Gene expression changes associated with electroconvulsive therapy (ECT).

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ECT is used for the therapy of severe major depression and other psychiatric disorders¹. To understand how ECT alters gene expression in the brains of patients being treated with convulsive seizures, we mined public and published microarray datasets²⁻⁵, comparing brain tissue from patients with bipolar disease treated with ECT with that of non ECT-treated bipolar patients, and from the brain tissues of mice treated with ECT experimentally. We found multiple significant changes in the brains of patients treated with ECT that in many cases could be validated in microarray data of the mouse brain with and without ECT. Validation of brain-derived neurotrophic factor (BDNF) as a differentially expressed gene after treatment with ECT⁶ suggests that other changes identified here may be reflective of actual transcriptional changes induced in the brain by electroconvulsive therapy.

Keywords: electroconvulsive therapy, ECT, ECT-induced gene expression changes.

Electroconvulsive therapy (ECT), or the application of an electrical current to induce a seizure in the brain, is clinically utilized worldwide for the purposes of achieving symptom relief in severe major depression and other psychiatric disorders¹. It is not understood how ECT functions to exert therapeutic relief. We sought to understand how ECT affects gene expression in the brain by mining published microarray datasets and identifying the most significant gene expression changes in the brains of the patients with bipolar disease receiving ECT or not², and from the brains of ECT-treated mice³⁻⁵. We found a series of genes whose differential expression could be observed both in mice experimentally treated with ECT and in ECT-treated human patients with bipolar disease. These data confirm published data indicating that ECT induces major changes in gene expression in the brain⁶ and identify individual gene expression targets of ECT.

Methods

We used datasets GSE5392², GSE38311³, GSE35259⁴, and GSE93732⁵ for this differential gene expression study in conjunction with GEO2R.

GSE5392 was generated with either orbitofrontal cortex or dorsolateral prefrontal cortex from patients post-mortem, and generated using Affymetrix Human Genome U133A Array technology, with n=36 patients with bipolar disease not having received ECT therapy and n=4 patients with bipolar disease receiving ECT therapy.

GSE38311 was generated with ventromedial hypothalamus from C57BL/6 mice using Affymetrix Mouse Genome 430A 2.0 Array technology, with n=1 sham-treated mouse (control) and n=4 ECT-treated mice (2 mice each receiving either 1 treatment or 7 treatments; collected either 2 or 6 hours post-seizure).

GSE35259 was generated with paraventricular hypothalamus from C57BL/6 mice using Affymetrix Mouse Genome 430A 2.0 Array technology with n=2 sham-treated mice (control) and

n=4 ECT-treated mice (all received one treatment; 2 mice each with tissue collected either 2 hours or 6 hours post-seizure).

GSE93732 was generated with dentate gyrus from C57BL/6 mice using Affymetrix Mouse Genome 430A 2.0 Array technology, with n=1 sham-treated mouse (control) and n=3 ECT-treated mice (1 mouse with tissue collected 1 hour after 1 ECT treatment, 1 mouse with tissue collected 1 hour after 11 ECT treatments, and 1 mouse with tissue collected 48 hours after 10 ECT treatments).

The Benjamini and Hochberg method of p-value adjustment was used for ranking of differential expression but raw p-values were used for assessment of statistical significance of global differential expression. Log-transformation of data was auto-detected, and the NCBI generated category of platform annotation was used. A statistical test was performed to evaluate whether gene expression was significantly different when comparing brain tissue from control groups (bipolar patients not having received ECT or sham-treated mice) and experimental groups (ECT-treated patients with bipolar disease or ECT-treated mice) using a two-tailed, unpaired t-test with Welch's correction. Only p-values less than 0.05 were considered statistically significant. We used PRISM for all statistical analyses (Version 8.4.0) (455).

Results

We compared transcriptome information from the post-mortem brains of patients with bipolar disorder - either having received ECT treatments or never having received ECT treatments - to understand how gene expression was most different in the brains of patients undergoing electroconvulsive therapy. We integrated these findings with data from studies wherein mice were treated with electroconvulsive therapy experimentally and brain tissue collected shortly thereafter.

Validation of brain-derived neurotrophic factor (BDNF) as a transcriptional change induced by ECT.

Brain-derived neurotrophic factor (BDNF) is associated with positive effects on mood^{7,8} and is released following activities such as exercise⁹. Changes in BDNF are among the most significant known changes in brain gene expression following ECT therapy⁶. We compared orbitofrontal cortex or dorsolateral prefrontal cortex tissue from patients with bipolar disease, either having received ECT therapy or not². This comparison revealed that changes in BDNF were among the most significant changes when comparing brain transcriptomes from bipolar patients based on ECT therapy. When sorting all of the transcripts measured by microarray based on change in expression when comparing ECT-treated bipolar patients and bipolar patients never having received ECT, BDNF ranked 181 out of 22283 transcripts. Differential expression of BDNF in ECT-treated bipolar patients was statistically significant (Table 1; $p=2.24E-02$). BDNF was expressed at higher levels in ECT-treated patients with bipolar disease; this difference was not statistically significant (Figure 1; $p=0.3696$). We calculated a fold change of 1.8074 ± 1.5323 in BDNF expression when comparing ECT-treated bipolar patients to non-treated bipolar patients (Table 1). This data demonstrates significant changes in BDNF in ECT-treated humans, and validates our method of identification of differentially expressed genes in the ECT-treated human brain.

Analysis of separate microarray data³ revealed that BDNF was differentially expressed in the mouse ventromedial hypothalamus following ECT therapy. When sorting all of the transcripts measured by microarray based on change in expression when comparing the ventromedial hypothalamus of ECT-treated mice with that of a sham-treated mouse, BDNF ranked 122 out of 22690 transcripts. Differential expression of BDNF in the ventromedial hypothalamus of ECT-treated mice was statistically significant (Table 2; $p=0.0025304$). BDNF expression was higher in the ventromedial hypothalamus of ECT-treated mice as compared to the ventromedial hypothalamus of a sham-treated mouse (Figure 2). We calculated a fold

change of 9.5286 ± 2.4891 in BDNF expression in the ventromedial hypothalamus when comparing ECT-treated mice to sham-treated mice (Table 2). Thus, we observed changes in BDNF expression associated with ECT in humans and induced by ECT in mice.

Expression of protocadherin alpha genes is decreased after therapy with ECT.

Mice with a targeted deletion at the protocadherin alpha locus exhibit significant depressive-like behaviors¹⁰, and patients resistant to SSRI therapy express significantly lower levels of PCDHA6 and PCDHA8 than those responsive to it¹¹. Comparing orbitofrontal cortex or dorsolateral prefrontal cortex tissue from patients with bipolar disease, either having received ECT therapy or not² revealed that changes in PCDHA2/PCDHA3 were among the most significant changes in ECT-treated bipolar patients. When sorting all of the transcripts measured by microarray based on change in expression when comparing ECT-treated bipolar patients and bipolar patients never having received ECT, PCDHA2/PCDHA3 ranked 248 out of 22283 transcripts. Differential expression of PCDHA2/PCDHA3 in ECT-treated bipolar patients was statistically significant (Table 3; $p=2.82E-02$). PCDHA2 was expressed at lower levels in ECT-treated patients with bipolar disease; this difference was not statistically significant (Figure 3; $p=0.1410$). We calculated a fold change of 0.8132 ± 0.1892 in PCDHA2/PCDHA3 expression when comparing ECT-treated bipolar patients to non-treated bipolar patients (Table 3).

In mice, we observed significant differential expression of a PCDHAC2/AC1/A12/9/1/10/11/4 transcript in the dentate gyrus⁵ and in the paraventricular hypothalamus⁴. When sorting all of the transcripts measured by microarray based on change in expression when comparing ECT-treated mice and a sham-treated mouse, PCDHAC2/AC1/A12/9/1/10/11/4 ranked 84 out of 22690 transcripts in the dentate gyrus. When sorting all of the transcripts measured by microarray based on change in expression when comparing ECT-treated mice and sham-treated mice, PCDHAC2/AC1/A12/9/1/10/11/4 ranked 89 out of 22690 transcripts in the paraventricular hypothalamus. Differential expression of PCDHAC2/AC1/A12/9/1/10/11/4 in ECT-treated mice was statistically significant, both in the dentate gyrus (Table 4; $p=0.0015803$)

