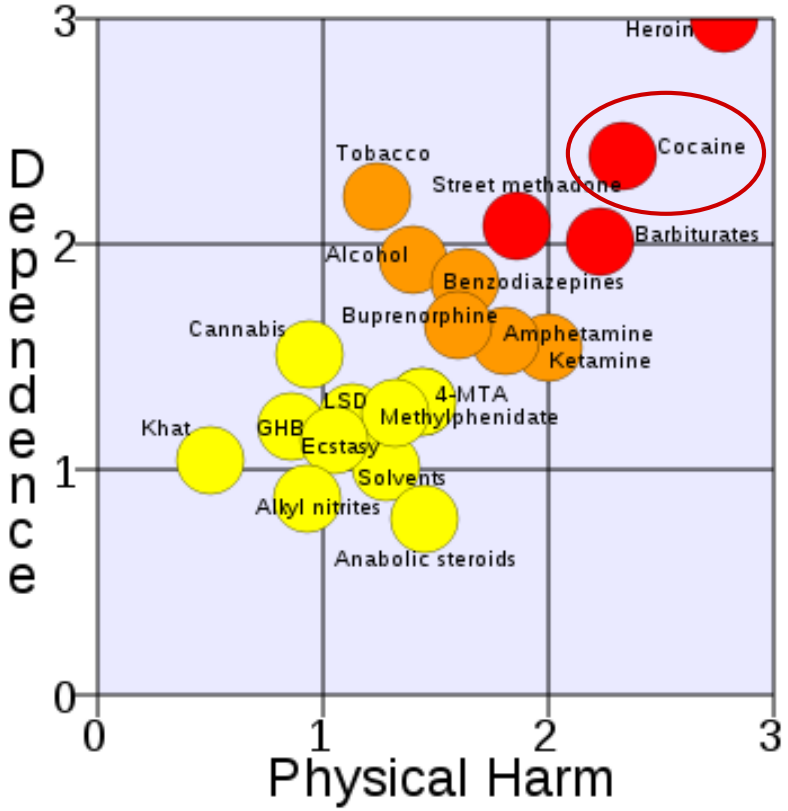



Estimated probability for addiction in specific substance user group

*Anthony 2002, updated*




Expert estimations (Delphi study) regarding the risk of drug consumption

*Nutt et al. 2007*

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# Addictive potential of cocaine



- 5-6% of cocaine users develop addiction in the first year of use, while 15-21% develop addiction during lifetime.
  *(Wagner and Anthony, 2002, Lopes-Quintero et al., 2011, Degenhardt and Hall, 2012)*

- Development of addiction is much faster compared to other drugs.
  *(Lopes-Quintero et al., 2011)*.

- 20% of all cocaine users in North America are heavy users, who are responsible for the consumption of 2/3 of the total available cocaine on the market.
  *(Kilmer et al 2014)*

- Cocaine addiction is afflicted with high relapse rates of 40-60% during or after specialized treatment.
  *(Simpson et al, 1999, McLellan et al., 2000)*

# Epidemiology of cocaine

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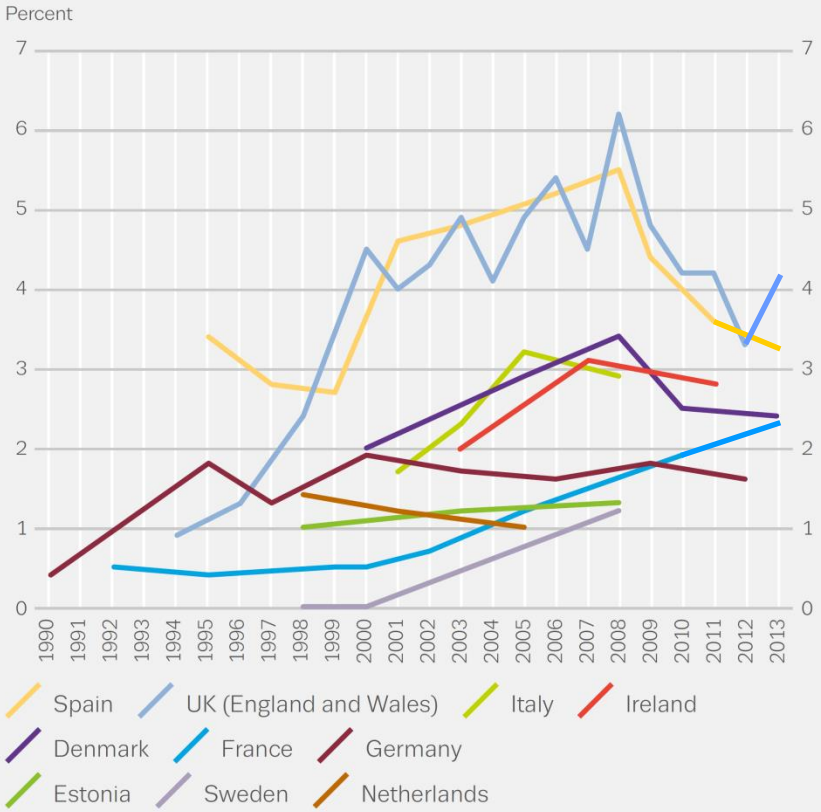
- Cocaine is worldwide as in Europe the second most prevalent illicit drug after cannabis.

Last year prevalence of cocaine use among young adults (15–34): selected trends (left) and most recent data (right)

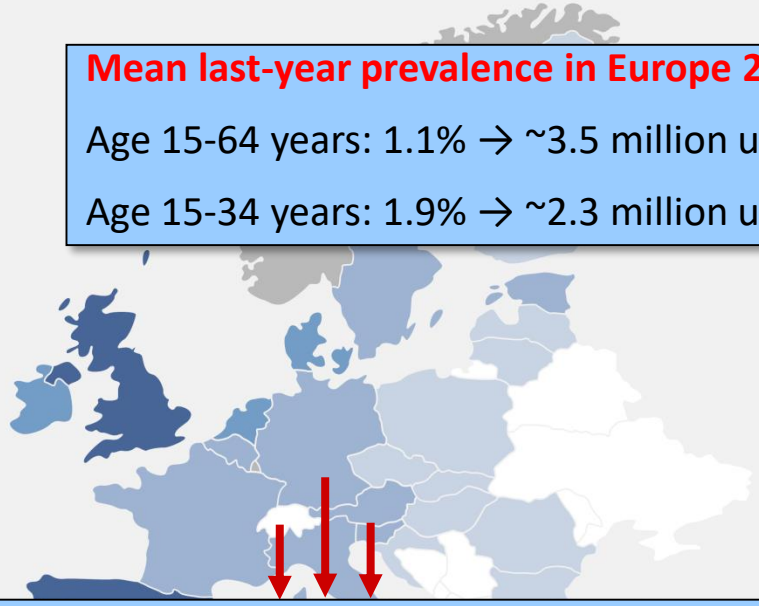
*EMCDDA, 2014, 2018*




**Mean last-year prevalence in Europe 2017**

Age 15-64 years: 1.1% → ~3.5 million users

Age 15-34 years: 1.9% → ~2.3 million users



**Austria:** Age 15-34: 0.4% → ~10k users (EMCDDA, 2017)
**Germany:** Age 15-34: 1.2% → ~300k users (EMCDDA, 2017)
**Switzerland**: Age 15-34: 1.7% → ~38k users (Gmel et al, 2017)

NB: Trends for ten countries with the highest prevalence and three or more surveys. Percent 0.1–1.0 1.1–2.0 2.1–3.0 >3.0 No data

# Wastewater epidemiology

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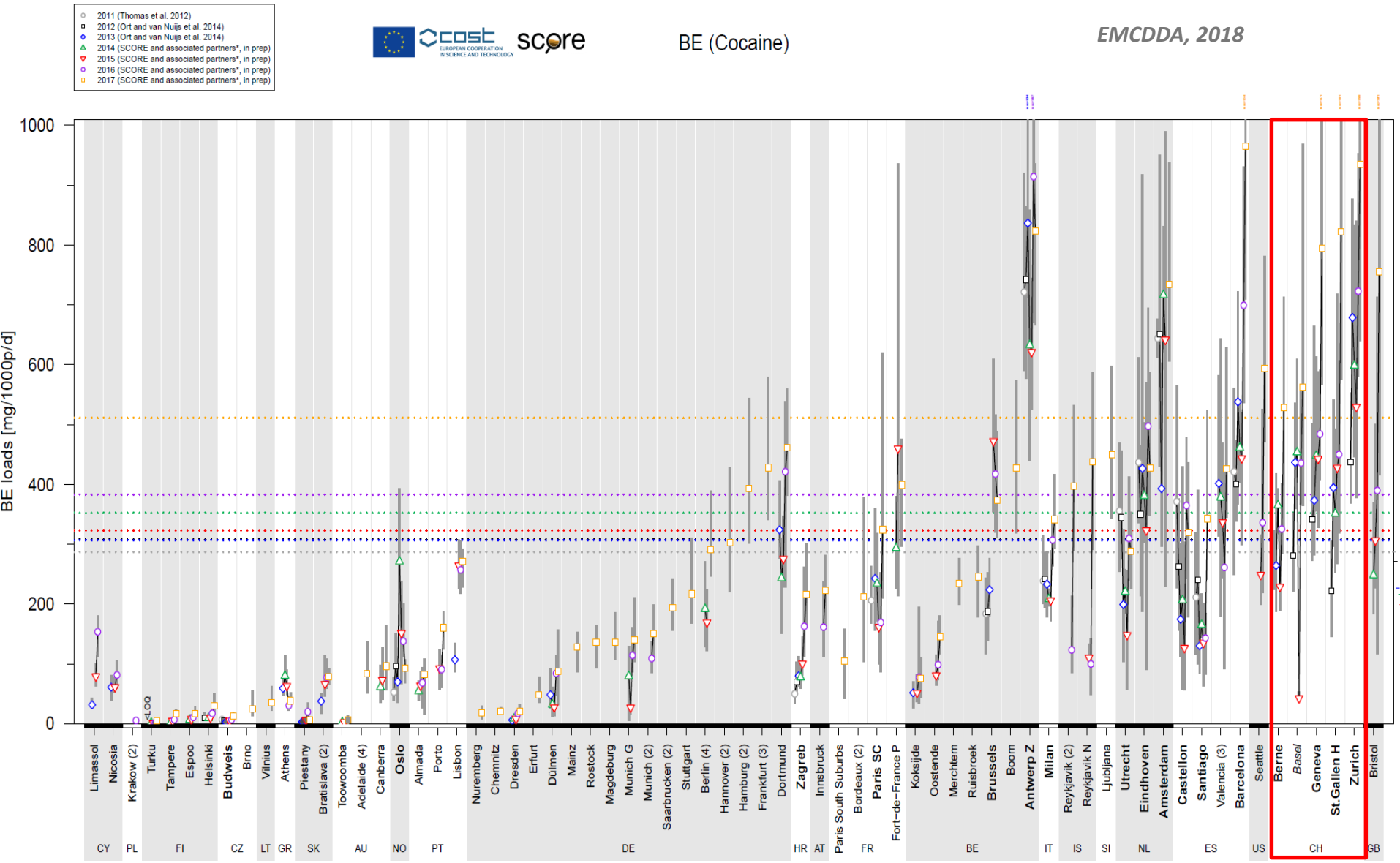
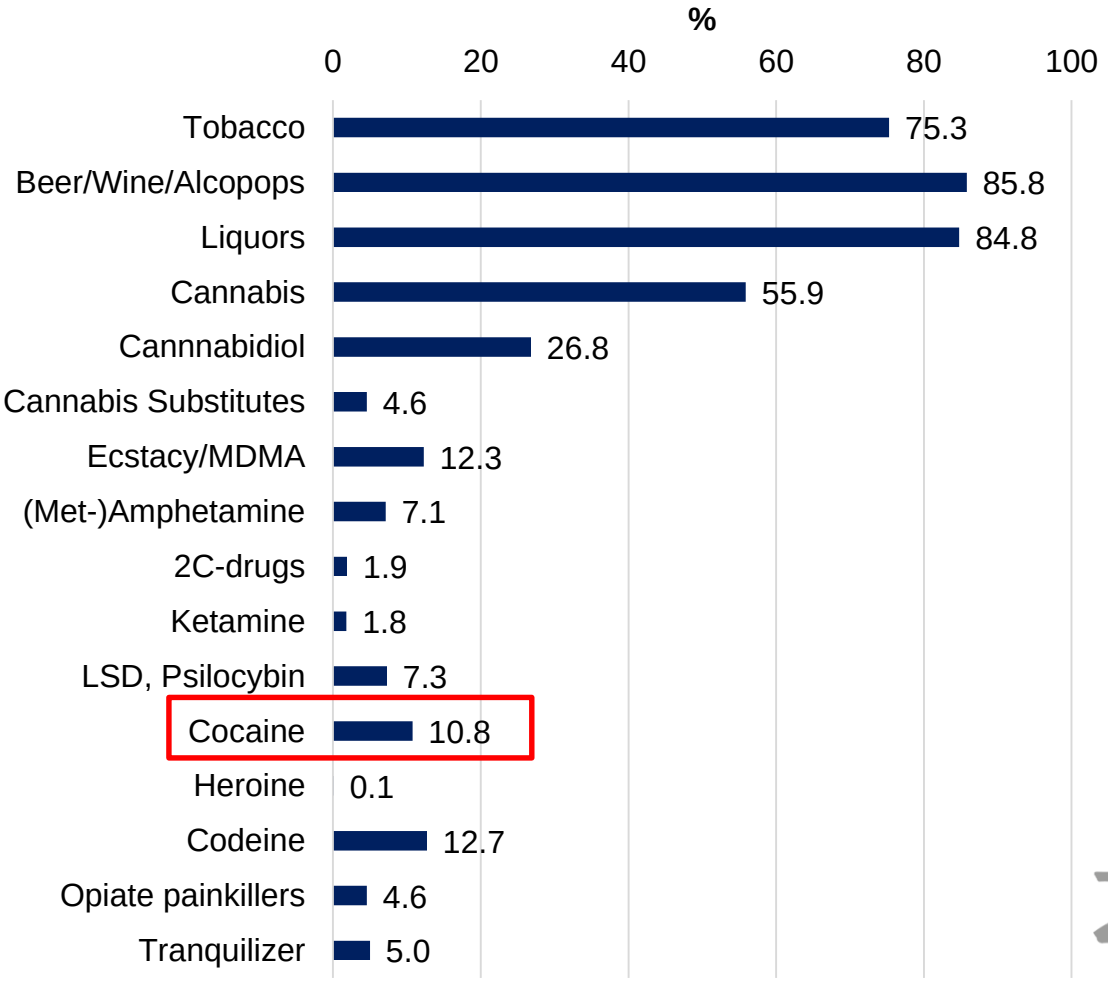


# Last-year prevalence of drug use in 2018 at age 20 in Zurich




*Quednow, et al., Shanahan, in preparation*

N= 1180
Community representative sample at age of 7 years

Z-proso
Zürcher Projekt zur sozialen Entwicklung von der Kindheit ins Erwachsenenalter

# Comorbidities of dependent cocaine use

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## Physical

- Cardiovascular diseases
  (e.g., cardiac and cerebral infarction, intracranial hemorrhage, hypertension, Arrythmia)
- Lung edema
- Epileptic seizures
- High vulnerability for infectious diseases

**Cause or consequence of use?**

## Mental

- Major Depression
- Anxiety disorders
- Suicidality
- Psychoses
- Sleep disorders
- Violence
- Social problems
- Cognitive deficits
  - Attention
  - Memory
  - Executive functions
    - Impulse control
    - Decision-making

# Study design: Zurich Cocaine Cognition Study

**Neuropsychology +**
**Psychophysiology +**
**Genetics**

**1. Baseline (cross-sectional)**

73 recreational users
35 dependent users
96 stimulant-naïve controls
204 participants

**12 month**

**Neuropsychology +**
**Psychophysiology**

**2. Follow-up (longitudinal)**

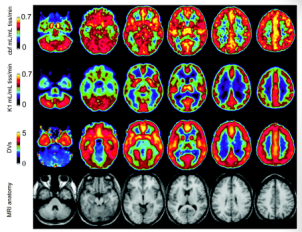
64 recreational users
17 dependent users
51 stimulant-naïve controls
132 participants

**PET + MRS + MRI**

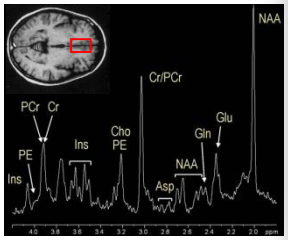
**Glutamate PET + MRS (cross-sect.)**
18 chronic users
18 stimulant-naïve controls
36 participants

**fMRI + resting-state + ASL (cross-sect.)**
25 chronic users
25 stimulant-naïve controls
50 participants

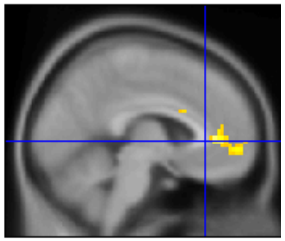
**Structural MRI + resting-state (longitud.)**
41 chronic users
43 stimulant-naïve controls
84 participants



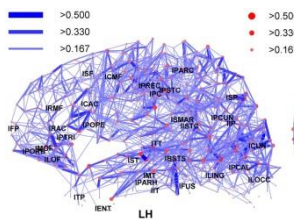
[$^{11}$C]-ABP688 PET




[$^{1}$H]NMR spectroscopy



Functional MRI




Resting-state connectivity

- Early information processing
- Classical neuropsychology
- Social Cognition
- Decision-making and impulsivity
- Social decision-making and neuroeconomics
- Genetics and gene expression
- Psychometrics

# In- and exclusion criteria

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**Inclusion criteria**

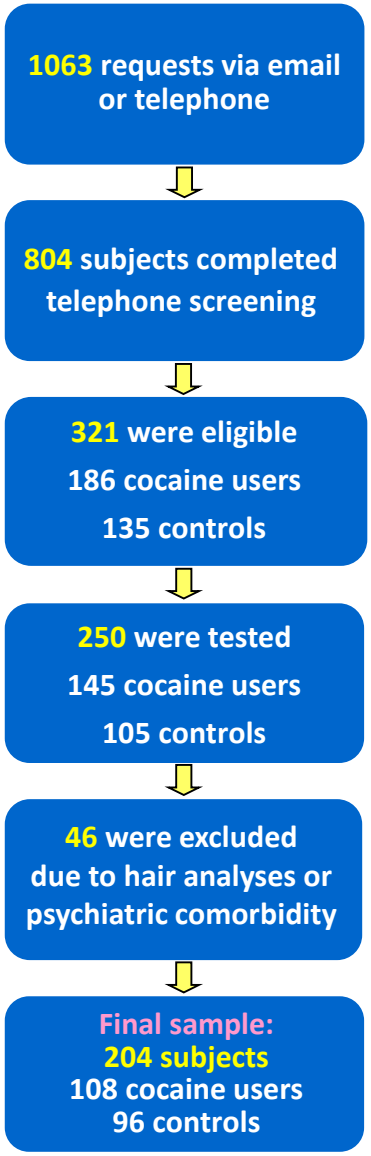
- Either: Regular but non-dependent use of cocaine (DSM-IV criteria not matched)
- Or: dependent use of cocaine (DSM-IV criteria matched)
- Consumption in the last 6 month and more than 1 g per month
- Age: 18 to 60 years

**Exclusion criteria**

- Polysubstance or opioid use
- OCD, schizophrenia, bipolar disorder, current depressive episode
- Neurological and severe somatic diseases
- Any prescribed medication with psychotropic substances
- ADHD and a history of depression was **not** excluded

**Additional requirements**

- Abstinence for illicit drugs: 3 days and alcohol: 24 h
- Urine, blood, and hair samples to control for recent drug use and chronic polysubstance and opioid abuse
- Approval of the Cantonal Ethics Committee Zurich (KEK)



