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Metabolic rate in the right amygdala predicts negative affect in depressed patients

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THE role of the amygdala in major depression was investigated. Resting regional cerebral metabolic rate ($rCMR_{glu}$) was measured with [^{18}F]fluorodeoxyglucose positron emission tomography (PET) in two samples of subjects using two different PET cameras. The samples consisted of 10 and 17 medication-free depressives and 11 and 13 controls, respectively. Using coregistration of PET and magnetic resonance images, regions were individually delineated for the amygdala and thalamus, the latter of which was used as a control region. Within the depressed groups, right amygdalar $rCMR_{glu}$ was positively correlated with negative affect. Thalamic $rCMR_{glu}$ was not related to negative affect, and amygdalar $rCMR_{glu}$ accounted for a significant portion of variance in depressives' negative affect scores over and above the contribution of thalamic $rCMR_{glu}$. *NeuroReport* 9: 3301–3307 © 1998 Lippincott Williams & Wilkins.

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Introduction

Based on animal and human studies, it is now well established that the amygdala subserves affective processes such as fear learning, perception of emotional stimuli, and experience of negative affect.[1–5] The role of the amygdala in psychopathology is just beginning to be elucidated, with only a few studies directly examining amygdala activity in mental disorders.[6,7] The aim of the current study was to examine amygdala activity in individuals suffering from Major Depressive Disorder.

Using $H_2{}^{15}O$ positron emission tomography (PET) to study cerebral blood flow in depression, Drevets and colleagues[6] found higher blood flow in the left amygdala of depressed patients than in healthy controls. They also reported a positive correlation between depression severity and left amygdalar blood flow. Also relevant to major depressive disorder are two studies using PET in normal individuals that examine amygdala activity associated with emotion-related cognitive processes. In a study designed to induce a sense of helplessness, Schneider and colleagues[8] found that while trying to solve unsolvable cognitive tasks, participants showed increased blood flow in the amygdala compared to a resting condition. The observation of amygdala activation during a transiently induced state of helplessness is consistent with increased amygdala activity occurring in depression. Cahill and colleagues[9] found that the magnitude of right amygdala activation during exposure to a story predicted the extent to which negative emotional events were remembered. In depression, the tenacity with which a negative event remains in memory[10] may be in part mediated by elevations in amygdala activity occurring during the event.

Drevets and colleagues' findings[6] were based upon images that were reconstructed to a transaxial resolution of 18 mm full width half maximum (FWHM), and the use of a procedure for anatomical localization that involved warping individual brain images to a standardized brain space. The low resolution afforded by the image acquisition and analysis procedures used in that study limit the certainty that their results actually reflect amygdala activity rather than activity in surrounding tissue, especially because the amygdala is a relatively small structure (2–3 cm^3). Using a phantom study, Hoffman and colleagues[11] showed that for accurate quantification of isotope

concentration in tissue, the size of the structure should be approximately double the resolution of the scanner. Because modern PET scanners have resolutions as low as 4 mm FWHM, accurate quantification of amygdala metabolism is possible.

In order to minimize inaccuracies in the estimation of regional metabolic rate ($rCMR_{glu}$), we coregistered each magnetic resonance image (MRI) to its corresponding PET scan and delineated regions of interest (ROIs) for each individual. This method did not require warping or smoothing of the PET data, and therefore did not reduce the resolution of the PET scans (i.e. 5 or 7 mm FWHM). We were interested in basal $rCMR_{glu}$ in the amygdala as opposed to amygdala activation related to a transiently induced psychological state. Therefore, we used [^{18}F]fluorodeoxyglucose (FDG) PET,[12] which provides the reliability and resolution appropriate for our research questions. We hypothesized that amygdala metabolic rate would be greater in depressed patients than in controls and would be positively correlated with depressive symptoms and negative affect in depressed patients. Furthermore, to ascertain the specificity of our findings, we examined the relation of negative affect and $rCMR_{glu}$ in a control region, the thalamus, which was hypothesized not to have a direct relation to depressive symptomatology.

