

Data supplement to Georgiades et al. New insights into the endophenotypic status of cognition in bipolar disorder: genetic modelling study of twins and siblings. Br J Psychiatry doi: 10.1192/bjp.bp.115.167239

Table DS1 Associations † between neurocognitive function and different classes of medication

	Mood Stabilising			Antipsychotic			Antidepressant			Hypnotic		
	Coeff.	LL	UL	Coeff.	LL	UL	Coeff.	LL	UL	Coeff.	LL	UL
WASI Full-Scale IQ	-5.57	-9.89	-1.25	-5.44	-9.98	-0.89	1.43	-2.98	5.85	0.05	-4.58	4.68
CVLT Immediate Recall/Learning	-0.50	-5.23	4.22	-1.24	-5.51	3.02	-1.70	-6.65	3.26	-4.58	-11.15	1.98
CVLT Delayed Recall	-0.42	-1.95	1.11	-1.36	-2.83	0.10	0.56	-1.01	2.14	-1.14	-3.10	0.83
CVLT Delayed Recognition	-0.23	-0.61	0.14	-0.46	-0.80	-0.11	0.07	-0.32	0.47	-0.14	-0.66	0.37
PAL Total Trials	0.98	-1.40	3.36	0.45	-2.12	3.03	0.30	-1.93	2.53	-0.00	-2.23	2.22
PRM Percent Correct	-0.93	-5.73	3.87	-2.18	-7.56	3.20	-1.24	-5.75	3.26	0.94	-3.71	5.60
PRM Mean Correct Latency	-47.94	-353.95	258.07	-13.71	-289.41	262.00	303.84	-13.93	621.62	-124.78	-441.14	191.58
SWM Between Errors	1.82	-7.88	11.53	7.87	-1.42	17.17	0.88	-8.36	10.11	-1.21	-14.36	11.95
SWM Strategy	0.76	-1.89	3.41	1.46	-1.02	3.94	0.92	-1.52	3.37	1.72	-0.68	4.12
RVP A Prime	-0.01	-0.04	0.01	-0.01	-0.04	0.01	0.00	-0.02	0.02	-0.01	-0.04	0.01

Abbreviations: CVLT, California Verbal Learning Test; DZ, Dizygotic; IED, Intra-Extra Dimensional Set Shifting; MZ, Monozygotic; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; RVP, Rapid Visual Processing; SWM, Spatial Working Memory; WASI, Wechsler Abbreviated Scale of Intelligence

Coeff.: Regression Coefficient; LL/UL: Lower Limit/Upper Limit of 95% Confidence Interval

† Associations were examined in the extended study sample (n=331) using a series of simple linear regression models for clustered observations including medication class (1='present'; 0='absent') as the predictor and neuropsychological score as the outcome.

Statistically significant at the 0.05 or 0.01 level (to survive correction for multiple comparisons, the P-value should be ≤ 0.001).

Table DS2 Associations † between neurocognitive function and medication dosage

	Antipsychotic Dosage (Converted to Chlorpromazine Equivalents) ^a			Valproate Sodium Dosage ^b			Lithium Dosage ^c		
	Coeff	LL	UL	Coeff	LL	UL	Coeff	LL	UL
WASI Full-Scale IQ	-0.01	-0.03	-0.01	-0.00	-0.01	0.01	-0.01	-0.03	0.01
CVLT Immediate Recall/Learning	-0.00	-0.02	0.00	0.00	-0.01	0.01	0.00	-0.01	0.02
CVLT Delayed Recall	-0.00	-0.01	0.00	-0.00	-0.00	0.00	-0.01	-0.01	0.00
CVLT Delayed Recognition	-0.00	-0.00	0.00	0.00	-0.00	0.00	-0.00	-0.00	0.00
PAL Total Trials	0.01	-0.00	0.02	0.00	-0.00	0.00	-0.00	-0.01	0.00
PRM Percent Correct	-0.01	-0.04	0.01	0.00	-0.00	0.01	0.01	-0.02	0.04
PRM Mean Correct Latency	0.15	-0.96	1.26	-0.17	-0.71	0.47	0.18	-0.60	0.97
SWM Between Errors	0.01	-0.03	0.06	0.00	-0.02	0.02	-0.03	-0.08	0.02
SWM Strategy	0.00	-0.00	0.01	-0.00	-0.01	0.01	-0.01	-0.02	0.01
RVP A Prime	-0.01	-0.03	-0.01	-0.00	-0.00	0.00	0.00	-0.00	0.00

