Annals of Depression and Anxiety

Open Access

Austin Publishing Group

Research Article

Understanding the Role of Glutamate and BDNF in Neurobiology of Depression: Data Mining of Stanley Neuropathology Consortium Integrative Database

Manish Kumar Jha[1]* and Shilpa Sachdeva[2]
[1]Department of Psychiatry, University of Texas Southwestern Medical Center, USA
[2]Department of Psychiatry and Behavioral Sciences, University of Kansas Medical Center, USA

***Corresponding author:** Manish Kumar Jha, Department of Psychiatry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA, Email: manish.jha@utsouthwestern.edu

Received: March 30, 2015; **Accepted:** May 28, 2015; **Published:** June 04, 2015

Abstract

Major Depressive Disorder is a common and chronic illness which is associated with significant impairment in quality of life. Rapid antidepressant effects of Ketamine have highlighted the role of glutamate neurotransmission and Brain Derived Neurotrophic Factor (BDNF) signaling in Major Depressive Disorder. Postmortem brain studies provide a valuable tool to study the molecular changes in brain; however, access to postmortem brain tissue is limited to major academic centers. In this report, we performed exploratory analyses on datasets generated by researchers across the world and made available publicly via the Stanley Neuropathology Consortium Integrative Database. Using in-built statistical analyses tool of this database, we found reports that depressed subjects had increased levels of GluA2 mRNA in dorsolateral prefrontal cortex while reduced levels of SLC1A2 mRNA in white matter of frontal cortex. We also found reports of reduced levels of PSD95, GluN1 and TrkB proteins in frontal cortical brain regions of depressed subjects as compared to control subjects. None of these comparisons were statistically significant after adjusting for multiple comparisons.

Keywords: BDNF; MDD; SNCID

Introduction

Major Depressive Disorder (MDD) affects 5 to 7 percent of adults in US every year [1,2]. It is associated with significant impairment in quality of life [3]. The medications which are commonly prescribed to treat depression target monoamine neurotransmission and are ineffective for a large number of patients [4]. Rapid antidepressant effect of Ketamine has highlighted the role of impaired glutamate neurotransmission in MDD [5,6]. Glutamate is a neurotransmitter which mediates fast excitatory neurotransmission in brain. Along with the Brain Derived Neurotrophic Factor (BDNF) it also affects neurogenesis and synaptic plasticity [7]. Impaired BDNF signaling has also been implicated in pathophysiology of MDD [8].

Consistent with the role of impaired excitatory neurotransmission, neuroimaging studies have also found reduced resting state brain activity in prefrontal cortex of MDD patients [9-14]. As the depressive symptoms resolve, there is an increase in activity in this brain region. Molecular changes in both glutamate and BDNF signaling may contribute to the frontal cortical deficits. Hence, there is a need to characterize the molecular changes in glutamate-BDNF signaling in major depressive disorder. Postmortem brain studies can help in improving our understanding of these molecular changes.

Only a few academic centers across US have postmortem brain collections or repositories for psychiatric diseases. Hence as described by Kim and Webster [15,16], the Stanley Neuropathology Consortium Integrative Database (SNCID) is an easy-to-use platform to analyze molecular changes associated with psychiatric illnesses. In this report, we have used the data mining approach to identify changes in glutamate-BDNF signaling in frontal cortex of subjects with MDD.

Methods

After registering for online access to SNCID, authors accessed the data mining tool of Neuropathology Consortium (http://sncid.stanleyresearch.org/DataExplorer.aspx) on September 22, 2014. Data exploration was restricted to the Neuropathology consortium database. Using the dropdown menu in the data explorer webpage, an exploratory search was conducted for all marker types in the frontal cortex brain region. Total of 909 records were then reviewed for reports on the following markers: BDNF and its receptor TrkB; GRIN1, GRIN2A, GRIN2B, GRIA1, and GRIA1; postsynaptic density protein (PSD95); and excitatory amino acid transporters SLC1A2 and SLC1A3. The link for statistical analysis was then used to perform non-parametric tests to compare the levels of above mentioned marker types in frontal cortical regions of brains from depressed and control subjects. The p values for Depression vs. Control comparisons were recorded and tabulated along with the name of the investigator, brain region, method, and sample size. The link for reference on each marker was checked to see if the data from these analyses have been reported previously.

