Thalamic Metabolic Rate Predicts EEG Alpha Power in Healthy Control Subjects But Not in Depressed Patients

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Background: *EEG alpha power has been demonstrated to be inversely related to mental activity and has subsequently been used as an indirect measure of brain activation. The hypothesis that the thalamus serves as a neuronal oscillator of alpha rhythms has been supported by studies in animals, but only minimally by studies in humans.*

Methods: *In the current study, PET-derived measures of regional glucose metabolism, EEG, and structural MRI were obtained from each participant to assess the relation between thalamic metabolic activity and alpha power in depressed patients and healthy controls. The thalamus was identified and drawn on each subject's MRI. The MRI was then co-registered to the corresponding PET scan and metabolic activity from the thalamus extracted. Thalamic activity was then correlated with a 30-min aggregated average of alpha EEG power.*

Results: *Robust inverse correlations were observed in the control data, indicating that greater thalamic metabolism is correlated with decreased alpha power. No relation was found in the depressed patient data.*

Conclusions: *The results are discussed in the context of a possible abnormality in thalamocortical circuitry associated with depression.* Biol Psychiatry 1999;45: 943–952

Key Words: EEG, PET, MRI, alpha, thalamus, depression

Introduction

Electroencephalographic (EEG) alpha power is reflective of an awake, but relaxed, state, and is commonly used as an indirect measure of brain activation (Shagass 1972). Past animal work implicates the thalamus as a neuronal oscillator of alpha rhythms (8 to 13 Hz). Early work demonstrated that electrical stimulation of the medial thalamic nuclei in anesthetized cats produced widespread cortical potentials (the putative "recruitment response") that bore a remarkable resemblance to spontaneous bursts of activity in the alpha band (Dempsey and Morison 1942).

Morison and co-workers (1943) found synchronous burst activity in the range of 8 to 12 Hz (spindles) in the thalamus and in the cortex of anesthetized cats. The thalamus exhibited normal burst activity even when deprived of all homolateral neocortical connections and most interhemispheric commissural systems. Morison and Bassett (1945) demonstrated that spindles could be seen in the thalamus of cats with complete bilateral decortication, thus indicating that spindle activity in the thalamus does not depend on the presence of the neocortex. Lopes da Silva et al (1973b, 1980) demonstrated that significant thalamocortical coherences existed, especially between the lateral geniculate nucleus and the cortical alpha rhythm. However, significant corticocortical coherences also existed, leading them to conclude that both coherences are important for the modulation of alpha rhythms.

Research by Steriade and colleagues has led to an increased understanding of thalamic rhythmic activity and its relation to cortical spindles (Steriade et al 1985, 1987). Steriade and colleagues suggest that only the nucleus reticularis (RE) is capable of producing spindle oscillations. In a study using cats, an abolition of spindle-wave rhythmicity and all-burst activity of neurons was observed in RE-deprived nuclei, whereas RE neurons preserved their rhythmicity after disconnection from their major (cortical and thalamic) input sources (Steriade et al 1985, 1987). The RE fits like a shell on the lateral, anterior superior, and anterior inferior surfaces of the thalamus, resulting in its penetration by virtually all fibers involved in thalamocortical and corticothalamic connections (Scheibel and Scheibel 1965). This position makes it ideal for potential monitoring of thalamocorticothalamic activity.

Steriade and colleagues further demonstrated that the thalamus produces not only spindle activity, but also slow and fast oscillations (Steriade and Deschenes 1984; Steriade et al 1991a, 1991b). Slow (0.5 to 4 Hz) and fast (20

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to 40 Hz) frequency oscillations depended upon either hyperpolarized or depolarized membrane potentials. In contrast, spindle oscillations (7 to 14 Hz) were associated with the resting membrane potentials (−55 mV) of RE neurons. The spindling activity of the RE was thought to be imposed on the cortex via thalamocortical connections. Since resting membrane potentials were associated with spindle oscillations, Steriade and colleagues concluded that an inverse relationship existed between cellular activity in the thalamus and cortical oscillations of 7 to 14 Hz. In other words, activity in the RE is inversely correlated with cortical alpha rhythms.

For decades, much work has been done to elucidate the relations of thalamocortical rhythmic activity using animal models. In the past, investigating the activity of subcortical brain structures required invasive techniques limiting researchers to studies using animals. With the advent of modern neuroimaging techniques, such as positron emission tomography (PET), came the first neurophysiologic examination of alpha rhythms in humans from our laboratory (Larson et al 1998). Using PET and EEG, we investigated the relation between the human alpha rhythm (8 to 13 Hz) and glucose metabolism in the thalamus in a mixed group of depressed and normal control subjects. More specifically, alpha EEG power, an indirect measure of regional brain activation (Shagass 1972), was correlated with thalamic metabolic activity. Based on the findings of Steriade and colleagues (1984), we hypothesized that greater activity in the thalamus would be correlated with greater alpha suppression.

EEG and [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG-PET) data were collected during the same session. Alpha power was aggregated over a 30-min period and correlated with every pixel of corresponding PET data to determine which areas of the brain would be the most negatively correlated. A robust inverse correlation was found between alpha EEG power and an area of the brain that included the thalamus. However, because of the limited sample, we could not investigate differences between the depressed and normal control subjects.

