

Exemplar Applications and Results From BRAINnet: What Are The Implications for Understanding, Modeling, Diagnosing and Treating Brain Disorders?

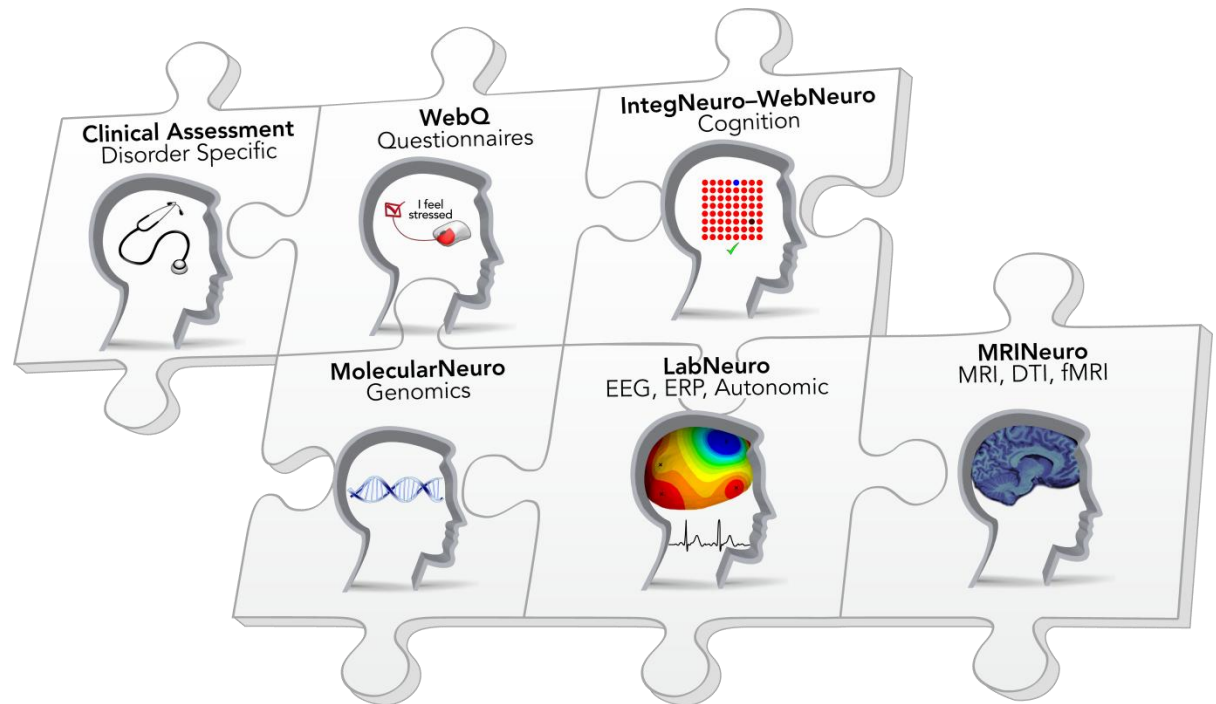
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Schizophrenia



A comparative study of the MATRICS and IntegNeuro cognitive assessment batteries

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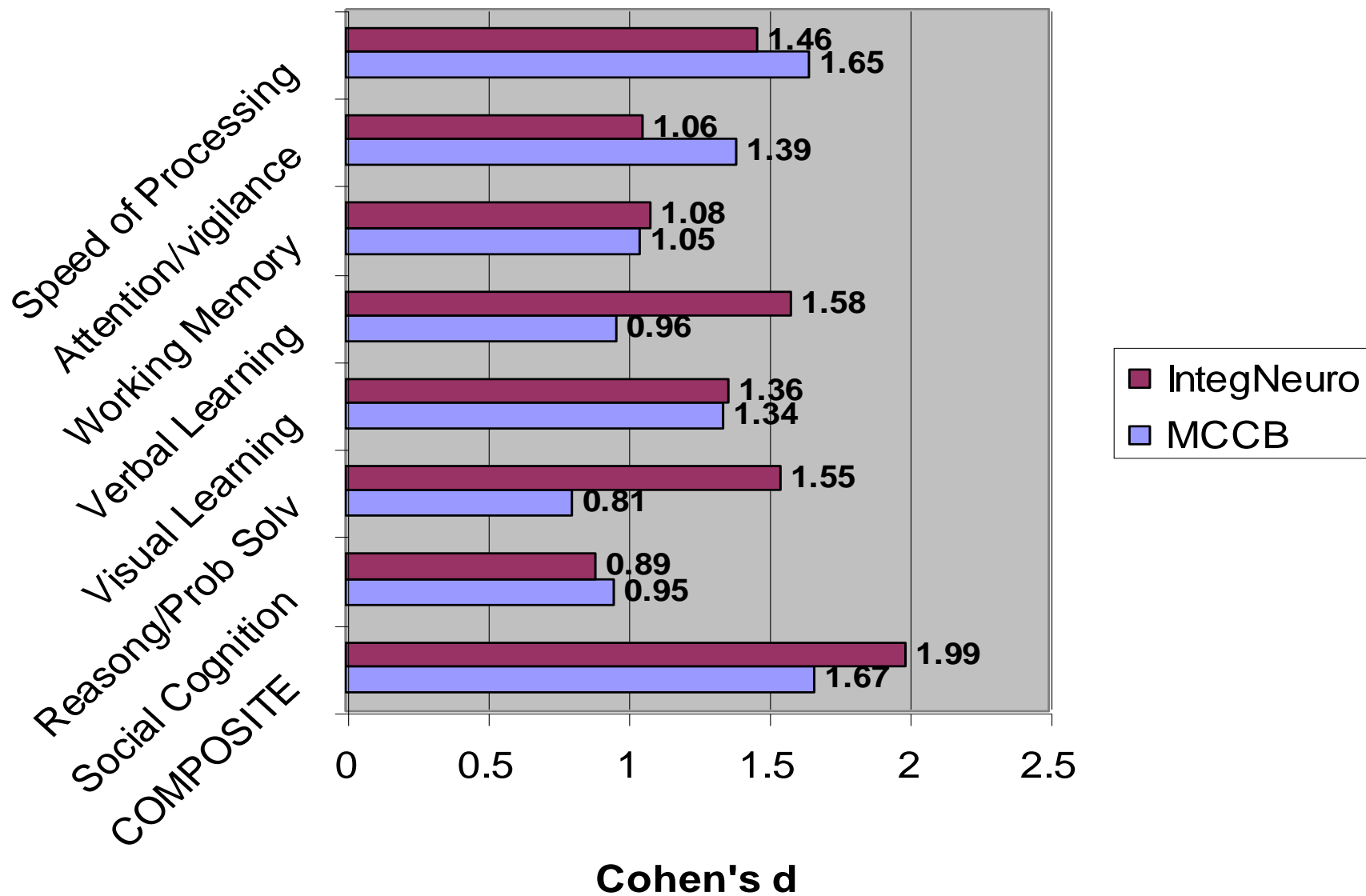
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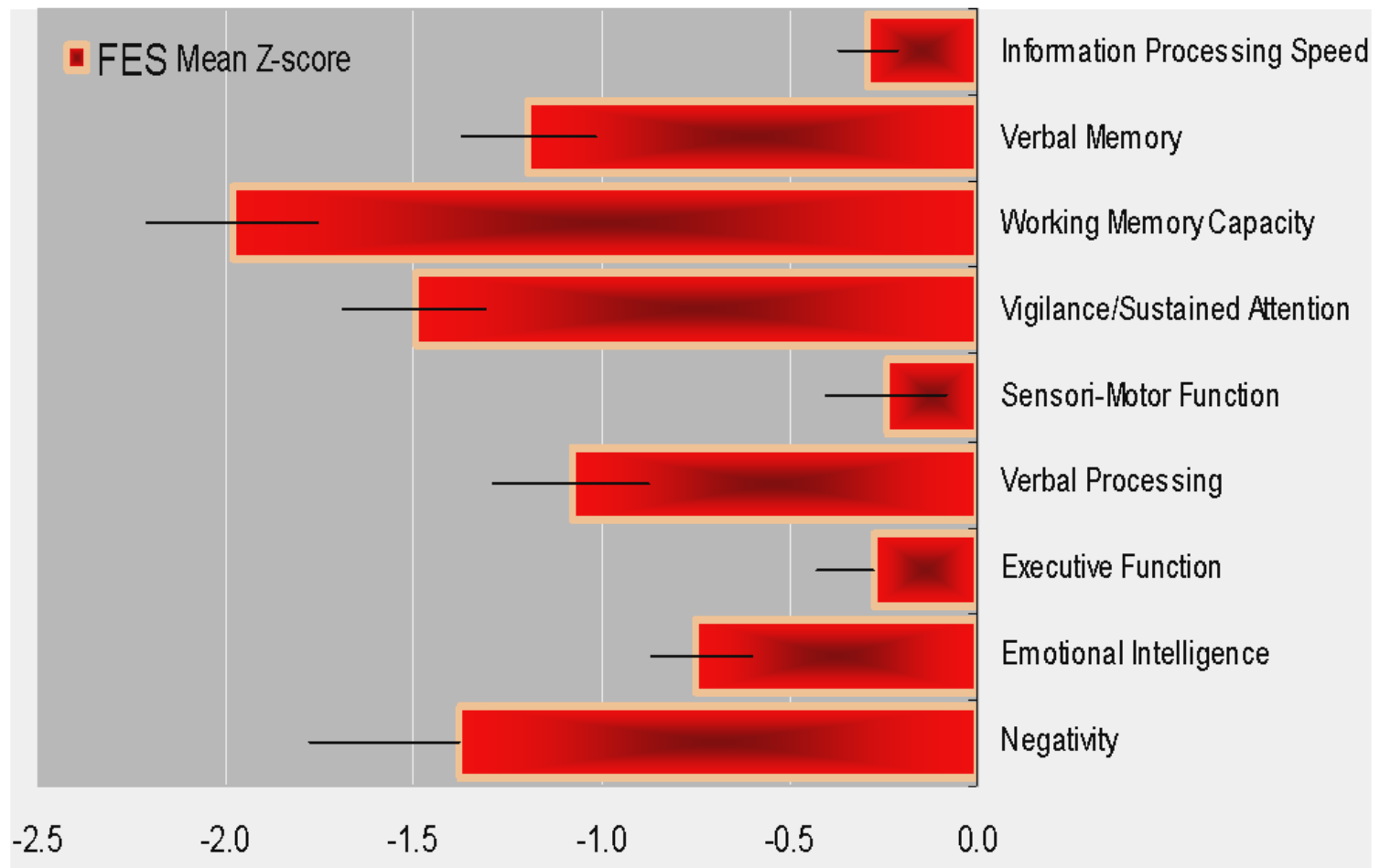
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1. Canonical correlation between sets of critical test scores in each battery = .91.
 2. Pearson r between composite scores = 0.85.

