A Magnetic Resonance Imaging Study of Cortical Thickness in Animal Phobia

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Background: *Despite the high prevalence of specific phobia (SP), its neural substrates remain undetermined. Although an initial series of functional neuroimaging studies have implicated paralimbic and sensory cortical regions in the pathophysiology of SP, to date contemporary morphometric neuroimaging methods have not been applied to test specific hypotheses regarding structural abnormalities.*

Methods: *Morphometric magnetic resonance imaging (MRI) methods were used to measure regional cortical thickness in 10 subjects with SP (animal type) and 20 healthy comparison (HC) subjects.*

Results: *Consistent with a priori hypotheses, between-group differences in cortical thickness were found within paralimbic and sensory cortical regions. Specifically, in comparison with the HC group, the SP group exhibited increased cortical thickness in bilateral insular, bilateral pregenual anterior cingulate, and bilateral posterior cingulate cortex as well as left visual cortical regions.*

Conclusions: *Taken together, these structural findings parallel results from initial functional imaging studies that implicate paralimbic and sensory cortical regions in the mediating anatomy of SP symptoms. Further research will be necessary to replicate these findings and to determine their specificity as well as their pathophysiologic significance.*

Key Words: Anxiety, cingulate cortex, insula, neuroimaging, specific phobia

Specific phobias (SP) are among the most common of psychiatric disorders, with lifetime prevalence estimates of ~10% (American Psychiatric Association 1994). Individuals with SP reliably exhibit exaggerated responses to specific phobic stimuli or situations, characterized by anxiety and distress upon exposure as well as anticipatory anxiety and avoidance (American Psychiatric Association 1994). Specific phobias are subdivided on the basis of the focus of the fear into the following types: animal, natural environment, blood-injection injury, and situational. Animal phobias typically have childhood onset and are more common in women than men (~3:1 ratio). Although the etiology of SP remains uncertain, data from family, epidemiologic studies, and clinical phenomenologic studies suggest that SP may have a genetic basis, and the pattern of occurrence does not suggest a learned etiology (see Kendler et al 2001). The neuropathophysiology of SP also remains poorly understood (Fyer 1998).

Animal research has provided some potentially relevant insight regarding the neurocircuitry of threat assessment, learning about potentially threatening stimuli or situations, and mounting physiologic responses to such conditions (see Aggleton 1992; LeDoux 1996). Briefly, sensory input signaling danger may gain rapid access to the amygdala through the thalamus as well as top-down through the sensory cortex. The amygdala appears to play a role both in assessment of threat and in fear conditioning as well as other associative forms of learning about potentially threatening stimuli (Aggleton 1992; LeDoux 1996). Infralimbic prefrontal cortex plays a critical role in modulating the amygdala response to threatening stimuli (such as via extinction; Milad and Quirk 2002; Morgan and LeDoux 1995). The hippocampus has been implicated in explicit learning and memory (Schacter 1997), as well as contextual conditioning (e.g., learning about safe vs. dangerous contexts; e.g., Sanders et al 2003). The amygdala also plays a central role in mediating relevant autonomic responses to threat through its descending projections to brain-stem nuclei (Davis 1997). Finally, the amygdala projects to multiple levels of the visual cortical stream, and it is believed that these projections can modulate sensory processing (Amaral et al 2003).

Likewise, in humans the normal functions of threat assessment, learning about potentially threatening stimuli, and mounting physiologic responses to perceived threat are purported to involve amygdalocortical circuitry. Conceptually, based on the clinical features of SP together with general knowledge about the functional organization of the brain, a hierarchy of relevant neural structures can be proposed (see Mesulam 1985). First, sensory cortical regions (e.g., somatosensory cortex and visual cortex) principally respond to the features of external stimuli in terms of their identity and location. Information from these sensory regions is then transmitted to so-called paralimbic cortical regions (e.g., posterior orbitofrontal, cingulate, insular, parahippocampal, and temporopolar cortex), composed of mesocortex (Mesulam 1985). Paralimbic cortex integrates the information from sensory input with collateral data about meaning and context from heteromodal association areas, to assign priority or importance to elements of a given situation and motivate selection among response options. Anatomically, paralimbic cortex provides a conduit from other (isocortical and heteromodal) cortical regions to deeper structures, such as the amygdala and hippocampus (so-called limbic structures), which in turn have direct projections to the hypothalamus and output nuclei of the brain stem. Hence, studies of normal human emotional responses (for review, see Phan et al 2002), as well as those of mood and anxiety disorders (see Drevets 2000; Mayberg 1997; Rauch 2003), have often focused on paralimbic cortical regions

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Received August 26, 2003; revised December 18, 2003; accepted December 23, 2003.

0006-3223/04/$30.00
doi:10.1016/j.biopsych.2003.12.022

along with the amygdala and hippocampus. Consequently, given the clinical features of SP, in which specific stimuli reliably provoke abnormal anxiety responses, there has been interest in the role of sensory and paralimbic cortical regions as well as the amygdala.

A few functional neuroimaging studies have been conducted to investigate the mediating neuroanatomy of SP in the context of symptom provocation paradigms. An initial study, employing positron emission tomography (PET), found no regional cerebral blood flow (rCBF) differences between patients with SP and matched healthy comparison subjects (HC; Mountz et al 1989); several subsequent PET studies have reported changes in rCBF within paralimbic and sensory areas, however (Fredrikson et al 1993, 1995; Rauch et al 1995; Wik et al 1993). More specifically, Fredrikson et al (1993) studied six women with snake phobia, and contrasted rCBF profiles during viewing of a video of snakes versus a video of neutral park scenes, as well as a generally aversive video (depicting physical abuse) unrelated to the phobic stimuli; they found significantly increased rCBF within visual cortex (Brodmann's areas 18 and 19). Additional analysis of the same data set (Wik et al 1993), again contrasting responses to the phobogenic versus control conditions, revealed reduced rCBF within orbitofrontal, temporopolar, and posterior cingulate cortex, as well as the hippocampus. Fredrikson et al (1995) replicated these findings in an analogous study of eight women with spider phobia; significant rCBF increases were found within secondary visual cortex, and significant rCBF decreases were found within orbitofrontal, temporopolar, and posterior cingulate cortex, as well as the hippocampus. In our own laboratory, we used PET to study eight subjects with a variety of small animal phobias (Rauch et al 1995), using a paradigm in which subjects were alerted to the presence of phobic versus control stimuli within the imaging suite, but then scanned while their eyes were closed. In a contrast between the phobic versus control conditions, we found increased rCBF within (pregenual) anterior cingulate, insular, and anterior temporal cortex as well as somatosensory cortex. Interestingly, upon debriefing, subjects described tactile imagery (i.e., imagining that the feared animal would actually touch them) as a powerful element of the phobic condition. Taken together, these symptom provocation studies suggested involvement of paralimbic cortex and sensory cortex that depended on the route of perceived exposure to the phobic stimulus (i.e., visual sensory cortex for visually presented stimuli and somatosensory cortex during tactile imagery). With respect to involvement of paralimbic cortex, despite the fact that one of these paradigms yielded findings of decreased rCBF and the other yielded findings of increased rCBF, it is most salient that all of these studies demonstrated modulation of these same regions. The disparity in the direction of rCBF changes is most likely due to methodological differences, including the mode of stimulus presentation (visual perception vs. imagery), timing of acquisition (during vs. immediately following exposure), or magnitude of the symptomatic state induced; prior functional imaging studies have documented such disparities in rCBF changes associated with induced anxiety states (e.g., Bystritsky et al 2001; Fischer et al 1998; Gur et al 1987; Javanmard et al 1999).

Of note, the contemporary symptom provocation studies of SP were limited by the absence of a group of psychiatrically healthy (i.e., nonphobic) comparison subjects. Therefore, these data do not provide empirical information about which specific territories are dysfunctional in SP, but rather implicate the systems that are involved in assessment of and response to phobogenic stimuli.

Table 1. Subject Group Characteristics

Characteristic	SP	HC	*p*
Number of Subjects	10	20	—
Sex (male:female)	4:6	8:12	—
Age (years)	32.1 ± 11.6	28.6 ± 6.5	.30
Education (years)	17.2 ± 2.5	16.8 ± 1.6	.55
Beck Depression Inventory	1.4 ± 1.1	1.8 ± 2.7	.70
Beck Anxiety Inventory	4.4 ± 5.0	2.7 ± 3.5	.27

Values are presented as means ± SD. Independent *t* tests were used to assess for between-group differences in quantitative variables. All $p > .25$.
HC, healthy comparison subjects; SP, specific phobia subjects.

More recently, using cognitive activation paradigms in conjunction with functional magnetic resonance imaging (MRI), we have found indications of abnormal insular cortical function in SP versus comparison subjects but detected no significant dysfunction in the amygdala (contrasting responses to fearful vs. neutral face stimuli; Wright et al 2003) or striatum (during performance of an implicit sequence learning task; Martis et al 2004). In contrast, a recent meta-analysis of symptom provocation studies of anxiety disorders, including SP, suggested that rCBF within the right amygdala may be correlated with the severity of symptoms provoked (Fredrikson and Furmark 2003).

Surprisingly, however, we could find no previous studies that used contemporary neuroimaging methods to test systematically hypotheses regarding structural brain abnormalities in SP. Therefore, in this experiment, we employed relatively new methods for measuring cortical thickness in conjunction with MRI (Fischl and Dale 2000; Rosas et al 2002; Kuperberg et al 2003) to test specific hypotheses regarding cortical thickness abnormalities in SP versus a psychiatrically healthy comparison (HC) group. On the basis of the theoretical considerations outlined earlier and the limited functional neuroimaging literature on SP, we sought in this preliminary experiment to test a priori hypotheses that between-group differences in cortical thickness would be found; more specifically, we hypothesized that regional differences in cortical thickness would be found within two principal search territories: 1) paralimbic cortex (i.e., posterior orbitofrontal, cingulate, insular, parahippocampal and temporopolar cortex) and 2) sensory cortex (specifically, somatosensory and visual cortex). Note that such a priori hypotheses are a critical aspect of initial imaging studies because they meaningfully constrain the number of multiple comparisons to be performed. This enables investigators to establish statistical thresholds that protect against type I error while maintaining power to mitigate the risk of type II error, despite studying a modest number of subjects.

Methods and Materials

Subjects

Written informed consent was obtained from each subject in accordance with the Institutional Review Board of Massachusetts General Hospital (MGH). Subjects participated as paid volunteers after being recruited through advertisements posted in the community. The study sample comprised 10 subjects with SP and 20 HC subjects, group matched for gender, age, and years of education (see Table 1); all subjects were right-handed (Oldfield 1971). A structured clinical interview (SCID; First et al 1994) was used to establish the DSM-IV diagnosis of SP in the SP group and its absence in the HC group, as well as to rule out all other Axis I diagnoses in both groups. The 10 SP subjects included in this

report were selected from 14 potential subjects who had consented; one subject was excluded for failure to meet full criteria for SP, two subjects were excluded because of the presence of psychiatric comorbidity (one with major depression and polysubstance abuse and one with bulimia), and one subject was excluded because of unusable MRI data. Likewise, the 20 HC subjects included in this report were distilled from 25 consented HC subjects, before morphometric analysis, based on optimal matching to the SP group with regard to age, gender, and education history. Data were also obtained from all subjects regarding depressive symptom severity (Beck Depression Inventory; Beck et al 1961) and general anxiety symptom severity (Beck Anxiety Inventory; Beck et al 1990); the two groups did not significantly differ on any of these clinical measures (see Table 1). All subjects were in good general health by self-report. All female subjects of child-bearing potential were administered urine tests before scanning to rule out pregnancy. All subjects denied the use of any psychotropic medication or other medications thought to affect brain structure or function at the time of scanning and for at least the 4 weeks before enrollment.

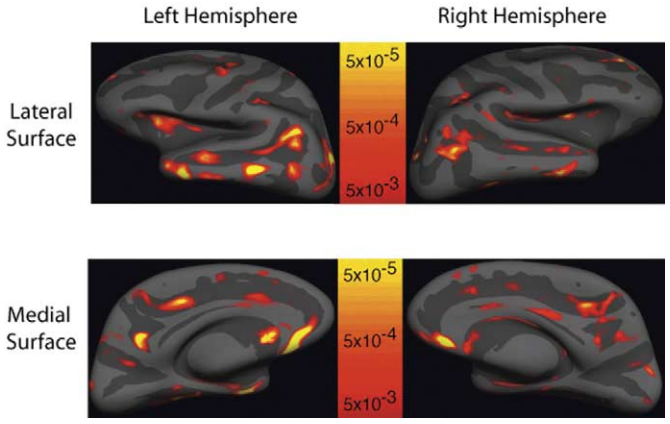

Figure 1. Regions with greater cortical thickness in specific phobia versus healthy control subjects.

Imaging

Acquisition. A Symphony/Sonata 1.5-Tesla whole body high-speed imaging device (Siemens Medical Systems, Iselin, New Jersey) was used with a three axis gradient head coil. Head movement was restricted using expandable foam cushions. After an automated scout image was acquired and shimming procedures were performed to optimize field homogeneity (Reese et al 1995), structural MRI data were gathered in replicate using a high-resolution three-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time = 7.25 msec, echo time = 3 msec, flip angle 7°) with an in-plane resolution of 1.3 mm and slice thickness of 1 mm.

Measurement of Cortical Thickness in Individual Subjects. These methods have been described in detail previously (Fischl and Dale 2000; Rosas et al 2002; Kuperberg et al 2003) but are reiterated here for clarity. The two structural scans for each participant were averaged, after motion correction, to create a single high signal-to-noise average volume. The resulting volume was used to segment cerebral white matter (Dale and Serenó 1993, Dale et al 1999) and to estimate the gray–white interface. Topological defects in the gray–white estimate were fixed (Fischl et al 2001), and this gray–white estimate was used as the starting point for a deformable surface algorithm designed to find the pial surface with submillimeter precision (Fischl and Dale 2000). The entire cortex in each individual subject was then visually inspected, and any inaccuracies in segmentation were manually corrected. All of these measurement procedures were carried out by investigators who were blind to subject group assignment and also to the nature of the hypotheses to be tested.

For each subject, thickness measures across the cortex were computed by finding the point on the gray–white boundary surface that was closest to a given point on the estimated pial surface (and vice versa) and averaging between these two values (Fischl and Dale 2000). The accuracy of the thickness measures derived from this technique have been validated by direct comparisons with manual measures on postmortem brains (Rosas et al 2002) as well as direct comparisons with manual measures on MRI data (Kuperberg et al 2003).

Inflation, Registration, and Intersubject Averaging. The surface representing the gray–white border was "inflated" (Dale and Sereno 1993; Fischl et al 1999a), differences among individuals in the depth of gyri–sulci were normalized, and each subject's reconstructed brain was then morphed and registered to an average spherical surface representation that optimally aligned sulcal and gyral features across subjects (Fischl et al 1999a, 1999b). This spherical morphing procedure was used to construct the cortical thickness difference brain maps, as described subsequently.

Computation of Mean and Statistical Cortical Thickness Difference Maps. The spherical transform was used to map the thickness measurements at each vertex on each subject's cortical surface into a common spherical coordinate system (Fischl et al 1999a, 1999b). The data were smoothed on the surface tessellation using an iterative nearest-neighbor averaging procedure (50 iterations were applied, equivalent to applying a two-dimensional Gaussian smoothing kernel along the cortical surface with a full-width/half-maximum of ~13 mm). Data were then resampled for participants into a common spherical coordinate system (Fischl et al 1999b).

Statistical Analysis. Statistical thickness difference maps were constructed using a t statistic (Figure 1). We used a General Linear Model in which the main effects of group (thickness differences between SP and HC) are shown. First we performed an omnibus test (two-tailed) at a statistical threshold of $p < .05$ to determine if there were between-group differences over the entire cortical surface, with follow-up tests of each hemisphere separately (see Results). Protected by significant unidirectional results for the omnibus test, and in each of the two hemispheres individually, we proceeded to investigate each hemisphere for loci of significant between-group differences in regional cortical thickness. We had a priori hypotheses that differences would be observed within paralimbic and sensory cortical regions. Given their surface area ($\leq 1.68 \times 10^4$ mm^2/search territory of interest) and the degree of surface smoothing applied (yielding ~169 mm^2/resolution element), we selected an uncorrected threshold of $p < 5 \times 10^{-4}$ (one-tailed), which corresponds to a threshold of $p < .05$ Bonferroni-corrected for the number of multiple comparisons within each of the two search territories (paralimbic cortex, sensory cortex) in each hemisphere. The regions reported all met this criterion (uncorrected $p < 5 \times 10^{-4}$) for significance; however, the figure displays (via color scale) all voxels meeting a $p < .005$ threshold to better illustrate the anatomic extent of areas exhibiting between-group differences in cortical thickness. We also provide a comprehensive list of all other loci, beyond the a priori search territories, that met the a priori statistical

Table 2. Loci of Significant Between-Group Differences in Cortical Thickness

Cortical Region	Coordinates (x, y, z)			*p* Value (*df* = 28)	Cortical Thickness			
					SP		HC	
					Mean	± SD	Mean	± SD
A Priori Regions								
Insular cortex								
L insular cortex	−27	25	10	4.0×10^{-4}	2.14	.41	1.75	.32
R insular cortex	33	0	9	4.8×10^{-4}	2.11	.29	1.76	.38
Cingulate cortex								
L pregenual anterior cingulate cortex	−7	34	−2	3.7×10^{-6}	2.08	.49	1.65	.22
R pregenual anterior cingulate cortex	6	35	−6	4.5×10^{-6}	2.55	.59	1.94	.27
L posterior cingulate cortex	−16	−31	23	4.4×10^{-5}	1.94	.37	1.58	.26
R posterior cingulate cortex	12	−46	22	4.2×10^{-4}	1.78	.35	1.51	.24
Visual cortex								
L superior occipital cortex	−24	−88	−16	6.5×10^{-6}	1.68	.28	1.44	.12
L medial occipitotemporal cortex	−30	−39	−29	2.1×10^{-4}	2.29	.40	1.97	.26
Post Hoc Regions								
Frontal cortex								
L superior frontal cortex	−23	52	27	1.2×10^{-4}	2.34	.40	2.09	.22
R superior frontal cortex	22	37	35	3.1×10^{-4}	2.35	.53	2.04	.22
Temporal cortex								
L middle temporal cortex	−61	−36	−23	2.1×10^{-5}	2.66	.61	2.11	.40
R inferior temporal cortex	51	−3	−25	2.6×10^{-4}	2.00	.42	1.64	.29
R superior temporal cortex	38	−61	−9	4.0×10^{-4}	1.79	.31	1.51	.28
L medial temporal cortex	−32	8	−28	5.5×10^{-5}	2.59	.72	2.05	.28
Parietal cortex								
L inferior parietal cortex	−50	−66	−1	3.3×10^{-6}	2.53	.55	1.97	.29
L subparietal cortex	−16	−59	4	1.7×10^{-5}	1.81	.28	1.53	.20

HC, healthy comparison subjects; L, left; R, right; SP, specific phobia subjects.

Coordinates are based on the Talairach and Tournoux (1988) system, given in mm; x > 0 indicates right hemisphere, y > 0 indicates anterior to the anterior commissure, and z > 0 indicates superior to the anterior commissure–posterior commissure plane. *p* values, based on *t* tests.

threshold ($p < 5 \times 10^{-4}$); this is done not to suggest that the findings at these post hoc loci are statistically significant but to obviate bias and demonstrate the relative specificity of results found within the a priori search territories. In this regard, the Bonferroni-corrected threshold for the cortical surface area of the entire brain would be $p < 3.25 \times 10^{-5}$; given that the total cortical area = $\sim 2.6 \times 10^5$ mm^2.

Results

The omnibus test for between-group differences in whole brain cortical thickness yielded significant results (mean cortical thickness ± SD: SP = 2.16 ± .42 mm, HC = 2.11 ± .45 mm; $t(1284) = 3.19$, $p = .001$). Likewise analogous omnibus tests of between-group differences in cortical thickness revealed significant findings separately for both the right (SP = 2.17 ± .43 mm, HC = 2.10 ± .45 mm; $t(642) = 2.33$, $p = .02$) and left hemispheres (SP = 2.16 ± .42 mm, HC = 2.09 ± .42 mm; $t(642) = 3.00$, $p = .003$).

The voxelwise maps depicting follow-up analyses of regional between-group differences in cortical thickness are shown in Figure 1, and coordinates reflecting the locations of centroids of significant differences as well as their respective *p* values are presented in Table 2. For SP versus HC, we found statistically significant increases in cortical thickness within the search territories of interest: 1) paralimbic cortex—bilateral insular cortex, bilateral pregenual anterior cingulate cortex, and bilateral posterior cingulate cortex; and 2) sensory cortex—occipital and left occipitotemporal cortex. No significant differences in cortical thickness were found within the subcallosal region, within the anterior temporal pole, or within parahippocampal cortex; no significant differences were found within somatosensory cortex.

Post hoc inspection of the entire brain, beyond the regions associated with a priori hypotheses, identified eight other loci where comparable increases in cortical thickness were found, and none of these were represented bilaterally. In the absence of corresponding a priori hypotheses, the post hoc loci may represent chance findings; they are listed solely for completeness and to illustrate the relative specificity of findings within a priori search territories. Among the listed post hoc findings, the left middle temporal, left inferior parietal, and left subparietal loci meet the Bonferroni-corrected criterion for significance in the context of a whole brain search. Finally, for completeness, across the entire brain surface, we tested for and found no areas of decreased cortical thickness (SP < HC), even at the more liberal $p < 5 \times 10^{-4}$ threshold.

Discussion

In comparison with a group of HC, a cohort of subjects with SP (animal type) were found to exhibit increased cortical thickness across several subterritories of paralimbic cortex as well as sensory cortex. This increase in thickness was found within insular, pregenual anterior cingulate, posterior cingulate, and

visual cortical regions, which have been implicated in previous functional neuroimaging studies of SP.

The strengths of this study include a well-characterized, diagnostically pure, clinical sample and the use of relatively new and innovative methods for measuring cortical thickness in vivo that have previously been shown to be reliable and valid. The hypothesis-driven nature of this investigation also represents a strength. Nonetheless, there are several limitations that we must acknowledge. The tools used for measuring cortical thickness do not extend to include the hippocampus. Therefore, future studies should be performed to assess for volumetric differences involving the hippocampus as well as subcortical structures. Given the intrinsic limitations of MRI methods, studies such as this one are subject to both false negative and false positive results. The number of subjects studied was modest, and the statistical thresholds applied were somewhat liberal, thereby accentuating these risks and underscoring the importance of replication. Note, however, that the bilateral and unidirectional nature of the results (i.e., that no regions of significant thinning were found) argue for the validity of the finding of increased cortical thickness in SP.

The significance of increased cortical thickness is unclear in terms of its etiology, pathogenesis, and pathophysiologic ramifications. The presence of regional structural abnormalities suggests potential dysfunction involving these same areas. Insular cortex has been implicated in mediating central representations of visceral sensation as well as disgust perception (e.g., Aziz et al 2000; Phillips et al 1997). Pregenual anterior cingulate cortex is implicated in emotional information processing; more specifically, this region appears to play a role in efficiently suppressing attention or response to emotionally relevant stimuli (Bush et al 2000; Vogt et al 1992; Whalen et al 1998). Finally, posterior cingulate cortex has also been implicated in emotion as well as the evaluation, prioritization, and memory for visual stimuli (Maddock 1999; Olson et al 1993; Vogt et al 1992, 2000). The occipital and occipitotemporal findings are within the ventral visual stream, which is implicated in identifying visual stimuli based on their physical features (Ungerleider and Haxby 1994) and receives substantial projections from the amygdala (Amaral et al 2003). Thus, dysfunction within this network of regions is consistent with the clinical features of animal phobia, which include acute sensitivity to specific stimuli, characterized by an exaggerated assessment of their threat value and an inability to suppress excessive anxiety responses, encompassing emotional, visceral, autonomic, cognitive, and attentional elements. Nonetheless, substantial and widespread cortical thickness abnormalities may seem counterintuitive for a disorder with such circumscribed symptoms. In fact, abnormalities in volume or thickness do not necessarily represent primary sites of pathology; equally plausible is that these represent the substrates of vulnerability factors, secondary changes, or compensatory changes. Furthermore, there is not necessarily a direct correspondence between regional volumetric abnormalities and the nature of functional abnormalities as detected by brain imaging methods; for instance, increased regional volume and thickness could be associated with increases or decreases in regional activity (rCBF or metabolism) or activation, depending on the nature of the underlying abnormalities at the cellular level.

Increased cortical thickness could be due to a greater number of neurons or greater volume per neuron, as might be the case with exuberant arbourization (although increased glial volume is also possible). With this in mind, we speculate that the observed increase in cortical thickness could be attributable to deficient pruning during development. Such a failure in normal pruning could lead to excessive cortical thickness that might precede or coincide temporally with the childhood onset of animal phobias (Landing et al 2002). Of note, the affected cortical regions are substantially interconnected (see Mesulam 1985) and are also known to share dense projections with the amygdala and other limbic brain structures (see Amaral et al 1992). Synaptic activity is believed to influence pruning in a competitive manner whereby more active synapses are preserved while relatively inactive ones are pruned (Hata et al 1999; Goldin et al 2001; Segal and Anderson 2000). Furthermore, during early development, excitatory connections predominate (De Felipe et al 1997), so that deficient pruning might lead to excessive mutually excitatory corticocortical or corticolimbic communication. Hence, pathologically deficient pruning could cause accentuation of species-specific behaviors, and especially their aberrant preservation into adulthood. This notion resonates with the fact that many specific phobias represent exaggerated versions of what might be considered normal fears from early development. It would be most interesting to explore whether manipulations during development in pruning of homologous brain regions in animals might produce analogous behavioral disturbances in adulthood. Moreover, computational modeling experiments could be informative by investigating the effects of excessive arbourization and connections within a selected circuit at the neural system level (see Hoffman and Dobscha 1989). Alternatively, it is possible that increased thickness in this network of regions represents a consequence rather than a cause of SP. The presence of SP symptoms might contribute to "overuse" of the implicated neuronal circuitry during critical stages of development or chronically, in a manner that produces the observed cortical thickening.

Our findings of increased cortical thickness appear to distinguish SP from other anxiety disorders, which, to date, have principally been characterized by diminished volumes in paralimbic cortical regions in comparison with HC subjects (e.g., posttraumatic stress disorder, Rauch et al 2003; panic disorder, Vythilingam et al 2000; obsessive–compulsive disorder; Szeszko et al 1999). Interestingly, SP is also distinguished from these other anxiety disorders on the basis of recommended pharmacologic treatment; although, as with other anxiety disorders, cognitive behavior therapy can be effective, unlike these other anxiety disorders, serotonergic reuptake inhibitors are not considered a first-line therapy for SP (e.g., see Nathan and Gorman 2002). In this regard, it is noteworthy that initial functional imaging studies of treatment response predictors in obsessive–compulsive disorder have indicated that response to serotonergic reuptake inhibitors may be inversely correlated with pretreatment activity within anterior paralimbic regions, whereas response to behavioral treatment is positively correlated with regional metabolism in these territories (e.g., see Brody et al 1998; Rauch et al 2002). Although it is premature to draw any conclusions with respect to treatment implications from our findings, future studies are indicated to determine whether the observed abnormalities in cortical thickness have predictive value with respect to subsequent treatment response and also to ascertain whether these abnormalities are reversible with successful treatment.

In conclusion, this initial MRI study of SP demonstrated cortical thickening within paralimbic and visual cortex. These results parallel functional imaging findings in SP and thus contribute further evidence toward a cohesive neurocircuitry model of SP. The unidirectional findings of increased regional cortical thickness may distinguish SP from other anxiety disorders. Future research will be necessary to replicate and extend these findings in SP, as well as to determine definitively their

specificity in contrast to other psychiatric disorders. In particular, future complementary studies should employ conventional volumetric methods to test for between-group differences with respect to paralimbic and visual cortical regions, as well as the amygdala and hippocampus, which were not measured in this study. Likewise, tandem studies are needed to determine the functional correlates of these structural findings, as well as their relationship to treatment response. Finally, complementary basic science research will be needed to elucidate the potential etiologic and pathophysiologic significance of increased cortical thickness in SP.

This work was supported in part by National Institute of Mental Health Grant No. RO1 MH60219 (SLR), National Institute of Mental Health Grant No. K23 MH64806 (CIW), the Robert Wood Johnson Foundation (CIW), National Center for Research Resources Grant Nos. RR16594 (BF) and P41RR14075 (BF), and the Mental Illness and Neuroscience Discovery Institute.

We thank Mary Foley, Jen Holmes, Linda Leahy, and Larry White for technical assistance.

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