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SUPPLEMENTARY MATERIAL

Supplementary Methods

Intracortical Myelin (ICM) Image Processing Methods

Image processing was performed predominantly in MIPAV v7.0.1 software (mipav.cit.nih.gov) using the JIST v3.0 (www.nitrc.org/projects/jist, TOADS-CRUISE vR3c (www.nitrc.org/projects/toads-cruise), and CBS High-Res Brain Processing Tools Version v3.0 (www.nitrc.org/projects/cbs-tools) plug-ins, and Amira v5.2 software (Visage Imaging). All processing was performed on the ratio image.

First, a mask of the cerebrum created from the SPECTRE 2010 algorithm [1] in MIPAV, was used to skull strip the ratio image. The skull-stripped ratio image was used as input to the Multiple Object Geometric Deformable Model (MGDM) Multi-contrast Brain Segmentation algorithm [2, 3] in MIPAV to generate initial probabilistic labels for tissue classes for each hemisphere of the brain. The probability labels generated for cerebral gray matter (GM) and white matter (WM) were used as the input to the CRUISE algorithm [4] to generate smoothed, topologically correct labels for the cerebrum. The CRUISE algorithm was performed in each hemisphere separately.

Subcortical structures and ventricles (as identified by the MGDM algorithm) were then removed from the labels for the left and right cerebrums and the labels remaining were combined. At this point, all GM segmentations were inspected and manual edits were made to replace missing cortex and to remove remaining dura mater arising from potential errors in the MGDM and CRUISE algorithms to ensure an accurate pial surface. This label for the entire cerebrum without the subcortical structures was then used to mask the Ratio image such that it only contained the cerebral cortex and underlying major white matter tracts.

The manually corrected, cerebrum-masked Ratio image was next segmented into two main tissue classes: WM and GM, taking into account lightly and heavily myelinated components of GM [5] using the FANTASM algorithm [6] in MIPAV, as we found that this yields a more accurate WM label for our ICM analysis than the output from CRUISE. The hemispheres were segmented together to avoid potential hemispheric bias, such that the algorithm used the entire cerebrum for its classification. Following segmentations,

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labels for each tissue class were split back into left and right hemispheres for subsequent processing. The labels near the GM/WM-boundary were morphologically processed to remove all WM tissue not connected to the largest WM mass.

The corrected GM labels from CRUISE representing the pial surface, and WM labels from FANTASM representing the GM/WM boundary surface were used as inputs to a volume-preserving cortical depth model to generate an intracortical surface at the ½ cortical depth to sample the T_1-weighted image signal [7, 8] (**Figure S1)**. Each subject's ½ depth surface was registered to the ½ depth surface generated from the MNI-152 atlas using a multi-contrast multi-scale surface registration approach [9]. In the analysis, the signal was first sampled onto the individual subject's surface, which was then deformed to be in register with the MNI-152 equivalent surface.

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Figure S1. Half depth metric visualization.