1 and in the paraventricular hypothalamus (Table 4; $p=0.0038553$). PCDHAC2/AC1/
2 A12/9/1/10/11/4 was expressed at lower levels in the paraventricular hypothalamus of ECT-
3 treated mice and this difference was statistically significant (Figure 4; $p=0.0003$). PCDHAC2/
4 AC1/A12/9/1/10/11/4 was also expressed at lower levels in the dentate gyrus of ECT-treated
5 mice. We calculated a fold change of 0.1639 ± 0.1243 in the paraventricular hypothalamus in
6 PCDHAC2/AC1/A12/9/1/10/11/4 expression when comparing ECT-treated mice to sham-treated
7 mice (Table 4), and a fold change of 0.3088 ± 0.0196 in the dentate gyrus in PCDHAC2/AC1/
8 A12/9/1/10/11/4 expression when comparing ECT-treated mice to sham-treated mice (Table 4).

9
10 Thus, in ECT-treated bipolar patients and in ECT-treated mice, we observed decreases
11 in expression at the protocadherin alpha gene cluster, a similar trend to the decreased
12 expression of PCDHA6 and PCDHA8 in SSRI-resistant patients (non-remitting patients with on
13 average 20% response to escitalopram or citalopram as compared to 70% response in
14 remitters). In mice, we observed a near loss of expression of a transcript produced at the
15 Pcdha gene cluster after therapy with ECT, a similar trend to that of Pcdha^{-/-} mice exhibiting
16 depressive-like behaviors.

17 18 Multiple transcriptional changes in ECT-treated humans and in ECT-treated mice.

19 We were able to identify several other changes in the orbitofrontal cortex and
20 dorsolateral prefrontal cortex of ECT-treated bipolar patients using published microarray data
21 which could be supported by similar findings in ECT-treated mice. Specifically, we observed
22 differential expression of FGFR4, ABCC9, CDX4, and MMP14 in the brains of ECT-treated
23 bipolar patients.

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25 When sorting all of the transcripts measured by microarray based on change in
26 expression when comparing ECT treated and bipolar patients never having received ECT,
27 FGFR4 ranked 152 out of 22283 transcripts. Differential expression of FGFR4 in ECT-treated
28 bipolar patients was statistically significant (Table 5; $p=1.96E-02$). FGFR4 was expressed at
lower levels in ECT-treated patients with bipolar disease; this difference was statistically

significant (Figure 5; $p=0.0353$). We calculated a fold change of 0.8316 ± 0.1014 in FGFR4 expression when comparing ECT-treated bipolar patients to non-treated bipolar patients (Table 5).

When sorting all of the transcripts measured by microarray based on change in expression when comparing ECT treated and bipolar patients never having received ECT, ABCC9 ranked 59 out of 22283 transcripts. Differential expression of ABCC9 in ECT-treated bipolar patients was statistically significant (Table 5; $p=7.97E-03$). ABCC9 was expressed at higher levels in ECT-treated patients with bipolar disease; this difference was not statistically significant (Figure 6; $p=0.2489$). We calculated a fold change of 1.1607 ± 0.2251 in ABCC9 expression when comparing ECT-treated bipolar patients to non-treated bipolar patients (Table 5).

When sorting all of the transcripts measured by microarray based on change in expression when comparing ECT treated and bipolar patients never having received ECT, CDX4 ranked 93 out of 22283 transcripts. Differential expression of CDX4 in ECT-treated bipolar patients was statistically significant (Table 5; $p=1.3E-02$). CDX4 was expressed at lower levels in ECT-treated patients with bipolar disease; this difference trended towards significance but was not statistically significant (Figure 7; $p=0.0639$). We calculated a fold change of 0.8303 ± 0.1232 in CDX4 expression when comparing ECT-treated bipolar patients to non-treated bipolar patients (Table 5).

When sorting all of the transcripts measured by microarray based on change in expression when comparing ECT treated and bipolar patients never having received ECT, MMP14 ranked 89 out of 22283 transcripts. Differential expression of MMP14 in ECT-treated bipolar patients was statistically significant (Table 5; $p=1.21E-02$). MMP14 was expressed at higher levels in ECT-treated patients with bipolar disease; this difference was statistically significant (Figure 8; $p=0.0076$). We calculated a fold change of 1.1365 ± 0.0542 in MMP14 expression when comparing ECT-treated bipolar patients to non-treated bipolar patients (Table 5).

