Mitochondrial Dysfunction as a Neurobiological Subtype of Autism Spectrum Disorder
Evidence From Brain Imaging

Suzanne Goh, MD; Zhengchao Dong, PhD; Yudong Zhang, PhD; Salvatore DiMauro, MD; Bradley S. Peterson, MD

**IMPORTANCE** Impaired mitochondrial function impacts many biological processes that depend heavily on energy and metabolism and can lead to a wide range of neurodevelopmental disorders, including autism spectrum disorder (ASD). Although evidence that mitochondrial dysfunction is a biological subtype of ASD has grown in recent years, no study, to our knowledge, has demonstrated evidence of mitochondrial dysfunction in brain tissue in vivo in a large, well-defined sample of individuals with ASD.

**OBJECTIVES** To assess brain lactate in individuals with ASD and typically developing controls using high-resolution, multiplanar spectroscopic imaging; to map the distribution of lactate in the brains of individuals with ASD; and to assess correlations of elevated brain lactate with age, autism subtype, and intellectual ability.

**DESIGN, SETTING, AND PARTICIPANTS** Case-control study at Columbia University Medical Center and New York State Psychiatric Institute involving 75 children and adults with ASD and 96 age- and sex-matched, typically developing controls.

**MAIN OUTCOMES AND MEASURES** Lactate doublets (present or absent) on brain magnetic resonance spectroscopic imaging.

**RESULTS** Lactate doublets were present at a significantly higher rate in participants with ASD (13%) than controls (1%) ($P = .001$). In the ASD group, the presence of lactate doublets correlated significantly with age ($P = .004$) and was detected more often in adults (20%) than in children (6%), though it did not correlate with sex, ASD subtype, intellectual ability, or the Autism Diagnostic Observation Schedule total score or subscores. In those with ASD, lactate was detected most frequently within the cingulate gyrus but it was also present in the subcortical gray matter nuclei, corpus callosum, superior temporal gyrus, and pre- and postcentral gyri.

**CONCLUSIONS AND RELEVANCE** In vivo brain findings provide evidence for a possible neurobiological subtype of mitochondrial dysfunction in ASD.
Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by disturbances in social interaction, communication, and behavioral flexibility. The diagnosis of ASD is at present based solely on behavioral phenotyping and its underlying etiology can be identified in only a minority of cases. An estimated 10% of ASD cases are associated with a known genetic syndrome (syndromic ASD) and the remainder, classified as primary or idiopathic ASD, have no clearly identifiable cause. A variety of genetic and environmental factors likely contribute to the notorious etiologic heterogeneity of this disorder.

Mitochondrial disease is an established cause of syndromic autism, generally believed until now to represent less than 1% of all cases of ASD. However, recent studies examining biomarkers of mitochondrial dysfunction obtained from peripheral or postmortem samples have detected impaired mitochondrial function in a much higher percentage of ASD cases. It is unclear whether these cases represent primary mitochondrial dysfunction or mitochondrial dysfunction secondary to other processes, such as increased oxidative stress. Moreover, peripheral markers do not necessarily represent in vivo disturbances in the brain. Thus, it remains unknown whether mitochondrial dysfunction is present in the brains of individuals with ASD and may play a role in its core cognitive and behavioral symptoms.

Three prior studies have used in vivo proton magnetic resonance spectroscopy to measure brain lactate, a marker of mitochondrial dysfunction in children with ASD. Lactate peaks were not detected at significantly higher rates in participants with ASD compared with controls. However, those studies had various limitations including small sample sizes; limited sampling of brain regions; averaging and potential dilution of lactate signal over large, heterogeneous regions of interest; reduced sensitivity due to low magnetic field strength (1.5 T); and data acquisition from a single volume coil rather than from multiple, more sensitive surface coils.

We acquired proton magnetic resonance spectroscopy data on a 3-T scanner to assess in vivo evidence of mitochondrial dysfunction directly in the brains of a large sample of children and adults with ASD.

Methods

Participants
Seventy-five individuals with ASD (simplex cases), aged 5 to 60 years, participated in this case-control study. They were recruited from child psychiatry clinics, schools, support groups, community events, and databases of research participants for other studies of ASD at our institution. The institutional review board of the New York State Psychiatric Institute approved the study and written informed consent was obtained from participants prior to their participation. For adult participants with ASD, an independent assessment of capacity to consent was conducted by a designated clinical monitor (a licensed psychologist or psychiatrist unaffiliated with the research study). If a participant was deemed by the monitor to lack capacity to consent, a participant-chosen surrogate then completed the consent process.