Abbreviations: CVLT, California Verbal Learning Test; DZ, Dizygotic; IED, Intra-Extra Dimensional Set Shifting; MZ, Monozygotic; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; RVP, Rapid Visual Processing; SWM, Spatial Working Memory; WASI, Wechsler Abbreviated Scale of Intelligence
Coeff.: Regression Coefficient; LL/UL: Lower Limit/Upper Limit of 95% Confidence Interval

† Associations with antipsychotic dosage, valproate sodium dosage and lithium dosage were examined in subgroups of 33, 20 and 26 participants with bipolar disorder, respectively, who received a daily dosage of the respective psychotropic drug; a series of simple linear regression models for clustered observations were used, including medication dosage as the predictor and neuropsychological variable as the outcome.

^a Mean (SD) antipsychotic dosage in chlorpromazine equivalents: 243.10 (179.62); range: 12.50 - 666.70 (based on 33 participants)

^b Mean (SD) valproate sodium dosage: 945.00 (417.35); range: 400.00 – 2000.00 (based on 20 participants)

^c Mean (SD) lithium dosage: 788.02 (243.84); range: 200.00 – 1400.00 (based on 26 participants)

Statistically significant at the 0.05 level (to survive correction for multiple comparisons, the P-value should be ≤0.002).

Table DS3 Daily psychotropic medication regimes of study participants with bipolar disorder (n=80)

Individual regimes of psychotropic medication in participants with bipolar disorder

1. Mirtazapine 30mg; Chlordiazepoxide 10mg; Temazepam 5mg
2. Citalopram 10mg
3. Citalopram 20mg
4. Fluoxetine 20mg; Dothiepin 50mg
5. Fluoxetine 20mg
6. Sertraline 50mg
7. Venlafaxine 220mg
8. Venlafaxine 150mg
9. Olanzapine 2.5mg
10. Amisulpride 600mg; Temazepam 10mg
11. Carbamazepine 800mg; Olanzapine 5mg
12. Flupentixol decanoate 30mg (at 3 week intervals)
13. Quetiapine 25mg daily
14. Quetiapine 600mg; Lorazepam 1mg; Zopiclone 7.5mg; Sertraline 150mg
15. Quetiapine 500
16. Quetiapine 300mg; Sertraline 20 mg
17. Risperidone (dose unknown); Fluoxetine 20mg
18. Quetiapine 50mg; Valproic Acid 600mg
19. Zopiclone 7.5mg; Lamotrigine 100mg
20. Divalproex Sodium 750mg; Citalopram 20mg; Zopiclone 7.5mg
21. Divalproex Sodium 1000mg; Citalopram 40mg
22. Divalproex sodium 1000mg
23. Divalproex sodium 1000mg; Olanzapine 2.5mg
24. Divalproex sodium 750mg; Risperidone 0.25mg; Bupropion 250mg
25. Divalproex sodium 750mg; Mirtazapine 30mg; Olanzapine 10mg
26. Divalproex sodium 500mg; Citalopram 40mg
27. Lamotrigine 15mg; Olanzapine x1 daily 15mg; Zopiclone 7.5mg
28. Lithium 1000mg
29. Lithium 200mg; Aripiprazole 30mg; Olanzapine 2.5mg (every other day)
30. Lithium 800mg; Risperidone 6mg
31. Lithium 600mg
32. Lithium 1000mg; Valproate Sodium 2000mg
33. Lithium 1200; Quetiapine 200mg
34. Lithium 600mg; Fluoxetine 20mg; Diazepam 5mg
35. Lithium 800mg
36. Lithium 1000mg; Valproate Sodium 1250mg
37. Lithium 1400mg; Lamotrigine 150mg; Quetiapine 325mg
38. Lithium 1000mg
39. Lithium 400mg; Thioridazine 250mg

Individual regime of psychotropic medication in participants with bipolar disorder (Table Cont.)

