Translational studies in addiction: a difficult path

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Head, Translational Addiction Research Laboratory, Campbell Family Mental Health Research Institute, CAMH

camh
mental health is health

UNIVERSITY OF TORONTO

Waypoint
CENTRE *for* MENTAL HEALTH CARE
CENTRE *de* SOINS *de* SANTÉ MENTALE

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NIH-NIDA and the NIDA drug supply program and NIH-NIAAA

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OPGRC, Ontario Lung Association, Heart and Stroke Foundation ; Narsad, MITACS, PSI Fondation, CAMH Fondation

Dr Le Foll' s industry support: Pfizer, **Bioprojet**, Alkermes, Aphria, Canopy, Indivior; Lilly; ACS
In kind support from GW Pharma and **Brainsway**, Aurora, Canopy, Filament for psilocybin product
Scientific Advisory Board for NFL biosciences; consulting for Changemark, Shinogy
Steering Committee for a trial for Indivior

CAMH is situated on lands that have been occupied by First Nations for millennia; lands rich in civilizations with knowledge of medicine, architecture, technology and extensive trade routes throughout the Americas. The site of CAMH appears in colonial records as the council grounds of the Mississaugas of the New Credit (as their name in 1860), today known as the Mississaugas of the Credit.

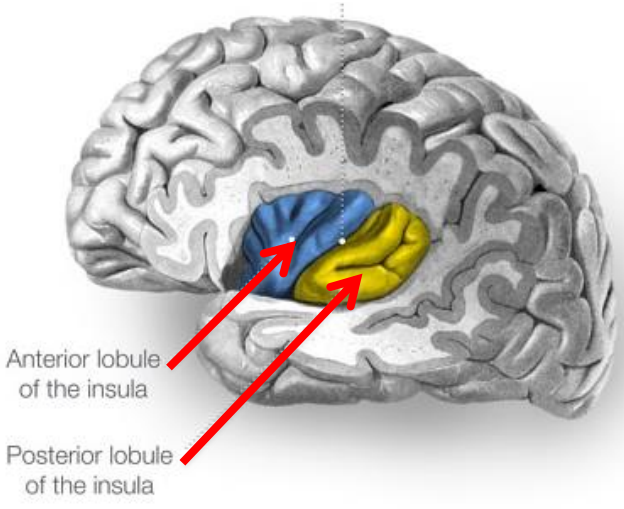
Presentation

- Role of insular cortex in Nicotine addiction
  - Preclinical (Inactivation/DBS)
  - TMS studies
- Exploring role of Histamine H3 in Alcohol addiction
  - Preclinical studies
  - Clinical studies
- Conclusion

Insula

- Part of the cerebral cortex, folded in the lateral sulcus
  - Divided into anterior (agranular) and posterior (granular) parts

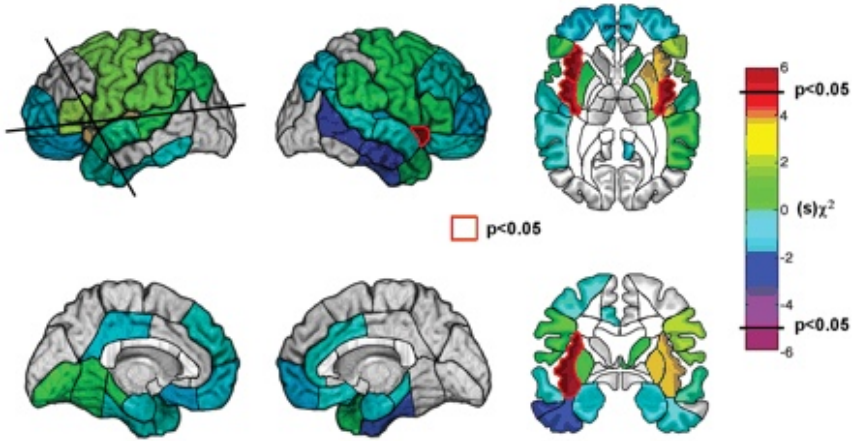
- Involved in feelings of anxiety, pain, cognition, mood, threat recognition, decision making, homeostasis (interoception) and conscious urges.



Beyond the dopaminergic system: Importance of the insula

Damage to the Insula Disrupts Addiction to Cigarette Smoking

Nasir H. Naqvi,[1] David Rudrauf,[1,2] Hanna Damasio,[3,4] Antoine Bechara[1,3,4]*

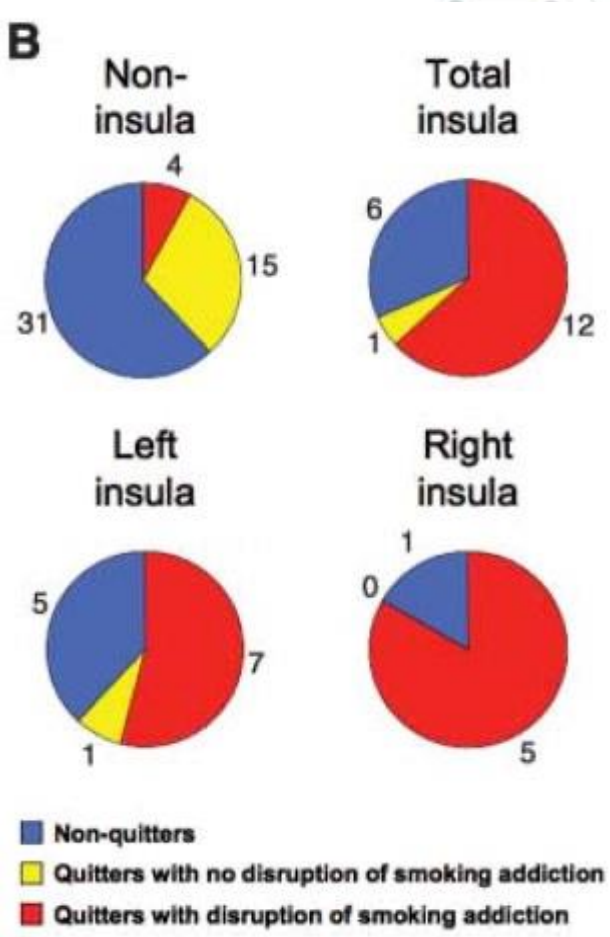


26 JANUARY 2007 VOL 315 SCIENCE www.sciencemag.org

Whole-brain region-by-region logistic regression analysis. Association between a lesion and a disruption of smoking addiction ($P < 0.05$, uncorrected) are highlighted in red. The insula is the only region on either side of the brain where a lesion was significantly associated with a disruption of smoking addiction.

- Lesion to the insula resulted in immediate smoking cessation without relapse

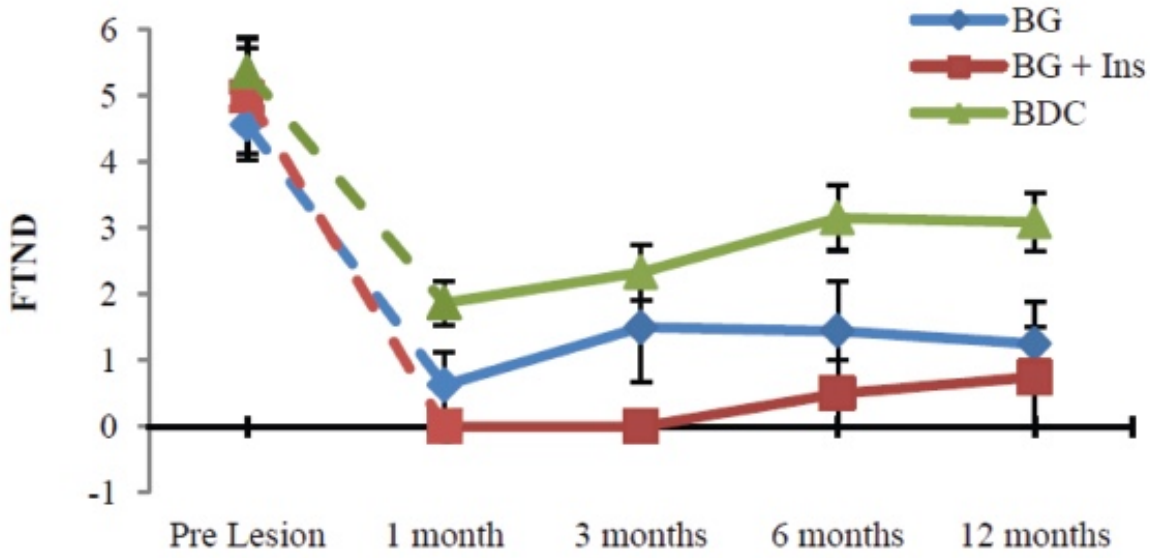
- Disruption of smoking addiction
  - Easily
  - Immediately
  - Without relapse
  - Without urge to smoke



From Naqvi *et al.*, 2007

Basal Ganglia Plus Insula Damage Yields Stronger Disruption of Smoking Addiction Than Basal Ganglia Damage Alone

Natassia Gaznick BS[1], **Daniel Tranel** PhD[1,2], **Ashton McNutt** BS[1], **Antoine Bechara** PhD[1,3]



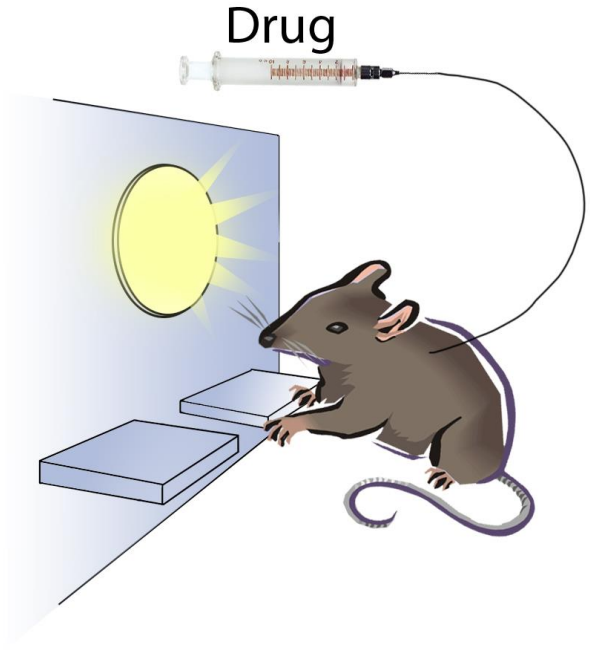
BG: Basal Ganglia; Ins: Insula; BDC: Brain Damaged Comparison

From Gaznick *et al.*, 2014

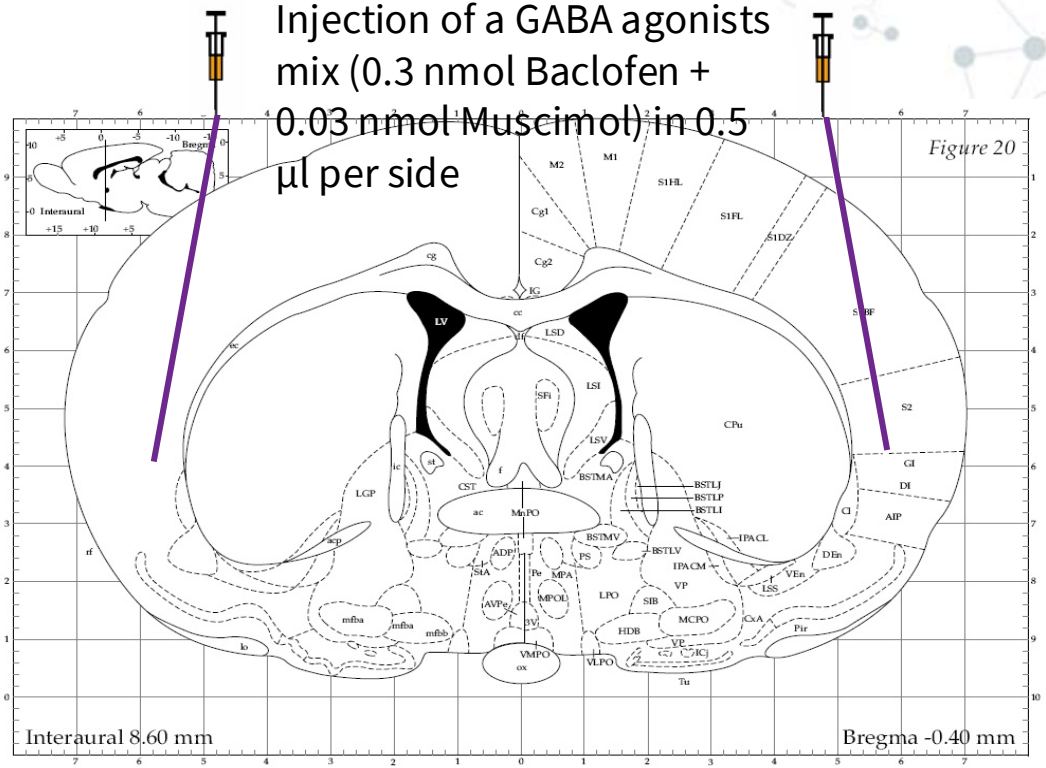
Question: can we directly implicate the insula in nicotine addiction processes ?

