From Pathophysiology to Novel Antidepressant Drugs: Glial Contributions to the Pathology and Treatment of Mood Disorders

Supplemental Information

Table S1. Postmortem studies examining glial cell pathology in brain regions associated with mood disorders.

BA24 & ACC			
DOWN	**NO CHANGE**	**UP**	**UNIQUE**
Ongur *et al.* (1998) (1): Glial number markedly reduced in both MDD and BD. Most prominent reductions in subgroups of subjects with familial MDD and BD.	**Chana *et al.* (2003) (2):** No statically significant difference in glial cell density was detected between MDD, BD, SCH and CS cases in a 2D analysis.		**Webster *et al.* (2005) (3):** GFAP mRNA levels decreased in the white matter of SCH and BD compared with CS cases. MDD group showed a statistically non-significant 15% reduction.
Cotter *et al.* (2001) (4): Glial cell density reduced in layer 6 of MDD cases relative to CS. Some evidence for reduced glial density in layer 6 SCH cases, before adjusting for multiple layer-wise comparisons. There was no evidence for differences in glial density in BD.	**Hercher *et al.* (2009) (6):** No difference in BA24a glial cell density between MDD suicide and CS cases.		**Choudary *et al.* (2005) (5):** Microarray analyses demonstrate significant down-regulation of the genes coding for EAAT1, EAAT2 and glutamine synthetase in the area 24 of MDD subjects.
Todtenkopf *et al.* (2005) (7): An analysis of 2 studies from the Benes laboratory using 2D counting methods demonstrated no significant difference in the density of glial cells in SCH or BD cases. In contrast, a single study employing the 3D optical dissector found significant reductions in glial density in layers III, V and VI of the SCH and BD cases.			**Torres-Platas *et al.* (2011) (8):** Hypertrophied fibrous astrocytes in a mix sample of MDD and BD cases compared to CS.
Gittins *et al.* (2011) (9): Mix of MDD and BD cases showed a decreased density of glial cells across all layers and a reduction in GFAP in white matter in area 24b.	**Khundakar *et al.* (2011) (10):** No difference in glial, cell density within individual layers (2-5) or the supragenual anterior cortex as a whole in late-life depression.		

BA 9 &10			
DOWN	**NO CHANGE**	**UP**	**UNIQUE**
Rajkowska *et al.* (2001) (11): Glial density reduced in sublayer IIIc in BD compared to non-psychiatric CS cases.	**Toro *et al.* (2006) (12):** No difference in GFAP immunoreactivity in area 9 of BD or MDD cases, but increased in SCH cases. No changes in GS immunoreactivity.		**Johnston-Wilson *et al.* (2000) (13):** Identified decreased levels of GFAP isoforms in MDD, BD and SCH in frontal cortex (BA10) compared with the non-psychiatric controls.
Cotter *et al.* (2002) (14): Reductions in glial cell density in layer 5 of MDD subjects. Also glial cell density was reduced in layer 5 in schizophrenia but not BD.			**Tkachev *et al.* (2003) (15):** Reduction of key oligodendrocyte-related and myelin-related genes in SCH and BD; expression changes for both disorders showed a high degree of overlap. MDD was not evaluated.
Uranova *et al.* (2004) (16): Significant reduction in numerical density of oligodendroglial cells was found in layer VI of subjects with SCH, BD and MDD as compared to controls. No change in adjacent white matter.			**Ernst *et al.* (2009) (17):** Expression of astrocyte-specific tropomyosin-related kinase-B receptor (TrkB.1) isoform and astrocyte connexins 30 and 43 are down-regulated area 10 suicide completers (areas 8,9,10).
DLPFC			
DOWN	**NO CHANGE**	**UP**	**UNIQUE**
Rajkowska *et al.* (1999) (18): Marked reductions in the density and size of neurons and glial cells were found in both supra- and infragranular layers DLPFC of MDD cases.	**Khundakar *et al.* (2009) (19):** No significant differences in glial density in the DLPFC as a whole.		**Davis *et al.* (2002) (20):** GFAP-immunoreactivity lower in DLPFC gray matter in layer V in MDD cases, but higher in DLPFC white matter compared to controls. GFAP-immunoreactivity significantly higher in layer I of the DLPFC in MDD cases vs. controls.

Miguel-Hidalgo *et al.* (2000) (21): A significant strong positive correlation between age and GFAP immunoreactivity was found in MDD cases. When the MDD group was divided into younger (30-45 years old) and older (46-86) adults, in the five younger MDD adults, areal fraction and packing density were smaller than the smallest values of the CS in areas II+IV and V.			**Ernst *et al.* (2011) (22):** Reduced expression of astrocyte specific Cx30 and Cx43 in DLPFC of suicide completers with mixed diagnoses.
Miguel-Hidalgo *et al.* (2002) (23): Glial density reduced in layers V and VI and in all layers combined in the alcohol dependent cases. The alcohol cases with depressive symptoms showed the lowest values of density. No difference in GFAP immunoreactivity was observed between groups.			**Choudary *et al.* (2005) (5):** Microarray analyses demonstrate significant down-regulation of the genes coding for EAAT1, EAAT2 and glutamine synthetase in areas 9 + 46 of MDD subjects.