Results

Data from 51 comparisons, most of them previously unpublished, were available for analyses. The name of investigator, the region of brain from which tissue was obtained, investigational method, sample sizes and p values were compiled in table 1. As shown in table 1, five analyses had p-values less than or equal to 0.05. Using quantitative Polymerase Chain Reaction (RT-PCR), Hemby et al. found that expression of GRIA2 mRNA was increased in Brodmann

Citation: Jha MK and Sachdeva S. Understanding the Role of Glutamate and BDNF in Neurobiology of Depression: Data Mining of Stanley Neuropathology Consortium Integrative Database. Ann Depress Anxiety. 2015;2(2): 1045.

Table 1: Five analyses had p-values less than or equal to 0.05.

	Investigator	Brain Region	Method	Sample size	pValue*
BDNF	SJ Watson	DLPFC layer I	in situ hybridization	15 Dep, 15 Con	0.36
BDNF	SJ Watson	DLPFC layer II	in situ hybridization	15 Dep, 15 Con	1.00
BDNF	SJ Watson	DLPFC layer III	in situ hybridization	15 Dep, 15 Con	0.41
BDNF	SJ Watson	DLPFC layer IV	in situ hybridization	15 Dep, 15 Con	0.49
BDNF	SJ Watson	DLPFC layer V	in situ hybridization	15 Dep, 15 Con	0.38
BDNF	SJ Watson	DLPFC layer VI	in situ hybridization	15 Dep, 15 Con	0.49
BDNF	Maree Webster	Frontal cortex layer I	in situ hybridization	15 Dep, 15 Con	0.30
BDNF	Maree Webster	Frontal cortex layer II	in situ hybridization	15 Dep, 15 Con	0.25
BDNF	Maree Webster	Frontal cortex layer III	in situ hybridization	15 Dep, 15 Con	0.32
BDNF	Maree Webster	Frontal cortex layer IV	in situ hybridization	15 Dep, 15 Con	0.68
BDNF	Maree Webster	Frontal cortex layer V	in situ hybridization	15 Dep, 15 Con	0.39
BDNF	Maree Webster	Frontal cortex layer VIa	in situ hybridization	15 Dep, 15 Con	0.06
BDNF	Maree Webster	Frontal cortex layer VIb	in situ hybridization	15 Dep, 15 Con	0.18
BDNF	Maree Webster	Frontal cortex layer all	in situ hybridization	15 Dep, 15 Con	0.39
GRIN1	Bill Deakin	Frontal cortex	in situ hybridization	15 Dep, 15 Con	0.37
GRIN1	Maria Karayiorgou	Frontal cortex	Western blot – total protein	15 Dep, 15 Con	0.10
GRIN1	Maria Karayiorgou	Frontal cortex	Western blot – phosphor protein	15 Dep, 15 Con	0.15
GRIN1	**Maria Karayiorgou**	**Frontal cortex**	**Western blot – phosphor protein/total**	**15 Dep, 15 Con**	**0.02**
NR1	Kotaro Hattori	Frontal cortex (BA6)	Dot blot/normalized to GAPDH	15 Dep, 15 Con	0.71
NR1	Bill Deakin	Orbital Frontal Cortex BA 22 grey matter	Immunoautoradiography using fixed section	15 Dep, 15 Con	0.17
NR1	Bill Deakin	Orbital Frontal Cortex BA 11 white matter	Immunoautoradiography using fixed section	15 Dep, 15 Con	0.47
NR1	Bill Deakin	Orbital Frontal Cortex BA 45 grey matter	Immunoautoradiography using fixed section	15 Dep, 15 Con	0.35
NR1	Bill Deakin	Orbital Frontal Cortex BA 45 white matter	Immunoautoradiography using fixed section	15 Dep, 15 Con	0.45
NR1	Bill Deakin	Orbital Frontal Cortex BA 32 grey matter	Immunoautoradiography using fixed section	15 Dep, 15 Con	0.55
NR1	Bill Deakin	Orbital Frontal Cortex BA 32 white matter	Immunoautoradiography using fixed section	15 Dep, 15 Con	0.68
NR2A	Kotaro Hattori	Frontal cortex (BA6)	Dot blot/normalized to GAPDH	15 Dep, 15 Con	0.30
NR2B	Kotaro Hattori	Frontal cortex (BA6)	Dot blot/normalized to GAPDH	15 Dep, 15 Con	0.13
TrkB (NTRK2)	Maree Webster	Orbital frontal cortex layer 1	in situ hybridization	15 Dep, 15 Con	0.17
TrkB (NTRK2)	Maree Webster	Orbital frontal cortex layer 2	in situ hybridization	15 Dep, 15 Con	0.31
TrkB (NTRK2)	Maree Webster	Orbital frontal cortex layer 3	in situ hybridization	15 Dep, 15 Con	0.48
TrkB (NTRK2)	Maree Webster	Orbital frontal cortex layer 4	in situ hybridization	15 Dep, 15 Con	0.20
TrkB (NTRK2)	Maree Webster	Orbital frontal cortex layer 5	in situ hybridization	15 Dep, 15 Con	0.33
TrkB (NTRK2)	Maree Webster	Orbital frontal cortex layer 6	in situ hybridization	15 Dep, 15 Con	0.25
TrkB	Carla Toro	Frontal cortex (BA6)	Immunoblot/normalized to actin	15 Dep, 15 Con	0.91
TrkB	Carla Toro	Frontal cortex (BA6)	Westerns - normalized to actin (background corrected	15 Dep, 15 Con	0.06
T-TrkB	Carla Toro	Frontal cortex (BA6)	Westerns - normalized to actin (background corrected	15 Dep, 15 Con	0.87
TrkB/T-TrkB	Carla Toro	Frontal cortex (BA6)	Westerns - normalized to T-TrkB (background corrected	15 Dep, 15 Con	0.06
TrkB/ p75	**Carla Toro**	**Frontal cortex (BA6)**	**Westerns - normalized to p75 (background corrected**	**15 Dep, 15 Con**	**0.02**
T-TrkB/ p75	Carla Toro	Frontal cortex (BA6)	Westerns - normalized to p75 (background corrected	15 Dep, 15 Con	0.58
PSD95	**Bill Deakin**	**Orbital frontal cortex BA11**	**Immunoautoradiography using fixed section**	**15 Dep, 15 Con**	**0.02**
PSD95	Bill Deakin	Orbital frontal cortex BA45	Immunoautoradiography using fixed section	15 Dep, 15 Con	0.96
SLC1A2	Cynthia Weickert	Frontal/superficial gray	in situ hybridization	15 Dep, 15 Con	0.07