Although these findings are in line with many earlier findings in animal studies, the previous study had several limitations that must be considered when interpreting the results. The statistical parametric mapping method used correlated global alpha EEG power with pixels from the entire brain volume. A more precise method using PET-magnetic resonance imaging (MRI) coregistration would allow us to uniquely define the region of the thalamus for each participant on his or her MRI and then extract the regional metabolic activity of the thalamus from the corresponding PET scan with no additional smoothing required. The extracted thalamic metabolic activity could then be correlated with the corresponding EEG data.

This more precise method for examining the neurophysiology of the human alpha rhythm forms the basis of the current study. FDG-PET, EEG, and MRI measures were obtained for each participant to assess the relation between thalamic metabolic activity and global alpha power. Structural MRIs were used to identify the left and right thalamus for each participant. The MRIs were then coregistered to their corresponding PET scans and metabolic activity from the specified regions of interest (ROIs) was extracted. Since the temporal resolution of PET is vastly inferior to that of EEG (collapsing over approximately 30 min of uptake for FDG-PET), we could not assess thalamic activity in relation to the phasic aspects of alpha rhythms. In addition, the spatial resolution of PET is not sufficient to examine the activity of separate nuclei within the thalamus. Therefore, metabolic activity from the entire thalamus was correlated with alpha power aggregated over the 30-min FDG-uptake period.

These data represent an expanded sample of those reported in the Larson et al (1998) paper and were collected as part of a study comparing resting regional brain activity in depressed patients and healthy control subjects. FDG-PET and EEG were recorded at the same session to assess the association between alpha power and thalamic glucose metabolism. Based on the findings of Steriade and colleagues (1984) and Larson and co-workers (1998), we predicted a robust negative correlation between metabolic activity in the thalamus and EEG alpha power would exist in the control data.

However, data from a number of sources suggest that dysfunction of anatomic circuits involving the frontal cortex, striatum, and thalamus are involved in the functional neuroanatomy of unipolar depression (Drevets and Raichle 1992; Swerdlow and Koob 1987; Baxter et al 1985). The exact nature of this dysfunction is yet unclear, as it has been reported in the overall synaptic activity of the circuit, the activity of particular structures within the circuit, and the amount of neurotransmitter acting on the circuit. In light of these suggestions highlighting the possibility of a thalamocortical abnormality, we did not predict to find the same strong relation between EEG alpha power and thalamic metabolism among the depressed patients.

Methods and Materials

Subjects

Subjects were recruited via advertisements in local media. Subjects were screened for psychopathology using the Structured Clinical Interview for DSM-III-R Patient Edition (SCID; Spitzer et al 1992). Depressed subjects were required to meet criteria for DSM-IV (1994) major depressive disorder and had a negative family history of mania and psychosis. Depressed subjects' mean

Beck Depression Inventory score was 28.72 (SD = 2.00) (BDI; Beck et al 1961). Control subjects had no past history of any Axis I disorders, and no family history of Axis I disorders. Control subjects' mean BDI score was 2.00 (SD = .71). All subjects were free of antidepressant medication for at least 4 weeks before testing. Subjects were right-handed as assessed by the Chapman Handedness Inventory (Chapman and Chapman 1987).

Thirty-nine subjects participated in the study, however 3 were dropped due to technical problems with their PET image data, and 5 others were dropped due to a lack of an MRI scan. Therefore, a total of 31 subjects (16 women) were used in analyses for this study, 18 depressed (9 women) and 13 nondepressed control subjects (7 women).[1] The two groups did not differ in age (depressed, mean = 35.11, SD = 9.83, range = 20 to 50; controls, mean = 34.31, SD = 11.60, range = 21 to 57; t (29) = .84, $p > .52$).

Procedures

Subjects completed a full day of testing including simultaneous EEG assessment and measurement of resting regional cerebral glucose metabolic rate (CMR_{glu}) using [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). Subjects fasted for at least 5 hours prior to arrival at the PET center. For 23 subjects, ERPs were recorded during a testing segment prior to the PET/EEG session, so these subjects arrived already fitted with the EEG and EOG recording electrodes. The electrode cap and EOG electrodes were rechecked for placement and impedances. For the 8 subjects who did not arrive with the electrodes already in place, the electrodes were placed at this time.

After the electrodes were connected, the left hand was placed into a heated handwarmer to maintain a skin surface temperature of 42°C, which allowed for rapid sequential sampling of "arterialized" blood. The right hand was also heated in order to equate thermal stimulation on both sides of the body. Two 22-gauge intravenous catheters were placed, one in the antecubital fossa of the right arm, and the other on the posterior aspect of the left hand.

Subjects were instructed that after the FDG was injected, the uptake period would last 30 min, during which the room would be kept as quiet as possible. A 1-2 mL blood sample was drawn to obtain an initial plasma glucose level. Just before injection of the radiotracer, the subject was informed that EEG recording was to start, and whether to hold their eyes open or closed. Approximately 5 mCi (range of 3.8 to 5.7 mCi) of FDG was then administered by bolus injection into the intravenous line in the right arm. Sequential 1 to 2 mL blood samples were collected throughout the 30 min following injection as follows: every 15 sec for 2 min; every 30 sec for the next 2 min; every min for the next 4 min; every 2 min for the next 10 min; and every 3 min for the next 12 min. To determine the time course of the concentration of tracer in plasma, two samples were obtained to measure plasma glucose levels at approximately 15 and 10 min postinjection. A technologist seated to the left of the subject drew blood samples from the left hand, and 1 to 2 laboratory assistants recorded the exact time of each draw.

