Cannabis in Palliative and Hospice Medicine

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Third Annual Palliative Care Institute Conference

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Honoring my teachers

Donald Abrams, MD
Head of Hematology and Oncology
University of California San Francisco

Neil McKinney, ND
Boucher College
Vancouver, BC

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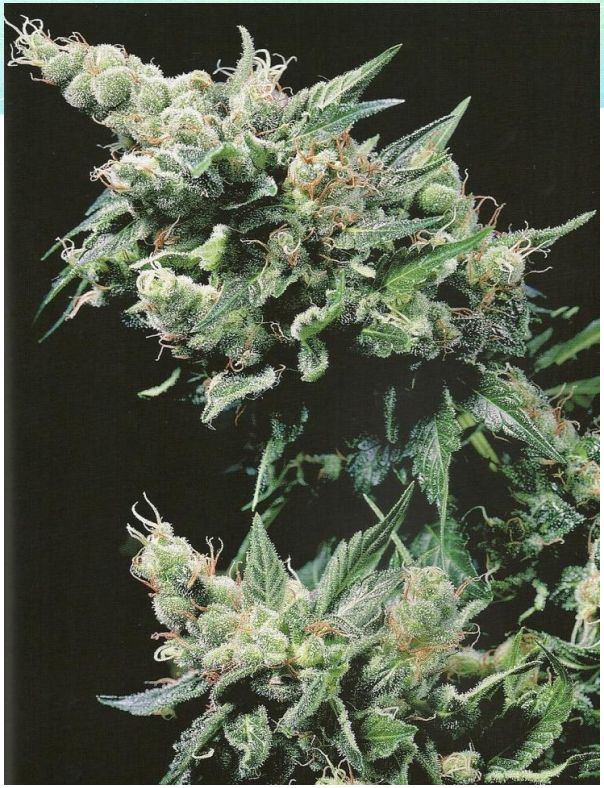
Cannabis as Medicine

- Cannabis (marijuana, hemp) is one of the oldest known psychoactive plants
- First reported use as medicine >3000 years ago
- Introduced into Western Medicine in 1840's by Dr. W.B. O'Shaughnessy
- Promoted for putative analgesic, sedative, anti-inflammatory, antispasmodic and anticonvulsant properties



Cannabis as Medicine

- Interest waned in early 1900's with advent of opiates, barbiturates, chloral hydrate, aspirin and syringes
- First federal restrictions in 1937 with Marihuana Tax Act ($1/oz for medical use, $100/oz for recreational users)
- AMA virtually alone in opposing act
  - Believed objective data re: harmful effects were lacking
  - Act would impede future clinical investigations
  - Removed from US Pharmacopoeia in 1942

Controlled Substance Act 1970

Schedule I Substances

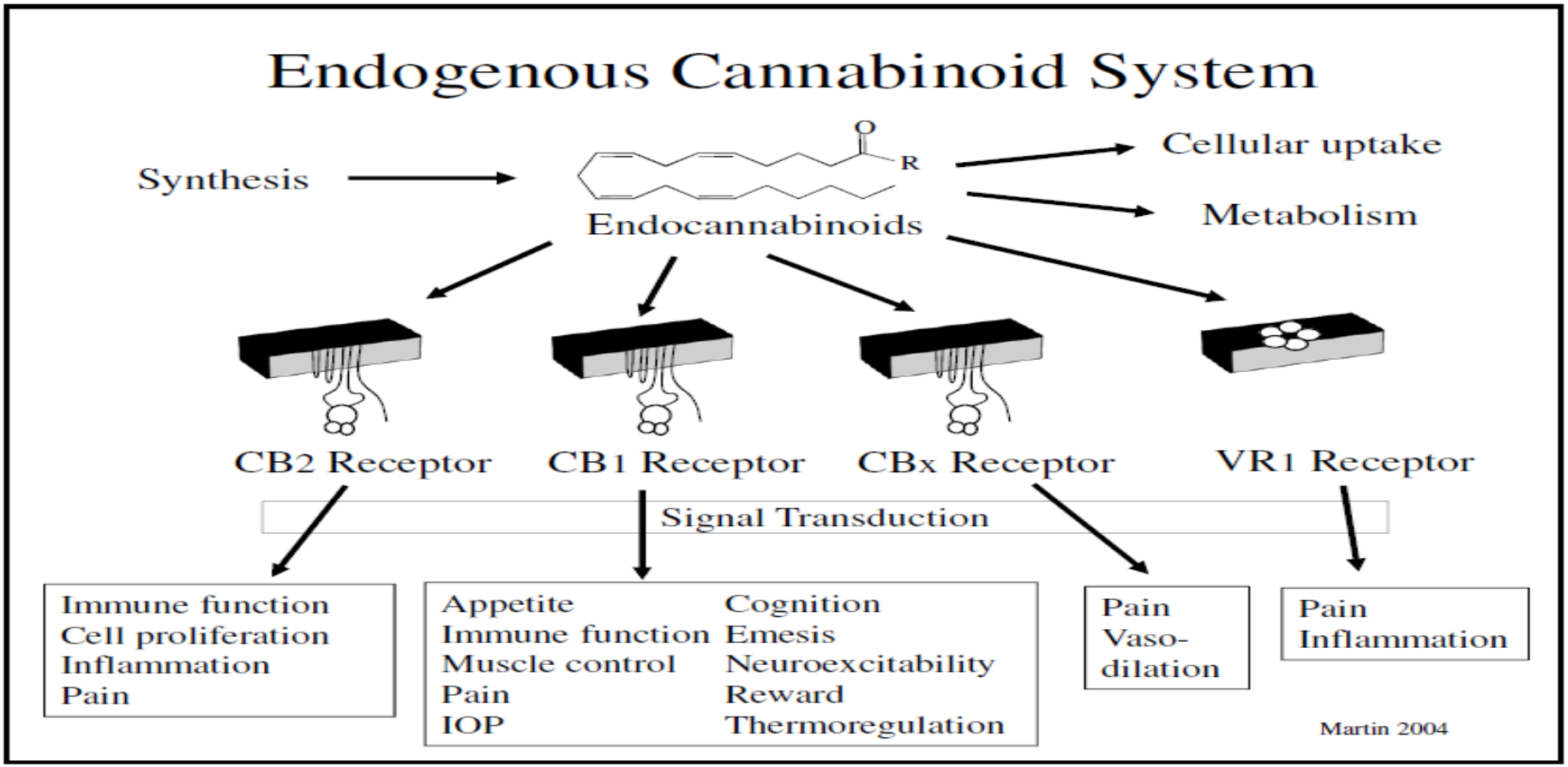
- Marijuana
- Heroin
- LSD
- Mescaline
- Other hallucinogenic amphetamine derivatives
- Methaqualone
- Illicit fentanyl derivatives
- Gamma hydroxybutyrate (GHB)

Cannabis as Medicine

- Contains over 400 chemical compounds
- Highest concentration of bioactive compounds in resin exuded from flowers of female plants
- Main psychoactive component believed to be delta-9-THC
- At least 70 other cannabinoids identified in pyrolysis products
- Delta-8-THC similar in potency but only in small concentration

Non-THC Components of Cannabis

- Δ9-tetrahydrocannabinol (THC) is the primary active ingredient of cannabis
- Secondary compounds may enhance the beneficial effects of THC
- Other cannabinoid and non-cannabinoid compounds may reduce THC-induced anxiety, anticholinergic effects and immunosuppression
- Terpenoids and flavonoids may increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens and provide anti-inflammatory activity



The Endocannabinoids

- Lipid (oil) soluble
- AEA anandamide (AEA). Binds to CB1 receptors. CBD in cannabis inhibits its enzymatic clearance.
- Two-aclglycerol, aka two-arachidonyl glycerol (2 AG). Acts on both CB1 and CB2 receptors. CBD in cannabis stimulates its release.
- We have more (endo)cannabinoid CB1 and CB2 receptors than opiate receptors.

Piomelli 2003

Endocannabinoid Receptors

* **CB1** receptors for AEA and 2AG endocannabinoids are particularly abundant in the **central nervous system**, also in adipose tissue, liver, lungs, uterus & placenta.
* Activation of CB1s in central and peripheral nerves can be **analgesic**.
* CB1s on GABA interneurons which can disinhibit **pain** projection neurons.
* **Neuro-transmitters** modulated include acetylcholine, norepinephrine, dopamine, 5-hydroxy-tryptamine, GABA and D-aspartate.

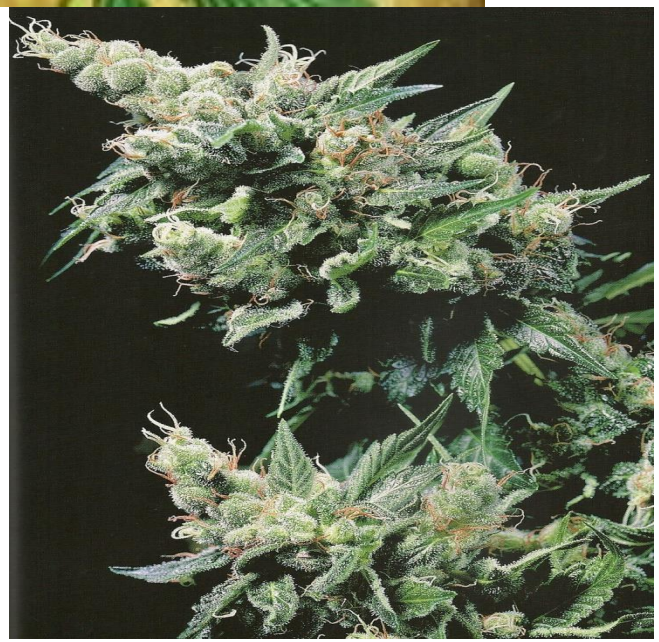
Exo-Cannabinoids

Cannabis contains at least 68 cannabinoids such as:

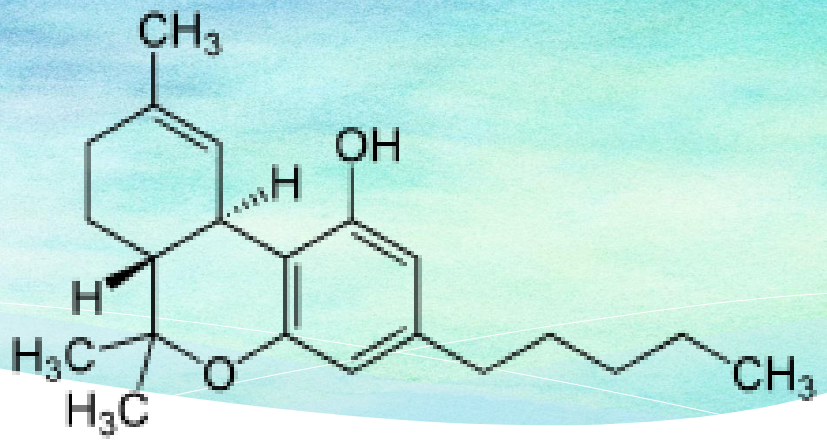
- THC – delta-9tetra-hydro-cannabinol
- CBD – cannabidiol
- CBN, CBG, CBC, THCV

Plus other bioactive components:

- Terpenes – the aromatic oils
- Flavonoids eg anti-inflammatory cannaflavins



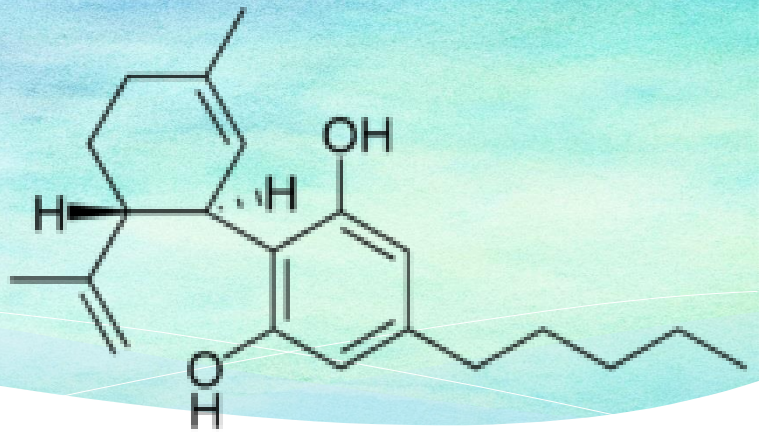
Δ9-THC



- delta-9-tetra-hydro-cannabinol
- Psychoactive "narcotic"– Sativa *high*, Indica *stone*

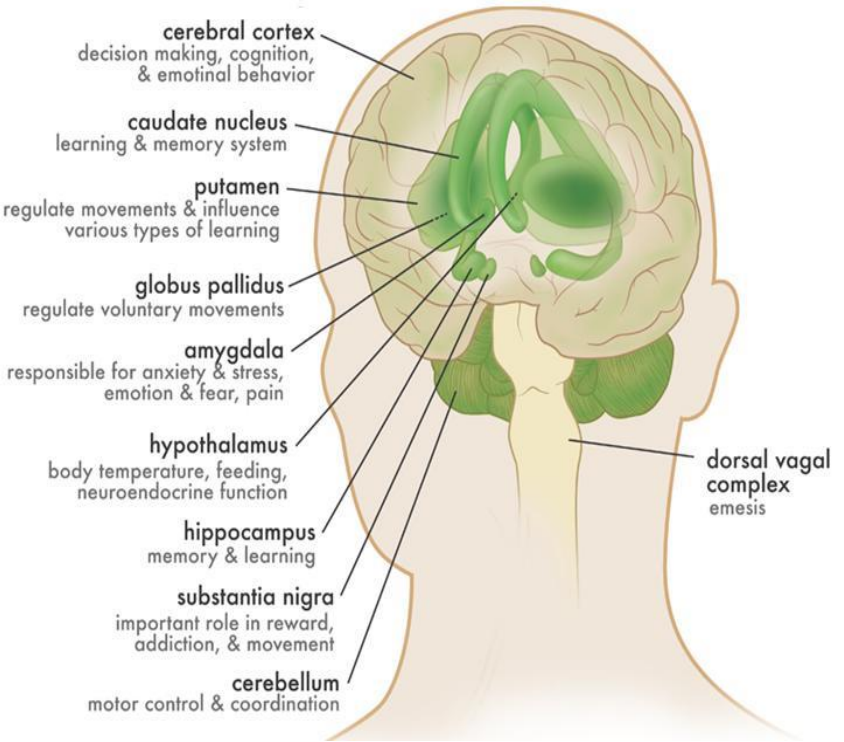
  Alters mood, behavior, perception & consciousness.
- CB1 - Receptors primarily in the CNS but also in peripheral nervous system and other organs.

CBD - Cannabidiol



- Stimulates release of endocannabinoid 2-AG which acts on CB1 and CB2 receptors.
- Balances psychotropic effects of THC at CB1s in CNS, reducing disorientation, tachycardia, drowsiness.
- Abundant in *Indica* leaf & bud.
- Immuno-modulator, anti-inflammatory, analgesic, anxiolytic, lowers BP, anti-nausea, neuroprotective.

Distribution of CB1 Receptors



CB1 receptors for AEA and 2AG endocannabinoids are particularly abundant in the **central nervous system**, also in adipose tissue, liver, lungs, uterus & placenta.

Activation of CB1s in central and peripheral nerves can be **analgesic**.

CB1s on GABA interneurons which can disinhibit **pain** projection neurons.

Neuro-transmitters modulated include acetylcholine, norepinephrine, dopamine, 5-hydroxy-tryptamine, GABA and D-aspartate.

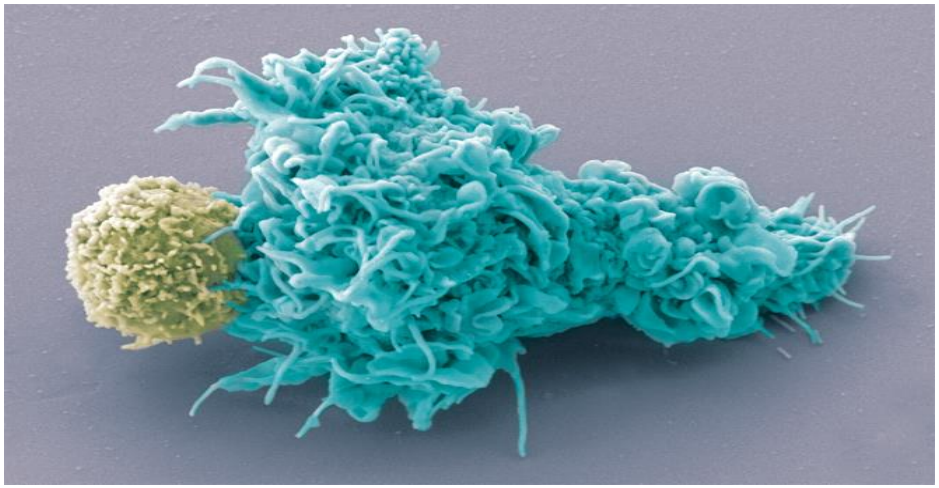
CB2 Receptors

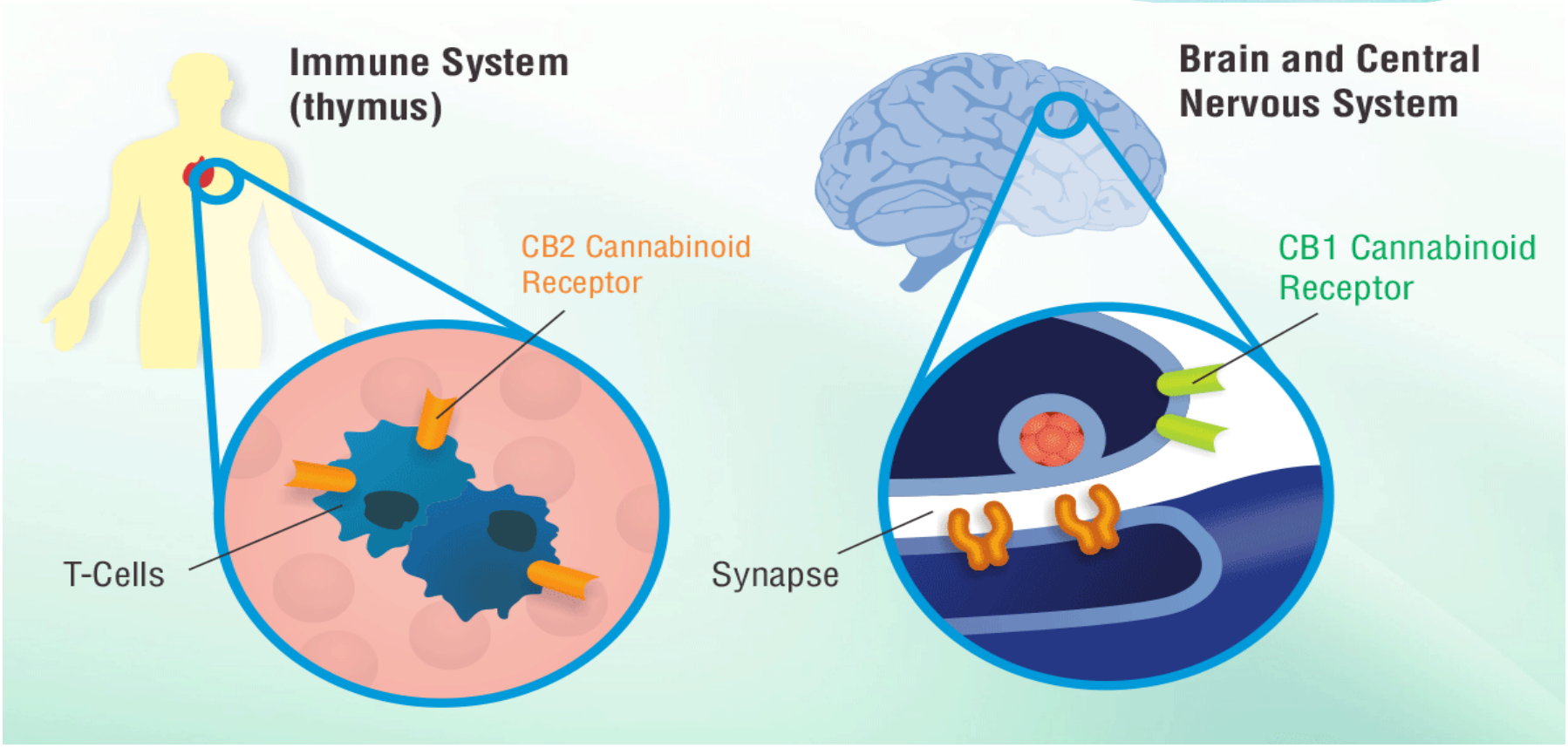
- **CB2** receptors for 2AG / CBD are found in liver, spleen, GI tract, heart, bones, kidneys, and in the peripheral nervous system.
- Many are in **immune** tissues such as spleen, tonsils, lymphatics and leucocytes including in order of concentration:

  B-cells, NK cells,

  Monos, PMNs,

  CD4 and CD8 T cells.





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Cannabinoids & Immune Function

Cannabinoids inhibit the TH1 immune response, with its pro-inflammatory cytokines IL-1, IL-2, IL-12, IL-18, and γIFN.

These may inhibit auto-immune diseases including multiple sclerosis, IDDM1, RA, psoriasis and Crohn's.

Stimulated by 2-AG and therefore by **CBD.**

Pharmacological Blockade of the eCB System

Pharmacologically induced deficiency of the eCB system by SR141716 or AM251 may lead to:

- suppressed feeding and weight loss Freedland et al. (2000) Pharmacol Biochem Behav; Rowland et al. (2001) Psychopharmacology
- increased anxiogenic-like behavior Haller et al. (2004) Behav Pharmacol; Navarro et al. (1997) Neuroreport
- attenuated responsiveness to rewarding stimuli (e.g., ethanol, sucrose, heroin, nicotine) Arnone et al. (1997) Psychopharmacology; Cohen et al. (2002) Behav Pharmacol; De Vries et al. (2003) Psychopharmacology
- reduced sensitivity to the reinforcing effects of electrical brain stimulation Deroche-Gamonet et al. (2001) Psychopharmacology
- increased duration of wakefulness, hyperarousal and vigilance Santucci et al. (1996) Life Sci

→ Similarities with melancholic depression

Courtesy of Dr. Patrik Roser

Terpenes

- Give the aroma and flavor to cannabis.
- D-limonene – see Boik 1998 – anti-mutagenic, immune modulator, anti-neoplastic. Gould 1997, Crowell 1999
- Pinene, linalool, terpeneols, citronellol, myrcene, caryophyllene, pulegone, cineole, cymene.
- *Sedative and anti-depressant effects*.
- *Lessen anxiety* from other cannabis bio-actives

Cannabis effects

- Topical, ingestible, suppository and vaporized for nausea, appetite, cachexia or pain.
- *Cannabis sativa* can be energizing.
- *Cannabis indica* is more sedating may cause dizziness and impaired memory.
- A balance in the ratio of CBD to THC can reduce intoxication ie indica leaf extract or juice.