Materials and Methods

Participants: Because it was necessary to switch scanners mid-way through data collection, two separate samples of subjects were tested. Participants for Sample 1 were 10 (six female) medication-free depressed participants and 11 (six female) controls. Participants for Sample 2 were 17 (nine female) medication-free depressed participants and 13 (seven female) controls. Recruitment procedures and selection criteria were identical for Samples 1 and 2. Participants were screened for psychopathology using the Structured Clinical Interview for DSM-III-R or for DSM-IV (SCID).[13,14] Depressed participants met DSM-IV criteria for major depressive disorder, 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. Control participants had no history of any Axis I disorder in themselves or their first-degree relatives. Reliability of the decision to accept or reject participants was evaluated through independent rating of 10 randomly chosen SCID audio tapes ($\kappa = 0.80$, one participant misclassified). All participants were right-handed and had no history of thyroid problems, ECT, diabetes, or brain injury. Participants signed an informed consent form that had been approved by the UW-Madison Center for Health Sciences Human Subjects Committee.

Procedure: The procedures for Samples 1 and 2 were identical with the exception of the PET camera used for the study. Resting cerebral glucose metabolism was measured using FDG and PET.[12] Injection of FDG was scheduled between 11:00 and 13:30 h. Participants fasted for at least 5 h before injection of FDG. A small i.v. catheter, used for injection of the radiotracer, was placed into the right antecubital fossa. A 22-gauge i.v. catheter, used for obtaining blood samples during FDG uptake, was placed into a vein on the posterior aspect of the left hand. Handwarmers were used to allow for rapid sequential sampling of arterialized venous blood.[15] Participants were informed that the uptake period would last 30 min and were instructed to remain still (allowing for periodic shifts in position if needed), sit quietly, and relax but stay awake during uptake. Eyes and ears were unoccluded. About 15 min after the i.v. catheters were placed, ~5 mCi (3.8–5.7 mCi) of FDG were administered by bolus injection. Following the uptake period, participants were positioned in the scanner after voiding the contents of their bladders.

Dispositional negative affect (PANAS-neg) was measured with the Positive and Negative Affect Schedule, trait version[16] and depression severity was measured with the Beck Depression Inventory (BDI).[17] For Sample 1, PANAS-neg was administered within 1.5 weeks of the PET scan for depressives and within 10 weeks of the PET scan for controls, and the BDI was administered on the day of the PET scan. For Sample 2, PANAS-neg and the BDI were administered on the day of the PET scan. Descriptive data are presented in Table 1. Structural MRI scans of the brain were obtained for all participants within 3 months of the PET scan.

PET and MRI data acquisition: ^{18}F fluoride was produced on a CTI RDS Cyclotron (Knoxville, TN) operated in the Department of Medical Physics. FDG was synthesized using the method of Hamacher.[18]

In both PET scanner systems laser beam positioning devices were used to guide positioning of the participant's head. Image planes were positioned parallel to the orbitomeatal line. Data for Sample 1 were collected on a CTI-Siemens ECAT 933/04 PET Scanner (Knoxville, TN; hereafter referred to as the ECAT). Over a period of ~60 min, the ECAT acquired two sets of 14 transaxial planes, each with two bed positions, each spanning an axial range of 9.45 cm. The data from the second set, which was offset from the first set in the caudal direction, was used for analysis because they sampled tissue low

Table 1. Age and self-report variables for Sample 1 and Sample 2.

