Neurobiology Disease Midterm-2

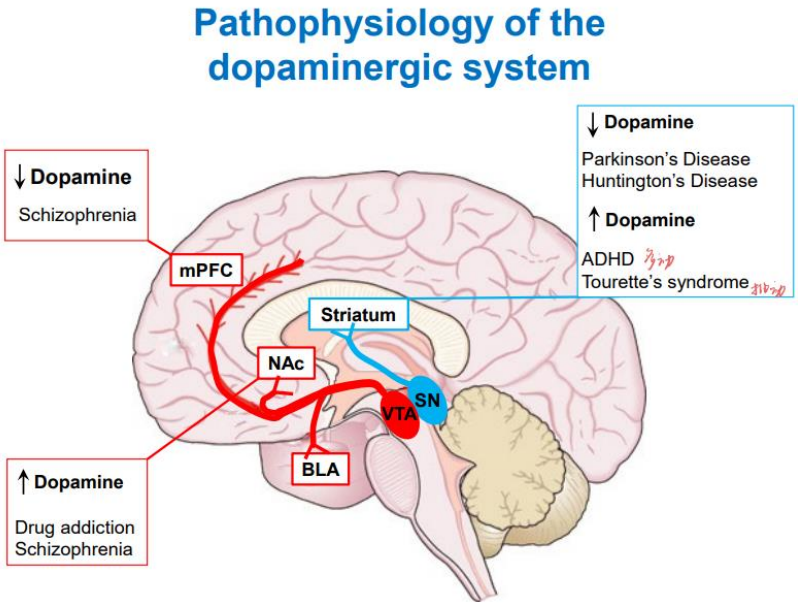
Reward Pathways in the Brain 170222

Neurotransmitter: Dopamine
DA lack → dopamine cells degenerate
Parkinson's Disease: dopamine cells degenerate

Dopamine neurons are located in the ventral midbrain[腹侧中脑]

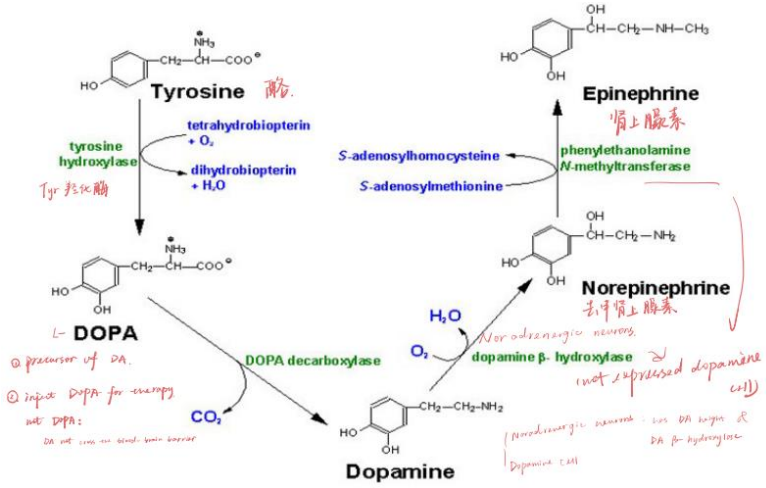
Dopaminergic Pathways

Pathways	Origin	Innervates[为(器官或其他身体部位)提供神经]	Function	
Nigro-striatal[黑质纹状体通路]	SNc	Dorsal Striatum CPu[背侧纹状体]	Control of Movement	
Mesolimbic[中脑边缘通路]	VTA	Ventral Striatum NAc, Ayg	Motivational Behavior	Schizophrenia
Mesocortical[中脑皮层通路]	VTA	Frontal Cortex (mPFC)[额叶皮层]	Learning and memory	

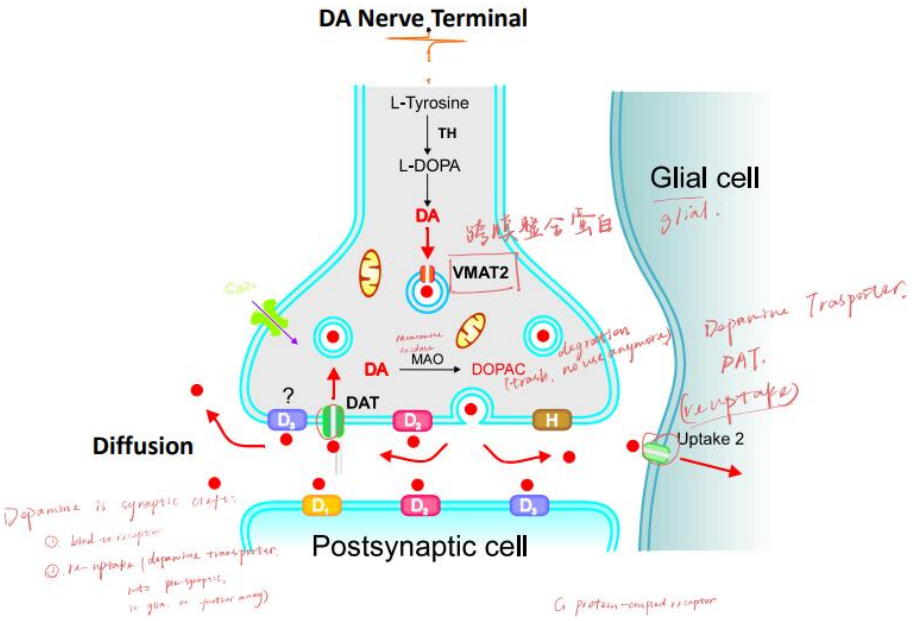


Dopamine Synthesis

Tyrosine hydroxylase[酪氨酸羟化酶] needed



Regulation of dopamine neurotransmission



Activation of D1 receptors increases the activity of AMPA receptors by PKA-mediated phosphorylation

Activation of D2 receptors decreases the activity of AMPA receptors by PKA-mediated phosphorylation

D1&D2 receptors balance each other

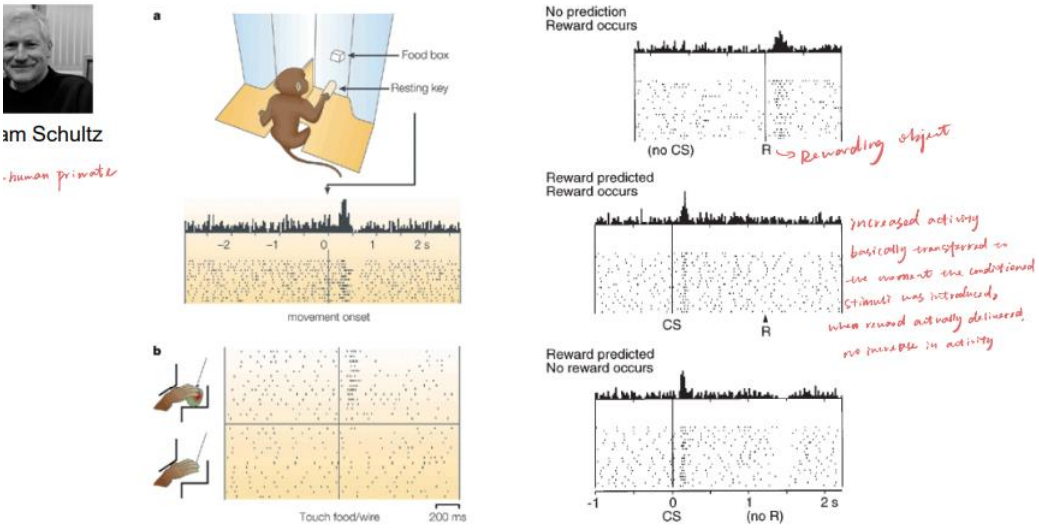
Dopamine is a neurotransmitter in the brain's reward system

nucleus accumbens (NAs): integration of reward signals in ventral striatum.

Discovery of the Brain Reward System

The discovery of intracranial self-stimulation (ICS) provided the first evidence for a brain 'reward' system: *When an animal is trained to deliver electrical shocks to certain regions of the brain (e.g. the VTA) it will press a lever to receive stimulation for extended periods at the expense of eating or drinking.*

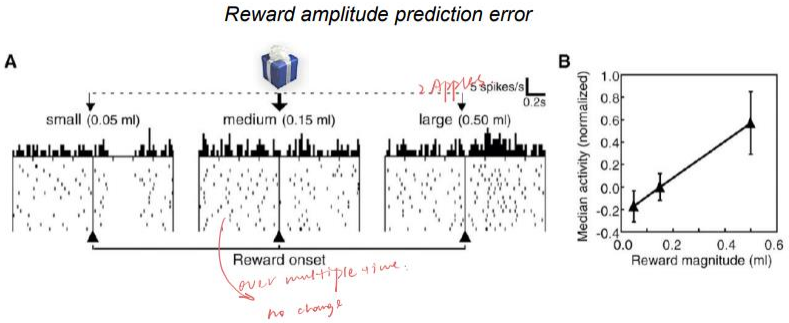
Responses of dopaminergic neurons in behaving primates following rewarding stimuli (Wolfram Schultz)



Phasic activation of midbrain dopamine neurons following food/liquid rewards and conditioned (CS), reward-predicting stimuli

Dopamine response = actual reward – expected reward

Phasic activity of dopamine neurons correlates with error of reward prediction



Larger than expected – increased activity of dopamine neurons
as expected – no change
Smaller than expected – reduced activity of dopamine neurons

fMRI – functional Magnetic Resonance Imaging

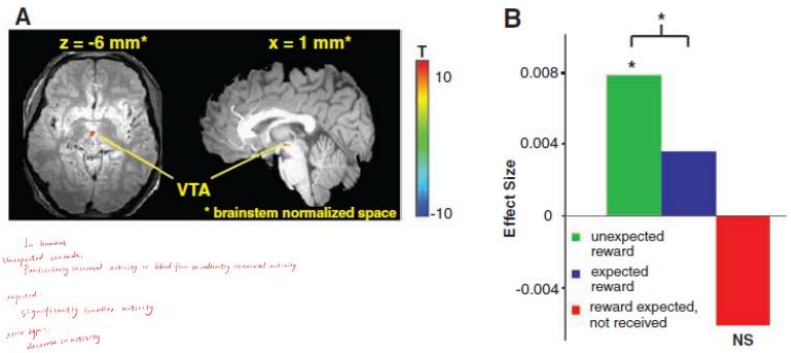
Measuring brain activity

BOLD fMRI (Blood Oxygen Level Dependent functional MRI): blood flow is associated with increased neural activity (indirect by the binding of Oxygen and hemoglobin), deoxyhemoglobin is paramagnetic and influences the MR signal unlike oxygenated hemoglobin.

Clinical use:

- Mapping the brain to plan a surgery
- Detect the effects of tumors, stroke, brain injury and diseases such as Alzheimer's

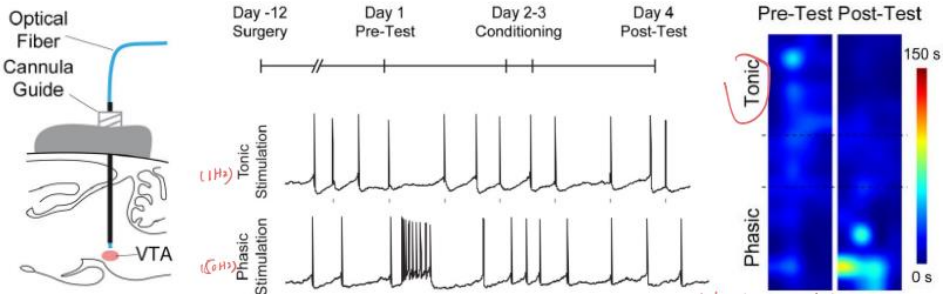
Reward-based learning – evidence from fMRI



Optogenetics: Controlling neural activity with light

Phasic firing in dopamine neurons is sufficient for behavioral conditioning

Express channelrhodopsin in VTA
Targeted dopamine cell: dopamine transporter Cre mouse line & TH(tyrosine hydroxylase) Cre mouse line

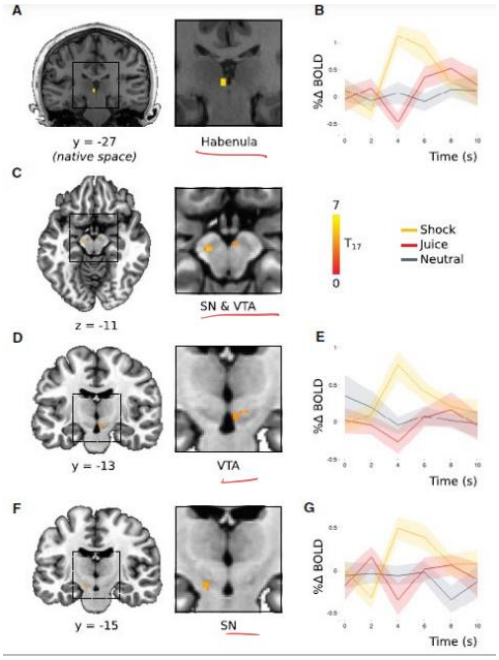


Phasic activation of DA neurons promotes preference for chamber associated with 50Hz stimulation.

Dopamine neurons can also be activated by negative experiences

footshock, airpuff...
→Not footshock, but the relief, turning off the electrical foot shock
→Not all dopamine cells are involved in reward, only in a particular location of the VTA, the activity rises. They project to different region, not to NAs, to the prefrontal cortex....to reinforce, warning...

Aversion Centers" in the brain? – evidence from fMRI



Take home

- Dopamine neuroanatomy and pathophysiology of dopamine system
- Dopamine biochemistry (synthesis, neurotransmission, receptors)
- Dopamine's role in reward and reinforcement learning
- fMRI
- Using optogenetics to study the dopamine system
- Brain regions involved in aversion-related behaviors

Drug Addiction 1 Cocaine 022222

Definition

'Compulsive out-of-control drug use despite serious negative consequences'
Addicts become progressively focused on obtaining, using a recovering from the effects of drugs, despite illness, disrupted relationships and failures in life roles.
Addiction is a cyclical, self-destructive pattern of behavior

Key Processes in Addiction

- Rewarding effects of drugs
- Adaptation to drugs – brain biochemistry and structure changes
- Disturbed decision making
- Craving associated with withdrawal – activation of stress axis

What happens during addiction?

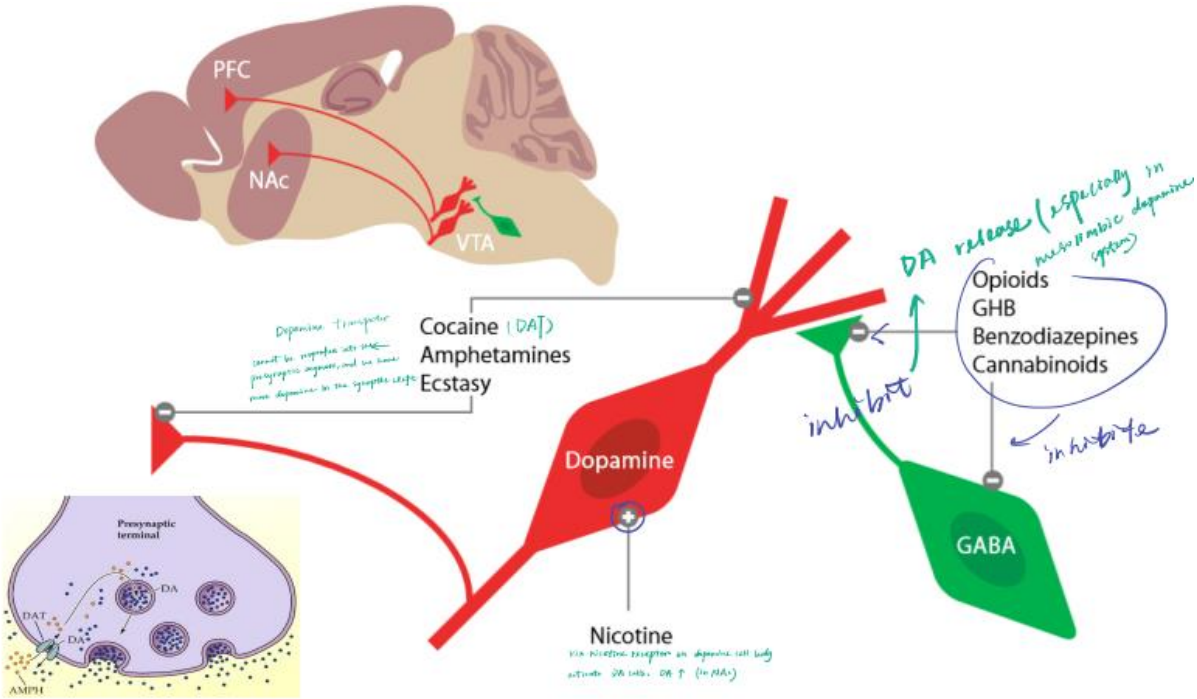
• When addictive drugs are used repeatedly, **molecular changes in the brain** promote continued drug taking that becomes increasing difficult for the individual to control.
• Addiction then follows a **chronic course**, in which periods of abstinence are followed by relapse to active drug use. **Relapse** is often triggered by associated or environmental cues.
• Addictive drugs can also produce **tolerance, sensitization and withdrawal.**

Tolerance: a decrease in the effect of a drug despite a constant dose, or a need to increase the dose to maintain a stable effect. Tolerance is developed to cocaine and heroin and can exacerbate[加剧] the molecular changes that lead to addiction.
Sensitization: Depending on the pattern of use, some drugs can produce sensitization (enhancement) of drug responses (e.g. cocaine, amphetamine).

Classes of drugs of abuse

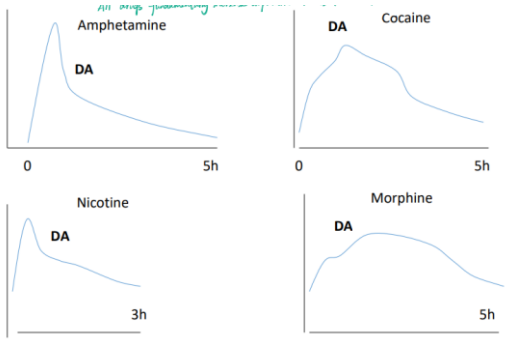
Stimulants	Amphetamines, cocaine, nicotine
Sedatives/Hypnotics[镇静/催眠]	Alcohol, barbiturates, benzodiazepines
Opiates	Morphine, heroin, oxycontin

Drugs of abuse activate the dopaminergic reward system and change the reward threshold



Cocaine, Amphetamines, Ecstasy function on DAT, dopamine transporter cannot be reuptake into the presynaptic anymore, and we have more dopamine in the synaptic cleft.
Nicotine: via nicotine receptor on dopamine cell body, activating DA cells in NAc, increase the DA.
Opioids, GHB, Benzodiazepines, Cannabinoids: inhibit GABAergic cells, which inhibit the DA cells, leading to DA release, especially in mesolimbic dopamine system.

Acute effects of addictive substances on NAc dopamine levels



All drugs fundamentally increase dopamine levels in the brain.

Drug use changes the brain in fundamental and long-lasting ways

- Addiction produces a change in brain structure and function (adaptation to the drug)
- Molecular changes in excitatory synapses on midbrain dopamine neurons
- This leads to changes in behaviors consistent with addicted states
- Addiction is therefore a form of drug induced neural plasticity

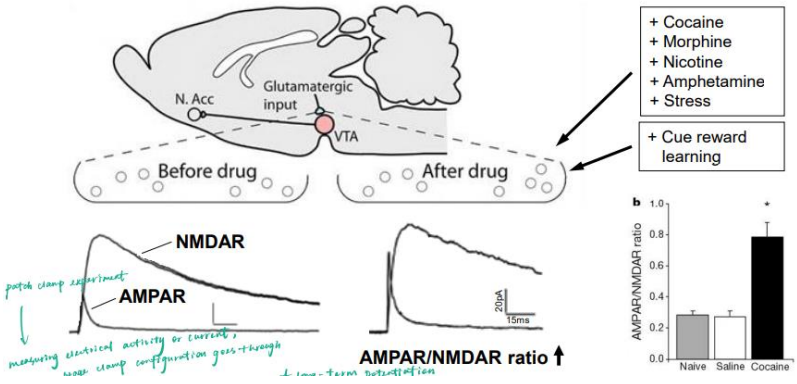
Subtypes of glutamate receptors in the brain

Ionotropic		
NMDA	AMPA	Kainate
NR1, NR2A-D, NR3A-B	GluR1-4	GluR5-7, KA1-2
Metabotropic		
Group 1	Group 2	Group 3
mGlu1,5	mGlu2,3	mGlu4,6-8

AMPAR/NMDAR →synaptic plasticity

There are some induced changes in plasticity happening at the synapse via the very simplified changes in current through NMDA and AMPA mediated glutamate receptors.

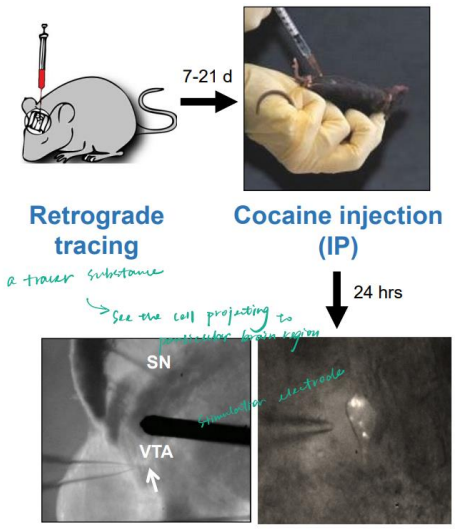
Drug-induced synaptic plasticity



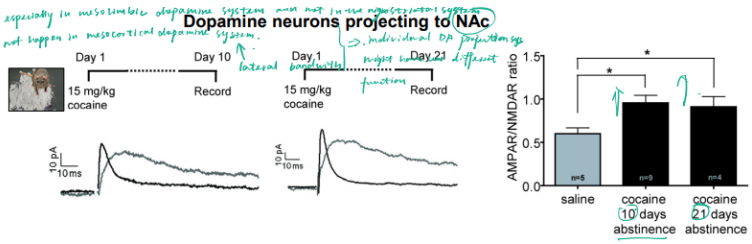
Synaptic potentiation of excitatory inputs on dopaminergic neurons following a single in vivo injection of cocaine

Patch clamp experiment: measuring electrical activity or current, in the voltage clamp configuration goes through certain ion channels, an indirect measure of long-term potentiation (because no ATP).

Studying synaptic plasticity in VTA dopamine neurons

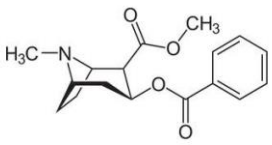


Long-lasting synaptic changes in excitatory synapses on dopamine neurons projecting to NAc by cocaine



Excitatory inputs to the DA or potentiate it after a single injection of cocaine, especially in mesolimbic dopamine system and not in the nigrostriatal system, not happen in mesocortical dopamine system
→individual DA projection system might have very different function.

Cocaine

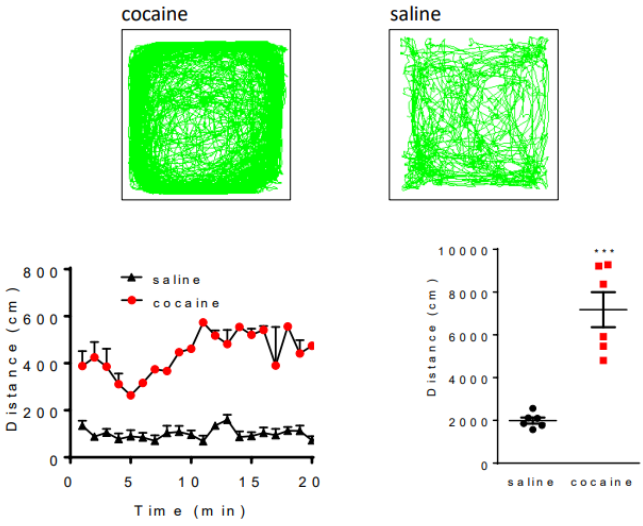


Effects and risks of cocaine use

Physical effects: Dry mouth, Sweating, Increased breathing and heart rate A single dose of cocaine has a rapid onset and last up to 30 mins
Good Feelings: • Alert • Energetic • Confident • Feelings of enhanced mental & physical powers
Bad Feelings: • Anxiety • Panic Attacks • Paranoia • Hallucinations • Fatigue & Depression (after)
Long-term effects:
• Restlessness[烦躁], nausea[恶心], hyperactivity[多动], insomnia, weight loss and exhaustion
• Psychological dependence and tolerance but no heroin-like withdrawal.
Risks:
• Impurities; Snorting: damages nasal membranes[损害鼻黏膜]; Smoking: breathing problems and voice loss; Injecting: Infections (Hepatitis[肝炎] & HIV)
• Respiratory or heart failure

• Pregnancy - babies are irritable, feed poorly, difficult to comfort

Cocaine administration increases locomotor activity in mice



Potential therapies for cocaine addiction

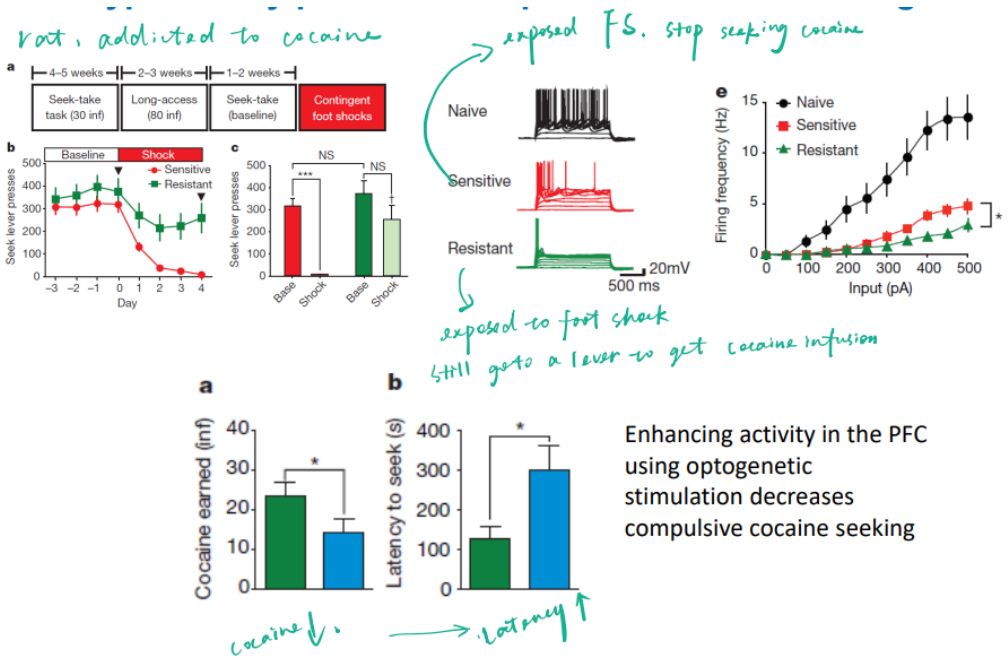
no really effective therapy method.

- Drug Addiction is considered to be a chronic, relapsing medical illness
- There are no current treatments for cocaine addiction (Pilot study using TMS; Terraneo et al., 2016)
- Addicts are usually weaned off but this is not a cure

Potential therapies need to:

- Prevent development addiction
- Treat withdrawal
- Prevent relapse (major problem)

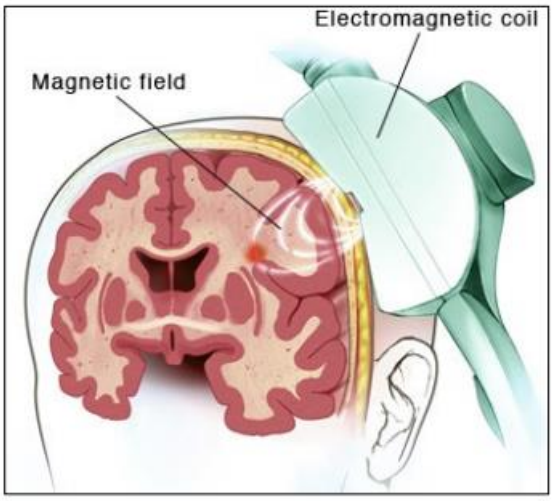
Using optogenetic discoveries to design and test a targeted treatment for cocaine addiction



Enhancing activity in the PFC using optogenetic stimulation decreases compulsive cocaine seeking

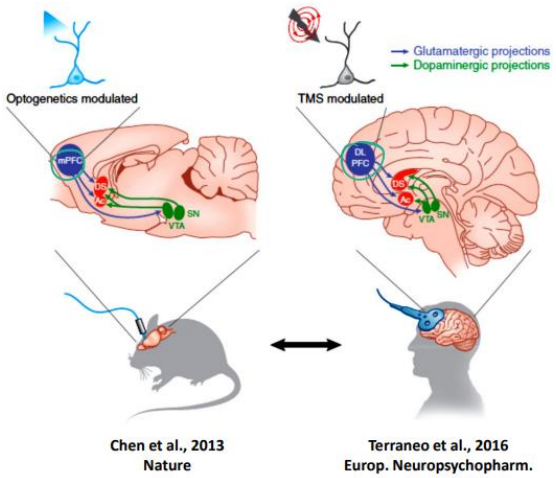
Rescuing cocaine-induced prefrontal cortex **hypoactivity** prevents compulsive cocaine seeking.

TMS = transcranial magnetic stimulation[经颅磁刺激]



- Treatments: neuropathic pain, schizophrenia, major depressive disorder (FDA), migraine (FDA)
- Mechanism: Electromagnetic induction[电磁感应]
- Targeting: Magnetic field pulse (2-3T) is directed at a specific brain region (cm scale)
- rTMS: repetitive pulses at 5-10Hz → potentiation-type plasticity?

Using optogenetic discoveries to design and test a targeted treatment for cocaine addiction



Transcranial magnetic stimulation of dorsolateral PFC[背外侧 PFC 的经颅磁刺激] reduces cocaine use

Take home

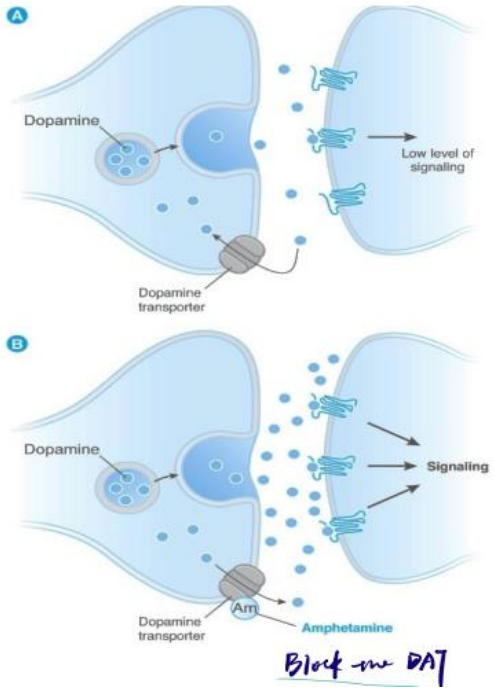
- Definition of “Addiction”
- Classes of drugs of abuse
- How do drugs of abuse interact with the dopamine system?
- Drug-evoked synaptic plasticity
- What are the effects of cocaine?
- Current and potential new treatments for cocaine addiction (e.g., TMS)

Drug Addiction 2 Amphetamines 240222

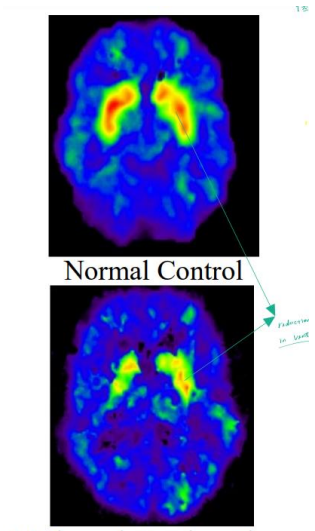
Effects and risks of amphetamine use

Physical effects: Dilates pupils[扩张瞳孔], increases breathing and heart rate
A single dose of amphetamine last up to 3-4 hrs, 2 to 3 days to feel normal
Good Feelings: • Alert • Energetic • Confident • Feelings of enhanced mental & physical powers
Bad Feelings: • Anxiety • Restlessness and irritable • Panic Attacks • Paranoia[偏执] and Hallucinations • Sleeplessness • Fatigue[疲劳] & Depression (after)
Long-term effects:
• Restlessness, hyperactivity, insomnia, aggressive behavior, mood swings, weight loss and exhaustion
• Psychological dependence and tolerance
Risks:
• Impurities also smoking- breathing problems and voice loss; Injecting- infections (Hepatitis & HIV)
• Sleeping and eating disorders, and reduced immune resistance

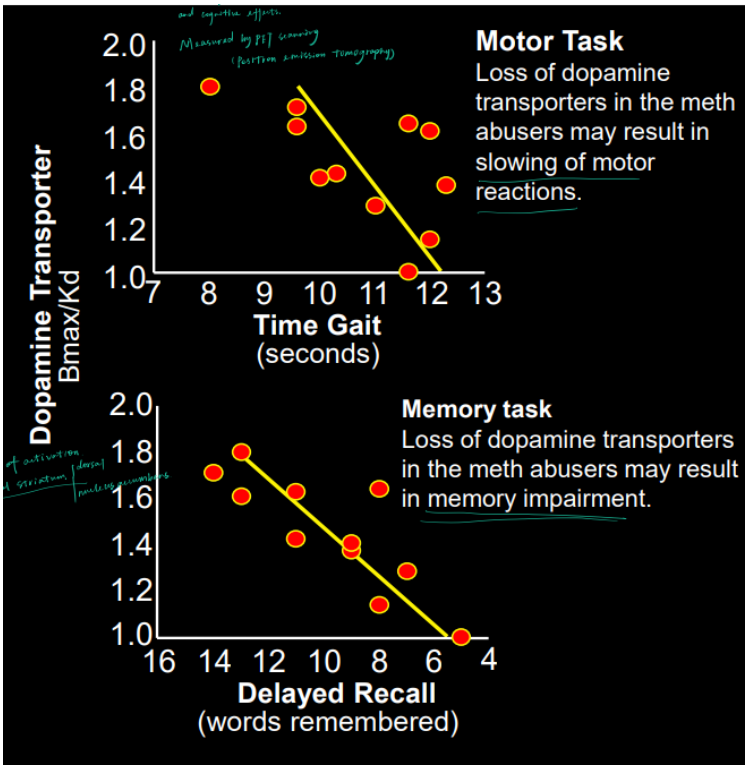
Mechanism of action of amphetamine



Dopamine transporters in methamphetamine[甲基苯丙胺] abusers



reduction of activation in ventral striatum, both in dorsal and nucleus accumbens



Methamphetamine has profound negative effects on both the physically and cognitive effects.
Measured by PET scanning (position emission tomography)
PET: position emission tomography, measuring the activity of a certain molecule by injecting a radio ligand/tracer to visualize (measure gamma rays using PET scanner → heat map) the molecule.

