Distinctive heritability patterns of subcortical-prefrontal cortex resting state connectivity in childhood: A twin study

Achterberg, M.; Bakermans, M.J.; IJzendoorn, M.H. van; Meulen, M. van der; Tottenham, N.; Crone, E.A.M.

Distinctive heritability patterns of subcortical-prefrontal cortex resting state connectivity in childhood: A twin study

Michelle Achterberg, MSc [1,2,3], Marian J. Bakermans-Kranenburg, PhD [1,3], Marinus H. van IJzendoorn, PhD [1], Mara van der Meulen, MSc[1,2,3], Nim Tottenham, PhD [4], & Eveline A. Crone, PhD [1,2,3]

Supplementary Materials

Affiliations:

[1] Leiden Consortium on Individual Development, Leiden University, the Netherlands

[2] Institute of Psychology, Leiden University, the Netherlands

[3] Leiden Institute for Brain and Cognition, Leiden University, the Netherlands

[4] Department of Psychology, Columbia University, New York City, NY, USA

Corresponding author: Michelle Achterberg, Faculty of Social and Behavioral Sciences, Leiden University, Wassenaarseweg 52, 2333AK Leiden, The Netherlands. Tel: +31 71 527 6861, E-mail: m.achterberg@fsw.leidenuniv.nl

Supplementary Figures

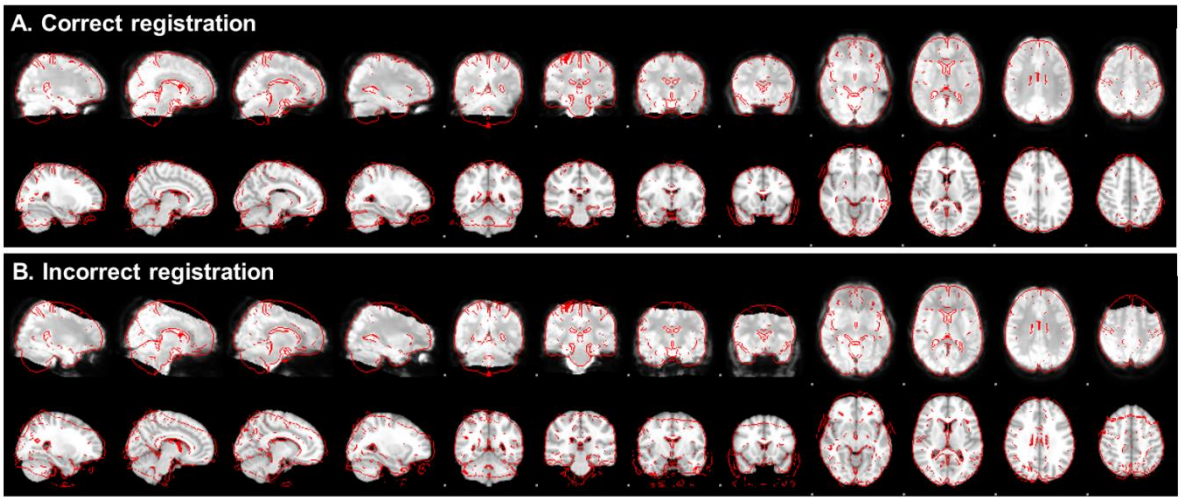

Figure S1. Example of correct (A) and incorrect (B) registration from subject specific functional data to standard MNI space.

