

Overt vs Non-overt Digital Cognitive Metrics and Vascular, Inflammatory, and Neurodegenerative Biomarkers in i3C

A-6635

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Across three digital neuropsychological tests, slower *"think-time"* and select *"ink-time"* tracked with greater vascular risk and higher *inflammatory* and *neurodegeneration biomarkers*. Discrete digital timing may flag emergent vascular and neurodegenerative disease before it's clinically obvious.

INTRODUCTION

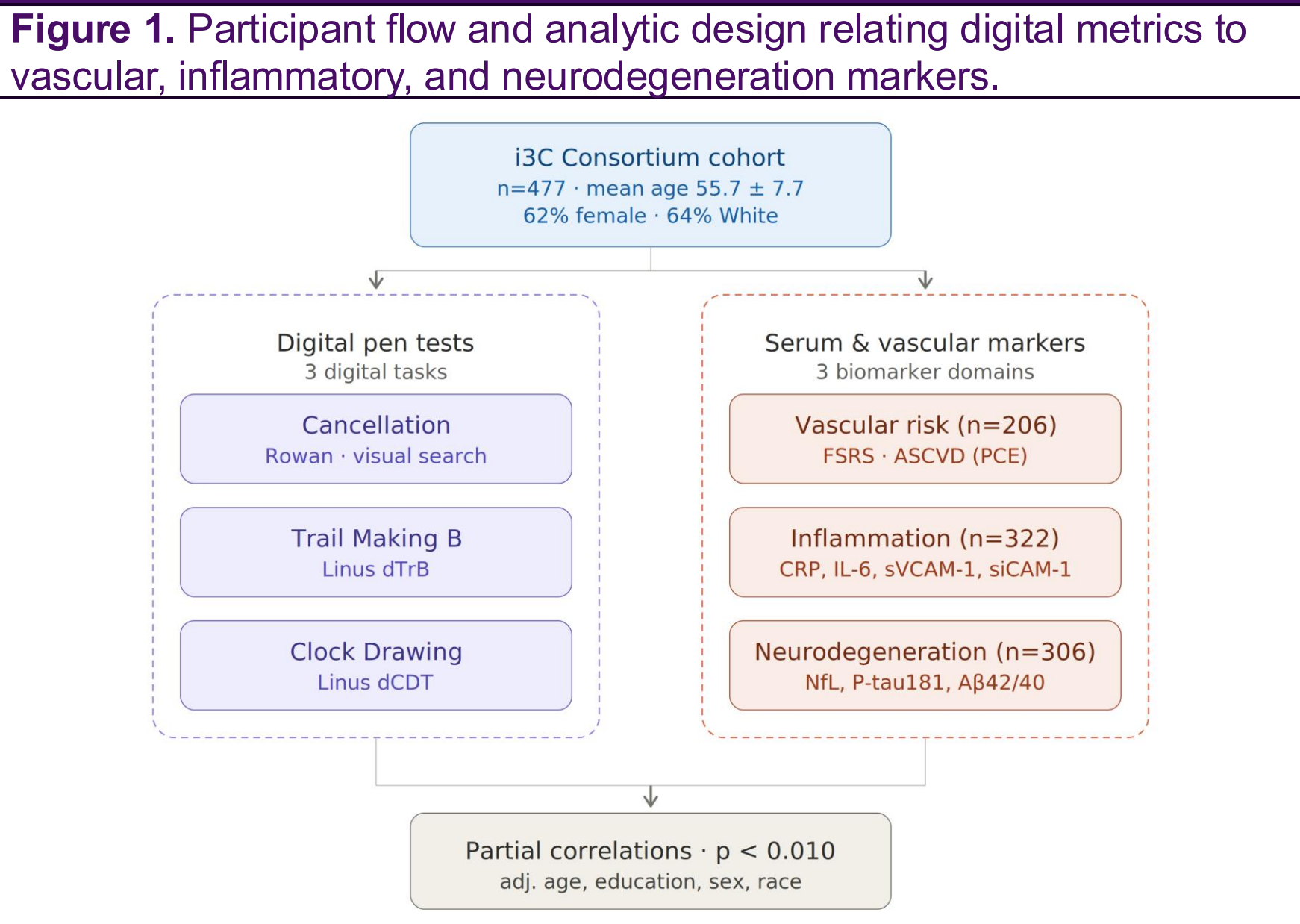
METHODS

Digital neuropsychological tests split a response into **non-overt "think-time"** (latency *between* pen strokes) and **overt "ink-time"** (latency *producing* strokes), timing impossible with paper/pencil.

Companion work links these metrics to cognition (Part 1) and brain structure on MRI (Part 3); whether they reflect **blood-based disease biology** was untested.

Vascular risk, inflammation, and neurodegeneration are all implicated in cognitive decline and may leave an early signature in processing speed.

OBJECTIVE: Test whether digital think-/ink-time relate to vascular risk indices and serum inflammatory and neurodegeneration biomarkers.



EXPOSURES: (digital metrics, 3 tests)

Rowan Cancellation, Linus dTrB, Linus dCDT (command + copy) each yielding think-time, ink-time, and (clock) component placement.

OUTCOMES: (3 biomarker domains):

- Vascular risk:* Framingham Stroke Risk Score (FSRS), ASCVD Pooled Cohort Equation (PCE).
- Inflammation:* CRP, IL-6, sVCAM-1, siCAM-1.
- Neurodegeneration:* NfL, P-tau181, Aβ42/40 ratio.