EEG collection began at the time of injection. Ten contiguous 3-min trials of EEG data were recorded to cover the entire 30 min. Each trial alternated between eyes open and eyes closed conditions, with the starting condition counterbalanced across subjects. The experimenter verbally informed the subject of the trial condition before beginning each 3-min trial. At the end of 30 min, the intravenous lines and electrodes were removed and subjects were directed to the restroom and encouraged to void their bladders. The subjects were then placed in the PET scanner bed to acquire a 30-min emission scan.

EEG Recording and Quantification

EEG was recorded using a modified lycra electrode cap (Electro-Cap), positioned on the subjects' head using known anatomic landmarks (Blom and Annevelt 1982). EEG was recorded at 28 scalp sites ($FP_{1/2}$, $F_{3/4}$, $F_{7/8}$, $FC_{3/4}$, $FC_{7/8}$, $C_{3/4}$, $T_{3/4}$, $T_{5/6}$, $CP_{3/4}$, $CP_{5/6}$, $P_{3/4}$, $PO_{3/4}$, F_{PZ}, F_Z, C_Z, and P_Z) referenced to the left ear (A_1). The right ear (A_2) was also recorded for rederivation of a linked ears reference off-line. In order to visually score data for eye movement artifact, two channels of EOG were recorded: horizontal (HEOG) from the external canthi of each eye; and vertical (VEOG) from the supra- to suborbit of one eye. All EEG electrode impedances were under 5000 ohms, and the impedance of homologous sites within 2000 ohms. EOG electrode impedances were under 20,000 ohms. The EEG and EOG were amplified with a Grass Model 12 Neurodata System using Model 12 C preamplifiers, with a bandpass of 1-300 Hz and a 60 Hz notch filter. The signal was also filtered with MF6 digital anti-aliasing low-pass filters set at 100 Hz, with a 36 dB/octave roll-off. The signals were digitized on-line at 250 Hz by a 486 DX2 33 MHz PC and an Analogic MS-DAS-12 A/D board.

The EEG was visually edited to remove artifact due to eye blinks, gross muscle activity, and movement. When artifact occurred in a given channel, data from all channels were removed. Artifact-free chunks of data were extracted through a Hamming window, which reduces spurious spectral power estimates at the beginning and end of each chunk. A Fast Hartley Transform (FHT; Bracewell 1984) was applied to all extracted artifact-free epochs of data 1.024 seconds in duration, with epochs overlapping 50%. The mean number of seconds of artifact-free data for control subjects was 1079.97 (SD = 248.31), and 1034.15 (SD = 234.25) for the depressed participants, ($t < 1$). Data were referenced off-line to the average reference. Power density (μV^2/Hz) was then computed for the alpha band (8 to 13 Hz). Power density (μV^2/Hz) was computed by summing power values across each 1 Hz bin within a band and dividing by the number of bins. Trials with less than 30 sec of artifact-free EEG were dropped from future computations. Mean alpha power was computed for the five trials in each condition (eyes open and eyes closed). All power density values were log transformed to normalize the distribution of the data. To compare whole-head alpha power with metabolic rate, mean alpha power across all 28 electrodes was computed for the eyes open and eyes closed conditions. Finally, mean whole-head alpha

[1] Of the 31 subjects, 21 (8 control, 13 depressed) were included in the analyses of both the current and the Larson et al (1998) paper.

power across the eyes open and eyes closed condition was also derived.

PET Data Collection and Reduction

^{18}F fluoride was produced by a CTI RDS Cyclotron (Knoxville, TN) in the Department of Medical Physics. FDG was synthesized using the modified method of Hamacher and colleagues (Hamacher and Coenen 1986).

Scans were performed by a GE Advance PET camera (Milwaukee, WI; in-plane and axial resolution approximately 5 mm FWHM). A laser positioning device was used to position the participant's head in the scanner. The image planes were positioned parallel to the orbitomeatal line. Thirty-five transaxial planes covering the entire brain were acquired during a 30-min emission scan. All images were reconstructed to 256 × 256 × 35 pixels, yielding pixel dimensions of 1.17 mm × 1.17 mm × 4.25 mm. Calculated attenuation correction was applied to the data.

The emission data were quantified using the following procedures. Blood samples were centrifuged. Aliquots of plasma were obtained from each blood sample and plasma radioactivity concentrations were measured. Radioactivity values were corrected for physical decay back to the time of injection. Previous measurements in our laboratory demonstrated the striking similarity, up to a multiplicative scale, of plasma FDG concentration time courses following the initial distribution of tracer into the plasma and extracellular spaces. The individual plasma time courses measured over the first 30 min were thus combined with previously measured normative data to provide tracer concentration time courses over the duration of the PET image data acquisition. These plasma time courses were combined with plasma glucose levels and image pixel values according to the Sokoloff method (Sokoloff et al 1977).

Estimates of global cerebral metabolic rate ($gCMR_{glu}$) were obtained using Statistical Parametric Mapping software (SPM 96; Wellcome Department of Cognitive Neurology). Each participant's $gCMR_{glu}$ value equals the average of all pixels in the image that fell above a threshold of 12.5% of the whole-volume mean.

MRI Data Acquisition

Structural MRI scans were performed on a 1.5 Tesla GE Signa scanner (Milwaukee, WI) within 3 months of the PET and EEG session. 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.

Determination of $rCMR_{glu}$

Regional cerebral metabolic rate values for each participant for the left and right thalamus were obtained using PET-MRI co-registration. MRI image sets were transformed into the coronal orientation for more reliable identification of the regions of interest (ROIs).