1 To determine whether these changes in gene expression were associated with the
2 disease process or disease severity, or whether these changes in gene expression could have
3 been caused by ECT, we probed independent microarray datasets³⁻⁵. We found similar
4 changes in FGFR4, ABCC9, CDX4, and MMP14 gene expression in the brains of ECT-treated
5 mice.

6 When sorting all of the transcripts measured by microarray based on change in
7 expression when comparing ECT-treated mice and sham-treated mice, FGFR4 ranked 114 out
8 of 22690 transcripts in the dentate gyrus⁵. Differential expression of FGFR4 in the dentate
9 gyrus of ECT-treated mice was statistically significant (Table 6; $p=0.0024483$). FGFR4 was
10 expressed at lower levels in the dentate gyrus of ECT-treated mice when compared to that of a
11 sham-treated mouse (Figure 5). We calculated a fold change of 0.2908 ± 0.0325 in the dentate
12 gyrus in FGFR14 expression when comparing ECT-treated mice to a sham-treated mouse
13 (Table 6).
14

15 When sorting all of the transcripts measured by microarray based on change in
16 expression when comparing ECT-treated mice and sham-treated mice, ABCC9 ranked 74 out of
17 22690 transcripts in the dentate gyrus⁵. Differential expression of ABCC9 in the dentate gyrus
18 of ECT-treated mice was statistically significant (Table 6; $p=0.0012294$). ABCC9 was expressed
19 at higher levels in the dentate gyrus of ECT-treated mice when compared to that of a sham-
20 treated mouse (Figure 6). We calculated a fold change of 7.500 ± 1.392 in the dentate gyrus in
21 ABCC9 expression when comparing ECT-treated mice to a sham-treated mouse (Table 6).
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23 When sorting all of the transcripts measured by microarray based on change in
24 expression when comparing ECT-treated mice and sham-treated mice, CDX4 ranked 79 out of
25 22690 transcripts in the paraventricular hypothalamus⁴. Differential expression of CDX4 in the
26 paraventricular hypothalamus of ECT-treated mice was statistically significant (Table 6;
27 $p=0.0031804$). CDX4 was expressed at lower levels in the paraventricular hypothalamus of
28 ECT-treated mice as compared to sham-treated mice, but this difference was not statistically
significant (Figure 7; $p=0.4046$). We calculated a fold change of 0.0718 ± 0.0178 in the

paraventricular hypothalamus in CDX4 expression when comparing ECT-treated mice to sham-treated mice (Table 6).

When sorting all of the transcripts measured by microarray based on change in expression when comparing ECT-treated mice and sham-treated mice, MMP14 ranked 98 out of 22690 transcripts in the ventromedial hypothalamus³. Differential expression of MMP14 in the ventromedial hypothalamus of ECT-treated mice was statistically significant (Table 6; $p=0.0019692$). MMP14 was expressed at higher levels in the ventromedial hypothalamus of ECT-treated mice as compared to that of a sham-treated mouse (Figure 8). We calculated a fold change of 10.2121 ± 0.8447 in the ventromedial hypothalamus in MMP14 expression when comparing ECT-treated mice to a sham-treated mouse (Table 6).

Thus, by integrating analysis of multiple published and public microarray datasets, we found significant changes in the global gene expression profiles of specific regions of the brain associated with ECT therapy: in mice and in humans, in the BDNF gene, transcripts from PCDHA gene cluster, FGFR4, ABCC9, CDX4, and MMP14.

Discussion

It is not understood how ECT functions to provide symptom relief in psychiatric disorders like major depression. We compared brain tissues from ECT-treated human and mice to that of human and mice never having received ECT using published microarray datasets and integrated findings of differential gene analyses to identify conserved gene expression changes induced by ECT.

Mice containing a deletion of the protocadherin alpha (Pcdha) gene cluster in serotonergic neurons possess defects in axonal tiling, wherein the axons of serotonergic neurons innervate the 3-dimensional space of the brain, with axon terminals arranging in a tiled fashion to allow optimal distribution of serotonin throughout the brain¹⁰. Pcdha2 is the only Pcdha isoform expressed in the serotonergic neurons of mice; loss of Pcdha2 expression was thus demonstrated as a specific cause of axon tiling defects¹⁰. Pcdha2 was expressed at lower

1 levels in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated bipolar
2 disease patients.

