Pharmaco-fMRI: a New Clinical Tool to Discover Anxiolytic Drugs

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Outline
1. Pharmaco-fMRI – where does it fit in?
2. What is fMRI and what it is not?
3. Biomarkers in anxiety
4. Pharmaco-fMRI studies
   - Lorazepam and emotional face processing
   - Lorazepam and risk-taking
5. fMRI study with high trait anxious subjects
6. Future directions

What Is the Problem?
• Anxiety disorders
  - Most common class of mental disorder
  - Point prevalence ~ 10%
• There are several promising drug classes
  - CRH-1 antagonists
  - Mglur2/3 and Mglur5 antagonists
  - NK1 antagonists
• But:
  - Big time lag:
    • From discovery to the demonstration of anxiolytic efficacy
    • Many failed compounds after many $ spent
What Is the Wish?

• To find shortcuts to drug development
• There is a huge leap of faith moving from phase I to phase II for anxiety
  - Drug shows some promise in preclinical anxiety models
  - Pick least toxic compound from platform
  - Administer to 500+ people in RCT
    • Dosing often uncertain
    • Clinical indications uncertain (which disorder?)
    • Failure likely

Then and Now:
The Different World of Drug Development

OLD: NEW:

We Need New Approaches

• U.S. Food and Drug Administration:
  - Mismatch between advancement in applied sciences (drug development) and basic sciences.
  - Need for new clinical endpoints.
• Pipeline problem:
  - “Our pipeline is rich with drugs that are unprecedented targets in unprecedented pathways”
  - But:
    • fewer innovative drugs move into development
    • fewer new drug applications
    • fewer innovative drugs approved each year.
What is Pharmaco-fMRI?

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

What Is fMRI (in 4 Steps)?

Step 1

- Protons when placed in a magnetic field
  - Align with the magnetic field
  - Flip between low and high energy states
- RF (radio frequency) pulses tip the net magnetization out of alignment
  - Signal: T2 - the rate of decay of the signal (out of alignment) back into alignment

What Is fMRI? - Step 2

- 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 Is fMRI? – Step 3

- The blood oxygen level dependent effect (BOLD) is complex
- Brain activation
  - ↑↑↑ Cerebral blood flow
  - ↑ Oxygen extraction
- Temporal delay of 4-6 seconds to the neural response
- The hemodynamic response lasts 12-16 seconds

What Is fMRI? – Step 4

- Where does the BOLD effect come from?
  - Expenditure of energy - restoration of ion gradients
  - Pumping sodium against the IC/EC gradient needs external energy
  - BOLD effect - excitatory synaptic activity
    - Glutamate opens sodium channels

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".
The Basic Premise Underlying Pharmaco-fMRI:

- Psychiatric disorders:
  - Brain disorders with altered metabolism in different brain structures.
- Treatments:
  - Affect neural metabolism by changing the firing rate of specific cells in different brain structures.
- Target processes:
  - Cognitive, affective or subjective/experiential processes related to the psychiatric disorder of interest.

What Can Pharmaco-fMRI Do?

- It can show:
  1. where in the brain a compound acts
  2. at what dose one observes changes in the brain
  3. whether a novel compound affects the brain similar to well-known therapeutics
- It cannot:
  1. Provide chemical specificity
  2. Differentiate which biological factors contribute to the brain change

Pharmaco-fMRI Versus PET

- Pharmaco-fMRI:
  - Can be used multiple times
  - Is available at many sites
  - Less expensive than PET (≈ 25 k / subject)
  - No ligands or radioactivity necessary
- But
  - No receptor specificity
  - Results from both neural and vascular effects
Where can Pharmaco-fMRI be useful?

- Phase I - Safety Studies
- Phase II - Clinical Trials

Proof of Principle Studies

Pharmaco-fMRI Study Protocols

- Depends on the question:
  - Acute protocol with
    - Healthy volunteers
    - Disorder population
  - Subchronic protocol
    - Healthy volunteers
    - Disorder population

Drug discovery and fMRI
Steps: fMRI Biomarker for Anxiety

- Identify brain areas
- Identify paradigms
- Anxiolytics should:
  - Alter fMRI BOLD in hypothesized brain areas
  - Magnitude of effect should correlate with anxiety changes
- Identify dose-response function
- Demonstrate effect size advantage over gold standard (current: rating scales)

Predictive Validity

Idealized scatterplot of ΔBOLD and Δanxiety responses with treatment for a critical task contrast in a key brain region (e.g., amygdala). Drugs which fall in the upper right quadrant would be predicted to have anxiolytic efficacy at those dose(s).

