Neuroanatomy of Verbal Working Memory as a Diagnostic Biomarker for Depression

Andre F. Marquand, Janaina Mourao-Miranda, Michael J. Brammer, Anthony J. Cleare and Cynthia H.Y. Fu
Silvain Dang

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Key Terms – Major Depressive Disorder
• DSM-IV Criteria:
  • One or more Major Depressive Episodes without mania or psychosis
• Major Depressive Episode:
  • depressed mood; lack of interest; weight, sleep, or motor disruption; fatigue; guilt; poor concentration; thoughts of death
  • two or more weeks; significant impairment/distress
  • not due to something else

Key Terms – Clinical Significance
• Statistical Significance:
  • Whether results are meaningful or due to chance
• Clinical Significance:
  • Whether results matter in real life and benefit the patient

Key Terms – Sensitivity, Specificity, and Accuracy
• Used to measure effectiveness of classification
  • Sensitivity: % of actual positives identified correctly
  • Specificity: % of actual negatives identified correctly
  • Accuracy: % of actual positives and actual negatives

Introduction
Relevant brain regions and activity:
• Frontal Cortical regions/Prefrontal Cortex
• Left Inferior Frontal Gyri
• Posterior Cortical regions
• Anterior Cingulate
• Limbic System
Changes related to working memory
• Cortical activity increases with difficulty of task
• Relevant regions overlap working memory circuit
Introduction

Neuroanatomy of working memory as biomarker:
- Working memory disruption common in depression
- Working memory has well-defined circuit
- Regions in circuit affected by depression

Biomarkers effective for classifying patients:
- Schizophrenia (structural imaging; accuracy 81%)
- Substance abuse (reward tasks; accuracy up to 83%)
- Depression (implicit processing of sad faces; 86%)

Prediction/Hypothesis:
- Neural correlates of working memory can discriminate patients from healthy controls for depression
- Less accurately than with affective processing task
- Less accurately than in schizophrenia
- Neural correlates of working memory can predict clinical response to treatment in patients
- Used patients participating in longitudinal drug treatment study

Methods

Subjects
Patients: 20 right-handed individuals (mean age 43.7, 14 women)
- Meet DSM-IV criteria for Major Depressive Disorder
- Minimum score = 18 on Hamilton Rating Scale for Depression
- Outpatients in prospective longitudinal drug treatment study

Controls: 20 right-handed individuals (mean age 43.7, 13 women)
- No history of psychiatric or neurological disorders and major head trauma
- Score < 7 on HRSD

Imaging
- 1.5T fMRI scanner measuring BOLD
- Cognitive Task: n-back test, with n = 1, 2, or 3
  - 14 stimuli (letters); 2 seconds between stimuli
  - Pressed button
  - 0-back (X) baseline
  - Presented in order: X1X2X3X1X2X3X1X2X3X1

Analysis
- Support Vector Machine, BOLD convolution model
- Cognitive subtraction of each difficulty level (n) from previous and subsequent baseline
- Each difficulty level was analyzed separately
- Looked for classification of patients vs. controls, and patients that respond “well” to treatment vs. those that respond “poorly”
- MAIN IDEA: each subject was compared against their own baseline, but subject pool was categorized into depressed or non-depressed

Results

Statistically significant classification between depressed and healthy subjects in 2-back task only
- Sensitivity = 65%; Specificity = 70%; Accuracy = 68%
  - P < 0.009

Statistically significant classification between “good” and “poor” response to treatment in 3-back task only
- Sensitivity = 85%; Specificity = 52%; Accuracy = 69%
  - P < 0.003
Results

Discussion

- Statistically significant
- Can distinguish between depression patients and healthy population
- Can distinguish between patients with good and poor responses to treatment

Clinical use limited by poor sensitivity, specificity, and accuracy
- Patients with stronger depression may show more accuracy
- Only 9 patients could be identified as having “good” or “poor” response to treatment

Conclusion

Functional neuroanatomy of working memory is a statistically significant but clinically limited diagnostic biomarker for depression

As a predictor of clinical response, requires more investigation

Review

Positives:
- Use of fMRI imaging with detailed statistical analysis
- Use of proven working memory test paradigm (n-back test)
- Compared results to healthy controls and 0-back background
- Considered clinical significance

Negatives:
- Poor sample size for second part of study
- No comment on whether areas activated actually related to working memory
- Insufficient comment on why there was low accuracy
- No comment on how and why this biomarker would be useful for diagnosis

Review

Future Investigations
- Investigate prediction of treatment outcome with more subjects
- Test patients prior to and after treatment
- Investigate biomarkers in other psychological disorders
- Investigate practical applications of implicit emotional processing as a diagnostic tool for depression
- Focusing on recognizing potential patients before onset of symptoms

Questions

Would defining psychological disorders via changes in neuroactivity be a beneficial step in psychopathology?