

Data supplement

Table DS1 Mean diffusivity (a) and fractional anisotropy (b) for the bipolar I group and their controls individually matched for age, gender and performance on National Adult Reading Test^a

(a)			
Mean diffusivity 10^{-6} mm ² /sec	Mean (s.d.)		2-tailed <i>P</i> (<i>U</i> -test)
	Bipolar I group, <i>n</i> = 20	Control group, <i>n</i> = 20	Regions of interest
Corpus callosum (total)	878 (45)	853 (39)	0.14
Corpus callosum (body)	1004 (138)	968 (89)	0.67
Left anterior	864 (62)	853 (60)	0.45
Right anterior	870 (64)	847 (54)	0.17
Left posterior	832 (51)	807 (78)	0.05*
Right posterior	831 (71)	784 (75)	0.02*
Left prefrontal	781 (28)	758 (22)	0.01*
Right prefrontal	770 (22)	747 (24)	0.002*
Left periventricular (1)	909 (54)	873 (34)	0.03*
Left periventricular (2)	861 (92)	793 (45)	0.01*
Right periventricular (1)	845 (33)	828 (34)	0.23
Right periventricular (2)	779 (31)	748 (30)	0.01*
Left central	717 (18)	711 (19)	0.45
Right central	709 (13)	704 (20)	0.45
Left occipital	738 (23)	724 (29)	0.06
Right occipital	745 (25)	728 (21)	0.04
(b)			
Fractional anisotropy $\times 10^{-4}$	Mean (s.d.)		2-tailed <i>P</i> (<i>U</i> -test)
	Bipolar I group, <i>n</i> = 20	Control group, <i>n</i> = 20	Regions of interest
Corpus callosum (total)	6787 (430)	7181 (436)	0.007*
Corpus callosum (body)	5950 (613)	6447 (590)	0.02*
Left anterior	6884 (509)	7155 (543)	0.10
Right anterior	6717 (535)	7142 (477)	0.01*
Left posterior	7327 (733)	7667 (686)	0.08
Right posterior	7101 (746)	7551 (637)	0.03*
Left prefrontal	3094 (229)	3185 (331)	0.28
Right prefrontal	3147 (267)	3198 (242)	0.40
Left periventricular (1)	3136 (696)	3137 (595)	0.69
Left periventricular (2)	3452 (674)	3530 (719)	1.00
Right periventricular (1)	3283 (579)	2989 (670)	0.13
Right periventricular (2)	3481 (829)	3235 (685)	0.26
Left central	4285 (433)	4479 (494)	0.20
Right central	4341 (369)	4470 (434)	0.52
Left occipital	3836 (435)	4077 (440)	0.06
Right occipital	3908 (355)	3928 (395)	0.81
<p>a. Statistical analysis yielded broadly similar results to the main comparison. For the sign test: mean diffusivity in the bipolar I group exceeded that of controls at all 15 independently measured sites (sign test ($P < 0.001$; two tailed). Fractional anisotropy in controls exceeded that in individuals in the bipolar I group at 13 of the 15 sites (sign test: $P = 0.008$; two tailed). For the individual between-group comparisons (<i>U</i>-test) the patterns of significant difference were broadly similar, except fewer of the differences in mean diffusivity and fractional anisotropy in the callosal regions reached statistical significance.</p> <p>*$P < 0.05$.</p>			

Table DS2 Mean diffusivity (a) and fractional anisotropy (b) subgroup analyses for participants in the bipolar group defined by past history of illicit substance use