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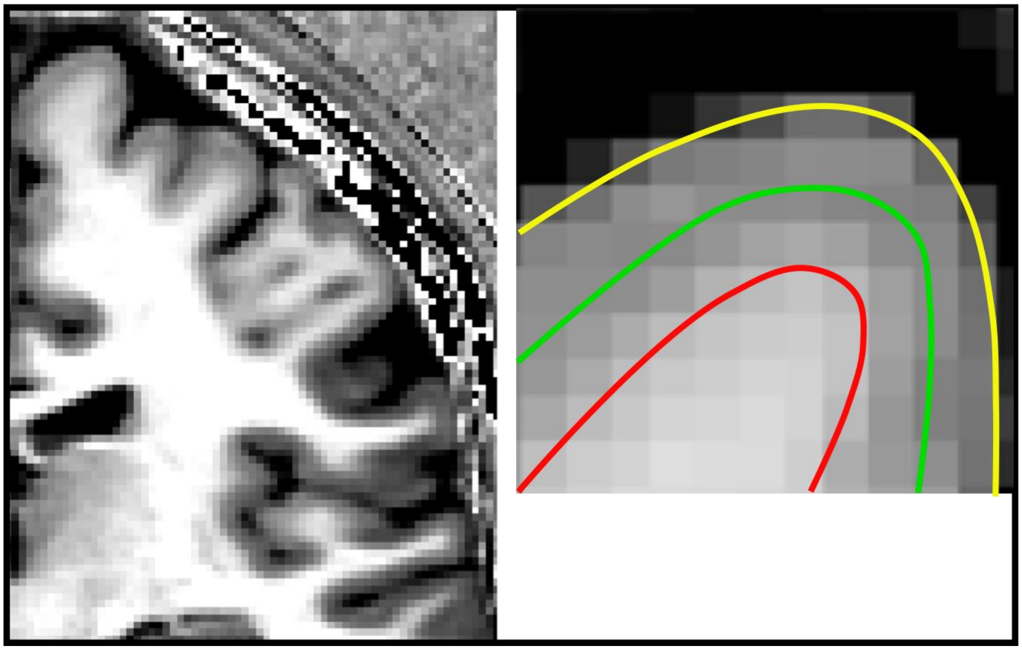

Left: T_1-weighted image with high intracortical contrast.
Right: Illustration of the half depth signal surface, which is calculated from the pial and white matter surfaces.

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Table S1. Significance of the Age*DX^2 term with and without bootstrapping (10 000 iterations, with replacement).

Cortical Region	Left Hemisphere				Right Hemisphere			
	2.5% CI	97.5% CI	Significance of Age*DX^2 with bootstrapping	Significance of Age*DX^2 without bootstrapping	2.5% CI	97.5% CI	Significance of Age*DX^2 with bootstrapping	Significance of Age*DX^2 without bootstrapping
Caudal Medial Visual Cortex	-0.000078	0.000001	NS	NS	-0.000064	0.000012	NS	NS
Lateral Visual Cortex	-0.000065	0.000007	NS	NS	-0.000078	-0.000007	*	*
Superior Visual Cortex	-0.000071	-0.000005	*	NS	-0.000071	-0.000001	*	NS
Cuneus	-0.000071	0.000006	NS	NS	-0.000071	0.000000	NS	NS
Caudal Middle Temporal Cortex	-0.000072	-0.000002	*	NS	-0.000083	-0.000011	*	*
Caudal Superior Temporal Cortex	-0.000087	-0.000005	*	*	-0.000085	-0.000004	*	*
Rostral Middle	-0.000076	0.000007	NS	NS	-0.000082	0.000002	NS	*

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Temporal Cortex								
Ventral Inferior Parietal Cortex	-0.000079	-0.000005	*	*	-0.000082	-0.000003	*	*
Dorsal Inferior Parietal Cortex	-0.000071	-0.000002	*	NS	-0.000080	-0.000010	*	*
Superior Parietal Cortex	-0.000073	0.000000	NS	NS	-0.000070	0.000001	NS	NS
Medial Superior Parietal Cortex	-0.000074	-0.000005	*	*	-0.000079	-0.000009	*	*
Medial Parietal Cortex	-0.000082	0.000006	NS	NS	-0.000081	0.000003	NS	NS
Posterior Cingulate Cortex	-0.000092	0.000005	NS	NS	-0.000083	0.000017	NS	NS
Ventral Somatosensory Cortex	-0.000077	0.000003	NS	NS	-0.000089	-0.000007	*	*
Dorsolateral Somatosensory Cortex	-0.000069	0.000003	NS	NS	-0.000083	-0.000008	*	*

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Dorsomedial Somatosensory Cortex	-0.000079	-0.000006	*	*	-0.000062	0.000011	NS	NS
Ventral Motor Cortex	-0.000080	0.000003	NS	NS	-0.000089	-0.000006	*	*
Dorsolateral Motor Cortex	-0.000099	-0.000019	*	*	-0.000108	-0.000023	*	*
Dorsomedial Motor Cortex	-0.000102	-0.000018	*	*	-0.000099	-0.000010	*	*
Rostral Ventral Premotor Cortex	-0.000091	-0.000006	*	*	-0.000088	0.000001	NS	NS
Dorsolateral Premotor Cortex	-0.000104	-0.000024	*	*	-0.000096	-0.000012	*	*
Dorsomedial Premotor Cortex	-0.000099	-0.000011	*	*	-0.000106	-0.000017	*	*
Caudal Dorsolateral Prefrontal Cortex	-0.000087	-0.000007	*	*	-0.000096	-0.000008	*	*
Caudal Dorsomedial	-0.000103	-0.000025	*	*	-0.000089	-0.000005	*	*

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Prefrontal Cortex								
Mid Cingulate Cortex	-0.000087	0.000009	NS	NS	-0.000094	0.000012	NS	NS
Rostral Ventrolateral Prefrontal Cortex	-0.000086	0.000000	NS	NS	-0.000084	-0.000005	*	*
Rostral Dorsolateral Inferior Prefrontal Cortex	-0.000071	0.000008	NS	NS	-0.000098	-0.000020	*	*
Rostral Dorsolateral Superior Prefrontal Cortex	-0.000073	0.000000	NS	NS	-0.000086	-0.000011	*	*
Rostral Dorsal Prefrontal Cortex	-0.000085	-0.000009	*	*	-0.000071	-0.000001	*	NS
Rostral Medial Prefrontal	-0.000089	-0.000011	*	*	-0.000072	0.000007	NS	NS

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Cortex								
Ventrolateral Orbito Frontal Cortex	-0.000095	-0.000005	*	*	-0.000091	0.000002	NS	NS
Ventral Orbito Frontal Cortex	-0.000076	0.000003	NS	NS	-0.000081	-0.000005	*	*
Ventromedial Orbito Frontal Cortex	-0.000071	0.000012	NS	NS	-0.000074	-0.000001	*	NS
Ventromedial Prefrontal Cortex	-0.000068	0.000007	NS	NS	-0.000062	0.000010	NS	NS
Anterior Cingulate Cortex	-0.000071	0.000013	NS	NS	-0.000086	0.000025	NS	NS

CI: Confidence Interval

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Table S2. Partial correlations with age of onset (years) and duration of illness (years) in BD subjects (N=45).

Cortical region	Left hemisphere			Right hemisphere		
	Partial R	P, uncorrected	P, corrected$^{\mu}$	Partial R	P, uncorrected	P, corrected$^{\mu}$
Age of onset						
Superior parietal cortex	0.17	0.16	1	0.25	0.04*	1
Medial parietal cortex	0.27	0.02*	1	0.34	0.006**	0.38
Dorsomedial somatosensory cortex	0.26	0.03*	1	0.20	0.10	1
Dorsolateral motor cortex	0.23	0.06	1	0.25	0.04*	1
Dorsomedial motor cortex	0.22	0.07	1	0.26	0.03*	1
Rostral ventral premotor cortex	0.15	0.21	1	0.26	0.03*	1
Dorsolateral premotor	0.26	0.03*	1	0.22	0.07	1

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cortex						
Dorsomedial premotor cortex	0.36	0.002**	0.17	0.28	0.02*	1
Caudal dorsolateral prefrontal cortex	0.29	0.02*	1	0.25	0.04*	1
Caudal dorsomedial prefrontal cortex	0.30	0.01	0.72	0.28	0.02*	1
Rostral ventrolateral prefrontal cortex	0.28	0.02*	1	0.24	0.049*	1
Rostral dorsolateral superior prefrontal cortex	0.25	0.04*	1	0.21	0.08	1
Rostral dorsal prefrontal cortex	0.27	0.03*	1	0.24	0.046*	1
Rostral	0.36	0.002**	0.14	0.32	0.007**	0.48

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medial prefrontal cortex						
Duration of illness (years)						
Caudal medial visual cortex	-0.33	0.005**	0.33	-0.31	0.009**	0.56
Lateral visual cortex	-0.26	0.03	1	-0.32	0.007**	0.43
Superior visual cortex	-0.26	0.03	1	-0.19	0.11	1
Cuneus	-0.33	0.006**	0.38	-0.26	0.03*	1
Caudal superior temporal cortex	-0.31	0.01*	0.60	-0.30	0.01	0.63
Dorsal inferior parietal cortex	-0.16	0.19	1	-0.25	0.03*	1
Superior parietal cortex	-0.21	0..09	1	-0.29	0.02*	0.84
Medial superior parietal cortex	-0.27	0.02*	1	-0.28	002*	0.85

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Medial parietal cortex	-0.33	0.005**	0.36	-0.37	0.002**	0.12
Posterior cingulate cortex	-0.33	0.005*	0.37	-0.30	0.01*	0.71
Dorsomedial somatosensory cortex	-0.30	0.01*	0.70	-0.18	0.13	1
Ventral motor cortex	-0.23	0.05	1	-0.25	0.04*	1
Dorsolateral motor cortex	-0.23	0.06	1	-030	0.01*	0.73
Dorsomedial motor cortex	-0.28	0.02*	0.87	-0.23	0.06	1
Rostral ventral premotor cortex	-0.24	0.049*	1	-0.23	0.06	1
Dorsolateral premotor cortex	-0.27	0.02*	1	-0.22	0.07	1
Dorsomedial premotor cortex	-0.29	0.01*	0.75	-0.27	0.03*	1
Caudal	-0.29	0.01*	0.75	-0.20	0.09	1

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dorsomedial prefrontal cortex						
Midcingulate cortex	-0.33	0.005**	0.37	-0.27	0.02*	1
Rostral ventrolateral prefrontal cortex	-0.24	0.04	1	-0.18	0.13	1
Rostral dorsolateral inferior prefrontal cortex	-0.25	0.04*	1	-0.29	0.02*	0.84
Rostral medial prefrontal cortex	-0.29	0.02*	0.85	-0.22	0.06	1
Ventrolateral orbitofrontal cortex	-0.24	0.048*	1	-0.20	0.09	1
Anterior cingulate cortex	-0.33	0.005**	0.33	-0.31	0.008**	0.53

µ p values corrected using Bonferroni correction.

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Table S3. Partial correlations with number of mood episodes in BD subjects (N=45).

Cortical Region	Left hemisphere			Right hemisphere		
	Partial R	P, uncorrected	P, corrected[µ]	Partial R	P, uncorrected	P, corrected[µ]
Number of manic episodes						
Rostral middle temporal cortex	-0.17	0.15	1	-0.24	0.047*	1
Number of hypomanic episodes						
Posterior cingulate cortex	-0.27	0.03*	1	-0.31	0.009**	0.67
Anterior cingulate cortex	-0.16	0.17	1	-0.27	0.02*	1

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Number of mixed episodes						
Lateral visual cortex	0.08	0.51	1	0.26	0.03*	1
Superior visual cortex	0.09	0.46	1	0.27	0.03*	1
Caudal middle temporal cortex	0.20	0.09	1	0.31	0.009**	1
Rostral middle temporal cortex	0.29	0.01*	1	0.19	0.10	1
Ventral inferior parietal cortex	0.12	0.31	1	0.27	0.02*	1
Dorsal inferior parietal cortex	0.10	0.40	1	0.26	0.03*	1
Superior parietal cortex	0.04	0.77	1	0.24	0.045*	1
Ventral somatosensory cortex	0.0009	0.99	1	0.29	0.02*	1

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Dorsolateral somatosensory cortex	0.18	0.14	1	0.26	0.03*	1
Rostral dorsolateral inferior parietal cortex	0.22	0.06	1	0.26	0.03*	1
Ventral orbitofrontal cortex	0.33	0.005**	1	0.29	0.01*	1
Ventromedial orbitofrontal cortex	0.37	0.001**	1	0.15	0.21	1
Ventromedial prefrontal cortex	0.42	0.0003***	0.04*	0.18	0.13	1

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µ p values corrected using Bonferroni correction.

