Two-dimensional Proton Echo-Planar Spectroscopic Imaging of Brain Metabolic Changes During Lactate-Induced Panic

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Background: A fast, proton echo-planar spectroscopic imaging (PEPSI) technique, capable of simultaneously measuring metabolites from multiple brain regions, was used to investigate the anatomical distribution and magnitude of brain lactate responses to intravenous lactate infusion among subjects with panic disorder and control subjects.

Methods: Fifteen subjects with panic disorder and 10 control subjects were studied. All subjects were medication free and met DSM-IV criteria for panic disorder, or, for controls, no Axis I psychiatric disorder. Two-dimensional axial metabolite images having 1-cm³ spatial resolution were acquired at 6 1/2-minute intervals during 3 conditions: a 20-minute baseline, 20-minute 0.5-mol/L sodium lactate infusion, and 15-minute postinfusion period.

Results: Intravenous lactate infusion increased brain lactate levels throughout the axial brain section studied in all subjects. Panic-disordered subjects had significantly greater global brain lactate increases in response to lactate infusion. Lateralization of brain lactate response did not occur, nor were discrete regional loci of elevated lactate observed. Cerebrospinal fluid lactate changes corresponded to lactate changes in brain tissue. Severity of symptoms provoked by lactate infusion did not directly correlate with brain lactate response.

Conclusions: Greater overall rises in brain lactate among subjects with panic disorder compared with controls occurred in response to lactate infusion. We were unable to detect a distinct regional pattern for magnitude differences in brain lactate rise by which to identify a specific neuroanatomical substrate underlying a lactate-induced panic response. The wide anatomical distribution of these brain lactate increases suggest metabolic and/or neurovascular mechanisms for the abnormal rise in subjects with panic disorder.

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INDIVIDUALS with panic attacks have a specific vulnerability to precipitation of acute anxiety and/or physiological arousal by intravenous sodium lactate infusion. Despite extensive investigation, mechanisms underlying this lactate sensitivity remain undetermined. One theory, that patients with panic disorder could be reacting to the effects of elevated brain lactate as a possible mechanism for lactate-induced panic, was postulated on the basis of study results in monkeys that directly measured lactate rises in cisternal fluid during intravenous lactate infusion. To address this proposed relationship between lactate-induced panic and elevated brain lactate, a newly emerging technology, magnetic resonance spectroscopy (MRS), has been used to noninvasively measure brain lactate changes during lactate infusion. Magnetic resonance spectroscopy studies of rats and healthy human controls demonstrate progressive brain lactate rises in response to lactate infusion. These increases in brain lactate levels during lactate infusion occur in subjects with panic disorder and are of greater magnitude and longer duration than in control subjects.

To date, most in vivo human MRS studies have used single-voxel MRS techniques that provide good time resolution but allow only a single predetermined region of interest (ROI) in the brain to be studied at one time. In previous single-voxel MRS studies, a large anatomical area (27 cm³) encompassing the insular cortex and adjacent regions, was chosen to be sampled on the basis of positron emission tomography studies indicating distinct blood flow abnormalities in that region among lactate-sensitive subjects with panic disorder. However, misinterpretation of extracranial signal artifact subsequently led to the retraction of those positron emission tomographic findings in panic disorder. Thus, it remains uncertain whether lactate abnormalities detected among patients with panic disorder are specific to the insular cortex or are representative of diffuse metabolic abnormalities. To address this
SUBJECTS AND METHODS

SUBJECTS

Fifteen subjects with panic disorder (7 men and 8 women) aged 33.1 ± 11.7 years (all values are mean ± SD), and 10 healthy control subjects (4 men and 6 women) aged 32.7 ± 7.4 years were studied. All subjects completed the study with the exception of 1 subject with panic disorder who stopped the study 10 minutes into the lactate infusion due to urinary urgency in the midst of a panic response (data from this subject are included through the first lactate infusion time point). In addition, incomplete MRS data sets were obtained for 3 subjects with panic disorder (2 with panic response to lactate infusion [panic responder] and 1 without panic response to lactate infusion [panic nonresponder]) and 1 control subject due to scanner malfunction.

All subjects were medication free for at least 1 month and were fasting at the time of MRS evaluation. Subjects with panic disorder had a diagnosis of panic disorder by structured psychiatric interview consistent with DSM-IV criteria, were free of other Axis I psychiatric diagnoses, and were actively experiencing panic attacks. Control subjects had no history of an Axis I psychiatric disorder. All subjects gave written informed consent for participation in the study, which was approved by the University of Washington Human Subjects Review Committee.

