Heterogeneity
And
Subject-Specific Heritabilities

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Epigenetic Origins of Heterogeneity across subjects

Molenaar, P.C.M., Boomsma, D.I., & Dolan, C.V. (1993). A third source of developmental differences. *Behavior Genetics*, *23*, 519-524.

Molenaar (2007). On the implications of the classical ergodic theorems: Analysis of developmental processes has to focus on intra-individual variation. *Developmental Psychobiology, 50*, 60-69.

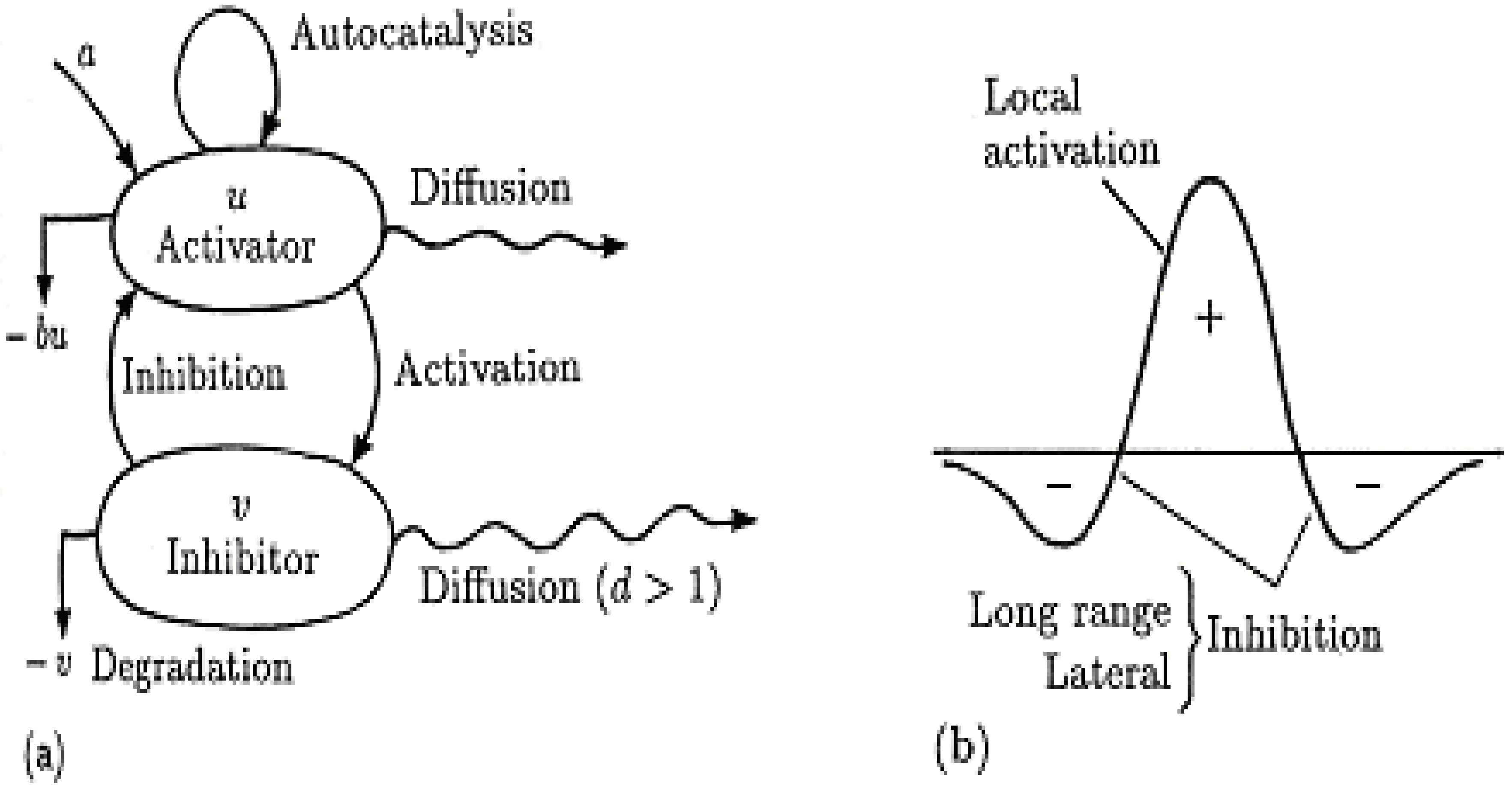


Fig. 14.3a,b. (a) Schematic representation of the activator-inhibitor system

$$u_t = a - bu + \frac{u^2}{v} + \nabla^2 u, \quad v_t = u^2 - v + d\nabla^2 v .$$

(b) Spatial representation of local activation and long range inhibition.

