

Neuro-circuitry and implications for drug development and study designs for treatment of apathy

KRISTA L. LANCTÔT, PHD

SENIOR SCIENTIST, SUNNYBROOK RESEARCH INSTITUTE;

HEAD, NEUROPSYCHOPHARMACOLOGY RESEARCH GROUP;

PROFESSOR OF PSYCHIATRY AND PHARMACOLOGY, UNIVERSITY OF TORONTO

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Apathy in Alzheimer's Disease

Characterized by lack of motivation, decreased initiative and emotional indifference

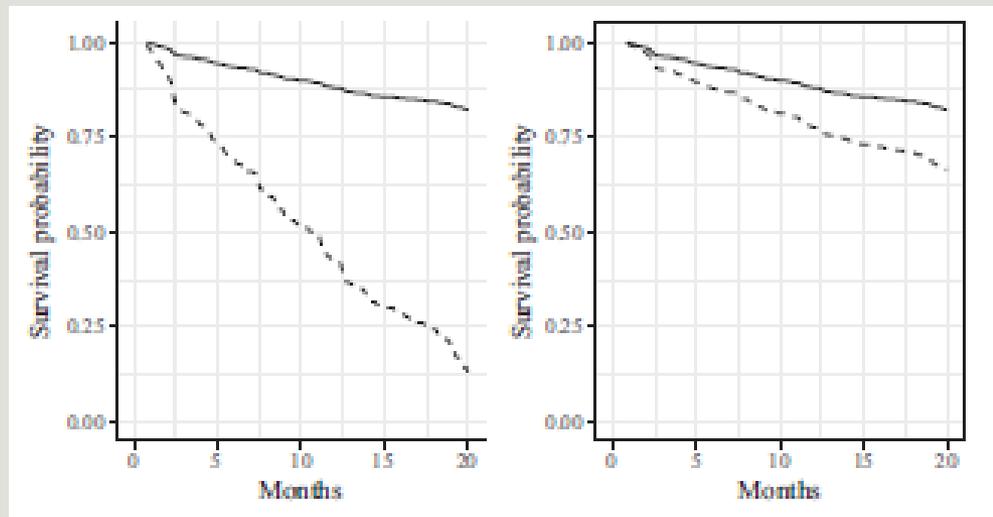
One of the most common BPSDs

Associated with

- decreased quality of life
- increased care needs and caregiver burden
- increased risk of institutionalization
- higher costs of care
- higher mortality

Apathy increases mortality in NH patients

1 SD increase in AES-10 score associated with 62% increase in mortality (HR = 1.62, 95% CI = 1.40–1.88, $P < .001$).



Survival probability in months for patients of SC (left) and DSC (right), for patients with apathy (dotted line) and patients without apathy (black line), apathy as categorical construct.

Treating Apathy

No current treatments specific to apathy

Cholinesterase inhibitors have been shown to improve apathy in some patients

- But, many patients do not improve despite improvements in cognition

Suggests a distinct neurocircuitry may underlie apathy

Apathy in AD is Linked to Specific Neurobiological Factors

Neurochemistry 4 studies

- low DA transporter in putamen
- low ACh binding in L frontal cortex
- low plasma GABA