DIP Station, version 1.0.6, (Hayden Image Processing Group) was used to manually draw thalamic ROIs on coronal MRI planes for each participant. Specific criteria were developed to minimize artifactual ROI metabolic rate estimates due to partial voluming in the PET scans. Therefore, the ROIs were drawn specifically for the purpose of extraction of PET-MRI co-registration-derived glucose metabolic rate and were not drawn for the purpose of morphometric analysis.

Tracing guidelines were developed through the use of neuroanatomic atlases (Matsui and Hirano 1978; DeArmond et al 1989), in consultation with colleagues experienced in neuroanatomy, and based on previous researchers' criteria for thalamic ROIs (Potts et al 1994). The method consisted of manually tracing the ROIs on every coronal slice in which the thalamus could be visualized (Figures 1–4).

ROIs for the thalamus were drawn on 25 to 41 coronal MRI planes. An outline was drawn just inside the gray/white matter interface of the thalamus. Because the thalamus is medially and superiorly bordered by the lateral and third ventricles and includes both white and gray matter, care was taken not to include any cerebral spinal fluid (CSF) or excess white matter. 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 of the thalamus. In other words, the most anterior slice of the thalamus was drawn when the inferior-most section of the ventricles became flattened by the appearance of the anterior nucleus of the thalamus. The most posterior slice of thalamus included was typically the slice just anterior to the appearance of the crus of fornix looping down to connect with the hippocampus.

After ROIs were delineated on each MRI scan, the ROIs were copied to a blank image set. The Automated Image Registration package (AIR; Woods et al 1993) was used to co-register the PET and MRI data. MRI scans were fit to PET scans, and then resliced to match the PET. The same manipulation was then applied to the blank image set containing the ROIs. The transformed ROIs were copied to the PET image and mean $rCMR_{glu}$ was extracted for the corresponding regions of the ROIs on the co-registered PET scan.

Statistical Analysis

ROI DELINEATION: INTER-RATER RELIABILITY OF $rCMR_{glu}$. Intraclass correlation coefficients were computed on absolute $rCMR_{glu}$ extracted from ROIs drawn by two independent raters on nine PET-MRI co-registered images. Participants used in reliability calculations were chosen randomly.

ADJUSTMENT OF REGIONAL METABOLIC RATE FOR VARIANCE IN GLOBAL METABOLIC RATE. Absolute $rCMR_{glu}$ 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 $rCMR_{glu}$ values). For analyses examining group differences in thalamic $rCMR_{glu}$, residualization of ROI scores was performed across hemisphere to preserve any hemispheric differences in metabolic rate.

TESTS OF GROUP DIFFERENCES IN EEG AND CMR_{glu} VARIABLES. Several tests were performed to examine group differences. First, an ANOVA was conducted to determine whether differences existed between the depressed and control

groups on alpha power averaged across all 28 electrodes between the eyes open and eyes closed conditions. A second ANOVA was performed to determine whether thalamic $rCMR_{glu}$ differences existed between the two groups (depressed or control), or the left and right thalamus. Finally, a between groups *t* test was performed to determine whether or not the two groups differed on $gCMR_{glu}$ (average CMR_{glu} from the entire brain volume).

CORRELATIONS BETWEEN ALPHA EEG POWER AND THALAMIC GLUCOSE METABOLISM. Several sets of correlations were run, the first of which compared a measure of alpha power with thalamic metabolic activity. The first correlations were performed between average alpha power from the whole head and thalamic glucose metabolic data using subjects from both depressed and control groups combined. A second set of correlations was run to examine any possible differences between the depressed and control groups. Correlations were also performed comparing thalamic metabolic activity with average alpha power from the two hemispheres separately (left, F_{P1}, $F_{3/7}$, $FC_{3/7}$, C_3, $T_{3/5}$, $CP_{3/5}$, P_3, PO_3; right, F_{P2}, $F_{4/8}$, $FC_{4/8}$, C_4, $T_{4/6}$, $CP_{4/6}$, P_4, PO_4), and cortical regions separately (frontal, $F_{P1/2}$, $F_{3/4}$, $F_{7/8}$, F_{PZ}, F_Z; central, $F_{C3/4}$, $F_{C7/8}$, $C_{3/4}$, $T_{3/4}$, C_Z, $CP_{3/4}$; parietal, $PO_{3/4}$, $T_{5/6}$, $P_{3/4}$, P_Z, $CP_{5/6}$). Lastly, because alpha power is generally more predominant during eye closure, the correlations examining the relation between thalamic metabolic rate and global alpha power were performed separately for the eyes open and eye closed conditions.

Results

Inter-rater Reliability of $rCMR_{glu}$

Intraclass correlations indicated reliable extraction of $rCMR_{glu}$ (right thalamus, $r = .97$, $p < .001$, left thalamus, $r = .94$, $p < .001$).

Test of Group Differences in Global Alpha Power

A 2 × 2 mixed model ANOVA (Group X Condition), comparing depressed and control participants on global alpha power, revealed a main effect for condition indicating that more alpha power existed during the eyes closed condition than during the eyes open condition ($F = 64.78$, $p < .001$). See Table 1 for means and standard deviations for global alpha power.

Test of Group Differences in Thalamic $rCMR_{glu}$

A 2 × 2 mixed model ANOVA (Group X Hemisphere) comparing participants on thalamic $rCMR_{glu}$ revealed no interaction and no differences between controls and depressives or left and right hemisphere, omnibus $F = .01$, $p > .93$. See Table 1 for means and standard deviations for thalamic $rCMR_{glu}$.

