ORIGINAL ARTICLE

Common Changes in Cerebral Blood Flow in Patients With Social Phobia Treated With Citalopram or Cognitive-Behavioral Therapy

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Background: Neurofunctional changes underlying effective antianxiety treatments are incompletely characterized. This study explored the effects of citalopram and cognitive-behavioral therapy on regional cerebral blood flow (rCBF) in social phobia.

Methods: By means of positron emission tomography with oxygen 15–labeled water, rCBF was assessed in 18 previously untreated patients with social phobia during an anxiogenic public speaking task. Patients were matched for sex, age, and phobia severity, based on social anxiety questionnaire data, and randomized to citalopram medication, cognitive-behavioral group therapy, or a waiting-list control group. Scans were repeated after 9 weeks of treatment or waiting time. Outcome was assessed by subjective and psychophysiological state anxiety measures and self-report questionnaires. Questions were readministered after 1 year.

Results: Symptoms improved significantly and roughly equally with citalopram and cognitive-behavioral therapy, whereas the waiting-list group remained unchanged. Four patients in each treated group and 1 waiting-list patient were classified as responders. Within both treated groups, and in responders regardless of treatment approach, improvement was accompanied by a decreased rCBF-response to public speaking bilaterally in the amygdala, hippocampus, and the periamygdaloid, rhinal, and parahippocampal cortices. Between-group comparisons confirmed that rCBF in these regions decreased significantly more in treated groups than control subjects, and in responders than nonresponders, particularly in the right hemisphere. The degree of amygdalar-limbic attenuation was associated with clinical improvement a year later.

Conclusions: Common sites of action for citalopram and cognitive-behavioral treatment of social anxiety were observed in the amygdala, hippocampus, and neighboring cortical areas, ie, brain regions subserving bodily defense reactions to threat.

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COMMUNITY SURVEYS indicate that at least 20% of the US population have anxiety disorders[1] and that the annual societal cost of these disorders exceeds $63 billion in 1998 dollars.[2] This underscores the importance of developing efficacious antianxiety treatments, which could be facilitated by a greater understanding of the brain regions involved in anxiety reduction. In the past decade, it was learned that selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, are helpful not only in depression but also for patients with anxiety disorders.[3] The SSRIs are generally considered to enhance serotonergic neurotransmission in the brain, but the neural mechanisms whereby these drugs alleviate anxiety symptoms are not well characterized. Similarly, psychological treatments such as cognitive-behavioral therapy are effective in reducing anxiety, but little is known about how successful psychotherapy exerts its beneficial effect in the central nervous system.

Extensive evidence indicates that the amygdala plays a major role in fear and anxiety reactions.[4] In animals, anxiolytic effects can be achieved by injections of benzodiazepines directly into the amygdaloid complex.[5,6] The hippocampus is also a part of the neural anxiety network, participating in the consolidation and retrieval of traumatic memories, behavioral inhibition, and contextual analysis of distressing situations.[7] Animal studies suggest that the effects of anxiolytic drug administration are paralleled by lesions to the hippocampus.[8] Although it can be hypothesized that the amygdala and hippocampus are important brain targets for traditional antianxiety pharmacotherapy, it remains unclear whether the SSRIs and efficacious psychotherapeutic techniques act on these or other regions in the brain. Neuroimaging techniques such as positron emission tomography (PET) provide the means to study these questions also in humans.

The principal aim of the present study was to examine neurofunctional changes associated with anxiety alleviation in pa-

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tients with social phobia (social anxiety disorder). Individuals with social phobia fear scrutiny, performance failure, and accompanying humiliation in social situations ranging from formal public appearances to casual conversations. Social phobia is arguably the most common anxiety disorder,[1,9] and public speaking is the most prevalent social fear.[10] Although it is known that patients with social phobia respond favorably to SSRIs[11] and cognitive-behavioral therapy,[12,13] the neural networks participating in the response to these 2 forms of treatment are not well understood. Thus, we used PET and water labeled with oxygen 15 (^{15}O) to assess regional cerebral blood flow (rCBF) in 18 patients with social phobia during a public speaking task, before and after 9 weeks of citalopram medication or cognitive-behavioral group therapy (CBGT). These treatments were compared with a waiting-list (WL) control group. Additional aims were to explore whether treatment responders and nonresponders differed in brain per-

SUBJECTS AND METHODS

SUBJECTS

Eighteen previously untreated patients (10 men and 8 women; mean ± SD age, 35.2 ± 7.3 years; range, 23-46 years) who fullfilled the *DSM-IV*[14] criteria for social phobia were recruited by means of newspaper advertising. The screening procedure included telephone questioning, self-report questionnaires, structured clinical diagnostic interviews[15], and a public speaking behavioral test. The structured clinical diagnostic interviews were performed by an experienced psychiatrist (I.M.). Criteria for exclusion were as follows: current psychiatric disorder (other than social phobia); neurologic disorders such as epilepsy, stroke, and brain hemorrhage; somatic disease; long-term use of prescribed medication; abuse of alcohol or narcotics; left-handedness; and pregnancy. Participants refrained from use of tobacco, alcohol, and caffeine for 12 hours before PET investigations. Participating women were premenopausal. Patients were, as far as practically possible, matched for severity, sex, and age in triplets. Severity matching was based on the Social Phobia Screening Questionnaire.[10] Age differences ranged from 7 to 12 years within triplets. One triplet did not have 3 members of the same sex. Patients were then, by means of sealed envelopes, randomized to citalopram (SSRI) medication, CBGT, or a WL control group, with 6 individuals in each group. There were 3 patients with generalized and 3 with nongeneralized social phobia in each group. Informed consent was obtained from all participants after the procedure had been fully explained. The study was approved by the Uppsala University Medical Faculty Ethical Review Board and the Uppsala University Isotope Committee, Uppsala, Sweden.