Regional neuropathology 2 studies

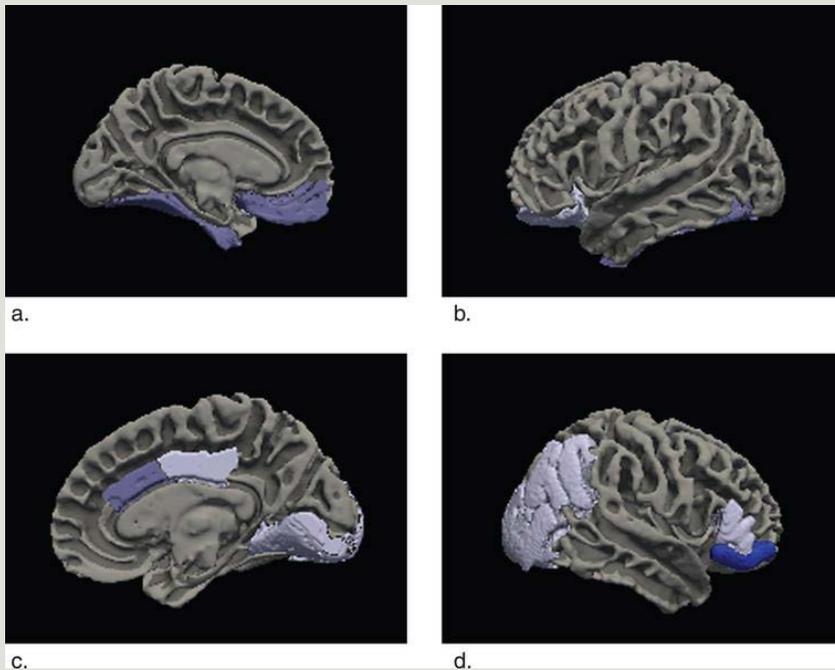
- NFTs in anterior cingulate

CSF biomarkers 2 studies

- no association with amyloid- β 1-42
- no association with/high total tau, and phosphorylated tau

Neuroimaging and apathy-- Regional atrophy

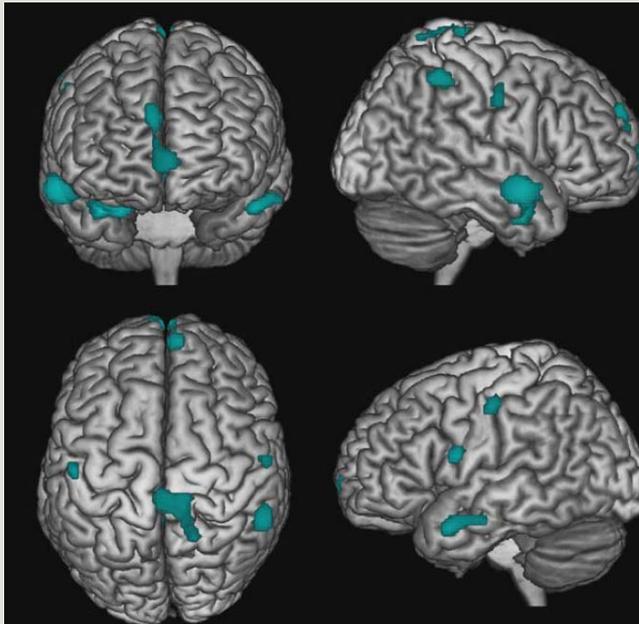
MRI--brain regions involved in arousal and reward processing (>8 studies)



- Atrophy of 4 regions independently associated with apathy:
 - ventromedial prefrontal cortex;
 - ventrolateral prefrontal cortex;
 - posterior cingulate cortex and adjacent lateral cortex;
 - bank of the superior temporal sulcus
- Replicate previous studies in FTD and CBS

Neuroimaging and apathy— regional hypoperfusion

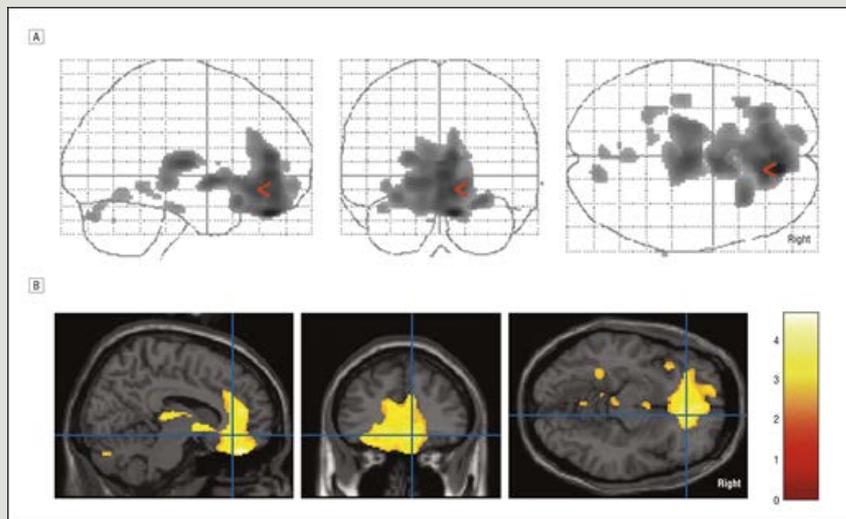
SPECT--alterations in rCBF in areas integrating sensory, affective, and motivational information to derive potential reward outcome (>7 studies)