INFUSION PROTOCOL

Following insertion of an intravenous catheter by an experienced anesthesiologist, subjects were moved to the Diagnostic Imaging Sciences Center and placed in the supine position into the scanner for the lactate infusion protocol. After optimization of imaging parameters (see below), a 20-minute baseline period was followed by intravenous infusion of 0.5 mol/L sodium lactate over 20 minutes (10 mL/kg total), followed by a 15-minute recovery period. At baseline and immediately following study completion, the Acute Panic Inventory (API), a panic severity rating scale (0-10; 0 = no panic, 10 = extreme panic) and anxiety severity rating scale (0-4; 0 = no anxiety, 4 = extreme anxiety) were administered to subjects. A carbon dioxide monitor (Puritan Bennett, Los Angeles, Calif) was used to continuously monitor end-tidal carbon dioxide (PETCO2) at baseline, during, and after lactate infusion.

We have demonstrated that the PETCO2–PaCO2 gradient within subjects is consistent under normal and hypocapnic conditions. In unpublished work (S.R.D. and A.A., 1994), sodium lactate infusion was found not to affect the PETCO2–PaCO2 gradient.

IMAGE ACQUISITIONS

PEPSI studies were performed by using a clinical 1.5-T Signa whole-body scanner equipped with Genesis version 5.4 operating system (General Electric Medical Systems, Milwaukee, Wis). An experimental receive-only bird cage coil designed and built at the University of Washington, Seattle, was used, which provided approximately 2 to 3 enhanced signal-to-noise ratio over conventional quadrature head coils (C.H., unpublished data, 1996). The coil incorporated a built-in head holder to immobilize the head during lactate infusion. High-resolution sagittal and axial T1-weighted magnetic resonance images were used for anatomical localization (repetition time, 600 milliseconds; echo time, 20 milliseconds; field of view, 23 cm; matrix, 256 × 128). An axial section at the level of the lateral ventricles was selected as the axial plane to be examined by PEPSI. This slice location was chosen to be consistent with prior single-voxel MRS studies of lactate infusion and hyperventilation. The PEPSI pulse sequence has been described in detail. Parameters used in data acquisition included echo time of 272 milliseconds, both to minimize lipid signal contribution and obtain an in-phase doublet of lactate, repetition time of 2 seconds to acquire partially relaxed spectra during signal acquisition; 32 × 32 spatial matrix; 22-cm field of view; 20-mm slice thickness; 32-kHz spectral width; 16 384 complex data points for frame size (32 spatial points convoluted with 512 spectral points with nominal voxel size of 1 cm), and 1.9-Hz/point spectral resolution; and 6 averages with acquisition of partial echoes to permit magnitude reconstruction. Following prescription and shimming, metabolic images were obtained during baseline (3 scans), lactate infusion (3 scans), and after infusion (2 scans).

IMAGE PROCESSING

Raw data traces from individual excitations were averaged, and separate even and odd echo data were combined.

RESULTS

Twelve of 15 subjects with panic disorder, but no control subjects, experienced a panic response to lactate infusion using criteria of sufficient API-rated symptoms to fulfill DSM-IV criteria for a panic attack and onset of moderate to severe feelings of panic that we have previously applied to studies of lactate infusion. Compared with control subjects, subjects with panic disorders showed significantly elevated API scores, and panic severity and anxiety severity scores at baseline and in response to lactate infusion, as shown in Table 1.

RM-ANOVA of PETCO2 levels found no significant difference in ventilatory response between diagnostic groups (group effect: F1,10 = 2.02, P = .17). PETCO2 levels did decrease over time in both groups (scan effect: F7,13 = 4.53, P < .001; ε = 0.43, GG-P < .001); however, no interaction was
Present (group × scan: \( F_{1,123} = 0.17, P = .99 \)). To investigate the concordance between brain lactate levels and \( P_{\text{ET}}\text{CO}_2 \) levels at each time point by group, correlational analyses were performed, which demonstrated an inverse relation at baseline and at completion of infusion (control group: \( r = -0.83, P = .02 \); panic group: \( r = -0.63, P = .04 \)) but not at other time points; this significance was lost with Bonferroni correction.