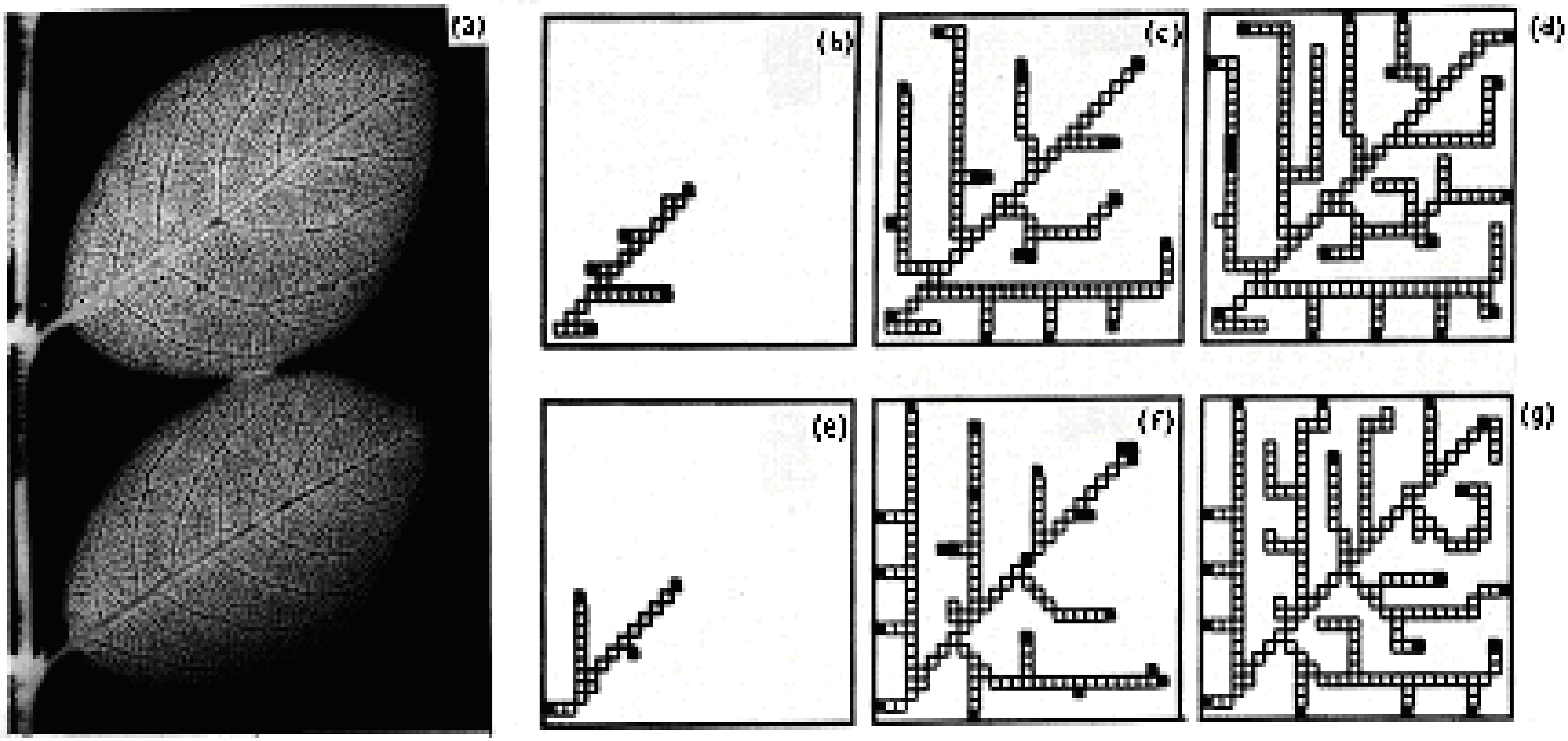


Fig. 15.5. Influence of random fluctuation on pattern formation. (a) Two leaves of the same tree. Their pattern formation is presumably controlled by the same genetic information. Nevertheless, the pattern is only similar, not identical. (b–d) and (e–g) Two simulations with the same parameters and the same initial condition but with different random fluctuation (3%) in the constant c, eq. 15.1a,b. The model reaction determines only properties of the overall pattern such as average net density. Fine details are influenced by small local differences.

