Mood and Motivation in Parkinson's Disease

Natalie Diaz, MD
Pacific Neuroscience Institute
Providence Little Company of Mary Medical Center

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Learning objective:

- What is mood and the biology of mood.
- Changes in mood and motivation in Parkinson's disease
- Treatment of mood disorders in Parkinson's disease.

The Clinical Spectrum of Parkinson's disease

Motor Symptoms

Tremor
Slow movement
Muscular stiffness
Problems with gait and balance
Loss of facial expression
Problems with speech and swallowing

Parkinson's disease

Non motor symptoms

Changes in mood and motivation
Problems with memory and thinking
Hallucinations
Impulse control disorders
Constipation
Urinary problems
Dizziness when standing
Insomnia
Acting out of dreams

What is Mood?

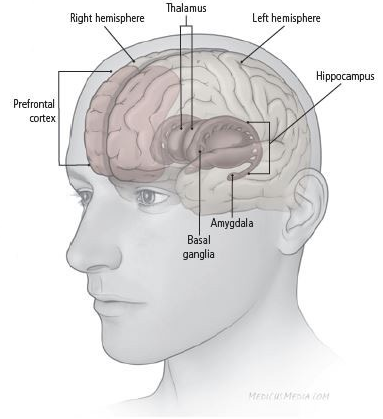
- Mood – a state of mind or feeling that is appropriate to the situational stimuli.
- Mood is a transient process and changes based on the stimuli and the situation.
- Mood disorder – mood that is persistently inappropriate or extreme in relation to the situational context.

The Biology of Mood

Chemical:

- 3 main neurotransmitters involved
  - Dopamine
  - Serotonin -
  - Norepinephrine
- Regulate mood, motivation and reward, appetite, sex drive, sleep, arousal and physical symptoms associated with mood.
- Other chemical involved:
  - Acetylcholine – attention and working memory
  - Glutamate – excitatory neurochemical involved in stabilization of cell energy

Structural:



The regions shown here are mirrored in both hemispheres of the brain. Also, these structures are interlocking; the illustration suggests location and relative region but not precise location.

Amygdala – understanding the emotional significant of different stimuli and experiencing emotions
Prefrontal cortex – regulating and controlling emotions
Ventral striatum – motivation, reward and learning

Other factors that can affect mood:

- Genetic vulnerability
- Stress
- Traumatic life events
- Inflammation
- Other medical problems – thyroid disease, anemia, low sodium or vitamin B12 deficiency, chronic infections.
- Medications – anti-seizure medications, blood pressure medications, sedatives, PD medications

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Changes in mood and motivation in Parkinson's disease

- Transient anger, frustration, irritability, demoralization are common feelings in Parkinson's disease.
- Disorders of mood and motivation, such as depression, anxiety or apathy may be more common in those with PD than with other medical conditions.
- Can occur at any stage – at diagnosis or as symptoms progress. Can also be a symptoms of medications wearing off. Predate motor symptoms in about 20-30% patient with mood disorders.
- Mood disorders associated with increased disability, worse quality of life and caregiver distress.

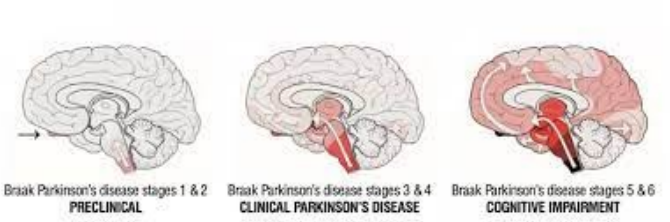
Changes in mood and motivation in Parkinson's disease

- Depression and anxiety can be an emotional response to diagnosis and living with PD.

- Mood disorders also thought to have a biological basis:

  - Reduction in levels of dopamine, serotonin, norepinephrine and their metabolites in the brain.

