Insular Hyperactivity in Anxiety Prone Individuals – A New Signature of Anxiety?

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Outline

• Why the insula?
• Insula: risk-taking and decision-making
• Insula and Anxiety Proneness
• Insula and Anticipation
• So what?

Insular Cortex: At the Computational Cross-Road between Cognition and Emotion

Afferents and Efferents

• Topographically specific afferents and efferents:
  - Cortex (parietal, temporal, orbitofrontal, ACC),
  - Thalamus (MD)
  - Striatum (both dorsal and ventral including accumbens)
  - Limbic system (amygdala, entorhinal cortex)

Computational Connections

• Insular-striatal connections provide the “gate”
  - Filtering body-relevant
  - Emotionally salient
  - Motivationally important
• signals to executive control areas:
  - ACC
  - mPFC
Neuroimaging Evidence:

- Insular Cortex:
  - Pain
    - Posterior – topographic organization
  - Emotion (Drive)
    - Anterior - agranular
  - Executive Functioning
    - Anterior - dysgranular

Insula – The Circuit

- Body state relevant valuation, motivation, and action selection.

Computational Role of the Insular Cortex

- 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 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
- Allocating attention, evaluating context, and planning actions
**Anatomy Of Interoception**
- Homeostatic neural system
- Signals from small-diameter primary afferents
- Creates an internal representation of the entire body
- Pathway:
  - Midbrain reticular nuclei
  - Ventromedial and ventroposterior thalamus
  - Interoceptive (posterior) insular cortex
  - Integrated in the anterior insular cortex of the dominant (right) hemisphere (Craig 2002)

**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)

**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)

**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

**Insular Cortex & Risk-taking and Decision-Making**
Risky Gains Decision-making

- Decide between:
  - A sure gain of 20 points
  - A risky gain of 40 or 80 points
  - Probability of punishment for 40 or 80 trials are such that there is no advantage of selecting the risky versus the safe option.

Less risky after punishment

- Subjects select the safe option 50% of the time.
- Subjects are less likely to select a risky option after punishment.
- Punishment leads to risk-aversion.

Insula response to risk

- Right Insula
  - Increased activation during risk-taking responses
  - Increased activation when response is punished
- Risk-taking decision-making:
  - Right anterior insula may process risks associated with a response

- Insula sensitivity to punishment predicts neuroticism
  - Subjects with a stronger insula activation during punishment had higher neuroticism and harm avoidance personality scores.
  - Insula sensitivity to punishment predicts a personality trait.

Insula Activation to Punishment and Temperament

Decision-making Processes

- Use time as the main independent variable:
  - Processes that are serialized in time:
    - Input
    - Assessment of Options
    - Process / Computation
      - Option – Value Association
    - Output
      - Selection of Action
      - Feedback
      - Learning, Option – Value Adjustment

Interpretation

- Right anterior insula (BA 13) activation:
  - larger when subjects selected a “risky” response versus selecting a “safe” response
  - larger when individuals were punished.
  - related to the probability of selecting a “safe” response
  - associated with neuroticism and harm avoidance
- Insula: critical role in the processing of risk during decision-making
- Greater insula response – less risk-taking behavior.
High / Low – Card Task

- Decide whether the next card is higher or lower
- Distinction between
  - Action Selection
  - Outcome Evaluation

Interpretation

- Bilateral anterior insula (BA 13) activation:
  - Selective involvement during action selection
  - Larger activation when more neurotic
  - No relationship to uncertainty of outcome
- Insula: signaling action (or action plans) in a decision-making situation
- Neuroticism:
  - Demand for greater brain processing resources to resolve appropriate action selection plans.

Action-Selection – Anterior Insula

- Bilateral anterior insula:
  - Selection of an action > experience of an outcome.
  - Activation correlated with neuroticism

Insular Cortex Hyperactivity in Anxiety Prone Individuals

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)

Anxiety Proneness

- Why Anxiety Prone?
  - Non-treatment seeking
  - Not treated
  - Subthreshold cases
  - High risk for future anxiety disorders
- Subjects recruited from San Diego State University
- Subjects comprised of two groups
  - Anxiety Prone (AP)
  - Non Anxiety Prone (NAP)

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

- Young 18-24 year old college students

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Results: fMRI - Amygdala

- HTA: Similar activation in medial
- Increased activation in dorsal amygdala

Results: fMRI - visual cortex

- HTA: No significant activation differences in fusiform gyrus or visual cortex.

Results: fMRI - Insula

- HTA:
  - Greater activation in bilateral anterior insula
  - Effect regardless of face type
- Significant correlation between anterior insula and anxiety sensitivity (ASI)

Altered Interoceptive Processing During Anticipation In Anxiety Prone Individuals

Emotion processing

- Anticipation
- Appraisal
- Reaction
- Regulation

Modified after: Neurobiology of Emotion Perception 1: The Neural Basis of Normal Emotion Perception

Van E. Nolte, Werner C. Denck, Ernst L. Koch and Richard Lane
Stimulus Anticipation Task

- Continuous performance task:
  - Blue circle LEFT button
  - Blue square RIGHT button
  - Tones: 250 msec long 500 Hz tone, 0.5 Hz
- Anticipate positive image
  - Blue (circle or square)
  - 250 Hz tone
- Anticipate negative image
  - Red (circle or square)
  - 1000 Hz tone

Task Performance

- No significant differences between AP and AN on:
  - Response Latency
  - Response Accuracy

Anticipation Effect

- Bilateral Insula activation during anticipation of negative images.

Anticipation: Group Difference

- AP individuals show greater activation in:
  - R anterior insula during anticipation of negative images
  - vACC during anticipation of all images

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)
See link: http://koso.ucsd.edu/~martin/index.html