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HUMAN
COGNITIVE AND BRAIN SCIENCES
LEIPZIG

Stress and Adaptive Learning in Alcohol Dependence "SALAD"

The influence of stress on behavioral adaptation, working memory and its neural correlates in alcohol use disorders

Zsuzsika Sjoerds, PhD

Max Planck-Fellow Group

"Cognitive and affective control of behavioural adaptation"

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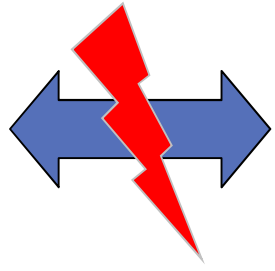
Leipzig, Germany

MAX-PLANCK-GESELLSCHAFT

Behavioral Adaptation:
Two parallel decision making systems:

goal-directed

"model-based"



habitual

"model-free"

flexible forward planning using internal representations (models) of the environment

Social use → Abuse / Harmful use → Dependence

Addiction
(Everitt and Robbins 2005)

Balleine and O'Doherty 2010, Neuropsychopharmacology; Dolan and Dayan 2013, Neuron

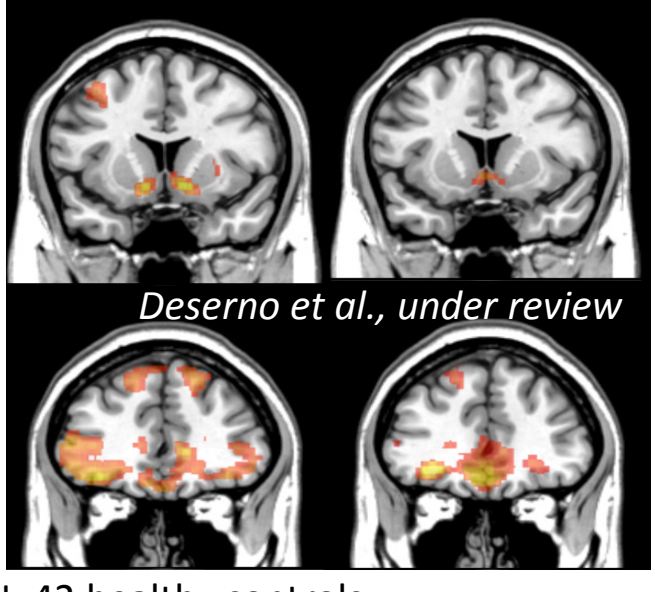
BEHAVIORAL ADAPTATION IN THE BRAIN:
Frontostriatal pathways

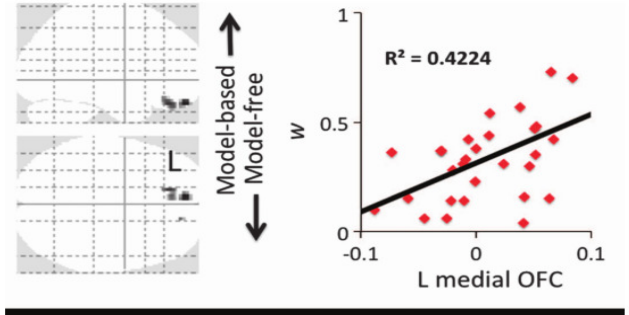
Single-update Prediction Error Model-free (habitual)

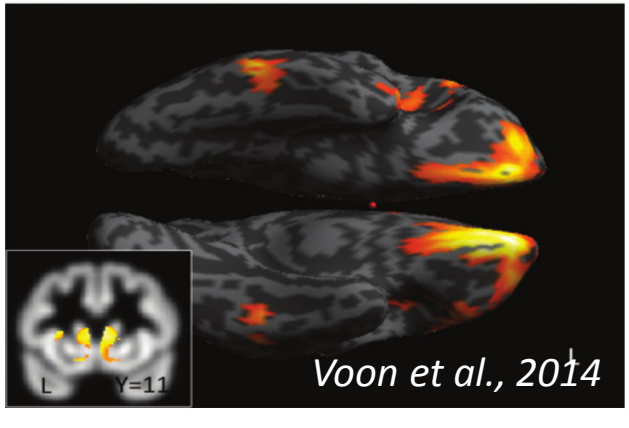
Double-update Prediction Error Model-based (goal-directed)

VS

PFC



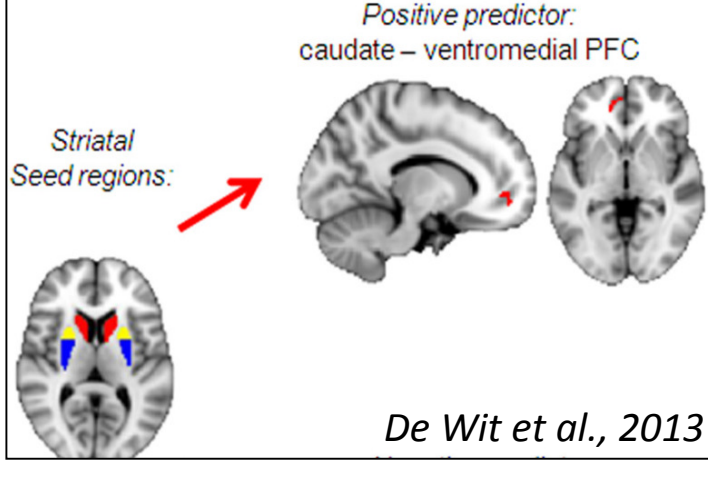




Behavioral/Systems/Cognitive

Corticostriatal Connectivity Underlies Individual Differences in the Balance between Habitual and Goal-Directed Action Control

a DTI predictors of goal-directed action



N=42 healthy controls,
p < .05 FWE-whole-brain-corrected

Functional

Morphometric

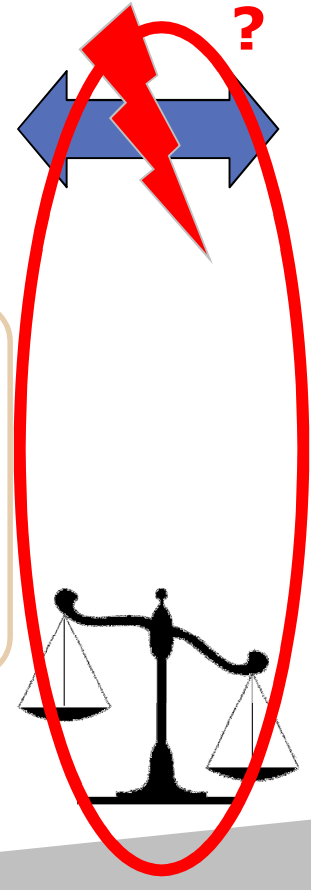
Connectivity

Behavioral Adaptation:
Two parallel decision making systems:

goal-directed

"model-based"

flexible forward planning using internal representations (models) of the environment



habitual

"model-free"

automatized responses to previously reinforced cues in the environment

Addiction
(Everitt and Robbins 2005)

