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Amygdalar interhemispheric functional connectivity differs between the non-depressed and depressed human brain

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The amygdalae are important, if not critical, brain regions for many affective, attentional and memorial processes, and dysfunction of the amygdalae has been a consistent finding in the study of clinical depression. Theoretical models of the functional neuroanatomy of both normal and psychopathological affective processes which posit cortical hemispheric specialization of functions have been supported by both lesion and functional neuroimaging studies in humans. Results from human neuroimaging studies in support of amygdalar hemispheric specialization are inconsistent. However, recent results from human lesion studies are consistent with hemispheric specialization. An important, yet largely ignored, feature of the amygdalae in the primate brain—derived from both neuroanatomical and electrophysiological data—is that there are virtually no direct interhemispheric connections via the anterior commissure (AC). This feature stands in stark contrast to that of the rodent brain wherein virtually all amygdalar nuclei have direct interhemispheric connections. We propose this feature of the primate brain, in particular the human brain, is a result of influences from frontocortical hemispheric specialization which have developed over the course of primate brain evolution. Results consistent with this notion were obtained by examining the nature of human amygdalar interhemispheric connectivity using both functional magnetic resonance imaging (FMRI) and positron emission tomography (PET). We found modest evidence of amygdalar interhemispheric functional connectivity in the non-depressed brain, whereas there was strong evidence of functional connectivity in the depressed brain. We interpret and discuss the nature of this connectivity in the depressed brain in the context of dysfunctional frontocortical–amygdalar interactions which accompany clinical depression.

Keywords: Amygdala; Frontal lobes; Hemispheric specialization; Connectivity; Affect

Introduction

From the standpoint of understanding the neurobiology of depression, (dys)function of the amygdalae is a critical component of both theoretical models and interpretations of empirical data (Davidson et al., 2002; Dougherty and Rauch, 1997; Drevets, 1998). With regard to affective processes, hemispheric differences in amygdalar function have been postulated, however, the extant findings are largely inconclusive (Davidson and Irwin, 1999b). Identifying the nature of hemispheric specialization in amygdalar function may be critical in helping to resolve the ambiguity in the extant literature and in elucidating the role of the amygdalae in affective processes in both the normal and depressed brain (Davidson et al., 2003; Pizzagalli et al., 2003). Below, we review the extant data which are consistent with the notion that there is hemispheric specialization of amygdalar function and that this specialization may be disrupted in the depressed brain. We examined the nature of amygdalar interhemispheric connectivity in both the non-depressed and clinically depressed brain and suggest a possible model which may account for the identified differences.

In the normal human brain, hemispheric functional differences of the amygdalae based on neuroimaging data suggest the roles of the amygdalae in information processing mirror the hemispheric specialization of the cerebral cortex, with the right and left hemispheres being associated with visuospatial and verbal processes, respectively (Markowitsch, 1998). In the past several years, hundreds of neuroimaging studies have reported on potential hemispheric lateralization/asymmetry in amygdalar function under various tasks and manipulations. These studies have been comprehensively reviewed by Zald (2003). With regard to affective processes, the extant data suggest that both negatively valenced visuospatial and verbal stimuli produce left amygdala activation. However, specifically about affective processes, such data are difficult to interpret due to methodological limitations, both concerning analytic procedures (Davidson and Irwin, 1999b; Jernigan et al., 2003), imaging techniques (e.g., Chen et al., 2003; LaBar et al., 2001) and the nature of affective challenges (cf. Davidson et al., 1990). With regard to amygdalar activation, to

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our knowledge, there is only one recent report which has statistically examined the Hemisphere by Stimulus Type (pictures versus faces) interaction. Their results suggest greater right amygdalar activation in response to pictorial stimuli (Keightley et al., 2003).

Compelling evidence which supports the proposal of amygdalar hemispheric specialization for processes (e.g., spatial versus verbal) involving affective stimuli comes from recent human lesion studies (Adolphs et al., 2000, 2001; Anderson and Phelps, 2000, 2001; Buchanan et al., 2001; Funayama et al., 2001; Peper et al., 2001). In general, these studies have demonstrated that the normative processing of negative affective stimuli which are visuospatial (e.g., mutilation pictures) is impaired by damage to the right amygdala, whereas the normative processing of affectively laden verbal stimuli (e.g., "taboo" words) is impaired with damage to the left amygdala.

Since the advent of methods for measuring cerebral blood flow and metabolism in vivo, there has been an interest in investigating regional interhemispheric connectivity in the normal resting brain (Blauenstein et al., 1977; Horwitz et al., 1984; Kuhl et al., 1982; Mazziotta et al., 1981; Metter et al., 1984; Prohovnik et al., 1980), as well and under various task-dependent conditions (Horwitz, 1990; Horwitz et al., 1992). This work continues today using more anatomically precise measures of brain activity (e.g., Biswal et al., 1995; Lowe et al., 1998, 2000). These studies have established that, in the resting normal brain, homologous cortical regions are positively and highly correlated. Moreover, there have been many attempts to distinguish patterns of interhemispheric connectivity in the normative brain from the psychopathological (Clark et al., 1984; Horwitz et al., 1991; Mallet et al., 1998), neurologic (Grady et al., 2001; Kuhl et al., 1980; Metter et al., 1982), developmentally disordered (Horwitz et al., 1988, 1990, 1998) and aged (Horwitz et al., 1986; Metter et al., 1983) brain. These investigations involved the imposition of some anatomical and/or functional parcellation of the cerebral cortex to obtain measures of regional cerebral metabolism and correlational analyses between homologous regions.

To date, the only known study in this tradition to examine the interhemispheric amygdalar functional connectivity (and functional connectivity with orbitofronal cortices), was that of Zald et al. (1998) under resting-state and an olfactory detection task condition. In the normal brain, they reported significant correlations between the right and left amygdala during the resting state which disappeared during the olfactory task. At first pass, these findings would be inconsistent with the neuroanatomical literature reviewed below, as well our findings in this report. We address this apparent inconsistency in Discussion. Finally, none of the studies in this tradition has examined the specific nature of amygdalar interhemispheric connectivity in the non-depressed compared to depressed brain.

In the rodent brain, all amygdaloid nuclei, except for possibly the cortical or dorsal nuclei, have dense and direct interhemispheric connections via the anterior commissure (AC) (Pitkanen, 2000). However, even the earliest neuroanatomical reports suggested that this was not the case in the non-human primate brain (Bailey et al., 1941; Fox et al., 1948; Lauer, 1945; McCulloch and Carol, 1941; Rundles and Papez, 1938; Whitlock and Nauta, 1956). More recent studies of amygdalar interhemispheric connectivity via the AC have continued to document this unique feature of the primate brain. Using various techniques, there are consistent findings of a lack of interhemispheric connectivity in the non-human primate brain (Jouandet and Gazzaniga, 1979; Pandya and Rosene, 1985; Pandya et al., 1973; Zeki, 1973), with occasional, but very sparse, labeling involving the dorsal nuclei in some species (Demeter et al., 1990; Jouandet et al., 1984; Turner et al., 1979). The most recent investigation of amygdalar interhemispheric connectivity via the AC in the non-human primate brain concluded that fiber labeling in the AC resulting from tracer injections into the cortical (i.e., dorsal) nuclei was very sparse, and no labeled fibers in the AC resulted from injections of tracer into the other nuclei (Demeter et al., 1990). Consistent with those findings, the only investigations of amygdalar interhemispheric connectivity in the human brain identified a few fibers possibly connecting the dorsolateral aspects of the amygdalar nuclei using both dissection (Klinger and Gloor, 1960) and staining (Virgilio et al., 1999) techniques. Thus, primate neuroanatomy suggests that the majority of amygdaloid nuclei are devoid of direct interhemispheric connections.

