GxE contributions to cognitive aging: An MZ twin pair comparison

CHANDRA A. REYNOLDS[1] & NANCY L. PEDERSEN[2,3]

[1]UNIVERSITY OF CALIFORNIA, RIVERSIDE [2]KAROLINSKA INSTITUTET [3]UNIVERSITY OF SOUTHERN CALIFORNIA

BACKGROUND

How GxE interactions affect aging processes are not well understood but evidence suggests GxE may shift over the life course [1]. GxE for cognitive decline may emerge after age 65 given increasing nonshared environment influences [2]. Genes in lipids and inflammatory/immune pathways may be particularly relevant.

- *APOE* maximally impacts Alzheimer's disease (AD) risk between 65-75 years [3], and likely cognitive decline [4].
- As *APOE* wanes, other genes or pathways may impact decline.
- Additional lipid and inflammatory/immune pathway genes have been identified [3], including *SORL1* [5].
- Comparing MZ within pair differences in cognitive change by genotypes may identify genes responsive to environments [2, 6-8].

METHODS

Participants (Analysis N= 1607)

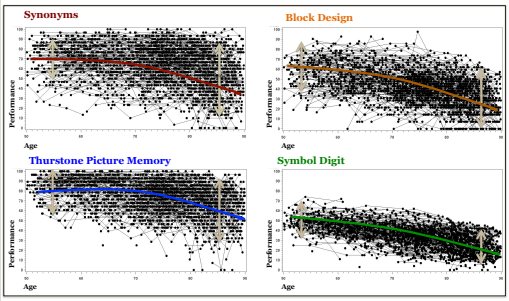
SATSA: The Swedish Adoption/Twin Study of Aging
- •Waves: M = 4.16 (SD=1.44; Max 6 waves)
- •Baseline Age: M = 64.75 (SD = 8.08)
- •N= 671 twins, 59% Female

GENDER: Sex Differences in Health and Aging Study
- •Waves: M = 2.4 (SD = 0.83; Max 3 waves)
- •Baseline Age: M = 74.44 (SD =2.63)
- •N= 446 twins, 50% female

OCTO-Twin: Study of Origins of Variance in the Oldest-Old
- •Waves: M = 3.67 (SD = 1.36; Max 5 waves)
- •Baseline Age: M = 83.16 (SD = 2.73)
- •N= 490 twins, 63% female

N= 269 MZ pairs from the SATSA and OCTO-Twin samples.
N = 198 - 216 MZ complete pairs had genotyping plus cognitive data.

Figure 1.
Cognitive Trajectories: Full sample.



Outcomes: Empirical Bayes estimates representing:
- Level @ 75 years
- Slope < 75 years
- Slope > 75 years

Growth models fitted to full information in SAS Proc Mixed (SAS, Cary NC). Data post-dementia onset excluded. Adjusted for practice effects. Rank-normalizations applied to adjust for non-normality.

Table 1. (a) Genes in lipid, inflammatory, and related pathways; (b) *SORL1* risk set construction.

Lipid	SNPs	Inflame	SNPs	Related	SNPs
ABCA1	48	*AGER*	12	*CDKN2A/B*	2
ABCA2	1	*APCS*	11	*FTO*	2
ACAT1	13	*BDNF*	11	*HHEX*	4
ACAT2	7	*CHRM2*	9	*IDE*	2
*APOA1**	17	*COMT*	1	*IGF2BP2*	2
APOB	26	*CRP*	6	*TCF7L2*	2
APOE	2	*FAS*	1	*SORL1*	15
CETP	29	*IL1A*	10		
CYP46A1	15	*IL1B*	9		
GALNT2	30	*IL6*	16		
GCKR/XAB1	11	*LTA*	6		
HMGCR	12	*NR1H2*	4		
LCAT	6	*NR1H3*	11		
LDLR	22	*PLA2G2A*	17		
LIPC	40	*PLA2G7*	20		
LIPG	16	*PTGS2*	12		
LPL	28	*REST*	2		
LRP1	19	*SAA1*	6		
MLXIPL/TBL2	13	*SAA2*	9		
PCSK9	24	*SAA4*	3		
PLTP	11	*SELS*	10		
SCARB1	32	*SERPINA3*	16		
*SORT1***	11	*SERPINE1*	11		
SREBF1	5	*TNF*	7		
SREBF2	15				

