Bewusstseinserweiternde Substanzen
als neue Möglichkeiten der Therapie

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The Psychedelic Renaissance

High hopes

Psychedelic drugs fell from grace in the 1960s. Now, scientists are rediscovering them as potential treatments for a range of illnesses.

By Kai Kupferschmidt
Towards rapid-acting Antidepressants

Ketamine
Zarate et al.
Arch Gen Psych, 2006.

Psilocybin
Carhart-Harris et al.

DMT / Ayahuasca
Palhano-Fontes et al.
Global Expansion of Ayahuasca

[Graph showing the increase in mentions of Ayahuasca over time]

**Nature**

**Ayahuasca psychedelic tested for depression**

Pilot study with shamanic brew hints at therapeutic potential.

Arran Froid

06 April 2015

Ayahuasca being prepared for a healing ritual in the Brazilian village of Novo Segredo.

[Image of Ayahuasca preparation]

Willka Tika

Essential Wellness

Rejuvenate with Pachamama in Peru’s Sacred Valley

[Image of Willka Tika]
Ayahuasca
Banisteriopsis caapi & Psychotria viridis

Santo-Daime-Community
Ceu do Mapia, Brazil
The Ayahuasca Experience
The Ayahuasca Experience

Robert Venosa: Ayahuasca Dream
The Ayahuasca Experience

„I feel more able to be with myself. I feel more capable of experiencing my emotions. So that I don’t go to those behaviors that shove those emotions down that I don’t want to experience anymore.“

(patient self-reports)

Lafrance et al.
"I did notice a huge, huge change [in eating disorder symptoms]. It’s just hard to describe but I felt like I had more distance between my behaviors and, you know the thought patterns and the triggers and just felt like I didn’t need to have those coping skills anymore. [...] It was like my brain was reprogrammed. It’s the only way I can describe it - I don’t know exactly how it works."

(patient self-report)
The Ayahuasca Experience

„Ayahuasca helped me deeply connect with myself so that self-love has been the prevalent priority over self-criticism that [...] self-love became more important and more prevalent. And that to me is the antidote for an eating disorder."

(patient self-report)

Lafrance et al.  
Ayahuasca may have clinical potential to alleviate symptoms of *depression, anxiety, auto-aggression, addictive cravings* and feelings of *disconnection*:

- **antidepressant effects** (Palhano-Fontes et al. 2017)
- **anxiolytic effects** (dos Santos et al. 2016)
- **anti-addictive properties** (Liester & Pricket, 2012)
- **eating disorder recovery** (Lafrance et al. 2014)
- **candidate therapy for PTSD** (Nielson et al. 2014)
- **potential for grief therapy** (Gonzales et al. 2017)
- **increased cognitive flexibility** (Kuypers et al. 2016)
- **increased mindfulness** (Soler et al. 2016)
- **possible role of DMT in immunomodulation, tissue protection and neuroregeneration** (Frecska et al. 2016)
Beta-carbolines, for example harmine, are inhibitors of the MAO enzyme, which has its role in the degradation of serotonin and other neurotransmitters.

DMT (N,N-dimethyltryptamine) is not active orally because it is destroyed by the action of the MAO enzymes in the gastrointestinal tract, but the combination with MAOI harmala alkaloids blocks its metabolic breakdown and renders it orally active.
Neuroprotective Effects of DMT via Sig-1R

Szabo et al.
Front Neurosci, 2016.
Ayahuasca Stimulates the Birth of New Brain Cells

**Distal region of Neurosphere**

**No effects after saline**

**Color code**
- **Blue staining:** cell nuclei (marks all cells)
- **Green staining:** young neurons
- **Red staining:** mature neurons

**Image Courtesy of Beckley Foundation**
Jordi Riba, Sant Pau Research Programme
Ayahuasca Stimulates the Birth of New Brain Cells

**Harmine Stimulates Neurogenesis in vitro...**

**Color code**
- *Blue staining*: cell nuclei (marks all cells)
- *Green staining*: young neurons
- *Red staining*: mature neurons

*Image Courtesy of Beckley Foundation*  
Jordi Riba, Sant Pau Research Programme
Ayahuasca Stimulates the Birth of New Brain Cells

