Imaging and Mood Disorders: Physiologic Biomarkers

PG4 New Frontiers in Neuropsychopharmacology, 1/9/07

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Why Biomarkers, generally?

- Problems with direct measures of the biological process you really care about
- Obtain data in a more useful timeframe
- Illuminate the causes, prevention, course, or mechanisms of treatment

Kraemer et al., Am J Geriatr Psychiatry 2002

Why Biomarkers in Mood Disorders?

- Enhance treatment outcomes by using physiologic guidance in treatment planning
- Examine biological heterogeneity in patients presenting with depressive symptoms, and relationship to outcome
- Differentiate between specific response to a treatment, and nonspecific response to the treatment process (placebo), for new drug discovery and development

Challenges in Managing MDD

- While antidepressants lead to symptomatic improvement in MDD, remission is not the common outcome
- Failure to enter remission with initial treatment has ominous consequences - symptomatic suffering, but also functional disability and impairments, and elevated risk of full relapse
- Evidence-based algorithms may enhance outcomes, but still have required the use of sequential treatment trials for each patient
- Biomarkers of remission could improve outcomes by guiding treatment plans
Predictors of Response I

- **Clinical & Demographic**: include specific symptom clusters (e.g. melancholia, anxiety), coexisting personality disorder, delusional features, medical comorbidities, psychomotor slowing, attunement, expectations, family history, functional impairment, episode duration …

- **Biological**: include presence of structural brain changes, auditory evoked potentials, dichotic listening tasks, REM latency, neuromotor slowing, thyrotropin releasing hormone stimulation test, dexamethasone suppression test …

- Tend to identify features separating responders and nonresponders, but they have not yet yielded a predictor of outcome that has been embraced in clinical practice.

Predictors of Response II

- **Neuroimaging** studies have pointed to
  - Increases in activity in paralimbic or caudate regions with treatment
  - Cortical activity decreases with effective treatment in prefrontal regions
  - Reports often assessed pre- to post-treatment changes; not in the timeframe useful for treatment planning
  - Some studies suggest changes arise in responders early in treatment (e.g. during index course of ECT), but prior studies did not indicate how early predictive changes might be found
  - Issues with dosimetry, cost, and access outside of research setting, may limit clinical application of PET and SPECT

Predictors of Response III

- **Neurophysiology** studies suggest a rationale for biomarkers based on monitoring brain function during treatment with surface EEG recordings
  - Prefrontal (PFC) and anterior cingulate cortex (ACC) are linked by white matter tracts as part of a neural circuit
  - In the theta band, EEG activity in PFC is correlated with MEG signals in ACC
  - Source localization techniques find differences in ACC theta currents between responders and nonresponders
  - Responders and nonresponders differ in theta EEG power
  - Deep brain stimulation of ACC leads to symptom improvement in MDD


Mayberg 1997; Drevets 1994; Sackeim 1988, 1994; Nobler 1994; Brody 2001

Classic Neuroimaging

Hippocampal Volume and Depression: A Meta-Analysis of MRI Studies

Meta-analysis examination of MRI studies of hippocampal volume in mood disorder

12 studies in unipolar depression had examined 351 patients and 279 healthy subjects

Depression was associated with an 8% reduction in hippocampal volume on the left (top) and 10% reduction on the right side (bottom)

Videbech & Ravnkilde
Am J Psychiatry 2004

Untreated Depression and Hippocampal Volume Loss

Study of relationship of hippocampal volume to duration of illness and to duration of untreated illness in MDD

Hippocampal volume was measured with MRI in 38 women with recurrent MDD in remission

Duration of untreated illness is better predictor of volume loss than overall illness, suggesting treatment may be neuroprotective

Sheline Am J Psychiatry 2003

Hippocampal Volume and First Major Depressive Episode After Cancer Diagnosis in Breast Cancer Survivors

Study of whether hippocampal volume was associated with developing a first episode of major depression after being diagnosed with breast Ca

Hippocampal volume was measured with MRI in 68 female survivors of breast cancer: 17 with a first MDE after dx, and 51 with no lifetime dx

First major depressive episodes after cancer diagnosis in female cancer survivors do not appear to be associated with hippocampal volume

Inagaki Am J Psychiatry 2004
**MRS in SSRI Discontinuation**

Study neurochemical changes associated with discontinuation of an SSRI medication ("drug holiday")

