Do the effects of Hormone Replacement Therapy during menopause differ by APOE genotype?

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Background

- Endocrine changes during menopause are critically implicated in the risk for Alzheimer's Disease (AD) being significantly higher in females.[1]
- Oestrogen appears neuroprotective, however, trials testing whether **Hormone Replacement Therapy (HRT)** (oestrogen/oestrogen+progesterone) benefits cognition and slows neurodegeneration have been inconsistent.[2]

97% of new patients at Newson Health report symptoms related with their memory or concentration (*n*=10,222)

- Interrelated factors contributing to brain function in mid-life, such as the **APOE-e4 genetic risk variant** for dementia and **cardiovascular health** may contribute to conflicting effects reported by clinical trials.[3:5]
- In addition, limited work has considered whether adding **testosterone** to HRT may offer increased cognitive protection, especially in APOE-e4 carriers (e4+). In older age, beneficial effects of testosterone against tau pathology and on cognition are selectively increased in female e4+.[6,7]

Aims

Investigate whether the introduction of HRT affects cognition longitudinally over 12 months, including whether predicted benefits differ by:

a. HRT formulation (HRT vs. HRT+ inclusion of testosterone).
b. APOE genotype (e4+ vs. APOE-e33 control group)
c. Cardiovascular risk score

Exploratory analyses will test if cognitive trajectories are modified by the timing of HRT initiation, non-cognitive menopause symptoms, and circulating hormone levels.

Methods

- 1000 perimenopausal and early postmenopausal females (aged ≤ 70 years) being newly prescribed HRT will be recruited from Newson Health specialist menopause clinics.
- The following data will be collected prior to the start of HRT (baseline), after 4-months and after 12-months of treatment:
  - Self-reported menopause symptoms (including subjective cognitive symptoms), reproductive & cardiovascular health.
  - Cognitive performance on tasks targeting domains first sensitive to AD pathology & menopause-related cognitive complaints (*see Table 1*).
  - HRT prescription.
  - Clinic data including hormone concentrations in serum.
  - Tissue sample for APOE genotype analysis.

Task	Cognitive Domain
Verbal fluency	Semantic & lexical access; Speech
Verbal memory	Episodic memory; Speech
Greebles 'odd-one-out' task	Visual perception
Stroop-switch task	Executive attention
N-back task	Working memory
Object Mnemonic Similarity task	Object recognition memory
Virtual Supermarket Task[8]	Spatial navigation

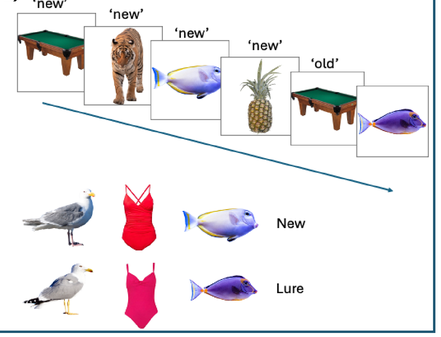
Table 1: *Cognitive tasks that will form the study's cognitive task battery*

- Participants will be grouped by HRT formulation, APOE genotype, and cardiovascular risk score.

Pilot Data

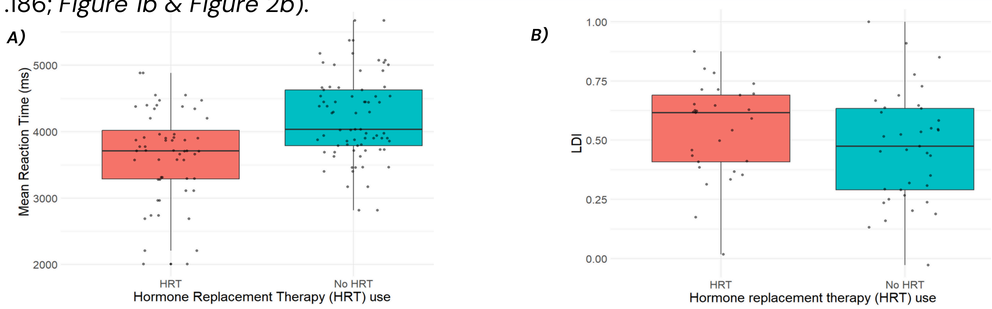
- Perimenopausal and postmenopausal women (*n* = 117, *mean age* = 57 years) completed an online cognitive task battery.
- Relative to women who were HRT-naïve, HRT users were significantly quicker on a perceptual 'odd-one-out' task (*d* = -.85, *p* = .001; *Figure 1a & Figure 2a*) and trended to show higher Lure Discrimination on an Object Mnemonic Similarity Task (MST) (*d* = .33, *p* = .186; *Figure 1b & Figure 2b*).

Figure 1.



A) *Example of a perceptual 'odd-one-out' 'Greebles' trial (above) and* ***B)*** *Schematic example of an Object MST (right).*[9-11]

Figure 2.



a) *The postmenopausal HRT-user group (M = 3643.48 ms, SD = 273.95 ms) correctly discriminated between 'Greebles' stimuli faster than the postmenopausal HRT-naive group (M = 4208.24 ms, SD = 186.45 ms).* ***b)*** *On an Object MST, the postmenopausal HRT-user group (M = .54, SD = .20) trended toward an elevated Lure Discrimination Index (LDI) in comparison to the postmenopausal HRT-naive group (M = .47, SD = .23). LDI is the key metric of mnemonic discrimination performance.*

Key hypotheses - Upcoming study

- HRT use is expected to benefit subjective and objective cognition across 12-months.
- HRT-associated improvements are predicted to be greatest in e4+ with good cardiovascular health receiving testosterone-containing HRT.
- HRT-associated improvements are predicted to be negligible in e4+ with poor cardiovascular health (regardless of HRT-type) as protective effects of oestrogen are theorised to be stronger in healthy cells.[12]

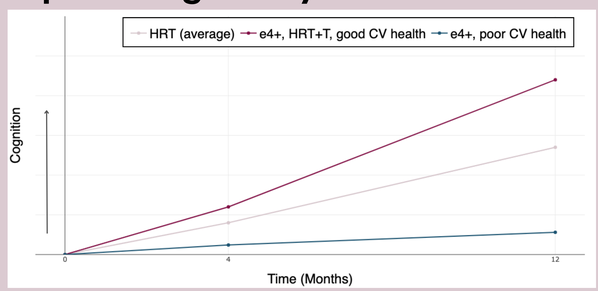


Figure 4: *Visualisation of overall predicted trajectories of cognitive change based on key study hypotheses*

Impact

Exploring the impact of HRT on cognition in interaction with the leading genetic risk factor for AD & cardiovascular health will:

- Advance research into how we can promote women's brain health in mid-life.
- Further establish whether HRT may be utilised to help prevent future AD.

Additionally, this project offers the opportunity to explore longer-term follow-up of the impact of HRT on cognitive health beyond mid-life.

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References: 1. Lindseth et. al., 2023; 2. Nerattini et. al., 2023; 3. Gannon et al, 2019; 4. Neu et. al., 2017; 5. Tai et. al., 2016 6. Sundermann et. al., 2020; 7. Dratva et al, 2024; 8. Tu et al, 2015; 9. Barense et. al., 2007; 10. Stark et. al., 2023; 11. Lancaster & Morcom, in prep; 12. Brinton, 2008.