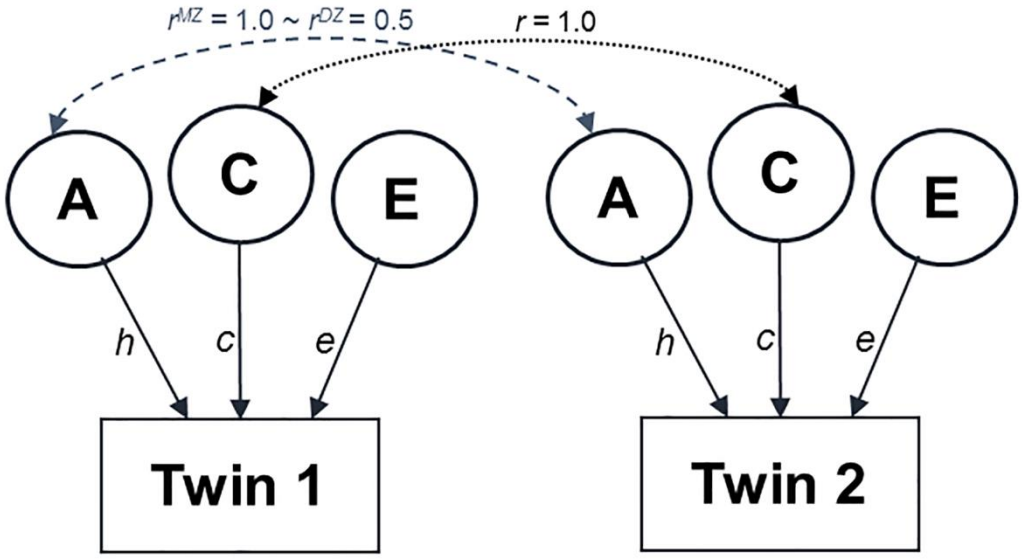

Figure S2. ACE model. Similarities among twin pairs are divided into similarities due to shared genetic factors (A) and shared environmental factors (C), while dissimilarities are ascribed to unique environmental influences and measurement error (E). The correlation of factor C within twins is 1 for both MZ and DZ twins, while the correlation of factor A is 1 within MZ twins and on average 0.5 within DZ twins.

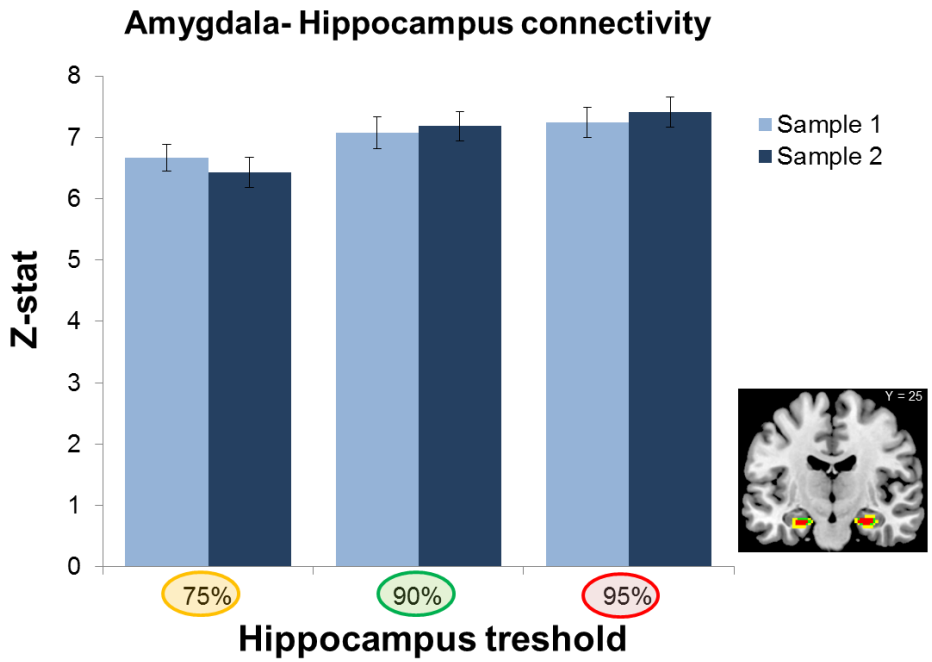

Figure S3. Amygdala-Hippocampus connectivity for different thresholds of the Harvard/Oxford hippocampus region: 75% (yellow), 90% (green), and 95% (red).

Supplementary Tables

Table S1. Sample selection

N		age (SD)	age range	% boys
512	Children included	7.94 (0.67)	7.02 - 9.68	48.80
- 69	No RS scan*	7.92 (0.69)	7.02 - 9.26	55.07
-3	Anomalous findings**	8.82 (0.03)	8.80 - 8.85	33.33
-209	Excessieve head motion***	7.90 (0.66)	7.02-9.68	55.02
-11	Registration errors	7.65 (0.64)	7.03 - 8.84	54.54
220	final sample	7.99 (0.67)	7.02 - 9.08	40.91

* due to no parental consent (4); MRI contra-indications (7); anxiety (14) or lack of time (44)

** as indicated by a radiologist

*** defined as 0.5 mm framewise displacement in >20% of the data

Table S2. Genetic modeling of framewise displacement (FD) for the initial sample (prior to motion exclusion, N=398) and the final sample (N=220).

