

Clinical Study of Stereotactic Surgery for Drug Addiction

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Drug Addiction

Definition of WHO :

Compulsive and spontaneous drug-taking behavior which is characterized by non-medical usage, long and repeated exposure to addictive drugs and gradually increasing drug-taking dose.



Problem around the world

200,000,000 People Drug Abuse

10,000,000 People Lose Labor Ability

100,000 People Lose Lives

Types of Clinical Manifestations

Physiological dependence

Psychological dependence

Physiological dependence

After repeated drug exposure, a sudden withdrawal would cause series of **withdrawal symptoms**, which would made the abuser reinstated into drug-taking.



withdrawal
symptoms

Dysphoria
Anxiety
insomnia
lachrymation
yawn

Psychological dependence

It means the **craving** for euphoria after withdrawal. It is the strong **desire** which drives the drug addicts to keeping their drug-taking behavior.

Effects of Conservative Therapies

- ❖ alleviating withdrawal symptoms (physiological dependence)  achieve detoxification
- ❖ hardly being helpful to craving (psychological dependence)  lead to relapse

Relapse rate after detoxification:

Within one month 90%

Within six months 97%

The drug abusers always fall into a vicious circle:



Neuroanatomy of drug addiction

Physiological dependence:

locus caeruleus (LC)

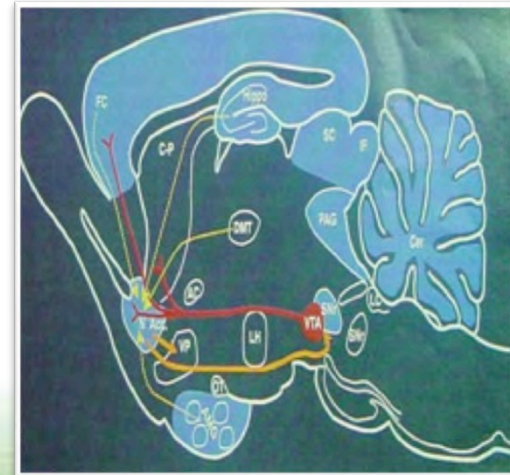
periaqueductal gray matter (PAG)



Psychological dependence:

nucleus accumbens (NAc)

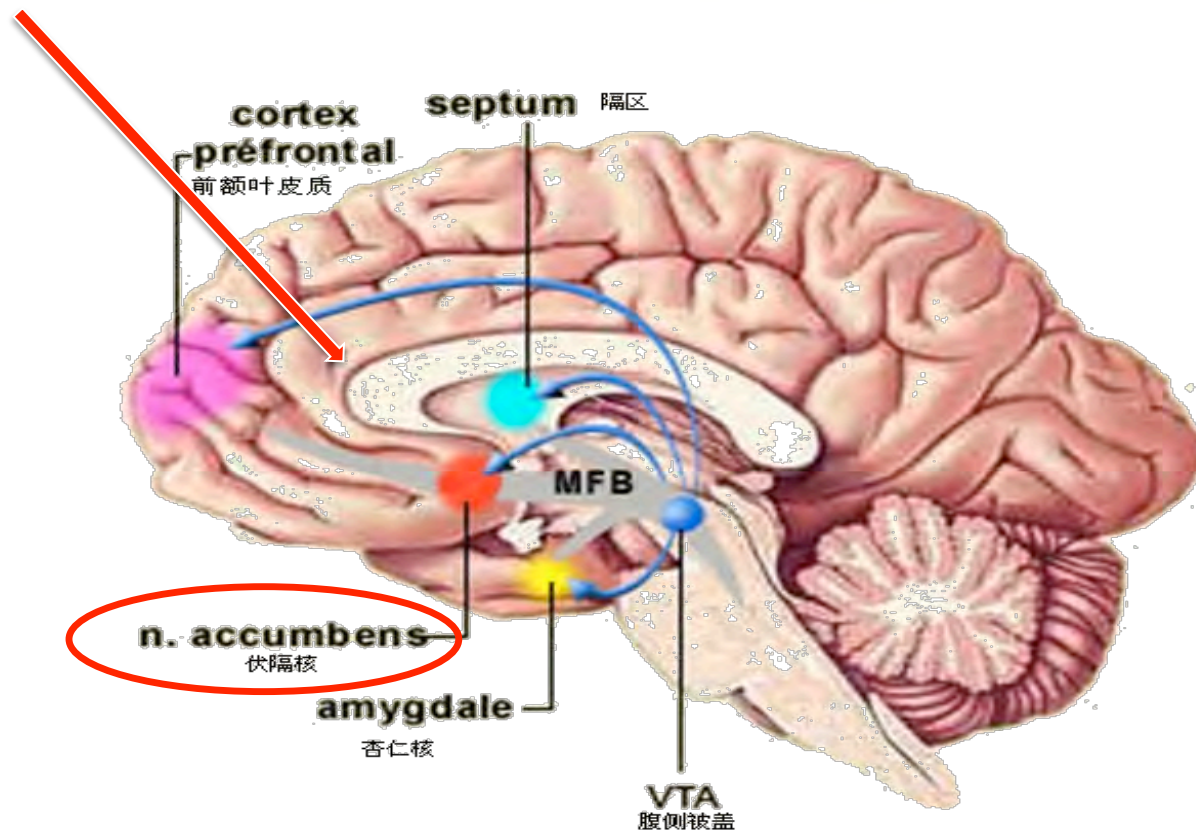
ventral tegmental area (VTA)



The **mesolimbic dopamine system** plays a central role in psychological dependence with the **nucleus accumbens (NAc)** serving as a key structure in mediating these effects.

NAc is located where the head of the caudate and the anterior portion of the putamen meet just rostral to the anterior commissure, which belongs to the basal ganglia of the brain.

