*Psychological Medicine*, 2004, **34**, 1059–1064. © 2004 Cambridge University Press
DOI: 10.1017/S0033291703001806 Printed in the United Kingdom

# Enlarged amygdala volume and reduced hippocampal volume in young women with major depression

C. LANGE AND E. IRLE*

*Department of Psychiatry and Psychotherapy, University of Göttingen, Germany*

## ABSTRACT

**Background.** Evidence is increasing that amygdala and hippocampus show significant structural abnormalities in affective disorders. Two previous studies found enlarged amygdala size in subjects with recent-onset major depression.

**Method.** Amygdala and hippocampal volumes were assessed in 17 young women with major depressive disorder and 17 healthy matched control subjects by use of three-dimensional structural magnetic resonance imaging. The severity of depressive symptoms was assessed using the Hamilton Depression Scale and the Beck Depression Inventory.

**Results.** Compared with control subjects, depressive subjects had significantly larger (+13%) amygdala volumes and significantly smaller (−12%) hippocampal volumes. Amygdala and hippocampal volumes were not significantly correlated with disorder-related variables.

**Conclusions.** Our results are consistent with previous findings of structural abnormalities of amygdala and hippocampus in subjects with recent-onset major depression. It may be suggested that the size of the amygdala is enlarged in the first years of the disorder, and may decrease with prolonged disorder duration.

## INTRODUCTION

Evidence is increasing that amygdala and hippocampus show significant structural abnormalities in affective disorders. In the majority of studies, individuals with major depressive disorder have been shown to have reduced hippocampal size (Sheline *et al*. 1996, 1999; Bremner *et al*. 2000; Mervaala *et al*. 2000; Shah *et al*. 2000; Frodl *et al*. 2002*a*; MacQueen *et al*. 2003). In contrast, individuals with bipolar I disorder according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; APA, 1994) were frequently shown to have normal hippocampal size (Pearlson *et al*. 1997; Altshuler *et al*. 1998; Strakowski *et al*. 1999, 2002; Hauser *et al*. 2000), although there has been a contrary report (Swayze *et al*. 1992).

* Address for correspondence: Dr Eva Irle, Department of Psychiatry and Psychotherapy, University of Göttingen, Von-Siebold-Str. 5, D-37075 Göttingen, FRG.
(Email: eirle@gwdg.de)

Structural abnormalities of the amygdala in affective disorders are a matter of dissent. Two earlier studies investigating individuals with bipolar I disorder measured the amygdala from two image slices and found a normal (Swayze *et al*. 1992) or reduced (Pearlson *et al*. 1997) amygdala size. Two recent studies using consecutive 1–1·4 mm coronal slices (Altshuler *et al*. 1998; Strakowski *et al*. 1999) found enlarged amygdala size in individuals with bipolar I disorder. The same was found in persons with temporal lobe epilepsy and dysthymia (Tebartz van Elst *et al*. 1999). Individuals with drug-resistant recurrent major depression (Mervaala *et al*. 2000) or depressive individuals with a broad age range (Sheline *et al*. 1999) were reported to have normal amygdala size, whereas two studies investigating middle-aged persons with major depression found enlarged amygdala size (Bremner *et al*. 2000; Frodl *et al*. 2002*b*).

In the present investigation amygdala and hippocampal volumes of 17 young women with

Table 1. *Demographic and clinical characteristics of depressive and control subjects*

| | Depressive subjects ($n=17$) | Control subjects ($n=17$) | $p$ |
|---|---|---|---|
| Age [years, mean (S.D.)] | 34 (10) | 32 (6) | N.S. |
| Height [cm, mean (S.D.)] | 167 (7) | 169 (6) | N.S. |
| Education [years, mean (S.D.)] | 11 (2) | 11 (2) | N.S. |
| IQ [mean (S.D.)]* | 111 (20) | 113 (13) | N.S. |
| Age at onset [years, mean (S.D.)] | 29 (10) | | |
| Duration of disorder [years, mean (S.D.)] | 5 (5) | | |
| Depressive episodes [mean (S.D.)] | 2 (1) | | |
| First episode ($n$) | 8 | | |
| Beck Depression Inventory [mean (S.D.)] | 26 (10) | | |
| Hamilton Depression Scale [mean (S.D.)] | 22 (4) | | |

* Wechsler Adult Intelligence Scale-Revised; IQ estimates were derived from Information, Similarities, Picture Completion and Block Design Scores.

