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

Larry Ereshefsky, PharmD, BCPP, FCCP

Chief Scientific Officer and Owner, Follow the Molecule: CNS LLC

Retired Professor of Pharmacy, Pharmacology and Psychiatry,
The University of Texas Health Science Center, San Antonio

Disclosures:
Consult for Abide Pharma, Intracellular Therapeutics, Lundbeck,
M3 Bio, Neuralstem, and Taisho R & D
CSO, Early Phase, Hassman Research Institute
Principal consultant, investigator, ProScience Research Group
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
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).

• 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

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

A New Perspective on Anhedonia in Schizophrenia

Gregory P. Strauss, Ph.D* 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
… but also in neurodegenerative disorders (typically under an apathy umbrella) …

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

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

Huey ED,1,2,3,4 Lee S4,5 Cheran G3, Grafman J6,7, Devanand DP2,4; Alzheimer's Disease Neuroimaging Initiative.

Auditory hedonic phenotypes in dementia: A behavioural and neuroanatomical analysis

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

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

David C. Perry, MD1, Virginia E. Sturm, PhD1, Kristie A. Wood, BS1, Bruce L. Miller, MD1, and Joel H. Kramer, PsyD1

1Department of Neurology, University of California, San Francisco, San Francisco, CA
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]
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?

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

**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

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