Neurophysiologic mechanism of psychological dependence



Brain reward system

Hypothesis

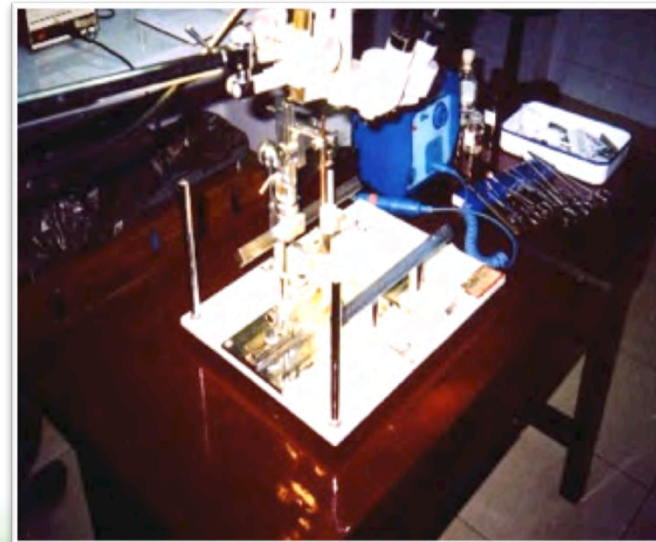
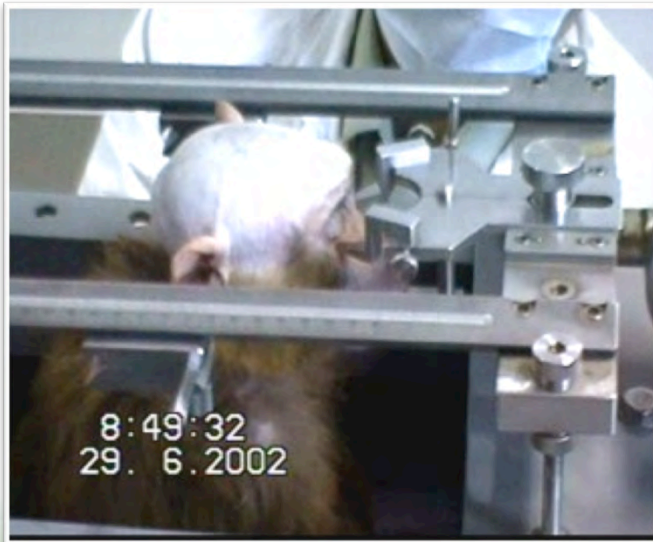
Ablation of the **NAc** with minimally invasive stereotactic neurosurgery would lead to blockage of the mesocorticolimbic dopamine circuit, which would prevent craving for drugs after detoxification and in this way prevent relapse

Our study

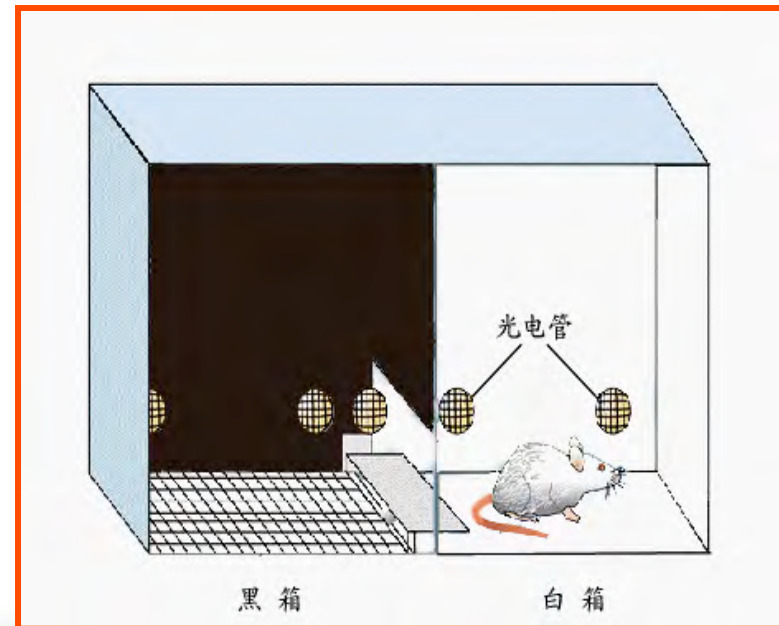
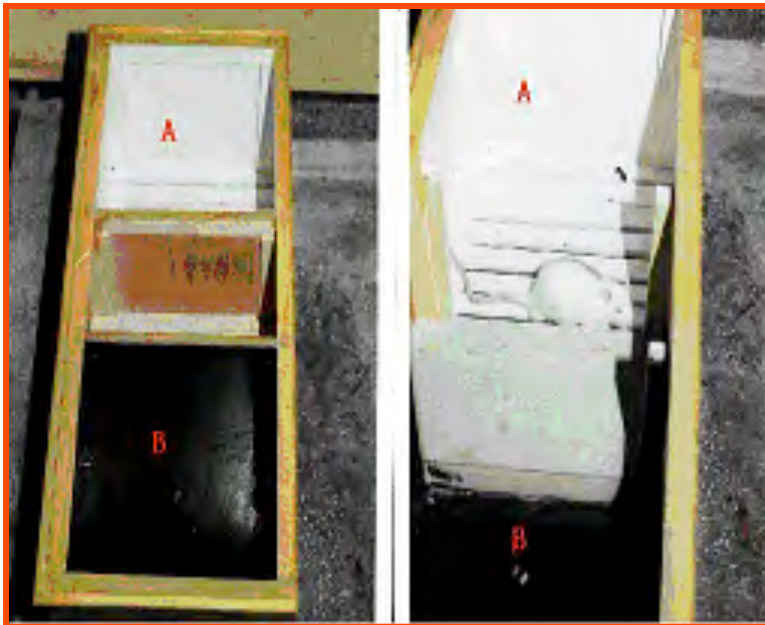
In 1998, we started preclinical and clinical exploration on the [NAc surgery for drug addiction](#), after sufficient discussion with experts in ethics, neuroscience, neurosurgery, neurology, psychology and psychiatry.

Animal Experiment

From May 1999, we studied experiments on rats and rhesus by ablating nucleus related to addiction, such as NAc and ventral globus pallidus (VP) for choosing the candidate target for clinical application.



