Neuron

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

NEUROTRANSMITTERS

- Glutamate (Glu): major excitatory NT; “on” switch
- GABA: major inhibiting NT
- Dopamine (DA): Prediction error (spike) and motivation (bath)
- Norepinephrine (NE) or Noradrenalin (NA): arousal, alarm system
- Serotonin (5-HT): mood regulation
- Endorphins: pain relief, euphoria
- Acetylcholine (Ach): memory and learning
- Anandamide and 2-Arachidonoylglycerol (2-AG)

Note: oxytocin (a hormone) reconfigures the mu opioid system so loved ones’ presence relieves stress and pain. Bonding raises pain threshold.
DOPAMINE NETWORKS

- Affect
- Attention
- Memory
- Reward/relief
- Behavioral control
- Motivation
- Prediction error

Serotonin Receptor Subtypes

- 5-HT1 = antidepressant & anxiolytic
- 5-HT1A – passive stress reduction
- 5-HT1B – ketamine binding in Nacc = antidepressant
- 5-HT2 = insomnia, anxiety, agitation, sexual dysfunction
  - 5-HT2A – context sensitization (LSD & psilocybin)
  - 5-HT2A block = lack of anxiogenic effects
  *5-HT2c antagonists = inc DA response to reinforcing drugs
- 5-HT3 = nausea
- 5-HT7 (thalamus, hypothalamus, cortex & hippocampus) – circadian rhythms, learning, memory, mood regulation.
NEUROPLASTICITY

Long Term Potentiation
Dendrite plasticity
Up and down regulation
Arborization and pruning
Sensitization
Tolerance
Conditioning:
  classical (Pavlovian)
  operant (Skinnerian)
Kindling
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; stimulus-reinforcement association learning

* Connections to amygdala and Nacc (emotional regulation)
* Assigns value to a stimulus
* Shows up in addiction through compulsivity and inability to change predictive value of behavior: drug expectation (Craving)
* Loss of control over initiation of behavior
* Disinhibition, irritability, social inappropriateness

Ventromedial: (vmpfc) (How much punishment)

* Mediates pain, sex, aggression, eating
* Monitor on-line emotional state
* Emotional triggers – cravings. (5-HT2A clusters ↓ cue-induced reinstatement)
* Decision making and inhibition of emotional responses (5-HT to amygdala)
* Damage leads to impulsivity, poor decision making
Dorsalmedial PFC
*neurons projecting to Nacc sensitize to reward-predictive cues; stimulation promotes conditioned reward-seeking (on switch)
*neurons projections to the thalamus inhibit responses to reward-predictive cues; stimulation suppresses both acquisition and expression of conditioned reward-seeking (off switch)

Dorsal lateral: (dlpfc) (How much responsibility)
*Reciprocal connections with ofc and vm
*executive function
*effortful sustained attention
*working memory processes – including drug related

Damage leads to impaired planning, working memory, cognitive flexibility, and mental control.

Cingulate Cortex

Anterior cingulate (ACC)- 3 functional subdivisions: Cognitive, affective, motor
*choose what to do; this not that: attentional bias
*maintenance of effort – sustained motivation
*Detects and monitor errors, evaluates, and suggests adjustments
*Dorsal connected to pfc and cognitive function in reward-based decision making- increase
*Activated by both emotional (e.g. being wrong) and physical pain
Ventral connected to hypothalamus, amygdala, insula, and NAcc and involved in emotional and motivational salience

Posterior cingulate (PCC):
Default Mode Network (DMN)
*activated by emotionally salient autobiographical retrieval, daydreaming, planning, self-reflection, rumination, worry
*Inactive during meditation and undistracted effortless mind wandering
*deactivated during externally directed, or presently centered attention
*activity reduced by psilocybin and LSD
INSULA (INSULAR CORTEX)

* Located between the frontal and temporal lobes, links body and mind
* Involved in perception of state of being: emotional, stress, energy levels.
* cue-induced drug craving
* Inputs from and outputs to:
  - Acc
  - Med PFC
  - AMYG
  - Nacc
* Thins in schizophrenia, PTSD, specific phobias
* Thickens with mindfulness meditation practices

Insula Continued

Lights up with:
- Drug craving
- Feeling pain
- Anticipating pain
- Empathizing
- Listening to jokes
- Seeing disgust on someone’s face
- Being shunned in a social setting
- Listening to music

* Anterior portion strengthened by mindful meditation
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/punishment

Habenula

- Input from basal ganglia and limbic
- Output to VTA and substantia nigra
- Supress motor activity under aversive conditions of pain, stress, and failure.
- Motivation and motor inhibition - Depression
- DA to VTA inhibited
- 5-HT to raphe nucleus inhibited
**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: Lose lottery (bad luck)
  - Mesolimbic: Lose bid (social status)

**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** (Caudate nucleus and putamen)
  - goal-directed behavior
  - Glu from motor cortex (compulsivity)
HIPPOCAMPUS

- Involved in short term storage
- Memory consolidation and retrieval through Glu LTP
- Important in connecting senses and emotions

*Growth with mindfulness meditation practice

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

The greatest sources of our suffering are the lies we tell ourselves.

Elvin Semrad
Opiates/opioids

- Endorphin mimics
- Half lives:
  - Heroin – few minutes (effects last c. 4 hrs) - metabolite 6-MAM gets into brain and activates DA; after 1 hr converts to morphine
  - OxyContin – 3.5-5 hrs
  - Morphine – 2-3 hrs
  - Fentanyl – (50-100 times more powerful than morphine
    - IV – 2-4 hrs (effects 30-60 min)
    - Transdermal – c. 24 hrs
  - Methadone – 15-60, average 22 hrs
  - Buprenorphine – 24-60 hrs

Oxytocin reconfigures the mu opioid system so that a loved one’s presence relieves stress and pain; and bonding raises the pain threshold.
**Ultram (tramadol)**

- Mu opiate agonist (naloxone only partially reverses analgesia)
- 5-HT and NE reuptake inhibitor
- NMDA Glu receptor antagonist
- Ach antagonist
- 5-HT2c antagonist (may be responsible for reducing depressive and OCD symptoms)

**Kratom—coffee family**

- Low dose stimulant – delta opioid receptors
- High dose sedative – mu opioid receptors
- 5-HT2A – loosen conditioning grip in ofc
- NMDA GLU antagonist – mild dissociation at high doses

- Active ingredients:
  Mitragynine and 7-hydroxymitragynine
### Clonidine (Catapres)

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<thead>
<tr>
<th>01</th>
<th>02</th>
<th>03</th>
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<tbody>
<tr>
<td>Stimulates presynaptic $\alpha_2$ NE receptors, reducing NE activity.</td>
<td>For ADHD it increases NE in the PFC through postsynaptic binding to $\alpha_2A$ receptors and indirectly by increasing NE input from the LC.</td>
<td>For withdrawal from opioids, alcohol, benzodiazepines, and nicotine, acts as a mild sedative.</td>
</tr>
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### Gabapentin and Pregabalin (Anticonvulsants)

- **Pregabalin (Lyrica)**
  - Stronger and more quickly absorbed
  - Neuropathic pain and fibromyalgia

- **Gabapentin (Neurontin)**
  - Postherpetic neuralgia and restless leg syndrome
• **OTHER PAIN MEDS**
  (Roughly 50% of individuals with mood disorders suffer from chronic pain)

- **CBD: Cannabidiol** (immune functions and appetite regulation too)
- **Octacosanol/policosanol** – reduce stress; promote sleep

* Low dose **nortriptyline**

Drugs with anxiolytic, antidepressant, and analgesic effects:
- **Cymbalta** (duloxetine)
  - Selective 5-HT and NE reuptake inhibitor
- **Strattera** (atomoxetine)
  - Selective NE reuptake inhibitor

**Positive allosteric modulators (PAM’s)**

- These work on secondary pain receptors instead of on primary ones where there is spillover
- PAM’s amplify anandamide and 2-arachidonoylglycerol (2-ag for our purposes), endogenous cannabinoids, at the right time to the right place.
- Delta-9 THC and opioids target primary receptors and affect receptor sites throughout the body.

[Image of 4Jointz logo]
• Negative feelings/fear/depression
• Neglect/abuse
• Trauma/ACE
• Bullying, violence, poverty, lack of opportunity
• Death of a parent, of a sibling, divorce

• My fault
• Something wrong with me
• Shame, self-loathing, low self esteem, alienation

**Adverse Childhood Events (ACE)**

• 1 out of eight has 4 or more
• Affect the Nacc, PFC and amygdala development and expression
• Affect the HPA axis and stress levels.
• Health outcomes across the board are affected, physical and mental.
• Elevated risk for heart disease, asthma, suicide, SUD’s, mental/emotional disorders.