Statistical comparison by $U$ test: N.S., not significant.

recent-onset major depressive disorder were compared to those of a healthy matched control group ($n=17$). The goals of our study were: (1) to investigate whether amygdala volumes are enlarged in a sample of young depressive subjects; (2) to investigate whether hippocampal volume reduction is present in the same sample of depressive subjects; and (3) to analyse how clinical variables are related to amygdala and hippocampal volumes of depressive subjects.

## METHOD

### Subjects

The sample comprised 17 right-handed young female in-patients with the diagnosis of major depressive disorder according to DSM-IV consecutively admitted to the Psychiatric Hospital of the University of Göttingen (Table 1). At time of assessment, all subjects met the DSM-IV criteria for a major depressive episode on the basis of interviews with the Structured Clinical Interview for DSM-IV (SCID; Wittchen *et al.* 1997). Subjects with signs of a manic, mixed or hypomanic episode in the past or present, as well as subjects with a history of neurological diseases, substance-related disorders or psychotic disorders were rigorously excluded. As reduced hippocampal volumes were reported to occur in subjects with post-traumatic stress disorder (Bremner *et al.* 1997) or borderline personality disorder (Driessen *et al.* 2000), subjects with these co-morbid disorders and subjects reporting traumatic events without fulfilling diagnostic criteria were excluded. Assessment took place when subjects were in a clinically stable phase, i.e. 3–6 weeks after admission. All subjects were on antidepressant medication (tricyclic antidepressants, selective serotonin reuptake inhibitors). Seven depressive subjects had a family history of major depressive disorder, but none of the subjects had a family history of bipolar or psychotic disorder.

Depressive subjects were compared with 17 right-handed healthy female control subjects matched for age, height and years of education. Control subjects were recruited for the study by an advertisement in a local newspaper and leaflets distributed in the hospital and town. Only subjects without a history of neurological or psychiatric (as assessed by the SCID) disorder were studied.

After a complete description of the study to the subjects, written informed consent was obtained.

### Clinical assessment

Depressive symptoms were assessed by means of the Beck Depression Inventory (Hautzinger *et al.* 1995) and the Hamilton Depression Scale (Hamilton, 1960). Intellectual functions were assessed by the Wechsler Adult Intelligence Scale-Revised (Tewes, 1991).

### Magnetic resonance imaging (MRI) acquisition and analysis

All subjects received a MR scan using a 1.5-T Philips Gyroscan machine. Scanning parameters of the $T_1$-weighted three-dimensional (3D) sequence were as follows: TE = 6·0 ms; TR = 24·0 ms; flip angle = 30°; FOV = 256; slice plane = sagittal; matrix = 256 × 256; slice thickness = 1·3 mm; slice number = 130; acquisition mode = 3D. Volumetric analysis was done on the basis of 3D MR images. The images were transferred to a computer workstation and processed using the CURRY® software (version 4.5; Compumedics, Melbourne, Australia). Images were reformatted into continuous slices of 1 mm thickness. Simultaneous 3D visualization of brain structures and manual tracing allowed a precise identification and differentiation of amygdala and hippocampus.

https://doi.org/10.1017/S0033291703001806 Published online by Cambridge University Press

Total brain volume was calculated with automated multistep algorithms and 3D region growing methods that are limited by grey value thresholds. Amygdala and hippocampus were separately disarticulated from surrounding tissue on coronal slices by means of manual tracing according to a standardized protocol (Pruessner *et al.* 2000) and with the aid of the atlas of Sims & Williams (1990) and the serial sections provided by Duvernoy (1998). Amygdala and hippocampus were separated by 3D visualization of the alveus and the inferior horn of the lateral ventricle (Pruessner *et al.* 2000).

For defining the intrarater reliability (a single rater being blind to the diagnosis) each one hemisphere of 11 randomly chosen cases was reassessed. The intra-class correlation coefficients for this procedure were $r = 0{\cdot}93$ for the amygdala and $r = 0{\cdot}94$ for the hippocampus.