# Sample characteristics

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| Mean and SD, numbers | Stimulant-naive controls (n=68) | Recreational cocaine users (n=68) | Dependent cocaine users (n=30) | F/Chi²/t | df/df$_{err}$ | *P* |
|---|---|---|---|---|---|---|
| Age | 30.3 (9.2) | 28.7 (6.2) | 32.5 (9.0) | 2.38 | 2/163 | 0.10 |
| Sex (m, f) | 47 / 21 | 50 / 18 | 22 / 8 | 0.38 | 2 | 0.83 |
| Years of school education | 10.7 (1.8) | 10.5 (2.0) | 9.5 (1.2) | 4.82 | 2/163 | **<0.01** |
| Verbal IQ (MWT-B) | 104.4 (9.7) | 103.2 (9.6) | 99.7 (9.1) | 2.46 | 2/163 | 0.09 |
| Smoker/non-smoker | 53 / 15 | 53 / 15 | 24 / 6 | 0.06 | 2 | 0.97 |
| Cocaine Craving (CCQ) | - | 19.0 (9.1) | 20.3 (11.4) | 0.36 | 96 | 0.55 |
| **Cocaine self report** | | | | | | |
| **g/week** | - | **1.1 (1.0)** | **7.9 (15.8)** | | | |
| **Duration (years)** | - | **6.5 (4.0)** | **9.4 (6.5)** | | | |
| **Cumulative lifetime dose (g)** | - | **520 (751)** | **5501 (9635)** | | | |
| **Last consumption (days)** | - | **27.5 (37.6)** | **21.0 (33.6)** | | | |
| **Quantitative hair toxicology** | | | | | | |
| **Cocaine (pg/mg)** | - | **2739 (4628)** | **22164 (32609)** | | | |
| **Benzoylecgonine (pg/mg)** | - | **546 (919)** | **5048 (7711)** | | | |
| **Cocaethylene (pg/mg)** | - | **276 (318)** | **2006 (3656)** | | | |
| **Norcocaine (pg/mg)** | - | **62.4 (100)** | **586 (758)** | | | |
| **Alcohol** (g/week) | 116.8 (122.6) | 167.8 (117.5) | 188.5 (260.6) | | | |
| **Amphetamine** (g/week) | - | 0.1 (0.2) | 0.0 (0.2) | | | |
| **MDMA** (tablets/week) | - | 0.1 (0.3) | 0.4 (1.8) | | | |
| **Cannabis** (g/week) | 0.5 (1.0) | 0.9 (2.1) | 1.2 (3.7) | | | |

*Vonmoos et al. 2013, Br J Psychiatry*

# Cognitive impairment and cocaine

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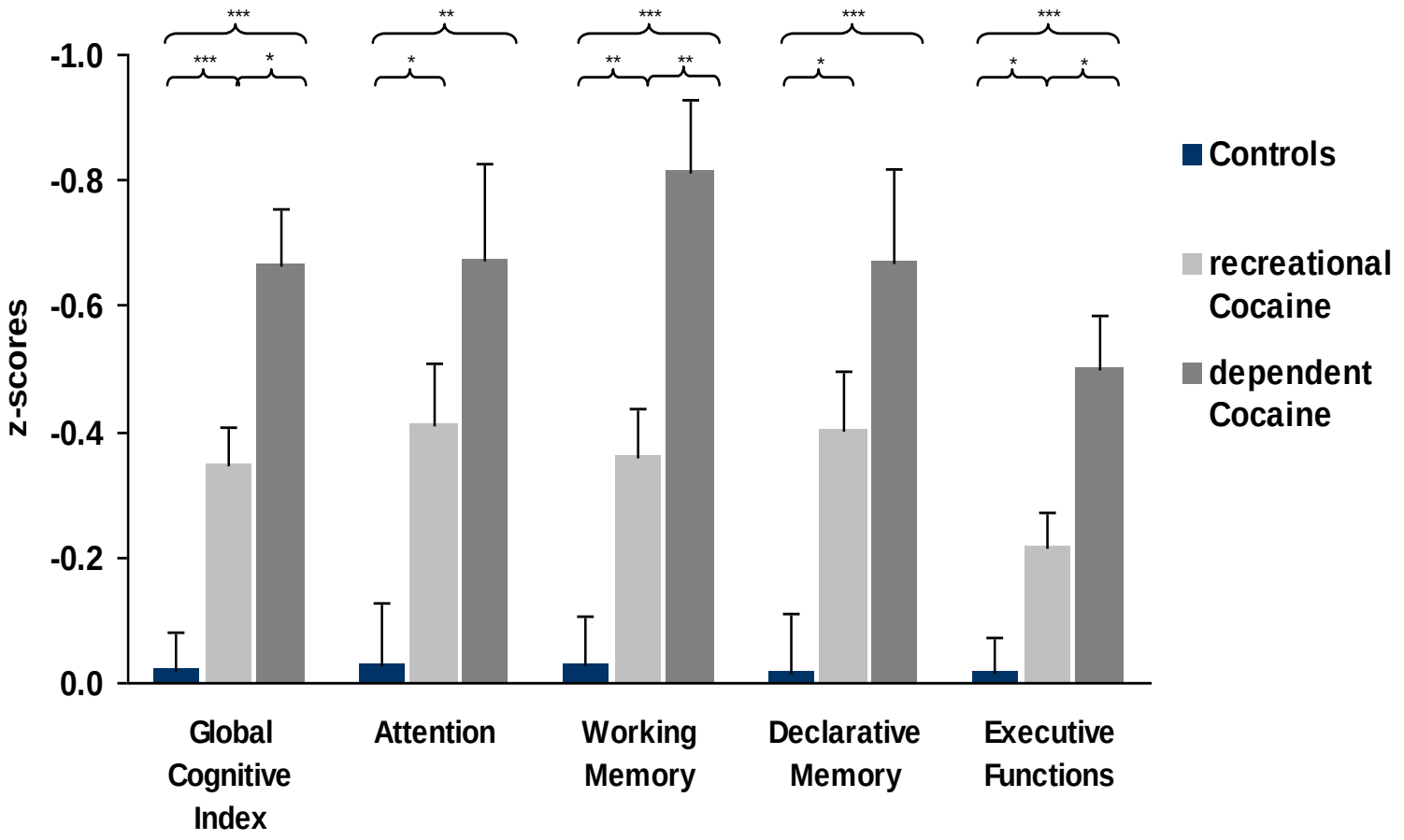


*Vonmoos et al. 2013, Br J Psychiatry*

**Sidak post hoc tests: *p<.05; **p<.01; ***p<.001**

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# Cognitive impairment in cocaine users

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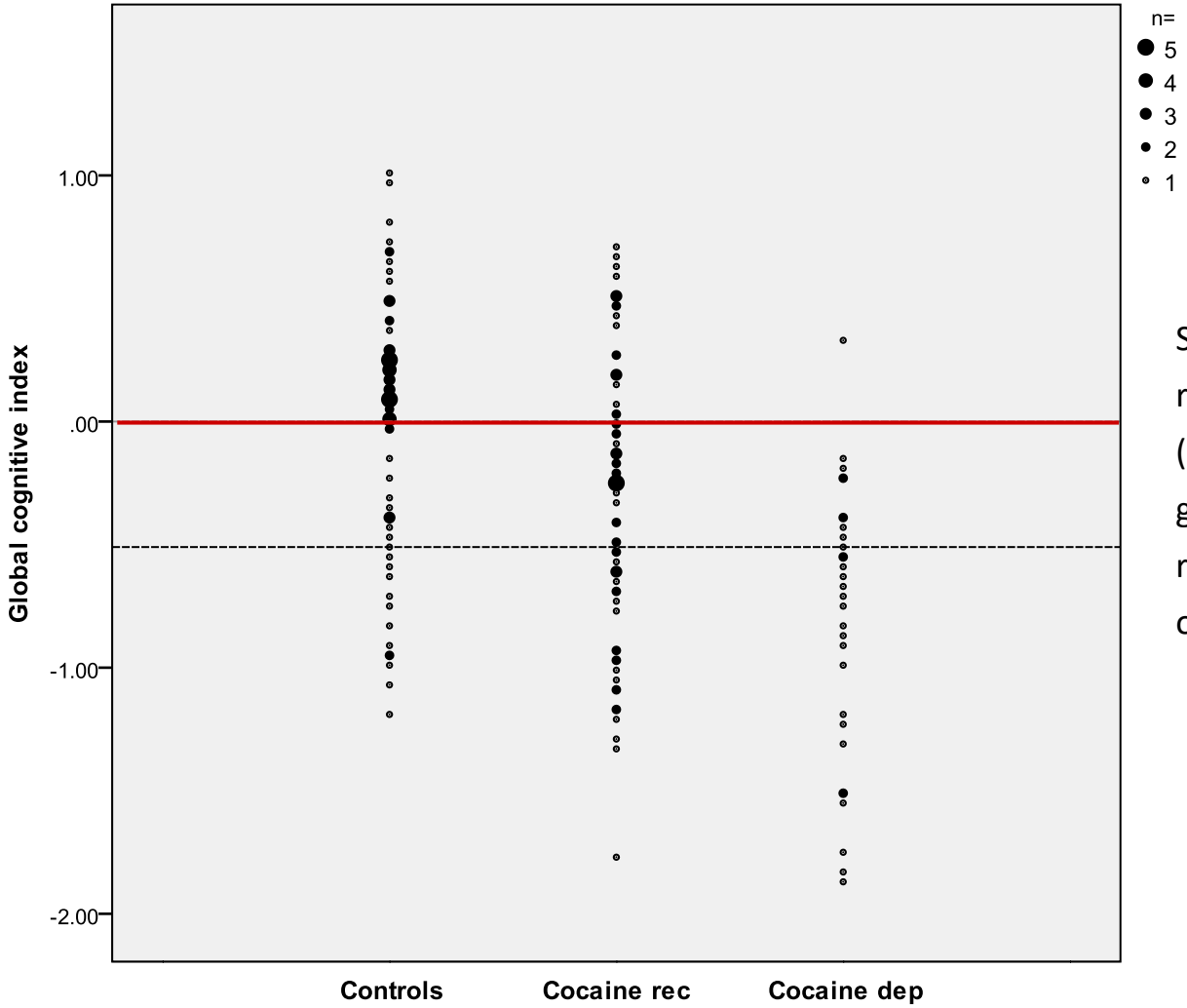
*Vonmoos et al. 2013, Br J Psychiatry*




Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). The dotted black line represents the (sub)clinical criterion of -1 SD of the control group.

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# Cognitive impairment and cocaine

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*Vonmoos et al. 2013, Br J Psychiatry*

| | n | Global Cognitive Index | Attention | Working memory | Declarative memory | Executive functions |
|---|---|---|---|---|---|---|
| **Cumulative dose (grams) log[a]** | 98 | ***-.50 | **-.31 | ***-.39 | ***-.43 | ***-.42 |
| **Cumulative dose (grams) log, adj. for age[b]** | 98 | ***-.47 | ***-.34 | ***-.34 | ***-.39 | ***-.37 |
| **Times per week[a]** | 98 | -.17 | | | | *-.25 |
| **Grams per week log[a]** | 98 | | | | | |
| **Years of use[a]** | 98 | ***-.33 | | ***-.33 | **-.29 | ***-.40 |
| **Years of use, adj. for age[b]** | 98 | **-.28 | | *-.25 | *-.22 | ***-.35 |
| **Maximum dose (grams/day)[a]** | 98 | **-.26 | *-.23 | | **-.27 | |
| **CCQ sum score (0-70)[a]** | 98 | | | -.18 | | |
| **Hair analysis Cocaine pg/mg[a]** | 97[c] | *-.22 | | | -.20 | -.18 |
| **Hair analysis Benzoylecgonine pg/mg[a]** | 97[c] | **-.29 | -.17 | *-.24 | **-.28 | *-.20 |
| **Hair analysis Cocaethylene pg/mg[a]** | 97[c] | | | | | |
| **Hair analysis Norcocaine pg/mg[a]** | 97[c] | **-.28 | | **-.26 | **-.27 | *-.21 |
| **Hair analysis Cocaine$_{total}$ pg/mg[a]** | 97[c] | *-.24 | | -.17 | *-.22 | -.19 |

Correlations with a p-level below 10% are shown, while significant correlations are marked: ***p<.05; **p<.01; ***p<.001**

[a] Pearson's product-moment correlation

[b] Partial Correlation corrected for age

[c] One hair sample of an RCU was deficient

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# Cognitive impairment in cocaine users

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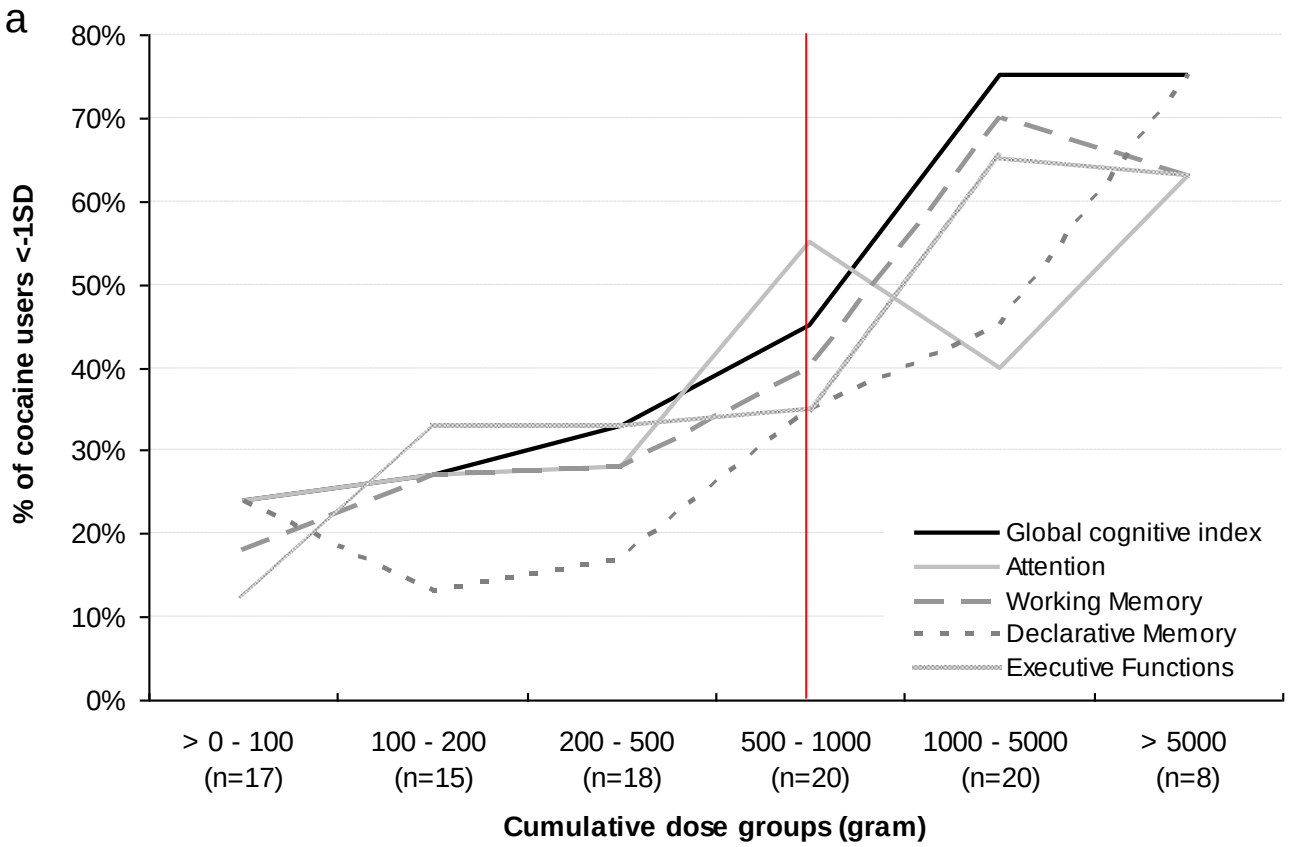
*Vonmoos et al. 2013, Br J Psychiatry*




- From a cumulative lifetime dose of 500-1000g cocaine ~50% of the users display subclinical deficits (>1 SD), while ~20% show clinically relevant cognitive decline (>1.5 SD).

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# The role of ADHD and age of onset

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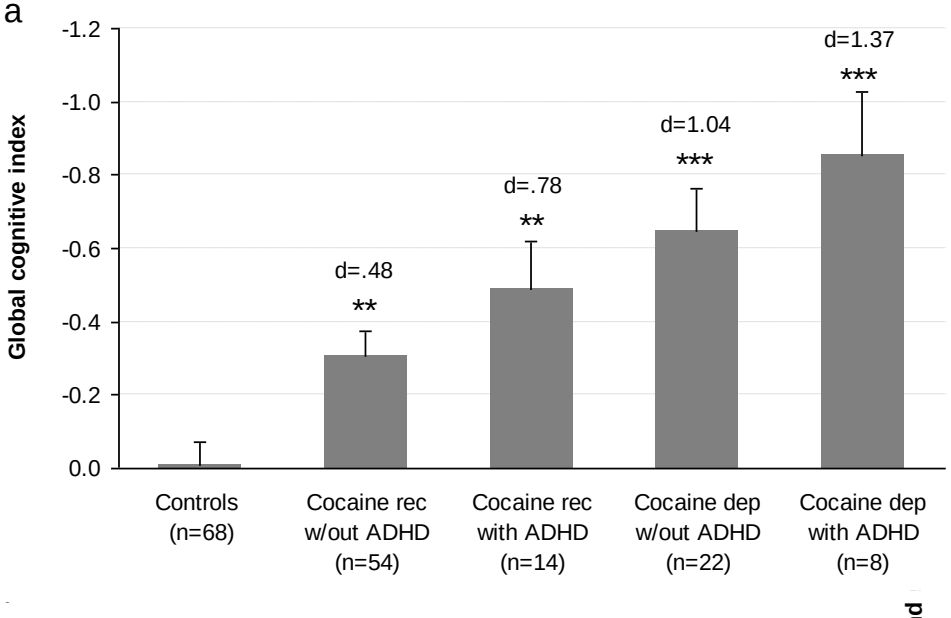
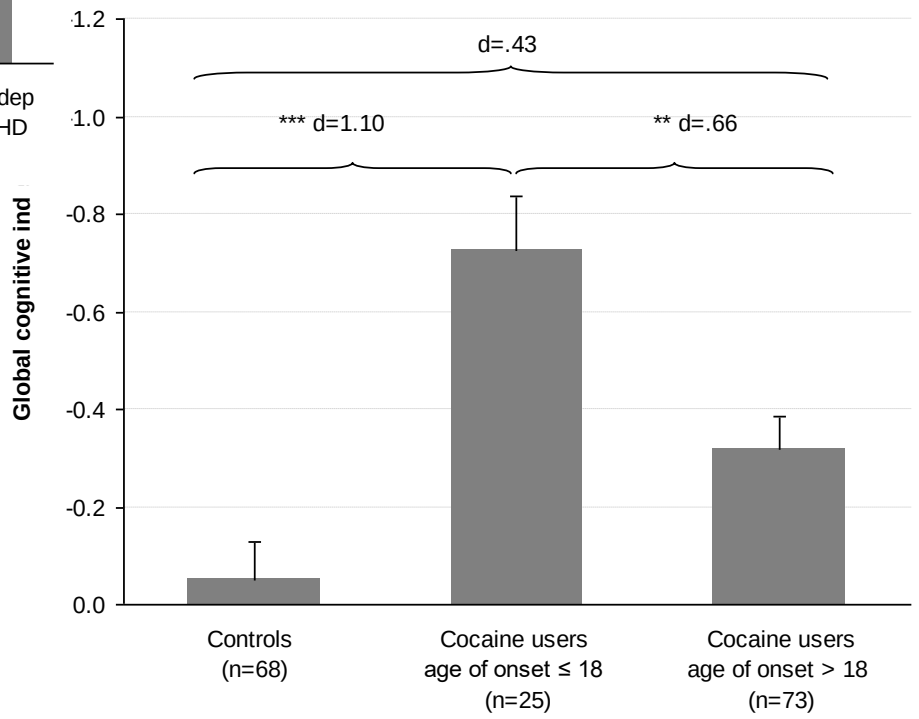
a




*Vonmoos et al. 2013, Br J Psychiatry*

- Early age of cocaine use onset had a great impact on cognitive performance.




- Comorbid ADHD had an additional impact on cognition but did not explain the impairment in general.

