

Accelerated age-related decrease in brain-derived neurotrophic factor levels in bipolar disorder



Received 3 June 2008; Reviewed 13 July 2008; Revised 31 July 2008; Accepted 21 August 2008;
First published online 10 October 2008

Age-related conditions, such as cognitive decline, cardiovascular disease, cancer and other medical morbidities have been associated with bipolar disorder (BD) (Kapczinski et al., 2008). However the biological mechanisms underlying these associations remain unclear.

It is well established that bipolar patients show greater cognitive impairment than age-matched controls, not only during mood episodes but also during euthymia (Torres et al., 2007). Further, recent evidence suggests that growth-factor family members, particularly the brain-derived neurotrophic factor (BDNF), may play an important role in the pathophysiology of BD (Kapczinski et al., 2008; Post, 2007) and in neuroplasticity associated with ageing (Lommatzsch et al., 2005; Mora et al., 2007). Notably, BDNF is essential for long-term memory as it promotes neuronal survival and maturation. Some studies have suggested that abnormalities in the BDNF-signalling pathway might be involved in the cognitive decline observed in neuropsychiatric disorders, including Alzheimer's (Laske and Eschweiler, 2006) and BD (Rybakowski et al., 2006). Interestingly, studies of normal ageing have shown that expression of BDNF in the hippocampus decreases with age (Hattiangady et al., 2005) and these decreases might contribute to age-related cognitive impairments (Gooney et al., 2004). To the best of our knowledge, the pattern of changes in BDNF levels in relation to age has not been examined in a clinical sample of patients with BD.

To explore this issue, we examined BDNF levels in 56 patients with bipolar I disorder and 56 healthy controls matched for age, gender and level of education. Patients were recruited from the first-episode mania programme of the University of British Columbia (UBC) Hospital, Vancouver, Canada ($n=26$) and from Bipolar Disorders Programme, Federal University of

Rio Grande do Sul (UFRGS), Porto Alegre, Brazil ($n=30$). Patients were not in an acute mood episode according to DSM-IV criteria and the diagnosis was confirmed with structured interview. The symptomatic status was assessed within 1 wk of blood sampling with clinical rating scales such as the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale, 21-item version (HAMD-21). Subjects enrolled in both centres received open-label maintenance treatment for BD from clinicians with expertise in management of mood disorders and familiar with the most recent clinical guidelines. Patients did not have significant comorbid medical conditions and they were not on medication other than those prescribed for their psychiatric condition. Clinical variables were collected using a standardized protocol. Controls were screened to rule out any history of psychiatric disorder, neurodegenerative disorder, mental retardation, cancer or chronic/acute infection and they were not on any medication. All of the procedures described in this report have received approval from the local clinical research ethics committees. Written informed consent was obtained from all patients and healthy subjects prior to conducting any study procedures. BDNF serum levels were measured with ELISA kit (Chemicon, Temecula, CA, USA). Total protein was measured by Lowry's method using bovine serum albumin as a standard. Results for BDNF are shown in $\text{pg}/\mu\text{g}$ protein. Statistical analyses such as Pearson's correlation followed by two-way ANOVA, were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

As expected, there was a significant negative correlation between BDNF levels and age in controls ($r=-0.29$, $p=0.027$) as well as in patients ($r=0.70$, $p<0.001$) (Figure 1). Interestingly, there was a significant difference between the slopes of patients and controls ($F=14.1$, $\text{d.f.}=1, 112$, $p<0.001$) indicating that the decrease in BDNF levels was accelerated with age in patients with BD compared with matched healthy controls. The correlation between age and BDNF levels was significant regardless of mood symptoms, in a regression model controlled for YMRS and HAMD scores ($\beta=-0.49$, $p=0.004$). This suggests that BD pathophysiology may involve not only changes in