TREATMENT

Subjects in the SSRI group were treated with citalopram by an experienced psychiatrist. Dosage was adjusted according to the individual's clinical response and experience of side effects. The daily mean (±SD) dosage was 40 ± 9.8 mg. Subjects came for checkups at weeks 2, 4, and 7. Assessments of compliance and side effect were then performed, but no systematic exposure instructions were given. The mean (±SD) plasma levels of citalopram and desmethylcitalopram at the time of the second PET assessment were 253 ± 46.0 and 118 ± 22.8 nmol/L, respectively.

The CBGT incorporated simulated exposures to feared situations, cognitive restructuring, and homework assignments according to principles described by Hope and Heimberg.[16] Because public speaking was the only target situation for in-session exposure, the treatment period was limited to 8 weekly sessions, each about 3 hours long. Sessions were led by 2 clinical psychologists (T.F. and M.T.) trained in cognitive-behavioral therapy. The treatment program was coplanned and supervised by a psychotherapist with considerable experience of CBGT for social phobia.

After the 9-week treatment period, subjects in the citalopram group could choose to continue medication and subjects in the CBGT group followed an individual maintenance program, whereas WL control subjects were treated with citalopram. No patients could receive any other form of treatment than the one to which they were allocated in the study.

BEHAVIORAL MEASURES

Nine outcome measures, evaluating symptom changes from pretreatment to posttreatment, were used. Four of these were public-speaking state anxiety measures, ie, the patient's ratings of fear and distress on a scale of 0 to 100 (minimum-maximum) and the Spielberger state anxiety inventory (STAI-S[17]), administered immediately after each scanned speech. Heart rate in beats per minute was also recorded during scans by means of the PSYLAB6 integrated system for psychophysiology (Contact Precision Instruments, London, England). In addition, patients completed a battery of social anxiety questionnaires: the Social Phobia Scale (SPS[18]), the Social Interaction Anxiety Scale (SIAS[18]), the Personal Report on Confidence as a Speaker (PRCS[19]), the Social Phobia Screening Questionnaire (SPSQ[10]), and the Global Assessment of Functioning (GAF[20]) Scale. The 5 questionnaires were completed before, immediately after, and 1 year after treatment. Data on heart rate and subjective anxiety during public speaking could not be collected at 1-year follow-up.

All subjects were interviewed immediately after the final PET examination by an independent assessor and were then asked to rate their phobic reactions after as compared with before the treatment or waiting period and to express any opinions about the treatment and assessments they had undergone.

PET ASSESSMENTS

An 8-ring brain PET scanner (GEMS PC2048-15B; General Electric Medical Systems, Uppsala, Sweden)[21] with a 10-cm axial field of view and an axial-transaxial resolution of approximately 6 mm was used. Subjects were positioned in the scanner and fixated in a commercial headholder by means of a fast-hardening foam. A venous catheter was inserted. Transmission measurements were performed with a rotating germanium 68 pin source. Roughly 20 minutes before the initial emission scan, patients were instructed to prepare a 2.5-minute speech about a vacation or travel experience. While being scanned, subjects performed the speech in the presence of a silently observing audience of 6 to 8 persons standing around the scanner bed. Patients were instructed to observe the audience. To

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heighten observational anxiety, the speech was recorded from close distance with a portable videocamera. Tracer injections, approximately 0.41 mCi (15 MBq)/kg of body weight, corresponding to 19 to 35 mCi (700-1300 MBq) of $H_2{}^{15}O$ dissolved in 3 to 4 mL of water, were performed at 12-minute intervals. Immediately after injections, patients were asked to start speaking and continue until they received instructions to stop. To improve signal-to-noise ratio, patients spoke twice in front of the audience both before and after treatment. At pretreatment, a final emission scan was acquired during which the couch was automatically translated back and forth between 2 fixed positions to obtain a scan with full axial coverage of the brain. This aids in the stereotactical normalization of PET images and movement corrections.