Schizophrenia Effect Sizes for IntegNeuro & MCCB Composites



Means (and SEs) for factor scores on PCA-derived domains of general and social cognition in first episode schizophrenia (FES) (N=56). FES scores were standardized to control (n=112) norms. Results confirmed in new sample of N=59

(from Williams, Whitford, Flynn, Wong, Liddell, Silverstein, Galletly, Harris, & Gordon *Schizophr Res.* 2008)





- ▶ General and Social-emotional cognitive measures predict functional status, explaining up to 79% variance in
 - ✓ Social and Occupational Functioning (SOFAS)
 - ✓ Quality of Life (WHOQOL)

Williams, Whitford, Flynn, Wong, Liddell, Silverstein, Galletly, Harris, & Gordon. (2008). *Schizophrenia Research*.

Neurodevelopmental context: Progressive Grey Matter Loss in Superior Temporal and Inferior Frontal Regions after 2.5 years from first onset of schizophrenia

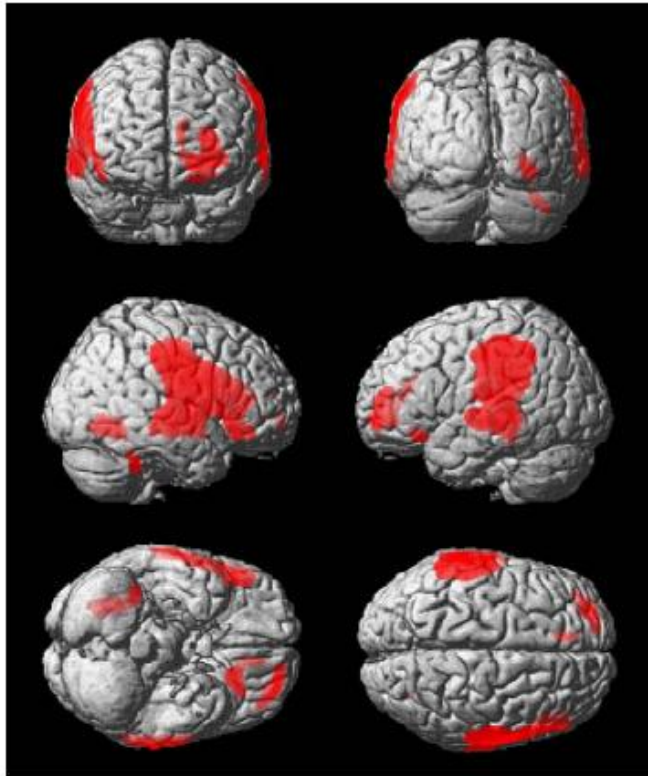


Fig. 1. Regions of reduced grey matter volume at baseline in 41 FES patients compared to 47 matched healthy controls. The regions of reduction are displayed as a rendered, three-dimensional statistical parametric map (SPM); height threshold: $P < 0.05$ corrected for family-wise error, extent threshold = 100 voxels.

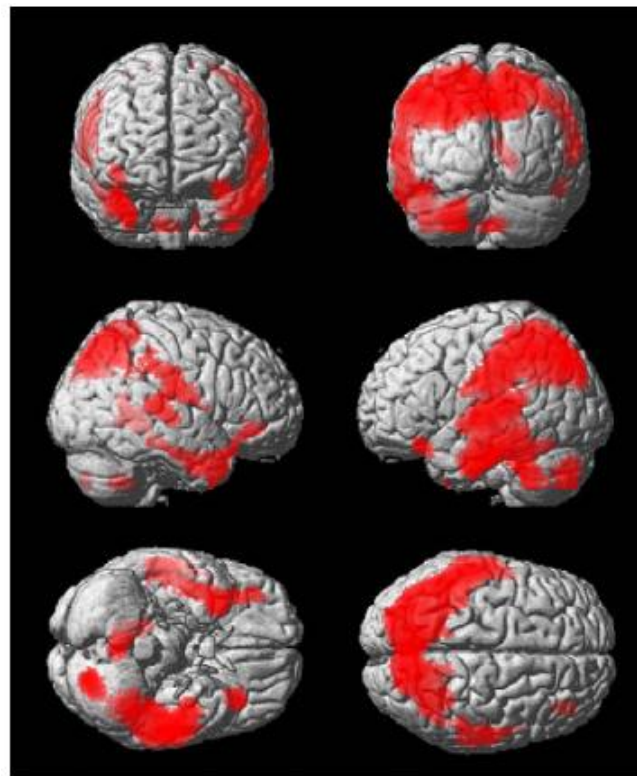


Fig. 3. Regions where 25 FES patients lost more grey matter volume over the 2- to 3-year follow-up interval compared to 26 matched healthy controls. These regions are displayed as a rendered, three-dimensional statistical parametric map (SPM); height threshold: $P < 0.05$ corrected for family-wise error, extent threshold = 100 voxels. There were no regions in

Neural synchrony in patients with a first episode of schizophrenia: tracking relations with grey matter and symptom profile