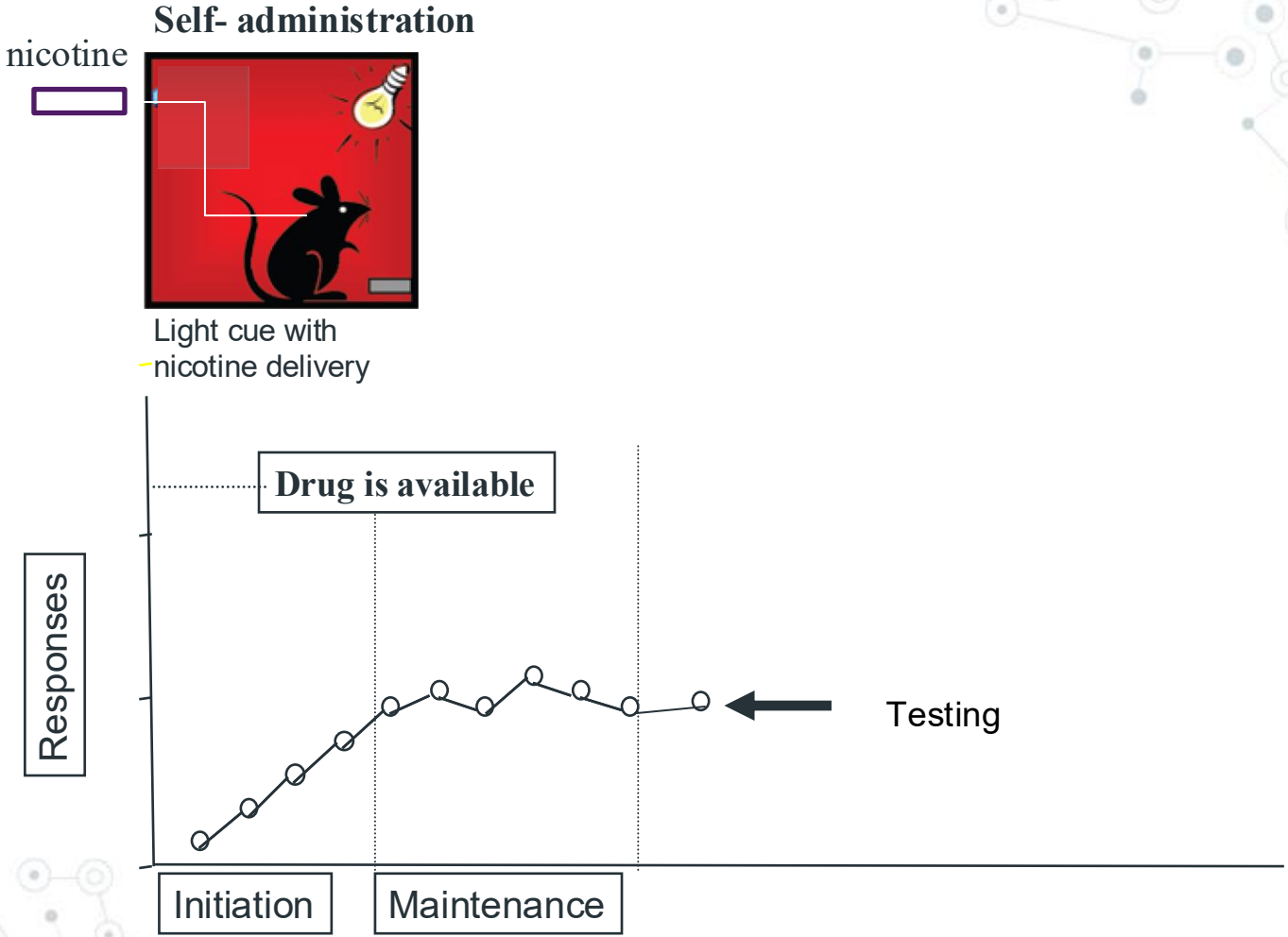
Reverse translational studies to directly implicate insula in nicotine addiction

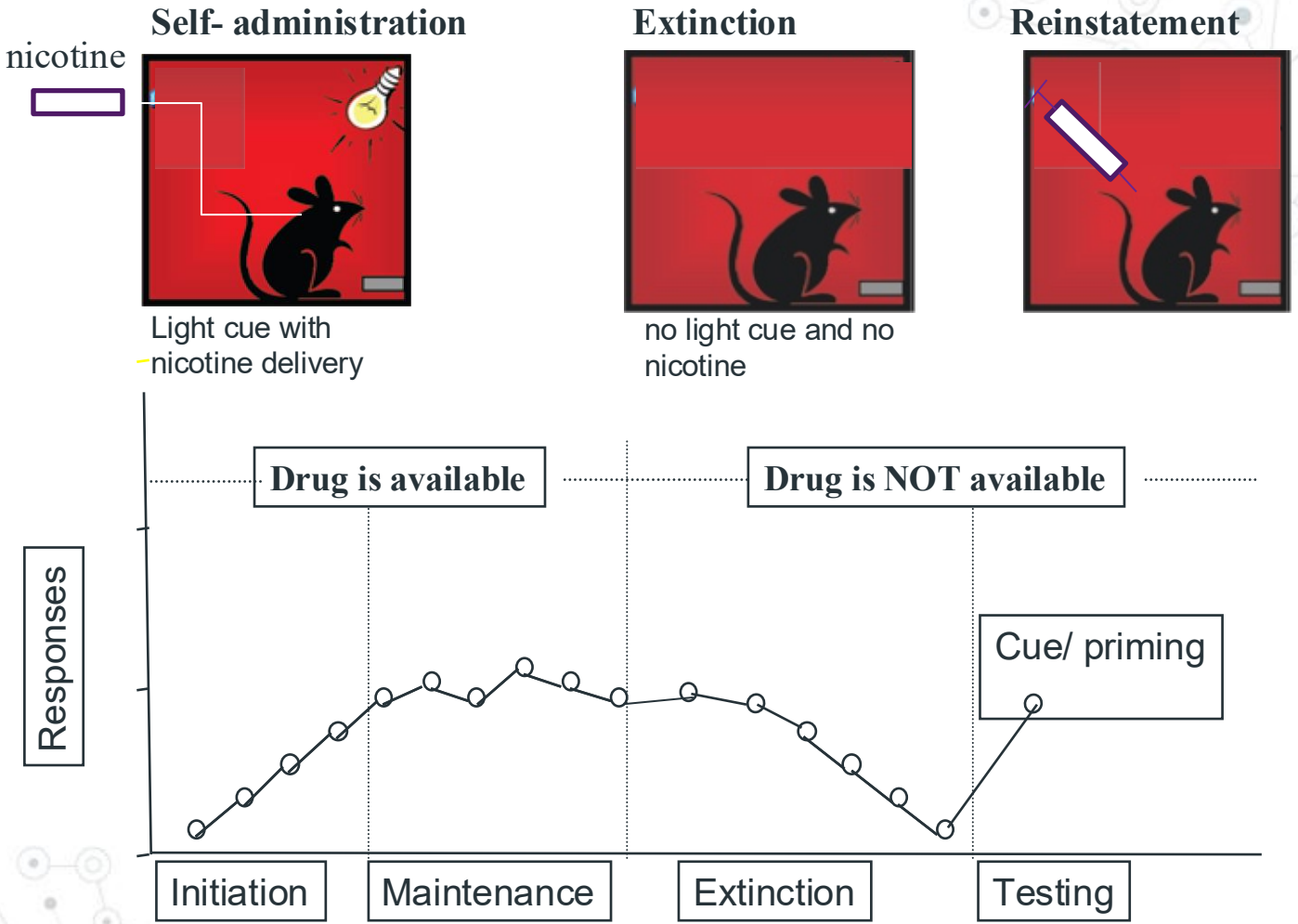
Preclinical models to assess drug-taking and drug seeking



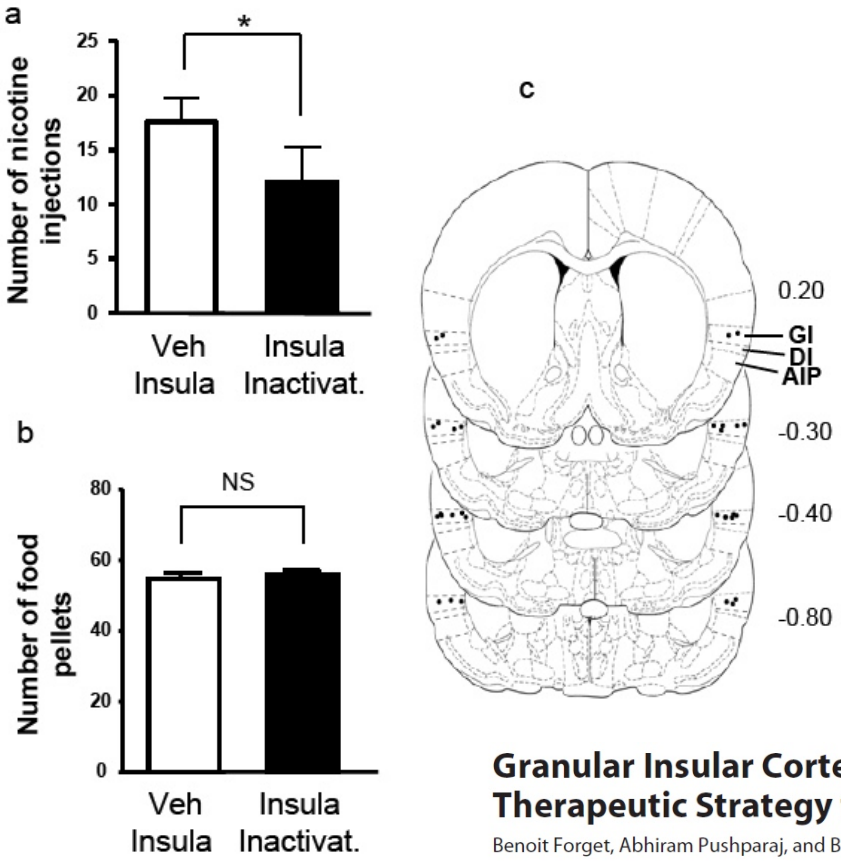
Injection of a GABA agonists mix (0.3 nmol Baclofen + 0.03 nmol Muscimol) in 0.5 µl per side




Self- administration
nicotine
Light cue with
nicotine delivery
Drug is available
Responses
Testing
Initiation
Maintenance


Self- administration
Extinction
Reinstatement
nicotine
Light cue with nicotine delivery
no light cue and no nicotine
Drug is available
Drug is NOT available
Responses
Cue/ priming
Initiation
Maintenance
Extinction
Testing

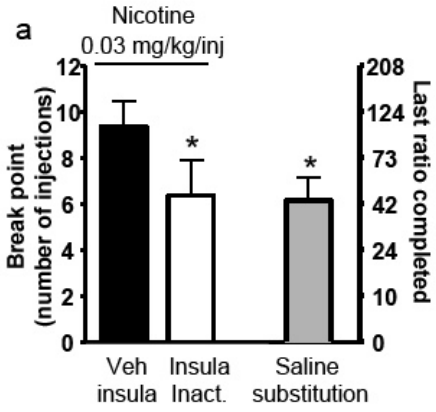
Granular Insula inactivation reduces nicotine-taking but not food taking under FR5

