

# **Introduction to Multivariate Genetic Analysis**

**Meike Bartels & Lucia Colodro Conde**

**With thanks to**

**Hermine Maes, Elizabeth Prom-Wormley, and many others**





# NATURE AND NURTURE: TWIN RESEARCH AND HUMAN GENETICS

🕒 SESSION 2: 18 JUL-1 AUG 2020 🎓 3 ECTS | ADVANCED BACHELOR/MASTER €1150 📱 VU AMSTERDAM

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# Looking for a PhD or Postdoc?

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## **PhD project:**

Social Media Language and Wellbeing; Understanding the Exposome-Genome interplay

4-years, paid position

## **Postdoc project**

A Comprehensive Framework for Well-being.

In this project we will use genomic, epigenomic, exposome, and well-being data and network approaches to understand the multi-layers interplay

3-years, paid position, 20-40% teaching

# **Introduction to Multivariate Genetic Analysis**

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# Research Questions

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## Univariate Analysis:

What are the contributions of additive genetic, dominance/shared environmental, and unique environmental factors to the variance?

## Bivariate Analysis:

What are the contributions of genetic, dominance/shared environmental, and environmental factors to the covariance between two traits?

# Example 1

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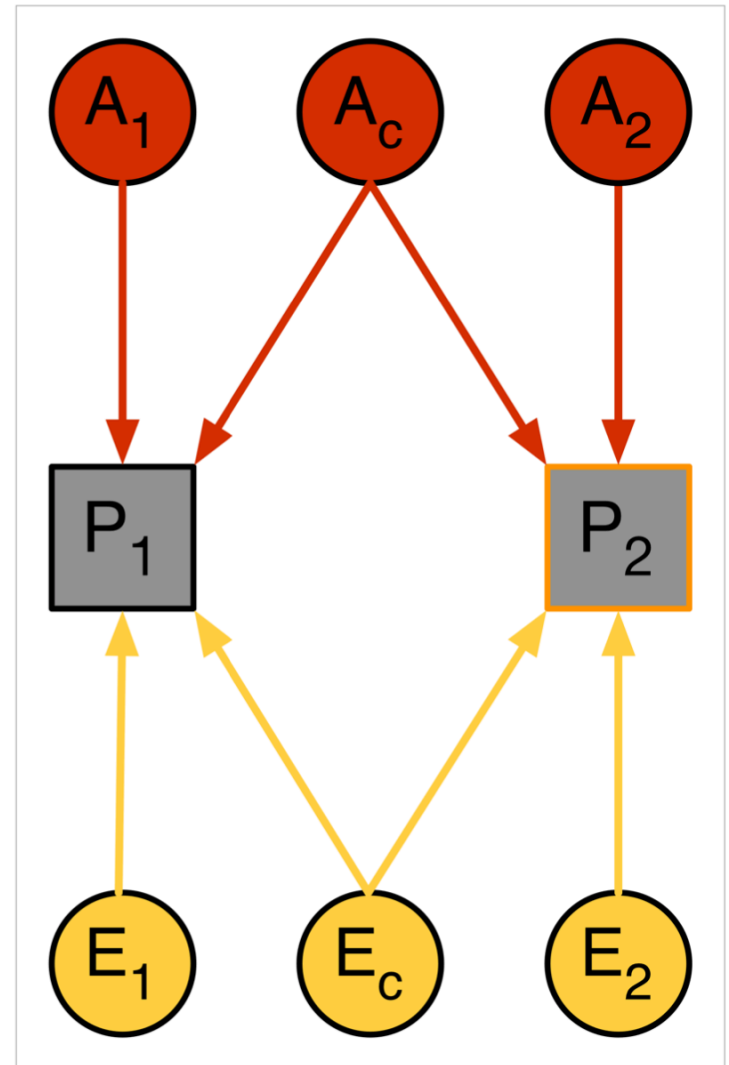
Why do traits correlate/covary?

How can we explain the association?

Shared Genes ( $r_G$ )

Shared shared environment ( $r_C$ )

Shared Non-shared environment ( $r_E$ )

