Post-stroke depression

We read with great interest the paper by Gainotti *et al* (1999) and we wish to raise some concerns about their study.

Description of the statistical analysis was omitted from the paper and it is impossible for the reader to know how the data were analysed. The authors did not mention whether the patients were administered drugs usually given to stroke patients (e.g. steroids, beta-blockers and anticonvulsant drugs) and which can induce some depressive symptoms. In the section entitled "Criteria used to make a diagnosis of major depression", the authors state that the validity of their diagnostic criterion (Hamilton Rating Scale for Depression (HAM–D) score >17) has been documented by others (Salzman *et al*, 1994). This assertion is false – we find no scientific support in the Salzman *et al* paper for Gainotti *et al*'s assertion. Also, information on the clinical features of Gainotti *et al*'s sample is limited by their omission to report standard deviations and the mean age of patients with endogenous depression (see Table 1, p. 164).

The most important problem, however, is with regard to the interpretation of HAM–D scores across groups. It is not made clear whether the mean HAM–D scores reported in Table 1 are calculated across the whole sample or only within the group with depression. In the psychiatric literature a HAM–D score of <12 is not generally considered clinically significant, so if Gainotti *et al* have calculated mean HAM–D score only within the group with depression, it is difficult to understand why the mean is so low (11.8 at <2 months post-stroke). Alternatively, if mean HAM–D scores were calculated across the whole sample (i.e. patients with and without depression), the increase in the mean with increasing time post-stroke may be due simply to the increase in the relative number of people with depression (27% at <2 and 2–4 months post-stroke *v.* 40% at >4 months post-stroke). In other words, the increase in the mean HAM–D score does not necessarily imply that the severity of depression in the whole sample increases from the acute to the later post-stroke period, but this tendency may be due simply to an increased proportion of patients with depression within the sample.

Finally, Cohen's κ for diagnostic concordance is not given by Gainotti *et al*. This index is routinely calculated when different diagnostic criteria are adopted for patient classification. Inspection of Table 1 shows that nine well subjects out of 43 were misclassified as having depression using the quantitative criterion of HAM–D score. This begs the question, how many patients with depression were classified as being well?

Gainotti, G., Azzoni, A. & Marra, C. (1999) Frequency, phenomenology and anatomical–clinical correlates of major post-stroke depression. *British Journal of Psychiatry*, **175**, 163–167.

Salzman, C., Schneider, L. S. & Alexopoulos, E. S. (1994) Pharmacological treatment of depression in late life. In *Psychopharmacology: The Fourth Generation of Progress* (eds F. E. Bloom & D. J. Kupfer), pp. 1471–1477. New York: Raven Press.

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Authors' reply: We would like to clarify some aspects of our paper in reply to the points highlighted by Di Michele & Bolino.

First, we would stress the fact that the preliminary analysis of our data had been extensive, but that only data relevant to the specific scope of our study, which consisted in checking the most recent version of Robinson and co-workers' biological theory of post-stroke depression, were included in the manuscript. Our data are clearly inconsistent with this theory.

Regarding our data analysis, continuous data were treated using one-way analysis of variance, whereas frequencies of distribution were analysed by means of χ^2 tests.

The possible influence of drugs was checked in our study by excluding all patients who were taking at the time of examination (or had taken in the previous four weeks) antidepressant drugs. We did not check other drugs (such as steroids, beta-blockers or anticonvulsants) which could induce depressive symptoms, since they were not considered relevant for the specific scope of our study.

The patients with endogenous depression were matched as for age (60.1 years) and educational level (7.9) with the three groups of post-stroke patients. Only a slight difference in gender distribution was observed between stroke patients and those with endogenous depression (a preponderance of females (20 : 10) among the group with endogenous depression). This not unexpected difference was not considered relevant with respect to the scope of the study.

Regarding interpretation of the HAM–D scores across groups, the main scope of our study consisted in determining whether the nature of post-stroke depression is different in the acute and in more chronic post-stroke periods. From this point of view, it was important to evaluate at various time intervals from stroke the qualitative aspects of depression and their anatomical–clinical correlates, whereas the severity of depression in patients with major depression was much less relevant. For this reason, the HAM–D scores were calculated, as the authors of the letter correctly argue, in each group as a whole (including subjects with and without depression) and the increment of the mean depression score across groups mainly reflected the relative increment of subjects with depression. Though this fact is not very relevant to the aim of our research, we must add that even considering only the patients with major post-stroke depression, we could observe a non-significant trend towards an increase in the mean HAM–D score from the acute (20.2) to the post-acute (21.8) and to the more chronic (23.5) post-stroke period.

Concerning the HAM–D score criterion for diagnosis of major depression and correlations between clinical and psychometric criteria, although different cut-off scores have been proposed in the literature, a score of 18 on the HAM–D is the most currently used (Endicott *et al*, 1981; Rapp *et al*, 1990). Furthermore, good concordance exists in our study between clinical (DSM–III–R) and psychometric (score >17 on the HAM–D) criteria. We have measured this concordance on our data by the κ statistic (Holman *et al*, 1982), which gives a numerical measure of chance-corrected categorical agreement. According to this index, which results from the ratio between the chance-corrected observed agreement and the chance-corrected perfect agreement, the perfect agreement corresponds to +1, the complete disagreement corresponds to −1 and the chance level is 0. The chance-corrected level of agreement between DSM–III–R criteria and HAM–D score >17 was quite satisfactory in our study (κ=0.84).

Endicott, J., Cohen, J., Nee, J., *et al* (1981) Hamilton Depression Rating Scale: Extracted from regular and change version of the Schedule for Affective Disorders

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and Schizophrenia. *Archives of General Psychiatry*, **38**, 98–103.

