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Correspondence

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Use of the first-person pronoun in schizophrenia

In their recent publication, Fineberg *et al* examined word use in first-person accounts of schizophrenia in comparison with word use in first-person accounts of mood and anxiety disorders.[1] One of their hypotheses concerned the use of the first-person singular pronoun 'I'. On the basis of research showing patients with mood disorders to be particularly self-focused, as well as phenomenological reports by patients suffering from schizophrenia describing a disrupted sense of self, they predicted that 'writers with schizophrenia would use "I" less often than persons with mood disorder'. They found this hypothesis to be supported by their data.

One obvious limitation of this study, admitted by the authors, is the lack of a healthy control group. Data from two such control groups, however, are readily at hand. First, one can compare the word frequencies found in their first-person accounts with their frequency in general language, as represented in reference corpora such as the Corpus of Contemporary American English.[2] Second, in order to compare a text format that is as similar as possible to first-person accounts of mental illness, one can make use of articles published in the *Schizophrenia Bulletin* under the rubric 'First-person account' that are not written by sufferers of schizophrenia, but by (supposedly) healthy family and friends of someone with schizophrenia (I will refer to those as 'second- person' accounts). Such comparison, based on analyses of a corpus of the *Schizophrenia Bulletin* using CQP software,[3] yields results that markedly differ from Fineberg *et al*'s findings (for a general introduction to corpus linguistics, see Lüdeling & Kytö[4]).

Since 1979, the *Schizophrenia Bulletin* has published 98 first-person accounts and 30 second-person accounts of schizophrenia. The frequency of 'I' in the first-person accounts is 34 621.67/106 words and 20 804.18/106 words in the second-person accounts. The authors of the first-person accounts use 'I' 3.34 times more often than it is used in general American English and 1.90 times more often than it occurs in general spoken American English. Comparing first- and second-person accounts, 'I' is used 1.66 times more often by people identifying as having schizophrenia spectrum disorders than by their mentally healthy friends and family members. The log likelihood test shows this difference to be significant ($P<0.01$).

Authors identifying as having schizophrenia thus use the first-person singular pronoun more often than healthy controls. Therefore, Fineberg *et al*'s finding that authors with schizophrenia use 'I' less often than authors with mood disorders does not warrant any inferences regarding pathologies of the self in schizophrenia. To further investigate the relationship between language and self-disturbances, it would be desirable to analyse linguistic data from people undergoing an acute psychotic episode as well as to consider pronouns in their wider grammatical context rather than looking at mere word frequencies.

1 Fineberg SK, Deutsch-Link S, Ichinose M, McGuiness T, Bessette AJ, Chung CK, et al. Word use in first-person accounts of schizophrenia. *Br J Psychiatry* 2014; doi: 10.1192/bjp.bp.113.140046.

2 Brigham Young University. *The Corpus of Contemporary American English*. Brigham Young University (http://corpus2.byu.edu/coca).

3 Hardie A. CQPweb – combining power, flexibility and usability in a corpus analysis tool. *Int J Corpus Linguist* 2012; **17**: 380–409.

4 Lüdeling A, Kytö M. *Corpus Linguistics – An International Handbook*. De Gruyter, 2009.

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Authors' reply: We very much appreciate the concerns Dr Maatz raises. Indeed, we raised many of them in our discussion. Here we'll take the opportunity to elaborate on our decision-making process with regard to the analyses we reported.

As Dr Maatz and we ourselves point out, we did not include a non-psychiatric control group in our analysis. We found it difficult to identify an appropriate control for our particular corpus. Writing about illness in a journal for medical professionals is a rather particular kind of enterprise that commands specific language. We considered the caregiver and family-member accounts in the *Schizophrenia Bulletin* (which Dr Maatz called 'second-person accounts'). However, we were concerned about comparing samples with different themes (writing about oneself in the first group, writing about other people in the proposed control group). That would almost certainly change pronoun use. Furthermore, family members can sometimes present with attenuated, subclinical versions of the experiences, behaviours and deficits observed in psychotic illness.[2] We thought these might detract from our original objective, which was to analyse word use by people with schizophrenia compared with that by individuals with another mental illness.