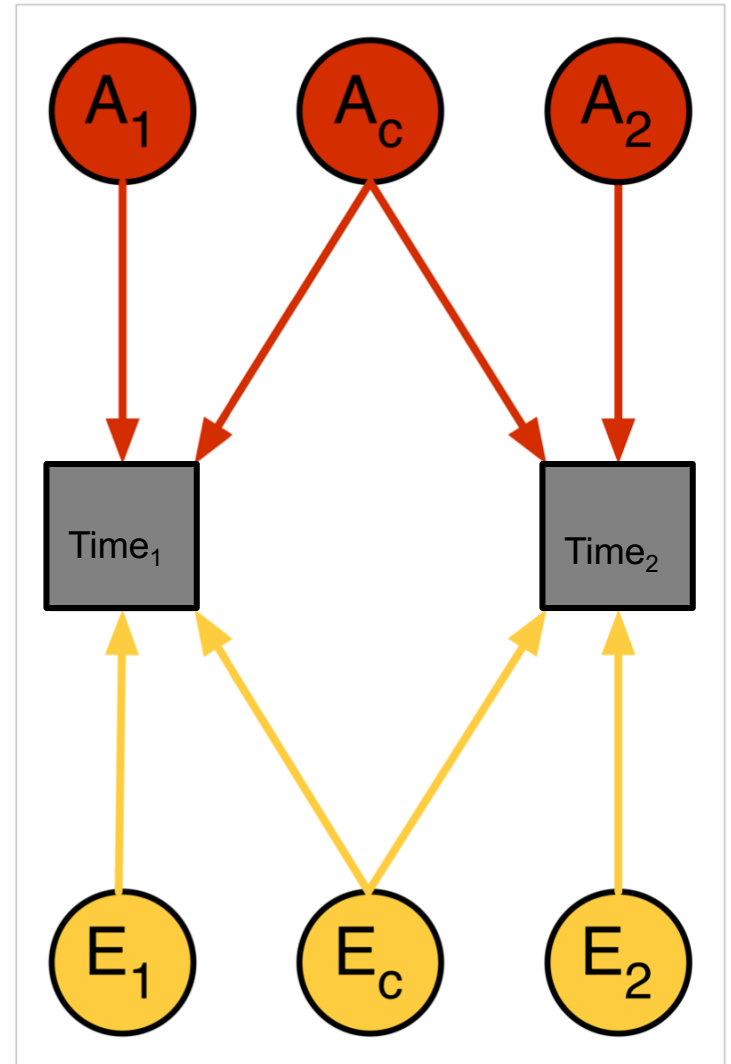




# Example 2

How do traits develop over time?  
Does one trait in childhood lead to another trait in adolescence?

Shared/ Stable Genes ( $r_G$ )  
Shared/ Stable shared environment ( $r_C$ )  
Shared/ Stable Non-shared environment ( $r_E$ )



# Sources of Information

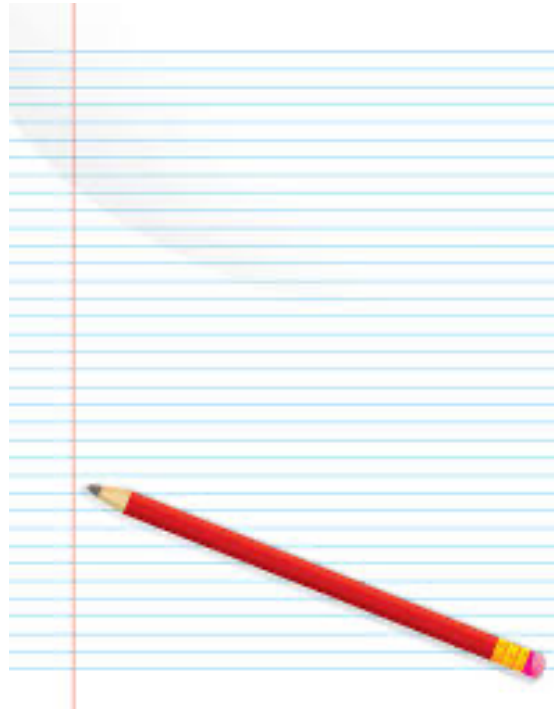
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- Two traits measured in twin pairs
- Interested in:
  - ◆ Cross-trait covariance *within* individuals
  - ◆ Cross-trait covariance *between* twins
  - ◆ MZ:DZ ratio of cross-trait covariance between twins



# Paper and Pencil Exercise

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# Observed Covariance Matrix- Univariate

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	Twin 1	Twin 2
Twin 1	Variance T1	
Twin 2	Covariance T1-T2	Variance T2

# Observed Covariance Matrix- Bivariate

		Twin 1		Twin 2	
		Phenotype 1	Phenotype 2	Phenotype 1	Phenotype 2
Twin 1	Phenotype 1	Variance P1			
	Phenotype 2	Covariance P1-P2	Variance P2		
Twin 2	Phenotype 1				
	Phenotype 2				

# Observed Covariance Matrix

		Twin 1		Twin 2	
		Phenotype 1	Phenotype 2	Phenotype 1	Phenotype 2
Twin 1	Phenotype 1	Variance P1			
	Phenotype 2	Covariance P1-P2	Variance P2		
Twin 2	Phenotype 1	Within-trait P1	Cross-trait	Variance P1	
	Phenotype 2	Cross-trait	Within-trait P2	Covariance P1-P2	Variance P2