**Sidak post hoc tests: *p<.05; **p<.01; ***p<.001**

# Cortical thickness an subcortical volumes in cocaine users

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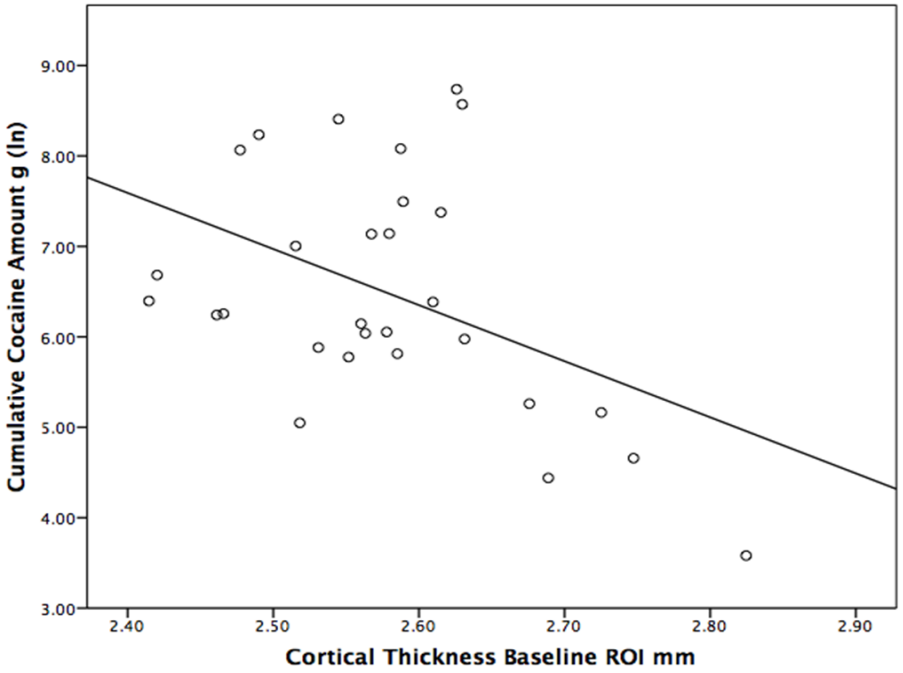
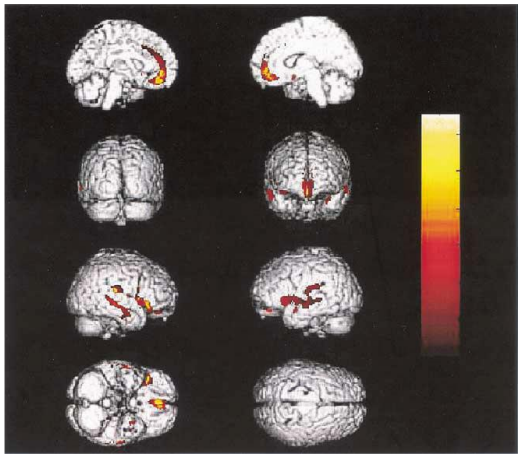
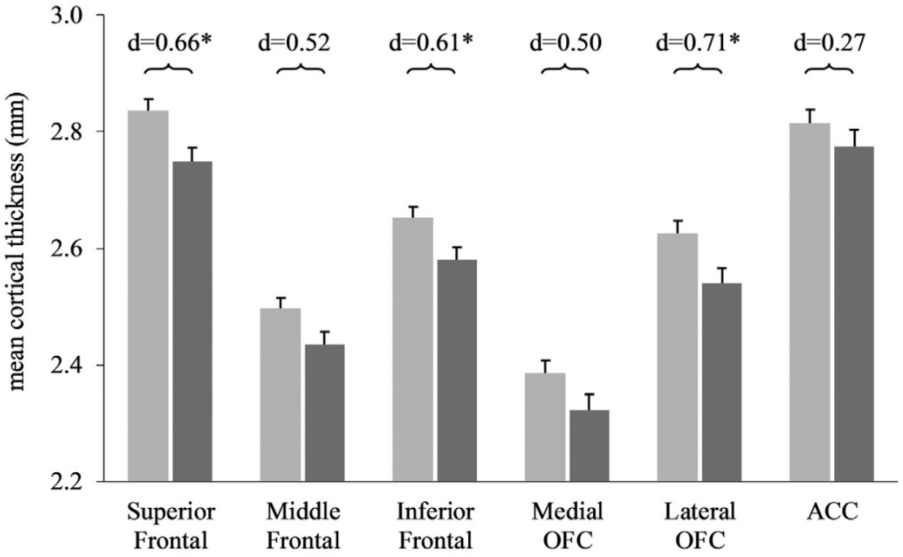


*Franklin et al. 2002, Biol Psychiatry*




- Cocaine users displayed reduced cortical thickness compared to controls within frontal regions, which are correlated with cumulative cocaine intake and attention.

*Hirsiger et al. 2019, Neuroimage Clin*

**Sidak post hoc tests: *p<.05**

# The role of adulderants

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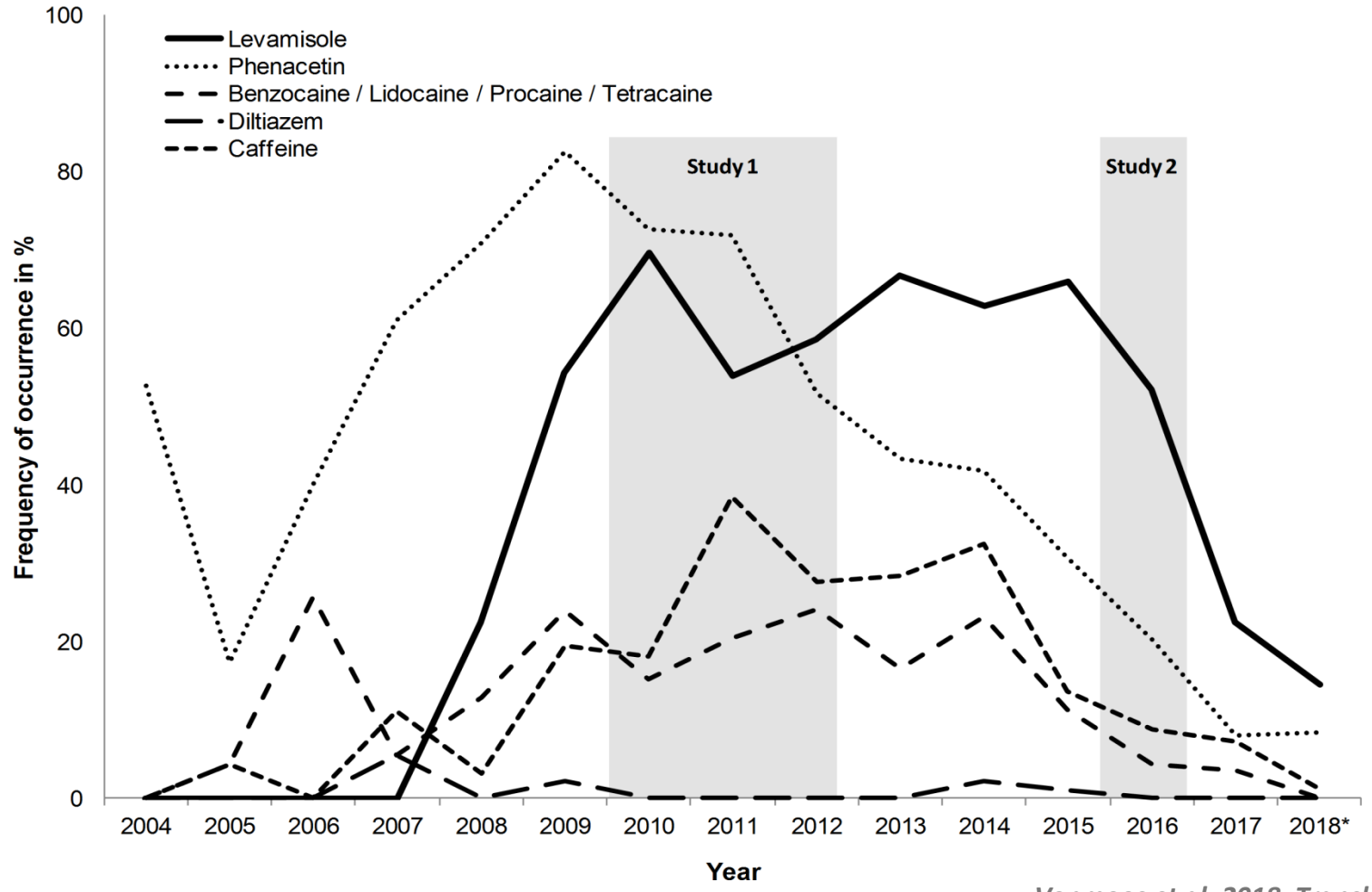


*Vonmoos et al. 2018, Transl Psychiatry*

# The role of adulderants

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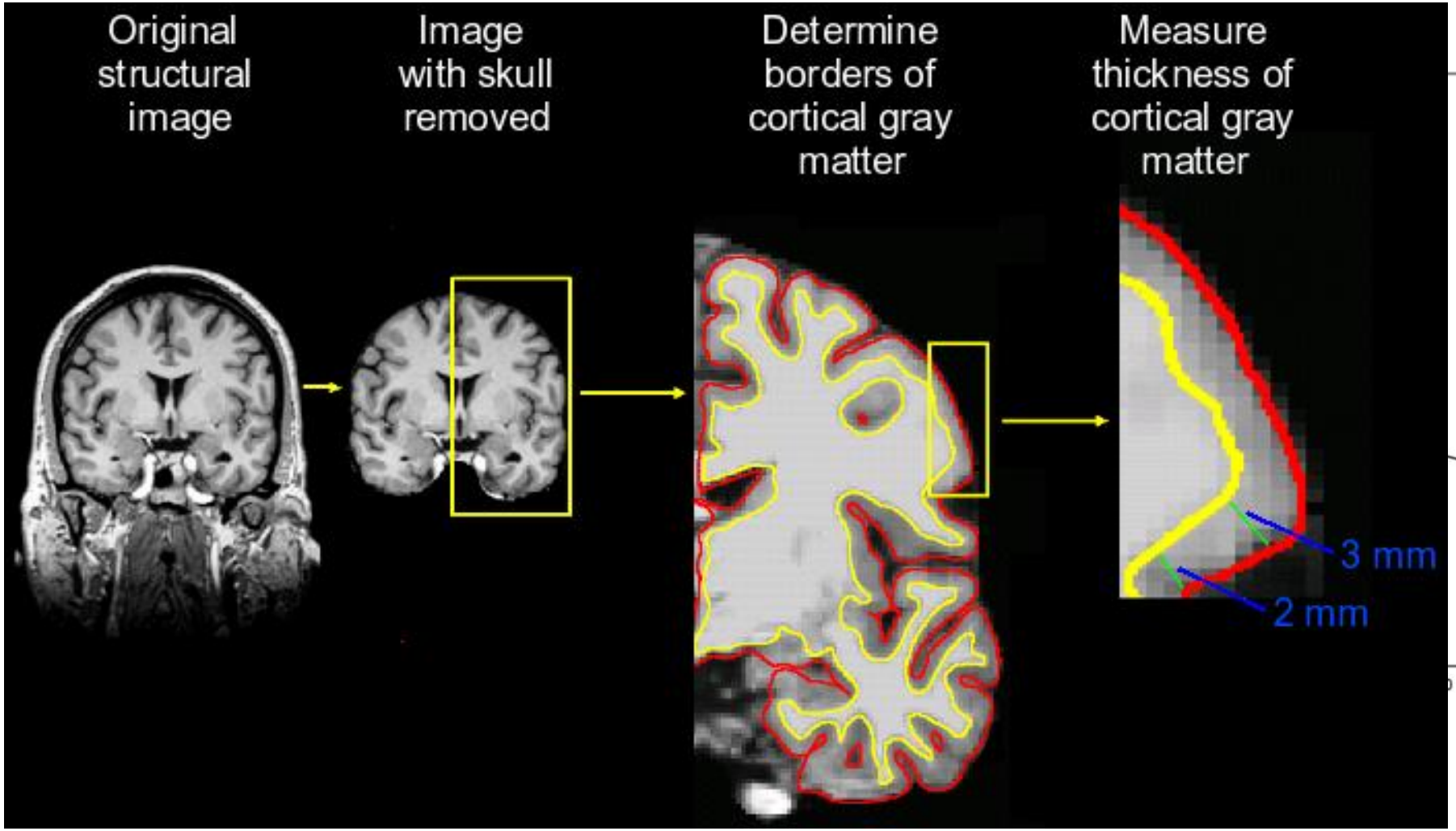


**Sidak post hoc tests: *p<.05; ***p<.01; p<.001, cov: age, verbal IQ, ADHS-SR**

*Vonmoos et al. 2018, Transl Psychiatry*

# Empathy

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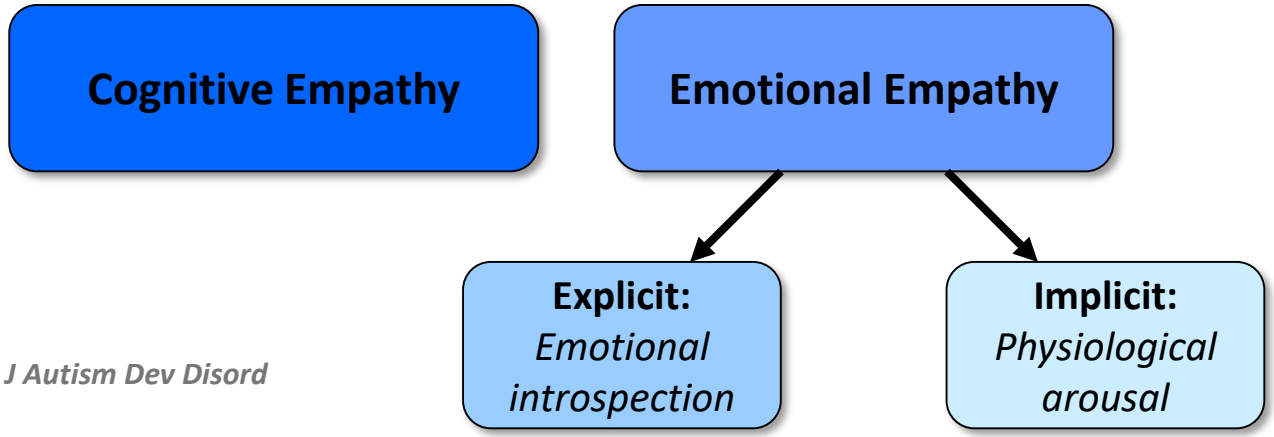
**Multifaceted Empathy Test (MET):**

- Complex fotorealistic stimuli
- 40 photos showing persons in emotional situations
- 3 questions with regard to each photo
- 3 subscales:
  - Cognitive Empathy (emotion recognition)
  - Emotional Empathy
    -> *explicit*: How much do you feel with this person?
    -> *implicit*: How much are you excited if you see this person?




*Dziobek et al. 2008, J Autism Dev Disord*

# Multifaceted Empathy Test (MET)

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**What does this person feel?**

**Cognitive Empathy**

1. ashamed
3. amused
2. embarrassed
4. charmed

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# Multifaceted Empathy Test (MET)

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**How much do you feel with this person?**

**Emotional Empathy**

**Explicit:** *Emotional introspection*

**1 2 3 4 5 6 7 8 9**

**not at all** **very**

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# Multifaceted Empathy Test (MET)

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**How much are you excited watching this picture?**

**Emotional Empathy**

**Implicit:** *Physiological arousal*

**1 2 3 4 5 6 7 8 9**

**not at all** **very**

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# Results: MET

*Preller et al. 2014, Addict Biol*

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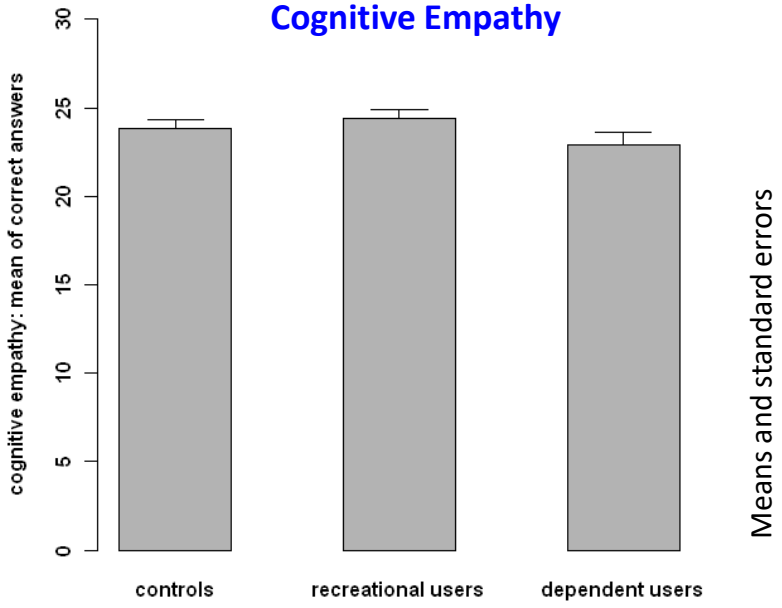
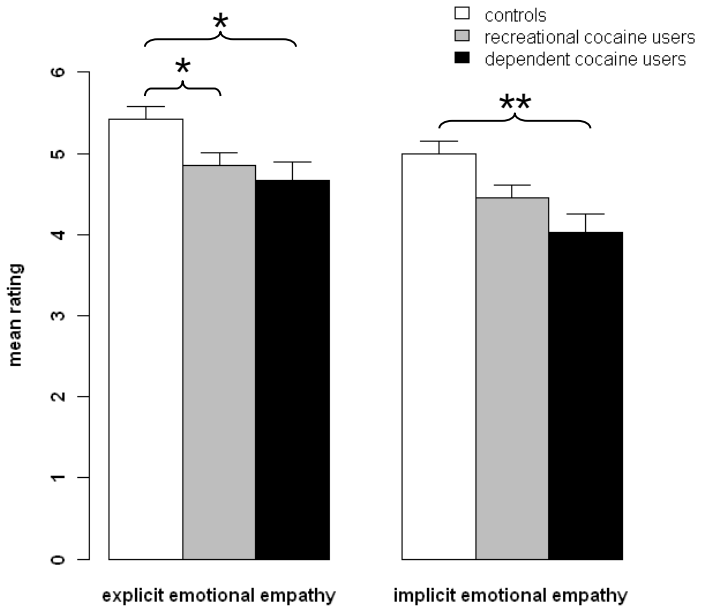
- Implicit Emotional Empathy was correlated with cumulative lifetime cocaine dose (r=.23, p<.05) and with cocaine g/week (r=.33, p<.01).




Means and standard errors

**Sidak post hoc Test: *p<.05, **p<.01**




Corrected for age & years of education

**Emotional Empathy**

- Emotion recognition is not impaired in cocaine users but implicit and explicit Emotional Empathy seem to decrease with increasing cocaine consumption.

# Results: Social Network

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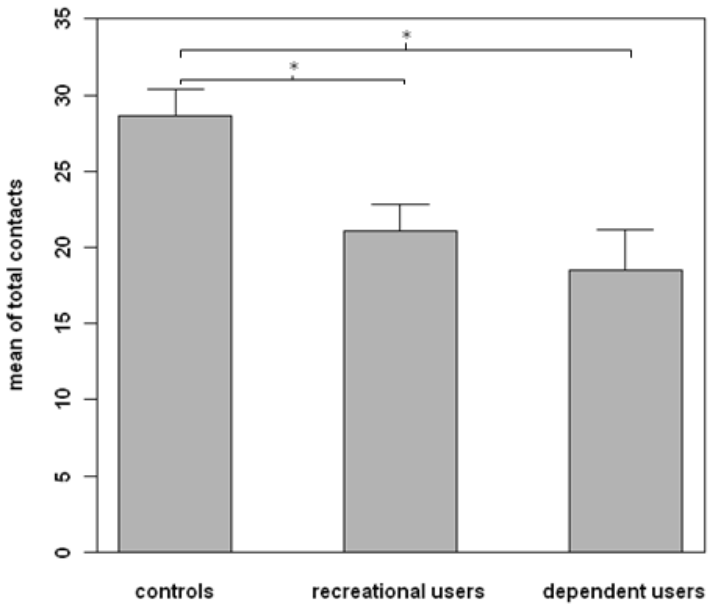
*Preller et al. 2014, Addict Biol*

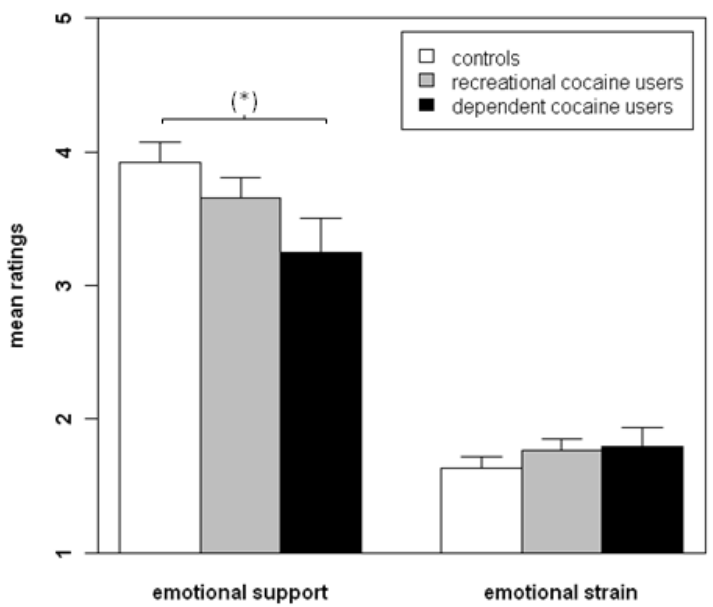
A

## Social Network Size




B

## Social Network Quality




- Recreational and dependent cocaine users display a smaller social network (friends, family) and they report less emotional support.
- The network was so much smaller as more ($r=-0.25$, $p<.01$) and longer ($r=-0.30$, $p<.01$) cocaine was used.
- Network size was correlated with emotional explicit empathy ($r=0.18$, $p<.05$).