...and so does THH

Color code
- Blue staining: cell nuclei (marks all cells)
- Green staining: young neurons
- Red staining: mature neurons

Image Courtesy of Beckley Foundation
Jordi Riba, Sant Pau Research Programme
Serotonin-related Psychedelics

DMT / Ayahuasca

\[
\begin{align*}
\text{DMT} & : \quad \text{N}(\text{Me})_2 \quad \text{H} \\
\text{5-HT} & : \quad \text{NH}_2 \quad \text{HO} \\
\text{5-MeO-DMT} & : \quad \text{N}(\text{Me})_2 \quad \text{MeO} 
\end{align*}
\]

Psilocybin

\[
\begin{align*}
\text{Psilocybin} & : \quad \text{HO} \quad \text{PO}_2^- \quad \text{N}(\text{Me})_2 \\
\text{Psilocin} & : \quad \text{OH} \quad \text{N}(\text{Me})_2 
\end{align*}
\]

Geyer et al.
Selected abbreviations and acronyms

- VR: Visionary restructuralization
- PPI: Prepulse inhibition
- PCP: Phencyclidine
- OB: Oceanic boundlessness
- NMDA: N-Methyl-D-aspartate
- MDMA: 3,4-Methylenedioxymethamphetamine
- MDE: 3,4-Methylenedioxyethylamphetamine
- LSD: Lysergic acid diethylamide
- 5-HT: 5-Hydroxytryptamine
- DMT: N,N-Dimethyltryptamine
- DA: Dopamine
- CSTC: cortico-striato-pallido-thalamic
- CSPT: cortico-striato-pallido-thalamic
- CMRglu: Cerebral metabolic rate of glucose
- ASC: Altered states of consciousness
- AED: Anxious ego-dissolution
- FDG: F-fluorodeoxyglucose

Pharmacological aspects

Psychedelic hallucinogens can be classified by either their chemical structure or their primary mode of action. They are closely related structurally to hallucinogenic phenylethylamines and stimulant amphetamines and include compounds such as mescaline and 2,5-dimethoxy-4-iodoamphetamine (2,5-DIM), whose most important representative is mescaline. Dissociative or psychotomimetic agents, such as phencyclidine (PCP), ketamine, and related drugs, provide psychedelic or dissociative anesthetics. These are used to study the neuronal basis of drug-induced altered states of consciousness and its relation to altered functional brain states, which can be investigated by exploring the effects of specific receptor mechanisms among the neurotransmitter systems involved.

Since then a number of newly discovered hallucinogens was investigated, such as psilocybin and LSD, and their so-called serotonergic hallucinogens include derivatives of the indolamines, such as mescaline and psilocybin/psilocin (the active principle of the sacred Aztec magic mushrooms). Serotonergic hallucinogens share close structural features with the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]). Dissociative or psychotomimetic agents, such as phencyclidine (PCP) and ketamine, have been used as models to study the shared psychedelic effects of serotonergic hallucinogens and NMDA antagonists can be understood as an effect downstream of a common neurotransmitter system or final pathway. First, both serotonergic hallucinogens and NMDA antagonists produce sufficient overlapping psychedelic effects and can be considered as psychotic agents, such as psilocybin and LSD, and their adrenergic counterparts, such as mescaline and 2,5-dimethoxy-4-iodoamphetamine. The second class of drugs is referred to as psychedelic or dissociative anesthetics, such as ketamine or phencyclidine.

The premise of the present review is that many of the neurobiological changes associated with hallucinogenic and related drugs have been investigated by exploring the effects of specific receptor mechanisms among the neurotransmitter systems involved, and information-processing functions, such as sensorimotor gating as indexed by prepulse inhibition (PPI) of startle and sensorimotor gating as indexed by prepulse inhibition (PPI) of startle.
Neurotransmitters

Serotonin
Dopamine
Acetylcholine
Noradrenaline
Neurotransmitters Regulate Biological Functions

- **Serotonin**
  - Pain
  - Motion
  - Sexuality
  - Emotions
  - Motivation
  - Learning & Memory
  - Sleep & Wakefulness