RESULTS

CONCLUSION

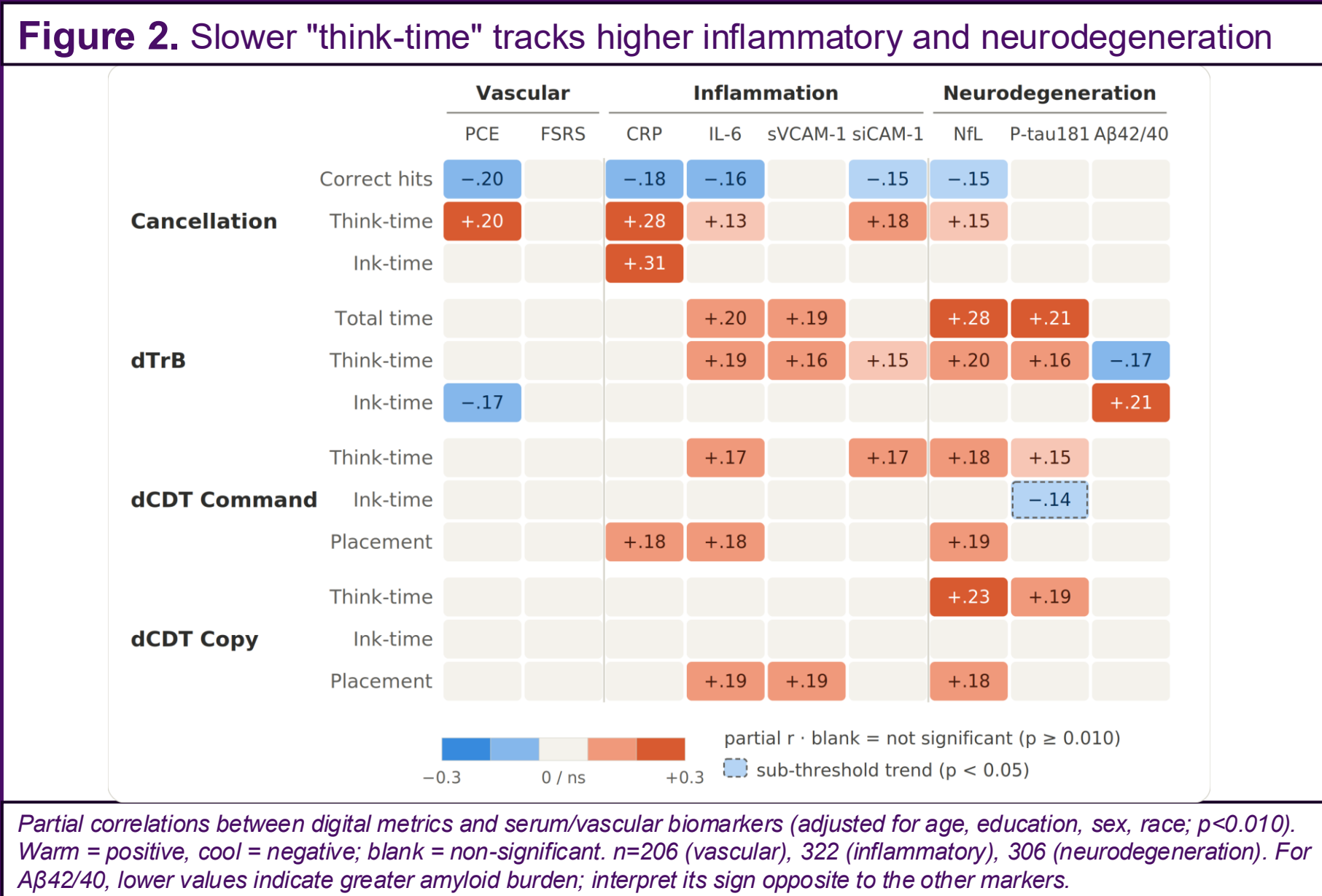
1. Inflammation is the strongest signal. Cancellation ink-time × CRP ($r=+0.314$, $p<0.001$) and think-time × CRP ($r=+0.281$, $p<0.001$) are the largest effects in the dataset — slower/less efficient performance with higher CRP.

2. Neurodegeneration tracks dTrB and dCDT. dTrB total time × NfL ($r=+0.276$) and × P-tau181 ($r=+0.211$); dCDT-Copy think-time × NfL ($r=+0.234$, $p<0.001$).

3. Vascular risk relates mainly to Cancellation. Fewer correct hits ($r=-0.197$) and slower think-time ($r=+0.200$) with higher ASCVD/PCE ($p<0.005$).

4. Think-time is the workhorse metric — significant across all three domains and all three tests; ink-time was significant more selectively (notably CRP, Aβ42/40).

5. Aβ42/40 behaves directionally opposite (lower ratio = worse): slower dTrB think-time ↔ lower ratio ($r=-0.168$), faster stroke velocity ↔ higher ratio ($r=+0.214$).



Greater vascular risk and higher inflammatory/neurodegeneration biomarkers consistently accompany **slower digital think-time** (and select ink-time), across all three tests.

The signal is **test-agnostic and domain-spanning**, suggesting think-/ink-time capture a general marker of subclinical disease burden rather than one pathway.

Brought to scale, these passively-captured timing metrics could **flag very early vascular and neurodegenerative illness** non-invasively.