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# Take-Give Game

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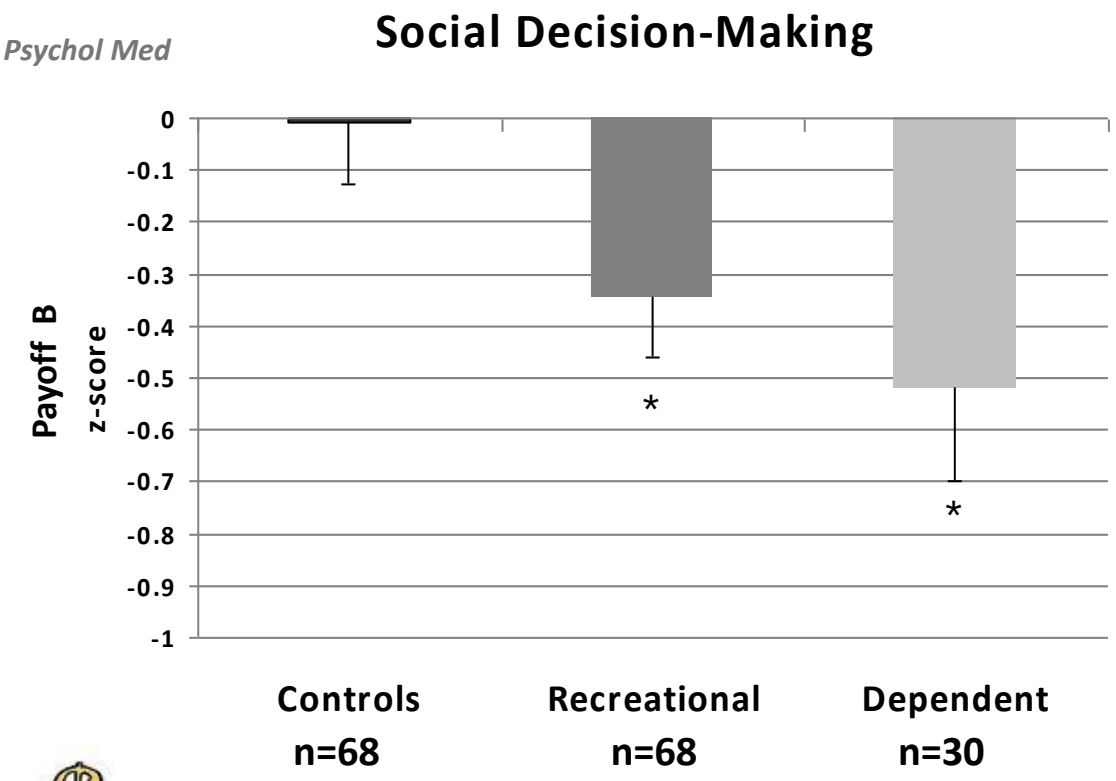
*Hulka et al. 2014, Psychol Med*




Z-transformed means of pay-off B from the subsequent Distribution Game and the Dictator Game.

Multiple regression analysis corrected for age, sex, years of education and dummy-coded groups: *p<.05

- Recreational and dependent users are less altruistic compared to controls in social money distribution games.

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# Longitudinal results

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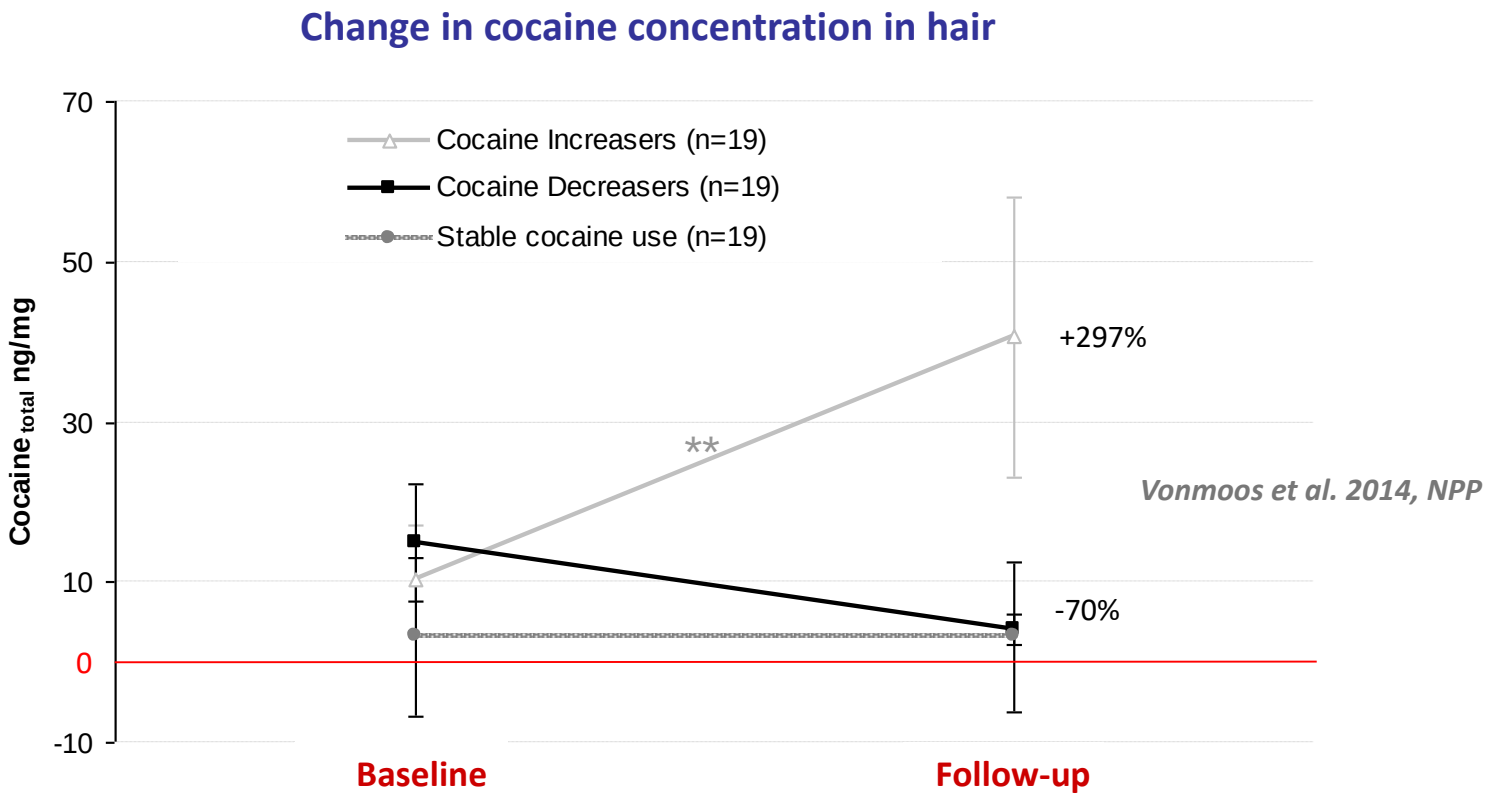


The criterion for group assignment was a combination of absolute and relative changes in cocaine concentration in hair samples between baseline (t1) and follow-up (t2):

- **Absolute criterion**: shift in cocaine concentration of at least ±500 pg/mg
- **Relative criterion**: minimal increase of 20% or a minimal decrease of 10% in the hair toxicology parameter $Cocaine_{total}$ (=Cocaine+Benzoylecgonine+Norcocaine)

# Longitudinal results

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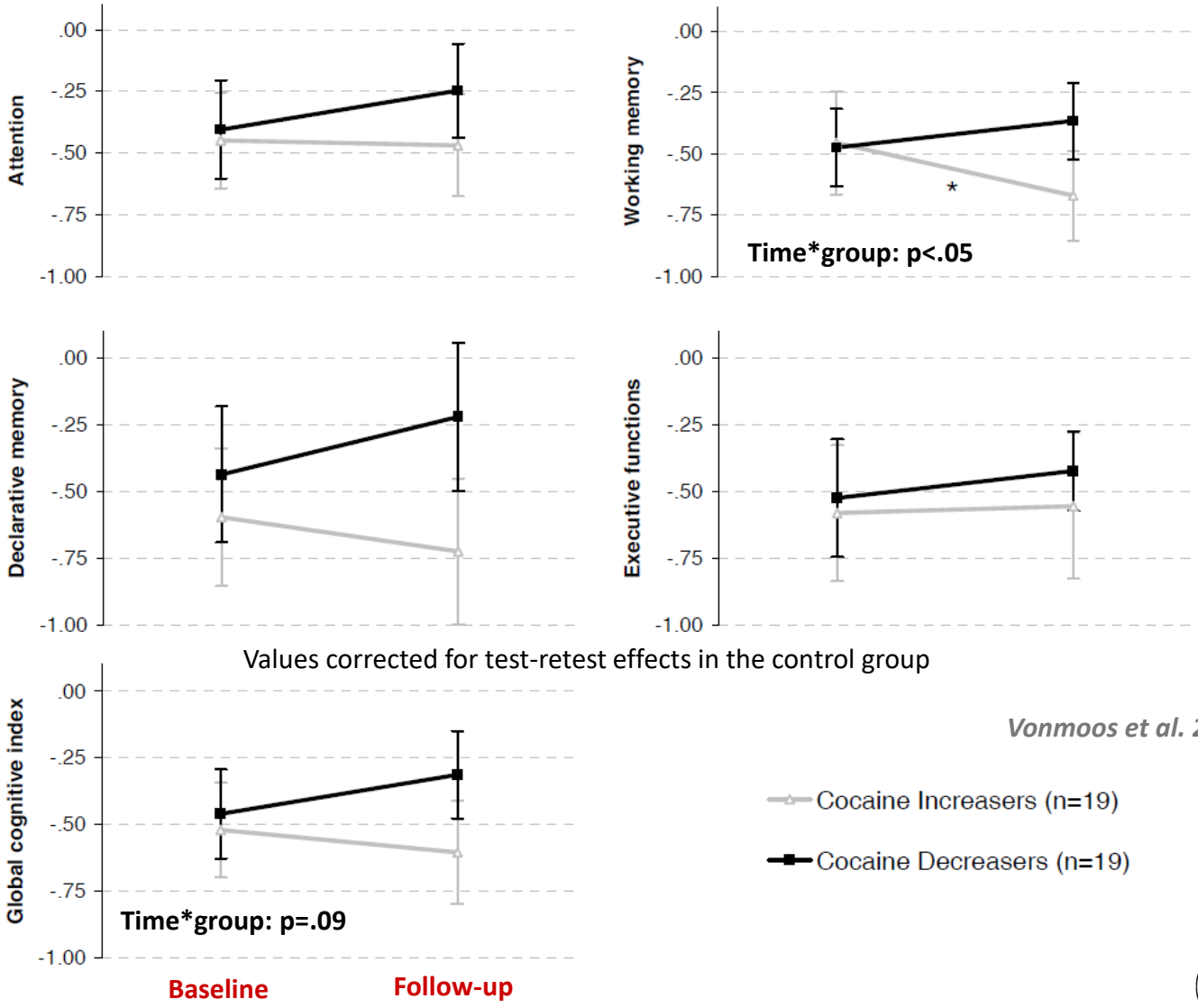


Values corrected for test-retest effects in the control group

*Vonmoos et al. 2014, NPP*

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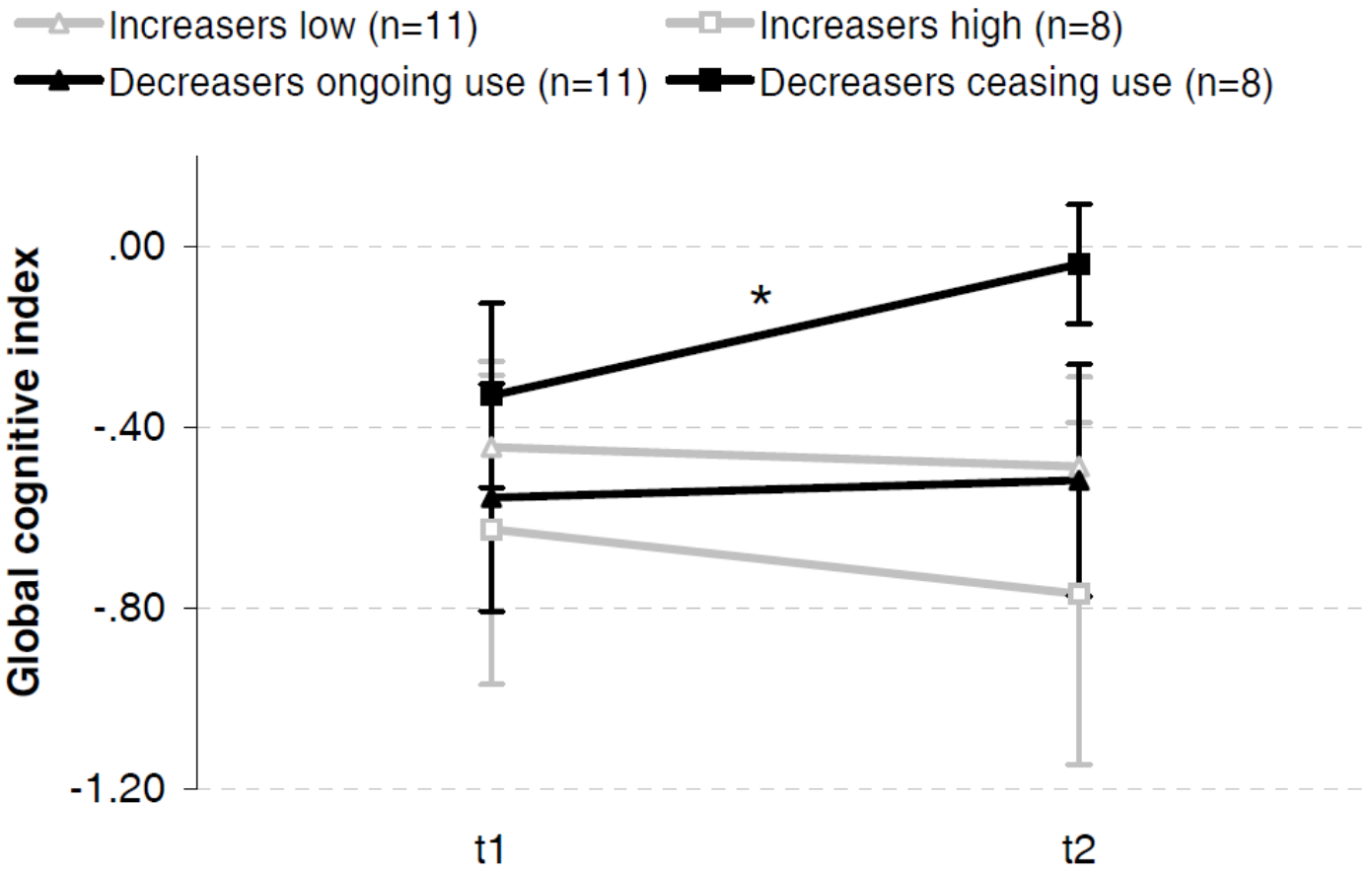
# Longitudinal results

Psychiatrische Universitätsklinik Zürich




*Vonmoos et al. 2014, NPP*

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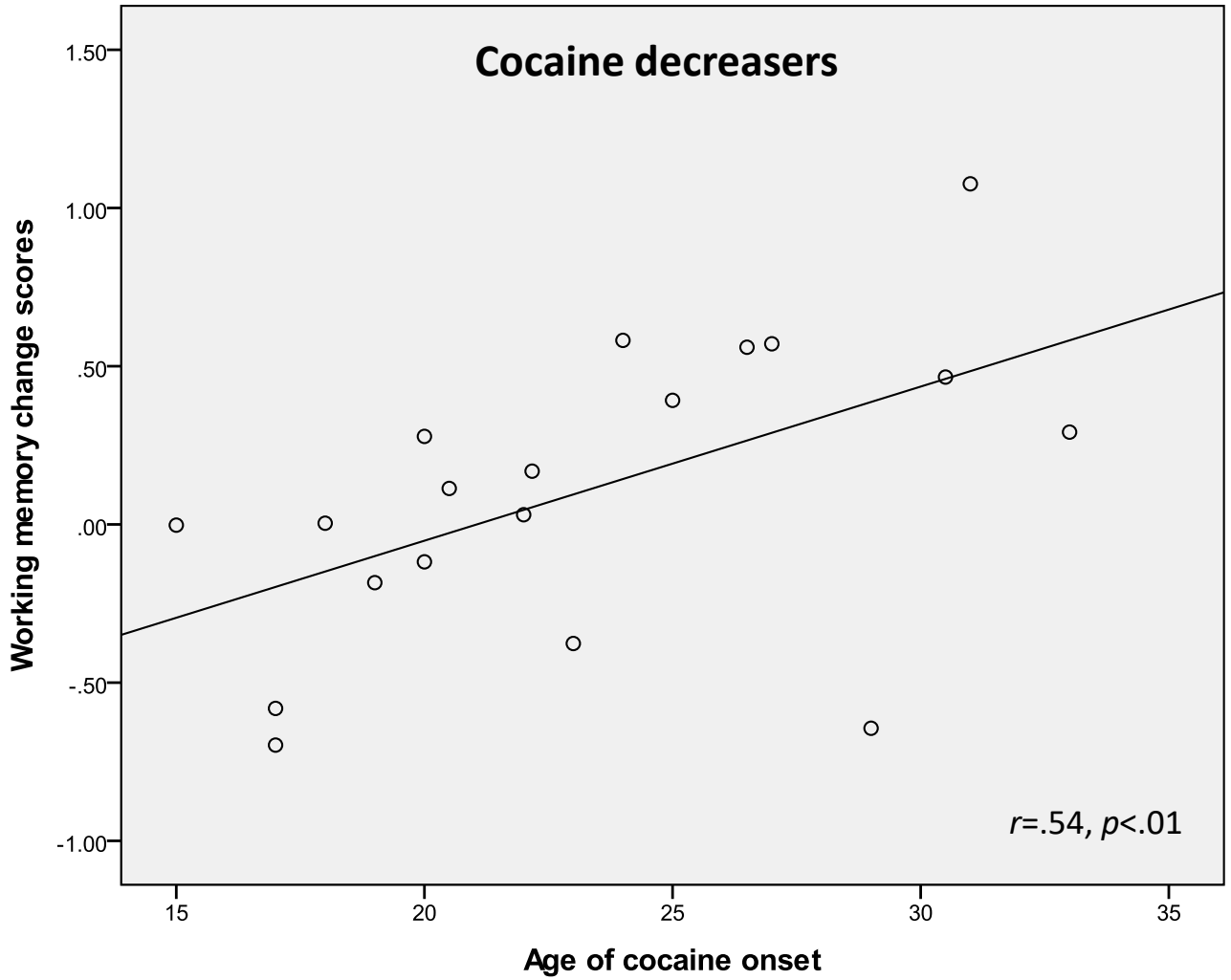
# Longitudinal results