*APOA1 resides in cluster of APOA5/APOA4/APOC3/APOA1.
** SORT1 resides in cluster of CELSR2/PSRC1/SORT1.

*SORL1****	Position	Tag	LD Spine
rs11600875	120862178	t	1
rs923893[1]	120870025	-	-
rs17245976[1]	120870930	-	-
rs12364988	120872836	t	1
rs668387	120873131	t	1
rs753780	120875926	t	1
rs689021	120876330	-	-
rs7105365[1]	120882005	t	1
rs641120	120886175	-	-
rs12285364	120898436	t	2
rs11512475	120902648	t	2
rs11820794[1]	120913165	t	2
rs2070045	120953300	t	3
rs3824968	120981132	t	3
rs2282649	120984168	t	3

Risk Sets	M (se)	Set 1	Set 2	Set 3
		0.88 (0.03)	-3.47 (0.06)	-0.92 (0.03)
Correlations	$r_{1,2}$	0.13		
	$r_{1,3}$	0.27		
	$r_{2,3}$	0.11		

*** Multilevel Logistic Regression in lme4 was fitted; empirical Bayes estimates saved [5]*

RESULTS

I. Initial Test of GxE: Mixture distributions

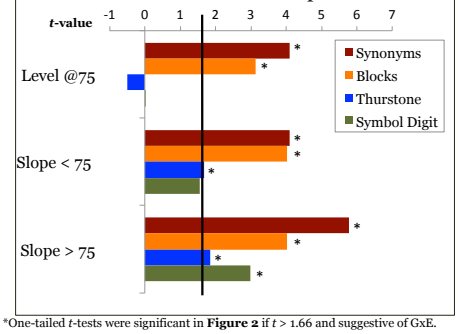
An initial test of GxE using MZ pairs [2, 6] was conducted, testing for heterogeneity of within-pair differences in rank-normalized cognitive trajectory traits. A t-test was constructed from comparing mean squared pair differences *vs.* mean absolute pair differences squared:

$$t = \mathbf{h}/\mathbf{s}$$

$$\mathbf{h} = \overline{d^2} - \frac{\pi}{2}\overline{d}^2 \qquad \mathbf{s} = \text{s.e.} = \frac{\overline{d^2}}{\sqrt{n}}(.5321)$$

Analyses were weighted by inverse s.e. of growth parameters.

Figure 2.
Test of mixture distributions: MZ pairs.

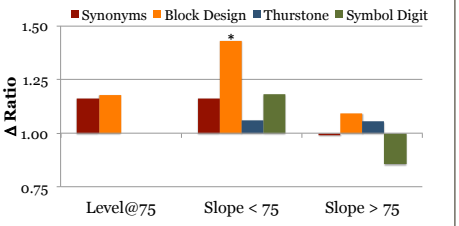


*One-tailed t-tests were significant in **Figure 2** if t > 1.66 and suggestive of GxE.

II. Evaluating *APOE* & *SORL1* associations

APOE e3/3 genotype shows greater variability in trajectories than *e2/+ or e4/+* for Block Design (p_{MV}=.0350), particularly for change before 75 (see **Figure 3**). Those with *APOE* e3/3 were 43% more variable (p=.0105).