The rCBF data were collected in fifteen 10-second frames during 150 seconds. Data from the first 70 seconds after arrival of the bolus to the brain were summed, and images were reconstructed from the summation after correction for dead time, scatter, and attenuation by means of the transmission scan.[22] All images were reconstructed to a 128×128 matrix with a pixel size of 2 mm by means of a 15-mm Hanning filter. The rCBF data were normalized for global flow by means of linear scaling,[23] thereafter reflecting relative (region to whole brain) values. Global flow was estimated with a predefined mask outlining the brain, but excluding all voxels that changed as a consequence of study conditions, by means of F-map masking.[24] Thus, brain regions exhibiting a change in perfusion resulting from the experimental design were excluded from the estimation of global flow, thereby ensuring independence between local and global flow.[24]

All images were anatomically normalized to a standard stereotactic space,[25] with the use of the software package CBA[26] (Computerized Brain Atlas; Applied Medical Imaging AB, Uppsala). This was performed automatically[27] by first matching the scan with full axial coverage of the brain to the CBA atlas template. Images from all other emission scans were automatically aligned to the full coverage scan, bringing them into the stereotactic space[25] and correcting for head movements between scans.[28,29] Because movements in any direction were always smaller than 5 mm, the attenuation correction was deemed satisfactory.[29]

The mean time from treatment onset to the second PET assessment was 62.7 days for the CBGT group and 66.5 days for the citalopram group. Subjects in the WL group were reassessed after a mean waiting period of 60.0 days.

DATA ANALYSIS

Within groups, behavioral measures were evaluated by paired *t* tests (2-tailed). In addition, between-group differences were evaluated by separate analyses of variance (ANOVAs). Because of small samples in each group, inflating the risk of type II errors, the SSRI and CBGT groups were merged (n=12) in the ANOVA group factor. Posttreatment differences between the citalopram and CBGT groups were evaluated separately by planned comparisons. In all tests, the α level used was $P<.05$.

At 9 weeks, patients who improved 1 SD or more from the pretreatment mean value on 7 to 9 outcome measures were labeled "much improved"; 4 to 6 measures, "moderately improved"; and 0 to 3 measures, "less improved." Patients who were at least moderately improved were considered to be responders. At 1-year follow-up, patients who improved 1 SD or more from the pretreatment mean value on 4 to 5 measures were labeled "much improved," and 0 to 3 measures, "less improved," similar to the approach that was used to categorize responders and nonresponders at 9 weeks.

The PET data were fitted to the general linear model[30] by means of a pixelwise multiple linear regression. Image data were averaged across the 2 repeated scans (both pretreatment and posttreatment) into mean images to be compatible with a random-effects model.[31] Image analyses were thus modeled as blocked ANOVAs where rCBF data, analogous to the behavioral measures, were evaluated by means of within- and between-group comparisons. Between-group differences were evaluated by group×time interactions in the form of double subtractions, such as $(CBGT_{post}-CBGT_{pre})-(WL_{post}-WL_{pre})$. Contrasts generated t-maps, subsequently converted to *z*-score maps through a probability-preserving transformation.[32] Local changes were evaluated by means of the spatial extent of connected clusters of voxels,[33] with a *z*-score more than 2.6 corresponding to $P<.01$ corrected for multiple comparisons. In addition to exploratory whole-brain analyses, directed region of interest (ROI) evaluations were planned a priori for the amygdala and hippocampus because of the large amount of previous research ascribing important roles to these regions in fear and anxiety.[4-8] For these areas, uncorrected *P* values are also reported.

Discriminant analysis was used to predict improvement at 1-year follow-up from initial attenuation of subcortical rCBF. Mean voxel values for each subject and condition were extracted from the subcortical ROIs implicated in the "Results" section (the amygdala, hippocampus, periaqueductal gray area, and left thalamus). The ROIs were anatomically predefined in the CBA.[25,26] Change scores (after–before treatment) in relative rCBF were calculated for each ROI and subject and then entered into a stepwise discriminant analysis[34] with the use of Statistica 4.1 for Macintosh (Statasoft, Inc, Tulsa, Okla).

To assess changes in verbal performance, number of spoken words before and after treatment was analyzed by means of repeated-measurement ANOVA and paired *t* tests (2-tailed). For each individual and condition, the number of words was sampled from a randomly chosen 20-second period from the videotape of the speech.

fusion and whether neural change was associated with long-term treatment outcome.

RESULTS

BEHAVIORAL MEASURES

There were no significant multivariate (Wilks $\lambda_{9,8}=0.50$, $F=0.89$, $P=.57$) or univariate ($F_{1,16}=0.04$-3.2, $P=.85$-$.09$) differences between treated and nontreated subjects on behavioral outcome measures before treatment. Means (±SD) at pretreatment were as follows: SPS, 28.9±14.4; SIAS, 34.3±18.0; PRCS, 24.4±3.1; SPSQ, 23.2±10.7; GAF, 76.5±11.6; heart rate, 94.7±15.5 beats/min; fear, 38.2±22.9; distress, 51.4±24.6; and STAI-S, 56.6±9.5.

Figure 1 displays within-group changes with treatment (pretreatment-posttreatment) for behavioral mea-