Psychiatrische Universitätsklinik Zürich




*Vonmoos et al. 2014, NPP*

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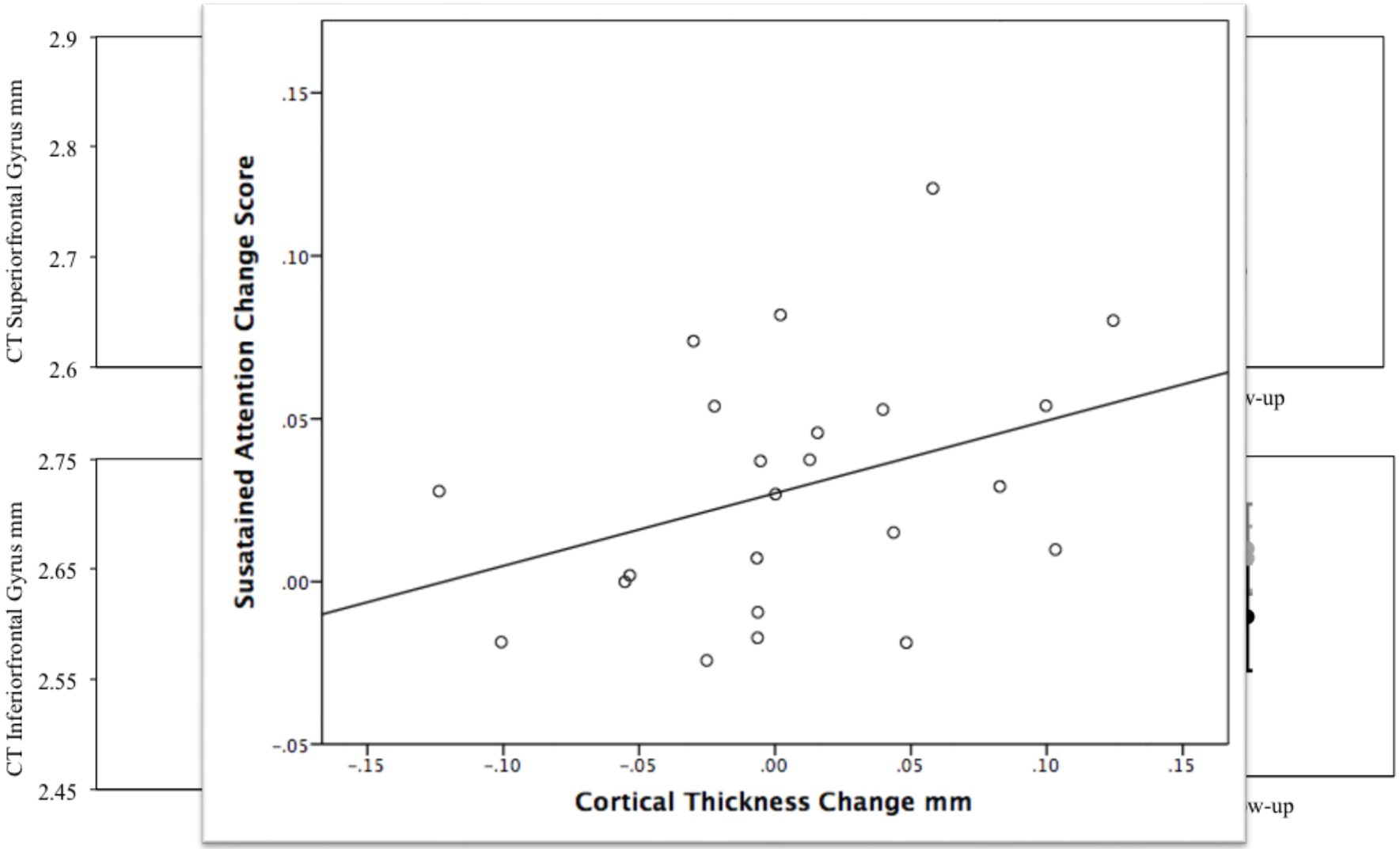
# Longitudinal results

Psychiatrische
Universitätsklinik Zürich




*Hirsiger et al. 2019, Neuroimage Clin*

# Longitudinal results

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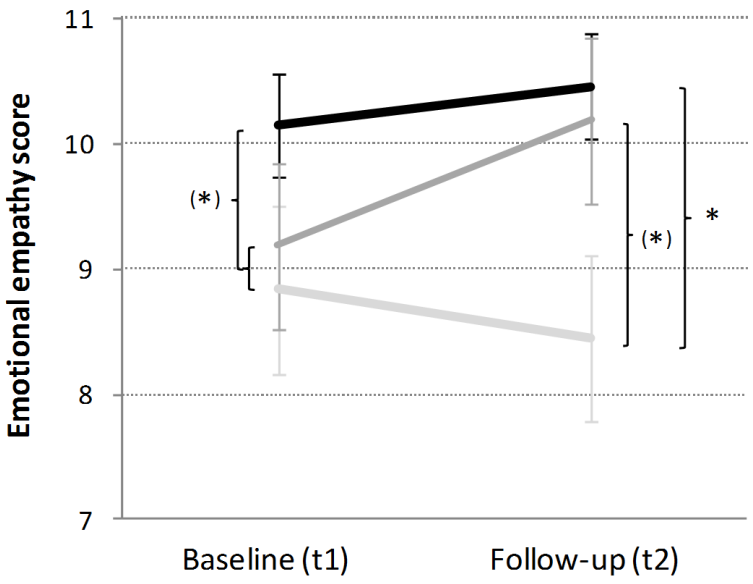
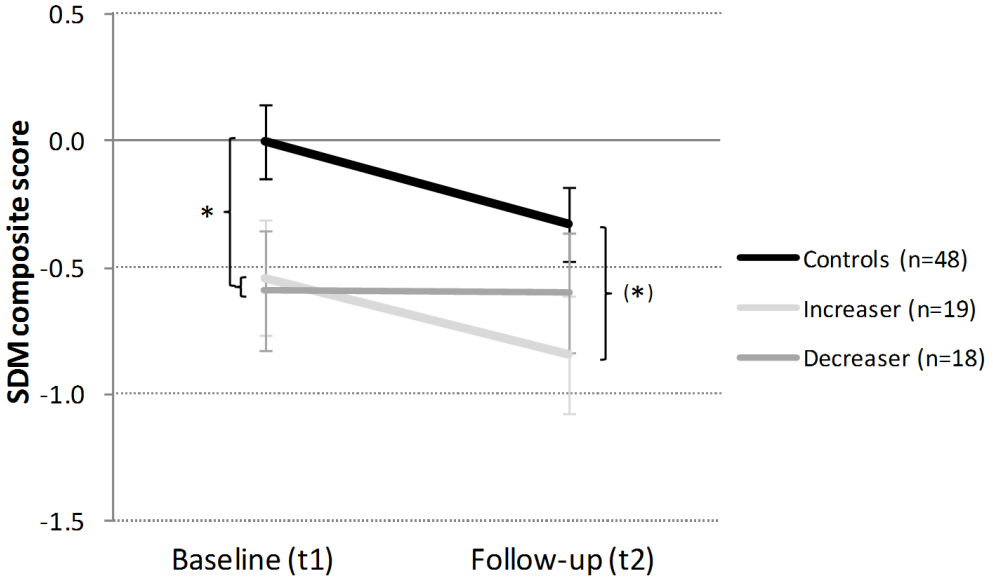
## Emotional Empathy




## Social decision-making




- Social and non-social cognitive deficits as well as associated cortical changes are at least in part drug-induced in cocaine users!

*Vonmoos, Eisenegger et al., in revission*

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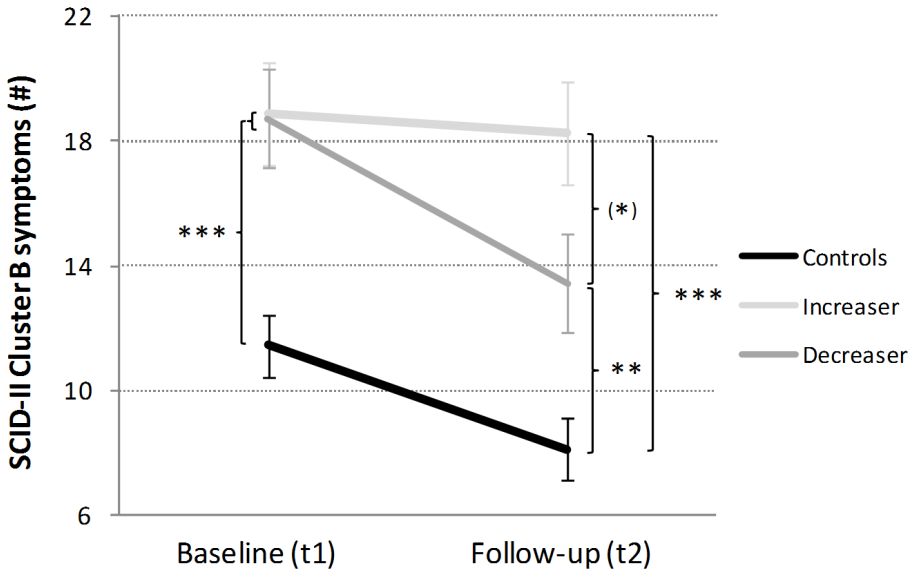
# Longitudinal results

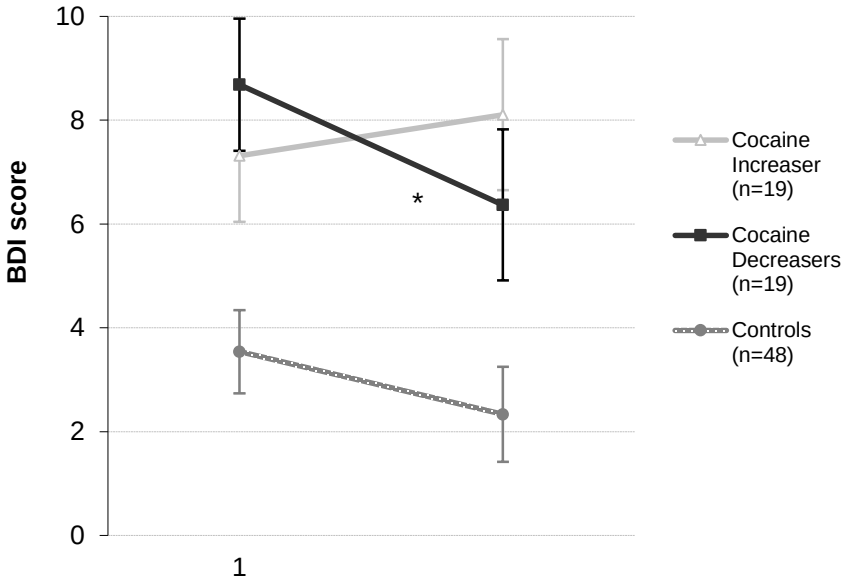
Psychiatrische Universitätsklinik Zürich

## Cluster B personality disorder




*Vonmoos, Eisenegger et al., in revision*

## Depressive symptoms




*Kluwe-Schiavon et al., in preparation*

- Personality disorder symptoms seem to be improve with abstinence and might also be partially drug-induced in cocaine users!

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# Summary

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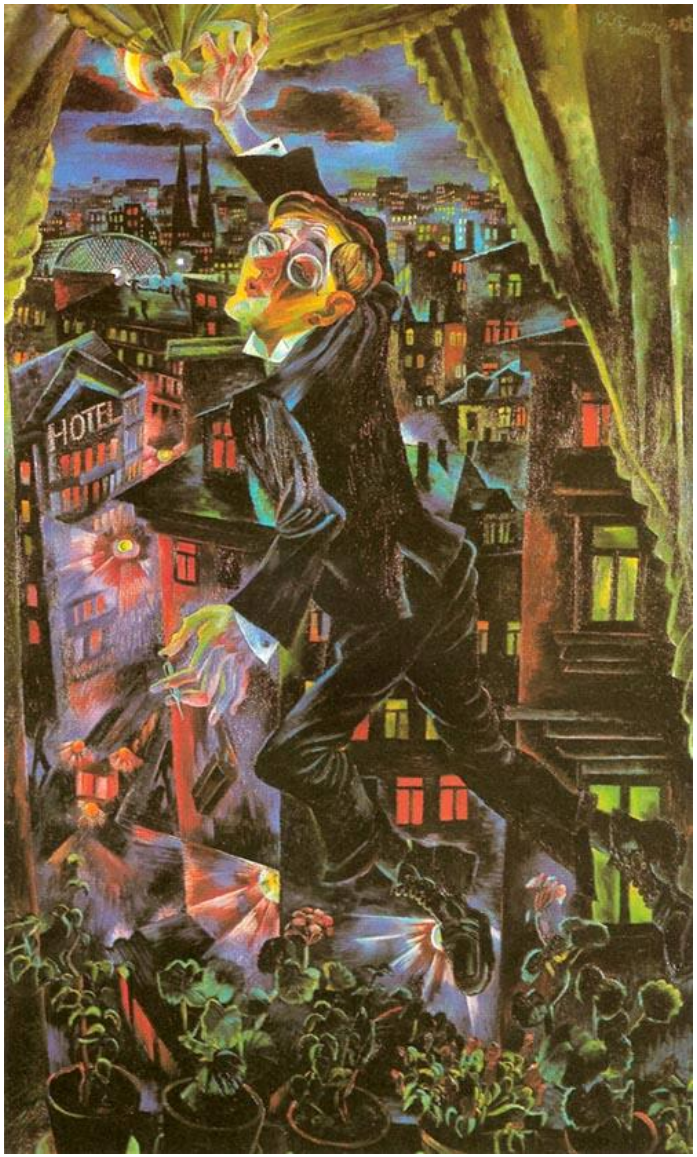
- Recreational and dependent cocaine users display broad cognitive impairments.
- Basal cognitive functions are correlated with several subjective and objective drug intake parameters.
- Emotional empathy, theory-of-mind, prosocial behaviour, and social network size are altered in cocaine users.
- Basal cognitive functions, impulsivity, emotional empathy, and prosocial behaviour covary with changing cocaine use. Thus, they are probably, at least in part, drug-induced. → Neuroplasticity!
- Age of onset and adulderants are important factors for impairment and recovery in cocaine users.




Conrad Felixmüller (1925), Der Tod des Dichters Walter Rheiner

# Acknowlegements

Psychiatrische Universitätsklinik Zürich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# Thank you for your attention!

Goa 2014

# Vicious circle of cocaine addiction

Psychiatrische Universitätsklinik Zürich

Chronic cocaine use

Neuroplastic changes in brain regions and neurotransmitter systems involved in social cognition, interaction, and reward processing

Deficits in socio-cognitive functions (empathy, theory-of-mind), prosocial behaviour, and blunted response to social reward

Decrease of social contact and support leading to an increase of social isolation, aggression, and depressive symptoms

Reduction of social reward resources

Ongoing social withdrawal

Cocaine use as the main source of reward

Maintenance of cocaine use and relapse

*Quednow, 2017, Curr Opin in Behav Sci*

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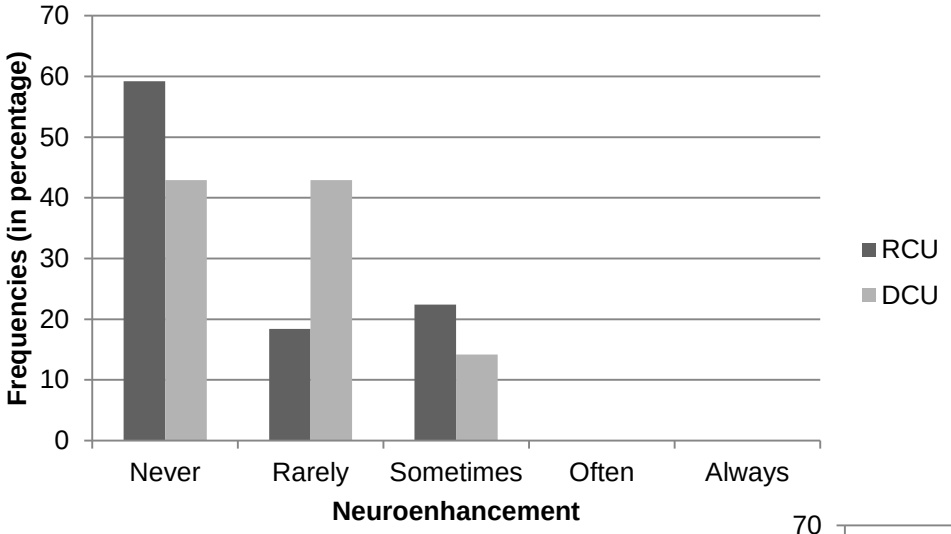
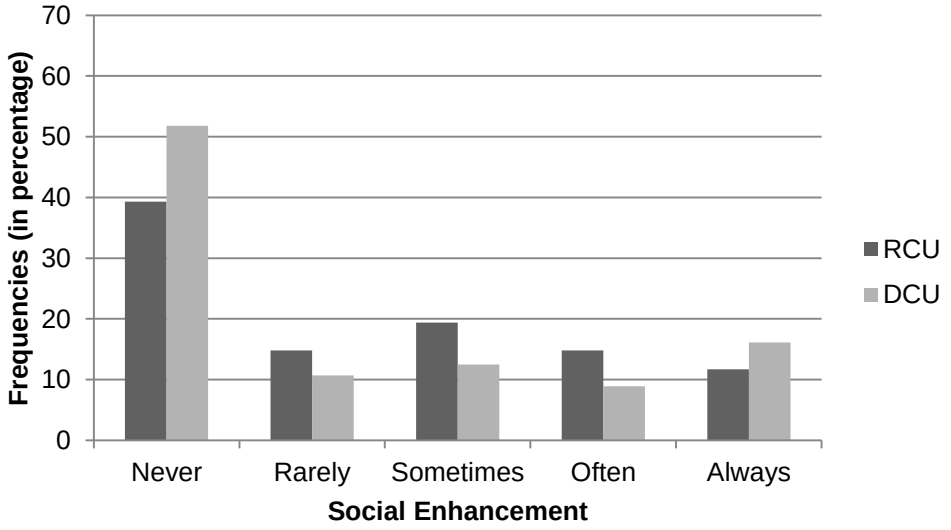
# Instrumentalization of cocaine use

Psychiatrische Universitätsklinik Zürich




- Recreational users employ cocaine more often for social enhancement than dependent users.

- The purpose of cocaine use for social enhancement is more frequent than for neuroenhancement.




*Kexel et al. in preparation*

# Social Interaction

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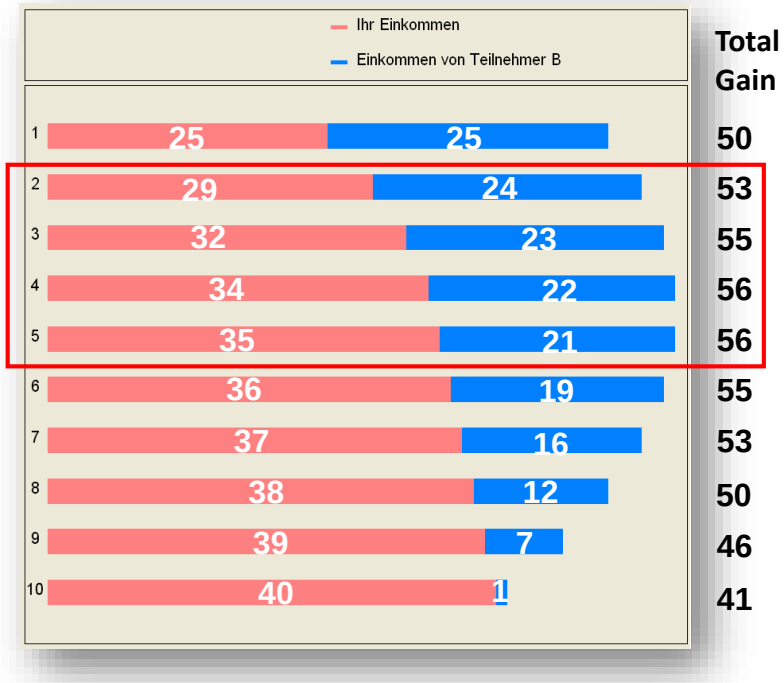
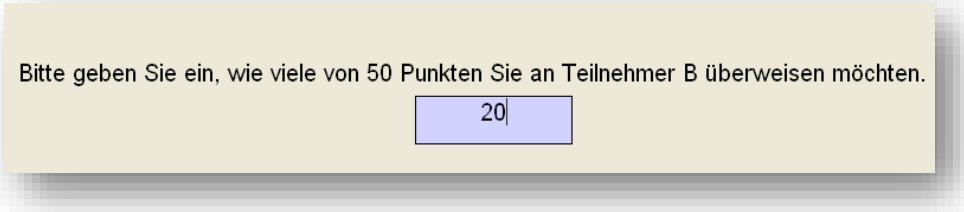



### 1. Stage

- Player A choose one of 10 possible point distributions for himself and player B.

### 2. Stage

- Player A has the oppurtunity to give player B any amount of points (0-50).




- Take-Give Game (social decision-making)
- Adaptation of the Dictator Game
- Two Player: A und B
- Two Stages (Taking and Giving)
- Points are converted to real money in the end.
- Measures fairness vs. efficiency preferences and altruism.

*Hulka et al. 2014, Psychol Med*

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# Sample characteristics

Psychiatrische Universitätsklinik Zürich

| *Preller et al. in press, Addict Biol* | *Control group (n = 68)* | *Recreational cocaine users (n = 69)* | *Dependent cocaine users (n = 31)* |
|---|---|---|---|
| Male/female participants (*n*) | 47/21 | 49/20 | 24/7 |
| Age | 29.81 (9.13) | 28.09 (6.60) | 34.81 (10.22)*,°° |
| Years of education | 10.62 (1.67) | 10.35 (1.91) | 9.47 (1.18)**,° |
| Verbal IQ | 104.87 (9.66) | 103.17 (9.28) | 101.81 (11.23) |
| Smoker/non-smoker (*n*) | 51/17 | 55/14 | 24/7 |
| FTND sum score (0–10)[d] | 2.45 (2.26) | 3.35 (2.22) | 4.79 (2.52)**,° |
| Craving for cocaine (0–70) | — | 19.14 (8.64) | 20.55 (11.65) |
| Antisocial PD (SCID II, 0–15)[e] | 2.40 (2.12) | 4.39 (3.23)** | 4.39 (3.83)** |
| Narcissistic PD (SCID II, 0–16)[e] | 3.06 (2.48) | 4.43 (2.56)* | 5.11 (3.49)** |
| ADHD-SR sum score (0–22) | 7.56 (5.05) | 13.43 (9.65)** | 17.00 (8.51)** |
| BDI sum score (0–63) | 3.66 (3.45) | 7.83 (6.58)** | 11.35 (8.66)**,° |
| Criminal offenses[f] | | | |
| Total | 0.54 (0.98) | 1.31 (2.07) | 1.84 (2.12)** |
| Drug related | 0.21 (0.45) | 0.65 (1.07)* | 1.40 (1.12)**;°° |
| Non-drug related | 0.33 (0.89) | 0.66 (1.74) | 0.44 (1.19) |
| Cocaine related | — | 0.24 (0.62)* | 0.80 (0.71)**,°° |
| Non-cocaine related | 0.54 (0.98) | 1.05 (1.93) | 1.04 (1.88) |
| Forfeit | 0.47 (0.89) | 1.13 (1.98) | 1.28 (1.54) |
| Conviction | 0.07 (0.26) | 0.18 (0.61) | 0.56 (1.23)**,° |

*Indicates post hoc (Sidak) versus control group P < 0.05 °Indicates post hoc (Sidak) versus recreational cocaine users group P <0.05.