Sequential lactate and NAA images acquired from a subject with panic disorder who reacted to lactate are shown in Figure 2 and Figure 3. Representative spectra at baseline and at completion of infusion are shown in Figure 4. Data on NAA demonstrated no significant group effects (\( F_{1,18} = 1.04, P = .32 \)), scan effects (\( F_{7,126} = 0.73, P = .65 \)), or group × scan effects (\( F_{7,126} = 1.66, P = .12 \)).

Significant differences in brain Lac/NAA were observed between subjects with panic disorder and controls: group (\( F_{1,18} = 5.77, P = .01 \)), across scans (\( F_{7,126} = 12.09, P < .001; \ e = 0.24, \ GG\text{-}P < .001 \)), and group × scan (\( F_{7,126} = 2.70, P = .006; \ GG\text{-}P = .05 \)). Because lactate sensitivity may demarcate a specific subgroup of subjects with panic disorder who have metabolic abnormalities, and consistent with our analytic approach in prior MRS studies, we analyzed brain Lac/NAA changes among groups differentiated by lactate response. Comparison of subjects with panic disorder who panicked in response to lactate infusion (panic responders) with controls revealed significant differences: group (\( F_{1,16} = 8.12, P = .006 \)), across scans (\( F_{7,112} = 12.44, P < .001; \ e = 0.23, \ GG\text{-}P < .001 \)), group × scan (\( F_{7,112} = 3.32, P = .002; \ GG\text{-}P = .03 \), as shown in Figure 5. No significant differences were observed between panic nonresponders and controls (group: \( F_{1,9} = 0.02, P = .88 \)), across scans: \( F_{7,63} = 5.92, P = .001 \)), group × scan: \( F_{7,63} = 0.28, P = .96 \).

**STATISTICAL ANALYSES**

SPSS software (version 6.1.1; SPSS Inc, Chicago, Ill) was used for statistical analyses. Clinical rating scales were compared between diagnostic groups by independent \( t \) tests. Differences in \( P_{\text{ET}}\text{CO}_2 \) were compared by repeated-measures analysis of variance (RM-ANOVA). Additionally, correlational analyses between \( P_{\text{ET}}\text{CO}_2 \) and brain lactate levels were performed for heuristic purposes. RM-ANOVA also was used to compare group differences in global brain Lac/NAA across the 8 PEPSI acquisitions. For RM-ANOVA reaching significance, independent \( t \) tests using pooled variances were applied to compare signal Lac/NAA between diagnostic groups at each time point. Paired \( t \) tests were used to assess whether control and subjects with panic disorder showed a similar rate of lactate response during and after infusion. RM-ANOVA was used to compare regional Lac/NAA and lactate signal amplitude changes. One-way ANOVAs were used for post hoc comparisons. As previous work found significant brain lactate elevations among subjects with panic disorder, which forms the basis for this work, 1-tailed \( P \) values were used as a statistical criterion in analyses of whole brain lactate. For regional analyses, 2-tailed \( P \) values were used, as no a priori hypotheses were posited. Both unadjusted \( P \) values and Geisser-Greenhouse (GG)\textsuperscript{24}—corrected \( P \) values are reported for all RM-ANOVA, although homogeneity of variance was satisfied in the majority of analyses. For post hoc analyses, both uncorrected and Bonferroni\textsuperscript{25}—corrected \( P \) values are reported.
or panic nonresponders and panic responders (group: $F_{1,9} = 1.85, P = .21$; scan: $F_{7,63} = 3.38, P = .004$; group $\times$ scan: $F_{7,63} = 0.57, P = .78$). Because only panic responders were significantly different from controls, and in keeping with our past approach toward differentiating panic-disordered subjects by lactate response, panic nonresponders were excluded in subsequent analyses.

Independent $t$ tests revealed elevated brain Lac/NAA among panic responders, compared with controls, at the first baseline, during lactate infusion, and after infusion as shown in Table 2. When the Bonferroni correction for multiple tests was applied, group differences remained statistically significant at scans 5 and 6 during lactate infusion and after infusion at scan 8, with other time points indicating trend differences. To investigate whether controls and panic responders had similar rates of brain Lac/NAA rise in response to lactate infusion, paired $t$ tests were used to compare the averaged baseline lactate level to subsequent scans within diagnostic groups (Table 2). Control subjects demonstrated significantly elevated Lac/NAA on the last infusion scan and on both postinfusion scans compared with baseline. In contrast, panic responders demonstrated significant Lac/NAA elevations during the first lactate infusion scan and on all subsequent scans compared with baseline. When $t$ tests were corrected for multiple comparisons using the Bonferroni adjustment ($P < .01$ for significance), Lac/NAA rise did not reach significance on the first infusion and first postinfusion scan for panic responders. Even with this correction, panic responders demonstrated earlier brain Lac/NAA increases compared with controls.