# Observed Covariance Matrix

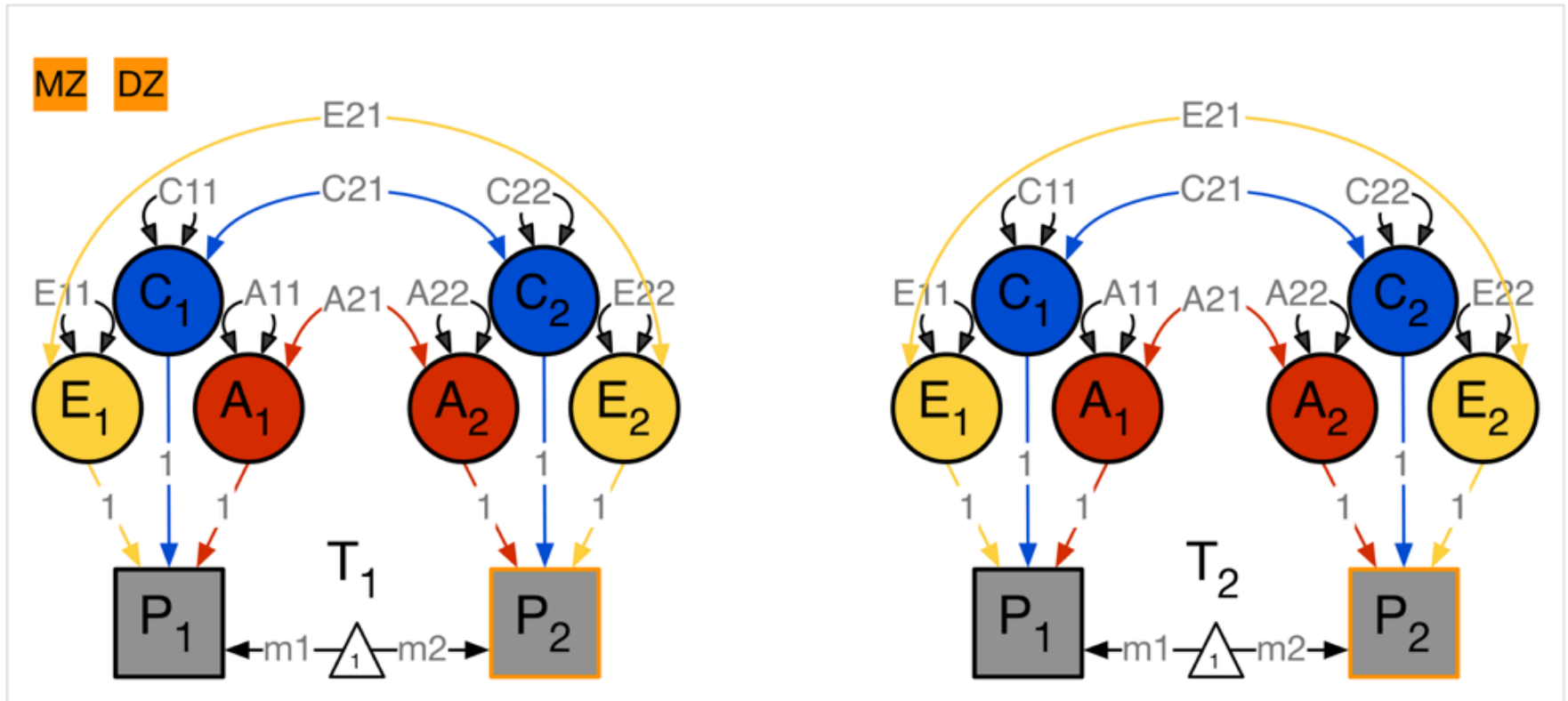
		Twin 1		Twin 2	
		Phenotype 1	Phenotype 2	Phenotype 1	Phenotype 2
Twin 1		<b>Within-twin covariance</b>			
	Phenotype 1	Variance P1			
	Phenotype 2	Covariance P1-P2	Variance P2		
Twin 2				<b>Within-twin covariance</b>	
	Phenotype 1	Within-trait P1	Cross-trait	Variance P1	
	Phenotype 2	Cross-trait	Within-trait P2	Covariance P1-P2	Variance P2



# Observed Covariance Matrix

		Twin 1		Twin 2	
		Phenotype 1	Phenotype 2	Phenotype 1	Phenotype 2
Twin 1		<b>Within-twin covariance</b>			
	Phenotype 1	Variance P1			
	Phenotype 2	Covariance P1-P2	Variance P2		
Twin 2		<b>Cross-twin covariance</b>		<b>Within-twin covariance</b>	
	Phenotype 1	Within-trait P1	Cross-trait	Variance P1	
	Phenotype 2	Cross-trait	Within-trait P2	Covariance P1-P2	Variance P2