Complimenting these neuroanatomical findings, there is abundant evidence for a lack of functional amygdalar interhemispheric connectivity in the human brain derived from electrophysiological studies of patients with bilaterally implanted electrodes. Nearly 50 years ago, it was observed that epileptic seizure discharge activity recorded from depth electrodes implanted in the amygdalae were uncorrelated (Ajmone-Marsan and Buren, 1958). Moreover, electrical stimulation of one amygdala does not spread to the contralateral amygdala (Brazier, 1964). The lack of coherent or correlated electrical activity between the two amygdalae—either spontaneous activity or activity evoked by electrical stimulation—has been consistently reported (e.g., Brazier, 1972a,b; Buser et al., 1973; Gloor et al., 1993; Kobayashi et al., 2000; Pagni and Marossero, 1965; Wilson et al., 1987, 1990, 1991). The independence of amygdalar electrical activity in the epileptic brain should, of course, be interpreted with caution, as such findings could be a result of the very pathophysiology causing epileptic activity. However, several lines of evidence argue against such an interpretation. Firstly, as reviewed above, at most, there are very few amygdalar interhemispheric connections via the AC and the few which do exist only connect the most dorsal regions. This neuroanatomical feature has been identified in both the monkey and human brain. Secondly, a lack of correlated amygdalar electrical activity has also been reported in the "psychotic", but non-epileptic, brain (Brazier, 1972b). Finally, the spread of amygdalar epileptic electrical activity contralaterally is not related to neuronal atrophy, which is putatively a result of the epileptic activity itself (Velasco et al., 2000), as measured with Magnetic Resonance Imaging (Bernasconi et al., 1999; Spanedda et al., 1997).

In preliminary investigations of task-induced human amygdalar activation in response to affectively laden visual stimuli using functional magnetic resonance imaging (FMRI) in normal subjects, we noted a striking absence of association between the activation levels of the right and left amygdalae ($r = -0.02$, $P = 0.95$ reported in Irwin et al., 1999), whereas the associations between various homologous cortical regions were high. This serendipitous observation was consistent with the evidence for independent amygdalar function reviewed above. In light of evidence suggesting dysfunctional intrahemispheric frontocortical–amygdalar connectivity in depression (Davidson et al., 2002) and presumed hemispheric specialized frontocortical–amygdalar interactions, it raised the question as to whether or not functional amygdalar "indepen-

dence" or differential functional coupling (Friston, 1994) would be present in the depressed brain.

Using region-of-interest analytic procedures with both task-induced amygdalar activation, acquired with echo-planar FMRI and resting-state amygdalar glucose metabolism, acquired with positron emission tomography (PET) and ^{18}F-fluorodeoxyglucose, from both non-depressed and depressed subjects, we investigated the patterns of amygdalar interhemispheric connectivity in three independent studies. Herein, we report findings which describe the nature of the interhemispheric functional connectivity of a human subcortical structure—the amygdala—and how that connectivity differs between the non-depressed and depressed brain. We support the specificity of this finding by examining the interhemispheric functional connectivity of another subcortical structure implicated in the neurobiology of depression, the thalamus.

Methods

Subjects

First, we detail the demographic data common to all subjects across studies; the specific demographic data for each of the samples investigated will be reported below. It should be noted that data reported from each of the three studies are based on independent samples. All subjects were right-handed (Chapman and Chapman, 1987) and provided informed written consent before participation in these studies according to guidelines of the Human Subjects Committee at the University of Wisconsin Medical School. Subjects were recruited through local newspaper advertisements and paid for their participation. The Structured Diagnostic Interview was administered to both non-depressed (Spitzer et al., 1990) and depressed subjects. Non-depressed subjects had no history of any Axis I disorder in themselves or their first-degree relatives. Depressed subjects met DSM-III-R (Spitzer et al., 1992) or DSM-IV (First et al., 1995) criteria for Major Depressive Disorder (MDD) were medication-free, had no history or current symptoms of mania or psychosis in themselves or their first-degree relatives and did not currently meet criteria for any other Axis I disorder with the possible exception of specific phobia or dysthymia. In addition, subjects were screened for neurological disorders and MRI safety standards. In each study, all depressed subjects were unmediated at the time of the first functional scan.

Anatomical image acquisition

Anatomical MRI volumes were acquired from all subjects. The scanning protocol used across all subjects utilized a 3-dimensional spoiled gradient-recalled (SPGR) echo sequence which yielded whole-brain coverage in 124 slices. All image data were acquired on a 1.5 Tesla General Electric (GE; Milwaukee, Wisconsin, USA) Signa or EchoSpeed scanner. For the FMRI study, this scan was acquired at the beginning of each scanning session, immediately after an initial localizer scan [echo time (TE) = 8 ms, repetition time (TR) = 35 ms, field of view (FOV) = 24 × 24 cm, flip angle (α) = 30°, number of excitations (NEX) = 1, acquisition matrix 256 × 128, reconstruction matrix 256 × 256, 124 slices, slice thickness = 0.9–1.2 mm]. For the PET studies, this scan was acquired within 3 months of the PET scan (TE = 14 ms, TR = 30 ms, FOV = 24 × 24 cm, α = 35°, NEX = 1, acquisition matrix 256 × 192, reconstruction matrix 256 × 256, 124 slices, slice thickness = 1.2 mm).

Functional magnetic resonance imaging study

Subjects

The data from 14 non-depressed (7 females; mean age 28 ± 2 years) and 12 depressed (8 females; mean age 38 ± 3 years) subjects were included in the study hereafter called "FMRI." In this study, there was a reliable difference in age between non-depressed and depressed subjects ($t_{(24)}$ = 2.84, P = 0.01). Some of the non-depressed and all of the depressed subjects were part of a longitudinal study examining the effects of antidepressant medication on brain function.

Experimental procedures

Subjects passively viewed alternating blocks of neutral (e.g., basket) and negatively valenced (e.g., body mutilation) visual stimuli (12 each) selected from the International Affective Picture System (Lang et al., 1997) presented via fiber-optic goggles. The blocks were composed of 12 valence-constant stimuli with the stimuli presented contiguously for 4 s each. Each stimulus appeared twice per trial, for a total of 132 stimulus exposures per trial. The stimuli were presented in a quasi-random order such that (a) a given stimulus was never repeated with fewer than 12 intervening stimuli, and (b) novel stimuli appeared up to three-quarters of the way through the trial. It has been previously demonstrated that such a paradigm is effective in eliciting affective reactions (Bradley et al., 1996; Sutton et al., 1997), and yielding amygdalar activation (Irwin et al., 1996). Further details of the experimental procedures have been previously published (Davidson et al., 2003).