Conditioned place preference (CPP) experiment was employed as addiction model and the animals was trained with morphine. Different targets was ablated to see the influence to animals' place preference.



The influence of CPP after NAc and VP lesion

	groups (n=10)	white box	black box
Pre-operation	NAc group	813.4±s30.1* #	86.6±s17.5
	VP group	806.5±s27.4 △	93.5±s16.5
	control	436.6±s21.7 *	463.4±s19.3
post-operation	NAc group	489.1±s21.3 #	410.9±s18.9
	VP group	594.7±s30.2 ☆ △	305.3±s14.5
	control	476.8±s19.6 ☆	423.2±s21.7

(* # △ $P < 0.01$ ☆ $P < 0.05$)

Animal experimental conclusion

- ❖ NAc is the main nucleus for modulating drug reinforcement
- ❖ Ablating the NAc could decrease drug-taking behavior of the addicted rats

Clinical Research

(2000.07—2010.12)

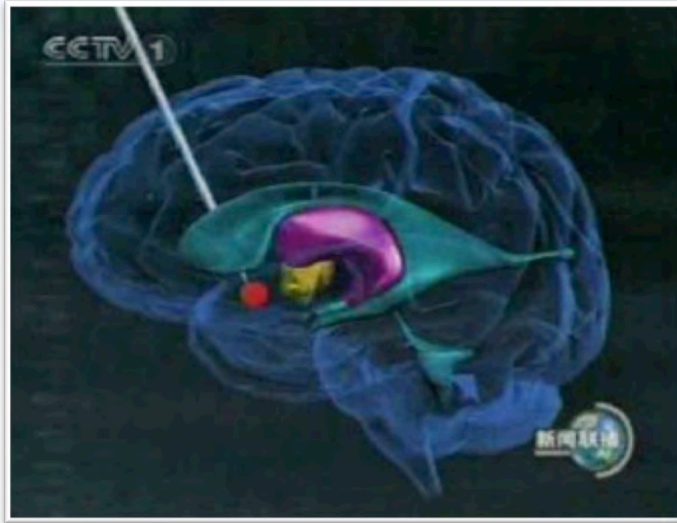
Bilateral ablation of NAc

- ❖ With great relationship to drug psychological dependence
- ❖ Inspired by the success of pallidotomy for Parkinson's disease
- ❖ Study on NAc as a sole target could obtain more explicit results than that on multiple targets

1. Inclusion and exclusion criteria

- (1) drug-taking history $\geq 3y$
- (2) times of treatment before ≥ 3
- (3) informed consent process
- (4) following physiological detoxification
- (5) without contraindications

Nucleus accumbens ablation



First case worldwide in July, 2000

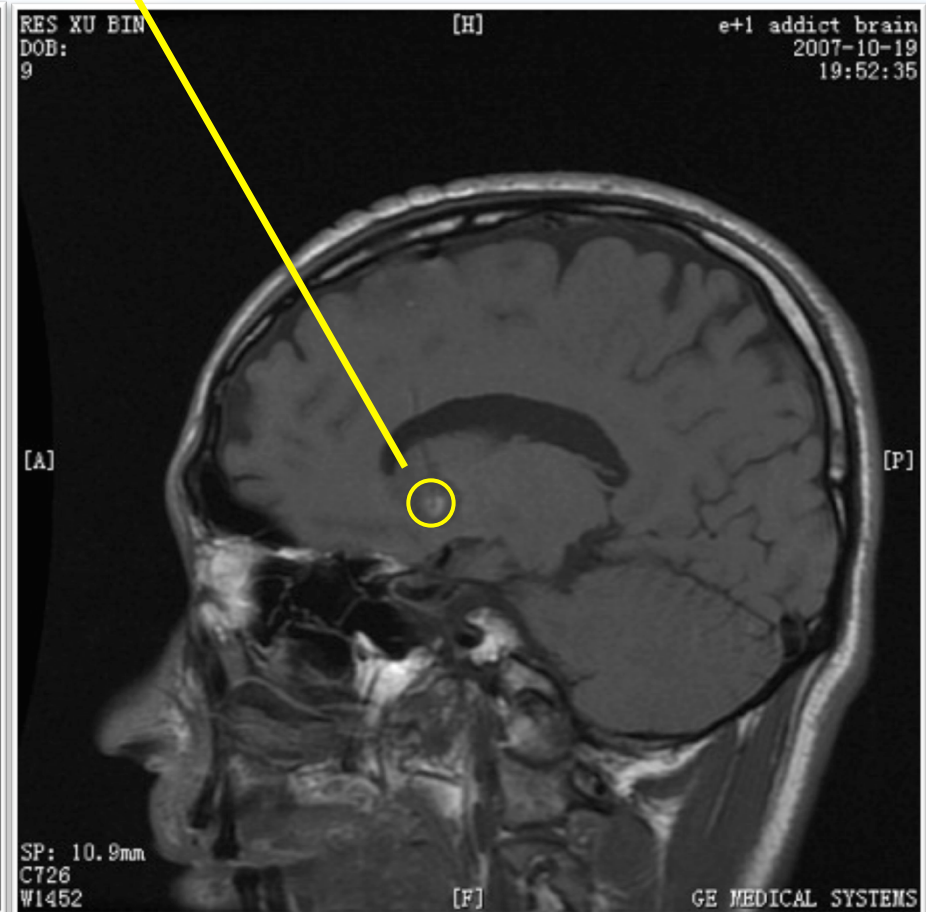
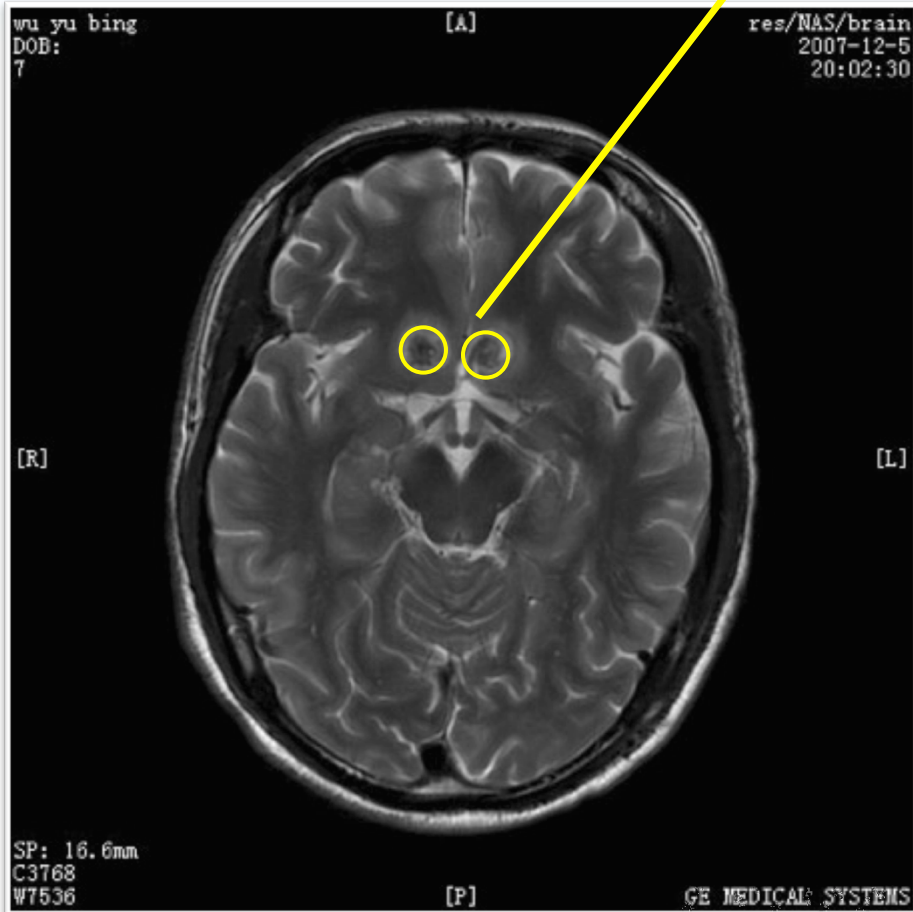
272 cases was included

