Reduced amygdalar and hippocampal size in adults with generalized social phobia

Eva Irle, PhD; Mirjana Ruhleder, PhD; Claudia Lange, PhD; Ulrich Seidler-Brandler, PhD; Simone Salzer, MS; Peter Dechent, PhD; Godehard Weniger, MD; Eric Leibing, PhD;* Falk Leichsenring, PhD*

Irle, Ruhleder, Lange — Department of Psychiatry and Psychotherapy; Seidler-Brandler, Salzer, Leibing — Department of Psychosomatic Medicine and Psychotherapy; Dechent — Magnetic Resonance-Research in Neurology and Psychiatry, University of Göttingen, Göttingen, Germany; Weniger — Department of Social and General Psychiatry, University of Zürich, Switzerland; Leichsenring — Department of Psychosomatic Medicine and Psychotherapy, University of Giessen, Giessen, Germany

Background: Structural and functional brain imaging studies suggest abnormalities of the amygdala and hippocampus in posttraumatic stress disorder and major depressive disorder. However, structural brain imaging studies in social phobia are lacking. **Methods:** In total, 24 patients with generalized social phobia (GSP) and 24 healthy controls underwent 3-dimensional structural magnetic resonance imaging of the amygdala and hippocampus and a clinical investigation. **Results:** Compared with controls, GSP patients had significantly reduced amygdalar (13%) and hippocampal (8%) size. The reduction in the size of the amygdala was statistically significant for men but not women. Smaller right-sided hippocampal volumes of GSP patients were significantly related to stronger disorder severity. **Limitations:** Our sample included only patients with the generalized subtype of social phobia. Because we excluded patients with comorbid depression, our sample may not be representative. **Conclusion:** We report for the first time volumetric results in patients with GSP. Future assessment of these patients will clarify whether these changes are reversed after successful treatment and whether they predict treatment response.

Introduction

Present evidence from functional brain imaging studies suggests that patients with social phobia, posttraumatic stress disorder (PTSD) or specific phobia share a pattern of hyperactivity of the amygdala and surrounding cortices, including the hippocampus, linked to negative emotional responses.[1] The majority of studies including patients with social phobia suggest that these changes may be most pronounced in the generalized subtype of social phobia (GSP).[2–4] A recent study suggests that these changes may resolve after successful psychotherapeutic or psychopharmacologic treatment of social phobia.[5]

There is now an extensive body of evidence suggesting that PTSD[6] and major depressive disorder[7,8] are related to abnormal amygdalar and hippocampal size. However, the mechanisms underlying these changes are not well understood. Research in nonhuman primates has suggested that stress and prolonged glucocorticoid exposure may damage the hippocampus,[9] thus raising the possibility that stress may also induce hippocampal degeneration in humans with anxiety or affective disorders. Another possibility is that preexisting small hippocampal size increases the risk for developing anxiety or affective disorders.[10,11]

However, structural brain imaging studies in social phobia are lacking. Given the fact that patients with traumatic and nontraumatic anxiety disorders share a pattern of medial temporal hyperactivity during functional neuroimaging,[1] investigation into structural aspects of the amygdala and hippocampus in social phobia are warranted. Furthermore, because the more severe form of social phobia (i.e., GSP) is likely associated with continuous and extreme stress, the possibility of a reduction of the size of the amygdala and hippocampus is likely.

We investigated amygdala and hippocampal volumes in adults with GSP and healthy controls. The goals of our study were to investigate whether amygdalar and hippocampal size

Correspondence to: Dr. E. Irle, Department of Psychiatry and Psychotherapy, University of Göttingen, Von-Siebold-Str. 5, D-37075 Göttingen, Federal Republic of Germany; fax 551-3912712; eirle@gwdg.de

*Both authors contributed equally to this study.

J Psychiatry Neurosci 2010;35(2):126-31.

Submitted Apr. 4, 2009; Revised Sept. 17, 2009; Accepted Oct. 30, 2009.

DOI: 10.1503/jpn.090041

are reduced in individuals with GSP, to investigate whether these changes are more pronounced in individuals with stronger disorder severity and to explore how specific clinical symptoms are related to amygdalar and hippocampal size.

