

# Treatment of Apathy in Psychiatric and Neurodegenerative disorders: Are Positive Valence Systems of Reward Shared in Common?

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Disclosures:

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# Research Domain Criteria Matrix

A suggested organizational structure for knowledge

<b>Domain</b> ▶ <b>Construct</b> ▶ <b>Subconstruct</b>	----- <b>Units of Analysis</b> -----							
	<b>Genes</b>	<b>Molecules</b>	<b>Cells</b>	<b>Circuits</b>	<b>Physiology</b>	<b>Behavior</b>	<b>Self-Reports</b>	<b>Paradigms</b>

**NIMH RDoC focused on Five Domains:**

- Negative Valence – responses to aversive situations
- **Positive Valence – responses to positive motivational contexts**
- Cognitive Systems
- Systems for Social processes—responses to interpersonal settings, perception interpretation
- Arousal/Modulatory Systems—activate neuronal systems, maintain homeostatic regulation of systems including energy balance and sleep

Regulation of positive valence constructs are not uniquely explained by a single domain

Modified from: Behavioral Assessment Methods for RDoC Constructs;  
 August 2016: Report by National Advisory MHC Workgroup on Tasks and Measures for RDoC



Parsing Anhedonia: Translational Models of Reward-Processing Deficits in Psychopathology  
*Curr Dir Psychol Sci.* 2013 June 1; 22(3): 244–249.  
 Michael T. Treadway<sup>1,2</sup> and David H. Zald<sup>3,4</sup>

# Applying RDoC (Research Domain Criteria) Strategies to BPSD

- Not advocating ‘acceptance’ of RDoC; rather does the framework have utility to understand and advance the treatment of apathy in AD?
- “To support an experimental therapeutics approach to interventions and facilitate strategies for translating scientific discovery into novel treatments for psychiatry.”

Jill Heemskerk, PhD (Aug 2016)

Deputy Director, Division of Adult Translational Research, National Institute of Mental Health, NIH

- Growing evidence that alterations in reward processes may underlie motivational and anhedonic symptoms in depression, schizophrenia, early AD, and Parkinson’s

## **Positive Valence domain**

- 1. Reward Responsiveness**
- 2. Reward Learning**
- 3. Reward Valuation**

- **How can we expand our growing understanding of ‘transdiagnostic’ psychiatric symptoms to inform development of novel treatments for BPSD?**

(PLOS ONE | DOI:10.1371/journal.pone.0157084 June 14, 2016).

[https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/rdoc\\_council\\_workgroup\\_report\\_153440.pdf](https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/rdoc_council_workgroup_report_153440.pdf)

- While definitions are overlapping and terminology is inconsistently used, ‘apathy/amotivational/anhedonic’ symptoms are present and prominent not only in psychiatric disorders...

Methodological approaches and magnitude of the clinical unmet need associated with amotivation in mood disorders

*Journal of Affective Disorders* 168 (2014) 439–451

Joseph R. Calabrese<sup>a,\*</sup>, Maurizio Fava<sup>b</sup>, George Garibaldi<sup>c</sup>, Heinz Grunze<sup>d</sup>, Andrew D. Krystal<sup>e</sup>, Thomas Laughren<sup>f</sup>, Wayne Macfadden<sup>c</sup>, Robert Marin<sup>g</sup>, Andrew A. Nierenberg<sup>b</sup>, Mauricio Tohen<sup>h</sup>

## **A New Perspective on Anhedonia in Schizophrenia**

*Am J Psychiatry*. 2012 April ; 169(4): 364–373.

**Gregory P. Strauss, Ph.D<sup>\*</sup>** and **James M. Gold, Ph.D.**

University of Maryland School of Medicine, Department of Psychiatry and Maryland Psychiatric Research Center

- **Negative symptoms, ISCTM/ECNP Sept 1, 2017**

Stephane Pollentier, Boehringer Ingelheim,

ECNP Experimental Medicine Network

Validation of Reward Processing tasks, 15<sup>th</sup> March 2017

... but also in neurodegenerative disorders (typically under an *apathy umbrella*) ...

**Hedonic and Behavioral Deficits Associated with Apathy in Parkinson's Disease: Potential Treatment Implications**

*Mov Disord.* 2013 August ; 28(9): 1301–1304.