- **Dopamine**

- **Acetylcholine**

- **Noradrenaline**
Pharmacological Simulation of Basic Human Values

Phenethylamines (MDMA, Mescaline)

Tryptamines (Psilocybin, DMT)

Stimulants (Cocaine, Amphetamines)

Sedatives (Opioids, Alcohol)

adapted from Schwartz
Basic human values, 2006
**Neurobiological Mechanisms**

### Image 1
- **Cortical layer V**
  - NMDAR
  - AMPAR
  - BDNF
- **Deep cortical layers**
  - 5-HT
  - Psilocin/LSD/DMT
- **Brainstem**
  - 5-HT neuron

### Image 2
- **Cortex**
  - Ketamine
  - NMDAR
  - AMPAR
  - BDNF
  - GABA
  - Interneuron
- **Subcortical areas**
  - NMDAR
  - Ketamine

### Annotations
- **DMT / Ayahuasca**
- **Psilocybin**
- **Ketamine**

**Text**

- Activation of the prefrontal network and glutamate release by psychedelics.
- The figure shows a model in which dissociative NMDA antagonists, such as ketamine, block their relative affinities at the NMDA receptor.
- In humans, fronto-limbic 5-HT receptors by stimulating corticofugal glutamate release in the prefrontal cortex (PFC)
- Psilocin reduces anxiety and pain in cancer patients.
- Dissociative anaesthetics.
- In addition to having these glutamatergic actions, certain dissociative agents block NMDA receptors on GABA-ergic interneurons in cortical and subcortical brain areas, leading to increased glutamate release in areas such as the prefrontal cortex.
- Indeed, recent studies showed that prefrontal 5-HT neurones may control serotonergic activity in the dorsal raphe nucleus, and in turn this dopaminergic and serotonergic activation is thought to ultimately lead to increased expression of brain-derived neurotrophic factor (BDNF).
- Finally, with regard to the finding that ketamine reduces anxiety and pain in cancer patients, ketamine reduces levels of 5-HT in the mPFC, which produces dose-dependent psychotropic effects of ketamine and PCP.

**References**

- Vollenweider & Kometer, 2010.
- © University of Zürich
Neurobiological Mechanisms

CSTC (cortico-striato-thalamo-cortical) loop

- CSTC feedback loops are involved in memory, learning, and self-nonself discrimination.
- The thalamus plays an important role in filtering out external and internal information to the cortex.
- Disruption of thalamic gating leads to sensory overload of the cortex and psychosis.
- The overwhelming flood of information affects cognitive integrity and self-referential information processing.

Vollenweider
Neurobiological Mechanisms

- Stimulation of 5-HT2A-receptors
  - Depolarization of pyramidal neurons of cortical layer V
    - Desynchronisation of cortical activity in associative brain areas
      - Destabilization of cortical networks
        - Increased metastability of cortical networks
          - Increased repertoire of connectivity motives
            - Facilitation of phase transitions
Neurobiological Mechanisms
**Neurobiological Mechanisms**

**Figure 4 | A combinatorial approach for treating depression based on the network hypothesis.** Depression might reflect disturbed information processing in neural networks (left panel). Antidepressant drugs, electroconvulsive shock and psychotherapy can all induce activity-dependent plasticity, which gradually leads to the recovery of connectivity in the affected neural networks (right panel).

**Castrén**
Nat Rev Neurosci 2005
Neurobiological Mechanisms

Task-negative network (default mode network: DMN)

Task-positive network (executive control network: ECN)

Fox & Greicius
Front Syst Neurosci, 2010
Neurobiological Mechanisms

*Increased mPFC activity and DMN connectivity in depression* (Farb et al. 2011)

\[ \Delta S, \Delta E \]

*metastable transition state*

*ruminative introspection (DMN)*

*extroception (TPN)*
Neurobiological Mechanisms

Psychedelics facilitate phase transitions through destabilization of networks

ΔS, ΔE

metastable transition state

phase shift

ruminative introspection (DMN)

extroception (TPN)
Neurobiological Mechanisms

FIGURE 7 | Increasing neural entropy elevates cognitive flexibility at the expense of a decrease in the cause-effect information specified by individual mechanisms.
Neurobiological Mechanisms