**Indicates post hoc (Sidak) versus control group P < 0.01. °°Indicates post hoc (Sidak) versus recreational cocaine users group P < 0.01.

| | *Control group (n = 68)* | *Recreational cocaine users (n = 69)* | *Dependent cocaine users (n = 31)* |
|---|---|---|---|
| Cocaine | | | |
| Times per week | — | 1.10 (1.08) | 2.63 (2.46) |
| Grams/week | — | 1.11 (1.43) | 6.72 (14.72) |
| Years of use | — | 6.32 (4.06) | 9.66 (6.42) |
| Maximum dose (24 hours) | — | 3.43 (2.45) | 9.48 (8.57) |
| Last consumption (days) | — | 27.45 (37.35) | 21.62 (35.58) |
| Cumulative dose (grams) | — | 504.32 (751.12) | 5 325.44 (9 505.37) |
| Urine toxicology (pos/neg) | — | 10/58 | 14/17 |
| Hair sample (pg/mg) | | | |
| COC | — | 2670.15 (4600.40) | 22 324.84 (32 083.52) |
| BEC | — | 537.57 (913.16) | 4 710.65 (7 284.00) |
| ECO | — | 258.71 (298.16) | 1 918.71 (3 583.17) |
| NOC | — | 61.60 (99.77) | 570.16 (733.30) |
| MDMA | | | |
| Pills/week | — | 0.08 (0.26) | 0.36 (1.79) |
| Years of use | 1.66 (11.15) | 2.29 (3.62) | 2.92 (5.19) |
| Last consumption (days) | — | 111.28 (110.63) (n = 22) | 81.00 (48.43) (n = 8) |
| Cumulative dose (pills) | 0.97 (2.96) | 31.91 (86.66) | 140.23 (387.41)**,° |
| Hair sample (pg/mg) | 1.78 (14.46) | 509.68 (1462.43)** | 218.55 (633.69) |
| Cannabis | | | |
| Grams/week | 0.56 (1.47) | 0.95 (2.08) | 1.20 (3.68) |
| Years of use | 5.45 (6.82) | 7.54 (5.91) | 9.78 (10.06)* |
| Last consumption (days) | 33.10 (46.98) (n = 30) | 19.81 (30.39) (n = 45) | 66.55 (218.64) (n = 17) |
| Cumulative dose (grams) | 821.85 (3433.07) | 1001.10 (1742.07) | 3259.86 (5957.33)**,° |
| Urine toxicology (pos/neg) | 10/58 | 15/53 | 10/21 |
| Amphetamine | | | |
| Grams/week | — | 0.06 (0.11) | 0.04 (0.18) |
| Years of use | 0.01 (0.06) | 1.53 (2.97)** | 1.49 (3.12)* |
| Last consumption (days) | — | 61.25 (51.84) (n = 25) | 78.38 (75.42) (n = 6) |
| Cumulative dose (grams) | 0.19 (1.42) | 17.02 (44.38)* | 21.49 (61.88)* |
| Hair sample (pg/mg) | 0.9 (7.39) | 84.85 (257.79)* | 57.74 (166.85) |
| GHB | | | |
| Cumulative dose (pipettes) | — | 1.64 (9.39) | 1.24 (2.85) |
| Halluzinogenes | | | |
| Cumulative dose (times) | 1.46 (6.88) | 6.45 (14.73)* | 6.57 (11.70) |
| Alcohol | | | |
| Grams/week | 119.11 (126.73) | 176.53 (115.95) | 192.32 (256.31) |
| Years of use | 13.23 (9.39) | 10.98 (5.22) | 13.92 (9.31) |
| Nicotine | | | |
| Cigarettes per day (CPD) | 9.18 (9.92) | 12.43 (9.00) | 15.70 (13.98)* |
| Years of use | 9.05 (9.75) | 9.39 (6.38) | 13.98 (9.24)*,° |

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*Indicates post hoc (Sidak) versus control group
P < 0.05

°Indicates post hoc (Sidak) versus recreational cocaine users group
P <0.05.

**Indicates post hoc (Sidak) versus control group
P < 0.01.

*Preller et al. in press, Addict Biol*

# Cognitive impairment and cocaine

Psychiatrische Universitätsklinik Zürich

| Measure | n[a] | Stimulant-naïve controls | Recreational cocaine users | Dependent cocaine users | F | df, $df_{err}$ | p | p, Sidak post-hoc: Controls vs. RCU | p, Sidak post-hoc: Controls vs. DCU | p, Sidak post-hoc: RCU vs. DCU | Cohen's d: Controls vs. RCU | Cohen's d: Controls vs. DCU | Cohen's d: RCU vs DCU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Global Cognitive Index | 68/68/30 | -0.02 (0.06) | -0.35 (0.06) | -0.67 (0.09) | 19.345 | 2, 161 | **<.001** | **<.001** | **<.001** | **.01** | 0.53 | 1.04 | 0.52 |
| *Neurocognitive domain scores* | | | | | | | | | | | | | |
| Attention | 68/68/30 | -0.03 (0.10) | -0.41 (0.10) | -0.68 (0.15) | 7.579 | 2, 161 | **<.001** | **.02** | **.001** | .38 | 0.44 | 0.74 | 0.30 |
| Working memory | 68/68/30 | -0.03 (0.08) | -0.36 (0.08) | -0.81 (0.12) | 16.312 | 2, 161 | **<.001** | **.007** | **<.001** | **.005** | 0.43 | 1.00 | 0.58 |
| Declarative memory | 68/68/30 | -0.02 (0.09) | -0.4 (0.09) | -0.67 (0.15) | 8.333 | 2, 161 | **<.001** | **.01** | **<.001** | .34 | 0.43 | 0.73 | 0.30 |
| Executive functions | 68/68/30 | -0.02 (0.06) | -0.22 (0.06) | -0.5 (0.09) | 11.388 | 2, 161 | **<.001** | **.03** | **<.001** | **.02** | 0.39 | 0.92 | 0.54 |
| *Neuropsychological test scores* | | | | | | | | | | | | | |
| *Attention* | | | | | | | | | | | | | |
| RVP Discrimination performance A' | 67/68/30 | 0.917 (0.0) | 0.899 (0.0) | 0.885 (0.0) | 6.254 | 2, 160 | **.002** | **.04** | **.004** | .43 | 0.42 | 0.72 | 0.31 |
| RVP Total hits | 67/68/30 | 18.3 (0.5) | 16.5 (0.5) | 15.3 (0.8) | 5.561 | 2, 160 | **.005** | **.05** | **.008** | .53 | 0.40 | 0.67 | 0.27 |
| RAVLT Supraspan trial 1 | 68/68/30 | 8.9 (0.2) | 8.4 (0.2) | 8.0 (0.4) | 2.407 | 2, 161 | .09 | .31 | .13 | .81 | 0.25 | 0.41 | 0.17 |
| *Working memory* | | | | | | | | | | | | | |
| LNST Score | 68/68/30 | 15.6 (0.3) | 14.5 (0.3) | 13.2 (0.5) | 8.320 | 2, 161 | **<.001** | .07 | **<.001** | .07 | 0.34 | 0.78 | 0.44 |
| SWM Total errors | 68/67/30 | 20.1 (1.9) | 23.3 (1.9) | 34.5 (2.9) | 8.727 | 2, 160 | **<.001** | .53 | **<.001** | **.005** | 0.19 | 0.84 | 0.65 |
| PAL First trial memory score | 68/67/30 | 15.6 (0.4) | 14.1 (0.4) | 13.4 (0.6) | 6.575 | 2, 160 | **.002** | **.02** | **.005** | .67 | 0.43 | 0.64 | 0.21 |
| *Declarative memory* | | | | | | | | | | | | | |
| RAVLT Learning performance (∑ trials 1-5) | 68/68/30 | 62.0 (0.9) | 58.0 (0.9) | 54.9 (1.4) | 9.612 | 2, 161 | **<.001** | **.009** | **<.001** | .22 | 0.45 | 0.80 | 0.35 |
| RAVLT Adjusted recognition performance p(A) | 68/68/30 | 0.873 (0.0) | 0.858 (0.0) | 0.823 (0.0) | 2.076 | 2, 161 | .13 | .83 | .12 | .39 | 0.13 | 0.44 | 0.31 |
| RAVLT Delayed recall trial 7 | 68/68/30 | 13.1 (0.3) | 11.9 (0.3) | 11.4 (0.5) | 6.046 | 2, 161 | **.003** | **.02** | **.009** | .75 | 0.44 | 0.63 | 0.19 |
| PAL Total errors adjusted | 68/67/30 | 10.6 (1.4) | 15.1 (1.4) | 16.9 (2.2) | 3.852 | 2, 160 | **.02** | .08 | .05 | .88 | 0.35 | 0.49 | 0.14 |
| PAL Total trials adjusted | 68/67/30 | 8.5 (0.3) | 9.5 (0.3) | 10.1 (0.5) | 4.231 | 2, 160 | **.02** | .09 | **.03** | .72 | 0.34 | 0.53 | 0.19 |
| *Executive functions* | | | | | | | | | | | | | |
| IED Total errors adjusted | 68/68/30 | 30.3 (4.1) | 31.3 (4.1) | 32.3 (6.3) | .039 | 2, 161 | .96 | 1.00 | .99 | 1.00 | 0.03 | 0.06 | 0.03 |
| IED Total trials adjusted | 68/68/30 | 104.1 (7.2) | 107.3 (7.3) | 108.5 (11.2) | .075 | 2, 161 | .93 | .98 | .98 | 1.00 | 0.05 | 0.07 | 0.02 |
| SWM Strategy score | 68/67/30 | 32.7 (0.6) | 33.4 (0.6) | 34.9 (0.9) | 1.887 | 2, 160 | .15 | .84 | .15 | .43 | 0.12 | 0.42 | 0.30 |
| RAVLT Recall consistency in % | 68/68/30 | 92.3 (1.1) | 88.1 (1.1) | 83.3 (1.6) | 11.004 | 2, 161 | **<.001** | **.02** | **<.001** | **.05** | 0.43 | 0.92 | 0.49 |

Means and standard errors. ANCOVA (all groups, corrected for age and verbal IQ). Significant p values are shown in bold.
GCI and cognitive domain scores are z-transformed values.
The robustness of these parametric tests was confirmed using bootstrap simulations with 1000 replications. Thereby, only one pairwise Sidak post-hoc comparison above turned from a significant group difference into a statistical trend (RAVLT recall consistency; cocaine rec vs. cocaine dep $p_{post\text{-}hoc}$=.08).
[a] Sample size control group/RCU/DCU. In each of the tasks RVP, PAL, and SWM one subject is missing due to a technical failure.

*Vonmoos et al. 2013, Br J Psychiatry*

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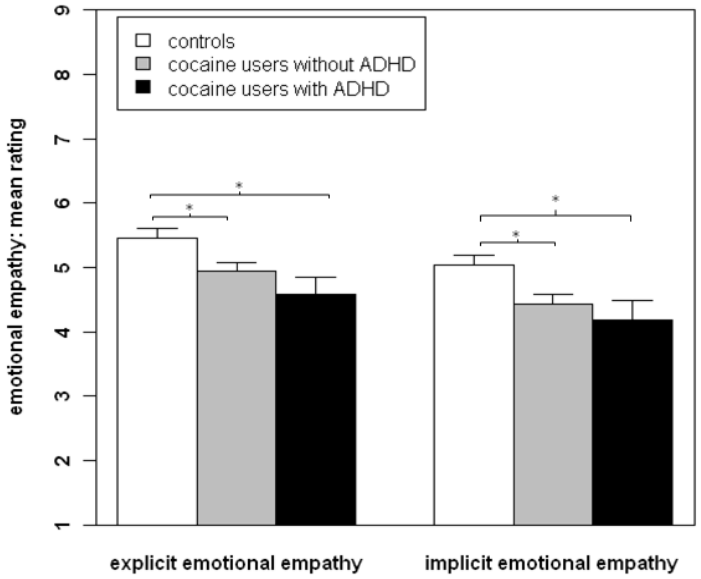
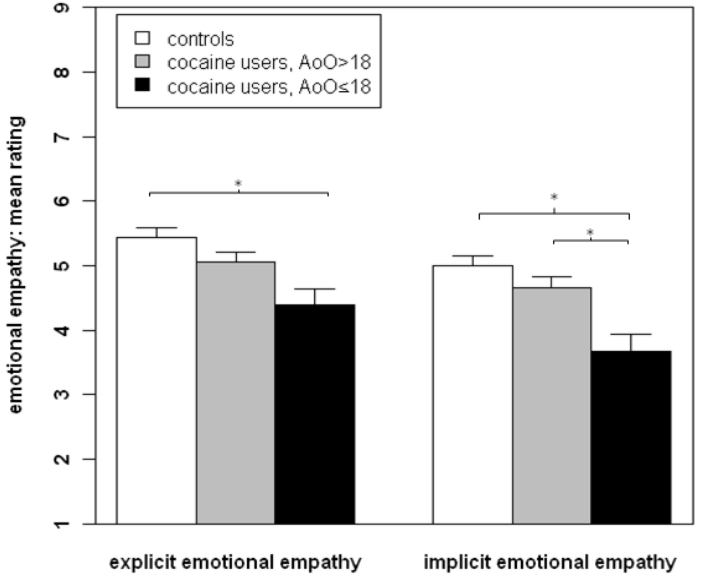
# The role of ADHD and age of onset

Psychiatrische Universitätsklinik Zürich




*Preller et al. Addict Biol, resubmitted*

- Early age of cocaine use onset had a great impact on empathy.

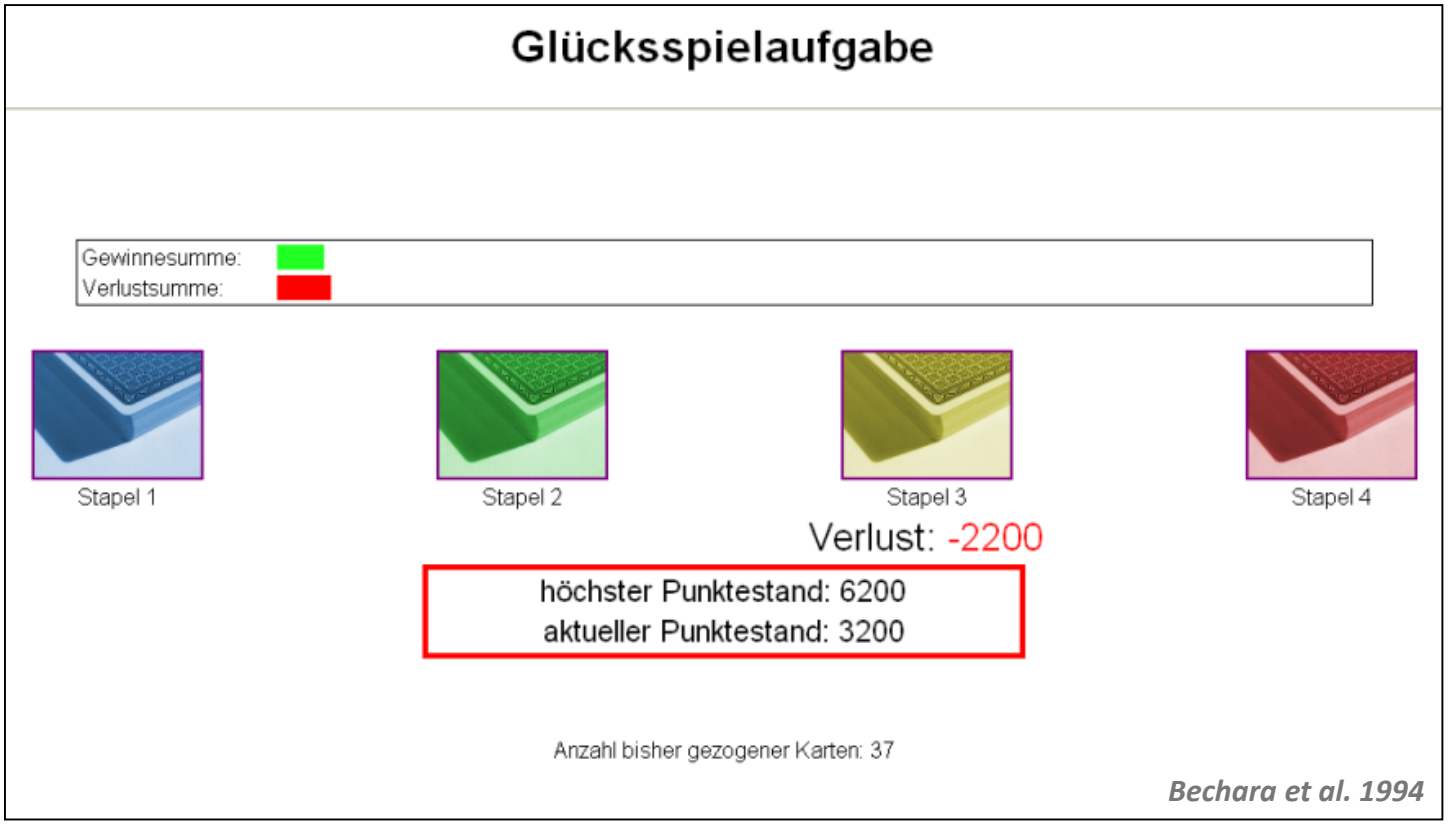



- Comorbid ADHD had an additional impact on empathy but did not explain the impairment in general.

**Sidak post hoc tests: *p<.05; **p<.01; ***p<.001**

# Iowa Gambling Task

Psychiatrische
Universitätsklinik Zürich




Disadvantageous card decks with higher gains but also higher losses

**vs.**

Advantageous card decks with smaller wins but also smaller losses

Universität Zürich[UZH]

# Delay Discounting

Psychiatrische Universitätsklinik Zürich

Do you prefere to receive 54.- today or 55.- in 117 days?

today 31.- or 85.- in 7 days?

today 54.- or 80.- in 30 days?

today 20.- or 55.- in 7 days?

- Fix set of 27 choices between smaller immediately available and larger but later available amounts of money (Kirby et al. 1999, J Exp Psychol).

Magnitude Effect:

- small delayed rewards (25-35 CHF)
- medium delayed rewards (50-60 CHF)
- large delayed rewards (75-85 CHF)

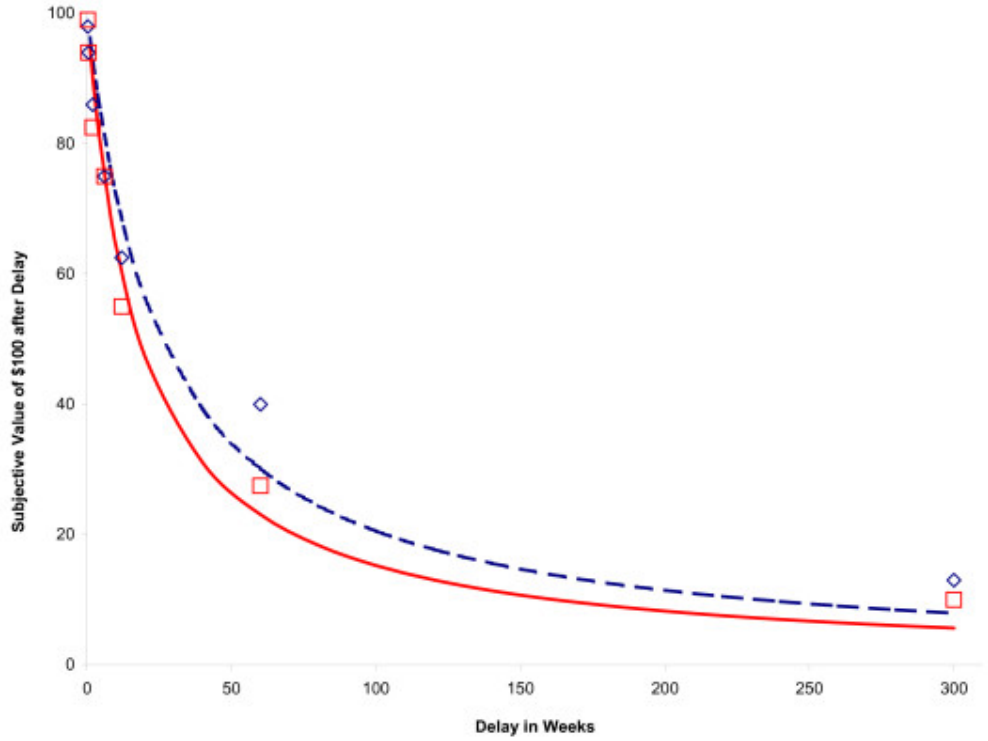
Dependent variables:

- k values for small amounts
- k values for medium amounts
- k values for large amounts

# Delay Discounting



- Delay discounting (DD): describes a decrease in the subjective value of a commodity as a function of delay to that commodity, or reward (Bickel & Johnson, 2003).
- DD is related to impulsive decision-making (being unable to wait for a reward) vs. self-control.
- DD is an important component in the development and maintenance of drug addiction.