We expected that individuals with GSP would have reduced amygdalar and hippocampal size. We hypothesized that stronger clinical symptoms in GSP patients would be related to smaller amygdalar and hippocampal size.

Methods

Participants

We included outpatients with GSP, admitted to the clinic of the Department of Psychosomatics and Psychotherapy of the University of Göttingen, Germany. The patients were recruited as part of a multicentre randomized controlled trial of psychotherapy for social phobia (pretreatment assessment)[12] (www.controlled-trials.com/ISRCTN53517394).

Our inclusion criterion were age 18–70 years with a diagnosis of social phobia (DSM-IV) and a score on the Liebowitz Social Anxiety Scale (LSAS) greater than 30.[13] We included only patients whose primary diagnosis was social phobia (i.e., the most severe disorder according to the Anxiety Disorders Interview Schedule Adult Version [ADIS-IV] rating[14]). We excluded patients with a history of neurologic disease, severe medical conditions, psychotic and affective disorders, prominent risk of self-harm, current substance-related disorders, PTSD, traumatic exposure or personality disorders except for avoidant personality disorder (APD) (as assessed by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders [SCID-II][15]). We excluded patients receiving concurrent psychotherapeutic or psychopharmacologic treatment.

We compared GSP patients with healthy controls matched for sex, age, height and years of education. We recruited controls through an advertisement in a local newspaper and leaflets distributed at the Hospital of the University of Göttingen and in town. We included only individuals without a history of neurologic or psychiatric disorders (as assessed by SCID-I[16] and SCID-II[15]).

We obtained written informed consent from all participants after providing them with a complete description of the study. The ethical committee of the medical faculty of the University of Göttingen approved the study design.

Clinical assessment

An experienced and trained interviewer (U.S.-B.) performed the diagnosis using SCID-I and SCID-II.[15,16] We verified the diagnosis of GSP by use of SCID-I with additional probes from the LSAS[17] (i.e., when more than 12 fears were present). Subscales of the LSAS were defined according to Heimberg and colleagues.[18] We further assessed clinical symptoms by the Social Phobia and Anxiety Inventory (SPAI)[19] and the State Trait Anxiety Inventory (STAI).[20] We assessed depressive symptoms by use of the Beck Depression Inventory (BDI).[21] We carefully screened all participants for traumatic exposure by use of the SCID-I and the Early Trauma Inventory–Short Form,[22] because amygdala and hippocampal size have been shown to be diminished in patients with PTSD.[6]

Magnetic resonance imaging assessment

We obtained images using a 3-T magnetic resonance imaging (MRI) scanner (MAGNETOM Trio; Siemens Healthcare). Parameters of the T_1-weighted 3-dimensional (3-D) sequence at 1 mm isotropic resolution were as follows: echo time 2.6 ms; repetition time 2250 ms; inversion time 900 ms; flip angle 9°; field-of-view 256; slice plane sagittal; matrix 256 × 256; slice thickness 1.0 mm; and 176 slices. We performed volumetric analysis on the basis of 3-D MRI scans. We transferred the images to a computer workstation and processed them using CURRY software, version 4.5 (Neurosoft Inc.).

We calculated intracranial volume and total brain volume with automated multistep algorithms and 3-D region growing methods limited by grey value thresholds. Simultaneous 3-D visualization of brain structures and manual tracing allowed a precise identification and delineation of the regions of interest. We separately disarticulated the amygdala and hippocampus from the surrounding tissue on coronal slices by means of manual tracing according to a standardized protocol.[23] We separated the amygdala and hippocampus by 3-D visualization of the alveus and the inferior horn of the lateral ventricle. The anterior border of the hippocampus was found on the coronal slice showing the alveus and/or the uncal recess of the inferior horn of the lateral ventricle, and the posterior border was found on the slice where an ovoid mass of grey matter appeared inferiomedially to the trigone of the lateral ventricle.

