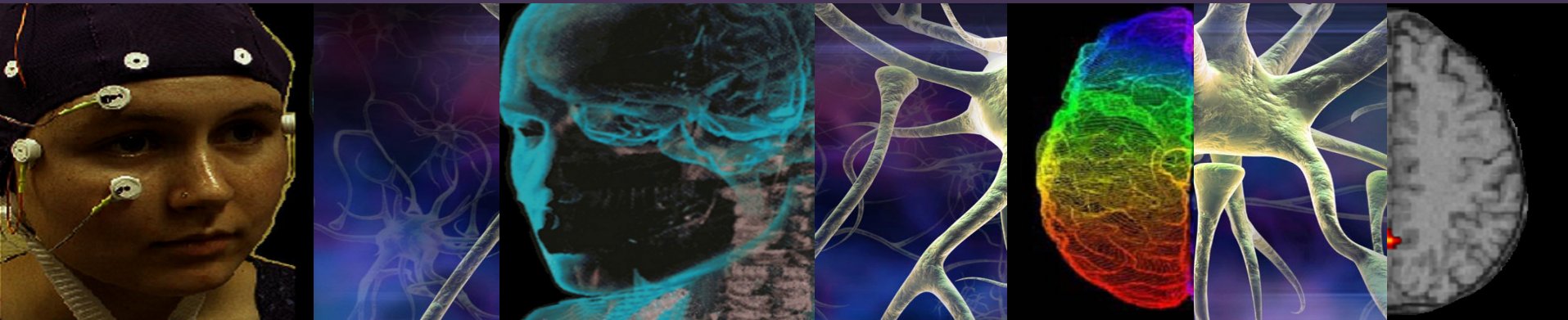


Biomarker predictions for treatment response in depression

Leanne (Lea) Williams, PhD



Disclosures

Brain Resource

Sponsor for iSPOT-D
Consultant

Context

Can neuroscience deliver clinically useful tools?

I propose the answer is “**Yes**”

We are in the midst of a paradigm shift

“Applied personalized neuroscience” is one way to harness this shift to achieve clinical translation

Integration of Psychiatry and Neuroscience



Neuroscience, Clinical Evidence, and the future of Psychiatric Classification in DSM-5.

Kupfer DJ & Regier DA
Am J Psychiatry. 168(7):672-674, 2011



Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders

Thomas Insel; et al.
Am J Psychiatry. 2010;167(7):748-751

**Clinical
tools?**

Applied Personalized Neuroscience

Established proof of concept in Sydney.
Illustration from first break schizophrenia



Now the first global practical trial
integrating neuroscience and clinical
outcomes for depression

Applied personalized neuroscience: What is it?

Discovering biomarkers
based on mechanisms

Predicting
clinical outcomes

Personalizing
to individuals in the clinic



Principles

- Grounding it in theories about mechanisms
- Clinicians and patients guide the questions to be answered
- Testing is standardized so different types of data can be connected
- Focus on collaboration and mix of strengths.
We can't do this in traditional scientific models
- Make it clinic friendly. Use web technology

Illustration #1

Brain Dynamics Center, University of
Sydney Medical School



<http://www.brain-dy>

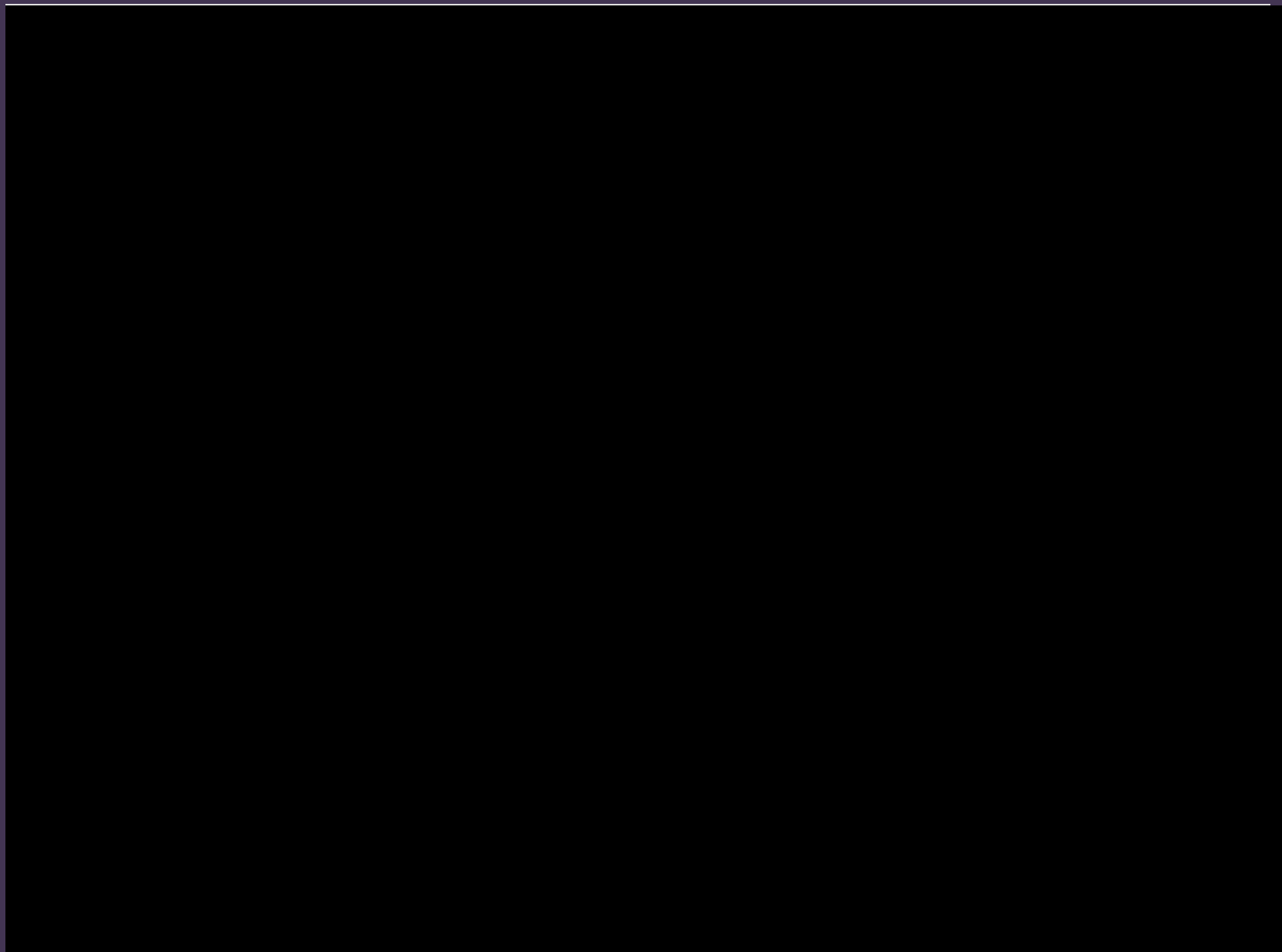
- **First break schizophrenia**, depression, anxiety (PTSD), ADHD
Risk and resilience
- **Clinical, self report, behavioral, physiological, imaging and genetic measures**

Matching environment to principles



1. Set realistic targets.
2. Patient and clinician needs guide research focus.
3. Connect outputs to
4. Interconnect
5. Standard applica

To make these concrete I will show you a 60 sec video of a day in the life



First break schizophrenia

Brain mechanisms

Reduced expression of markers for GABA-ergic interneurons that synapse with pyramidal neurons

Especially in frontal and temporal cortex

This creates a loss of real time synchrony, needed for a coherent gestalt of the internal and external worlds

It fits with other evidence

Smaller pyramidal neurons and dendritic spines

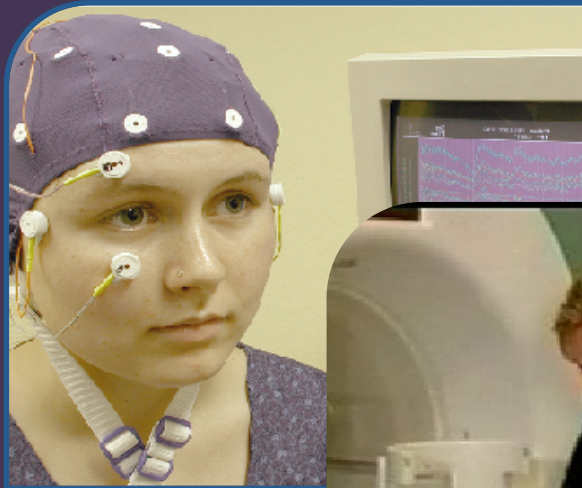
Regions of grey matter reduction present from first break

Whitford et al (2007). American J Psychiatry
Williams (2008) Expert Reviews in Neurotherapeutics
Lee et al (2003) Brain Research Reviews