13 subjects with MDD stabilized on FLU and 13 on PAR underwent PBO substitution for 1 week

Plate A: voxel placement in rostral anterior cingulate
Plate B: spectra while on paroxetine (lower trace) and after 3d on PBO (upper)

Ch:Cr ratio was decreased in subjects reporting discontinuation symptoms, compared with asymptomatic subjects

May reflect altered activity in ACC associated with discontinuation syndrome

Kaufman Biol Psychiatry 2003

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**Regional Brain Activity in MDD Tx**

Study of changes in brain metabolism during treatment for MDD with paroxetine or interpersonal therapy (IPT)

24 MDD and 16 controls had FDG-PET before and after 12 wks of treatment

PAR - bilateral PFC decr
IPT - Right PFC only
Both groups - L Ant cing decr

Two interventions yield some similar yet some contrasting patterns of change in brain activity

Brody Arch Gen Psychiatry 2001

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**SSRIs in MDD vs OCD**

- SSRIs are effective treatments for both MDD and OCD
- OCD response correlated with higher pre-tx metabolism in R caudate
- MDD response correlated with higher pre-tx in medial PFC, and rostral ACC (above), and lower values in amygdala and thalamus
- Suggests different substrates in different disorders

Saxena Amer J Psychiatry 2003

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**Predictors of Lithium Response**

- **Positive Response:**
  - Loudness-dependent AEP; higher brain [Li]; lower inositol monophosphatase mRNA expression; higher 5HT-induced Ca mobilization; increased NAA peak and decreased myo-inositol peak on MRS; white matter hyperintensities; decreased intracellular pH; higher frequency of phospholipase C gamma-1 (PLCγ1)-5 repeat and PLCγ1-8 repeat; C973A polymorphism in inositol polyphosphate 1-phosphatase gene

- **Negative Response:**
  - Epileptiform abnormalities on EEG; human leukocyte antigen A3; decreased phosphocreatine peak after photic stimulation; homozygotes for short variant of serotonin transporter gene.

- Most predictors of good response are also risk factors for BAD, so lithium-responsive BAD may be a distinct subtype with special neurobiological basis.

- "The search for biological predictors of lithium response is still in its infancy"

Deep Brain Stimulation

• Electrodes have been implanted into brain tissue to manage movement disorders.
• At Brown (Butler Hospital) 5 patients with MDD were implanted in the ventral striatum; 3 of 5 met response criteria, the other two slowed lesser improved.
• At Univ. of Toronto (Rotman Inst.) 6 patients with MDD were implanted into the subgenual cingulate white matter (BA 25) and underwent high frequency stimulation (130Hz, 60µS pw). At 6 months, 66% met response criteria, and 50% met remission (though 2/6 required explantation).

Friehs Proc Int Funct Electr Stim Soc 2005 Ann Meeting; Mayberg Neuron 2005

rCBF changes from DBS

• Compared with matched controls, baseline differences include:
  * high subgenual cingulate (Cg25)
  * low dorsal anterior cingulate (Cg24)
  * low dorsolateral PFC (F9)
  * low ventromedial PFC (F47)
• After 3 months of DBS:
  * ACC, F9/46 PFC now high
  * subgenual now low
  * orbitofrontal (oF11) low
  * medial frontal (mF10) low
  * hypothalamus (hth) low

Mayberg Neuron 2005

Physiologic Biomarkers

• Study regional brain activity during treatment to detect early changes that are related to outcome
• Develop tools that could be scaled for use in clinical practice

Quantitative EEG

• Computer processing calculates “power spectrum”
• Interpretations have limited integration with other measures of brain activity (e.g. PET, SPECT, fMRI)
• Can a measure combine values derived from power spectra into more meaningful and interpretable measures?
Methodology: QEEG Cordance

- Calculated from quantitative EEG power values - integrates absolute and relative power information
- Moderately strong association with regional cerebral perfusion
- Provides information on regional activity that is interpretable in the context of PET and SPECT neuroimaging studies of depression


Cordance in Depression: Pilot Data

- EEG spectral power in the theta band (4-8 Hz) had been shown to exhibit group differences between responders and nonresponders, but with limited individual predictive value
- In case series of patients treated naturallyistically, responders and nonresponders showed difference patterns of change in cordance in the theta band
- Physiologic changes were detectable within the first few days of treatment
- Prefrontal region was of particular interest (Fp1, Fp2, Fpz)


Randomized Clinical Trials

- 51 subjects with DSM-IV MDD, Ham-D \textsubscript{17} score \geq 16
- Random assignment to either:
  - fluoxetine 20 mg or placebo
  - venlafaxine 150 mg or placebo
- 25 subjects on active medication,
  26 subjects on placebo
- One-week placebo lead-in, then eight week double-blind treatment
- Serial cordance studies to examine regional changes
- Response defined as final Ham-D score < 10

Cook et al., Neuropsychopharmacology 2002
HAM-D\textsubscript{17} Ratings over Time

Early Prefrontal Decrease in M-R

Prefrontal Decreases in M-R

PFC Decrease is Unique to M-R

Cook et al., Neuropsychopharmacology 2002

Cook et al., Neuropsychopharmacology 2002

Cook et al., Neuropsychopharmacology 2002

Cook et al., Neuropsychopharmacology 2002
Early Changes on Med and 8 week Ham-D

Week 1 Test Performance

- Using a cut-point of “0” (so any decrease is considered predictive of response) how does this relate to final outcome?
- Sensitivity - 69%
  - True Positivity - rate correctly classified by test has having the “condition” (response)
- Specificity - 75%
  - True Negativity - rate correctly classified by test as not having the condition
- Test Accuracy - 72%
  - overall “correctness” of classification

Week 2 - ROC Analysis

- Data re-analyzed at 2 week point, as this was a common decision point in clinical care, and might be a point where clinicians would be open to biomarker guidance
- Receiver Operating Characteristic (ROC) curve analysis suggested cut-point of -0.5
- Sensitivity - 77%
- Specificity - 92%
- Test Accuracy - 84%
Replication & Extension: Stage 1 Treatment Resistant Depression

- 12 subjects were treated naturalistically with an SSRI and failed to respond (3 FLX, 3 SER, 1 PAR, 5 CIT)
- Next treatment* was selected by their physician, blinded to EEG results
- EEGs recorded at cross-over and after ~1-2 weeks
- 9/12 were classified correctly (5/6 R, 4/6 NR) - sensitivity 83%, specificity 67%, test accuracy 75%, effect size .53
- Findings support the use of cordance biomarkers in TRD patients, without imposing a washout period
- Difference in accuracy (v 84%) ? due to TRD and/or carry-over effect of medication on-board and/or small N

*Subsequent Treatments: in-class switch n=2; out-of class switch n=4 augmentation n=6 (bupropion, buspirone)

Cook et al., J Psychiatry Res 2005

Independent TRD Replication

- Bareš and colleagues at the Prague Psychiatric Centre (Czech Republic) independently implemented cordance
- Enrolled 17 inpatients with Stage 1 TRD in a 4 wk trial
- Next treatments* were chosen clinically (open label)
- Measured EEGs and clinical symptoms (MADRS) at baseline and after 1 and 4 weeks, with ≥50% improvement as threshold for response (5 of 17, 29%)
- Sensitivity: 100% - 5 of 5 responders decreased
- Specificity: 83% - 10 of 12 nonresponders did not decr.
- Test accuracy: 88% - 15 of 17 correctly predicted by changes in prefrontal cordance at week 1

*Bares et al., J Psychiatry Res 2006
*Next Tx: 4 SSRI, 8 SNRI, 2 NDRI, 2 TCA, 1 other

Biomarkers of Remission in MDD

- In an experiment to learn how cordance changes in never-depressed subjects during medication exposure, 32 healthy adults received venlafaxine and EEGs
- Hierarchical cluster analysis identified electrodes with high inter-correlation in midline and right frontal cortical areas (“MRFC”):
  - FPz, Fz, FP2, AF2, F4, F8
- 37 subjects from our RCTs were then reanalyzed using this ROI and Ham-D17 ≤5 as remission (13 FLX, 24 VLX).
  - 11 of 37 remitted (30%)
- With logistic regression, decrease in MRFC at 1 wk was associated with remission (p=0.02) (trend at 2 wks, p=0.06)
- Using ROC analysis, area under the curve was 0.73. With cutpoint of 0, prediction of remission with 68% accuracy (90% sensitivity, 58% specificity)