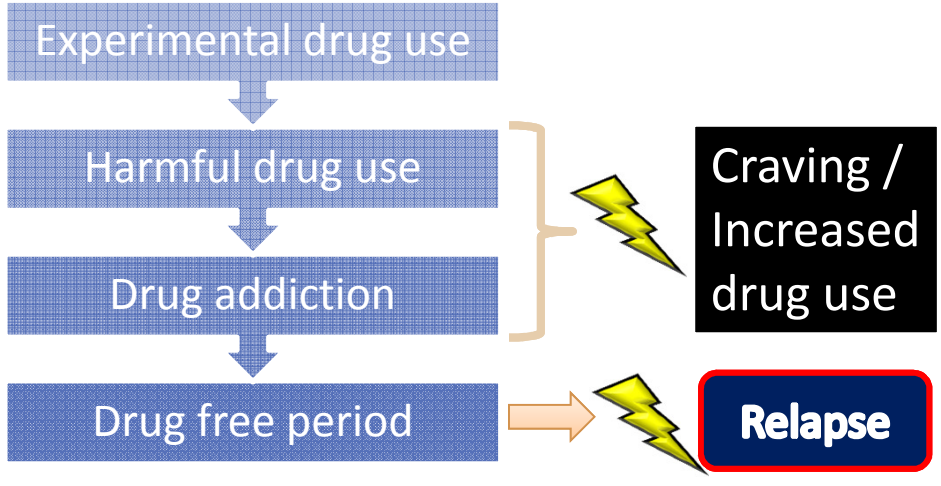
Balleine and O'Doherty 2010, Neuropsychopharmacology; Dolan and Dayan 2013, Neuron

The Journal of Neuroscience, June 3, 2009 • 29(22):7191–7198 • 7191

Behavioral/Systems/Cognitive

Stress Prompts Habit Behavior in Humans

Lars Schwabe and Oliver T. Wolf
Department of Cognitive Psychology, Ruhr University Bochum, 44780 Bochum, Germany



PNAS

Working-memory capacity protects model-based learning from stress

A. Ross Otto[a,1], Candace M. Raio[b], Alice Chiang[b], Elizabeth A. Phelps[a,b,c], and Nathaniel D. Daw[a,b]

[a]Center for Neural Science and [b]Department of Psychology, New York University, N

Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approve

Accounts of decision-making have long posited the operation of separate, competing valuation systems in the control of choice behavior. Recent theoretical and experimental advances suggest two dec rier

Stress, September 2006; 9(3): 133–141

Psychosocial stress impairs working memory at high loads An association with cortisol levels and memory retrieval

N. Y. L. OEI[1], W. T. A. M. EVERAERD[2], B. M. ELZINGA[1], S. VAN WELL[2], &

informa
healthcare

Psychoneuroendocrinology (2008) 33, 643–653

Psychosocial stress induces working memory impairments in an *n*-back paradigm

Daniela Schoofs, Diana Preuß, Oliver T. Wolf*

Department of Cognitive Psychology, Ruhr-University Bochum, Universitätsstr. 150, D-44780 Bochum, Germany

MAIN AIMS

1. To investigate the effects of stress on behavioral adaptation, working memory and its neurobiology in alcohol use disorders compared with HC.

2. To determine if stress-induced behavioral and/or neurobiological alterations predict relapse after 3 months in treatment seeking alcohol dependents and heavy drinkers.

Exclusion: MRI-contraindications, psychopharmacological medication, psychiatric / neurological comorbidity

Alcohol dependents (AD)
DSM/ICD diagnosis
N=30 men

AD patients following ICD-10 criteria, recruited from the Soteria Addiction Clinic in Leipzig

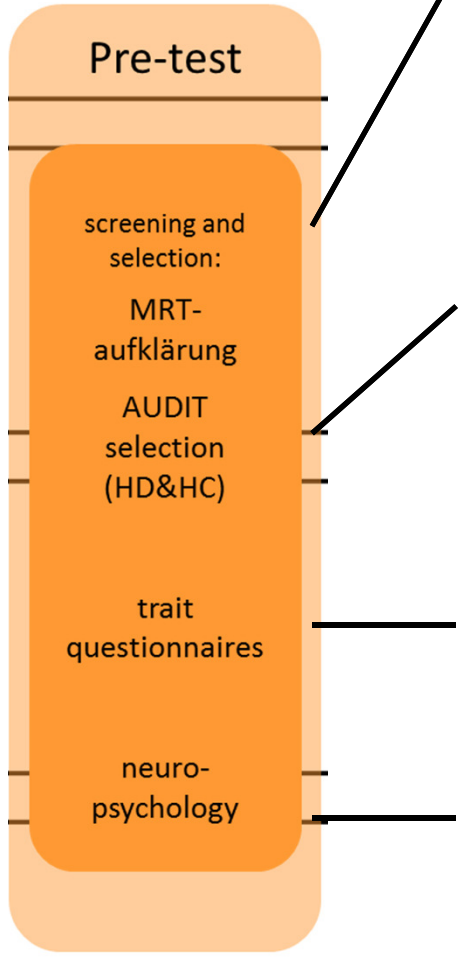
Non-treatment seeking heavy drinkers (HD)
AUDIT > 16
N=30 men

Non-treatment seeking heavy drinkers (HD), age, education matched, and alcohol use disorder test (AUDIT) score >16

Healthy controls (HC)
AUDIT < 8
N=30 men

Age, education matched healthy controls (HC) without history of psychiatric disorders, alcohol use disorder test (AUDIT) score <8 non-smoking?

SELECTION & TRAIT ASSESSMENT



MRT briefing of (new)probands/patients by medical doctor

Alcohol Use Disorder Identification Test (AUDIT)

Score 0 – 8: no problem drinking HC

Score 9 – 15: simple advice focused on the reduction of hazardous drinking

Score 16 and up: hazardous drinking or even dependence (20-40) HD

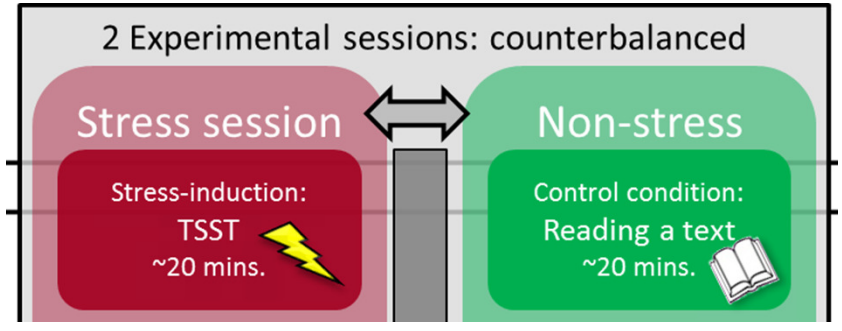
e.g. Chronic/lifetime stress, impulsivity, compulsivity, depression, anxiety, chronotype, stressor appraisal scale (PASA), work history (interviews experience)

Working memory, intelligence, cognitive flexibility

PSYCHOSOCIAL STRESS INTERVENTION:

TRIER SOCIAL STRESS TEST

Stress condition:
Interview & Calculus in front of committee

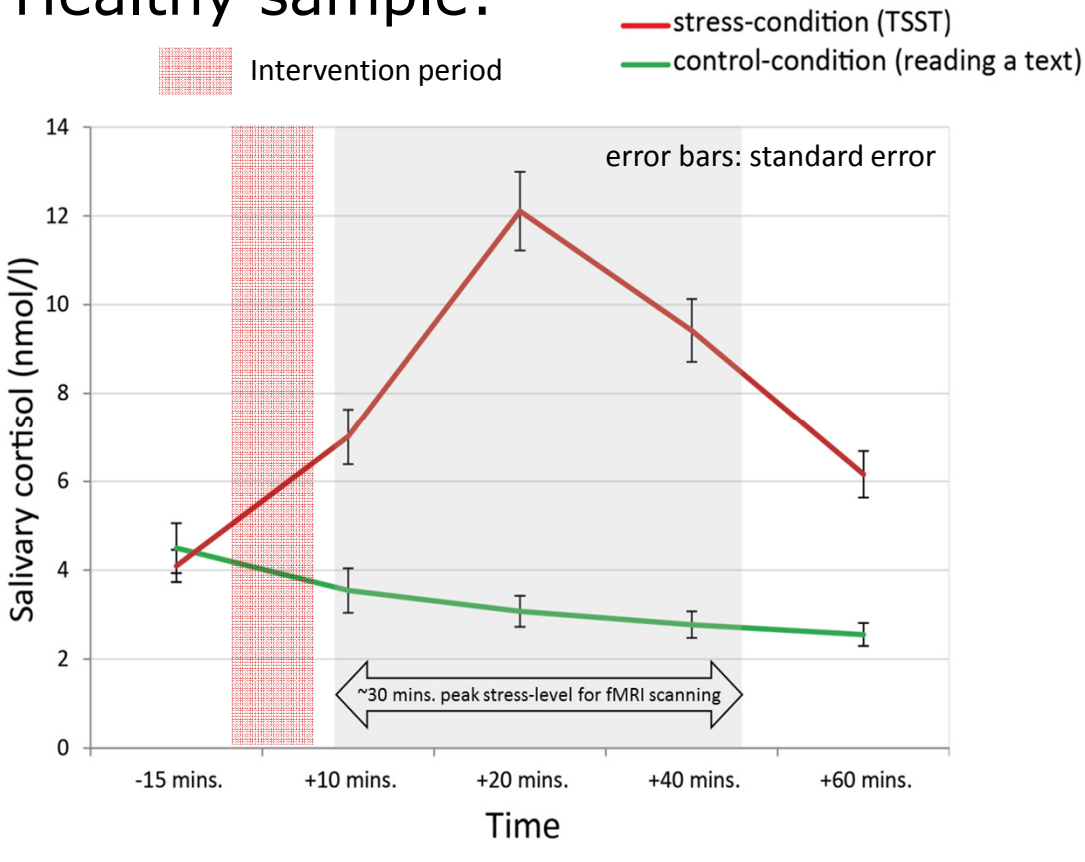


Control condition:
Reading a neutral text in a non-stress environment

Kirschbaum et al., 1993

TSST & CORTISOL LEVELS

Healthy sample:



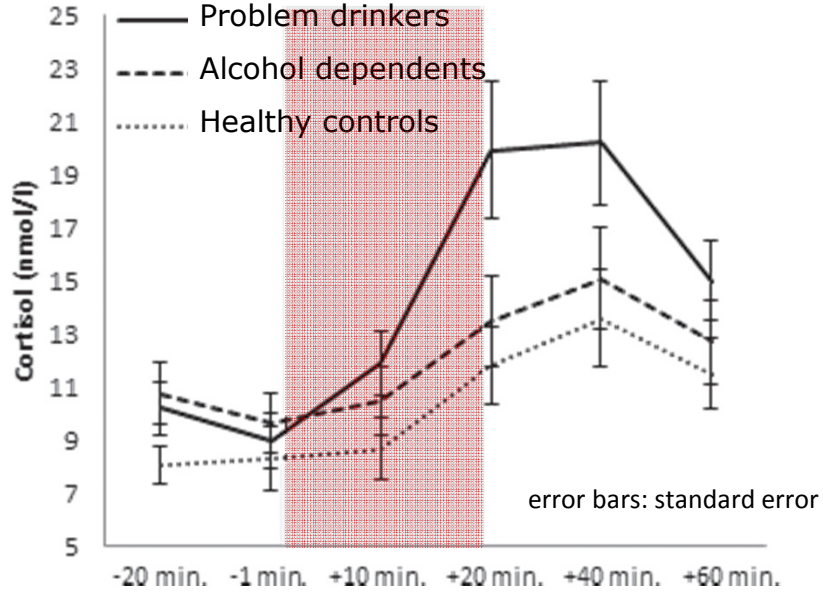
Time x Condition interaction: p<0.001

Radenbach, Reiter et al., in revision

Alcohol dependence:

Psychosocial stress increases craving / drug seeking behavior

Cortisol in AD comparable with HC:



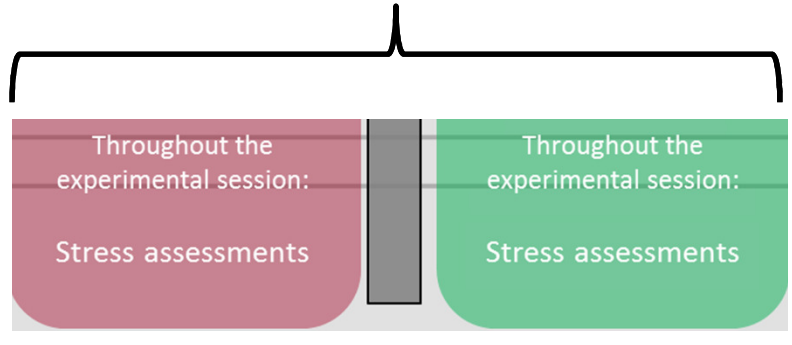
Starcke et al. 2013

STRESS ASSESSMENT

Endocrine:
- Cortisol levels – salivettes
- Catecholamines – blood drawings

Subjective arousal: questionnaires
- STAI State Anxiety Scale
- Emotion grid / visual analog scale
- PANAS positive, negative affect