- R amygdala
 - Middle temporal gyri
 - Posterior cingulate
 - Right superior frontal, postcentral, left superior temporal gyri
- Compared with depressed-no-apathy group, distinct regions

Neuroimaging and apathy— regional hypometabolism

FDG-PET—regions of the brain that modulate behavioural initiation, motivation, interest and reward mechanisms

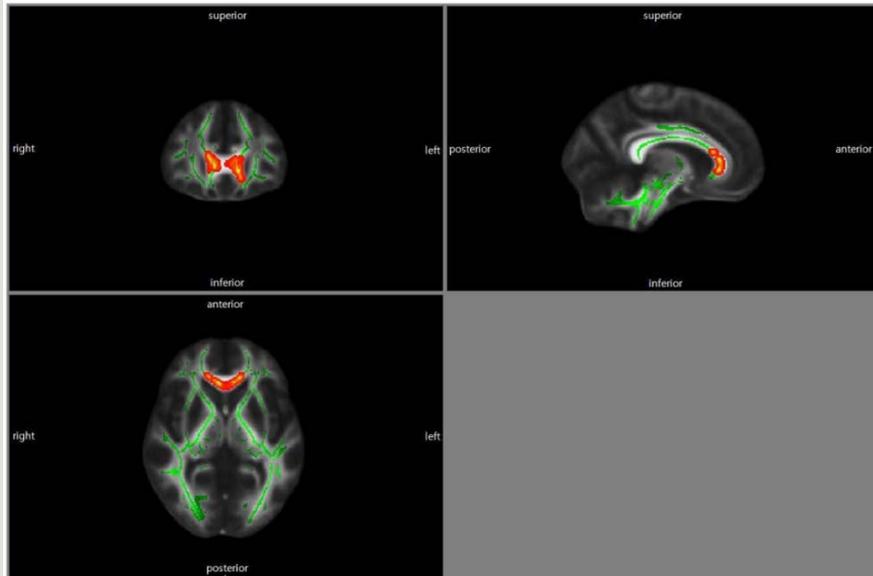


- reduced activity in bilateral anterior cingulate region, medial orbitofrontal cortex, and the bilateral medial thalamus (Marshall 2007)
- positive association between posterior cingulate hypometabolism and apathy at baseline and over time (Gatchel 2017)

Neuroimaging and apathy— white matter

WMH-Frontal or diffuse white matter hyperintensities (>2 studies)

DTI- impaired white matter integrity in the tracts associated with motivation (3 studies)



- impaired white matter integrity anterior cingulate and medial thalamus (Ota 2012)
- reduced FA values in genu of corpus callosum
 - Interconnecting fibres from prefrontal cortex - motivation.

Neuroimaging and apathy-- summary

Structural neuroimaging studies in AD

- atrophy in frontal regions, particularly PFC (e.g., orbitofrontal [motivational significance, reward], anterior cingulate [initiate behaviour]) and insula

Functional neuroimaging studies in AD

- abnormal perfusion in the cingulate and orbitofrontal regions
 - loss of white-matter connectivity
- Regions of the brain that modulate motivation, interest, behavioural initiation, and reward mechanisms

Neuroimaging and apathy

More recent data from AAIC 2017

- Apathy positively correlated to tau depositions (AD, MCI)
 - bilateral anterior cingulate cortex, bilateral dorsolateral prefrontal (DLPF), bilateral orbitofrontal, right superior parietal and right middle temporal gyrus (You, P2-267)
- Apathy Inventory scores positively correlated with functional connectivity of the default mode network (DMN) (30 AD vs controls)
 - left anterior cingulate cortex (Won, P2-350)
- Apathy related to decreased connectivity between the salience network (SN) and DMN, and increased connectivity between two SN components (MCI)
 - (dorsal anterior cingulate cortex and insula) (Opmeer, P3-307)

specificity

regions intrinsic to apathy

- suggested by frontal involvement

regions typically affected in early AD

- suggested by involvement of parietal and temporal lobes

Consistency of findings— prodromal

Continuum--clinically normal elderly, MCI and mild AD from ADNI

Structural MRI

- no association with cortical thickness at baseline
- reduced baseline cortical thickness in inferior temporal regions predictive of apathy over time