Characteristics: Behavioral Paradigm

- Behavioral effect sensitive to anxiety
- No ceiling / floor effects
- Repeatable
- Simple
- Sensitive to pharmacological manipulations
- Activates relevant brain areas
- Behavioral effects correlate with levels of anxiety
- Imaging effects correlate with anxiety
Anxiety – What to Target?

- What are measurable targets for behavior and fMRI?

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

Behavioral Targets for Anxiety

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Description</th>
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<tr>
<td>Ambiguity/Uncertainty processing:</td>
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<tr>
<td>Attentional bias paradigms (Mathews et al., 1989)</td>
<td>Ambiguous Face Classification (Richards et al., 2002)</td>
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<td>Attentional distractor paradigms (Mathews et al., 1990)</td>
<td>Ambiguous events task (Hamann et al., 2009)</td>
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<td>Continuous Performance Test (Ballard, 1996)</td>
<td>Emotional events task (Shanyashin et al., 2001)</td>
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<td>Anterior cingulate cortex task (Raison et al., 2003)</td>
<td>Decision making task (Wager et al., 2004)</td>
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<td>Memory recall task (Reidy &amp; Richards, 1997)</td>
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<td>Decision-making:</td>
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<td>Interference Working Memory task (Calvo &amp; Eysenck, 1996)</td>
<td>Gambling task (Aftanas et al., 1996)</td>
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<td>Behavioral control:</td>
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<td>Risk-taking decision-making (Schmitt et al., 1999)</td>
<td>Emotion or Face processing:</td>
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<td>Fear conditioning (Elliott et al., 2000)</td>
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<td>Emotional go/no-go task (Elliott et al., 2000)</td>
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<tr>
<td>Implicit or explicit Emotion or Face processing:</td>
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<td>Real/imagined conflict exposure:</td>
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<td>Probe detection task (Mogg et al., 1995; Bradley et al., 1997)</td>
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<td>Simulated public speaking (Fabere et al., 1998)</td>
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<td>Public Speaking Task (Dumontier-Bois et al., 2002)</td>
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<td>Viewing standardized pictures (Fabere et al., 1998)</td>
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<td>Viewing standardized pictures (Lang et al., 2000)</td>
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<td>Viewing standardized pictures (Kang et al., 2002)</td>
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<tr>
<td>Other:</td>
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<tr>
<td>Directed imagery of neutral, moderate and high anxiety situations (Bystritsky et al., 2001)</td>
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<td>Implicit association task (Egloff &amp; Schmukle, 2002)</td>
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<td>Anticipation of electroshocks (Boucsein &amp; Wendt-Suhl, 1976)</td>
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<td>Conditioned Tasks (Schneider et al., 1999)</td>
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<td>Avoidance control paradigm (Wright, 1984)</td>
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Anxiety Circuitry

- Amygdala
- Insula
- Medial Prefrontal Cortex

Brain Activation

<table>
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<tr>
<th>% BOLD Difference</th>
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<tr>
<td>0.7</td>
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<td>0.5</td>
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<td>0.3</td>
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<td>0.1</td>
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<td>-0.5</td>
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<tr>
<td>-0.7</td>
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<tr>
<td>Dose</td>
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</table>

Anxiety Circuitry

- Amygdala
- Insula
- Medial Prefrontal Cortex
Our Targets

• Emotional face processing

• **Anticipation** of aversive visual stimuli

• Risk-taking decision-making (conflict)

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.

Paulus MP et al., Arch Gen Psychiatry 2005
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

Paulus MP et al., Arch Gen Psychiatry 2005

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)

Paulus MP et al., Arch Gen Psychiatry 2005

Scanning / Processing

- 1.5-Tesla Siemens (Erlangen, Germany) scanner
- T2*-weighted echo planar imaging:
  - TR = 2000 ms, TE = 40 ms, 64 x 64 matrix, 20 4-mm axial slices, 256 repetitions)
- T1-weighted image
- Structural and functional image processing: Analysis of Functional Neuroimages software package (AFNI) package.