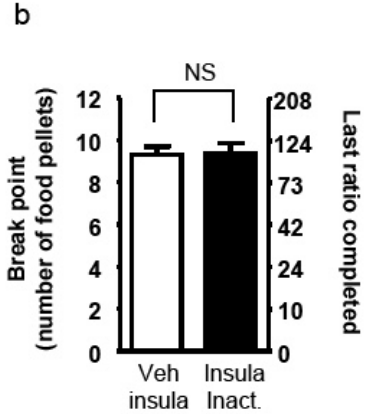


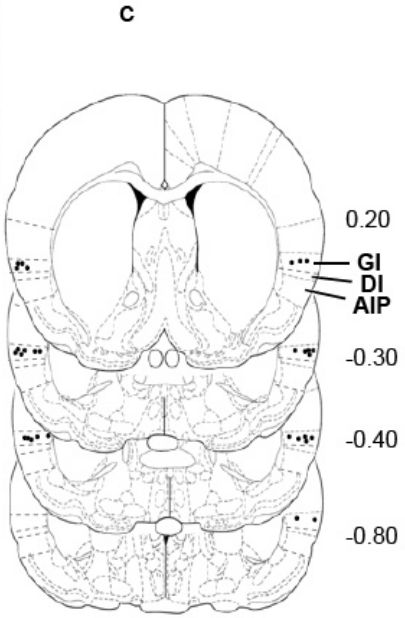
Granular Insular Cortex Inactivation as a Novel Therapeutic Strategy for Nicotine Addiction

Benoit Forget, Abhiram Pushparaj, and Bernard Le Foll

Granular insula inactivation reduces motivation for nicotine (but not for food)



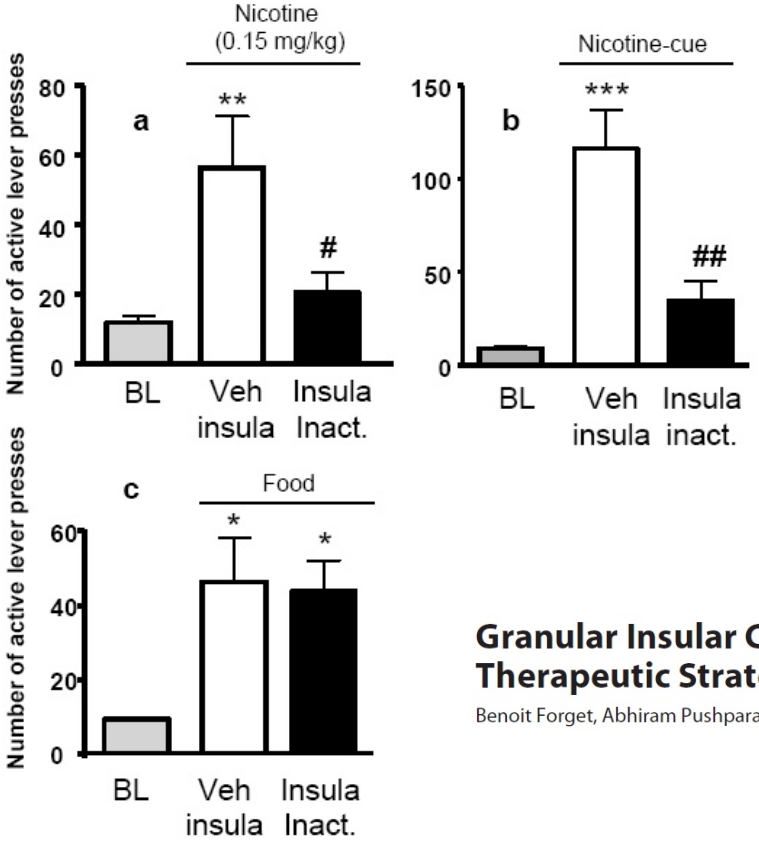




Granular Insular Cortex Inactivation as a Novel Therapeutic Strategy for Nicotine Addiction

Benoit Forget, Abhiram Pushparaj, and Bernard Le Foll

Granular insula inactivation reduces reinstatement for nicotine, but not for food



Granular Insular Cortex Inactivation as a Novel Therapeutic Strategy for Nicotine Addiction

Benoit Forget, Abhiram Pushparaj, and Bernard Le Foll

Is inactivation a reasonable goal? Will it predict the effect of DBS/rTMS?

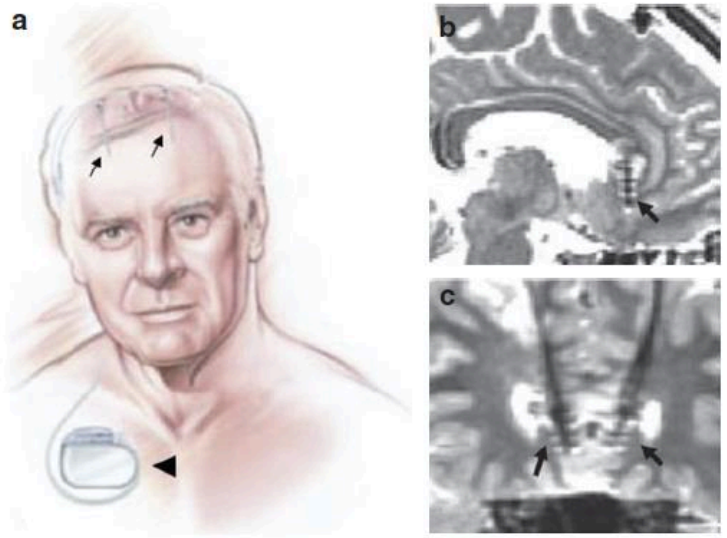


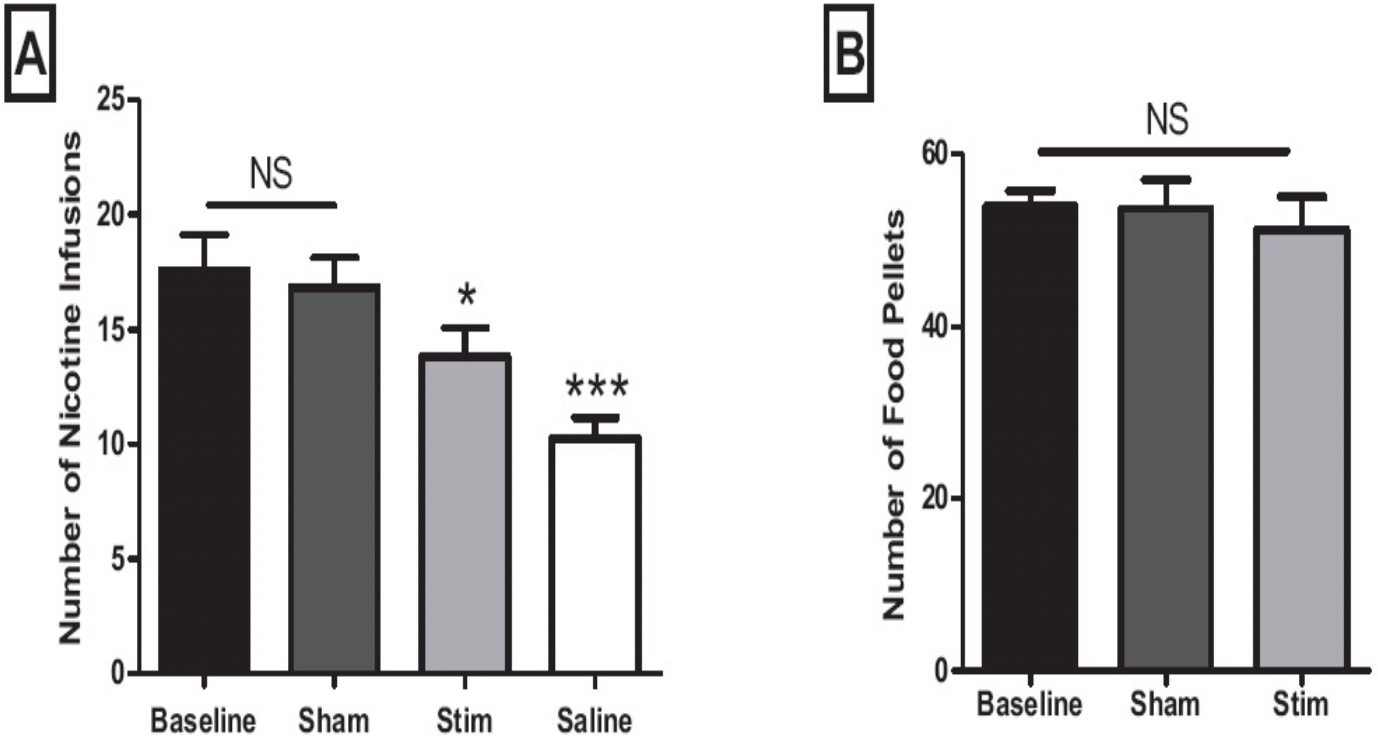
Figure 1 Deep brain stimulation system. (**a**) Schematic representation of a deep brain stimulation system as implanted in a patient. Electrodes (arrows) placed into the brain parenchyma deliver pulses via a pulse generator (arrowhead) (© 2010 Medtronic, Inc.). In **b** and **c**, sagittal and coronal magnetic resonance images of electrodes (arrows) implanted in the subgenual cingulate gyrus in a patient with depression (reprinted from ref. 20 with permission from Elsevier).

From Hamani *et al.*, 2010

Deep Brain Stimulation Methods

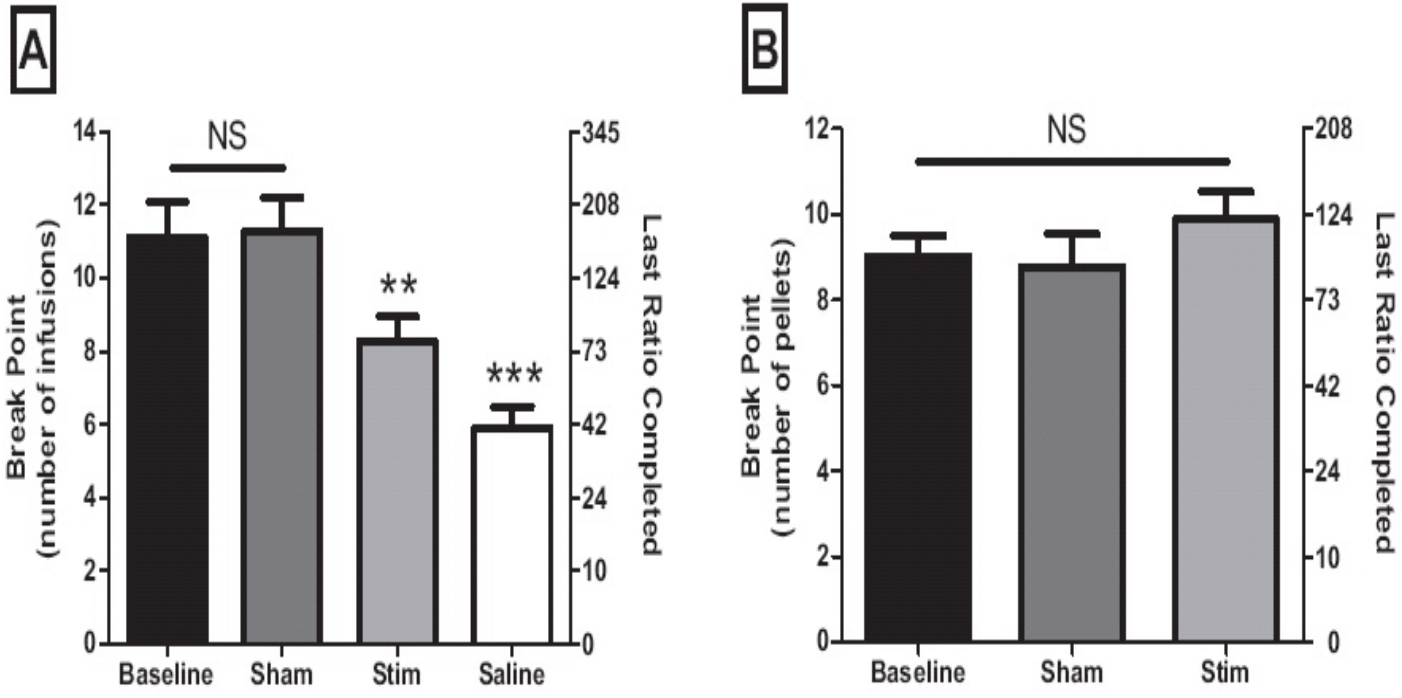
- Insulated stainless steel electrodes were bilaterally implanted and used as cathodes
- Electrode with similar characteristics attached to epidural screws were used as an anode
- After connection to a plastic pedestal, electrodes were fixed to the skull with dental acrylic cement
- Stimulation was conducted with a handheld device (ANS model 3510, Plano, TX), connected to the animals through extension cables and a multi-channel commutator
- Animals were stimulated at 200µA, 90 µs of pulse width and 130 Hz starting approximately 5 min prior to the start of the session