% frames >0.5 mm FD	model	A^2	C^2	E^2	LTR	AIC
Initial sample	ACE	0.38	0.06	0.56		3146.62
(prior to motion exclusion)	*95% CI*	0.26-0.56	0.00-0.42	0.44-0.72		
	*** AE**	**0.44**	**-**	**0.56**	**0.08**	**3144.7**
	CE	-	0.35	0.65	2.49	3147.11
	E	-	-	1	>26.72	3171.83
Final sample	ACE	0.00	0.15	0.85		670.68
(after motion exclusion)	*95% CI*	0.00-0.35	0.00-0.38	0.62-1.00		
	AE	0.11	-	0.89	0.93	669.61
	CE	-	0.15	0.85	<.001	668.68
	*** E**	**-**	**-**	**1**	**<1.53**	**668.21**

Table S3. MNI coordinates and local maxima for whole brain connectivity clusters from Sample I, with $Z>3.09$, $p<.05$ cluster correction. Anatomical regions were derived from the Harvard-Oxford atlas in FSL.

Sample I	voxels	max zstat	max x	max y	max X	anatomical regions
VS positive	10712	16	12	8	-12	Medial prefrontal cortex, anterior cingulate cortex, paracingulate gyrus, superior frontal gyrus, frontal pole, subcallosal cortex, thalamus, orbitofrontal cortex, putamen, pallidum, caudate, nucleus accumbens
	2128	6.39	38	12	10	Right frontal operculum cortex, right insula, right inferior frontal gyrus, right precentral gyrus, right postcentral gyrus
	374	4.7	50	-34	-22	Right inferior temporal gyrus, right teporal fusiform cortex
	352	5.31	66	-6	-20	Right middle temporal gyrus, right superior temporal gyrus
	271	4.02	-56	-10	-6	Left insula, left Heschl's gyrus
	214	4.75	-44	50	20	Left frontal pole
VS negative	3368	5.38	-38	10	40	Left middle frontal gyrus, left precentral gyrus, left inferior frontal gyrus, left superior frontal gyrus, left lateral occipital cortex, left superior parietal lobule
	3064	5.59	24	-34	14	Hippocampus, Thalamus, brainstem, parahippocampal gyrus
	2230	5.13	36	-20	42	Right postcentral gyrus, right precentral gyrus, right supramarginal gyrus
	671	6.71	-46	30	-8	Left frontal pole, left orbitofrontal gyrus, left inferior frontal gyrus
	477	5.22	42	50	-8	Right frontal pole, right orbitofrontal gyrus, right inferior frontal gyrus
	461	4.91	50	8	40	Right middle frontal gyrus, right precentral gyrus
	353	4.92	36	-56	60	Right lateral occipital cortex
AMY positive	15999	15.2	-22	-4	-18	Hippocampus, parahippocampal gyrus, putamen, pallidum, thalamus, brainstem, Fusiform cortex, insula, temporal pole, subcallosal cortex, orbitofrontal cortex
AMY negative	66829	7.31	-2	-30	2	supplementary motor cortex, superior frontal gyrus, paracingulate gyrus, anterior cingulate gyrus, middle frontal gyrus, frontal pole, precentral gyrus, precuneus, postcentral gyrus, lateral occipital cortex, inferior frontal gyrus, precentral gyrus, central opercular cortex

Table S4. MNI coordinates and local maxima for whole brain connectivity clusters from Sample II, with $Z>3.09$, $p<.05$ cluster correction. Anatomical regions were derived from the Harvard-Oxford atlas in FSL.