  - Impaired activation and connectivity between prefrontal cortex, amygdala and ventral striatum on resting state fMRI



Depression

- Most common psychiatric disorder in PD (25-50% of PD patients)
- Depression can overlap with other symptoms of PD – psychomotor slowing, loss of facial expression, insomnia, loss of energy.
- Increased risk:
  - Women > men
  - Advanced stage of PD
  - Patients with cognitive problems
- In most mild to moderate depression. < 20 % have severe depression.
- Non motor symptom most correlated with poor quality of life.
- Can affect long-term outcomes by causing social withdrawal, lack of exercise, more reluctant to seek care.

Symptoms of depression (DSM-5 criteria)

- Persistent sadness
- Feelings of hopelessness or pessimism
- Feelings of guilt, worthlessness or helplessness
- Loss of interest or pleasure in daily activities
- Diminished ability to concentrate or indecisiveness
- Psychomotor agitation
- Significant change in weight (loss or gain)
- Insomnia or excessive sleeping
- Recurrent thoughts of death or suicide

*Symptoms present for at least 2 weeks and are a change from previous functioning

Anxiety

- Occurs in 20-40% of PD patients.
- Often occurs together with depression but can occur in isolation
- Can manifest in several ways:
  - Generalized anxiety
  - Panic attacks – unprovoked or during periods of medication wearing off
  - Agoraphobia
  - Social phobia
- Can worsen motor symptoms such as tremor

Symptoms of Anxiety

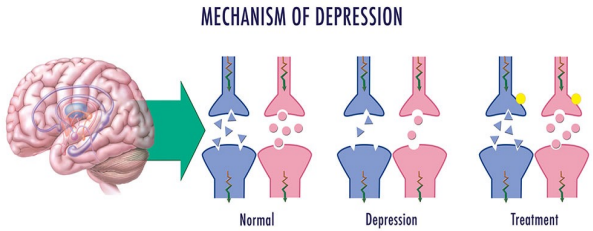
- Excessive feelings of fear, nervousness or worry associated for at least 6 months associated with at least 3 other symptoms:
  - Restlessness or frequently feeling on edge
  - Easily fatigued
  - Difficulty concentrating
  - Frequent irritability
  - Increased muscle tension
  - Sleep disturbance
- Patient may also experience physical symptoms such as unexplained bouts of nausea, shortness of breath, racing heart or sweating that occur for no reason
- Symptoms cause distress or impairment in functioning
- Not attributable to other condition or medication

Treatment of depression and anxiety in PD

- Adequate treatment of motor symptoms of Parkinson's.
- Medications – antidepressants, anxiolytics
- Therapy or counseling– i.e. talk therapy
- Lifestyle changes – regular exercise, social activities, support groups
- Other interventions – relaxation techniques, biofeedback, meditation, massage, acupuncture, aromatherapy

Medications:

- Tricyclics – 1st generation
  - **Nortriptyline**, doxepin, desipramine, imiprimine
  - May be slightly helpful in tremor. May help sleep
  - Potential side effects – dry mouth, urinary retention, constipation, sedation and confusion, lowering of blood pressure
  - Avoid use if cardiac problems, narrow angle glaucoma
  - Highly lethal in overdose



- Selective serotonin reuptake inhibitors (SSRIs)
  - Increase serotonin levels
  - Sertraline (Zoloft), citalopram (Celexa) , escitalopram (Lexapro) paroxetine (Paxil), fluoxetine (Prozak)
  - Possible side effects – nausea, may aggravate tremor, changes in weight, sexual dysfunction.

- Selective norepinephrine reuptake inhibitors (SNRIs)
  - Increase both serotonin and norepinephrine
  - Venlafaxine (Effexor), duloxetine (Cymbalta)
  - Also help with neuropathic type pain

Medications:

- Other atypical antidepressants:
  - Bupropion (Wellbutrin) – increases norepinephrine and dopamine activity. Most activating antidepressant. Least likely to cause sexual side effects.
  - Mirtazepine (Remeron) – enhances release of norepinephrine and serotonin by different mechanism. Can stimulate appetite and improve sleep

- Other treatments for anxiety:
  - Buspirone (Buspar) – directly stimulates serotonin receptors
  - Benzodiazepines –
    - Alprazolam (Xanax), lorazepam (Ativan), clonazepam (Klonopin), diazepam (Valium)
    - Stimulate inhibitory GABA receptors in the brain
    - Fast-acting, good for episodic anxiety
    - Drawback – tolerance, dependence, sedation. Long-term may be associated with dementia.