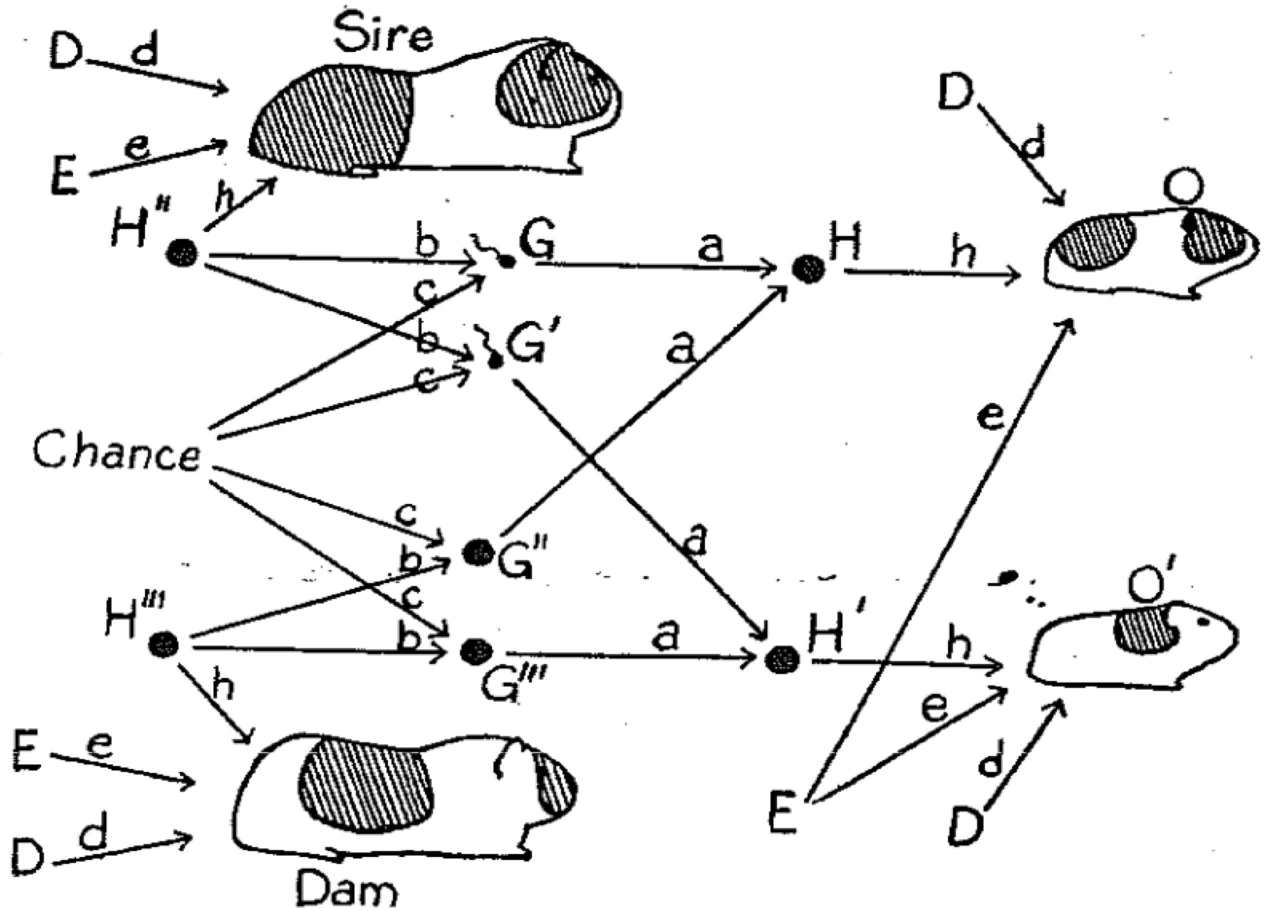


Diagram illustrating the casual relations between litter mates (O, O′) and between each of them and their parents. H, H′, H″, H,‴ represent the genetic constitutions of the four individuals, G, G′, G″, and G‴ that of four germ cells. E represents such environmental factors as are common to litter mates. D represents other factors, largely ontogenetic irregularity. The small letters stand for the various path coefficients.

Figure 5.5. Diagram illustrating the relations between two mated individuals and their progeny.

Subject-Specific Heritabilities

Molenaar, P.C.M. (2010) On the limits of standard quantitative genetic modeling of inter-individual variation: Extensions, ergodic conditions and a new genetic factor model of intra-individual variation. In: K.E.Hood, C.T. Halpern, G. Greenberg, & R.M. Lerner (Eds.), *Handbook of developmental science, behavior, and genetics*. Malden, MA: Blackwell.

Nesselroade, J.R., & Molenaar, P.C.M. (2010). Analyzing intra-person variation: Hybridizing the ACE model with P-technique factor analysis and the idiographic filter. *Behavior Genetics*, *40*, 776-783.

Longitudinal Genetic Factor Model (Inter-Individual Variation)

Let $\mathbf{y}_{ijkmt}$ denote the observed phenotypic score at the *m*th observed variable (m = 1,2,…,M) for the *j*th member (j = 1,2) of the *i*th twin pair (i = 1,2,…,N) of type *k* (k = 1 for MZ and k = 2 for DZ) at the *t*th measurement occasion *t* (t = 1,2,…,T)

$$\mathbf{y}_{ijkmt} = \alpha_{mt}A_{ijkt} + \delta_{mt}\mathbf{C}_{ijkt} + \phi_{mt}\mathbf{E}_{ijkt} + \varepsilon_{ijkmt}$$

A_{ijkt} is the additive genetic factor score of the *j*th member of the *i*th twin pair of type *k* at measurement occasion *t*

$\mathbf{C}_{ijkt}$ is the common environmental factor score of the *j*th member of the *i*th twin pair of type *k* at measurement occasion *t*

