Measuring response to L-DOPA challenge as a biomarker for outcomes in late-life depression: A pilot feasibility study

Nicholas J. Ainsworth, MD; Kevin R. Smith, MD; Iva Cheung, PhD; Daniel M. Blumberger, MD; Sophia Frangou, MD, PhD; Raymond W. Lam, MD; Mary Pat McAndrews, PhD; Bruce G. Pollock, MD, PhD; Angela Russolillo, PhD; Benoit H. Mulsant, MD MS on behalf of the LLDOPA study team

Background

- Late-life depression (LLD) is a common condition affecting older adults (prevalence ~10%)
- LLD is frequently associated with psychomotor retardation
- Pre-clinical evidence supports a link between dopaminergic dysfunction and psychomotor retardation in LLD
- Early clinical evidence suggests that psychomotor retardation in LLD responds to levodopa (L-DOPA)
- Aims: 1) assess feasibility of administering a L-DOPA challenge to participants with LLD; 2) measure post-L-DOPA psychomotor/cognitive/psychiatric changes; 3) explore association between L-DOPA effects and treatment response

Methods

Main inclusion criteria:

- Outpatients age ≥60 years with MDD
- Moderate-severe depressive symptoms (MADRS ≥15)
- Able to ambulate independently

Main exclusion criteria:

- Major medical or neurological illness
- Presence of dementia (clinical diagnosis/MMSE <24)
- Psychotic features or active suicidality

L-DOPA challenge:

- Week 1: levodopa/carbidopa 150mg/37.5mg once daily
- Week 2: levodopa/carbidopa 150mg/37.5mg twice daily

Study measures:

- Psychomotor: 4-metre walk test, CORE instrument
- Cognitive: NIH Toolbox Cognitive Battery
- Psychiatric: PHQ-9, MADRS

Significance & Future directions

- First trial to evaluate psychomotor response to L-DOPA as possible biomarker for LLD treatment response
- Preliminary results suggest clinical effects of L-DOPA in LLD
- Recruitment and post-treatment follow-up is ongoing