To investigate whether brain Lac/NAA response was lateralized, ROIs in each hemisphere were pooled (lateralization effect) (Figure 1). Consistent with whole brain analyses, significant effects of group ($F_{1,37} = 10.94, P = .002$), scan ($F_{7,259} = 13.12, P < .001$; $\epsilon = 0.48$, GG-$P < .001$), and group $\times$ scan ($F_{7,259} = 2.68, P = .01$, GG-$P = .04$) were shown for this subset of combined brain regions. However, no significant lateralization effect ($F_{1,37} = 0.02, P = .90$) or interactions of lateralization by group or scan were demonstrated (all $F$ values $< 1.02$, $P$ values $>.20$).

To evaluate regional differences (region) in brain Lac/NAA response, RM-ANOVA was conducted on all ROIs,
excluding CSF regions, as shown in Figure 1. No significant region effects were demonstrated (all F values < 1.28, P values > .22). To maximize signal-to-noise ratio, scans were combined to provide an average baseline, average lactate infusion, and average postinfusion measure. Consistent with 2-dimensional axial brain results, significant group, scan, and group × scan effects were demonstrated (all F values > 11.14, P values < .001). Although no region (F16,252 = 1.35, P = .17) or group × region (F16,252 = 0.92, P = .55) effects were shown, a region × scan interaction was demonstrated (F12,306 = 1.49, P = .04; η = 0.81, GG-P = .06) as shown in Figure 6. One-way ANOVA comparing region × scan showed a significant baseline effect (F16,360 = 3.14, P < .001), accounted for by elevated lactate in the left frontal region (P < .05, Bonferroni corrected). Although, there was a significant infusion effect (F16,338 = 1.72, P = .04), no individual ROIs reached significance. There was no postinfusion effect by region (F16,320 = 0.84, P = .63).

We further compared CSF with other brain regions. Consistent with metabolite ratio analyses for averaged time points, group, scan, and group × scan effects were again demonstrated using absolute lactate signal intensity (all F values > 9.71, P values < .001). Consistent with regional results using metabolite ratios, no region (F18,273 = 1.18, P = .27) or group × region (F18,273 = 0.60, P = .90) effects were shown but there was a consistent region × scan interaction (F10,546 = 1.45, P = .05; η = 0.82, GG-P = .06). One-way ANOVA revealed baseline differences (F16,392 = 1.68, P = .04) that remained significant for the left frontal region (P < .05, Bonferroni corrected), but not regional differences during infusion (F18,369 = 0.95, P = .52) or after infusion (F18,348 = 1.18, P = .27), as shown in Figure 7.

Figure 3. Corresponding N-acetylaspartate (NAA) metabolic proton echo-planar spectroscopic images for the same subject in Figure 2, acquired every 6 1/2 minutes at baseline (3 scans, top), during lactate infusion (3 scans, middle), and after infusion (2 scans, bottom). These images demonstrate the stability of NAA levels across the experimental protocol.

Figure 4. A subset of characteristic spectra, acquired using proton echo-planar spectroscopic imaging, for a 3 × 3 voxel array from the left insular cortex region of a subject with panic disorder at baseline (left) and at completion of lactate infusion (right), which demonstrates the increase in lactate resonance (arrows). NAA indicates N-acetylaspartate; Cho, choline; and Cre, creatine.

Figure 5. Mean ± SD global brain lactate/N-acetylaspartate (NAA) metabolite ratio response for control subjects (n = 10), panic responders (subjects with panic disorder who had lactate-induced panic) (n = 12), and panic nonresponders (subjects with panic disorder who did not have lactate-induced panic) (n = 3). Partial data sets are included for 1 control, 2 panic responders, and 1 panic nonresponder due to system failure during lactate infusion. In addition, 1 panic responder discontinued the study following the first infusion scan.
The relationship between psychiatric symptom severity (API, panic, and anxiety scales) and whole brain Lac/NAA was evaluated at baseline and for maximal response to lactate infusion across all subjects with panic disorder and for panic responders without evidence of significant correlation (all r values < 0.33, P values > .20). To address whether left frontal region Lac/NAA elevations at baseline corresponded to baseline anxiety levels, we further evaluated this relationship for the above-noted symptom scales across all subjects and for subjects with panic disorder without evidence of significant correlation (all r values < 0.15, P values > .96).

