Sensitizing and Kindling in Co-occurring Disorders

Nicolas Ruf, MA, LADC

nickruf@msn.com
Biochemical  CNS  Phenomenological

Reflective  Affective  Motive

Sensory Input  Arousal  Cue
| Selection     | Appraisal | Thought |
|              |           | Impulse |
| Cognitive Map | Emotional incentive | Compulsion |

PSYCH/B PROGRAM

E
Relevant Studies

* Dietrich Lehmann , Pascal L. Faber, Shisei Tei, Roberto D. Pascual-Marqui, Patricia Milz, Kieko Kochi:

Reduced functional connectivity between cortical sources in five meditation traditions detected with lagged coherence using EEG tomography, Neurolmage 60 (2012) 1574–1586
Closed Systems

- Kindling
- Extremist beliefs
- Denial
- Self-fulfilling prophecies
- Homeostasis
- Conditioning
Neuron

- Average 10,000 dendritic spines and axon terminals per cell
- Input plasticity due to LTP
- Up to 50 action potentials/second
- Action potential all or nothing

NEUROPLASTICITY

Long Term Potentiation
Dendrite plasticity
Up and down regulation
Arborization and pruning
Sensitization
Tolerance
Conditioning:
    classical (Pavlovian)
    operant (Skinnerian)
Kindling
NEUROTRANSMITTERS

- Glutamate (Glu): major excitatory NT; “on” switch
- GABA: major inhibiting NT
- Dopamine (DA): motivation and association
- Norepinephrine (NE) or Noradrenalin (NA): arousal, alarm system
- Serotonin (5-HT): mood regulation
- Endorphins: pain relief, euphoria
- Acetylcholine (Ach): memory and learning
MONOAMINERGIC PATHWAYS

NORADRENERGIC PATHWAYS

Nucleus accumbens
Amygdala
Hypothalamus
Locus coeruleus

DOPAMINERGIC PATHWAYS

Nucleus accumbens
Substantia nigra
Amygdala
Ventral tegmental area

SEROTONERGIC PATHWAYS

Nucleus accumbens
Amygdala
Hypothalamus
Raphe nuclei
Hippocampus
Prefrontal Cortex (pfc)

* Focusing attention
* Organizing thoughts and problem solving
* Foreseeing and weighing possible consequences of behavior
* Considering the future and making predictions
* Forming strategies and planning
* Ability to balance short-term rewards with long term goals
* Shifting/adjusting behavior when situations change
* Impulse control and delaying gratification
* Modulation of intense emotions
* Inhibiting inappropriate behavior and initiating appropriate behavior
* Simultaneously considering multiple streams of information when faced with complex and challenging information
**PREFRONTAL CORTEX**

- Orbitofrontal cortex (OFC) – good/bad; assess risk; approach/withdraw
  * Connections to amygdala and NAcc
  * Shows up in addiction through compulsivity and inability to change predictive value of behavior. (Craving)
  * Loss of control over initiation of behavior
  * Modulate maladaptive behaviors

- Anterior cingulate (ACC)- 3 functional subdivisions: Cognitive, affective, motor
  * Choose what to do; this not that.
  * Monitors behavioral outcomes and makes adjustments
  * Dorsal connected to pfc and cognitive function in reward-based decision making.

- Ventral connected to hypothalamus, amygdala and nacc and involved in emotional and motivational salience
PFC cont.

Ventral medial:
mediates pain, sex, aggression, eating

Dorsal lateral:
Reciprocal connections with ofc and vm
executive function
effortful sustained attention
working memory processes
INSULA (INSULAR CORTEX)

*Located between the frontal and temporal lobes.
*Involved in perception of state of being: emotional, stress, energy levels.
*Inputs from and outputs to:
  Acc
  Med PFC
  AMYG
  NAcc
AMYGDALA

- Sends connections to hypothalamus to activate SNS
- Sends to VTA for da
- Sends to LC for ne
- Records emotional memories
- Sensitizes to cues predicting reward
Ventral Tegmental Area

