Brain Resource Limited

24 January 2011

Presentation at the Personalized Medicine World Conference

Please see attached a copy of the presentation given by Dr Evian Gordon, CEO, at the Personalized Medicine World Conference being held in Silicon Valley this week. This conference examines the advances and challenges of Personalized Medicine through a practical lens and brings together the thought-leaders of business, government, healthcare-delivery, research and technology.

The main feature of this presentation is to demonstrate the power of our methodology for identifying Biomarkers and translating them into having both clinical and drug development utility.

We have many outcomes from our 10 years of building the Brain Resource International Database, including the iSPOT study, and we are planning a cascade of campaigns to demonstrate their value.

This presentation is part of a systematic campaign beginning 2012 to:

1) lodge the first Personalized Medicine predictive diagnostics for the Brain with the FDA (we anticipate receiving feedback from the FDA on next steps very soon);
2) identify the right marketing partner for co-distribution of a companion diagnostic once approved for the 3 antidepressants tested in iSPOT – note as all three drugs are generic from March this year, there is the opportunity to leverage this diagnostic as a strong differentiator for driving sales of these three drugs;
3) find the right partner to further develop Molecular Assays based on our iSPOT brain data and blood samples;
4) showcase power of our methodology for helping pharmaceutical companies to develop companion diagnostics for drugs in their pipeline; and
5) showcase the benefits of our companion diagnostics to Payers to aid their cost efficiencies.

About Brain Resource
Brain Resource Ltd translates the most useful new brain findings from the Brain Resource International Database into: (i) scalable web products that empower individual users to assess and train their brain to be more effective at work and in life; and (ii) new tests anticipated to help predict which individuals will best respond to what medication.

For more information, please visit www.brainresource.com or Media contact Julian Brophy (julian@perceptionpartners.com.au, 0408 276 749) or Dr Evian Gordon (CEO) +61 407 272 000.

Personalized Medicine and Companion Diagnostics

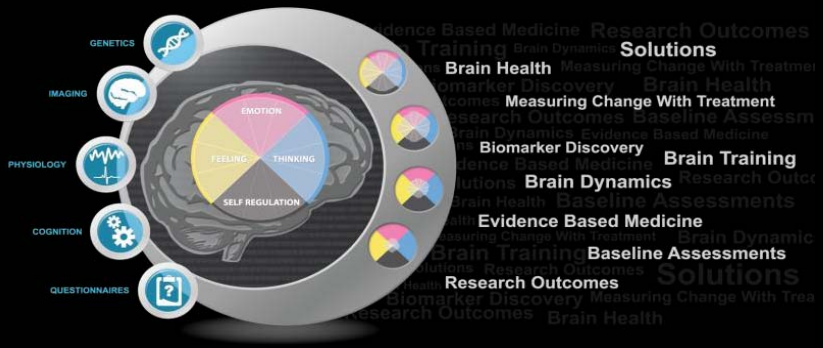
The role of a standardized platform

Dr. Evian Gordon
Executive Chairman
Brain Resource

PMWC 2012
PERSONALIZED MEDICINE WORLD CONFERENCE
- SILICON VALLEY -

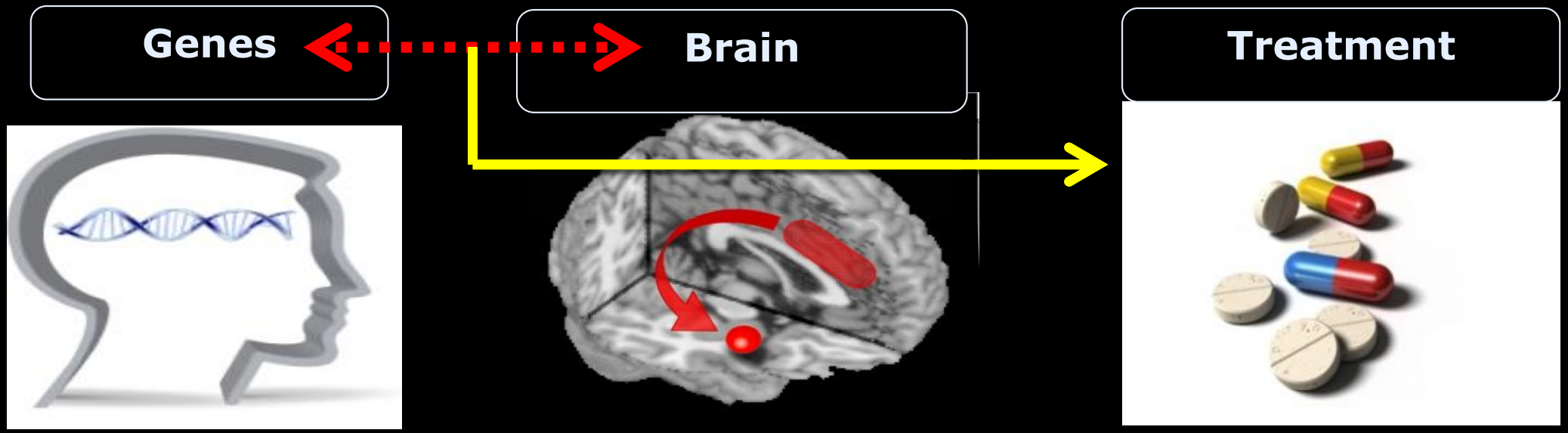
A Standardized Integrative Platform

to find Biomarkers at unprecedented speed and unparalleled efficiency



Expands the Biomarker discovery methodology beyond Genomics, to integrate Neuroimaging and Cognition

Biomarkers Predict Treatment Response



Brain Resource is conducting the largest Biomarker Personalized Medicine global study: 2,000 MDD subjects.

Goal: Companion Diagnostic Biomarkers for Rx prediction in the 3 most commonly prescribed medications in Depression.

First 1,000 subject's are being analyzed.

FDA Pre-IDE interactions underway.