1 year non-relapse rate: 69.5%

Specific complications : 5.9%



Nucleus accumbens



81 | 1-4 | 03

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**Stereotactic
and Functional
Neurosurgery**

Clinical Study for Alleviating Opiate Drug Psychological Dependence by a Method of Ablating the Nucleus accumbens with Stereotactic Surgery

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Xian, China

Key Words

Stereotactic surgery · Drug abstinence · Nucleus accumbens ·
Psychological dependence

Abstract

The aim of this study was to explore a new way of treating drug addiction by ablating the nucleus accumbens (NA_C), which has a close relationship with drug-induced psychological dependence, using stereotactic surgery, blocking the mesocorticolimbic dopamine circuit, alleviating craving for drugs and lowering the relapse rate after detoxification. On the basis of animal experiments, stereotactic surgery was performed in 28 patients by making a lesion in the NA_C bilaterally to treat opiate drug dependence. Indications, the criterion of therapeutic effect, treatment process and the therapeutic and safety evaluation index of the surgery were formulated particularly. The mean follow-up period was 15 months. Relapse has not occurred in 11 cases up till now. Drug-free time in these patients has been more than half a year in 4 cases (more than a year in 3 cases), and less than half a year in 7 cases. Relapse occurred in 15 cases after surgery. Drug-free time in these patients was more than half a year in 3 cases, between 1 month and half a year in 10 cases and less than 1 month in 2 cases. The therapeutic effect was excellent in 7 cases (26.9%), good in 10 cases (38.5%) and poor in

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02/10/03

Dear Dr. Guodong,

I'm pleased to tell you that your abstract has been accepted for platform presentation for the Quadrennial meeting of the American Society of Stereotactic and Functional Neurosurgery to be held in New York from May 18-21st, 2003. Your paper will be given 12 minutes of platform presentation time. Your presentation should be limited to 9 minutes and you should allow 3 minutes for discussion.

Please send in your presentation to the New York University Continuing Medical Education office by e-mail (keith.varney@med.nyu.edu), to be received no later than May 2nd, 2003. Your presentation is scheduled to take place on May 19th 2003 at 2:39pm.

This promises to be an exciting meeting for which we have received a record number of abstracts and I feel the quality is exceptional. Thank you for taking part in the ASSFN meeting and for your contributions.

Yours sincerely,

Andres Lozano MD, PhD, FRCSC

Scientific Program Coordinator
Secretary/Treasurer, ASSFN

Lecture

1. Conference of stereotactic and functional neurosurgery (USA, 2003.5)
2. Other four international conferences

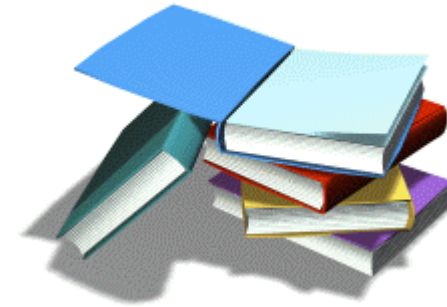
- ❖ After publication of our work, more than 10 hospitals carried out similar clinical studies in China.
- ❖ Most of the studies confirmed the therapeutic effect of NAc ablation for drug addiction but Incurred doubt
- ❖ A national survey on this treatment was performed in 2009, which was assigned and funded by Chinese Ministry of Science & Technology

National Survey

1 year
Short term
Single center



5-year
Long term
Multi-center



Effectiveness

Safety

Department of Neurosurgery, Tangdu Hospital
& National Institute on Drug Dependence