Sample	Group	Age	PANAS-neg (range 10-50)	BDI (range 0-63)
Sample 1 (ECAT Scanner)	Depressed ($n = 10$)	31.1 ± 10.7	27.7 ± 6.6	33.2 ± 8.1
	Controls ($n = 11$)	38.0 ± 14.0	13.1 ± 4.5	1.5 ± 3.2
Sample 2 (Advance Scanner)	Depressed ($n = 17$)	34.6 ± 9.9	22.6 ± 8.1	28.8 ± 8.8
	Controls ($n = 13$)	34.3 ± 11.6	10.8 ± 1.5	2.0 ± 2.5

The groups did not differ significantly on age, Sample 1, t = 1.27, $p = 0.22$; Sample 2, t = 0.07. PANAS-neg, PANAS negative affect, trait version;[16] BDI, Beck Depression Inventory.[17] Values are means ± s.d.

enough in the brain to reliably include the amygdala. In-plane and axial resolution were ~7 mm FWHM. Images were reconstructed to $256 \times 256 \times 14$ pixels. In-plane pixel dimensions were 0.97×0.97 mm with a plane thickness of 6.75 mm. Calculated attenuation correction was applied to the data. Data for Sample 2 were collected on a GE Advance PET Camera[19] (Milwaukee, WI; hereafter referred to as the Advance). Over a 30 min period, the Advance acquired 35 transaxial planes for a field of view of 15.2 cm, which covered the entire brain. In-plane and axial resolutions for the Advance were ~5 mm FWHM. Images were reconstructed to $256 \times 256 \times 35$ pixels. Pixel dimensions were 1.17×1.17 mm in plane with a plane thickness of 4.25 mm. Calculated attenuation correction was applied to the data.

Structural MRI scans were performed on a 1.5 T GE Signa scanner (Milwaukee, WI). The MRI protocol consisted of an axial 3D SPGR, with 24 cm FOV, TE = 14, TR = 30, 256×192 matrix, NEX = 1, flip angle = 35°, and a 1.2 mm slice thickness, for a total of 124 slices.

Quantification of emission data: Sequential 1–2 ml blood samples were collected during the 30 min uptake period. Pixel absolute radioactivity concentration values and blood radioactivity values were corrected for physical radionuclide decay back to the time of tracer injection. Previous measurements in our laboratory indicate similarity among participants, up to a multiplicative scale, of plasma FDG concentration time courses following the initial distribution of tracer into the plasma and extracellular spaces. Therefore, individual plasma time courses measured over the first 30 min were combined with previously measured normative data to provide tracer concentration–time courses over the duration of the PET image data acquisition. 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 Sokoloff method.[20]

Determination of metabolic rate values: Global metabolic rate ($gCMR_{glu}$) values were obtained for each individual using Statistical Parametric Mapping software (Wellcome Department of Cognitive Neurology). The automated image registration package (AIR)[21] was used to co-register each MRI scan to its corresponding PET scan. Image sets were transformed into the coronal orientation for identification of the regions of interest (ROIs). DIP Station, version 1.0.6, (Hayden Image Processing Group) was used to draw ROIs for each participant (Fig. 1). ROIs for the amygdalae were drawn on 5–8 coronal MRI 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. ROIs for the thalamus were drawn on 25–41 coronal planes. The internal capsule was used as a guide for the lateral and inferior boundaries. The shape of the lateral ventricles typically differentiated the anterior aspect, i.e. the most anterior slice was drawn when the inferior-most section of the lateral ventricles became flattened by the anterior nucleus of the thalamus. The posterior boundary was typically the slice just anterior to the crus of fornix looping down to connect with the hippocampus. There were no volumetric differences in ROIs between controls and depressives for either Sample 1 (left amygdala, t = –0.0013; right amygdala, t = 0.19; left thalamus, t = 0.55; right thalamus, t = –0.10) or Sample 2 (left amygdala, t = –0.85; right amygdala, t = 0.08; left thalamus, t = 0.15; right thalamus, t = –0.33).