MAO-B Inhibitors and SSRIs

- MAO-B Inhibitors – selegiline, rasagiline
- Labeling on MAO-B inhibitors stress caution when combining with antidepressants.
- Potential risk of serotonergic syndrome (serotonin excess)
  - Agitation and restlessness
  - Confusion
  - High blood pressure and rapid heart rate
  - Diarrhea
  - Muscle twitching, worsening tremor
- Pooled analysis of 8 studies:
  - no cases of serotonin syndrome > 1,500 patients taking rasagiline and SSRIs
  - 11 cases of serotonin syndrome in > 4,500 patients taking selegiline and SSRIs

  - *Can J Hosp Pharm. 2018 May-Jun;71(3):196-207.

Non-Pharmacological Approach

- Psychotherapy - Cognitive Behavioral Therapy (CBT):
  - Helps people better understand their illness
  - Helps you recognize patterns of negative thoughts
  - Teaches coping skills and how to think positively

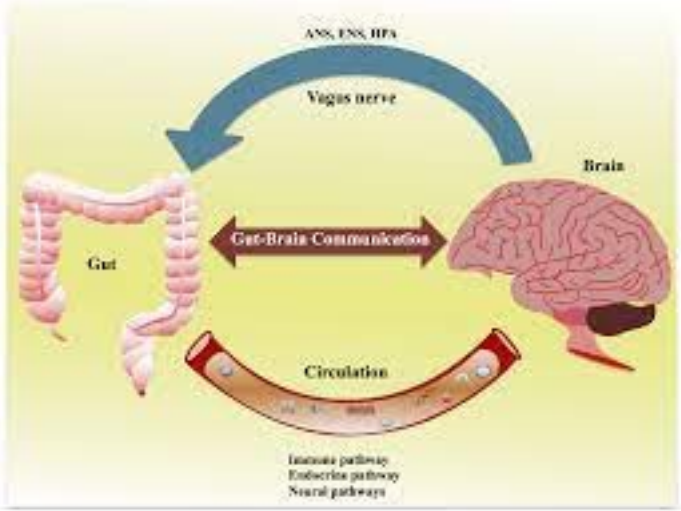
- Complementary Therapies:
  - Meditation and mindfulness
  - Music therapy
  - Massage therapy
  - Light therapy

Exercise and mood

- Robust efficacy in the treatment of mood symptoms in the general population.
- Moderate aerobic activity and resistance training shown to significantly improve depression and anxiety in Parkinson's.
- Also improves sleep and appetite.
- Improves concentration and memory.
- Lowers stress and inflammation

The Gut Microbiome and Mood

- Bi-directional communication between the gut and the brain
- In animal studies, transplantation of gut bacteria from animal expressing depressive behavior into normal animals produced similar behavior.
- In humans, severe interventional trials have shown that a mainly plant-based diet or Mediterranean diet has shown improvement in depression

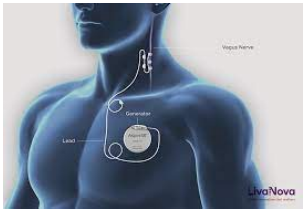


Other FDA Approved Therapies

- Electroconvulsive Therapy:
  - Electric current applied through the scalp
  - Effective in severe or refractory depression
  - May also help motor symptoms
  - Drawbacks – requires general anesthesia, temporary confusion and/or short-term memory problems.