Insula DBS reduces nicotine-taking but not food taking under FR5



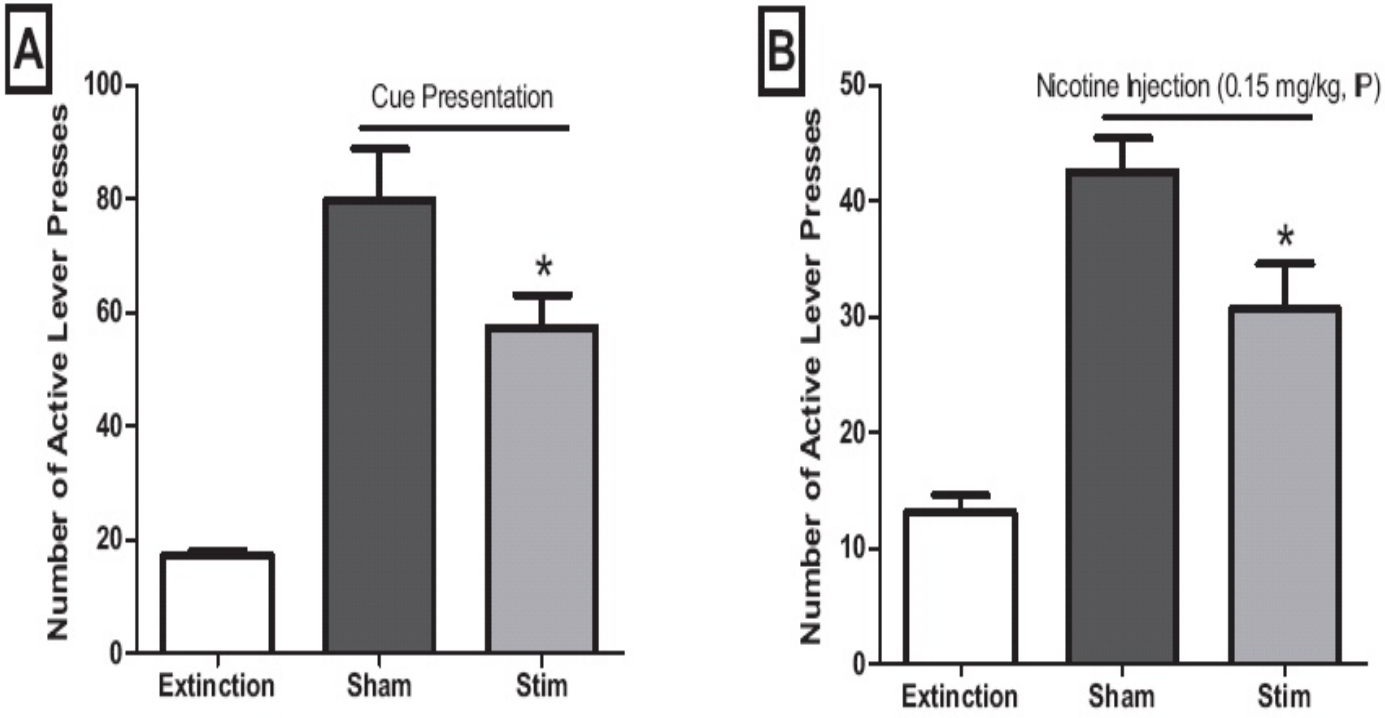
From Pushparaj *et al.*, 2013

Insula DBS reduces motivation for nicotine but not motivation for food



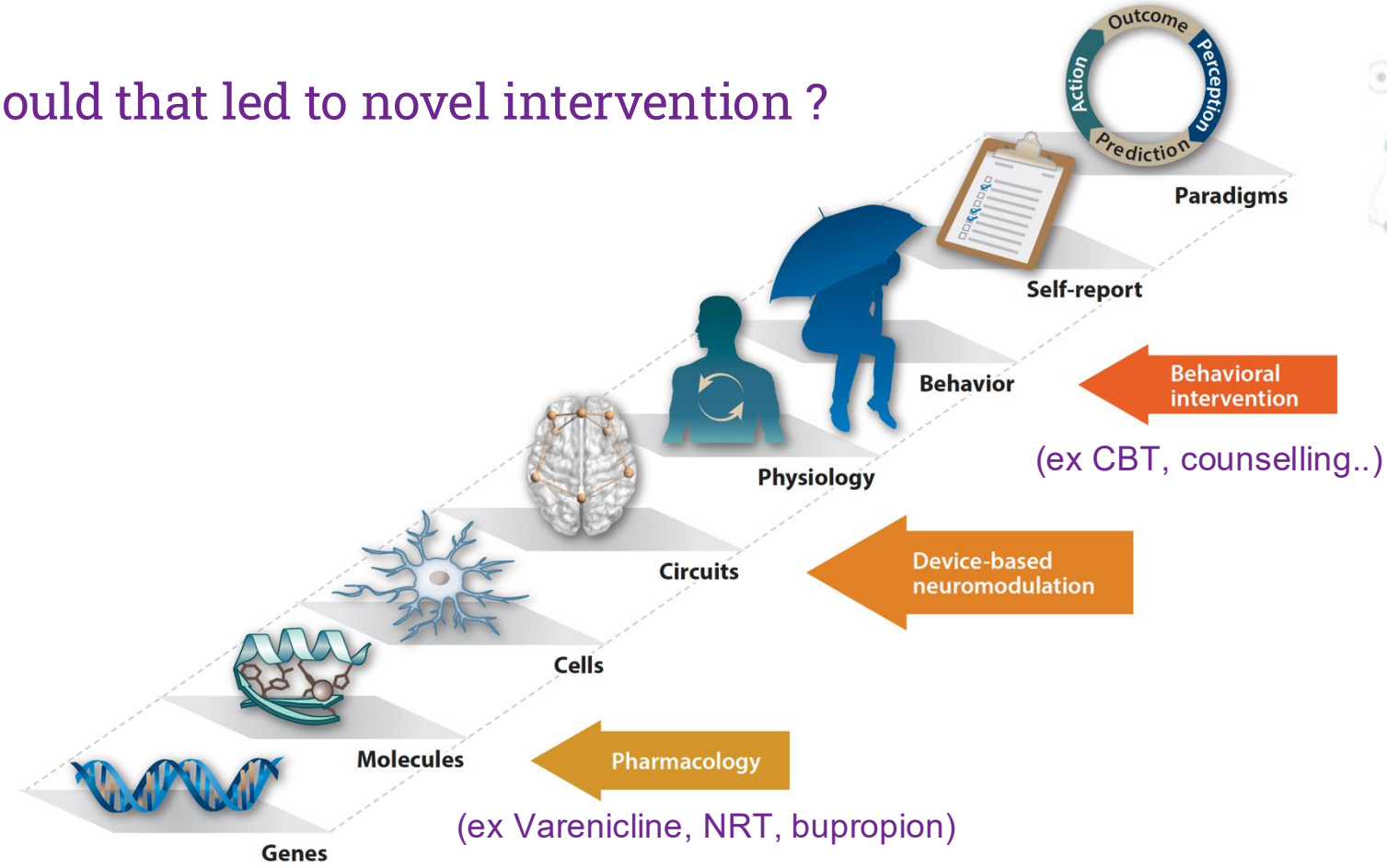
From Pushparaj *et al.*, 2013

Insula DBS reduces reinstatement for nicotine seeking



From Pushparaj *et al.*, 2013

Could that led to novel intervention ?

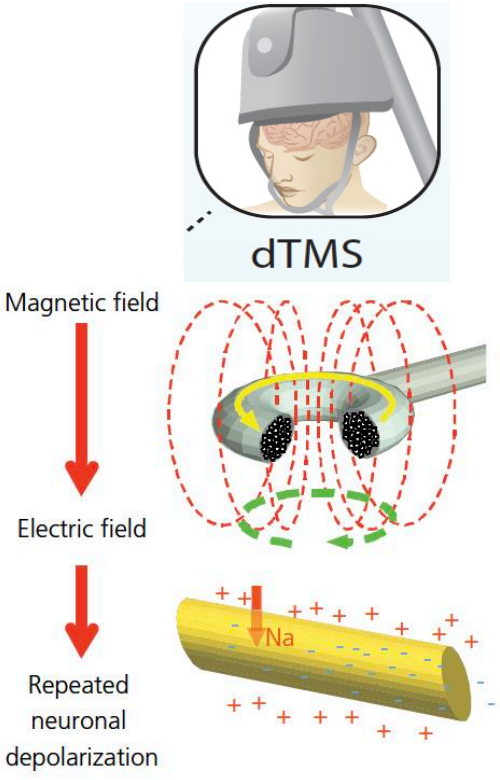


(ex CBT, counselling..)

(ex Varenicline, NRT, bupropion)

Deng et al. (2020) *Ann Rev Pharm Tox*

Deep repetitive Transcranial Magnetic Stimulation (Deep rTMS) targeting insula/DPFC



Non-invasive stimulation with electromagnetic coil to induce electric field in brain

Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial

Table 1 Demographic and clinical features of patients randomized to receive active or sham repetitive transcranial magnetic stimulation

	Active (N=123)	Sham (N=139)	p
Gender (% female)	48.8	47.5	0.834
Age (years, mean±SD)	45.0±13.0	44.8±13.4	0.946
Age started smoking (years, mean±SD)	16.9±4.0	17.4±5.3	0.390
Total years smoking (years, mean±SD)	27.1±13.0	26.2±13.7	0.597
N. cigarettes/day (mean±SD)	18.3±7.7	18.2±7.2	0.874
Desire to quit (from 1 - low to 10 - high, mean±SD)	8.8±1.4	9.0±1.3	0.238
N. tries to stop (%)			
One	14.3	21.9	0.283
Two	10.9	16.1	
Three	23.5	18.2	
Four	11.8	9.5	
Five	12.6	7.3	
More than five	26.9	27.0	

