Morphological effects of chronic drug use in the brain and functional consequences

Christian P. Müller
SGDP Center, Institute of Psychiatry
King‘s College London
normal behavioural repertoire: • driven by natural reinforcers
• spectrum of behaviours
Drug addiction is a syndrome in which the use of a drug gets a higher priority than all other behaviours which previously had a high priority.

(WHO, 1981)
Chronic drug intake

- Drug repeatedly interacts with chemical structure of the brain
  - Acute neurochemical effects
  - Acute subjective and behavioural effects
  - Chronic changes in brain structure and function
  - Chronic changes in subjective perception and behaviour
Changes in brain structure and function

establishing addiction-related behaviours

compromise normal reinforcement-related behaviours

loss of function in other behavioural domains
  e.g.
  • emotion
  • attention
  • cognition
Changes in brain structure and function

- Establishing addiction-related behaviours
- Drug seeking and drug taking behaviours
- Established within brain reinforcement systems
- Systematic synaptic and morphological adaptations are induced
- Adaptations can be very long lasting
Changes in brain structure and function

establishing addiction-related behaviours

oppose each other

increase of likelihood to perform drug-related behaviour reduces likelihood for non-drug related behaviour: ‘collateral inhibition’

non-drug related behavioural repertoire
• studies of dendritic branching and spine density in various brain regions
• after experimenter administered drugs and after self-administration
Structural plasticity associated with exposure to drugs of abuse
Terry E. Robinson a,*, Bryan Kolb b


enhanced dendritic branching and spine density in the ncl. accumbens after cocaine and amphetamine treatment
Structural plasticity associated with exposure to drugs of abuse

Terry E. Robinson a, b, Bryan Kolb b


Table 1
Effects of stimulant drugs on spine density

<table>
<thead>
<tr>
<th></th>
<th>Acb</th>
<th>mPFC</th>
<th>oPFC</th>
<th>Par1</th>
<th>Oc1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>SA</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>NC</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>EA</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>NC</td>
</tr>
<tr>
<td>SA</td>
<td>–</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Nicotine</td>
<td>EA</td>
<td>–</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Abbreviations: EA, experimenter-administered; SA, self-administered; C, core; S, shell; A, apical; B, basilar; NC, no change; –, no data; ↑, increase; ↓, decrease (see text for references).

Table 2
Effects of stimulant drugs on dendritic branching

<table>
<thead>
<tr>
<th></th>
<th>Acb</th>
<th>mPFC</th>
<th>Par1</th>
<th>Oc1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>–</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>SA</td>
<td>–</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>EA</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Nicotine</td>
<td>EA</td>
<td>–</td>
<td>↑</td>
<td>NC</td>
</tr>
</tbody>
</table>

Abbreviations: see Table 1.
Structural plasticity associated with exposure to drugs of abuse
Terry E. Robinson a,⁎, Bryan Kolb b


Table 3
Effects of morphine in spine density and dendritic branching

<table>
<thead>
<tr>
<th></th>
<th>Ach</th>
<th>mPFC</th>
<th>nPFC</th>
<th>Par1</th>
<th>Oc1</th>
<th>HPC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Spines</td>
<td>EA</td>
<td>–</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>SA</td>
<td>–</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>NC</td>
</tr>
<tr>
<td>Branches</td>
<td>EA</td>
<td>–</td>
<td>↓</td>
<td>↓</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: EA, experimenter-administered; SA, self-administered; C, core; S, shell; A, apical; B, basilar; NC, no change; –, no data; ↑, increase; ↓, decrease (see text for references).

Structural plasticity is region specific and depends on the drug
Is drug-induced structural plasticity required for the establishment of addiction-related behaviours?

- rats self-administering (SA, i.v.) cocaine either 1h or 6h/day (= short and long access)
- then 47d days forced abstinence
- test of cocaine seeking (not rewarded)
- neuronal morphology in PFC and Ncl. accumbens

- Long access SA of cocaine establishes higher consumption and stronger cocaine seeking after abstinence

Ferrario et al. (2005)
Is drug-induced structural plasticity required for the establishment of addiction-related behaviours?