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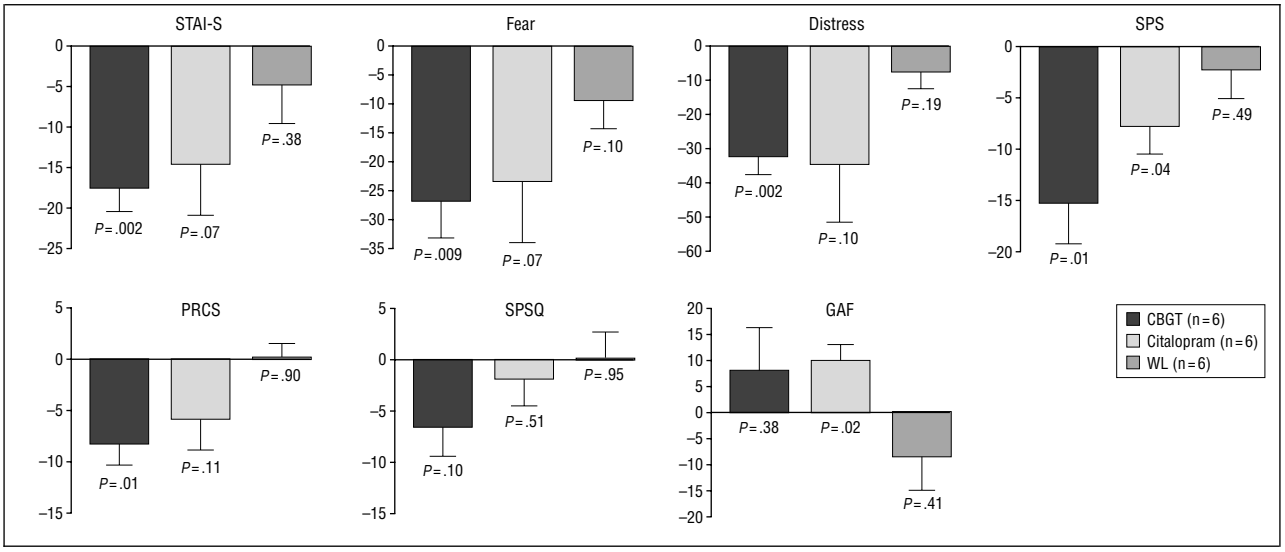

Figure 1. Change scores (mean±SE) reflecting social phobia symptom changes with 9 weeks of treatment or waiting time. CBGT indicates cognitive-behavioral group therapy; WL, waiting-list control group; STAI-S, Spielberger State Anxiety Inventory[17]; SPS, Social Phobia Scale[18]; PRCS, Personal Report on Confidence as a Speaker[19]; SPSQ, Social Phobia Screening Questionnaire[10]; and GAF, Global Assessment of Functioning self-report.[20] Heart rate and scores on the Social Interactional Anxiety Scale[18] did not change markedly ($P>.10$) and are not displayed.

sures that were at least at the $P\leq.10$ level according to paired t tests. The CBGT group improved significantly on the STAI-S, fear, distress, SPS, and PRCS ($t_5=3.7$-5.9; $P=.01$-$.002$), whereas the citalopram group improved significantly on the SPS and GAF scales ($t_5=2.8$-3.6; $P=.04$-$.02$). On several measures, these subjects also exhibited changes that were marginally above the 2-tailed $P<.05$ α level (Figure 1). The WL group did not change significantly on any measure ($t_5=0.1$-2.0; $P=.95$-$.10$).

Separate ANOVAs confirmed that treated subjects collectively improved more than WL controls. Significant group×time interactions were noted for the SPS ($F_{1,16}=4.9$, $P=.04$), PRCS ($F_{1,16}=6.9$, $P=.02$), and GAF scale ($F_{1,16}=5.5$, $P=.03$). Follow-up Fisher least significant difference tests showed that the treated subjects improved significantly more than controls (SPS, $P<.001$; PRCS, $P<.01$; GAF, $P<.05$). Borderline significant group×time interactions were obtained on ratings of distress ($F_{1,16}=4.1$, $P=.06$) and the STAI-S ($F_{1,16}=3.7$, $P=.07$). Treated subjects were more improved ($P\leq.05$; Fisher least significant difference) than WL subjects on both of these measures at posttreatment.

Planned comparisons did not show statistical differences between the CBGT and citalopram groups on any outcome measure after therapy. The number of responders was 4 each (67%) in the CBGT and citalopram groups, with 2 patients being much improved and 2 moderately improved in both groups, suggesting that the 2 interventions were about equally beneficial. One patient in the WL group was also classified as a moderately improved responder, possibly because of habituation effects. All responders (n=9) confirmed symptom improvement in individual posttreatment interviews.

REGIONAL CEREBRAL BLOOD FLOW

Therapeutic effects on rCBF were first evaluated by contrasting public speaking after and before treatment within each group (CBGT, citalopram, WL) separately. In CBGT- and citalopram-treated patients, symptom improvement was accompanied by a significantly reduced rCBF response bilaterally in the amygdala, hippocampus, and anterior and medial temporal cortex, including the entorhinal, perirhinal, parahippocampal, and periamygdaloid areas. No significant rCBF alterations were observed in WL controls. To verify that brain perfusion changed as a function of treatment, the same contrast was run for responders regardless of treatment modality. Consistently, responders decreased their neural response to public speaking in the same regions. Significant within-group decreases of temporal lobe rCBF are displayed in **Table 1** and **Figure 2**A.

Between-group comparisons confirmed that the rCBF response to public speaking decreased significantly more in both treated groups relative to WL control subjects in the previously implicated temporal lobe regions, albeit mainly in the right hemisphere. Consistently, the rCBF response also decreased more in responders relative to nonresponders in the right amygdala, hippocampus, and rhinal and periamygdaloid areas (**Table 2**, Figure 2B). The citalopram and CBGT groups differed only with regard to perfusion in the right thalamus (x 17, y −14, z 11; $z=4.82$), which increased more with citalopram than CBGT.