3 While we found changes thought to be associated with improvement or enhancement of
4 mood in ECT-treated patients (e.g., BDNF) we also found changes that are reflective of gene
5 expression in the brains of patients with the worst response to SSRI medications (e.g., PCDHA
6 gene cluster transcripts)¹¹. Though analysis of human data alone² would be inconclusive as to
7 whether these differences are induced by ECT or simply a reflection of gene expression in the
8 brain of a more acutely depressed patient, we found similar changes for each of the genes
9 described here in mice experimentally treated with ECT³⁻⁵. This suggests that each of these
10 changes are reflective of actual transcriptional modulation in the brain caused by
11 electroconvulsive therapy.
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13 Future studies can determine whether ECT dosage correlates with magnitude of
14 expression changes in the brain for any of these genes¹², and whether modeling any of these
15 changes in the mouse brain can mimic therapeutic efficacy or associated cognitive sequelae¹³.
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Rank	ID	p-value	t	B	Fold change	Gene	Gene name
181	206382_s_at	2.24E-02	2.36884264	-3.718	1.8074 ± 1.5323	BDNF	brain derived neurotrophic factor

Table 1: BDNF is differentially expressed in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of gene expression between groups compared, the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Fold change	Gene	Gene name
122	1422169_a_at	0.0025304	5.08	-1.1456	9.5286 ± 2.4891	Bdnf	brain derived neurotrophic factor

Table 2: BDNF is differentially expressed in the ventromedial hypothalamus of ECT-treated mice.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of gene expression between groups compared, the gene and gene name are listed in this chart.

Figure 1: BDNF is expressed at higher levels in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease as compared to patients with bipolar disease never receiving ECT.

The mRNA expression of BDNF in brain tissues from patients with bipolar disease never receiving ECT (left) and in brain tissues from bipolar patients receiving ECT treatments (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in BDNF expression between the brains of control bipolar patients and brains of bipolar patients receiving ECT, a p-value, listed above.

Figure 2: BDNF is expressed at higher levels in the ventromedial hypothalamus of ECT-treated mice.

The mRNA expression of BDNF in brain tissues from sham-treated mice (left) and in brain tissues from ECT-treated mice (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in BDNF expression between a sham-treated mouse and ECT-treated mice, a p-value, listed above.

Rank	ID	p-value	t	B	Fold change	Gene	Gene name
248	210572_at	2.82E-02	2.27089121	-3.805	0.8132 ± 0.1892	PCDHA2///PCDHA3	protocadherin alpha 2///protocadherin alpha 3

Table 3: PCDHA2/3 is differentially expressed in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of gene expression between groups compared, the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Fold change	Gene	Gene name
89	1425017_at	0.0038553	-4.41	-2.242	0.1639 ± 0.1243	Pcdhac2///Pcdhac1///Pcdha2///Pcdha12///Pcdha9///Pcdha1///Pcdha10///Pcdha11///Pcdha4	protocadherin alpha subfamily C, 2///protocadherin alpha subfamily C, 1///protocadherin alpha 2///protocadherin alpha 12///protocadherin alpha 9///protocadherin alpha 1///protocadherin alpha 10///protocadherin alpha 11///protocadherin alpha 4
84	1427687_at	0.0015803	-9.38	-0.3953523	0.3088 ± 0.0196	Pcdhac2///Pcdhac1///Pcdha2///Pcdha12///Pcdha9///Pcdha1///Pcdha10///Pcdha11///Pcdha4	protocadherin alpha subfamily C, 2///protocadherin alpha subfamily C, 1///protocadherin alpha 2///protocadherin alpha 12///protocadherin alpha 9///protocadherin alpha 1///protocadherin alpha 10///protocadherin alpha 11///protocadherin alpha 4

Table 4: A transcript produced at the PCDHA locus is differentially expressed in the brains of ECT-treated mice, in the dentate gyrus and in the paraventricular hypothalamus.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of gene expression between groups compared, the gene and gene name are listed in this chart.

Figure 3: PCDHA2/3 is expressed at lower levels in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease.

The mRNA expression of PCDHA transcript in brain tissues from patients with bipolar disease never receiving ECT (left) and in brain tissues from bipolar patients receiving ECT treatments (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in PCDHA transcript expression between the brains of control bipolar patients and brains of bipolar patients receiving ECT, a p-value, listed above.