Autonomic:
- Outside scanner: Heart rate & heart rate variability – heart belt & watch
- During scanning: Heart rate & heart rate variability – ECG
  Respiration – respiration belt
  Skin conductance level

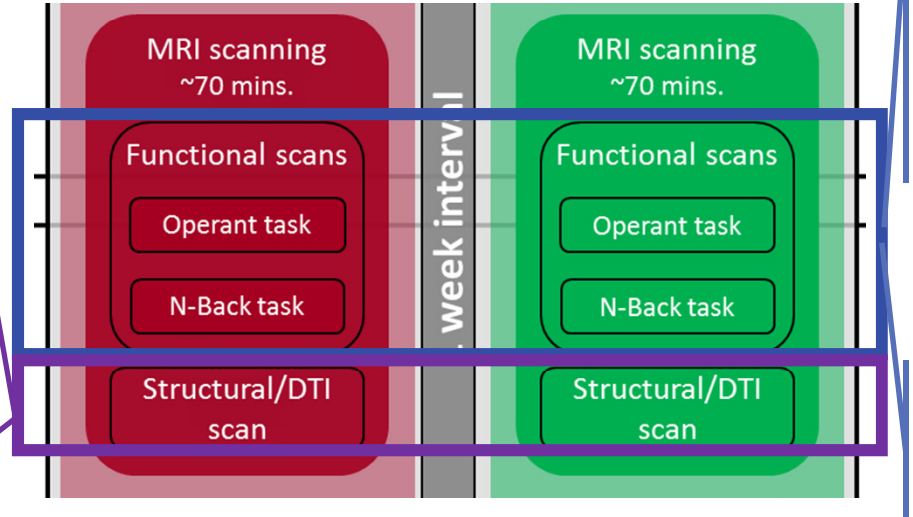


MRI scanning

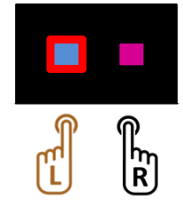
Two sessions a 70 mins, one week interval. Same time (afternoon).

Diffusion MRT:
ep2d_DTI
Corticostriatal connectivity

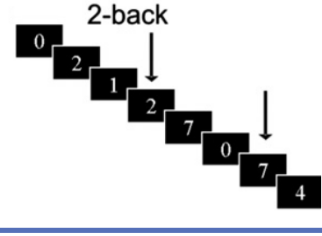
Structural scanning:
MPRAGE
Registration of functional & diffusion scans
Voxel-based morphometry
Cortical thickness