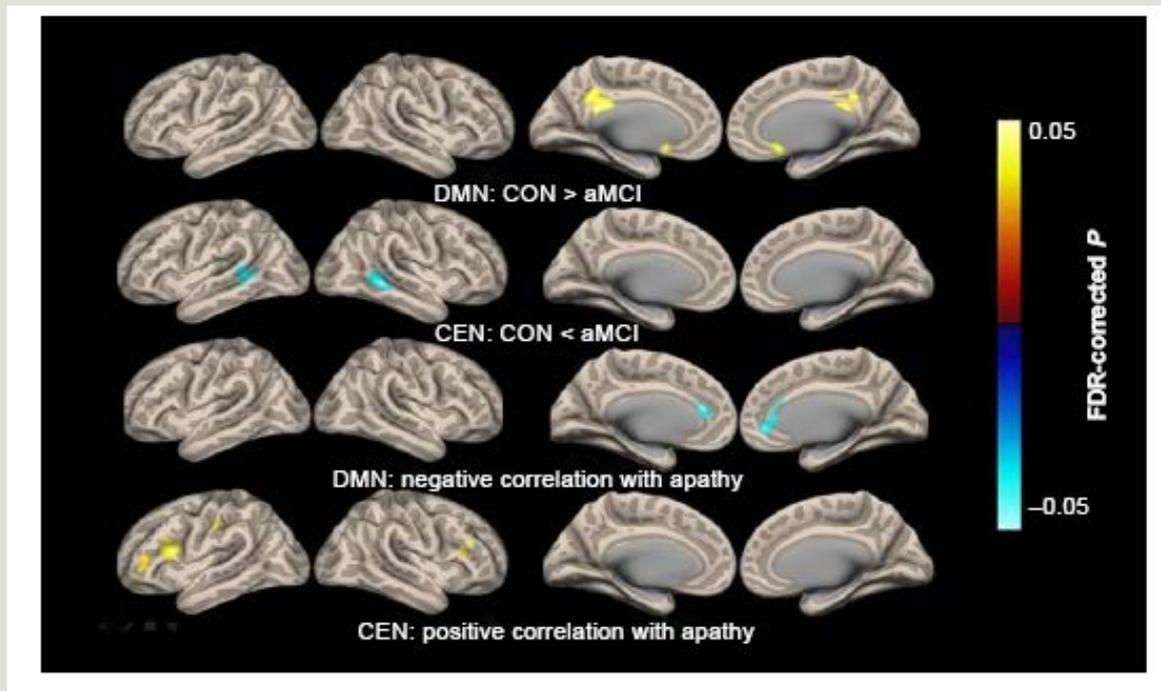
CSF concentrations of amyloid- β 1-42, total tau, and phosphorylated tau

- not related to severity of apathy in cross-sectional or longitudinal analyses

Hypertension and white matter lesions independently associated with apathetic behavior in healthy elderly subjects

