iSPOT-D: International Study to Predict Optimized Treatment – in Depression

Investigators from 20 sites across 5 countries

22 publications: www.BrainResource.com/Research/iSPOT/iSPOTD
iSPOT-D: Objective and Overview

- **Objective**: Identify pre-treatment markers of MDD response and remission (after 8 weeks of treatment) to three common antidepressants.

- **Overview**: This is an open-label, randomised (effectiveness) study (i.e. comparison of active treatments) to identify genetic markers, brain function, brain structure, psychological and cognitive indicators (or a combination of markers) in MDD subjects versus healthy controls.

- Approximately 1,700 subjects with major depressive disorder (MDD) across 20 international sites (USA, Europe, Australia) are randomised to one of three treatment arms:
  - Treatment A: Escitalopram
  - Treatment B: Sertraline
  - Treatment C: Venlafaxine XR

- **Training cohort** (n=1008) and **Replication cohort** (n=702) are complete.

![Clinical Evaluation & Self Report](image1.png)
![Genomic](image2.png)
![Cognition](image3.png)
![EEG, ERP, Heart Rate](image4.png)
![MRI, DTI, fMRI](image5.png)

In males, non-remitters to sertraline can be identified with 91% accuracy in the training set.

Non-remitters are identified by a specific profile of poor cognitive functioning - slow motor coordination, poor impulse control and executive functioning, and poor emotion identification.
Predicting treatment outcome: ABCB1 gene

In a functional polymorphism upstream from ABCB1 gene (rs10245483), G/G common allele homozygotes have greater remission to SSRIs escitalopram and sertraline. T/T minor allele homozygotes have greater remission to SNRI venlafaxine-XR.

**Remission by Genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Escitalopram</th>
<th>Sertraline</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td></td>
<td>*</td>
<td></td>
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</tbody>
</table>

% patients who remit
Predicting treatment outcome: SSRIs – EEG resting asymmetry


Female remitters to SSRIs escitalopram and sertraline have more left lateralized activity frontal activity at rest (right lateralized alpha).

**Baseline EEG alpha asymmetry**

$p<.001$; ES=0.55

HRSD17 Non-Remission
HSRD17 Remission
**iSPOT-D: international Study to Predict Optimized Treatment in Depression**

**Predicting treatment outcome: SNRI - Theta EEG**


Responders to the SNRI venlafaxine-XR have lower frontal and rACC theta.

**Responders < Non-Responders to Venlafaxine-XR (p<.05)**

Decreased theta mainly at BA6 (Medial Frontal Gyrus), BA24 (Cingulate Gyrus) and BA31 (Paracentral Lobule).
Replicated:

A subgroup of 52% of non-remitters can be identified with 82% accuracy, combined across treatment with escitalopram, sertraline and venlafaxine-XR. Non-remitters are identified by a combination of smaller left medial frontal volume and larger the right angular gyrus volume.
ADDICTION: Training Reduces Clinical Symptoms

Exercises played

- Relaxation Room
- eCatch the feeling
- Thought Tamer

Symptom Level

- Low
- High

Amount of Gameplay

- Low Gameplay (z < -0.5)
- High Gameplay (z > 0.5)
**Biomarker Findings in Psychiatry**

**Depression:** Shows the highest % Negativity Bias

![Graph showing % Classification for Depression, PTSD, Panic Disorder, ADHD, Anxiety, MCI, Controls.](image)

**Anxiety:** Correlates with high HR and low HRV

<table>
<thead>
<tr>
<th>Heart Rate (HR)</th>
<th>Heart Rate Variability (HRV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Controls</td>
</tr>
<tr>
<td>Controls</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Controls</td>
<td>Controls</td>
</tr>
</tbody>
</table>

**ADHD:** Increased EEG Theta in ADHD

![EEG Theta maps for ADHD and Controls.](image)

**PTSD:** Greater activation in Amygdala to nonconscious fear faces

![Brain images showing Amygdala activation in Controls and PTSD.](image)