A single rater (C.L.), who was unaware of the diagnosis, performed the assessment. To define intrarater reliability, the analyst reassessed 1 hemisphere of 10 randomly chosen cases. The intraclass correlation coefficients for this procedure were $r = 0.94$ for the amygdala and $r = 0.95$ for the hippocampus. Interrater reliabilities, including that of this rater, have been published previously (hippocampus: $r = 0.96$; amygdala: $r = 0.96$).[24,25]

Statistical analysis

We used t tests to compare differences between groups for demographic and clinical variables and for intracranial and total brain volume. We compared amygdalar and hippocampal volumes of GSP patients and the control group using analyses of covariance (ANCOVA) with group and sex as the between-subjects factors and hemisphere as the within-subjects factor and with adjustment for total brain volume. We used multiple stepwise regression analyses with a significance level for selecting variables of $\alpha = 0.05$ to examine the relations between amygdalar and hippocampal volumes and clinical variables. We used left- and right-sided amygdalar and hippocampal volumes and total brain volume as explanatory variables and clinical scores as dependent variables. All analyses were 2-tailed; we set the level of statistical significance at $p < 0.05$. We corrected the results of clinical instruments for multiple testing (Bonferroni correction: α level

for the LSAS = 0.016). We performed statistical analyses using the Statistical Package for the Social Sciences (SPSS for Windows, Version 14.0).

Results

Participants

Our sample comprised 24 outpatients with GSP and 24 healthy matched controls. Participant characteristics are provided in Table 1. Four GSP patients had a history of psychotherapeutic treatment (18, 3, 1 or 1/2 years) before the present assessment. Four patients had a history of psychopharmacologic treatment. Three had received antidepressant drugs about 10 years before the present assessment; 1 patient was irregularly taking benzodiazepines 2 years before the present assessment.

The male (n = 12) and female (n = 12) GSP patients did not differ significantly in terms of age, education, age at disorder onset, disorder duration or for any of the clinical variable in Table 1. Comorbid diagnoses and clinical measures for all GSP patients are summarized in Table 1. Results from the SCID-I and the Early Trauma Inventory–Short Form revealed that none of the GSP patients or control participants experienced childhood physical or sexual abuse or other traumatic exposure.

Brain measures: group comparisons

An overall 2 × 2 × 2 (group × sex × hemisphere) ANCOVA comparing the amygdalar volumes of GSP patients and controls and adjusting for total brain volume yielded a significant effect of group, indicating that GSP patients had smaller amygdalar volumes than controls (Table 2). The group × sex interaction was also significant, indicating stronger amygdalar size reduction in men than in women in the GSP group. The following F values were obtained: group, $F_{1,43}$ = 11.46, p = 0.002; sex, $F_{1,43}$ = 0.14, p = 0.71; hemisphere, $F_{1,43}$ = 0.03, p = 0.87; group × hemisphere, $F_{1,43}$ = 1.43, p = 0.24; group × sex, $F_{1,43}$ = 9.77, p = 0.003; sex × hemisphere, $F_{1,43}$ = 0.38, p = 0.54; group × sex × hemisphere, $F_{1,43}$ = 0.04, p = 0.85.

Table 1: Clinical and socio-demographic characteristics of patients with generalized social phobia and healthy controls

Characteristic	Group; mean (SD)*	
	GSP patients, n = 24	Controls, n = 24
Age, yr, mean (SD) [range]	32 (10) [19–49]	31 (9) [19–47]
Education, no. of yr	15 (2)	15 (2)
Sex, male:female, no.	12:12	12:12
Handedness, right:left, no.	23:1	22:2
Duration of disorder, yr	15 (10)	–
Age at disorder onset, yr	17 (5)	–
DSM-IV diagnoses, no. of patients		–
GSP	15	–
GSP, avoidant personality disorder	7	–
GSP, bulimia nervosa	1	–
GSP, panic disorder with agoraphobia	1	–
Liebowitz Social Anxiety Scale[17] score		–
Anxiety	38 (9)	–
Avoidance	29 (9)	–
Number of fears	18 (3)	–
Social Phobia and Anxiety Inventory[19] score†	4 (1)	–
State Trait Anxiety Inventory,[20] state anxiety score	45 (10)	–
Beck Depression Inventory[21]	13 (7)	–

GSP = generalized social phobia; SD = standard deviation.
*Unless otherwise indicated.
†German version with 22 items (range: 0–6).