### Statistical analyses

Because of the small number of subjects in each group, all statistical comparisons were performed using non-parametric statistical methods. Mann–Whitney *U* tests were applied to compare differences between groups on demographic and cognitive variables and on total brain volume. Partial correlation coefficients controlling for total brain volume were used to examine the relationship between amygdala and hippocampal volumes and demographic, cognitive and clinical variables.

Amygdala and hippocampal volumes of depressive and control subjects were compared by non-parametric analyses of covariance (ANCOVA; Brunner *et al.* 2002) with the between-subjects factor group (depressive, control subjects) and the within-subjects factor hemisphere (left, right) adjusting for total brain volume. The multivariate model was followed up by separate one-way ANCOVAs ($p < 0{\cdot}025$) in the case of a significant group × hemisphere interaction.

All analyses were two-tailed and the alpha was defined as $p < 0{\cdot}05$. Statistical computations were performed using the Statistical Analysis System (SAS for Windows; Version 8.01; nonparametric ANCOVAs: http://www.ams.med.uni-goettingen.de/Projekte/LD/Makros_LD.html; MACRO:NPAR. SAS) and the Statistical Package for the Social Sciences (SPSS for Windows, Version 10.0).

## RESULTS

### General

Depressive subjects did not differ significantly from control subjects with respect to demographic or cognitive variables. Depressive symptoms were rated as moderate to strong (Beck Depression Inventory, Hamilton Depression Scale). Depressive subjects had a short illness history and were young at illness onset (Table 1). Total brain volumes were not significantly different between depressive and control subjects (Table 2).

### Amygdala and hippocampal volume: group comparisons

Compared with control subjects, depressive subjects had larger volumes of the left (+15%) and right (+11%) amygdala and smaller volumes of the left (−7%) and right (−16%) hippocampus.

The 2 (group) × 2 (hemisphere) ANCOVAs adjusting for total brain volume revealed significantly larger amygdala volumes and significantly smaller hippocampal volumes of depressive subjects when compared with control subjects. Considering hippocampal volumes, the interaction of group and hemisphere also yielded significance. The follow-up regional ANCOVA models revealed that depressive subjects had significantly smaller hippocampal volumes in the right hemisphere when compared with control subjects. For detailed results of all statistical comparisons see Table 2.

### Relationship between amygdala and hippocampal volume and demographic, clinical and cognitive variables

In depressive subjects ($n = 17$), left or right amygdala volumes and left or right hippocampal volumes were not significantly correlated with demographic (age, education, height), cognitive (IQ), or clinical (age at onset, duration of disorder, number of episodes, Beck Depression Inventory, Hamilton Depression Scale) variables.

## DISCUSSION

### Structural changes of amygdala and hippocampus in affective disorders

Compared with control subjects, our depressive subjects had significantly larger amygdala

https://doi.org/10.1017/S0033291703001806 Published online by Cambridge University Press

Table 2. *Brain volume measures of depressive and control subjects*

| Volume (ml) | Depressive subjects ($n=17$) Mean (S.D.) | Control subjects ($n=17$) Mean (S.D.) | Difference (%)* | Statistic | $p$ |
|---|---|---|---|---|---|
| Total brain† | 1136 (97) | 1132 (93) | +0·4 | $U=141·5$ | 0·919 |
| Amygdala‡ | | | | | |
| Total | 2·55 (0·49) | 2·26 (0·33) | +12·8 | $T=4·05$ | **0·044** |
| Left | 1·29 (0·26) | 1·12 (0·17) | +15·2 | | |
| Right | 1·26 (0·26) | 1·14 (0·20) | +10·5 | | |
| Hippocampus§ | | | | | |
| Total | 5·46 (0·83) | 6·19 (0·71) | −11·8 | $T=11·61$ | **<0·001** |
| Left¶ | 2·79 (0·41) | 2·99 (0·46) | −6·7 | $T=3·33$ | 0·068 |
| Right¶ | 2·67 (0·50) | 3·19 (0·37) | −16·3 | $T=16·07$ | **<0·001** |

Bold face indicates significance.

* Percentage of difference in regional volumes is relative to control subjects.

† Mann–Whitney $U$ test.