40. Lithium 400mg; Paroxetine 20mg
41. Lithium 800mg; Carbamazepine 400mg; Olanzapine 7.5mg
42. Lithium 600mg
43. Lithium 700mg; Aripiprazole 20mg; Escitalopram 10mg; Diazepam 15mg
44. Lithium 800mg
45. Lithium 800mg
46. Lithium 800mg; Olanzapine 10mg; Lorazepam (dose unknown); Zopiclone (dose unknown)
47. Lithium 800mg; Zolpidem Tartrate 10mg (twice a week)
48. Lithium 800mg; Olanzapine 10m; Flupenthixol 2mg
49. Lithium 800mg; Valproate Sodium 400mg; Thioridazine 400mg
50. Lithium 800mg; Paroxetine 30mg
51. Lithium 800mg; Sertraline 150mg
52. Lithium 800mg; Carbamazepine 1000mg; Methotrimeprazine 50mg; Lorazepam 2mg
53. Lithium (dose unknown); Thioridazine (dose unknown)
54. Valproate Sodium 600mg; Quetiapine 25mg; Sertraline 100mg; Diazepam 8mg; Temazepam 20mg
55. Valproate Sodium 1200mg; Carbamazepine 1000mg; Venlafaxine 300mg
56. Valproate Sodium 500mg
57. Valproate Sodium 800mg; Amisulpiride 400mg
58. Valproate Sodium 1400mg; Sulpiride 600mg
59. Divalproex sodium 1000mg; Amisulpride 200mg
60. Valproate Sodium 1600mg; Risperidone 3mg; Temazepam 10mg
61. Valproate Sodium 500mg; Trifluoperazine 4mg
62. Carbamazepine 300mg
63. Carbamazepine 200mg; Flupentixol decanoate 30mg (at 4-week intervals); Citalopram 30mg
64. Carbamazepine 600mg; Aripiprazole 30mg; Olanzapine 2.5mg (every other day); Clomipramine 50mg
65. Carbamazepine 400mg; Venlafaxine 75mg; Mirtazapine 15mg
66. Lamotrigine 50mg daily; Venlafaxine 75mg
67. None
68. None
69. None
70. None
71. None
72. None
73. None
74. None
75. None
76. None
77. Information missing
78. Information missing
79. Information missing
80. Information missing

Table DS4 Mean (SD) Neurocognitive Scores in 4 Study Groups ¹

Cognitive Variable	PARTICIPANTS FROM TWIN AND SIBLINGS PAIRS AFFECTED WITH BIPOLAR / SCHIZOAFFECTIVE DISORDER						CONTROL TWINS AND SIBLINGS (N=203)	
	CASES (N=80)		NONBD MEMBERS ‡				Mean	SD
	Mean	SD	MZ CO-TWINS (N=22)		DZ CO-TWINS AND SIBLINGS (N=26)			
			Mean	SD	Mean	SD		
WASI Full-Scale IQ	109.76	12.21	113.18	9.98	117.69	7.27	115.08	9.85
CVLT Immediate Recall/Learning	48.23	9.9	50.95	9.69	53.6	11.21	53.6	9.91
CVLT Delayed Recall	10.03	3.46	11.09	3.19	11.92	3.07	12.06	3.24
CVLT Delayed Recognition	2.78	0.84	3.06	0.75	3.23	0.82	3.26	0.74
IED Total Trials	94.7	29.93	93.64	32.39	81.38	30.21	91.85	45.40
PAL Total Trials	14.08	5.44	13.68	4.87	11.29	2.42	12.05	3.42
PRM Percent Correct	88.71	10.25	88.26	10.58	90.28	9.08	91.81	7.94
PRM Mean Correct Latency	2260.55	615.32	2136.19	680.37	1954.65	556.84	2075.55	519.58
SWM Between Errors	31.08	21.12	27.14	14.54	20.5	18.90	21.97	17.17
SWM Strategy	33.32	5.65	32.41	5.51	30.92	5.79	31.20	6.30
RVP A Prime	0.89	0.05	0.91	0.05	0.9	0.06	0.92	0.05
RVP B Double Prime	0.93	0.12	0.86	0.42	0.94	0.07	0.94	0.07