Case file provided by 7 hospitals

Up to July, 2009 Total cases: 769cases

Tangdu Hospital: 272 cases

Guangdong 999: 203 cases

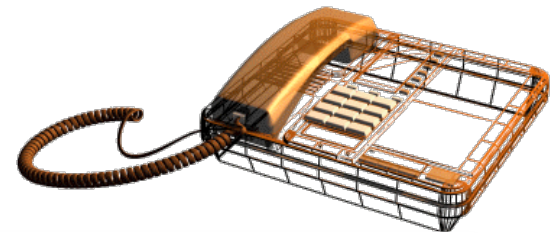
Guangzhou 458: 185 cases

Sichuan Luzhou: 56 cases

Naval General Hospital: 32 cases

Shenyang 463: 10 cases

Shanghai Ruijing: 11 cases



Because of funds limit, a 150 cases sample investigation was carried on at last

Random select 150 patients
from cases file

5 areas, appoint 1-2 hospitals as
the center of follow-up study

Set up a healthy person group
as control

**Face
to
Face**

The content of follow-up visit



Non-Relapse rate
Craving of drugs
Withdrawal syndrome

Complications
Craving of food, sex
Personality
Mental health
Life Quality

Face to Face



Image



The result of urine test (-)

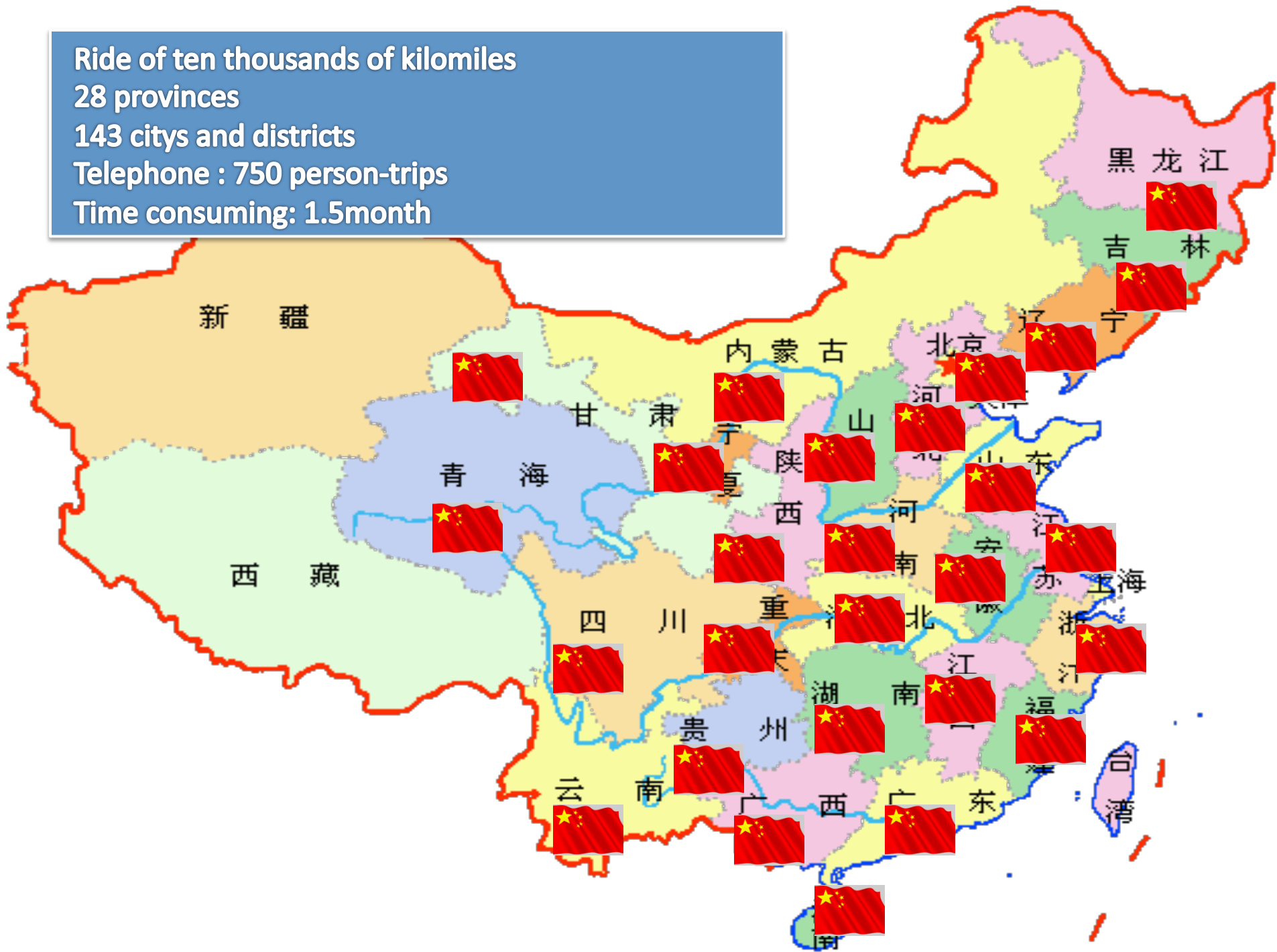
Ride of ten thousands of kilomiles

28 provinces

143 cities and districts

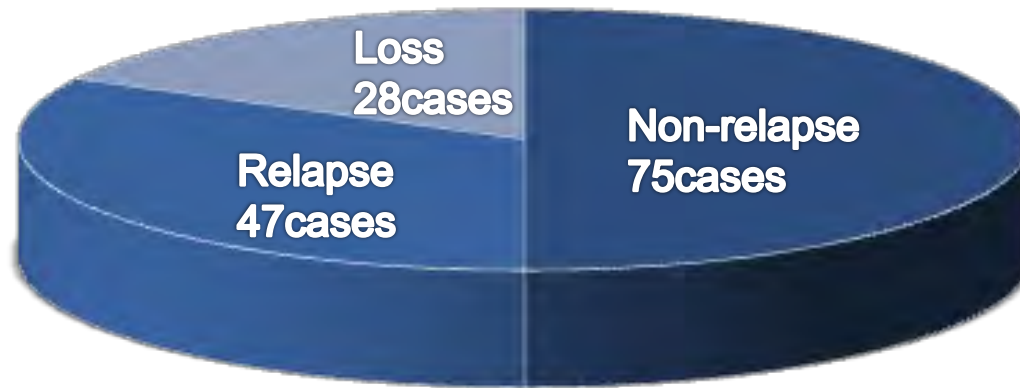
Telephone : 750 person-trips

Time consuming: 1.5month



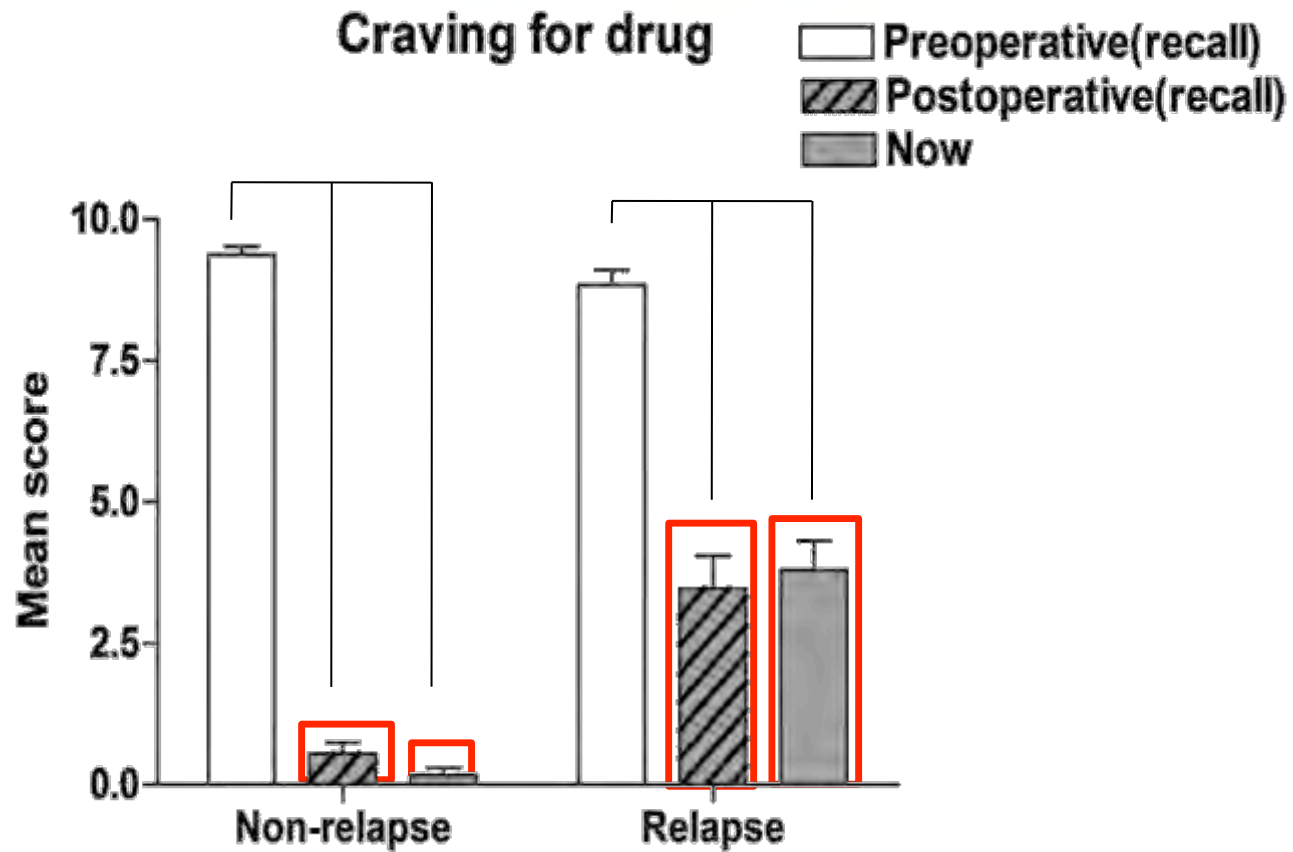
Efficacy

150 patients



5-year Non-relapse rate: 50%

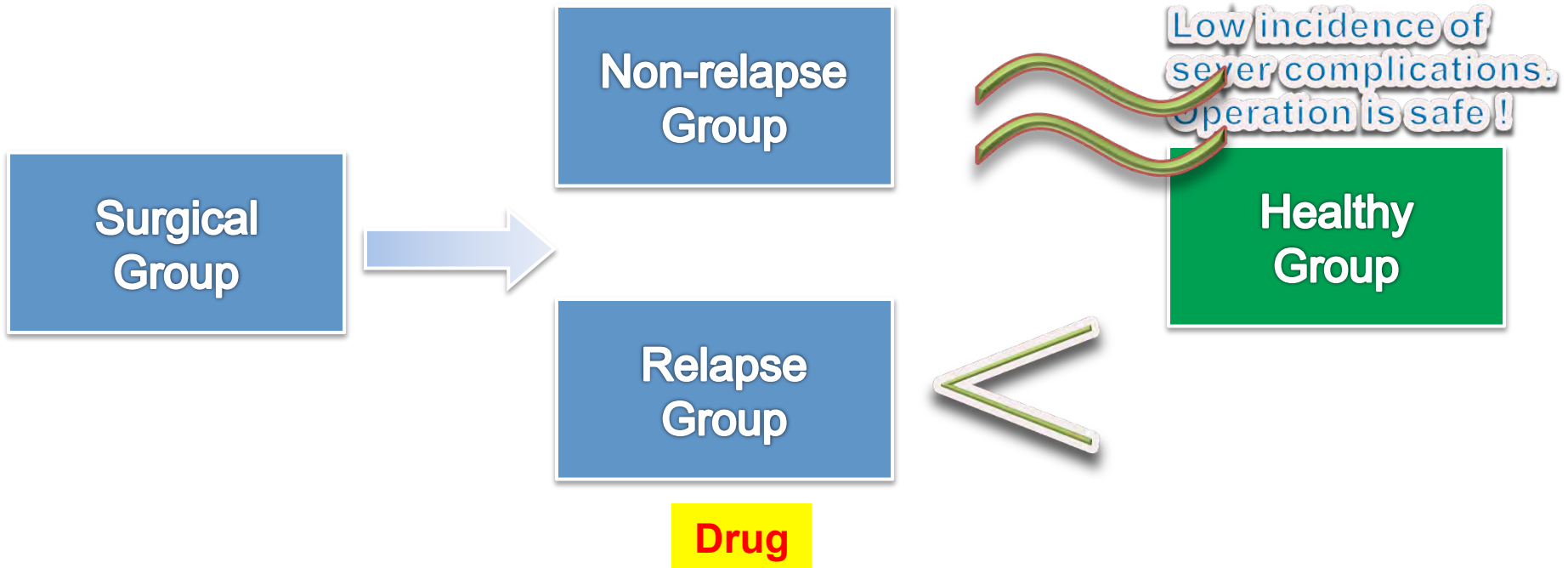
Efficacy



Conclusion

1. Long term efficacy (**good**)

2. Long term safety



Conclusion

- ❖ **Surgical treatment for addiction is one of the most important and effective method for drug addiction.**
- ❖ **Comprehensive treatment is helpful.**
 - **drug detoxification**
 - **surgical treatment**
 - **psychological rehabilitation**
 - **return to society**

Conference

1. Meeting of the American Society of Stereotactic and Functional Neurosurgery, New York (2003.5)
2. Chinese Congress of Stereotactic and Functional Neurosurgery, Shanghai (2004.6)
3. international forum of minimal invasive neurosurgery, Beijing (2004.9)