Cook et al. NCDEU poster, 2006; Leuchter et al., in submission

Cordance Changes in Remission

Cook et al. NCDEU poster, 2006
Treatment Resistant Depression

• “Response Variability in Treatment Resistant Depression” Collaborative R01 Project, Ancillary Study to STAR*D
• UCLA and Mass General Sites
• Enroll 200 subjects with unipolar MDD and treat with an SSRI (escitalopram); EEG at start and after 2 wks
• Those who do not remit by week 12 can be treated with a second agent (sertraline); another pair of EEGs at cross over and 2 weeks into the second treatment
• Examine robustness of the biomarker predictions in this effectiveness trial setting

Alternative Technology: BRITE-MD

• Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression
• Multi-center study of a reduced-montage EEG system for biomarkers of response and remission
• One-week challenge with escitalopram, then randomized assignment to 12 weeks of escitalopram, bupropion, or combination
• Ten sites: Baylor, Cedars-Sinai, Harbor UCLA, MGH, Northwestern, UCLA/Semel, UCSD, UPMC/WPIC, UT Southwestern, R/D Clinical Research

Specificity of Biomarkers: SPARC-MD

• Specific Prediction of Antidepressant Responses with Concordance in Major Depression: collaborative R01 application (UCLA, UT Southwestern)
• Examine whether the biomarker predicts a likelihood of remission with a specific antidepressant or a more general likelihood of remission
• Measure two biomarkers prior to the treatment trial (escitalopram and bupropion) and test associations between biomarker predictions with the treatment agent vs those with the other medication
SPARC-MD Design

- 172 adults with MDD (86/site)
- Test specificity of the prediction using Biomarkers for T1, T2, and T3 periods
- Outcomes for TxA and TxB periods

Integrating Biomarker Guidance into Treatment Management

Patient category | Possible immediate impact | Possible long-term impact
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Predicted Remitter | • Encourage treatment adherence | More patients achieve response / remission
 | • Avoid unnecessary switching and/or augmentation | Patients achieve response / remission sooner
Predicted Non-Remitter | • Progress to next step(s) in treatment sequence more quickly | Less cost, less impairment/disability, less relapse
 | • Prevent treatment discontinuation before achieving remission |  

EEG tests at baseline and after 1 week of treatment

Side Effect Biomarkers

- Adverse effects may be related to pharmacodynamic and/or nonpharmacodynamic effects (e.g., nocebo phenomena)
- 32 never-depressed adults randomized to placebo (n=15) or venlafaxine IR (n=17)
- 1 week PBO lead-in, 4 weeks treatment
- Medication side effects - semi-structured interview
- SE burden was associated with prefrontal EEG changes at the end of lead-in \( r = -0.67 \ p < 0.003 \) at 2 weeks \( r = -0.77 \ p < 0.002 \) and 4 weeks \( r = -0.77 \ p < 0.004 \) post-randomization
- Variance in SE burden is explained by EEG changes during lead-in; subsequent changes do not add greater explanatory power.

Side Effect Biomarkers

Hunter et al., Neuropsychopharmacology 2004
Pretreatment Features

• Pizzagalli built on the PET work from Mayberg (1997) and Wu (1999), by using LORETA - low resolution electromagnetic tomography, with 18 adults treated with nortriptyline for MDD.

• Theta activity in the rostral-most anterior cingulate (Brodman 32, 24, some of 10) was related to outcome - better response accompanied higher pretreatment values (but only 2 NR).

Nonspecific vs Specific Response

Placebo vs “Specific” Response

• Classically, response to placebo is marked by a quick but transient improvement in symptoms.

• Placebo lead-in is intended to remove them from most RCTs.

• How is placebo response related to specific response - time course, physiologic changes?

HAM-D Ratings over Time
Later Changes Characterize P-R

Identification of PBO Response

- Responders to PBO had at baseline
  - Lower frontocentral cordance (AF1, AF2)
  - Faster cognition (digit-symbol)
  - Less terminal insomnia
- Logistic regression model identified 97.6% of PBO-responders
- Extension project now funded (NCCAM)

Conclusions

- Functional neuroimaging with PET and related techniques continues to reveal features of neurobiology in mood disorders in a research setting
- Physiologic neuroimaging with EEG may be better suited to clinical application in a treatment setting
- Decreases in prefrontal cordance characterized the medication responders, and were found as early as 48 hours into treatment
- Replication with SSRI and mixed-action meds; biomarker now undergoing large-scale tested in the effectiveness setting
- Prefrontal activity may be associated with side effects as well as with therapeutic effects