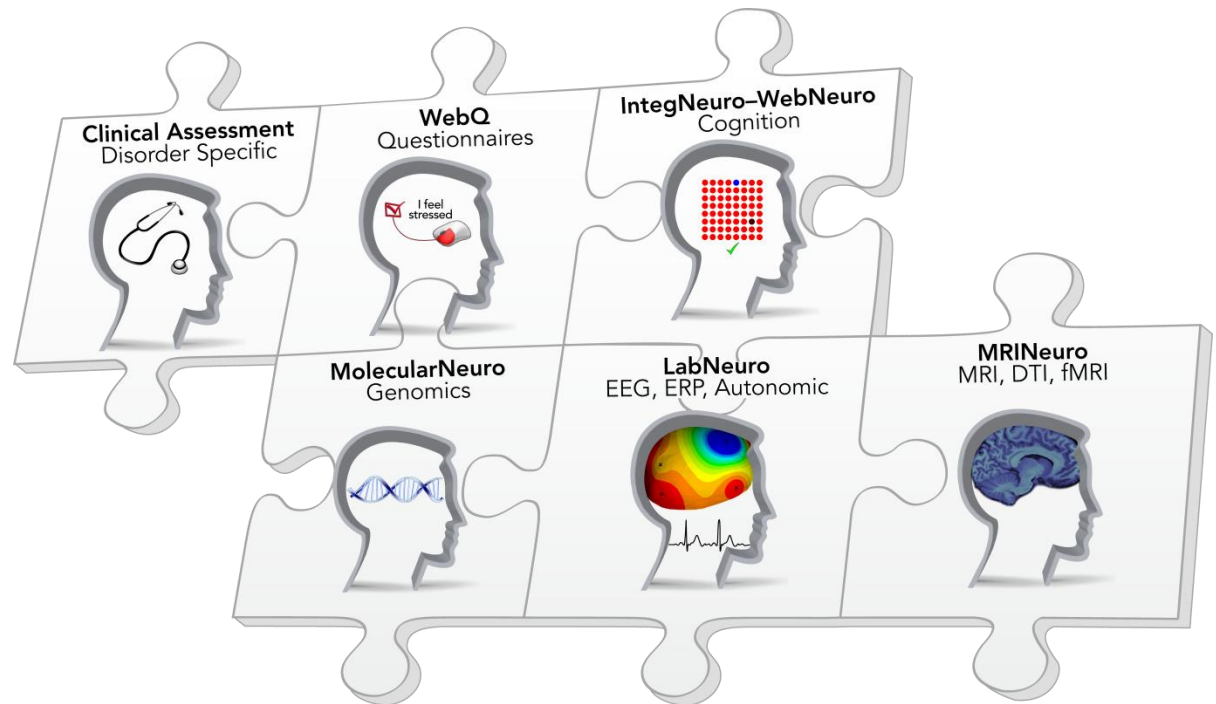
Leanne M. Williams, PhD; Thomas J. Whitford, PhD; Evian Gordon, PhD, MBBCh; Lavier Gomes, MBBS; Kerri J. Brown, MClinPsych, PhD; Anthony W.F. Harris, PhD, MBBS

Williams, Whitford, Gordon, Brown, Harris — Brain Dynamics Centre, Westmead Millennium Institute and Western Clinical School; Williams, Gordon, Brown, Harris — Department of Psychological Medicine, Faculty of Medicine, University of Sydney; Gordon — The Brain Resource International Database, Ultimo; Gomes — Department of Radiology, Westmead Hospital, Westmead, Australia

Background: Although schizophrenia has been characterized by disruptions to neural synchrony, it remains unknown whether these disturbances are related to symptoms and loss of grey matter. We examined relations between 40 Hz Gamma band synchrony and grey matter in patients with schizophrenia at first episode and after 2.5 years. **Methods:** From an initial recruitment of 35 medicated patients with a first episode of schizophrenia, 25 patients completed clinical and oddball task-elicited Gamma synchrony within 3 months of health service contact and again after 2.5 years, 23 completed magnetic resonance imaging (MRI) at these time points, and 13 completed all sessions. We compared patients with 35 matched healthy controls. We identified early (0–150 ms) and late (250–500 ms) peaks in Gamma synchrony locked to oddball targets, and we analyzed MRI data using voxel-based morphometry. We evaluated group and test–retest differences using repeated-measures analyses of variance. **Results:** Compared with controls, at first contact, patients with a first episode of schizophrenia showed a disruption to the laterality of early Gamma synchrony and global reduction in late Gamma synchrony, with a corresponding loss of fronto–temporal–parietal grey matter. Gamma synchrony was increased at follow-up among patients with a first episode of schizophrenia. It related negatively to further loss of grey matter, but positively to improvement in reality distortion symptoms. These relations could not be explained by medication dose. **Limitations:** Our study did not include unmedicated patients or normative follow-up testing. **Conclusion:** Gamma synchrony may track the progression of schizophrenia from first episode. An increase in Gamma synchrony over time might reflect an attempt to adapt to a progressive loss of cortical grey matter and associated changes in cognitive and emotional function.

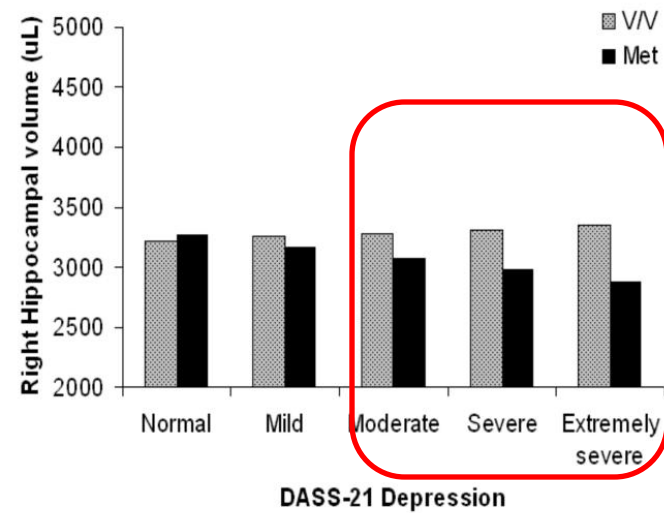
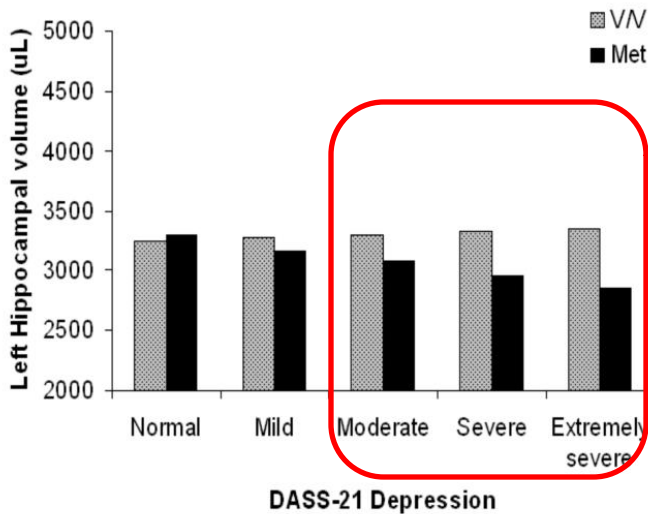


Depression





In people with moderate+ depression, the BDNF Met allele is Associated with loss of hippocampal grey matter (n=467)