4. International forum of stereotactic and functional neurosurgery, Beijing (2005.12)
5. Future of Neuromodulation Therapy in Clinical Neuroscience, seoul, Korea (2007.1)
6. The 6th Asian Society for Stereotactic, Functional and Computer Assisted Neurosurgery, Mt. Fuji Resort, Japan (2007.5)
7. 2010 CNS annual meeting, san francisco (2010.10)
8. The 8th AASSFN, Jeju, Korea(2011.6)



Top 10 Abstract (CNS annual meeting)

Top Ten Abstracts – Section on Stereotactic and Functional Neurosurgery

Moderators: *Brian H. Kopell, Konstantin V. Slavin*

1:30 – 1:39 PM

961

**Treatment of Medically Intractable Mesial Temporal Epilepsy
with Responsive Brain Stimulation: Results of a Subset
Analysis from the RNS® System Pivotal Investigation**

*Robert R. Goodman, Peter B. Weber, Thomas C. Witt,
Robert M. Worth, Ryder Guinn, Louis A. Whitworth,
Joseph R. Smith, David W. Roberts, Charles Y. Liu,
Steven S. Glazier, Ashutni Dayal Sharan, James W. Leiphart,
George I. Jallo, Kost Elisevich, Richard W. Byrne, Karl A. Sillay,*


2:51 – 3:00 PM

970

**Nucleus Accumbens Lesioning Appears to Reduce Opiate
Dependence: Target Location Correlates with Outcome**

*Wang Xuelian, Paul S.A. Kalanithi, John Adler, Chang Chongwang,
Ge Shunnan, Li Nan, Geng Ning, Ma Jiubong, Wu Heming,
Fang Wei, Gao Guodong*

**Stereotactic
and functional
Neurosurgery**

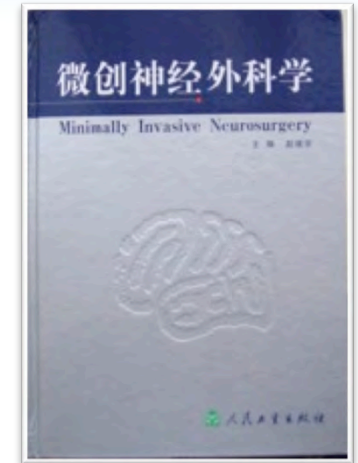


Publication

1. Gao G, Wang X, He S, Li W, Wang Q, Liang Q, Zhao Y, Hou F, Chen L, Li A. Clinical study for alleviating opiate drug psychological dependence by a method of ablating the nucleus accumbens with stereotactic surgery. *Stereotact Funct Neurosurg.* 2003;81(1-4):96-104.
2. He F, Guan H, Zhao Z, Miao X, Zhou Q, Li L, Huang D, Liu A, Miao D. Evaluation of short-term psychological functions in opiate addicts after ablating the nucleus accumbens via stereotactic surgery. *Stereotact Funct Neurosurg.* 2008;86(5):320-329.