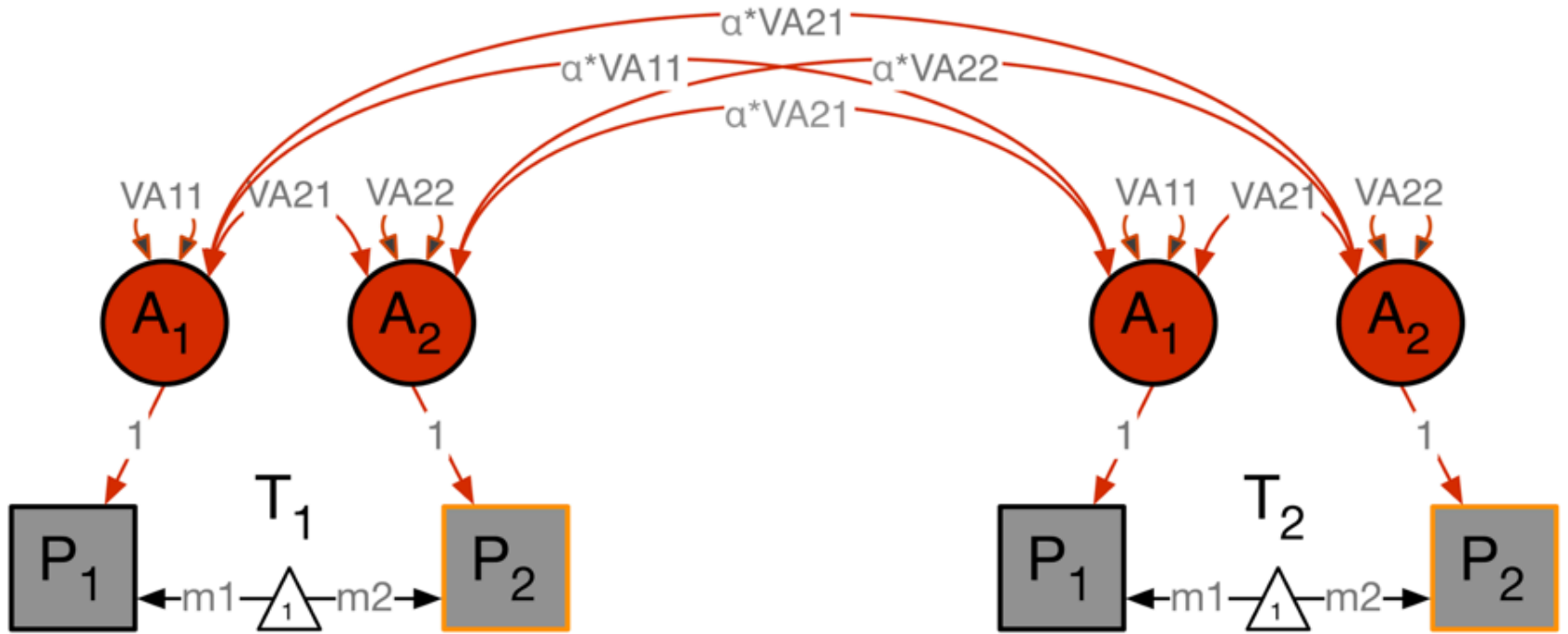
# Within-Twin Covariance



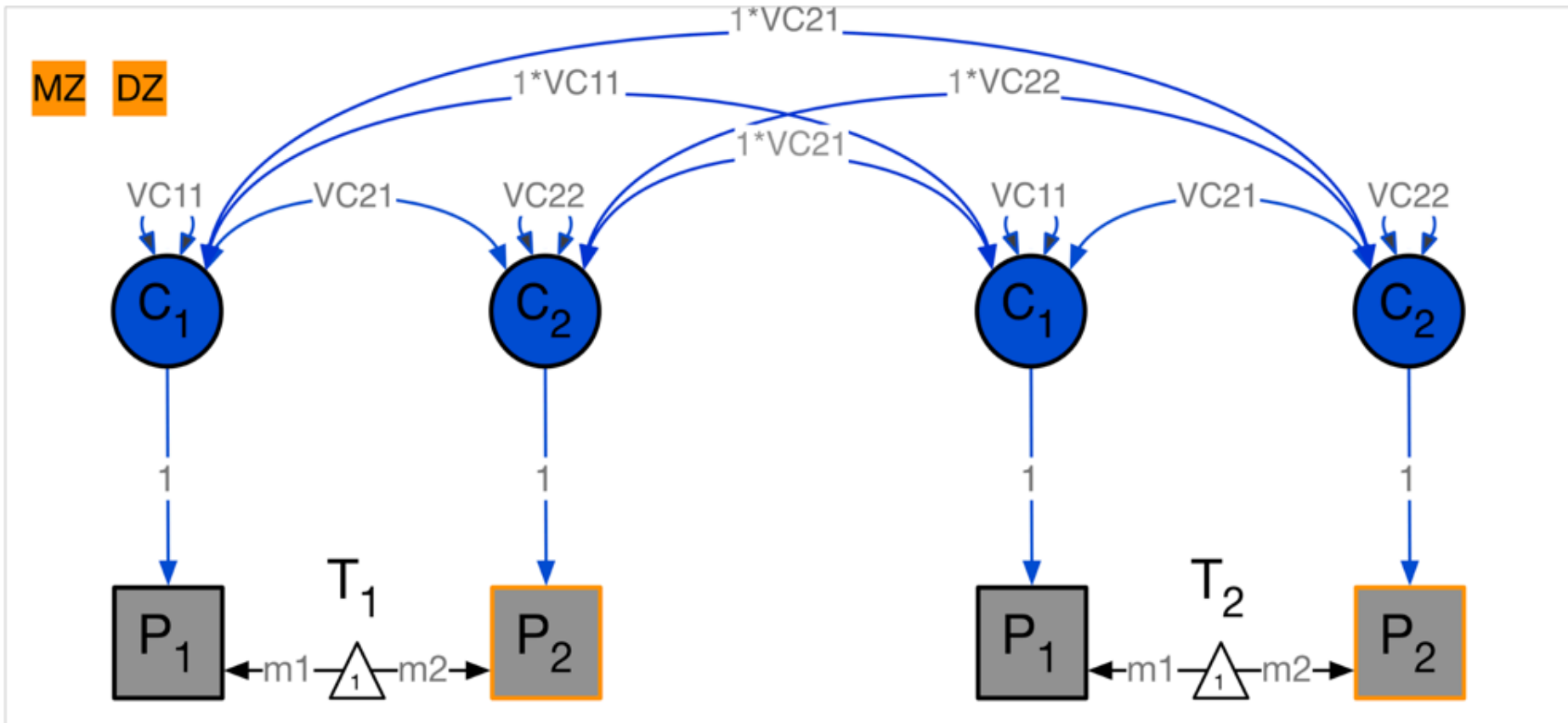


# A Cross-Twin Covariance

MZ DZ

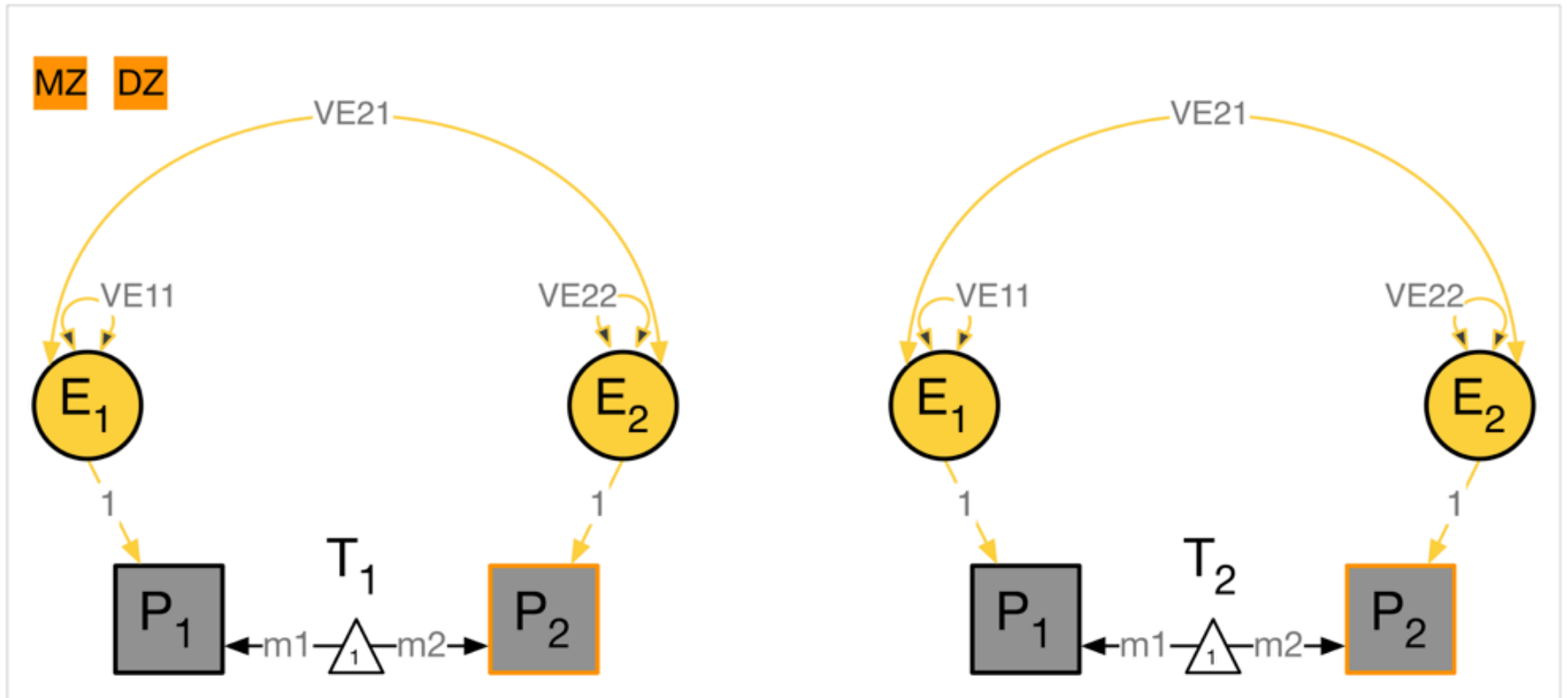


# C Cross-Twin Covariance

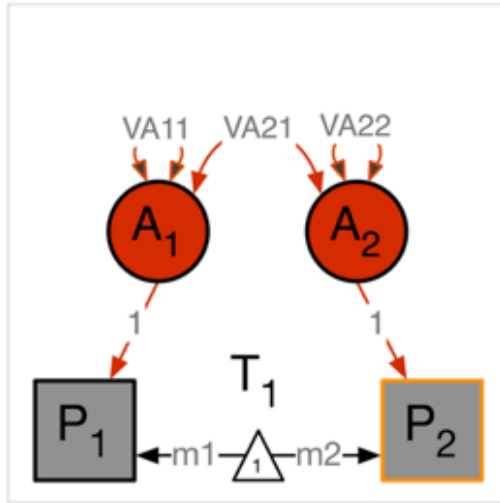




# E Cross-Twin Covariance



# Bivariate within Twin Covariance Matrix

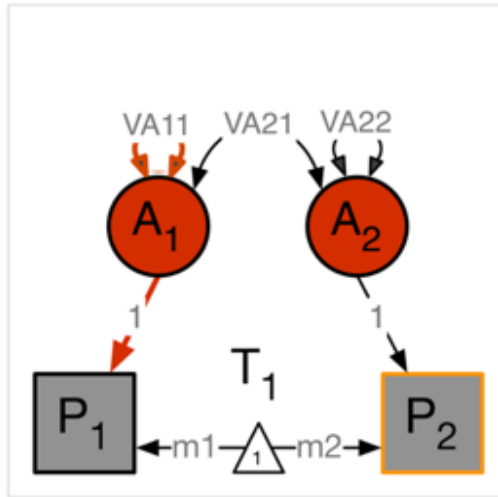


TWIN 1

TWIN 1