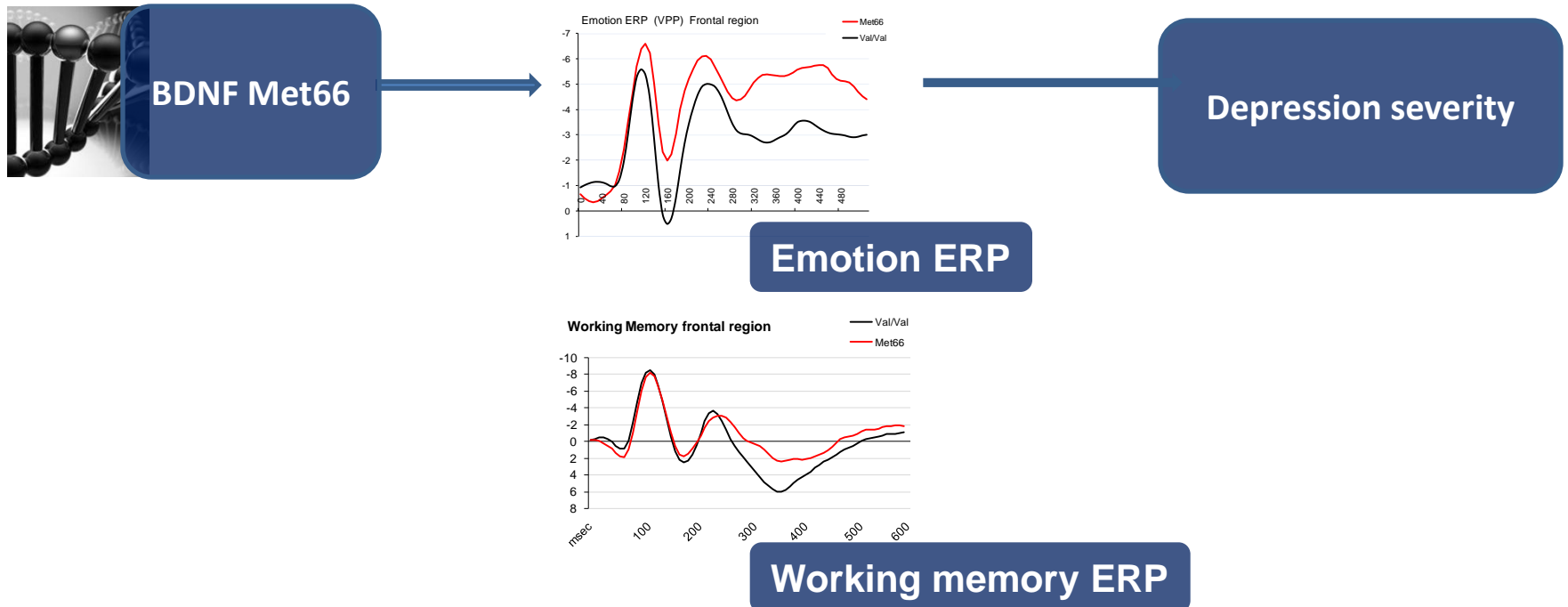


Joffe et al (2009) Human Brain Mapping



The relationship between the BDNF Met66 allele and altered brain activity predicts symptoms of depression .

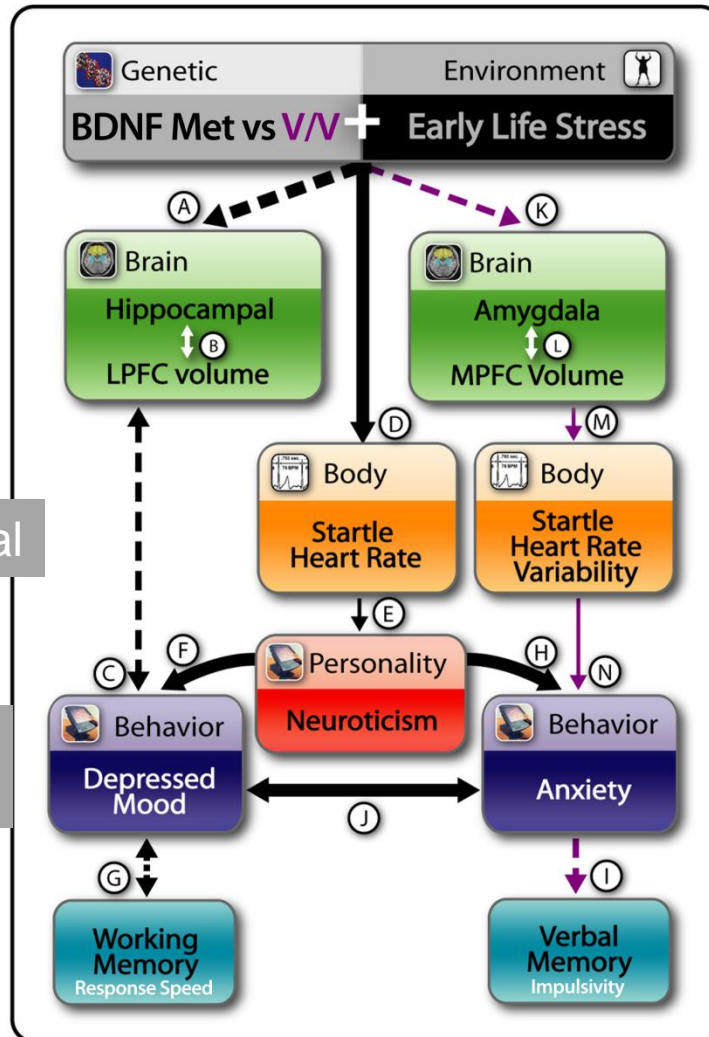
Brain activity is assessed by ERPs for Emotion and Thinking (working memory) tasks



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 Nemeroff³, C Dobson-Stone^{4,5,6}, RH Paul⁷, RA Bryant^{1,8}, PR Schofield^{4,5,6}, E Gordon^{1,2,9}, AH Kemp^{1,2} and LM Williams^{1,2}



Genetic

Brain

Body arousal

Symptoms & Cognition

A pathway to depression and anxiety

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

- loss of brain grey matter
- increased heart rate
- increased depression and anxiety symptoms
- associated cognitive thinking problems in response speed and impulsivity

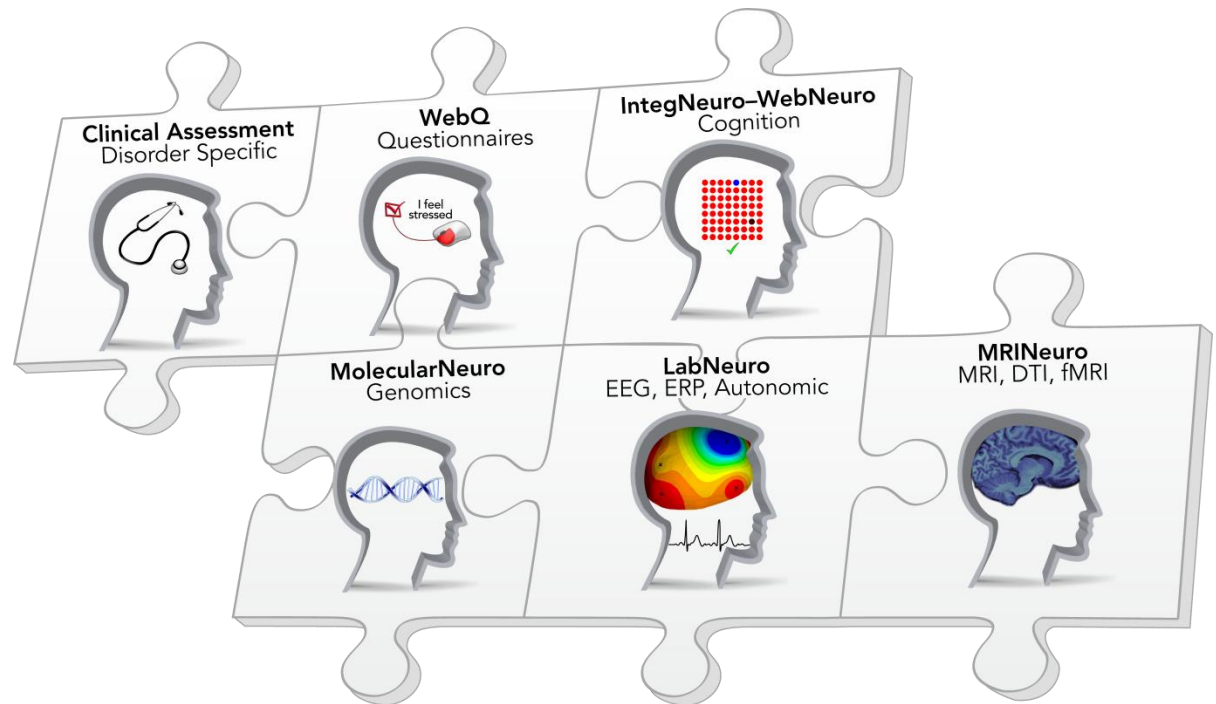
iSPOT

- Large, multi-site clinical trial for depression treatment, to determine which treatments work for whom
- 19 sites – across USA, Europe, Australia, and Africa
- N = 910 as of August 30, 2010
- First publications will report on N=1000
- Head of Publication Committee: A. John Rush
- All sites acquiring cognition, ERP, and symptom data
- 300 SNPs
- 4 sites for MRI/fMRI/DTI