- Long access to cocaine produces stronger morphological changes than short access in the Nac but not PFC

Ferrario et al. (2005)
normal learning and addiction establishment induce same type of cellular plasticity in overlapping circuitry in the brain
Changes in brain structure and function

- establishing addiction-related behaviours
- compromise normal reinforcement-related behaviours

- present circuits can be weakened
- drugs induce unspecific activation (noise) in the system
Amphetamine or cocaine limits the ability of later experience to promote structural plasticity in the neocortex and nucleus accumbens

Bryan Kolb**, Grazyna Gorny*, Yilin Li*, Anne-Noël Samaha*, and Terry E. Robinson*

PNAS | September 2, 2003 | vol. 100 | no. 18 | 10523–10528

- amphetamine prevents plasticity induced by environmental enrichment
- amphetamine alone enhances dendritic branching and spine density
- amphetamine effects last at least 3.5 months after discontinuation of drug treatment
Amphetamine or cocaine limits the ability of later experience to promote structural plasticity in the neocortex and nucleus accumbens

• amphetamine effects on spine density accumulate with repeated administration

C – complex enriched environment
S - standard environment
Amphetamine or cocaine limits the ability of later experience to promote structural plasticity in the neocortex and nucleus accumbens

Bryan Kolb*, Graziya Gorny*, Yilin Li*, Anne-Noël Samaha*, and Terry E. Robinson*

PNAS | September 2, 2003 | vol. 100 | no. 18 | 10523–10528

- cocaine prevents plasticity induced by environmental enrichment
- no effects of cocaine alone
Changes in brain structure and function

- establishing addiction-related behaviours
- compromise normal reinforcement-related behaviours
- loss of function in other behavioural domains
  - e.g.
  - emotion
  - attention
  - cognition

Drug Toxicity
MDMA/Ecstasy

- 3,4-methylendioxymethamphetamine (MDMA = Ecstasy)
- popular club drug
MDMA/Ecstasy

animal studies:

- neurotoxine in humans and rodent and primate species
- repeated high doses and even single doses can cause serotonin depletion in rats and primates
- depletion of 5-HT and metabolite 5-HIAA
- long term upregulation of 5-HT₂ receptors

Ricaurte et al. (1992)
animal studies:
- reduced density of serotonin transporters
- mechanisms not completely understood: presumably by formation of free radicals in the presynapse
**MDMA/Ecstasy**

*animal studies:*

- depletion lasts for few weeks when abstinent
- full recovery after 1 year, but not in all individuals achieved
- recovery requires reinnervation
- regrowth of axons from serotonergic neurons
MDMA/Ecstasy

animal studies:

Altered Serotonin Innervation Patterns in the Forebrain of Monkeys Treated with (±)3,4-Methylenedioxymethamphetamine Seven Years Previously: Factors Influencing Abnormal Recovery

George Hatzidimitriou, Una D. McCann, and George A. Ricaurte


- monkeys treated twice daily with MDMA or saline
- 7 year survivor group (had received MDMA before)
- immunocytochemistry

- reduced serotonin innervation in the brain
- recovers with abstinence
MDMA/Ecstasy

animal studies:

- monkeys treated twice daily with MDMA or saline
- 7 year survivor group (had received MDMA before)
- immunocytochemistry

- no sign. loss of serotonergic cell bodies

Table 3. 5-HT-IR cell counts in the rostral raphe nuclei of squirrel monkeys treated with MDMA 2 weeks and 7 years previously

<table>
<thead>
<tr>
<th>Raphe nucleus</th>
<th>Cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRN Control</td>
<td>8269 ± 1965</td>
</tr>
<tr>
<td>2 week</td>
<td>8359 ± 2183</td>
</tr>
<tr>
<td>7 year</td>
<td>8996 ± 1927</td>
</tr>
<tr>
<td>MRN Control</td>
<td>7034 ± 1364</td>
</tr>
<tr>
<td>2 week</td>
<td>6366 ± 1100</td>
</tr>
<tr>
<td>7 year</td>
<td>6882 ± 1245</td>
</tr>
</tbody>
</table>
MDMA/Ecstasy

*humans:*

- reduced 5-HT and 5-HIAA in blood and CSF – proxy marker for brain serotonin activity
- women more susceptible to serotonin toxicity of MDMA than men
- recovery after abstinence
MDMA/Ecstasy

**humans:**

- reduced serotonin transporter density after MDMA use
- decrease correlates with extend of MDMA use
- no gross change to brain morphology
- no evidence for brain atrophy

- PET study labeling SERTs
- previous MDMA users (3 w abstinence) vs. controls

Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings

**U D McCann, Z Szabo, U Scheffel, R F Dannals, G A Ricaurte**

*Lancet* 1998; 352: 1433–37
Serotonergic system

Serotonin (5-Hydroxytryptamin, 5-HT)

5-HT important for:

- general locomotor activity
- sensory processing
- emotion
- learning and memory
- hedonic tone
Serotonergic system

Serotonin (5-Hydroxytryptamin, 5-HT)