From Zangen et a*l.*, 2021

Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial

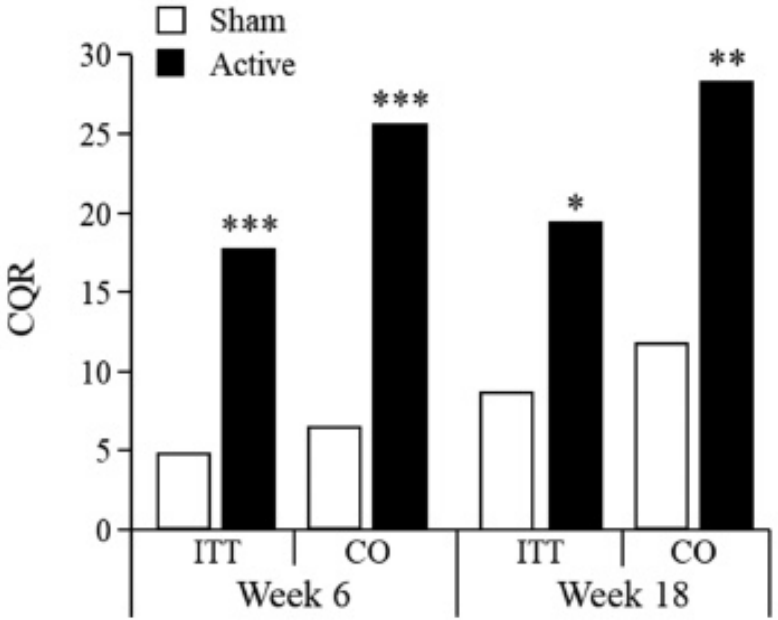
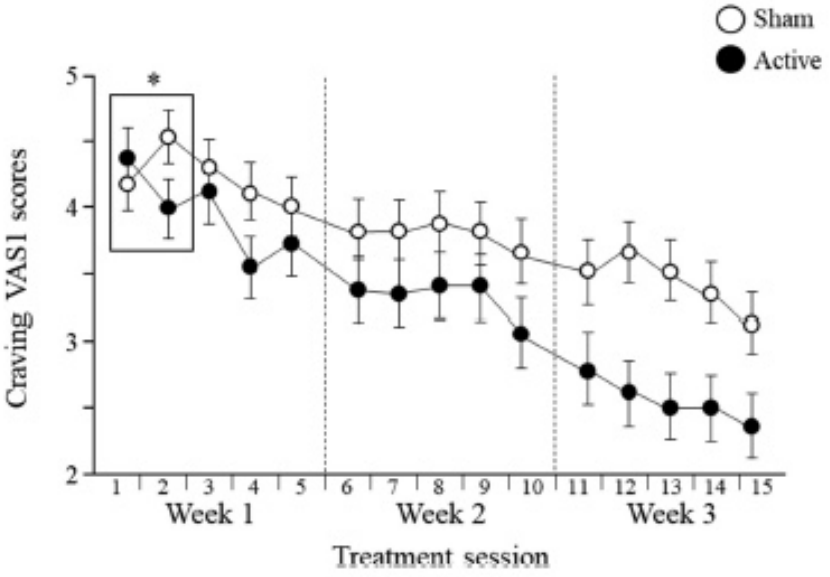
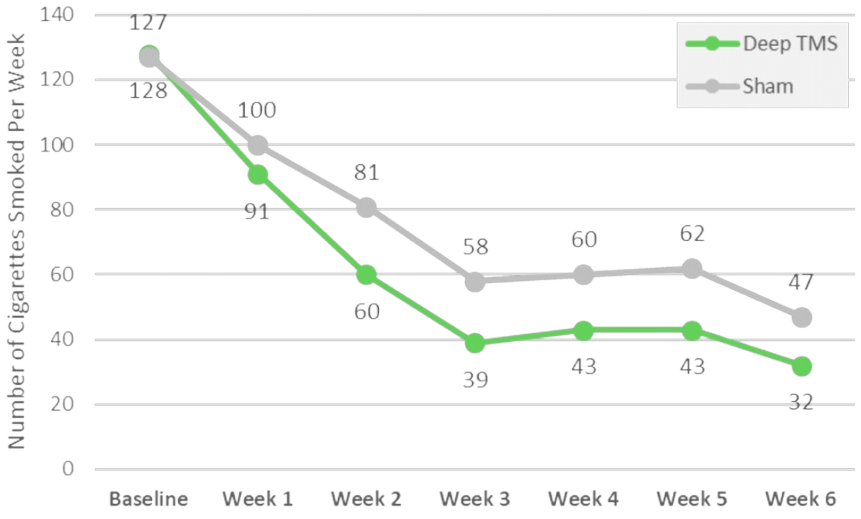


Figure 2 Four-week continuous quit rate (CQR) until Week 6 and Week 18 in patients receiving active or sham repetitive transcranial magnetic stimulation. Only participants who were abstinent at Week 6 were followed up to Week 18. ITT – intent-to-treat set, CO – completer analysis set. *p<0.05, **p<0.01, ***p<0.001.

From Zangen et a*l.*, 2021

Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial





From https://www.brainsway.com/treatments/smoking-addiction/

Craving Score

Cigarettes per week

From Zangen et a*l.*, 2021

2020: First FDA Clearance for Deep rTMS for smoking cessation
2022: Approval from Health Canada

BrainsWay®

BrainsWay Receives FDA Clearance for Smoking Addiction in Adults

Email | Print Friendly | Share

August 24, 2020 07:00 ET | **Source:** BrainsWay

Company Intends to Execute a Controlled U.S. Market Release in Early 2021

This is the Company's third FDA-cleared indication for its Deep TMS System, and is the first FDA clearance in the addiction space for any TMS device

CRESSKILL, N.J. and JERUSALEM, Aug. 24, 2020 (GLOBE NEWSWIRE) -- BrainsWay Ltd. (NASDAQ & TASE: BWAY) ("BrainsWay" or the "Company"), a global leader in the advanced non-invasive treatment of brain disorders, today announced that it has received 510(k) clearance from the U.S. Food and Drug Administration (FDA) for the Company's deep transcranial magnetic stimulation (Deep TMS) system for its use as an aid in short-term smoking cessation in adults.

"This FDA clearance represents a significant milestone for BrainsWay and our Deep TMS platform technology," stated Christopher von Jako, Ph.D., President and Chief Executive Officer of BrainsWay. "Smoking is one of the leading causes of death in the U.S. and also leads to other serious conditions, such as lung cancer and heart disease. While other therapies are currently available, a substantial medical need continues to exist for treatments that can increase the continuous quit rate among smokers. Based on the compelling data from our large, randomized pivotal study of 262 subjects, we are confident that our Deep TMS technology can play an important role in treating cigarette smokers who seek to quit. We look forward to executing a controlled U.S. market release of our newly cleared and proprietary H4 Deep TMS coil for this indication early next year."

Dr. von Jako added, "Importantly, this is the first FDA clearance in the addiction space for any TMS device, and it represents BrainsWay's third FDA-cleared coil and indication, following the clearance of our H1-coil for patients suffering from major depressive disorder and the H7-coil as an adjunct therapy for the treatment of OCD. This latest clearance cements BrainsWay's status as an industry leader, and further demonstrates our commitment to leveraging our platform technology to advance innovative therapeutic solutions across multiple patient populations."

Next steps for implementation in clinic

Psychiatry Research 326 (2023) 115340

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Review article

Repetitive transcranial magnetic stimulation for smoking cessation: Next steps for translation and implementation into clinical practice

Victor M. Tang [a,b,c,d,e,f,*], Rachel Goud [a,c], Laurie Zawertailo [a,d,e,g], Peter Selby [a,b,c,d,e,h,i], Adina Coroiu [a,d], Matthew E. Sloan [a,b,c,d,e,g], Meghan Jo-Ann Chenoweth [c,d,g], Daniel Buchman [d,i], Christine Ibrahim [a,b,j], Daniel M. Blumberger [b,c,d,f], Bernard Le Foll [a,b,c,d,e,g,h,i,j,k]

Insula Highlights

- Series of preclinical, imaging and lesion studies suggest a critical role of the insula in addiction
- Translation of clear lesion findings in humans have led to approval of Hcoil from Brainsway for smoking cessation
- Possible other interests (other SUDs, gambling), but some unclear translation for alcohol
- Challenges remain: dissemination of this novel therapeutic option, cost, infrastructure required, how/when to use (alone, combination with pharmacotherapies)…

Histamine H3 Receptor and its therapeutic potential

Histamine

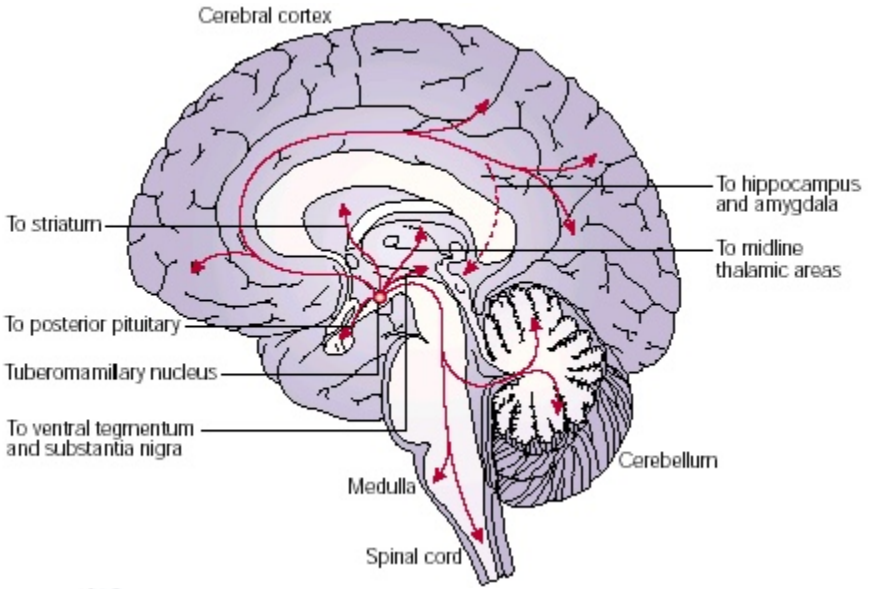
- Biogenic amine with four main receptors: H1-H4
- H1 and H2 are the most known ones

Receptor	Indications	Notes
H1	Allergy	Antagonists have sedating effects. It is used as an OTC sleep aid. Cholinergic actions give it side effects (Cetirizine, Zyrtex; loratadine Claritin)..
H2	Gastric acid release	First blockbuster drug: Cimetidine (Tagamet). Rarely considered as a CNS drug
H3	**Recently uncovered**	**Primarily expressed in brain. H3 is an auto-receptor and heteroreceptor**
H4	Asthma and allergy	Not considered for CNS disorders

Histamine H3 Receptor (H3R)

- H3R was first characterized in 1983 as an autoreceptor that regulates histamine
- H3R was also identified as an hetero-receptor that modulates the activity of other neurotransmitters (DA, Ach, 5-HT, GABA and Glu)
- Antagonism of H3 receptors increases Ach, NE and DA, as well as histamine

The Histaminergic System in the Brain

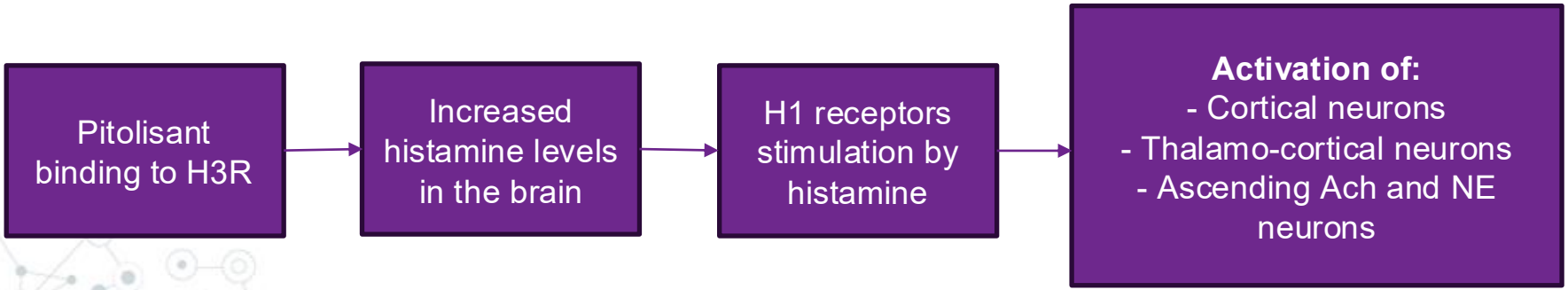


bioprojet

- The localization and pharmacology of the H3R receptor suggests it may be relevant in psychiatric/ substance use disorders.
- To-date, histamine H3 receptors have been studied mostly for their role in wakefulness as a treatment for narcolepsy.