	$P_{1T_1}$	$P_{2T_1}$
$P_{1T_1}$	Variance $P_{1T_1}$	Covariance $P_{1T_1}P_{2T_1}$
$P_{2T_1}$	Covariance $P_{1T_1}P_{2T_1}$	Variance $P_{2T_1}$

# Bivariate within Twin Covariance Matrix

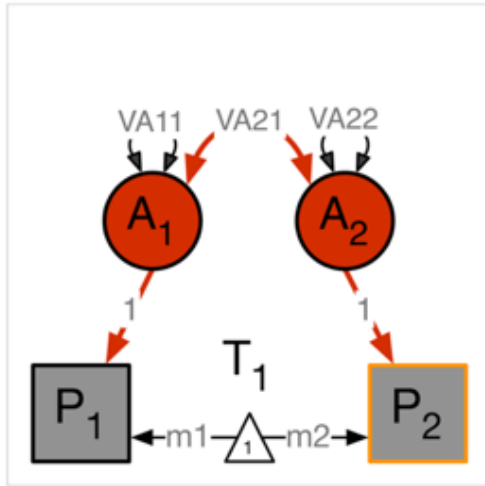


TWIN 1

TWIN 1

	$P_{1T_1}$	$P_{2T_1}$
$P_{1T_1}$	<b>VA11</b>	Covariance $P_{1T_1}P_{2T_1}$
$P_{2T_1}$	Covariance $P_{1T_1}P_{2T_1}$	<b>Variance</b> $P_{2T_1}$