Test of Group Differences in $gCMR_{glu}$

Control and depressed participants did not differ on $gCMR_{glu}$, $t\ (29) = .84$, $p > .52$. See Table 1 for means and standard deviations for $gCMR_{glu}$.

Correlations Between Global Alpha Power (8-13 Hz) and Thalamic $rCMR_{glu}$

When both groups were combined, no significant correlations between whole head alpha power from the 8 to 13 Hz band and thalamic $rCMR_{glu}$ were observed (right thalamus, $r = -.24$, $p =$ ns, left thalamus, $r = -.24$, $p =$ ns). The correlations examining the same relation for each group separately revealed a robust inverse correlation for the control subjects (right thalamus, $r = -.68$, $p < .01$, left thalamus, $r = -.70$, $p < .01$) but no relation for the depressed patients (right thalamus, $r = .20$, $p =$ ns, left thalamus, $r = .23$, $p =$ ns; see Figure 5 for scatterplots). The correlations were significantly different between control subjects and the depressives ($p < .01$). See Table 2 for correlation coefficients by group.

Correlations Between Hemispheric and Regional Alpha Power and Thalamic $rCMR_{glu}$

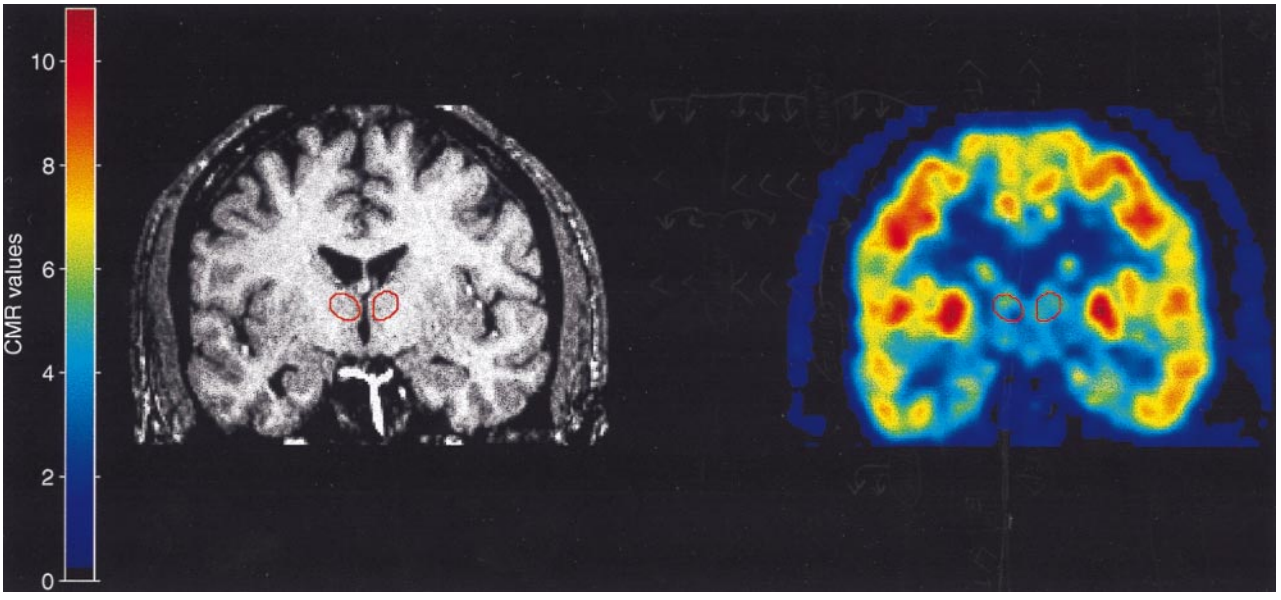
A similar trend of group (depressed and control) differences was observed when the correlations comparing thalamic $rCMR_{glu}$ with alpha were performed separately for left and right hemispheric average alpha power. Finally, correlations between alpha power and thalamic $rCMR_{glu}$ were also very similar for EEG alpha power from the frontal, central, and parietal regions. All correlations were significantly different between controls and depressives ($p < .05$). See Table 2 for correlation coefficients.

Correlations Performed Separately by Condition

The correlations between thalamic $rCMR_{glu}$ and global alpha power did not differ for the eyes open and eyes closed conditions. The results were consistent with the group differences observed across condition. The correlations were significantly different between the controls and depressives ($p < .05$). See Table 2 for correlation coefficients.

Discussion

Our results indicate that in healthy control subjects, an aggregate measure of power in the alpha band over a 30-min time period is inversely correlated with glucose metabolic rate in the thalamus derived from the same period. The data also indicate that although no group differences were found in the mean or variance of whole head alpha power, thalamic $rCMR_{glu}$, or $gCMR_{glu}$, there is



Figures 1–4. Anterior-to-posterior illustration of PET-MRI co-registration of thalamic ROI delineation. These figures present representative image planes in the coronal orientation for one participant. PET image planes are presented to the right of their corresponding co-registered (using AIR; Woods et al 1993) MRI plane. Figure 1 represents an anterior thalamic slice, Figures 2 and 3 represent more medial slices, and Figure 4 represents a posterior thalamic slice. Each actual ROI included data from 25 to 41 planes. Units of the PET color scale are in mg/100g/min.

no relation between thalamic $rCMR_{glu}$ and global alpha power in the depressed subjects. Despite the fact that alpha rhythms are generally more predominant during eye closure, there were no differences between the correlations for the eyes open and eyes closed conditions. This pattern of strong correlations between alpha power and thalamic $rCMR_{glu}$ in the control subjects and no correlation in the depressed group was observed even when the correlations were done separately for hemisphere, eyes open and eyes closed condition, or for frontal, central, and parietal regions. Moreover, for each set of correlations between alpha power and thalamic metabolic rate, significant differences were observed between the correlations for the controls and the patients.