WAKIX® (pitolisant)

- FDA approved to treat excessive daytime sleepiness (EDS) or cataplexy in people 6 years of age and older with narcolepsy
- Inverse agonist and competitive antagonist at the H3R
- Wakix® does not show preclinical abuse potential
- Suggested wakefulness effect mechanism:



Translational Psychiatry

▸ Transl Psychiatry. 2026 Jan 29;16:55. doi: 10.1038/s41398-026-03807-y

Histamine H3 Receptor as a target for alcohol use disorder: challenging the predictability of animal models for clinical translation in drug development

Bernard Le Foll [1,2,3,4,5,6,7,✉,#], Mickael Naassila [8,#], Jérôme Jeanblanc [8,#], Christian S Hendershot [9], Jesus Chavarria [10], Thierry Calmels [11], Stéphane Krief [11], Isabelle Berrebi-Bertrand [11], Marilyne Uguen [11], David Perrin [11], Xavier Ligneau [11], Isabelle Boileau [4,5,6,12], Pablo M Rusjan [13], Patricia Di Ciano [2,7,14], Pamela Sabioni [1,2], Marc Capet [10], Philippe Robert [10], Olivier Finance [10], Jeanne-Marie Lecomte [15], Jean Charles Schwartz [11,15]

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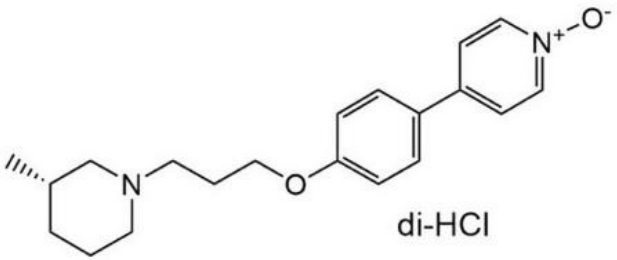
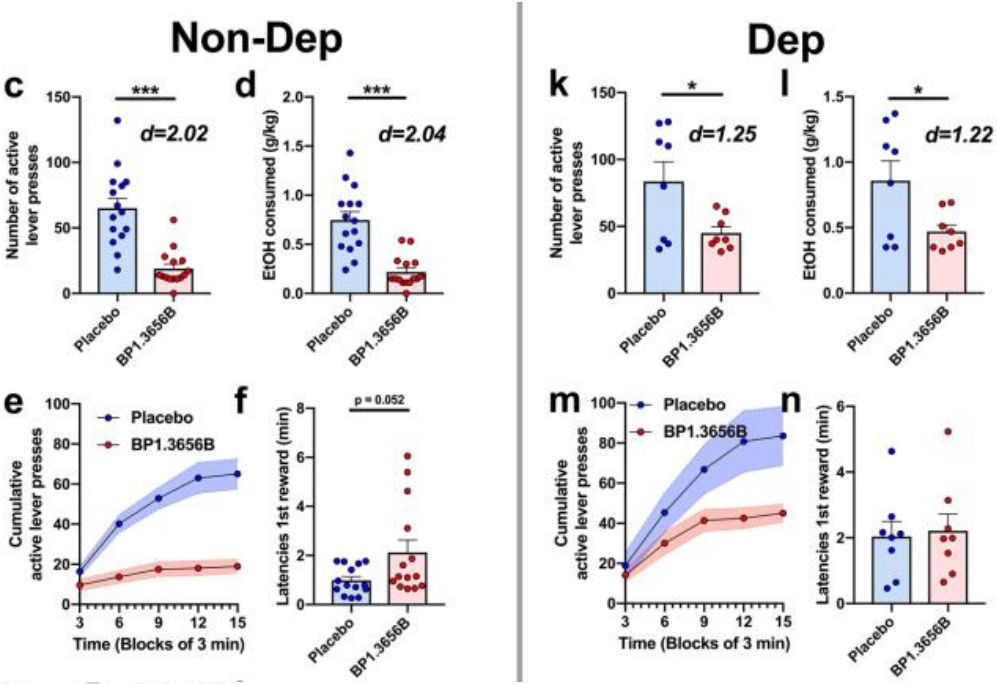
BP1.3656B Pharmacology



Structure of BP1.3656B, (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy] phenyl}pyridine 1-oxide, dihydrochloride

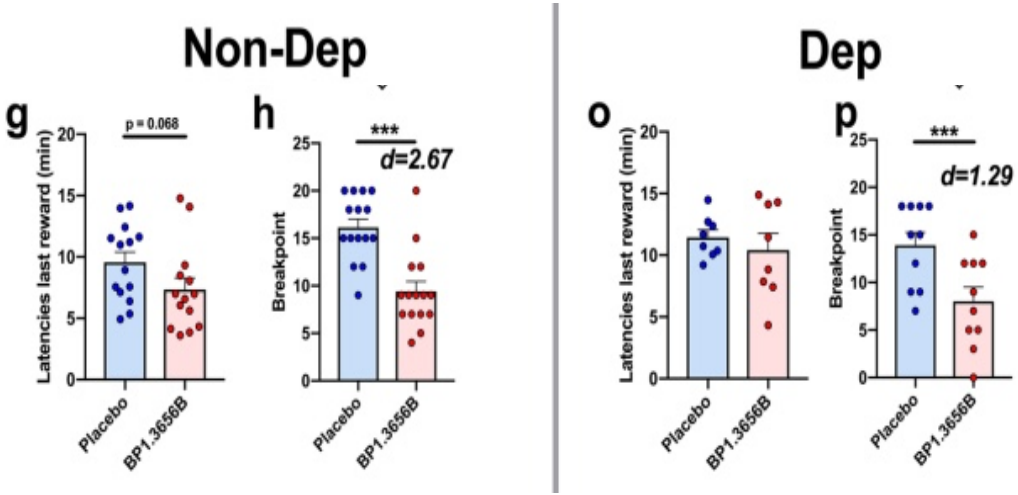
- High affinity and potent inverse agonist/ antagonist activity at the human H3R
- Highly selective and functionally active H3R antagonist
- Minimal off-target or cardiotoxic liability

BP1.3656B on Alcohol Self-Administration



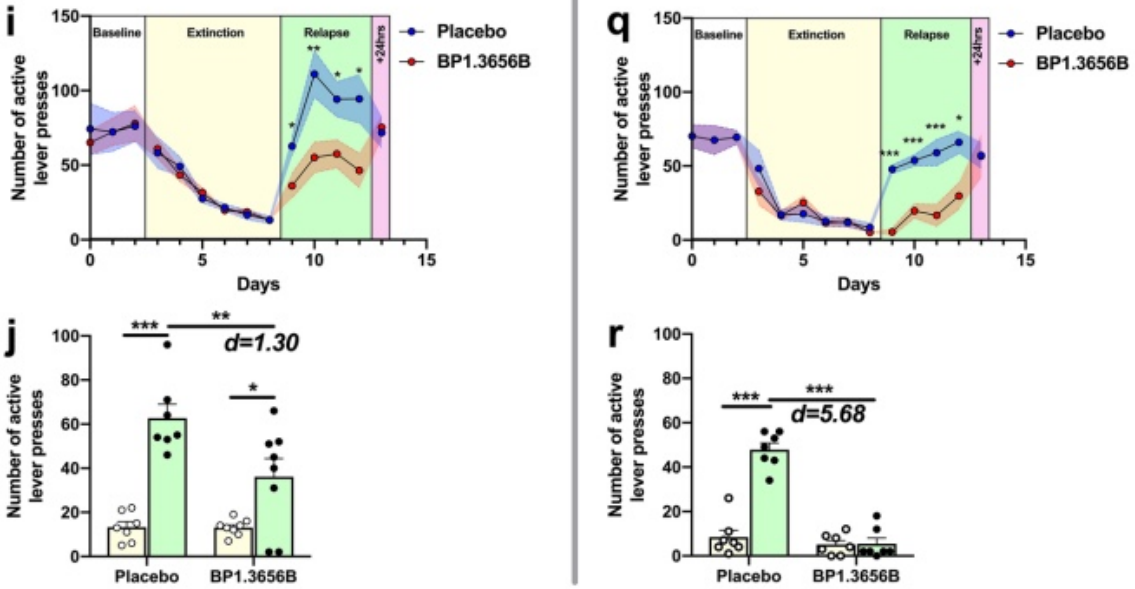
Alcohol self-administration is reduced by BP1.3656B (0.3 mg/kg, i.p.) in both dependent (right) and non-dependent (left) rats

BP1.3656B on Alcohol Motivation



Alcohol motivation is reduced by BP1.3656B (0.3 mg/kg, i.p.) in both dependent (right) and non-dependent (left) rats

BP1.3656B on Relapse after Extinction



Top: Effect of sub-chronic (4 consecutive days) BP1.3656B administration on the relapse after extinction

Bottom: Effect of acute BP1.3656B administration on the relapse after extinction

Occupancy of BP1.3656B at the H3R

PET study in healthy subjects

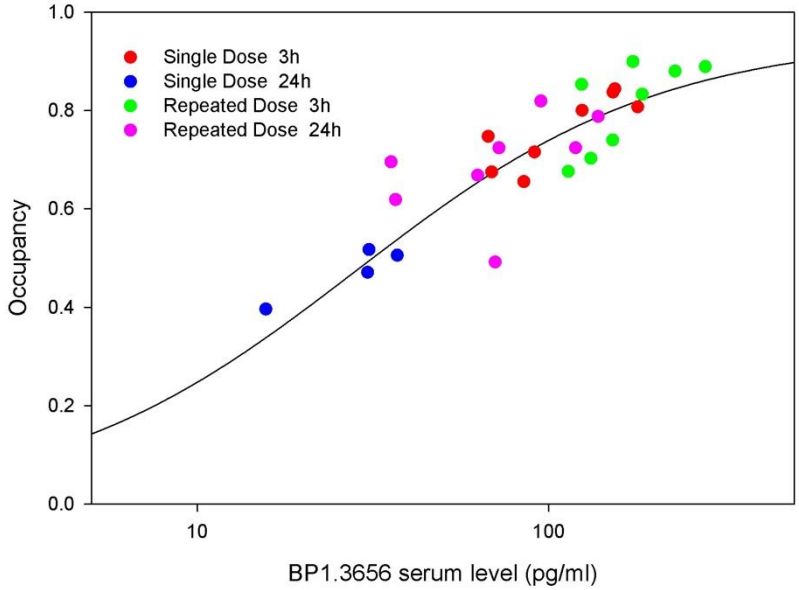
Acute administration:

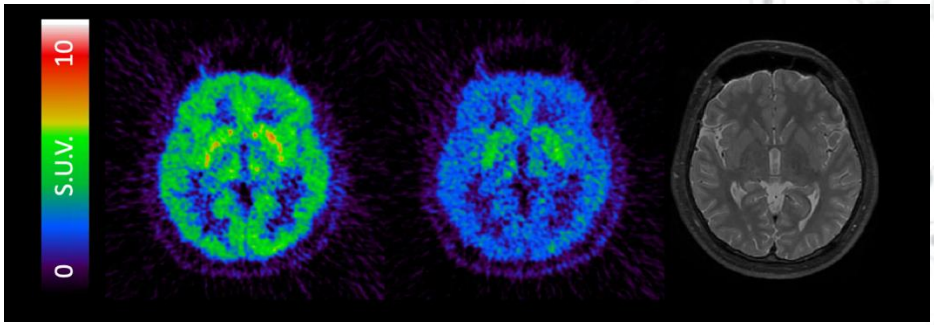
- Participants were given a single dose of BP1.3656B (30 µg or 60 µg) → scanned with [^{11}C]-GSK189254 either 3 h or 24 h after dosing.

Subchronic administration

- Participants were given BP1.3656B (30 µg or 60 µg) sub chronically for 5 to 10 days → scanned with [^{11}C]-GSK189254 either 3 h or 24 h after last dosing.