COMMENT

Lactate elevations in control subjects and the greater lactate elevations exhibited by subjects with panic disorder in response to lactate infusion are widely distributed across a 2-dimensional axial brain section. This dynamic spectroscopic imaging study, by demonstrating the generalized nature of abnormal brain lactate increases among subjects with panic disorder, greatly extends our prior single-voxel MRS studies of lactate infusion.3,4 There did not appear to be any hemispheric lateralization, nor a discrete anatomical locus for metabolic response to lactate-induced panic. Furthermore, comparison of ventricles with other brain regions shows a similar time course for response, suggesting that brain lactate increases do not differentially reflect the CSF compartment. Consistent with results of prior single-voxel MRS lactate studies,6,7 subjects with panic disorder are well able to tolerate the combined stress of magnet confinement and lactate infusion and panic provocation.

Regional brain lactate increases can be detected in response to neuronal activation from sensory stimulation,12,26 and are thought to reflect decoupling of neuronal blood flow and energy requirements.7 There also is evidence of regional reductions of cerebral blood flow in the context of lactate-induced panic28 or a spontaneously occurring panic attack.29 On this basis, we might expect regionally specific magnitude differences in brain lactate elevation in response to lactate-induced panic. Although power issues may have limited our ability to detect regional differences, similar lactate rises in all regions indicate the diffuse nature of this effect. It is conceivable that administration of a large lactate load obscured small regionally specific lactate increases arising from neuronal activation related to a panic response. The 1-cm³ spatial reso-

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Scan No.</th>
<th>Controls, Mean (SD) Lac/NAA</th>
<th>Controls % Change From Averaged Baseline (Paired t)</th>
<th>Panic Responders, Mean (SD) Lac/NAA</th>
<th>Panic Responders % Change From Averaged Baseline (Paired t)</th>
<th>Independent t Controls vs Panic Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1</td>
<td>0.045 (0.005)</td>
<td>0.052 (.008)</td>
<td>0.053 (.009)</td>
<td>0.053 (.009)</td>
<td>t20 = 2.37, P = .01</td>
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<td></td>
<td>2</td>
<td>0.050 (0.007)</td>
<td>. . .</td>
<td>0.052 (.009)</td>
<td>. . .</td>
<td>t20 = .50, P = .63</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.049 (0.009)</td>
<td>. . .</td>
<td>0.053 (.009)</td>
<td>. . .</td>
<td>t20 = 1.11, P = .28</td>
</tr>
<tr>
<td>Lactate infusion</td>
<td>4</td>
<td>0.052 (0.007)</td>
<td>8 (t8 = 1.56, P = .16)</td>
<td>0.063 (.012)</td>
<td>21 (t20 = 2.06, P = .03)</td>
<td>t20 = 2.33, P = .02</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.053 (0.013)</td>
<td>10 (t8 = 1.47, P = .18)</td>
<td>0.077 (.007)</td>
<td>48 (t8 = 3.20, P = .006)</td>
<td>t20 = 3.17, P = .004</td>
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<tr>
<td></td>
<td>6</td>
<td>0.060 (0.013)</td>
<td>25 (t8 = 3.36, P = .005)</td>
<td>0.087 (.026)</td>
<td>57 (t8 = 3.77, P = .002)</td>
<td>t20 = 2.85, P = .006</td>
</tr>
<tr>
<td>After infusion</td>
<td>7</td>
<td>0.062 (0.012)</td>
<td>29 (t8 = 4.53, P = .001)</td>
<td>0.091 (.042)</td>
<td>75 (t8 = 2.56, P = .02)</td>
<td>t20 = 2.04, P = .33</td>
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<tr>
<td></td>
<td>8</td>
<td>0.059 (0.014)</td>
<td>23 (t8 = 3.05, P = .008)</td>
<td>0.084 (.025)</td>
<td>52 (t8 = 3.61, P = .004)</td>
<td>t20 = 2.59, P = .10</td>
</tr>
</tbody>
</table>

* Lac/NAA indicates lactate/N-acetylaspartate (metabolite ratio); ellipses, not applicable.

Figure 6. Regional analysis of lactate/N-acetylaspartate (NAA) response within discrete brain regions (mean ± SD) across averaged baseline, infusion, and postinfusion periods. Both subjects with panic disorder and control subjects are included as no differential group response by region was shown. For the majority of regions sampled, there was a rise in lactate level during and after lactate infusion. Some regions (ie, frontal lobe and cingulate) had reduced numbers of subjects with valid spectra due to lipid contamination and inhomogeneity effects.