Abbreviations: CVLT, California Verbal Learning Test; DZ, Dizygotic; IED, Intra-Extra Dimensional Set Shifting; MZ, Monozygotic; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; RVP, Rapid Visual Processing; SWM, Spatial Working Memory; WASI, Wechsler Abbreviated Scale of Intelligence

¹To identify performance patterns indicative of potential endophenotypes (degree of neurocognitive impairment increasing with degree of genetic susceptibility to bipolar disorder), it was essential to divide the non-bipolar members of the discordant pairs (NonBD members) by zygosity.

‡ NonBD MEMBERS: Twins and siblings with no personal history of bipolar or psychotic-spectrum disorders, but with a co-twin or same-sex sibling with bipolar or schizoaffective disorder

Table DS5 Post-Hoc Comparisons † in Neurocognitive Function between Cases and Controls and between NonBD Co-Twins/Siblings and Controls

Cognitive Variable	CASES VERSUS CONTROLS		NONBD MZ Co-Twins ‡ VERSUS CONTROLS		NONBD DZ Co-Twins/Siblings ‡ VERSUS CONTROLS	
	<i>t</i> Score	<i>P</i> Value	<i>t</i> Score	<i>P</i> Value	<i>t</i> Score	<i>P</i> Value
WASI Full-Scale IQ	-3.21	0.002	-0.83	0.406	1.41	0.160
CVLT Immediate Recall/Learning	-2.91	0.004	-1.29	0.199	0.18	0.854
CVLT Delayed Recall	-3.56	<0.001	-1.38	0.171	-0.04	0.971
CVLT Delayed Recognition	-3.51	0.001	-1.21	0.227	0.00	0.998
PAL Total Trials	2.26	0.025	1.57	0.119	-1.51	0.134
SWM Between Errors	3.16	0.002	1.49	0.137	-0.27	0.791
SWM Strategy	2.60	0.010	0.94	0.347	-0.14	0.890
RVP A Prime	-3.89	<0.001	-0.46	0.646	-1.69	0.094

Abbreviations: CVLT, California Verbal Learning Test; DZ, Dizygotic; MZ, Monozygotic; PAL, Paired Associates Learning; RVP, Rapid Visual Processing; SWM, Spatial Working Memory; WASI, Wechsler Abbreviated Scale of Intelligence

† Planned post-hoc comparisons were performed between cases and controls and between NonBD co-twins/siblings and controls in neurocognitive variables that elicited statistically significant ($P < 0.05$) differences across groups in a series of regression analyses for clustered observations.

‡ NONBD Co-Twins/Siblings: Twins and siblings with no personal history of bipolar or psychotic-spectrum disorders, but with a co-twin or same-sex sibling with bipolar or schizoaffective disorder

Statistically significant ($P < 0.05$)

Table DS6 Within-Twin/Sibling Cross-Trait Correlations between Neurocognitive Measures and Bipolar Disorder

	R	LL	UL
WASI Full-Scale IQ	-0.20	-0.30	-0.09
CVLT Immediate Recall/Learning	-0.20	-0.30	-0.10
CVLT Delayed Recall	-0.23	-0.33	-0.12
CVLT Delayed Recognition	-0.21	-0.31	-0.10
IED Total Trials	0.05	-0.07	0.17
PAL Total Trials	0.16	0.06	0.26
PRM Percent Correct	-0.13	-0.23	-0.03
PRM Mean Correct Latency	0.13	0.03	0.23
SWM Between Errors	0.22	0.11	0.32
SWM Strategy	0.17	0.07	0.27
RVP A Prime	-0.24	-0.34	-0.13
RVP B Double Prime	0.02	-0.10	0.13

