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Amygdalar atrophy in panic disorder patients detected by volumetric magnetic resonance imaging

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Abstract

It has been suggested that the pathophysiology of panic disorder (PD) may involve abnormalities in several brain structures, including the amygdala. To date, however, no study has used quantitative structural neuroimaging techniques to examine amygdalar anatomy in this disorder. Volumetric magnetic resonance imaging (MRI) studies of the amygdalas, hippocampi, and temporal lobes were conducted in 12 drug-free, symptomatic PD patients (six females and six males), and 12 case-matched healthy comparison subjects. Volumetric MRI data were normalized for brain size. PD patients were found to have smaller left-sided and right-sided amygdalar volumes than controls. No differences were found in either hippocampi or temporal lobes. These findings provide new evidence of changes in amygdalar structure in PD and warrant further anatomical and MRI brain studies of patients with this disorder.
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Introduction

The biological basis of panic disorder (PD) remains unknown, despite the fact that a large number of hypotheses have been proposed. In the puzzling task of identifying the exact mechanisms underlying its pathophysiology, one of the main current lines of research focuses on brain circuitry.

Multiple preclinical studies with animals have provided detailed descriptions of the brain pathways involved in conditioned fear responses (for a review, see LeDoux, 1996 and Davis, 1992), and recent review articles have suggested that abnormalities in similar circuits may be involved in the pathophysiology of human anxiety disorders, and more specifically of PD (Coplan and Lydiard, 1998; Gorman et al.,

2000). According to these authors, the amygdalar region, near-by structures, its projections, and the medial prefrontal cortex may be abnormally sensitive in PD. It is suggested that that there may be a deficit in the relay and coordination of "upstream" (cortical) and "downstream" (brain stem) sensory information, which results in heightened amygdalar activity with resultant behavioral, autonomic, and neuroendocrine activation.

To date, although few papers have focused on the possible abnormalities of the amygdala in PD, structural and functional neuroimaging techniques have provided indirect evidence of abnormalities in the mesial areas of the temporal lobe. Qualitative magnetic resonance imaging (MRI) studies in PD have identified structural temporal lobe lesions, mainly located in the mesiotemporal area (Ontiveros et al., 1989; Fontaine et al., 1990). In addition, a high frequency of structural septohippocampal abnormalities has been reported in PD associated with nonepileptic EEG abnormalities (Dantendorfer et al., 1996). The only study

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using quantitative MRI (Vythilingam et al., 2000) found a bilateral decrease in temporal lobe volume in PD patients. Functional neuroimaging studies have also been used to study patients with PD. Reiman et al. (1986) found an abnormal hemispheric asymmetry of parahippocampal blood flow and oxygen metabolism in PD patients in the resting, nonpanic states. Although the study presented important methodological limitations, this asymmetry was interpreted by the authors as an abnormal increase in right parahippocampal measurements. An asymmetry in the glucose metabolism of both the hippocampal and parahippocampal structures has since been reported (Nordahl et al., 1990), also suggesting an increase in glucose metabolic rates on the right side. Similar results were found by Nordahl et al. (1998) in a study of asymptomatic, imipramine-treated PD patients, suggesting that this abnormality could reflect a trait marker for the illness. De Cristofaro et al. (1993) found lower perfusion indices in both right and left hippocampal regions, and Bisaga et al. (1998) found a significant increase in glucose metabolism in the left hippocampus and parahippocampal area in women. Using proton magnetic resonance spectroscopy, our group (Massana et al., 2002) found decreased levels of creatine plus phosphocreatine in the right medial temporal lobe region of PD patients compared to healthy matched controls. Moreover, a decrease in measures of benzodiazepine receptor binding has recently been found in the left hippocampus and precuneus in PD patients relative to controls (Bremner et al., 2000a).

The aim of our study was to examine possible alterations in the brain amygdalar anatomy in PD by means of quantitative MRI. As part of the study, the temporal lobes and the hippocampi were also assessed. To our knowledge, amygdalar volume in PD has not been examined to date.

Methods

Subjects

The study was carried out at the Hospital Clínic i Provincial de Barcelona (Catalonia, Spain), and was approved by the Local Research Ethics Committee. All patients and comparison subjects signed written informed consent agreements following detailed explanation of the study and procedure.

Twelve individuals with PD (six male, six female), aged 26 to 43 years, were included in the study. Screening visit included a detailed medical history, physical, and neurological examination, and the Structured Clinical Interview for the DSM-IV to ascertain the diagnosis of PD and to rule out other past or current Axis I diagnoses. Patients who had medical contraindications for an MR examination were excluded. None of the patients had a past or current diagnosis of traumatic brain injury or other neurological disorders. All patients were actively experiencing panic attacks, were right-handed, and had been off medication for at least 2 weeks. None had ever been treated with antidepressants. Ten out of 12 had some degree of agoraphobia. As part of the clinical assessment, the Hamilton Anxiety Rating Scale, the Mobility Inventory for Agoraphobia (Chambless et al., 1985), and the Body Sensations Questionnaire (Chambless et al., 1984) were administered.

The comparison group comprised 12 healthy subjects recruited from the hospital staff after completing clinical assessment to rule out past or current medical and psychiatric diagnoses. All these subjects were matched for age (within 6 months) and gender. Although the findings in the literature are inconclusive, there is some evidence that age (Pruessner et al., 2001; Mu et al., 1999) and gender (Durston et al., 2001; Goldstein et al., 2001; Pruessner et al., 2001) may bias amygdalar and/or hippocampal volume determinations in humans. Similarly, because handedness seems to affect right-to-left amygdalar and hippocampal volume ratios (Szabo et al., 2001), comparison subjects were case-matched for handedness. Finally, the groups were very similar in socioeconomic status, which was assessed using the Hollingshead Four Factor Index (Hollingshead, 1975). Demographic and clinical data are presented in Table 1, which shows that gender, age, and handedness were adequately matched.

Magnetic resonance imaging (MRI) study

MRI acquisition

Axial three-dimensional T1-weighted spoiled gradient echo MRI scans were performed on a 1.5 Tesla General Electric Signa MR System (Milwaukee, WI, USA), with the following parameters: TR = 12.5 ms, TE = 2.2 ms, flip angle = 20°, field of view = 24 cm, slice thickness = contiguous 1.2 mm, NEX = 3, matrix = 256 × 160. This sequence provides a voxel of $1.2 \times 0.9 \times 0.9 \text{ mm}^3$. We obtained 119 contiguous slices. During the study, subjects reclined in a supine position on the bed of the scanner and a RF coil was placed over the participant's head. Other precautions were taken to minimize subject motion during the entire course of the MR study, by instructing subjects to remain still and packing foam padding around their heads. Thanks to these measures, all scans were finally judged as being of good quality and none was excluded on the basis of unacceptable amount of motion. The MR image data were recorded on an optical disk for morphometric analysis. Anatomical 3D-MR images were examined by an expert neuroradiologist (JMM), and no gross abnormalities were noted in any of the 24 subjects. All subjects tolerated the procedure well. No sedation was used.

Morphometric analysis

The image data sets were processed on a SUN Solaris ultra 60 workstation (Sun Microsystems Inc.) with the ANALYZE 2.5 software (Mayo Foundation, Rochester, MN, USA). First, the images were resized with *Force Cubic*

Table 1
Demographic and clinical features of the sample

	Age	Gender	Handedness	HFFI	DS	NPA	HAMA	MIA	BSQ
Mean	35.33 (35.00)			37.33 (38.42)		12.33	27.42	49.67	41.25
SD	5.6 (5.9)			6.2 (5.9)		11.26	10.00	31.59	13.11
Statistic[a]	$P = .220$ ($t = 1,30$, $df = 11$)			$P = .266$ ($t = -1.17$, $df = 11$)					
Patient									
1	38 (37)	F (F)	R (R)	48 (45)	>6 months	8	12	56	27
2	26 (25)	F (F)	R (R)	42 (45)	<6 months	14	30	43	55
3	42 (43)	F (F)	R (R)	31 (36)	>6 months	8	42	79	55
4	28 (29)	M (M)	R (R)	32 (30)	>6 months	6	29	0	39
5	40 (39)	M (M)	R (R)	41 (38)	>6 months	40	14	50	27
6	40 (40)	F (F)	R (R)	35 (32)	>6 months	3	28	76	54
7	38 (37)	F (F)	R (R)	31 (35)	>6 months	9	32	39	51
8	33 (32)	M (M)	R (R)	30 (34)	<6 months	4	23	44	39
9	32 (31)	F (F)	R (R)	44 (47)	>6 months	13	45	114	53
10	43 (44)	M (M)	R (R)	40 (39)	<6 months	7	19	40	27
11	31 (31)	M (M)	R (R)	32 (34)	>6 months	30	32	55	48
12	33 (32)	M (M)	R (R)	42 (46)	<6 months	6	23	0	20

Note. Data corresponding to healthy matched comparison subjects is in parentheses. SD, standard deviation; F, female; M, male; R, right; DS, duration of symptoms; HFFI, Hollingshead Four Factor Index; NPA, number of panic attacks during the last 4 weeks; HAMA, Hamilton Anxiety Rating Scale; MIA, Mobility Inventory for Agoraphobia; BSQ, Body Sensations Questionnaire.

[a] Two-tailed Student's *t* Test for paired samples.

option, to obtain an isotropic voxel ($1.2 \times 1.2 \times 1.2$ mm^3). Images were processed with the region of interest (ROI) feature of the ANALYZE program. ROI tracing was drawn manually. The volume measures were then quantified automatically.

Amygdala. To measure amygdala, we used axial and coronal planes, following Pruessner et al. (2000). First, the axial view was used to delimit the lateral and medial border of the amygdala. In the inferior slice, amygdala was delimited as gray matter adjacent anteriorly and laterally to the entorhinal area, and posteriorly to the temporal horn of lateral ventricle and the hippocampus. In the more superior slices, the anterior limit was the gyrus ambiens and the posterior limit was the lateral ventricle. The coronal plane was used to delimit the posterior end of the amygdala more exactly, at the point where gray matter first started to appear above the alveus and lateral to the hippocampus (Fig. 1A, B, and C).

Hippocampus. Following Bigler et al. (1997), the posterior boundary of the hippocampus was identified (1) at the level of the superior colliculi and (2) when the oblong position of the hippocampus was visible at the level of the crura of the fornices. Laterally, hippocampus was delimited by the temporal horn of the lateral ventricle and/or white matter adjacent to hippocampal gray matter. The anterior boundary was defined in the slice where the lateral ventricle separated the hippocampus and amygdala. Using the *Orthogonal sections* tool in the ANALYZE software, we obtained a more exact definition of the limit between the posterior end of the amygdala and the anterior boundary of the hippocampus.

The measure included hippocampus, *gyrus dentate, alveus,* fimbria, and subiculum (Fig. 1D, E, and F).

Temporal lobe. Temporal lobe was measured in the coronal view, following Giedd et al. (1996). The Sylvian fissure was used to separate the temporal lobe from the frontal and parietal lobes. The internal lateral boundary of the temporal lobe was delimited tracing a line connecting the lowest point of the insular cisterns to the most lateral point of the hippocampal or amygdaloid fissure. The coronal slice containing the most posterior aspect of the corpus callosum defined the posterior boundary of the temporal lobe. Amygdala and hippocampus were so included in the temporal lobe segmentation.

Measurements of the amygdala, hippocampus, and temporal lobe were normalized for differences in total intracranial volume (Free et al., 1995). The intracranial volume was obtained after a segmentation process; whole-brain T1-weighted images were automatically segmented using the automatic image processing approach integrated in SPM99 (Wellcome Department of Cognitive Neurology, University College, London, UK: a complete reference for SPM99 can be found on http://www.fil.ion.ucl.ac.uk/spm). Automatic image processing algorithms combined pixel intensity and a priori knowledge, and were completed by the "lots of inhomogeneity correction" option (Ashburner and Friston, 2000). If required, the remaining skull around the gray matter was removed by applying a brain mask.

Volumetric measurements were performed by a trained, reliable rater (JMS), who was blind to the names and diagnoses of the subjects. Test–retest reliability was sufficient,
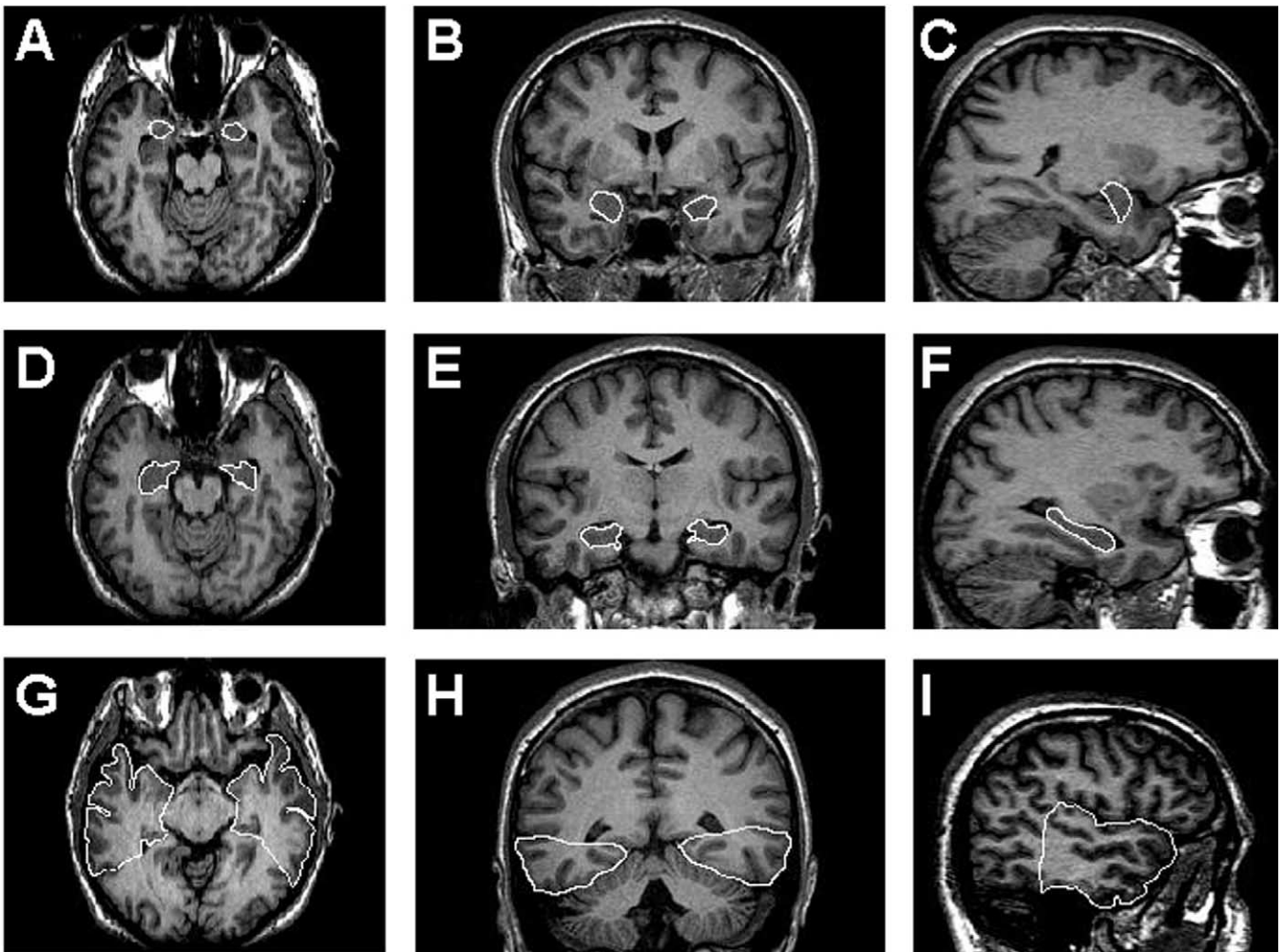
Fig. 1. T1-weighted MRI showing boundaries for volumetric measures of amygdala (A, B, C), hippocampus (D, E, F), and temporal lobe (G, H, I).

with intercorrelation coefficients ranging from 0.89 to 0.95 (median 0.94).

Statistical analysis

The statistical analyses were performed using SPSS version 10.0. Two-tailed Student *t* test for paired samples was used to assess differences in volumes of amygdala, hippocampus, and temporal lobe between subjects in the same group (patients vs patients or comparison subjects vs comparison subjects) and, in view of the very close matching of PD patients and comparison subjects, between patients and comparison subjects as well. Correlation analyses between volume measurements and clinical and demographic variables were carried out by means of two-tailed Pearson's correlation coefficients.

Results

Volumetric measurements did not reveal group differences in the brain measurements, i.e., intracranial volume,

cerebrospinal fluid, cerebral gray matter, and cerebral white matter (Table 2). However, the PD group had significantly lower absolute and normalized mean amygdalar volumes, with reductions, for normalized volumes, of 31.85% (right hemisphere, $t = 4.807$, $df = 11$, $P = .001$) and 23.44% (left hemisphere, $t = 4.107$, $df = 11$, $P = .002$) compared to the healthy comparison group (Table 3 and Fig. 2A and 2B). The level of significance was $P < .002$, and the results remained significant when the Bonferroni correction was applied. Right hippocampus, left hippocampus, right temporal lobe, and left temporal lobe did not differ between groups (Table 3).

An asymmetry of the hippocampal absolute mean volumes was found for PD patients (left < right, $t = 2.872$, $df = 11$, $P = 0.15$) and for healthy matched comparison subjects (left < right, $t = 2.214$, $df = 11$, $P = .049$) (Table 3). When comparing hippocampal normalized mean volumes, the same asymmetry was still found in PD patients (left < right, $t = 2.950$, $df = 11$, $P = .013$), but not in the healthy matched comparison group, although there was a trend toward an asymmetry that did not reach statistical

Table 2
Global brain volumes of panic disorder patients and healthy subjects

Structure (cm³)	PD patients (N = 12)		Healthy subjects (N = 12)		Statistic[a]	
	Mean	SD	Mean	SD	t(df = 11)	P
Intracranial volume	1293.96	±102.62	1299.02	±111.72	0.108	.916
Cerebrospinal fluid	232.57	± 28.56	221.28	± 37.55	−0.903	.386
Cerebral gray matter	696.29	± 51.23	708.96	± 53.60	0.505	.623
Cerebral white matter	365.09	± 35.64	368.77	± 39.42	0.279	.785

[a] Two-tailed Student's t test for paired samples.

significance (left < right, t = 2.170, df = 11, P = .053) (Table 3 and Fig. 3A and B). No left-to-right asymmetries of the amygdalas or of the temporal lobes were found in either group (Table 3).

There were no significant correlations between right and left amygdalar, hippocampal, and temporal lobe absolute and normalized mean volumes as regards the clinical and demographic variables used to assess our patients (age, sex, months of duration of the symptoms, number of panic attacks during the 4 weeks prior to the study, or the scores on the Hamilton Anxiety Rating Scale, the Mobility Inventory for Agoraphobia, and the Body Sensations Questionnaire).

Discussion

Patients with PD had smaller right and left amygdalar volumes than healthy matched comparison subjects. To our knowledge, this is the first study to examine the amygdalar volume in PD patients, and our results are the first MRI

Table 3
Absolute and normalized regional brain volumes of panic disorder patients and healthy comparison subjects

Structure (cm³)	PDP (N = 12)		HCS (N = 12)		Statistic[a] (between group)		Statistic[b] (within group)			
					PDP vs HCS		PDP vs PDP		HCS vs HCS	
	Mean	SD	Mean	SD	t(df = 11)	P	t(df = 11)	P	t(df = 11)	P
Right amygdala										
Absolute	1.19	±0.25	1.75	±0.29	3.841	.003*				
Normalized	0.92	±0.16	1.35	±0.19	4.807	.001*				
							−1.758	.107	2.030	.067
							−1.760	.106	1.878	.087
Left amygdala										
Absolute	1.27	±0.22	1.66	±0.25	3.323	.007*				
Normalized	0.98	±0.12	1.28	±0.18	4.107	.002*				
Right hippocampus										
Absolute	2.82	±0.29	3.04	±0.56	1.096	.296				
Normalized	2.19	±0.23	2.34	±0.42	1.156	.272				
							2.872	.015*	2.214	.049*
							2.950	.013*	2.170	.053
Left hippocampus										
Absolute	2.62	±0.36	2.83	±0.44	1.198	.256				
Normalized	2.03	±0.27	2.19	±0.33	1.204	.254				
Right temporal lobe										
Absolute	25.95	±13.15	29.81	±10.79	0.872	.402				
Normalized	19.85	±9.15	22.77	±7.58	0.988	.344				
							−0.597	.562	0.377	.713
							−0.635	.538	0.318	.756
Left temporal lobe										
Absolute	28.34	±8.85	28.49	±7.03	0.044	.966				
Normalized	21.80	±6.32	21.88	±4.86	0.040	.969				

PDP, panic disorder patients; HCS, healthy comparison subjects.

[a] Two-tailed Student's t test for paired samples between the absolute and normalized mean volume of the same structure between different groups (i.e., right amygdala of patients vs right amygdala of healthy subjects).

[b] Two-tailed Student's t test for paired samples between the absolute and normalized mean volume of bilateral structures within the same group (i.e., right amygdala of patients vs left amygdala of patients, etc.).
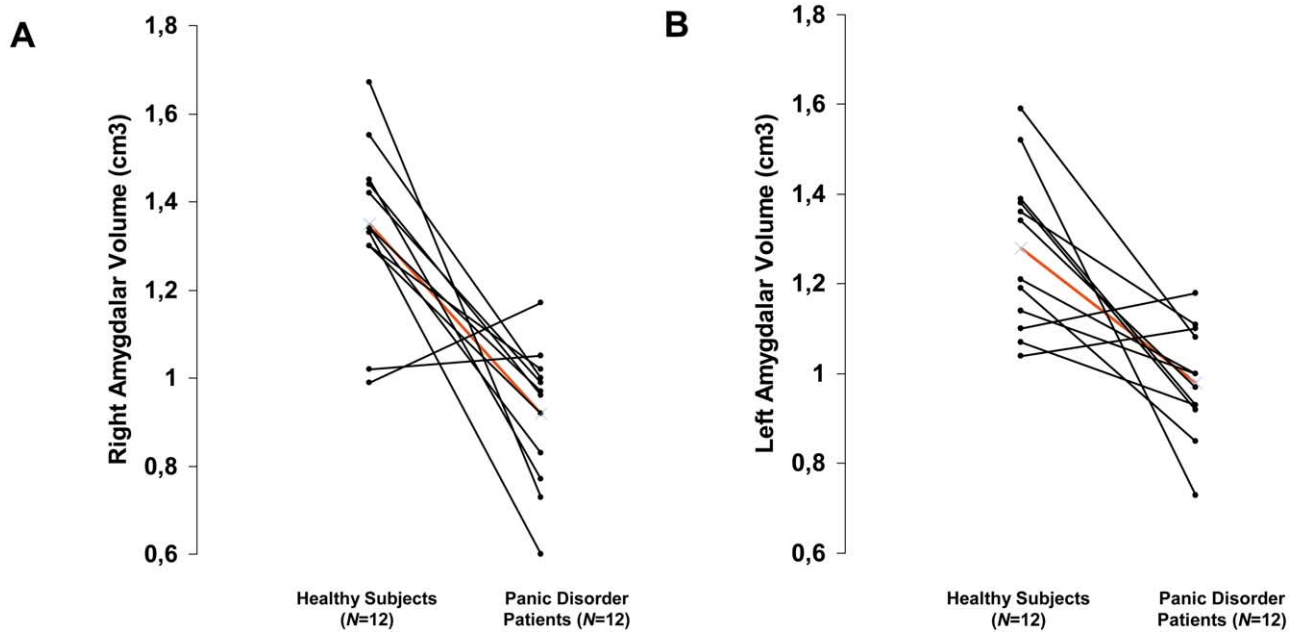
* Statistically significant.

Fig. 2. Right (A) and left (B) normalized amygdalar volume in panic disorder patients and healthy matched comparison subjects. Individual symbols represent right (A) or left (B) normalized amygdalar volume in patients and healthy subjects, and the lines connect patients with the individual matches. Red line connects mean values for right (A) and left (B) normalized amygdalar volumes of patients and healthy matched comparison subjects.

evidence of reduced amygdalar volume in this disorder. No differences were found for the right and left hippocampi nor for the right and left temporal lobes between PD patients and healthy matched subjects. Of particular note is the fact that these findings were obtained in a sample of patients with a "pure" panic disorder, i.e., without any past or cur-

rent major psychiatric comorbidity with the exception of agoraphobia, which was present to some degree in 10 out of 12 of our patients. Another important feature of the study was the close matching between each patient and its healthy comparison subject, which minimized possible confounding factors such as gender (Durston et al., 2001; Goldstein et al.,
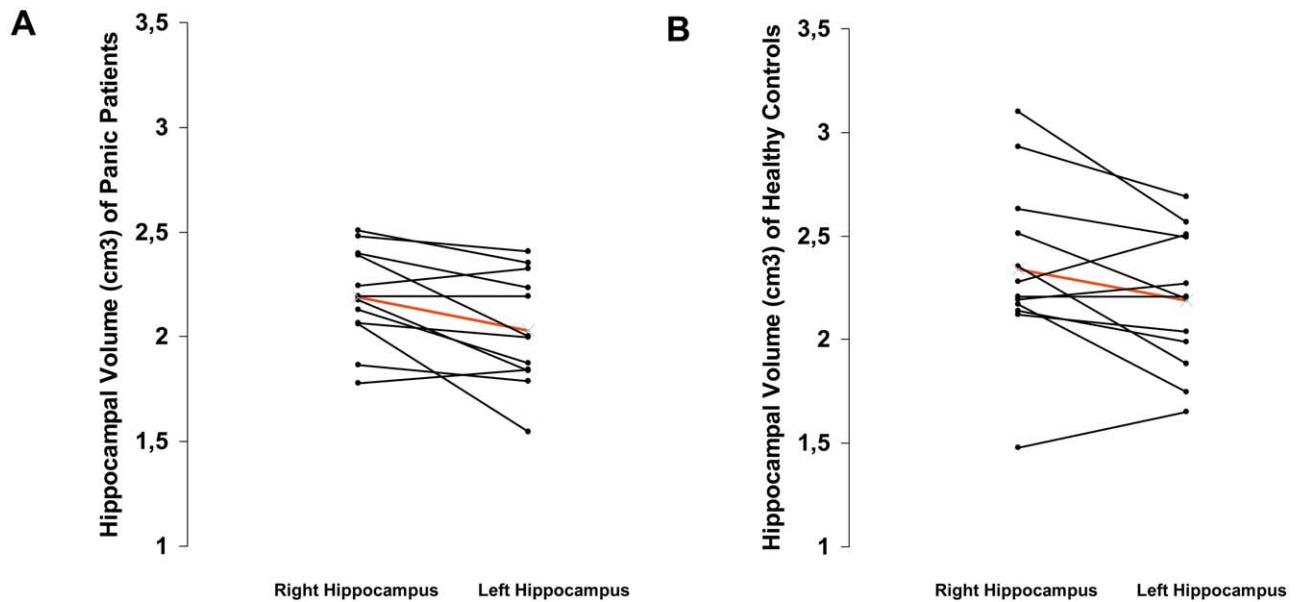

Fig. 3. Right and left normalized hippocampal volume in panic disorder patients (A) and healthy matched comparison subjects (B). Individual symbols represent right and left normalized hippocampal volumes, and the lines connect the right hippocampus with the left hippocampus of the same individual. Red line connects right and left normalized hippocampal mean values for patients (A) and comparison healthy subjects (B).

2001; Pruessner et al., 2001), and age (Pruessner et al., 2001; Mu et al., 1999).

Our findings of decreased right and left amygdalar volumes in patients with PD are consistent with the structural lesions detected by means of qualitative MRI in mesiotemporal areas in PD patients (Ontiveros et al., 1989; Fontaine et al., 1990; Dantendorfer et al., 1996).

Our findings may also be interesting in view of recent pathophysiological hypotheses proposed concerning the extended amygdala complex. A large body of preclinical research with animal models has provided strong evidence that this system underlies conditioned fear responses (Ledoux, 1996). In fact, well-known projections from the amygdala to motor areas (locus coeruleus, vagus, pontine respiratory centers, areas of the dorsal PAG, and the periventricular nucleus of the hypothalamus) could well underlie most if not all panic symptoms (Coplan and Lydiard, 1998). Although this evidence is more basic than clinical, it has led to the publication of several review articles hypothesizing the involvement of the extended amygdala complex (due to its alleged abnormal sensitivity) in the pathophysiology of PD. In humans, the amygdala plays a role in certain—but not all—forms of emotional processing. Specifically, research so far indicates that the amygdala has paramount importance in the recognition and learning of cues of threat or danger (for a review, see Davidson, 2002, Phan et al., 2002). Our finding of lower amygdalar volume in PD patients than in healthy comparison subjects further supports the possibility that anatomical changes in this region may underlie the symptomatology of PD. It is true, however, that one would expect the amygdala to be larger, not smaller, if it were abnormally sensitive in PD. Thus, our findings are relevant to this theory, but do not entirely support it. However, the possibility of the amygdala being reduced in volume and abnormally sensitive at the same time cannot be entirely ruled out. In fact, using proton magnetic resonance spectroscopy we recently detected biochemical abnormalities in the right medial temporal lobe region (encompassing the amygdala and part of the hippocampus) in PD patients, which may indicate a hypermetabolism of some kind (Massana et al., 2002). It could well be that a "very marked" atrophy of the amygdala (i.e., greater than 50% of its volume) may lead to a decrease in anxiety responses, while a "not so marked" atrophy (i.e., not greater than 50% of its volume) may lead to an increase of anxiety responses. Another important point is the anatomy of the amygdala itself; as is well known, the amygdala is formed by several subnuclei, and the effect of the atrophy may vary depending on which subnuclei are involved. Moreover, regional atrophy (e.g., restricted to the GABAergic intercalated cell masses or even the BLA) within the amygdala could be consistent with increased sensitivity or hyperexcitability.

The design of our study does not allow establishing either the time of onset or the mechanisms of the amygdalar atrophy observed in PD patients. In fact, these marked changes in adults may well originate from early developmental processes such as abnormal synaptic arborization or mielination (or may have nothing at all to do with gray matter and be restricted to white matter) or, rather, suggest some kind of neuronal damage that would involve the amygdala, but not the hippocampus. The similarity in hippocampal volume between patients with PD and healthy controls has also been documented by Vythilingam et al. (2000); these authors did not examine the amygdala but, unlike us, found a decrease in left and right temporal lobe volumes in PD patients. Mechanisms underlying possible neuronal damage in PD could be related to stress. In fact, research with animal models has provided evidence that stress is associated with damage to specific neurons (McEwen et al., 1992). So it seems that exposure to high levels of excitotoxic glucocorticoids, which are released during stress, may lead to amygdalar and hippocampal changes (Sheline et al., 1996; Sapolsky, 1990). Glucocorticoids may affect brain structures through two different mechanisms: interaction with the genome and interaction with cell membranes (McEwen et al., 1979). Their actions include a large biochemical cascade leading to profound changes in brain function and morphology, most probably involving the participation of excitatory amino acids such as glutamate. Neurons containing glucocorticoid-specific receptors are densely located in hippocampus, septum, and amygdala, regions believed to be directly involved in the mechanisms of anxiety and depression. Many authors think that the hippocampal atrophy widely observed in recurrent depression (Bremner et al., 2000b) may be linked to this process (Wolkowitz and Reus, 1999). Our results, however, indicate amygdalar—but not hippocampal—atrophy. Interestingly, evidence of hypercortisolism in PD is rather inconsistent (Goldstein et al., 1987; Holsboer et al., 1987). The conclusion of the large series of studies is that abnormalities of the hypothalamic–pituitary axis function in panic patients tend to be similar to those found in depression, but that their presence is significantly lower. Under these conditions it is difficult to interpret the reduction of the amygdalar volume observed in our study. At first sight it seems unlikely that the amount of "circulating" glucocorticoids in panic disorder would be "sufficient" to explain the amygdalar atrophy (and, if this were the case, why the amygdala only?) as it does in the hippocampus of depressed patients. The same question has been raised in relation to the finding that elevated cortisol levels can underlie the hippocampal atrophy in posttraumetic stress disorder (PTSD). As is known, hippocampal atrophy has also been documented in PTSD (Bremner et al., 1995, 1997; Gurvits et al., 1996), although in this condition, glucocorticoids levels are low. It has been hypothesized that cortisol levels at the time of the stressor may be relevant for the atrophic phenomena (Bremner et al., 1997). However, it does not seem that a significant stressor is a necessary condition to trigger the first panic attack. This means that the amygdalar atrophy is unlikely to be the consequence of stress, and other possibilities should be

considered, such as genetic, postnatal developmental processes, or environmental factors such as vascular abnormalities, which have also been documented in PD (Cerisoli et al., 1996; Ball and Shekhar, 1997; Owega et al., 2001), or a combination of these factors.

We did not obtain significant correlations between amygdalar volumes and the clinical anxiety ratings used to assess our patients. This suggests that amygdalar atrophy is unlikely to be related to the severity of PD. Interestingly, however, reduced amygdalar volumes were observed both in the group of PD patients with long (>6 months) duration of major PD symptoms (panic attacks, agoraphobia, and anticipatory anxiety) and in those in whom these symptoms first appeared during the 6 months prior to the study. This finding, if confirmed in further studies (our sample was obviously too small to allow reliable statistical comparisons between these two groups of patients), may indicate that amygdalar abnormalities are likely to appear before the onset of the illness, and so represent a risk factor for the illness. Further research is necessary to clarify whether decreased amygdalar volume may predispose to PD, or rather reflect a neurodegenerative process which occurs sometime during the first few months of symptoms and is thus a consequence of the disorder.

The small amygdalar volume reported here cannot be considered specific to PD. Different types of reduction (either bilateral or unilateral) in amygdalar volume have also been documented in obsessive-compulsive disorder (Szeszko et al., 1999), in adolescent and young adult offspring from families at high risk for developing alcoholism (Hill et al., 2001), in women with borderline personality disorder and early traumatization (Driessen et al., 2000), in nonmentally retarded autistic adolescents and adults (Aylward et al., 1999a), in demented adults with Down's syndrome (Aylward et al., 1999b) and, although the results are not entirely consistent, in certain depressed patients (von Gunten et al., 2000). On the other hand, right and total amygdala volumes have been found to be significantly larger in generalized anxiety disorder subjects (De Bellis et al., 2000), while no amygdalar changes in volume have been detected in PTSD (Gurvits et al., 1996; Bremner et al., 1997).

Reduced amygdalar volume has also been described in temporal lobe epilepsy (TLE) (Cendes et al., 1993; Kalviainen et al., 1997; Pitkanen et al., 1998). This finding is interesting, in view of the suggested link between panic disorder and TLE (Dantendorfer et al., 1995; Handal et al., 1995; Harter et al., 2000). Dantendorfer et al. (1996) found that more than half of PD patients with morphological abnormalities in the temporal lobe had EEG abnormalities as well. In fact, some specific EEG patterns may accompany certain symptoms observed during panic attacks, such as depersonalization (Locately et al., 1993). Nevertheless, Roy-Birne et al. (1986), studying patients with PD, found no EEG abnormalities of the kind seen in patients with temporal lobe epilepsy. In addition, the amygdalar atrophy seen

in temporal lobe epilepsy is consistently accompanied by hippocampal atrophy, which does not seem to occur in PD. Finally, some medications used in the treatment of PD (e.g., antidepressants) lower the seizure threshold.

In our study, both patients and controls had larger absolute hippocampal volumes on the right side. When comparing normalized volumes, the same asymmetry was found in PD patients, but not in the healthy matched comparison group, although there was a trend toward an asymmetry that did not reach statistical significance. These findings could also be relevant to functional neuroimaging studies (PET and SPECT), that have provided strong evidence for an abnormal function of the hippocampal and parahippocampal regions in PD. Reiman et al. (1986) found an abnormal hemispheric asymmetry of parahippocampal blood flow and oxygen metabolism in PD patients in the resting, nonpanic states. Despite some relevant methodological limitations, such asymmetry was interpreted by the authors as an abnormal increase in right parahippocampal measurements. Moreover, an asymmetry in glucose metabolism of both the hippocampal and parahippocampal structures was later reported (Nordahl et al., 1990), also suggesting an increase in glucose metabolic rates on the right side. Similar results were found (Nordahl et al., 1998) studying assymptomatic, imipramine-treated PD patients, suggesting that such abnormality could reflect a trait marker for the illness. However, the picture is not that clear because other authors have reported opposite results. De Cristofaro et al, (1993) found lower perfusion indices both in the right and left hippocampal regions, and Bisaga et al, (1998) found a significant increase in glucose metabolism in the left hippocampus and parahippocampal area in women. Moreover, a decrease in measures of benzodiazepine receptor binding has also been reported in left hippocampus and precuneus in PD patients compared to controls (Bremner et al., 2000a). Despite these rather inconsistent findings, the structural hippocampal asymmetry observed in our study could suggest that the left-to-right parahippocampal asymmetries described in most functional neuroimaging studies could reflect some kind of compensatory mechanisms. However, the fact that in our study healthy controls also showed a structural asymmetry in absolute hippocampal volumes and a trend toward the same asymmetry when comparing normalized hippocampal volume, makes the authors think that, overall, our findings seem more consistent with studies carried out in large samples of healthy individuals, which point to the existence of a "physiological" right-greater-than-left asymmetry of the hippocampal volume measurements in right-handed individuals (Bilir et al., 1998; Mervaala et al., 2000; Szabo et al., 2001).

Finally, unlike Vythilingam et al. (2000), we did not find differences in temporal lobe volumes between PD patients and healthy matched subjects. Further research is also necessary to clarify this point. One possible explanation for these discrepancies could be the procedure used for the volumetric measures, as our colleagues used a more con-

servative approach, measuring only the midsegment of the temporal lobe (15 mm), tracing the ROI on five contiguous coronal sections of 3 mm, and excluding the hippocampus and the amygdala volumes from the ROI. In our case, we used a more precise approach (described in the Methods section) delimiting the temporal lobe from the frontal lobe by the Sylvian fissure, and defining the posterior extent of the temporal lobe by the coronal slice containing the posteriormost aspect of the corpus callosum (inclusive) (Giedd et al., 1996), including a mean of 74.5 slices in the ROI. Another possible reason for the differences in the results may be the characteristics of the patient sample. Whereas we decided to include patients with no other past or current Axis I diagnoses (although assessed retrospectively), some of the patients reported in Vythylingam et al. (2000) presented a substantial level of comorbidity.

Overall, our study has some limitations. First, morphometric analyses were conducted using edge tracing. As has been pointed out (Gundersen et al., 1999), edge tracing does not offer the precision that unbiased stereological volumetric determination of volumes allows. So far, stereological methods have been used to estimate the volume of the hippocampus (Keller et al., 2002), the amygdala (Sheline et al., 1998), and other structures (for a review, see Roberts et al., 2000). Compared to manual ROI tracing, stereological volumetric methods provide an unbiased volume estimation of the structure of interest, being an accurate and efficient method for the volumetry of those objects whose segmentation from images is not feasible (i.e., when the boundaries are nor clear). Moreover, they are less time consuming when trying to obtain structural measures than hand tracing ROIs (Rajapakse, 2000).

A second limitation has to do with the boundaries of the structures examined. It is important to note that the amygdala boundaries especially and also hippocampus boundaries used in volumetric studies have varied considerably (Pruessner et al., 2000). For example, differentiation between the amygdala and the anterior hippocampus is difficult, because the posterior part of the amygdala is partly overlapping the anterior part of the hippocampal head (Duvernoy, 1991). As it was described in Pruessner et al., the use of arbitrary landmarks to demarcate boundaries of the amygdala results in a wide variety of outcomes, being difficult to compare between studies. To reduce such arbitrary landmarks, in our study we used the three-dimensional protocol for manual segmentation of the amygdala described in Pruessner et al., which results in a more reliable segmentation. On the other hand, hippocampal boundaries can also be established using a three-dimensional approach. Overlapping between hippocampal head and posterior amygdala can be disclosed using simultaneous sagittal and coronal views. In terms of the posterior hippocampal boundaries, hippocampal tail (HCT) is diffuclt to differentiate from adjacent structures. To delimitate HCT, we used an arbitrary criterium described previously (Bigler et al., 1997). This is a conservative criterium, because a small portion of HCT was excluded from the segmentation. However, individual landmarks could be consistently identified. The use of this protocol gave us a reliable measure of the whole hippocampus and is more precise than the protocol used by Vythilingam et al. (2000). In this previous study, the authors did not find hippocampal volume differences between PD patients and controls, but they only measured the hippocampal body: in our study we measured nearly the whole hippocampus.

In conclusion, our results so far point to the existence of significant differences in bilateral amygdalar volumes between PD patients and healthy matched comparison subjects. The number of subjects in our study is small, and thus the results will obviously need to be replicated. However, because the sample is so "pure" this is less of a problem than in a less carefully selected population. The implications of our findings are still to be determined. On the one hand, amygdalar atrophy seems relevant to the hypothesis of an abnormally sensitive "fear network," comprising the prefrontal cortex, the amygdala, its near-by structures and its projections to motor areas of the brain stem, and the hypothalamus in the pathophysiology of PD. On the other hand, it seems unlikely that amygdalar volume reduction could be explained by the theories currently relating neuronal atrophy with stress pathophysiology. To rule out this possibility, however, further studies with larger samples allowing comparison between patients with long vs short durations of PD symptoms are needed. If the amygdalar atrophy is not a consequence of the illness, it could then be a cause, a trait marker, or a risk or vulnerability factor enhancing the possibility of full-blown PD development. So far, however, a causal relationship between the amygdalar atrophy and PD is impossible to establish from our study. Moreover, the amygdalar atrophy observed in other psychiatric conditions argues against a specific relationship with PD. Further research aimed at disentangling the circuitry of all these conditions could shed some light on the questions posed here.

Acknowledgments

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