Sample II	voxels	max zstat	max x	max y	max X	anatomical regions
VS positive	9397	14.3	10	10	-8	Medial prefrontal cortex, anterior cingulate cortex, paracingulate gyrus, superior frontal gyrus, frontal pole, subcallosal cortex, thalamus, orbitofrontal cortex, putamen, pallidum, caudate, nucleus accumbens
	1503	5.18	-38	-20	4	Left insula, left middle temporal gyrus, left inferior frontal gyrus
	443	4.58	46	-12	16	Right central opercular cortex, right inferior frontal gyrus
	336	3.95	50	-54	-12	Right inferior temporal gyrus, right temporal gyrus, right temporal fusiform cortex
	204	4.42	46	18	-32	Right temporal pole, right middle temporal gyrus
VS negative	7743	6.23	-10	2	38	Middle frontal gyrus, precentral gyrus, left inferior frontal gyrus, superior frontal gyrus, lateral occipital cortex, superior parietal lobule, postcentral gyrus
	3191	4.97	-6	-70	2	Hippocampus, Thalamus, brainstem, parahippocampal gyrus
	356	4.7	50	10	40	Right middle frontal gyrus, right precentral gyrus, right inferior frontal gyrus
AMY positive	17843	16.3	-24	-2	-20	Hippocampus, parahippocampal gyrus, putamen, pallidum, thalamus, brainstem, Fusiform cortex, insula, temporal pole, subcallosal cortex, orbitofrontal cortex
AMY negative	61466	7.8	2	16	48	Supplementary motor cortex, superior frontal gyrus, paracingulate gyrus, anterior cingulate gyrus, middle frontal gyrus, frontal pole, precentral gyrus, precuneus, postcentral gyrus, lateral occipital cortex, inferior frontal gyrus, precentral gyrus, central opercular cortex, left inferior frontal gyrus
	884	5.5	58	14	2	Right inferior frontal gyrus, right precentral gyrus, right central opercular cortex

Table S5. Mean and standard deviations of Z-values for all subcortical-cortical and subcortical-subcortical connectivity patterns. Differences in connectivity between different samples were tested with independent sample T-tests. Asterisks indicate significant differences between samples.

Seed	ROI	Sample I mean (SD)	Sample II mean (SD)	*T*	*p*	
Ventral Striatum	vmPFC	1.66 (1.34)	1.69 (1.60)	-0.12	0.905	
	vACC	1.05 (1.04)	0.86 (1.14)	1.07	0.287	
	OFC	1.31 (0.88)	1.09 (0.89)	1.54	0.125	
	dmPFC	-0.29 (0.61)	-0.05 (0.54)	-2.68	0.008	*
	dACC	-0.54 (1.03)	-0.73 (1.21)	1.10	0.274	
	dlPFC	-0.48 (0.59)	-0.31 (0.55)	-1.95	0.053	
	Thalamus	0.51 (1.37)	0.50 (1.37)	0.03	0.980	
	Hippocampus	-0.52 (1.87)	-0.41 (2.10)	-0.36	0.716	
	Amygdala	0.34 (2.17)	0.40 (2.04)	-0.17	0.862	
Amygdala	vmPFC	-0.04 (1.45)	0.26 (1.03)	-1.51	0.134	
	vACC	-0.25 (0.93)	0.06 (0.86)	-2.16	0.032	*
	OFC	1.13 (1.11)	1.28 (0.76)	-1.02	0.308	
	dmPFC	-0.75 (0.62)	-0.72 (0.59)	-0.28	0.777	
	dACC	-0.38 (1.11)	-0.29 (1.14)	-0.50	0.616	
	dlPFC	-0.88 (0.67)	-0.88 (0.54)	0.04	0.969	
	Thalamus	-0.43 (1.47)	-0.15 (1.32)	-1.24	0.218	
	Hippocampus	6.67 (1.93)	6.43 (2.17)	0.72	0.471	

Table S6. Simple T-tests for all subcortical-cortical and subcortical-subcortical connectivity patterns. Bold statistics indicate connectivity that was not significantly different from zero. For means and standard deviations, see **Table S5**.