3. Wang J, Zhao Z, Liang Q, Wang X, Chang C, Wang J, Gao G. The nucleus accumbens core has a more important role in resisting reactivation of extinguished conditioned place preference in morphine-addicted rats. *J Int Med Res.* 2008;36(4):673-81.
4. Heng LJ, Yang J, Liu YH, Wang WT, Hu SJ, Gao GD. Repeated morphine exposure decreased the nucleus accumbens excitability during short-term withdrawal. *Synapse.* 2008;62(10):775-82.
5. Wu HM, Wang XL, Chang CW, Li N, Gao L, Geng N, Ma JH, Zhao W, Gao GD. Preliminary findings in ablating the nucleus accumbens using stereotactic surgery for alleviating psychological dependence on alcohol. *Neurosci Lett.* 2010;473(2):77-81.
6. Wu HM, Wang C, Wang XL, Wang L, Chang CW, Wang P, Gao GD. Correlations between angiotensinase activity asymmetries in the brain and paw preference in rats. *Neuropeptides.* 2010;44(3):253-259.
7. Zhao HK, Chang CW, Geng N, Gao L, Wang J, Wang X, Wang YR, Wang XL, Gao GD. Associations between personality changes and nucleus accumbens ablation in opioid addicts. *Acta Pharmacol Sin.* 2012 May;33(5):588-93.
8. Li N, Gao L, Wang XL, Chen L, Fang W, Ge SN, Gao GD. Deep brain stimulation of bilateral nucleus accumbens in normal rhesus monkey. *Neuroreport.* [Epub ahead of print].
9. Li N, Wang J, Wang XL, Chang CW, Ge SN, Gao L, Wu HM, Zhao HK, Geng N, Gao GD. Nucleus Accumbens Surgery for Addiction. *World Neurosurgery.* [Epub ahead of print].
10. Ge SN, Chang CW, Kalanithi P, Adler JR, Zhao HK, Chang XZ, Gao I, Wu HM, Wang J, Li N, Wang XL, Gao GD. Long-term changes in the personality and psychopathological profile of opiate addicts after nucleus accumbens ablative surgery are associated with treatment outcome. 2013;91:30–44.