	First Onset Psychosis	Controls
Demographics	Mean (SD) or sample size	Mean (SD) or sample size
Sample Size	n=108	n=108
Age	20.71 (2.91)	20.49 (3.05)
Gender	70 Male, 38 Female	70 Male, 38 Female
Diagnoses		
Schizophrenia	n=51	-
Schizophreniform	n=20	-
Psychosis NOS	n=15	-
Schizoaffective disorder	n=6	-
Bipolar disorder with psychosis	n=6	-
Substance induced psychosis	n=6	-
MDD with psychosis	n=2	-
Delusional disorder	n=2	-
Medication		
Second Generation Antipsychotic	n=76	-
First Generation Antipsychotic	n=1	-
Unknown	n=13	-
CPZ equivalent dose (mg)	390.31 (193.58)	-
Symptoms		
DUP (weeks)	26.73 (55.34)	-
PANSS - Positive	24.99/49 (6.35)	-
- Negative	26.12/49 (7.00)	-
- General	40.03/112 (8.49)	-
- Total	81.14/210 (18.25)	-
CDSS	3.74/27 (4.01)	-

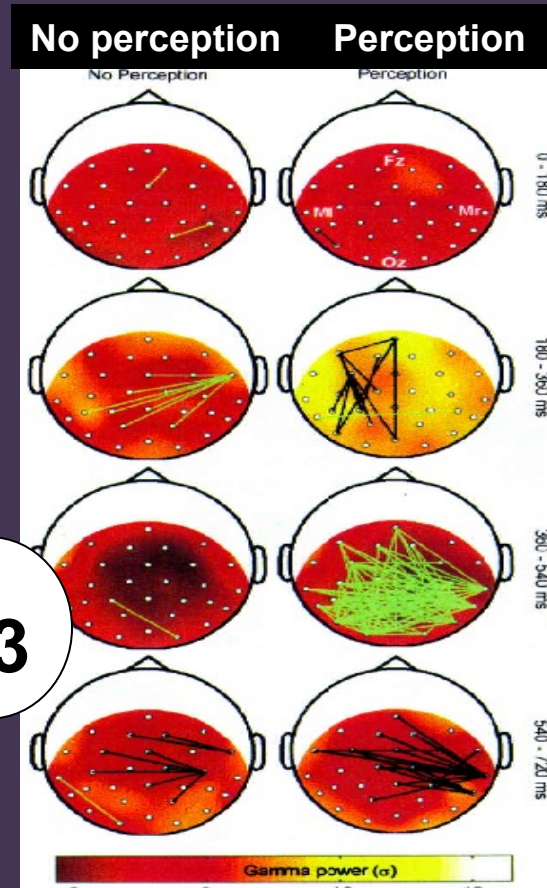
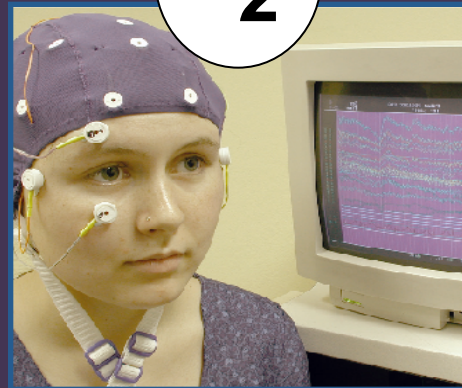
Note: NOS=not otherwise specified; MDD=major depressive disorder; CPZ=Chlorpromazine; DUP=duration of untreated psychosis; PANSS=Positive and Negative Syndrome Scale; CDSS = Calgary Depression Scale for Schizophrenia

Multiple measures of these mechanisms



How can we look at this in schizophrenia patients?

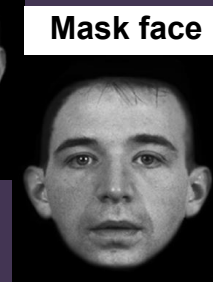
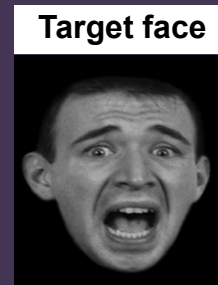
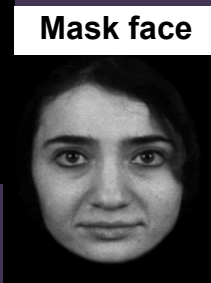
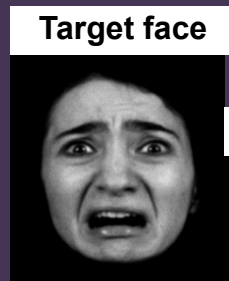
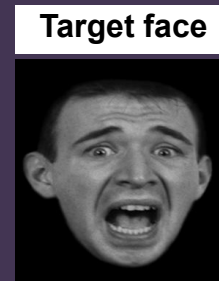
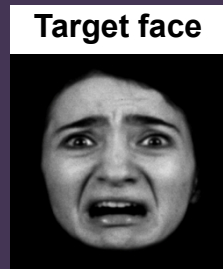
Option 1: “EEG Gamma synchrony”



Rodriguez et al. (1999). Nature.

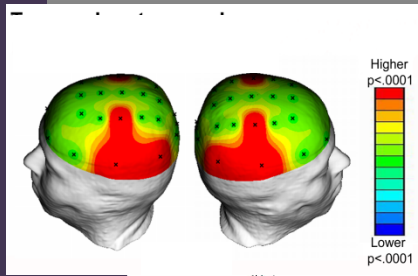
Lee et al. (2003). Brain Research Reviews
Symond et al (2005). American J Psychiatry
Slewa-Younan et al. (2005). American J Psychiatry

Viewing facial expressions of emotion task

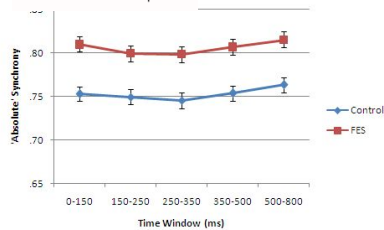


Williams et al. (2004). Human Brain Mapping;
Williams et al. (2006). Human Brain Mapping
Williams et al. (2006). J Neuroscience

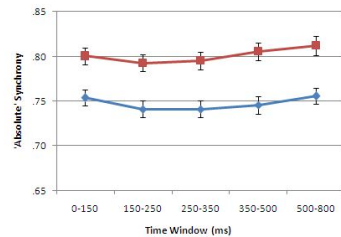
Too MUCH baseline synchrony in first break schizophrenia patients



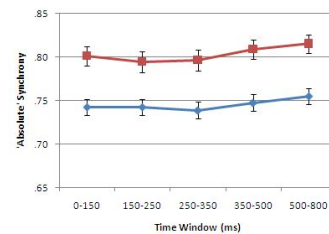
Fear



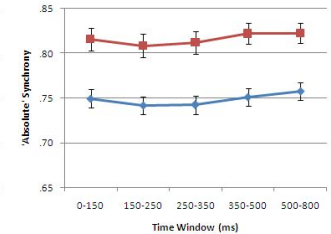
33-37 Hz



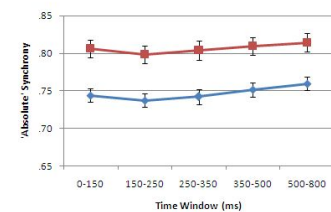
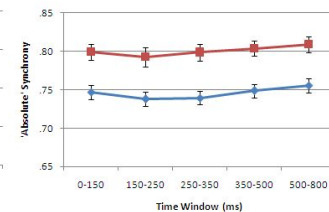
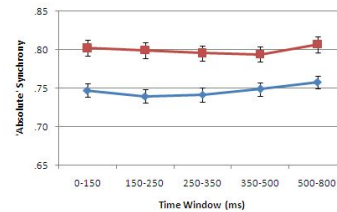
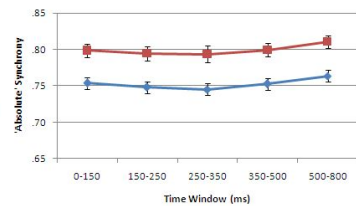
37-41 Hz



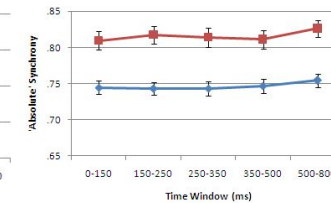
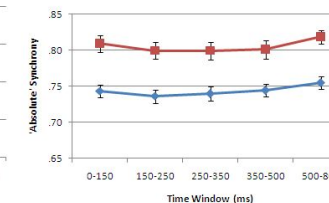
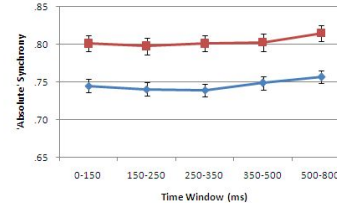
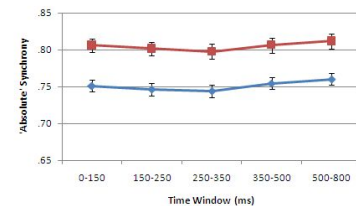
41-45 Hz



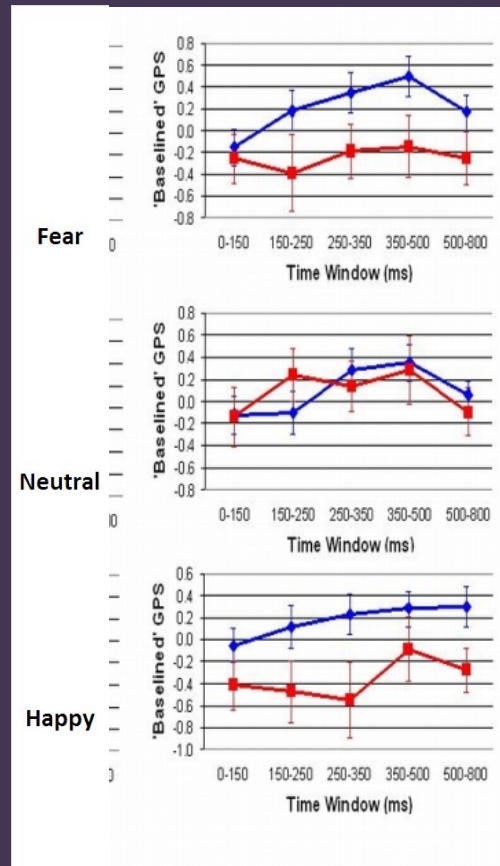
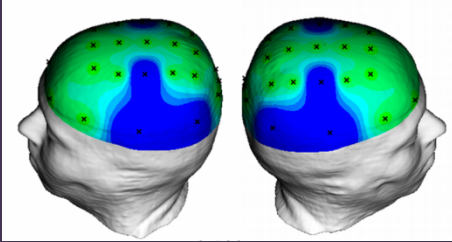
Neutral



Happy



Too MUCH baseline synchrony in first break schizophrenia patients



Brennan et al. (in review)
Williams et al. (2009) J Psychiatry and Neuroscience

How can we look at this in schizophrenia patients?

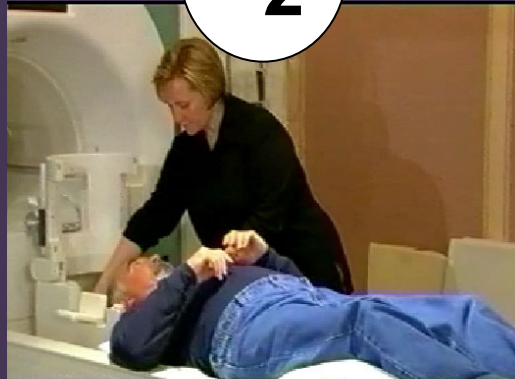
Option 2: fMRI brain circuit connectivity

1

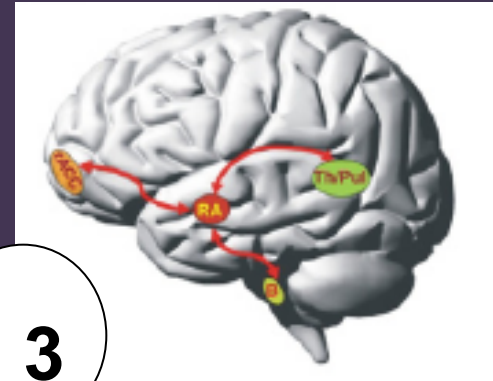
Target face



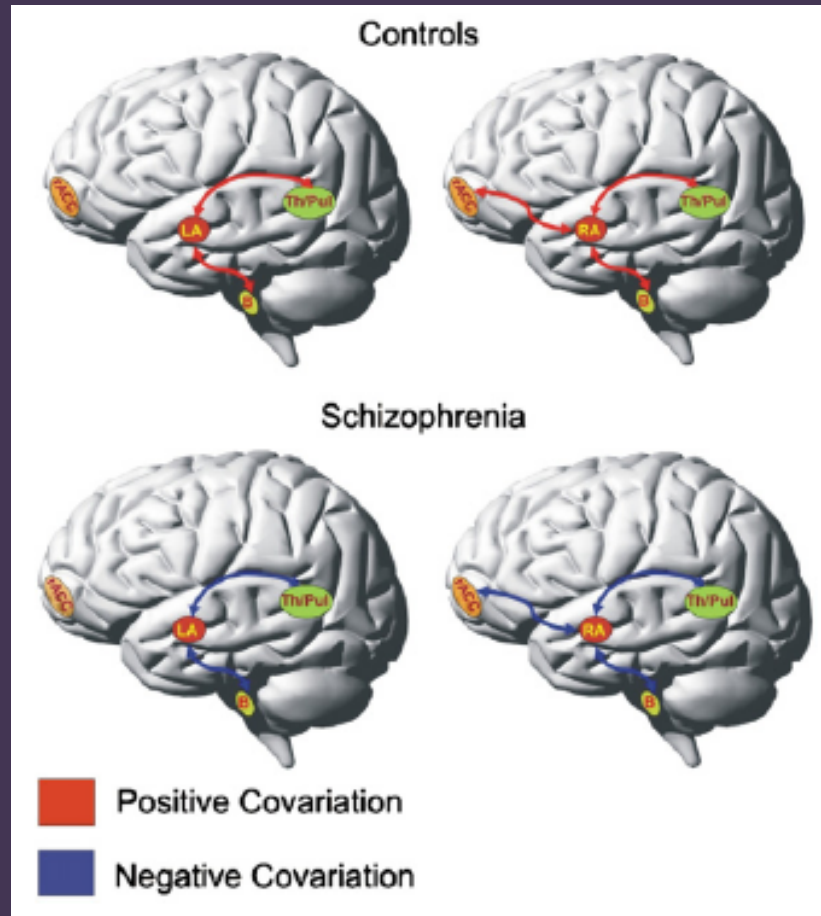
2



3



Reversed connectivity from functional MRI

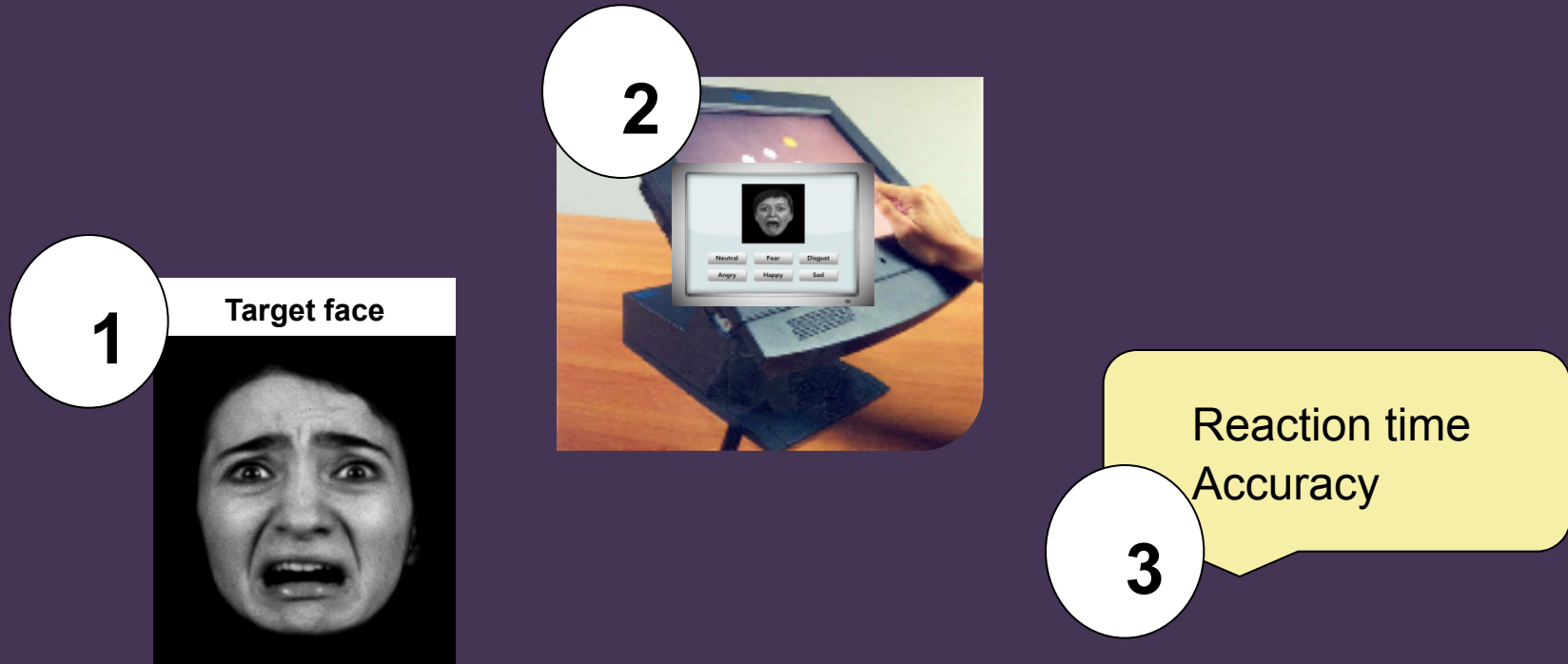


Williams et al. (2004). American J Psychiatry

Williams et al. (2006). Journal of Neuroscience Das, et al. (2007). Schizophrenia Research

How can we look at this in schizophrenia patients?

Option 3: Emotional behavior

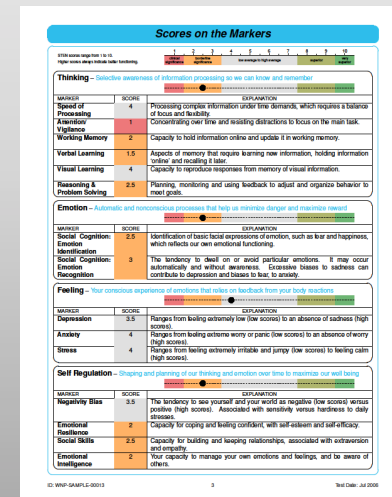
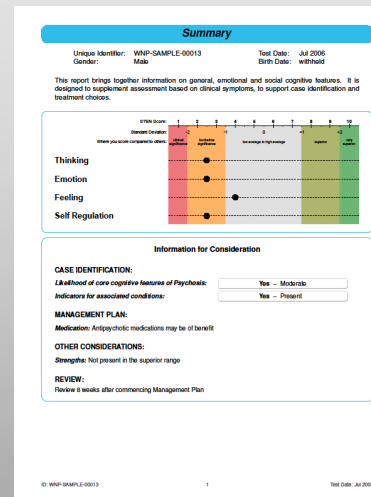
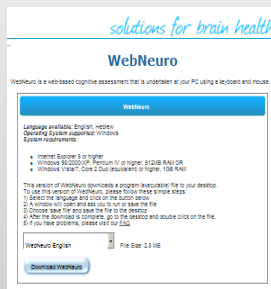


These brain measures predict function, relevant to the clinic

- Abnormal synchrony predicted ↓ social functioning
- Reversed connectivity predicted ↓ social functioning
- Poorer behavior predicted ↓ social functioning
↓ quality of life
- No relationships for symptoms

How can this be applied in the clinic?

- Example of “return to school” decision support



Web to patient, then report to clinician in a few minutes

Illustration #2



iSPOT-D.
Focus of my visiting position
here at Stanford

**Academic PI for
International Study to Predict
Optimized Treatment in Depression
(iSPOT-D)**

iSPOT-D is running across 20 sites in 5 countries.
N=1008 patients and 336 controls have completed phase 1



USA

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*
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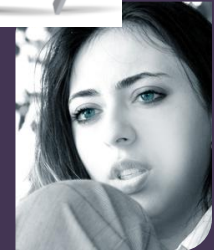
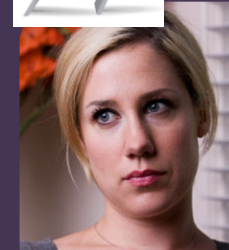
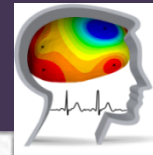
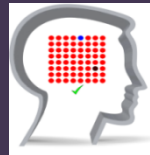
Africa

Johannesburg	University of Witwatersrand, Johannesburg*
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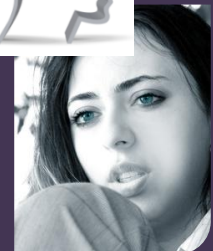
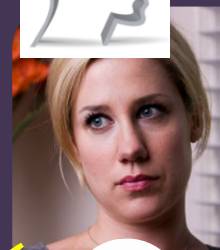
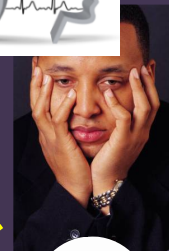
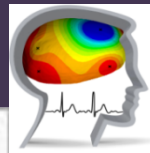
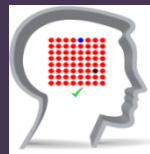
*Sites contributing to recruitment of the first n=1008 patients

Identify markers that link neuroscience mechanisms to treatment outcomes

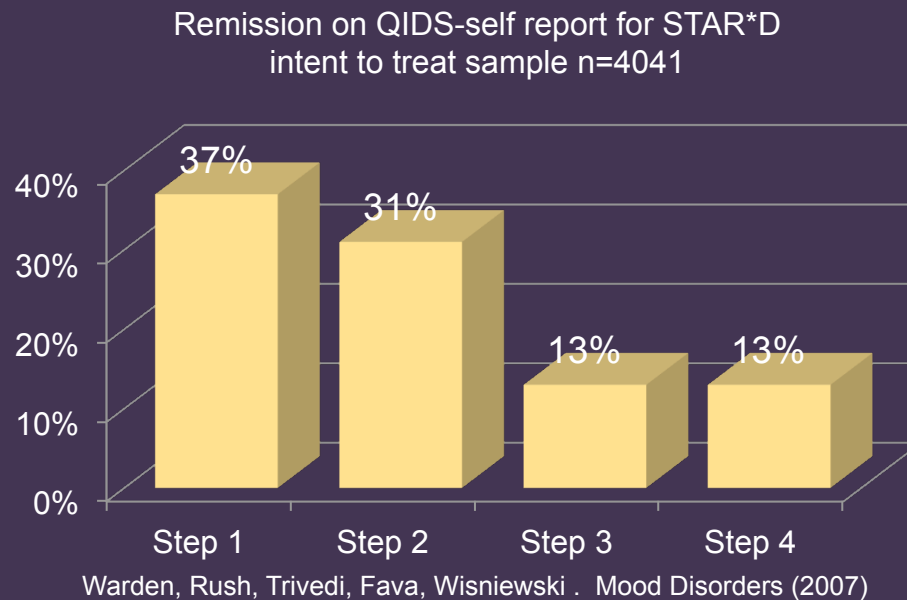
What markers define disorder and subtypes?



What markers predict antidepressant treatment outcomes?



The rationale is that neuroscience markers are needed to improve patient outcomes at step 1