- by expanding the reality cone and promoting conceptual overlap, the high entropy state facilitates creativity, novel thinking, and imagination.
- conceptual blending could result in a failure to distinguish concepts related to self from concepts related to other, perhaps explaining the “ego dissolution” and the sense of “oceanic boundlessness”.
- as psychotherapeutic agents psychedelics break out the inflexible and circular modes of thinking that characterize psychiatric disorders.
Neurobiological Mechanisms

Mckenna & Riba et al.
Curr Topics Behav Neurosci, 2016.
Neurobiological Mechanisms

Bipartite model of brain serotonin function

1) Post-synaptic 5-HT1AR-mediated passive coping • Modulated by SSRIs (chronic-use)

- Basic action
  - Post-synaptic 5-HT1AR signalling ↑
  - Limbic responsivity ↓

- Functions reduced
  - Stress, impulsivity, aggression, anxiety ↓

- Functions enhanced
  - Resilience ↑
  - Patience ↑
  - Emotional blunting ↑
  - Tolerance of stress ↑

Pathway 1 (modulated by conventional antidepressants)

2) 5-HT2AR-mediated active coping • Modulated by psychedelics

- Basic action
  - 5-HT2AR signalling ↑
  - Cortical entropy ↑

- Functions reduced
  - Rigid thinking ↓
  - Pessimism ↓

- Functions enhanced
  - Plasticity ↑
  - Environmental sensitivity ↑
  - Learning & unlearning ↑
  - Adaptability/change ↑

Pathway 2 (modulated by 5-HT2AR agonist psychedelics)

Depression ↓
Well-being ↑

Carhart-Harris & Nutt et al.
Transformative psychotherapy involves the transformation of maladaptive into more adaptive states of consciousness. Therapeutic transformation through altered states of consciousness involves continuous learning and experiencing with improvements and relapses. Psychotherapy and substitution-based pharmacotherapy are also important components of this approach.
Transformational Psychotherapy

sub-critical system
- low entropy
- stable
- insensitive for change

critical system
- metastable
- sensitive for change

Max. 30-35°

super-critical system
- high entropy
- instable
- prone to avalanches

adapted from Carhart-Harris et al.
Front Hum Neurosci, 2014
Transformational Psychotherapy

Phase transition

Secondary consciousness ↔ Primary consciousness

Sub-critical system
- coma / anaesthesia
- deep sleep
- depression
- obsessive-compulsive / rigid thinking

Everyday consciousness

Super-critical system
- psychedelic state
- REM sleep / dreaming
- psychosis
- magical / creative thinking

Adapted from Carhart-Harris et al.
Front Hum Neurosci, 2014
Therapeutic transformation through altered states of consciousness

Transformational Psychotherapy

Stuck in a rut: rethinking depression and its treatment

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Transformational Psychotherapy

Roland Fischer
Science 1971
Results

Figure 1 shows the scores obtained for the study variables before and 24 h after the ayahuasca session. The MINDSENS composite index showed a statistically significant increase following the ayahuasca session ($F(1,24)=6.78, p=0.016$).

The analysis of the individual questionnaires showed a significant effect of ayahuasca session on the EQ score ($F(1,24)=8.55, p=0.007$). Two of the five subscales of the FFMQ also showed significant increases in the 24 h following ayahuasca: Non-Judge ($F(1,24)=7.86, p=0.010$) and Non-React ($F(1,24)=5.06, p=0.034$).

The introduction of the prior experience with ayahuasca as a covariate in the analysis did not greatly modify the results for the MINDSENS composite index ($F(1,23)=5.26, p=0.031$). However, it decreased significance of changes on the EQ questionnaire score ($F(1,23)=6.45, p=0.018$) and increased significance of the pre- vs. post-comparison of scores on the FFMQ Non-Judge ($F(1,24)=8.39, p=0.008$) and Non-React ($F(1,24)=5.06, p=0.009$) subscales.

Despite the changes in $F$ and $p$ values, the overall pattern of results remained unchanged.