Consistency of findings— RS-fMRI in aMCI

RS-fMRI—regions of the brain that modulate motivation

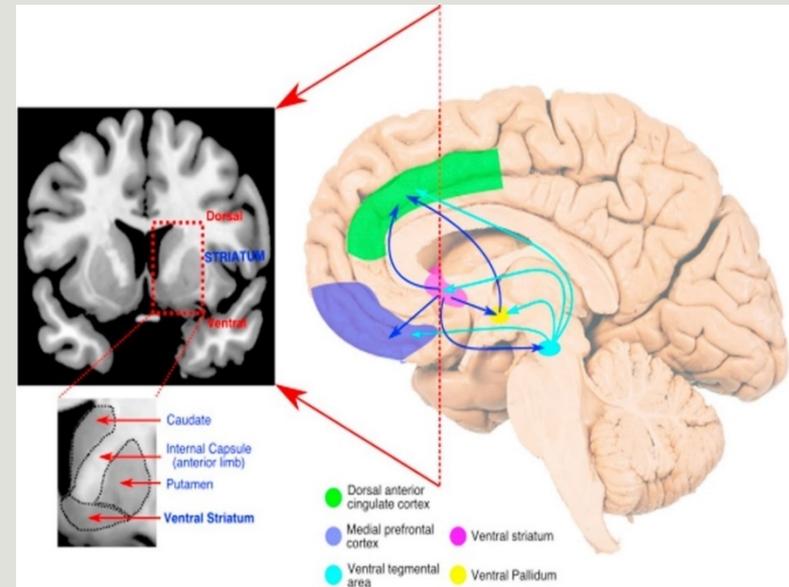


- Total IA score in aMCI n=50
 - negatively correlated with FCs of the anterior cingulate within the DMN
 - positively correlated with FCs of the middle frontal, inferior frontal, and supramarginal gyrus within the CEN (central executive network)

Consistency of findings — across disorders

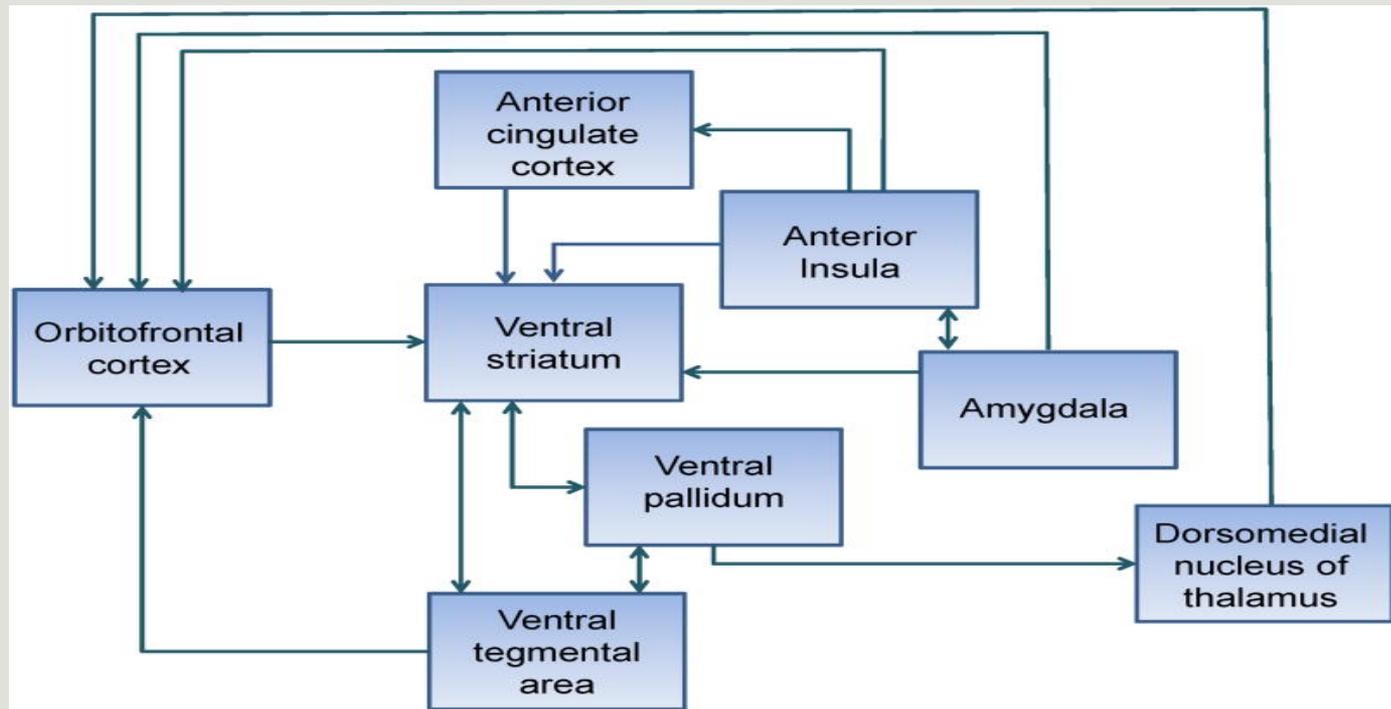
Consistent across a variety of neurocognitive disorders

