How do Anxiolytics influence Neural Circuitry?

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Outline

- Anxiety – a neuroscience perspective
- Functional magnetic resonance imaging (fMRI)
- Pharmaco-fMRI Study
  - Lorazepam
  - Escitalopram
- Insular Cortex and Interoception
- Anxiety – altered interoception

Psychology Meets Brain Science

- Psychological constructs: Anxiety etc.
- Tests:
  - Behavioral Tasks
  - Self-assessments etc.
- Neuroscience:
  - Brain Imaging
  - Brain Lesions
  - Animal Experiments
  - Pharmacology
Anxiety – What Target Processes?

- What are **measurable targets** for behavior and fMRI?

- Anxiety: a future oriented cognitive and emotional state/trait characteristic
  - Anxious apprehension/ anticipation and worry
  - Affective/behavioral conflict
  - Altered approach/avoidance behavior
  - Hyperarousal

Our Target Processes

- Emotional face processing
- **Anticipation** of aversive visual stimuli
- Risk-taking decision-making (**conflict**)
What Is functional Magnetic Resonance Imaging (fMRI)?

- Hemodynamic activity is closely linked to neural activity
- When nerve cells are active, they consume oxygen supplied by local capillaries
- Hemoglobin is
  - Diamagnetic (weak form of magnetism) when oxygenated
  - Paramagnetic when deoxygenated

What does fMRI measure?

- Subject perform different types of “tasks”
- MRI images are acquired continuously.
- Changes in blood oxygenation alter the image intensity in areas of the brain that are “involved in the task”.

What is Pharmaco-fMRI?

- Combine:
  - Human pharmacology
  - Magnetic Resonance Imaging
  - Blood Oxygen Level Dependent (BOLD) Contrast
  - Specific Brain Processes: Behavioral Tasks
  - Target Brain Structures
Pharmaco-fMRI Studies

Benzodiazepine & Anxiety

- Benzodiazepines:
  - GABA<sub>A</sub> Receptor Agonists
  - Complex subtypes – α<sub>3,5</sub> "anxiolysis?"

Lorazepam Study

- Goal - to show that the extended anxiety circuitry (amygdala, insula, medial prefrontal cortex):
  - Responds to a particular behavioral paradigm
  - Shows predictable changes to a standard benzodiazepine at anxiolytic doses
  - Demonstrates dose-dependency.

Paulus MP et al., Arch Gen Psychiatry 2005
Methods: Subjects

- Fifteen healthy, non-smoking, individuals.
- 6 females, 9 males
- Aged 18–39 years (mean 27.6 +/- 1.4 years)
- 12-18 years of education (mean 15.6 +/- 0.3 years)
- Recruited via general advertisement in local newspapers.

Procedures

- Acute, double-blinded administration of lorazepam or placebo
- Three conditions in randomized order between 1-3 weeks apart
- Subjects arrived at the MRI facility 60-90 minutes prior to the MRI scan
- Subjects received orally placebo, 0.25 mg or 1.0 mg lorazepam suspension mixed in diet, decaffeinated cola

Emotion Face Assessment Task

- Based on Hariri et al. 2002
- Decide:
  - Which bottom face matches the emotion expressed by the top face
  - 5-second trials
  - Presentation of angry, fearful, and happy target faces (Matsumoto & Ekman 1998)
Results: Behavioral Ratings

- Lorazepam - no effect on level of anxiety
- No effect of lorazepam on:
  - Tension, trembling, other psychomotor symptoms
- Increased sleepiness after 1.0 mg lorazepam

Paulus MP et al., Arch Gen Psychiatry 2005

Results: Task Performance

- Accuracy: 97% +/- 0.7:
  - Not affected by 0.25 mg or 1.0 mg lorazepam
- Latency: longer for matching angry or fearful faces relative to happy faces and circles or squares.
  - Not affected by lorazepam

Paulus MP et al., Arch Gen Psychiatry 2005

Results: fMRI - Amygdala

- BOLD-fMRI signal in amygdala:
  - 1.0 mg lorazepam < 0.25 mg
  - 1.0 mg lorazepam < placebo.
  - No significant difference between placebo and 0.25 mg lorazepam

Paulus MP et al., Arch Gen Psychiatry 2005
Results: Insula

- BOLD-fMRI signal in insula:
  - 1.0 mg lorazepam < 0.25 mg
  - 1.0 mg lorazepam < placebo.
  - No significant difference between placebo and 0.25 mg lorazepam

Paulus MP et al., Arch Gen Psychiatry 2005

Results: Visual Cortex

- No significant effect of lorazepam on the activation in bilateral visual cortex for placebo or the two doses of lorazepam

Paulus MP et al., Arch Gen Psychiatry 2005

Summary of Lorazepam fMRI Study

- Lorazepam, a known anxiolytic dose-dependently attenuates task-induced activation in bilateral amygdala and insula but has no effect in the visual cortex.
- BOLD-fMRI studies:
  - Where do benzodiazepines alter behavioral processes related to anxiety?
- First evidence of a dose-dependent change in fMRI:
  - by an established therapeutic agent
  - in brain regions critical for the mediation of anxiety.
**Objective**

- Within-subject chronic administration
- Healthy volunteers
- SSRI: Attenuate limbic and paralimbic activation during emotion processing?