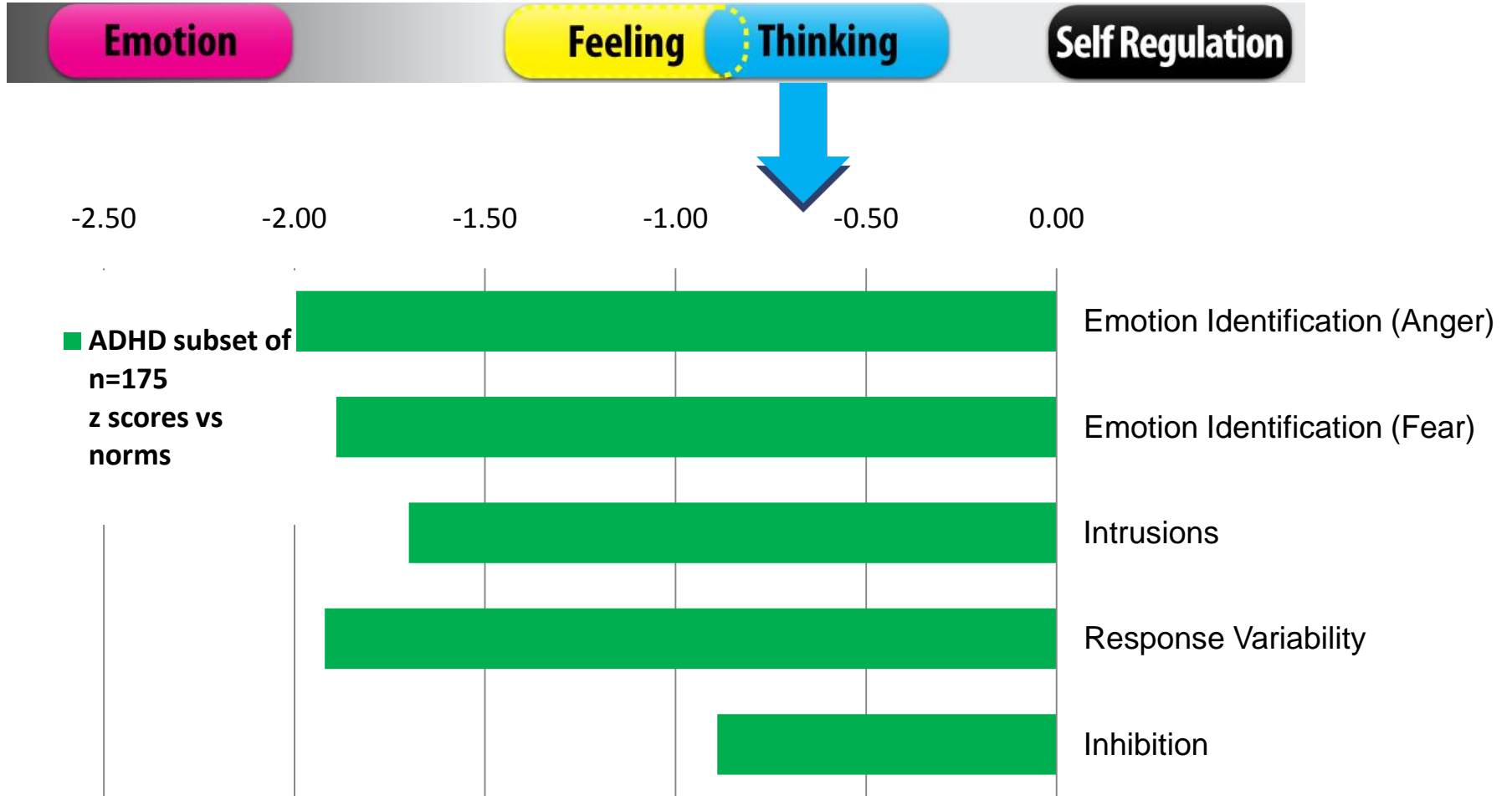




ADHD



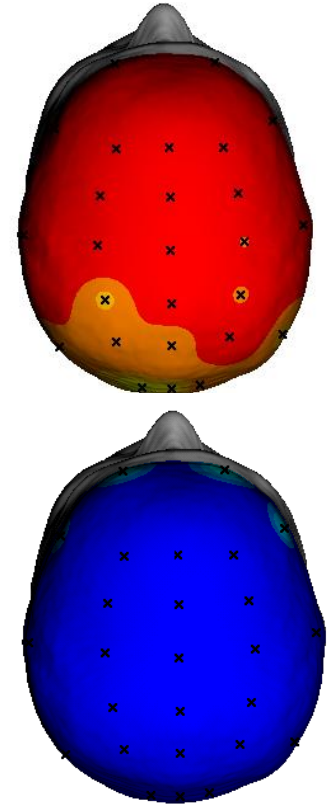
Thinking markers of general cognition. ADHD: n=175 Confirmed in second n=175