**Schizophrenia:** Reversed fMRI connectivity to Fear

![fMRI connectivity maps for Controls and Schizophrenia.](image)

**Alzheimer’s:** Memory deficits in mild cognitive impairment (MCI), Subjective Memory Complaint (SMC), and Alzheimer’s Disease (AD) from normal controls

![Graph showing Memory Recall Score by Age (years) for Normals, SMC, MCI, AD.](image)

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*Brain Resource International Database*

*Findings Published via BRAINnet.net*

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P.T.O. for references
Disruptive Technology Gets Personal
BrainFutures 2015
U.S. Military Tests Predictive Analytics to Better Treat Depression in War Veterans

Joel Schectman
Reporter

The military is testing whether a cloud-based predictive analytics tool that identifies when soldiers are at higher risk for depression can help doctors do a better job treating depression in military personnel.
Predictive Analytics Using Quantitative EEG
An analysis that displays outcomes for neurosimilar patients:

- by medication class
- by medication
- with PPV/NPV
- builds evidence with “machine learning” algorithms
Open Science – machine-learning

Peer Summary

PEER ID: R-131211
Patient: Details

Request Date: 9/2/2014 11:58 AM
Physician: Demo Carpenter

PEER Report Fluoxetine

Drug Detail

Fluoxetine report

- Known Non-Responses
- Known Responses

Similarity to known non-responders

Likelihood of Response
How we build evidence

A “crowdsourced” clinical registry built by physicians

n >= 10,000 unique patients
n >= 38,000 outcome correlations
> 1 year follow period
Evidence
Elliot Spitzer’s \textit{other} scandal

- Only 51% positive trials, NOT 94%  
- Only 2 PTSD on-label meds  
- Zoloft example: mostly negative studies, 1 positive with $n = 283$
A growing literature designates medication-free baseline EEG data as the independent variable and predicts medication response as the dependent variable, which demonstrates a clear relationship between neurophysiologic findings and treatment response.

Stephen C. Suffin, MD
Chief Lab Officer, Quest Labs

We can predict non-responders using “an easy, relatively inexpensive, predictive, objective office procedure that builds upon clinical judgment to guide antidepressant choice.”

Charles DeBattista, MD et al
Stanford University School of Medicine

100+

peer-reviewed clinical trials have demonstrated successful correlations of digital EEG data to medication response

www.PEERDossier.com
<table>
<thead>
<tr>
<th>Authors</th>
<th>Publication Title</th>
<th>Trial Design</th>
<th>Enrolled subjects</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>PEER</th>
<th>Control</th>
<th>Summary/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeBattista, C, et al., Journal of Psychiatric Research, 2010</td>
<td>The use of Referenced-EEG (rEEG) in assisting medication selection for the treatment of depression</td>
<td>DB-RCT</td>
<td>114</td>
<td>Treatment Resistant Depression</td>
<td>QIDS-SR16; Q-LES-Q-SF</td>
<td>65%</td>
<td>39%</td>
<td>rEEG-guided pharmacotherapy was more effective in subjects with depression than employing a treatment algorithm derived from the most effective medications in the STAR*D study. rEEG may represent an easy, inexpensive, predictive, objective office procedure that builds on clinical judgment to guide antidepressant choice.</td>
</tr>
<tr>
<td>DeBattista, C, et al., NCDEU Poster, 2009</td>
<td>Review of current results in the use of Referenced-EEG in the guidance of psychotropic medication selection for treatment-resistant depressed patients</td>
<td>SB-RCT</td>
<td>18</td>
<td>Treatment Resistant Depression</td>
<td>QIDS and Q-LES-Q scores</td>
<td>58%</td>
<td>0%</td>
<td>rEEG group had better outcomes than those medicated per TMAP standard, regardless of sub-grouping by equivalency. Depression scores (QIDS) and quality of life scores (Q-LES-Q) were significantly improved vs. TMAP. Results consistent with prior trials investigating the use of rEEG efficacy in guiding Treatment Resistant patients.</td>
</tr>
<tr>
<td>Suffin, S, et al., Journal of American Physicians &amp; Surgeons, 2007</td>
<td>A QEEG Database Method for Predicting Pharmacotherapeutic Outcome in Refractory major Depressive Disorders</td>
<td>DB-RCT</td>
<td>13</td>
<td>Treatment Resistant Depression</td>
<td>Ham-D, BDI, CGI scale</td>
<td>85%</td>
<td>17%</td>
<td>Prospective, randomized, blinded, controlled study comparing outcomes in refractory major depressive disorder (MDD) guided by electroencephalography-based medication outcome prediction. There were statistically significant differences between the two groups in pretreatment vs. treatment HAM-D and Beck Depression Inventory scores (P&lt;.009) and CGI scores (P = .02).</td>
</tr>
<tr>
<td>Schneider, B, et al, Neuropsychiatric Disease and Treatment</td>
<td>The use of the Psychiatric Electroencephalography Evaluation Registry (PEER) to personalize pharmacotherapy</td>
<td>DB-RCT</td>
<td>150</td>
<td>MDD</td>
<td>QIDS-SR16, CHRT, PCL</td>
<td>x</td>
<td>x</td>
<td>Peer-reviewed and accepted 6/14; release s.t. Walter Reed</td>
</tr>
</tbody>
</table>
PEER Randomized Controlled Trials