Our finding of a relation in the control group is consistent with previous findings from our laboratory and

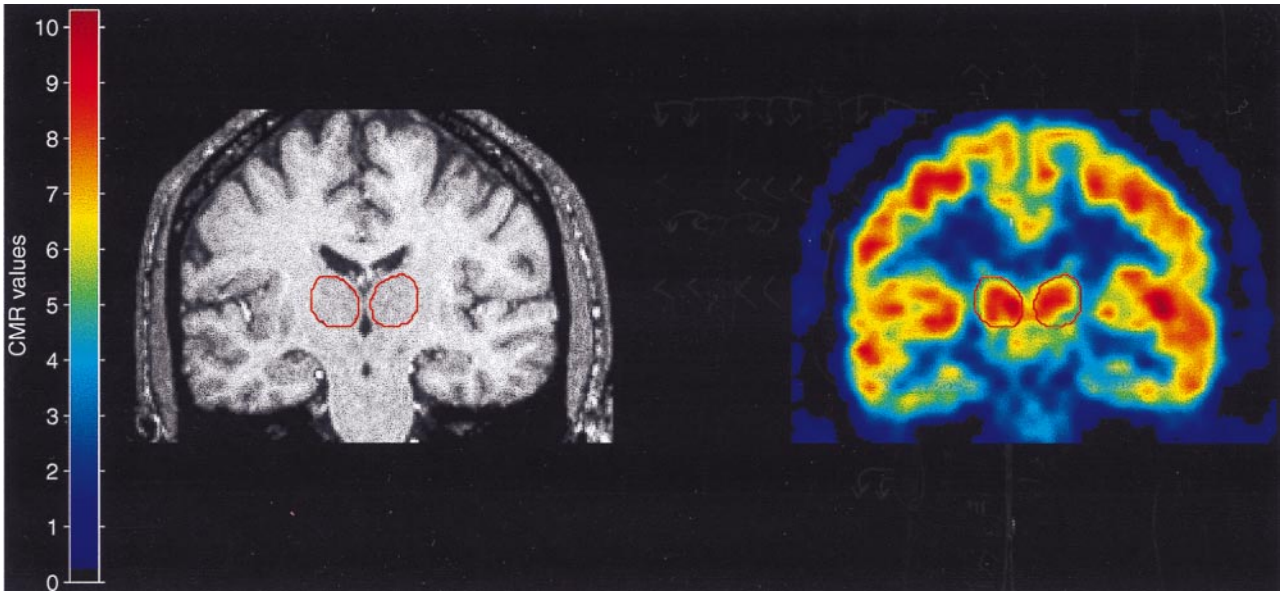


Figure 2.

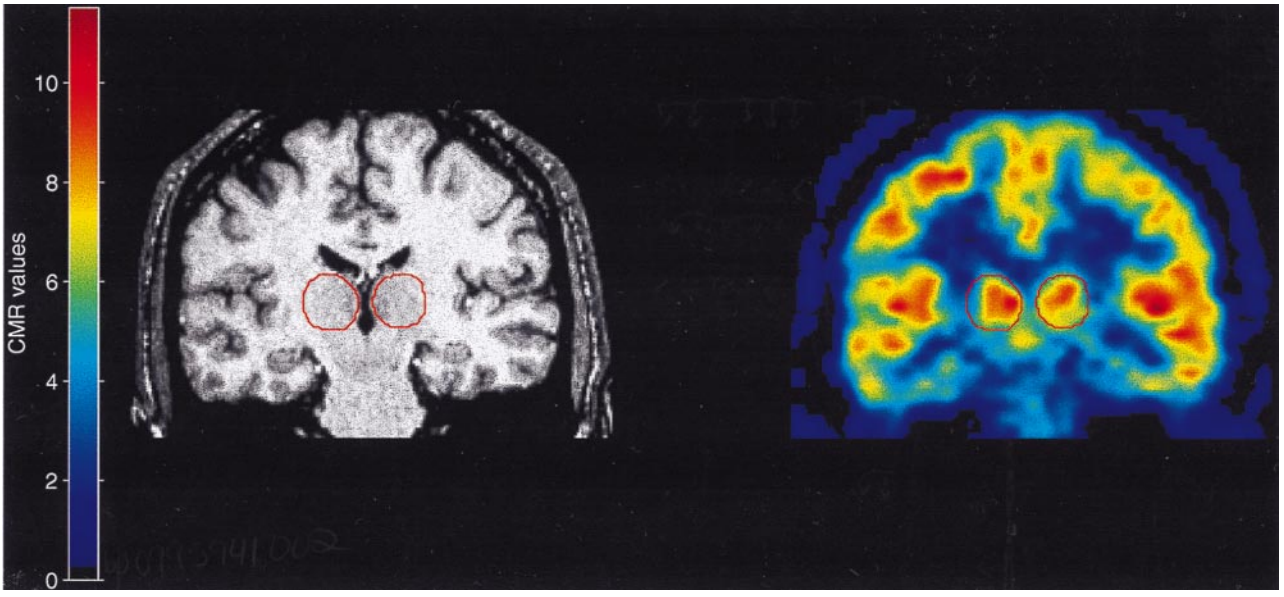


Figure 3.