Ecstasy/MDMA

Schedule 1 drug: MDMA, psychedelics[迷幻药], High potential for addiction potential, no therapeutic use.
Schedule 2 drug: Cocaine, amphetamine

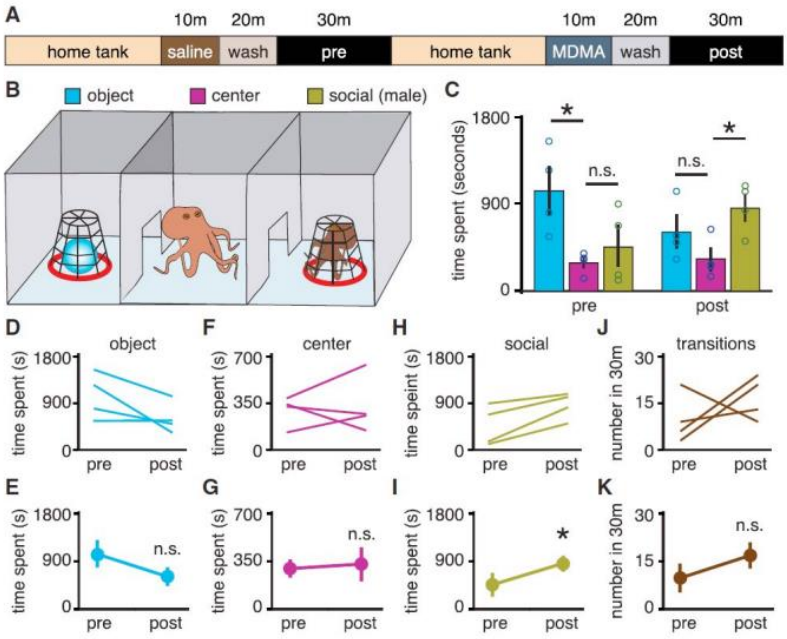
MDMA: a fully synthetic drug, with properties of amphetamine and hallucinogen.

- MDMA = 3,4-methylene dioxy-N-methyl amphetamine (Schedule 1)

- Shares properties of amphetamines and hallucinogens
- Associated with electronic music dance parties (“raves”)
- May have psychotherapeutic value (empathogens) [心理治疗的价值]
- Associated with 5-HT (serotonin) neurotoxicity

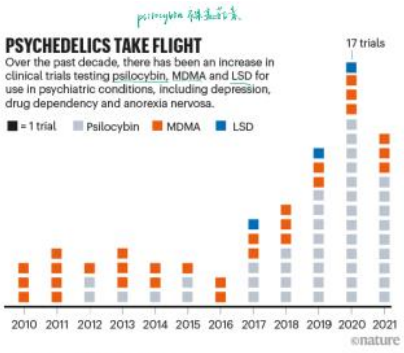
  MDMA interacts with the serotonin system, basically leading to toxicity within the serotonin dopamine system. A direct ligand at the serotonin transporter, responsible for the reuptake of serotonin. Blocks the transporter and increase serotonin levels.
- Ecstasy – hangover: Depression, Memory Impairment, Difficulty concentrating Causes: Neurotoxicity, acute decrease in 5HT

Prosocial Effects(亲社会效应) of MDMA in Octopus bimaculoides[章鱼，反社会の物]



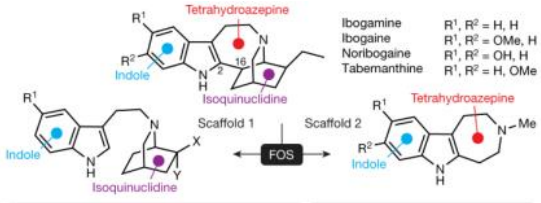
The rise of psychedelic psychiatry[迷幻精神病学]

Clinical trials testing psilocybin, MDMA and LSD for use in psychiatric conditions, including depression, drug dependency, and anorexia nervosa.



Tullis, 2021; Nature

High-toxicity



redesign to

Function-oriented synthesis to identify the key structural elements of the therapeutic potential of **ibogaine → tabernanthalog**

Cameron et al., 2019; Nature

Function-oriented synthesis to identify the key structure elements of the therapeutic potential of ibogaine→ tabernanthalog
ibogaine: hallucinogenic potential & toxicity, but can decrease the withdraw symptoms of drug addiction
redesign totabernanthalog: similar effects in the treatment of drug addiction and lacks the toxicity potential.

Opiates(addictive pain killer)

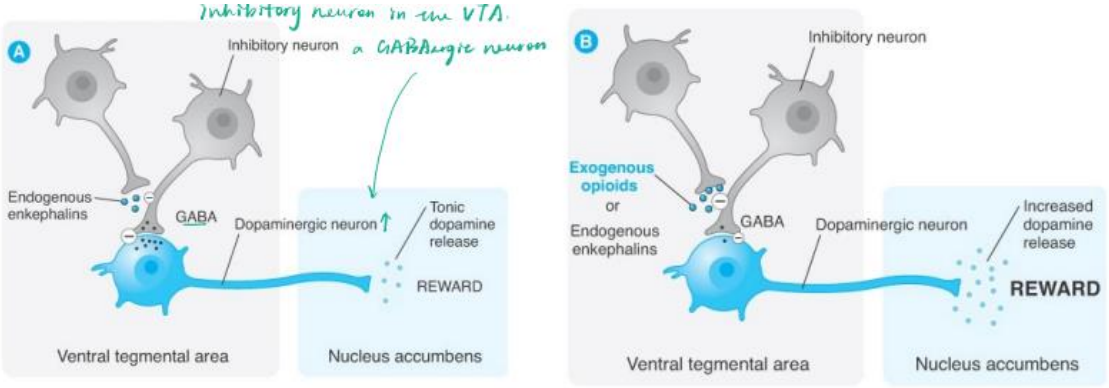
• Opium extracts isolated from opium poppies (Papaver somniferum)
• Friedrich Serturner isolated the primary active ingredient in opium and named in morphium, now better known as morphine
• Heroin synthesized in 1897 by Bayer (Germany)
• Heroin was sold in Germany until 1958 as antitussive[镇咳药] and analgesic[镇痛药]
• Synthetic analogs of morphine used in clinical settings as analgesic

Opiate receptor subtype

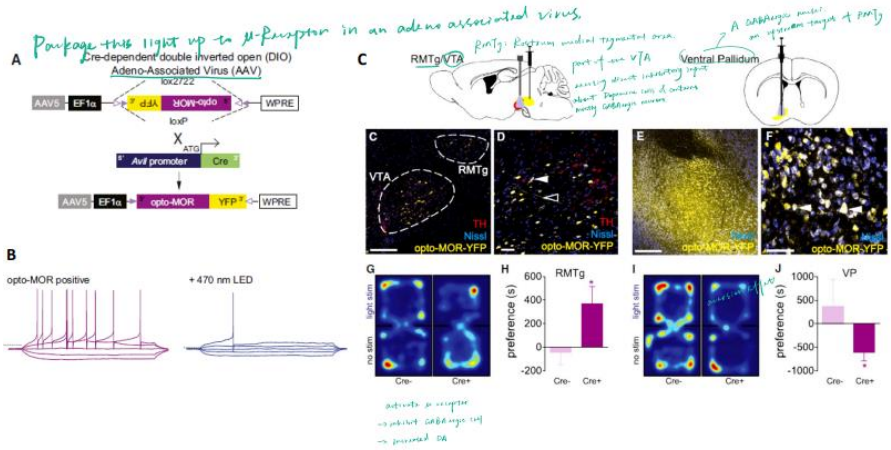
μ (mu) – high affinity for **morphine and related opiates**
δ (delta) – similar distribution to μ
κ (kappa) – named for high affinity for ketocyclazocine, high affinity for endogenous opiate dynorphin A

Reward pathways: Role of opiates

Mesolimbic system has been associated with its rewarding effect.
Opioid receptor expressed on inhibitory neuron in the VTA, a GABAergic neuron.



Generation and characterization of a new photosensitive mu-opioid-like receptor (opto-MOR)



A: Package this light-up to μ-Receptor in an Adeno-Associated Virus (AAV)
C: **RMTg/VTA:** RMTg (Rostromedial tegmental area), part of the VTA, exerting direct inhibitory input about dopamine cells and containing mostly GABAergic neurons.
Ventral Pallidum: a GABAergic nuclei, an upstream target of RMTg.
Activate μ receptor → inhibit GABAergic cell → increased DA

Effects of opiates

Analgesia, Respiratory, depression, Euphoria, Relaxation and sleep, Tranquilization, Blood pressure↓, Constipation, Pupil constriction, Flushed and warm skin, Drying of secretion.

OxyContin: addictive & high potential to abuse

Opiate overdose symptoms and treatment

- (Respiratory depression) Ventilate the patient with a bag valve mask device via a basic airway adjunct and start CPR
- Check his heart rhythm on an EGG monitor, possibly defibrillate (除顫)
- administer naloxone (opioid receptor antagonist)

Withdrawal symptoms are opposite of acute actions of opiates

Acute action	Withdrawal sign
Analgesia	Pain and irritability
Respiratory depression	Panting and yawning
Euphoria	Dysphoria and depression
Relaxation and sleep	Restlessness and insomnia
Tranquilization	Fearfulness and hostility
Decreased blood pressure	Increased blood pressure
Constipation	Diarrhea
Pupil constriction	Pupil dilation
Hypothermia	Hyperthermia
Drying of secretions	Tearing, runny nose
Reduced sex drive	Spontaneous ejaculation
Flushed and warm skin	Chilliness and "gooseflesh"

Withdrawal: not life threatening
Treatment: symptomatically with antiemetic, antidiarrheal, muscle relaxant, NSAIDS, BZD[对症止吐药、止泻药、肌肉松弛药、非甾体抗炎药、BZD]

Treatment – Opiate use disorder

- Support, education, skills building, psychiatric and psychological treatment
- Methadone (opioid substitution)
  - Mu agonist
  - needs to be enrolled in a certified opiate substitution program
- **Naltrexone**
  - opioid antagonist

Smoking, tobacco & nicotine

- **Prevalence**: 22.3% of Americans smoke. Equivalent to 67.2 million people in USA
- **Lifetime risk of Smoking**: 1 in 2 chance of dying from a smoking-related disease.
- **Worldwide prevalence**: 1.3 billion people smoke worldwide.
- **Average life years lost for Smoking**: 12 years
- **Organs Affected by Smoking**: Nose, throat, larynx, trachea, bronchi, and lungs (respiratory tract).
- **Conditions**: Chronic bronchitis, Emphysema, wide variety of cancers, linked to heart disease, linked to artery disease

- **Deaths**: 440,000 annual deaths in US each year are smoking-associated (CDC)

Effects of nicotine

Nicotine has predominantly [主要是] stimulant effects.

Central nervous system

- Pleasure
- Arousal, enhanced vigilance [唤醒，提高警惕]
- Improved task performance
- Anxiety relief

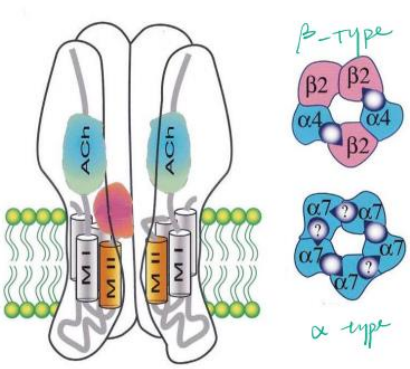
Cardiovascular system

- ↑ Heart rate [心率]
- ↑ Cardiac output [心输出量]
- ↑ Blood pressure [血压]
- Coronary vasoconstriction [冠状血管收缩]
- Cutaneous vasoconstriction [皮肤血管收缩]

Other

- Appetite suppression [食欲下降]
- Increased metabolic rate
- Skeletal muscle relaxation [骨骼肌放松]

Nicotine binds to DA cell body on Nicotinic Acetylcholine Receptors (nAChR)



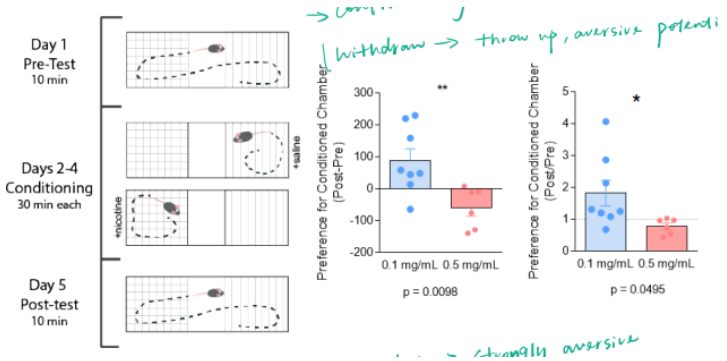
•Ligand gated ion channel

- •Pentamer
- •α and β subunits
- •Twelve known subunits $\alpha_{2\text{-}10}$ and $\beta_{2\text{-}4}$
- •Two main types present in brain
  - •α_7 nAChR subtype
    - •High affinity for α-bungarotoxin [银环蛇毒素]
  - •$\alpha_4\beta_2$ nAChR subtype
    - •High affinity for nicotine
    - •Believed to upregulate in response to nicotine

Behavioral effects of nicotine are dose dependent

30µl infusions every 5 minutes based on weight, 6 infusions over 30 minutes

→ Rewarding dose: 0.75 mg/kg Aversive dose: 3.75 mg/kg



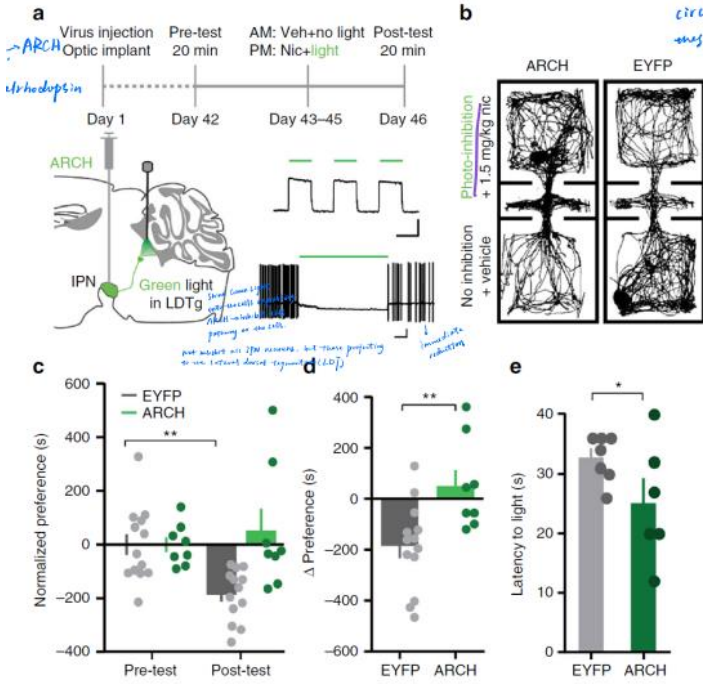
small does→ high rewarding→continuously intake

→withdraw→throw up, aversive potential

High does→strongly aversive→block the use of frugs

Inhibition of IPN terminals in LDT blocks nicotine conditioned place aversion

an example: a brain circuity might be important for the nicotine induced aversive behavior



a: Express an inhibitory opsin[抑制性视蛋白] (ARCH), an opposite thing of channelrhodopsin.

shine green light onto the cells expressing ARCH → inhibit this pathway or the cells.

not inhibit all IPN neurons, but those projecting to the ***lateral dorsal tegmentum*** *(LDT, 外侧背被盖)*

Nicotine tolerance & withdrawal

- Mild tolerance to behavioral and cardiovascular [心血管] effects
- **Upregulation of receptors** has been interpreted as a compensation to desensitization of nicotinic acetylcholine receptors, and this prolonged desensitization has been proposed as the mechanism of chronic tolerance to nicotine
- Withdrawal may start after as little as one hour, may last for as long as several months, can include:
  – Craving – Irritability – Anxiety – Dysphoria – Anger
  – Difficulty concentrating – Restlessness – Impatience – Increased appetite, weight gain – Insomnia

Treatment options

- Behavior modification

- Substitute nicotine
  Nicotine gum/ Nicotine patches/ Nicotine inhaler/ Nicotine nasal spray
- Nicotine antagonist
  Bupropion

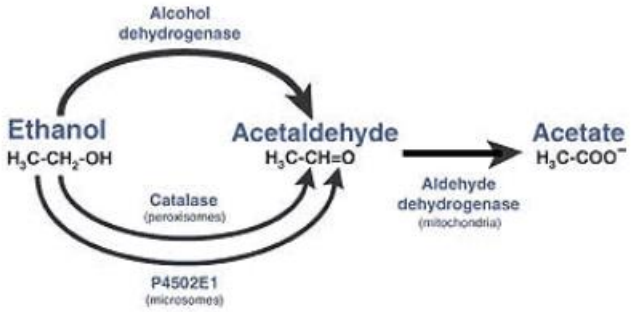
Alcohol consumption

- **Tissue damage** – alcohol is an irritant[刺激性] to the mouth, throat, and stomach and can raise the risk of cancers to these structures
- **Liver Damage** – the liver can be overwhelmed by fatty acid, causing it to swell and lose its ability to filter the body of other toxins
- **Brain damage and dependence** – alcohol can permanently damage brain cells, particularly in brains that are still developing and maturing (the brain does not finish maturing until age 20-25)
- **Weight gain** – alcohol has 7 calories per gram. This is almost as high as pure fat (9 Cal) and higher than carbohydrates (4 Cal/g)
- **Skin Damage** – the conversion of alcohol into acetaldehyde causes inflammation.
  Excess consumption will cause excess inflammation that can lead to the rupture of blood vessels in the skin creating blotchy scarring.
- **Accidents** – impaired judgment, lost coordination, and an increased sense of confidence is a deadly and all-too-often fatal combination.

Alcohol addiction treatment

Alcohol processing in the liver:

1. Alcohol arrives at the liver via the bloodstream
2. ADH turns alcohol into acetaldehyde
3. ALDH converts acetaldehyde into acetate
4. Acetate is converted into CO_2, H_2O, and fatty acids by liver cell mitochondria. If fatty acids accumulate too fast, cirrhosis can occur



Disulfiram[双硫仑](using aversion potential as a treatment): an aversion-based pharmacotherapy[药物疗法] for alcohol addiction

Inhibits ALDH to allow **acetaldehyde accumulation**, which is associated with adverse side effects: Nausea[恶心], vomit[呕吐], headaches, chest pain after only five to ten minutes after drinking.

Take home

- What are amphetamines and how do they influence the dopamine system?
- Effects of MDMA on serotonin system and their influence on social behavioral
- What are opiates? Effects on CNS?
- Role of opiates on the reward system
- Different types of opiate receptors

- Opiate overdose and withdrawal symptoms
- Effects of nicotine on the brain (IPN to LDT) and animal behavior (aversive effects of nicotine and its brain circuitry)
- Treatment of nicotine and alcohol addiction

Depression

- If untreated, depression leads to suicide in about 15% of the people it affects
- Depression is the leading cause of disability and premature death in adults and is predicted to be the leading cause of disability in people of all ages by the year 2020
- 6.7% of adults in the US (30% severe)
- 11.2% of 13-18 yr. old in the US (3.3% severe)
- Women are affected twice as often as men
- Cost to society: $83+ billion per year

Risk factors

• Genetic risk (heritability ~40%)
• Stressful life events
• Disease genes unknown; can be idiopathic; drug side effects; secondary to systemic illness[全身性疾病] (e.g., stroke)

Depression symptoms

• **Motivation** Apathy[冷漠的], loss of energy and interest: things seem pointless, hopeless, worthlessness
• **Emotional** Low mood, emptiness[空虚], anger or resentment[怨恨], anxiety, shame, guilt, negative views, guilt
• **Cognitive** Poor concentration, negative ideas about the self, the world and the future.
• **Behavior** Lowered activity, social withdrawal, agitation[激动] or retardation[迟缓]
• **Biological** Sleep disturbance, loss of appetite, loss of weight, changes in circadian rhythms[昼夜节律], hormones and brain chemicals.

Types of depression

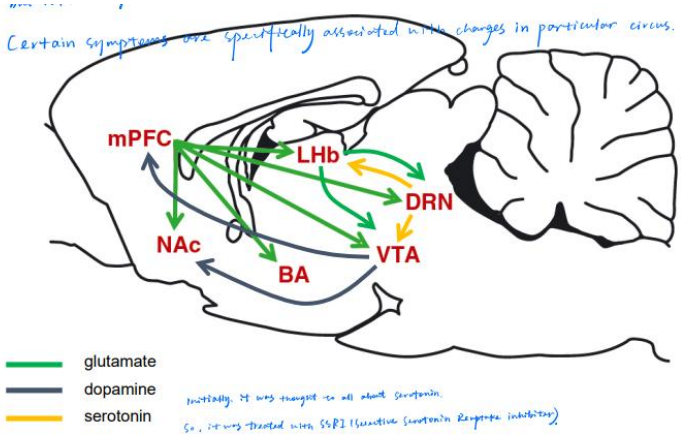
- Major depression
- Chronic depression (Dysthymia)
- Atypical depression
- Bipolar disorder/Manic depression
- Seasonal depression (SAD)

Diagnosis of depression

- Duration > 2 weeks depressed mood or marked loss of interest or pleasure in normal activities
- Plus 4 of:
  i. Significant change in weight
  ii. Significant change in sleep pattern
  iii. Agitation or retardation
  iv. Fatigue or loss of energy
  v. Guilt / worthlessness
  vi. Can’t concentrate or make decisions
  vii. Thoughts of death or suicide

Dysregulated circuits in depression

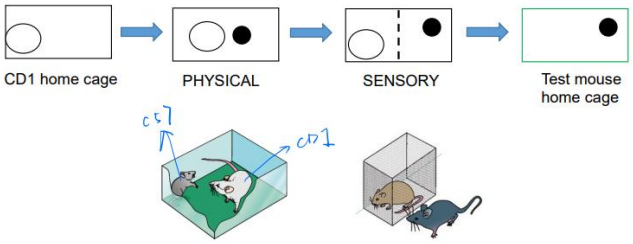
A disease is not associate with a single neurotransmitter, but rather a system. Certain symptoms are specifically associated with changes in particular circuits.



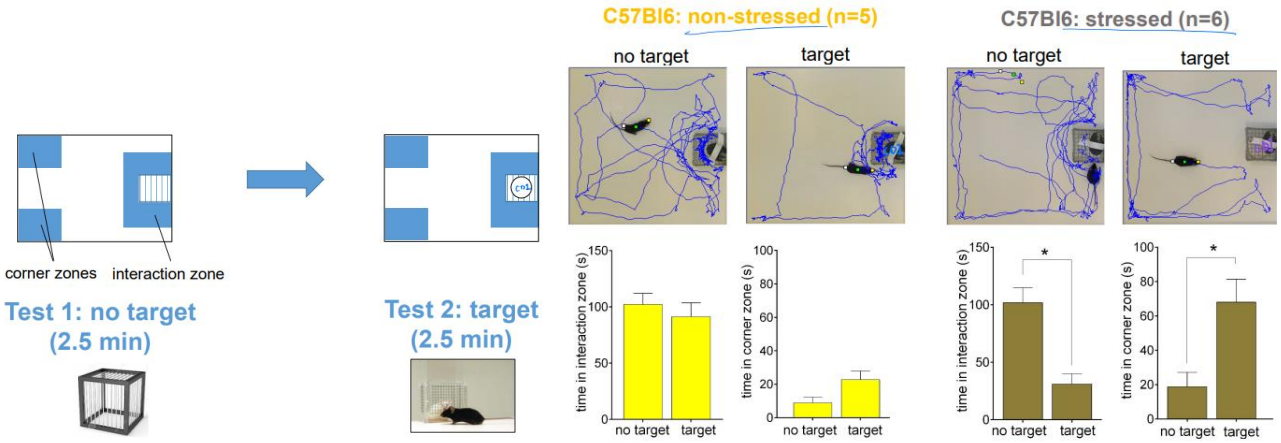
Initially, it was thought to all about serotonin, so it was treated with SSRI (Selective Serotonin Reuptake Inhibitor) to increase the serotonin in the brain.

Animal models of depression

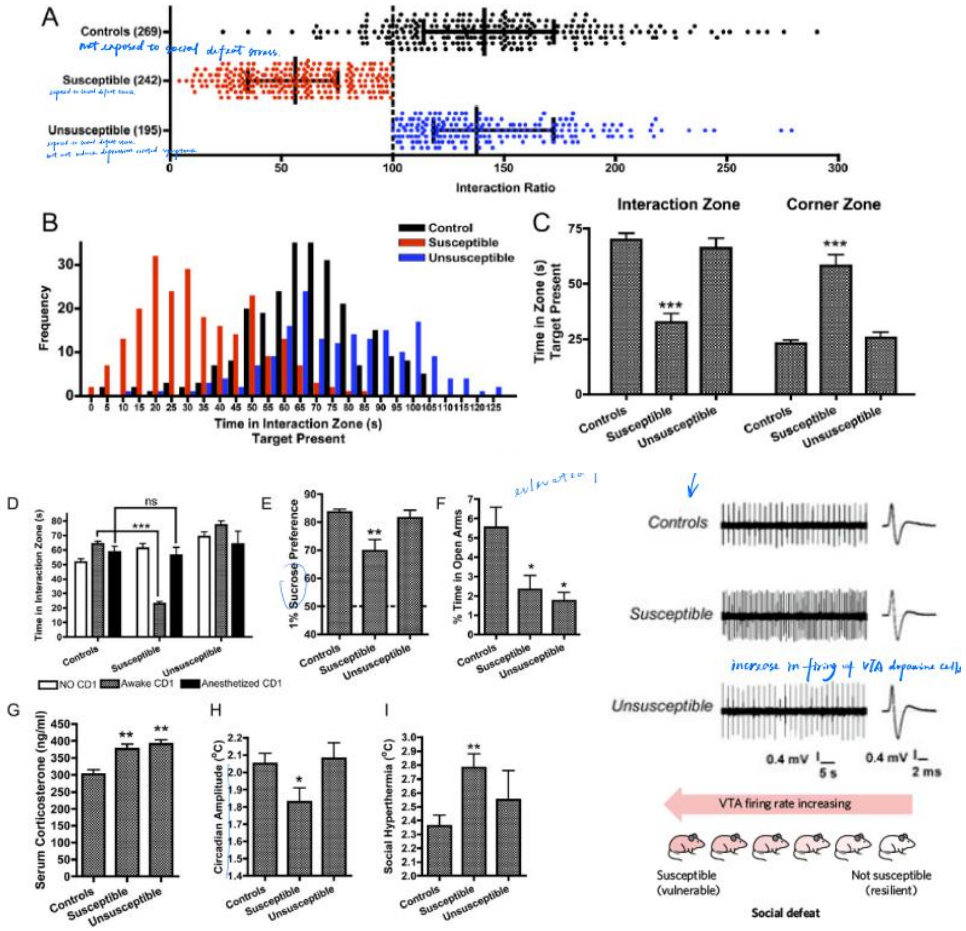
Inducing depression-related behaviors in rodents: social defeat; CMS; Restraint; Learned helplessness
Assessing depression-related behaviors in rodents: immobility; Sociability; Helplessness; Exploration; Anhedonia



Social defeat stress is used as an animal model of depression



Social interaction test for assessing depression-related behavior in mice



Susceptible and unsusceptible phenotypes

Controls: not exposed to social defeat stress

Susceptible: expose to social defeat stress, inducing depression related symptoms

Unsusceptible: expose to social defeat stress, but not induce depression related symptoms

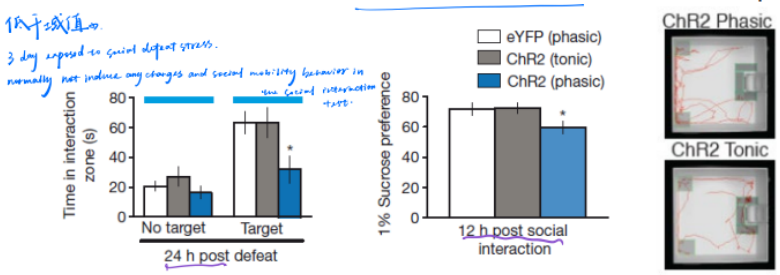
The underlying changes in behavior associated with changes in the VTA cell activity. In unsusceptible ones, the firing of VTA dopamine cells increases.

Light stimulation of VTA dopamine neurons induces a depression phenotype

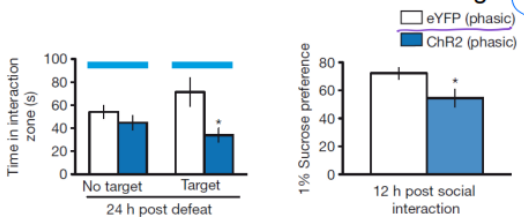
Subthreshold (3d) exposed to social defeat stress normally not induce any changes in social mobility behavior in the social interaction test.

10d social defeat stress: VTA DA stimulation changes from resilient to susceptible

- Subtreshold social defeat stress: VTA DA stimulation induces susceptibility



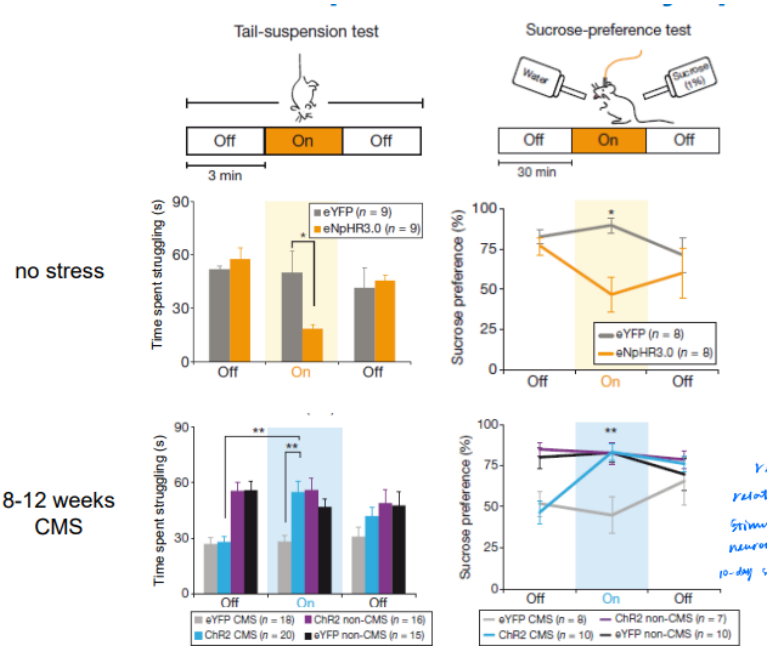
- 10d social defeat stress: VTA DA stimulation changes resilient → susceptible



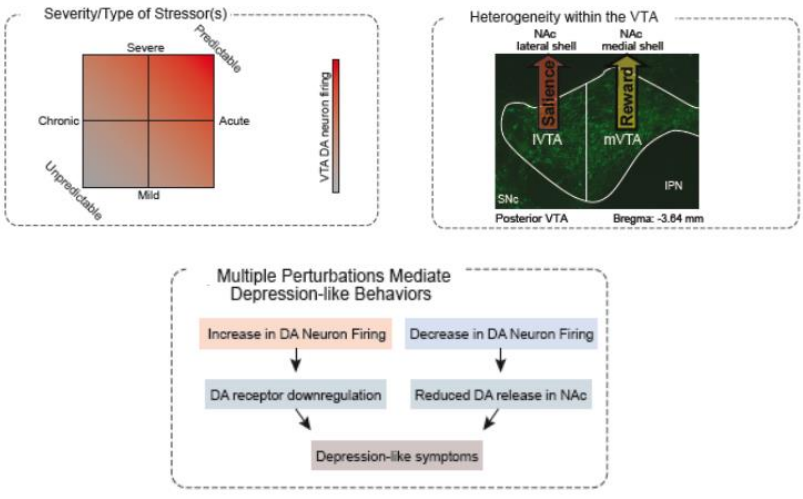
Chronic mild stress as an animal model of depression

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 1			Day: white noise Night: tilted cage	Day: shaking Night: wet bedding	Day: strobe light Night: food deprivation	Light cycle inversion	Light cycle inversion
Week 2	Day: crowded housing Night: tilted cage	Day: strobe light Night: water deprivation	Day: shaking Night: bedding removal	Day: bobcat urine Night: tilted cage	Day: crowded housing Night: wet bedding	Light cycle inversion	Light cycle inversion
Week 3	Day: bobcat urine Night: bedding removal	Day: crowded housing Night: wet bedding	Day: strobe light Night: food deprivation	Day: shaking Night: bedding removal	Day: white noise Night: tilted cage	Light cycle inversion	Light cycle inversion
Week 4	Day: strobe light Night: food deprivation	Day: shaking Night: bedding removal	Day: crowded housing Night: tilted cage	Day: bobcat urine Night: wet bedding	Day: white noise Night: water deprivation	Light cycle inversion	Light cycle inversion
Week 5	Day: bobcat urine Night: wet bedding	Day: crowded housing Night: food deprivation	Day: shaking Night: bedding removal				

Bidirectional control of dopamine neurons modulates depression-related symptoms

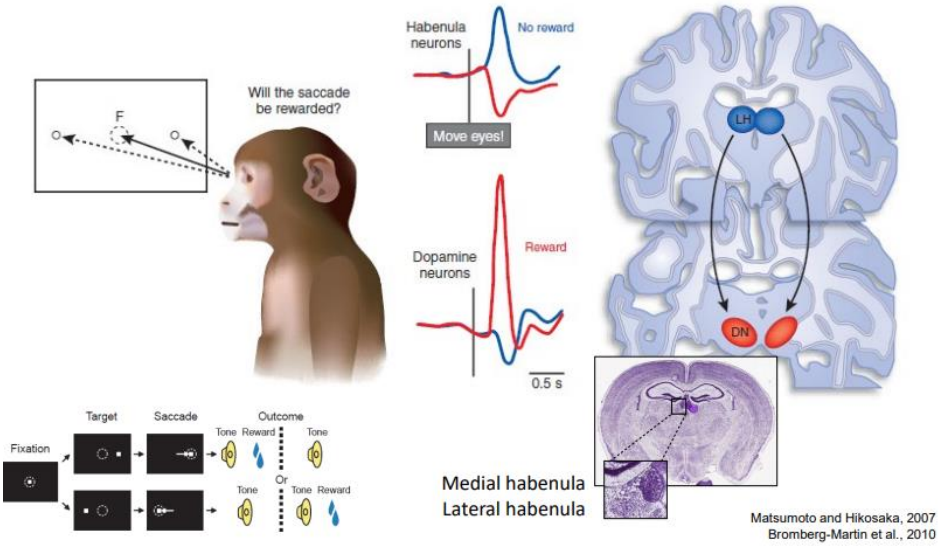


Duration, severity and type of stressors may generate specific behaviors

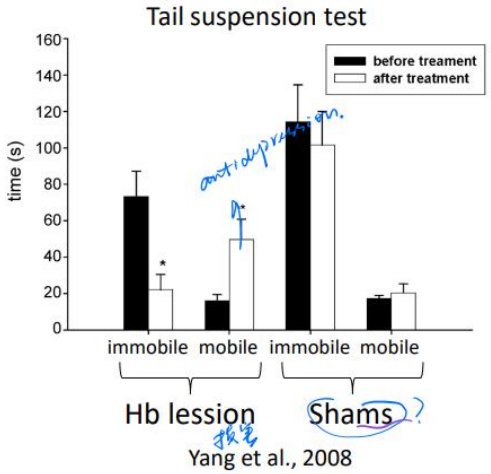


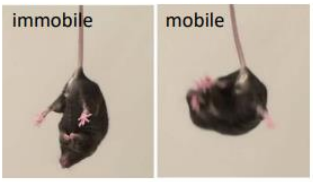
Lateral habenula neurons carry negative reward signals

activated after aversive stimuli, inhibited after rewarding stimuli.

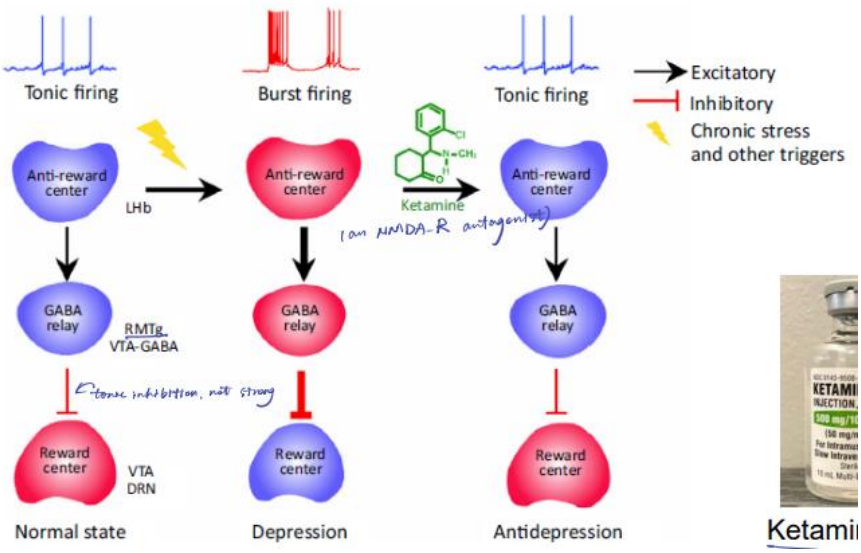


Relevance of lateral habenula hyperactivity in depression-like states





A conceptual model of how depressive state and ketamine bidirectionally regulate burst firing of lateral habenula neurons



Ketamine (an NMDA-R antagonist) for depression:

- immediate effect with an anti-depression effect.
- more potent compared to SSRI
- S ketamine for nasal spray

Depression Treatments / Medications

Popular types of antidepressant medications include (SSRI):

- Fluoxetine (Prozac)
- Citalopram (Celexa)
- Paroxetine (Paxil)
- Sertaline (Zoloft)

SSRIs side effects:

- Nausea/vomiting
- Drowsiness or somnolence
- Headache
- Dizziness
- Changes in sexual behavior

Many disappear within 4 weeks (adaption phase; usually no anti-depressive effect in this phase)

Side effects more manageable compared to MAOIs

Alternative Treatments:

- **Psychotherapy**

Two main types of psychotherapies-cognitive-behavioral therapy (CBT[认知行为疗法]) and interpersonal therapy (IPT,人际关系疗法) have been shown to be effective in treating depression by teaching new ways of thinking and behaving.

- **Electroconvulsive (high relapse rate) Therapy**

Can provide relief for people with severe depression who have not been able to feel better with other treatments.

- **Deep Brain Stimulation**

Medial forebrain bundle, nucleus accumbens, habenula, thalamus anterior gyrus cinguli (Brodman area Cg25)[内侧前脑束、伏隔核、缰核、丘脑扣带前回（布罗德曼区 Cg25）]

Serotonin and norepinephrine [去甲肾上腺素] reuptake inhibitors (SNRIs) are similar to SSRIs and include:

- Venlafaxine (Effexor)
- Duloxetine (Cymbalta)

MAO inhibitors: Tranylcypromine

Atypical: Bupropion, Mirtazapine
Everyone reacts differently. There is no one-size-fits-all approach to medication.

Take home

- Depression: types, symptoms, diagnosis, treatment
- Animal models of depression and assays to test depression-related behaviors
- Neurobiology of depression in the dopamine system (social defeat vs. CMS)
- Role of the lateral habenula in depression
- SSRIs and Ketamine in depression treatment

Bipolar Disorder

- Life time prevalence 0.4 – 1.6%
- Characterized by episodes of
  Depression, mania or mixed states separated by periods of normal moods
- Mania[狂躁]
  Features include elevated expansive euphoric mood, irritability, hyperactivity, decreased need for sleep, disorganized behavior, delusions, hallucinations and functional impairment

Bipolar Disorder Treatment

Lithium:
Side effects/drawbacks: Blood levels drawn frequently, Weight gain, Increased thirst, increased urination[排尿增加], water retention, Nausea[恶心], diarrhea[腹泻], Tremor[震颤], Cognitive dulling (mental sluggishness[精神迟钝]), Dermatologic conditions[皮肤病], Hypothyroidism[功能减退], Birth defects[出生缺陷]
How does Li+ act? Bipolar Disorder Treatment Unknown. All ideas about Li+ assume an intracellular target (intracellular concentrations of Li+ are probably several mM). Some ideas about Li+ involve enzyme inhibition.

Anxiety

Normal vs. pathologic anxiety

- Normal anxiety is **adaptive**. It is an inborn response to threat or to the absence of people or objects that signify safety can result in cognitive (worry) and somatic (racing heart, sweating, shaking, freezing, etc.) symptoms.
- Pathologic anxiety is anxiety that is **excessive**, impairs function.

Anxiety disorders

- Specific phobia [特定恐惧症]
  Marked or persistent fear (>6 months) that is excessive or unreasonable cued by the presence or anticipation of a specific object or situation
  - *Anxiety must be out of proportion to the actual danger or situation*
  - *It interferes significantly with the persons routine or function*
- Social anxiety disorder (SAD) [社交焦虑症]
- Panic disorder (PD)
- Generalized anxiety disorder (GAD) [广泛性焦虑症]
  - *Excessive worry more days than not for at least 6 months about a number of events and they find it difficult to control the worry.*

• 3 or more of the following symptoms:

• Restlessness or feeling keyed up or on edge, easily fatigued, difficulty concentrating, irritability, muscle tension, sleep disturbance

• Causes significant distress or impairment

• Epidemiology: 4-7% of general population median onset=30 years, female:male 2:1

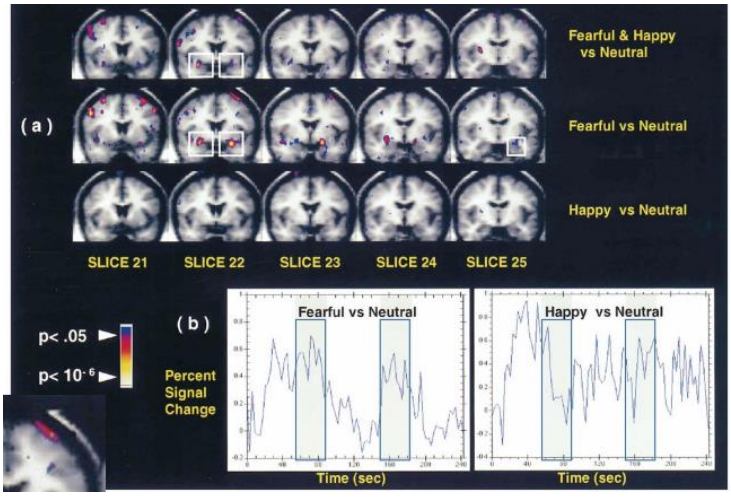
- Anxiety Disorder due to a General Medical Condition
- Substance-Induced Anxiety Disorder

Signs and symptoms of anxiety

- Feelings of panic, fear, and uneasiness
- Uncontrollable, obsessive thoughts
- Repeated thoughts or flashbacks of traumatic experiences
- Nightmares
- Ritualistic behaviors, such as repeated hand washing
- Problems sleeping
- Cold or sweaty hands and/or feet
- Shortness of breath
- Palpitations [心悸]
- An inability to be still and calm
- Dry mouth
- Numbness or tingling in the hands or feet [手脚麻木或刺痛]
- Nausea [恶心]
- Muscle tension
- Dizziness

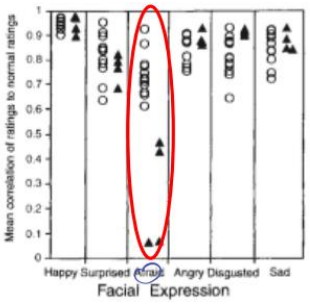
Amygdala[杏仁核] responses to fearful faces (Breiter et al., 1996; Neuron)

Insights on the role of the amygdala in appraising emotions from patient S.M.

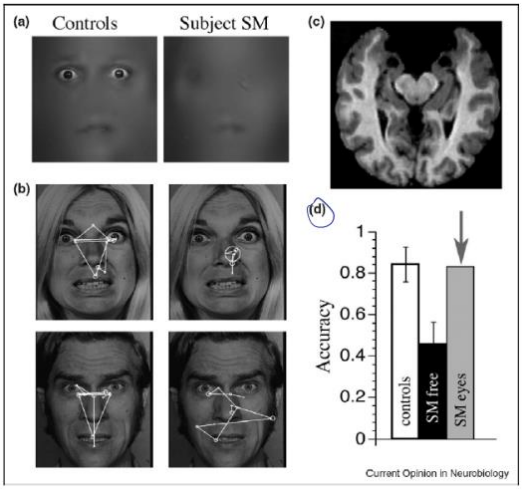


Insights on the role of the amygdala in appraising emotions from patient S.M.

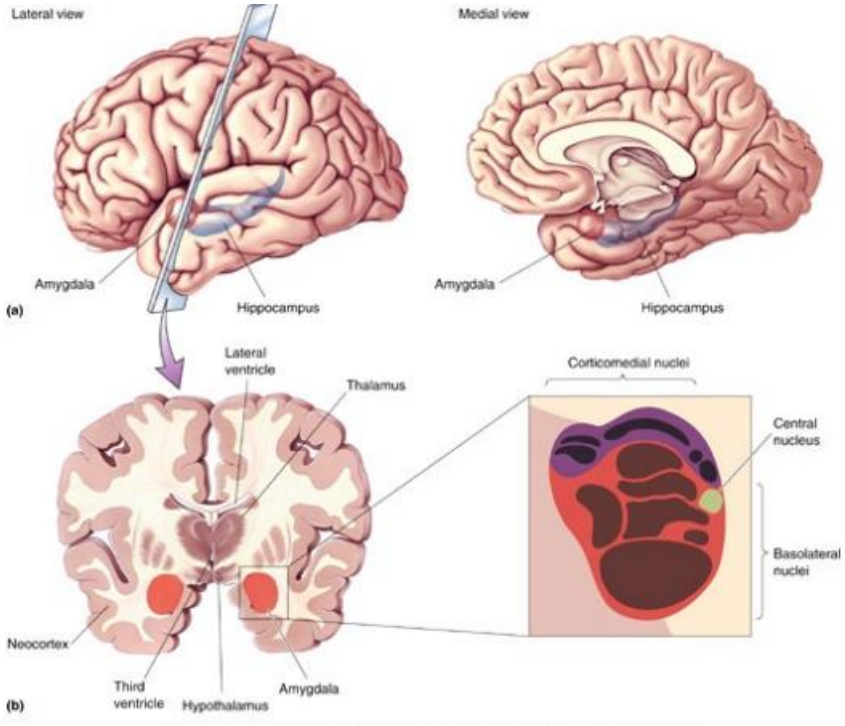
patient S.M. : in certain situations he had these dramatic reduced fear & anxiety feelings.



Selective defect in recognizing expression of fear by neglect of fearful eyes



The amygdalae are almond[杏仁状] shapes bodies located in bilateral medial temporal lobe[双侧颞叶内侧]



Brain circuits involved in fear responses

inputted by what you see

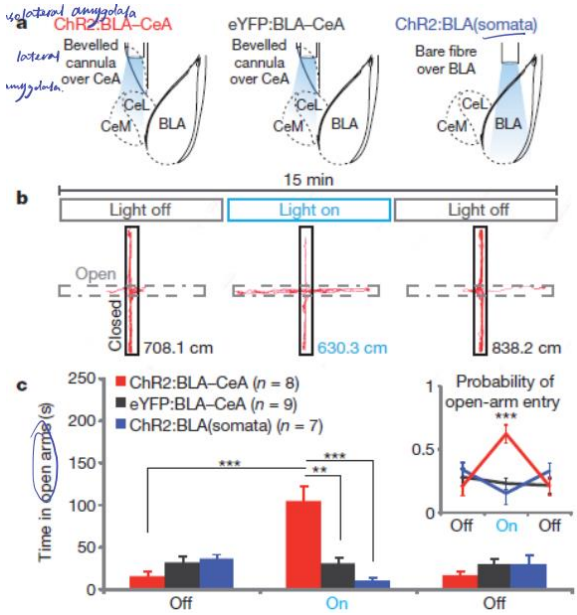
Parts of the brain involved in fear response: thalamus, amygdala, hypothalamus, which then instruct the endocrine glands and autonomic NS.

1. Thalamus[丘脑] receives stimulus and sends to both amygdala and cortex

2. Amygdala registers danger
3. Amygdala triggers fast response
4. More considered response based on cortical processing

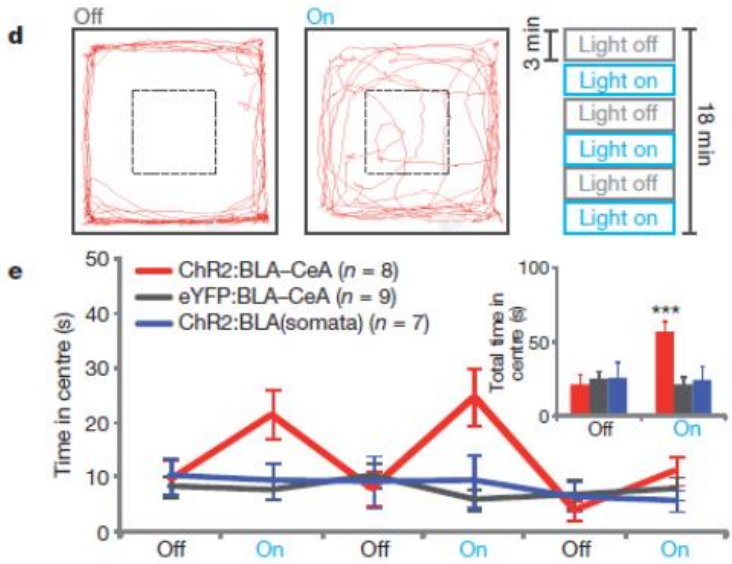
Amygdala circuitry mediating reversible and bidirectional control of anxiety

a: express ChR2 in basolateral amygdala; optical fiber over the lateral part of the central amygdala.



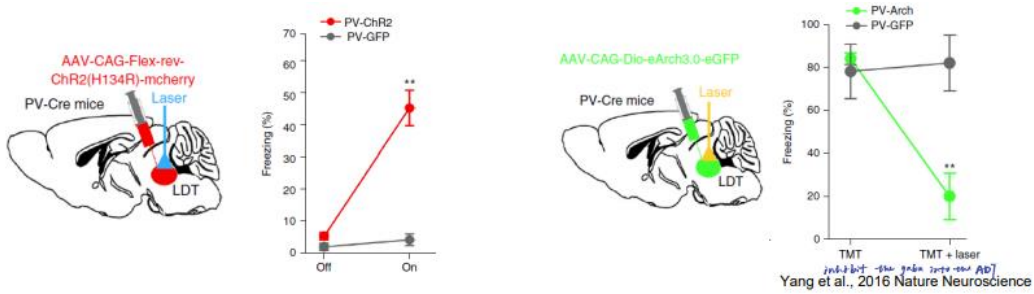
Acute reversible anxiolysis by stimulating BLA terminals in the CeA: Elevated plus maze

Acute reversible anxiolysis by stimulating BLA terminals in the CeA: Open field test



Open field chamber

Role of latero-dorsal tegmentum interneurons for regulating innate fear



Yang et al., 2016 Nature Neuroscience

Inhibit the GABA in the LDT

Anxiety Treatment

- Medication: Drugs used to reduce the symptoms of anxiety disorders include anti-depressants (SSRIs), anxiety-reducing drugs (benzodiazepines), antihistamine (hydroxyzine), gabapentin (useful for comorbidity)
- Psychotherapy: Dealing with their disorder.
- Cognitive-behavioral therapy: The person learns to recognize and change thought patterns and behaviors that lead to troublesome feelings.
- Dietary and lifestyle changes
- Relaxation therapy

Benzodiazepines

• Sedation [镇静]
• Hypnosis［催眠］
• Anesthesia [麻醉]
• Anticonvulsant effects [抗惊厥作用]
• Muscle relaxation
• Effects on respiration and cardiovascular function

Molecular pharmacology of the GABA-A receptor

• Structure: 5 subunits: 2 α (bind GABA), 2 β (bind barbiturates), 1 γ (bind BZD)
• Benzodiazepines increase the affinity of the receptor for GABA, and thus increase Cl^- conductance and hyperpolarizing current
• Benzodiazepines are indirect agonists of the GABA-A receptor

Schizophrenia 1 080322

Historical facts

First mention of a disorder (Dementia praecox: Premature loss of mind) sharing symptomology was by Emil Kraepelin (1856-1926):

- Catatonia[紧张症] (disorder of movement involving immobility or excited agitation)
- Hebephrenia (silly and immature emotionally)
- Paranoia (delusions of grandeur persecution[迫害妄想症])

The first use of the term (Schizophrenia: 'Split of mind') was by Eugen Bleuler (1857-1939):

- Dissociation/Associative splitting[不协调;损害] of basic functions or alterations of personality (cognition, emotions, perception etc.)
- Not mean split of personality or multiple personality

Schizophrenia is diagnosed based on positive and negative symptoms

Positive symptoms[阳性症状]

- Delusions[妄想]:
  disorder of thought content, strong beliefs that misrepresent reality. Delusion of grandeur, delusions of persecution, Capgra's syndrome[卡普拉格妄想症：自己的爱人被一个具有同样外貌特征的人取代], Cotard's syndrome[Cotard 综合征: 临床表现患者感到自己已不复存在，或是一个没有五脏六腑的空虚躯壳，并认为其他的人，甚至整个世界包括房子、树木都不存在]
- Hallucinations[幻觉]:
  Perceptual disturbance in which things are seen or otherwise sensed although they are not real or actually present.
- Disorganized speech & behavior:
  lack of insight; jump from topic to topic, talk illogically, lack of coherence; laugh or cry at improper times; motor dysfunctions (agitation[激动] or immobility)

Negative symptoms[阴性症状]

- Avolition[意志]:
  = apathy[冷漠], inability to initiate and persist in activities
- Alogia[逻辑]:
  Absence of speech (poor communication skills)
- Anhedonia[失欢]:
  Lack of pleasure
- Affective flattening[情感缺失]:
  Don't show emotions when a reaction would be expected.

We have a lot of drugs or pharmacology to address the positive symptoms, they can be very effective at controlling things like delusions and hallucinations. There's much less that we have available to treat these negative symptoms.

Prevalence and cause of schizophrenia

- 0.2% to 1.5% of population, equivalent for men and women
- Onset in early adulthood (16-25)
- Children who later develop schizophrenia have abnormal emotional reactions very early (less positive and more negative affect)
- Genetic vulnerability factors
  Family studies, twin studies, adoption studies, genetic markers
- Environmental risk factors
  In-utero events, infectious pathogens, nutritional factors, stressful life events

Diagnostic criteria

- two or more of the following, for at least 1 month:
  delusions; hallucinations; disorganized speech; disorganized behavior; negative symptoms

Only 1 required if delusions are bizarre; or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or 2 or more voices conversing with each other.

- symptoms cause social/occupational dysfunction
- some sign of the disturbance has lasted at least 6 months
- not caused by a substance or a medical illness

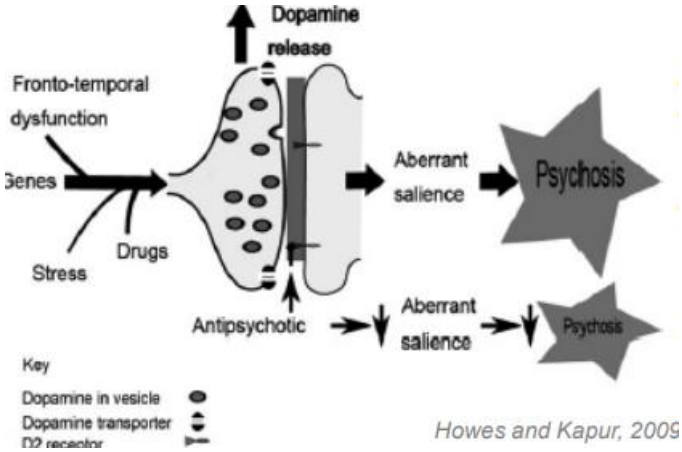
Structural brain abnormalities (Macro)

- Increased ventricle size (Weinberger, NIH):
  Ventriculomegaly: enlarged lateral ventricle, temporal ventricular horn, 3rd and 4th ventricles, septum pellucidum
  Brain region volume changes
- Brain region volume changes (Shenton et al., 1992):
  Decreased total gray matter volumes: Overall 7%, regionally-frontal(PFC, 部分额叶), parietal(P, 顶叶), temporal(T, 颞叶)

Reduced total brain volume

Dopamine dysfunction (Cellular molecular level)

In schizophrenia, there appear to be dysregulation of dopamine signaling within specific circuits in the brain



- Mesolimbic: hyperdopaminergic
  e.g., ventral striatum (nucleus accumbens, olfactory tubercle), amygdala
- Mesocortical: hypodopaminergic
  e.g., prefrontal cortex (PFC) including dorsolateral PFC, orbitofrontal PFC, and anterior cingulate cortex

Results in overactive limbic areas (hallucinations) and poor prefrontal/executive function

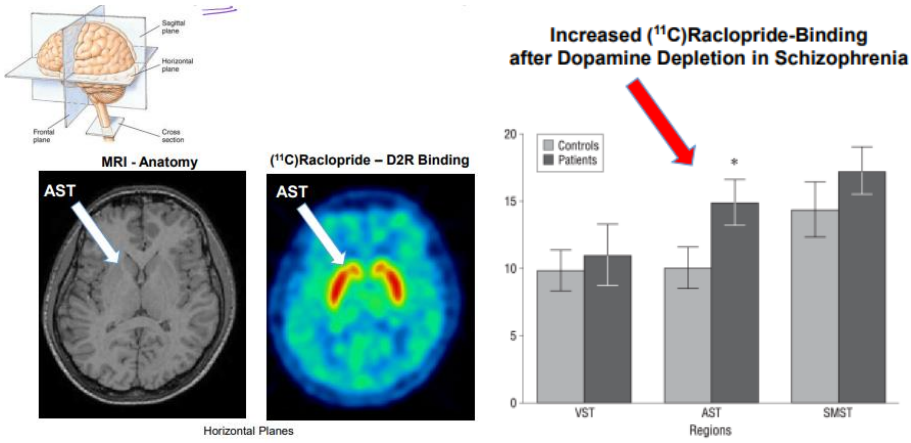
(positive symptoms) In the **striatum**, dopamine dysregulation is hypothesized to alter the appraisal[评估] of stimuli, perhaps through a process of aberrant salience[异常显著性]. Increased dopamine activity in the **striatum** of SZ (schizophrenia) may attribute INCENTIVE SALIENCE [激励显著性]to otherwise irrelevant stimuli. This mechanism is postulated to underlie delusion formation

(negative symptoms) In the PFC, chronic low levels of dopamine, and compensatory increases of D1 receptors, may play a role in cognitive impairment.

From altered dopamine release to D2R dysregulation to pathophysiology (Kegeles et al. 2010)

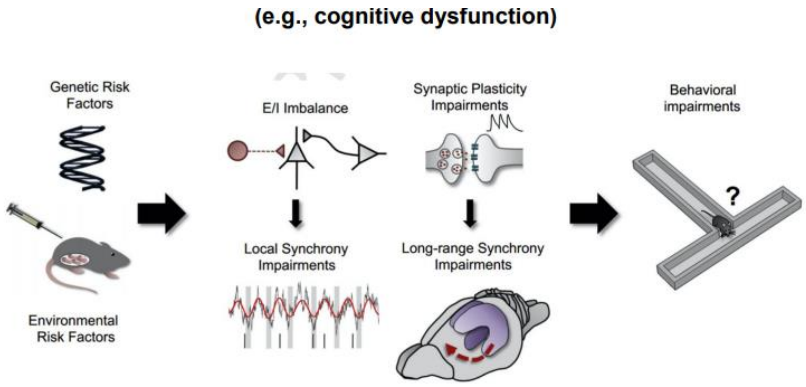
There is indeed kind of overactive or expression perhaps of D2 receptors in individuals with schizophrenia. Increase Dopamine-binding to D2R is brain region-specific (AST = associative striatum, which is thought to be of integrating different inputs from all over the brain and making decisions about which actions to select.) in Schizophrenia

- Inject individuals with a radioactive tracer called Raclopride.
- (^{11}C)Raclopride-binding to D2R, PET scan



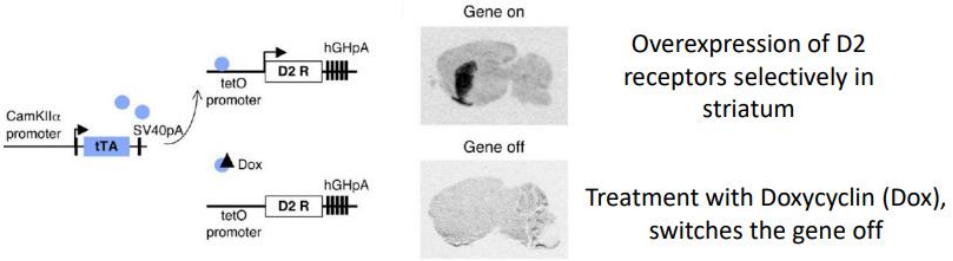
This kind of fits the idea that D2R blockers or antagonists are effective anti-psychotic drugs.

Animal models of endophenotypes related to Schizophrenia

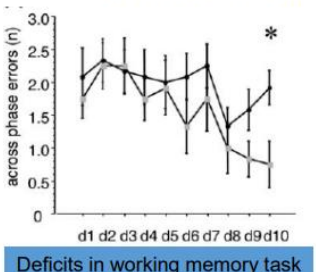


Construct validity of different genetic and pharmacological* mouse models
(* amphetamine, ketamine)

D2R-O: An animal model for cognitive deficits(Kellendonk et al., 2006; Neuron)



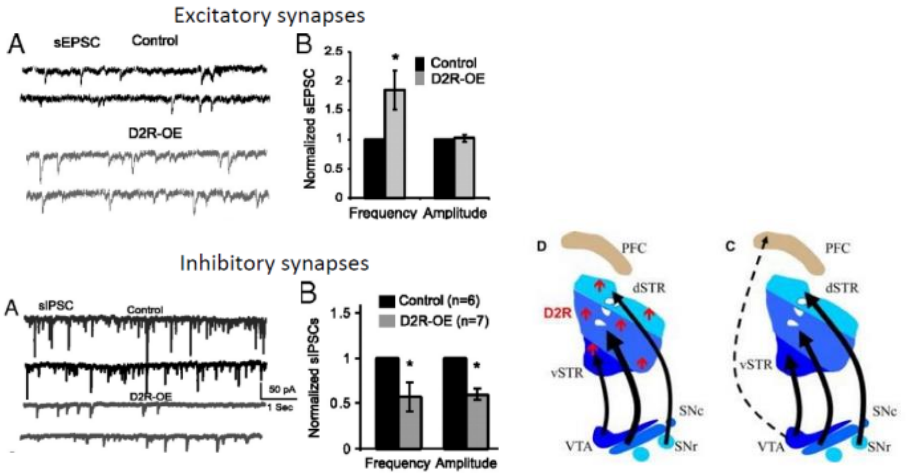
Radial arm task to measure working memory



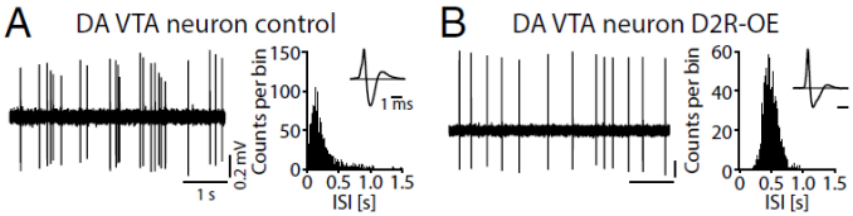
Deficits in working memory task and behavioral flexibility

Overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning(Li et al., 2011; PNAS)

In striatum-D2R overexpressing mice, there is increased excitatory synaptic function and decreased inhibitory synaptic function in the prefrontal cortex. sE/IPSC(自发性 E/IPSC, Excitatory/Inhibitatory Postsynaptic Current)



Striatal D2 overexpression alters firing pattern of VTA dopamine neurons. (Krabbe et al., 2015; PNAS)

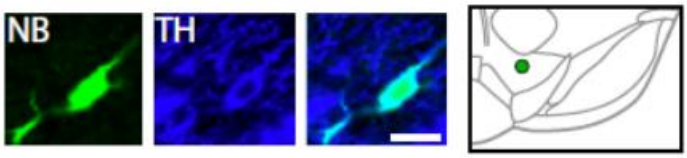


(A Left) The activity in VTA neurons projecting to ventral striatum part of the mesolimbic pathway. Each of these lines represents an action potential that's recorded extracellularly.