Medication efficacy doubled:
Mean change from baseline was -43% when guided by PEER vs -20% for Treatment as Usual.

50% improvement in Treatment Efficiency — PEER surpassed Control group in half the number of visits.
<table>
<thead>
<tr>
<th>QEEG Controlled Trials</th>
<th>Trial Design</th>
<th>n</th>
<th>Diagnosis</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arns M, Bruder, Hegerl, Spooner, Palmer, Etkin, Fallahpour, Gatt, Hirshberg, Gordon.</td>
<td>DB-RCT</td>
<td>1344</td>
<td>MDD</td>
<td>AD</td>
</tr>
<tr>
<td>Thiago M. Fidalgo, MD, Journal of ECT &amp; Volume 00, Number 00, Month 2013</td>
<td>Systematic Review</td>
<td>12</td>
<td>MDD</td>
<td>rTMS</td>
</tr>
<tr>
<td>Turker Tekin Erguzel et al., Psychiatry Investig 2015;12(1):61-65</td>
<td>Open label</td>
<td>55</td>
<td>MDD</td>
<td>rTMS</td>
</tr>
<tr>
<td>Khodayari-Rostamabad A, Conference Proceedings, 2011</td>
<td>Open label</td>
<td>27</td>
<td>MDD</td>
<td>rTMS</td>
</tr>
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</table>
Frontocingulate Dysfunction in Depression: Toward Biomarkers of Treatment Response

Results from the current meta-analysis indicate that increased pre-treatment rACC activity is a reliable marker of treatment response in depression, which is associated with a large effect size (Cohen's d value: 0.918) and has been replicated across 19 studies.

Highlighting the robustness of this finding, a link between increased rACC activity and positive antidepressant response has emerged across treatments, including various classes of antidepressant drugs (eg, SSRIs, atypical antidepressants, ketamine), sleep deprivation, and rTMS.

The clinical and research implications of these findings are substantial. From a clinical perspective, the current meta-analysis indicates that it is possible to identify a priori individuals with a low probability of response to monotherapy, who might benefit from a combination of treatment interventions at the outset.
PEER Replication Trials

Southern California PEER Trial:
- Real-world evidence trial “outside the fenceline”
- Substantially similar design and protocol
- Target enrollment $N = 468$

NATO PEER Trial:
- Led by Canadian Forces
- Substantially similar design and protocol
- Target enrollment $N = 300$

Defense Health Agency:
- Continuing current protocol at large active bases
QEEG predictive analytics

Baseline EEG

Standard International 10-20
Every prescribing decision involves weighing risks vs benefits

“the art of medicine is the art of balancing probabilities.”
— Sir William Osler, 19th century physician