Address for correspondence: L. N. Yatham, MBBS, FRCPC, MRCPsych (UK), Professor of Psychiatry and Associate Head, Research and International Affairs Department of Psychiatry, University of British Columbia, Room 2C7, 2255 Westbrook Mall, Vancouver, BC, V6T 2A1 Canada.
Tel.: 1-604-822-7325 Fax: 1-604-822-7922
E-mail: yatham@exchange.ubc.ca

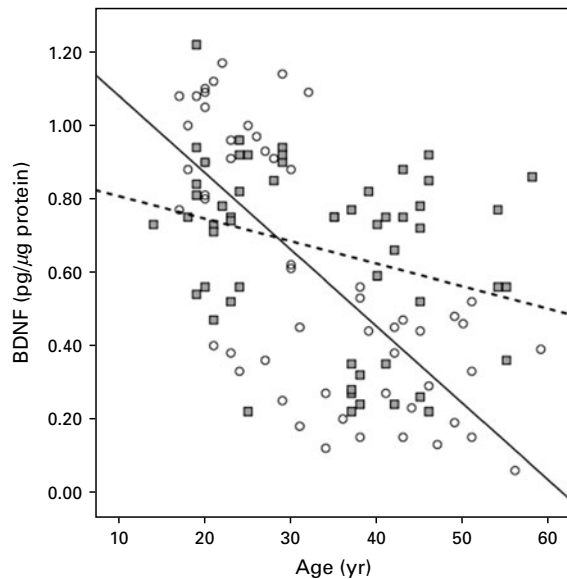


Figure 1. Correlation between brain-derived neurotrophic factor (BDNF) levels and age in patients with bipolar disorder (○) and in healthy controls (■). Significant negative correlation between BDNF levels and age in controls ($r = -0.29$, $p = 0.027$) and in patients ($r = 0.70$, $p < 0.001$). Significant difference between the slopes of patients (—) and controls (---) ($F = 14.1$, d.f. = 1, 112, $p < 0.001$).

biochemistry that result in mood episodes, but also changes associated with accelerated ageing processes.

Some limitation should be considered when interpreting the results. First, BDNF levels were only assessed in the serum, however, it has been demonstrated that there is a high positive correlation ($r = 0.81$) between serum and cortical BDNF levels (Karege et al., 2002). Moreover, there is evidence that serum levels of BDNF might reflect aspects of neuronal integrity given the association with *N*-acetylaspartate levels (Lang et al., 2007). Second, all patients were on medication at the time of blood sampling, mostly mood stabilizers, such as lithium and divalproex. The use of these medications and improvement in symptoms has previously been reported to be associated with normalization of BDNF levels in previous studies. This would suggest that the decrease of BDNF with age would be even more marked if these patients had not been taking medication.

The finding of accelerated age-related decrease in BDNF levels in BD is in line with recent reports suggesting accelerated ageing in BD (Simon et al., 2006). For instance, the telomere length, which has been used as a marker of ageing, was significantly shorter in those with mood disorders, representing as much as 10 yr of accelerated ageing (Simon et al., 2006). Indirect evidence

also comes from studies showing increased oxidative stress in BD, which is also known to increase with ageing (Andreazza et al., 2007). Notably, oxidative stress is associated with DNA damage, endothelial dysfunction and telomere shortening. These findings of accelerated age-related processes provide further support for investigating the therapeutic role of the long-term effects of agents with neurotrophic, anti-inflammatory and antioxidant properties in the treatment of BD.

Acknowledgements

The First-episode Program (UBC) was funded by an unrestricted grant from AstraZeneca to Dr Yatham. The Bipolar Disorders Program (HCPA) was supported by CNPq and FIPE-HCPA.