(A right) The interspike interval histogram, kind of to the left, meaning they're generally pretty short interspike interval, having burst.

(B) No such bursting pattern anymore, we have this kind of more regular tonic activity. And the distribution is shifted to the right. so we have longer interspike intervals.

There are cellular level changes happening in these cortical striatal circuits, these mesolimbic dopamine circuits.



Approach to know that these spikes are coming from a dopamine neuron: combined extracellular single-unit recordings with juxtacellular single-cell labeling and post hoc immune-histochemistry (labor intensive and low throughput)

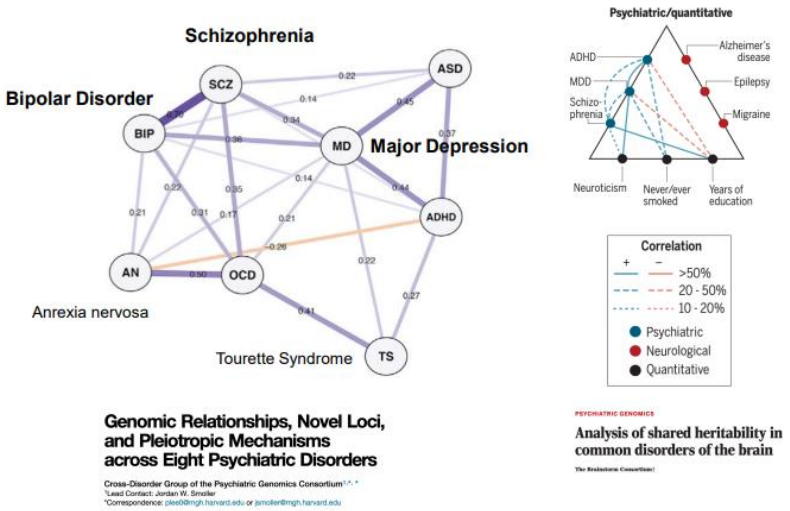
(NB) juxtacellular single-cell labeling: Whereby this neuron that's nearby will be a fluorescent.

(TH) post hoc immune-histochemistry: do this post-hoc immunostaining for something like tyrosine hydroxylase to know whether that's always a dopamine neuron.

Genetics of Schizophrenia

Twin studies suggest high heritability of mental disorders (50-80%)

Gene wide association studies (GWAS): Identification of schizophrenia-associated loci

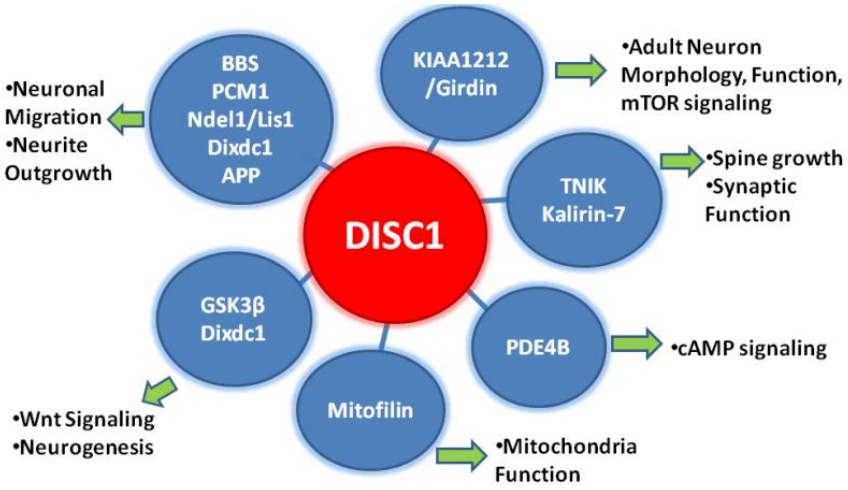


Evidence for significant genetic overlap between different mental disorder. The lines between them are showing kind of the degree of shared genetic risk between different disorders.

Schizophrenia susceptibility gene: DISC1

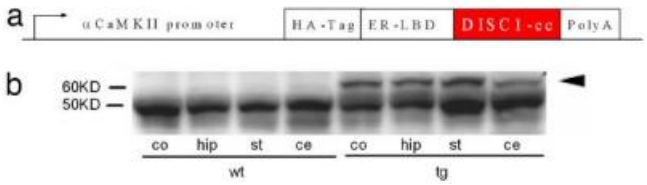
- DISC1 = 'Disrupted-in-schizophrenia 1'
- localized in the nucleus, cytoplasm, and mitochondria
- involved in neurite outgrowth and cortical development Schizophrenia susceptibility gene: DISC1
- the DISC1 gene is disrupted by a balanced chromosomal translocation co-segregating with schizophrenia (7 cases), bipolar affective disorder (1 case), and related affective disorders (10 cases) in a large Scottish family
- disruption of DISC1 for generating a genetic mouse model of schizophrenia

DISC1 has multiple interaction partners and functions in the brain

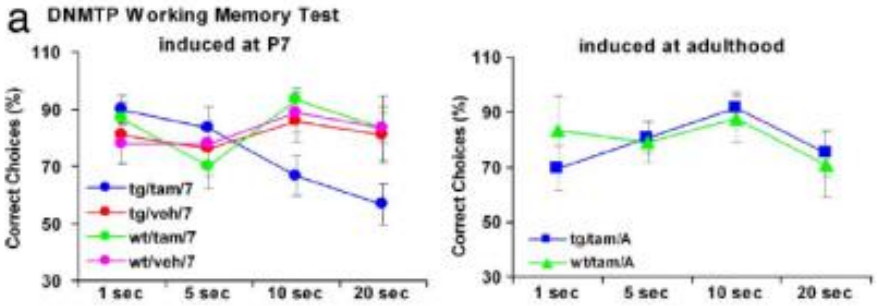


Specific developmental disruption of DISC1 function results in schizophrenia-related phenotypes in mice (Li et al., 2007; PNAS)

- Inducible over-expression of DISC1 c-terminal fragment causes dominant-negative disruption of endogenous DISC1



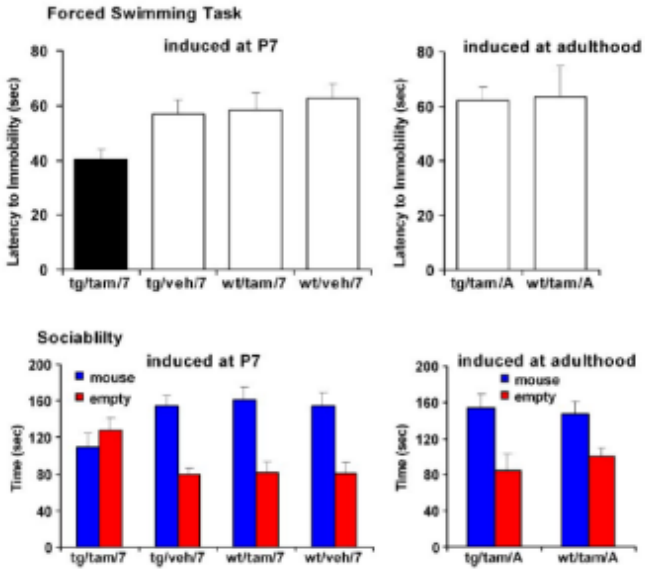
- Working memory deficit due to early post-natal disruption of DISC1



the relevant group is the blue line, the others are controls.

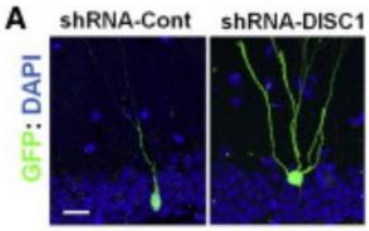
When induced in adulthood, after every neural circuits have fully formed, they don't see it as working memory deficit.

- Depressive-like behavior and reduced sociability due to disruption of DISC1

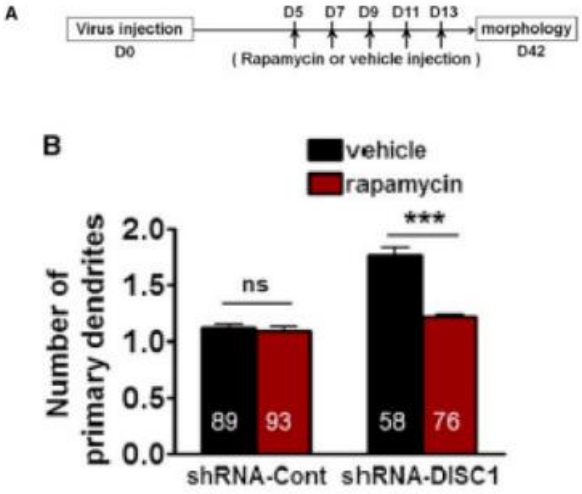


mTOR inhibition ameliorates cognitive and affective deficits caused by DISC1 knockdown in dentate granule neurons (Zhou et al., 2013; Neuron)

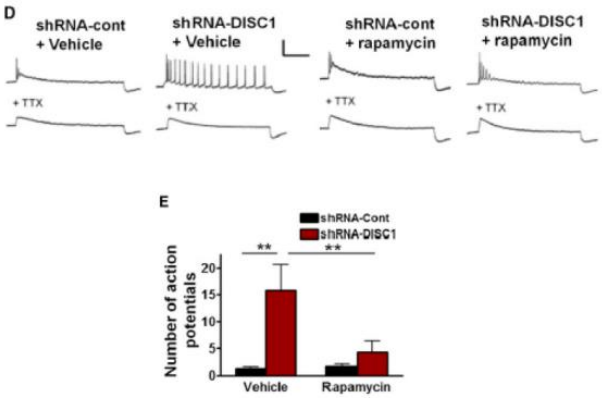
- Knock-down of DISC1 by shRNA(short hairpin RNA) in newborn dentate gyrus granule cells causes schizophrenia-related cellular and behavioral changes



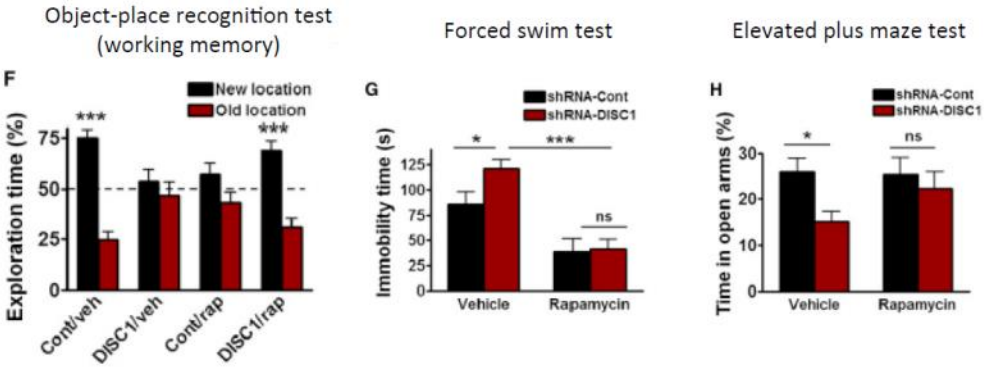
- Rapamycin treatment rescues dendrite morphology changes



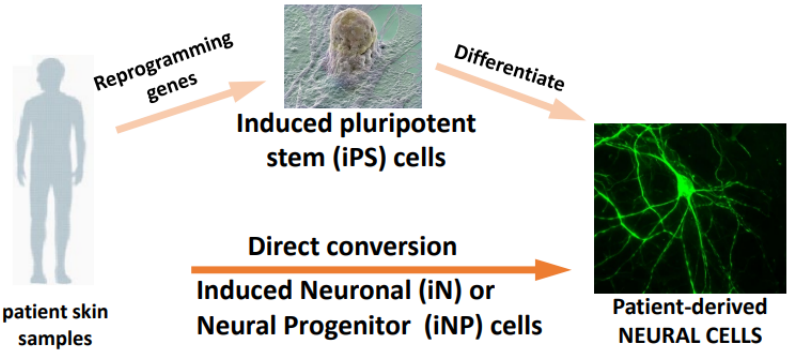
- Rapamycin treatment rescues neuronal hyperexcitability.



- Rapamycin treatment rescues behavioral alterations



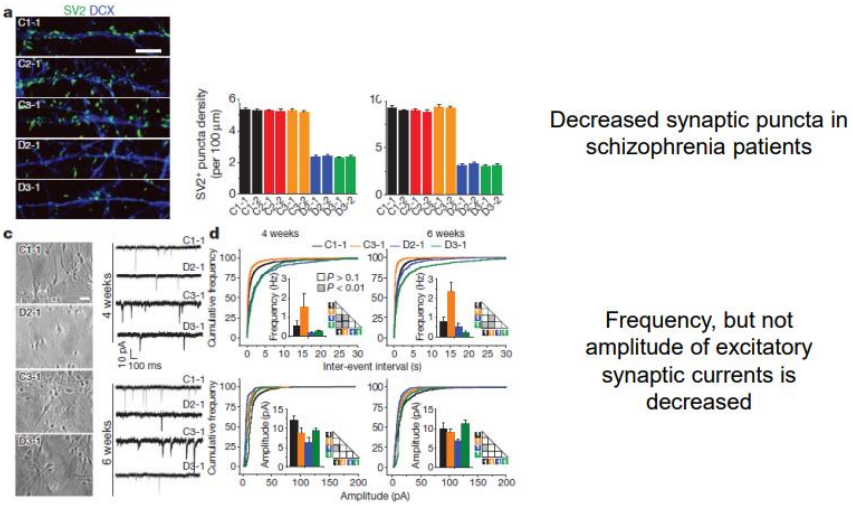
Human cellular reprogramming to create patient-derived neural cells



ADVANTAGES of Direct Conversion:

1. Faster than iPS method
2. Epigenetic signature of patient cell is likely preserved
3. Specific Neuronal subtype generation (Spinal Motor, Dopaminergic)

Synaptic dysregulation in a hiPS cell model of patients with a DISC1 mutation



Post Traumatic Stress Disorder & Schizophrenia 2: Cognitive Deficits, Treatments 100322

Post Traumatic Stress Disorder(PTSD)

Exposure to actual or threatened death, serious or sexual violence in one or more of the following ways:

- Direct experiencing of traumatic event(s)
- Witnessed in person the events as it occurred to others
- Learning that the traumatic events occurred to person close to them
- Experiencing repeated or extreme exposure to aversive details of trauma

PTSD comorbidities

- Depression
- Other anxiety disorders
- Substance use disorders
- Somatization
- Dissociative disorders

PTSD Epidemiology

- 7-9% of general population
- 60-80% of trauma victims
- 30% of combat veterans[退伍军人]
- 50-80% of sexual assault victims[性侵犯受害者]
- Increased risk in women, younger people
- Risk increases with “dose” of trauma, lack of social support, pre-existing psychiatric disorder

Functional neuroimaging in PTSD

- Increased **amygdala**[杏仁核] activation is seen in PTSD patients compared to controls
- Hypoactivation of the medial prefrontal cortex [内侧前额叶皮层]including the orbitofrontal cortex and anterior cingulate cortex (area implicated in affect regulation[情感调节区域])

PTSD Treatment

- Cognitive-behavioral therapy
- Group therapy
- Medications – antidepressants, mood stabilizers, beta-blockers, clonidine

It really depends on the individual diagnosis of the patient.