# Bivariate within Twin Covariance Matrix

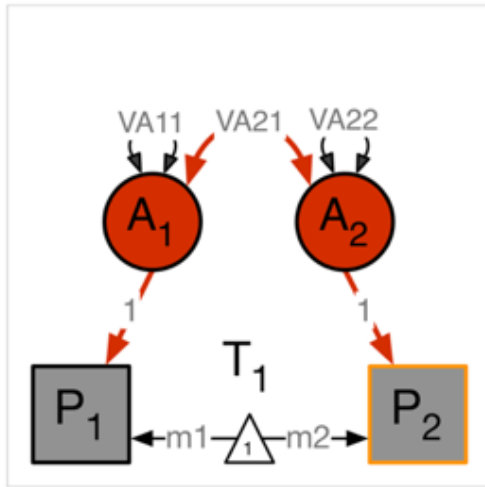


TWIN 1

TWIN 1

	$P_{1T_1}$	$P_{2T_1}$
$P_{1T_1}$	<b>VA11</b>	Covariance $P_{1T_1}P_{2T_1}$
$P_{2T_1}$	<b>VA21</b>	Variance $P_{2T_1}$

# Bivariate within Twin Covariance Matrix



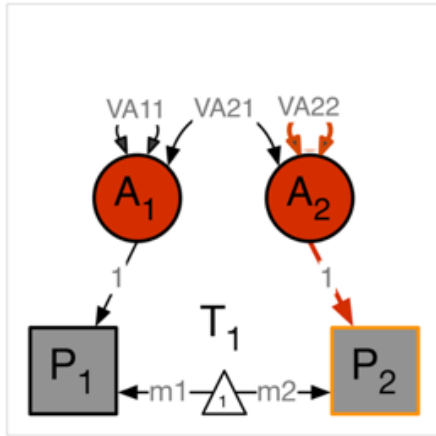
TWIN 1

TWIN 1

	$P_{1T_1}$	$P_{2T_1}$
$P_{1T_1}$	<b>VA11</b>	<b>VA21</b>
$P_{2T_1}$	<b>VA21</b>	Variance $P_{2T_1}$



# Bivariate within Twin Covariance Matrix



TWIN 1

	$P_{1T_1}$	$P_{2T_1}$
$P_{1T_1}$	$VA_{11}$	$VA_{21}$
$P_{2T_1}$	$VA_{21}$	$VA_{22}$

TWIN 1

# Bivariate cross Twin Covariance Matrix

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TWIN 1

	P1 <sub>T1</sub>	P2 <sub>T1</sub>
P1 <sub>T1</sub>	VA11 + VE11	VA21 + VE21
P2 <sub>T1</sub>	VA21 + VE21	VA22 + VE22

TWIN 1

# Bivariate cross Twin Covariance Matr

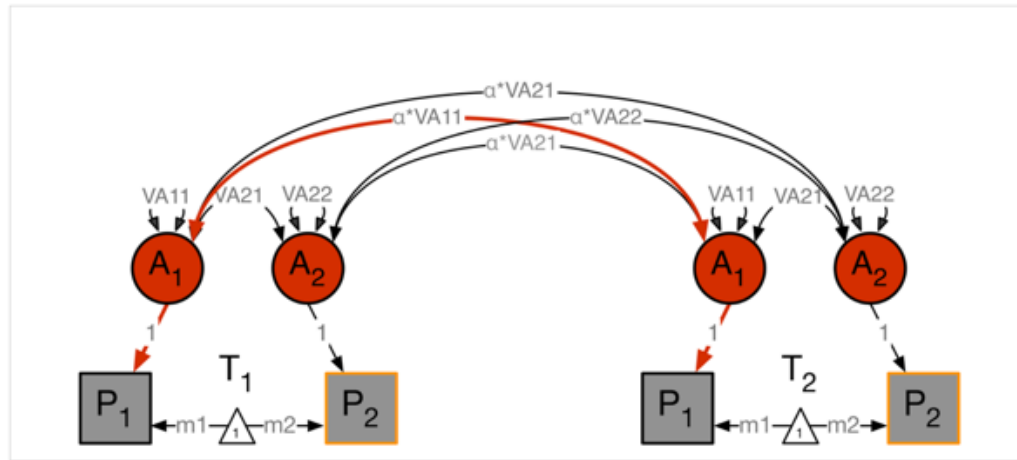
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TWIN 1

TWIN 2

	P1 <sub>T1</sub>	P2 <sub>T1</sub>
P1 <sub>T2</sub>	Within-Trait P1 <sub>T1</sub> P1 <sub>T2</sub>	Cross-Trait P1 <sub>T1</sub> P2 <sub>T2</sub>
P2 <sub>T2</sub>	Cross-Trait P2 <sub>T1</sub> P1 <sub>T2</sub>	Within-Trait P2 <sub>T1</sub> P2 <sub>T2</sub>

# Bivariate cross Twin Covariance Matr

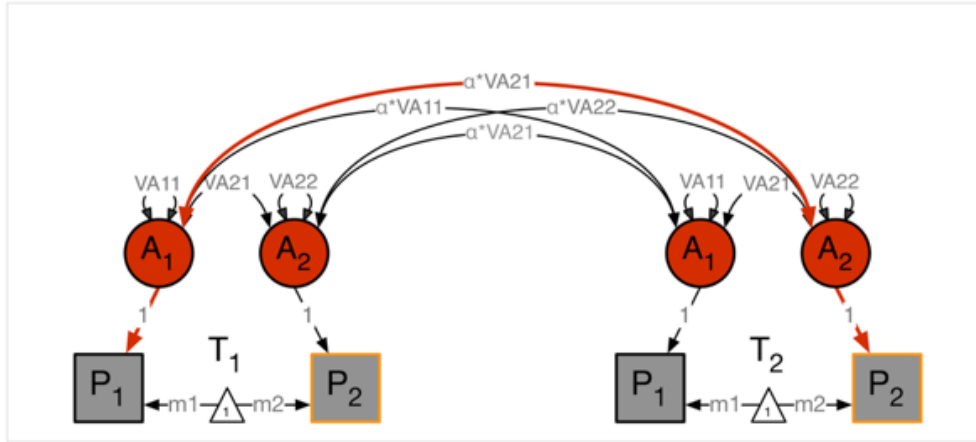


TWIN 1

TWIN 2

		P1 <sub>T1</sub>	P2 <sub>T1</sub>
P1 <sub>T2</sub>		<b>1/0.5 * VA11</b>	Cross-Trait P1 <sub>T1</sub> P2 <sub>T2</sub>
P2 <sub>T2</sub>		Cross-Trait P2 <sub>T1</sub> P1 <sub>T2</sub>	Within-Trait P2 <sub>T1</sub> P2 <sub>T2</sub>