‡ The hypothesis-driven group × hemisphere (2 × 2) ANCOVA-type statistic using total brain volume as covariate had the following $T$ values: group, $T(1)=4·05$, $p=0·044$; hemisphere, $T(1)=0·01$, $p=0·934$; group × hemisphere, $T(1)=1·09$, $p=0·296$.

§ The hypothesis-driven group × hemisphere (2 × 2) ANCOVA-type statistic using total brain volume as covariate had the following $T$ values: group, $T(1)=11·61$, $p<0·001$; hemisphere, $T(1)=0·31$, $p=0·582$; group × hemisphere, $T(1)=5·57$, $p=0·018$.

¶ One-way ANCOVA-type statistic controlling for total brain volume; Box-Approximation df = 1.

volumes. Our results replicate two previous findings of amygdala enlargement in individuals with recent-onset major depression (Bremner *et al.* 2000; Frodl *et al.* 2002*b*). Two other studies investigating individuals with drug-resistant recurrent major depression (Mervaala *et al.* 2000) or depressive individuals with a broad age range (Sheline *et al.* 1999) did not find enlarged amygdala size. It may be suggested that the size of the amygdala is enlarged in the first years of a major depressive disorder and may decrease with prolonged disorder duration.

So far, enlarged amygdala size has only been found in individuals with bipolar I disorder or major depressive disorder, or in dysthymic persons with temporal lobe epilepsy (Altshuler *et al.* 1998; Strakowski *et al.* 1999; Tebartz van Elst *et al.* 1999; Bremner *et al.* 2000; Frodl *et al.* 2002*b*). Thus, it might be speculated that amygdala enlargement is directly related to as yet unknown factors of these affective disorders. Individuals with major depression were reported to have sustained elevated resting metabolism in the amygdala (Drevets *et al.* 1992), which possibly could result in increased amygdala volumes (i.e. by enhanced blood flow). However, a possibly pre-existing large amygdala size could also result in an elevated physiological activity.

Research in non-human primates has suggested that stress and prolonged glucocorticoid exposure may damage the hippocampus (Sapolsky *et al.* 1990; Gould *et al.* 1998), thus raising the possibility that chronic stress may induce hippocampal degeneration in humans. Hypercortisolism and insensitivity to feedback suppression is a common phenomenon in major depression, rendering the hypothesis of hippocampal neurotoxicity in depressive individuals likely. However, small hippocampal size could also be an unspecific feature of many neuropsychiatric disorders. Hippocampal size reduction has been frequently reported in individuals with schizophrenia (Wright *et al.* 2000). A recent study (Gilbertson *et al.* 2002) found evidence that reduced hippocampal size may be a risk factor for developing post-traumatic stress disorder in individuals having been exposed to traumatic stress.

We could not find correlations between hippocampal or amygdala volumes and age, disorder duration, number of depressive episodes or age at disorder onset. Most of the other studies (Altshuler *et al.* 1998; Strakowski *et al.* 1999; Bremner *et al.* 2000; Mervaala *et al.* 2000; Frodl *et al.* 2002*a*, *b*; Strakowski *et al.* 2002) also failed to detect these relationships. These results might argue against the assumption that the structural abnormalities of amygdala and hippocampus are related to the disease process itself. However, two studies investigating

https://doi.org/10.1017/S0033291703001806 Published online by Cambridge University Press

depressive individuals with a broad age range (Sheline *et al*. 1999; MacQueen *et al*. 2003) found smaller hippocampal volumes in individuals with longer illness duration, indicating that hippocampal size reduction may increase in the course of the illness.

### Functional significance of enlarged amygdala size and reduced hippocampal size in major depression

We report enlarged amygdala size and reduced hippocampal size in the same sample of depressive individuals. Animal experimentation has shown that lesions of the hippocampus destroy the ability to passively avoid stressful stimuli ('behavioral inhibition system'; Gray & McNaughton, 2000). It may thus be possible that depressive individuals with hippocampal size reduction have also deficits to avoid and cope with stressful stimuli. Studies on posttraumatic stress disorder have repeatedly shown that persons with this disorder display hippocampal size reduction and that the amount of hippocampal size reduction is related to the severity of anxiety symptoms (Bremner *et al*. 1997; Gilbertson *et al*. 2002; Villarreal *et al*. 2002).