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At baseline, lactate level in the left frontal region was elevated compared with other regions; however, there was no significant correlation with anxiety or arousal. As the frontal regions, in particular, suffer from susceptibility artifacts when using spectroscopic imaging techniques, this finding from the left frontal region must be viewed with caution until confirmed by further studies.

A lack of correlation between (1) API symptoms, (2) anxiety, panic severity, and brain lactate measurements at baseline, or (3) in response to lactate infusion suggests that brain lactate elevations are not directly related to symptom severity, although we are unable to account for possible threshold effects. There were insufficient numbers of panic nonresponders to show differences from controls or panic responders, although lactate insensitivity among these few panic-disordered subjects suggests clinical heterogeneity in the sample. As the study design did not include a placebo cell and no subjects panicked during the baseline period, we also are unable to address potential effects of generalized arousal on brain lactate findings. In this regard, prior work demonstrating greater brain lactate rises during controlled hyperventilation among subjects with panic disorder in remission who were previously lactate responders, although lactate insensitivity among these panic nonresponders to show differences from controls or possible threshold effects. There were insufficient numbers of panic disorder in remission who converted to a negative lactate response, indicates that symptom provocation, per se, is not a necessary requirement for abnormal brain lactate rises among subjects with panic disorder. Instead, a role for metabolic and/or neurovascular blood flow dysregulation is suggested by the widely distributed abnormal brain lactate rises observed in this study, that would be in keeping with results of prior reports of systemic lactate abnormalities associated with “anxiety neurosis” or panic disorder.

Although brain lactate and P_{CO2} levels were negatively correlated only in the postinfusion period, hyper-ventilation, among all subjects, undoubtedly contributed to brain lactate rise in response to lactate infusion. In conjunction with the similar overall decrease in P_{CO2} for both panic-disorder and control subjects during lactate infusion, hypocapnia can decrease the cerebral perivascular hydrogen concentration, resulting in cerebral vasoconstriction. Vasconstriction, in addition to its effects on lactate clearance, may increase lactate levels in 1 of 2 ways: first, by stimulating the release of the vasodilatory chemicals that normally counteract excessive vasoconstriction, and second, as a result of anaerobic metabolism of glucose (when excessive vasoconstriction causes areas of relative ischemia). As lactate itself is one of the chemical metabolic vasodilators released to antagonize cerebral vasoconstriction, if other vasodilatory mechanisms are more active in controls, they will antagonize hypocapnia-induced vasoconstriction and little stimulus for lactate release will be present. On the other hand, greater adrenergic nerve activity in subjects with panic disorder and increased cellular release of endothelin, endothelial-derived constricting factor, prostaglandins, thromboxanes, and leukotrienes, would accentuate vasoconstriction with resultant greater anaerobic metabolism and increased lactate production.

We were unable to measure T2 relaxation times (ie, spin-spin relaxation or transverse relaxation time) for lactate due to its low concentration at baseline and rapidly changing concentration during and after lactate infusion. It is conceivable that T2 relaxation time differences between NAA and lactate, within the context of diverse metabolic effects, such as pH changes during lactate infusion, could have affected our measurements using metabolic ratios. But, this is unlikely to have differentially affected measurements between diagnostic groups. Furthermore, assessment of absolute lactate signal also differentiated subjects with panic disorder from control subjects and demonstrated the same pattern of metabolic response to lactate infusion. It is possible that only a portion of brain lactate is being measured due to a bound component that is “magnetic resonance invisible,” but this
should only affect the relative signal-to-noise ratio for lactate measurement among all subjects and not affect the measurement of changes between groups over time.

Fast, spectroscopic imaging offers a powerful new tool for serially measuring brain chemistry using the intrinsic hydrogen signal of brain regions sampled. Our application using PEPSI to map the brain distribution of metabolic conditions during lactate precipitation of panic indicates that generalized or diffuse brain lactate elevations occur, with a time course and magnitude of rise between diagnostic groups consistent with findings of earlier single-voxel studies. In the present study, no temporal relationship between lactate changes and discrete neuroanatomical loci was found. Regional brain lactate measurements demonstrate that the brain lactate abnormality associated with lactate-induced panic is diffuse, opening up new directions of inquiry for understanding pathological mechanisms underlying panic disorder.

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