(a)					
Mean diffusivity $\times 10^{-6}$ mm ² /sec	Bipolar group any previous substance use, <i>n</i> = 14 Mean (s.d.)	2-tailed <i>P</i> (<i>U</i> -test) Regions of interest	Bipolar group no previous substance use, <i>n</i> = 14 Mean (s.d.)	Controls for bipolar group no previous substance use, <i>n</i> = 14 Mean (s.d.)	2-tailed <i>P</i> (<i>U</i> -test) Regions of interest
Corpus callosum (total)	885 (46)	0.29	864 (55)	840 (40)	0.17
Corpus callosum (body)	1029 (159)	0.23	947 (87)	946 (66)	0.65
Left anterior	857 (58)	0.93	851 (61)	841 (49)	0.61
Right anterior	870 (63)	0.65	858 (62)	829 (43)	0.18
Left posterior	847 (54)	0.10	811 (67)	797 (72)	0.38
Right posterior	855 (90)	0.38	825 (90)	769 (60)	0.08
Left prefrontal	785 (19)	0.08	768 (36)	757 (28)	0.36
Right prefrontal	777 (19)	0.04*	756 (34)	744 (32)	0.20
Left periventricular (1)	930 (38)	0.04*	891 (56)	881 (32)	0.75
Left periventricular (2)	893 (81)	0.17	858 (93)	802 (47)	0.15
Right periventricular (1)	866 (41)	0.08	841 (44)	825 (36)	0.65
Right periventricular (2)	804 (38)	0.02*	770 (40)	746 (40)	0.15
Left central	724 (15)	0.04	709 (22)	709 (18)	0.75
Right central	714 (14)	0.03	700 (17)	700 (16)	0.89
Left occipital	738 (22)	0.22	727 (25)	714 (26)	0.17
Right occipital	745 (26)	0.13	732 (25)	724 (26)	0.31
(b)					
Fractional anisotropy $\times 10^{-4}$	Bipolar group any previous substance use, <i>n</i> = 14 Mean (s.d.)	2-tailed <i>P</i> (<i>U</i> -test) Regions of interest	Bipolar group no previous substance use, <i>n</i> = 14 Mean (s.d.)	Controls for bipolar group no previous substance use, <i>n</i> = 14 Mean (s.d.)	2-tailed <i>P</i> (<i>U</i> -test) Regions of interest
Corpus callosum (total)	6777 (446)	0.55	6677 (452)	7227 (326)	0.002*
Corpus callosum (body)	5879 (664)	0.55	5963 (581)	6469 (569)	0.048
Left anterior	6941 (501)	0.61	6896 (481)	7184 (445)	0.14
Right anterior	6771 (609)	0.41	6665 (472)	7277 (435)	0.002*
Left posterior	7262 (714)	0.75	7167 (742)	7722 (511)	0.06
Right posterior	6922 (853)	0.61	6987 (903)	7671 (346)	0.02*
Left prefrontal	3169 (271)	0.12	3023 (192)	3196 (277)	0.06
Right prefrontal	3215 (207)	0.07	3070 (277)	3233 (238)	0.08
Left periventricular (1)	3140 (495)	0.71	3043 (755)	3164 (581)	0.65
Left periventricular (2)	3519 (528)	0.75	3498 (738)	3670 (644)	0.58
Right periventricular (1)	3209 (322)	0.96	3189 (853)	3335 (721)	0.75
Right periventricular (2)	3453 (599)	0.36	3453 (1066)	3569 (820)	0.90
Left central	4276 (477)	0.85	4328 (306)	4390 (403)	0.71
Right central	4192 (462)	0.18	4433 (259)	4416 (399)	0.55
Left occipital	3791 (487)	0.25	3924 (239)	4129 (363)	0.11
Right occipital	3862 (442)	0.68	3922 (267)	4147 (352)	0.12

This table presents two subgroup comparisons. First, data from patients with a history of substance use were compared with those of patients with no such history. Mean diffusivity was significantly increased in the right prefrontal region and in two periventricular regions in patients with a positive history of substance use (*U*-test). Second, patients with no history of substance use were compared with their control group. Using the sign test to examine the data-sets, mean diffusivity was greater at 13 sites and fractional anisotropy was reduced at 14 sites (*P* < 0.01, two-tailed, for both comparisons). Comparing individual sites (*U*-test), there were significant decreases in fractional anisotropy at some callosal sites and prefrontal fractional anisotropy decreases approached significance. However, the pattern of increased prefrontal and periventricular mean diffusivity evident in the main group comparison (Table 1) was not found.
**P* < 0.05.

Table DS3 Mean diffusivity (a) and fractional anisotropy (b) subgroup analyses for participants with bipolar disorder defined by lithium treatment^a

(a)						
Mean diffusivity $\times 10^{-6}$ mm ² /sec	Bipolar participants on lithium, <i>n</i> = 16 Mean (s.d.)	Controls for bipolar participants on lithium, <i>n</i> = 16 Mean (s.d.)	2-tailed <i>P</i> (<i>U</i> -test) Regions of interest	Bipolar participant not on lithium, <i>n</i> = 12 Mean (s.d.)	Controls for bipolar participants not on lithium, <i>n</i> = 12 Mean (s.d.)	2-tailed <i>P</i> (<i>U</i> -test) Regions of interest
Corpus callosum (total)	870 (57)	852 (36)	0.40	881 (44)	838 (45)	0.05*
Corpus callosum (body)	996 (142)	945 (97)	0.21	977 (124)	964 (75)	0.95
Left anterior	851 (70)	850 (56)	0.90	858 (41)	825 (57)	0.07
Right anterior	854 (68)	839 (56)	0.52	877 (52)	827 (46)	0.02*
Left posterior	823 (61)	820 (81)	0.52	837 (66)	784 (59)	0.04*
Right posterior	830 (100)	801 (81)	0.43	854 (76)	763 (52)	0.006*
Left prefrontal	774 (31)	760 (27)	0.14	779 (28)	754 (24)	0.05*
Right prefrontal	762 (29)	752 (30)	0.20	773 (29)	739 (27)	0.01*
Left periventricular (1)	899 (60)	870 (49)	0.14	925 (32)	890 (36)	0.04*
Left periventricular (2)	855 (97)	795 (48)	0.08	902 (68)	806 (46)	0.001*
Right periventricular (1)	840 (38)	836 (52)	0.68	871 (47)	818 (39)	0.02*
Right periventricular (2)	774 (33)	754 (50)	0.10	804 (48)	741 (36)	0.004*
Left central	714 (22)	709 (17)	0.37	720 (17)	707 (22)	0.17
Right central	705 (18)	704 (17)	0.68	710 (15)	699 (22)	0.39
Left occipital	734 (23)	724 (30)	0.23	730 (26)	713 (27)	0.12
Right occipital	741 (26)	732 (27)	0.27	735 (26)	726 (22)	0.60
(b)						
Fractional anisotropy $\times 10^{-4}$	Bipolar participants on lithium, <i>n</i> = 16 Mean (s.d.)	Controls for bipolar participants on lithium, <i>n</i> = 16 Mean (s.d.)	2-tailed <i>P</i> (<i>U</i> -test) Regions of interest	Bipolar participant not on lithium, <i>n</i> = 12 Mean (s.d.)	Controls for bipolar participants not on lithium, <i>n</i> = 12 Mean (s.d.)	2-tailed <i>P</i> (<i>U</i> -test) Regions of interest
Corpus callosum (total)	6792 (357)	7277 (332)	0.001*	6640 (544)	7110 (481)	0.07
Corpus callosum (body)	5956 (599)	6575 (558)	0.01*	5874 (657)	6341 (581)	0.13
Left anterior	6923 (530)	7320 (473)	0.03*	6911 (434)	7054 (512)	0.56
Right anterior	6775 (532)	7274 (379)	0.007*	6642 (559)	7103 (578)	0.12
Left posterior	7316 (694)	7701 (631)	0.06	7079 (754)	7672 (640)	0.07
Right posterior	7088 (667)	7606 (619)	0.007*	6776 (1077)	7584 (483)	0.07
Left prefrontal	3133 (234)	3215 (259)	0.29	3047 (254)	3203 (350)	0.18
Right prefrontal	3141 (289)	3221 (187)	0.24	3145 (202)	3215 (292)	0.45
Left periventricular (1)	3044 (757)	3183 (632)	0.50	3155 (424)	3257 (566)	0.60
Left periventricular (2)	3430 (747)	3494 (684)	0.91	3613 (438)	3779 (713)	0.73
Right periventricular (1)	3103 (699)	2972 (568)	0.62	3327 (536)	3436 (796)	0.86
Right periventricular (2)	3323 (1003)	3310 (660)	0.71	3626 (581)	3549 (748)	0.77
Left central	4391 (373)	4498 (402)	0.35	4183 (406)	4356 (492)	0.60
Right central	4355 (390)	4462 (378)	0.85	4257 (394)	4405 (492)	0.69
Left occipital	3912 (308)	4163 (462)	0.02*	3784 (468)	3881 (218)	0.73
Right occipital	4001 (302)	4072 (439)	0.55	3745 (392)	3885 (317)	0.42

a. Comparing data-sets from the lithium and non-lithium treated bipolar subgroups directly, mean diffusivity in the non-lithium treated group was higher than in the lithium group at 12 of the 15 sites (sign test: *P*=0.04; two tailed). Fractional anisotropy was lower at 10 of the 15 sites (sign test: *P*=0.30; two tailed). Comparing individual regions of interest directly, no significant differences were found in diffusion parameters (these data are not shown in the table). When the non-lithium-treated bipolar group (*n* = 12) compared with their individually matched controls, the pattern of increased prefrontal, periventricular and callosal mean diffusivity previously observed in the main group comparison persisted. This pattern was not seen in the lithium-treated group in comparison with their controls (*n* = 16). For fractional anisotropy, the pattern of significant results did not differ markedly between treatment groups.
**P* < 0.05.