Lizabeth L. Jordan, M.S.<sup>1,2</sup>, Laura B. Zahodne, Ph.D.<sup>1,5</sup>, Michael S. Okun, M.D.<sup>1,3,4</sup>, and Dawn Bowers, Ph.D.<sup>1,2,3,6</sup>

**Apathy as a feature of prodromal Alzheimer's disease: an FDG-PET ADNI study**

*Int J Geriatr Psychiatry* 2015; 30: 470–477

Julien Delrieu<sup>1</sup>, Thomas Desmidt<sup>2</sup>, Vincent Camus<sup>2</sup>, Sandrine Sourdet<sup>1</sup>, Claire Boutoleau-Bretonnière<sup>3</sup>, Emmanuel Mullin<sup>4</sup>, Bruno Vellas<sup>1,5</sup>, Pierre Payoux<sup>6,7</sup>, Thibaud Lebouvier<sup>3</sup> and Alzheimer's Disease Neuroimaging Initiative<sup>†</sup>

- Apathy is related to reduced VTA function in Early AD with frontotemporal degeneration and subjective cognitive impairment (n=54);
- Apathy is linked to medial frontal areas in Probable AD (n=41)
  - Both studies implicate the motivational DA network

Schroeter ML, et al., *Psychiatry Res.* 2011;194:235-244

Marshall GA, et al., *Arch Neurol* 2007;64:1015-20

# Lack of precision in the use of Anhedonia, Amotivation, Apathy: Behaviorally (psychodynamically) Differentiated -- Yet are they Inter-related at a Neurocircuitry, Brain Function Level?

J Alzheimers Dis. 2017;55(2):551-558.

## **Brain Regions Involved in Arousal and Reward Processing are Associated with Apathy in Alzheimer's Disease and Frontotemporal Dementia.**

Huey ED<sup>1,2,3,4</sup>, Lee S<sup>4,5</sup>, Cheran G<sup>3</sup>, Grafman J<sup>6,7</sup>, Devanand DP<sup>2,4</sup>; Alzheimer's Disease Neuroimaging Initiative.

## **Auditory hedonic phenotypes in dementia: A behavioural and neuroanatomical analysis**

CORTEX 67 (2015) 95-105

*Phillip D. Fletcher, Laura E. Downey, Hannah L. Golden, Camilla N. Clark,  
Catherine F. Slattery, Ross W. Paterson, Jonathan M. Schott,  
Jonathan D. Rohrer, Martin N. Rossor and Jason D. Warren\**

*Alzheimer Dis Assoc Disord. 2015 ; 29(2): 161-164. doi:10.1097/WAD.0000000000000012.*

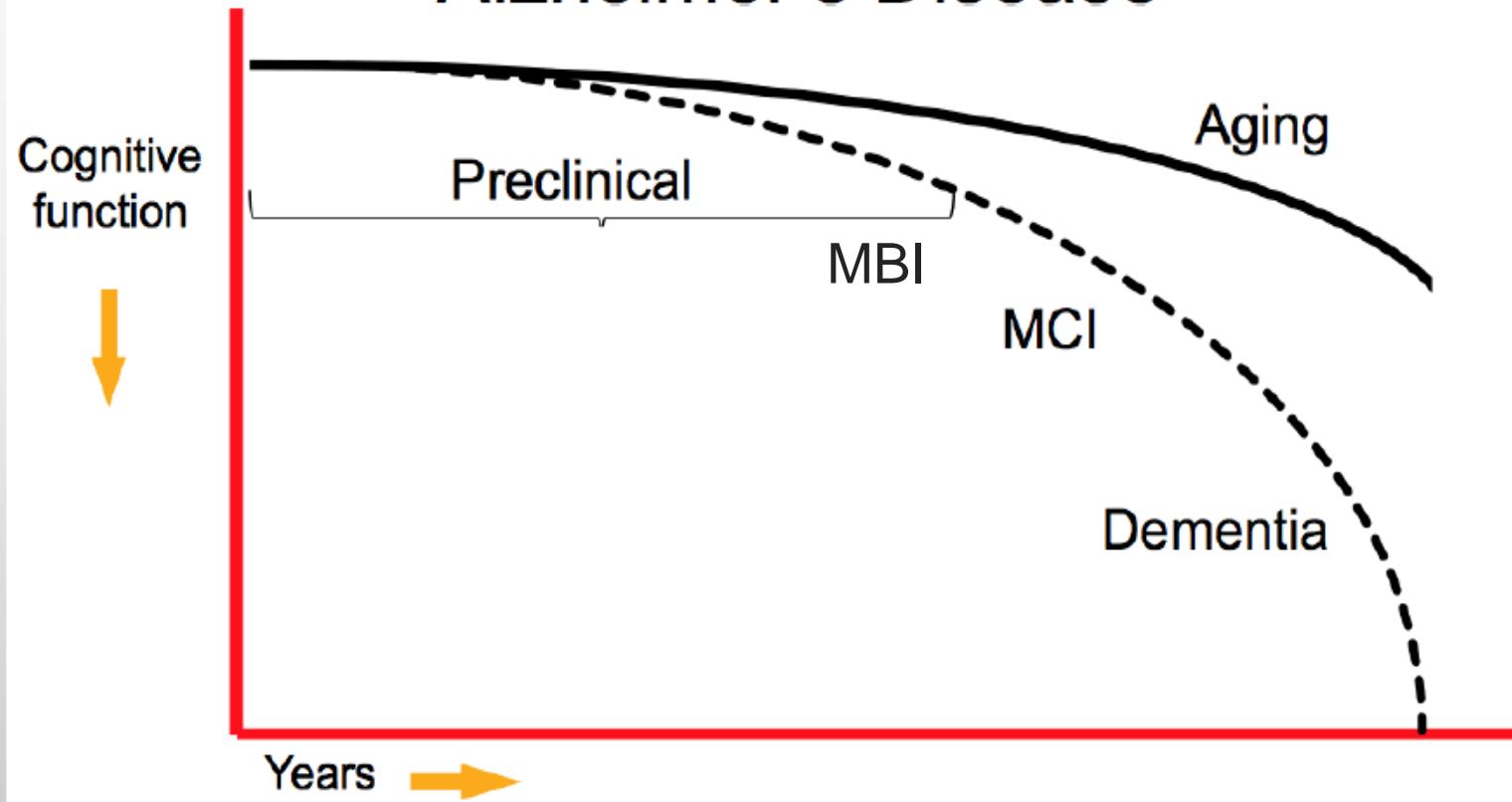
## **Divergent processing of monetary and social reward in behavioral variant frontotemporal dementia and Alzheimer's disease**