# Bivariate cross Twin Covariance Matr



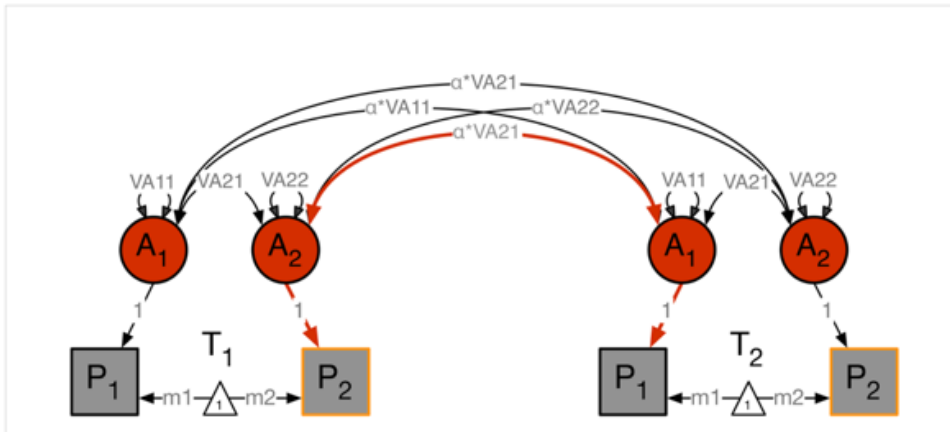
TWIN 1

TWIN 2

	P1 <sub>T1</sub>	P2 <sub>T1</sub>
P1 <sub>T2</sub>	$1/0.5 * VA11$	Cross-Trait P1 <sub>T1</sub> P2 <sub>T2</sub>
P2 <sub>T2</sub>	$1/0.5 * VA21$	Within-Trait P2 <sub>T1</sub> P2 <sub>T2</sub>



# Bivariate cross Twin Covariance Matr

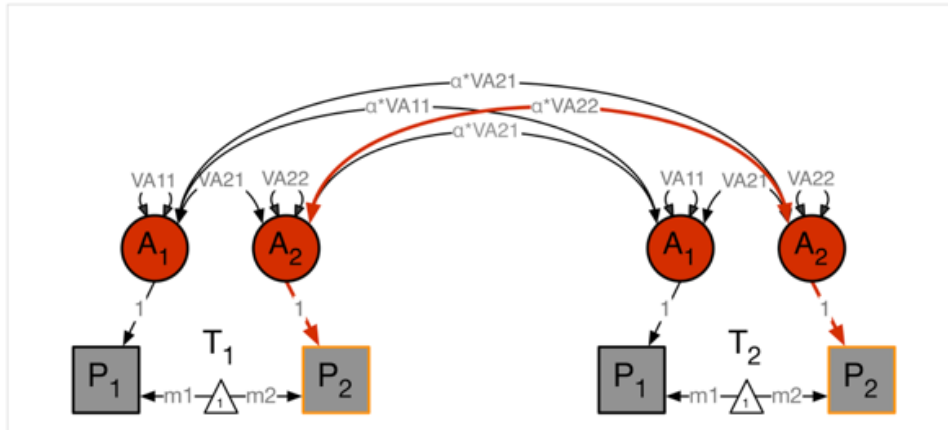


TWIN 1

TWIN 2

	P1 <sub>T1</sub>	P2 <sub>T1</sub>
P1 <sub>T2</sub>	1/0.5 * VA11	1/0.5 * VA21
P2 <sub>T2</sub>	1/0.5 * VA21	Within-Trait P2 <sub>T1</sub> P2 <sub>T2</sub>

# Bivariate cross Twin Covariance Matr



TWIN 1

	P1 <sub>T1</sub>	P2 <sub>T1</sub>
TWIN 2 P1 <sub>T2</sub>	$1/0.5 * VA11$	$1/0.5 * VA21$
P2 <sub>T2</sub>	$1/0.5 * VA21$	$1/0.5 * VA22$

# Predicted Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VA11$ $+VC11 +VE11$	$VA21$ $+VC21 +VE21$	$1/0.5 * VA11$ $+VC11$	$1/0.5 * VA21$ $+VC21$
	$P2_{T1}$	$VA21$ $+VC21 +VE21$	$VA22$ $+VC22 +VE22$	$1/0.5 * VA21$ $+VC21$	$1/0.5 * VA22$ $+VC22$
twin 2	$P1_{T2}$	$1/0.5 * VA11$ $+VC11$	$1/0.5 * VA21$ $+VC21$	$VA11$ $+VC11 +VE11$	$VA21$ $+VC21 +VE21$
	$P2_{T2}$	$1/0.5 * VA21$ $+VC21$	$1/0.5 * VA22$ $+VC22$	$VA21$ $+VC21 +VE21$	$VA22$ $+VC22 +VE22$

