Cross-Diagnostic Disorders of Cognition/Motivation
The Why and the What

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Disclosure:

The presenter is an employee and share holder of F. Hoffmann La Roche

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Problem Statement – The WHY

NS innovative therapy development lack biological tractability:

– Poor understanding of the pathophysiology
– Animal models do not represent the target diseases
– Lack of translatability of effect from healthy individuals to patients
– Diagnostic entities in NS disorders are heterogeneous and may have different underlying biology
Cross Diagnostic Symptom Domains - the **WHAT**

- Cognition and motivation:
  - Are these discrete continuous entities? Are they measurable?
  - Is there a unique biology underlying these domains?
  - How do these domains manifest themselves across diagnoses?
  - Do they predict functioning?
Nomenclature

• **Apathy** (used in AD, PD, depression): absence or suppression of passion, emotion, or excitement

• **Avolition** (used in schizophrenia): “poverty of will”, lack of drive, or motivation to pursue meaningful goals

• **Amotivation**: a state of lacking any motivation to engage in an activity, characterized by a lack of perceived competence and/or a failure to value the activity or its outcomes

www.selfdeterminationtheory.org
Motivation A Discrete Entity?

• What is normal and abnormal motivation?
• How is it called by clinicians and researchers across disease areas?
• Can we propose a uniform nomenclature?
• Can we propose a classification for all disorders of motivation?
Is Motivation a Discrete Entity?

• Normal motivation could be “intrinsic” or “controlled”

• Both autonomy and control are types of motivation. They energize people’s actions.

• Amotivation refers to a lack of motivation. When amotivated there is little or no intention or action.
Intrinsic Motivation

• Doing an activity because it is interesting and enjoyable

• Satisfies people’s basic psychological needs for competence, autonomy, and relatedness

• It’s the prototype of autonomy
Positive Feedback
Increases intrinsic motivation

Negative Feedback
Decreases intrinsic motivation

Why?
Because we also have a fundamental psychological need to be competent
Extrinsic Motivation

Doing an activity specifically because it leads to a separate consequence such as receiving a reward, avoiding a punishment, or getting parents love and approval.
The Interface Between “Intrinsic and “Controlled” Motivation

• Controlled motivation can be internalized
  – People tend to internalize aspects of the environment that are endorsed by important others – They have a need for relatedness

• Controlled motivation is fostered by parents’ attention and affection depending children’s behavior.
  – Love and attention when children do what their parents desire.
From Health to Pathology

• **Autonomous motivation** (integration), results from need satisfaction; is the basis of health and flexibility

• **Controlled motivation** (pressure), results from thwarting of the autonomy need; is the basis of rigidity, ill-being, and some pathologies

• **Amotivation** (poor regulation), results from thwarting the autonomy and either competence or relatedness needs; involves lack of intentionality and relates to some pathologies
Disorders Associated with Controlled Motivation

• Rigid Character Disorders
  • Act strong, show no weakness, do not give in to barricades,
  • Inner rigidity and inflexibility

• Obsessive compulsive disorders
  • Repetitive behavior, easily upset when routine is interrupted
  • A power dynamic with authority
  • Feels compulsion and no sense of choice
  • Inner rigidity and inflexibility
Disorders Associated with Controlled Motivation

• **Paranoid Personality**
  - Projects introjected demands onto other authorities
  - Believes those authorities want to harm them, suspicious of others
  - Extreme rigidity and inflexibility

• **Anorexia nervosa**
  - Focuses on controlling one’s eating
  - Obsessed with body image and weight
  - A power dynamic with authorities
  - Inner rigidity and inflexibility
Disorders Associated with Amotivation

• Impulsive disorders
• Borderline personality
• Anaclytic Depression
  • Lack of intention to behave
  • Overcome by sadness
  • Lack of self-worth
  • Results from loss of loved one
  • Based in thwarting of autonomy & relatedness needs
Disorders of Motivation Across Neuropsychiatric Disorders

AMOTIVATION

Idiopathic

Secondary

Pathology

Neuro-Development

Neuro-Degeneration

Drug Induced

Mental Disorders
Amotivation in MDD

• Described as a syndrome in itself (Chase 2011)
• Correlation with mood varies depending on the definition (Marin 1991, Brogard 2011)
• Prevalence 19 to 88% in MDD, specially older with poor executive functioning.
• Severity of interest activity and mood predictive of outcome in GENEDEP and STAR*D (Uher 2012)
• Most focus on unipolar than bipolar depression.
Methodological Questions

• Confounders:
  – Population: distinction between mood symptoms and amotivation
  – Fatigue
  – Concomitant medications

• Assessment tools
  – Apathy Evaluation Scale (AES) is the most used
  – Sheehan Disability, QoL scales
Amotivation in Neurodegenerative Disorders

• Present in most NDDs (AD, PD, HD, MS, PSP, FTD)

• AD and PD could be used as research models. Can the findings be extrapolated to other NDDs)

• Prevalence: AD 25-90%; PD 20-70% (Aarsland 2007, Oguru 2010)
Methodological questions

• Confounders
  – Diagnosis: motivation versus mood symptoms
  – Psychosis
  – Concomitant medications

• Clinical outcomes:
  – NPI – Apathy subscale
  – AES and the AES-derived apathy subscale
  – Key secondary outcomes: ADLs, cognition, caregiver burden, QoL
Conclusions

• Motivation:
  – Is a discrete continuous entity
  – It is measurable
  – It manifest itself across many diagnoses. More research needed
  – It’s impact on functioning across different disorders should be further evaluated
  – Is there a common underlying biology?
Panel Discussion:
Introduction to the HOW
Pathways to Evaluate the Effect of an NME on Motivation

• Motivation (/cognition) is observed in multiple diagnostic entities.
• There are subgroups of patients who, despite treatment with existing therapies, still present persistent symptoms of amotivation.
• Improvement of motivation in these patients will lead to an improvement in overall functioning.
Approaches to Evaluate Motivation

• Psychiatric illnesses:
  – Schizophrenia
  – Major depressive disorders

• Neuro-degenerative disorders:
  – Alzheimer’s disease
  – Parkinson’s disease

• Neurodevelopmental disorders
  – Autism
Proposed Methodology to Assess the Effect of NMEs on Motivation

• Major Depressive Disorders
  – Population:
    • Euthymic patients who, despite optimal treatment with SOC, still present residual amotivation
  – Assessment: AES
  – Duration: 6 to 12 weeks

• Hypothesis:
  – NME adjunctive to SOC has a superior efficacy on motivation compared with placebo adjunctive to SOC
Proposed Methodology to Assess the Effect of NMEs on Motivation

- Alzheimer’s disease
  - Population:
    - Patients with AD who, despite optimal treatment with SOC, present predominant amotivation
  - Assessment: AES
  - Duration: 6 to 12 weeks

- Hypothesis:
  - NME adjunctive to SOC has a superior efficacy on motivation compared with placebo adjunctive to SOC