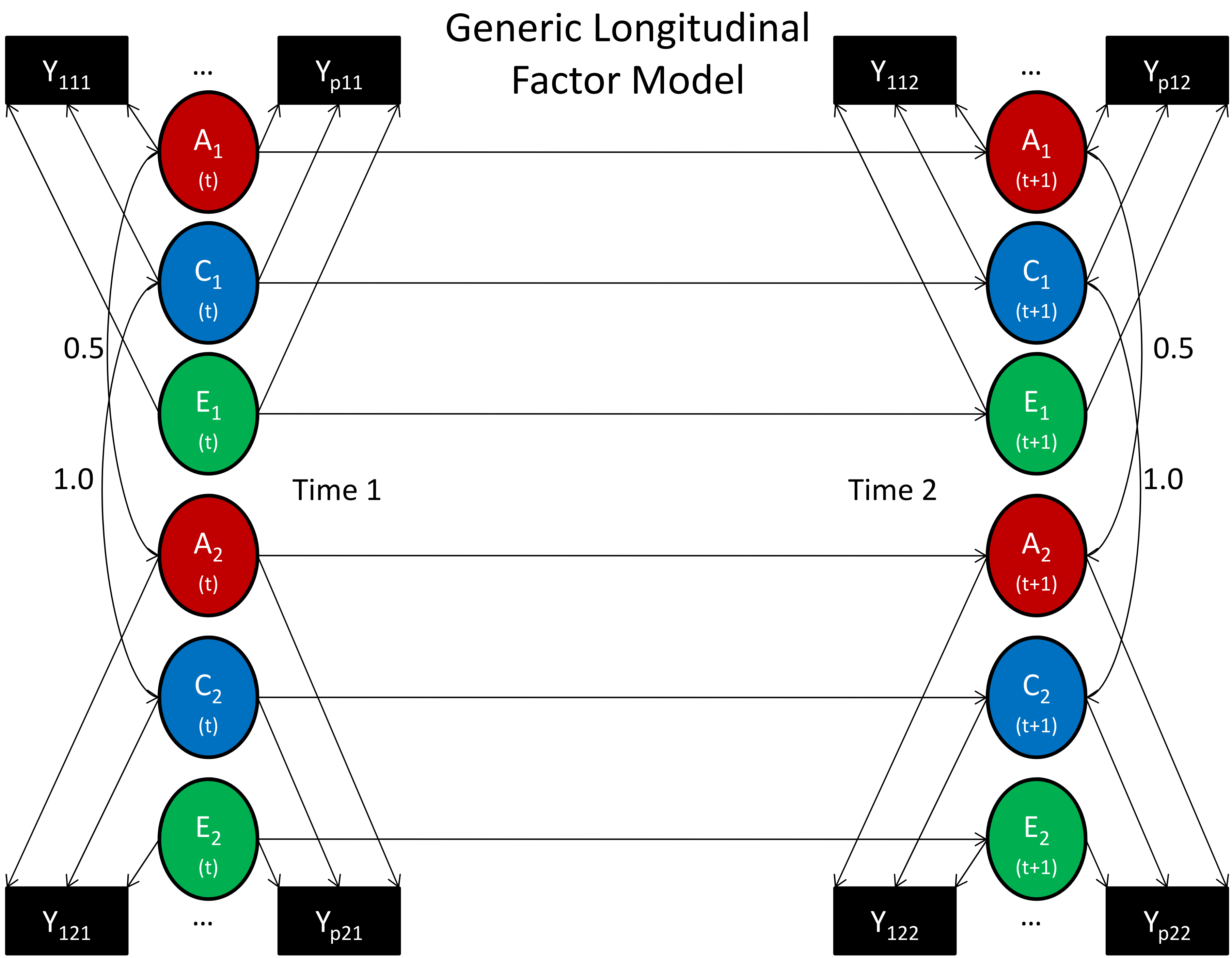
$\mathbf{E}_{ijkt}$ is the specific environmental factor score of the *j*th member of the *i*th twin pair of type *k* at measurement occasion *t*

Longitudinal Evolution of Factor Scores

$$\mathbf{A}_{ijkt} = \beta_{t,t-1}\mathbf{A}_{ijkt-1} + \zeta_{ijkt}$$

$$\mathbf{C}_{ijkt} = \gamma_{t,t-1}\mathbf{C}_{ijkt-1} + \xi_{ijkt}$$

$$\mathbf{E}_{ijkt} = \nu_{t,t-1}\mathbf{E}_{ijkt-1} + \sigma_{ijkt}$$


Generic Longitudinal Factor Model
Y_{111}
...
Y_{p11}
Y_{112}
...
Y_{p12}
A_1 (t)
C_1 (t)
E_1 (t)
A_2 (t)
C_2 (t)
E_2 (t)
A_1 (t+1)
C_1 (t+1)
E_1 (t+1)
A_2 (t+1)
C_2 (t+1)
E_2 (t+1)
0.5
1.0
0.5
1.0
Time 1
Time 2
Y_{121}
...
Y_{p21}
Y_{122}
...
Y_{p22}

The general Longitudinal Genetic Factor Model is based on the strong assumption that all parameters (genetic, common and specific environmental factor loadings and lagged regression coefficients) are invariant across subjects.

Genetic Factor Model for **Intra**-Individual Variation (iFACE).

Application to **single** DZ twin pair (i and k subscripts fixed).