Paulus MP et al., Arch Gen Psychiatry 2005
fMRI Analysis

- Four orthogonal regressors
  - (1) happy, (2) angry, (3) fearful, (4) circle/oval sensorimotor condition
- Additional regressors:
  - residual motion (roll, pitch, and yaw), baseline and linear trend
- A priori regions of interest:
  - bilateral amygdala, medial prefrontal cortex, primary visual cortex and insula.

Paulus MP et al., Arch Gen Psychiatry 2005

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

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

Results: Visual Cortex

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

• Lorazepam, a known anxiolytic dose-dependently attenuates the task-induced activation in bilateral amygdala and insula but has no effect in the visual cortex.
• BOLD-fMRI studies can provide robust data to determine the site of action of putative anxiolytics.
• First evidence of a dose-dependent change induced by an established therapeutic agent in brain regions known to be critical for the mediation of anxiety.

Risk and Decision-making

• Risk-taking occurs within the framework of the decision-making
  – selecting an option that is associated with a potential loss, danger, or other aversive consequence.
• Subjective versus objective definitions of risk
  – ratings of preferences or behavioral patterns.
  – experimental parameter.

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.
Lorazepam - Behavioral Effects

- No significant change in Frequency of Risky Responses (with or without prior punishment)

BOLD fMRI Effects – Response Selection Phase

- Dose-dependent attenuation in left amygdala and medial prefrontal cortex.

BOLD fMRI Effects – Outcome Phase

- Dose dependent attenuation in bilateral insular cortex and right amygdala
Summary

• Lorazepam did not affect risky behavior at the doses tested
• Lorazepam dose-dependently attenuated activation:
  – In the amygdala and medial prefrontal cortex during the response selection phase
  – In the bilateral insular cortex and amygdala during the outcome phase

HTA – Amygdala Processing

• Goal - to show that the extended anxiety circuitry (amygdala, insula, medial prefrontal cortex):
  – Is sensitive to levels of anxiety
  – Is hyper-responsive in subjects with high trait anxiety

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)
**Results: fMRI - Amygdala**

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

- **Hariri: HTA versus NTA**
  -0.2
  -0.1
  0
  0.1
  0.2
  0.3
  0.4
  0.5
  0.6
  0.7

Angry - Oval Fear - Oval Happy - Oval Angry - Oval Fear - Oval Happy - Oval

**Right Amygdala Left Amygdala**

**Activation Area**

**% Signal Difference**

**NTA**

**HTA**

**Results: fMRI - Insula**

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

- **Spielberger Trait Anxiety**
  -70.060.050.040.030.0
  - Insula: Angry - Oval

  0.40
  0.20
  0.00
  -0.20
  -0.40
  -0.60
  -0.80 Rsq = 0.3214

- **Spielberger State Anxiety**
  -80.070.060.050.040.030.020.0
  - Insula: Angry - Oval

  0.40
  0.20
  0.00
  -0.20
  -0.40
  -0.60
  -0.80 Rsq = 0.0909

**Results: fMRI – visual cortex**

- **HTA**
  - No significant activation differences in fusiform gyrus or visual cortex.
Summary / Conclusion: HTA Study

- Individuals with high trait anxiety
  - exaggerated response in bilateral amygdala and anterior insula.
- Direct evidence that the combination of this task and BOLD-fMRI can detect
  - Attenuation with an anxiolytic
  - Increase with high trait anxiety in important target areas for anxiety processing.

The Road Ahead

- fMRI and behavioral paradigms:
  - Promising biomarkers for psychiatric disorders
  - Need a comprehensive screen of various fMRI/behavioral task paradigms as candidates
  - Need more rigorous pharmacofMRI studies
    - Establish utility of pharmacofMRI assay with established anxiolytic compounds
    - Demonstrate consistent within-class effects
    - Demonstrate across-class effects
  - Study new anxiolytic compound
    - PharmacofMRI in 20 subjects as part of Phase 1.5
      - Proceed to RCT
    - Learn about predictive utility...

Where Does fMRI Fit in?

- fMRI:
  - Does the drug get into the brain?
  - Where does it act?
  - Does it generate a profile similar to those of standard anxiolytics?
  - Is there a new indication of an existing drug?
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- For more information go to:
  http://koso.ucsd.edu/~martin/