Biomarkers complementing Genomics

Circuits provide a framework that incorporate ALL Biomarkers:

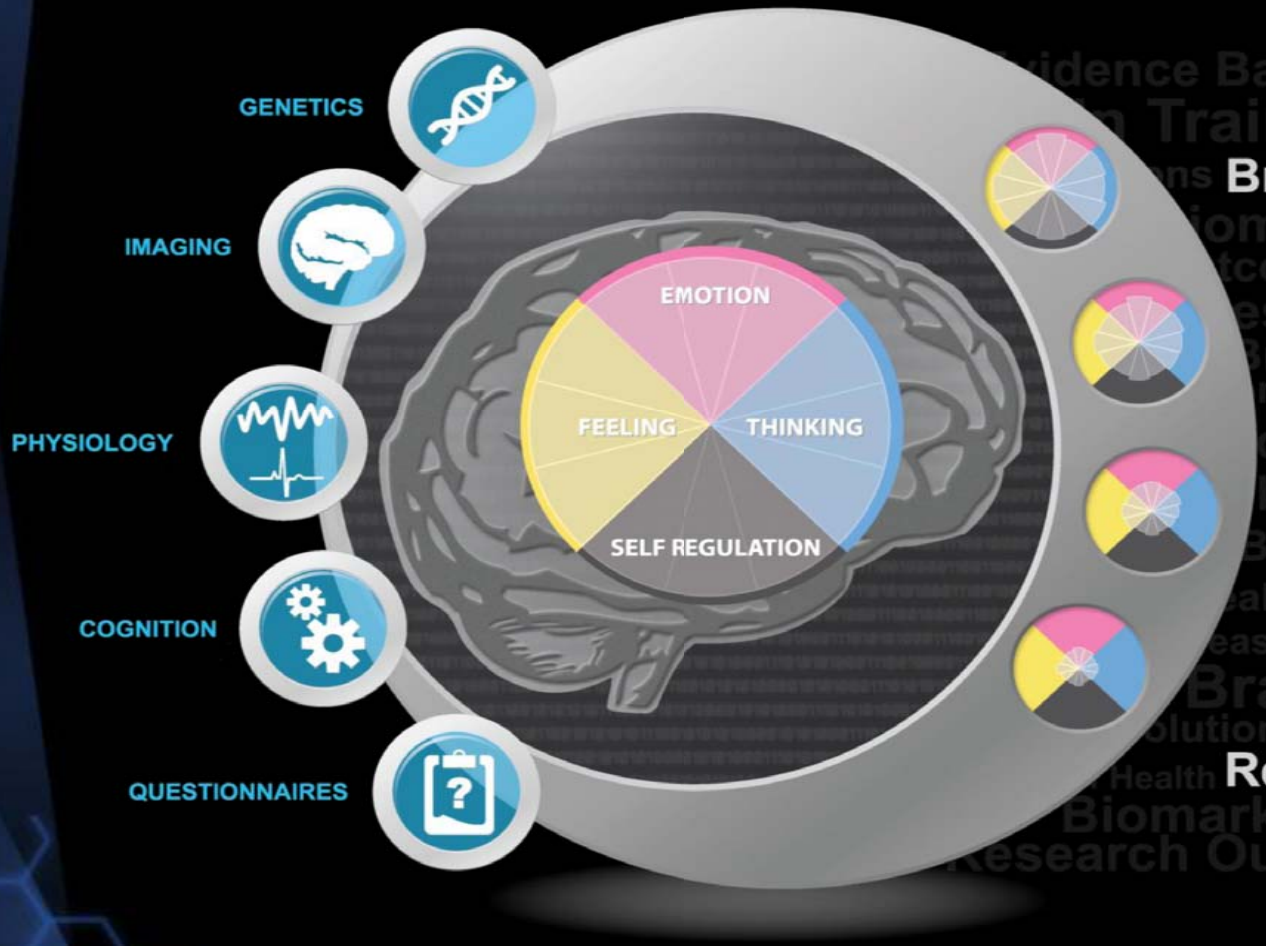
- Genomic Biomarkers
- Circuitry Biomarkers (MRI; DTI)
- Physiological Biomarkers (EEG; ERPs)
- Behavioral Biomarkers (Cognition)

Clear “end points” (outcomes) to predict:

- Overall Response
  No/Yes: defined by symptom remission
- Different responses to different Types of treatment
  (Escitalopram; Zoloft; Venlafaxine)
- Dose
  (Ex. Venlafaxine: SSRI <150mg; SNRI>150mg)
- Side effects
- Long Term Remission

"Nothing Scales Without Standardization"

Standardized + Integrative Platform



Solutions

Brain Health

Measuring Change With Treatment

Biomarker Discovery

Brain Training

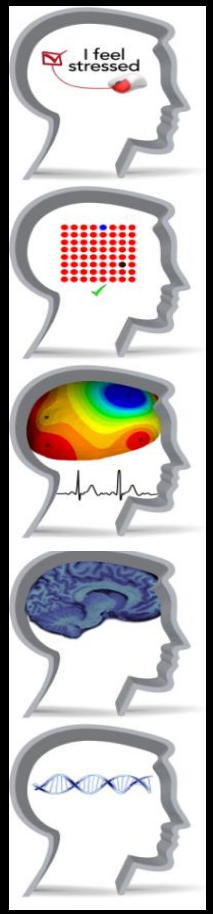
Brain Dynamics

Evidence Based Medicine

Baseline Assessments

Research Outcomes

Standardized and Integrative Platform



Psychology. *Self-report*

Behavior. *Tasks for cognition and emotion*

Physiology. *EEG, Event-related potentials, Heart Rate*

Brain imaging. *MRI, Functional MRI, DTI*

Genetics. *Bloods for GWAS, Gene Expression, Proteomics, Metabolomics*

Standardized Work-up

Identical software, accessed from internet

Identical touchscreens and software

Identical lab specs and EEG Amplifiers

Same GE 3T scanners and paradigm software.

