Cognitive advantages in young APOE ε4-carriers: The how, why and when

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APOE ε4 & cognition – lifetime trajectory

Possession of an APOE ε4-allele (ε4+) is the strongest **genetic risk factor** for developing mild cognitive impairment (MCI) or Alzheimer's disease (AD). It is associated with poorer cognition in 'normal' aging (Wisdom et al., 2011). Yet, evidence is emerging of a potential cognitive advantage for ε4 carriers in youth.

APOE ε4 - cognitive advantage in youth

Cognitive advantages seen for ε4+ carriers in:

- Verbal fluency (Alexander et al., 2007; Marchant et al., 2010)
- Attention (Marchant et al., 2010; Rusted et al., 2013)
- Episodic memory (Mondadori et al., 2007)
- General cognitive ability (Schultz et al., 2008)
- Mental development index scores in infants (Wright et al., 2003).

Cognitive advantage – what drives it?

However, ε4+ cognitive advantages have not always been reported (Bloss et al., 2007, Bunce et al., 2011; Deary et al., 2003; Duchek et al., 2006; Plomin et al., 1995; Ruiz et al., 2009; Turic et al., 2001).

Furthermore, some studies have demonstrated an ε4+ advantage only when other factors were present, such as decreased low-density lipoprotein cholesterol levels (Puttonen et al., 2003), high infant illnesses generally resulting in poorer cognition (Oriá et al., 2005), or traumatic brain injury (Han et al., 2007). Other authors suggest that ε4+ may have an enhanced resistance to cognitive fatigue (Dowell et al., 2013; Evans et al., 2013). It may therefore be that ε4+ benefits mainly appear under **cognitively challenging** conditions.

Overall question: Do young ε4+ show different reactivity to cognitive challenge?
If so, do early life experiences interact with this reactivity?

Research questions	Rationale	Potential methods
1. Do young ε4+ show differential reactivity to cognitive challenge?	Young ε4+ advantage may only be seen under cognitively challenging conditions	We will design an experimental paradigm to **manipulate cognitive challenge**.
2. Do early life experiences differently impact APOE genotypes?	The cognitive consequences of APOE genotype may vary due to different early life experiences	We will explore cognitive challenge response across differing **early life experience** by comparing ε4+ carriers with low & high 'young life reserve'
3. Does APOE genotype result in trajectory differences in academic and occupational achievement?	ε4+ carriers may show greater potential to higher educational and occupational achievement	We will analyse lifespan performance in **cohort data** to assess the impact of APOE on education and occupation over four decades

Cognitive reserve and APOE

Cognitive reserve (CR) is thought to reduce risk of AD and delay AD onset (Stern, 2002). CR may interact with APOE genotype (Jonaitis et al., 2013; Shpanskaya et al., 2014), or have an independent, additive effect (Pettigrew et al., 2013; Soldon et al., 2015), in AD patients and cognitively normal elderly. For example, Ferrari et al. (2013) observed that CR reduced ε4+ risk to ε4- levels in elderly (CR estimates based on education and leisure).

Specifically looking at education and APOE:
- ε4+ show higher educational attainment (Hubacek et al., 2001)
- More pronounced cognitive decline is seen in low education vs high education ε4+ (Mayeux et al., 2001)

'Young life reserve'

In earlier work young ε4+ carriers:
- Young ε4+ showed higher WAIS performance IQ (Yu et al., 2000) .
- Young ε4+ trend towards advantage in all cognitive tests, and significantly higher nonverbal IQ (Oriá et al., 2005)

In the proposed studies, we will assess cognitive reserve development by measuring education, IQ, social activities, and cognitively stimulating activities. The first task in my PhD will be to develop this hypothetical construct of 'young life reserve'.