Discussion

By exploring the effects of ayahuasca intake on mindfulness capacities, the present study aimed to better understand the psychological mechanisms underlying the therapeutic potential of ayahuasca. Our findings indicate that ayahuasca intake leads to a rapid increase in several mindfulness-related parameters. Two FFMQ facets changed after ayahuasca, suggesting a decrease in the judgmental processing of personal experiences, along with a reduction in inner reactivity. Additionally, decentering ability was also increased after ayahuasca intake. These combined modifications provide an explanatory mechanism that could contribute to the beneficial effects reported for ayahuasca in the treatment of addiction and depression (Thomas et al. 2013; Osório et al. 2015). It is worth mentioning that prior studies showing benefits associated with long-term ayahuasca use have the confounding factor of participants being members of a religious group (Fábregas et al. 2010; Bouso et al. 2012). The present results obtained in a lay setting support the notion that ayahuasca may have therapeutic potential per se in the absence of the religion confound.

The scores in some mindfulness capacities observed after ayahuasca are analogous to those of experienced meditators (Soler et al. 2014a). Thus, Soler and colleagues report the following average scores in their experienced meditator sample: $B_{Non-react}^\text{post} = 24.84$, $B_{Non-judge}^\text{post} = 30.61$, EQ = 41.07, and MINDSENS = 3.70. These values are very close and in some cases lower than those obtained here in the post-ayahuasca assessment: $B_{Non-react}^\text{post} = 25.56$, $B_{Non-judge}^\text{post} = 33.16$, EQ = 41.41, MINDSENS = 3.66. The similar values obtained in the MINDSENS are a relevant finding. The MINDSENS index was created with those FFMQ and EQ items that were more sensitive.
Transformational Psychotherapy

ACT-Hexaflex Model
Fig. from Prevedini et al. 2011
Transformational Psychotherapy

Andrews-Hanna et al.
Neuron, 2010

Self > Control

Default Mode Network (PCC)
Dorsal Nexus (DMPFC)
Affective Network (sgACC)
DMN (PACC/MPFC)

Scheidegger et al.
PloS One, 2012

Meditation (Brewer et al. 2011)
Psilocybin (Carhart-Harris et al. 2012)
Ayahuasca (Palhano-Fontes et al. 2015)

Carhart-Harris et al.
Nature, 2012
Transformational Psychotherapy

Imaginationen, Regressionen und Übertragungsphänomene

mystische Erfahrungen und ekstatische Zustände
Transformational Psychotherapy

Adaptation

Begreifen
(emotional/kognitiv)

Anpassung der Grenzfläche

Perspektive bleibt erhalten
(personal, biographisch)

Wachstum

mehrere Sitzungen
(niedrige-moderate Dosen)

Transformation

Ergriffen-Sein
(existenziell)

Auflösung der Grenzfläche

Perspektive wird aufgelöst
(transpersonal, mystisch)

Wiedergeburt

1-3 Sitzungen
(hohe Dosen)

Psycholytische Therapie

Psychodelische Therapie
Transformational Psychotherapy

„The future may teach us how to exercise a direct influence, by means of particular chemical substances, upon the amounts of energy and their distribution in the apparatus of the mind. It may be that there are other undreamed of possibilities of therapy. But for the moment we have nothing better at our disposal than the technique of psychoanalysis...“

Sigmund Freud: An Outline of Psychoanalysis, 1949
Transformational Psychotherapy

„I believe that if people would learn to use LSD's vision-inducing capability more wisely, under suitable conditions, in medical practice and in conjunction with meditation, then in the future this problem child could become a wonder child.“