Hyperbolic discounting curve

$$v = V/(1 + kD)$$

v = subjective value of the later available value V at the delay D

k = free parameter that determines the discounting rate

*Kirby et al. 1999, J Exp Psychol*

# Decision-making

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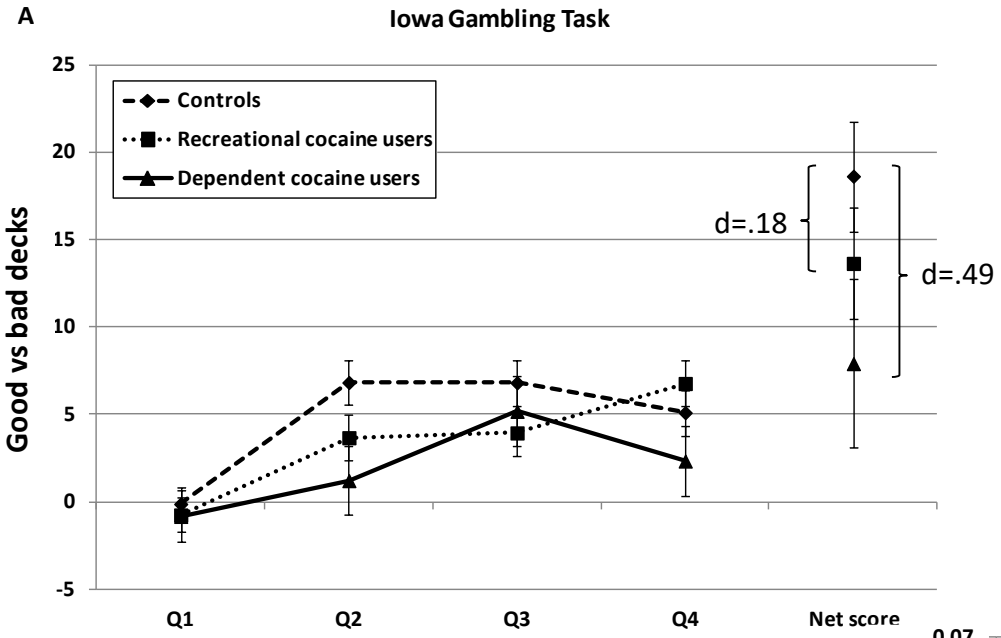
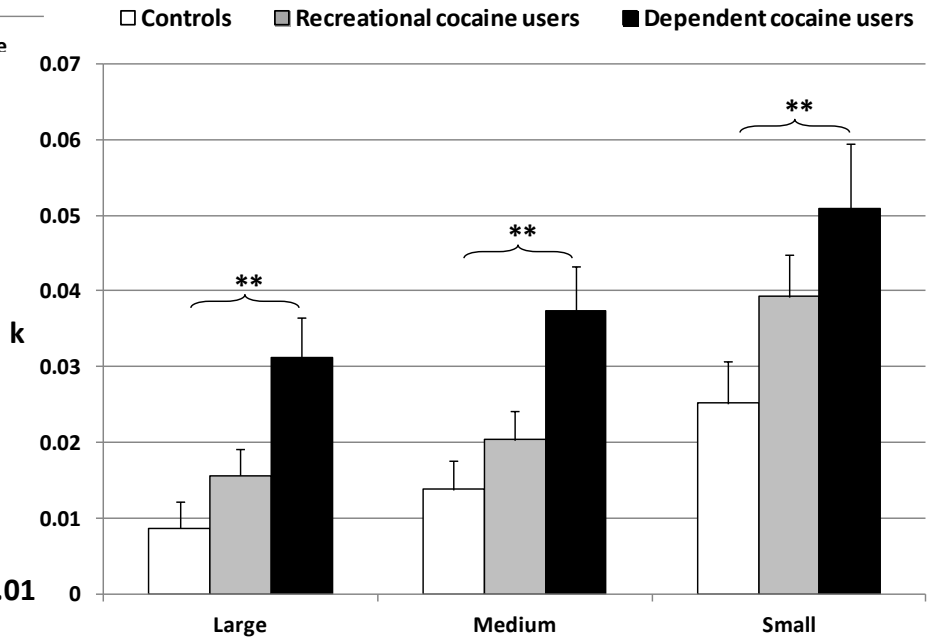



*Hulka et al. 2014, Psychol Med*

- Primarily dependent cocaine users were less foresighted in the IGT and more impulsive regarding immediate reward in the Delay Discounting Task (DD).

- In multiple regressions the IGT netscore was predicted cumulative cocaine dose ($p<.05$), while DD was predicted by cumulative cocaine dose ($p<.01$) and years of use ($p<.01$).




**Sidak post hoc tests: **p<.01**

# Impulsivity measures

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**Table 4**
Correlations between cocaine use parameters, ADHD, BDI, and measures of impulsivity in cocaine users.

| | BIS-11 | | | | TCI NS | | | | | RVP | | | | SST | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FI | FII | FIII | Total score | NS1 | NS2 | NS3 | NS4 | Total score | B" | M. Lat. | Total FA | Imp.-score | p[c] (corr. inhib) | RT[d] go trials | p[c] (corr. resp) | RT[d] s-r trials | SSRT | ADHD[e] | Depr.[f] |
| Times per week[a] | .19 | | | | −.18 | | | −.19 | −.19 | | | | | | | | | | | |
| Grams per week log[a] | | | | | −.05 | | | *−.21 | | | | | | | | | | | | |
| Years of use[a] | *.24 | *.24 | *.25 | **.29 | | | | | | | | | | | | | | | *.21 | .19 |
| Years of use, adj. for age[b] | **.30 | **.30 | **.33 | ***.37 | | .17 | | | | | | | | | | | | | *.24 | *.22 |
| Age of onset[a] | −.18 | −.19 | *−.22 | *−.24 | | | | | | | | | | | | | .19 | | | |
| Cumulative dose (grams) log[a] | **.27 | **.28 | *.23 | **.31 | −.18 | | .20 | | | | | | | | | | | | **.28 | ***.33 |
| Cumulative dose (grams) log, adj. for age[b] | **.28 | **.30 | *.25 | ***.33 | −.19 | | | | | | | | | | | | | | **.29 | ***.35 |
| Maximum dose (grams/day)[a] | | | | | −.18 | | | | | | | | | | | | | | **.26 | **.27 |
| CCQ sum score (0–70)[a] | ***.33 | | | *.22 | −.19 | | | | | | | .19 | | | | | *−.22 | | **.29 | ***.33 |
| Hair analysis $Cocaine_{total}$ pg/mg[a] | | | | | *−.25 | | | | | | | | | | | | | | | |
| Hair analysis Cocaine pg/mg[a] | | | | | *−.23 | | | | | | | | | | | | | | | |
| Hair analysis Benzoylecgonine pg/mg[a] | | | | | **−.32 | | | | | | | | | | | | | .19 | | |
| Hair analysis Cocaethylene pg/mg[a] | | | | | | | | | | | | | | | | | | | | |
| Hair analysis Norcocaine pg/mg[a] | | | | | *−.26* | | | | −.18 | | | | | | | | | | | |

Correlations with a *p*-level below 10% are shown, while significant correlations are marked: *$p < .05$; **$p < .01$; ***$p < .001$.

**Table 5**
Correlation matrix for impulsivity measures, ADHD, and BDI in cocaine users.

| | 2) | 3) | 4) | 5) | 6) | 7) | 8) | 9) | 10) | 11) | 12) | 13) | 14) | 15) | 16) | 17) | 18) | 19) | 20) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1) BIS-11 FI Attentional Imp. | ***.51 | ***.43 | ***.75 | | **.23 | .14 | **.24 | *.19 | | | | | | | | | | ***.75 | ***.50 |
| 2) BIS-11 FII Motor Imp. | 1 | ***.66 | ***.88 | | ***.50 | ***.32 | ***.37 | ***.49 | *−.20 | | *.18 | *.16 | −.13 | | | | | ***.47 | ***.31 |
| 3) BIS-11 FIII Nonplanning Imp. | | 1 | ***.85 | | ***.51 | ***.40 | ***.41 | ***.47 | | | | | **−.21 | *−.19 | | *−.16 | | ***.36 | ***.27 |
| 4) BIS-11 Total score | | | 1 | | ***.51 | ***.35 | ***.41 | ***.47 | −.15 | | .13 | | *−.18 | −.13 | | | | ***.61 | ***.42 |
| 5) TCI NS1 Exploratory excitability | | | | 1 | **.21 | *.16 | .13 | ***.57 | | | | | | | | | *−.16 | | ***−.37 |
| 6) TCI NS2 Impulsiveness | | | | | 1 | ***.34 | ***.35 | ***.74 | −.15 | | .14 | *.19 | | | | | | *.16 | |
| 7) TCI NS3 Extravagance | | | | | | 1 | ***.42 | ***.70 | | | | | | | | | | .13 | |
| 8) TCI NS4 Disorderliness | | | | | | | 1 | ***.69 | | | | | | **−.22 | | *−.18 | | ***.28 | |
| 9) TCI Novelty seeking Total score | | | | | | | | 1 | | | | *.16 | | −.15 | | | | *.17 | |
| 10) RVP Response bias B" | | | | | | | | | 1 | **−.23 | ***−.96 | ***−.69 | | | | | .14 | | |
| 11) RVP Mean latency | | | | | | | | | | 1 | ***.27 | ***−.51 | | | | | | | |
| 12) RVP Total false alarms | | | | | | | | | | | 1 | ***.69 | | | | | | | |
| 13) RVP Impulsivity-score | | | | | | | | | | | | 1 | | | | | | | |
| 14) SST *p*(correct inhibition)[c] | | | | | | | | | | | | | 1 | ***.63 | ***−.32 | ***.56 | ***−.40 | | |
| 15) SST RT on go trials[d] | | | | | | | | | | | | | | 1 | ***−.51 | ***.95 | **−.25 | | |
| 16) SST *p*(correct resp. on go trials)[c] | | | | | | | | | | | | | | | 1 | ***−.54 | ***.52 | | |
| 17) SST RT on signal-respond trials[d] | | | | | | | | | | | | | | | | 1 | ***−.32 | | |
| 18) SST Stop-signal reaction time | | | | | | | | | | | | | | | | | 1 | | |
| 19) ADHD[a] | | | | | | | | | | | | | | | | | | 1 | ***.56 |
| 20) Depression[b] | | | | | | | | | | | | | | | | | | | 1 |

Pearson's product-moment correlation. Correlations with a *p*-level below 10% are shown, while significant correlations are marked: *$p < .05$; **$p < .01$; ***$p < .001$.

# Impulsivity measures

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**Table 3**
Impulsivity measures.

| Measure | $n^a$ | Controls | RCU | DCU | F | $df$, $df_{err}$ | $p$ | $p$, Sidak post hoc: Controls vs. RCU | Controls vs. DCU | RCU vs. DCU |
|---|---|---|---|---|---|---|---|---|---|---|
| Barratt Impulsiveness Scale (BIS-11) | | | | | | | | | | |
| FI Attentional Impulsiveness | 68/68/30 | 14.7 (0.4) | 16.3 (0.4) | 18.7 (0.7) | 12.982 | 2, 162 | **<.001** | **.03** | **<.001** | **.01** |
| FII Motor Impulsiveness | 68/68/30 | 22.5 (0.5) | 24.3 (0.6) | 25.9 (0.8) | 6.435 | 2, 162 | **.002** | .06 | **.003** | .33 |
| FIII Nonplanning Impulsivenes | 68/68/30 | 26.3 (0.5) | 27.9 (0.5) | 29.1 (0.8) | 4.570 | 2, 162 | **.01** | .11 | **.02** | .56 |
| BIS-11 Total score | 68/68/30 | 63.4 (1.3) | 68.5 (1.3) | 73.6 (1.9) | 10.803 | 2, 162 | **<.001** | **.02** | **<.001** | .08 |
| Temperament and Character Inventory | | | | | | | | | | |
| NS1 Exploratory excitability | 67/68/28 | 7.5 (0.3) | 8.0 (0.3) | 7.2 (0.4) | 1.904 | 2, 159 | .15 | .34 | .92 | .24 |
| NS2 Impulsiveness | 67/68/28 | 4.8 (0.3) | 5.9 (0.3) | 6.0 (0.5) | 4.258 | 2, 159 | **.02** | **.03** | .09 | 1.00 |
| NS3 Extravagance | 67/68/28 | 5.8 (0.2) | 7.1 (0.2) | 7.4 (0.4) | 9.486 | 2, 159 | **<.001** | **<.001** | **.002** | .89 |
| NS4 Disorderliness | 67/68/28 | 4.4 (0.2) | 5.8 (0.2) | 5.7 (0.4) | 10.348 | 2, 159 | **<.001** | **<.001** | **.008** | 1.00 |
| Novelty seeking Total score | 67/68/28 | 22.5 (0.7) | 26.8 (0.7) | 26.3 (1.1) | 11.384 | 2, 159 | **<.001** | **<.001** | **.009** | .96 |
| Rapid Visual Processing Task | | | | | | | | | | |
| Response bias B' | 67/68/30 | .949 (0.0) | .937 (0.0) | .928 (0.0) | 1.160 | 2, 161 | .32 | .67 | .39 | .90 |
| Mean latency (ms) | 67/68/30 | 404.7 (11.0) | 418.3 (11.0) | 416.2 (16.6) | .421 | 2, 161 | .66 | .76 | .92 | 1.00 |
| Total false alarms | 67/68/30 | 1.3 (0.2) | 1.9 (0.2) | 2.1 (0.4) | 2.850 | 2, 161 | .06 | .19 | .11 | .89 |
| Impulsivity-score | 67/68/30 | .00 (0.2) | .23 (0.2) | .44 (0.3) | 1.114 | 2, 161 | .33 | .70 | .40 | .88 |
| Stop-Signal Task | | | | | | | | | | |
| $p$(correct inhibition)[b] | 67/67/29 | 54.8 (1.4) | 54.7 (1.4) | 50.4 (2.1) | | | | | | |
| RT on go trials (ms)[c] | 67/67/29 | 765.2 (23.2) | 728.7 (23.3) | 734.4 (35.6) | .671 | 2, 159 | .51 | .61 | .85 | 1.00 |
| $p$(correct responses on go trials)[b] | 67/67/29 | 94.4 (1.4) | 90.9 (1.4) | 94.0 (2.1) | 1.759 | 2, 159 | .18 | .21 | 1.00 | .53 |
| RT on signal-respond trials (ms)[c] | 67/67/29 | 672.9 (21.6) | 651.1 (21.7) | 647.1 (33.2) | .339 | 2, 159 | .71 | .86 | .89 | 1.00 |
| Stop-signal reaction time, SSRT (ms) | 65/65/27 | 298.1 (7.8) | 277.1 (7.8) | 292.9 (12.1) | 1.885 | 2, 153 | .16 | .17 | .98 | .62 |

Means and standard errors. ANCOVA (all groups, corrected for age). Significant $p$ values are shown in bold.

*Vonmoos et al. 2013, DAD*

# Impulsivity measures

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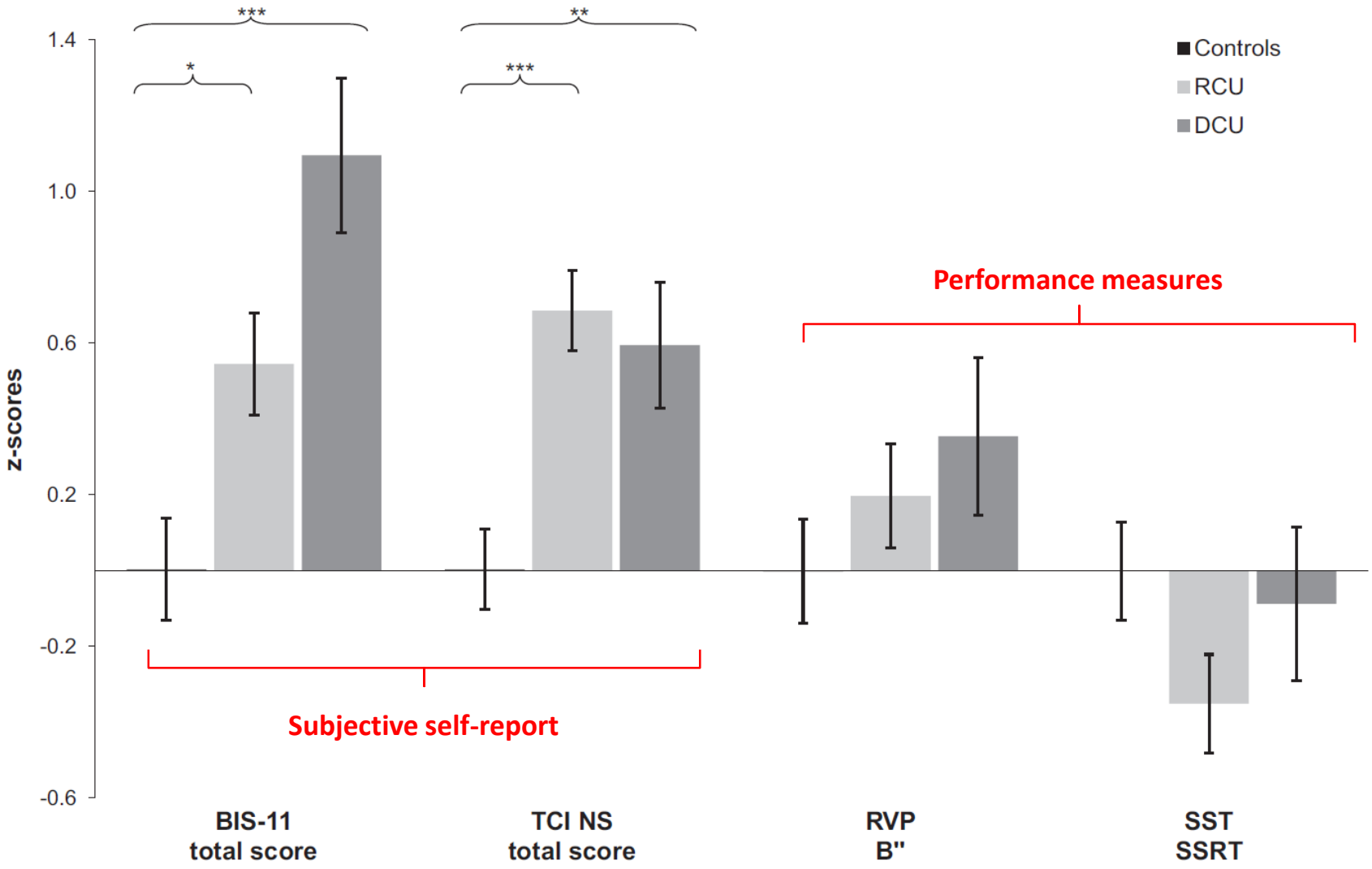