SLC1A2	Cynthia Weickert	Frontal/deep	in situ hybridization	15 Dep, 15 Con	0.16
SLC1A2	**Cynthia Weickert**	**Frontal/white matter**	**in situ hybridization**	**15 Dep, 15 Con**	**0.05**
SLC1A3	Cynthia Weickert	Frontal/superficial gray	in situ hybridization	15 Dep, 15 Con	0.93
SLC1A3	Cynthia Weickert	Frontal/deep	in situ hybridization	15 Dep, 15 Con	0.77
SLC1A3	Cynthia Weickert	Frontal/white matter	in situ hybridization	15 Dep, 15 Con	0.53
GRIA1	Scott Hemby	Frontal cortex BA46	RT-PCR	15 Dep, 15 Con	0.07
GRIA2	**Scott Hemby**	**Frontal cortex BA46**	**RT-PCR**	**15 Dep, 15 Con**	**0.02**
GRIA2	Scott Hemby	Frontal cortex BA46	RT-PCR/flip	15 Dep, 15 Con	0.20
GRIA2	Scott Hemby	Frontal cortex BA46	RT-PCR/flop	15 Dep, 15 Con	0.30

*p Value – rounded off to two digits.

Area 46 in depressed subjects as compared to controls. Weickert et al. found reduced expression of SLC1A2 mRNA in white matter of frontal cortex using in situ hybridization. Reduced levels of PSD95, GRIN1 and TrkB proteins in depressed subjects as compared to controls were reported by Deakin et al., Karayiorgou et al., and Toro et al. respectively. None of these comparisons were significant after adjusting for multiple comparisons using Bonferroni correction.