We agree with Dr Maatz that this comparison between two illness groups limits the conclusions we can draw. We felt we were suitably circumspect but we are happy to rehearse the point. We are gathering new data, in which process we ask standard questions of participants (including questions that engage discussion of self, others, and impersonal topics). Furthermore we are gathering those data from participants at various illness phases (prodrome, acute psychosis, chronic illness) in order to examine the hypotheses suggested by our initial study of the *Schizophrenia Bulletin* corpus.

With respect to context analysis (how words co-occur), we agree that this is an interesting and important issue. We do not think that our word-counting approach is the final word on meaning in computational linguistics (no pun intended). We are eager to analyse larger meaning structures in our corpus using the new computational techniques Dr Maatz suggests,[3] among others.[4] We look forward to reading more about the analyses of the *Schizophrenia Bulletin* corpus she mentions in the peer-reviewed literature.

Indeed, we hope that this approach, analysing the writing and speech of patients with mental illness using computational linguistics, becomes another tool employed by those committed to understanding and treating mental illness. We are glad that Dr Maatz is interested in joining us in this venture.

1 Callicott JH, Egan MF, Mattay VS, Bertolino A, Bone AD, Verchinksi B, et al. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry* 2003; **160**: 709–19.

2 Hardie A. CQPweb – combining power, flexibility and usability in a corpus analysis tool. *Int J Corpus Linguistics* 2012; **17**: 380–409.

3 Brown C, Snodgrass T, Kemper SJ, Herman R, Covington MA. Automatic measurement of propositional idea density from part-of-speech tagging. *Behav Res Methods* 2008; **40**: 540–5.

4 Mota NB, Vasconcelos NA, Lemos N, Pieretti AC, Kinouchi O, Cecchi GA, et al. Speech graphs provide a quantitative measure of thought disorder in psychosis. *PLoS One* 2012; **7**: e34928.

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BDNF and proBDNF as biomarkers for bipolar disorder

I read with great interest the recent article by Li *et al*, describing plasma levels of brain-derived neurotrophic factor (BDNF) in patients with bipolar disorder in their first depressive episode.[1] A total of 203 patients with a first major depressive episode, as well as 167 healthy controls, were enrolled. After 3 years of bi-annual follow-up, 164 patients with a major depressive episode completed, and of these, 21 patients were diagnosed as having bipolar disorder and 143 patients were diagnosed as having major depressive disorder. At baseline, patients with bipolar disorder and depression showed significantly lower BDNF mRNA levels ($P<0.001$ and $P=0.02$, respectively) and plasma BDNF levels ($P=0.002$ and $P=0.01$, respectively) compared with healthy controls. Interestingly, plasma BDNF levels in patients with bipolar disorder were lower than those in patients with depression.

This study suggests that the model for predicting bipolar disorder during a first depressive episode is a combination of BDNF mRNA with plasma BDNF levels.[1] BDNF (mature BDNF) is a 13 kDa polypeptide, which is initially synthesised as a precursor protein, preproBDNF, in the endoplasmic reticulum. Following cleavage of the signal peptide, proBDNF (~32 kDa) is converted to mature BDNF by extracellular proteases. It was initially thought that only secreted, mature BDNF was biologically active, and that proBDNF, localised intracellularly, served as an inactive precursor. However, accumulating evidence shows that both proBDNF and mature BDNF are active, eliciting opposing effects via the p75NTR and TrkB receptors, respectively, and that both forms play important roles in several physiological functions.[2]

The enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems) used by Li *et al* recognise both proBDNF (precursor of BDNF) and mature BDNF, because of the limited specificity of the BDNF antibody.[3] Using newly available human proBDNF and mature BDNF ELISA kits, which differentiate between the BDNF forms, we have reported high levels of both proBDNF and mature BDNF in human serum.[3] We reported that serum levels of mature BDNF, but not proBDNF, in patients with major depressive disorder were significantly lower than those in healthy controls.[4] And we recently found that serum levels of mature BDNF and the ratio of mature BDNF to proBDNF in mood-stabilised patients with bipolar disorder were significantly higher than in healthy controls.[4] Interestingly, serum levels of proBDNF in mood-stabilised patients with bipolar disorder were significantly lower than those in healthy controls.[5] These findings were confirmed in two independent cohorts (Sahlgrenska set and Karolinska set in Sweden).[5] Considering the high levels of both proBDNF and mature BDNF in human serum, and their putative opposing functions, it would be clinically and scientifically interesting to measure the individual serum levels of proBDNF and mature BDNF in this cohort study.