*See Nadine Burke Harris’ TED talk on ACE’s*
Pain of being wrong (ACC): Do or say something wrong

To feel better: avoid, repress, or escape pain (DA to Nacc)

Cognitive Dissonance

Cognitive Dissonance

Pain/discomfort ➔ Little white lie ➔ Split (dissociation between reality and lie) ➔ Belief ➔ The cure is the problem
placebo

- Increased placebo effect with better emotional regulation.
- Open-label effectiveness with detailed explanation
- As George tells Jerry before the lie-detector test: “Jerry, Just remember, it’s not a lie if you believe it.”

THE LIES

Maintain homeostasis (deal with stress) through defenses (tolerance):
- Denial
- Excusing
- Rationalization
- Dissociation
- Fantasy
- Blame
- Humor

*Conditioning deepens
*Sensitization broadens
*Increased sensitivity to perceived threat
*Increased tolerance to the progression of negative outcomes.
Dissociation

- Dissociative identity disorder (DID)
- State-dependent learning.
- Blackouts
- Muscle memory
- Cult membership
- Mental disorders like depression, anxiety
- Addiction
- Habits
- Hypnosis

The easy fix

Dissociation:
Denial of feelings, suppression (deadening), avoidance strategies (lies, humor), escape (fantasizing)
Self-fulfilling prophecy
Denial of responsibility: excuses, rationalization, blame
Denial of implication: minimizing, discounting, dismissing
Denial of fact: didn’t happen, wasn’t me, meant nothing.
**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.

![Diagram showing the cycle of chronic stress effects](diagram.png)

**BDNF**

- *BDNF strengthens glutamergic synapses and weakens GABAergic synapses.
- *Drugs of abuse increase acutely BDNF expression leading to long-lasting elevation of D3 receptors 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
If an already stressed system, seek relief through repression, avoidance, aggression – anxiety, depression, anger, impulsivity, PTSD, SUD’s

Fear paths → sustained stress → sensitized amygdala → SNS habitual

Sensory thalamus → Amygdala

Emotional stimulus → Emotional response (SNS: Flight, fight, freeze)

• Painful experience → stress → escape/avoid/repress → SUD, depression, anxiety, PTSD
• LC: NE → cortisol
• Amygdala sensitized

(G B-ball)

https://youtu.be/IGQmdoK_ZfY
THE PROCESS

- Painful thought or feeling (PFC or amygdala)
- Conditioning and sensitization
- Reinforcement through hippocampus
- Resetting of hypothalamic controls of mood, sleep, arousal, libido, appetite
- Connection to stress hormones and SNS

Confirmation Bias

- “In fact, one could say the brain is hardwired to accept, reject, misremember or distort information based on whether it is viewed as accepting of or threatening to existing beliefs.”

- American Psychological Assn: ScienceDaily, 10 August 2018.
  <www.sciencedaily.com/releases/2018/08/180810120037.htm>
Closed Systems

- Kindling
- Extremist beliefs
- Denial
- Self-fulfilling prophesies
- Homeostasis
- Conditioning
- State-dependent learning
- Catch-22
- Muscle memory
- Bootcamp tx practices

Closed systems

- Kindled
- Autonomous
- Self-reinforcing
- Automatic
OCD – the cure is the problem

Pathological uncertainty

* Compulsive behavior triggers doubt: “Maybe it didn’t work.”
* Doubt triggers anxiety
* Anxiety triggers obsessive perseveration
* Obsession triggers stress, sensitization to cues, and overestimation of payoff.
* Stress et al trigger compulsive behavior
Animal Experiments

• Animals force fed drugs do not become addicted although they show reinforcement: place preference, ICSS, etc.
  
  Change their diet, their environment, their circumstances and they will alter their drug taking behavior.

• Animals that have freely chosen to take the drug do not alter their addictive pattern if external circumstances change.

  There is some initial receptiveness or anticipatory state, some place in their systems for the substance effect: negative reinforcement.