Seed	ROI	Sample I	Sample II
Ventral Striatum	vmPFC	t(77)=10.94, *p*<.001	t(77)=9.31, *p*<.001
	vACC	t(77)=8.95, *p*<.001	t(77)=6.71, *p*<.001
	OFC	t(77)=13.09, *p*<.001	t(77)=10.86, *p*<.001
	dmPFC	t(77)=-4.30, *p*<.001	**t(77)=-.80, *p*=.428**
	dACC	t(77)=-4.59, *p*<.001	t(77)=-5.37, *p*<.001
	dlPFC	t(77)=-7.29, *p*<.001	t(77)=-4.93, *p*<.001
	Thalamus	t(77)=3.29, *p*=.002	t(77)= 3.25, *p*=.002
	Hippocampus	t(77)=-2.47, *p*=.016	**t(77)= -1.71, *p*=.091**
	Amygdala	**t(77)=1.40, *p*=.167**	**t(77)=1.74, *p*=.085**
Amygdala	vmPFC	**t(77)=-.261, *p*=.795**	t(77)=2.24, *p*=.028
	vACC	t(77)=-2.37, *p*=.021	**t(77)=.63, *p*=.532**
	OFC	t(77)=8.95, *p*<.001	t(77)=14.92, *p*<.001
	dmPFC	t(77)=-10.77, *p*<.001	t(77)=-10.90, *p*<.001
	dACC	t(77)=-3.04, *p*=.003	t(77)=-2.25, *p*=.027
	dlPFC	t(77)=-11.59, *p*<.001	t(77)=-14.50, *p*<.001
	Thalamus	t(77)=-11.59, *p*<.001	**t(77)= -1.00, *p*=.321**
	Hippocampus	t(77)=30.45, *p*<.001	t(77)=26.12, *p*<.001

Genetic modeling - comparison of parsimonious models

Similarities among twin pairs are divided into similarities due to shared genetic factors (A) and shared environmental factors (C), while dissimilarities are ascribed to unique environmental influences and measurement error (E). Behavioral genetic modeling with the OpenMX package (Neale et al., 2016) in R (R Core Team, 2015) provides estimates of these A, C, and E components. For each of the 17 connections, four different models (ACE, AE (with C set to zero), CE (with A set to zero), and E (with A and C set to zero)) were estimated and a log likelihood was calculated. Each model was then compared to a more parsimonious model (e.g. ACE vs. AE; ACE vs. CE; AE vs. E and CE vs. E) by subtracting the log likelihoods, resulting in an estimate of the Log- Likelihood Ratio Test (LRT). Given that the LRT follows the $\chi 2$-distribution, an LRT<3.85 would indicate that the more parsimonious model has no worse fit to the data. The Akaike Information Criterion (AIC; Akaike (1974) was used to determine the best model for equally parsimonious non-nested models (i.e. AE and CE), with better model fit being indicated by a lower AIC. When ACE models show the best fit, both heritability, shared and unique environment are important contributors to explain the variance in the outcome variable. AE models indicate that genetic and unique environmental factors play a role; whilst CE models indicate influences of the shared environment and unique environment. If the E model has no worse fit than AE or CE models, variance in the outcome variable is accounted for by unique environmental factors and measurement error.

Table S7. Genetic modeling of Ventral Striatum-Cortical connectivity: full ACE model versus more parsimonious models.

Start Seed	ROI	model	A²	C²	E²	LRT	AIC
Ventral	vmPFC	ACE	0.67	0.00	0.33		182.29
Striatum		*** AE**	**0.67**	**-**	**0.33**	**<0.001**	**182.29**
		CE	-	0.44	0.56	5.68	187.97
		E	-	-	1.00	>14.03	200.00
	vACC	ACE	0.12	0.17	0.71		138.13
		AE	0.32	-	0.68	0.19	136.31
		*** CE**	**-**	**0.27**	**0.73**	**0.07**	**136.20**
		E	-	-	1.00	>4.71	139.03
	OFC	ACE	0.32	0.09	0.59		83.87
		*** AE**	**0.42**	**-**	**0.58**	**0.05**	**81.92**
		CE	-	0.34	0.66	0.58	82.44
		E	-	-	1.00	>8.09	88.54
	dmPFC	ACE	0.36	0.01	0.63		-41.82
		*** AE**	**0.37**	**-**	**0.63**	**0.001**	**-43.82**
		CE	-	0.27	0.73	0.65	-43.17
		E	-	-	1.00	>5.00	-40.17
	dACC	ACE	0.46	0.00	0.54		165.63
		*** AE**	**0.46**	**-**	**0.54**	**<0.001**	**163.63**
		CE	-	0.27	0.73	4.00	167.62
		E	-	-	1.00	>4.97	170.60
	dlPFC	ACE	0.19	0.00	0.81		-50.46
		AE	0.19	-	0.81	<0.001	-52.46
		CE	-	0.12	0.88	0.73	-51.73
		*** E**	**-**	**-**	**1.00**	**<1.74**	**-52.72**

[1] LRT < 3.85 equals no worse fit of the model (p<.05)

[2] Lower AIC values indicate a better model fit

* Asterisks indicate the best model fit

Table S8. Genetic modeling of Amygdala-Cortical connectivity: full ACE model versus more parsimonious models.