Adverse Effects

Dry mouth, **dehydration**, reduced saliva and tears, reduced energy, weakness, light-headedness, **dizziness**, postural hypotension, syncope, immobility ("couch-lock"), mental clouding, confusion, dysphoria, lethargy, **anxiety** (often re: death or loss of control), impaired memory, amnesia, increased reaction time, reduced motor performance, decreased attention, reduced coordination, nausea, stomachache, colored stool or urine, conjunctival injection (bloodshot eyes), bronchitis, **tachycardia**.

Intoxication is aggravated by MSG!

Cannabinoid Analgesia

- Somatic pain
- Visceral pain
- Neuropathic pain
- Hyperalgesia
- Allodynia, pain of inflammation
- Muscle spasticity

Severe pain requires both THC and CBD.

Abrams 2011 Martin-Sanchez 2003

Cannabinoids and Pain

- Elevated levels of the CBI receptor – like the opioid – are found in areas of the brain that modulate nociceptive processing
- CB1 and CB2 agonists have peripheral analgesic actions
- CBs may also exert anti-inflammatory effects
- Analgesic effects not blocked by opioid antagonists

Cannabinoid: Opioid Interactions

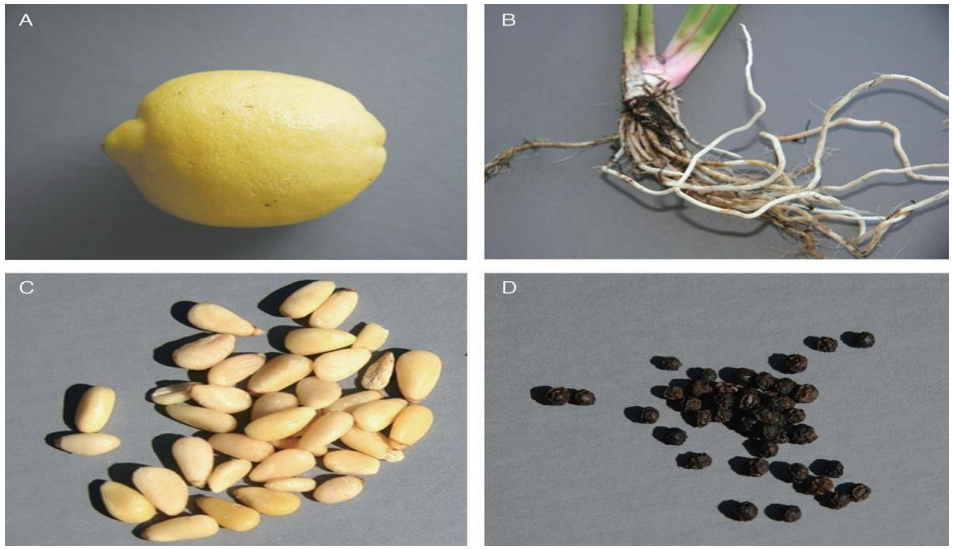
- In mice and rats, THC greatly enhances analgesic effect of morphine in a synergistic fashion
- Increased potency of other mu opioids (hydromorphone and oxymorphone) seen with oral-Δ-9-THC in mouse models
- Possibility of enhanced and persistent analgesic effect at lower opioid doses

PTSD, opiates, neurological disorders

- PTSD – Pruning memory, time distortion, altered perceptual state and disinheriting may be useful in moving trauma into long-term memory – "just one of the things that happened in my life". Rx 8+ mg
- Cannabinoids can reduce opiate use and dependence, and may stand-in for alcohol and other psychoactive drugs.
- May ease anxiety (CBD), Tourrete's, epilepsy, MS, agitated dementia.
- *Caution: Sedative drugs interact strongly!*

Traditional Antidotes to Intoxication

- Citrus fruit – eg lemons, rind zest.
- Pine nuts
- Black pepper
- Calamus root



Russo 2011

Danger To Children

- At age 13 a human child has well-developed pleasure/reward centres so can get high, but has not fully developed pre-frontal cortex until age 24.
- Cannabis primarily acts in the pre-frontal cortex of adults, who are able to use that area to create forethought of consequences of action and to control impulses.
- Early exposure to cannabis may damage brain development and may increase risk of psychoses.

Dependence

Risk of dependency is about 9%, less than for tobacco, alcohol (15%), cocaine (17%) or heroin (23%).

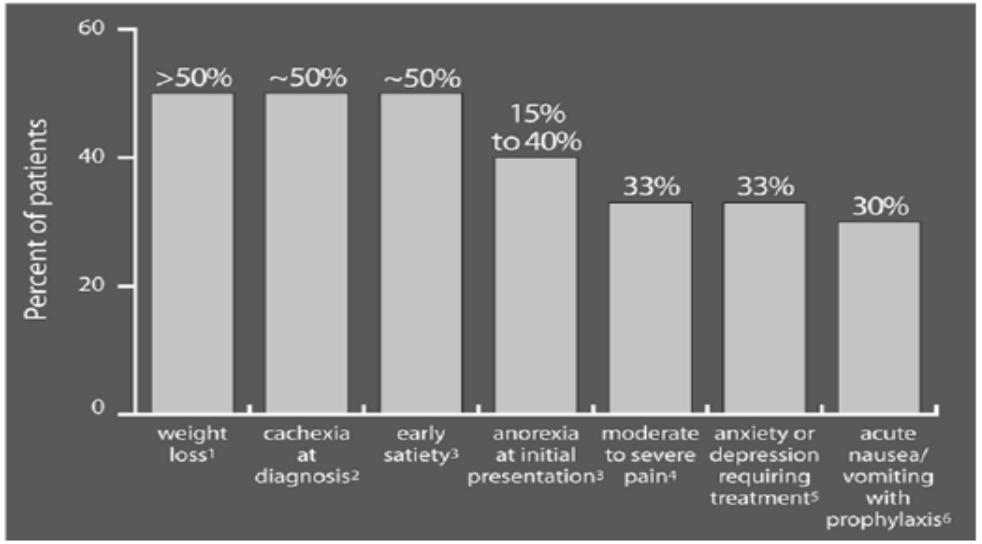
The hallmarks of dependency are compulsion, craving, loss of control of intake, continuing to use despite negative consequences in physical health or social, recreational or work activities or relationships, tolerance, persistent desire to reduce intake but inability to do so, and withdrawal reactions.

N-acetyl-cysteine helps break dependence Gray 2012

Drug Withdrawal

- Heavy users who suddenly withdraw may have mild irritability, anger, aggression, restlessness, agitation, sleep disorder, strange dreams, depression, hyperhidrosis, loss of appetite, weight loss, rebound intraocular pressure increase.
- Withdrawal symptoms tend to peak at day 2 to 4, and end by 7 to 14 days.
- THC will clear off in about 35 days, metabolites can be detected in urine for up to 80 days.

Symptom Management Challenges Associated with Cancer and Its Treatments



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Cannabinoids and Appetite

- Anandamide in low concentrations in mice leads to a potent enhancement of appetite
- CBI receptors implicated in food intake control (hypothalamus and limbic system)
- CB1 knockout mice eat less than wild type litter mates
- CB1 receptors involved in motivational/reward aspects of eating

Cannabis and Chemotherapy N & V

* Interest in 70's prompted by anecdotal reports when available antiemetics were inadequate
* In randomized trials, oral THC better than placebo and equivalent or superior to prochlorperanzine
* Smoked THC appeared superior to oral
* THC <metoclopramide <5-HT_3 antagonists

2015 Cochran Review

Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy (Review)

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Cochrane review conclusions

- 23 RCTS
- N&V decreased in those who received verum vs placebo
- Similar to conventional anti-nausea medicines. However, more people experienced side effects such as 'feeling high', dizziness, sedation, dysphoria and left the study due to the side effects with cannabis-based medicines, compared with either placebo or other anti-nausea medicines.
- In trials where people received cannabis-based medicines and conventional medicines in turn, overall people preferred the cannabis-based medicines

Medical Cannabis and cancer. Joan Cramer, MD. CA Cancer J Clin 2015;65:109-122.

Pain → 9 RCTS 1975-2011. 9/9 positive benefit. Dose dependent response

Appetite ad weight → 5 RCTS 1986 -2007. 5/5 increased appetite and weight with dose dependence

Drug: herb interactions → none with taxanes or irinotecan

No evidence of lung cancer or COPD risk with smoking.

Oncologists' THC Survey

- 1000 responses from randomly selected members of American Society of Clinical Oncology surveyed in 1990
  - 44% had recommended marijuana to at least one patient
  - Marijuana believed to be more effective than dronabinol by 44%; dronabinol more effective by 13%
    - Doblin et al JCO 1991

THC and Analgesia

- In cancer trials, oral THC 20 mg was comparable to codeine 120 mg but with marked psychological effects

- Cannabinoids also effective in rat model of neuropathic pain

Cannabis in HIV Neuropathy

- HIV-related painful distal symmetric polyneuropathy is a common problem
- Current therapy for HIV neuropathy pain is inadequate
  - Opioids generally ineffective
  - Anticonvulsants in common use currently
  - Anecdotal reports of marijuana's efficacy
- Cannabinoids effective in preclinical models of neuropathic pain

Supported in part by UC CMCR and NIH GCRC Funds

Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

D.I. Abrams, MD; C.A. Jay, MD; S.B. Shade, MPH; H. Vizoso, RN; H. Reda, BA; S. Press, BS; M.E. Kelly, MPH; M.C. Rowbotham, MD; and K.L. Petersen, MD

Abstract—*Objective:* To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model. *Methods:* Prospective randomized placebo-controlled trial conducted in the inpatient General Clinical Research Center between May 2003 and May 2005 involving adults with painful HIV-associated sensory neuropathy. Patients were randomly assigned to smoke either cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Primary outcome measures included ratings of chronic pain and the percentage achieving >30% reduction in pain intensity. Acute analgesic and anti-hyperalgesic effects of smoked cannabis were assessed using a cutaneous heat stimulation procedure and the heat/capsaicin sensitization model. *Results:* Fifty patients completed the entire trial. Smoked cannabis reduced daily pain by 34% (median reduction; IQR = −71, −16) vs 17% (IQR = −29, 8) with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($p \leq 0.05$) but appeared to have little effect on the painfulness of noxious heat stimulation. No serious adverse events were reported. *Conclusion:* Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

NEUROLOGY 2007;68:515–521

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Cannabis: Opioid Conclusions

- Co-administration of vaporized cannabis with oral sustained release opioids is safe
- Co-administration of vaporized cannabis in subjects on stable doses of morphine or oxycodone appears to enhance analgesia
- Co-administration of vaporized cannabis trends towards lowering concentration of the opioids
  - The PK effects would be expected to reduce the analgesic effects of the opioids
  - The effect of vaporized cannabis to enhance opioid analgesia occurs by a pharmacodynamics, not a pharmacokinetic mechanism

IOM: Efficacy of Cannabinoid Drugs

- The accumulated data indicate a potential therapeutic value for cannabinoid drugs
  - Pain relief
  - Control of nausea and vomiting
  - Appetite stimulation
- THC therapeutic effects best established
- Effects of cannabinoids generally modest; usually there are more effective medications

Cannabis-Induced Euphoria

* Often described as a “side–effect” of Rx
* Is it really an “adverse experience” particularly in the terminal patient?
* Is a single treatment that increases appetite, decreases nausea and vomiting, relieves pain and improves mood and sleep a potentially useful tool in palliative medicine?