The posthoc 2 × 2 (group × sex) ANCOVA adjusting for total brain volume confirmed these results for the left and right amygdala. The following F values were obtained for the left amygdala: group, $F_{1,43}$ = 13.29, p = 0.001; sex, $F_{1,43}$ = 0.48, p = 0.49; group × sex, $F_{1,43}$ = 6.80, p = 0.012. The values for the right amygdala were as follows: group, $F_{1,43}$ = 4.20, p = 0.046; sex, $F_{1,43}$ = 0.00, p = 0.98; group × sex, $F_{1,43}$ = 6.68, p = 0.013. The posthoc 1-way ANCOVA revealed that male GSP patients had smaller left ($F_{1,21}$ = 12.89, p = 0.002) and right ($F_{1,21}$ = 13.33, p = 0.001) amygdalar volumes compared with male controls. However, female GSP patients did not differ significantly from female controls.

The overall 2 × 2 × 2 (group × sex × hemisphere) ANCOVA comparing the hippocampal volumes of GSP patients and controls and adjusting for total brain volume yielded a significant effect of group, indicating that GSP patients had smaller hippocampal volumes than controls (Table 2). The sex × hemisphere interaction was also significant, indicating a stronger left–right asymmetry in women (right hippocampus > left hippocampus) relative to men. The following F values were obtained: group, $F_{1,43}$ = 8.17, p = 0.007; sex, $F_{1,43}$ = 0.30, p = 0.86; hemisphere, $F_{1,43}$ = 2.42, p = 0.13; group × hemisphere, $F_{1,43}$ = 0.01, p = 0.97; group × sex, $F_{1,43}$ = 0.45, p = 0.50; sex × hemisphere, $F_{1,43}$ = 4.47, p = 0.040; group × sex × hemisphere, $F_{1,43}$ = 0.84, p = 0.36.

The posthoc 2 × 2 (group × sex) ANCOVA confirmed reduced left and right hippocampal volumes of GSP patients (Table 2): left hippocampus, group, $F_{1,43}$ = 8.08, p = 0.007; sex, $F_{1,43}$ = 0.93, p = 0.34; group × sex, $F_{1,43}$ = 0.10, p = 0.75; right hippocampus, group, $F_{1,43}$ = 6.39, p = 0.015; sex, $F_{1,43}$ = 0.31, p = 0.58; group × sex, $F_{1,43}$ = 0.82, p = 0.37.

The relation between brain and behaviour

The volumes of the left- and right-sided amygdala and hippocampus of GSP patients (n = 24) were entered as predictors into multiple regression analyses (method: stepwise; significance level for selecting variables: α = 0.05). Total brain volume was entered as a further predictor to control for the effects of global brain size. Clinical scores (LSAS anxiety score, LSAS avoidance score, LSAS number of fears, SPAI, STAI and BDI; Table 1) were used as dependent variables.

When the LSAS scores were considered, right-sided hippocampal volumes significantly predicted the number of social fears (β = –0.533, p = 0.014), indicating higher scores (i.e., stronger disorder severity) in patients with smaller right hippocampal volumes. For the STAI scores, smaller right-sided amygdalar volumes significantly predicted stronger state

anxiety (β = –0.615, p = 0.001). Regression models with the same predictors and BDI or SPAI as dependent variables were not significant.

Multiple regression analyses (method: stepwise; significance level for selecting variables: α = 0.05) were also performed with the predictors age, age at disorder onset and disorder duration and left and right amygdalar volume and left and right hippocampal volume as dependent variables, respectively. None of the predictors significantly predicted left or right hippocampal volumes or left amygdalar volumes of the GSP patients. However, right amygdalar volumes were significantly predicted by age (β = –0.475, p = 0.019), indicating smaller volumes in older GSP patients.

Influence of comorbid APD on brain and behaviour

The GSP patients with comorbid APD (n = 7, 5 men) did not differ significantly from those without APD (n = 17, 7 men) for left and right hippocampal volume or left and right amygdalar volume (ANCOVA adjusting for total brain volume). The overall 2 × 2 × 2 (group × sex × hemisphere) ANCOVA adjusting for total brain volume were repeated for GSP patients without APD (n = 17) and controls (n = 24). The ANCOVA comparing amygdalar volumes yielded a significant effect of group ($F_{1,36}$ = 6.33, p = 0.017) and group × sex ($F_{1,36}$ = 10.00, p = 0.003), indicating that male GSP patients had smaller amygdalar volumes. The ANCOVA comparing hippocampal volumes yielded a significant effect of group ($F_{1,36}$ = 5.47, p = 0.025), indicating smaller hippocampal volumes in GSP patients. None of the other terms were statistically significant.