others (Larson et al 1998; Steriade and Deschenes 1984; Steriade et al 1991a, 1991b) supporting the idea that the thalamus serves as a neuronal pacemaker of human alpha rhythms. The methodology adopted in our earlier study necessitated including all pixels from the entire brain volume in the correlation and using atlas-based coordinates for localizing the thalamus in stereotactically transformed brain images. Using this SPM method, we demonstrated that alpha EEG power is inversely correlated with an area of the brain that includes the thalamus. In the current study, the thalamus was individually identified for each participant using PET-MRI coregistration. MRI scans were co-registered to their corresponding PET scans and metabolic activity from the region of the thalamus extracted. This methodology allowed for correlation of average whole head alpha power with glucose metabolic activity from a region of the brain that included only the thalamus. Even with this more stringent method of analysis, a robust inverse correlation was demonstrated in the controls indicating that greater metabolic activity in the thalamus is associated with alpha suppression.

The lack of correlation observed in the depressed

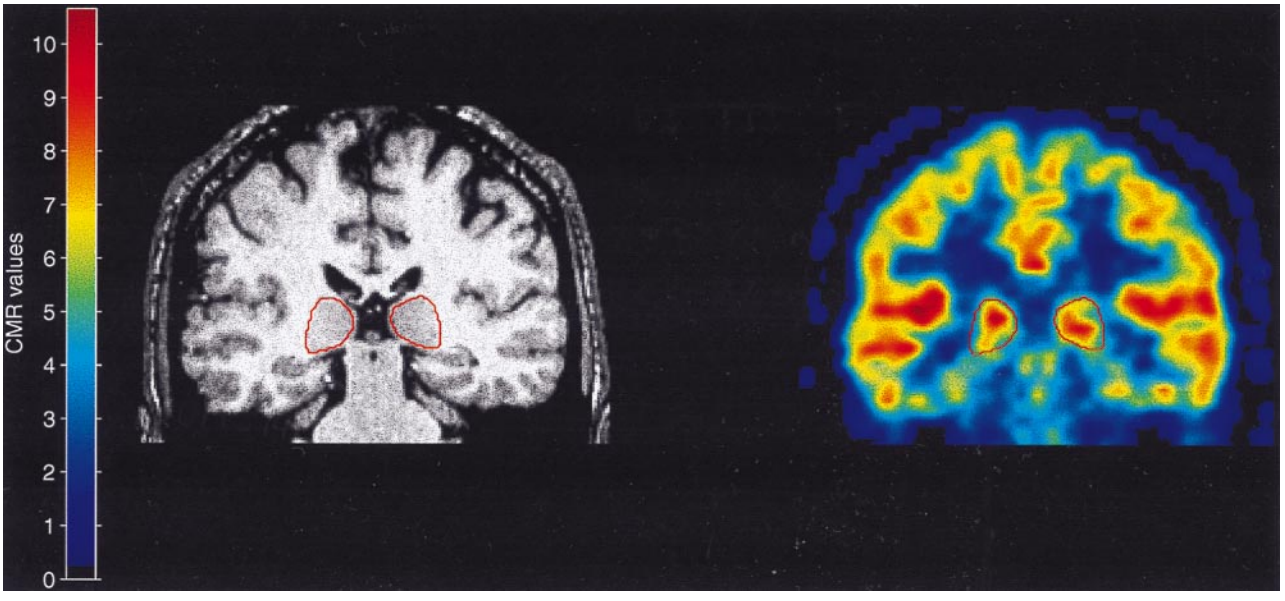


Figure 4.

Table 1. Global and Regional Metabolic Rate and Global Alpha Power Listed by Group

	Controls (n = 13)		Depressives (n = 18)	
	Mean	SD	Mean	SD
Metabolic Rate				
$gCMR_{glu}$	5.35	0.81	5.07	0.98
Absolute $rCMR_{glu}$				
Right thalamus	1.59	0.15	1.61	0.15
Left thalamus	1.59	0.12	1.62	0.16
Residualized $rCMR_{glu}$				
Right thalamus	0.00	0.73	0.00	0.55
Left thalamus	0.00	0.61	0.00	0.55
Global Alpha Power				
Eyes open	0.30	0.33	0.35	0.24
Eyes closed	0.89	0.30	0.83	0.25

Absolute $rCMR_{glu}$ and $gCMR_{glu}$ values are metabolic rate in mg/100g/min, and global alpha power values are power density in log μV^2/Hz.

patient data is not surprising when recent investigations of the complex neuroanatomic circuitry involved in depression are considered. Data from several sources suggest that anatomic circuits involving the frontal cortex, striatum, and thalamus are involved in the functional neuroanatomy of unipolar depression (Soars and Mann 1997; Afifi 1994; Cummings 1993; Drevets and Raichle 1992; Mayberg et al 1992; Drevets et al 1992; Folstein et al 1991; Swerdlow and Koob 1990, 1987; McHugh 1989). Using PET to examine cerebral blood flow in participants with familial pure depressive disease (FPDD), Drevets and Raichle (1992) obtained evidence of increased flow in the left prefrontal cortex, the left amygdala, and the left medial thalamus and decreased flow in the left medial caudate. In combination with previous evidence, they interpreted the data to suggest that the limbicothalamocortical circuit may be engaged in abnormal reverberatory activity that maintains the fixed cognitive and emotional set of depression.