BP1.3656B/Pitolisant H3R Occupancy





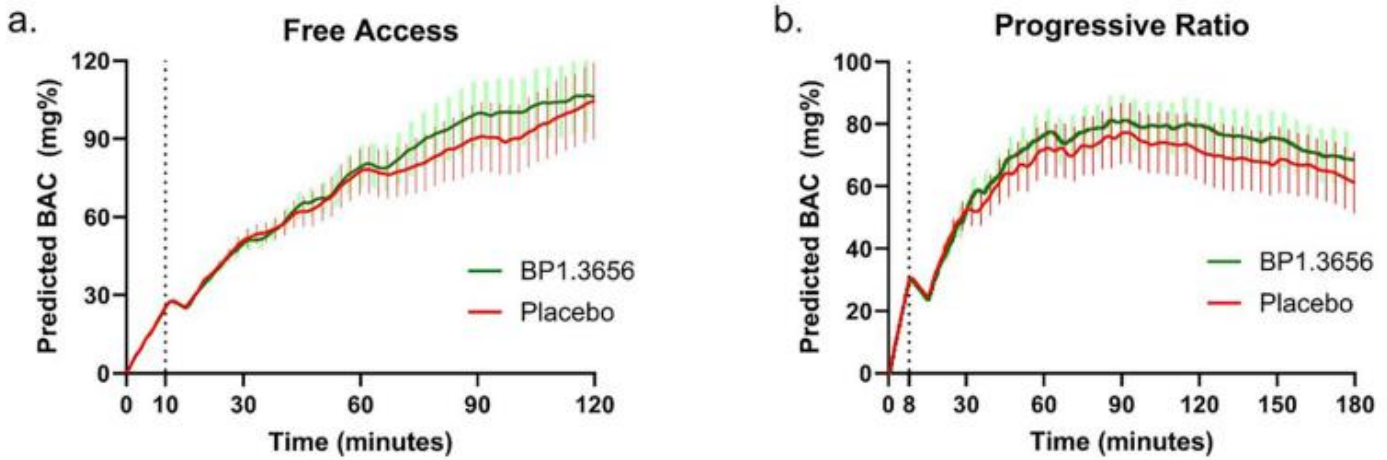
Mean SUV of [^{11}C]GSK189254 PET in human 3 hours after placebo (left) or 40 mg pitolisant (middle). Structural MRI (right). **84 %occupancy on average**

	Acute Dosing			Subchronic Dosing			
	30 µg 3hr	30 µg 24hr	60 µg 3hr	30 µg 3hr	30 µg 24hr	60 µg 3hr	60 µg 24hr
Average	70%	48%	82%	74%	62%	88%	76%
SEM	2%	3%	1%	3%	5%	1%	3%

Effects of BP1.3656B and placebo on intravenous alcohol self-administration (IV-ASA) in individuals with AUD

- Double-blind, within-subjects, counterbalanced design.
- Non-treatment-seeking adults who met criteria for past-year AUD were recruited from the community (36 randomized)
- Participants were randomized to treatment order (BP1.3656 first or placebo first) prior to sub-acute treatment with BP1.3656B and placebo.
- Target duration of treatment: at least 10 days (range: 10–14 days)
- 14-day washout period between treatments.
- Each treatment phase concluded with two laboratory visits involving operant IV-ASA procedures, consisting of one free-access (FA) IV-ASA session phase and one progressive ratio (PR) IV-ASA session phase (fixed order with sessions separated by at least one day).
- FA and PR sessions served as laboratory assays of alcohol liking and alcohol motivation/wanting, respectively

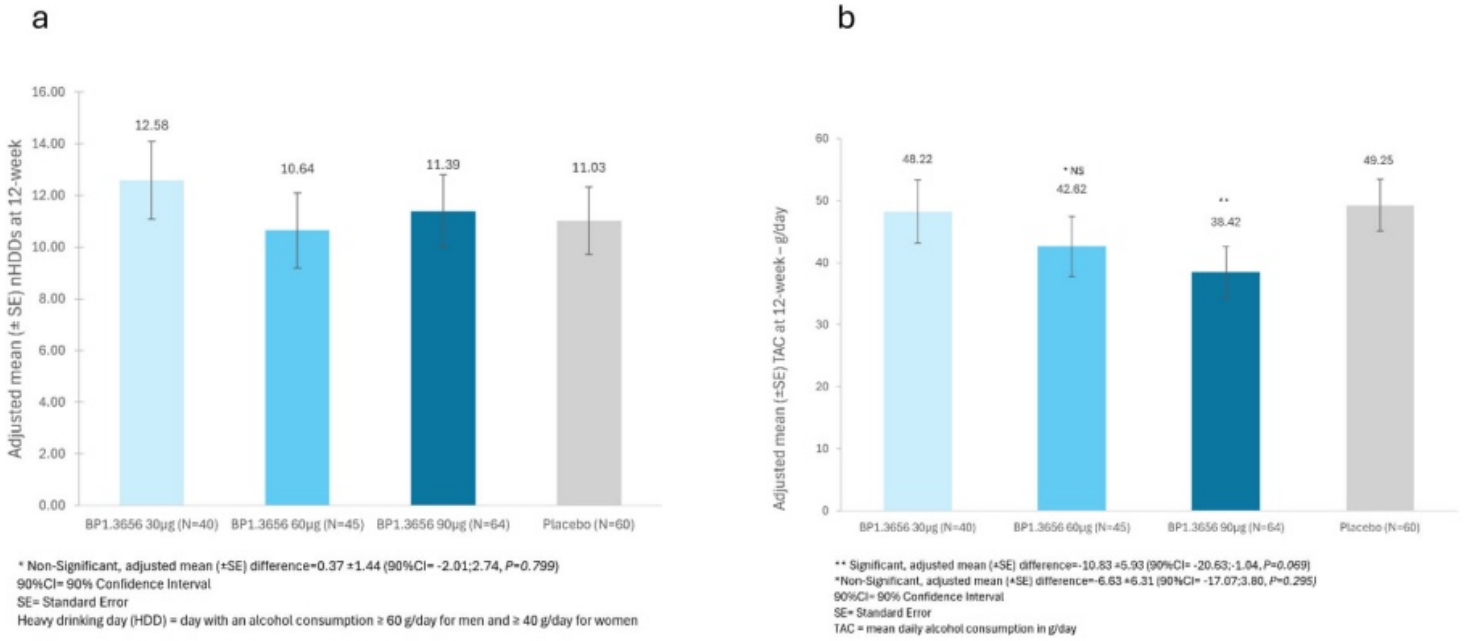
Effects of BP1.3656B and placebo on intravenous alcohol self-administration (IV-ASA) in individuals with AUD



Effects of BP1.3656B in individuals with AUD - RCT

- Multicenter, randomized, double-blind, placebo-controlled phase II trial
- Male and female patients with moderate to severe AUD
- Parallel groups to evaluate the effectiveness and the safety of BP1.3656B 30 µg or 60 µg or 90 µg OD compared to placebo in reducing alcohol consumption (sample size ~ 43/ active group)
- 12-week double blind treatment followed by a one-week wash out period under single blind placebo.
- Eighteen active centers within 3 countries (France, Bulgaria, Russia) participated in the trial.

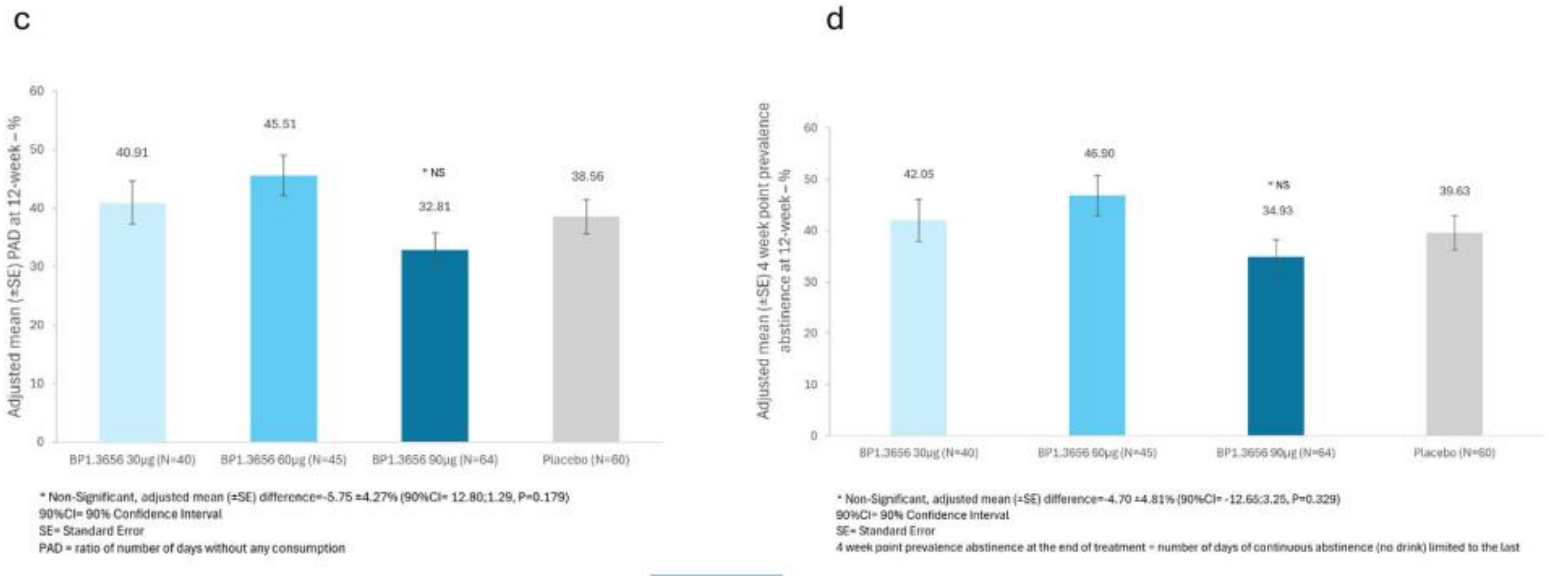
Effects of BP1.3656B in individuals with AUD - RCT



a. Heavy Drinking Days (nHDDs) during 12-week double-blind period

b. Total daily Alcohol Consumption (TAC) from baseline to the end of treatment

Effects of BP1.3656B in individuals with AUD - RCT



c. Percent of Abstinent Days (PAD) during 12-week double-blind period

d. 4-week point prevalence abstinence (PPA) at the end of treatment

H3 Highlights

- BP1.3656B showed a promising profile for AUD across multiple preclinical models (alcohol self-administration, motivation, alcohol relapse, both in the non-dependent and dependent rats).
- Good tolerability and good brain penetration and occupancy
- However, no effect on motivation for alcohol using a human laboratory self-administration paradigm
- No significant effects on multiple drinking measures across a range of doses in a multi-center RCT in treatment seekers individuals

Final Conclusions

- Preclinical models are useful to generate ideas and hypothesis
- However, clinical translation is often difficult. The insula story that started with a clear human signal based on lesion work highlight the importance of human validation early on for success
- For target with no clear human data, it may be important to use earlier behavioral pharmacology laboratory experiments, due to their lower cost compared to clinical trials to de-risk the translation
- Possible that AUD may be more complex than other SUDs to translate due to the multiplicity of receptors involved and various reasons to drink alcohol

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Collaborating CAMH Researchers: Boileau I, Rehm J, Fisher B, George TP, Selby P, Quilty L, Hendershot C, Mann, B Brands, C Wickens, Tyndale R, Kennedy J, Sloan M, Hassan A, Kloiber S, Chavez S, Bozinoff N, Blumberger D, Tang, Selby P, Zawertailo L, Zack M, Kahana D., **Isabelle Boileau, Christian Hendershot, Pablo Rusjan**

Collaborating Scientists: Nielsen S, Lintzeris N, Khor K, Farrell M, Hall W, Gates P, Marshall K, Gowing L, Ali R, Copeland J, Huestis M, Barnes A, Goldberg SR, Justinova Z, Makriyannis A, Zangen A**, Naassila Michael, Jerome Jeanblanc, Jean Charles Schwartz, Jeanne Marie Lecomte, Bioprojet staff,** Sokoloff P, Daskalakis J