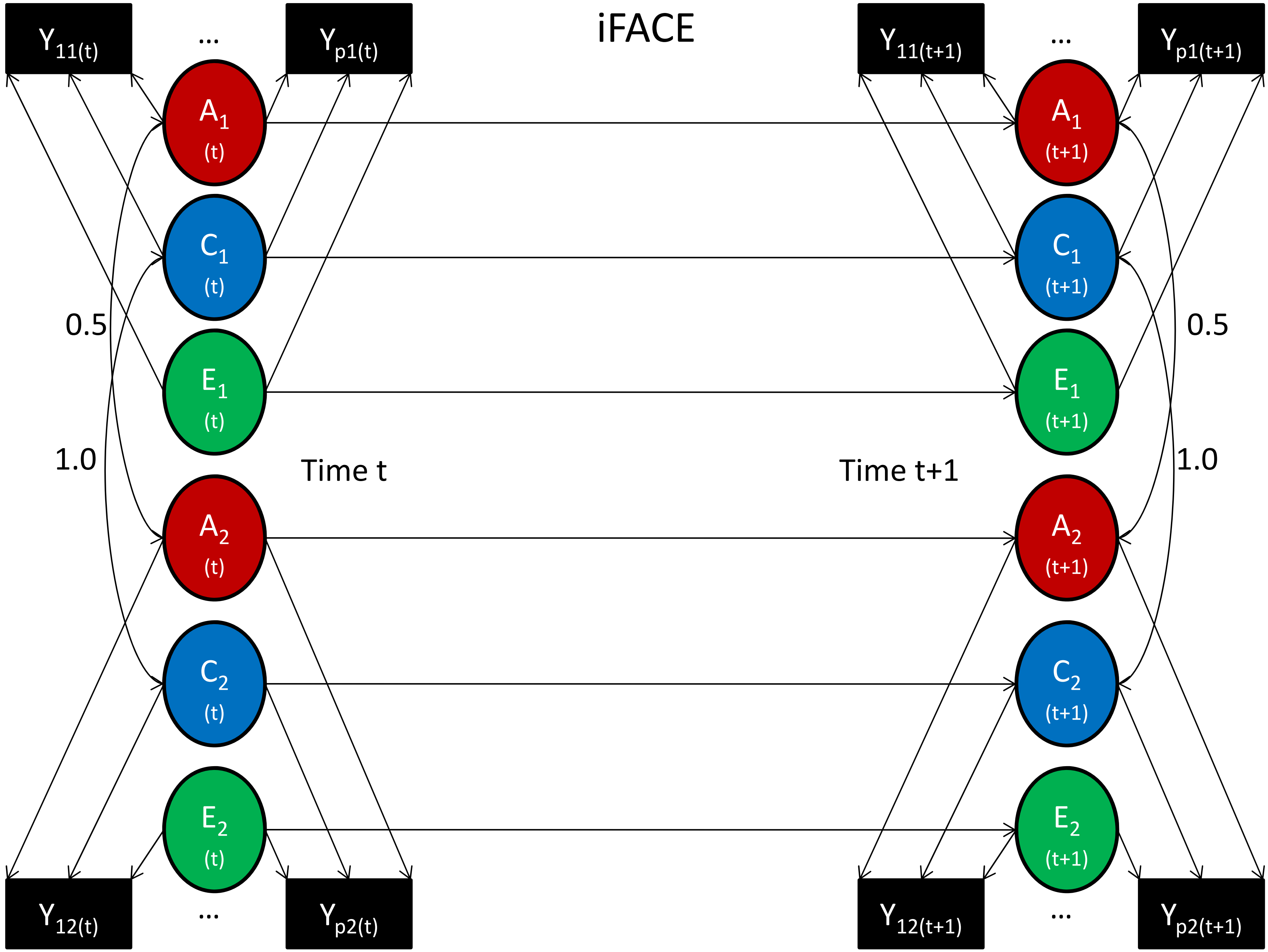
$$\mathbf{y}_{jmt} = \alpha_{jm}A_{jt} + \delta_{jm}\mathbf{C}_{jt} + \phi_{jm}\mathbf{E}_{jt} + \varepsilon_{jmt}$$

$$A_{jt} = \beta_j A_{jt-1} + \zeta_{jt}$$

$$\mathbf{C}_{jt} = \gamma_j \mathbf{C}_{jt-1} + \xi_{jt}$$

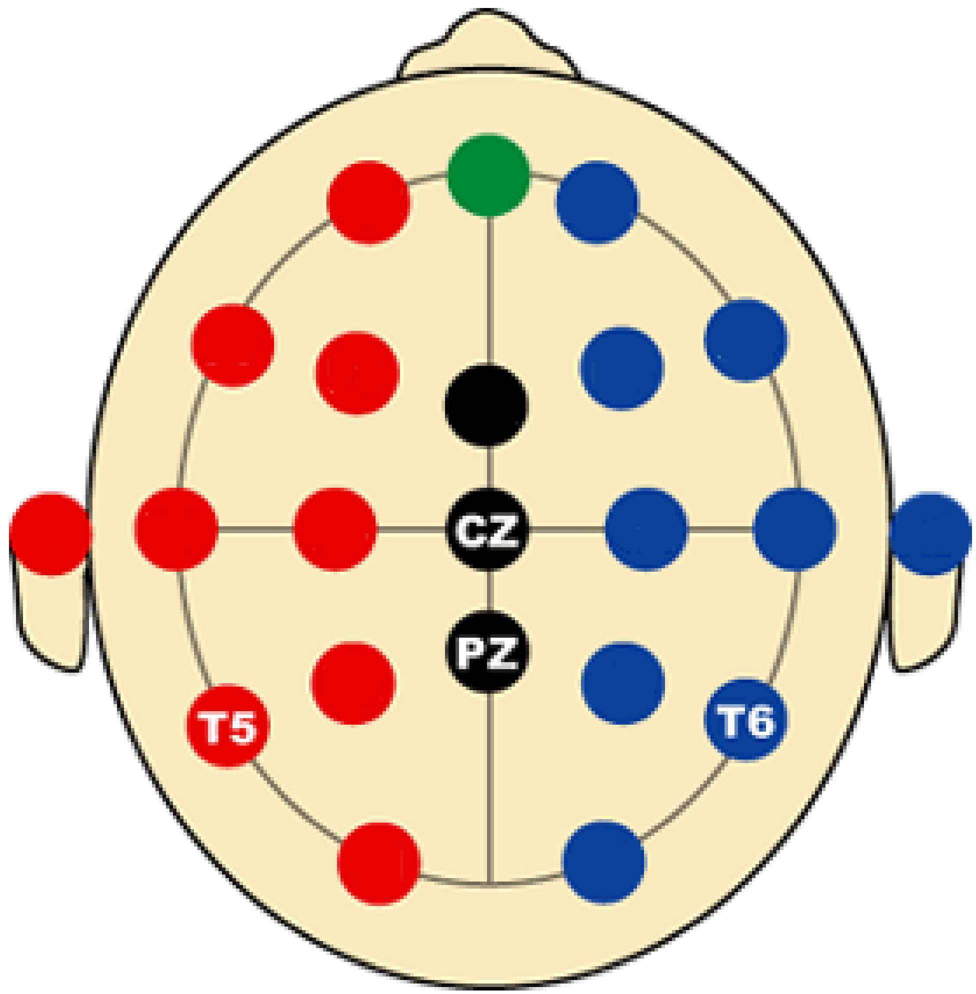
$$\mathbf{E}_{jt} = \nu_j \mathbf{E}_{jt-1} + \sigma_{jt}$$