Table S4. Partial correlations with medication use in BD subjects (N=45).

Cortical Region	Left hemisphere			Right hemisphere		
	Partial R	P, uncorrected	P, correctedµ	Partial R	P, uncorrected	P, correctedµ
Anticonvulsant use						
Rostral dorsolateral inferior prefrontal cortex	-0.24	0.04*	1	-0.09	0.46	1
Rostral dorsal prefrontal cortex	-0.25	0.04*	1	-0.25	0.03*	1
Ventromedial	-0.12	0.34	1	-0.25	0.04*	1

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orbitofrontal cortex						
Antipsychotic use						
Caudal medial visual cortex	-0.33	0.005**	1	-0.16	0.18	1
Cuneus	-0.23	0.06	1	-0.30	0.01*	1
Medial superior parietal cortex	-0.25	0.04*	1	-0.27	0.02*	1
Medial parietal cortex	-0.14	0.24	1	-0.25	0.04*	1
Posterior cingulate cortex	-0.29	0.02*	1	-0.26	0.03*	1
Dorsolateral motor cortex	-0.27	0.02*	1	-0.25	0.04*	1
Midcingulate cortex	-0.26	0.03*	1	-0.32	0.008**	1
Anterior cingulate cortex	-0.10	0.39	1	-0.35	0.003**	1
Total medication load						
Caudal medial	-0.38	0.001**	0.70	-0.27	0.02*	1

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visual cortex						
Cuneus	-0.17	0.16	1	-0.27	0.03*	1
Medial parietal cortex	-0.13	0.25	1	-0.28	0.02*	1
Posterior cingulate cortex	-0.25	0.04*	1	-0.22	0.07	1
Dorsolateral somatosensory cortex	-0.13	0.28	1	-0.24	0.04*	1
Dorsolateral motor cortex	-0.30	0.01*	1	-0.30	0.01*	1
Dorsomedial motor cortex	-0.28	0.02*	1	-0.28	0.02*	1
Total medication count						
Caudal medial visual cortex	-0.33	0.006**	1	-0.22	0.06	1
Caudal middle temporal cortex	-0.06	0.62	1	-0.26	0.03*	1
Ventral inferior parietal cortex	-0.14	0.26	1	-0.27	0.03*	1
Dorsal	-0.16	0.19	1	-0.26	0.03*	1

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inferior parietal cortex						
Superior parietal cortex	-0.13	0.28	1	-0.24	0.049*	1
Medial parietal cortex	-0.08	0.50	1	-0.25	0.03*	1
Dorsolateral somatosensory cortex	-0.18	0.12	1	-0.33	0.005**	1
Dorsomedial somatosensory cortex	-0.17	0.17	1	-0.25	0.03*	1
Dorsolateral motor cortex	-0.23	0.05	1	-0.29	0.02*	1
Dorsomedial motor cortex	-0.26	0.03*	1	-0.32	0.008**	1
Dorsolateral premotor cortex	-0.20	0.10	1	-0.25	0.04*	1
Dorsomedial premotor cortex	-0.25	0.03*	1	-0.31	0.009**	1
Caudal	-0.22	0.06	1	-0.25	0.04*	1

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dorsomedial prefrontal cortex						
Rostral dorsolateral inferior prefrontal cortex	-0.29	0.02*	1	-0.15	0.23	1
Ventral orbitofrontal cortex	-0.31	0.01*	1	-0.22	0.07	1

µ p values corrected using Bonferroni correction