- Activated by Glu
- Sends DA to Nacc
- Receives messages about how efficiently basic needs are being met
- Processes messages from amygdala conditioning body against fear
- Creates avoidance strategies for safety
- Origin of two major Da pathways
  - Mesocortical
  - Mesolimbic
STRIATUM

- Involved in decision-making & motivational salience

- Ventral striatum = **nucleus accumbens (Nacc)**
  - Subject to sensitization and kindling (impulse)
  - Gets da from VTA
  - Increase in da with possibility of reward
  - Glu from pfc, amygdala, and hippocampus

- **Dorsal striatum**
  - Glu from motor cortex (compulsivity)
HIPPOCAMPUS

- Involved in short term storage
- Memory consolidation and retrieval through Glu LTP
- Important in connecting senses and emotions
- Vulnerable to kindling
LOCUS CERULEUS

- Contains 70% of NE neurons
- Cognitive arm of SNS
- Functions in neuroplasticity, arousal, attention and memory, emotions, stress
- Efferents to amygdala relevant to stress induced fear responses (e.g. PTSD)
HYPOTHALAMUS

- Links nervous system to endocrine system via pituitary gland
- Regulation of body temp, thirst, hunger, moods, sex drive, fatigue, sleep, circadian rhythms
- Controls homeostasis through set points
- Responsive to and regulated by DA, NE, and 5-HT
UP AND DOWN REGULATION

Example of Behavioral Effect

1. HR normal
2. HR ↑
3. HR normal
4. HR ↑
5. HR normal
6. HR normal
7. HR ↑
8. HR normal
GLU LTP

- With enough Glu stimulation of AMPA receptors, Mg unblocks NMDA Glu to Ca influx
- Glu receptors in storage are activated at post-synaptic membrane
- Receptors are modified (phosphorylated) to stay open longer
- Dendrite changes shape to spread wavelet
- Retrograde NT’s (like NO) are released back to pre-synaptic cell signaling manufacture of more Glu
OCD

Pathological uncertainty

Compulsive behavior triggers doubt
Doubt triggers anxiety
Anxiety triggers obsessive perseveration
Obsession triggers stress
Stress triggers compulsive behavior
OFC underactivity
LIKE-WANT-NEED

- Like = activation of reward/reinforcement Nacc endorphin pathway
- Stimulation near the hypothalamus in the medial forebrain bundle activates Da release in the ventral tegmental area (VTA) to the forebrain
- Glu release from the amygdala and Da release from the VTA to the nucleus accumbens (Nacc) – the crossroads of emotion and behavior
- ICSS, brain stimulation, place preference, and injections of cocaine or amphetamine studies show Da release in the nucleus accumbens (Nacc)
- Da rises in Nacc in response to natural rewards and CS, and Da antagonists block reward and place preference
Impulsivity to Compulsivity

- Impulsivity or sensation-seeking may predate compulsive drug use
- An inability to wait and sample predictive stimuli before responding
- Devolution of drug-seeking behavior from the ventral (Nacc) to the dorsal striatum
- Low D2 and/or D3 receptors in the ventral but not dorsal striatum predict escalating cocaine use in impulsive animals
- Low D2 and/or D3 receptor availability in the dorsal striatum is found in chronic drug-abusers.
Glu Input to Nacc input from:

- PFC for predicted reward
- Amygdala for emotional cue
- Hippocampus for recall
DRUG ACTIONS

- Drugs like cocaine and amphetamines work directly on Da
- Opiates work directly with endorphin receptors
- Other mind altering drugs of abuse work through Glu or GABA to activate Da or endorphins

http://learn.genetics.utah.edu/content/addiction/drugs/mouse.html
THREE PHASES OF ADDICTION

1- Binge/intoxication:
   - Nacc and amygdala
   - DA from VTA
   - Endos from hypothalamus

2- Withdrawal/negative affect:
   - Decreased DA in Nacc
   - Increased stress in amygdala
   - Increased CRF and NE

3- Preoccupation/anticipation:
   - Glu to Nacc and amygdala
ADDICTION

Pleasure/Relief \rightarrow System bias
LTP \rightarrow Cues for possible reward

Intermittent reinforcement

Overvaluation of predicted reward
Sensitized amygdala and nucleus accumbens
Kindling