- apathy consistently associated with the dorsal anterior cingulate cortex and the ventral striatum
- Other regions sometimes implicated: insula, DLPFC and OFC



Key reward circuit structures and pathways that can be affected in neurodegenerative disease

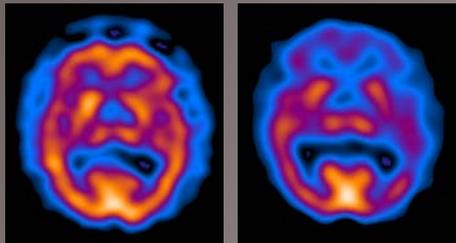
- selective vulnerability of different regions associated with variable disease process



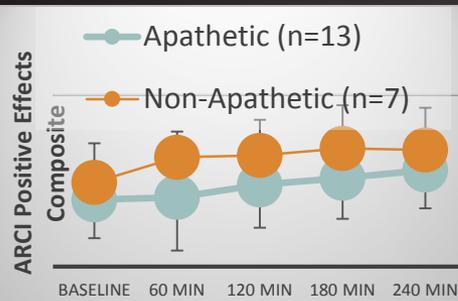
Why look at markers?

These data can inform clinical trials

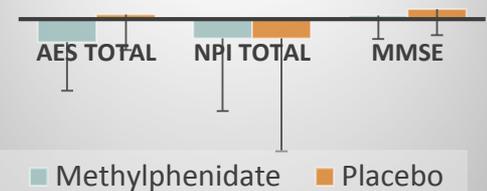
Research implicating brain reward system



Pharmacologic challenge suggests differences in DAergic system between apathetic and non-apathetic



Pilot data shows apathy decreases following methylphenidate



Apathy in Dementia Methylphenidate Trial (ADMET)

FOCUS ON ALZHEIMER'S DISEASE AND RELATED DISORDERS

Safety and Efficacy of Methylphenidate for Apathy in Alzheimer's Disease: A Randomized, Placebo-Controlled Trial

Paul B. Rosenberg, MD; Krista L. Lanctôt, PhD; Lea T. Drye, PhD;
Nathan Herrmann, MD; Roberta W. Scherer, PhD; David L. Bachman, MD;
and Jacobo E. Mintzer, MD, MBA, for the ADMET investigators

ABSTRACT

Objective: In a recent crossover trial, methylphenidate treatment decreased apathy in Alzheimer's disease. We further assessed this finding in the Alzheimer's Disease Methylphenidate Trial (ADMET).

Method: Six-week, randomized, double-blind, placebo-controlled multicenter trial enrolling Alzheimer's disease participants (NINCDS-ADRDA criteria) with apathy assigned to methylphenidate 20 mg daily or placebo, conducted from June 2010 to December 2011. Primary outcomes were change in Apathy Evaluation Scale (AES) score and modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGI-C). Secondary outcomes included change in Neuropsychiatric Inventory (NPI) apathy score, Mini-Mental State Examination (MMSE) score, and safety.

Results: 60 participants were randomly assigned (29 methylphenidate, 31 placebo). At baseline, mean (SD) age = 76 (8) years, MMSE score = 20 (5), AES score = 51 (12), NPI total score = 16 (8), and 62% of the participants (n = 37) were female. After 6 weeks' treatment, mean (SD) change in AES score was -1.9 (1.5) for methylphenidate and 0.6 (1.4) for placebo (P = .23). Odds ratio for improvement in ADCS-CGI-C was 3.7 (95% CI, 1.3 to 10.8) (P = .02), with 21% of methylphenidate versus 3% of placebo rated as

Alzheimer's disease is the major neurodegenerative disease of aging, affecting an estimated 5.1 million persons in the United States in 2010 and increasing to 11 to 16 million by 2050.¹ Neuropsychiatric syndromes affecting behavior are near-universal in Alzheimer's disease.² Apathy is one of the most common syndromes, with a 5-year prevalence estimate of 71%.² Apathy in Alzheimer's disease is described as loss of interest and motivation in daily activities in the absence of depression or other mood changes.³ Because apathy in Alzheimer's disease is associated with poorer quality of life,^{4,5} greater functional impairment,⁶ greater caregiver burden,⁷ increased risk of institutionalization,⁸ and higher costs of care,⁹ it is an important treatment target.