Publication (Book chapters)

- ❖ Gao GD, Wang XL and He SM. Stereotactic Neurosurgical treatment of brain disorders associated with drug dependence. Minimally Invasive Neurosurgery by Jizong Zhao, People's Medical Publishing House, 2005: 546-551
- ❖ Gao GD. Stereotactic technique for the management of drug dependence. Operative techniques of Stereotactic Neurosurgery by Wang YH and Wu CY, People's Medical Publishing House, 2005: 305-317



Foundation

❖ This research has been supported by several grants

❖ In progress

Assigned program in the Eleventh
Five-Year Plan of China----clinical study
led by MHC

National Natural science foundation
of China----basic research on
DBS application to addiction

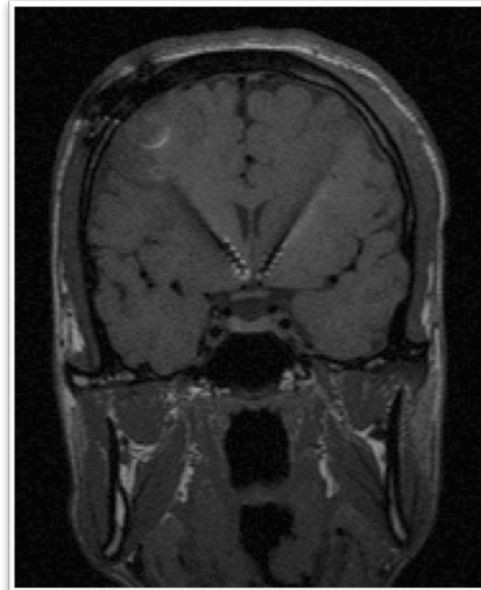
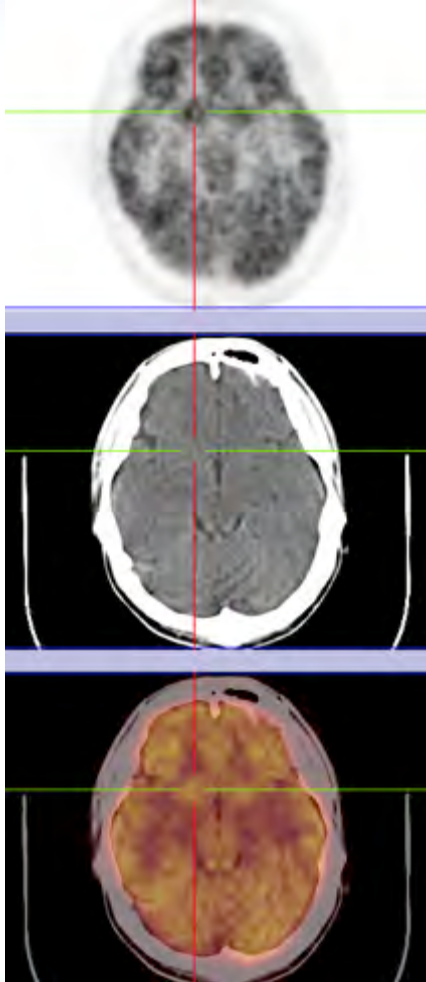
Shortage of ablation

- ❖ **Hard to accepted ethically**
 - irreversible injury
- ❖ **Natural reward, character change?**
- ❖ **Ablation intensity is difficult to control**
 - poor outcome if insufficient
 - more complication if severe
- ❖ **Addiction can be cured but lesions are permanent**

Prospect of DBS

- ❖ **DBS is a possible better way**
 - mimic the functional effect of lesion
 - non-invasive, reversible, adjustable
- ❖ **Addiction is prevalent and similar to psychiatric disorders**
- ❖ **More acceptable ethically and draw great interest**

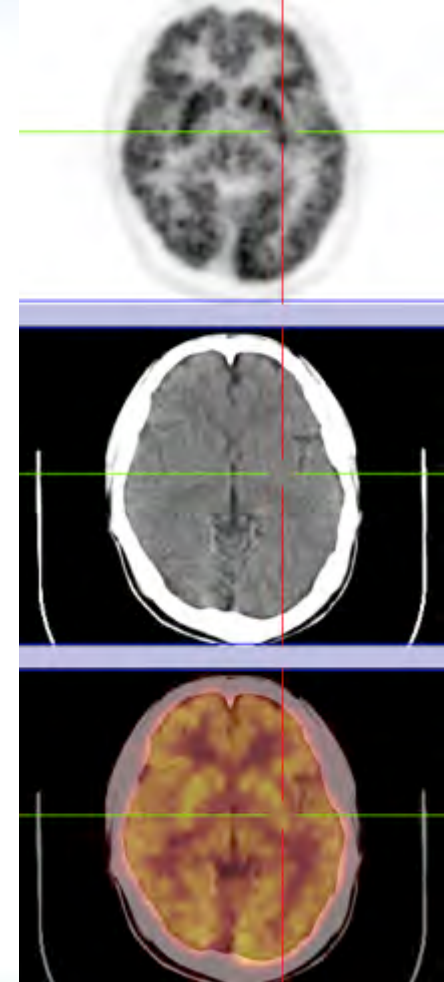
NAc-DBS for Drug Addiction



2011-04-20 First Case

2011-11-08 second Case

Both are effective





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唐都脑科医院
Tangdu Neurology & Neurosurgery Hospital

Thank You