- Repetitive transcranial magnetic stimulation (rTMS)
  - Non-invasive coils to produce magnetic pulses that stimulate specific brain regions

- Vagus nerve stimulation (VNS)
  - Surgically implanted pacemaker-like device that electrically stimulates the vagus nerve in the neck
  - Not an immediate effect



Pseudobulbar Affect

- Described as brief episodes of emotional lability that do not match a person's feelings or situation.
- Uncontrollable or inappropriate laughing or crying
- Frequently mistaken for depression
- Damage to brain areas that control normal expression of emotion.
- Can cause stress or frustration or avoidance of social interaction due to lack of emotional control.
- Nuedexta – only FDA-approved therapy

Apathy

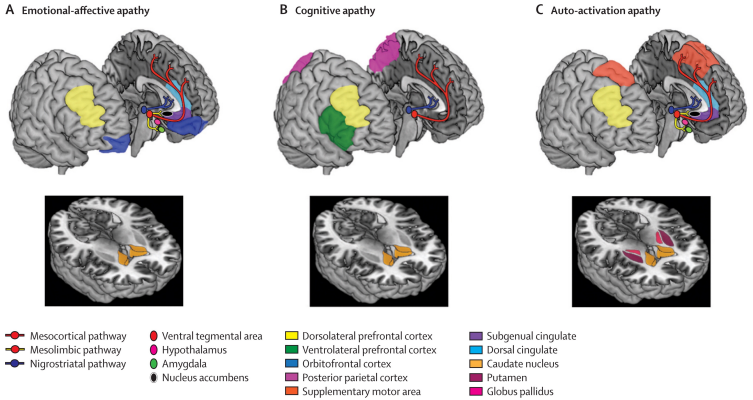
- Greek phrase meaning “without passion”
- A state of indifference, characterized by lack of interest or motivation in the world around oneself.
- In contrast to depression, a person with apathy lacks emotion. No feeling of sadness, guilt or hopelessness.
- Apathy can occur on its own or can co-exist along with depression or cognitive problems.

The different dimensions of apathy

- **Cognitive/Behavioral**:
  - Little or no-goal directed behavior, inability to “get up and go”
  - Trouble initiating activities/tasks, needs to be prompted
  - Loss of curiosity in learning new things

- **Emotional:**
  - Emotional indifference or inability to express emotion
  - Lack of passion related to activities or situations that previously provoked emotion
  - Less empathy toward feelings of others

- **Social:**
  - Less interest in participating in social or leisure activities
  - Less interest in family or interest in meeting new people
  - Less participation in conversation
  - Reduced spontaneous interactions with others



The Effects of Apathy

- **On the patient:**
  - Can have negative effects on physical and mental health
  - Lack of motivation to participate in exercise or rehab
  - Withdrawal from hobbies and social activities
  - Lack of self-awareness therefore do not seek help or understand why those around them are frustrated

- **Family and caregivers**
  - Can put a strain on relationships
  - A person with apathy may be thought to be lazy, defiant, unwilling/not wanting to help themselves.
  - Sensation that patient does not want to spend time or care about their feeling

Treatment of Apathy

- No approved therapies

- Medications that may be helpful:
  - Dopaminergic therapy – levodopa, dopamine agonists
  - Rivastigmine
  - Antidepressants that activate dopamine and enhance cholinergic function

- TMS

Coping with Apathy – non-pharmacological approaches

- Maintain a regular schedule of structured activities:
  - Focus on more relevant activities first – medical and therapy appointments
  - Chores, household duties
  - Keep a calendar and check tasks off as they are done

- Avoid isolation:
  - Schedule time with family and friends
  - Support groups

- Tips for caregivers:
  - Be patient
  - Provide positive feedback when goals are reached.

In Summary

- Mood is a state of mind associated with environmental situations.
- Regulation of mood is a complex interplay of brain chemicals and connections.
- Mood changes are common in Parkinson's disease.
- Mood disorders can be a reaction to the diagnosis and living with Parkinson's disease but is thought to have a biological basis.
- Treatment option for mood disorders include medications, psychotherapy, lifestyle changes, complementary therapies.
- Other procedures are FDA approved for severe or refractory depression