The GSP patients with comorbid APD did not differ significantly from those without APD in terms of age, education and age at disorder onset. However, patients with comorbid APD had a longer disorder duration (t_{22} = –2.34, p = 0.029) and showed stronger anxiety (t_{22} = –3.63, p = 0.001) and avoidance (t_{22} = –4.02, p = 0.001) on the LSAS and had a higher SPAI score (t_{22} = –4.13, p < 0.001) than patients without comorbid APD. Comparisons of the BDI and the STAI score were not significant.

Discussion

To our knowledge, our study is the first structural 3-D MRI study of social phobia and the first study to investigate amygdalar and hippocampal size in this disorder. Our results indicate reduced amygdalar and hippocampal size in individuals with GSP. None of our patients received psychopharmacologic or psychotherapeutic treatment at the time of the assessment. None of our patients had experienced traumatic exposure, which is associated with amygdalar and hippocampal size reduction.[6] We excluded patients with comorbid depression because major depressive disorder was shown to be also related to small hippocampal size.[7]

We found significant relations between right hippocampal volume and social phobia severity, indicating smaller volumes in GSP patients with a more generalized disorder. Furthermore, a relation between right amygdalar size and state anxiety emerged, indicating smaller amygdalar size in patients with stronger anxiety. Significant negative relations between hippocampal size and PTSD severity have been well established.[6] There is also evidence that the small hippocampal size of individuals with major depressive disorder is related to stronger anxiety symptoms.[25] Animal experiments have shown that lesions of the hippocampus destroy the ability to avoid stressful stimuli.[26] Accordingly, recent studies involving healthy individuals suggest that individuals with small hippocampal and amygdalar size may have deficits in inhibiting stressful thoughts and feelings.[27,28]

The mechanisms underlying amygdalar and hippocampal size reduction in anxiety disorders are not well understood. Research involving nonhuman primates has suggested that stress and prolonged glucocorticoid exposure may damage the hippocampus.[9] There is also evidence that hyperglutamatergic activity may contribute to neural toxicity (i.e., hippocampus degeneration) in individuals who had been exposed to extreme stress.[29] Animal studies demonstrated that activation of N-methyl-D-aspartate glutamate receptors inhibits neurogenesis in the hippocampus[30] and increases the excitability of amygdala neurons.[31]

In contrast, it can be argued that pre-existing small hippocampal and amygdalar size increases the risk of developing anxiety or affective disorders. A twin study investigating hippocampal size in Vietnam veterans suggested that individuals with smaller hippocampal size were at greater risk for developing PTSD,[10] rendering it likely that genetic factors contribute to the small hippocampal size of individuals with PTSD. Polymorphisms in the promoter region of the serotonin

Table 2: Morphometric measures of patients with generalized social phobia and healthy controls

Brain volume, mL	Group; mean (SD)*		Statistical test	p value
	GSP patients, n = 24	Controls, n = 24		
Intracranial volume	1552 (139)	1550 (109)	t_{46} = –0.06	0.96
Total brain volume	1225 (119)	1233 (86)	t_{46} = 0.27	0.79
Amygdala				
Left	0.96 (0.14) [–17.2]	1.16 (0.20)	$F_{1,43}$ = 13.29	0.001
Right	0.98 (0.19) [–9.3]	1.08 (0.19)	$F_{1,43}$ = 4.20	0.046
Hippocampus				
Left	2.79 (0.36) [–7.9]	3.03 (0.26)	$F_{1,43}$ = 8.08	0.007
Right	2.97 (0.36) [–7.8]	3.22 (0.34)	$F_{1,43}$ = 6.39	0.015

GSP = generalized social phobia; SD = standard deviation.
*Values in square brackets indicate the percentage difference in regional volume relative to controls.