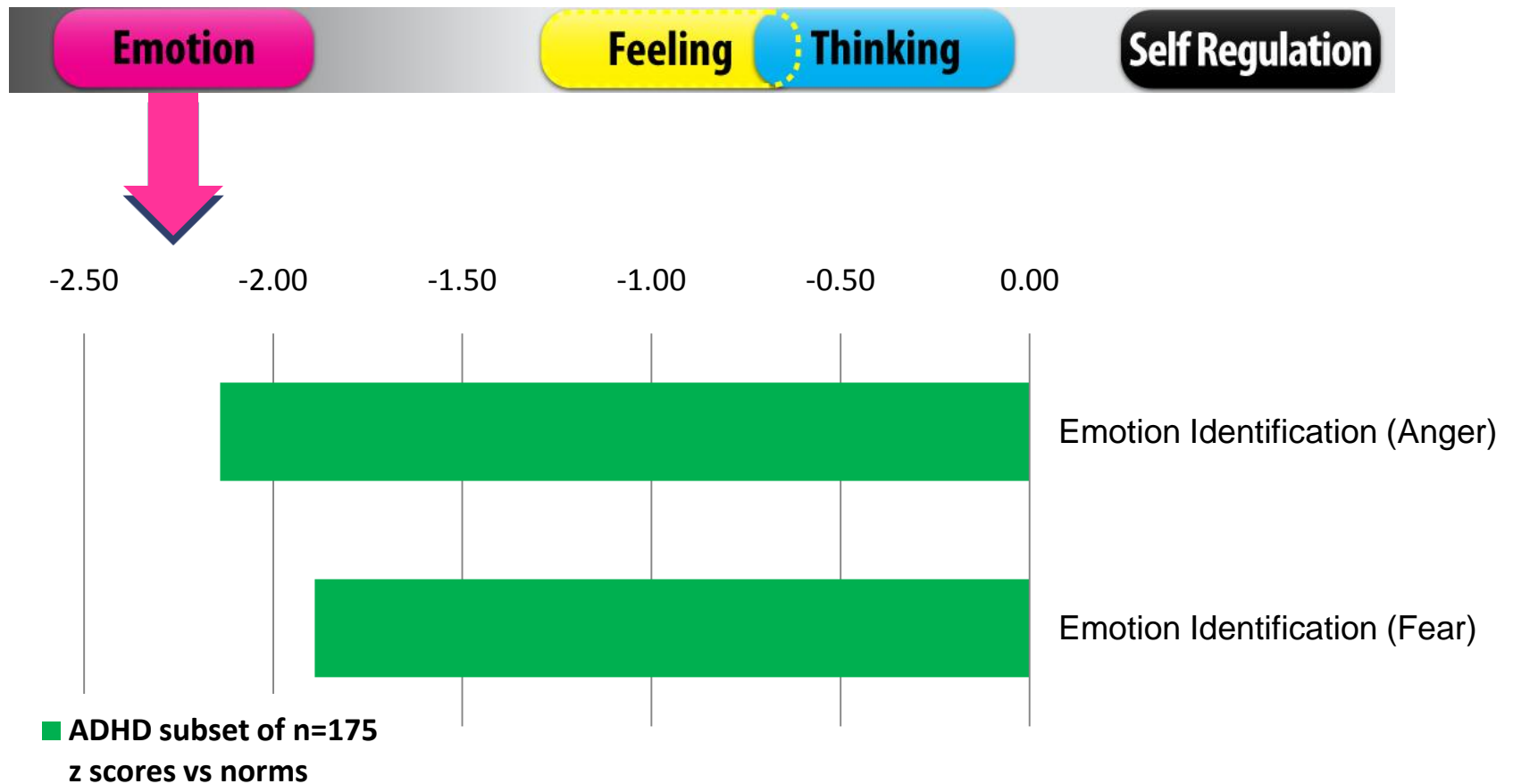
ADHD: markers: brain basis

They correlate with

- Enhanced EEG Theta power (relative to Beta)
- Reduced brain activity in Sustained Attention & Impulsivity tasks (P450 ERP for CPT N200 ERP for Go-NoGo)
- Reduced body arousal (heart rate)



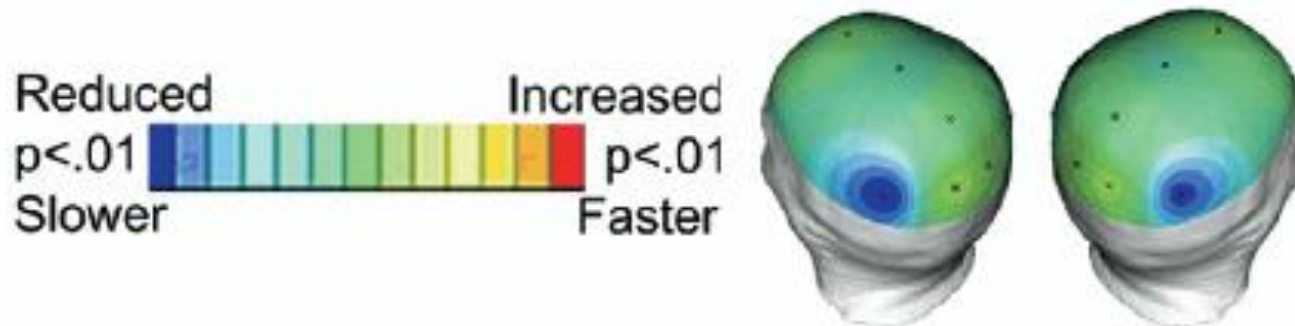
Emotion markers of emotional cognition. ADHD: n=50 (subset of n=175)



ADHD: **Emotion** markers: brain basis

They correlate with
alterations in emotional brain activity.

Reduced and slowed activity in occipital cortex, measured by ERPs

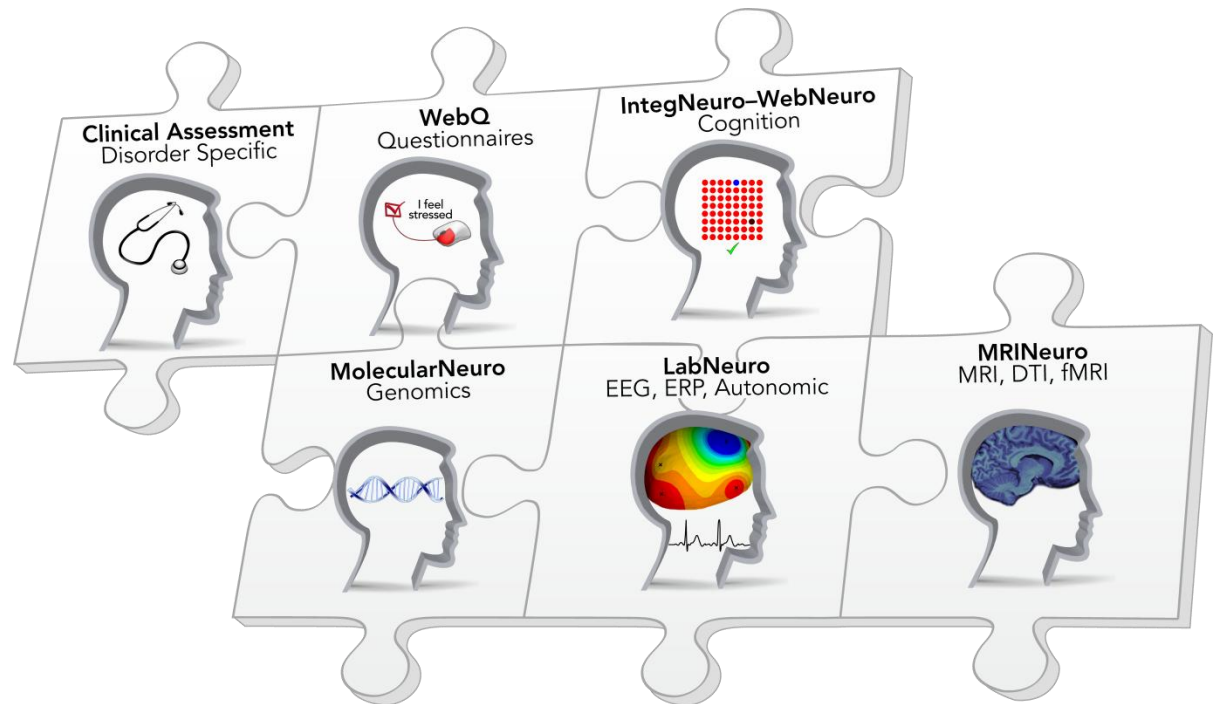


Misinterpreting Emotional Expressions in Attention-Deficit/Hyperactivity Disorder: Evidence for a Neural Marker and Stimulant Effects

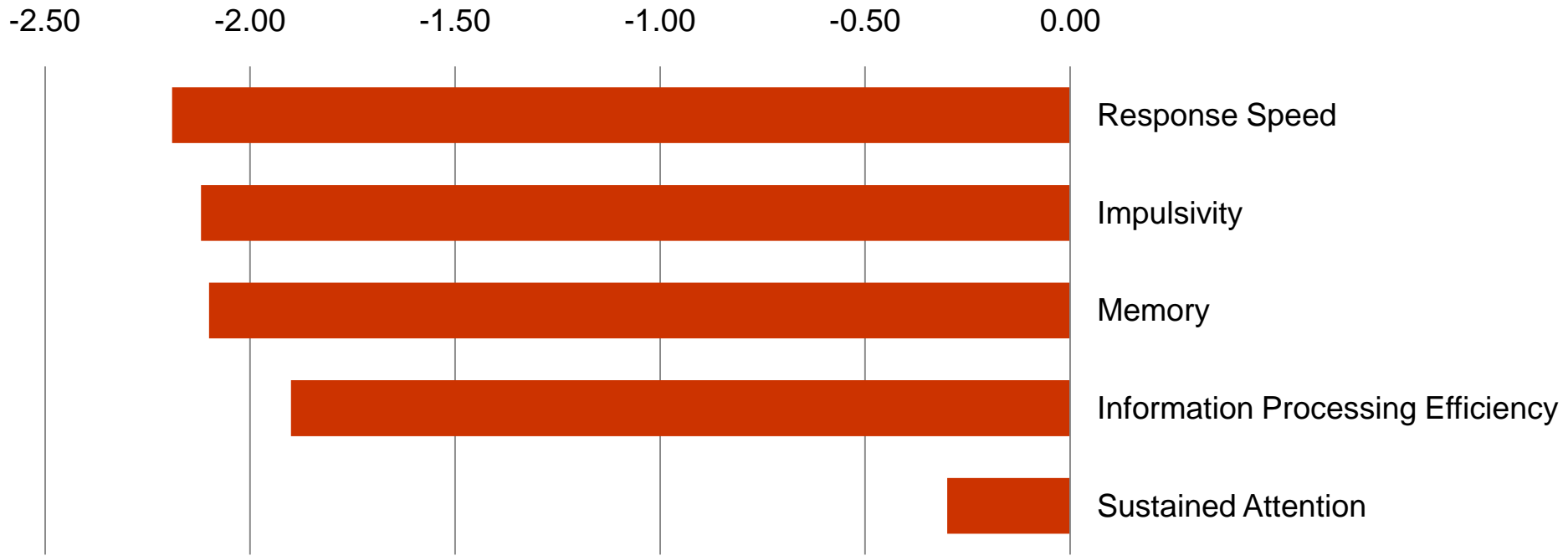
Leanne M. Williams, Daniel F. Hermens, Donna Palmer, Michael Kohn, Simon Clarke, Hannah Keage,
C. Richard Clark, and Evian Gordon