Addiction and the brain

- Initial prediction error (reward/relief) triggers Glu LTP in VTA (like)
- VTA sends dopamine to Nacc and PFC (like)
- Endorphins released in Nacc (like)
- PFC reacts to cues predicting reward/relief (dopamine spike) in Nacc motivationg behavior. (want)
- Conditioning deepens and sensitization broadens pathways.
- Increased motivation with intermittent reinforcement drives loss of control over behavior (need)
- Behavior kindles and detaches from results (need)
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

What happens if reward is less than expected?
ADDICTION

Pleasure/Relief → System bias LTP → Cues for possible reward

- Overvaluation of predicted reward
- Stress
- Failure reinforced through craving, denial, increased motivational Da, compromised Acc and Ofc

- Sensitized amygdala and nucleus accumbens
- Kindling
- Stereotyped, autonomous, compulsive B

Intermittent reinforcement
... what we see is not a direct reflection of the world but a mental representation of the world that is infused by our emotional experiences.

Siegal, EH et al in Psychological Science, 2018

REALITY

- Reality is what we take to be true.
- What we take to be true is what we believe.
- What we believe is based upon our perceptions.
- What we perceive depends on what we look for.
- What we look for depends on what we feel*.
- What we feel* depends on what we perceive.
- What we perceive determines what we believe.
- What we believe determines what we take to be true.
- What we take to be true is our reality.

*think in original

David Bohm
**GAD, MDD and the Default Mode Network (DMN)**

- Disruption between mind and body motivated by an attempt to avoid unpredictability and acute intense emotionality brought about by actual or perceived threat (GAD) or by actual or perceived loss or deprivation (MDD).

- Worry or rumination are invoked for control and predictability and, when momentarily successful in warding off aversive experiences of strong emotional responses, these self-evaluative processes are then reinforced.

- What starts off feeling like a hug turns into a viselike grip in the DMN

---

**DEPRESSION**

- **PSYCHOLOGICAL/EMOTIONAL PAIN**
  - THE LIE: I CAN TURN DOWN MY FEELINGS SO IT DOESN’T HURT/I CAN TAKE IT (COGNITIVE)
  - TEMPORARY RELIEF THROUGH LTD
  - TOLERANCE
  - FLATTENED AFFECT (EMOTIONAL)
  - HYPOTHALAMUS RESET (BEHAVIORAL)

- Mpfc influence over DMN
- LOW D2 IN Nacc due to stress
What does DEPRESSION look like in the brain?

- Hyperactive amygdala
- Smaller hippocampus
- Reduced striatal connectivity and response to reward

DOPAMINE PATHWAYS IN DEPRESSION

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

Mesocortical
- Hyperactive ofc
  - stimulus-reinforcement
- 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
### DEPRESSION

<table>
<thead>
<tr>
<th>phenomenon</th>
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<tr>
<td>SELF-CRITICISM (fight - SNS)</td>
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<tr>
<td>SELF-ISOLATION (flight –SNS)</td>
</tr>
<tr>
<td>SELF-ABSORPTION (freeze/collapse/passivity/dissociation - PNS)</td>
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<table>
<thead>
<tr>
<th>experience</th>
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<tr>
<td>Feeling (sad)</td>
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<tr>
<td>Belief (worthless)</td>
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<tr>
<td>Memory(neglect/abuse)</td>
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“**The gray drizzle induced by depression,**” William Styron wrote in his *classic memoir of what depression is really like*, “**takes on the quality of physical pain.**” In my own experience, the most withering aspect of depression is the way it erases, like physical illness does, the memory of wellness. The totality of the erasure sweeps away the elemental belief that another state of being is at all possible — the sensorial memory of what it was like to feel any other way vanishes, until your entire being contracts into the state of what is, unfathoming of what has been, can be, and will be. If Emily Dickinson was correct, and correct she was, that “confidence in daybreak modifies dusk,” the thick nightfall of depression smothers all confidence in dawn.

