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. 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. 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, yields results that markedly differ from Fineberg et al’s findings (for a general introduction to corpus linguistics, see Lüdeling & Kyto). 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 34,621/106 words and 20,804/106 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.

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. 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, among others. 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.


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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.2 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 (~32kDa) 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 recognised 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.4 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).6 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.


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 reported that the ratio of mBDNF to proBDNF differs in a sex-specific manner in zebrafish. 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.

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)


Chen Zhang, MD, PhD; Zehui Li, MD, PhD; Yun Fang, MD, PhD, Professor, Division of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China. Email: yyrongtong@gmail.com
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Early and delayed treatment of bipolar disorder

Using Danish registry data, Kessing et al examined the relationship between lithium response and the timing of treatment (early v. delayed).1 Early treatment was associated with an increased probability of lithium response. This is a clinically important finding, given the increasing emphasis on early intervention in bipolar disorder. The results of the Kessing et al study are sobering. Only few patients, particularly among those for whom treatment was delayed, responded to lithium. Several factors may have contributed to the reported results.

The study did not – and possibly could not – control for the cycle shortening that is observed after successive episodes of bipolar disorder. Although the interpretation of such cycle shortening has been debated,2 it is well established that early cycles are significantly longer than those occurring later; consequently, early in the course of illness one would expect longer spontaneous remissions regardless of treatment. This effect may be partially responsible for the greater treatment response in patients receiving early intervention in the Kessing et al study.

Naturalistic studies typically demonstrate full response in about 30% of participants3 (that is, no recurrences, or the Kessing et al criterion, in treatment-adherent patients), which is markedly greater than the response rate observed by Kessing et al. This discrepancy could be related to age at first contact. The average age of participants whom Kessing et al reported as having received early and late treatment was 46.7 years and 49.1 years, respectively.

The natural history of bipolar disorder includes an average age at onset in the second or third decade of life. The trajectory of the illness, where mania typically develops as the last stage, delays the diagnosis of bipolar disorder. Also, there is often a substantial delay in starting treatment even following the diagnosis of bipolar disorder.4,5 These reports, in conjunction with the advanced age at index presentation, and high rates of antidepressant, antipsychotic and anticonvulsant use in the Kessing et al study suggest that participants may have been afflicted with bipolar disorder for some time before ‘first contact’. In a sample of 450 participants, Baldessarini et al reported a negative relationship between treatment latency and effect of treatment on time spent ill.6 If the aforementioned findings are generalisable to the Danish sample, the reduced overall treatment responses may be interpreted as a consequence of relatively advanced participant age.

Finally, Kessing et al analysed data collected since 1995. Is it possible that participants had received lithium during the years prior? This would further complicate the interpretations of sample responsiveness to lithium, regardless of early or late initiation. In conclusion, we suggest that the findings presented by Kessing et al are limited by the lack of control for inter-participant differences in the manifestation of the natural history of bipolar disorder. Such control may be difficult, or in some cases impossible, to achieve using registry-based observational data, but is nevertheless imperative to understanding the effects of early v. late treatment prophylaxis in relapsing–remitting illnesses such as bipolar disorder.


5 Baldessarini RJ, Tondo L, Hennen J. Treatment-latency and previous episodes: relationships to pretreatment morbidity and response to maintenance treatment in bipolar I and II disorders. Bipolar Disord 2003; 5: 169–79.

Authors’ reply: We are confident that the relatively low response rates to lithium in our study relate to the narrow definition of lithium response, rather than to characteristics of the included patients.7 Thus, we intended to characterise patients who had an excellent response to lithium monotherapy; that is, patients who were ‘cured’ from further affective episodes following a start-up period of lithium as in a prior study.2 We used two robust clinical indicators to define excellent lithium response: (a) lithium prescribed in monotherapy; and (b) no need for psychiatric hospital admission. By doing this, we defined lithium response in a rather rigorous way, resulting in relatively low rates of response. We do not find that our definition of lithium response hampered the finding of the study that early treatment with lithium was associated with increased probability of excellent lithium response compared with delayed treatment, or hampered the generalisability of this finding. Although cycle acceleration occurs on average in bipolar disorder2,4 the results of our study may suggest that early treatment with lithium might prevent progression of bipolar disorder.


‘Reasonable adjustments’ for vulnerable patients

We support the views of Tuffrey-Wijne & Hollins1 and their argument for the NHS to take an organisational approach to embed documentation and provision of reasonable adjustments for those with protected characteristics under the Equalities Act 2010. Lord Darzi defined quality for the NHS as comprising three dimensions: safety, effectiveness and patient experience.2 The provision of reasonable adjustments is central to each of these.

Safety – Tuffrey Wijne & Hollins rightly identify the lack of provision of reasonable adjustments as being a patient safety issue. The Confidential Inquiry into Premature Deaths of People with
Learning Disabilities (CIPOLD)\textsuperscript{3} demonstrated an underlying culture in which people with intellectual disabilities were disadvantaged in accessing equitable healthcare and at risk of premature death because equality for disabled people was assumed to mean treating them the same as others. It does not. Alternative methods of making services available have to be found in order to achieve equality of outcomes. Mizen \textit{et al}, for example, demonstrated that clinical guidelines can actually increase health inequalities for people with intellectual disabilities if reasonable adjustments are not made.\textsuperscript{4} If the lack of reasonable adjustments threatens to compromise safety as, in very many cases, it does for people with intellectual disabilities, this needs to be reported and reviewed as a patient safety issue.

Effectiveness – evidence put forward by Tuffrey-Wijne \textit{et al} suggests that ward culture, staff attitudes and staff knowledge are crucial in ensuring that hospital services are accessible to vulnerable patients.\textsuperscript{5} Effective care is that which is tailored to the needs of the patient, and this must involve an understanding of the adjustments they need in order to be able to receive appropriate medical and nursing care. In our view, we should go further than Tuffrey-Wijne & Hollins’ requirement for Care Quality Commission inspections in England and Wales to oversee patient-specific recording of reasonable adjustments. We also need to be confident that such adjustments are being delivered, and for evidence to be provided of adequate arrangements being in place.

Patient experience – Turner & Robinson note that it is difficult for people with intellectual disabilities and their families to influence policy and practice in healthcare systems if they are not visible within them and if involvement mechanisms such as surveys and focus groups are not accessible to them.\textsuperscript{6} Both the Death by Indifference\textsuperscript{7} and CIPOLD reports highlighted the lack of attention paid to the views of patients and their families, preventing them from becoming active partners in their care; the CIPOLD report additionally noted the devastating impact on future care that a poor experience of healthcare can have for some people with intellectual disabilities. The provision of reasonable adjustments needs to extend to the ways in which we garner the views of people with intellectual disabilities, communicate with them, and place them at the centre of their care.

The CIPOLD report made 18 recommendations, which included (a) clear identification of people with intellectual disabilities on the NHS central registration system and in all health care records, and (b) reasonable adjustments required by, and provided to, individuals, to be audited annually and examples of best practice shared across agencies and organisations.\textsuperscript{3} It is now 4 years since the Equalities Act 2010 came into force. Our adherence to the Act must be sharpened in the light of the health inequalities faced by people with protected characteristics, including those with intellectual disabilities, so clearly demonstrated in successive reports. We all have a responsibility, and we all have a role to play, in ensuring equal outcomes for vulnerable people through the provision of reasonable adjustments, but strong leadership is central to making it happen.

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