A change in perfusion was noted in a few other regions outside the temporal lobe. In the CBGT group, rCBF decreased in the periaqueductal gray area (x 4, y −33, z −13; $z=3.17$), while increases were noted in the right cerebellum (x 16, y −51, z −11; $z=3.70$) and the secondary visual cortex (area 19; x 37, y −64, z −11; $z=2.88$). In the citalopram group, rCBF decreased in the left thalamus (x −10, y −14, z 6; $z=4.66$) and left inferior frontal cortex (area 10/47; x −17, y 35, z −10; $z=4.74$). Responders exhibited rCBF decreases in the right inferior frontal (area 47; x 19, y 14, z −11; $z=3.79$), right dorsolateral prefrontal (area 9; x 37, y 0, z 21; $z=4.72$), and bilateral

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Table 1. Brain Regions Exhibiting Significantly Decreased Within-Group Activation After Treatment of Social Phobia

Brain Region*	Coordinates† x	y	z	Maximum *z* Value‡
CBGT (n = 6)				
L amygdala	–16	–7	–12	3.23
R amygdala	20	–2	–16	2.75§
L hippocampus	–25	–24	–9	3.23
R hippocampus	21	–28	–10	3.17
L temporal cortex (15, 34)	–18	–1	–8	3.64
R temporal cortex (27, 28, 36)	18	–32	–10	3.55
Citalopram (n = 6)				
L amygdala	–19	–4	–17	3.60
R amygdala	19	–4	–17	4.23
L hippocampus	–27	–22	–13	2.60§
R hippocampus	17	–10	–17	4.61
L temporal cortex (15, 20, 21, 36, 38)	–55	–24	–22	4.42
R temporal cortex (15, 34, 35, 36, 37, 38)	14	–6	–17	5.04
Responders (n = 9)				
L amygdala	–15	–6	–12	4.56
R amygdala	24	–10	–9	4.23
R hippocampus	25	–10	–21	4.61
L temporal cortex (15, 21, 34, 38)	–52	–22	–22	4.86
R temporal cortex (15, 20, 34, 36, 38)	26	–15	–21	4.91

*CBGT indicates cognitive-behavioral group therapy; L, left hemisphere; and R, right hemisphere. Approximate Brodmann areas are within parentheses. Location of maximum voxel value is underlined. No significant change was seen in waiting-list control subjects.

†Coordinates in millimeters correspond to the stereotactic atlas of Talairach and Tournoux.[35]

‡Unmarked *z* scores correspond to $P<.01$ or better, corrected for multiple comparisons.

§$P<.005$ uncorrected (region evaluated with a priori hypothesis).

anterior cingulate (area 25/32; x –4, y 27, z –7; $z=5.11$) cortices (**Figure 3**). In the between-group comparison, rCBF decreased more in responders than nonresponders in the right dorsolateral prefrontal (area 9; x 24, y 29, z 35; $z=5.19$) and bilateral anterior cingulate (area 24/33; x 1, y 34, z 14; $z=3.71$) cortices (Figure 3).

At 1-year follow-up, 7 of the originally treated patients were classified as much improved, on the basis of the questionnaire results, whereas the remaining 5 patients were less improved. A stepwise discriminant analysis examined whether initial attenuation of subcortical rCBF (after–before change scores) was associated with the level of improvement a year later. The periaqueductal gray area ($P=.005$), left thalamus ($P=.006$), right amygdala ($P=.02$), and left amygdala ($P=.06$) combined to yield a significant discrimination (Wilks $\lambda=0.16$, $F=9.4$, $P<.006$) that was 100% accurate in predicting the 2 levels of improvement. Favorable outcome at 1-year follow-up was associated with a greater initial attenuation of the subcortical rCBF response to public speaking (**Figure 4**).

VERBAL PERFORMANCE

An ANOVA evaluating data for treated subjects and controls did not show significant time ($F_{1,16}=0.14$, $P=.71$) or group × time ($F_{1,16}=0.26$, $P=.62$) interaction effects with regard to number of spoken words. Paired *t* tests also indicated that the mean number of spoken words did not change significantly from pretreatment to posttreatment for subjects in the CBGT (+3.5 words; $t_5=0.72$, $P=.50$), citalopram (–4.2 words; $t_5=2.2$; $P=.08$), and WL (+2.2 words; $t_5=0.51$, $P=.63$) groups.

COMMENT

Social phobia symptom severity was significantly and about equally reduced after 9 weeks of either cognitive-behavioral or SSRI treatment, whereas WL control subjects did not improve. Alleviation of social anxiety was associated with an attenuated neural activity during public speaking in the amygdala, hippocampus, and the neighboring rhinal, parahippocampal, and periamygdaloid cortices. This neural pattern was observed within both treated groups, and in responders regardless of treatment approach, but not in WL control subjects. Between-group comparisons confirmed that the rCBF response to the anxiogenic public speaking task was significantly more suppressed after treatment in the citalopram and CBGT groups relative to WL control subjects, and in responders relative to nonresponders, particularly in the right hemisphere.

Furthermore, discriminant analysis showed that rCBF diminution in the amygdala, in conjunction with the periaqueductal gray area and left thalamus, could accurately discriminate much improved from less improved patients a year later. Hence, the degree of limbic response attenuation with treatment was associated with long-term clinical outcome. Because of small samples, this should be interpreted cautiously. However, according to the discriminant score plot, the closest distance between the much improved and less improved groups was roughly 1 SD, suggesting that the groups were well separated with regard to predicting variables and that the accurate discrimination was statistically reliable. Significant response decrement in limbic brain territories could thus be crucial for long-term improvement.

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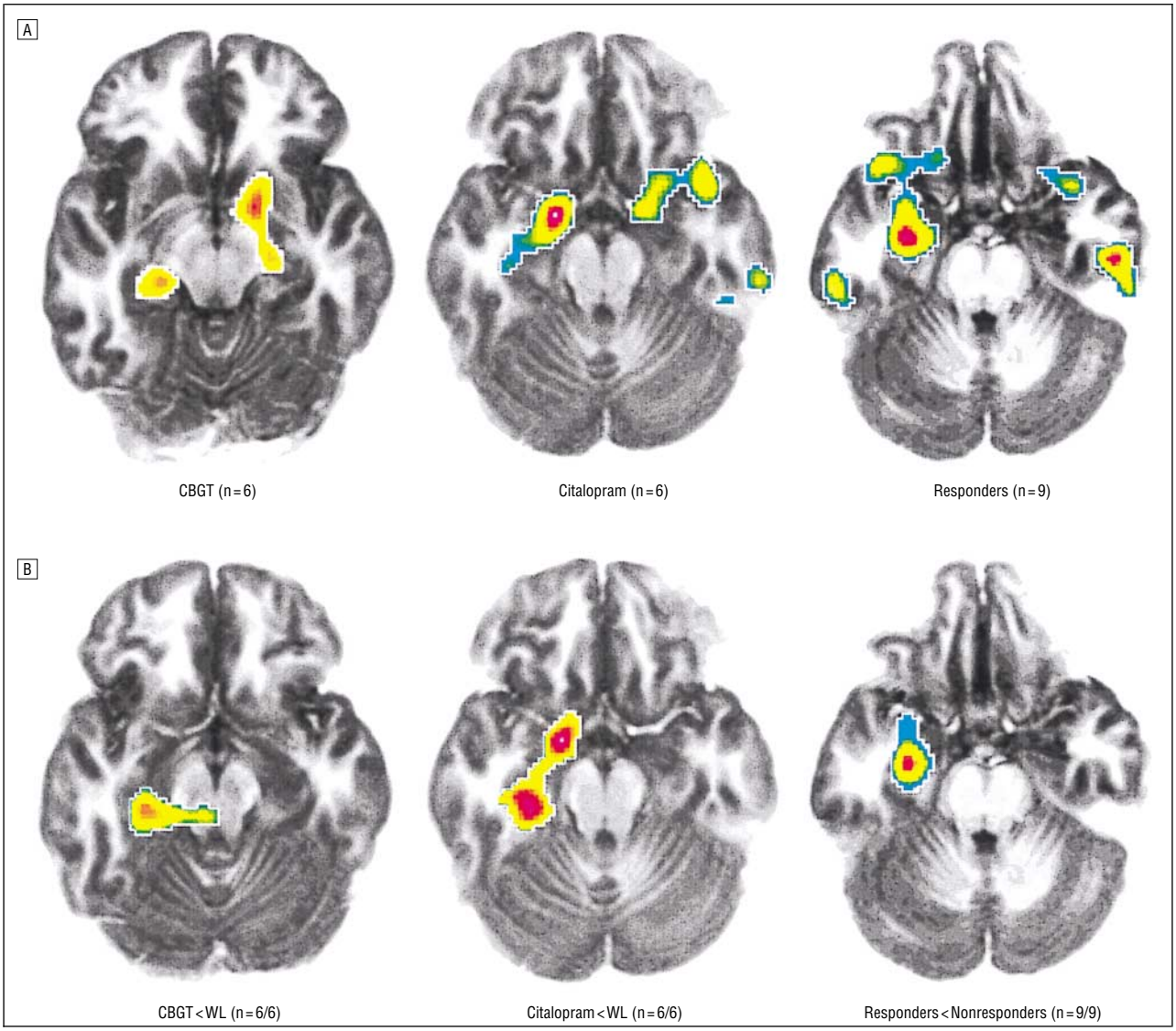

Figure 2. A, Transverse positron emission tomographic images, superimposed on a magnetic resonance reference image, showing significant decreases in the regional cerebral blood flow response to an anxiogenic public speaking task as a function of cognitive-behavioral group therapy (CBGT; left) or citalopram treatment (middle), and for responders regardless of treatment approach (right). Points of neural convergence were observed in the amygdala, hippocampus, and surrounding temporal cortical regions. B, Corresponding between-group differences in the amount of change in regional cerebral blood flow with treatment. Images show a greater reduction in the neural response to public speaking in CBGT relative to the waiting-list (WL) group (left), citalopram relative to the WL group (middle), and responders relative to nonresponders (right).