**Hypothesis**: Escitalopram attenuates BOLD-fMRI activation in amygdala and insula during emotion processing.

**Methods**

- 13 healthy volunteers participated in double-blind, placebo controlled, randomized study.
- After 21 days of treatment with Escitalopram (5mg x 3 days + 10mg x 18 days) or placebo:
  - functional magnetic resonance imaging (fMRI, 3.0 Tesla-GE scanner)
  - Urine was collected previous to scanner session to assess Escitalopram levels.
  - Emotion Face Assessment Task
- Neuroimaging analyses:
  - ROI analysis included (1) amygdala and (2) insular cortex and (3) medial prefrontal cortex.
Urine-level dependent SSRI Effects:

- Escitalopram attenuated bilateral amygdala and insular cortex activation during the processing of emotional faces.
- This attenuation was most pronounced in individuals who had significant urine concentration of Escitalopram at the end of the 21 day administration period.

Attenuation of Amygdala Activation

Summary: SSRI Effects on Emotion Face Processing

- The SSRI Escitalopram attenuated activation of limbic neural substrates (amygdala & insula) during emotion processing dependent on urine drug concentration.
- Sub-chronic treatment with an antidepressant and acute administration of an anxiolytic show comparable effects on neural substrates.
- The dependency on the urine concentration points toward the importance of monitoring compliance to achieve reduction of limbic activation.
Insular Cortex:
Interoception: Linking Cognition and Emotion

Insular Cortex

- **Interoception:**
  - the sense of the physiological condition of the entire body (Craig 2002)
  - “How do you feel”
  - “How might you feel if…”
  - “What does your body tell you?”

Insula – The Circuit

- Body state relevant valuation, motivation, and action selection.
Computational Role of the Insular Cortex

“Is it good for me or not?”

Regulatory role:
- Computation of homeostatic demands
- Anticipation of homeostatic perturbation
- Signaling initiation of homeostatic-maintenance actions

Interoception

“Sense of the physiological condition of the entire body” (Craig 2002)
- Monitoring sensations important for integrity of internal body state:
  - Temperature, pain, itch, tickle, sensual touch, muscular and visceral sensations, vasomotor flush, hunger, thirst, air hunger, self awareness and others
- Important for allocating attention, evaluating context, and planning actions – decision-making

Interoceptive Pathways

Special nerve fibers:
- Information about body state via the midbrain into the insula cortex!
Characteristics Of The Interoceptive System

- Interoceptive sensations:
  - Intense affective and motivational components
  - Evaluation is highly dependent on the homeostatic state

- Interoceptive state:
  - Integrated in the anterior insula
  - Relayed to the anterior cingulate cortex (control and action network)

Error Processing, Learning And Prediction

- Evolutionary advantage of cortical circuitry:
  - Top-down modulation of ascending sensorimotor information
  - Ability to predict future states

- Learning associations between stimuli and future pleasant or aversive outcomes

- Discrepancy between:
  - The actual occurrence of reward and
  - The predicted occurrence of reward - ‘reward prediction error’ (Schultz et al 1997)

Anterior Insula – Prediction Of Aversive States

- Anterior insular cortex:
  - Receives:
    - Information about stimuli associated with aversive body states
  - Integrates:
    - Current body state with prediction of future body state
  - Sends out:
    - Signal to brain areas that are critical for the allocation of attention and the execution of actions
    - Signal of an impending aversive body state
Disorders of Interoception

- Anxiety:
  - Anxious Thoughts
  - Possible infringement of real or imagined body integrity
  - Body Sensations
  - Hyperarousal
  - Increased Aversive Prediction Signal

- Depression:
  - Enhanced Affective Bias

Insula – so what

- Utility of examining insular functioning in anxiety
  - Processing Target:
    - Risk-taking
    - Decision-making
    - Anticipation
  - Biomarker Target
    - Processing Differences in Anxiety disorders
    - Severity marker
    - Response to interventions

Insula – the future

- Insular function in Anxiety
  - Intervention Target (DBS?)
  - Identifying individuals at risk
  - Monitoring long-term outcome
  - Developmental Aspects

- Neural systems approach
  - Processes (risk-taking, decision-making)
  - Computational Models
  - Molecular mechanisms (gene-fMRI)
Thanks Goes To

For more information:
http://koso.ucsd.edu/~martin