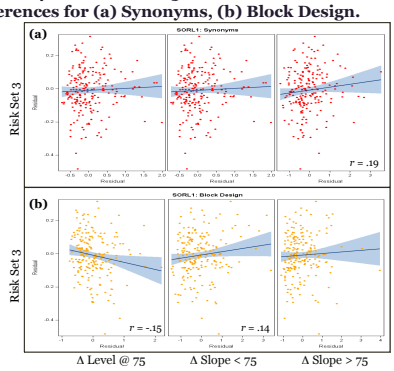
Figure 3.
***APOE* e3/3 *vs.* e2/+ & e4/+: Ratio of intrapair differences.**



*Adjusted for sex, age, sex*age, pair sums and weighted by inverse standard errors.*

SORL1 risk sets predict variability with effects observed for sets 1-3 for Block Design (Wilks Λ =.91 - .96, p =0.0003 - 0.0474), and set 3 for Synonyms (Wilks Λ =.96, p = 0.0278). **Figure 4** presents set 3 effects from weighted multivariate regression analyses adjusted for all covariates (SAS Proc Reg, Cary NC).

Figure 4. *SORL1* set 3 risk scores and intrapair differences for (a) Synonyms, (b) Block Design.

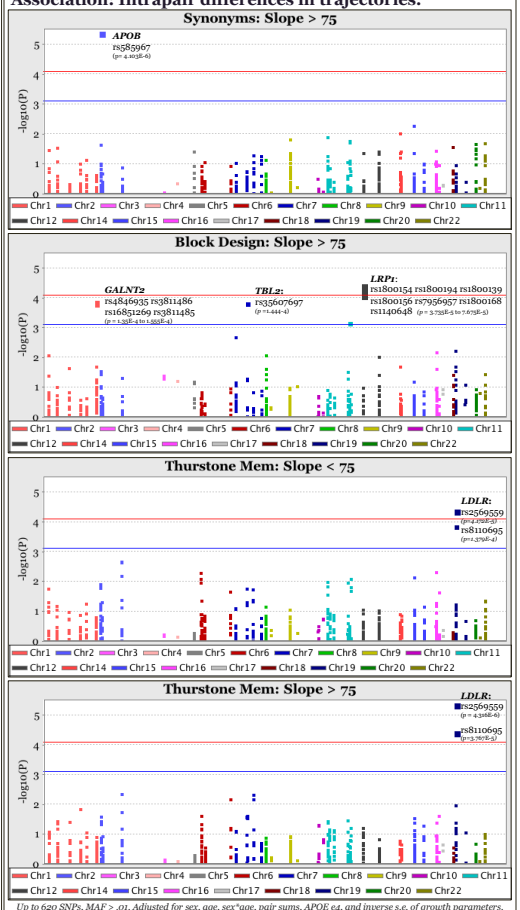


*Adjusted for sex, age, sex*age, pair sums, APOE e4, and weighted by inverse standard errors.*

III. Association with lipid and inflammation candidates: controlling for *APOE* e4

Intrapair differences in trajectory features were subjected to association tests [8], using PLINK [9]. A 2-degree-of-freedom test was conducted agnostic to the genetic model for up to 620 SNPs. **Figure 5** suggests other lipid pathway genes may be associated with variability in cognitive change after age 75 years.

Figure 5.
Association: Intrapair differences in trajectories.



*Up to 620 SNPs, MAF > .01. Adjusted for sex, age, sex*age, pair sums, APOE e4, and inverse s.e. of growth parameters.*

CONCLUSIONS

- Responsiveness to environments, perhaps indicative of *plasticity*, is evident for cognitive change across domains.
- *APOE e3/3* genotype shows greater variability in spatial trajectories especially before 75 years, consistent with prior work on semantic memory [2].
- Higher *SORL1* risk scores predict greater variability in verbal and spatial trajectories, particularly for risk set 3 capturing the 3' end of *SORL1*.
- Other *lipid pathway* genes may be important to consider for GxE after age 75 (e.g., *APOB*, *LRP1*, *LDLR*)
- Larger samples are needed, especially to evaluate sex effects. Follow-up is planned within IGEMS [10].

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