Statement of Interest

Dr Yatham is on speaker/advisory boards for, or has received research grants from: AstraZeneca, Bristol-Myers Squibb, Canadian Institutes of Health Research, Canadian Network for Mood and Anxiety Treatments, Eli Lilly, GlaxoSmithKline, Janssen, Michael Smith Foundation for Health Research, Pfizer, Servier and Stanley Foundation. Dr Kauer-Sant'Anna has been an investigator in clinical trials sponsored by Servier, CIHR, and Stanley Foundation; has received an APA/AstraZeneca unrestricted educational grant and a NARSAD Young Investigator Award and is supported by CNPq. Dr Kapczynski has been an investigator in clinical trials sponsored by CNPq, CIHR, Stanley Foundation and Servier. He has worked as consultant/speaker for Servier, AstraZeneca, Eli Lilly and Abbott. Dr Bond has been an investigator in clinical trials sponsored by Sanofi-Aventis, GlaxoSmithKline, and Servier, and has received speaking fees from AstraZeneca and the Canadian Network for Mood and Anxiety Treatments. Dr Lam is on speaker/advisory boards for, or has received research grants from: ANS Inc., AstraZeneca, Biovail, Canadian Institutes of Health Research, Canadian Network for Mood and Anxiety Treatments, Eli Lilly, GlaxoSmithKline, Great West Life, Janssen, Litebook Company Ltd, Lundbeck, Sanofi-Aventis, Servier, VGH and UBC Hospital Foundation, and Wyeth. Dr Andreazza is supported by CNPq.

References

- Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Ceresér KM, Santin A, Gottfried C, et al. (2007). Serum S100B and antioxidant

- enzymes in bipolar patients. *Journal of Psychiatric Research* 41, 523–529.
- Gooney M, Messaoudi E, Maher FO, Bramham CR, Lynch MA** (2004). BDNF-induced LTP in dentate gyrus is impaired with age: analysis of changes in cell signaling events. *Neurobiology of Aging* 25, 1323–1331.
- Hattiangady B, Rao MS, Shetty GA, Shetty AK** (2005). Brain-derived neurotrophic factor, phosphorylated cyclic AMP response element binding protein and neuropeptide Y decline as early as middle age in the dentate gyrus and CA1 and CA3 subfields of the hippocampus. *Experimental Neurology* 195, 353–371.
- Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, Kauer-Sant'Anna M, Grassi-Oliveira R, Post RM** (2008). Allostatic load in bipolar disorder: implications for pathophysiology and treatment. *Neuroscience and Biobehavioral Reviews* 32, 675–692.
- Karege F, Schwald M, Cisse M** (2002). Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. *Neuroscience Letters* 328, 261–264.
- Lang UE, Hellweg R, Seifert F, Schubert F, Gallinat J** (2007). Correlation between serum brain-derived neurotrophic factor level and an in vivo marker of cortical integrity. *Biological Psychiatry* 62, 530–535.
- Laske C, Eschweiler GW** (2006). Brain-derived neurotrophic factor: from nerve growth factor to modulator of brain plasticity in cognitive processes and psychiatric diseases. *Der Nervenarzt* 77, 523–537.
- Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, Virchow JC** (2005). The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiology of Aging* 26, 115–123.
- Mora F, Segovia G, del Arco A** (2007). Aging, plasticity and environmental enrichment: Structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Research Reviews* 55, 78–88.
- Post RM** (2007). Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. *Journal of Psychiatric Research* 41, 979–990.
- Rybakowski JK, Borkowska A, Skibinska M, Hauser J** (2006). Illness-specific association of val66met BDNF polymorphism with performance on Wisconsin card sorting test in bipolar mood disorder. *Molecular Psychiatry* 11, 122–124.
- Simon NM, Smoller JW, McNamara KL, Maser RS, Zalta AK, Pollack MH, Nierenberg AA, Fava M, Wong KK** (2006). Telomere shortening and mood disorders: preliminary support for a chronic stress model of accelerated aging. *Biological Psychiatry* 60, 432–435.
- Torres IJ, Boudreau VG, Yatham LN** (2007). Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatrica Scandinavica* (Suppl.) 434, 17–26.
- Lakshmi N. Yatham¹, Flavio Kapczinski², Ana C. Andreazza^{1,2}, L. Trevor Young¹, Raymond W. Lam¹, Marcia Kauer-Sant'Anna¹**
- ¹ *Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Canada*
- ² *Molecular Psychiatry Laboratory, Department of Psychiatry, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil*