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Cingulate function in depression: a potential predictor of treatment response

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THE relationship between pretreatment regional cerebral glucose metabolism and eventual antidepressant drug response was measured using positron emission tomography (PET) in hospitalized patients with unipolar depression. Rostral anterior cingulate metabolism uniquely differentiated eventual treatment responders from non-responders. Hypometabolism characterized non-responders when compared with controls, in contrast to responders who were hypermetabolic. Metabolism in no other region discriminated the two groups, nor did associated demographic, clinical or behavioral measures, including motor speed, cognitive performance, depression severity or illness chronicity. Cingulate hypermetabolism may represent an important adaptive response to depression and failure of this response may underlie poor outcome. A critical role for rostral cingulate area 24a/b in the limbic-cortical network involved in abnormal mood states is proposed.

Key words: Cingulate; Depression; Limbic; Metabolism; PET; Prognosis

Introduction

This study evolved from two converging but unresolved lines of evidence from studies of patients with depression. First, there is the repeated clinical observation that while generally treatable, a significant number of depressed patients fail to improve with standard treatment, and there are no reliable neuropsychological, biochemical, or hormonal predictors of this response failure.[1] Second, while functional brain imaging has been used to study patients with depression, and abnormalities have been described in frontal (dorsal prefrontal) and to a lesser extent limbic (amygdala, cingulate), paralimbic (ventral-orbital frontal, anterior temporal) and subcortical (basal ganglia, thalamus) regions, there is clear variability among studies.[2–5] The incongruities in the published literature are more than casual, as increases, decreases and absence of change in regional flow or metabolism have all been reported. Both clinical and technical factors, including differences in classification criteria, disease subtypes, medication status, illness severity, disease chronicity, imaging methods, behavioral conditions during scanning and heterogeneity of associated clinical symptoms such as anxiety, motor slowing or cognitive impairment, have been proposed to explain this variability. There is not yet a consensus, however. This study hypothesed that differences in eventual treatment response is a major source of the limbic and paralimbic metabolic variability seen in positron emission tomography (PET) studies of patients with depression. This was tested by examining pretreatment regional metabolism as a function of treatment outcome.

Patients and Methods

Patient selection: Unipolar depressed patients with symptoms requiring hospitalization and treatment with antidepressant medications were recruited. The clinical diagnosis of major depression was made by two independent psychiatrists using DSM-IIIR criteria. Patients with cerebrovascular risk factors or a previous stroke, documented head trauma or neurodegenerative disorders, other Axis I psychiatric diagnoses, or evidence of global cognitive impairment were excluded, as were patients with psychotic symptoms, alcohol or substance abuse, or recent electroconvulsive therapy. Eighteen depressed patients (15 men, 3 women; mean age 45 ± 12 years) meeting

these criteria were identified. Fifteen non-depressed volunteers (12 men, 3 women; mean age 38 ± 11 years) with normal neurological and psychiatric histories and examinations were also enrolled. Written informed consent was obtained from all subjects, and the experiment was conducted as approved by the University of Texas Health Science Center's Institutional Review Board.

Imaging studies: Regional cerebral glucose metabolism was measured in patient and control subjects using 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) and PET. All subjects were scanned under identical conditions: supine, awake, in the resting state with eyes closed and ears uncovered.[5] A 5 mCi dose of FDG was injected i.v., with image acquisition beginning after 40 min (GE/Scanditronix 4096 camera; 15 parallel slices; 7 mm center-to-center inter-slice distance; attenuation correction with 68Ge/68Ga transmission scans; final reconstructed resolution in-plane of 8 mm, FWHM). Absolute glucose utilization rate was not measured. An anatomical magnetic resonance imaging (MRI) scan was also acquired in each subject for the purposes of spatial transformation of the PET data, region of interest analysis and parametric image display (Elscint Gyrex 2T-DLX; 3D-GRASS sequence: TR = 33 ms; TE = 12 ms; flip angle = 60°; 256 × 256 × 127 volume, spatial resolution of 1 mm^3).

Baseline evaluation and treatment response assessment: On or within one day of the PET study, a standardized behavioral test battery[6] and the Hamilton Rating Scale for Depression (Ham-D) were performed on all subjects to assess mood, anxiety, motor speed and cognitive performance. These data were used to examine directly the relationship between regional metabolic abnormalities and disease symptom heterogeneity, as well as to evaluate any potential interaction between clinical characteristics and treatment response.

Following the PET study, antidepressant treatment was initiated in all patients. Drug response was assessed with a chart review at 6 weeks. Non-responders were defined by an extended hospital stay, need for re-hospitalization, physician notes describing deterioration in clinical symptoms, or need for supplemental medications. A subset of patients also participated in an in-patient treatment study which included a pre- and post-treatment Ham-D assessment. Responders identified by chart review all had at least a 45% drop in this measure.

Data analysis: Two independent statistical methods were used to assess regional metabolic differences between responders, non-responders and controls: a hypothesis-driven, region of interest (ROI) analysis and a pixel-by-pixel, ROI-free image subtraction strategy. Both analyses were performed, using in-house software, following spatial transformation of PET and MR images into proportional bi-commisural coordinate space[7] relative to the 1988 stereotaxic atlas of Talairach,[8] and global normalization of regional tissue uptake of FDG to whole brain mean relative cerebral metabolic rate for glucose (rCMRGlc) scaled to an arbitrary mean of 1000. Finally, value and spatially normalized images were interpolated trilinearly, resampled (60 slices, 8 mm^3 voxels) and gaussian filtered to a final resolution of 8.7 mm (FWHM) prior to statistical analysis.

For Method 1, a mixed design, repeated-measures analysis of variance was used to evaluate the effects of group (control, responders, non-responders), hemisphere (right, left) and region (rostral anterior cingulate (Brodmann areas 24a/b), basal ventral frontal (BA 10/11/47), anterior insula, anterior-inferior temporal (BA21/38), dorsal lateral prefrontal (BA 9/10/46), inferior parietal (BA 40) and striatum) with *post hoc* Fisher's protected least-significant difference tests to characterize significant interactions. Using coordinates defined in the Talairach atlas for inclusion in gray matter, a standardized set of brain regions (ROI size = 128 mm^3) sampled by Brodmann area on each subject's MRI and PET scans were first identified. For the ANOVA, these Brodmann regions were secondarily collapsed into seven functional groupings based on human and primate definitions of limbic, paralimbic and neocortical brain regions as used in our previous depression studies.[5]

For Method 2, a statistical parametric image (SPI) analysis was performed using a pixel-by-pixel group mean subtraction strategy to avoid the potential bias introduced by the ROI method, where critical areas may have been undersampled, or functional groupings may have been overly inclusive. Spatially normalized data from each subject were averaged by group. Grand-mean images for each group (all depressed patients, depressed responders and depressed non-responders) were compared with controls, creating three group-mean subtraction images. For each of the three difference images, omnibus significance was tested using change distribution analysis.[9] When significant, subtraction images were converted to statistical parametric images of z-score maps based on the variance of all local changes within the images. Locations of local maximal and minima exceeding a z-score of 1.96 (two-tailed $p < 0.05$) are listed in table 1, with the peak voxel (search cube volume = 125 mm^3) of each local maximal/minima point described in x-, y- and z-coordinates as mm relative to the anterior commissure.

Table 1. Baseline clinical measurements

	Responders ($n = 8$)	Non-responders ($n = 10$)	Controls ($n = 13$)
Present illness duration (weeks)	23 ± 19	16 ± 18	–
Depressive episodes (lifetime number)	2.6 ± 2	2.7 ± 1.4	0
Hamilton Depression Scale	29 ± 3	28 ± 7	NA
Spielberger State Anxiety Scale	58 ± 11	51 ± 14	NA
Stroop word–color time (s)	82 ± 19	79 ± 18	61 ± 13[a]
Trails B time (s)	75 ± 15	83 ± 42	55 ± 13[a]
Minnesota Rate of Manipulation (s)	50 ± 11	56 ± 17	39 ± 5[a]

Values are mean ± s.d. NA = not assessed.
[a]Non-responders + responders *vs* controls, $p < 0.01$. Responders *vs* non-responders, NS.

Results

Clinical response: At the time of the PET study, all patients had a Ham-D score ⩾ 20. Thirteen patients were either naive to medication or medication-free for a minimum of 2 weeks; five had been newly started on antidepressant medication within days of the scan session. After 6 weeks of therapy, eight patients met the criteria for a therapeutic response, 10 did not. All patients were treated with a single medication. Thirteen patients were treated with a selective serotonin reuptake inhibitor; five received either a tricyclic or bupropion. There were no significant differences between responders and non-responders in age, gender, illness duration, number of previous episodes, past-medication use, suicidality or baseline measures of mood severity, motor slowing or cognitive impairment (MANOVA), although depressed patients as a whole showed performance deficits on a subset of tests compared with healthy controls (Table 1).

Scan results: Metabolism in rostral anterior cingulate (BA 24a/b)[10] uniquely differentiated eventual treatment responders from non-responders, using both the pixel-by-pixel parametric approach (Table 2) and regional ANOVA (response × region interaction $F(2,12) = 2.04$; $p = 0.024$; *post hoc* $t = 3.09$, $p < 0.008$). Responders were hypermetabolic (24a/b mean rCMLGlc = 1270 ± 70) and non-responders hypometabolic (1134 ± 111) compared with controls (1198 ± 85; Fig. 1). No other brain region showed this inverse pattern in responders and non-responders relative to controls. Responders and non-responders did show clear differences however, in the magnitude and extent of bilateral dorsal lateral prefrontal (BA 45/46/9), premotor (BA 44), basal-ventral frontal (BA 47) and anterior insula hypometabolism (Table 2, images not shown). While the ANOVA demonstrated no significant lateralized effects (response × region × hemisphere interaction $F(12,180) = 0.65$, $p = 0.80$; rCMLGlc: responders right (R) Cg = 1271 ± 81, left (L) Cg = 1268t ± 82; non-responders R-Cg = 1123 ± 108, L-Cg = 1144 ± 138; controls R-Cg = 1193 ± 106, L-Cg = 1203 ± 84), the SPI analysis demonstrated the cingulate changes to be right lateralized, a finding also not seen in other regions.

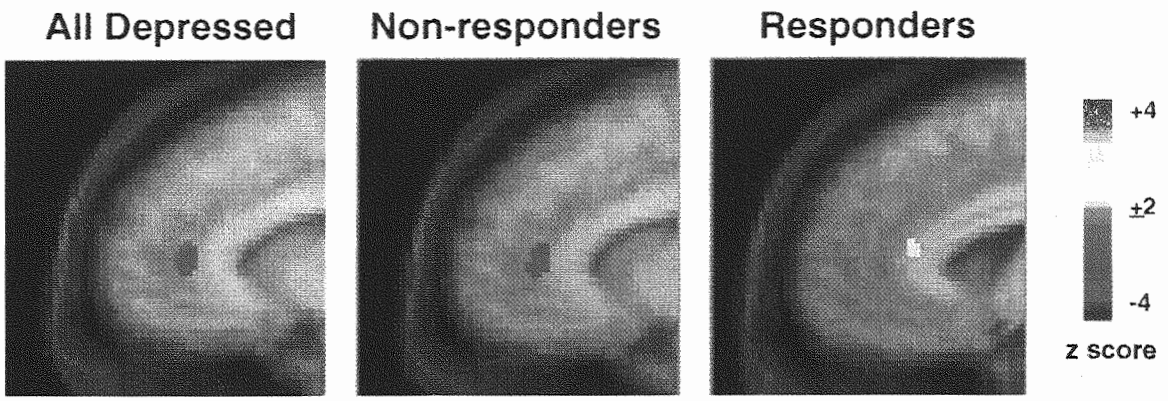

FIG. 1. Positron emission tomography/magnetic resonance imaging superimposition, sagittal view. z-score maps demonstrating differences in direction, magnitude and extent of changes seen in rostral cingulate glucose metabolism (BA 24a/b) in the three groups of depressed patients compared with healthy controls. Cingulate hypometabolism (negative z-values, shown in green) characterized the non-responder group in contrast to hypermetabolism (positive z-values, shown in yellow) seen in the eventual treatment responders. Table 2 lists the coordinates of local cingulate maxima and minima.

Table 2. Location of significant differences in regional glucose metabolism identified in depressed patient groups relative to healthy controls identified using statistical parametric image analysis.

Region	BA	Side	All depressed				Responders				Non-responders			
			Coordinates[a]			z-value	Coordinates[a]			z-value	Coordinates[a]			z-value
			x	y	z		x	y	z		x	y	z	
Ant cingulate	24a/b	R	12	40	10	−2.96	1	44	10	+2.10	10	38	12	−3.21
Post cingulate	29/30	R	4	−40	18	−2.87	14	−48	12	−4.09				
Ant insula		L	−28	18	10	−3.24	−32	24	12	−2.68	−30	16	8	−3.44
		R	30	16	10	−3.84	32	24	10	−4.70	32	12	7	−2.19
		L									−38	4	2	−2.00
		R									42	6	4	−3.75
Ventral frontal	47	L									−32	32	−6	−2.17
	47	R									44	30	−6	−2.44
Premotor	44	L	−36	4	28	−4.78	−34	0	30	−3.06	−36	4	28	−5.02
	44	R	42	4	28	−3.10					44	6	26	−3.46
Dorsolateral	45/46	L	−44	18	14	−2.24	−34	38	14	−2.35	−43	20	18	−1.98
Prefrontal	45/46	R	40	24	22	−2.40	44	40	8	−2.55	42	24	22	−2.10
	46/9	L	−34	22	28	−2.49					−32	20	26	−2.33
	46/9	R	28	34	26	−3.26	27	22	30	−2.20	26	34	26	−3.48
Inf parietal	40	L	−42	−50	28	−3.99	−42	−48	28	−3.33	−42	−50	28	−3.35
	40	R	44	−46	28	−3.68	46	−44	28	−3.62	44	−46	30	−2.64
Inf temporal	21	L	−46	−38	2	−2.8	−48	−38	2	−2.5	−46	−38	0	−2.1
	21	R	46	−34	−4	−3.2	46	−50	−2	−3.0	46	−34	−2	−3.8

Coordinates, mm relative to anterior commissure: x: right (+)/left (-); y: ant (+)/post (-); z: sup (+)/inf (-)
z-scores: $|z| > 1.96$, $p < 0.05$ (two-tailed); $|z| > 2.6$, $p < 0.01$; $|z| > 3.3$, $p < 0.001$; $|z| > 3.9$, $p < 00001$.

No other measured clinical variable could account for this response-predictive change in rostral cingulate metabolism, including the number of previous depressive episodes, duration of present illness, time of initiation of drug treatment relative to the PET scan, or medication type. Furthermore, rostral anterior cingulate metabolism did not correlate with depression severity, or measurements of anxiety, cognitive performance or motor speed. No endocrine or biochemical markers were examined.

Discussion

As first suggested by Broca, and later Papez, Yakovlev and MacLean,[11] the cingulate gyrus is recognized for its role in the integration of emotional behaviors. Modern comparative cytoarchitectural and connectivity studies have further characterized segregated, but interactive, pathways linking different subdivisions of the cingulate with specific brain stem, subcortical, paralimbic and neocortical target sites.[10,12–15] These functional connections are supported by behavioral literature which implicates a rostral-caudal and dorsal-ventral division of labor.[16] Parallel anatomical and imaging studies[17,18] further demonstrate that posterior cingulate regions are preferentially involved in sensorimotor and visual-spatial processing: anterior zones participate in autonomic, affective, and motivational behaviors (rostral and ventral regions), and pain perception, attention to action and response selection (dorsal regions).

The specific changes observed in this study in rostral anterior cingulate (BA 24a/b) are of particular interest because this region has unique reciprocal connections not only with dorsal anterior cingulate, but also with selective dorsal neocortical (lateral prefrontal) and ventral paralimbic (insula, basal frontal) regions. These rostral cingulate projection sites are the same areas where metabolic changes were seen in this study across the entire depressed patient group, and also in the majority of previous studies.[2–5] The finding that metabolic activity in the rostral cingulate discriminates eventual responders from non-responders suggests that this area may function as a bridge linking dorsal and ventral pathways necessary for the normal integrative processing of mood, motor, autonomic and cognitive behaviors, all of which are disrupted in depression. The fact that responders and non-responders show an inverse pattern compared with controls further suggests that an adaptive hypermetabolic change in the rostral cingulate may be required to facilitate response to treatment, a compensatory response not present in the non-responder group.

Neurochemical mechanisms that can account for these selective but divergent metabolic changes in the rostral cingulate are more circumstantial. While there is a large literature describing changes in a variety of monaminergic and peptidergic markers in depression, there has been little focus on the target regions identified in this or previous imaging studies.[19–21] There is, however, clear evidence of both direct and indi-

rect monoaminergic modulation of intrinsic cingulate neurons and their afferent and efferent projections, although regional specificity within the cingulate has not been fully examined.[22] Changes in anterior cingulate function and neuroreceptor markers have also been reported using functional imaging following treatment with antidepressant medications, electroconvulsive therapy and sleep deprivation.[23–25] The direction and precise localization of changes has been variable, and reported findings generally involve dorsal rather than rostral cingulate regions. Mechanisms that might explain these results is an ongoing area of basic research.[26]

The logical inference from the data presented in this report is that rostral cingulate metabolism has value as a prognostic marker in actively depressed patients. There are however, several unresolved issues. While 6 weeks is a standard endpoint in studies of drug response, it is common for patients to show only partial resolution of depressive symptoms over this time, and some patients may require a longer time for a maximum therapeutic effect. It is possible that some of the non-responders would have eventually improved with higher medication doses or a change in drug class. The standard deviation was, in fact, greater in the non-responder group, consistent with this proposition. The time course of these changes and the contribution of disease chronicity also are unknown. It should be noted however, that cingulate metabolism in first episode depressives was no different from that seen in patients with multiple episodes in either the responder or non-responder group. Prospective longitudinal studies of new onset and chronic patients may help clarify these issues.

Conclusion

This study identified selective metabolic changes in the rostral anterior cingulate (BA regions 24a/b) that predicted eventual treatment response in a clinically homogeneous group of unipolar depressed patients. We propose a central role for this region in the normalization of cortical and paralimbic dysfunction that accompanies recovery from depression. Failure of this adaptive response may underlie poor outcome, and presence of this metabolic signature in individual patients may prove useful in identifying those at risk for a difficult disease course.

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General Summary
Brain glucose metabolism was measured using positron emission tomography in a group of acutely ill patients with depression. To test the hypothesis that specific metabolic patterns can predict the response of depressed patients to antidepressant medication, baseline metabolism was examined in separate groups of responders and non-responders. In both groups, decreases were found in frontal, insula, and parietal regions, consistent with previous reports. In contrast, metabolism in the rostral anterior cingulate uniquely distinguished the two groups. Patients with high pretreatment cingulate metabolism went on to show a good response, while those with low metabolism remained significantly depressed after 6 weeks of treatment. These results focus attention on the role of the rostral cingulate in brain circuits required for recovery from depression. Additional studies will be required to test the clinical utility