via image processing

Same blood draw and storage specs

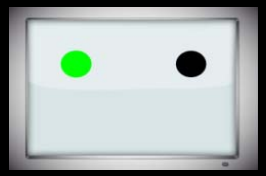
via DNA service

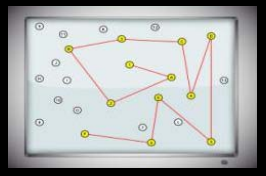
Centralized Relational Database for integrating Data

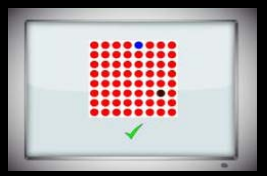
Standardized Cognition Markers

Questions *[Feeling and Self Regulation]* (5 min)

Objective Cognitive Tasks *[Thinking and Emotion]* (30 min)

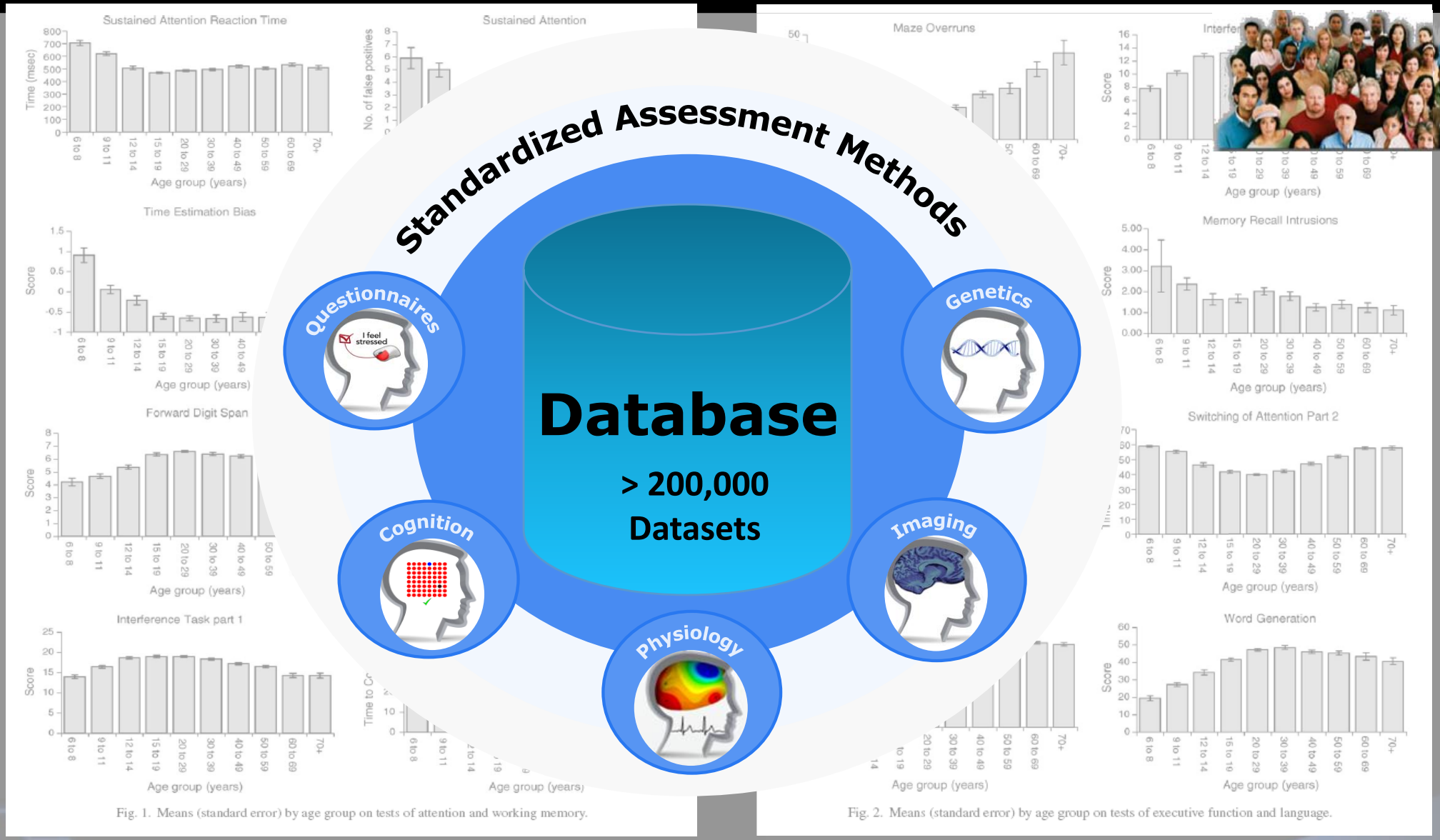






English, Mandarin, Arabic, Hebrew, Spanish, Dutch Language Versions

Brain Resource International Database



Clark et al., 2006; Mathersul et al., 2009; Williams et al. 2009

Depression: Proof of Concept

n=128 patients enrolled.
Outcomes for
n=30 followed up after
antidepessant treatment

Treatment Response

Candidate behavioral markers
Assessed with touchscreen cognitive tasks

Group	% improvement with SSRI
Depressed patients **Impulsivity** Biomarker	76%
Depressed patients Impulsivity plus Emotion Biomarkers	84%
Compared to average for total group	39%

Treatment Response

Candidate cognitive markers of response to SSRI – Response Speed plus Emotion Identification