AMYGDALA			
DOWN	**NO CHANGE**	**UP**	**UNIQUE**
Bowley *et al.* (2002) (24): Glial density and the glia/neuron ratio were substantially reduced in MDD cases. Average glia measures not reduced in BD cases; however, BD cases not treated with lithium or valproate had significant glial reduction. Similar but smaller changes were found in the entorhinal cortex.	**Bezchlibnyk *et al.* (2007) (25):** No change in number or density of glial cells in MDD, BD, or SCH cases.		**Hamidi *et al.* (2004) (26):** Follow up on Bowley *et al.* (2002) (24) found the density of total glia and oligodendrocytes in the amygdala was significantly lower in MDD than CS cases, but not significantly lower in BD compared with control subjects. The decreases were largely accounted for by differences in the left hemisphere. There was no significant decrease in astrocyte or microglia density in MDD or BD cases.
Altshuler *et al.* (2010) (27): Reduced GFAP-immunoreactive astrocytes density in MDD cases but not in BD or SCH cases.			

HIPPOCAMPUS			
DOWN	**NO CHANGE**	**UP**	**UNIQUE**
Muller *et al.* (2001) (28): Decreased GFAP-immunoreactive astrocytes in CA1 and CA2 areas, in MDD and steroid treated cases compared to CS. However, differences should be interpreted with caution.	**Boldrini *et al.* (2013) (29):** No difference in glial number quantified in the DG was observed in a small subset of MDD cases (either treated or not treated) compared to CS.	**Stockmeier *et al.* (2004) (30):** Glial density in the DG and all CA subfields are increased in MDD cases. Differences may be accounted for by a reduction of neuropil per cell.	
	Cobb *et al.* (2013) (31): No significant difference in glial cell number between MDD and CS cases in CA1, CA2/3, or hilus.		

LOCUS COERULEUS			
DOWN	**NO CHANGE**	**UP**	**UNIQUE**
			Ordway *et al.* (2012) (32): Laser capture microdissection of astrocytes from the LC revealed that BMP7 gene expression was reduced in depression. BMP7 has unique developmental and trophic actions on catecholamine neurons and these findings suggest that reduced astrocyte support for pontine LC neurons may contribute to pathology of brain noradrenergic neurons in MDD.
			Bernard *et al.* (2011) (33): Microarray gene expression findings reveal multiple signaling pathway alterations in the LC of MDD but not BD subjects. These include glutamate signaling genes, SLC1A2, SLC1A3 and GLUL, growth factor genes FGFR3 and TrkB, and several genes exclusively expressed in astroglia.

BA, Brodmann area; BD, bipolar disorder; BMP7, bone morphogenetic protein 7; CS, control subject; DG, dentate gyrus; DLPFC, dorsolateral prefrontal cortex; EAAT1, 2, excitatory amino acid transporters 1 and 2; FGFR3, fibroblast growth factor receptor 3; GFAP, glial fibrillary acidic protein; GLUL, glutamate-ammonia ligase, coding for GS; GS, glutamine synthetase; LC, locus coeruleus; MDD, major depressive disorder; SCH, schizophrenia; SLC1A2, solute carrier family 1 member 2, coding for EAAT2; SLC1A3, solute carrier family 1 member 3, coding for EAAT1; TrkB, tyrosine-related kinase B, neurotrophin receptor.