Data acquisition

Only the scanning protocols relevant to this report are described. A coronal T1-weighted spin-echo protocol (TE = 20 ms, TR = 500 ms, α = 90°, NEX = 1, FOV = 24 × 24 cm, matrix = 256 × 128, reconstructed to 256 × 256, 23 slices, slice thickness = 7 mm, interslice spacing = 1 mm) provided the slice locations from which functional image data would be acquired. This scan was manually prescribed (WI) such that one slice was "centered" on the amygdalae. This was defined such that the posterior edge of this slice was positioned 1 mm anterior to the location where the hippocampus could first be identified in high-resolution images acquired just prior. A T2*-weighted gradient-echo echo-planar protocol (TE = 50 ms, TR = 3000 ms, α = 90°, NEX = 1, FOV = 24 × 24 cm, matrix = 64 × 64) based on the Mansfield (Mansfield, 1977) and the blood oxygen level dependent contrast (Ogawa et al., 1992) methods was used to acquire functional image data. A functional time series composed of 191 images was acquired from each subject during this scan. Image data were acquired with either a GE Signa or EchoSpeed scanner as described above.

Image processing

All individual subject time series data sets were adjusted to correct for any head movement (Cox and Jesmanowicz, 1999). To

identify paradigm-correlated MR signal increases, the time series from each voxel was fitted to a hemodynamically delayed box-car reference function which modeled the alternating stimulus blocks using a three-parameter (i.e., amplitude, mean, slope) least-squares method (Lowe and Russell, 1999). The hemodynamic delay was estimated to be 6 s by examining signal changes in the amygdalae. The first five images acquired while subjects viewed the word "Begin" were discarded. Thus, for each subject, 184 images (i.e., 191 acquired images−5 discarded images−2 images to account for hemodynamic delay) were included in the fitting procedure which yielded a statistical volume where the voxel values were the Student's t statistic.

Using Analysis of Functional NeuroImages (AFNI, Version 2.00, Cox, 1996; Cox and Hyde, 1997), each subject's anatomical data were transformed into the Talairach and Tournoux (1988) stereotaxic coordinate system. Then, the statistical volumes were coregistered to the anatomical data using nearest-neighbor interpolation and resampled to 1 mm isotropic voxels to create new statistical volumes. Separately, for the non-depressed and depressed subjects, these statistical volumes were combined across subjects using in-house code by summing the square of the positive unthresholded voxel values to create group-wise t^2 volumes. The t^2 is distributed as the χ^2 with the degrees of freedom equal to the number of subjects (Hotelling, 1931; Worsley et al., 1995).

Region-of-interest

Using a maximal estimation of the search volume for the region of the amygdalae (Pruessner et al., 2000), the group-wise statistical volumes were thresholded to visualize contiguous clusters of activation >10 mm^3, corresponding to a corrected false−positive rate of $P < 0.05$ per amygdala, as estimated using the simultaneous inference tool within AFNI. The ROI for each amygdala was defined by the region of suprathreshold activation common to *both* the non-depressed and depressed subjects. Using in-house code written in Interactive Data Language (Version 5.2, Research Systems, Inc., Boulder, Colarado, USA), image masks based on the group-wise amygdalar ROIs were applied to individual subject data to compute mean subject-wise Student's t values which were used as the indices of amygdalar activation.

Positron emission tomography studies

Subjects

The data from 11 non-depressed (6 females; mean age 31 ± 3 years) and 10 depressed (6 females; mean age 38 ± 4 years) subjects were included in the study hereafter called "PET_1." The data from 13 non-depressed (7 females; mean age 33 ± 3 years) and 18 depressed (9 females; mean age 37 ± 4 years) subjects were included in the study hereafter called "PET_2." There were no differences in age between non-depressed and depressed subjects for either study (PET_1: $t_{(19)} = 1.40$, $P > 0.24$; PET_2: $t_{(29)} = 0.84$, $P > 0.52$). All subjects were part of longitudinal studies examining the effects of different types of therapeutic interventions (e.g., cognitive versus pharmaceutical) on brain function.

Data acquisition

Resting cerebral glucose metabolism was measured using ^{18}F-fluorodeoxyglucose (FDG) and PET (Phelps et al., 1979). The data for PET_1 were acquired with a CTI-Siemens ECAT 933/04 PET camera (Knoxville, TN, USA), and the data for PET_2 were acquired with a GE Advance PET camera. The cameras had full-width-half-maximum in-plane and axial resolutions of approximately 7 mm and 5 mm, respectively. Further details of the PET procedures have been reported elsewhere (Abercrombie et al., 1998).

Experimental procedures

The procedures for PET_1 and PET_2 were identical wherein subjects fasted for at least 5 h before injection of FDG which was scheduled between 11:00 a.m. and 1:30 p.m. Two 22-gauge intravenous catheters were placed, one into the right antecubital fossa for injection of the radiotracer and one into a vein on the posterior aspect of the left hand for obtaining blood samples during FDG uptake (Phelps et al., 1979). Roughly 15 min after the intravenous catheters were placed, approximately 5 mCi (3.8–5.7 mCi) of FDG were administered by bolus injection. Subjects were informed that the uptake period would last 30 min and were instructed to sit quietly and stay awake during this period. Every 3 min, subjects were instructed to alternately open or close their eyes. Following the uptake period, subjects voided their bladders and were positioned in the camera.

Image processing

All PET data were corrected for calculated attenuation and plasma time courses were combined with plasma glucose levels and image pixel values to estimate the rate of glucose utilization in each image pixel by the method of Sokoloff et al. (1977). Additional details on the processing of the PET data have been previously reported (Abercrombie et al., 1998).

Automated Image Registration (Woods et al., 1993) was used to coregister the MRI and PET images for each subject. Glucose global cerebral metabolic rate ($gCMR_{glu}$) values were obtained for each subject using Statistical Parametric Mapping (Wellcome Department of Cognitive Neurology, London, UK). Glucose regional cerebral metabolic rate ($rCMR_{glu}$) values were regressed on $gCMR_{glu}$ values to remove the variance in absolute $rCMR_{glu}$ that was due to $gCMR_{glu}$. Hereafter, "$rCMR_{glu}$" refers to residualized $rCMR_{glu}$ in units of milligrams per 100 g per min.

Regions-of-interest

Right and left amygdalar ROIs were drawn on MRI images for each subject using DIP Station (Version 1.0.6, Hayden Image Processing Group). ROIs for the amygdalae were drawn on 5 to 8 coronal planes. The posterior boundary of the amygdala was always anterior to the basilar artery. The temporal horn of the lateral ventricle was also used as a guide; the ROI was never drawn lateral to or inferior to the ventricle (Fig. 2). Additional details about these ROIs have been reported elsewhere (Abercrombie et al., 1998; Schaefer et al., 2000). The mean $rCMR_{glu}$ for these ROIs were the indices of amygdalar activation.

In addition, for the subjects in the PET studies, ROIs for the right and left thalami were drawn and indices of thalamic activation were obtained using the same procedures as those described above for the amygdalae. Additional details of these procedures have been reported elsewhere (Lindgren et al., 1999).

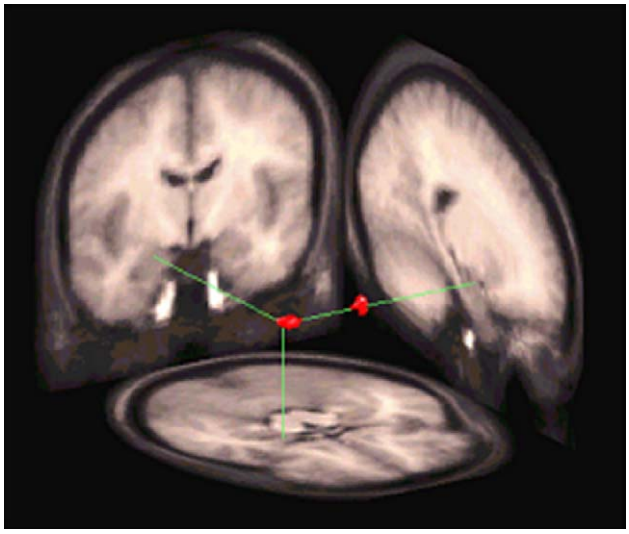

Fig. 1. Right and left amygdalar ROIs from the FMRI study. The visualizations correspond to amygdalar activation common to both non-depressed and depressed subjects. These statistical ROIs were derived by including only those voxels common to both non-depressed and depressed group-wise analyses of amygdalar activation in response to negative (compared to neutral) stimuli. The descriptive characteristics of the ROIs are presented in Table 1. The cross-hairs are positioned at the center-of-mass of the right amygdala (see Table 1). The background anatomy is the mean of the 14 non-depressed and 12 depressed subjects.

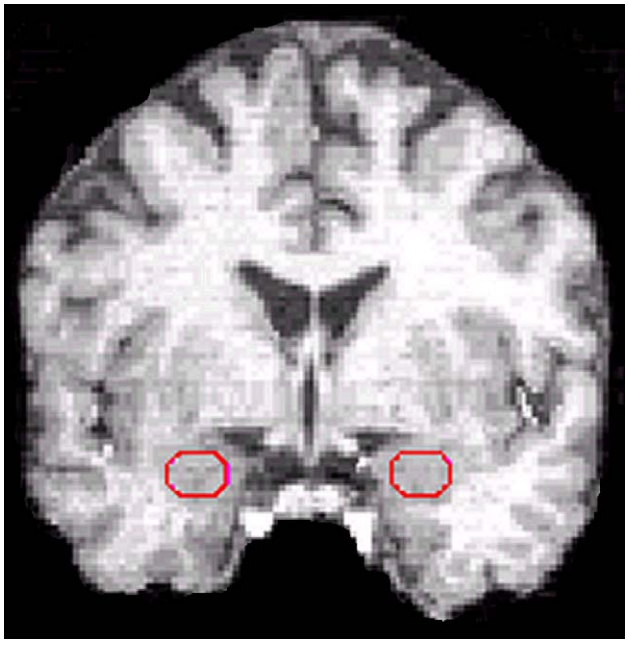

Fig. 2. Right and left amygdalar ROIs from an individual subject from the PET studies. ROIs were manually drawn on 5–7 coronal plans on subjects' individual anatomical planes and then coregistered to their corresponding PET image volumes. Note the conservative nature of the boundaries used to delineate the ROIs (see Table 2).

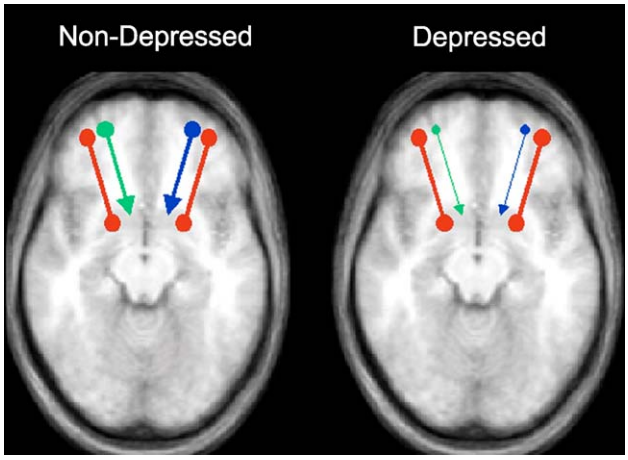

Fig. 4. Schematic representation of frontocortical–amygdalar connectivity in the non-depressed (left) and depressed (right) brain on axial sections (top is anterior). Red lines in both hemispheres represent "common" interactions between frontal cortices and specific amygdalar nuclei. Green and blue lines indicate hemispheric specific interactions between frontal cortices and specific amygdalar nuclei. In the non-depressed brain, the integrated amygdalar activation is comprised of substantial portions of hemispheric-specific influence, thus, yielding unreliable right–left amygdalar associations. In the depressed brain, due to frontocortical–amygdalar dysfunction, the hemispheric-specific influence is reduced yielding more similar integrated amygdalar activation, and, thus, high reliable right–left amygdalar associations.

Statistical analyses

The Wilcoxon Signed-Rank test was used to assess mean interhemispheric amygdalar differences within sample (e.g., right versus left amygdalae for the non-depressed subjects from the FMRI study). The Mann–Whitney *U* test was used to assess intrahemispheric amygdalar differences between groups, within study (e.g., the right amygdala of non-depressed versus the right amygdala of depressed subjects from the FMRI study). In the tradition of the electrophysiology literature (cf. Tomarken et al., 1990), right-minus-left amygdalar difference indices within subject were computed and the Mann–Whitney *U* test was used to assess differences in hemispheric asymmetry between groups (e.g., right-minus-left indices for non-depressed subjects versus right-minus-left indices for depressed subjects from the FMRI study). The Pearson product moment correlation coefficient was used to assess interhemispheric connectivity (cf. Horwitz, 1990) within sample (e.g., correlation between right and left amygdalar indices for non-depressed subjects from the FMRI study). The Fisher *r*-to-*z* transformation and test was used to assess differences between right–left amygdalar correlations within study, between samples (e.g., right–left correlation for non-depressed subjects versus right–left correlation for depressed subjects from the FMRI study). Throughout, the terms *reliable* and *unreliable* are used to indicate "statistically significant" and "not statistically significant", respectively ($\alpha \leq 0.05$).

For the PET studies, differences in amygdalar ROI volumes were assessed using the Wilcoxon Signed-Rank (e.g., right versus left amygdalae for the non-depressed subjects from the PET_1 study) and Mann–Whitney *U* test (e.g., the right amygdala of non-depressed versus the right amygdala of depressed

Table 1
Descriptive characteristics for amygdalar ROIs in the FMRI study as visualized in Fig. 1

Hemisphere	Volume (mm^3)	Center of Mass (x, y, z)[a]
Right	100	20, −4, −10
Left	70	−21, −6, −9

Hemisphere	Non-Depressed (n = 14)	Depressed (n = 12)
	Mean ± SEM (Student's t)[b]	Mean ± SEM (Student's t)
Right	2.04 ± 0.23	2.25 ± 0.28
Left	1.88 ± 0.15	2.08 ± 0.28

SEM = standard error of the mean.
[a] Coordinates based on the Talairach and Tournoux (1988) system.
[b] These values reflect the mean Student's t values across subjects from the least-squares fit between the paradigm reference function and the functional time course data (see Methods).

subjects from the PET_1 study) tests. All statistical analyses were conducted using SPSS (Version 11.0.1, Chicago, IL, USA).

Results

Regions-of-interest: FMRI study

There was reliable bilateral amygdalar activation both for non-depressed and depressed subjects. The regions of activation for non-depressed and depressed subjects for the right and left amygdalae which were common to two both groups are visualized as the ROIs in Fig. 1. These regions are in the dorsal regions of the amygdalae, with some extension into the basal forebrain regions. The descriptive characteristics of these regions are given in Table 1.

Regions-of-interest: PET studies

The reliability of our ROI drawing procedure from brain to brain was high (Abercrombie et al., 1998; Schaefer et al., 2000). Within study, there were no reliable volumetric differences between right and left amygdalae ($PET_{1\text{-non-depressed}}$: $z = 0.09$, $P = 0.93$; $PET_{1\text{-depressed}}$: $z = 0.56$, $P = 0.56$; $PET_{2\text{-non-depressed}}$: $z = 0.04$, $P = 0.97$; $PET_{2\text{-depressed}}$: $z = 0.97$, $P = 0.33$; all two-tailed tests). Within study and between non-depressed and depressed subjects, there were no reliable volumetric differences between the right (PET_1: $z = 0.17$, $P = 0.86$; PET_2: $z = 0.26$, $P = 0.79$) or left (PET_1: $z = 0.00$, $P = 1.00$; PET_2: $z = 0.80$, $P = 0.44$; all two-tailed tests) amygdalae. As visualized in Fig. 2, the amygdalar ROIs were drawn very conservatively to minimize any partial volume effects in the PET data and included the core nuclei with the near complete exclusion of the most dorsal regions. The descriptive characteristics of the ROIs are presented in Table 2. The right and left amygdalar ROI volumes represent approximately one-third of an amygdala (Pruessner et al., 2000).

Hemispheric differences

Firstly, there were no reliable differences in mean amygdalar activation between groups in any study for either the right (FMRI: $z = 0.72$, $P = 0.49$; PET_1: $z = 0.04$, $P = 0.97$; PET_2: $z = 0.16$, $P = 0.89$) or left (FMRI: $z = 0.41$, $P = 0.71$; PET_1: $z = 0.28$, $P = 0.81$; PET_2: $z = 0.14$, $P = 0.89$; all two-tailed tests) amygdalae (Tables 1 and 2). Secondly, with one exception, there were no reliable right–left differences in mean amygdalar activation for any sample across studies ($FMRI_{non\text{-}depressed}$: $z = 0.41$, $P = 0.68$; $FMRI_{depressed}$: $z = 1.10$, $P = 0.27$; $PET_{1\text{-non-depressed}}$: $z = 0.18$, $P = 0.86$; $PET_{1\text{-depressed}}$: $z = 1.01$, $P = 0.31$; $PET_{2\text{-non-depressed}}$: $z = 0.84$, $P = 0.40$; all two-tailed tests). The one exception was a reliable ($z = -2.24$, $P = 0.03$) right–left difference in mean amygdalar activation for the depressed patients from the PET_2 study, where the mean ($rCMR_{glu}$ in mg/100 g/min ± standard error of the mean) of the left amygdala (70.68 ± 2.06) was reliably greater than the right (67.45 ± 1.55). Thirdly, there were no reliable differences in the mean right-minus-left indices of amygdalar activation asymmetry between groups in any study (FMRI: $z = 0.31$, $P = 0.78$; PET_1: $z = 0.63$, $P = 0.56$; PET_2: $z = 0.22$, $P = 0.83$; all two-tailed tests). Thus, with one exception, there were no reliable mean differences between right and left amygdalar activation at any level of analysis, nor were there any reliable hemispheric asymmetries. In particular, there were no reliable differences between non-depressed and depressed subjects in any study. It should be underscored that our statistical analysis of differences between right-minus-left indices is equivalent to assessing the condition (neutral versus negative stimuli) by group (non-depressed versus depressed) by hemisphere (right versus left) interaction for the FMRI study, and the group-by-hemisphere interaction for the PET studies. Such statistical procedures are necessary to assess the presence or absence of hemispheric asymmetries (Davidson and Irwin, 1999a; Jernigan et al., 2003). The standard analytic strategy would be to conduct an Analysis of Variance (ANOVA) to test the group-by-

Table 2
Descriptive characteristics for amygdalar ROIs from the PET studies

Hemisphere[a]	PET_1		PET_2	
	Non-depressed (n = 11)	Depressed (n = 10)	Non-depressed (n = 13)	Depressed (n = 18)
Right				
Volume ± SEM (mm^3)	431.00 ± 35.66	421.80 ± 31.90	471.00 ± 31.60	458.72 ± 28.93
Mean ± SEM ($rCMR_{glu}$)	102.69 ± 2.19	103.36 ± 2.91	67.90 ± 1.77	67.45 ± 1.55
Left				
Volume ± SEM (mm^3)	433.64 ± 35.74	433.70 ± 31.50	484.69 ± 41.60	452.28 ± 29.68
Mean ± SEM ($rCMR_{glu}$)	102.52 ± 2.39	105.01 ± 3.36	69.65 ± 1.69	70.68 ± 2.06

SEM = standard error of the mean.
$rCMR_{glu}$ = residualized glucose cerebral metabolic rate in mg/100 g/min (see Methods).
[a] An example from a single subject is visualized in Fig. 2.

hemisphere interaction (for an expanded discussion of this issue see Davidson and Irwin, 1999a,b), which was not the aim of the current report. Instead, we chose to exhaustively test for any possible right–left amygdalar differences and hemispheric asymmetries using individual non-parametric tests, due to the non-normal distributions of our amygdalar indices, to highlight the fact that interhemispheric connectivity can exist (or not) in the absence of mean hemispheric differences or asymmetries. When ANOVA is employed, there were no reliable group-by-hemisphere interactions for any study [FMRI: $F(1, 24) = 0.004$, $P = 0.95$; PET_1: $F(1, 19) = 0.46$, $P = 0.50$; PET_2: $F(1, 29) = 0.46$, $P = 0.50$].

Finally, it should be noted that we conducted many statistical tests to reveal any possible hemispheric differences between non-depressed and depressed subjects in each study, without applying any correction for multiple comparisons. Any such correction would have increased the critical values needed to claim reliable differences, and thus our null findings would still have obtained. Additionally, it should be pointed out that despite the large number of comparisons reported within study, there were actually few, and can be reasonably considered independent. For example, within study, there was a comparison between right and left amygdalar activation for both groups (e.g., non-depressed and depressed). Within study, there was a comparison between groups for both right and left amygdalar activation. These two sets of analyses examine two very distinct possible differences. Keeping in mind that a statistical interaction can be obtained in the absence of main effects, our comparison between non-depressed and depressed subjects using the right-minus-left hemispheric asymmetry indices addressed this issue.

Age and sex differences

Because there was a reliable difference in age between the non-depressed and depressed subjects in the FMRI study, we examined the possible effects on our between-group findings. Using first-order part correlation, the correlations between right and left amygdalar activation indices (separately for each group) were controlled for age. The right–left amygdalar correlations remain unchanged to two decimal places for both the non-depressed ($r = 0.38$) and depressed ($r = 0.89$) subjects. There were no effects of age on our results for the 2 PET studies for which there were no reliable differences in age between the non-depressed and depressed subjects.

Despite the growing evidence for sex-related differences in the study of "emotional memory", it was not possible to address this issue in our studies due to the small sample sizes. Furthermore, it was not the aim of the current studies to examine memorial processes. Rather, it was to examine similarities and differences between non-depressed and depressed brain function. Several recent human neuroimaging which have documented sex-related differences in emotional memory have used stimuli similar to those in our FMRI study. Therefore, we present the results of analyses to examine the effects of sex for that study. There were no reliable sex differences between either the non-depressed ($M_{\text{male-right}} = 1.79 \pm 0.23$, $M_{\text{female-right}} = 2.29 \pm 0.38$, $z = -0.70$, $P = 0.54$; $M_{\text{male-left}} = 1.77 \pm 0.26$, $M_{\text{female-left}} = 1.99 \pm 0.17$, $z = -0.45$, $P = 0.71$) or depressed ($M_{\text{male-right}} = 2.58 \pm 0.79$, $M_{\text{female-right}} = 2.09 \pm 0.21$, $z = -0.34$, $P = 0.81$; $M_{\text{male-left}} = 2.05 \pm 0.69$, $M_{\text{female-left}} = 2.09 \pm 0.28$, $z = -0.51$, $P = 0.68$; Mean $\pm$ standard error of the mean; all Mann–Whitney U tests) subjects. Additionally, there were no reliable sex differences in the PET studies.

Amygdalar interhemispheric functional connectivity

For the non-depressed subjects in all studies, the associations between right and left amygdalar activation were positive, but unreliable (FMRI: $r = 0.38$, $P = 0.18$; PET_1: $r = 0.56$, $P = 0.08$; PET_2: $r = 0.38$, $P = 0.20$; all one-tailed tests). In contrast, for the depressed subjects in all studies, the associations were positive, strong and reliable (FMRI: $r = 0.89$, $P < 0.001$; PET_1: $r = 0.90$, $P < 0.001$; PET_2: $r = 0.80$, $P < 0.001$). Most importantly, for each study, the differences in right–left amygdalar associations between non-depressed and depressed subjects were reliable (FMRI: $z = 2.22$, $P = 0.01$; PET_1: $z = 1.65$, $P = 0.05$; PET_2: $z = 1.71$, $P = 0.04$).

Thus, the right–left amygdalar associations were positive and reliable only for the depressed subjects, and, for each study, they were reliably greater in the depressed compared to the non-depressed subjects (Fig. 3)[1]. It should be underscored that this difference in interhemispheric functional connectivity between non-depressed and depressed subjects was identified in the absence of any mean differences between right and left amygdalae or hemispheric asymmetry.

Interhemispheric functional connectivity specificity

To address the issue of the specificity of subcortical differences between the non-depressed and depressed brain in interhemispheric functional connectivity, we examined the associations between right and left thalamic activation using the data from the PET_1 and PET_2 studies. In contradistinction to the amygdalae, across studies there were no reliable differences between non-depressed (PET_1: $r = 0.95$, $P < 0.001$; PET_2: $r = 0.92$, $P < 0.001$) and depressed (PET_1: $r = 0.95$, $P < 0.001$; PET_2: $r = 0.94$, $P < 0.001$) subjects for the thalami. While there is little evidence for direct interhemispheric connectivity between the two thalami, the high correlations between the right and left thalami likely result from corticothalamic pathways (Jones, 1985). These results for non-depressed and depressed subjects are consistent with other human neuroimaging studies (Mallet et al., 1998). A similar analysis of

[1] As we note in the discussion, the right–left amygdalar activation correlations, while not reliable, are not zero for the non-depressed subjects across studies. A reviewer raised the issue of pooling data across the three studies to increase statistical power and potentially reveal a different pattern of correlations between non-depressed and depressed subjects. However, there are numerous methodological issues in attempting to conduct such analyses. For example, the FMRI data were derived from a task-induced study and the PET data were acquired with different cameras. One analytic strategy—albeit exploratory—seemed reasonable. Within study, within group (e.g., non-depressed subjects), within sex, and then across studies the indices of amygdalar activation were standardized (i.e., z-score transformed). The same right–left correlational analysis as reported for each of the three studies were conducted on the standardized variables. The right–left amygdalar associations between non-depressed subjects was reliable ($r = 0.43$, $P = 0.004$, $N = 38$), as it was for the depressed subjects ($r = 0.85$, $P = 10^{-12}$, $N = 40$). Most importantly, the right–left amygdalar correlations were reliably different between the non-depressed and depressed subjects ($z = 3.41$, $P = 0.0003$), which is the major finding we have underscored in this report.

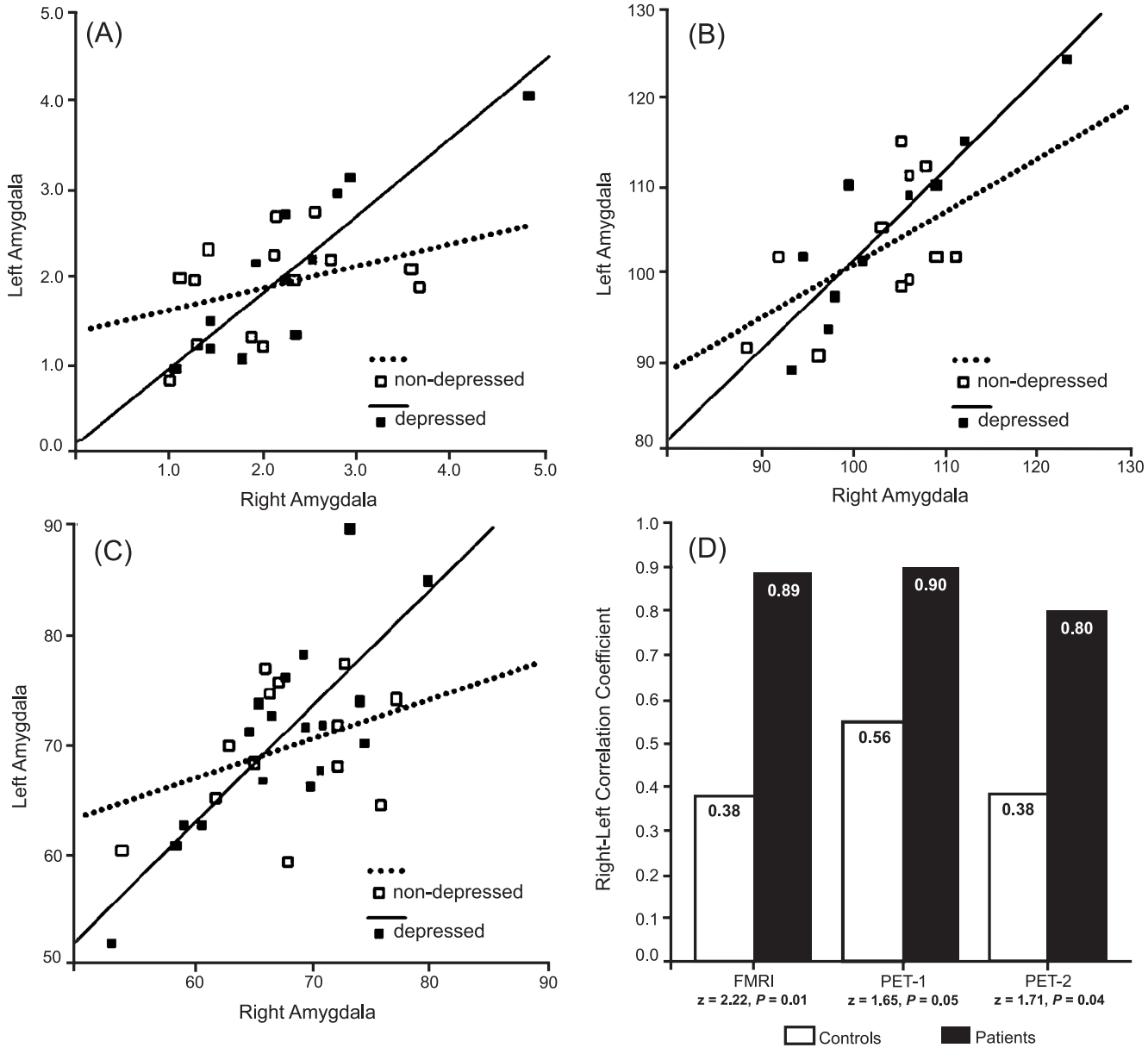

Fig. 3. Right–left amygdalar scatterplots for the non-depressed (open squares, dotted lines) and depressed (solid squares, solid lines) subjects in the (A) FMRI, (B) PET_1 and (C) PET_2 studies. In (A), the units are the mean Student's *t* values for the right and left amygdalae ROIs in Fig. 1 for each subject. In (B) and (C), the units are the mean $rCMR_{glu}$ (mg/100 g/min) for the right and left amygdalae based on each subjects' individual amygdalar ROIs (see Fig. 2). (D) Summary bar plot of the right–left amygdalar correlation coefficients for each group from each study. The right–left correlations were reliably different between non-depressed and depressed subject in each study.

specificity was not possible in the FMRI study, as there were no other common subcortical statistical ROIs.

Discussion

Amygdalar interhemispheric functional connectivity

Utilizing region-of-interest methods, we have demonstrated that amygdalar interhemispheric functional connectivity—correlated right–left amygdalar activation—differs between the non-depressed and depressed brain. These results were derived from data obtained from three independent studies—a total of 38 non-depressed and 40 depressed subjects—utilizing different methodologies. An FMRI study provided data which measured state-dependent changes in amygdalar activation in response to an affective challenge. Two PET studies provided data which measured trait-dependent amygdalar activation in a resting baseline-state condition. In all three studies, the association between right and left amygdalar activation was positive, but unreliable for non-depressed subjects, and positive, reliable and strong for depressed subjects. More importantly, the differences in the magnitudes of right–left amygdalar associations between non-depressed and depressed subjects were reliable across all three studies. We wish to underscore the fact that our findings of differences in amygdalar interhemispheric functional connectivity between non-de-

pressed and depressed subjects were found in the absence of any differences between groups in mean amygdalar activation or hemispheric asymmetry. Furthermore, we examined subcortical specificity by demonstrating that there were no differences between the non-depressed and depressed brain in interhemispheric functional connectivity of the thalami. Finally, it is important to note that identical selection criteria for both non-depressed and depressed subjects were used across studies, and all depressed subjects were in an acute episode of depression and off medication at the time of data acquisition.

Anatomical and methodological considerations

Throughout this report, we have broadly referred to the ROIs visualized in Figs. 1 and 2 as "amygdalar." While not necessarily visible in Fig. 1, the ROIs at the most dorsal aspects extend into the basal forebrain or "extended amygdala" (Alheid and Heimer, 1988), including ventral sublenticular regions of the substantia innominata (Heimer et al., 1997; Lauer, 1945). In part, this is one reason we chose to use ROIs which were common to both non-depressed and depressed subjects. Nonetheless, the ROIs in Fig. 1 clearly occupy the regions of the dorsal or cortical nuclei of the amygdalae to the exclusion of the deep core and ventral nuclei. Finally, although the volumes of the right and left amygdalar ROIs do differ, the descriptive characteristics presented in Table 1 support the assertion of reasonable hemispheric homology in terms of their locations.

The characteristics of the amygdalar ROIs visualized in Fig. 2 used in the analyses of the PET data are very different from those used in the analyses of the FMRI data (Fig. 1). Firstly, the right and left amygdalar ROIs were manually drawn on (coronal) MRI sections for each individual subject. Secondly, the ROIs were intentionally drawn with a conservative bias to exclude the potential influence from signal in the neighboring periamygdalar cortices and hippocampus and to reduce partial volume effects; these ROIs (Fig. 2 and Table 2) represent about one third of the volumes of the amygdalae (Brierley et al., 2002). Finally, these ROIs (Fig. 2) largely exclude the dorsal or cortical nuclei which the ROIs in the FMRI study include (Fig. 1), keeping in mind differences in the effective spatial resolution of the FMRI and PET data. Nevertheless, the sign and magnitude of our indices of amygdalar interhemispheric connectivity are strikingly similar across studies. Specifically, across studies, there are strikingly similar—and reliable—differences between non-depressed and depressed subjects, despite the differences across the studies in the index of amygdala activation (e.g., task-induced versus resting state).

As this report was being prepared, Drevets et al. (2002) reported findings which are both consistent and inconsistent with ours. First, they reported a difference in left amygdalar metabolism between a particular subtype of depressed subjects compared to control subjects, whereas we report above no differences in amygdalar metabolism between non-depressed and depressed subjects. Second, the sign and magnitude of right–left amygdalar correlation is virtually identical to that reported herein for control subjects ($r = 0.35$, Drevets et al., 2002, p. 435); however, they did not find positive high correlations for any of their clinical samples as we report herein. Drevets et al. only tested patients with recurrent MDD and there were several other differences in diagnostic criteria between studies. It is likely that heterogeneity within the depressive spectrum is associated with different patterns of right–left amygdalar functional connectivity.

The relevance of brain, sex and age, particularly psychopathology, is of great import. To the extent that we could examine possible sex and age differences between the non-depressed and depressed brain, we found no impact of either. While there is cumulating evidence of sex differences in emotional memory as reviewed in Introduction, it is important to note the conclusions of two recent reviews. Wager et al. (2003) concluded "Activations from both males and females were represented approximately equally in the amygdala, and peaks for both genders were distributed fairly evenly in the right and left amygdalae, with a moderate leftward bias in both genders …"(p. 521), and Zald (2003) concluded "Thus, while there is emerging evidence of gender effects on lateralization related to memory for emotional material and aspects of processing facial emotion, the gender effects are likely to be relatively specific to the domains in question…" (p. 113).

Functional implications

While the magnitudes of the right–left associations in the non-depressed subjects were not zero, those associations were not reliable, which is consistent with the independence of the amygdalae as suggested by primate neuroanatomy and electrophysiology, as reviewed in Introduction. Recent data from our laboratory have again provided consistent evidence for this claim. Using FMRI and a threat-of-shock paradigm, we identified robust bilateral amygdalar activation in the normal non-depressed brain, but the right–left amygdalar associations were unreliable ($r = 0.16$, $N = 17$, $P = 0.54$; Dalton, personal communication). In fact, specifically with regard to affective processes, Doty (1989) has suggested that, normatively, the amygdalae operate in independence.

Given that there are no direct amygdalar interhemispheric connections, the extent to which the amygdala in one hemisphere has access to the information in the contralateral amygdala must be a function of a series of relay nodes which are part of an interhemispheric network. Drawing on evidence recently reviewed elsewhere (Davidson et al., 2002; Drevets, 2001; Ghashghaei and Barbas, 2002), important parts of this network include regions of the frontal lobes. Unique functional evidence for this proposition comes from the analysis of seizure propagation in epilepsy. In patients with bilaterally implanted electrodes in both the temporal lobes, including the amygdalae, and frontal lobes, it has been demonstrated that information (i.e., discharge) travels from the ipsilateral temporal lobe to the ipsilateral frontal lobe and then crosses (via the anterior portion of the corpus callosum) to the contralateral frontal lobe and finally reaches the contralateral temporal lobe (Lieb et al., 1991; Wilson and Engel, 1993a,b). This information route has also been demonstrated in both non-epileptic (Wada et al., 1981) and "epileptic" non-human primates (Wada and Komai, 1985; Wada and Mizoguchi, 1984). Finally, we believe the findings (Zald et al., 1998) of amygdalar functional coupling during the resting state and functional de-coupling during an olfactory task—which are in apparent contradiction to those reported herein—support our proposition of both independent interhemispheric amygdalar function and potent intrahemispheric frontocortical–amygdalar influence. Given the apparent left hemisphere lateralization for olfactory processes (Zald and Pardo, 2000), an olfactory challenge would differentially increase frontocortical–amygdalar interactions and thus decrease the functional connectivity between the right and left amygdalae.

Dysfunction of the frontal lobes and amygdalae are consistent findings in depression (Davidson et al., 2002; Drevets, 2001). However, the functional, modulatory relations between ipsilateral frontal lobe and amygdala have not been sufficiently detailed, particularly in the human brain. The phylogenetic development of the brain supports the observation that with the increasing size and complexity of the frontal lobes, there have been concomitant changes in amygdalar structure. For example, the ratio of the size of the lateral nuclei to the central nuclei of the amygdalae is approximately 1:1 in the rodent brain and approximately 1:15 in the human brain; the ratios for the basal (including accessory basal) nuclei are approximately 1:1 and 1:12 in the rodent and human brain, respectively (adapted from Brodal, 1981, p. 654; also see Scott et al., 1991). Both the lateral and basal nuclei have prominent connections with the frontal lobe, with particularly dense reciprocal projections to orbitofrontal, mediofrontal and anterior cingulate cortices (Amaral et al., 1992). These cortical regions are critical nodes in the distributed network which regulates both normative and disrupted affective processing (Davidson and Irwin, 1999b; Davidson et al., 2002; Drevets, 1998).

These neuroanatomical features and the fact of functional hemispheric specialization in humans at the cortical level (Geschwind and Galaburda, 1985a,b,c) provide the substrates for the influence of specialized cortical processes on amygdalar processes. Thus, certain amygdalar nuclei may be selectively modulated by cortical hemispheric specialization such that right hemisphere amygdalar nuclei are influenced by visuospatial processes and left hemisphere amygdalar nuclei are influenced by verbal processes. As noted in Introduction, in humans, there are both recent neuroimaging (Markowitsch, 1998; Wright et al., 2001) and lesion (Adolphs et al., 2000, 2001; Anderson and Phelps, 2000, 2001; Buchanan et al., 2001; Funayama et al., 2001; Peper et al., 2001) data to support this assertion. Thus, the many nuclei that compose the amygdalae could be conceptualized as being either "common" (e.g., central nuclei) which are relatively uninfluenced by cortical processing, and thus, hemispherically similar, or "specialized" (e.g., lateral and basal nuclei) which are heavily influenced by hemispherically specialized processing at the cortical level.

In the depressed brain, we propose that the predominant finding of hypoactivation of the frontal lobes results in dysfunctional frontocortical–amygdalar connectivity, such that the influences of frontocortical processes on lateral and basal nuclei of the amygdalae are reduced. Therefore, the integrated activity of the amygdalae—which we indexed in the studies reported herein—is less influenced by hemispheric-specialized activation; however common activation, for a given state, is similar in both the normal and depressed brain. Thus, the variance of the integrated activity of the amygdalae in the non-depressed brain is composed of putatively equal proportions of both common and frontocortical–amygdalar-specialized activation. Due to dysfunction of frontocortical–amygdalar (functional) connectivity in the depressed brain, the integrated activity of the amygdala is composed of differential proportions of specialized frontocortical influences (Fig. 4). The description of this model is based on the assumption that the influences of the frontal lobes on the amygdalae are excitatory. At the level of integrated amygdalar activation, the decrease in specialized activation and sustained common activation results in more similar right–left activation variance, and, thus, results in higher right–left amygdalar correlations.

There are many additional unanswered questions raised by these data. For example, specifically in the case of MDD, does functional or effective connectivity change at the time of remission? Are there certain experimental manipulations or challenges which could yield similar patterns—increased or decreased—functional coupling between depressed and non-depressed brains? How might specific pharmacological treatments affect interhemispheric amygdalar connectivity in the depressed brain? Using neuroimaging data and structural equation modeling techniques (cf. Iidaka et al., 2001), we now have the opportunity to pursue the answers to these questions and other questions, non-invasively, in the human brain. We believe such approaches will provide new critical details about both normal and abnormal brain function as it relates to affective behavior.

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