In individuals with social phobia, the amygdala and hippocampus have previously been implicated in the processing of conditioned aversive stimuli, as well as facial and unpleasant odor stimulation.[36,37] It has been proposed that the amygdaloid-hippocampal region forms an alarm system that is activated by threatening stimulation.[38] Presumably, the rhinal, parahippocampal, and periamygdaloid cortices transit sensory and/or memory information into this system.[4] Suppression of neural activity in the amygdalohippocampal and surrounding cortical regions might be an important mechanism by which both pharmacologic and psychological therapies exert their anxiolytic effect. Exposure-based behavior therapy may act by permitting systematic habituation of neuronal activity in these brain structures.[8] Consistently, recent studies suggest that repetition of emotionally salient stimuli results in neural habituation in the medial temporal lobe including the amygdala[39,40] and hippocampus.[39] The SSRIs could produce similar effects, eg, by correcting for median raphe nucleus malfunction with resultant attenuation of cortical and amygdalohippocampal activation.[41] An increase of serotonin may inhibit thalamic and cortical inputs from activating the amygdala.[42]

In a recently completed report, our group[43] noted that the amygdalohippocampal activity during public speaking stress was more elevated in untreated patients with social phobia than in normal healthy volunteers. However, neural activation patterns in the 2 groups differed also in widespread cortical areas including the secondary visual, retrosplenial, parietal, temporal pole, insular, and orbitofrontal cortices.[43] Thus, pretreatment abnormalities and therapeutic change patterns overlap only partly, suggesting that treatment involves both nor-

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Table 2. Brain Regions Exhibiting Significantly Decreased Between-Group Activation After Treatment of Social Phobia

Brain Region*	Coordinates† x	y	z	Maximum *z* Value‡
CBGT <waiting list (n = 6/6)				
L amygdala	−20	−8	−9	2.85§
L hippocampus	−25	−24	−9	2.71§
R temporal cortex (28, 35, 36, 37)	27	−34	−18	4.40
Citalopram <waiting list (n = 6/6)				
L amygdala	−21	−4	−21	2.37‖
R amygdala	17	−5	−17	3.15
L hippocampus	−26	−17	−17	2.37‖
R hippocampus	16	−9	−17	3.52
R temporal cortex (15, 27, 28, 34, 35, 36)	13	−6	−17	3.44
Responders <nonresponders (n = 9/9)				
R amygdala	25	−4	−21	3.01
R hippocampus	24	−11	−21	4.10
R temporal cortex (34, 36)	25	−16	−21	4.88

*CBGT indicates cognitive-behavioral group therapy; L, left hemisphere; and R, right hemisphere. Approximate Brodmann areas are within parentheses. Location of maximum voxel value is underlined. The first group exhibited lowered activity relative to the second group after treatment.

†Coordinates in millimeters correspond to the stereotactic atlas of Talairach and Tournoux.[35]

‡Unmarked *z* scores correspond to $P<.01$ or better, corrected for multiple comparisons.

§$P<.005$, uncorrected (region evaluated with a priori hypothesis).

‖$P<.01$, uncorrected (region evaluated with a priori hypothesis).

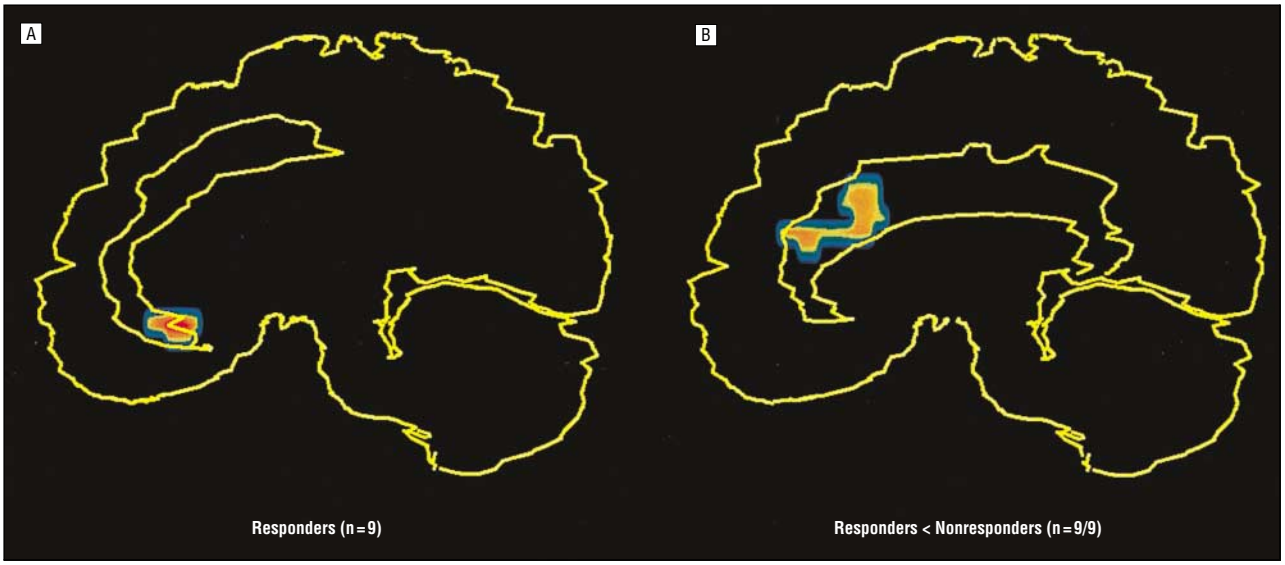

Figure 3. Sagittal positron emission tomographic images displaying significantly reduced regional cerebral blood flow in the rostral-ventral (subgenual) cingulate cortex corresponding to areas 25/32 for treatment responders (A) and a greater reduction in regional cerebral blood flow in the responders relative to nonresponders in the affective division of the anterior cingulate cortex corresponding to areas 24/33 (B).