# Predicted MZ Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VA11$ $+VC11 +VE11$	$VA21$ $+VC21 +VE21$	$VA11$ $+VC11$	$VA21$ $+VC21$
	$P2_{T1}$	$VA21$ $+VC21 +VE21$	$VA22$ $+VC22 +VE22$	$VA21$ $+VC21$	$VA22$ $+VC22$
twin 2	$P1_{T2}$	$VA11$ $+VC11$	$VA21$ $+VC21$	$VA11$ $+VC11 +VE11$	$VA21$ $+VC21 +VE21$
	$P2_{T2}$	$VA21$ $+VC21$	$VA22$ $+VC22$	$VA21$ $+VC21 +VE21$	$VA22$ $+VC22 +VE22$

# Predicted DZ Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VA11$ $+VC11 +VE11$	$VA21$ $+VC21 +VE21$	$0.5 * VA11$ $+VC11$	$0.5 * VA21$ $+VC21$
	$P2_{T1}$	$VA21$ $+VC21 +VE21$	$VA22$ $+VC22 +VE22$	$0.5 * VA21$ $+VC21$	$0.5 * VA22$ $+VC22$
twin 2	$P1_{T2}$	$0.5 * VA11$ $+VC11$	$0.5 * VA21$ $+VC21$	$VA11$ $+VC11 +VE11$	$VA21$ $+VC21 +VE21$
	$P2_{T2}$	$0.5 * VA21$ $+VC21$	$0.5 * VA22$ $+VC22$	$VA21$ $+VC21 +VE21$	$VA22$ $+VC22 +VE22$

# Bivariate Twin Covariance Matrix

twin 1

twin 2

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$		$CP1_{T1}P2_{T1}$	<div style="border: 1px solid black; padding: 5px; text-align: center;">                     Variances of P1 &amp; P2                      same across twins and                      zygosity groups                 </div>	
	$P2_{T1}$	$CP1_{T1}P2_{T1}$			
twin 2	$P1_{T2}$	$CP1_{T1}P1_{T2}$	$CP2_{T1}P1_{T2}$		$CP1_{T2}P2_{T2}$
	$P2_{T2}$	$CP1_{T1}P2_{T2}$	$CP2_{T1}P2_{T2}$	$CP1_{T2}P2_{T2}$	

# Bivariate Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$		Covariances of P1& P2 same across twins and zygosity groups	
	$P2_{T1}$		$VP2_{T1}$		
twin 2	$P1_{T2}$	$CP1_{T1}P1_{T2}$	$CP2_{T1}P1_{T2}$	$VP1_{T2}$	
	$P2_{T2}$	$CP1_{T1}P2_{T2}$	$CP2_{T1}P2_{T2}$		$VP2_{T2}$

# Bivariate Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$	$CP1_{T1}P2_{T1}$	Cross-Twin Within-Trait Covariances differ by zygosity	
	$P2_{T1}$	$CP1_{T1}P2_{T1}$	$VP2_{T1}$		
twin 2	$P1_{T2}$		$CP2_{T1}P1_{T2}$	$VP1_{T2}$	$CP1_{T2}P2_{T2}$
	$P2_{T2}$	$CP1_{T1}P2_{T2}$		$CP1_{T2}P2_{T2}$	$VP2_{T2}$



# Bivariate Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$	$CP1_{T1}P2_{T1}$	Cross-Twin Cross-Trait Covariances differ by zygosity	
	$P2_{T1}$	$CP1_{T1}P2_{T1}$	$VP2_{T1}$		
twin 2	$P1_{T2}$	$CP1_{T1}P1_{T2}$		$VP1_{T2}$	$CP1_{T2}P2_{T2}$
	$P2_{T2}$		$CP2_{T1}P2_{T2}$	$CP1_{T2}P2_{T2}$	$VP2_{T2}$

# Bivariate MZ Twin Covariance Matrix

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		twin 1		twin 2	
		P1 <sub>T1</sub>	P2 <sub>T1</sub>	P1 <sub>T2</sub>	P2 <sub>T2</sub>
twin 1	P1 <sub>T1</sub>	1			
	P2 <sub>T1</sub>	0,26	1		
twin 2	P1 <sub>T2</sub>	0,64	0,21	1	
	P2 <sub>T2</sub>	0,25	0,7	0,31	1

# Bivariate DZ Twin Covariance Matrix

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		twin 1		twin 2	
		P1 <sub>T1</sub>	P2 <sub>T1</sub>	P1 <sub>T2</sub>	P2 <sub>T2</sub>
twin 1	P1 <sub>T1</sub>	1			
	P2 <sub>T1</sub>	0,31	1		
twin 2	P1 <sub>T2</sub>	0,2	0,12	1	
	P2 <sub>T2</sub>	0,12	0,53	0,27	1

# Bivariate Twin Covariance Matrix

MZ

	twin 1		twin 2		
	P1 <sub>T1</sub>	P2 <sub>T1</sub>	P1 <sub>T2</sub>	P2 <sub>T2</sub>	
twin 1	1				
	P2 <sub>T1</sub>	0,26	1		
twin 2	P1 <sub>T2</sub>	0,64	0,21	1	
	P2 <sub>T2</sub>	0,25	0,7	0,31	1

DZ

	twin 1		twin 2		
	P1 <sub>T1</sub>	P2 <sub>T1</sub>	P1 <sub>T2</sub>	P2 <sub>T2</sub>	
twin 1	1				
	P2 <sub>T1</sub>	0,31	1		
twin 2	P1 <sub>T2</sub>	0,2	0,12	1	
	P2 <sub>T2</sub>	0,12	0,53	0,27	1

# Summary

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- Within-individual cross-trait covariance implies common aetiological influences
- Cross-twin cross-trait covariance implies common aetiological influences are familial
- Whether familial influences are genetic or environmental shown by MZ:DZ ratio of cross-twin cross-trait covariances