David C. Perry, MD<sup>1</sup>, Virginia E. Sturm, PhD<sup>1</sup>, Kristie A. Wood, BS<sup>1</sup>, Bruce L. Miller, MD<sup>1</sup>,  
and Joel H. Kramer, PsyD<sup>1</sup>

<sup>1</sup>Department of Neurology, University of California, San Francisco, San Francisco, CA

Stephane Pollentier, Boehringer Ingelheim,  
ECNP Experimental Medicine Network  
Validation of Reward Processing tasks, 15<sup>th</sup> March 2017

# The Continuum of Alzheimer's Disease



Do early stage patients with AD, i.e., MBI or MCI, (biomarker positive) manifest the same reward neurocircuitry dysfunction (fMRI, rsMRI, connectivity, ERP), transmitter/receptor dynamics, and response to drugs as psychiatric patients?

Could we screen new treatments in early stage illness to increase success of later phase studies in AD?

RA Sperling et al <http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011000999.pdf>

# Treatment of Apathy in Psychiatric and Neurodegenerative disorders: Are Positive Valence Systems of Reward Shared in Common?

- If reward processing circuitry activity changes, linked to the generation of motivational states, overlap for CNS disorders, then would pseudo-specificity concerns be allayed, i.e., apathy improvement and cognition?
  - What about pharmacological specificity, i.e., dopaminergic interventions?
    - The differing dynamics of dopamine concentration during reward learning, tonic (reward prediction errors) vs phasic (reward value)
    - D1 vs D2 signaling, PDE10a inhibitors
- If we can demonstrate target engagement with a ‘logical’ mechanism of action;
  - Show the intervention causes a change in relevant brain activity or mental process; and
  - Show that the intervention is associated with beneficial changes in the clinical phenomenon of relevance, then would we be on the path of de-risking drug development for Apathy in dementia?
- How might this construct inform the path forward to accelerate drug development? (*Experimental Therapeutics Approach to Interventions*, Sarah H. Lisanby, M.D., Director, Division of Translational Research, <https://www.nimh.nih.gov/outreach/coalition/coalition-for-research-progress-meeting-summary-march-30-2017/index.shtml>)



# RDoCs Style Anhedonia 'Fast-Fail' Early Phase Development Study in Early MCI with Apathy (Decreased Motivation/Indifference)

## Early MCI meeting Apathy Diagnostic Criteria

### Screening/Subject enrichment?

Subjects able to perform reward tasks

Patients functioning below age-matched norms

Pharmacological challenge strategy

**I/E:** Behavioral symptoms sufficient to produce minimal impairment; BPSD not attributable to current psychiatric disorder

Does not meet criteria for any Dementia

Presence/absence of depression

### Primary: Circuit measure of expected effect of drug on the brain

Measure engagement of circuitry related to hedonic experience/ motivational responses, i.e., Monetary Incentive Delay.

DMN/Connectivity

*Experimental Therapeutics Approach to Interventions*, Sarah H. Lisanby, Director, Division of Translational Research

<https://www.nimh.nih.gov/outreach/coalition/coalition-for-research-progress-meeting-summary-march-30-2017/index.shtml>

## Key secondary

Behavioral intermediate phenotype assessment (more closely linked to neural circuitry than clinical outcome but also linked to clinical outcome)

Probabilistic Reward Task assesses capacity to learn based on reward

Clinical Outcome: Measured with clinical scales: NPI Apathy, CGIC

Cognition measure

What would be a functional measure in early MCI for a short Early Phase trial?

### Exploratory: Additional circuit measure

QEEG measures, ERP,

Effort Expenditure for Rewards Task assesses the degree to which one is motivated by reward as demonstrated by effort