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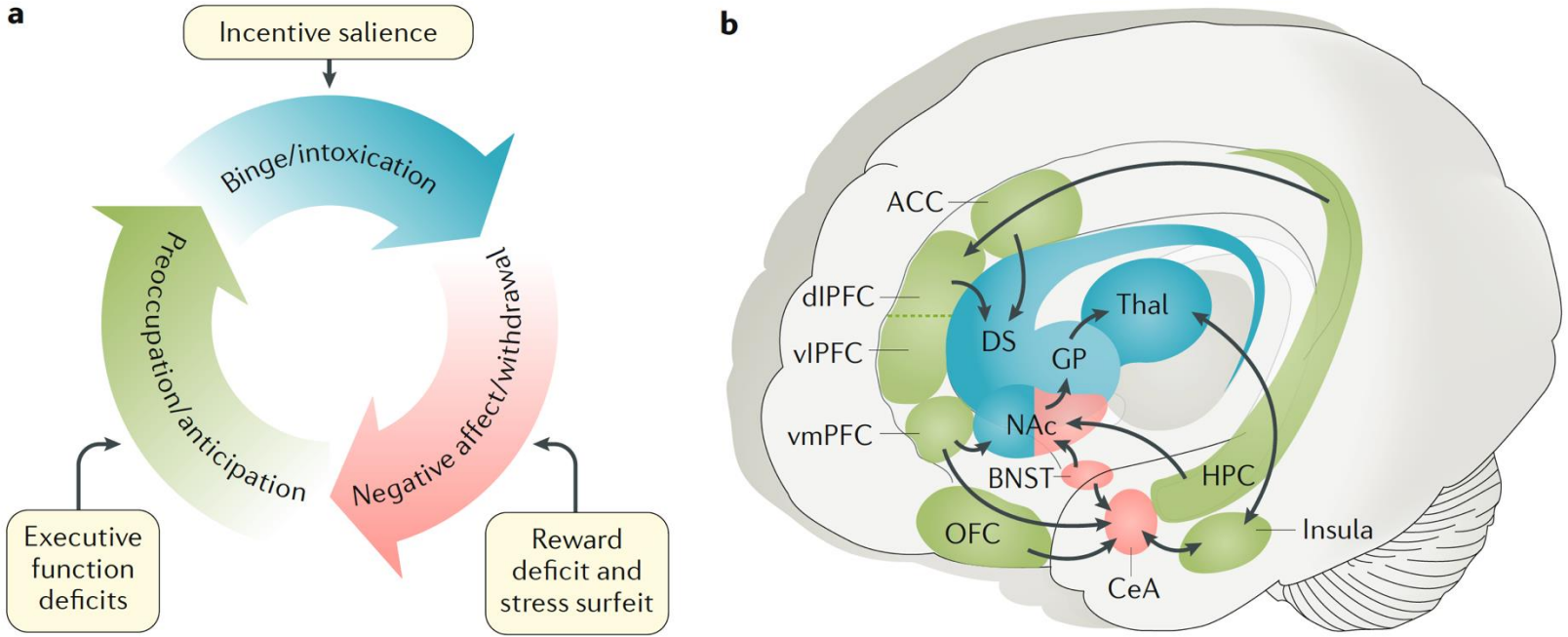
It's all in the brain
Neurobiological Framework for Addiction



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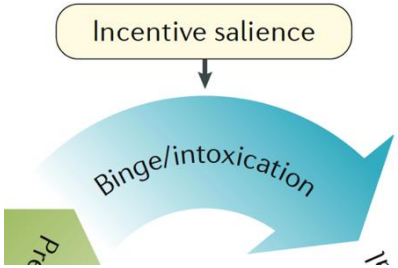
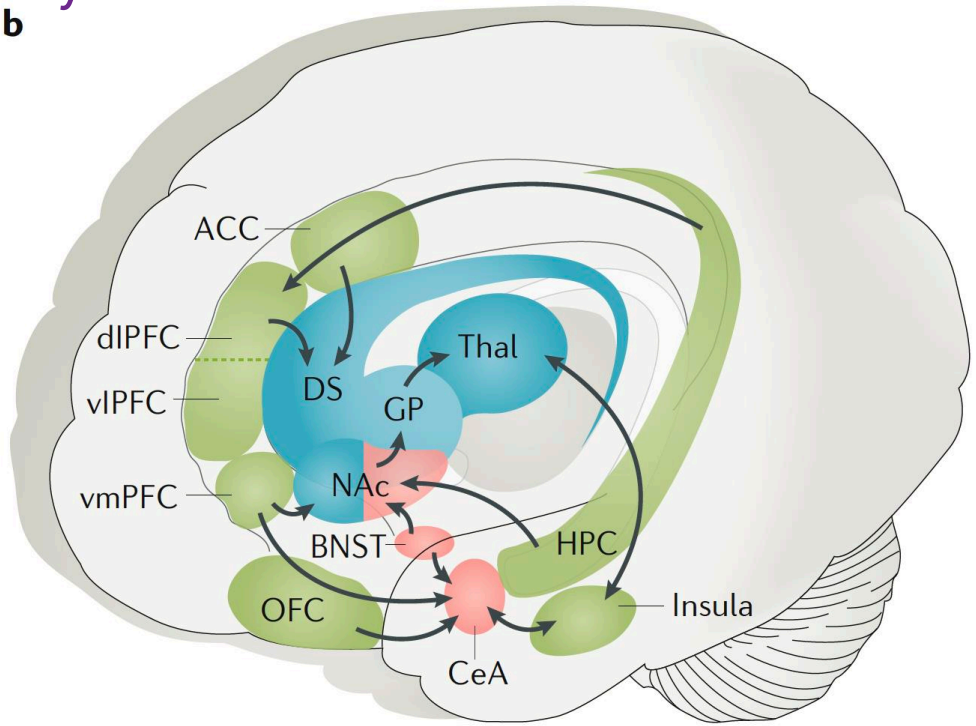
Incentive Salience Circuitry



- Reward Systems
- Associative learning
- Habit
- Basal ganglia
  - Nucleus Accumbens (Nac)
  - Dorsal Striatum (DS)
    - Caudate
    - Putamen



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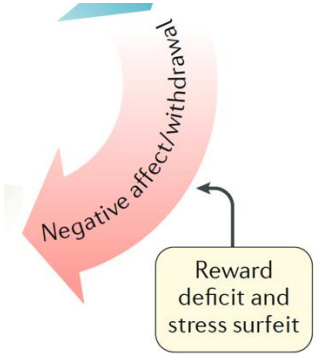
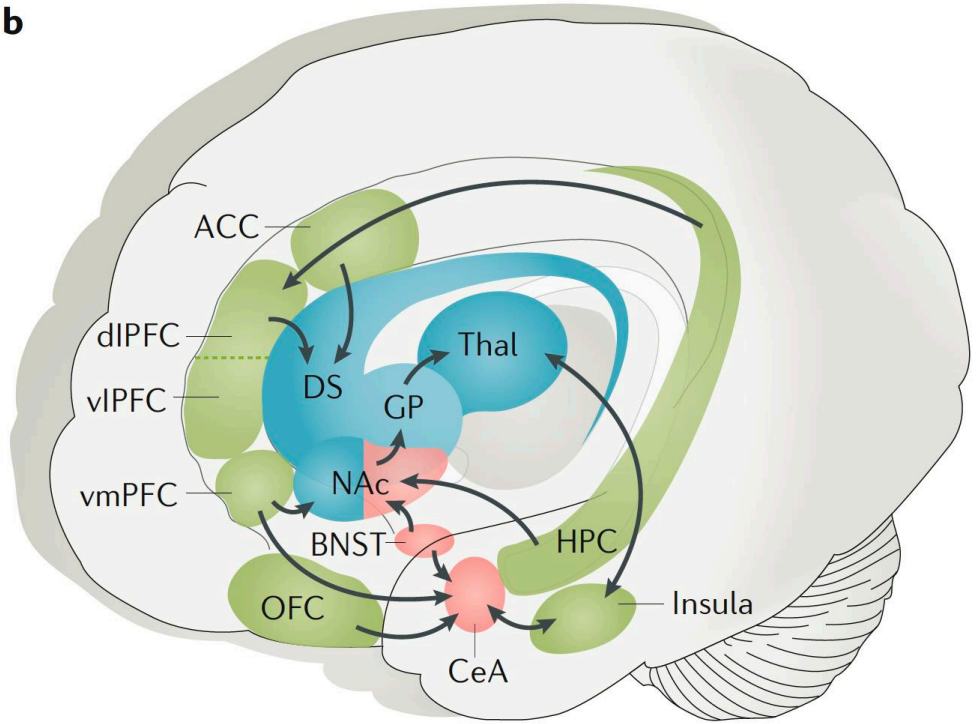
Withdrawal Circuitry



- Aversive/stress systems
- Extended amygdala
  - Bed nucleus stria term
  - Medial NAc



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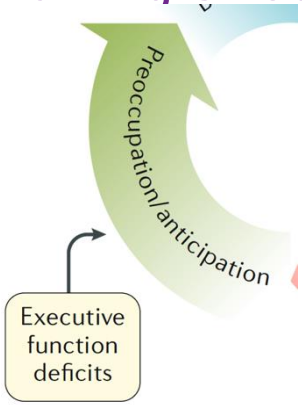
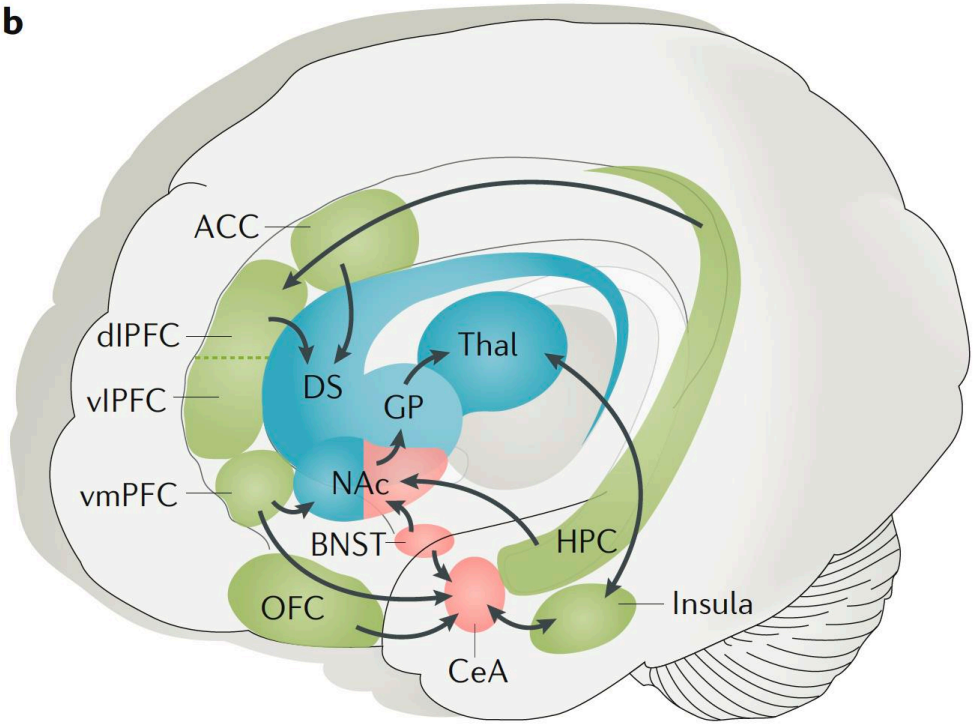
Craving Circuitry



- Executive Function
- Craving Stage
- Prefrontal Cortex (PFC)
  - Orbitofrontal (OFC)
  - Ventromedial (vmPFC)
  - Ventrolateral (vlPFC)
  - Dorsolateral (dlPFC)
- Insula



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Imaging studies are consistent for insula activation during drug urges

Functional imaging studies demonstrating insular activity during drug urges

Study	Drug	INSULA	OFC/VMPFC	ACC	DLPFC	Amygdala	VS	HF
McBride et al. (2006)	Cigarettes	L	L	L,R	L[a]			
Franklin et al. (2007)	Cigarettes	L	R		L[a]	L,R	L,R	L, R
Brody et al. (2002)	Cigarettes	L[a],R[a]	L[a],R[a]	L,R	L[a],R[a]	L		
Brody et al. (2007)	Cigarettes	L[a],R[a]		L[a],R[a]	L[a]			
McClernon et al. (2005)	Cigarettes	L,R		L[a],R[a]	L[a],R[a]			
Lee et al. (2005)	Cigarettes	R	L	L	R			
Wang et al. 2007	Cigarettes	R[a]	R[a]	R[a]	R[a]	R[a]	R[a]	L[a], R[a]
Kilts et al. (2004)	Cocaine	L		R		L,R	R	
Bonson et al. (2002)	Cocaine	L[a]	L[a]		R[a]	L[a]		
Kilts et al. (2004)	Cocaine	L[a],R[a]	L[a],R[a]	L		L,R	R	
Wang et al. (1999)	Cocaine	L,R[a]	L[a],R[a]					
Garavan et al. (2000)	Cocaine	R		L	L,R			
Wexler et al. (2001)	Cocaine	R		L,R	L			
Myrick et al. (2004)	Alcohol	L,R	L[a],R[a]	L[a],R			L[a],R	L
Tapert et al. (2004)	Alcohol	L,R		L	L			
Sell et al. (1999)	Heroin	L	L	L,R				

Naqvi & Bechara, 2010