This interpretation is compatible with the neural model of depression proposed by Swerdlow and Koob (1987). They suggest a limbicocorticostriatopallidothalamic circuitry comprised of three "feedback loops." One of these loops, the corticothalamocortical loop, serves to primarily maintain a continuous stream of cognitive thought and emotional impulses, achieved through positive feedback. A second positive feedback loop consisting of the cortex, nucleus accumbens, pallidum, and thalamus is also capable of exciting the corticothalamocortico loop through inhibition of an inhibitory input. The third loop in this circuitry consisting of the nucleus accumbens, pallidum, and tegmentum is a negative feedback loop, which provides a means to disrupt or switch the ongoing activity of the corticothalamocortical loop. Swerdlow and Koob (1987) predict that disruption in any of these integrative circuitry loops would result in severe disturbances in cognitive or emotional processes. They propose that enhancement of the corticothalamocortical positive feedback loop would most likely result in the perseveration of a fixed set of cortical activity, manifested by the emotional, cognitive, and motor processes of depression.

These observations suggest that dysfunction at multiple points within this system may give rise to depression. Imbalances within these circuits, rather than overall increased or decreased synaptic activity within a particular

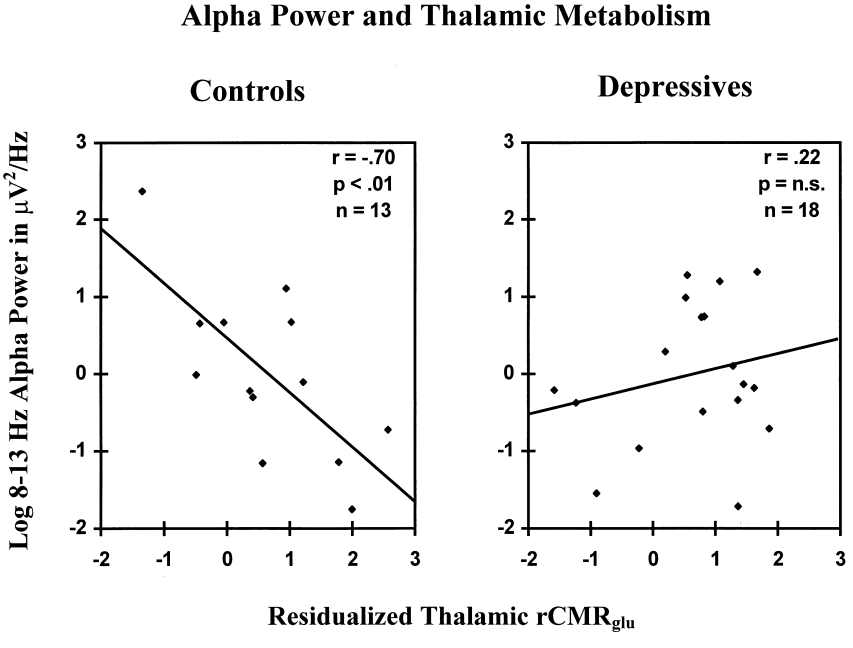


Figure 5. Scatterplots of the correlation between residualized thalamic $rCMR_{glu}$ and global alpha power in the control and depressed groups. Thalamic $rCMR_{glu}$ is presented as an average of the left and right hemispheres.

Table 2. Correlations Between Average Alpha Power (8 to 13 Hz) and Thalamic Metabolism by Group

	Controls ($n = 13$)		Depressives ($n = 18$)	
	Right	Left	Right	Left
Whole head correlations	−0.68[a]	−0.70[a]	0.20	0.23
Hemispheric correlations				
Right hemisphere	−0.70[b]	−0.71[b]	0.03	−0.02
Left hemisphere	−0.71[b]	−0.71[b]	0.03	−0.01
Regional correlations				
Frontal sites	−0.65[b]	−0.67[b]	0.18	0.23
Central sites	−0.73[b]	−0.74[b]	0.25	0.30
Parietal sites	−0.69[b]	−0.70[b]	0.19	0.23
Condition correlations				
Eyes open	−0.62[a]	−0.60[a]	0.24	0.25
Eyes closed	−0.71[a]	−0.74[a]	0.18	0.22

All correlations are significantly different between depressives and controls ($p < .05$).
[a] $p < .05$.
[b] $p < .001$.

structure, may be associated with depression (Drevets et al 1992). In light of these data underscoring the importance of functional neuroanatomic circuitry, the lack of relation between thalamic metabolic activity and global alpha power in the participants suffering from depression is better understood. If the thalamus is to impose its control over cortical alpha rhythms via thalamocortical connections, depression-associated disruption in these connections could potentially impede that control, resulting in a loss of correspondence between the thalamus and cortex. In other words, depression-associated disruption in the thalamocortical circuit itself or its excitatory and/or inhibitory inputs may be responsible for the lack of relation between thalamic metabolic activity and cortical alpha power observed in our depressed patient data.

While recent research has demonstrated thalamocortical relations exist in human subjects, this is the first study to report on differences in this relation in depressed and control participants. It must be noted that although the depressed and control groups were matched in gender (roughly 50% women) and race (100% Caucasian), other potentially influential factors such as health related practices were not measured or taken into account (e.g., smoking status). It must also be underscored that the effects we describe were obtained in the "resting" state. It will be of interest in future studies to use measures of thalamic functional activity that provide increased temporal resolution (e.g., PET-derived measures of blood flow; fMRI) to determine if the absence of an inverse relation between EEG alpha power and thalamic activation observed in the present study in depressed patients, varies with shifts in affective or cognitive processing or in clinical state. The functional consequences of this abnormal pattern of thalamocortical function also requires further study.

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