Albert Hofmann
LSD - My Problem Child (1980)
Nutzen, Risiken und Grenzen

- Auf ein geeignetes **Set** (innerer Zustand) und **Setting** (Umfeld) ist aufgrund der stark **kontextsensitiven Wirkung** dieser Substanzen unbedingt zu achten.
- **Supportive Psychotherapie im Plastizitätsintervall** um korrektive Bewusstseinserfahrungen weiter zu stabilisieren
- Aufklärung, **Nutzen-Risiko-Analyse** und Einverständniserklärung
- Pharmakologisch induzierte veränderte Bewusstseinzustände können aufgrund ihrer ungewohnten Intensität bei entsprechender Prädisposition akut auch **Angst, Panik oder Gefühle von Kontroll- und Realitätsverlust** auslösen.
- **Psychiatrische Kontraindikationen**: akute Suizidalität, emotionale Instabilität oder Psychoseanfälligkeit
- **kardiales Screening und regelmässiges Monitoring** der Vitalparameter während der Sitzung (BD-/Pulsanstieg)
- **Medikamenteninteraktionen**: Antiglutamaterge und GABAerge Medikamente (z.B. Antiepileptika, Benzodiazepine), Opiode und SSRIs mildern die Wirkung serotonerger Psychedelika ab, während MAO-Hemmer zu einer unvorhersehbaren Wirkungsverstärkung beitragen und wegen der Gefahr eines Serotonin Syndroms daher kontraindiziert sind.
Toxikologisch gelten glutamaterge und serotonerge psychoaktive Substanzen bei den im therapeutischen Rahmen üblichen Dosierungen und Behandlungsfrequenzen als hinreichend sicher.

Im Gegensatz zu häufig verschriebenen Betäubungsmitteln wie Benzodiazepinen und Opiaten, weisen serotonerge psychoaktive Substanzen kein Risiko für eine Abhängigkeitsentwicklung auf.

Entgegen früheren Annahmen liess sich nicht bestätigen, dass die Lebenszeitprävalenz der Einnahme von Psychedelika mit einem erhöhten Risiko für psychiatrischen Erkrankungen assoziiert ist, im Gegenteil zeigte sich ein signifikant vermindertes Auftreten von Suizidgedanken und -versuchen bei Menschen, die regelmässig Psychedelika konsumieren.

Das Risiko für Langzeitnebenwirkungen wird zudem durch die unregelmässige und limitierte Anzahl an Behandlungen gesenkt, was auch gesundheitsökonomische Vorteile hat.

Da die meisten Wirkstoffe und Präparate allerdings nicht patentierbar sind, sinken die Anreize für industrielle Forschung und pharmazeutische Entwicklung im Bereich von serotonergen psychotropen Substanzen.
Take Home Messages

• Der klinisch-experimentelle Einsatz psychoaktiver Substanzen wird seit einigen Jahren wieder vermehrt wissenschaftlich untersucht.

• Abhängigkeitserkrankungen, Stress- und Traumafolgestörungen sowie Angststörungen und Depression bei lebensbedrohlicher körperlicher Erkrankung stellen derzeit die am besten evaluierten Indikationen für die substanzunterstützte Psychotherapie mit serotonergen psychoaktiven Substanzen dar.

• Der Behandlungsansatz mit psychoaktiven Substanzen beruht nicht auf einer längerdauernden pharmakologischen Substitution von Neurotransmittern, sondern zielt als transformationsorientiertes Paradigma auf die rasche Veränderung dysfunktionaler neuronaler Regelkreise ab.

• Psychoaktive Substanzen zeigen in einem kontrollierten klinisch-experimentellen oder wissenschaftlichen Setting ein relativ gutes Sicherheitsprofil und eine gute Verträglichkeit.

• Die experimentelle Behandlung mit nicht verkehrsfähigen Substanzen unterliegt der Bewilligungspflicht durch die kantonalen Ethikkommissionen sowie des BAGs und ist vorerst nur in wissenschaftlich begleiteten Kontexten oder für experimentelle individuelle Heilungsversuche möglich.
Reconnect Foundation

**Deep Cognitive Tools for Transformational Healthcare**

- Developing a **standardized botanical extract** analogue to traditional ayahuasca
- Assessing **safety and tolerability** including pharmacokinetics and brain dynamics (phEEG)
- Multimodal neuroimaging of neural correlates of emotional regulation, cognitive flexibility, and mindfulness-related capabilities
- Clinical studies about efficacy of **ayahuasca-based psychotherapy** for stress-related affective disorders

*Psychiatrische Universitätsklinik Zürich*
Reconnect Team
Vielen Dank für Ihre Aufmerksamkeit...

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