transporter (5-HTTLPR) were shown to influence hippocampal size in individuals with depression[11] and to influence the reactivity of the amygdala of healthy people[32] and those with social phobia[33] toward salient environmental cues. A longitudinal study found that genetic variation of the serotonin transporter was associated with the development of depression following stressful life events, suggesting a gene-by-environment interaction in which the response to environmental insults is moderated by genetic factors.[34]

There is preliminary evidence of the beneficial effects of antidepressant pharmacologic treatment on hippocampal size reduction in mood and anxiety disorders.[35,36] Several recent findings suggest that structural magnetic resonance imaging may also predict response to treatment.[37] Results from our multicentre trial of psychotherapy for social phobia[12] will elucidate whether treatment responders have less decline or even an increase in amygdalar and hippocampal size when compared with nonresponders and with patients without treatment (on waiting lists). These forthcoming results may also provide clues as to whether amygdalar and hippocampal size reductions in social phobia are related to environmental influences or predisposition, or both.

Limitations

Our sample included only patients with the generalized subtype of social phobia. Furthermore, we excluded patients with comorbid depressive disorders, because major depressive disorder has been shown to be related to small hippocampal size.[7] Thus, our sample may not be considered representative. Future studies will show whether individuals with the nongeneralized subtype of social phobia also have reduced amygdalar and hippocampal size. Furthermore, it seems important to compare GSP patients with social phobia patients with only performance fears, because these subgroups may be biologically heterogeneous.[38]

We found statistically significant amygdalar size reductions in male but not female GSP patients. However, the number of male and female GSP patients included were small. We are not aware of clear sex differences in amygdalar or hippocampal size reduction in PTSD[6] or major depressive disorder.[7,8] However, functional brain imaging has revealed differential emotion processing between men and women.[39] Future studies using larger patient series are needed to clarify whether men with anxiety disorders are more prone to amygdalar size reduction than women are.

Acknowledgements: The authors thank Lena-Sophie Tanneck and Astrid Bohl for assistance in participants' assessments and Dr. Steffen Luntz (Koordinierungszentrum Klinische Studien, Heidelberg, Federal Republic of Germany) for support in data management and on-site monitoring. This research was supported by grant BMBF 01GV0607 (Ministry of Education and Research, Germany).

Competing interests: None declared.

Contributors: Drs. Irle, Leichsenring and Leibing made substantial contributions to the study conception and design. Drs. Ruhleder, Seidler-Brandler, Salzer and Dechent acquired the data, which Drs. Irle, Ruhleder, Lange and Weniger analyzed. Dr. Irle wrote the first draft of the article. All authors revised and gave final approval of the article to be published.

References

1. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry* 2007;164:1476-88.
2. Stein MB, Philip R, Goldin MS, et al. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Arch Gen Psychiatry* 2002;59:1027-34.
3. Phan KL, Fitzgerald DA, Nathan PJ, et al. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry* 2006;59:424-9.
4. Blair K, Shaywitz J, Smith BW, et al. Response to emotional expressions in generalized social phobia and generalized anxiety disorder: evidence for separate disorders. *Am J Psychiatry* 2008;165:1193-202.
5. Furmark T, Tillfors M, Marteinsdottir I, et al. Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Arch Gen Psychiatry* 2002;59:425-33.
6. Karl A, Schaefer M, Malta LS, et al. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev* 2006;30:1004-31.
7. Campbell S, Marriott M, Nahmias C, et al. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry* 2004;161:598-607.
8. Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-anlysis of magnetic resonance imaging studies. *Mol Psychiatry* 2008;13:993-1000.
9. Sapolsky RM, Uno H, Rebert CS, et al. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci* 1990;10:2897-902.
10. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci* 2002;5:1242-7.
11. Taylor WD, Steffens DC, Payne ME, et al. Influence of serotonin transporter promotor region polymorphisms on hippocampal volumes in late-life depression. *Arch Gen Psychiatry* 2005;62:537-44.
12. Leichsenring F, Hoyer J, Beutel M, et al. The social phobia psychotherapy research network. *Psychother Psychosom* 2009;78:35-41.
13. Mennin DS, Fresco DM, Heimberg RG, et al. Screening for social anxiety disorder in the clinical setting using the Liebowitz Social Anxiety Scale. *J Anxiety Disord* 2002;16:661-73.
14. Brown TA, di Nardo P, Barlow DH. *Anxiety disorders interview schedule adult version*. Oxford (UK): Oxford University Press; 1994.
15. First MB, Gibbon M, Spitzer RL, et al. *Structured clinical interview for DSM-IV axis II personality disorders (SCID-II)*. Washington (DC): American Psychiatric Press; 1997.
16. First MB, Spitzer RL, Gibbon M, et al. *Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition.* (SCID-I/P) New York (NY): Biometrics Research, New York State Psychiatric Institute; 2002.
17. Liebowitz MR. Social phobia. *Mod Probl Pharmacopsychiatry* 1987; 22:141-73.
18. Heimberg RG, Horner KJ, Juster HR, et al. Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychol Med* 1999;29:199-212.
19. Beidel DC, Turner SM, Cooley MR. Assessing reliable and clinically significant change in social phobia: validity of the social phobia and anxiety inventory. *Behav Res Ther* 1993;31:331-7.