All parameters in iFACE are subject-specific.



iFACE
Y11(t)
...
Yp1(t)
Y11(t+1)
...
Yp1(t+1)
A1 (t)
C1 (t)
E1 (t)
A2 (t)
C2 (t)
E2 (t)
A1 (t+1)
C1 (t+1)
E1 (t+1)
A2 (t+1)
C2 (t+1)
E2 (t+1)
0.5
1.0
0.5
1.0
Time t
Time t+1
Y12(t)
...
Yp2(t)
Y12(t+1)
...
Yp2(t+1)

Application iFACE to Multi-Lead EEG Data Obtained in Oddball Task


CZ
PZ
T5
T6

DZ Twin Pair (cor[A_1,A_2] = .40)

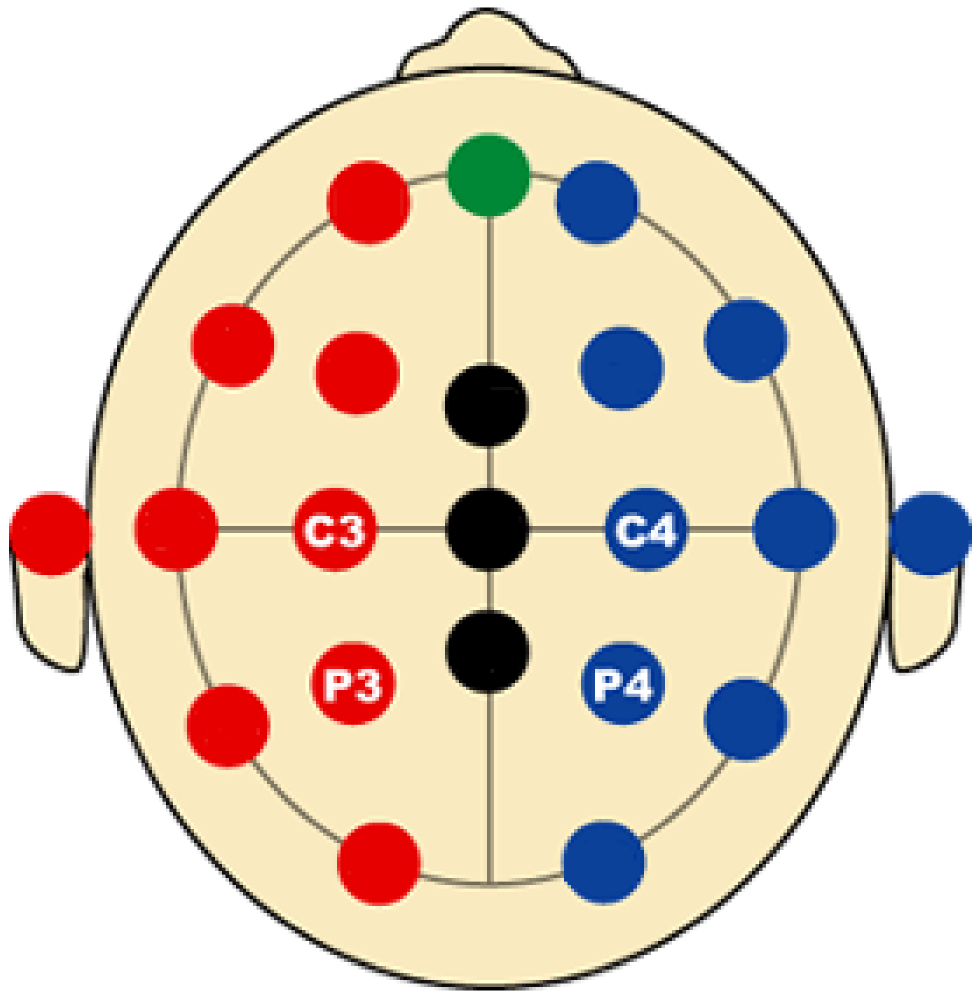
Twin 1

	a^2	c^2	e^2	res
Cz	.000	.016	.980	.703
Pz	.736	.039	.226	.063
T5	.285	.005	.710	.052
T6	.022	.000	.977	.000