Current evidence suggests that apathy in Alzheimer's disease is associated with a decrease in dopaminergic neurotransmission. Lower dopamine transporter binding in the bilateral putamen has been associated with poor initiative.¹⁰ It has been proposed that dopaminergic circuits between the basal ganglia, anterior cingulate, and frontal cortex, which are involved in motivation and reward, are dysfunctional in Alzheimer's disease patients with apathy.¹¹ Alzheimer's disease patients with apathy have a blunted subjective response to dextroamphetamine challenge,¹² a potential biomarker of the brain reward system. Therefore it has been hypothesized that treatments that enhance dopamine (such as methylphenidate) could be effective for apathy in Alzheimer's disease. Methylphenidate improved apathy more than placebo in a recent crossover trial¹³ while modafinil

Double blind, placebo-controlled, 6-week, 3-centre* RCT in 60 patients with AD

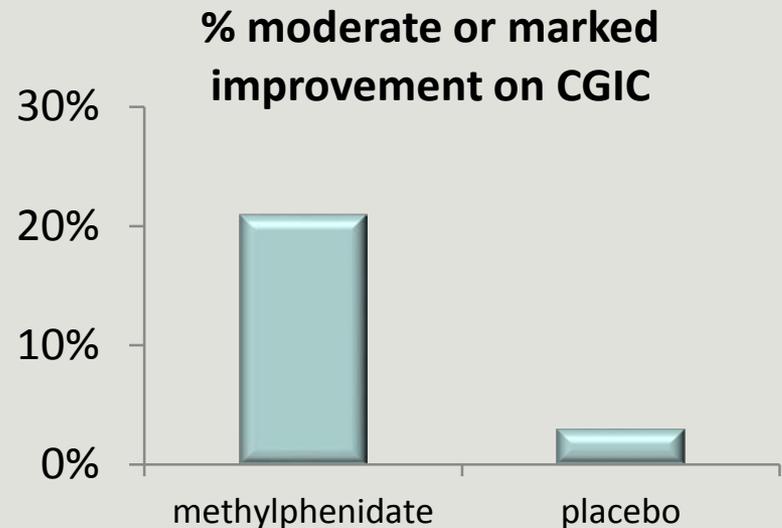
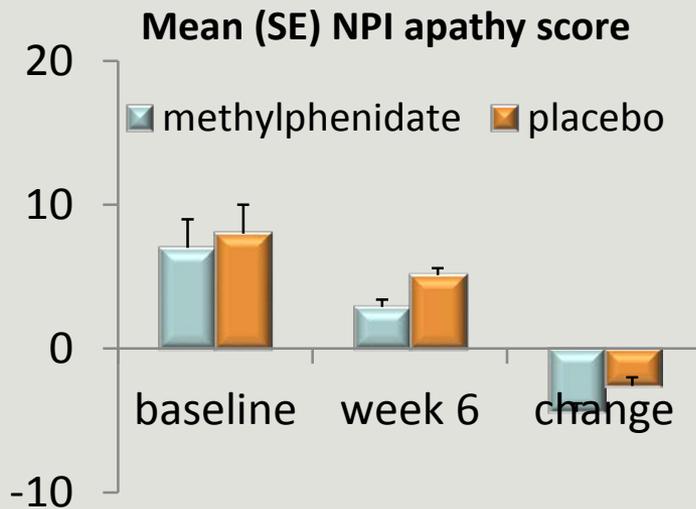
efficacy and safety of methylphenidate (20 mg/d) for clinically significant apathy in AD

ADMET apathy outcomes

NPI Apathy score improvement 1.8 points (95% CI 0.3, 3.4) greater in methylphenidate vs. placebo (p=0.02)

Odds ratio (95% CI) for improvement in CGI-C was 3.7 (1.3, 10.8) (p=0.02)