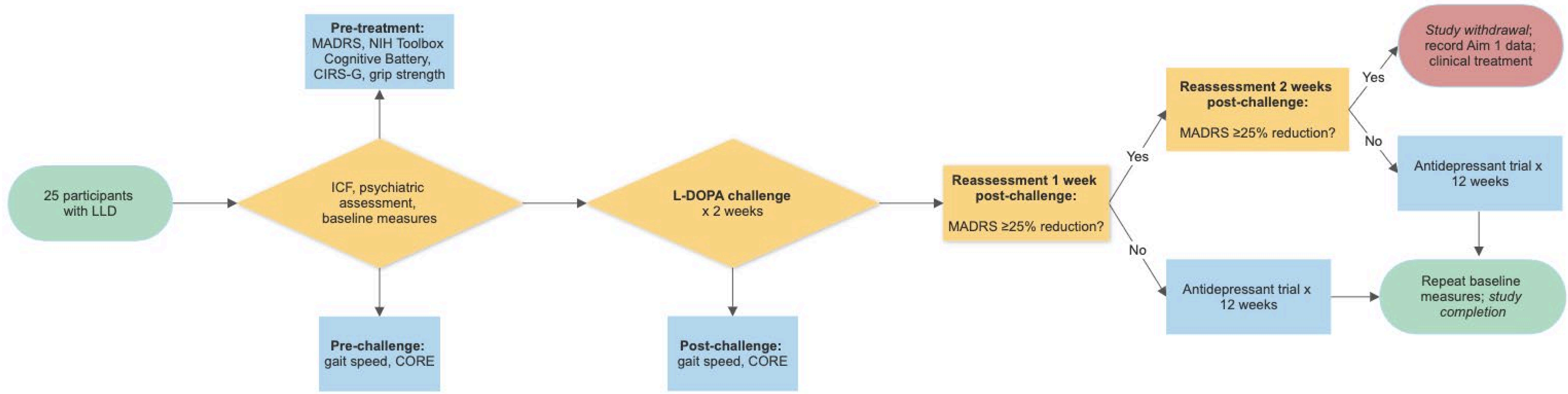

Figure 1. Diagram of overall clinical trial design

Results

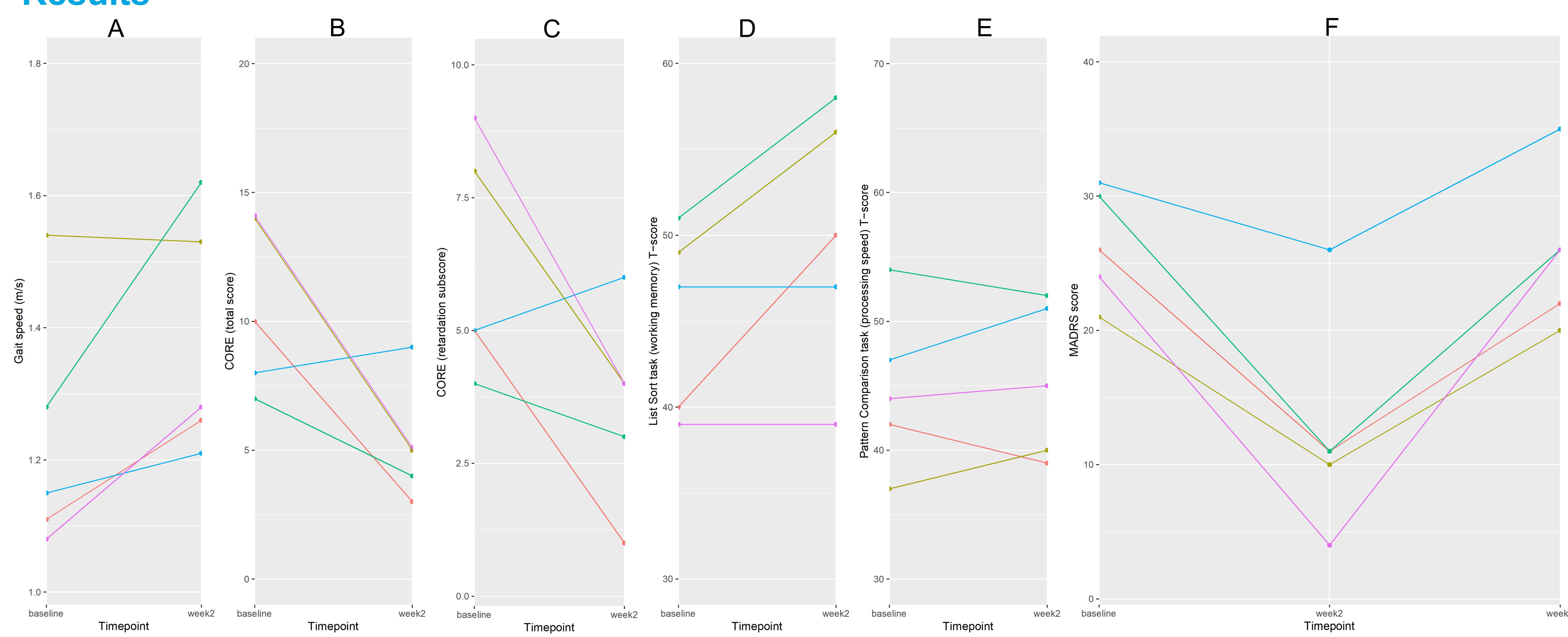

Figure 2 (A-F). Preliminary data from L-DOPA challenge

Lines represent individual participants.
Baseline: before L-DOPA challenge; Week 2: Immediately following challenge; Week 3: Following 1-week washout period
A: Gait speed (m/s); B: CORE total score (psychomotor dysfunction); C: CORE retardation sub-score (psychomotor slowing); D: List Sort task T score (working memory); E: Pattern Comparison task T score (processing speed); F: MADRS score (depressive symptoms)

Selected References

1. Buyukdura JS, McClintock SM, Croarkin PE. Psychomotor retardation in depression: Biological underpinnings, measurement, and treatment. Prog Neuro-Psychopharm Biol Psych. 2011;35(2):395-409.
2. Rutherford BR, Slifstein M, Chen C, et al. Effects of L-DOPA Monotherapy on Psychomotor Speed and [11C]Raclopride Binding in High-Risk Older Adults With Depression. Biol Psychiatry. 2019;86(3):221-229.
3. Cham R, Studenski SA, Perera S, Bohnen NI. Striatal dopaminergic denervation and gait in healthy adults. Exp Brain Res. 2008;185(3):391-398.
4. Taylor WD, Zald DH, Felger JC, et al. Influences of dopaminergic system dysfunction on late-life depression. Mol Psychiatry. 2022;27(1):180-191.

THE UNIVERSITY OF BRITISH COLUMBIA
Providence HEALTH CARE
Funding Partners
CANTRAIN
Michael Smith Health Research BC
UBC IMH Institute of Mental Health