DZ Twin Pair ($cor[A_1,A_2] = .40$)

Twin 2

	a^2	c^2	e^2	res
Cz	.045	.492	.463	.779
Pz	.048	.400	.551	.471
T5	.002	.018	.981	.041
T6	.109	.138	.753	.062


C3
C4
P3
P4

DZ Twin Pair (cor[A_1,A_2] = .37)

Twin 1

	a^2	c^2	e^2	res
C3	.019	.532	.449	.743
P3	.187	.749	.063	.013
C4	.186	.508	.305	.009
P4	.151	.828	.021	.321

DZ Twin Pair (cor[A_1,A_2] = .37)

Twin 2

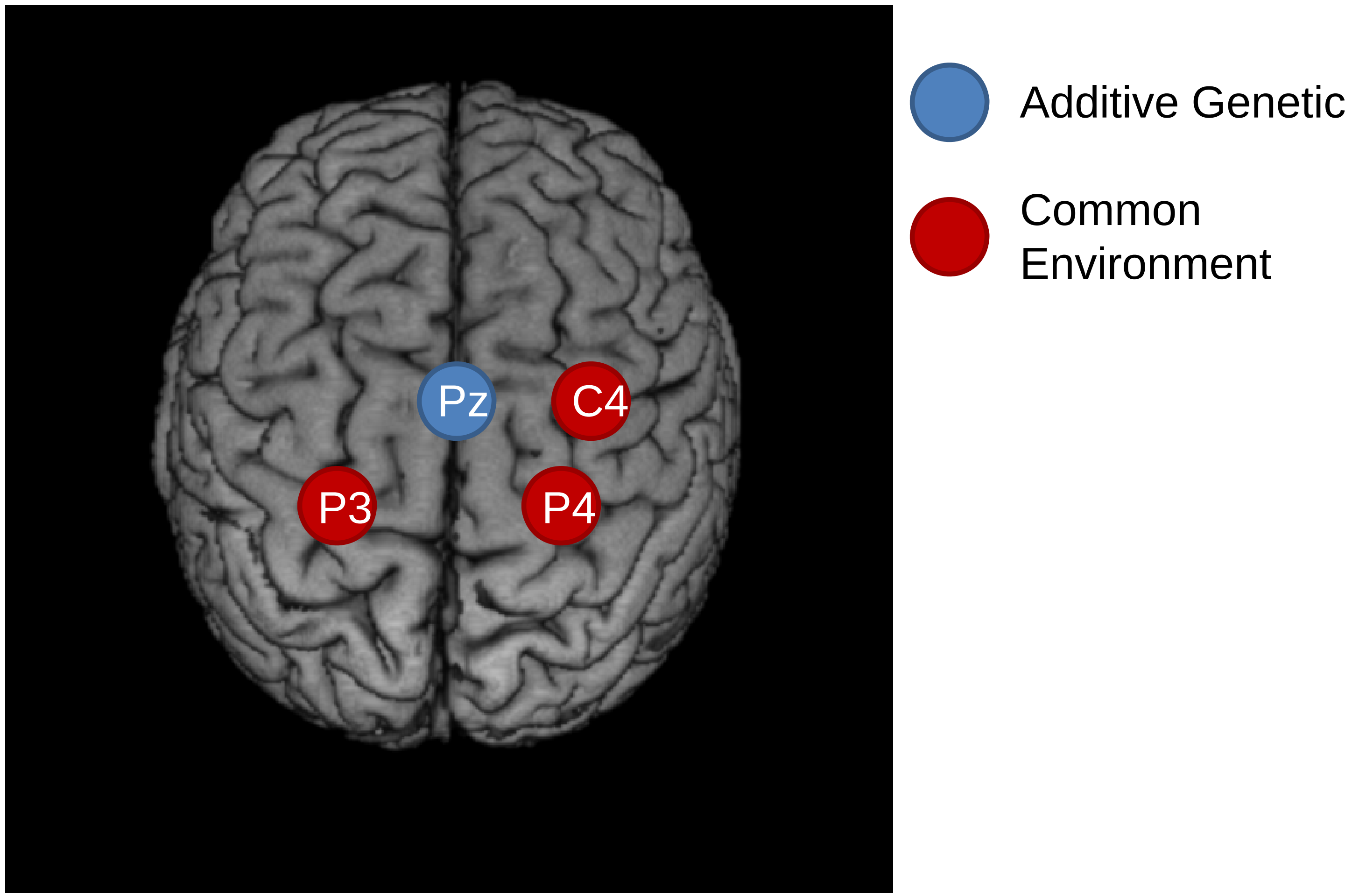
	a^2	c^2	e^2	res
C3	.159	.007	.834	.092
P3	.450	.008	.543	.173
C4	.842	.094	.065	.846
P4	.456	.007	.538	.262

Heritability is high for a few leads which differ across subjects (Pz for twin 1; P3 and P4 for twin 2)