After ROIs were delineated on each MRI scan, mean $rCMR_{glu}$ was extracted for the exact corresponding regions on the co-registered PET scan. For calculation of inter-rater reliability coefficients, second sets of ROIs were drawn independently, and intraclass correlations (IC) were performed on absolute $rCMR_{glu}$ values (for the amygdala, Sample 1 ($n = 8$): left, IC = 0.94, right, IC = 0.95; Sample 2 ($n = 4$): left, IC = 0.95, right, IC = 0.96; and for the thalamus, Sample 1 ($n = 4$): left, IC = 0.91, right, IC = 0.99; Sample 2 ($n = 5$): left, IC = 0.97, right, IC = 0.95).

Data analysis: Analysis procedures were identical for Samples 1 and 2. Absolute $rCMR_{glu}$ values were regressed on $gCMR_{glu}$ values to remove the variance

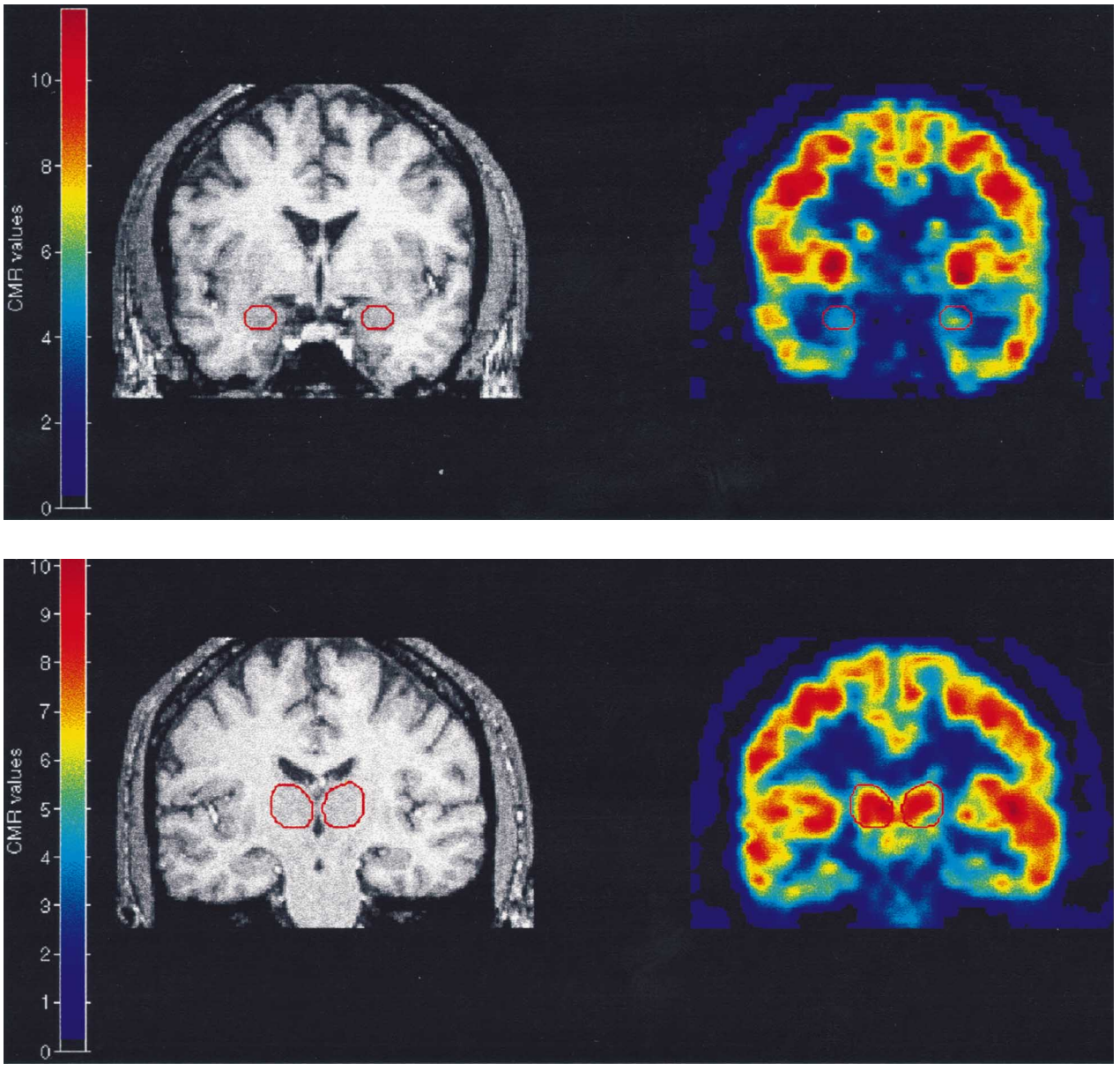

FIG. 1. PET–MRI co-registration and amygdalar (**a**) or thalamic (**b**) ROI delineation. This figure presents representative image planes in the coronal orientation for one participant. The PET image planes are presented beside their corresponding co-registered MRI planes.[21] Each actual amygdalar ROI included data from 5–8 planes and thalamic ROIs contained data from 25–41 planes. The PET image of absolute $rCMR_{glu}$ is from a GE Advance PET camera[19] (in-plane resolution ~5 mm FWHM). Units of the PET color scale are in mg/100g/min.

in absolute $rCMR_{glu}$ that was due to $gCMR_{glu}$ (hereafter $rCMR_{glu}$ refers to residualized $rCMR_{glu}$ values). Between-group *t*-tests were performed on amygdalar $rCMR_{glu}$ and $gCMR_{glu}$ values to test for differences in metabolic rate between depressed and control participants. Within the groups of depressed patients, Pearson r correlations were computed between amygdalar $rCMR_{glu}$ values and BDI and PANAS-neg scores.

Because specific predictions were made for each analysis performed, corrections for multiple comparisons were not applied. Within the control groups, there were restrictions of range and skewed distributions for the BDI and PANAS-neg (with all but a few controls obtaining the lowest possible scores). Thus, tests of correlations including control subjects were not performed. Power analyses[22] were computed to determine whether the sample sizes in the current study were sufficiently large to detect a group difference in amygdala activity of the magnitude reported by Drevets *et al.*[6] To establish the regional specificity of our findings, the relation between thalamic $rCMR_{glu}$ and negative affect was examined.

Results

Sample 1: Control and depressed participants did not differ on $gCMR_{glu}$ or on left or right amygdalar $rCMR_{glu}$ (t's ranging from –0.35 to 0.52). Although correlations for the depressed patient group between amygdalar $rCMR_{glu}$ and self-report measures did not reach significance, right and left amygdalar $rCMR_{glu}$ were positively correlated with PANAS-neg (left, r[8] = 0.39; right, r[8] = 0.41, see Fig. 2) and BDI scores (left, r[8] = 0.25; right, r[8] = 0.45).

Sample 2: Control and depressed participants did not differ on $gCMR_{glu}$ or on left or right amygdalar $rCMR_{glu}$ (t's ranging from –0.29 to 0.94). Right amygdalar $rCMR_{glu}$ and PANAS-neg scores were positively correlated within the depressed patient group (r[15] = 0.56, $p < 0.02$, two-tailed; Fig. 2). Left amygdalar $rCMR_{glu}$ was not correlated with PANAS-neg for depressives (r[15] = 0.12). The correlations between amygdalar rCMRglu and PANAS-neg were significantly different for the left and the right amygdala (t = 2.2, $p < 0.05$). Correlations between the BDI and both right and left amygdalar $rCMR_{glu}$ were not significant, (left, r[15] = 0.31; right, r[15] = 0.23).

Control region analyses: Within the depressed group, thalamic $rCMR_{glu}$ was not significantly correlated with PANAS-neg for either Sample (Sample 1: right thalamus, r[8] = 0.25; Sample 2: right thalamus, r[15] = 0.24). For Sample 2, a hierarchical regression analysis with PANAS-neg as the dependent variable, with right thalamic $rCMR_{glu}$ entered as the first independent variable, and with right amygdalar $rCMR_{glu}$ entered second, revealed that amygdalar $rCMR_{glu}$ accounted for a significant portion of variance in negative affect scores after variance due to thalamic $rCMR_{glu}$ had been removed (increment in $R^2 = 0.26$, $p < 0.05$).

Power analysis: The effect size in the Drevets *et al.* study[6] for the group difference in mean blood flow in the left amygdala was computed using the t-value and sample sizes they reported (d = 1.0). For this effect size at a significance level of 0.05, the power to detect a group difference in amygdala activity in the current study was 0.70 for Sample 1 and 0.83 for Sample 2. These values indicate a sufficient degree of power in the current study, particularly in Sample 2.

Discussion

The primary finding in the current study was a positive correlation between dispositional negative affect and right amygdalar $rCMR_{glu}$ for the groups of depressed patients. Midway through subject recruitment for our study, we were forced to switch PET scanners, leaving each portion of the total sample (i.e. Sample 1 and Sample 2) under-powered. Although the finding was significant only in Sample 2, the effect size in Sample 1 was comparable, thus providing a between sample replication. This finding is consistent with the corpus of literature indicating the importance of the amygdala for negative affective processes.[1–9] The analysis of the thalamus as a control region suggested that the relation between negative affect and amygdala metabolism was regionally specific, particularly when examined using hierarchical regression, which showed that amygdalar $rCMR_{glu}$ predicted negative affect scores over and above the contribution of the thalamic $rCMR_{glu}$.

The correlation between negative affect and amygdala metabolism for Sample 2 was unilateral, apparent only on the right. The literature is mixed with regard to the laterality of the relation between negative affective processes and amygdala activity, with some studies finding results on the right,[7,9] others on the left,[4,6] and some bilaterally.[3,5] In order to disentangle the inconsistent findings with regard to laterality,

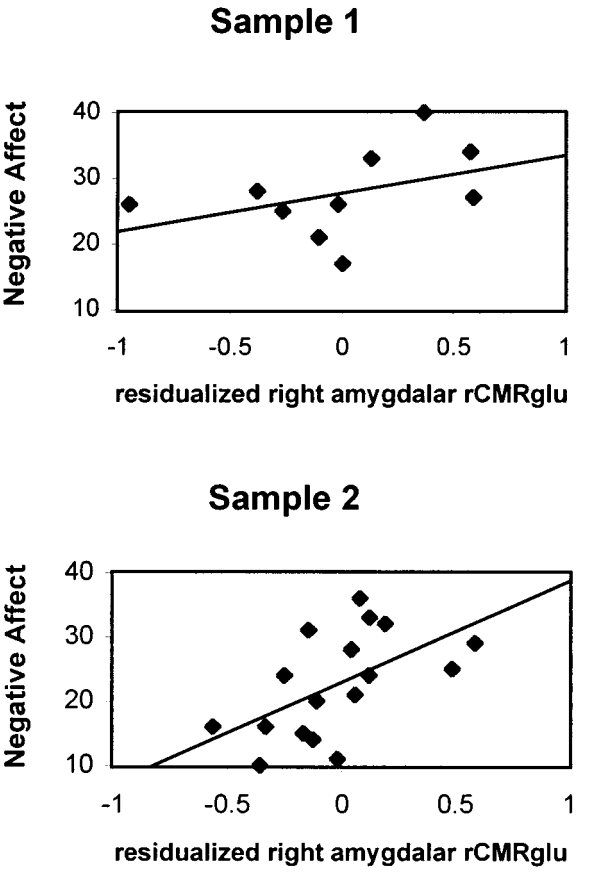

FIG. 2. Scatter plots of the correlations within the depressed groups between dispositional negative affect (assessed with the PANAS Negative Affect Scale, trait version[16]) and residualized $rCMR_{glu}$ in the right amygdala, Sample 1, r(8) = 0.41, $p = 0.24$; Sample 2, r(15) = 0.56, $p < 0.02$.

future studies should be designed to determine under what conditions the right and left amygdala are differentially as well as bilaterally activated.