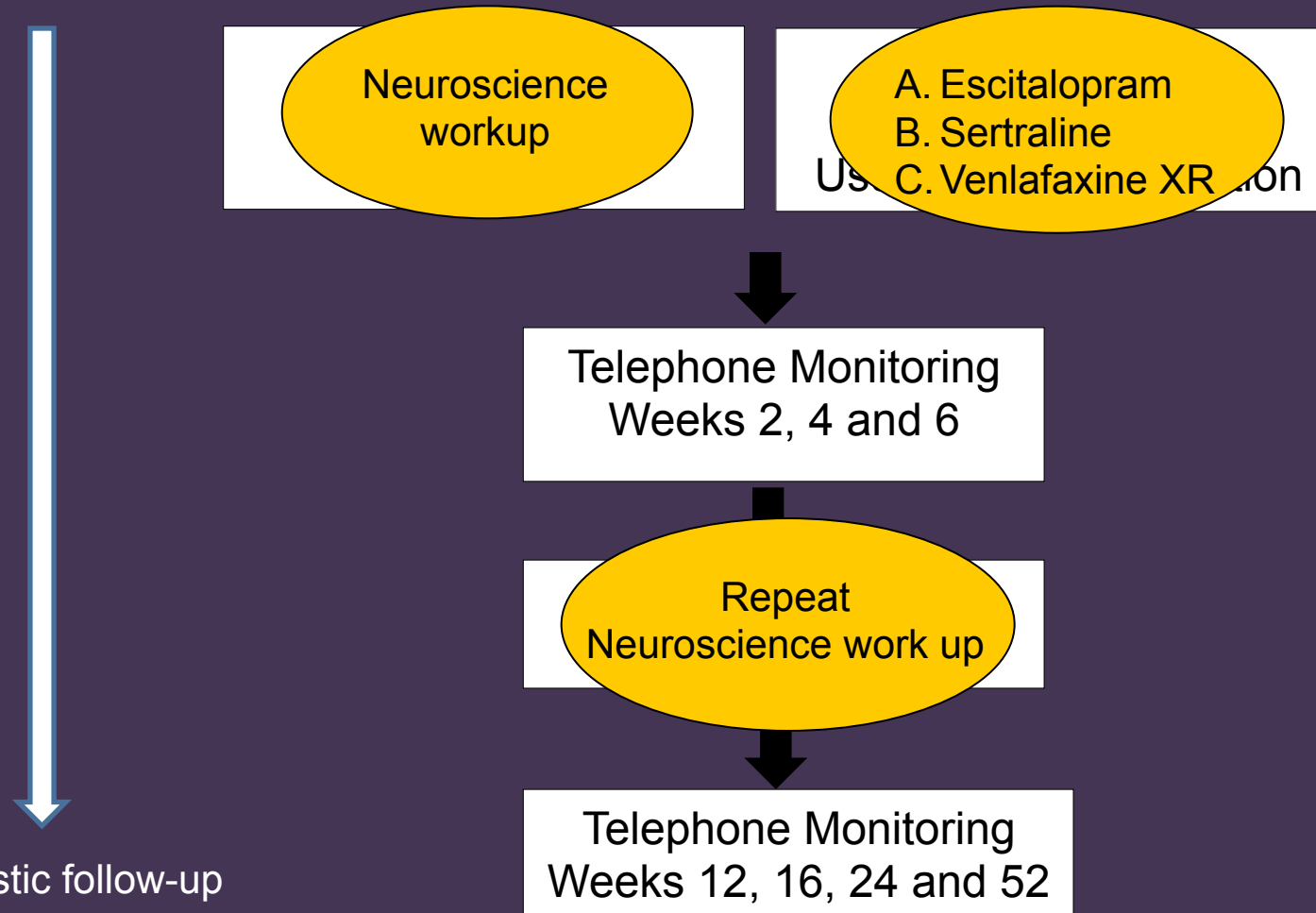


Protocol

- It's a practical trial mirroring routine practice
- Along with clinical information, we collect neurobiological and genetic information
- Standardized methods make this feasible



Primary phase of study



Recruitment strategy attains a broad sample of treatment seekers

Source	% of 1008	% prior Tx
Primary Care services at sites	<u>No difference across sources in response to Tx</u>	50%
Specialty Care services at sites		52%
Advertisement		62%
Other, via family/ friend		62%

Screened for palpable psychopathology,
and eligibility for testing and treatment

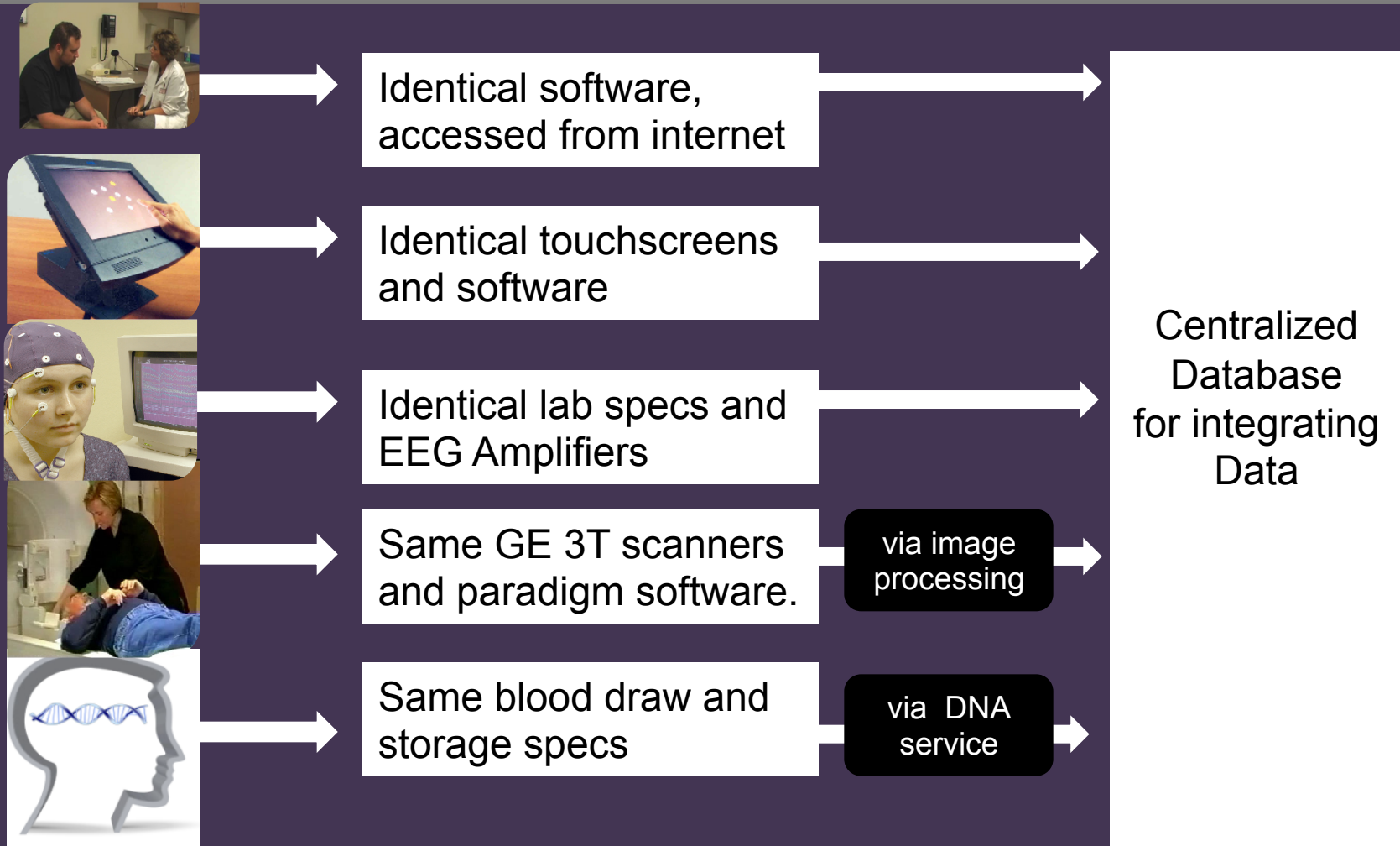
Inclusion Criteria

- DSM criteria for Major Depression (MINI-Plus)
- Age 18-65
- Hamilton Depression Rating ≥ 16

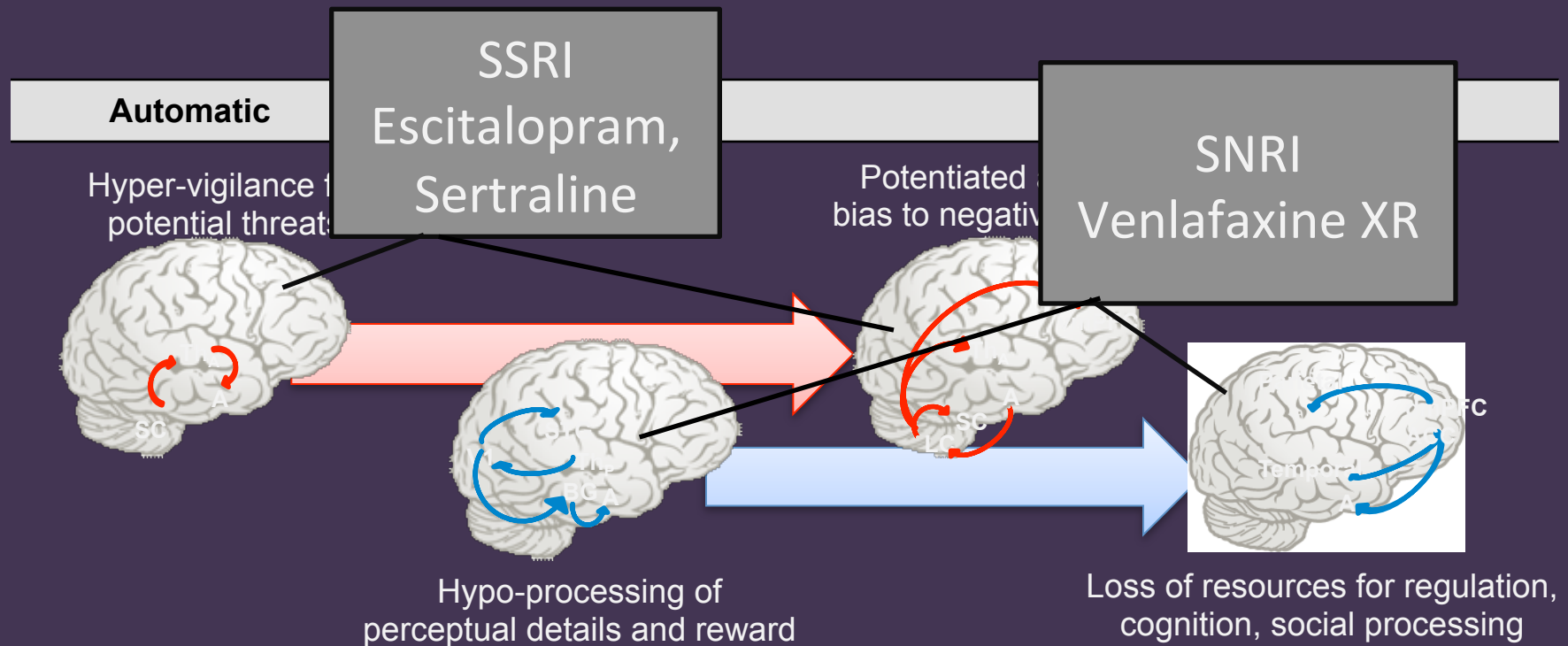
Major exclusion criteria

- Suicidal planning
- Psychosis
- Contraindication to study medications

Standardized measures



A unifying theoretical context drove the selection of measures



Demographics reflect the community of treatment seekers

Feature	1008 MDD
	Mean
Age	37.8 years
Education	14.5 years
Gender	%
Female	57%
Race	
White	62%
Black	17%
Other	21%
Ethnicity	
Hispanic	8%

Escitalopram	Sertraline	Venlafaxine XR
<p><u>No difference</u> across these treatment arms</p>		

Demographics reflect the community of treatment seekers

Feature	1008 MDD	Escitalopram	Sertraline	Venlafaxine XR
	%			
Employment		<u>No difference</u> across these treatment arms		
<i>Employed</i>	50%			
<i>Unemployed</i>	7%			
<i>Retired</i>	4%			
<i>Student</i>	19%			
<i>Other*</i>	7%			
<i>Unknown</i>	13%			
Marital Status				
<i>Single**</i>	61%			
<i>Married/cohabiting</i>	20%			
<i>Divorced/separated</i>	14%			
<i>Widowed</i>	1%			
<i>Unknown</i>	4%			

Saveanu et al. in prep

* Includes 'homemaker' ** Includes patients cohabiting but identify as single, consistent with legal definition of country in which tested.

Clinical features also reflect this community

Feature	1008 MDD
	Mean
Age at first episode	22.9 years
Duration of MDD	14.4 years
Comorbidity	N
<i>Dysthymia</i>	219
<i>Panic Disorder</i>	85
<i>Agoraphobia</i>	74
<i>Social Phobia</i>	93
<i>Specific Phobia</i>	55
<i>GAD</i>	69
<i>No Comorbidities</i>	636

Escitalopram	Sertraline	Venlafaxine XR
<p><u>No difference</u> across these treatment arms</p>		

As expected, the sample is heterogenous

Feature	1008 MDD
	%
<i>Previous suicide attempt</i>	12%
MDD Recurrence	
<i>Recurrent MDD</i>	87%
<i>Non-recurrent MDD</i>	10%
<i>Unknown</i>	3%
MDD Subtypes	
<i>Melancholic</i>	39%
<i>Atypical</i>	28%
<i>Anxious</i>	42%

Escitalopram	Sertraline	Venlafaxine XR
<p><u>No difference</u> across these treatment arms</p>		

The sample is moderately severe on average

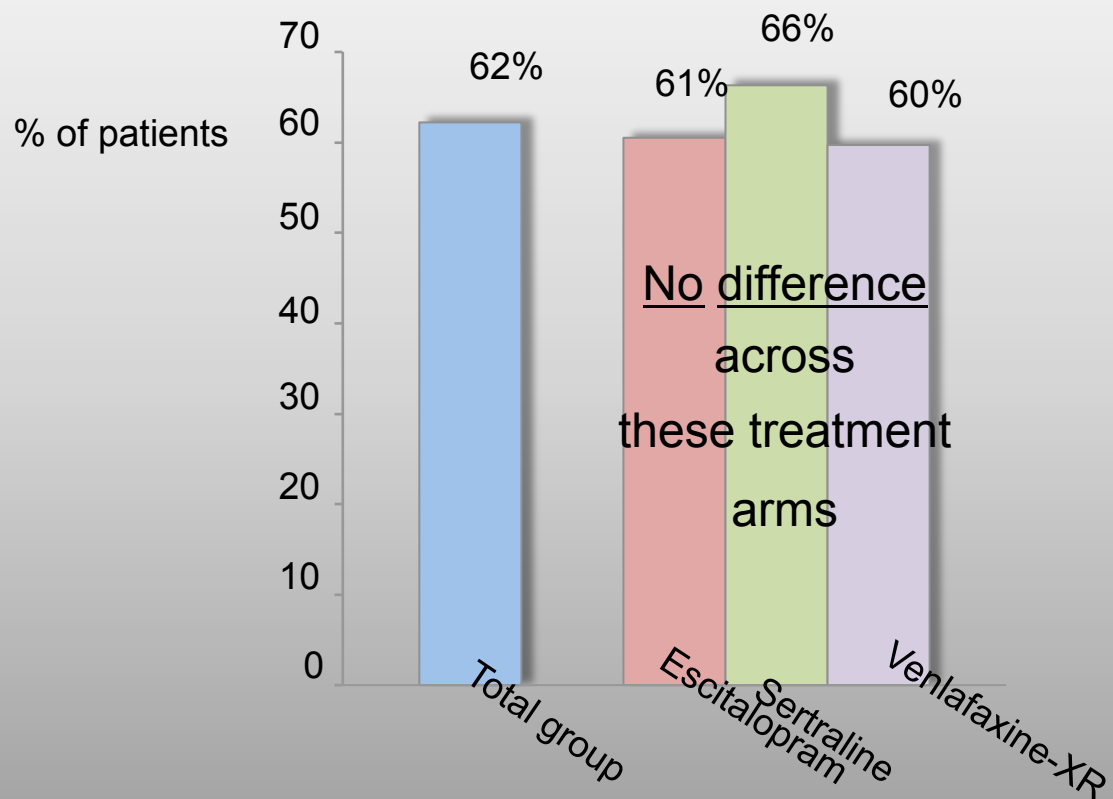
Feature	1008 MDD
Clinician-Rated symptoms	
HRSD17 Score	21.9
Self-reported symptoms	
QIDS-SR16 Score	14.5
DASS score out of 42	
DASS Depression	22.2
DASS Anxiety	8.8
DASS Stress	18.2

Escitalopram	Sertraline	Venlafaxine XR
<u>No difference</u> across these treatment arms		

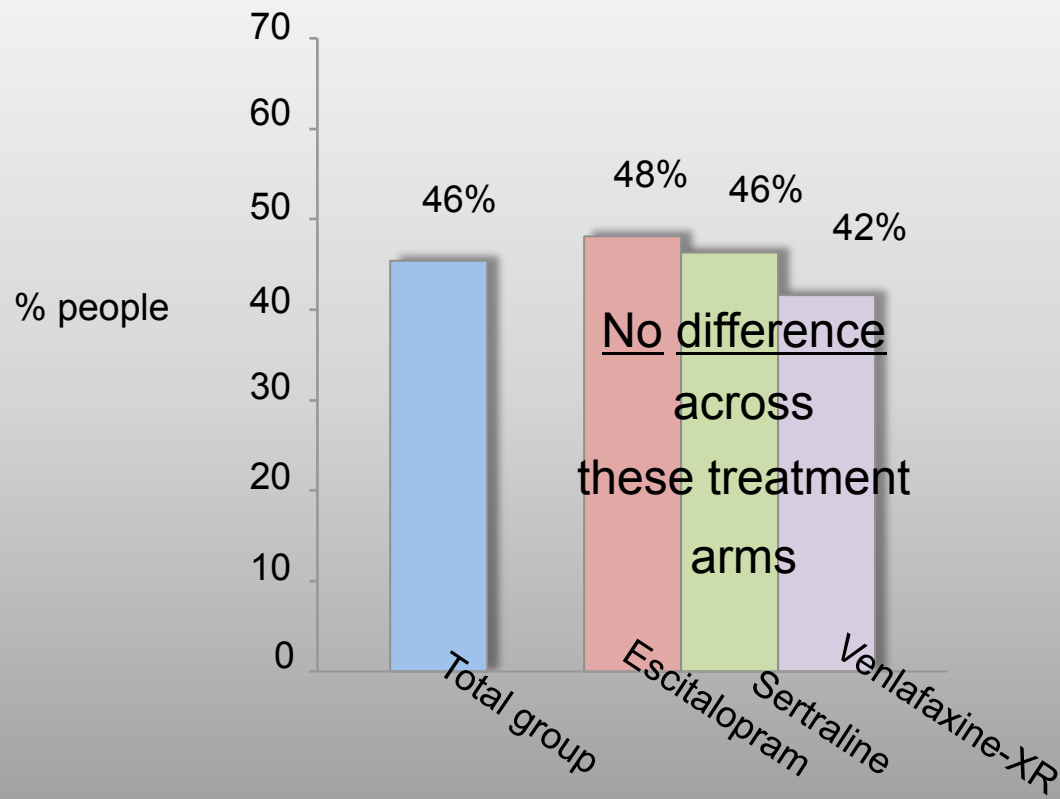
Functional capacity is impaired

Feature	1008 MDD Mean	Escitalopram	Sertraline	Venlafaxine XR
		<u>No difference</u> across these treatment arms		
<i>Social-Occupational Functioning</i>	56 / 100			
<i>Satisfaction With Life Scale</i>	12 / 35			
<i>Quality of Life – Physical</i>	52 / 100			
<i>Quality of Life Psychological</i>	35 / 100			
<i>Quality of Life – Social</i>	39 / 100			
<i>Quality of Life – Environmental</i>	52 / 100			

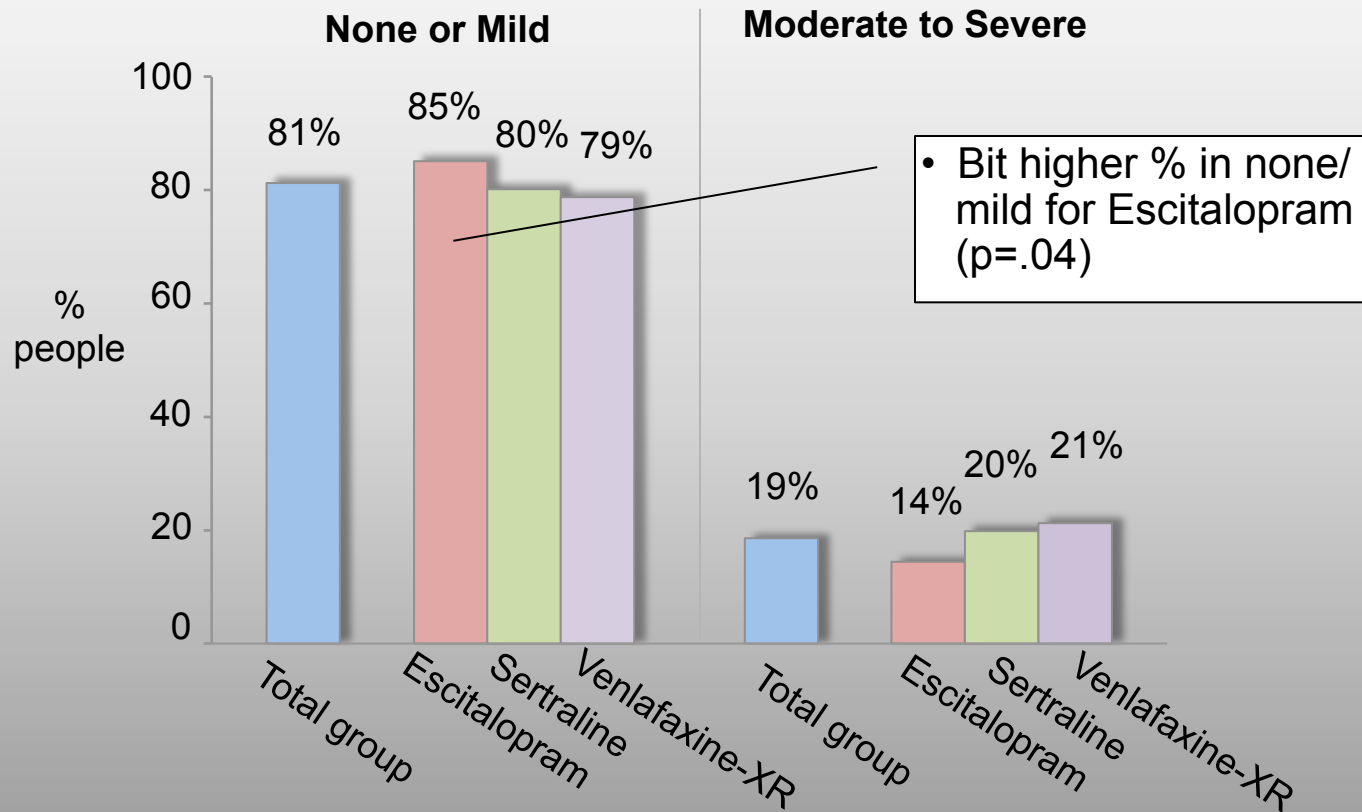
Response rate on primary outcome measure: ≤50% reduction on HDRS₁₇



Remission rate on primary outcome measure: Score of ≤ 7 on HDRS₁₇



Side effect outcomes



Intensity data are displayed. Same pattern for Frequency and Burden

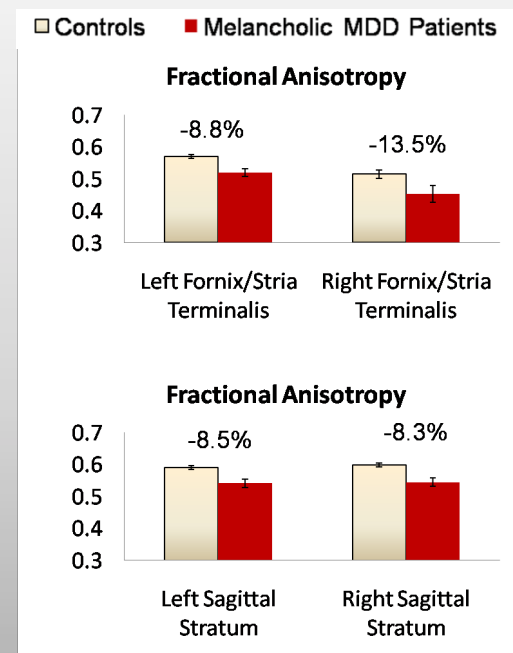
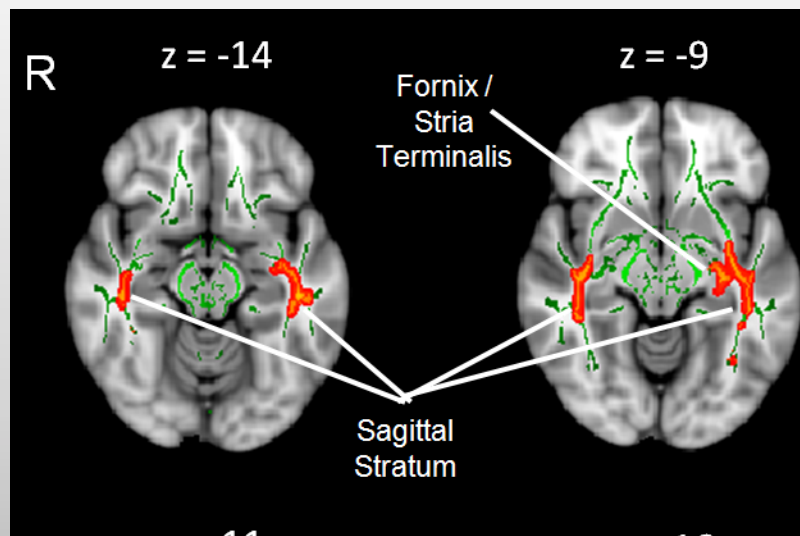
Functional capacity improved

Feature	1008 MDD	Escitalopram	Sertraline	Venlafaxine XR
	% change	<u>No difference</u> across these treatment arms		
<i>Social-Occupational Functioning</i>	24.5%			
<i>Satisfaction With Life Scale</i>	37.1%.			
<i>Quality of Life – Physical</i>	23.9%			
<i>Quality of Life Psychological</i>	47.9%			
<i>Quality of Life – Social</i>	31.1%			
<i>Quality of Life – Environmental</i>	15.1%			

Findings from n=1008

- These clinical findings provide a “level playing field” for identifying neuroscience markers

White matter connectivity: a candidate marker for the Melancholic subtype



The melancholic subtype has reduced white matter connectivity (fractional anisotropy) on DTI scans (red colors)

Functional MRI

COGNITION

Attention: Oddball paradigm

Working memory:
n-Back continuous performance paradigm

Cognitive control: Go-NoGo paradigm



B G G

PRESS
PRESS

EMOTION

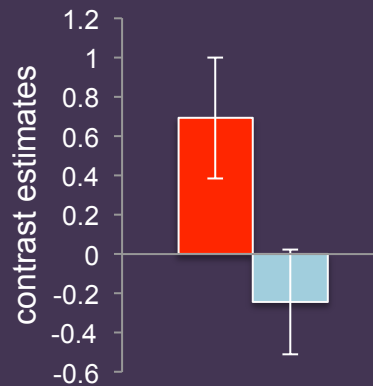
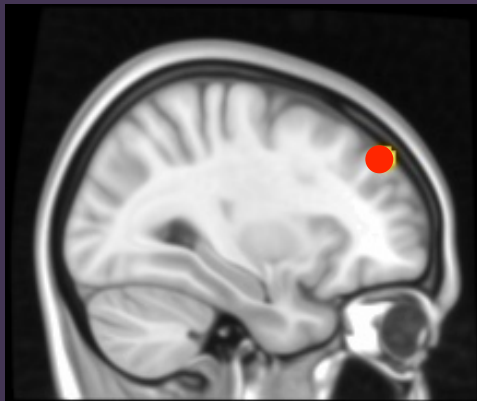
Viewing of Emotion Faces paradigm

Masked viewing of Emotion Faces
paradigm

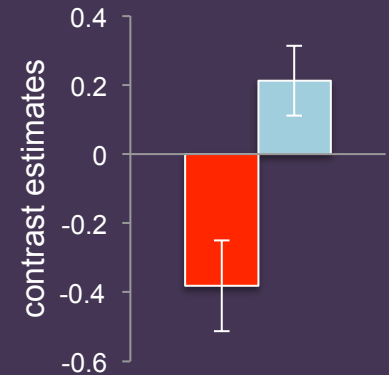


Frontal circuitry

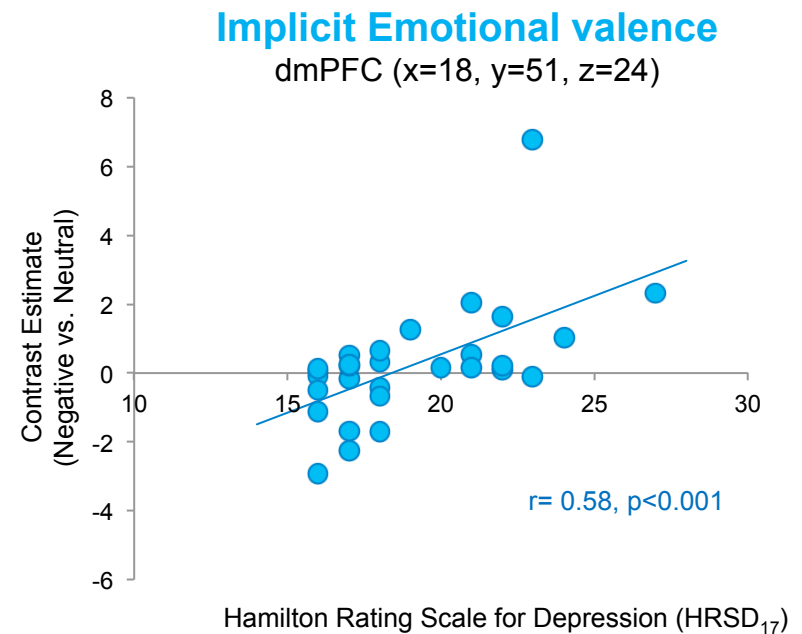
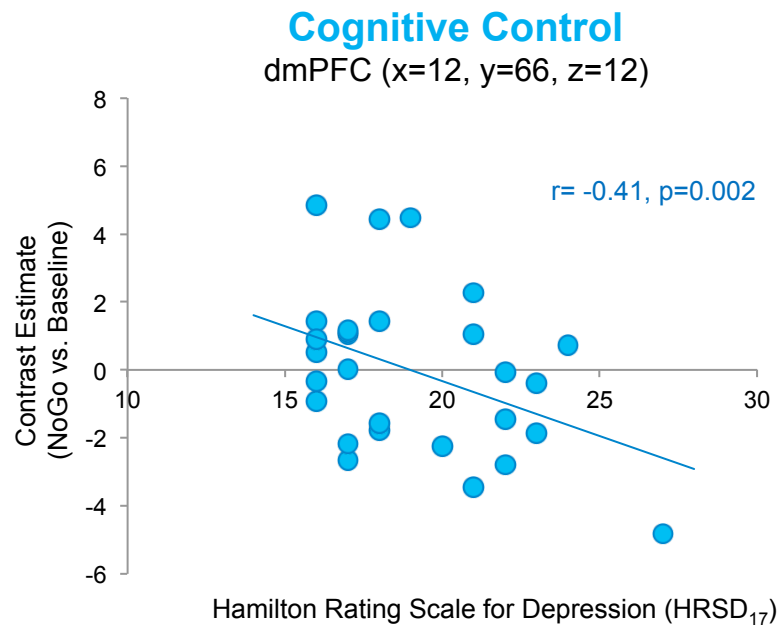
**Hyper activation in DLPFC
for Emotion: Fear**



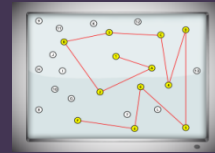
**Hypo activation in ACC for
Cognition: control**



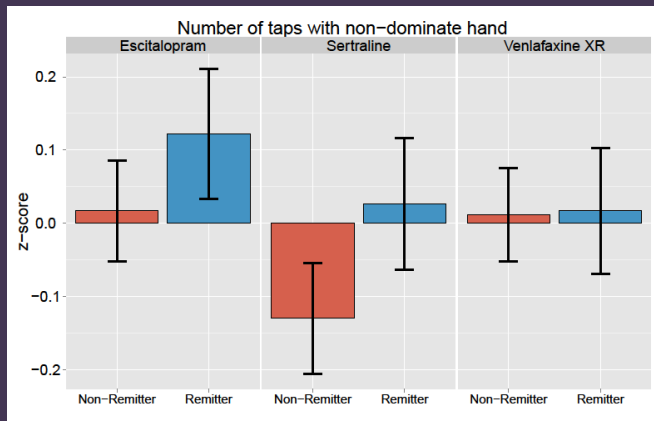
Hypo-activation for cognition and hyper-activation for emotion correlate with symptom severity



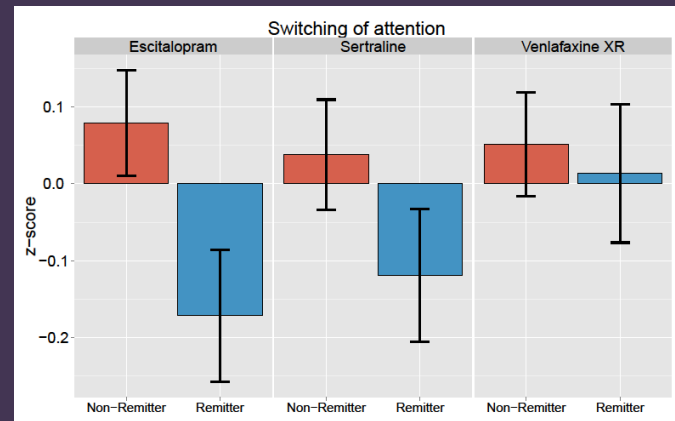
Cognition predictors for SSRI: Escitalopram and Sertraline



Psychomotor speed



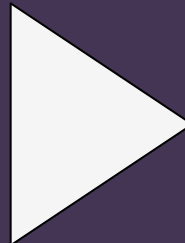
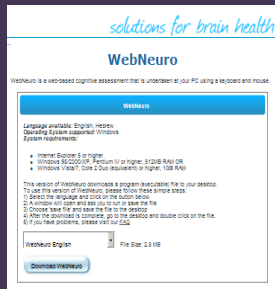
Cognitive Control



What does it mean?

- Neuroscience offers viable biomarkers for what predicts outcome
- They are grounded in neuroscience of depression
- They are independent of symptom severity.
- They do correlate with real-world functional capacity

Translation to the clinic



Building the family of “iSPOTs”

Anxiety
Risk and Resilience
Non-medication treatments
Novel treatments, inc web



International Study to Predict
Optimized Treatment in
ADHD (iSPOT-A)

Leading the integration of Psychiatry and Neuroscience, through to **application in the clinic**

THE AMERICAN JOURNAL OF PSYCHIATRY

Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders

Thomas Insel; et al.

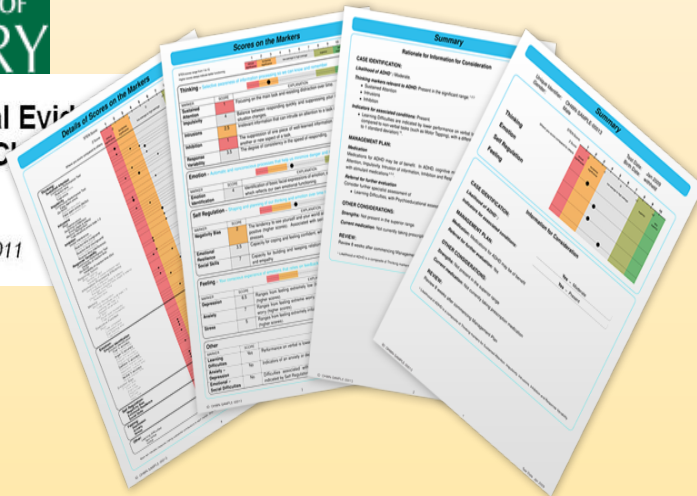
Am J Psychiatry. 2010;167(7):748-751

THE AMERICAN JOURNAL OF PSYCHIATRY

Neuroscience, Clinical Evidence the future of Psychiatric Classification DSM-5.

Kupfer DJ & Regier DA

Am J Psychiatry. 168(7):672-674, 2011



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Brain Resource

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Keith Sudheimer
Jill Waring
Fellowship program

