Nikotinsucht: Neuroadaptative Änderungen und Implikationen für die Behandlung

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Outlook

- Introduction:
  - Nicotine addiction: burden and characteristics
  - Nicotine addiction: criteria and use

- The cerebral reward system
- The cerebral reward system and nicotine addiction
- Neurobiological model of Substance Use Disorders (SUD):
  - Neuroadaptative changes in nicotine addiction

- Implication for treatment
- Discussion and conclusion
Nicotine addiction: Burden and characteristics

- Smoking is associated with 20% mortality in men, and 1/3 of deaths in the 35-69 years old
- 1 milliard smokers worldwide
- High relapse rate

In Switzerland:
- 1 person on 4 (over 15 years old) is smoking
- More than 50% of the smokers report desire to stop
- 1 of 3 persons exposed to tobacco smoke
- Prevalence: 30% in men, 24% in women
- 24% among the 14-19 years old
- No change during the last 5 years, while decrease in other western countries

Panorama des addictions, 2017
Nicotine in the field of substance use disorders (SUDs)

- Amongst most significant public health problems worldwide
  - High societal/economic costs
  - Substantial suffering on individual level
- SUDs often resist/recur after treatment → chronic aspect

Nicotine use disorder: Diagnostic criteria (DSM-5)

Substance use disorder

1) Consuming more of the substance than planned.
2) Persisting desire or unsuccessful efforts to cut down or control substance use.
3) Spending a large amount of time using, obtaining and recovering from the substance.
4) Craving
5) Failure to fulfill major role obligations as a consequence of substance use.
6) Continuing the use of the substance despite its having negative effects on important relationships or on health.
7) Giving up or reduce important activities because of the substance use.
8) Tolerance
9) Withdrawal symptoms

Changes with DSM-IV:
No differentiation between Substance abuse and substance dependence

Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, 2013
Nicotine use disorder

Patterns of use:

- 9.9 mia cigarettes sold in Switzerland in 2015 (1400 cigarettes per inhabitants over 15)
- 40% of rolled cigarettes
- 2.8% use of snus

E-cigarettes

- 14% of the population >15 years tried at least once
- 0.3% regular consumers
- Unclear effect for tobacco smoking cessation

Development of new products: potentially reduced risks products

- Tobacco warming products
A little bit of history

- Intracranial self-stimulation (ICSS) behavior discovered by Olds and Milner (1953).
- Evidence for chemical specificity of ICSS: main implication of mesolimbic and mesocortical dopamine (DA) system.
- Further evidence for implication of dopamine in reward processing given in pharmacological and electrophysiological studies.
Cerebral reward system and substance of abuse

- All substances of abuse are associated with increase of dopamine transmission in nucleus accumbens
- Common denominator between all substances
- Direct effect on the cerebral reward system
- «Hijacking» of the reward system by the drugs
What is reward?
Cerebral reward system

- Reward is a positive reinforcer as well as an incentive stimulus.
- Reward is involved in motivation and learning.
- The mesolimbic dopamine system is involved in the processing of reward information.
- The ventral striatum in general, and the nucleus accumbens in particular are crucial regions for reward processing.

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(Tremblay & Schultz, 1999)
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Reduced brain responses to reward

Monetary reward versus baseline:

Striatum

No mood increase in response to reward in smokers.

Reduced responses to reward

- No correlations between monetary rewards and mood in smokers and cannabis smokers.
- No correlations between striatal responses to reward and mood changes.

A. All subjects

B. Nonsmokers

C. Smokers

Martin-Soelch et al., 2003, Eur.J Neurosci., 18(3)
Reduced responses to reward

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Neurobehavioral model of SUD

First contact
Experimenting phase

- Substance availability
- Interest / curiosity
- Positive effects of substance
- Peer pressure
- Model learning

Regular use / abuse

- Positive reinforcement
- Behavioral effects of substance
- Biochemical effects of drug
- Drug use as coping strategy
- Positive expectations

Dependence / SUD
Neurobehavioral model of SUD

First contact
Experimenting phase

Regular use / abuse

Dependence/ SUD

Development of drug conditioning (craving)

Drug availability

Curiosity
Peer pressure
personality traits
(impulsivity, sensation-seeking)

Drug use

Pleasant feelings
Increase of dopamine transmission in the NAc

Other stimuli

Association
Attribution of positive motivational value

Association
Attribution of positive motivational value

Mechanisms of negative reinforcement in SUD

Koob GF., Brain Res. 2010, 1314:3-14.