Anorexia Nervosa

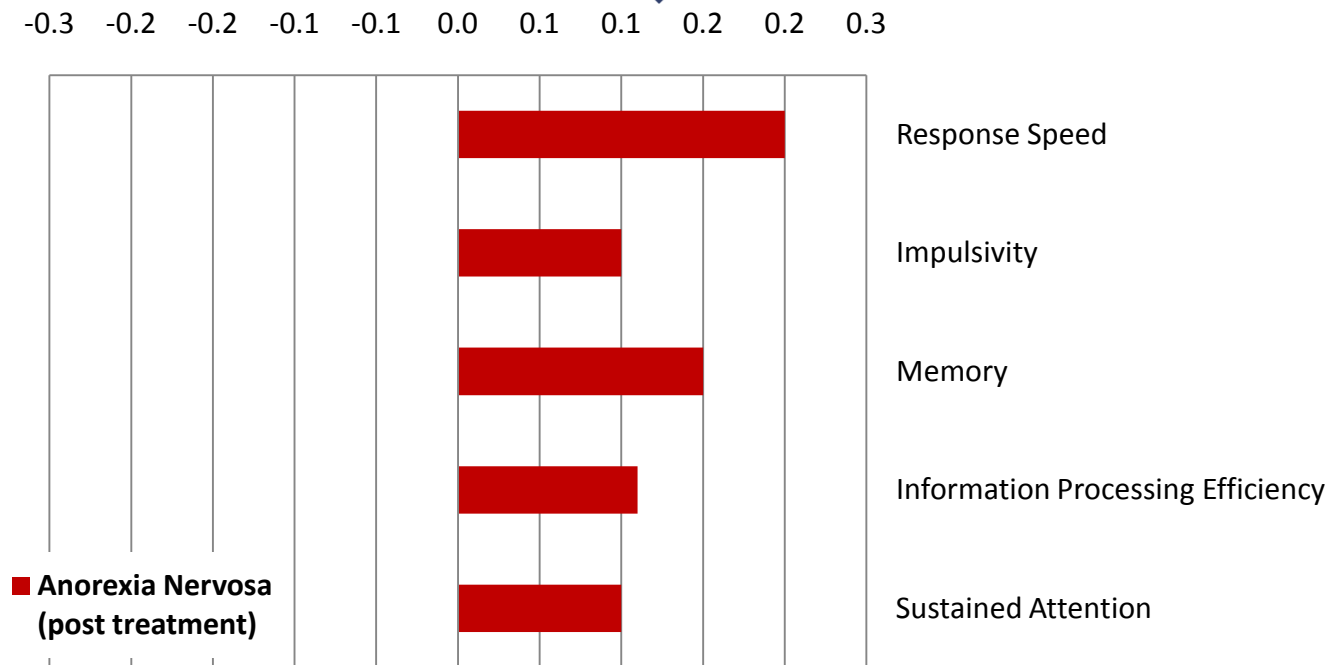


Thinking markers of general cognition. Anorexia Nervosa: n=42



■ Anorexia Nervosa; n=42; z scores vs norms

Thinking markers improve with refeeding treatment in Anorexia Nervosa



In First Presentation Adolescent Anorexia Nervosa, Do Cognitive Markers of Underweight Status Change with Weight Gain Following a Refeeding Intervention?

Ainslie Hatch, BA^{1,2*}
 Sloane Madden, MBBS,
 FRANZCP³
 Michael R. Kohn, MBBS,
 FRACP^{1,4}
 Simon Clarke, MBBS, FRACP^{1,4}
 Stephen Touyz, PhD²
 Ewan Gordon, PhD^{1,5}
 Leanne M. Williams, PhD^{1,6}

ABSTRACT
Objective: To determine the nature and severity of cognitive functioning impairment in adolescent anorexia nervosa (AN) when underweight and following weight gain.
Method: In 37 first admission adolescent (12–18 year) AN patients and 45 matched controls, general cognitive functions were assessed at baseline and follow-up using the IntegNeurocomputerized battery. AN participants were tested between days 5 and 10 of their admission when underweight, with retesting conducted after weight restoration.
Discussion: Cognitive impairments in adolescent AN appear to normalize with refeeding and weight gain. © 2009 by Wiley Periodicals, Inc.

Hatch et al (2010). Int J Eating Disorders

Anorexia Nervosa:

Emotional processing task performance and ERPs (shown here) DO NOT improve after treatment.

