Alternative Brain–Body Communication Pathways

Focusing on Placebo Effect and Psychoneuronimmunology
Examples to Consider: (not memorize)

- Mind over Matter
  - Walking on coals
- Positive Thinking
- Placebo Effect
- Convincing yourself of illness
  - Headache, cold, H1N1, food poisoning
- Getting “buzzed” from a non-alcoholic drink
- Hives from Stress
- Hysterical pregnancy
  - (Symptoms of pregnancy but no fetus)
- Somatoform Disorders
Is this real or is it all in your head??

Yes and Yes

An increasing number of studies have found that we can imagine and convince ourselves of various realities (in our head)

But…

Sometimes they are also being carried out on the anatomical, physiological, and molecular, level (it is real)
What we will focus on to explore this process, (overview of today’s lecture)

- Some communication methods we already know
- Classically conditioning the immune system?
- Psychoneuroimmunology
  - Definition
  - Nervous and Immune system interface: the BBB
- Top Down vs. Bottom Up
- Placebo Effect
  - Definition
  - Examples of use
    - Placebo and Depression
  - Possible structures involved
Brain–body communication we have covered:

- Somatic Pathways
  - Muscle Stimulation Output
  - Sensory Information Input

- Autonomic Pathways (rest and digest/fight or flight)
  - Sympathetic and Parasympathetic
  - Two Patterns
    - Direct innervation via Neuron (ACh→Heart)
    - Hormone released into the bloodstream (from hypothalamus/pituitary)

- Pharmacology of Drugs
  - Injection, ingestion, inhalation, etc
  - We take cocaine, it passes the BBB, and our DA reuptake is blocked.

- All of these systems have a sender and receiver who can understand the messages being exchanged
  - Presynaptic neuron can synthesize ACh → Postsynaptic neuron has an ACh receptor

- Old idea: the immune system and nervous system do not possess this ability
Classically Conditioning the Immune System?

- 1975 Psychosomatic Medicine, Robert Ader

Basic Set-up:
- Step 1: associate something that affects the immune system with something that doesn’t in a population of rats
- Step 2: Test to see if the immune system can be controlled by the non-immune related drug

Components for Step 1
- Saccharin (nothing) = Neutral Stimuli
- Immunosuppressive agent (decrease immune activity/strength) = Unconditioned Response

Components for Step 2
- Antigen=Foreign agent that should be attacked by the immune system if it is at full strength and not suppressed by anything
# Results from Antigen Exposure:

<table>
<thead>
<tr>
<th>Non conditioned</th>
<th>Immune response was high</th>
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</thead>
<tbody>
<tr>
<td>Conditioned with a placebo</td>
<td>Immune response was high</td>
</tr>
<tr>
<td>Conditioned rats but not exposed to saccharin or immunosupressor when antigen is introduced</td>
<td>Immune response was high</td>
</tr>
<tr>
<td>Conditioned and given the immunosuppressent when the antigen is introduced</td>
<td>Immune response was low</td>
</tr>
<tr>
<td>Conditioned and given only saccharin at the same time as antigen</td>
<td>Immune response was low</td>
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So the Immune System and the Brain Can Talk?

- Discovery that each system secretes and receives compounds the other is capable of reciprocating
  - Previously thought to be exclusive to specific tissues

- Immune cells secrete hormones and are affected by them
  - Secrete Growth Hormone (GH)
  - Have adrenergic receptors for epinephrine → sympathetic innervation!

- Neurons have receptors for cytokines
  - These are important signaling molecules for the immune system
Definition from the National Institutes of Health:

- “the field concerned with the interrelationship between the brain, behavior, and the immune system”
Where do they exchange their information?

The **Blood Brain Barrier (BBB)** previously thought to divide the immune and central nervous systems may not only be a key interface for interaction, it may also have a regulatory role.
The Immune system can be classically conditioned

Immune System and CNS share some of the exact same signaling molecules and receptors

The location of interaction and regulation is thought to be the BBB
Placebo Effect
Two theories on information control and processing:

- **Top-Down Processing**
  - Idea that experience and perception is based on expectations from the top which influences lower areas
  - Forebrain (especially the cortex) is essentially in charge

- **Bottom Up-Processing**
  - Idea that experience is dictated by our senses (the bottom) which influence the top
  - The senses and lower brain structures are essentially in charge
Bottom up processing can also come from a non-native compound such as a **drug** taken for a specific problem.
Examples of Placebo

- Placebo drugs
  - Painkillers, antidepressants, antiparkinsonian drugs

- Placebo Acupuncture
  - (Streitberger needle)

- Placebo Surgeries
Placebo and Pain
Set up:
- Two groups in a double blind test (researchers and patients don’t know)
- Patients with depression were given either Placebo or Fluoxetine (an antidepressant)

Results:
- The two groups showed no difference in amount improved when tested qualitatively using a depression scale and questionnaires

- PET scans looking at changes in metabolic activity in the brain had the same locations of activity in the placebo as in the Fluoxetine – but the Fluoxetine group showed greater change in activity and in more places
Relationship of Early Metabolic Changes to Eventual Clinical Response

- **Expectation**: 1 week of treatment
  - MFC
  - PFC
  - VST
  - OFC

- **Recovery**: 6 weeks of treatment
  - MFC
  - PFC
  - ACing25
  - ACing24

**Groups**:
- **Fluoxetine Non-responders**
- **Fluoxetine responders**
- **Placebo responders**

+4z to -4z ArcminGlc
Top-Down and Bottom Up with Placebo and Fluoxetine

Placebo from the posterior cingulate?

Fluoxetine only areas due to bottom-up drug pathways?
Common areas seen in multiple placebo studies:

- Parts of the limbic system
  - Often associated with emotional responses
  - Includes the posterior cingulate as seen in the Fluoxeine study

- Parts of the prefrontal cortex
  - Associated with planning and executive function

- Mesolimbic Dopaminergic Pathways
  - Sometimes associated with reward in the BG and reward expectation in the frontal cortex

- But…there is ALSO activation in areas specific to each placebo effect
Criteria for placebo to work

- Personality and attitude towards the treatment
  - A strong desire to be a good patient or for the treatment to work
- Aware that they are being given a treatment
- Have an expected outcome in mind
- Be convinced it is real
  - Color of the pills, given in a Dr.’s office, from a Dr. wearing a white coat

- Related to reward and planning?
How placebo effect may effect immune related diseases
Placebo Summary

- Placebo effects can be many things including medications and surgery
- Each placebo effect can be seen in unique areas specific to the process
- There may involvement of the prefrontal cortex as well as the limbic and mesolimbic dopaminergic systems
- Patients must desire its effect, and be aware of and believe that treatment is being given
- It is also possible to have placebo when unaware if it is classically conditioned
- The workings of the mind can become the reality of the brain and body