Koob GF., Brain Res. 2009, 1293:61-75
Neurobehavioral model of SUD

First contact
Experimenting phase

Regular use / abuse

Dependence/ SUD

Development of drug conditioning (craving)
Compulsive use

SUD Maintenance
• Negative reinforcement:
• Substance is used to reduce withdrawal symptoms
• Dysfunctional cognitions
Interaction between positive (cerebral reward system) and negative (neurobiological stress system) reinforcements

Neuroadaptation of motivational systems («anti-reward system»)
Neuroadaptation of motivational systems

- Neuroreceptor studies of DA generally point to a reduced DA function in smokers.
- Nicotine-dependent men exhibit lower putamen D2/D3 dopamine-receptor availability than non-smokers (Fehr et al., 2008)
- Reduced dopamine transporter (DAT) availability in smokers (Leroy et al., 2011; Yang et al., 2008)
- Lower dopamine synthesis capacity in nicotine-dependent smokers that appears to normalize with abstinence (Rademacher et al., 2016).

Rademacher et al., 2016)
Interaction between positive (cerebral reward system) and negative (neurobiological stress system) reinforcements

Neuroadaptation of motivational systems.

Development of drug habits

Koob, G.F., Pharmacopsychiatry 2009; 42, p.33
Development of drug habits

Smoking behavior becomes automatized in frequent smokers

(Isik et al., 2017)
Interaction between positive (cerebral reward system) and negative (neurobiological stress system) reinforcements.

Neuroadaptation of motivational systems.

Development of drug habits

Increased salience of stimuli associated with the substance («craving»)
Increased salience of stimuli associated with the substance («craving»)

- Higher fMRI activations in smokers than nonsmokers evidenced when viewing smoking-related compared to control images in the dorsal striatum, the premotor cortex, the superior parietal lobule and the right lateral cerebellum (Yalachkov et al., 2009)

- Correlations between severity of dependence and brain activity in regions involved in motor preparation in response to smoking cues in a group of smokers (Smolka et al., 2006)

- Greater fMRI activity during extended abstinence compared to before smoking cessation in the dorsal striatum in response to smoking cues (Janes et al., 2009)

- The neural reaction to smoking cues before entering a smoking cessation program predicted relapse, especially the activation in the insula and in the dorsal striatum (Janes et al., 2010).
Increased salience of stimuli associated with the substance («craving»)

- Greater fMRI activity during extended abstinence compared to before smoking cessation in the dorsal striatum in response to smoking cues (Janes et al., 2009)
Neurobiological model of substance dependance

- Interaction between positive (cerebral reward system) and negative (neurobiological stress system) reinforcements.
- Neuroadaptation of motivational systems.
- Development of drug habits
- Increased salience of stimuli associated with the substance («craving»)
- Decreased top-down control (impulsivity)

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Interaction between positive (cerebral reward system) and negative (neurobiological stress system) reinforcements.

Neuroadaptation of motivational systems.

Development of drug habits

Increased salience of stimuli associated with the substance («craving»)

Decreased top-down control (impulsivity)

Decision-making impairments

(Koob, G.F., Pharmacopsychiatry 2009; 42, p.33)