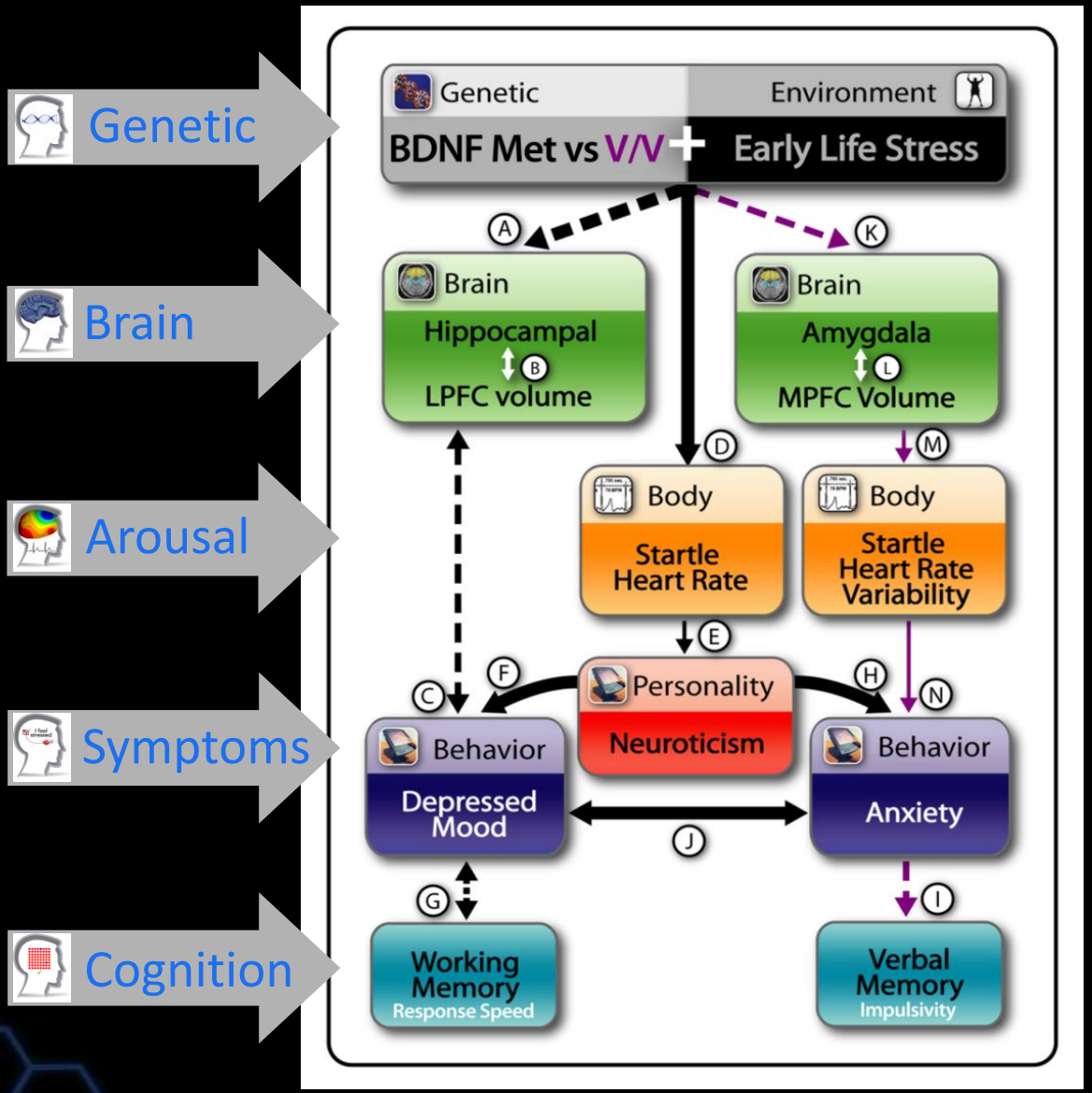
Group	% Improvement with SNRI
Depressed patients with **Response Speed** Biomarker	69%
Depressed patients with Response Speed plus Emotion Biomarkers	74%
Compared to average for total group	39%

Treatment Response

Findings link back to Genetic predictors

Genes	Response status	Analysis
BDNF Val 5HTT Short COMT Met	Responders $HDRS_{17}$ ≥50%	Logistic regression
BDNF Met 5HTT Long COMT Val	Non-Responders $HDRS_{17}$<50%	Logistic regression

Consistent with other Circuit Gene-Neuroimaging Biomarkers



Molecular Psychiatry (2009) 14, 681–695

www.nature.com/mp

ORIGINAL ARTICLE

Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety

JM Gatt[1,2], CB Nemeroff[3], C Dobson-Stone[4,5,6], RH Paul[7], RA Bryant[1,8], PR Schofield[4,5,6], E Gordon[1,2,9], AH Kemp[1,2] and LM Williams[1,2]

Interaction of BDNF and Early life stress predicted a cascade of effects:

- Loss of gray matter
- Increased Heart Rate
- Depression and Anxiety Ss
- Cognitive thinking problems in response speed and impulsivity

iSPOT Depression Protocol

- It's a "practical trial" mirroring routine practice in 2000 MDD
- Along with Clinical information, Genomic and Neurobiological measures
- Standardized methods


STUDY PROTOCOL

TRIALS

Open Access

International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol

Abstract

Background: Clinically useful treatment moderators of Major Depressive Disorder (MDD) have not yet been identified, though some baseline predictors of treatment outcome have been proposed. The aim of iSPOT-D is to identify pretreatment measures that predict or moderate MDD treatment response or remission to escitalopram, sertraline or venlafaxine, and develop a model that incorporates multiple predictors and moderators.

Methods/Design: The International Study to Predict Optimized Treatment - in Depression (iSPOT-D) is a multi-centre, international, randomized, prospective, open label trial. It is enrolling 2016 MDD outpatients (ages 18-65) from primary or specialty care practices (972 per treatment arm; 622 age-, sex- and education-matched healthy controls). Study-eligible patients are antidepressant medication (ADM) naive or willing to undergo a one-week washout of any non-protocol ADM, and cannot have had an adequate response to protocol ADM. Baseline assessments include symptoms; distress; daily function; cognitive performance; electroencephalogram and event-related potentials; heart rate and genetic measures. A subset of these baseline assessments are repeated after eight weeks of treatment. Outcomes include the 17-item Hamilton Rating Scale for Depression (primary) and self-reported depressive symptoms, social functioning, quality of life, emotional regulation, and side-effect burden (secondary). Participants may then enter a naturalistic telephone follow-up at weeks 12, 16, 36 and 52. The first half of the sample will be used to identify potential predictors and moderators, and the second half to replicate and confirm.

Discussion: First assessment was in December 2008, and is ongoing. iSPOT-D evaluates clinical and biological predictors of treatment response in the largest known sample of MDD collected worldwide.

Trial registration: International Study to Predict Optimized Treatment - in Depression (iSPOT-D) ClinicalTrials.gov identifier: NCT00693849

URL: http://clinicaltrials.gov/ct2/show/NCT00693849?term=International+Study+to+Predict+Optimized+Treatment+in+Depression+(iSPOT-D)&rank=1

Background

Major depressive disorder (MDD) is the fourth most disabling medical condition worldwide (based on disability-adjusted life-years) and is expected to be ranked second by year 2020 [1,2]. MDD is typically recurrent, often chronic and disabling, with a lifetime prevalence rate of over 15% [3]. Women are approximately twice as likely to develop MDD as men. MDD is associated with high health care costs [4]. Antidepressant medications (ADMs) are effective, [5-9], but only about 50% of patients with MDD show a response (>50% reduction in baseline symptoms) and only about one in three attain remission (virtual absence of symptoms) within the first eight weeks of treatment [10-12]. Those who do not attain remission remain at high risk for subsequent depression, functional impairment and serious general

Williams, Rush, Koslow, Wisniewski, Cooper , Nemeroff, Schatzberg, Gordon, *Trials,* 4, 2011

USA	**(*Site Replication of Results)**
California	Stanford University*
	Shanti Clinical Trials Colton*
	Center for Healing the Human Spirit Tarzana*
Florida	Miami University
Missouri	University of Missouri St Louis*
New York	Cornell University
	Brain Resource Center, NYC*
North Carolina	Skyland Behavioral Health Associates*
Ohio	Ohio State University*
Rhode Island	NeuroDevelopment Center, Providence*
Virginia	University of Virginia*
Australia & New Zealand	
Sydney	University of Sydney*
Melbourne	Monash University & Swinburne University
Adelaide	Flinders University*
Auckland	University of Auckland, New Zealand
Europe	
Netherlands	Brainclinics Diagnostics & Treatment, Nijmegen*
Africa	
Johannesburg	University of Wittswatersrand, Johannesburg*

*Sites contributing to recruitment of the first n=1000 patients

iSPOT Protocol

Primary phase of study

Baseline Visit
Week 0

Randomized to Medication
Usual Care and Titration

Genetics and
Neurobiology workup

Telephone Monitoring
Weeks 2, 4 and 6

Repeat Visit
Week 8

Repeat
Neurobiology work up

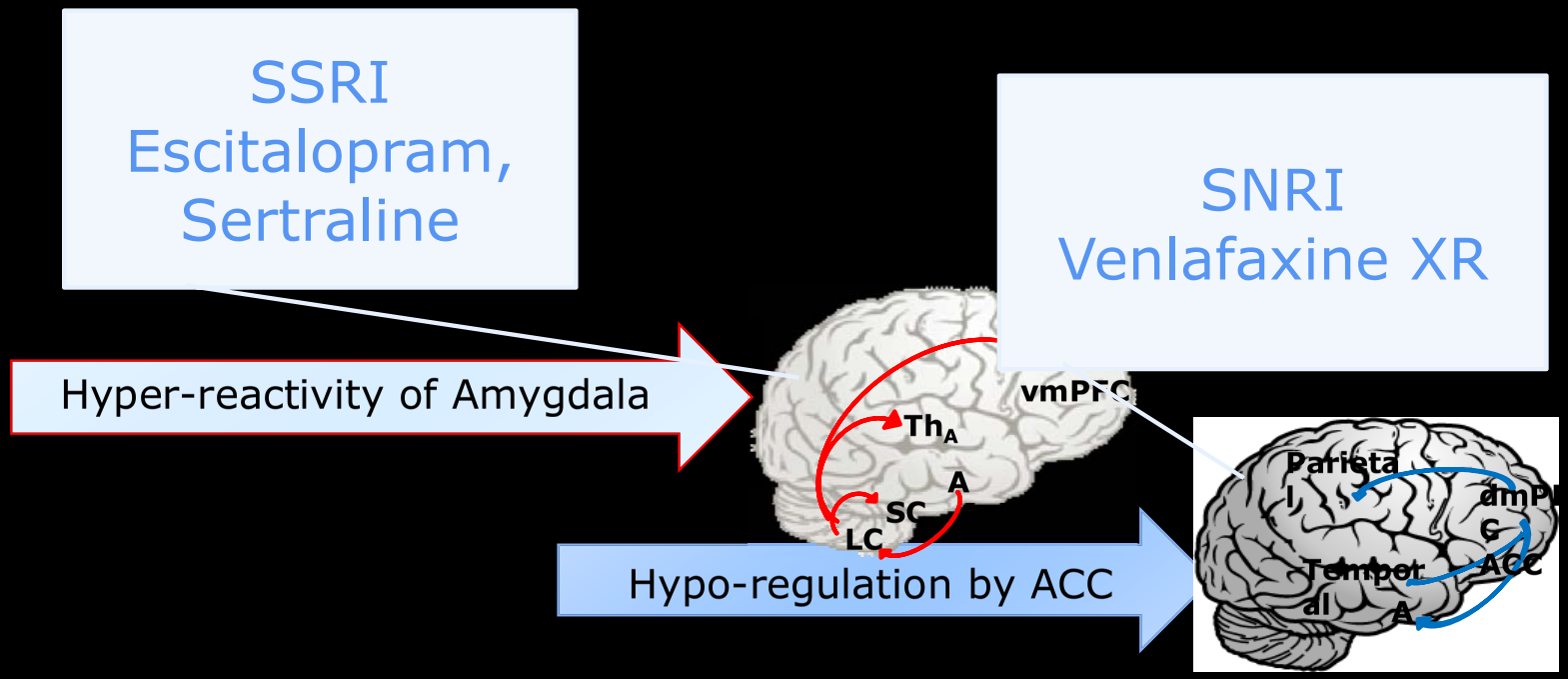
Telephone Monitoring
Weeks 12, 16, 24 and 52

Naturalistic follow-up

Williams, Rush, Koslow, Wisniewski, Cooper , Nemeroff, Schatzberg, Gordon, *Trials,* 4, 2011

A unifying theoretical context

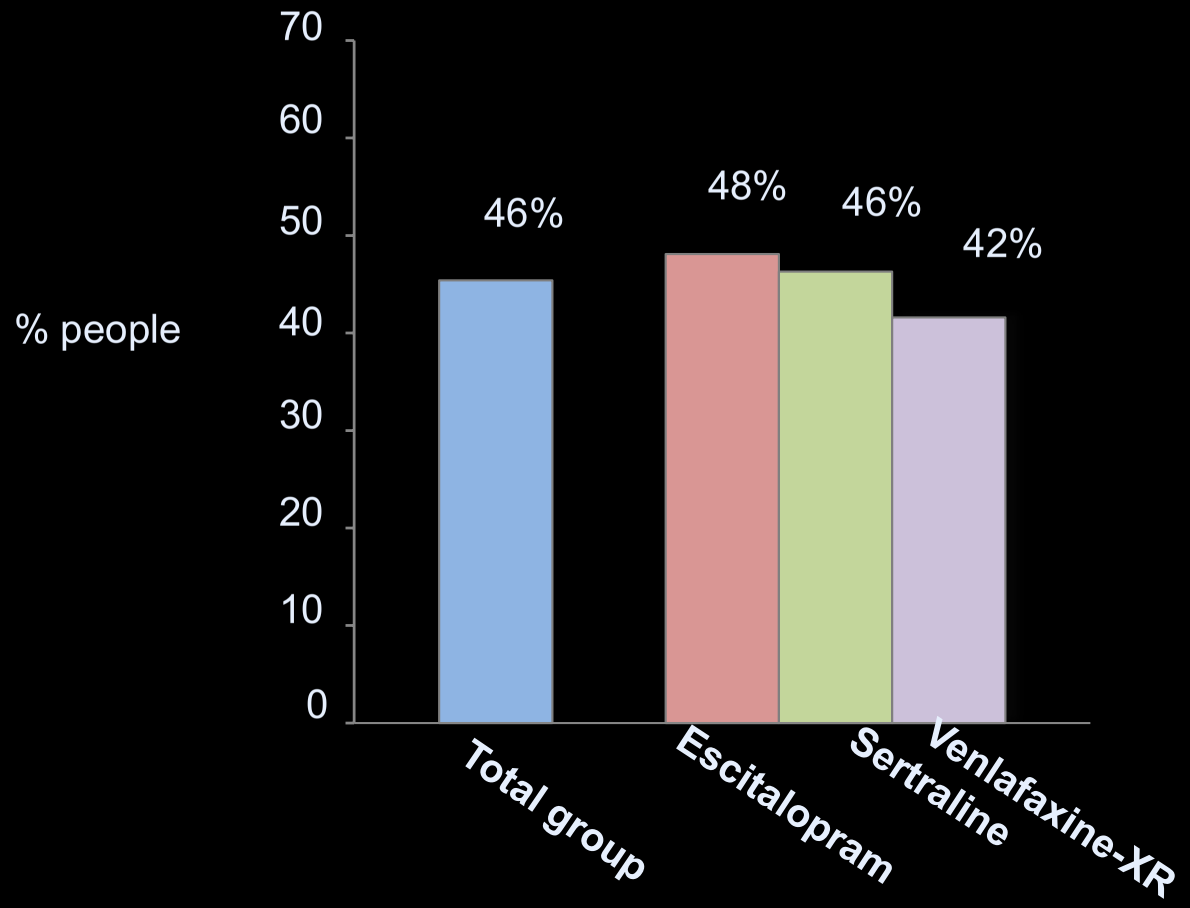
- **Hyper-reactivity of amygdala circuits**
- **Hypo-regulation by anterior cingulate circuits**
  - **These are circuits modulated by Serotonin and Norepinephrine**
- **Flow on consequences are to deplete resources for cognition**



Gordon, Williams (2010). In "Integrative Neuroscience and Personalized Medicine", OUP

Remission rate on primary outcome measure: Score of <=7 on HDRS17

No difference across these treatment arms



Functional capacity improved

Feature	1008 MDD
	% change
Social-Occupational Functioning	24.5%
Satisfaction With Life Scale	37.1%.
Quality of Life – Physical	23.9%
Quality of Life Psychological	47.9%
Quality of Life – Social	31.1%
Quality of Life – Environmental	15.1%

Escitalopram Sertraline Venlafaxine XR

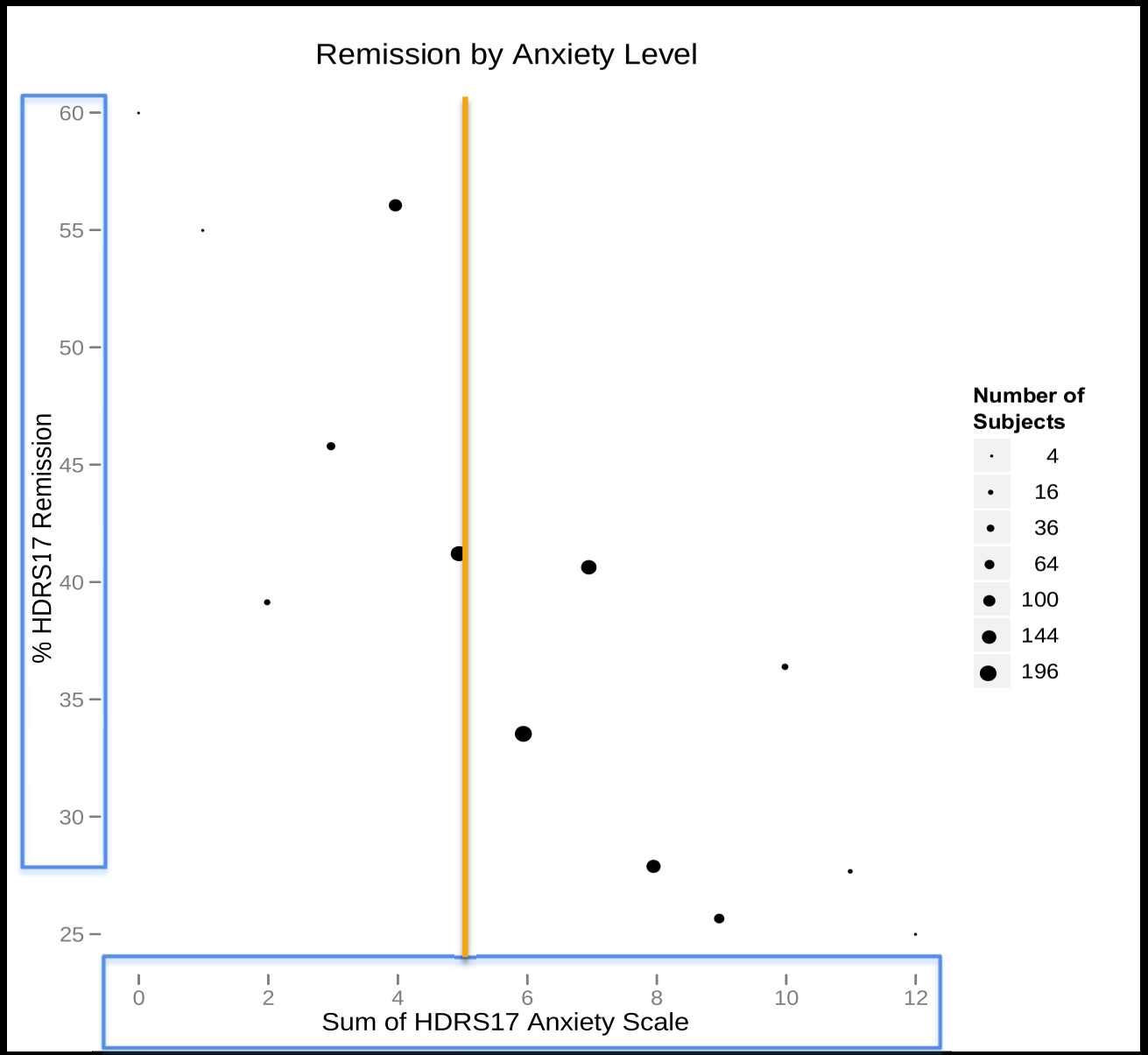
No difference across these treatment arms

Findings from n=1000 MDD

- The importance of considering sub-type and dimensions, specifically for anxiety

First 1000 MDDs from iSPOT-D

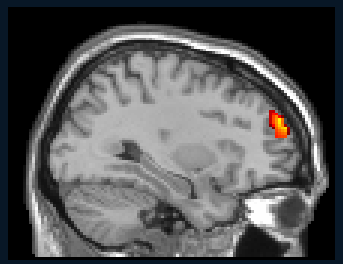
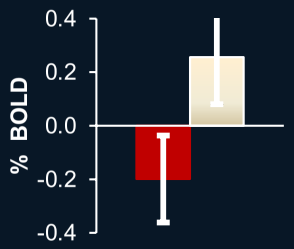
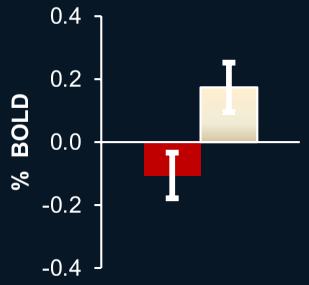
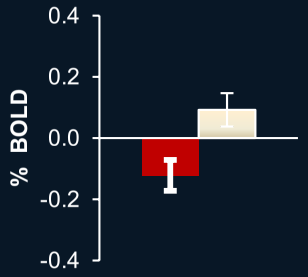
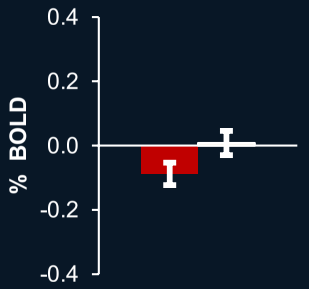
Higher Anxiety Leads to Poorer Outcomes



Better Response ➔
(% of MDD responding to treatment)

Higher Anxiety ➔

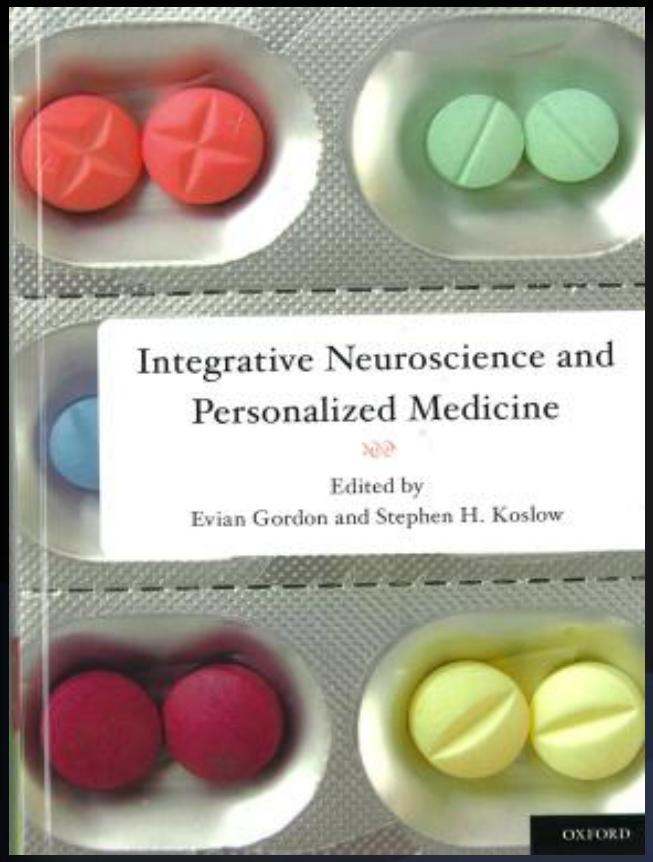
Cognitive deficit in MDD in Hypo-active Frontal Circuitry (Convergence of 5HT and Norepinephrine)

Attention	Working memory	Response Inhibition	Explicit Emotion
MDD < Control	MDD < Control	MDD < Control	MDD < Control
			
Right ACC (3, 51, 9)	Right DLPFC (33, 54, 27)	Right mPFC (27, 30, 24)	Right mPFC, ACC (6, 30, 33)
			

Korgaonkar MS, et al. In review

Using Brain Resource Standardized and Integrative Platform

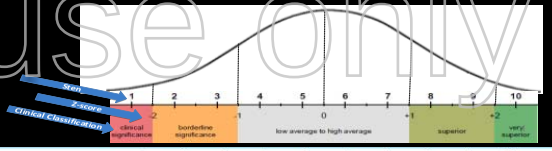
OTHER EXAMPLES OF CIRCUITS-BIOMARKERS IN DIFFERENT DISORDERS



www.BRAINnet.net

ADHD

iSPOT ADHD



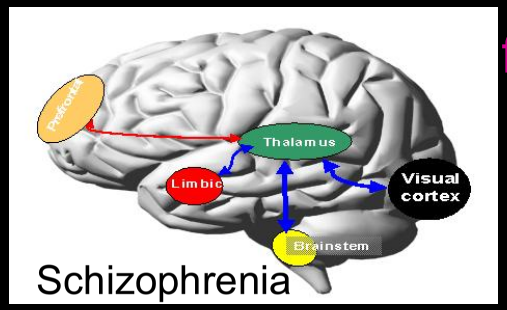
STEN scores range from 1 to 10.
Higher scores always indicate better functioning.

Thinking – Selective awareness of information processing so we can know and remember

MARKER	SCORE	EXPLANATION
Sustained Attention	1	Focusing on the main task and resisting distraction over time.
Impulsivity	4	Balance between responding quickly and suppressing your responses as the situation changes.
Intrusions	2.5	Irrelevant information that can intrude on attention to a task or memory.
Inhibition	1	The suppression of one piece of well-learned information in order to focus on another or new aspect of a task.
Response Variability	3.5	The degree of consistency in the speed of responding.

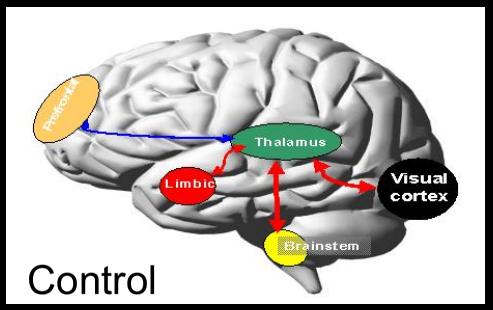
Schizophrenia

4 Studies



Schizophrenia

fMRI

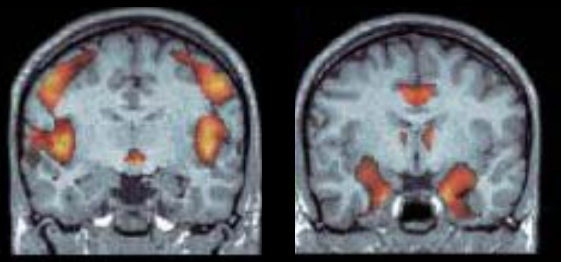


Control

- Positive Functional Connectivity
- Negative Functional Connectivity

Alzheimer's

Aspect study



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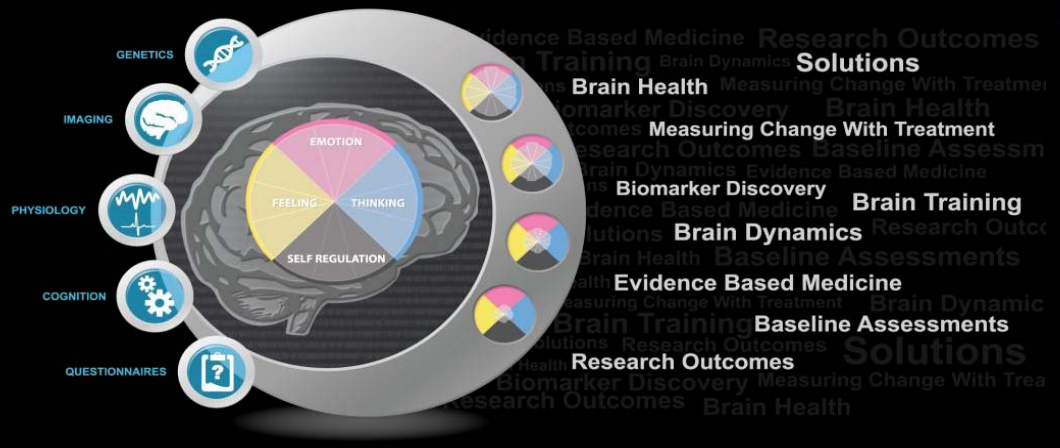
Standardized Integrated Biomarker Platform



- Overall Response
  No/Yes: defined by symptom remission
- Different responses to different Types of treatment
- Dose
- Side effects
- Long Term Remission
- New Drug Discovery

BRC: Current Discussions

FDA: Communications underway with FDA (CDRH+CDER) regarding Biomarkers (filing PMA for marketing iSPOT claims). *Data acquisition methodology covered by our existing FDA 510k.*

In discussion with interested stakeholders in Co-marketing iSPOT Biomarkers with the 3 Rx constituting 40% market share. (And exploring Biomarkers 6ml Blood all options of Molecular Outcomes).

Pharma: Rapid 'Companion Diagnostics'.

Payer (Medicaid): Rx cost savings.

BRC: Contacts

Biomarker Platform for 'Companion Diagnostics' and Co-development of New drug Candidates.

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