Functional imaging studies have shown that depressive individuals have an exaggerated amygdala response to emotional stimuli (Sheline *et al*. 2001), and that these responses are sustained significantly longer than those of healthy controls (Siegle *et al*. 2002). Depressive individuals are known to involuntarily ruminate negative topics, which may result in a 'negative response bias' (Beck, 1976). It has been speculated that the same mechanisms underlying sustained amygdala activation are also involved in the experience of depressive rumination (Siegle *et al*. 2002). Future studies should clarify whether enlarged amygdala size of depressive individuals is related to depressive rumination and to an increased metabolism of the amygdala during the depressive state.

## ACKNOWLEDGEMENTS

We express our appreciation to the subjects who participated in this study. Research was supported by grants IR 15/6-3 and IR 15/8-1 from the Deutsche Forschungsgemeinschaft.

## REFERENCES

**Altshuler, L. L., Bartzokis, G., Grieder, T., Curran, J. & Mintz, J.** (1998). Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: an MRI study demonstrating neuroanatomic specifity. *Archives of General Psychiatry* **55**, 663–664.

**APA** (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV). American Psychiatric Press: Washington, DC.

**Beck, A. T.** (1976). *Cognitive Therapy and the Emotional Disorders*. International Universities Press: New York.

**Bremner, J. D., Randall, P. R., Vermetten, E., Staib, L., Bronen, R. A., Mazure, C., Capelli, S., McCarthy, G., Innis, R. B. & Charney, D. S.** (1997). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse – a preliminary report. *Biological Psychiatry* **41**, 23–32.

**Bremner, J. D., Narayan, M., Anderson, E. R., Staib, L. H., Miller, H. L. & Charney, D. S.** (2000). Hippocampal volume reduction in major depression. *American Journal of Psychiatry* **157**, 115–117.

**Brunner, E., Domhof, S. & Langer, F.** (2002). *Nonparametric Analysis of Longitudinal Data in Factorial Experiments*. Wiley: New York.

**Drevets, W. C., Videen, T. O., Price, J. L., Preskorn, S. H., Carmichael, S. T. & Raichle, M. E.** (1992). A functional anatomical study of unipolar depression. *Journal of Neuroscience* **12**, 3628–3641.

**Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., Osterheider, M. & Petersen, D.** (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of General Psychiatry* **57**, 1115–1122.

**Duvernoy, H. M.** (1998). *The Human Hippocampus. Functional Anatomy, Vascularization, and Serial Sections with MRI*. Springer: Berlin, Germany.

**Frodl, T., Meisenzahl, E., Zetzsche, T., Born, C., Groll, C., Jäger, M., Leinsinger, G., Bottlender, R., Hahn, K. & Möller, H.-J.** (2002*a*). Hippocampal changes in patients with a first episode of major depression. *American Journal of Psychiatry* **159**, 1112–1118.

**Frodl, T., Meisenzahl, E., Zetzsche, T., Bottlender, R., Born, C., Groll, C., Jäger, M., Leinsinger, G., Hahn, K. & Möller, H.-J.** (2002*b*). Enlargement of the amygdala in patients with first episode of major depression. *Biological Psychiatry* **51**, 708–714.

**Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P. & Pitman, R. K.** (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience* **5**, 1242–1247.

**Gould, E., Tanapat, P., McEwen, B. S., Flügge, G. & Fuchs, E.** (1998). Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proceedings of the National Academy of Sciences USA* **95**, 3168–3171.

**Gray, J. A. & McNaughton, N.** (2000). *The Neuropsychology of Anxiety: an Enquiry into the Functions of the Septo-hippocampal System* (2nd edn). Oxford University Press: Oxford.

**Hamilton, M.** (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–62.

**Hauser, P., Matochik, J., Altshuler, L. L., Denicoff, K. D., Conrad, A., Li, X. & Post, R. M.** (2000). MRI-based measurements of temporal lobe and ventricular structures in patients with bipolar I and bipolar II disorders. *Journal of Affective Disorders* **60**, 25–32.