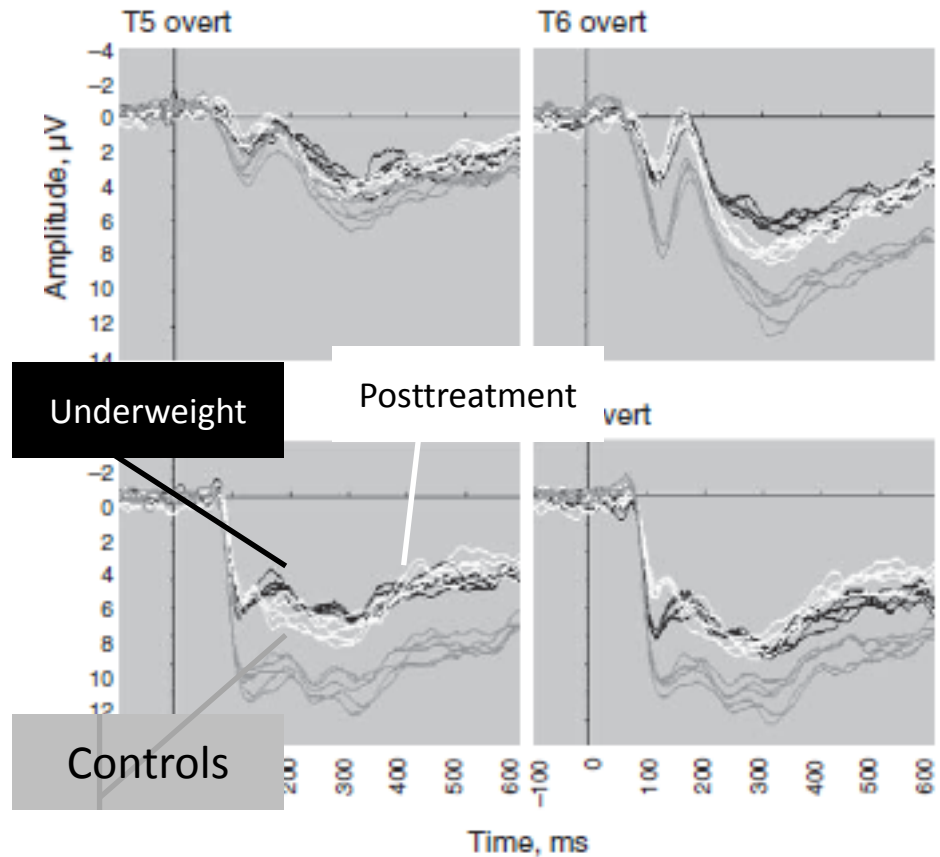
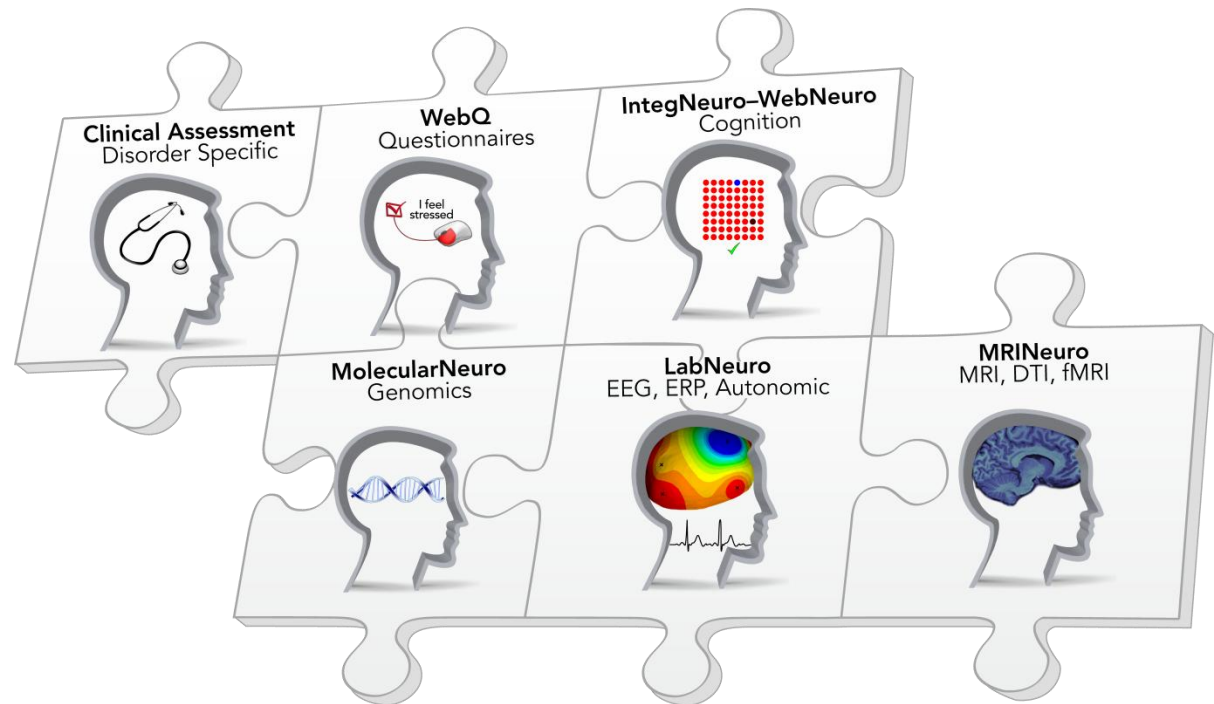


fig. 1: Event-related potential waveforms for the frontal (Fz), temporal (left T5 and right T6 sites) and occipital (left O1 and right O2) regions elicited by overt facial expressions of happy, fearful, anger and disgust in participants with anorexia nervosa who are underweight (black), after weight gain (white) and in matched healthy controls (grey).

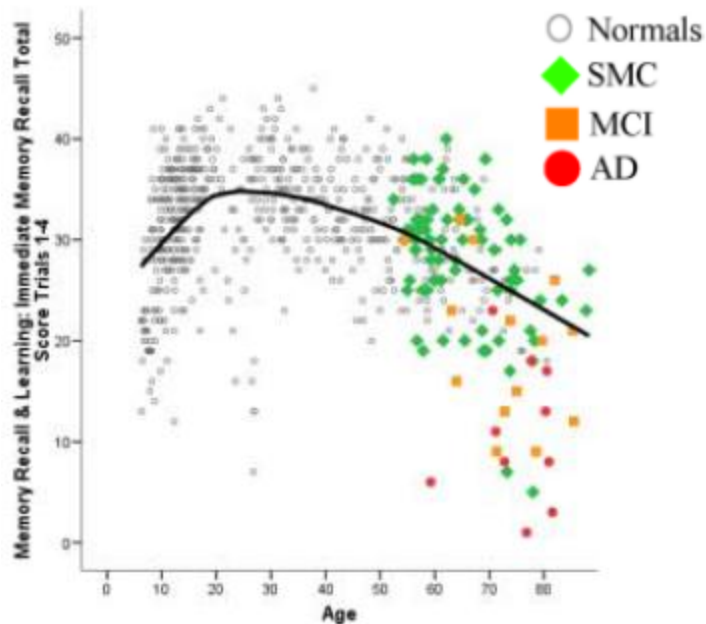


MCI, Alzheimers



Thinking

Memory marker shows distinct profile of correlates with brain measures (EEG/ERP) in MCI and Alzheimers Disease



(a) Verbal Memory: Immediate Recall

Table 5. Correlations between memory performance and EEG/ERP measures for normal, SMC, MCI and AD subjects. Pearson's r-values are presented, and strength of correlation is marked in color: yellow ($p < 0.05$), orange ($p < 0.01$), red ($p < 0.001$).

State	EEG Band	Region	Correlations			
			Normals	SMC	MCI	AD
EO	Delta	Central			$r = 0.767$	
		Temporal			$r = 0.761$	
		Parietal-Occipital			$r = 0.758$	
EC	Delta	Central	$r = 0.197$			
		Parietal-Occipital	$r = 0.235$			
EO	Theta	Frontal		$r = -0.228$		
		Central		$r = -0.209$		
EC	Theta	Parietal-Occipital				$r = -0.627$
EC	Alpha Peak Amplitude	Central	$r = 0.242$			
		Parietal-Occipital	$r = 0.252$			
EO	Alpha Peak Freq	Frontal		$r = 0.269$		
		Central		$r = 0.256$		
		Temporal		$r = 0.283$		
		Parietal-Occipital		$r = 0.256$		
EC	Alpha Peak Freq	Frontal				$r = 0.779$
		Central				$r = 0.901$
		Temporal				$r = 0.671$
		Parietal-Occipital				$r = 0.82$
EO	Theta:Alpha Ratio	Frontal				$r = -0.719$
		Central				$r = -0.661$
		Temporal		$r = -0.193$		$r = -0.644$
		Parietal-Occipital				$r = -0.724$
EC	Theta:Alpha Ratio	Frontal				$r = -0.64$
		Central				$r = -0.635$
		Temporal				$r = -0.645$
		Parietal-Occipital				$r = -0.678$

Research Report

RATES OF DECLINE DISTINGUISH ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT RELATIVE TO NORMAL AGING: INTEGRATING COGNITION AND BRAIN FUNCTION



Implications - I

- Integration of genetic, psychophysiological, cognitive, life history, and personality data can increase our ability to model the etiology and development of psychopathology.
- Large normative database, and common testing platform for studies of multiple disorders can assist in identifying common vs. unique mechanisms and pathways across disorders.
- Consistent with the NIMH Research Domain Criteria (RDoC) initiative, this can lead to more effective ways of conceptualizing, classifying, diagnosing, and treating mental illness.



Implications - II

- Treatment effects can be examined at multiple levels, in an integrated fashion, with clear reference to age- and gender-matched population norms.
- Large and growing database can serve as the basis for a personalized approach to treatment and prognosis.
- BrainNet approach can address 2 major reasons cited by pharmaceutical companies for abandonment of CNS R&D efforts:
 - 1) lack of appropriately characterized patient and control subjects
 - by having large normative and clinical groups (e.g., 1000 depressed patients for iSPOT)
 - 2) lack of valid biomarkers of endpoints for the condition being studied