Abbreviations: CVLT, California Verbal Learning Test; IED, Intra-Extra Dimensional Set Shifting; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; RVP, Rapid Visual Processing; SWM, Spatial Working Memory; WASI, Wechsler Abbreviated Scale of Intelligence

R: Correlation Coefficient; LL/UL: Lower Limit/Upper Limit of Confidence Interval

Statistically significant correlation (the 95% Confidence Interval excludes 0)

Table DS7 Cross-Twin/Sibling Within-Trait Correlations and Cross-Twin/Sibling Cross-Trait Correlations †

Cognitive Variable	CROSS-TWIN/SIBLING WITHIN-TRAIT CORRELATIONS ^a						CROSS-TWIN/SIBLING CROSS-TRAIT CORRELATIONS ^b					
	MZ TWINS			DZ TWINS/SIBLINGS			MZ TWINS			DZ TWINS/SIBLINGS		
	R	LL	UL	R	LL	UL	R	LL	UL	R	LL	UL
WASI Full-Scale IQ	0.70	0.60	0.78	0.36	0.11	0.54	-0.22	-0.33	-0.11	0.02	-0.13	0.16
CVLT Immediate Recall/Learning	0.50	0.33	0.64	0.38	0.19	0.54	-0.16	-0.28	-0.05	-0.03	-0.17	0.11
CVLT Delayed Recall	0.55	0.39	0.67	0.18	-0.03	0.37	-0.18	-0.29	-0.07	-0.05	-0.19	0.10
CVLT Delayed Recognition	0.49	0.30	0.62	0.30	0.10	0.47	-0.17	-0.28	-0.06	-0.04	-0.19	0.10
PAL Total Trials	0.39	0.23	0.52	0.41	0.09	0.60	0.18	0.07	0.29	-0.06	-0.20	0.09
PRM Percent Correct	0.37	0.20	0.52	0.13	-0.14	0.36	-0.15	-0.26	-0.04	-0.08	-0.23	0.07
PRM Mean Correct Latency	0.51	0.35	0.63	0.43	0.21	0.59	0.04	-0.07	0.15	-0.08	-0.22	0.06
SWM Between Errors	0.61	0.47	0.72	0.29	0.07	0.47	0.17	0.05	0.28	0.02	-0.13	0.16
SWM Strategy	0.24	0.04	0.41	0.35	0.14	0.53	0.16	0.03	0.27	0.02	-0.12	0.17
RVP A Prime	0.54	0.37	0.66	0.14	-0.11	0.36	-0.14	-0.25	-0.03	-0.19	-0.33	-0.04

Abbreviations: CVLT, California Verbal Learning Test; DZ, Dizygotic; IED, Intra-Extra Dimensional Set Shifting; MZ, Monozygotic; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; RVP, Rapid Visual Processing; SWM, Spatial Working Memory; WASI, Wechsler Abbreviated Scale of Intelligence

R: Correlation Coefficient; LL/UL: Lower Limit/Upper Limit of 95% Confidence Interval

† Only results for neurocognitive measures that showed statistically significant Within-Twin/Sibling Cross-Trait Correlations with Bipolar Disorder (Table DS1) are reported.

^a Correlation of twin/sibling 1 with co-twin/sibling 2 on each neurocognitive measure. The cross-twin/sibling within-trait correlation for bipolar disorder was constrained to 0.88 in MZ twins and 0.44 in DZ twins/siblings based on the literature and a 1% prevalence.

^b Correlation of neurocognitive score of twin/sibling 1 with genetic liability to bipolar disorder of co-twin/sibling 2.

Statistically significant correlation (the 95% Confidence Interval excludes 0)

Table DS8 Additive Genetic, Common Environmental and Unique Environmental Estimates of the Full ACE Genetic Model for Neurocognitive Endophenotypes after Co-varying for Affective Symptoms † ^a

	h^2	LL	UL	c^2	LL	UL	E^2	LL	UL
WASI Full-Scale IQ	0.50	0.16	0.74	0.17	0.00	0.49	0.33	0.24	0.45
CVLT Delayed Recall	0.51	0.18	0.65	0.01	0.00	0.26	0.48	0.35	0.65
CVLT Delayed Recognition	0.44	0.00	0.63	0.05	0.00	0.41	0.51	0.38	0.69
PAL Total Trials	0.13	0.02	0.43	0.29	0.01	0.44	0.58	0.47	0.71
SWM Between Errors	0.52	0.12	0.70	0.07	0.00	0.40	0.40	0.29	0.56

Abbreviations: CVLT, California Verbal Learning Test; IED, Intra-Extra Dimensional Set Shifting; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; RVP, Rapid Visual Processing; SWM, Spatial Working Memory; WASI, Wechsler Abbreviated Scale of Intelligence
† Only results for neurocognitive measures that showed statistically significant Within-Twin/Sibling Cross-Trait Correlations with Bipolar Disorder (Table DS1) are reported.

^a h^2 , c^2 , and e^2 indicate heritability, shared environmental, and unique environmental effects, respectively. Parameters for bipolar disorder are fixed based on a prevalence of 1% and the following genetic model: $h^2=0.81$, $c^2=0.07$, $e^2=0.12$.

Statistically significant point estimate (the 95% Confidence Interval excludes 0)

Table DS9 Phenotypic Correlations between Bipolar Disorder and Neurocognitive Measures, the Decomposed Sources of These Correlations as Predicted by the Full ACE Models, and A, C and E Correlation Estimates after Co-varying for Affective Symptoms †^a

	r_{ph-a}	r_{ph-c}	r_{ph-e}	r_{ph}	LL	UL	r_g	LL	UL	r_c	LL	UL	r_e	LL	UL
WASI Full-Scale IQ	-0.29	0.11	0.06	-0.12	-0.22	-0.01	-0.45	-0.99	-0.13	0.99	0.57	1.00	0.29	0.01	0.54
CVLT Delayed Recall	-0.17	0.02	-0.01	-0.16	-0.26	-0.05	-0.26	-0.74	0.02	1.00	-0.99	1.00	-0.05	-0.33	0.26
CVLT Delayed Recognition	-0.20	0.06	-0.01	-0.15	-0.26	-0.05	-0.34	-0.99	0.13	0.99	-0.99	0.93	-0.04	-0.33	0.24
PAL Total Trials	0.32	-0.14	-0.01	0.17	0.07	0.26	1.00	0.34	1.00	-0.26	-1.00	0.18	-0.03	-0.28	0.20
SWM Between Errors	0.19	-0.07	0.01	0.13	0.03	0.23	0.30	-0.08	0.89	-1.00	-1.00	0.60	0.05	-0.23	0.34

Abbreviations: CVLT, California Verbal Learning Test; IED, Intra-Extra Dimensional Set Shifting; PAL, Paired Associates Learning; PRM, Pattern Recognition Memory; RVP, Rapid Visual Processing; SWM, Spatial Working Memory; WASI, Wechsler Abbreviated Scale of Intelligence

† Only neurocognitive measures that showed statistically significant Within-Twin/Sibling Cross-Trait Correlations with Bipolar Disorder (Table DS1) were entered in this analysis.

^a r_{ph-a} , r_{ph-c} , and r_{ph-e} indicate the phenotypic correlations due to additive genetic, shared environmental, and unique environmental influences, respectively; r_{ph} indicates the total phenotypic correlation; r_g , r_c , and r_e indicate the genetic, shared environmental, and unique environmental correlations, respectively. The fixed genetic model for bipolar disorder used the following parameters: $h^2=0.81$, $c^2=0.07$, $e^2=0.12$.

Statistically significant point estimate (the 95% Confidence Interval excludes 0)