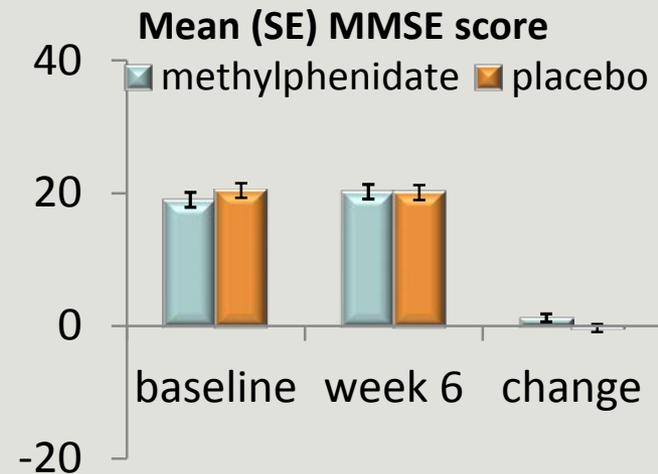
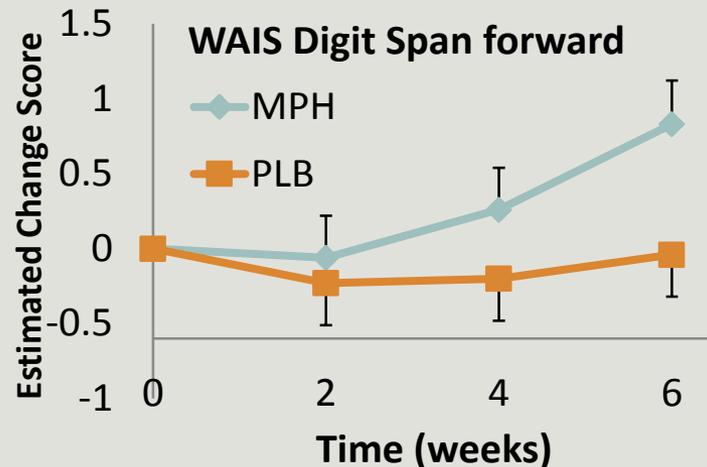
AES n.s.



ADMET cognitive outcomes

- ✓ change in DS forward (selective attention) favoured MPH over placebo ($\delta=0.87$ 95% CI: 0.06-1.08, $p=0.03$)
- ✓ change in DS total (selective attention plus working memory) favoured MPH over placebo ($\delta=1.01$ [0.09-1.93], $p=0.03$)

- ✓ MMSE trend favouring methylphenidate: estimated difference of 1.5 (95% C.I. -0.1, 3.1) ($p=0.06$)





ADMET 2-Apathy in Dementia Methylphenidate Trial 2

A phase III randomized multi-center placebo-controlled trial of 6 months 20 mg methylphenidate versus placebo for apathy in Alzheimer's disease

9 sites across US and Canada

- Krista Lanctôt & Nathan Herrmann, Sunnybrook Research Institute
- Paul Rosenberg, Johns Hopkins University
- Suzanne Craft, Wake Forest University
- Christopher van Dyck, Yale University
- Alan Lerner, University Hospitals-Case Medical Center
- Allen Levey, Emory University
- Olga Mintzer, Roper-St. Francis Healthcare
- Prasad Padala, University of Arkansas
- Anton Porsteinsson, University of Rochester

- Study Chair: Jacobo Mintzer, Medical University of South Carolina
- Coordinating Center: Roberta W. Scherer, Johns Hopkins University



ADMET 2-Study design

200 individuals with apathy in AD

- NPI-apathy subscale ≥ 4
- Corresponds with Apathy criteria (Lanctot et al, AAIC 2017)

Methylphenidate (20 mg/day) vs placebo (1:1 ratio)

Psychosocial intervention for both groups

Primary outcomes

- NPI apathy (change from baseline to 6 months)
- CGIC apathy (rating of change at 6 months)

Secondary outcomes

- Cognition, ADLs, resource utilization

6 months follow-up with monthly in-person visits

Discussion

Apathy is common, and has an important impact on patients and caregivers

Current treatments which improve cognition do not improve apathy

Apathy has a distinct neurocircuitry

Apathy has been successfully targeted using pharmacotherapy

These data suggest that apathy can be defined as a future treatment target

Moving forward

- Defining apathy: apathy versus anhedonia, apathy subdomains
- Measuring apathy: Reliability, validity, change over time, change with treatment
- Symptoms across neurodegenerative disorders
- Impact of apathy: not as well recognized

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