Maria Pavlova
Anxiety
(Arousal in situations others do not find fearful)

- LTP and sensitization of amygdala
- Decreased DA from amygdala
- Hippocampal atrophy
- Increased stress response
- SNS activation
- Read neutral expressions as angry or threatening

ANXIETY

- FEAR
- THE LIE: I CAN AVOID, ESCAPE, OUTRUN IT
- RELIEF (LTP)
- SENSITIZATION
- NEUTRAL STIMULI ANXIOGENIC
- RESET
• Double projecting hippocampal neurons to amygdala and mPFC

• Reduced Da = anhedonia

• Hippocampus encodes contextual cues and atrophies due to glucocorticoids

• Amygdala stores associations between context and aversive event

• mPFC signals whether a defensive response is appropriate in the present context

• Sensitized amygdala and habituation in ventral ACC

**PTSD**
• Release of NE increases arousal

• Release of endorphins inhibits pain

• Both inhibit memory consolidation

Subtypes of Anxiety and Depression

• **Tension:** This type is defined by irritability. People are overly sensitive, touchy, and overwhelmed. The anxiety makes the nervous system hypersensitive.

• **Anxious arousal:** Cognitive functioning, such as the ability to concentrate and control thoughts, is impaired. Physical symptoms include a racing heart, sweating, and feeling stressed. “People say things like ‘I feel like I’m losing my mind,’” Williams says. “They can’t remember from one moment to the next.”

• **Melancholia:** People experience problems with social functioning. Restricted social interactions further cause distress.

• **Anhedonia:** The primary symptom is an inability to feel pleasure. This type of depression often goes unrecognized. People are often able to function reasonably well while in a high state of distress. “We see it in how the brain functions in overdrive,” Williams says. “People are able to power through but at some time become quite numb. These are some of the most distressed people.”

• **General anxiety:** A generalized type of anxiety with the primary features involving worry and anxious arousal—a more physical type of stress.
Correlates of Anxiety and Depression

- Lower levels of 5-HT, DA, and NE
- Deactivation of cognitive control brain regions (ACC & PFC)
- Higher emotional reactivity (amygdala)
- Greater DMN
- Higher memory processing (hippocampus)
- Reflects higher salience and inability to govern ruminations
- Resetting hypothalamus controls for mood, fatigue, appetite, libido

THERE IS A CRACK IN EVERYTHING: THAT’S HOW THE LIGHT GETS IN

Leonard Cohen
Short term stress:
Relief through direct addressing, both cortical and limbic systems (LTP)

1: THALAMUS (SENSORY INPUT)

2: AMYGDALA: (EMOTIONAL SIGNIFICANCE)

3: HIPPOCAMPUS

4: ANTERIORcingulate cortex

5: Prefrontal cortex

4: Sympathetic = Fight or Flight!

3: HYPOTHALAMUS (STRESS HORMONES)
Early Warning Signs

- Physical symptoms
- Change in daily activities
- Sleep patterns
- Work, school, social activities
- Sexual behavior
- Eating
- Substance abuse
- Spending

Behavior Activation Therapy

- Best outcomes with unipolar depression
- What behaviors are being or have been eliminated
- Challenging but effective
**CONVERGENT LINES**

*Hypnosis & placebo

* Research on psychedelics (5-HT2A): psilocybin, LSD, ketamine

*Research on mindfulness meditation: Mindfulness-based Stress Reduction (MBSR), Mindfulness-based Relapse Prevention (MBRP), Acceptance and Commitment Therapy (ACT)

*Mindfulness-oriented recovery enhancement (MORE) – eight week program reduced pain severity in chronic pain opioid-abusing clients at 3 month follow-up (Garland et al 2014)

*Research on transcranial low voltage brain stimulation, neurofeedback, deep brain stimulation (DBS), and the like.

*Research on dangers, side effects, or ineffectiveness of psychotropic meds: Opiates, benzodiazepines, antidepressants.

---

Our brains secrete thoughts and feelings like the stomach secretes digestive juices or the pancreas secretes insulin.
Mindful Meditation

- Open monitoring (OM) refers to noticing negative emotions without judging or emotional secondary reactions to them.
  - Leads to improvement in emotional non-reactivity
*Focused attention (FA) refers to maintaining focus – like on breathing – to disengage from negative emotions.
  - Improves attentional control

15 minutes a week reduces worry.
MINDFUL MEDITATION

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 oneness and dissolution of ego borders during meditation.

Lehmann, Faber, et al 2012

www.elsevier.com/locate/ynimg

Lehmann, Faber, et al 2012

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, NeuroImage 60 (2012) 1574–1586


MORE STUDIES