**Hautzinger, M., Bailer, M., Worall, H. & Keller, F.** (1995). *Beck Depressions Inventory* (*BDI*). Huber: Bern, CH.

**MacQueen, G. M., Campbell, S., McEwen, B. S., Macdonald, K., Amano, S., Joffe, R. T., Nahmias, C. & Young, L. T.** (2003). Course of illness, hippocampal function, and hippocampal volume in major depression. *Proceedings of the National Academy of Sciences USA* **100**, 1387–1392.

**Mervaala, E., Föhr, J., Könönen, M., Valkonen-Korhonen, M., Vainio, P., Partanen, J., Tihonen, J., Viinamäki, H., Karjalaien, A.-K. & Lehtonen, J.** (2000). Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychological Medicine* **30**, 117–125.

**Pearlson, G. D., Barta, P. E., Powers, R. E., Menon, R. R., Richards, S. S., Aylward, E. H., Federman, E. B., Chase, G. A., Petty, R. G. & Tien, A. Y.** (1997). Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. *Biological Psychiatry* **41**, 1–14.

**Pruessner, J. C., Li, L. M., Serles, W., Pruessner, M., Collins, D. L., Kabani, N., Lupien, S. & Evans, A. C.** (2000). Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. *Cerebral Cortex* **10**, 433–442.

**Sapolsky, R. M., Uno, H., Rebert, C. S. & Finch, C. E.** (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience* **10**, 2897–2902.

**Shah, P. J., Ebmeier, K. P., Glabus, M. F. & Goodwin, G. F.** (2000). Cortical gray matter reductions associated with treatment-resistant chronic unipolar depression: controlled magnetic resonance imaging study. *British Journal of Psychiatry* **172**, 527–532.

**Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. G. & Vannier, M. W.** (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences USA* **93**, 3908–3913.

**Sheline, Y. I., Sanghavi, M., Mintun, M. A. & Gado, M. H.** (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience* **19**, 5034–5043.

**Sheline, Y. I., Barch, D. M., Donnelly, J. M., Ollinger, J. M., Snyder, A. Z. & Mintun, M. A.** (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological Psychiatry* **50**, 651–658.

**Siegle, G. J., Steinhauer, S. R., Thase, M. E., Stenger, V. A. & Carter, C. S.** (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biological Psychiatry* **51**, 693–707.

**Sims, K. S. & Williams, R. S.** (1990). The human amygdaloid complex: a cytologic and histochemical atlas using nissl, myelin, acetylcholinesterase and nicotinamide adenine dinucleotide phosphate diaphorase staining. *Neuroscience* **36**, 449–472.

**Strakowski, S. M., DelBello, M. P., Sax, K. W., Zimmermann, M. E., Shear, P. K., Hawkins, J. M. & Larson, E. R.** (1999). Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Archives of General Psychiatry* **56**, 254–260.

**Strakowski, S. M., DelBello, M. P., Zimmerman, M. E., Getz, G. E., Bills, N. P., Ret, J., Shear, P. & Adler, C. M.** (2002). Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. *American Journal of Psychiatry* **159**, 1841–1847.

**Swayze II, V. W., Andreasen, N. C., Alliger, J. R., Yuh, W. T. C. & Ehrhardt, J. C.** (1992). Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. *Biological Psychiatry* **31**, 221–240.

**Tebartz van Elst, L., Woermann, F. G., Lemieux, L. & Trimble, M. R.** (1999). Amygdala enlargement in dysthymia – a volumetric study of patients with temporal lobe epilepsy. *Biological Psychiatry* **46**, 1614–1623.

**Tewes, U.** (1991). *Hamburg–Wechsler Intelligenztest für Erwachsene. Revision 1991*. Huber: Bern, CH.

**Villarreal, G., Hamilton, D. A., Petropoulos, H., Driscoll, I., Rowland, L. M., Griego, J. A., Kodituwakku, P. W., Hart, B. L., Escalona, R. & Brooks, W. M.** (2002). Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. *Biological Psychiatry* **52**, 119–125.

**Wittchen, H. U., Zaudig, M. & Frydrich, T.** (1997). *Strukturiertes Klinisches Interview für DSM-IV*. Hogrefe: Göttingen, FRG.

**Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W. R., David, A. S., Murray, R. M. & Bullmore, E. T.** (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry* **157**, 16–25.