Type of file: table
Label: Table S1
Filename: Supplemental_Table_1A-B.doc

Supplemental Table 1A. Additional Findings in Wholebrain Analysis of BD vs. UD Comparison of Diffusivity Measures : BD [15] > UD [16]

WHOLEBRAIN REGIONS		Voxels		EMM FA* 95% Confidence Intervals			FA		λ‖		λ⊥	
					Lower	Higher	t-test **	P value	t-test **	P value	t-test **	P value
RIGHT UNCINATE FASCICULUS	**[subgenual cortex]**	**20**	BD	0.29	0.26	0.32	**3.8**	**<0.05#**	0.6	.454	0.1	.803
[MNI coordinates x, y, z: 14,13,-10]			UD	0.24	0.21	0.26						

** Estimated Marginal Means (EMM) are evaluated at the covariate value of age = 34.5.*

* Positive values on t-student tests refer to diffusivity measures greater in BD than UD adults, while negative values refer to diffusivity measures less in BD depressed than UD adults.

Supplemental Table 1B . Additional Findings in Wholebrain Analysis of BD vs. HC Comparison of Diffusivity Measures: BD [15] < HC [24]

WHOLEBRAIN REGIONS		Voxels		EMM FA* 95% Confidence Intervals			FA		λ‖		λ⊥	
					Lower	Higher	t-test **	P value	t-test **	P value	t-test **	P value
RIGHT SUPERIOR LONGITUDINAL FASCICULUS	**[primary sensory cortex]**	**22**	BD	0.32	0.29	0.35	**-3.9**	**<0.05#**	-2.5	0.124	**4.7**	**0.037**
[MNI coordinates x, y, z: 40,-27,51]			HC	0.39	0.36	0.41						

** Estimated Marginal Means (EMM) are evaluated at the covariate value of age = 31.0.*

* Positive values on t-student tests refer to diffusivity measures greater in UD than HC adults, while negative values refer to diffusivity measures less in UD depressed than HC adults.

** Monte Carlo simulation with alphasim correction was run on uncorrected t statistical maps ($p<0.001$), obtaining a dual thresholding of both type I error (alphasim $p<0.05$, corrected) and cluster-size thresholding (t-tests CST$\geq$18 voxels)

FA: Fractional Anisotropy; λ||: Longitudinal Diffusivity; λ⊥: Radial Diffusivity; BD; Bipolar Disorder individuals; UD: Unipolar Disorder individuals; HC: Healthy Control individuals.

Significant between-group comparisons in **bold;** trend between-group comparisons in *italic*

Type of file: table
Label: Table s2a
Filename: Supplemental_Table_2A.doc

Supplemental Table 2A. Spearman Correlations Between Diffusivity Measures in Regions that Significantly Differentiated BD, UD Depressed and HC Adults and Demographic and Clinical Variables in 15 BD, 16 UD and 24 HC.