*Vonmoos et al. 2013, DAD*

Sidak post hoc tests: *p<.05; **p<.01

# The effect of recent cocaine use

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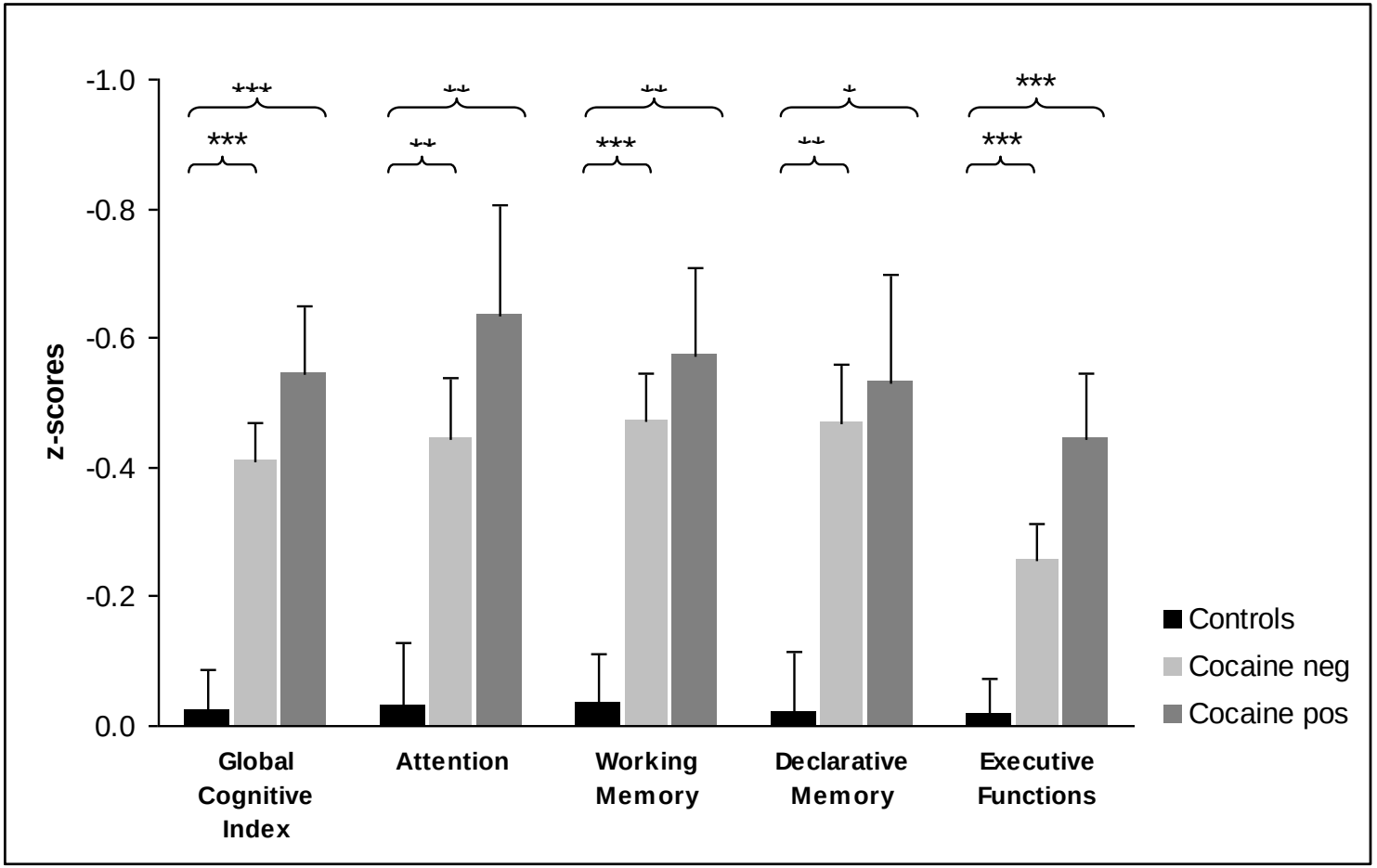
*Vonmoos et al. BJP, in press*




Mean z-scores and standard errors for the global cognitive index and the four cognitive domains (values corrected for age and verbal IQ) in groups with controls (n=68), negative (n=75), and positive (n=22) urine samples. One hair sample (recreational cocaine user) was deficient. Sidak post-hoc tests: *p<.05; **p<.01; ***p<.001.

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# Sample characteristics

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| | Baseline (t1) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Controls ($n = 48$)** | **Cocaine increaser ($n = 19$)** | **Cocaine decreaser ($n = 19$)** | **$F/\chi^2/T$** | **d.f., $d.f._{err}$** | ***p*** | **Effect size** |
| Age, years | 30.3 (8.9) | 31.5 (9.4) | 31.4 (8.3) | 0.20[b] | 2, 83 | 0.82 | ${}_p\eta^2 = 0.00$ |
| Sex (female/male) | 16/32 | 3/16 | 5/14 | 2.11[c] | 2 | 0.35 | $V = 0.16$ |
| Verbal IQ (MWT-B)[d] | 107.6 (10.0) | 102.9 (9.7) | 103.8 (7.1) | 2.20[b] | 2, 83 | 0.12 | ${}_p\eta^2 = 0.05$ |
| Education, years | 10.8 (1.8) | 10.4 (1.8) | 10.0 (1.5) | 1.30[b] | 2, 83 | 0.28 | ${}_p\eta^2 = 0.03$ |
| ADHD-SR score (0–22) | 7.7 (5.2) | 13.5 (9.4)** | 14.1 (6.8)** | 8.83[b] | 2, 83 | **<0.001** | ${}_p\eta^2 = 0.18$ |
| ADHD DSM-IV (y/n)[e] | 0/48 | 4/15 | 3/16 | 7.02[c] | 2 | **0.03** | $V = 0.28$ |
| Weeks between t1 and t2 | 58.2 (10.1) | 59.3 (12.1) | 61.9 (14.5) | .69[b] | 2, 83 | 0.50 | ${}_p\eta^2 = 0.02$ |
| BDI score (0–63) | 3.5 (3.3) | 7.3 (8.0)* | 8.7 (6.5)** | 7.53[b] | 2, 83 | **<0.001** | ${}_p\eta^2 = 0.15$ |
| BDI depression (y/n)[f] | 0/48 | 1/18 | 1/18 | 2.59[c] | 2 | 0.27 | $V = 0.17$ |
| *Cocaine* | | | | | | | |
| Times per week[g] | — | 1.6 (1.8) | 1.0 (1.3) | 1.17[h] | 36 | 0.25 | $d = 0.38$ |
| Grams per week[g] | — | 2.0 (2.5) | 1.7 (2.3) | 0.41[h] | 36 | 0.68 | $d = 0.12$ |
| Years of use | — | 7.0 (5.5) | 8.2 (5.4) | 0.68[h] | 36 | 0.50 | $d = 0.22$ |
| Maximum dose (g/day)[i] | — | 4.7 (4.4) | 5.9 (6.4) | 0.71[h] | 36 | 0.48 | $d = 0.22$ |
| Cumulative dose (g)[i] | — | 1182 (1635) | 3698 (8585) | 1.25[h] | 36 | 0.22 | $d = 0.41$ |
| Last consumption (days) | — | 18.5 (25.1) | 20.8 (22.2) | 0.29[h] | 36 | 0.77 | $d = 0.08$ |
| Cocaine craving (0–70)[j] | — | 19.8 (9.5) | 17.7 (7.2) | 0.79[h] | 36 | 0.44 | $d = 0.25$ |
| *Hair analysis (ng/mg)*[k] | | | | | | | |
| $Cocaine_{total}$ | — | 10.3 (29.2) | 14.9 (32.2) | 0.46[h] | 36 | 0.65 | $d = 0.15$ |
| Cocaine | — | 8.2 (23.3) | 11.4 (23.9) | 0.42[h] | 36 | 0.68 | $d = 0.14$ |

# Take-Give Game

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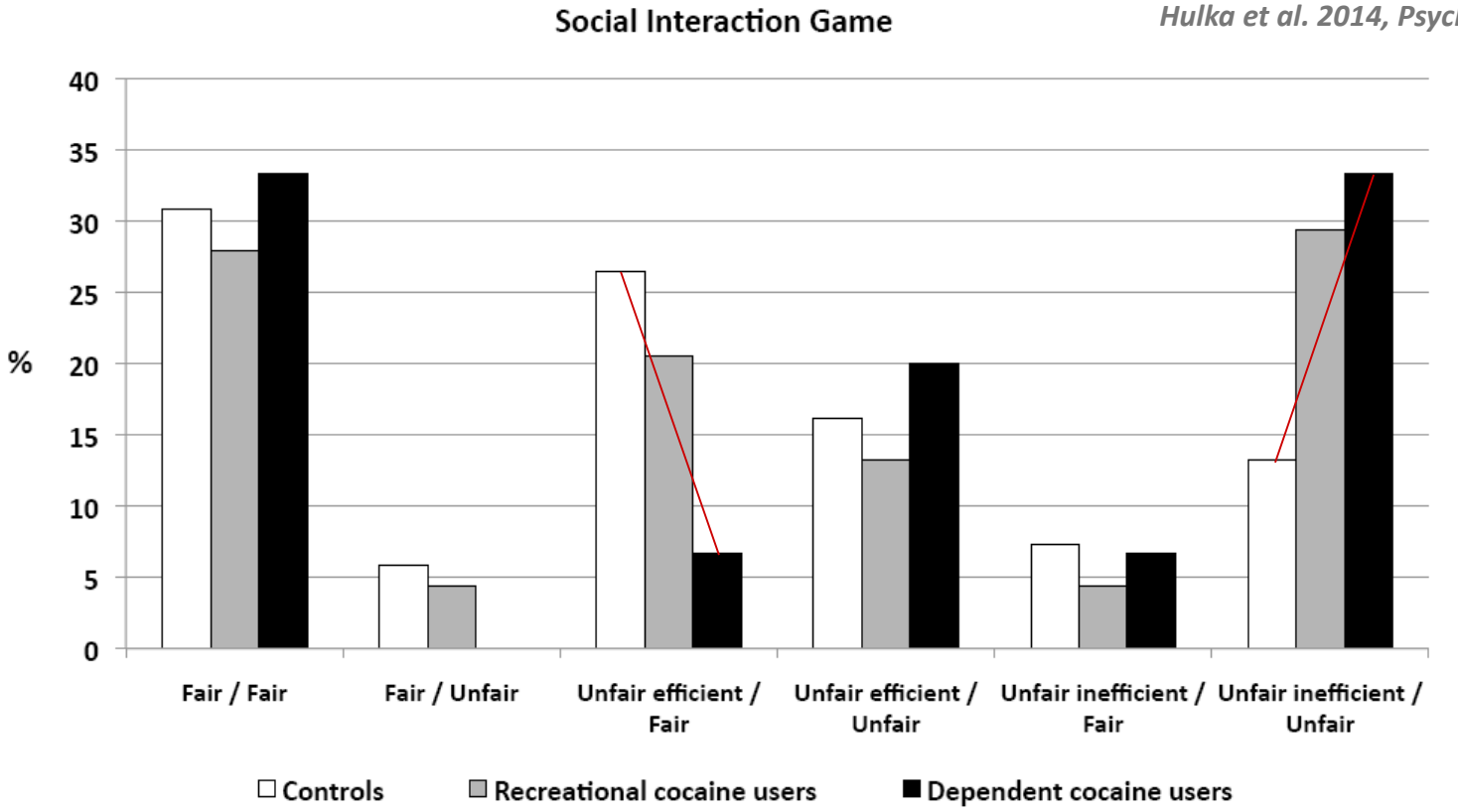


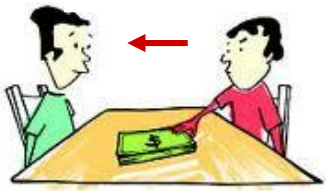


- While most of initially unfair controls changed to fair behaviour at the second stage, most cocaine users remained unfair after initial unfairness.

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# Take-Give Game

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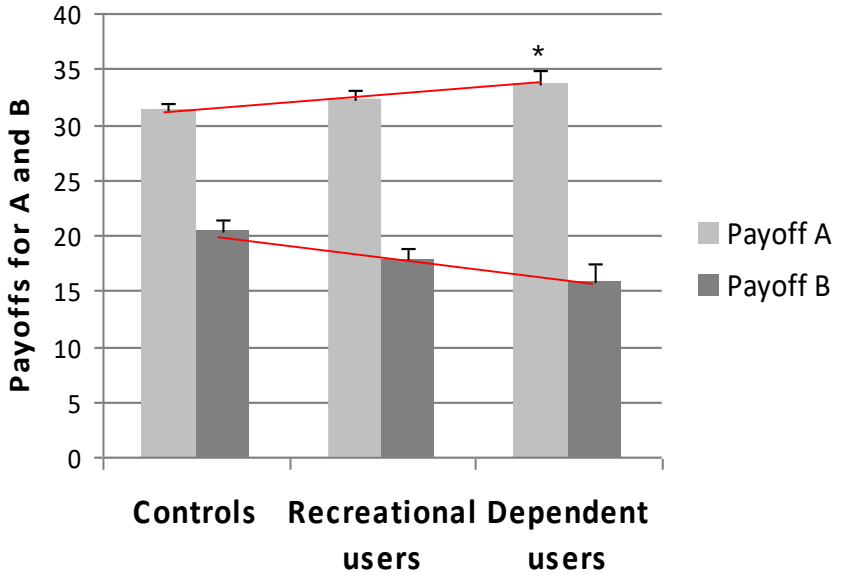
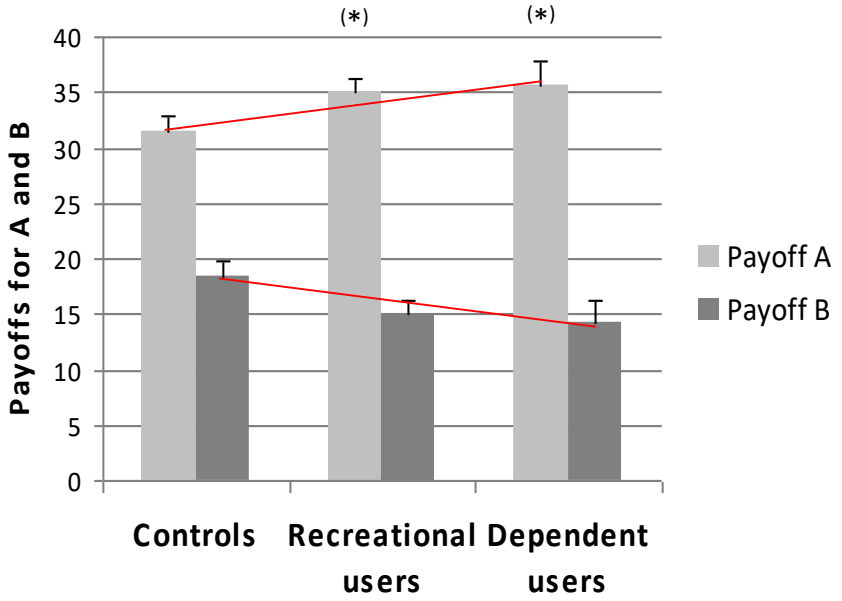



Multiple regression analysis with age, sex, years of school education, and dummy-coded groups: vs. controls *p<.05, (*)p<.10

- Age was strongly correlated with payoffs.
  → The older the more fair!
- No relationship with drug use pattern!
  → Social decision-making as a trait?




- Cocaine users are more concerned with their own monetary gain.

*Hulka et al. 2014, Psychol Med*

# Comorbidities of cocaine use

*Quednow und Herdener, 2018*

**BOX 8.1**

**Klinische Begleit- und Folgeerscheinungen des Kokaingebrauchs (modifiziert und erweitert nach Treadwell und Robinson 2007)**

**Psychiatrisch:**
- Depressive Störungen
- Angststörungen
- Suizidalität
- Paranoia
- Delirium
- Stimulanzieninduzierte Psychosen
- Schlafstörungen
- Persönlichkeitsstörungen (insbesondere Cluster B)
- Aggressivität
- Soziale Probleme
- Kognitive Störungen

**Neurologisch:**
- Kopfschmerzen
- Bewegungsstörungen
- Krampfanfälle
- Apoplex
- Hirnblutungen
- Zerebrale Vaskulitis
- Zerebrale Atrophien

**Ophthalmologisch:**
- Sehnervschädigungen
- Farbsehstörungen (meist auf der Blau-Gelb-Achse)

**Kardiologisch:**
- Myokardinfarkt
- Kardiomyopathie
- Myokarditis
- Arrhythmien
- Arterielle und venöse Thrombosen
- Plötzlicher Herztod

**Pulmologisch:**
- Pneumothorax
- Mediastinalemphysem
- Lungenembolie
- Lungenödem
- Pulmonale Blutungen
- Bronchiolitis obliterans

**Otorhinolaryngologisch:**
- Chronische Rhinitis
- Perforation der Nasenscheidewand
- Osteolytische Sinusitis
- Abnormale Riechfunktionen
- Granulomatose mit Polyangiitis

**Dentologisch:**
- Erosion des Zahnschmelzes
- Ulzerationen des Zahnfleischs

**Gastroenterologisch:**
- Ischämische Kolitis

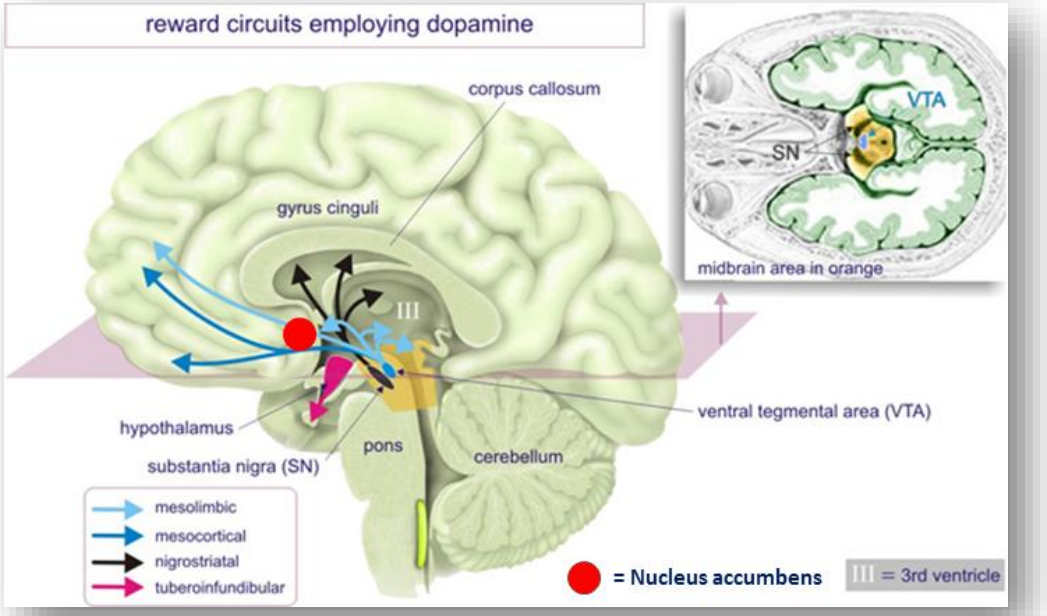
**Endokrinologisch:**
- Gynäkomastie
- Galaktorrhö
- Sexuelle Dysfunktion

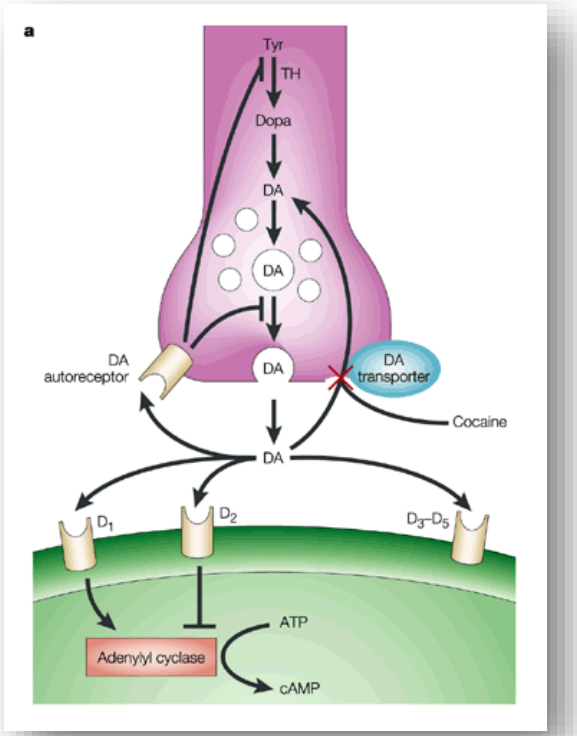
**Infektiologisch** (primär bei intravenösen Konsumenten):
- Bakterielle Endokarditis
- HIV
- Hepatitis
- Injektionsabszesse
- Zellulitis

**Weitere Störungen:**
- Gewichtsverlust
- Rhabdomyolyse

# Acute effects of cocaine

- Blockade of presynaptic dopamine, serotonin, and noradrenalin transporters
- Transient increase of neurotransmitter concentration in the synaptic cleft
- Intense stimulation of the fronto-limbic reward system by dopamine release in the ventral tegmental area, nucleus accumbens, and prefrontal cortex.




*Kreek et al. 2002*

- Acute subjective effects: euphoria, increased drive and energy, enhanced vigilance and thoughts, and elevated self-confidence.

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