Decision making:
Operant learning task

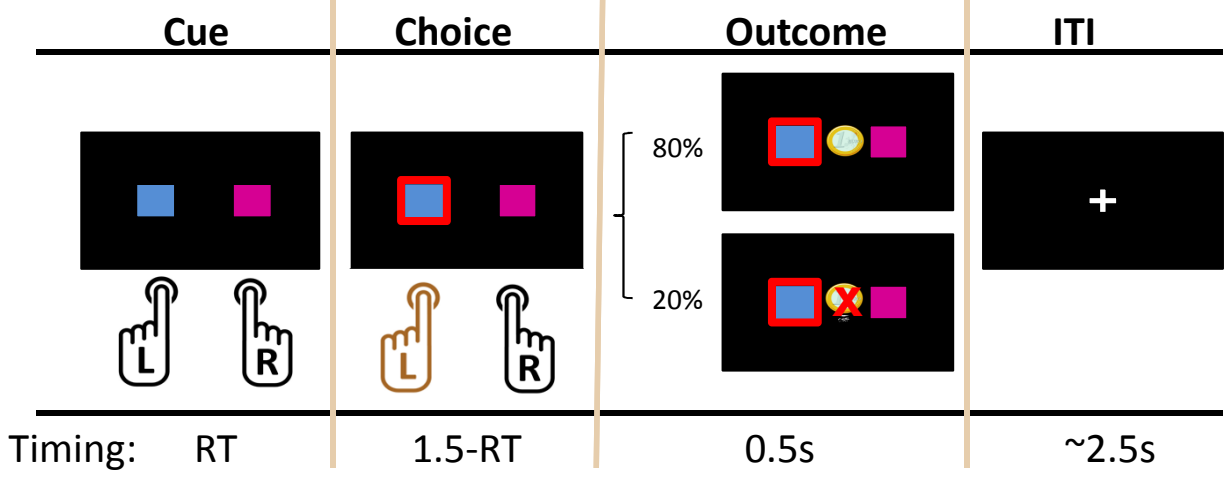


Working memory:
N-Back task



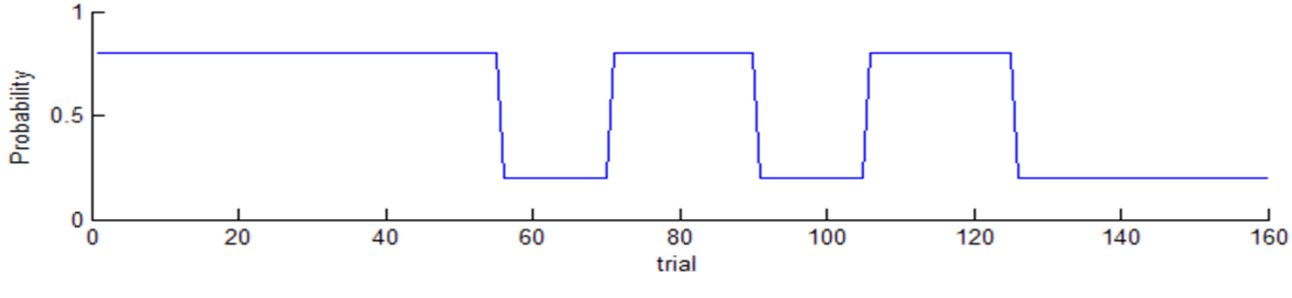
OPERANT LEARNING TASK

To test behavioral adaptation by using computational modeling

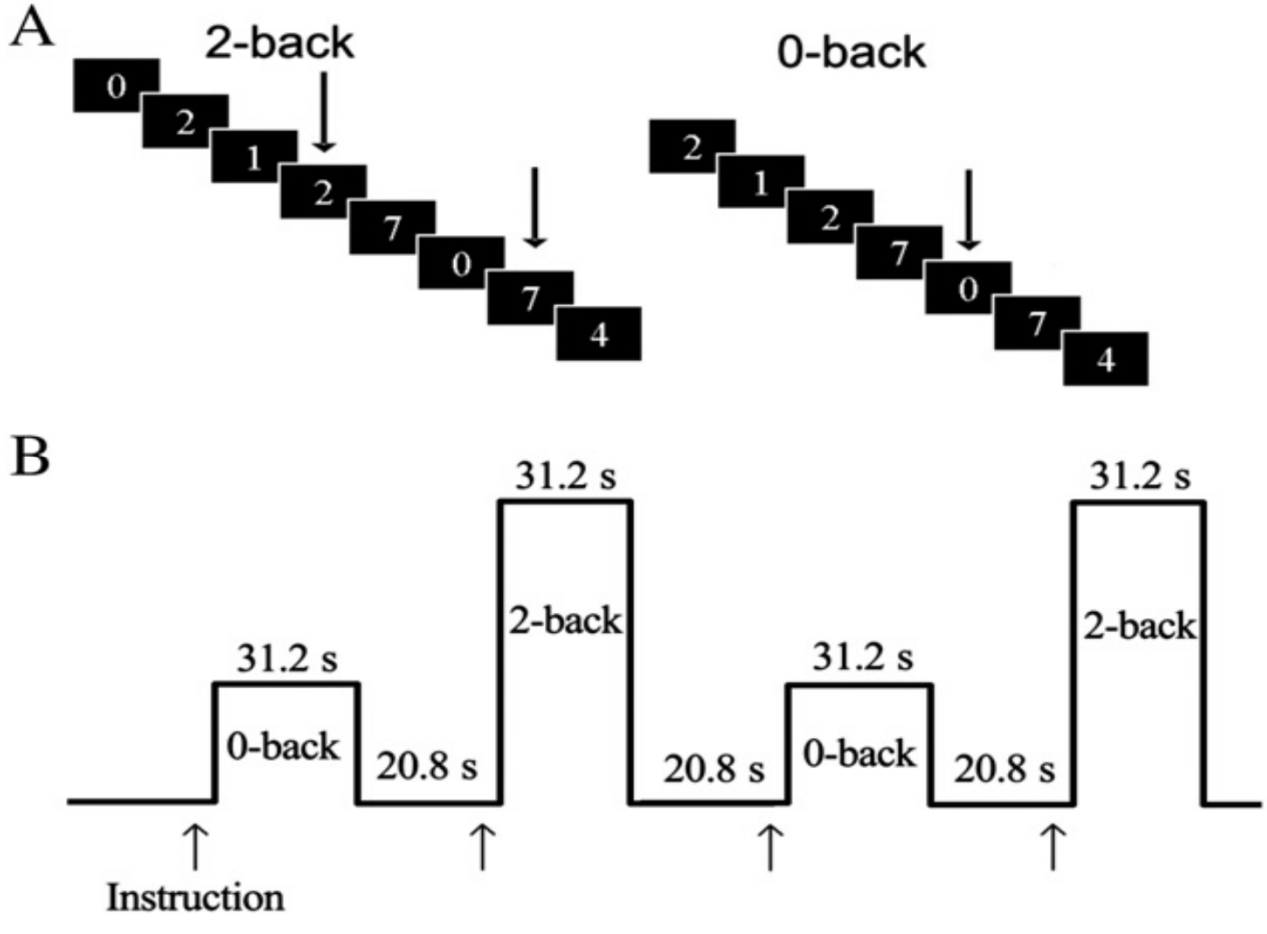


2s + 2.5s ITI * 160 trials
→ 12 min
+ 32 Nullevents 4.5s

Total → 14.5 min



2-BACK TASK



Schlagenhauf et al., 2008

Timeplanning experimental day		Minutes
Arrival, resting period, fill in first questionnaires (administration, state), fMRI task training		45
1st stress assessment: **Baseline**	t1: Cortisol, blood, arousal, HR	5
TSST speech preparation / Control condition introduction		10
2nd stress assessment: **Anticipation**	t2: Cortisol, blood, arousal, HR	5
Intervention: TSST / Control condition (counterbalanced)		20
3rd stress assessment: **Intervention (stress/control) effect**	t3: Cortisol, blood, arousal, HR	5
Walking to MRI scanner + MRI preparation		5
4th stress assessment: **Pre-scan**	t4: Cortisol, blood, arousal, HR	5
MRI scanning (total: 70 min) **+ ongoing physiological measurements (Biopack?)**	Pre-scans (quinpilot, fieldmaps)	5
	Operant task	15
	N-Back task	10
5th stress assessment: **Mid-scan** (+ coil change?)	t5: Cortisol, arousal	10
	Flair (only patients), Diffusion / T1	20
6th stress assessment: **Post-scan**	t6: Cortisol, blood, arousal, HR	5
Debriefing		**15**
	Total	**180 min.**
Trait questionnaires / neuropsychological testing on a separate day		60

RESOURCES

- Pre-test day - selection, trait assessment & neuropsychological testing: test-room, computer

~ 60 minutes

- Stress Intervention: 2 independent committee members, stress-room, video/audio recorders; Control Condition: relaxation room

~20 minutes

- MRT: (N=)3x30 x 2 sessions x ~70 minutes = ~210 h scanning time in 1 year. 3 Tesla Scanner, one afternoon a week, same time (possible: 3 scans per day)

1. Task fMRI (EPI): TR 2s, TE 22ms, voxel size: 3mm iso, 36 slices, flip 90°
2. Structural scanning (MPRAGE): TR 1.3s; matrix = 240 x 256, voxel size: 1mm iso (BUT for cortical thickness: 0.8 mm iso), 170 slices
3. Diffusion MRI (ep2d_DTI): TR 12 s, TE 100ms, voxel size: 1.72x1.72x1.7mm, 67 volumes, 88 axial slices

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Danke!