1 Li Z, Zhang C, Fan J, Yuan C, Huang J, Chen J, et al. Brain-derived neurotrophic factor levels and bipolar disorder in patients in their first depressive episode: 3-year prospective longitudinal study. *Br J Psychiatry* 2014; **205**: 29–35.

2 Hashimoto K. Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. *Psychiatry Clin Neurosci* 2010; **64**: 341–57.

3 Yoshida T, Ishikawa M, Iyo M, Hashimoto K. Serum levels of mature brain-derived neurotrophic factor and its precursor proBDNF in healthy subjects. *Open Clin Chem J* 2012; **5**: 7–12.

4 Yoshida T, Ishikawa M, Niitsu T, Nakazato M, Watanabe H, Shiraishi T, et al. Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. *PLoS One* 2012; **7**: e42676.

5 Södersten K, Pĺlsson E, Ishima T, Funa K, Landén M, Hashimoto K, et al. Abnormality in serum levels of mature brain-derived neurotrophic factor (BDNF) and its precursor proBDNF in mood-stabilized patients with bipolar disorder: a study of two independent cohorts. *J Affect Dis* 2014; **160**: 1–9.

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Declaration of interest

K.H. is a holder of the patents 'Diagnostic and examination method for eating disorder' (US 7,754,434 B2) and 'Diagnostic agent for ischemic heart disease risk group' (US 2013/0310321A1), which pertain to the measurement of BDNF as a biomarker. In addition, He has served as a scientific consultant to Astellas and Taisho and he has received research support from Abbvie, Dainippon Sumitomo, Otsuka and Taisho.

Authors' reply: While we agree with Professor Hashimoto's comments regarding the predictive role of mature brain-derived neurotrophic factor (mBDNF) and its precursor, proBDNF, in bipolar disorder, several points merit further discussion.

First, we presented preliminary data describing a potential role for BDNF as a biomarker for predicting bipolar disorder in major depressive disorder, although we detected the serum BDNF level using commercial kits that do not differentiate between mBDNF and proBDNF. When we reviewed the literature regarding mBDNF and proBDNF in bipolar disorder and major depressive disorder, we noticed that lower serum levels of mBDNF and higher serum levels of proBDNF were found among patients with major depressive disorder.[1,2] Södersten *et al* also reported that higher serum levels of mBDNF and lower proBDNF were observed among patients with bipolar disorder.[3] These disparate results suggest that levels of mBDNF and proBDNF, as well as the ratio of mBDNF to proBDNF, might be sensitive enough to help differentiate bipolar disorder from major depressive disorder.

Second, our previous studies indicated that BDNF probably has some sex-specific characteristics. Tang *et al*[4] reported that the ratio of mBDNF to proBDNF differs in a sex-specific manner in zebra finches. These findings suggest that mBDNF and proBDNF are different in males and females and should be further investigated.

Third, the findings of one of our previous studies implied that genetic interactions between genes encoding BDNF and its receptor enhance the risk of treatment-resistant depression.[5] Recent studies have found that mBDNF and proBDNF elicit biological effects via interaction with their respective receptors, p75NTR and TrkB. Accordingly, we concluded that evaluations of mBDNF and proBDNF should also consider their receptors. On the whole, we appreciate Professor Hashimoto's insightful comments in directing our future work.

1 Yoshida T, Ishikawa M, Niitsu T, Nakazato M, Watanabe H, Shiraishi T, et al. Decreased serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. *Plos One* 2012; **7**: e42676.

2 Zhou L, Xiong J, Lim Y, Ruan Y, Huang C, Zhu Y, et al. Upregulation of blood proBDNF and its receptors in major depression. *J Affect Disord* 2013; **150**: 776–84.

3 Södersten K, Palsson E, Ishima T, Funa K, Landen M, Hashimoto K, et al. Abnormality in serum levels of mature brain-derived neurotrophic factor (BDNF)

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