WHOLEBRAIN REGIONS		Group [N]	Continuous Variables: Age		Age of Illness Onset		Illness Duration		HDRS-25		Medication Load	
			Spearman	P value	Spearman	P value	Spearman	P value	Spearman	P value	Spearman	P value
LEFT SUPERIOR LONGITUDINAL FASCICULUS [inferior temporal cortex] [MNI coordinates x, y, z: -50,-38,-15]	FA	**BD[15]**	***-0.5***	***0.038$^{\&}$***	-0.1	0.849	-0.4	0.101	0.0	0.965	-0.2	0.581
		UD[16]	0.2	0.528	0.1	0.586	0.3	0.295	-0.3	0.280	0.0	1.000
		HC[24]	-0.1	0.744	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ||	**BD[15]**	0.4	0.173	0.4	0.144	0.1	0.621	0.1	0.632	0.2	0.375
		UD[16]	0.1	0.787	-0.1	0.807	-0.2	0.549	-0.2	0.353	-0.2	0.574
		HC[24]	-0.1	0.595	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ⊥	**BD[15]**	***0.6***	***0.014$^{\$}$***	0.3	0.255	0.4	0.095	0.0	0.990	0.5	0.081
		UD[16]	-0.1	0.737	-0.1	0.833	-0.3	0.295	0.2	0.402	0.0	1.000
		HC[24]	0.1	0.764	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
LEFT SUPERIOR LONGITUDINAL FASCICULUS [primary sensory cortex] [MNI coordinates x, y, z: -47,-19,47]	FA	**BD[15]**	0.0	0.990	-0.4	0.142	0.3	0.283	-0.1	0.655	-0.1	0.622
		UD[16]	0.1	0.820	-0.4	0.175	0.3	0.259	-0.4	0.114	0.0	0.879
		HC[24]	0.1	0.619	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ||	**BD[15]**	-0.4	0.182	0.1	0.732	-0.4	0.147	0.0	0.939	0.0	0.878
		UD[16]	-0.1	0.644	0.2	0.435	-0.3	0.266	0.1	0.601	-0.1	0.782
		HC[24]	0.2	0.443	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ⊥	**BD[15]**	-0.5	0.087	0.2	0.579	-0.5	0.076	0.1	0.819	-0.1	0.784
		UD[16]	-0.1	0.680	0.4	0.135	-0.4	0.134	***0.5***	***0.047$^{\$}$***	0.0	0.968
		HC[24]	0.0	0.912	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
LEFT INFERIOR LONGITUDINAL FASCICULUS [lateral occipital cortex] [MNI coordinates x, y, z: -28,-66,40]	FA	**BD[15]**	-0.1	0.603	-0.3	0.291	0.2	0.413	-0.1	0.693	0.5	0.078
		UD[16]	-0.2	0.499	-0.3	0.313	0.1	0.688	-0.3	0.335	0.1	0.751
		HC[24]	-0.3	0.205	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ||	**BD[15]**	0.3	0.226	0.3	0.291	0.1	0.752	0.2	0.441	0.2	0.447
		UD[16]	0.1	0.696	***0.6***	***0.011$^{\$}$***	-0.2	0.431	0.3	0.341	-0.2	0.374
		HC[24]	0.2	0.473	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ⊥	**BD[15]**	0.2	0.567	0.3	0.215	-0.2	0.428	0.1	0.651	-0.3	0.285
		UD[16]	0.2	0.520	***0.5***	***0.028$^{\$}$***	-0.1	0.602	0.2	0.371	-0.1	0.658
		HC[24]	0.3	0.150	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
RIGHT UNCINATE FASCICULUS [orbitofrontal cortex] [MNI coordinates x, y, z: 26,26,-11]	FA	**BD[15]**	-0.2	0.483	0.1	0.689	-0.1	0.648	0.0	0.934	0.1	0.725
		UD[16]	-0.2	0.471	-0.1	0.854	0.0	0.940	0.1	0.768	***0.5***	***0.036$^{\$}$***
		HC[24]	0.1	0.760	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ||	**BD[15]**	0.1	0.737	0.3	0.294	0.0	0.970	-0.3	0.249	0.3	0.320
		UD[16]	0.0	0.974	0.3	0.294	-0.4	0.184	-0.3	0.258	-0.2	0.528
		HC[24]	-0.1	0.627	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ⊥	**BD[15]**	0.2	0.467	0.0	0.990	0.1	0.781	-0.1	0.770	-0.1	0.745
		UD[16]	0.3	0.309	0.3	0.311	-0.2	0.578	-0.2	0.498	-0.4	0.091
		HC[24]	0.0	0.936	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

RIGHT UNCINATE FASCICULUS [subgenual cortex] [MNI coordinates x, y, z:: 14,13,-10]	FA	**BD[15]**	-0.1	0.603	-0.1	0.708	0.0	0.990	-0.1	0.674	-0.1	0.608
		UD[16]	-0.4	0.107	-0.2	0.506	-0.3	0.244	-0.2	0.535	-0.2	0.480
	λ||	**BD[15]**	***0.6***	***0.024$***	0.3	0.347	0.4	0.160	-0.1	0.770	0.2	0.572
		UD[16]	0.1	0.649	0.4	0.152	-0.4	0.161	0.0	0.952	0.0	0.906
	λ⊥	**BD[15]**	***0.7***	***0.007$***	0.2	0.521	0.5	0.062	0.0	0.977	0.0	0.911
		UD[16]	0.2	0.368	0.3	0.239	-0.2	0.387	0.0	0.857	0.0	0.937
RIGHT SUPERIOR LONGITUDINAL FASCICULUS [primary sensory cortex] [MNI coordinates x, y, z:: 40,-27,51]	FA	**BD[15]**	0.1	0.612	-0.1	0.859	0.2	0.576	0.0	0.970	-0.2	0.590
		HC[24]	0.1	0.677	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ||	**BD[15]**	-0.4	0.114	-0.2	0.385	0.0	0.899	0.0	0.965	0.0	0.929
		HC[24]	0.1	0.700	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	λ⊥	**BD[15]**	-0.3	0.265	-0.1	0.624	0.0	0.980	-0.1	0.679	0.3	0.343
		HC[24]	-0.1	0.497	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

FA: Fractional Anisotropy; λ||: Longitudinal Diffusivity; λ⊥: Radial Diffusivity; BD; Bipolar Disorder individuals; UD: Unipolar Disorder individuals; HC: Healthy Control individuals.

BD and UD: Statistical threshold of p=0.05/10=0.005, **in bold** to control for multiple comparisons; trend range of 0.005<p≤0.05, ***in bold-italic***.

HC: Statistical threshold of p=0.05, **in bold**; trend range of 0.05<p≤0.099, ***in bold-italic***.

$ Positive relationship; & negative relationship.

Type of file: table
Label: Table s2b
Filename: Supplemental_Table_2B.doc

Supplemental Table 2B. Relationships Between Diffusivity Measures in Regions that Significantly Differentiated BD and UD Depressed Adults and Dichotomous Clinical Variables in 15 BD and 16 UD Depressed Adults.

WHOLEBRAIN REGIONS		Group [N]	Dichotomous Variables: MS		AP		AD		BDZ		Drugs/Alcohol[#]	
			MWU	P value	MWU	P value	MWU	P value	MWU	P value	MWU	P value
LEFT SUPERIOR LONGITUDINAL FASCICULUS [inferior temporal cortex] [MNI coordinates x,y,z:-50,-38,-15]	FA	**BD[15]**	23.0	0.859	24.0	0.953	25.0	0.779	16.0	0.224	16.0	0.622
		UD[16]	n/a	n/a	3.0	0.500	14.0	1.000	24.0	0.743	15.0	0.611
	λ‖	**BD[15]**	21.0	0.679	15.0	0.254	13.0	0.094	22.0	0.607	12.0	0.284
		UD[16]	n/a	n/a	1.0	0.250	11.0	0.700	23.0	0.661	17.0	0.800
	λ⊥	**BD[15]**	22.0	0.768	17.0	0.371	15.0	0.152	18.0	0.328	14.0	0.435
		UD[16]	n/a	n/a	3.0	0.500	13.0	0.933	26.0	0.913	15.0	0.611
LEFT SUPERIOR LONGITUDINAL FASCICULUS [primary sensory cortex] [MNI coordinates x,y,z:-47,-19,47]	FA	**BD[15]**	23.0	0.859	19.0	0.513	20.0	0.397	26.0	0.955	9.0	0.127
		UD[16]	n/a	n/a	4.0	0.625	11.0	0.700	15.0	0.180	17.0	0.800
	λ‖	**BD[15]**	22.0	0.768	23.0	0.859	25.0	0.779	24.0	0.776	14.0	0.435
		UD[16]	n/a	n/a	7.0	1.000	13.0	0.933	23.0	0.661	8.0	0.146
	λ⊥	**BD[15]**	21.0	0.679	24.0	0.953	19.0	0.336	16.0	0.224	18.0	0.833
		UD[16]	n/a	n/a	6.0	0.875	10.0	0.600	15.0	0.180	15.0	0.611
LEFT INFERIOR LONGITUDINAL FASCICULUS [lateral occipital cortex] [MNI coordinates x,y,z:-28,-66,40]	FA	**BD[15]**	14.0	0.206	14	0.206	21.0	0.463	16.0	0.224	16.0	0.622
		UD[16]	n/a	n/a	4.0	0.625	12.0	0.817	21.0	0.510	7.0	0.111
	λ‖	**BD[15]**	25.0	1.000	24.0	0.953	19.0	0.336	26.0	0.955	18.0	0.833
		UD[16]	n/a	n/a	0.0	0.125	13.0	0.933	14.0	0.145	6.0	0.082
	λ⊥	**BD[15]**	16.0	0.310	19.0	0.513	16.0	0.189	16.0	0.224	17.0	0.724
		UD[16]	n/a	n/a	1.0	0.250	11.0	0.700	20.0	0.441	5.0	0.057
RIGHT UNCINATE FASCICULUS [orbitofrontal cortex] [MNI coordinates x,y,z:26,26,-11]	FA	**BD[15]**	23.0	0.859	21.0	0.679	12.0	0.072	24.0	0.776	16.0	0.622
		UD[16]	n/a	n/a	2.0	0.375	7.0	0.333	21.0	0.510	11.0	0.296
	λ‖	**BD[15]**	14.5	0.206	24.5	0.953	13.5	0.094	21.0	0.529	18.5	0.833
		UD[16]	n/a	n/a	0.0	0.125	7.0	0.333	12.0	0.090	19.0	1.000
	λ⊥	**BD[15]**	25.0	1.000	25.0	1.000	18.0	0.281	26.0	0.955	16.0	0.622
		UD[16]	n/a	n/a	0.0	0.125	14.0	1.000	13.0	0.115	13.0	0.439
RIGHT UNCINATE FASCICULUS [subgenual cortex] [MNI coordinates x,y,z:14,13,-10]	FA	**BD[15]**	24.0	0.953	16	0.310	24.0	0.694	13.0	0.113	14.0	0.435
		UD[16]	n/a	n/a	2.0	0.375	13.0	0.933	23.0	0.661	16.0	0.704
	λ‖	**BD[15]**	24.0	0.953	18.0	0.440	23.0	0.613	23.0	0.689	13.0	0.354
		UD[16]	n/a	n/a	6.0	0.875	13.0	0.933	16.0	0.221	15.0	0.611
	λ⊥	**BD[15]**	21.5	0.679	21.5	0.679	20.5	0.397	19.5	0.388	9.0	0.127
		UD[16]	n/a	n/a	6.0	0.875	12.0	0.817	19.0	0.377	15.0	0.611
RIGHT SUPERIOR LONGITUDINAL FASCICULUS [primary sensory cortex] [MNI coordinates x,y,z:40,-27,51]	FA	**BD[15]**	23.0	0.859	15.0	0.254	23.0	0.613	27.0	1.000	20.0	1.000
		HC[24]	n/a	n/a	7.0	1.000	10.0	0.600	18.0	0.320	19.0	1.000
	λ‖	**BD[15]**	23.0	0.859	23.0	0.859	25.0	0.779	17.0	0.272	17.0	0.724
		HC[24]	n/a	n/a	1.0	0.250	5.0	0.200	11.0	0.069	16.0	0.704
	λ⊥	**BD[15]**	18.0	0.440	17.0	0.371	26.0	0.867	25.0	0.864	15.0	0.524
		HC[24]	n/a	n/a	2.0	0.375	12.0	0.817	18.0	0.320	19.0	1.000

BD=Bipolar Disorder individuals; UD=Unipolar Disorder individuals; MS= mood stabilizer; AP=antipsychotics; AD=antidepressants; BDZ=benzodiazepines; Drugs/Alcohol= lifetime prevalence of drugs/alcohol abuse/dependence; $\lambda||$=Longitudinal Diffusivity; $\lambda\perp$=Radial Diffusivity.

BD: Statistical threshold of p=0.05/10=0.005, to control for multiple comparisons; trend range of $0.005<p\leq0.05$, ***in bold-italic***.

Missing information in 2 BD (females; 41 and 28year-old) about lifetime history of drug/alcohol abuse/dependence.

Type of file: table
Label: Tables s3a-b
Filename: Supplemental_Table_3A-B.doc

Supplemental Table 3A. Main Effect of Group in Wholebrain Analysis of Diffusivity Measures in females only: BD [14], UD [12] and HC [15]

WHOLEBRAIN REGIONS		Voxels		EMM FA*	95% Confidence Intervals		FA		λ‖		λ⊥	
					Lower	Higher	f-test **	P value	f-test *	P value	f-test *	P value
RIGHT UNCINATE FASCICULUS [MNI coordinates x, y, z: 26,26,-12]	**[orbitofrontal cortex]**	**14**	BD	0.29	0.24	0.33	**13.4**	**<0.05#**	**3.6**	**0.036**	1.6	0.208
			UD	0.36	0.32	0.41						
			HC	0.40	0.35	0.44						
LEFT SUPERIOR LONGITUDINAL FASCICULUS [MNI coordinates x, y, z: -51,-38,-16]	**[inferior temporal cortex]**	**14**	BD	0.30	0.24	0.37	**10.7**	**<0.05#**	2.0	0.148	**6.0**	**0.005**
			UD	0.47	0.40	0.54						
			HC	0.38	0.32	0.44						
LEFT SUPERIOR LONGITUDINAL FASCICULUS [MNI coordinates x, y, z: -48,-48,-1]	**[middle temporal cortex]**	**10**	BD	0.44	0.39	0.49	**11.1**	**<0.05#**	1.5	0.230	**3.2**	**0.051**
			UD	0.54	0.49	0.59						
			HC	0.50	0.45	0.54						

** Estimated Marginal Means (EMM) are evaluated at the covariate value of age = 33.9.*

** Monte Carlo simulation with alphasim correction was run on uncorrected f statistical maps (p<0.001), obtaining a dual thresholding of both type I error (alphasim p<0.05, corrected) and cluster-size thresholding (f-tests CST≥10 voxels)

Supplemental Table 3B. Post-hoc Comparisons in Wholebrain Analysis of Diffusivity Measures in females only: BD [14], UD [12] and HC [15]

WHOLEBRAIN REGIONS		Voxels		EMM FA*	95% Confidence Intervals		FA		λ‖		λ⊥	
					Lower	Higher	t-test **	P value	t-test *	P value	t-test *	P value
BD < UD												
LEFT SUPERIOR LONGITUDINAL FASCICULUS [MNI coordinates x, y, z: -48,-48,-1]	**[middle temporal cortex]**	**22**	BD	0.43	0.38	0.47	**-4.7**	**<0.05#**	-1.0	0.382	**4.2**	**0.022**
			UD	0.52	0.47	0.57						
LEFT SUPERIOR LONGITUDINAL FASCICULUS [MNI coordinates x, y, z: -51,-38,-16]	**[inferior temporal cortex]**	**20**	BD	0.30	0.23	0.37	**-4.6**	**<0.05#**	-2.1	0.137	**6.9**	**0.003**
			UD	0.47	0.39	0.54						

** Estimated Marginal Means (EMM) are evaluated at the covariate value of age = 31.8.*

BD < HC

LEFT SUPERIOR LONGITUDINAL FASCICULUS [MNI coordinates x, y, z: -38,-26,44]	**[primary sensory cortex]**	**22**	BD	0.34	0.31	0.38	**-4.4**	**<0.05#**	**-5.8**	**0.006**	*2.7*	*0.077*
			HC	0.44	0.40	0.47						
RIGHT UNCINATE FASCICULUS [MNI coordinates x,y,z: 26,26,-12]	**[orbitofrontal cortex]**	**22**	BD	0.29	0.24	0.34	**-5.1**	**<0.05#**	*-3.0*	*0.063*	1.8	0.178
			HC	0.40	0.35	0.44						

** Estimated Marginal Means (EMM) are evaluated at the covariate value of age = 31.0.*

UD < HC and UD > HC

LEFT SUPERIOR LONGITUDINAL FASCICULUS [MNI coordinates x, y, z: -53,-41,-16]	**[inferior temporal cortex]**	**25**	UD	0.42	0.34	0.50	**4.8**	**<0.05#**	1.3	0.282	**-4.6**	**0.016**
			HC	0.29	0.22	0.36						
LEFT UNCINATE FASCICULUS [MNI coordinates x, y, z: -31,-24,-28]	**[entorhinal cortex]**	**25**	UD	0.32	0.28	0.37	**-4.0**	**<0.05#**	-0.2	0.858	0.9	0.428
			HC	0.36	0.32	0.40						

** Estimated Marginal Means (EMM) are evaluated at the covariate value of age = 29.7.*

** Monte Carlo simulation with alphasim correction was run on uncorrected t statistical maps (p<0.001), obtaining a dual thresholding of both type I error (alphasim p<0.05, corrected) and cluster-size thresholding (t-tests CST≥18 voxels)

FA: Fractional Anisotropy; λ||: Longitudinal Diffusivity; λ⊥: Radial Diffusivity; BD; Bipolar Disorder individuals; UD: Unipolar Disorder individuals; HC: Healthy Control individuals.

Significant between-group comparisons in **bold;** trend between-group comparisons in *italic*. λ|| and λ⊥ extracted only in WM regions showing significant between-group differences upon FA; wholebrain analyses and/or corrections of these two diffusivity measures were not performed.