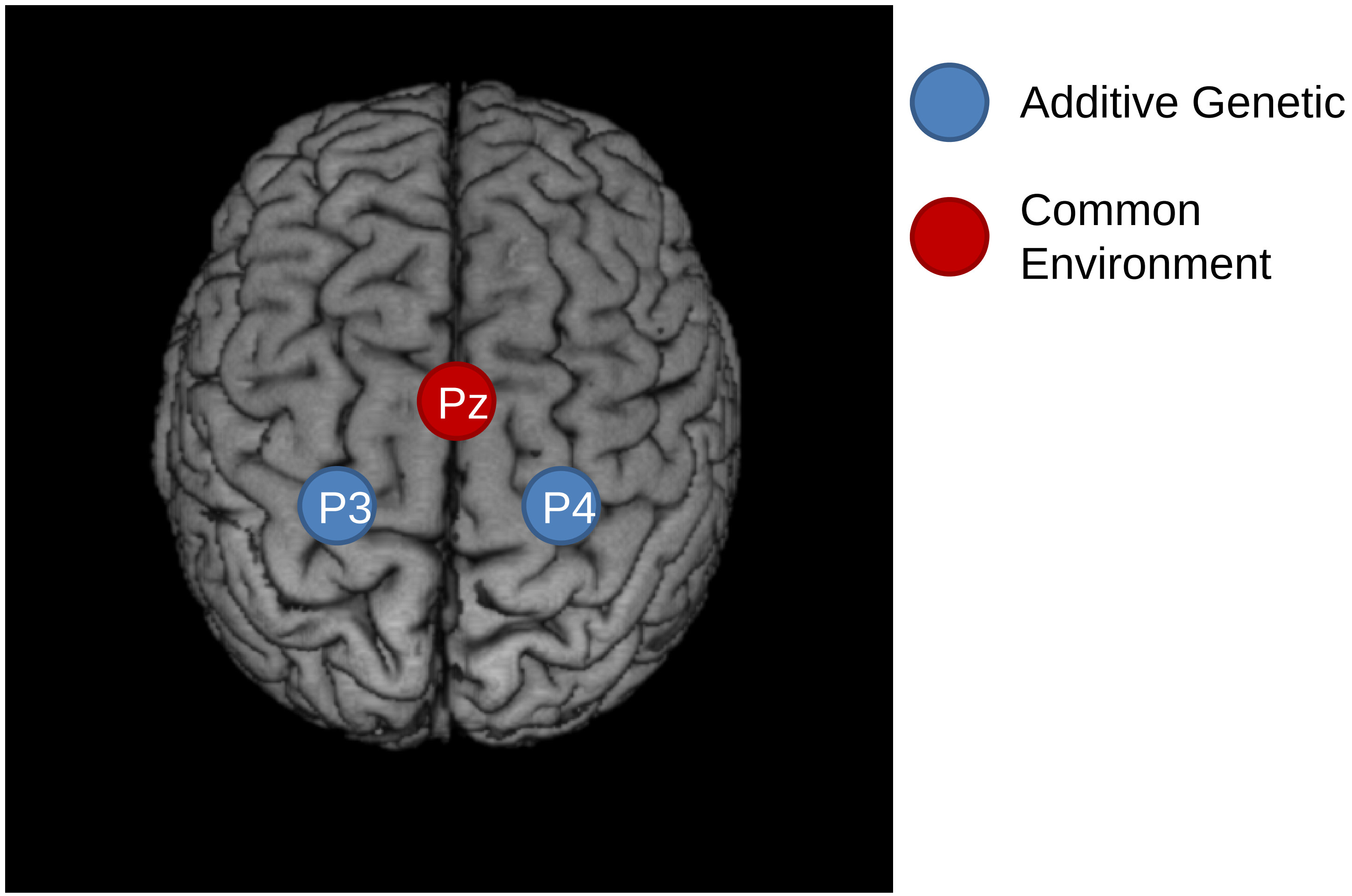
The effects of common environment are high for leads neighboring the ones with high heritability (P3 and P4 for twin 1; Pz for twin 2), possibly due to A x C interaction (Molenaar et al., *Genetic Epidemiology*, 1990)

Analogous results are obtained for other DZ twin pairs

Twin 1



Twin 2



Application of iFACE to multi-lead EEG preliminary and can be generalized in several respects, including:

- Alternative estimation techniques
- Alternative model variants
- Application to complete set of leads (19)
- Application to separate ERP components
- Frequency domain analysis

Conclusions

- iFACE (combination of IF and the ACE model) provides a principled new methodology to assess heterogeneity (subject-specificity).

- It is expected that iFACE will help better understand the relationships between genetic influences and phenotypes mediated by subject-specific physiological and brain systems.

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Simulation Study

Twin 1

true $(h_1)^2 = .34$ est $(h_1)^2 = .36$

true $(h_2)^2 = .86$ est $(h_2)^2 = .86$

true $(h_3)^2 = .35$ est $(h_3)^2 = .36$

true $(h_4)^2 = .57$ est $(h_4)^2 = .60$

Twin 2

true $(h_1)^2 = .73$ est $(h_1)^2 = .62$

true $(h_2)^2 = .20$ est $(h_2)^2 = .15$

true $(h_3)^2 = .54$ est $(h_3)^2 = .45$

true $(h_4)^2 = .49$ est $(h_4)^2 = .40$

Idiographic Filter is:

- Based on analysis of intra-individual variation

- Involves a new definition of measurement equivalence at the level of latent variables

- Allows for subject-specific factor loadings

Nesselroade, J.R., Gerstorf, D., Hardy, S.A., & Ram, N. (2007). Idiographic filters for psychological constructs. *Measurement*, *5*, 217-235.