Table S2. Studies examining riluzole's effects in mood and anxiety disorders

MDD									
Studies	**Diagnosis**	**Design**	**Subjects**	**Age**	**Concomitant medications**	**Dose**	**Duration**	**Primary outcome measures**	**Secondary outcome measures**
			M=Male F=Female when available	range and (mean) when available		Specified in protocol and (mean) when available	Specified in protocol		
Zarate *et al.* (2004) (34)	MDD,TRD	Open-label, Monotherapy	9M, 10F	18-70	Medication free for at least 1 week	50-200 mg/day (168.8)	6 weeks	Significant improvement in MADRS occurred on weeks 3 through 6.	CGI severity and HAM-A scores significantly improved weeks 3 through 6. Depression response rates at week 6 for all patients and trial completers were 32% and 46%, respectively. Remission rates at week 6 for all patients and completers were 21% and 31%, respectively.
Sanacora *et al.* (2007) (35)	MDD,TRD	Open-label, Augmentation	6M, 7F	21-65 (47.9)	Variety, majority on >2 antidepressant meds	100 mg/day (95.0)	6 week initial phase with an additional 6 week continuation	Significant improvement in HAM-D at week 6 endpoint.	Significant improvement in HAM-A over the period of the study. Depression response rates at week 6 were 40%. Remission rate was 30%. HAM-A scores by 31%. Significant reductions from baseline scores were seen as early as week 1 for both the HAM-D and HAM-A and remained significant for every week thereafter (all adjusted $p < .05$).
Mathew *et al.* (2010) (36)	MDD,TRD	Randomized 72 hrs post ketamine (0.5 mg/kg IV over 40 min) infusion and 300 mg lamotrigine or placebo by mouth, if meeting response criteria. Primary goal to determine if riluzole could delay time to relapse after ketamine response.	14 subjects 6 riluzole 8 placebo	21-70 (48.2)	None after ketamine / lamotrigine drug study	100–200 mg/day (116.7)	32 days	There were no differences in time-to-relapse between groups (log-rank $\chi^2 = 0.17$, $df = 1$, $p = 0.68$)	Mean time-to-relapse for the riluzole group was 24.4 d (95% CI 15.9–33.0), while mean time-to-relapse for the placebo group was 22.0 d (95% CI 14.9–29.1). MADRS scores at study exit (LOCF) did not differ between groups.
Ibrahim *et al.* (2012) (37)	MDD, TRD	Randomized 4-6 hrs post ketamine (0.5 mg/kg IV over 40 min) infusion.	42 subjects 21 riluzole 21 placebo	18–65 (47.2)	None after ketamine	100-200 mg/day (173.8)	4 weeks	Significant improvement in MADRS scores was found over time, but the differences between treatment groups and the interaction between time and treatment group were not significant.	Kaplan–Maier survival analysis showed a non-significant weak trend riluzole to extend to relapse (log rank test, $\chi 2 = 2.50$, $p = 0.11$). Ketamine–riluzole group took 17.2 (SE = 3.1) days and the ketamine–placebo group took 9.8 days (SE = 2.8) to relapse on average.

BD									
Studies	**Diagnosis**	**Design**	**Subjects**	**Age**	**Concomitant medications**	**Dose**	**Duration**	**Primary outcome measures**	**Secondary outcome measures**
Zarate *et al.* (2005) (38)	BD I (*n* = 6), BD II (*n* = 8)	Open-label, Augmentation of lithium treatment	10M, 4F	18–70 (49.5)	Minimum of 4 weeks lithium treatment prior to riluzole	100-200 mg/day (171.4)	8 weeks	Significant decrease in MADRS at weeks 5–8.	Significant improvement in weeks 6–8 for the CGI. Scores on the YMRS did not change significantly during the study. The response and remission rates at week 8 were both 50%.
Brennan *et al.* (2010) (39)	BD I (*n* = 4), BD II (*n* = 10)	Open-label, Augmentation of mood stabilizing or antidepressant treatment for 7, monotherapy for 7	7M, 7F	18–65	Various mood stabilizers and antidepressants, excluding lithium and lamotrigine	100-200 mg/day (181.8)	6 weeks	Significant improvement on HAM-D scales for both longitudinal and endpoint analyses.	Highly significant decrease, with very large effect sizes (Cohen's d > 2.0), in MADRS, and CGI-S scores. YMRS scores decreased significantly in the end point analysis, but not in the random regression analysis.
OCD									
Studies	**Diagnosis**	**Design**	**Subjects**	**Age**	**Concomitant medications**	**Dose**	**Duration**	**Primary outcome measures**	**Secondary outcome measures**
Coric *et al.* (2005) (40)	OCD, treatment resistant, 10 patients with comorbid MDD	Open-label, Monotherapy	5M, 8F	18-65 (40.9)	Mixed SRIs	100 mg/day	6 weeks with extension to 12 weeks	Significant improvement in Y-BOCS over time.	HAM-D significantly decreased. HAM-A significantly decreased. CGI/GI significantly improved.
Grant *et al.* (2007) (41)	OCD, 5 with comorbid MDD Pediatric	Case series, Mixed monotherapy and augmentation	5M, 1F	8-16 (14.4)		Up to 120 mg/day (101)	12 weeks	39.3 +/- 19.7% reduction in Y-BOCs	4 subjects were considered "responders"
Pittenger *et al.* (2008) (42)	OCD, 9 with comorbid MDD	Case series, Augmentation	9M, 4F	42.3	Mix therapies	100 mg/day	12 Weeks	Average Y-BOCS decreased by 26%	6 subjects were considered "responders". Mean HAM-D decreased 28%. Mean HAM-A decreased by 31%.
GAD									
Studies	**Diagnosis**	**Design**	**Subjects**	**Age**	**Concomitant medications**	**Dose**	**Duration**	**Primary outcome measures**	**Secondary outcome measures**
Mathew *et al.* (2005) (43)	GAD, but comorbid panic attacks, dysthymia, social anxiety disorder and specific phobia present in over 50% of the subjects	Open-label, Monotherapy	6M, 12F	33.6	Medication free for at least 2 weeks	100 mg/day	8 weeks	Significant improvement in HAM-A score across the duration of the trial.	Significant decrease in Mean Anxiety Sensitivity Index scores, and HAM-D scores at endpoint.

BD, bipolar disorder; CGI, Clinical Global Impression; CI, confidence interval; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; IV, intravenous; LOCF, last observation carried forward; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SE, standard error; SRI, serotonin reuptake inhibitor; TRD, treatment resistant depression; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; YMRS, Young Mania Rating Scale.

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