The Phineas Gage story

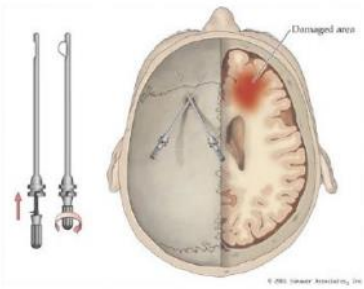
Early evidence for functional segregation from damage
Phineas Gage, 1823-1860

[菲尼亚斯·盖奇（Phineas P. Gage），1823 年生。25 岁在美国佛蒙特州铁路工地工作时发生意外，被铁棍穿透头颅，从颧骨下面进入，从眉骨上方出去，但却依然存活。此事被誉为“十大起死回生事件”，他本人也成为医学研究的热点。37 岁时因癫痫死去。]

The first time where we can make associations between brain damage with behaviors.

Psychosurgery of frontal cortex

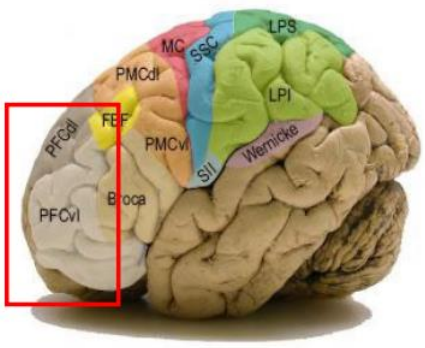
Egas Moniz & Walter Freeman

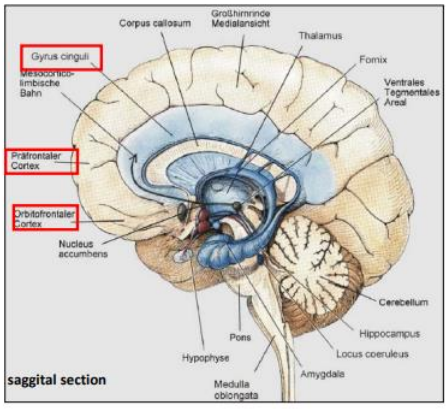


“Frontal leucotomy, despite certain limitations of the operative method, must be considered one of the most important discoveries ever made in psychiatric therapy”

——(Nobel Prize Ceremony Speech by Prof. Olivecrona, Royal Caroline Institute)

Macroscopic anatomy of the human prefrontal cortex





human PFC:

1. dorsolateral PFC
2. ventrolateral (orbito-frontal) PFC
3. medial PFC (anterior cingulate cortex, ACC)

function:

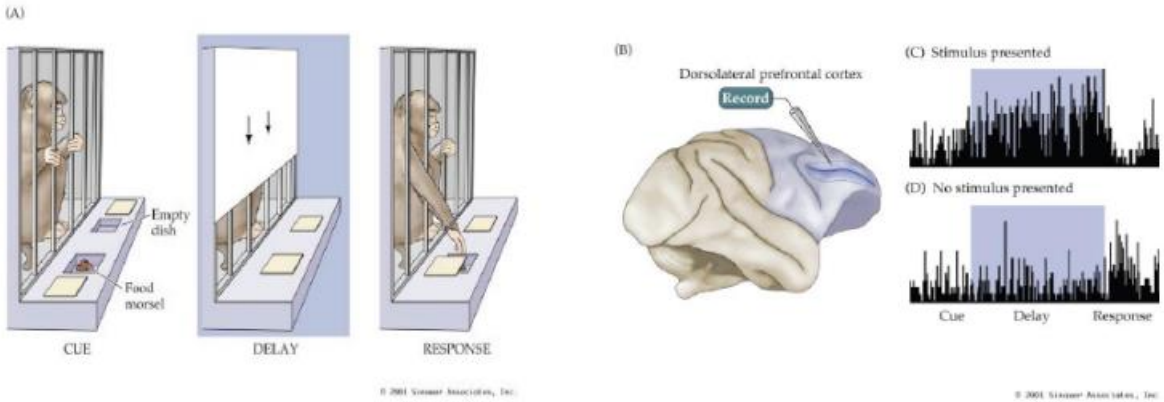
- working-memory (1)
- planning and social restraint function (2+3)

Do mice have a prefontal cortex? and do mice have all these different sub-regions as well?

Although hey have dopamine cells, It's a very controversial topic. Some researchers say, yes, there is something which is reminiscent of the human dorsolateral prefrontal cortex. Other researchers strongly argue against it. What we now as that from an anatomical perspective, we don't have this typical structure of the dorsolateral prefrontal cortex in mice. But functionally, the dorsolateral prefrontal cortex, more or less responds to medial prefrontal cortex. So when we talk about the medial prefrontal cortex function in mice, then associate this with the dorsolateral function in humans.

"Planning-neurons" in the dorsolateral PFC

working memory: **temporary** memory system used to hold specific information mental "on-line"

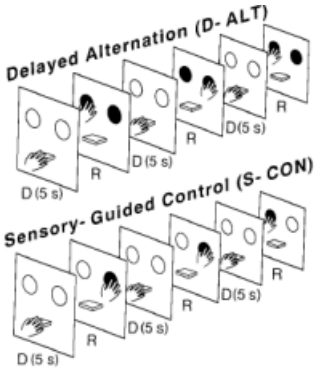


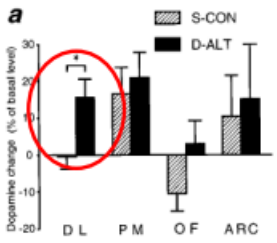
- A primate performing a behavior experiment
- Measure the activity during this delay paste here in neurons in the **dorsolateral prefrontal cortex**
- It's obvious that during the delay phase here in this case, we see this increased neural activity patterns that is associated with working memory function.

Dopamine input to the PFC regulates working memory and higher cognition (mesocortical dopamine pathway)

pioneering work: selective 6-OH-dopamine depletion in the PFC of monkey and rat
Watanabe et al., 1997:

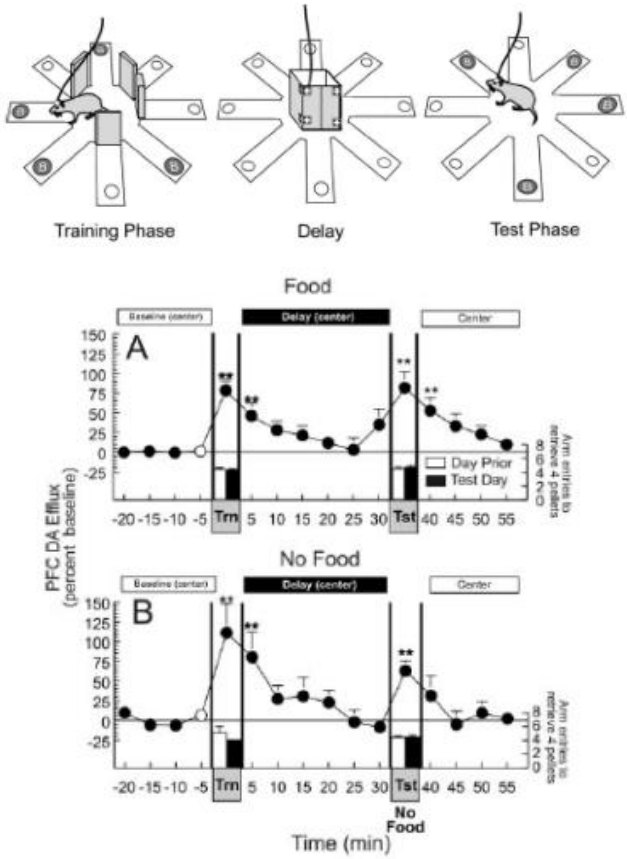
Delayed Alternation Task (D-ALT) → working memory
Sensory Guided Control Task (S-CON) → motivational component





dorsolateral prefrontal (DL), premotor (PM), orbitofrontal (OF), arcuate (ARC)

delayed response task on a radial arm maze(Phillips et al., 2004; J. Neurosci.)

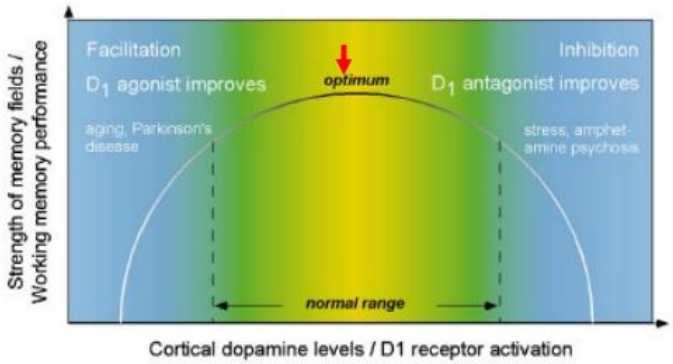


- dopamine signal represents the ability to use – not to store information, we need an optimal dopamine levels basically in order to perform adequately during working memory experiences
- phasic dopamine release in the mPFC is not related to the "reward-prediction error" theory (!)
- mPFC dopamine release is negatively correlated with the numbers of errors committed during memory retrieval

We increase this delay period. Let's say we go from 30 minute up to six hours. Then we see that dopamine levels are not increased anymore.

An optimal level of cortical dopamine is required for adequate working memory performance

PFC function depends on an optimized cortical dopamine level



Neuronal activity in the PFC is regulated by D1 receptors

Cognitive deficits in schizophrenia

Damage to DLPFC causes characteristic deficits:

- Poor cognitive flexibility due to difficulty shifting attention; impaired working memory

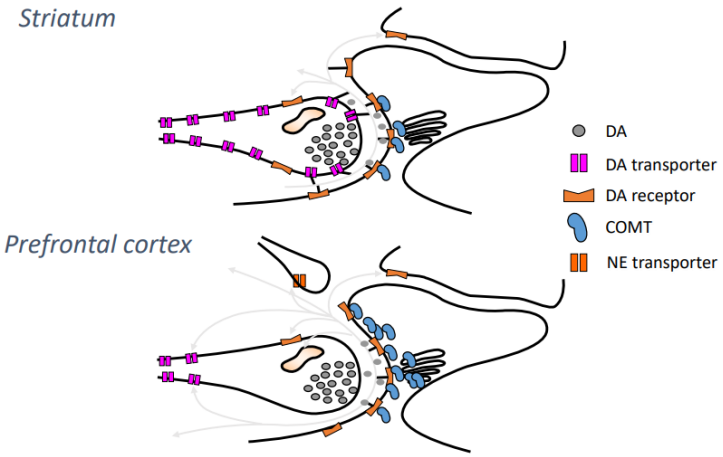
- Lack of emotional spontaneity (abulia) probably due to poor perception of hedonic events
- Decrement in interpersonal involvement
- Poor self care due to lack of initiation, decreased ability to learn from complex social feedback

These deficits are essentially identical to the negative symptoms of schizophrenia.

Working memory deficits in schizophrenia: Dysfunction of the DLPFC and abnormal prefrontal connectivity

Wisconsin Card Sorting Task: Flexible use of working memory following changing rules

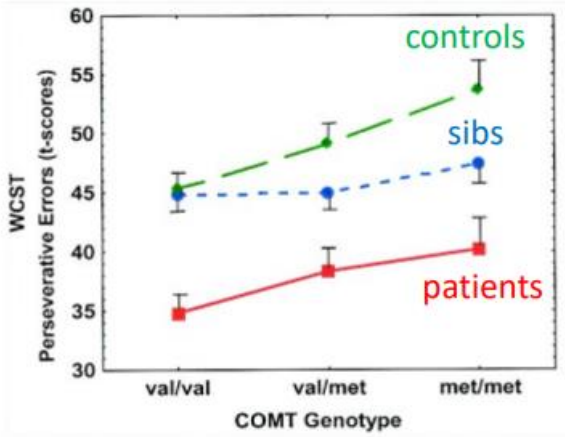
Dopamine terminals in striatum and in prefrontal cortex are not the same



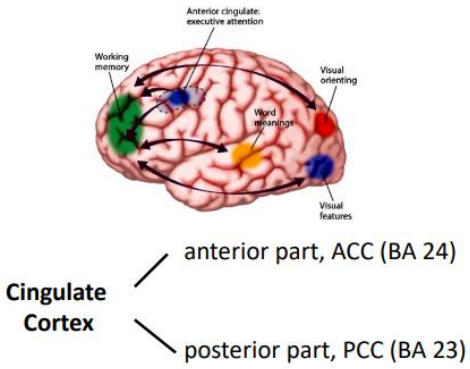
More DA transporter (reuptake) in Striatum
More COMT (metabolize dopamine and norepinephrine at the synapsis)

Catechol-O-methyltransferase (COMT)

- Enzyme involved in the metabolic degradation of dopamine.
- COMT appears to be the major contributor to the termination of dopamine action in the prefrontal cortex due to low levels of the dopamine transporter.
- Val108/158Met polymorphism
- Val variant has 4-fold greater activity than Met variant, leading to decreased prefrontal dopamine levels.
- Schizophrenic individuals with val/val variant show greater impairments on working memory tasks.



Cingulate cortex[扣带回皮层] – Interface between emotion and cognition



- part of the limbic system
- some functions: **i)** emotional self-control **ii)** focused problem-solving (activation of the ACC during stroop test) **iii)** pain perception (emotional component)
- cingulotomy: "ultimo ratio" in intractable chronic pain and depression, obsessive-compulsive disorders

Schizophrenia treatment

Therapeutic Goals

- minimize symptoms
- minimize medication side effects
- prevent relapse
- maximize function
- "recovery"

Types of Treatment

- pharmacotherapy
- psychosocial/psychotherapeutic

The first modern antipsychotic——Chlorpromazine(Thorazine)

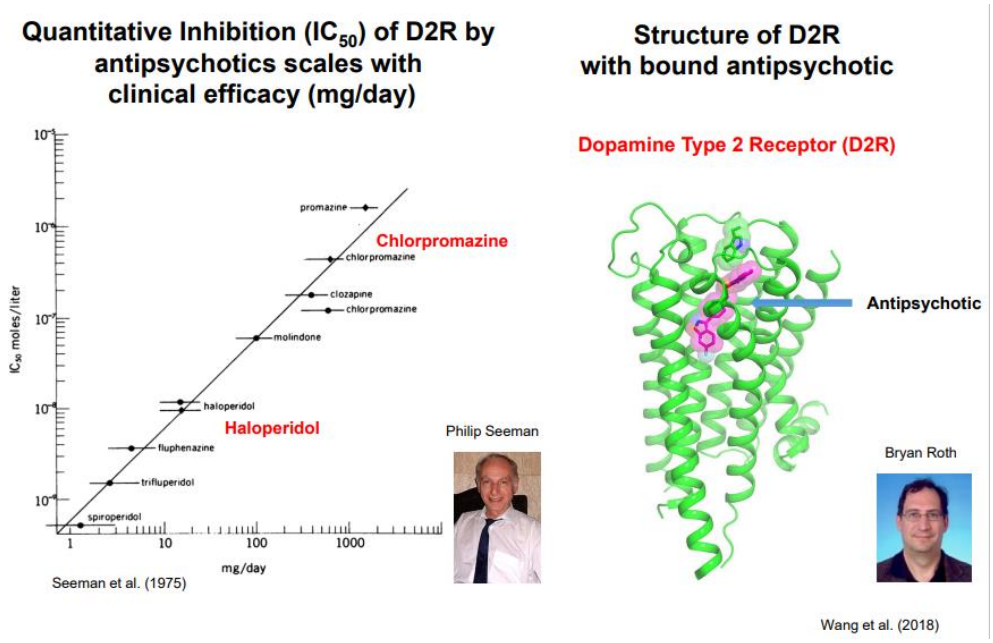
- Antipsychotic properties discovered in 1952
- Studied originally for usefulness as a sedative
- Found to be useful in controlling agitation in patients with schizophrenia
- Introduced in U.S. in 1953

"Typical" antipsychotic drugs

"First-generation, conventional, neuroleptics, major tranquilizers"

- High potency: haloperidol, fluphenazine
- Mid potency: loxapine, perphenazine
- Low potency: chlorpromazine, thioridazine

Antipsychotics act on D2 receptors (D2R)



Antipsychotic medication: Problems & side effects

cause Parkinsonian side effects (EPS)

- Parkinsonism
- Tardive dyskinesia
- Dystonia • Akathisia

not fully effective at reducing symptoms in all patients

frequently do not reduce negative symptoms as effectively as they do positive symptoms

"Atypical" antipsychotic drugs

- Improve the negative symptoms of schizophrenia
- They rarely cause EPS or tardive dyskinesia
- Disadvantage of atypical drugs is their increase in cost over the typical anti-psychotic drugs
- Cost is outweighed by improved effectiveness and quality of life experienced by patients
- Less D2 receptor affinity, more 5-HT2a