20. Spielberger CD, Gorsuch RL, Lushene RE. *Manual for the State-Trait Anxiety Inventory*. Palo Alto (CA): Consulting Psychologists Press; 1970.

21. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-71.

22. Hyman SM, Garcia M, Kemp K, et al. A gender specific psychometric analysis of the early trauma inventory short form in cocaine dependent adults. *Addict Behav* 2005;30:847-52.

23. Pruessner JC, Li LM, Serles W, et al. Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. *Cereb Cortex* 2000;10:433-42.

24. Irle E, Lange C, Sachsse U. Reduced size and abnormal asymmetry of parietal cortex in women with borderline personality disorder. *Biol Psychiatry* 2005;57:173-82.

25. Weniger G, Lange C, Irle E. Abnormal size of the amygdala predicts impaired emotional memory in major depressive disorder. *J Affect Disord* 2006;94:219-29.

26. Gray JA, McNaughton NJ. *The neuropsychology of anxiety*. Oxford (UK): Oxford Medical Publications; 2000.

27. Cherbuin N, Windsor TD, Anstey KJ, et al. Hippocampal volume is positively associated with behavioural inhibition (BIS) in a large community-based sample of mid-life adults: the PATH through life study. *Soc Cogn Affect Neurosci* 2008;3:262-9.

28. Barros-Loscertales A, Meseguer V, Sanjuan A, et al. Behavioral inhibition system activity is associated with increased amygdala and hippocampal gray matter volume: a voxel-based morphometry study. *Neuroimage* 2006;33:1011-5.

29. Chambers RA, Bremner JD, Moghaddam B, et al. Glutamate and post-traumatic stress disorder: toward a psychobiology of dissociation. *Semin Clin Neuropsychiatry* 1999;4:274-81.

30. Cameron HA, McEwen BS, Gould E. Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. *J Neurosci* 1995;15:4687-92.

31. Shekhar A, Truitt W, Rainnie D, et al. Role of stress, corticotropin releasing factor (CRF) and amygdala plasticity in chronic anxiety. *Stress* 2005;8:209-19.

32. Munafo MR, Brown SM, Hariri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biol Psychiatry* 2008;63:852-7.

33. Furmark T, Tillfors M, Garpenstrand H, et al. Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. *Neurosci Lett* 2004;362:189-92.

34. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003; 301:386-9.

35. Vermetten E, Vythilingam M, Southwick SM, et al. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biol Psychiatry* 2003;54:693-702.

36. Frodl T, Jäger M, Smajstrlova I, et al. Effect of hippocampal and amygdala volume on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. *J Psychiatry Neurosci* 2008;33:423-30.

37. MacQueen GM. Magnetic resonance imaging and prediction of outcome in patients with major depressive disorders. *J Psychiatry Neurosci* 2009;34:343-9.

38. Stein MB, Torgrud LJ, Walker JR. Social phobia symptoms, subtypes, and severity. Findings from a community survey. *Arch Gen Psychiatry* 2000;57:1046-52.

39. Hamann S, Canli T. Individual differences in emotion processing. *Curr Opin Neurobiol* 2004;14:233-8.