PCDHAC2/AC1/A2/A12/A9/A1/A10/A11/A4

PCDHAC2/AC1/A2/A12/A9/A1/A10/A11/A4

Figure 4: A transcript produced at the PCDHA locus is expressed at lower levels in the brains of ECT-treated mice, in the dentate gyrus and in the paraventricular hypothalamus.

The mRNA expression of the PCDHA transcript in brain tissues from sham-treated mice (left) and in brain tissues from ECT-treated mice (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in PCDHA transcript expression between a sham-treated mouse and ECT-treated mice, a p-value, listed above.

Rank	ID	p-value	t	B	Fold change	Gene	Gene name
152	204579_at	1.96E-02	-2.42468912	-3.667	0.8316 ± 0.1014	FGFR4	fibroblast growth factor receptor 4
93	221340_at	1.3E-02	-2.59260155	-3.51	0.8303 ± 0.1232	CDX4	caudal type homeobox 4
89	160020_at	1.21E-02	2.6204698	-3.483	1.1365 ± 0.0542	MMP14	matrix metalloproteinase 14
59	208561_at	7.97E-03	-2.78360432	-3.324	1.1607 ± 0.2251	ABCC9	ATP binding cassette subfamily C member 9

Table 5: FGFR4, CDX4, ABCC9, and MMP14 are differentially expressed in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of gene expression between groups compared, the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Fold change	Gene	Gene name
114	1427776_a_at	0.0024483	-8.20	-0.722816	0.2908 ± 0.0325	Fgfr4	fibroblast growth factor receptor 4
79	1421552_at	0.0031804	-4.58	-2.154	0.0718 ± 0.0178	Cdx4	caudal type homeobox 4
98	1448383_at	0.0019692	5.35	-0.95548	10.2121 ± 0.8447	Mmp14	matrix metalloproteinase 14 (membrane-inserted)
74	1420408_a_at	0.0012294	1.01E	-0.2234303	7.500 ± 1.392	Abcc9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9

Table 6: FGFR4, CDX4, ABCC9, and MMP14 are differentially expressed in the brains of ECT-treated mice.

The rank of differential expression, the probe/transcript ID, the p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, the fold change of gene expression between groups compared, the gene and gene name are listed in this chart.

Figure 5: FGFR4 is expressed at lower levels in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease and in the dentate gyrus of ECT-treated mice.

The mRNA expression of FGFR4 transcript in brain tissues from patients with bipolar disease never receiving ECT and in brain tissues from bipolar patients receiving ECT treatments (left), and in a sham-treated and ECT-treated mice (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in FGFR4 transcript expression between the brains of control bipolar patients and brains of bipolar patients receiving ECT, a p-value, listed above.

Figure 6: ABCC9 is expressed at higher levels in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease and in the dentate gyrus of ECT-treated mice.

The mRNA expression of ABCC9 transcript in brain tissues from patients with bipolar disease never receiving ECT and in brain tissues from bipolar patients receiving ECT treatments (left), and in a sham-treated mouse as compared to ECT-treated mice (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in ABCC9 transcript expression between the brains of control bipolar patients and brains of bipolar patients receiving ECT, a p-value, listed above.

Figure 7: CDX4 is expressed at lower levels in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease and in the paraventricular hypothalamus of ECT-treated mice.

The mRNA expression of CDX4 transcript in brain tissues from patients with bipolar disease never receiving ECT and in brain tissues from bipolar patients receiving ECT treatments (left), and in sham-treated mice as compared to ECT-treated mice (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in CDX4 transcript expression between the brains of control bipolar patients and brains of bipolar patients receiving ECT, or between sham-treated mice and ECT-treated mice, a p-value, listed above.

Figure 8: MMP14 is expressed at higher levels in the orbitofrontal cortex and dorsolateral prefrontal cortex of ECT-treated patients with bipolar disease and in the ventromedial hypothalamus of ECT-treated mice.

The mRNA expression of MMP14 transcript in brain tissues from patients with bipolar disease never receiving ECT and in brain tissues from bipolar patients receiving ECT treatments (left), and in a sham-treated mouse as compared to ECT-treated mice (right) is represented with mean mRNA expression level marked and the result of a statistical test evaluating the significance of difference in MMP14 transcript expression between the brains of control bipolar patients and brains of bipolar patients receiving ECT, a p-value, listed above.