Holman, C. D. J., James, J. R. & Helman, P. J. (1982) An improved method of analysis of observer variation between pathologists. *Histopathology*, **6**, 581–589.

Rapp, S. R., Smith, S. S. & Britt, M. (1990) Identifying comorbid depression in elderly medical patients: use of the extracted Hamilton Depression Rating Scale. *Psychological Assessment*, **2**, 243–247.

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Correlation between cerebral perfusion and depressive symptom scores from morning to evening

I am writing to point out an error in our paper on cerebral perfusion correlates of depressed mood (Ebmeier *et al*, 1997). Although the description of methods in the paper is accurate, the interpretation of the interaction between condition (time of day) and depression scores (Befindlichkeitsscale (BFS)) is not accurate. This interaction does not represent the "within-subjects correlation with BFS change", but the change in correlation between cerebral perfusion and symptom scores from morning to evening.

Consequently, "correlations with BFS" in the text ought to read "diurnal changes in correlations". The reported "positive correlation between severity of depression and anterior limbic perfusion" is, in fact, a significantly stronger correlation between symptom scores and cerebral perfusion in the morning *v.* evening. In other words, there is a relatively greater (positive) slope of the regression line between perfusion and symptoms in the morning, whereas the slope in the evening is significantly less positive. The correlations reported with factor scores were interpreted accurately and, for example, support the claim for a positive correlation between severity of depression/weakness/fatigue and anterior limbic perfusion.

Although this may seem an arcane point, the additional change in the 'tightness' of the mood–brain perfusion association from morning to evening implied by these results is actually rather exciting. It could reflect the difference between a direct and a compensatory relationship between brain activity and behaviour at different times of the day and should provide a motive for follow-up experiments.

Ebmeier, K. P., Cavanagh, J. T., Moffoot, A. P. R., *et al* (1997) Cerebral perfusion correlates of depressed mood. *British Journal of Psychiatry*, **170**, 77–81.

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Lithium-induced hypothyroidism

I would like to congratulate Johnston & Eagles (1999) on the scale of their study and for providing a clearer idea regarding the prevalence of hypothyroidism related to lithium and the potential risk factors. I would like to comment on several important issues, including the presence of pre-existing thyroid disease prior to initiation of lithium, the presence of antibodies and the possibility of diagnosis as a risk factor.

With regard to the presence of pre-existing hypothyroidism (as suggested by patients receiving replacement thyroxine) the study excluded a total of 18 cases, which, given the total number of cases on thyroxine, is a substantial proportion of the sample. This would suggest that patients who have hypothyroidism are more likely to suffer from conditions that require treatment with lithium.

It is unfortunate that thyroid antibodies were not measured more frequently. The finding that 13 out of 15 patients with hypothyroidism were positive for antibodies would suggest that the prevalence of antibodies would have been high and would have clarified the role played by autoimmunity in contributing to hypothyroidism. Thyroid autoimmunity mediating the hypothyroid effect of lithium has been studied extensively and there is considerable evidence to support this. As early as 1973, Crowe *et al* (1973) suggested that two different types of hypothyroidism occur with lithium, one with evidence of underlying autoimmune hypothyroidism and one without, based on a review of cases reported. Studies by Lazarus *et al* (1981) and Leroy *et al* (1988) suggest a high prevalence for antithyroid antibodies in patients who are hypothyroid on lithium, thus supporting the role of autoimmmunity mediating this effect. Indirect evidence that autoimmune factors may mediate the actions of lithium on the thyroid comes from cases of hyperthyroidism, a well-documented side-effect of lithium, that cannot be explained on the basis of a direct pharmacological effect of lithium on the thyroid.

The issue of a particular diagnosis being a potential risk factor for lithium-induced hypothyroidism has not been highlighted in the literature although it has been studied, albeit indirectly. It is reasonable to conclude from the literature that thyroid autoimmunity is increased in conditions in which lithium is likely to be prescribed (i.e. bipolar affective disorder and depressive disorders). A study by Lazarus *et al* (1986), in which thyroid antibodies were investigated prior to the prescription of lithium, reported a prevalence of 43%. Importantly, the entire group had a diagnosis of bipolar affective disorder. This compares with only 8.6% in a study of unipolar depression (Joffe, 1987). This would indicate that there is a case for studying the relationship between the psychiatric diagnosis, thyroid autoimmunity and the hypothyroid effect of lithium. This could answer the question raised by the authors as to why hypothyroid patients on lithium are selected to remain on both treatments. It is possible that lithium is more likely to be continued when the diagnosis is that of bipolar affective disorder than depression alone.

I hope that further studies in this area will help to dissect out the factors that play a role in lithium-induced hypothyroidism.

Crowe, M. J., Lloyd, G. G., Bioch, S., *et al* (1973) Hypothyroidism in patients treated with lithium: a review and two case reports. *Psychological Medicine*, **3**, 337–342.

Joffe, R. T. (1987) Antithyroid antibodies in major depression. *Acta Psychiatrica Scandinavica*, **76**, 598–599.

Johnston, A. M. & Eagles, J. M. (1999) Lithium-associated clinical hypothyroidism. Prevalence and risk factors. *British Journal of Psychiatry*, **175**, 336–339.

Lazarus, J. H., John, R., Bennie, E. H., *et al* (1981) Lithium therapy and thyroid function. *Psychological Medicine*, **11**, 85–92.

___, McGregor, A. M., Ludgate, M., *et al* (1986) Effect of lithium carbonate therapy on thyroid immune status in manic depressive patients: a prospective study. *Journal of Affective Disorders*, **11**, 155–160.

Leroy, M., Villeneuve, A. & Lajeunesse, C. (1988) Lithium and antithyroid antibodies. *American Journal of Psychiatry*, **145**, 534.

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