The Safety of Cannabis

* No deaths have been reported from OD
* Estimate 800 cigarettes required to kill (death secondary to CO not cannabinoid poisoning)
* By comparison, 300 ml of vodka or 60 mg of nicotine would be lethal
* Addictive potential and minor withdrawal syndrome less than or equal to caffeine

Cannabis and MS-related Incontinence

The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicenter, randomized placebo-controlled trial

Freeman et al 2006

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Cannabis as an Anti-Cancer Agent

- Increasing body of preclinical evidence suggests cannabinoids may have activity
- Anti-oxidant and anti-inflammatory effects
- Possibility of anti-tumor activity via cannabinoid receptors inducing apoptosis and impairing tumor vascularization
- Gliomas and skin tumors seem responsive in animal models

Cannabinoids and Cancer

* Cannabinoid administration to nude mice curbs growth of various tumor xenografts
  - Lung carcinoma
  - Thyroid epithelioma
  - Lymphoma
  - Skin carcinoma
  - Glioma

Cannabinoids and Cancer

- Cannabinoids induce apoptosis in gliomas
- Cannabinoids administration in mouse models differentiates tumor vascular hyperplasia
  - Associated with reduced expression of VEGF and VEGF receptors
- Cannabinoids decrease the activity of matrix metalloproteinase-2; hence may also modify glioma invasiveness
  - All of the above in mice with gliomas

Velasco Neuropharmacology 04

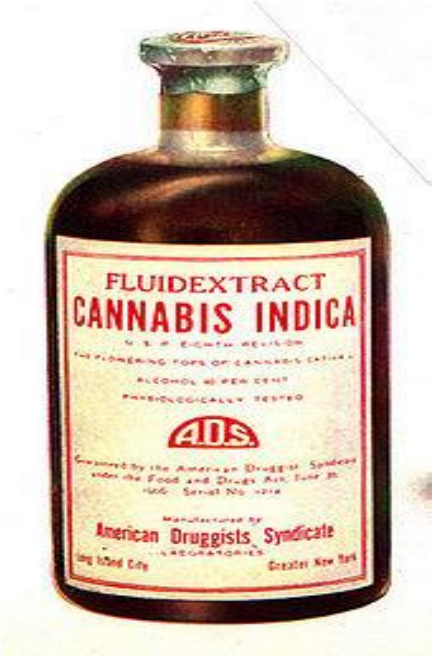
Cannabidiol and Colon Cancer

- In colorectal cancer cell lines, CBD
  - Protected DNA from oxidative damage
  - Increased endocannabinoid levels
  - Reduced cell proliferation
- In mice treated with azoxymethane, CBD 1 mg/kg decreased aberrant crypt foci polyps and tumor formation
- At non-cytotoxic concentration, CBD anti-proliferative vs colorectal cancer cell lines

Aviello et al. J Moi Med 2011

Cannabinoids for Cancer

- Cannabinoids inhibit cancer gene expression of Id-1 protein involved in aggressive growth and metastasis of breast & ovarian cancer. McAllister 2007
- Cannabinoids retard angiogenesis Freimuth 2010
- Cannabinoids inhibit inflammation via TNFα Chianchi 2008



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Cannabinoids have anti-cancer activities

- directly retard cancer cell growth, eg CBD inhibits proliferation by antagonizing GPR55 receptors. Kotsikorou2013
- selectively kill cancer cells, mutated cells
- THC inhibits angiogenesis Blazquez 2004
- THC inhibits cancer cell respiration even where there are no cannabinoid receptors. Ruiz 1999
- CBD + THC inhibit metastasis Murase 2013
- CBD + THC reduce free radicals of oxygen.

Cannabis for Cancer

- Cannabinoids inhibit the TH1 immune response, with its pro-inflammatory cytokines IL-1, IL-2, IL-12, IL-18, TNFα and γIFN. Borgelt 2013
- Modulate inflammatory growth factors
- THC inhibits EGFR. Blasquez 2004
- THC is anti-cachexic, THC + CBD are anti-nausea.
- Terpenes such as D-limonene also have anti-tumor activity.

Oral THC Pharmacology

- Low (6-20%) and variable bioavailability
- Peak [Plasma] within 1-6 hr; may remain elevated for several hrs
- Initially oxidized in liver to 11-OH-THC, as potent psychoactive metabolite
- Further oxidation of 11-OH-THC leads to elimination products (urine and feces)
- Terminal half life 20-30 hrs

Smoked THC Pharmacology

- Rapidly absorbed into blood stream and redistributed
- Considerable amount of dose lost in smoke and destroyed by pyrolysis
- Peak blood levels achieved at end of smoking decline rapidly over 30 minutes
- Smoking achieves higher peak concentration but shorter duration of effect
- Smaller amts 11-OH-THC formed

Sativex®

- GW Pharmaceuticals, England
- ~ 50 : 50 mix of THC & CBD
- **Whole plant extract** – terpenes, flavonoids
- Oral spray – corrosive to gingiva
- Approved in Canada. Expensive
- Rx for neuropathic pain and muscle spasticity
- Gets many patients too high

  Johnson 2013

Marinol® (dronabinol)

- THC pill – 2.5, 5 or 10 mg
- High blood levels of psychoactive 11-hydroxy-THC
- Expensive, less effective than cannabis Cooper 2013

Nabilone®

- Synthetic THC from Cesamet, circa 2006
- For pain, chemo nausea, vomiting, loss of appetite
- 50% drop out: dizziness, sedation, dysphoria
- Most users prefer cannabis

Cannabis Dose Guidelines

- Multiple variables dictate that dosing be highly individualized
- A patient-determined self-dosing model is recommended
- Self titration model acceptable in view of the plant and host variables and the low toxicity of cannabis
- Gabapentin and example of another drug with relatively low toxicity and high dosing limits titrated to effect

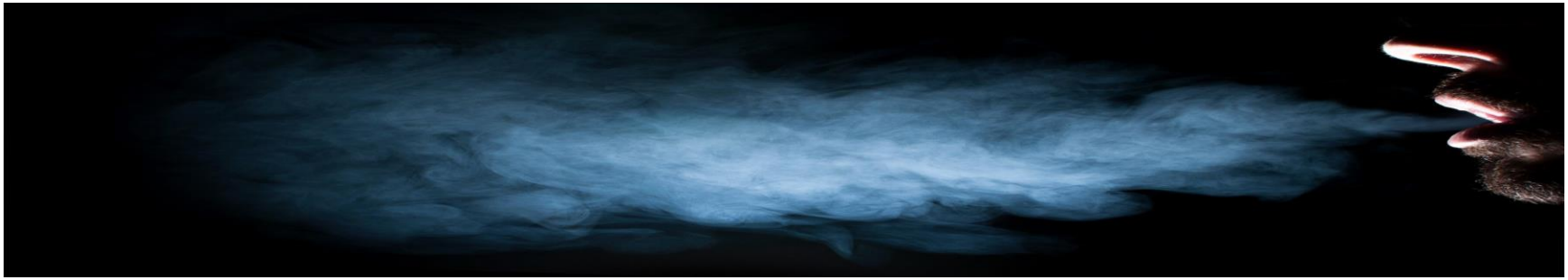
Carter et al IDrugs 2004

Smoking cannabis

- A joint = 0.5 to 0.8 grams of cannabis with about 4 to 8% THC
- About 20 to 70% of that ~ 5 mg of THC reaches the lungs.
- 5 to 50% of the THC is bioavailable - into systemic circulation,
- 31% of CBD - cannabidiol reach systemic circulation,
- 38% of CBN - cannabinoids reach systemic circulation.
- Plasma peaks of THC occur in 3 to 10 minutes, often before finishing a joint.
- The most psychoactive metabolite 11-hydroxy-THC reaches a peak in 13 minutes.
- It rapidly moves into highly vascular tissues, then slowly distributes into fatty tissue.
- Plasma clears in about 3 hours, and the high usually lasts about 1 to 2 hours, sometimes up to 4 hours. The Pot Book 2010

Vaporization

- Lower temperature, low particulates and markedly less of toxic carbon monoxide make this much safer and cleaner than smoking
- There is markedly better THC delivery to blood compared to smoking - 30% of THC content is lost to pyrolysis (combustion)in smoking.



“Hash Oil”

- Ambrosia hybrid iso/ethyl extract contains 48 mg/mL THC + 8 mg CBD. Thinned in MCT to 12-24 mg THC/mL .
- Regular strength morning dose for pain, spasm, anxiety, depression, PTSD, etc. 0.15 mL which delivers 0.3 mg CBD, 1.8 mg THC.
- A larger dose later in the day may be 0.25 mL, yielding 0.5 mg CBD and 3 mg THC. Like smoking hash.
- “High Test” dose: 0.40 mL = 0.8 mg CBD & 4.8 mg THC
- At 24% an *Extra Strength HT* 0.4 mL cap = 9.6 mg THC

Edibles

- http://www.cbc-canada.ca/recipes/cbcoc-official-recipe-book
- www.hempology.ca Ted Smith
- Cannoil: 43 gm bud, 1 litre olive oil, strain, add 11 Tbsp. lecithin
- Green butter: 2 oz. leaf, 1 lb butter, strain, add 5 Tbsp. lecithin
- Buddha oil: 4 2/3 oz leaf, 1 litre olive or grapeseed oil, strain, add 11 Tbsp. lecithin

Cannabutter

- Kettle of water – bring to a boil and add
- 1 pound butter.
- 1 ounce good bud
- Boil 2 hours, making sure temp doesn't exceed 212° F - don't let the pot boil dry.
- Strain out plant material, add water, re-boil.
- Mix both batches, let cool. The butter will congeal on top.
- Store butter covered, in fridge.

Olive Oil Infusion

* Decarboxylate herb 15 minutes in oven at 250° (or 1 hour at 150°).
* One ounce of bud, leaf or "shake" per cup of oil
* Put in crock pot on LOW setting for 20+ minutes
* Strain through cheesecloth

* Coconut or grapeseed oil as also used.

Buddha Balls for Cachexia

Buddha Balls are carefully designed to be easy on compromised digestive systems such as those with Crohn's disease and diabetics, and are a complete meal replacement. They contain oats, hemp protein, hemp hearts, soy protein, whey protein, coconut, sunflower seeds, almond powder, honey, and cannabis infused olive oil.

Buddha Balls Recipe

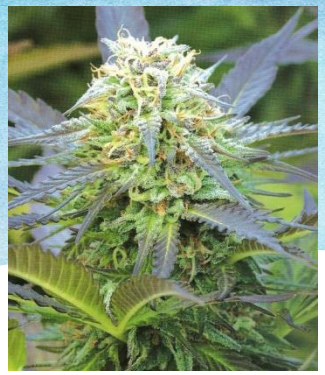
Combine :

4 cups oats
3 cups coconut
1 cup raw unsalted sunflower seeds
1 ½ cups whey protein
1 ½ cups soy protein
½ cup hemp protein
½ cup hemp hearts
Mix.....
1 cup Buddha Ball Oil (Cannabis infused olive oil)
Mix.....
400g honey (2 ½ ladles)
Mix thoroughly.....
Put 1 cup almond powder in a small bowl
Form the balls and use almonds to coat the outside
Add ½ cup chocolate chips for ½ the batch
.....Makes 24

Topical Cannabis Oil

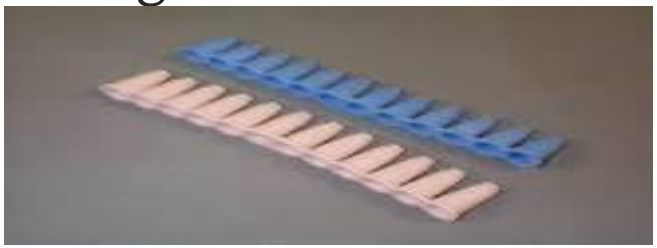
Olive or coconut oil extracts are effective for many skin disorders, and can be rubbed into sore joints. 4 2/3 oz leaf, 1 liter oil, ½ bottle vitamin E oil

Rick Simpson dilutes the *phoenix tears* type oil in 5 parts 99% iso-propyl alcohol for topical use, and claims this "most medicinal plant in the world" cured his skin cancer.



Cannabis Suppositories

- Grind decarboxylated bud 15'@ 250° to flour consistency
- Melt cocoa butter and/or beeswax in a double-boiler Coconut oil can also be used.
- Mix equal parts cannabis flour, or 1 – 2 gm RSO hemp oil, per 100 gm cocoa butter.
- Add up to 4% beeswax for shape and healing.
- Pour into moulds or shape into cylinders on wax paper.
- Refrigerate/freeze until needed.



Cannabis as a Cancer Treatment?

Active against cholangiocarcinoma, glioblastoma, carcinoid, breast, lung, prostate, pancreatic,

leukemia – *in vitro* and in pre-clinical animal studies

via ceramide, akt/mTOR, MMP, PPARɣ, autophagy, EGFR, apoptosis, etc……..

Abrams, Weil, Guzman 2009

Singh & Bali 2013 – a case report

“Rick Simpson Hemp Oil”

- Rick Simpson used one pound of high THC *Indicas* .
- 8 litres of toxic and dangerous naptha or butane solvents.
- Short contact of herb with solvent www.phoenixtears.ca
- Yield – about 60 grams of thick, greasy oil.
- Consume 60 + grams RSO in 90 days

Phoenix Tears Oil Today

- Ideal is 1:1 mix of ethyl and isopropyl alcohols.
- Iso yields ~ 25 gm oil / lb > than pure ethanol.
- 15 minute ice-cold maceration maximizes bio-actives and GI tolerability of the oil.
- Using high CBD:THC hybrids: *Cannatonic* - 6%/6% Romano 2013



Taking "RSO" hemp oil

- Warm the syringe in hot water.
- Dose 4 to 72 insulin units, up to 1 gm/day.
- Start at bedtime, as needed add doses at breakfast, lunch and 5 pm.
- Use citicoline to prevent excess intoxication, or lemonade, pine nuts.
- Ψ A/Es – avoid alcohol & sedatives!

Grain of Rice – RSO Starting Dose

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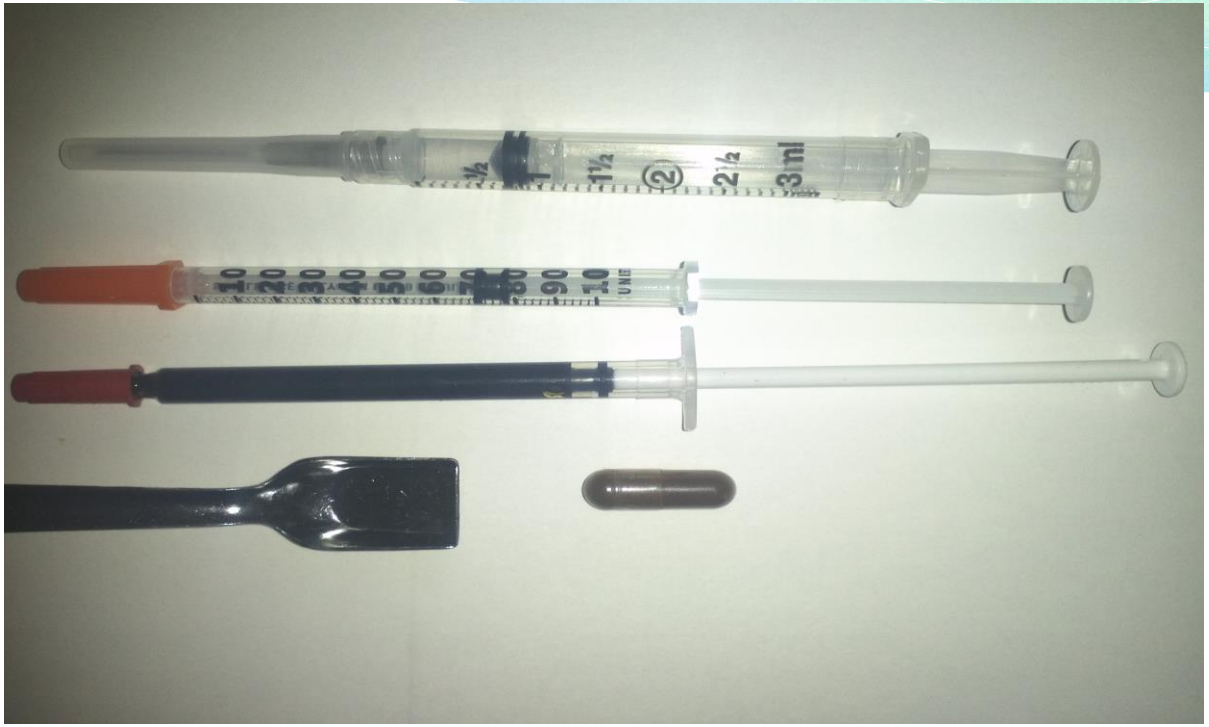
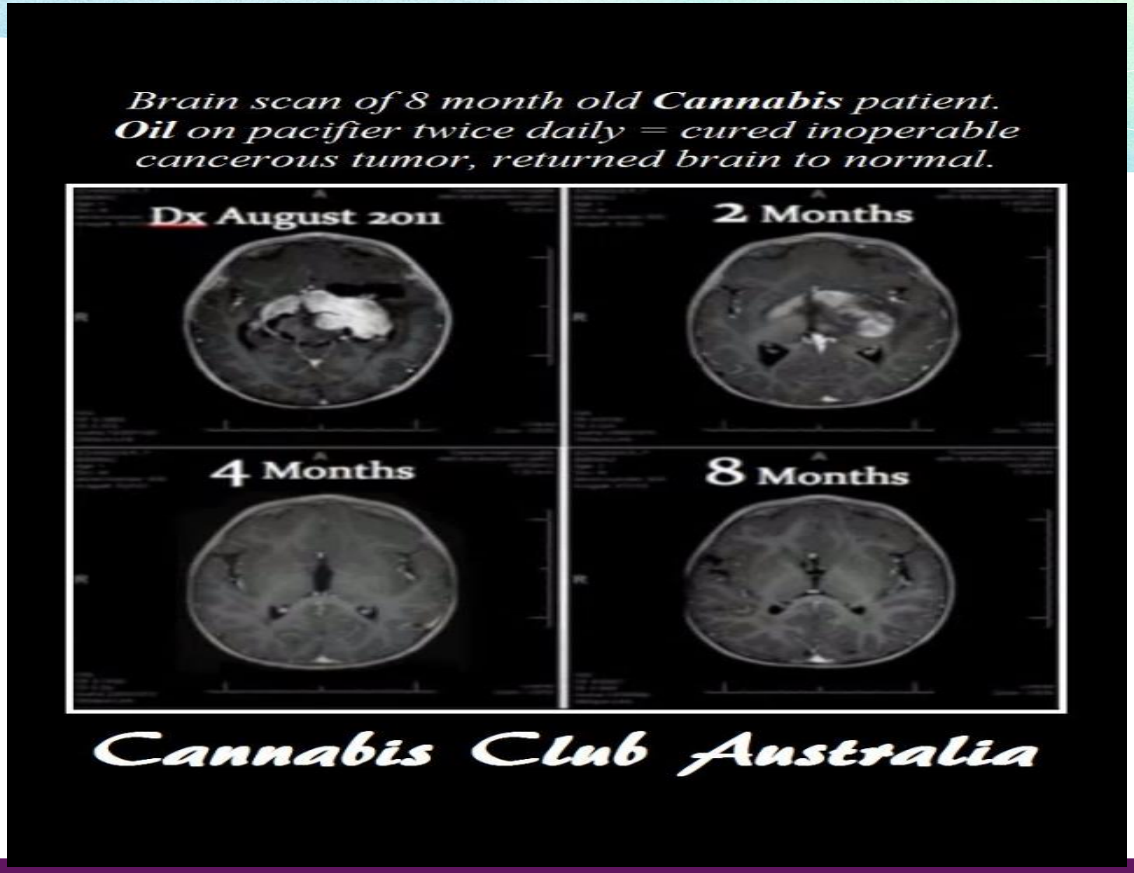
1 gram oil = 0.71 mL = “00” capsule = ¼ tsp



Anecdotes and Legends



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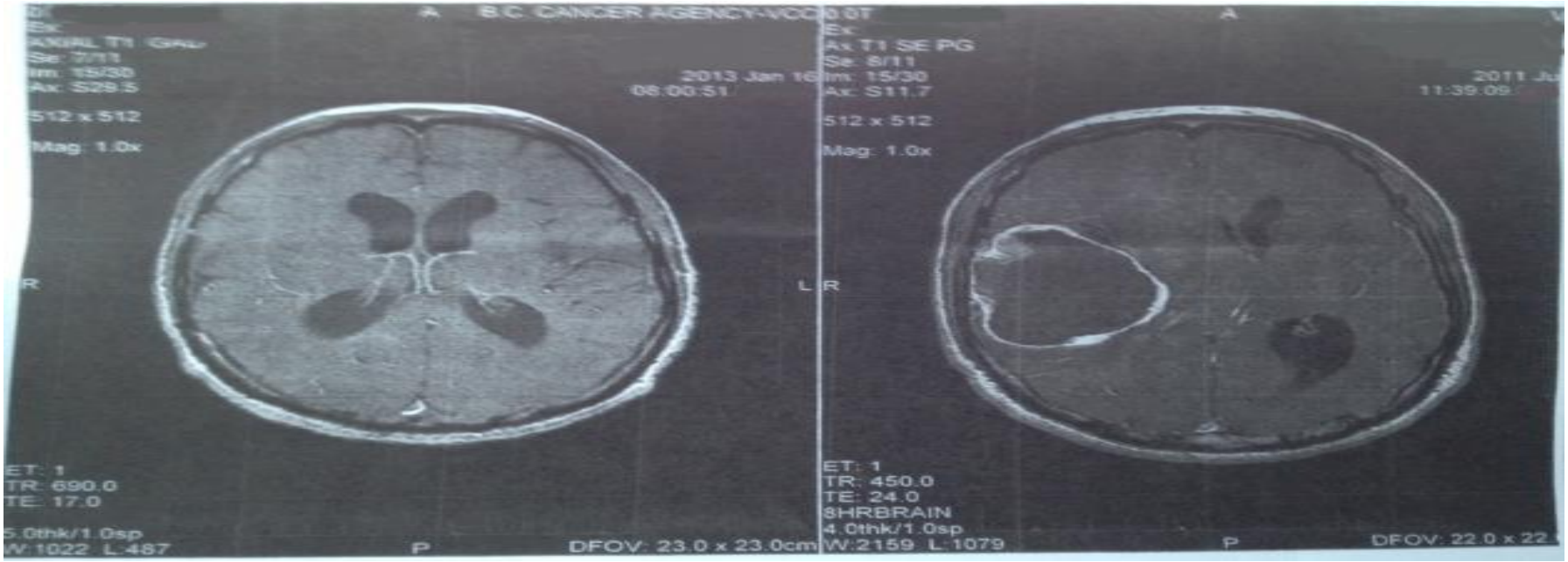
Brain tumour cured by cannabis ? No chemotherapy, no diet change – just RSO



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Print on tamper proof Rx paper

Your name
Address
Phone
fax

Documentation of healthcare professional's authorization to engage in the Medical Use of Cannabis in the State of Washington

Authorization for: **Patient name here** **DOB:** _____

Designation of **insert another close person who is authorized to pick up medicine at dispensary** as PRIMARY CAREGIVER under Wash. Rev. Code §§69.51A.010, 69.51A.040 (2007).

I, your name, am a licensed naturopathic physician in the State of Washington under Washington statute 18.36A, and I have diagnosed the above individual as having a debilitating condition as defined in RCW 69.51A.010(6).

I have advised the above named individual about the potential risks and benefits of the medical use of cannabis. I have a long medical relationship with this person and am familiar with the extent and nature of their disease state; in my medical opinion they will likely benefit from medical cannabis.

Your name and credentials . WA License _____

_____ Signed on _____

This recommendation expires on _____

Documentation of risk/benefit is in the medical record.

CBD rich concentrated extract: A 30-day supply as stipulated in WA RCW 69.51A.010(6) for this person is 60 mL Tincture, two ounces dry marijuana or 60 mL Oil Infusion / extract, 1 Gram Co2-Raw Oil-CBD Rich or 60 mL. Refill PRN.

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- *Marijuana – Gateway to Health – How Cannabis Protects Us from Cancer and Alzheimer's Disease*, Clint Werner, 2011, Dachstar Press.
- *Cannabis – A History*, Martin Booth, 2003,Picador – St. Martin's Press.

Websites of interest

* www.hempology.ca
* www.rxmarijuana.com
* www.marijuanauses.com
* www.medicalmarijuanastrains.com
* www.cbc-canada.ca/recipes/cbcoc-official-recipe-book
* http://safeaccess.ca
* www.phoenixtears.ca
* www.leafly.com
* www.cbdproject.org

Take home

1. Cannabis is useful therapy for some patients. Don't be afraid to recommend to your patients. Ask about prior use.
2. Visit your local cannabis dispensary and ask for a tour.
3. Start small dose orally. 5 mg CBD and 1 mg THC. Take before bed. Increase dose until JND in mood, pain, appetite.
4. Wide therapeutic dose range.
5. Refer your pt to a trusted medical dispensary near you.
6. Tell the dispensary to provide a low dose capsule or high dose oil in a 1 ml syringe. Call the dispensary and consult with them.
7. Certified organic cannabis may be hard to obtain. So teach pts how to grow make their own at home.

End of presentation

Will western palliative and hospice medicine be using psychedelic drugs to improve QOL and the death and dying experience?

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Is there a role for psychedelic medicines in modern western end-of-life care?

* Some Central America indigenous groups use psilocybe mushrooms as a sacrament.
* Some Southwest American indigenous groups use peyote as a sacrament.
* 78% of Amazonian basic tribal indigenous groups use ayahuasca as a sacramental tea
* Used in tribal groups as a community and family medicine.
* Most psychedelic natural and synthetic products are powerful 5-HT1a receptor agonists.
* Santo Daime Church and Uñiao do Vegetal Church use ayahuasca as a sacramental tea

Psychedelic medicine clinical trials and practice

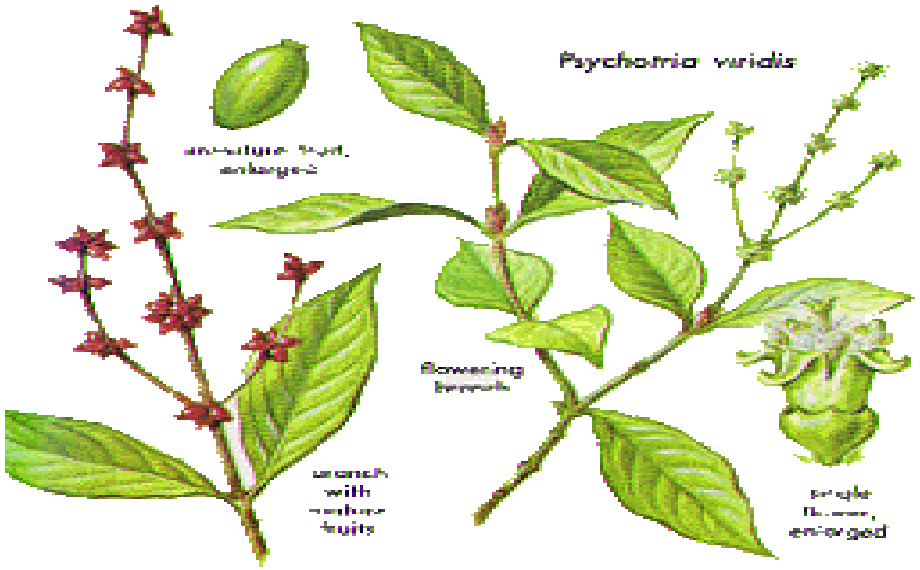
- LSD used by psychiatrists in 1960's and 70's dose 1 mcg/kg = 0.001 mg/kg for treating anxiety, depression, drug and alcohol dependence and OCD.
- Became FDA schedule I in 1970 and LSD research stopped and use went underground
- Psilocybin reduced fear of death in psilocybin trial at UCLA (Grob et al 2010) 0.2 mg/kg dose
- Psilocybin human studies at Johns Hopkins and NYU in normal adults
- MDMA trial starting soon for PTSD.

Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance.

Griffiths RR, Richards WA, McCann U, Jesse R.
Psychopharmacology (Berl). 2006 Aug;187(3)

B. caapi vine/stem

Psychotria viridis leaves and flowers



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P. Viridis in cultivation in Peru

Towards an FDA, IRB and DEA approval clinical trial of ayahuasca for the treatment of moderate recurrent depression in adults

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Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin

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Edited by Leslie Lars Iversen, University of Oxford, Oxford, United Kingdom, and approved December 20, 2011 (received for review December 3, 2011)

Psychedelic drugs have a long history of use in healing ceremonies, but despite renewed interest in their therapeutic potential, we continue to know very little about how they work in the brain. Here we used psilocybin, a classic psychedelic found in magic mushrooms, and a task-free functional MRI (fMRI) protocol designed to capture the transition from normal waking consciousness to the psychedelic state. Arterial spin labeling perfusion and blood-oxygen level-dependent (BOLD) fMRI were used to map cerebral blood flow and changes in venous oxygenation before and after intravenous infusions of placebo and psilocybin. Fifteen healthy volunteers were scanned with arterial spin labeling and a separate 15 with BOLD. As predicted, profound changes in consciousness were observed after psilocybin, but surprisingly, only decreases in cerebral blood flow and BOLD signal were seen, and these were maximal in hub regions, such as the thalamus and anterior and posterior cingulate cortex (ACC and PCC). Decreased activity in the ACC/medial prefrontal cortex (mPFC) was a consistent finding and the magnitude of this decrease predicted the intensity of the subjective effects. Based on these results, a seed-based pharmaco-physiological interaction/functional connectivity analysis was performed using a medial prefrontal seed. Psilocybin caused a significant decrease in the positive coupling between the mPFC and PCC. These results strongly imply that the subjective effects of psychedelic drugs are caused by decreased activity and connectivity in the brain's key connector hubs, enabling a state of unconstrained cognition.

default mode network | hallucinogens | serotonin | depression | 5-HT2A receptor

Psilocybin is the prodrug of psilocin (4-hydroxy-dimethyltryptamine), the primary hallucinogenic component of magic mushrooms, and a classic psychedelic ("mind-manifesting") drug. Psilocybin has been used for centuries in healing ceremonies (1) and more recently in psychotherapy (2); it is capable of stimulating profound existential experiences (3), which can leave a lasting psychological impression (4). However, despite a wealth of literature on its phenomenology, we currently know very little about how its effects are produced in the brain. The present study sought to address this question using complementary functional MRI (fMRI) techniques and a protocol designed to image the transition from normal waking consciousness to the psychedelic state. Two groups of healthy subjects were scanned using arterial spin labeling (ASL) perfusion and blood-oxygen level-dependent (BOLD) fMRI during intravenous infusion of psilocybin. Infused over 60 s (2 mg in 10-mL saline), psilocybin's subjective effects begin within seconds (5), allowing the capture of the corresponding change in brain state.

Results

ASL Perfusion fMRI. Fifteen healthy, hallucinogen-experienced subjects (five females), mean age 34.1 (SD 8.2) were scanned with ASL. Subjects underwent an anatomical scan followed by two task-free functional scans, each lasting 18 min. Subjects were instructed to relax and a fixation cross was displayed. Solutions were infused manually over 60 s, beginning 6 min after the start of each functional scan. Subjects received placebo (10-mL saline) in the first scan and psilocybin (2 mg in 10-mL saline) in the second. The intensity of the subjective effects was rated via button press on a 0–10 visual analog scale (10 = extremely intense effects) at the start of each functional scan, just before infusion, 5-min postinfusion, and 12-min postinfusion. The average rating 5-min postinfusion was 6.7 (±1.9), and 5.2 (±2.3) 12-min postinfusion. Earlier work showed that the effects of 2 mg i.v. psilocybin are comparable with ~15 mg of orally administered psilocybin, which is considered a moderate dose (6). Nineteen additional items were rated immediately after each ASL scan. Fig. 1 displays the top 10 rated items from the two studies. Ratings for all of the items used in the ASL and BOLD studies can be found in Table S1.

The interaction between cerebral blood flow (CBF) and the infusion event was modeled, contrasting CBF before and after infusion. The subjective effects began toward the end of the infusion period and reached a sustained peak after ~4 min (5). The first level results were entered into a higher level analysis, contrasting CBF after psilocybin with CBF after placebo for all 15 subjects. Fig. 2 displays these results.

The group level results (Fig. 2) revealed significant CBF decreases in subcortical (bilateral thalamus, putamen, and hypothalamus) and cortical regions [the posterior cingulate cortex (PCC), retrosplenial cortex, precuneus, bilateral angular gyrus, supramarginal gyrus, rostral and dorsal anterior cingulate cortex (ACC), paracingulate gyrus, medial prefrontal cortex (mPFC), frontoinsular cortex, lateral orbitofrontal cortex, frontal operculum, precentral gyrus, and superior, middle and inferior frontal gyrus] (Fig. S1). The decreases were localized to high-level association regions (e.g., the PCC and mPFC) and important connector hubs, such as the thalamus, PCC and ACC/mPFC.

To assess the temporal dynamics of the CBF changes postinfusion, thalamic, ACC, and PCC masks were made; voxels within these were restricted to those that were significantly decreased after psilocybin. For each region of interest (ROI), the percent CBF change postinfusion was plotted against time (Fig. 3). All ROIs showed steep decreases in CBF after psilocybin that were sustained for the duration of the scan.

Author contributions: R.L.C.-H., J.E., R.G.W., and D.J.N. designed research; R.L.C.-H., D.E., T.W., J.M.S., L.J.R., A.C., R.J.T., R.L., A.L.M., K.M., P.H., J.E., A.F., and R.G.W. performed research; R.L.C.-H., K.M., and R.G.W. analyzed data; and R.L.C.-H., K.M., R.G.W., and D.J.N. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

See Commentary on page 1820.

[1]To whom correspondence should be addressed. E-mail: d.nutt@imperial.ac.uk.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1119598109/-/DCSupplemental.

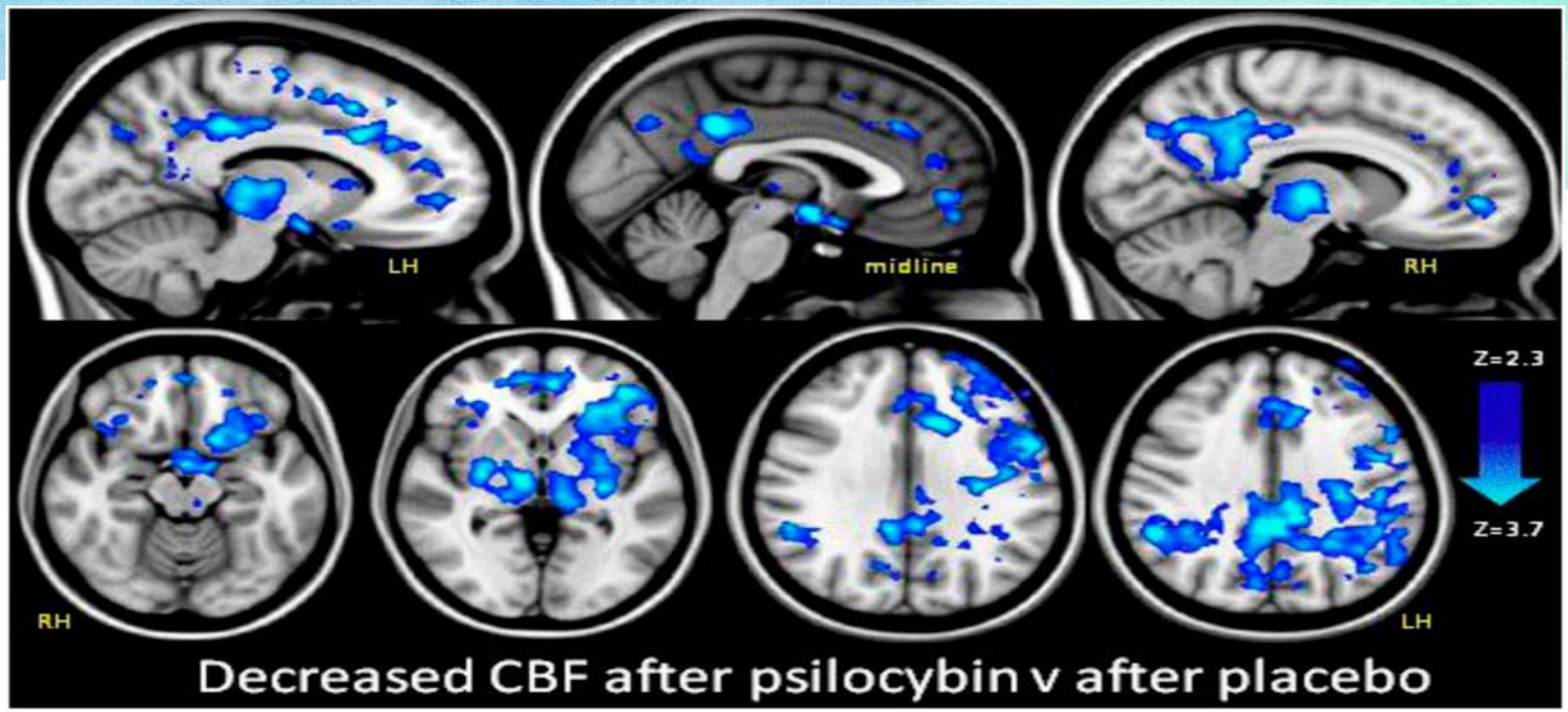

Fig. 2. Decreased CBF after psilocybin (ASL perfusion fMRI). Regions where there was significantly decreased CBF after psilocybin versus after placebo are shown in blue (z: 2.3–3.7). Mixed effects analysis, $z > 2.3$, $P < 0.05$ whole-brain cluster-corrected, $n = 15$. LH, left hemisphere; RH, right hemisphere. Note, we observed no increases in CBF in any region.

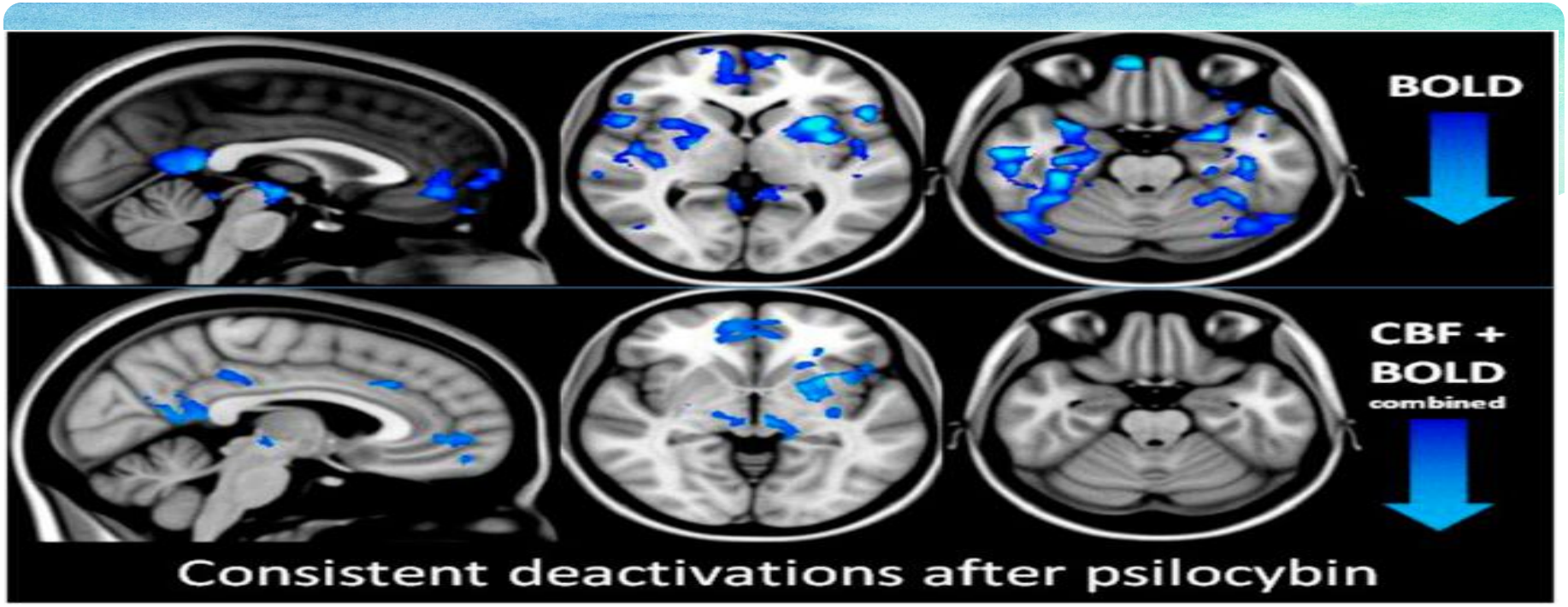

Fig. 4. Brain deactivations after psilocybin. (Upper) Regions where there was a significant decrease in the BOLD signal after psilocybin versus after placebo (z: 1.8–3). Mixed-effects analysis, $z > 1.8$, $P < 0.05$ whole brain cluster corrected, $n = 15$. (Lower) Regions where there was a consistent decrease inCBF and BOLD after psilocybin. For display purposes, significant BOLD decreases were calculated within a mask based on the ASL result (Fig. 2) atan uncorrected voxel level threshold of $P = 0.05$. Note, we observed noincreases in CBF or BOLD signal in any region.

PubMed Central, Fig 1: PLoS One. 2015; 10(2): e0118143. Published online 2015 Feb 18. doi: 10. - HSL — UW Health Sciences Libr

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4334486/figure/pone.0118143.g001/

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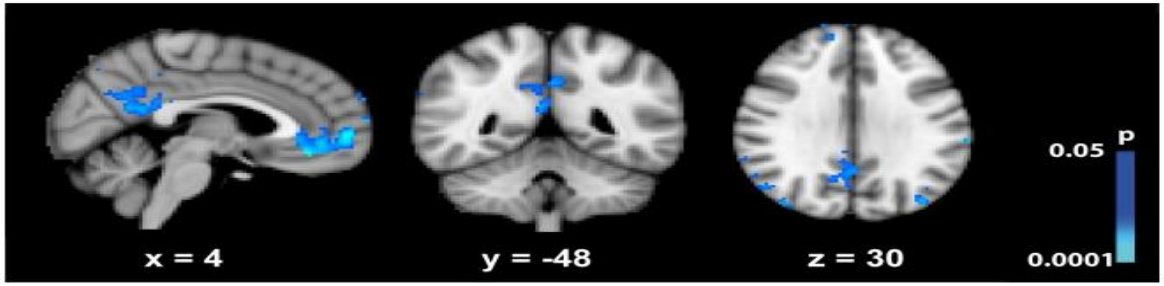
PMC full text: PLoS One. 2015; 10(2): e0118143.
Published online 2015 Feb 18. doi: 10.1371/journal.pone.0118143

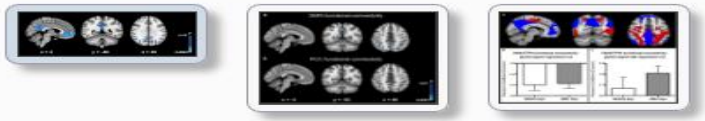
Fig 1



Statistical maps showing regions where BOLD signal of the DMN (rest > task) decreases after Ayahuasca ingestion.

P < 0.05 uncorrected.

Images in this article



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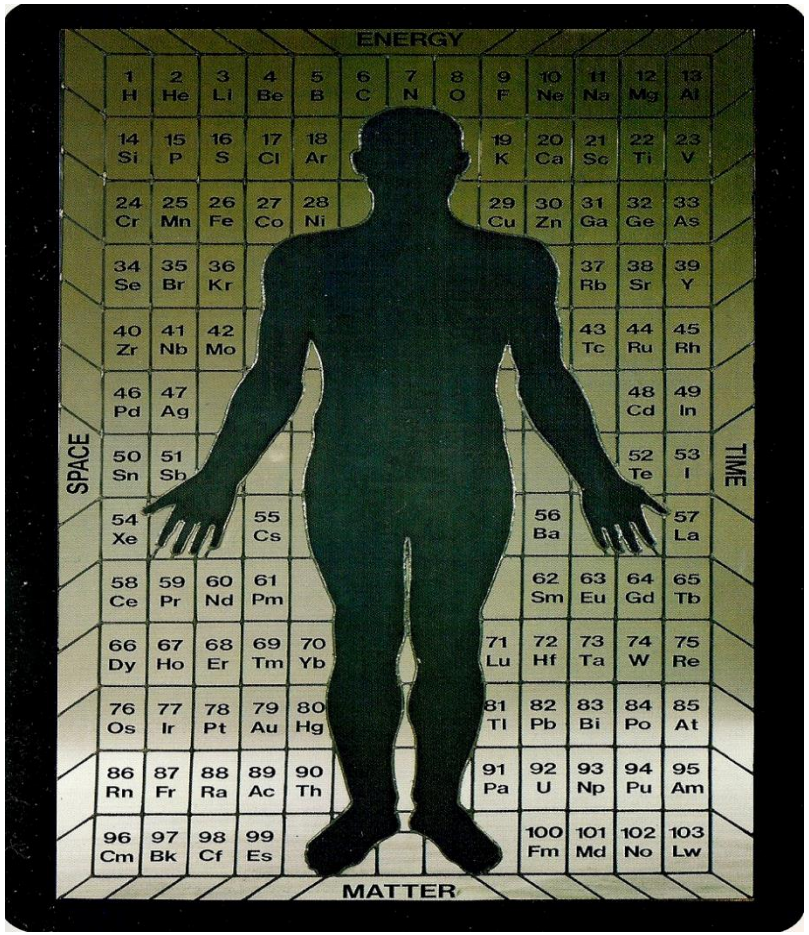

Alex Grey Sacred Mirrors

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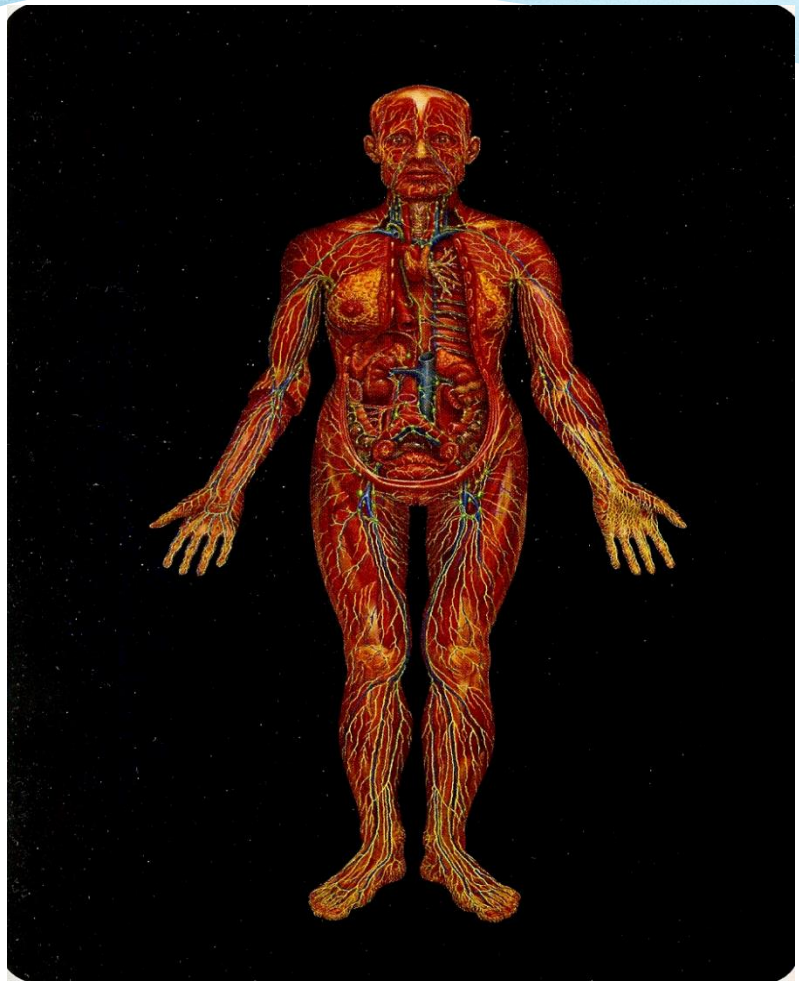

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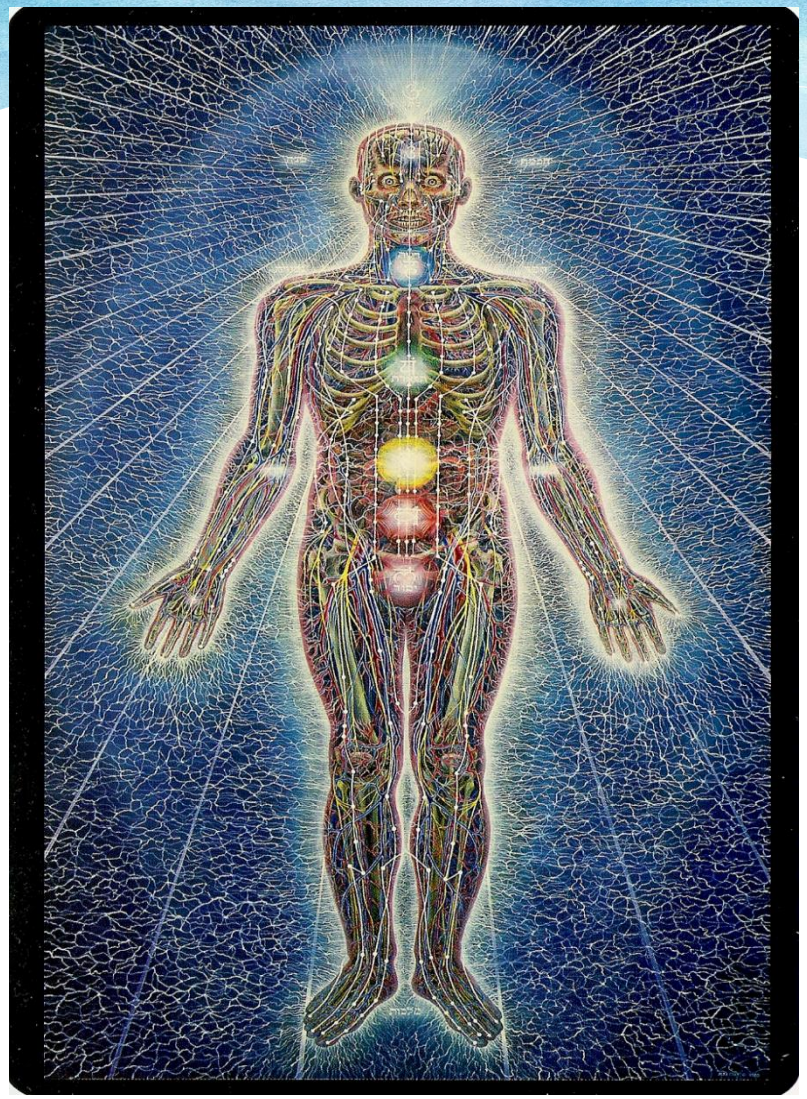

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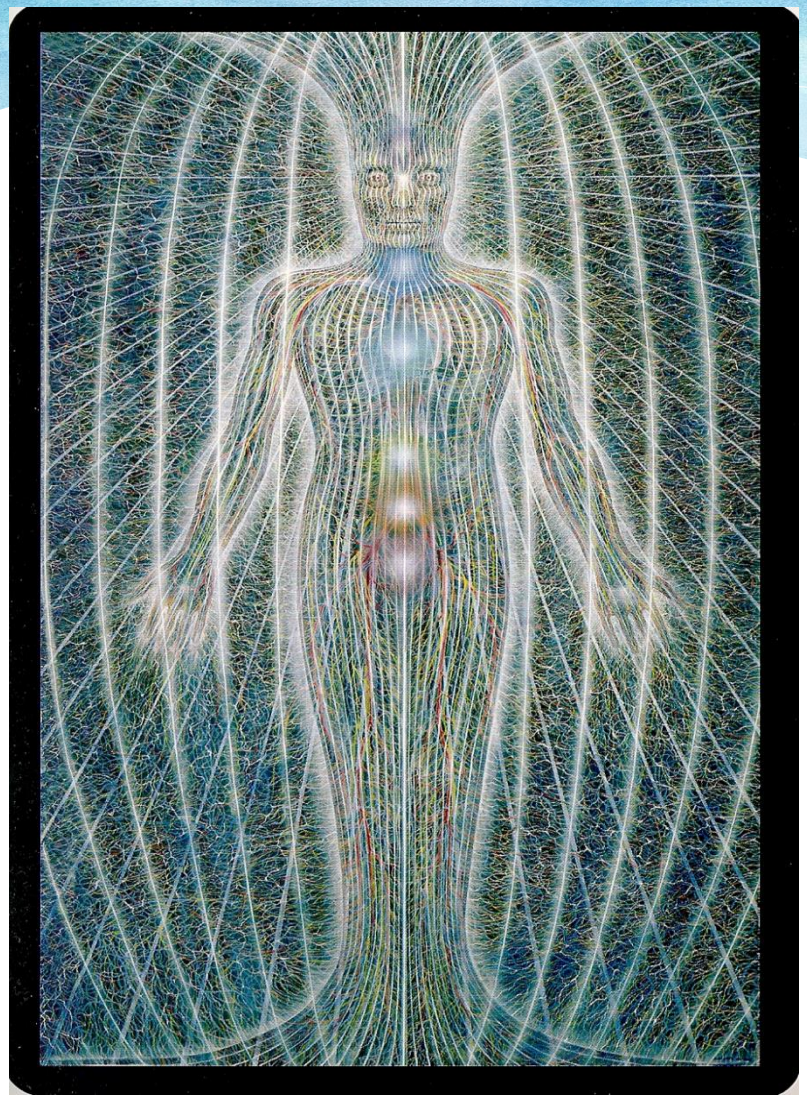

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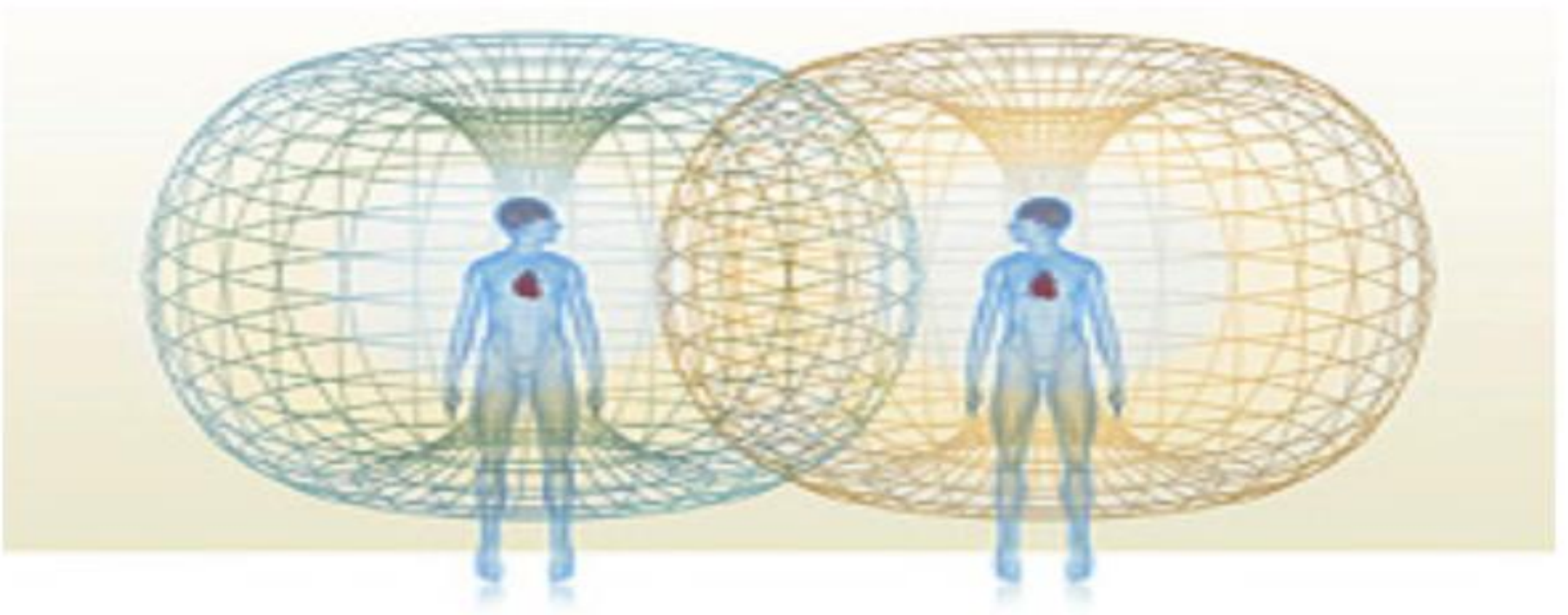
The human heart generates the largest electromagnetic field.
We really are interconnected.



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