Discussion

An exploratory analysis of the Stanley Neuropathology Consortium Integrative Database using a web-based tool suggests aberrant glutamate-BDNF neurotransmission. Consistent with findings of neuroimaging studies, our exploratory analyses suggests that markers related to glutamate-BDNF signaling are reduced in frontal cortical regions. Reduced levels of PSD95, GRIN1 and TrkB in this database have not been reported previously. Reduced levels of GRIN1 as reported in this study are consistent with previous findings of and Beneyto and Meador-Woodruff [17]. Similarly, reduced levels of TrkB have also been reported by Qi et al. [18].

There are several limitations of this study. As listed in the disclaimers section of SNCID website (http://sncid.stanleyresearch.org/Disclaimer.aspx), this database has been generated with multiple datasets provided by research groups across the world. Hence, the research methods vary between these groups. Additionally, the use of in-built statistical analyses tool limits the kind of statistical analyses. Effects of confounding variables like age, postmortem interval, pH, duration of illness, suicide status, use of antidepressant medications etc. were not evaluated in these analyses.

This report demonstrates the utility of this easily accessible database in exploration of the molecular basis of Major Depressive Disorder. Despite the limitations as listed above, this database allows for exploratory analyses which in turn can be used to generate hypotheses for future research. With increasing emphasis on sharing data by the national institute of health (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html) and other governmental agencies (https://www.whitehouse.gov/sites/default/files/omb/memoranda/2013/m-13-13.pdf), this report andStanley Neuropathology Consortium Integrative Database serve as a model for using these publicly available databases for future studies.

References

1. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry. 2005; 62: 1097-1106.
2. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289: 3095-3105.
3. Jha MK, Minhajuddin A, Thase ME, Jarrett RB. Improvement in self-reported quality of life with cognitive therapy for recurrent major depressive disorder. J Affect Disord. 2014; 167: 37-43.
4. Murrough JW, Charney DS. Is there anything really novel on the antidepressant horizon? Curr Psychiatry Rep. 2012; 14: 643-649.
5. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry. 2013; 170: 1134-1142.
6. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, Collins KA, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013; 74: 250-256.
7. Mattson MP. Glutamate and neurotrophic factors in neuronal plasticity and disease. Ann N Y Acad Sci. 2008; 1144: 97-112.
8. Kerman IA. New insights into BDNF signaling: relevance to major depression and antidepressant action. Am J Psychiatry. 2012; 169: 1137-1140.
9. Baxter LR Jr, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry. 1989; 46: 243-250.
10. Brody AL, Saxena S, Mandelkern MA, Fairbanks LA, Ho ML, Baxter LR. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. Biol Psychiatry. 2001; 50: 171-178.
11. Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry. 2004; 61: 34-41.
12. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry. 2000; 48: 830-843.
13. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry. 1999; 156: 675-82.
14. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005; 45: 651-660.
15. Kim S, Webster MJ. The Stanley neuropathology consortium integrative database: a novel, web-based tool for exploring neuropathological markers in psychiatric disorders and the biological processes associated with abnormalities of those markers. Neuropsychopharmacology. 2010; 35: 473-82.
16. Kim S, Webster MJ. Postmortem brain tissue for drug discovery in psychiatric research. Schizophr Bull. 2009; 35: 1031-1033.

17. Beneyto M, Meador-Woodruff JH. Lamina-Specific Abnormalities of NMDA Receptor-Associated Postsynaptic Protein Transcripts in the Prefrontal Cortex in Schizophrenia and Bipolar Disorder. Neuropsychopharmacology. 2007; 33: 2175-2186.

18. Qi XR, Zhao J, Liu J, Fang H, Swaab DF, Zhou JN. Abnormal retinoid and TrkB signaling in the prefrontal cortex in mood disorders. Cereb Cortex. 2015; 25: 75-83.

Ann Depress Anxiety - Volume 2 Issue 2 - 2015
ISSN : 2381-8883 | www.austinpublishinggroup.com

Citation: Jha MK and Sachdeva S. Understanding the Role of Glutamate and BDNF in Neurobiology of Depression: Data Mining of Stanley Neuropathology Consortium Integrative Database. Ann Depress Anxiety. 2015;2(2): 1045.