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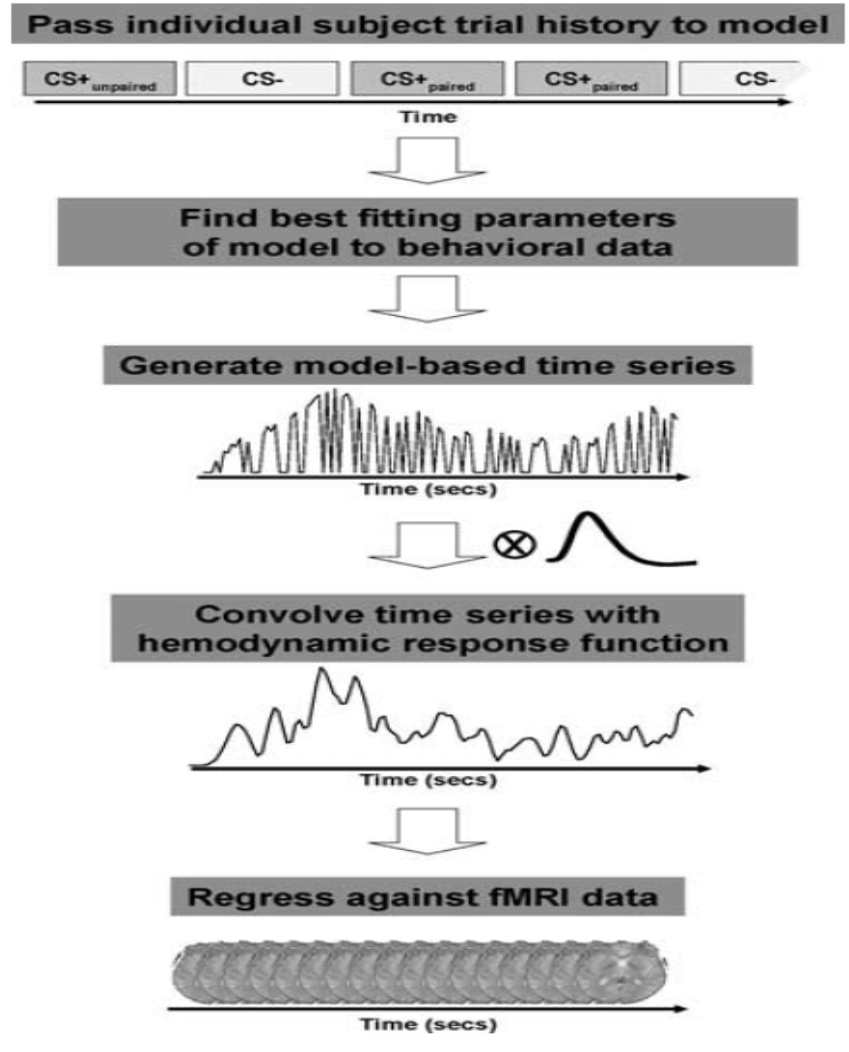
Model-based task analysis
Reinforcement Learning (RL) Algorithm

- Prediction error (PE) = received – expected outcome

$$\delta_t = R_t - Q(chosen)_t$$

- Action value updated for chosen target

$$Q_{t+1} = Q_t + \alpha \times \delta_t$$



Brain: CORTICOSTRIATAL DISFUNCTIONS

Structural connectivity within corticostriatal pathway implicated in goal-directed vs. habitual behavior

12066 • The Journal of Neuroscience, August 29, 2012 • 32(35):12066–12075

Behavioral/Systems/Cognitive

Corticostriatal Connectivity Underlies Individual Differences in the Balance between Habitual and Goal-Directed Action Control

Sanne de Wit,[1,2,3*] Poppy Watson,[1*] Helga A. Harsay,[1] Michael X. Cohen,[4] Irene van de Vijver,[1,4] and K. Richard Ridderinkhof[1,2]

[1]Amsterdam Center for the Study of Adaptive Control in Brain and Behavior, Department of Developmental Psychology, [2]Cognitive Science Center Amsterdam, and Departments of [3]Clinical Psychology and [4]Brain and Cognition, University of Amsterdam, 1018 XA Amsterdam, The Netherlands

BACKGROUND:
SECOND AIM

To study structural brain connectivity in AD, and whether altered connectivity underlies the hypothesized decrease in goal-directed responding in AD patients.

STRUCTURAL CONNECTIVITY: DIFFUSION WEIGHTED IMAGING

White matter tract strength in AD:

Tract based spatial statistics (TBSS) *Smith et al., 2006*

Probabilistic Tractography

- Striatum (caudate, anterior/posterior putamen) & ventromedial prefrontal cortex
  - (Harvard-Oxford cortical & subcortical atlases)

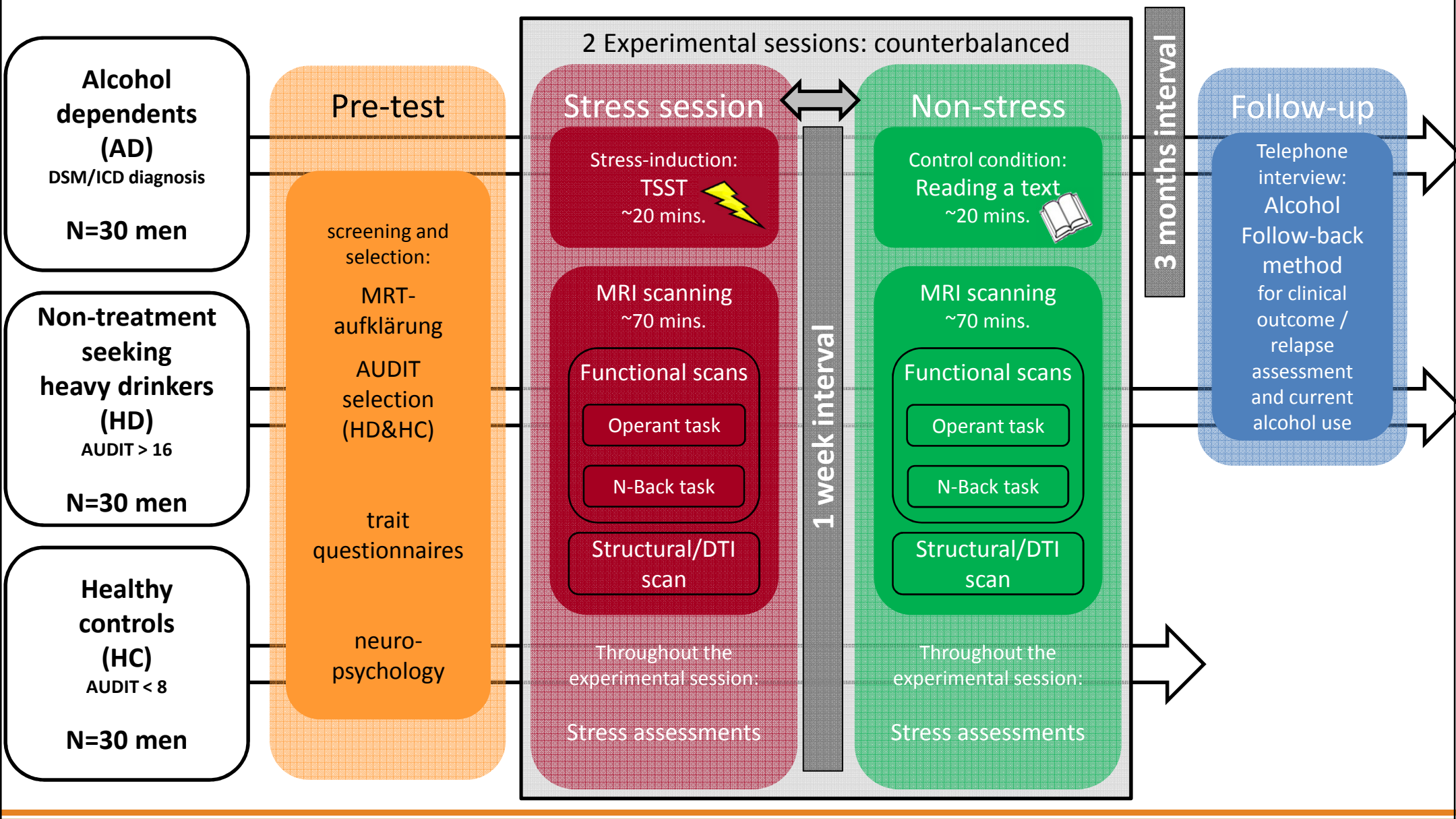
HYPOTHESES:
OPERANT LEARNING TASK

AD patients compared with healthy controls show:

- Impaired behavioral adaptation as mirrored in more unsucessful choices → decreased goal-directed responding

- Reduced prefrontal learning signals related to goal-directed learning

This is more pronounced under stress


Alcohol dependents (AD)
DSM/ICD diagnosis
N=30 men
Non-treatment seeking heavy drinkers (HD)
AUDIT > 16
N=30 men
Healthy controls (HC)
AUDIT < 8
N=30 men
Pre-test
screening and selection:
MRT-aufklärung
AUDIT selection (HD&HC)
trait questionnaires
neuro-psychology
2 Experimental sessions: counterbalanced
Stress session
Stress-induction: TSST ~20 mins.
MRI scanning ~70 mins.
Functional scans
Operant task
N-Back task
Structural/DTI scan
Throughout the experimental session:
Stress assessments
1 week interval
Non-stress
Control condition: Reading a text ~20 mins.
MRI scanning ~70 mins.
Functional scans
Operant task
N-Back task
Structural/DTI scan
Throughout the experimental session:
Stress assessments
3 months interval
Follow-up
Telephone interview:
Alcohol Follow-back method
for clinical outcome / relapse assessment and current alcohol use

OPERANT LEARNING TASK

Tests behavioral adaptation

by using computational modeling

Two parallel decision making systems:

goal-directed "model based"	habitual "model free"
Flexible, goal-oriented, high-demand	Inflexible, automatic, low-demand
- Flexible forward planning using internal representations (models) of the environment (the task)	- No representation of task structure - Automatized responses to cues in the environment by reinforcement

Dolan and Dayan, 2013

INNOVATION

Translating knowledge on mechanisms in healthy populations to an addicted population

Identifying factors, such as stress, that increase relapse-associated behavior in addiction

Needed for prevention of detrimental stress effects on relapse-associated behaviour in addiction

ALCOHOL USE DISORDERS (AUD)

Key to clinical diagnosis, DSM-5:

- Excessive drug use & preoccupations with obtaining the drug
- Inability to inhibit these excessive behaviors, despite inference with person‘s daily goals (e.g. work, social life)

- Flexible, goal-directed control is compromised in alcohol dependence

Sjoerds et al. 2013, Translat Psychiat

HABIT THEORY OF ADDICTION

Everitt & Robbins, 2005 / Vanderschuren & Everitt, 2005

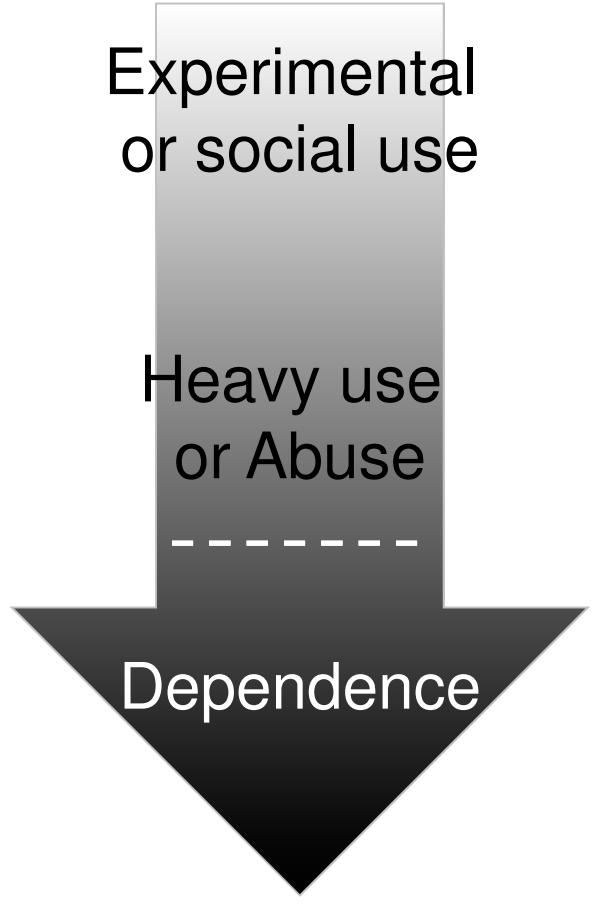
Initial drug use:
Reward-guided drug intake / hedonic effects

↓

Repeated drug intake:
Habit formation

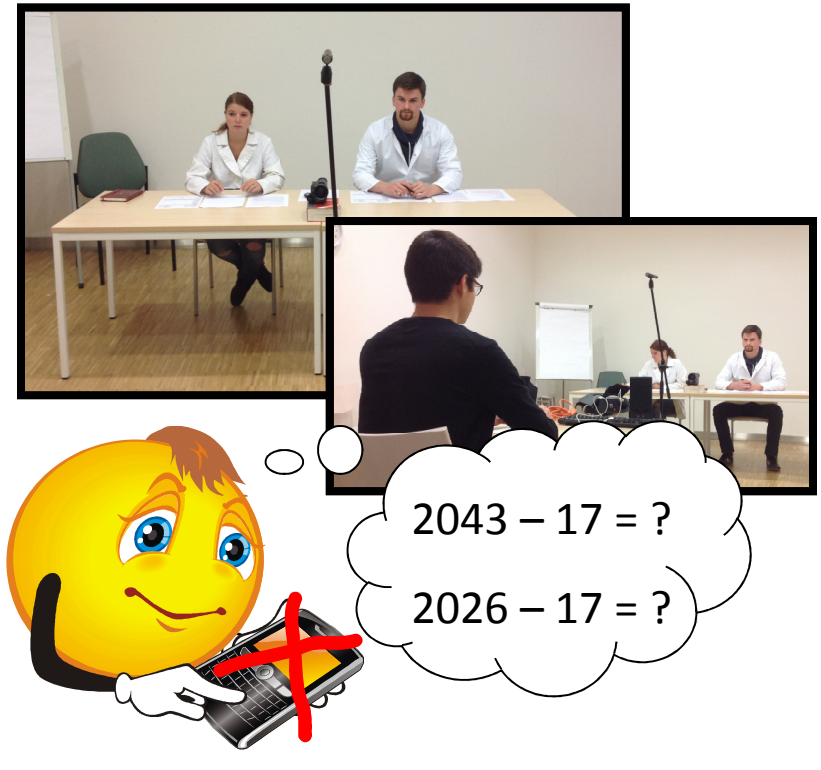
↓

Chronic drug use:
Drug compulsion & high relapse



PSYCHOSOCIAL STRESS INTERVENTION: TRIER SOCIAL STRESS TEST

Stress condition: Interview & Calculus in front of committee



Control condition: Reading a neutral text in a non-stress environment

ALCOHOL DEPENDENCE AND STRESS

Psychopharmacology
DOI 10.1007/s00213-011-2263-y

REVIEW

Translational and reverse translational research on the role of stress in drug craving and relapse