5-HT system is highly plastic

> 80% rule
MDMA/Ecstasy

Functional consequences in humans:

- Low 5-HT associated with depression, suicidality, aggressiveness, and impulsiveness

- BUT: behavioral deficits are rather subtle in animals and humans

- Deficits in:
  - episodic learning and memory
  - increased impulsiveness
  - depressed mood
  - emotional instability
  - anxiety
  - hostility/aggression
  - heightened psychological distress
MDMA/Ecstasy

Functional consequences in humans:

still unclear whether deficits caused by drug or whether these factors predispose to the drug
amphetamine

- abused by various populations (e.g. students, sports professionals, truck drivers)

$\beta$-phenyl-isopropylamin = amphetamine
methamphetamine

- methamphetamine known as „crank“, „meth“, „crystal“, and „speed“ wide spread use in rural areas of the US

<table>
<thead>
<tr>
<th>Crank</th>
<th>foul smelling yellow powder, sniffed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lith</td>
<td>slightly cleaner, smokeable paste, induces strong rush</td>
</tr>
<tr>
<td>Ice</td>
<td>highest purity, induces most intense rush</td>
</tr>
</tbody>
</table>
methamphetamine

animal studies:

- neurotoxine in humans and rodent and primate species
- high or repeated doses of AMPH or METH induce wide spread degeneration of presynaptic serotonergic and dopaminergic axon terminals
- reduced density of serotonin- and dopamine transporters of 20-45%
- persistent up to 4 years in primates
- reduced dopamine transporter and DA D2 receptor level in former METH users
- reduced serotonin transporter level
- reduced hippocampal volume
- enlarged striatal volume
- white matter hypertrophy
- altered glucose metabolism
Serotonergic system

Dopaminergic system

human

rat

Mesolimbic/Mesocortical Dopamine System
Functional consequences in humans:

- no gross motor disturbances
- behavioral deficits are rather subtle in animals and humans despite DA and 5-HT toxicity
- deficits in:
  - learning and memory
  - attentional control
alcohol

ethyl alcohol (ethanol)
alcohol

• morphological changes in moderate drinkers difficult to assess
• morphological and cognitive deficits are reversible in moderate drinkers
• in alcoholics: morphological changes increase with consumed amount of alcohol
**CNS-impairment:**

- shrinking of brain volume and brain weight
- increased ventricle and sulci size
- white matter: volume reduction (esp. prefrontal)
- grey matter: shrinking and reduction of neurons and glia in frontal but not motor cortex
CNS-impairment:

- neuronal dendritic shrinking (shorter terminals) in frontal regions
- little changes in basal ganglia, nucleus basalis (ACh) and raphe ncl. (5-HT)
alcohol

Functional consequences in humans:

Deficits in:
  • abstract problem solving
  • visuospatial and verbal learning
  • memory function
  • perceptual motor skills
  • motor function
alcohol

CNS-impairment: the cerebellum

- cerebellar atrophy in Wernicke-Korsakoff Syndrome
- shrinkage of cerebellar vermis
- loss of Purkinje cells in vermis
- compromised pontocerebellar system
- compromised cerebellothalamocortical system

- disturbed fine motor control
- ataxia
- unsteadiness
specific syndroms:

- Marchiafava-Bignami disease
  - necrosis of the corpus callosum and neighbouring brain areas
  - dementia, spasticity, locomotor impairments
- Wernicke-Korsakoff syndrome
alcohol

Wernicke-Korsakoff syndrome

- after long time, intensive alcohol abuse in relation with a thiamine-deficiency (vitamin B1)
- initially peripheral neuritis $\rightarrow$ sensory impairment in extremity (hyperesthesia)
- later amnestic-confabulatory (loss of long term memory, confabulatory pseudo-memory)
- anterograde amnesia
- can be treated in early stage with thiamine
alcohol

Mechanisms of toxicity

90% alcohol metabolism in the liver

Ethanol $\xrightarrow{\text{ADH}}$ Acetaldehyde $\xrightarrow{\text{AcDH}}$ Acetate

Lipid peroxidation $\rightarrow$ aldehydic products
alcohol

Mechanisms of toxicity

- Alcohol metabolism generates highly active oxygen-containing molecules (oxygen radicals), e.g. hydroxyethyl radical (HER).
- Oxygen radicals generate oxidative stress which leads to cell damage.
- Oxygen radicals cause lipid (fat) peroxidation producing other reactive molecules, e.g. malondialdehyde (MDA).
Methanisms of toxicity

Interaction of reaction products with cellular structural proteins and immune mechanisms

Literature