Start Seed	ROI	model	A²	C²	E²	LRT	AIC
Amygdala	vmPFC	ACE	0.23	0.00	0.77		184.64
		AE	0.23	-	0.77	<0.001	182.64
		CE	-	0.07	0.93	1.43	184.08
		*** E**	**-**	**-**	**1.00**	**<1.79**	**182.43**
	vACC	ACE	0.00	0.35	0.65		84.01
		AE	0.34	-	0.66	1.12	83.14
		*** CE**	**-**	**0.35**	**0.65**	**<0.001**	**82.01**
		E	-	-	1.00	>7.41	88.55
	OFC	ACE	0.54	0.00	0.46		84.33
		*** AE**	**0.54**	**-**	**0.46**	**<0.001**	**82.33**
		CE	-	0.46	0.54	1.79	84.11
		E	-	-	1.00	>15.30	97.41
	dmPFC	ACE	0.08	0.00	0.92		-14.87
		AE	0.08	-	0.92	<0.001	-16.87
		CE	-	0.00	1.00	0.24	-16.62
		*** E**	**-**	**-**	**1.00**	**<0.24**	**-18.62**
	dACC	ACE	0.08	0.00	0.92		130.54
		AE	0.08	-	0.92	<0.001	128.54
		CE	-	0.03	0.97	0.22	128.77
		*** E**	**-**	**-**	**1.00**	**<0.27**	**126.82**
	dlPFC	ACE	0.14	0.00	0.86		-4.94
		AE	0.14	-	0.86	<0.001	-6.94
		CE	-	0.04	0.96	0.68	-6.26
		*** E**	**-**	**-**	**1.00**	**<0.76**	**-8.18**

[1] LRT < 3.85 equals no worse fit of the model (p<.05)

[2] Lower AIC values indicate a better model fit

* Asterisks indicate the best model fit

Table S9. Genetic modeling of Subcortical-Subcortical connectivity: full ACE model versus more parsimonious models.

Start Seed	ROI	model	A^2	C^2	E^2	LRT	AIC
Ventral Striatum	Hippocampus	ACE	0.37	0.00	0.63		266.12
		*** AE**	**0.37**	**-**	**0.63**	**<0.001**	**264.12**
		CE	-	0.32	0.68	0.74	264.87
		E	-	-	1.00	>6.95	269.81
	Thalamus	ACE	0.04	0.15	0.81		175.08
		AE	0.21	-	0.79	0.13	173.21
		*** CE**	**-**	**0.18**	**0.82**	**0.01**	**173.08**
		E	-	-	1.00	<2.10	173.18
	Amygdala	ACE	0.42	0.00	0.58		281.83
		*** AE**	0.42	-	0.58	**<0.001**	279.83
		CE	-	0.36	0.64	0.92	280.75
		E	-	-	1.00	>9.07	287.83
Amygdala	Hippocampus	ACE	0.32	0.00	0.68		277.93
		*** AE**	**0.32**	**-**	**0.68**	**<0.001**	**275.93**
		CE	-	0.19	0.81	2.24	278.18
		E	-	-	1.00	>2.27	278.44
	Thalamus	ACE	0.35	0.00	0.65		154.42
		*** AE**	0.35	-	0.65	**<0.001**	152.42
		CE	-	0.23	0.77	1.98	154.40
		E	-	-	1.00	>3.47	155.87

[1] LRT < 3.85 equals no worse fit of the model (p<.05)

[2] Lower AIC values indicate a better model fit

* Asterisks indicate the best model fit

References

Akaike, H., 1974. New Look at Statistical-Model Identification. Ieee Transactions on Automatic Control Ac19, 716-723.

Neale, M.C., Hunter, M.D., Pritikin, J.N., Zahery, M., Brick, T.R., Kirkpatrick, R.M., Estabrook, R., Bates, T.C., Maes, H.H., Boker, S.M., 2016. OpenMx 2.0: Extended Structural Equation and Statistical Modeling. Psychometrika 81, 535-549.

R Core Team, 2015. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.