Rajita Sinha · Yavin Shaham · Markus Heilig

Review

CellPress

Stress and alcohol interactions: animal studies and clinical significance

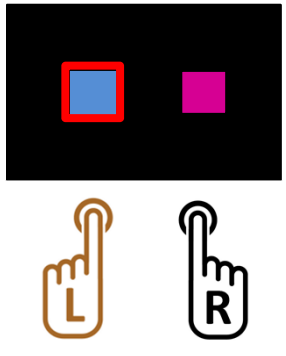
Rainer Spanagel[1], Hamid R. Noori[1], and Markus Heilig[2]

[1] Institute of Psychopharmacology, Central Institute of Mental Health (CIMH), University of Heidelberg, Medical Faculty Mannheim, Germany
[2] Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism (NIAAA), Bethesda, USA

MRI scanning:

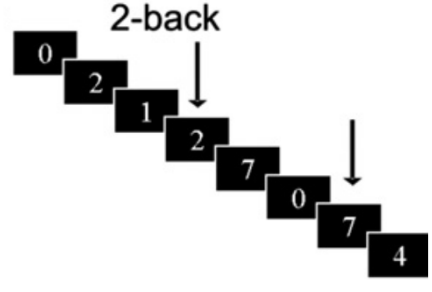
- Structural scanning (T1)
- Diffusion Weighted Imaging (ep2d_DTI)
- Functional task-MRI (2 tasks):

1. Decision making



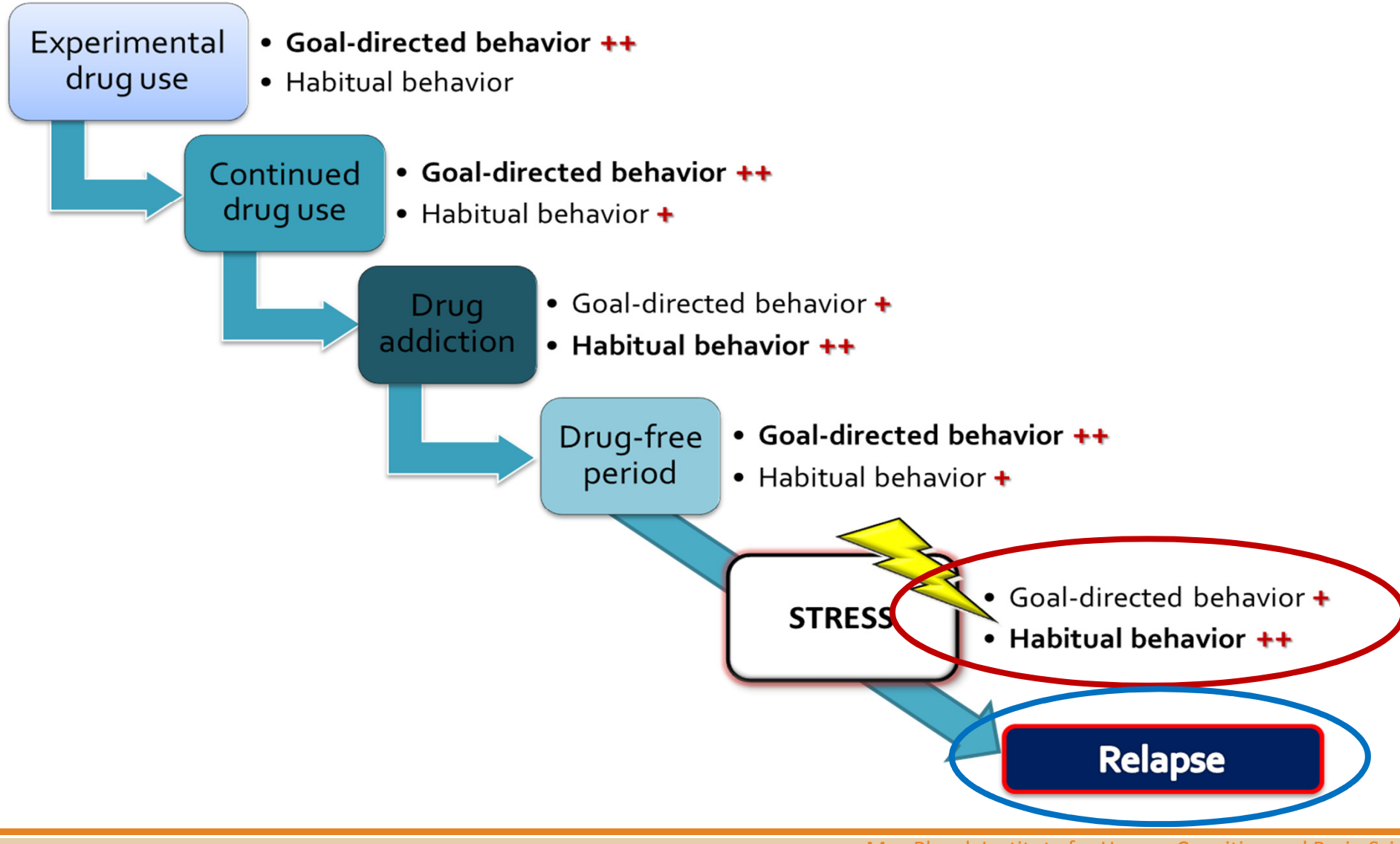
Operant learning task

2. Working memory



2-back task

MODEL


Experimental drug use
• Goal-directed behavior ++
• Habitual behavior
Continued drug use
• Goal-directed behavior ++
• Habitual behavior +
Drug addiction
• Goal-directed behavior +
• Habitual behavior ++
Drug-free period
• Goal-directed behavior ++
• Habitual behavior +
STRESS
• Goal-directed behavior +
• Habitual behavior ++
Relapse

MAIN HYPOTHESES

- Stress increases inflexible habitual- over goal-directed actions and affects brain activity in habit-related limbic regions and goal-directed related frontal regions in AD, more pronounced than in HC.

- Stress impairs working memory capacity and affects brain activity in cortical brain areas implicated in working memory processes.

- Stronger influence of stress on behavioral adaptation and its neurobiological profile predict relapse at follow-up.