malization and other adaptive metabolic changes in the brain. Some anomalies may persist after therapy. This has been noted also in mood disorders.[44] Resting-state amygdala hypermetabolism in depressed patients appears to decrease toward normality after antidepressant pharmacotherapy,[45] suggesting that the amygdala could be a general target for treatments of negative affect.

Only a few regions outside the temporal lobe exhibited altered activity after treatment. Patients who received CBGT showed decreased neuronal activity in the periaqueductal gray area, which is involved in defense behaviors in animals and probably also in humans.[46] Moreover, a decrement in rCBF was noted in the left thalamus (citalopram group), the affective division of the anterior cingulate cortex[47] (responders), and the inferior and medial prefrontal cortices (responders). The thalamus relays afferent anxiogenic information to the amygdala and cortical areas.[7] Both the left inferior frontal[48] and anterior cingulate[49] cortices participate in affective regulation and perception of facial emotions. Decreased flow in these areas might reflect downgraded emotional evaluative functions, suggesting that the affective value assigned to facial or other exteroceptive stimuli is lessened after treatment. Reduced prefrontal and cingulate activity could also reflect an alteration of the emotional experience[38] or a reduction in catastrophic or negative thinking.[41]

In patients with social phobia, Van der Linden and coworkers[50] recently reported that 8 weeks of citalo-

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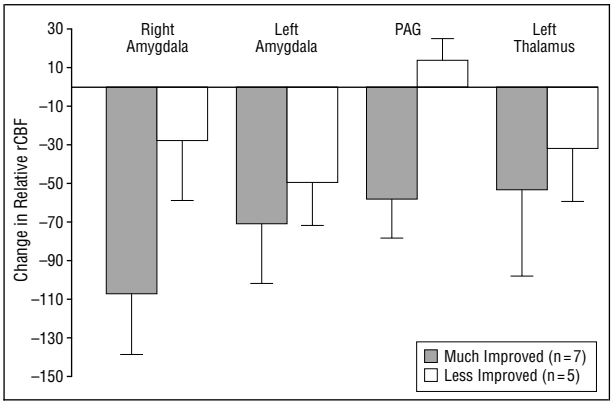

Figure 4. Regional cerebral blood flow (rCBF) redistribution after treatment (mean relative rCBF±SE, after minus before therapy) in 4 subcortical regions of interest. Discriminant analysis showed that the initial degree of rCBF change in these regions was associated with clinical status (much or less improved) in patients with social phobia at 1-year follow-up assessment. Favorable long-term outcome was associated with a greater initial suppression of subcortical rCBF. PAG indicates periaqueductal gray area.

pram medication reduced resting-state neuronal activity in the left-sided temporal, midfrontal, and cingulate cortices, whereas bilateral increases were noted in occipital regions. Other brain imaging reports on antianxiety treatments are scarce, but landmark PET studies suggest that both pharmacotherapy[51] and behavioral therapy[51,52] normalize resting-state glucose metabolism in the right caudate nucleus in patients with obsessive-compulsive disorder. To our knowledge, the present investigation is the first study incorporating comparative evaluations of the effects that SSRI and psychological treatments exert on brain activity during provoked anxiety states.

An important limitation of the present study is the small number of subjects in each group, restricting statistical power and enhancing the risk of type II errors (false-negative results). Even so, a consistent pattern of change in behavioral measures and rCBF was demonstrated in both within- and between-group analyses. Because both CBGT- and citalopram-treated subjects improved while WL control subjects did not, it is unlikely that the beneficial effects can be attributed to repeated testing, statistical regression, or other potentially confounding factors. The number of spoken words did not change from before to after treatment for the groups, making it unlikely that rCBF changes reflect verbal performance shifts rather than anxiety reduction. We argue that the consistent pattern shown by the subtractive and discriminant analyses supports a true causal link between the alterations in brain activity and symptom change.

Future imaging studies could compare treatment groups not only with WL control groups but also with attentional (eg, educational-supportive) psychotherapy and pill placebo groups. Future studies could also investigate whether the combination of cognitive-behavioral and SSRI treatments amplifies the effect on brain activity. Moreover, the direct physiological effects of citalopram and other SSRIs could be unraveled by administering these drugs to normal healthy volunteers. A recent report, however, indicated that long-term administration of fluoxetine did not change regional or global CBF in healthy volunteers.[53]

In conclusion, the neural sites of action for citalopram and cognitive-behavioral treatments of social anxiety converged in the amygdala, hippocampus, and neighboring cortical areas, possibly representing a final common pathway in successful antianxiety treatments. Thorough suppression of amygdalar-limbic activity with therapy was associated with favorable long-term outcome and may be a prerequisite for clinical improvement.

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