(Martin-Soelch, 2010; 2013)
Cognitive control and decision making changes

- Nicotine has enhancing properties on cognitive performance
- Enhanced connectivity strength in the presence of an acute nicotine patch in smokers in circuits consistent with those implicated in the performance-enhancing properties of nicotine (Heischmann et al., 2010; Hong et al., 2009).
- Reduced prefrontal cortical activity in current smokers compared to ex-smokers in response to smoking cues and to a motor response inhibition task (Nestor et al., 2011).
- Association between smoking withdrawal and the greater recruitment of insular, frontal and parietal cortical areas during a gambling task (Addicott et al., 2012).
- Reduced cortical grey matter volumes in the frontal and temporal lobes of smokers (Brody et al., 2004).
Neuroadaptive Changes Associated with Smoking: Structural and Functional Neural Changes in Nicotine Dependence

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Implications for treatment

Pharmacological interventions

- Nicotine replacement therapy (NRT): patches, gums,…
- Bupropion: inhibitor of noradrenalin and dopamine reuptake
- Vareniclin: nicotine receptor partial agonists
- Bupropion and NRT more efficient than placebo
- More NRT methods = more efficient
- Vareniclin more efficient than 1 NRT, but not than placebo (Cahill, Perera & Lancaster, 2013)
- Bupropion useful in «difficult» patients, for instance COPD and depressive patients (Richmond et al., 2003)
Implications for treatment

Pharmacological interventions

Reactivity to pleasant cues before treatment predicts cessation treatment outcomes (Versace et al., 2012)

“Smokers with higher activation to cigarette-related vs. pleasant stimuli (C > P) had 99% chances of increased benefit from varenicline compared to placebo at both time points, but only 67 and 43% with bupropion at the EOT and 3-month follow-up “ (Cinciripini et al., 2017)
Developing behavioral treatment targeting the cerebral reward system

The Mindfulness-Oriented Recovery Enhancement (MORE Treatment, Garland et al., 2014; 2017)

**Aims:**
- Distract from stimuli associated with the substance and re-orient attention towards pleasant experiences.
- Develop the consciousness for emotions and cognitions related to pleasant experiences at a meta-cognitive level.
- Group training, manualized, 8 to 10 meetings
Developing behavioral treatment targeting the cerebral reward system

Effect of MORE treatment in smokers (Froeliger et al., 2017)

Significant reduction of smoking and significant increase of positive affect

**Figure 1**: fMRI contrast of the group × time interaction on positive ER-BOLD response. A significant group (MORE, control) × time (Pre, Post) interaction was found in left ventral striatum (VS: −9, 14, −12; $F(1, 22) = 12.4, d = 2.13$) and right vmPFC (9, 26, −16; $F(1, 22) = 19.4, d = 2.66, K_{v} = 1648$) ($p_{v|n|< 0.05, \alpha = .05}$, Monte Carlo). Parameter estimates from the model indicate a relative increase in BOLD response from baseline to 8 weeks post-MORE relative to the control group, who evidenced a decrease in BOLD response.
### Implications for treatment

#### Cognitive-behavioral methods
- Contingency management
- Cognitive-behavioral therapy
- Motivational interview
- Relapse prevention using mindfulness
- Use of technology-based interventions (for instance, applications for smartphones)

#### Interventions based on the neurobehavioral research
- Cognitive and motor training reduces approach behaviors toward the substance (Wiers et al., 2010 et 2011; Eberl et al., 2013).
- Short-term memory training to better the top-down control (Houben et al., 2011; Bickel et al., 2011)
Takiwasi Addiction Treatment/ Rehabilitation Center

- Peru, upper Amazon
- Founded in 1992 by French MD Dr. Jacques Mabit
- Therapeutic protocol combining
  - Western contemporary &
  - Amazonian traditional
treatment methods for SUDs

(Berlowitz et al., 2017, 2018)
Conclusions

- Strong evidence for reduced neural responses to reward in SUD
  - «Anti-reward» system
  - Hijacking of the brain by the substances
- Nicotine use disorder as model for neurobiological investigation of SUD
- Interaction between positive and negative reinforcement in SUD
  - Important role of stress and motivation at neurobiological level
- These changes influence the therapeutic work.
- Interventions working on motivation are efficient.
- Responses to rewards as indicator resp. predictor of treatment responses.
- Pharmacological and non-pharmacological interventions are efficient
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QUESTIONS?