Stressed

Failure reinforced through craving, denial, increased motivational Da, compromised Acc and Ofc

Stereotyped, autonomous, compulsive B
Anxiety

Arousal in situations others do not find fearful

- LTP and sensitization of amygdala
- Hippocampal atrophy
- Increased stress response
- SNS activation
PTSD

Traumatic or long term stress:

- CS elicit UR
- Sensitization and conditioning
- Reduced Da = anhedonia
- LTP, Sensitization & kindling in amygdala
- Hippocampal atrophy due to glucocorticoids
PTSD Continued

Release of NE increases arousal

Release of endorphins inhibits pain

Both inhibit memory consolidation
PTSD

Emotional stimulus → Sensory thalamus → Amygdala → Emotional response

Medial prefrontal cortex

Emotional response (SNS: Flight, fight, freeze)
Depression

- The end result of a reversible, organic, neurodegenerative disease involving the health and functioning of neurons in the hippocampus and frontal cortex.
- Stress & other insults lead to decreased “Brain-derived neurotropic factors” (BDNF) resulting in atrophy of hippocampal and cerebral neurons.

*Child & Adolescent Psychopharmacology News, June 2007*
ACTUAL OR PERCEIVED HELPlessness & LOSS OF CONTROL

HYPERAROUSAL OF THE LIMBIC SYSTEM & DYSREGULATION IN SYSTEMS GOVERNING REWARD, INHIBITION, SLEEP, AND COGNITION

Negative thinking

Depression

Isolation
DOPAMINE PATHWAYS

Depression
  Mesolimbic
    Feeling sad
    Believe worthless
    Memory of abuse/neglect/trauma

Mesocortical
  hyperactive ofc
  hyperactive vmpfc
    increased sensitivity to pain
    anxiety
    depressive ruminations
    tension
  hypoactive dlpfc
    psycho-motor retardation
    apathy
    deficits in working memory and attention

Acc – amygdala pathway weakened:
  ACC loses emotional regulation control
STATE-DEPENDENT LEARNING

Both acquisition and extinction associations can be context dependent.

Changes in contextual setting often result in immediate recovery of original learning.
Sensitization of AMPA Glu in Nacc in early abstinence to pick up cues

Cues signal intermittent reward which ramps up Da release twice that for 100% predictable reward

Powerful craving/motivation/goal-directed behavior
CHRONIC STRESS AND CORTISOL

- Cortisol acts as a neurotoxin and destroys brain cells:
- In the PFC it tends to fix patterns of response.
- In the hippocampus it reduces choices and behavioral options.
CHRONIC STRESS

• Chronic stress boosts cortisol levels and downregulates neural glucocorticoid receptors trying to compensate for excess hormone.

• The brain underestimates circulating glucocorticoid values and fails to tell the pituitary to slow down.
BDNF

• Brain derived neurotrophic factor (BDNF) levels are increased in the VTA and Nacc.
  • Sensitized recognition of cues and motivation to seek predicted rewards
  • Levels are reduced in the hippocampus and PFC.
  • Reduced ability to modify behavior according to results
  • Fixing responses to established rewards and reducing behavioral options
RELAPSE PREVENTION

Jeffrey Schwartz’s & Gabor Mate’s 5 R’s:

1. Relabel
2. Reattribute
3. Refocus
4. Revalue
5. Recreate
The globally reduced functional interdependence between brain regions in meditation suggests that interaction between the self process functions is minimized, and that constraints on the self process by other processes are minimized, thereby leading to the subjective experience of non-involvement, detachment, and letting go, as well as of all-oneness and dissolution of ego borders during meditation.

Lehmann, Faber, et al 2012

www.elsevier.com/locate/ynimg
REFERENCES


REFERENCES Cont.

Neuropharmacology, Volume 56, Supplement 1, Pages 1-278 (2009)

Frontiers in Addiction Research: Celebrating the 35th Anniversary of the National Institute on Drug Abuse: Edited by David Shurtleff, Rita Liu and Catherine Sasek


Http://criticalthinkrx.org/