The current study provides a partial replication of Drevets and colleagues' findings.[6] Both studies provide evidence for the involvement of the amygdala in the severity of distress experienced by depressed individuals. However, in the Drevets *et al.* study, a different measure of distress was used (Hamilton Rating Scale for Depression[23]), and it was the left rather than the right amygdala that showed the association. The lack of correlation between amygdalar $rCMR_{glu}$ and the depression severity measure used in the current study, the BDI,[17] may be due to heterogeneity in the psychological constructs measured by the BDI. It may be that only certain depressive symptoms are related to amygdalar function. Further study is required to clarify which aspects of depressive symptomatology are specifically related to amygdalar function.

Drevets and colleagues[6] found that depressives had greater mean blood flow in the left amygdala than control subjects, whereas no group differences in mean amygdalar $rCMR_{glu}$ were revealed for either sample in the current study. Our lack of a group difference in amygdalar $rCMR_{glu}$ is not likely merely a consequence of low power due to small sample sizes. Power analyses revealed that the sizes of the samples used in the current study were sufficiently large to reveal a group difference of the magnitude reported by Drevets and colleagues, particularly in our Sample 2. A number of other factors could account for the discrepancy between the studies. The resolution of the images used in the Drevets *et al.* study (~18 mm FWHM) was substantially lower than the resolutions of the images used in the current study (~5 and 7 mm FWHM with no additional smoothing). Furthermore, Drevets and colleagues used an atlas-based approach for identification of the amygdala whereas the current study individually identified amygdala ROIs for every subject. Our data, obtained on a modern scanner using more precise amygdala delineation, were unable to differentiate depressives and controls based on basal $rCMR_{glu}$ in the amygdala. Although controls do not show levels of distress commensurate with depressives, other psychological factors (e.g. arousal) may be related to variation in amygdala activity in control subjects. The depressives studied by Drevets *et al*. may have consistently shown elevated activity in the amygdala because they suffered relatively severe affective illness and were a highly homogeneous group. Although BDI[17] scores indicated moderate to severe depression in the current study, possibly these depressives were not consistently severely depressed enough to reveal a mean difference in amygdala activity when compared to controls. Variables such as the measurement of blood flow *vs* metabolism, the precision of estimation of amygdalar activity, and the severity of depression could all contribute to the discrepancy in results. Future PET studies of severely depressed individuals must use high resolution images with precise delineation of the amygdala to resolve the inconsistency.

A number of studies of depression using PET have been conducted previously.[24] The amygdala has not typically emerged in *post hoc* analyses of group differences in regional activity, and the exact role of the amygdala in the etiology of depression remains unknown. Because of the theoretical import of the amygdala and its known involvement in affective processes, the role of the amygdala in Major Depressive Disorder should be more explicitly and precisely studied.

Conclusion

This study demonstrated that individuals with major depressive disorder who have greater baseline right amygdala glucose metabolism experience more severe negative affect. The thalamus, selected as a control region, showed no relation with negative affect, thus providing evidence for the specificity of the finding with the amygdala. Our finding is consistent with results from human and non-human studies that indicate the importance of the amygdala in negative affective processes.[1–9] Our study provided partial replication of another study[6] of amygdala activity in depression, which showed that blood flow in the left amygdala predicted depression severity and that depressed patients had higher blood flow rates in the left amygdala than controls. The current study, using precise methods for estimation of amygdalar metabolic rates, did not reveal a group difference in amygdalar metabolism for depressives and controls. Future research is needed to more definitively reveal the role of the amygdala in Major Depressive Disorder.

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