Each participant underwent a diagnostic evaluation by a psychiatrist, neurologist, or psychologist with expertise in the diagnosis of ASD. Diagnosis was made according to DSM-IV-TR criteria for autistic disorder (45%), Asperger disorder (32%), or pervasive developmental disorder not otherwise specified (23%). Assessments generally included the Autism Diagnostic Interview-Revised in children and the Autism Diagnostic Observation Schedule in children and adults. Exclusion criteria included identifiable genetic or metabolic abnormalities (eg, Fragile X, tuberous sclerosis complex, or known mitochondrial disease), a history of neurological injury (eg, cerebral ischemia, inflammation, infection, malignancy, status epilepticus, or perinatal or postnatal trauma), seizure activity during the 6 months prior to the magnetic resonance imaging (MRI) scan, medical contraindications to MRI scanning (including claustrophobia), or inability to cooperate with study procedures. A detailed list of current medications was recorded for every participant, with particular attention to those associated with mitochondrial toxicity (available on request). Dietary restrictions, the use of dietary supplements, and sleep habits were not routinely assessed.

Ninety-six typically developing controls matched by age and sex participated in the study. Controls were recruited from community-based telemarketing lists of households in the same geographic regions as the ASD cohort. A detailed clinical interview was performed that included the Kiddie Schedule for Affective Disorders and Schizophrenia for children or the Structured Clinical Interview for DSM-IV Axis I Disorders for adults. Individuals with a current or previous psychiatric or neurological disorder were excluded. Control participants were also screened using the Social Communication Questionnaire and Social Responsiveness Scale. All control participants scored below threshold for ASD on these instruments (Social Responsiveness Scale score cutoff, 70 for males and 65 for females; Social Communication Questionnaire score cutoff, 15 for both males and females). None of the control participants were taking prescription or over-the-counter medications; however, the use of dietary supplements was not assessed.

Each participant (or guardian) was asked to classify the participant’s race according to options defined by the investigator. Race was deemed to be relevant to this study because of differences in mitochondrial traits across races.

Participants were evaluated using the 4-subtest format of the Wechsler Abbreviated Scale of Intelligence. Intelligence testing was generally performed on the same day as the MRI scan and always occurred within 1 month of the MRI scan.

Magnetic Resonance Imaging
All magnetic resonance data were acquired on a 3-T whole-body scanner (GE Signa) equipped with an 8-channel surface coil for parallel imaging. Head positioning was standardized using canthomeatal landmarks. No sedation was used at any time during the study. Participants’ faces were monitored dur-
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Preprocessing Procedures | The entire raw data set acquired by the 8-channel coil was separated into subsets for individual coils. The k-space data for each individual coil were multiplied by a Hamming window function for spatial filtering, prior to spatial transform to suppress signal contamination stemming from the effect of the point-spread function. We applied a 2-dimensional fast Fourier transform to the data to transform it into image space on a slicewise basis. Water residues were removed using a high-pass filter. Time domain echoes were zero-filled to 2048 points, followed by application of a spectral fast Fourier transform to transform the time-domain echoes into the spectral domain. For spectral registration, we set the frequency of the singlet of N-acetylaspartate (NAA) (the CH$_3$ group) to 2.01 ppm. We then performed zero-order and first-order phase correction so that the 3 prominent singlets of NAA, creatine, and choline were all in absorption (real) mode.

MPSI Data Quality and Criteria for Exclusion | Participant MPSI data were deemed unusable if they met any of the following criteria:
- Signal-to-noise ratio (SNR) of NAA was less than 10 in the sensitive region of any single coil.
- Linewidth was broad, manifesting as overlapping creatine and choline signals (the value at which the peaks overlap was greater than 75% of the height of the lower peak) in more than 33% of the voxels in the sensitive region of the individual coil.
- Motion artifact was substantial, manifesting as overall low SNR, broad linewidth, the presence of a large water residue, and lipid contamination.

Using these criteria, 13 patient scans and 4 control scans were excluded from the study.

Rationale for Screening the Spectra of the Component Coils | We screened the spectra of individual coil components instead of the spectra combined across all coil elements for the following reasons: (1) The combination of the spectra of the coil array requires phase alignment across coils, a procedure that requires a reference signal. Although NAA is commonly used as a reference, we found that the SNRs of NAA varied widely across coils. The errors of the phases of NAA in low-sensitivity regions in some coils could be large because of the low SNRs of NAA, likely introducing phase errors in the combined spectra that could adversely affect our ability to detect lactate peaks, which are phase sensitive. When combining spectra in absolute mode, phase alignment is not necessary; on the other hand, the valuable phase information of lactate, one of the important criteria for the detection of lactate, is lost. (2) Different coils may fluctuate in their degree of lipid contamination because of their differing positions relative to the skull and the outer volume suppression bands. Therefore, screening the spectra of individual coil components may allow us to detect lactate in 1 coil that has no lipid contamination and avoid obscuring it by combining it with the spectrum from another coil that contains severe lipid contamination (eFigures 1, 2, 3, 4, 5, and 6 in Supplement).

Criteria for Defining Lactate Doublets | Each voxel (1-cm$^3$ volume, 900-1200 per brain) was visually inspected for the presence of a lactate doublet by 2 trained personnel and then confirmed by a senior spectroscopy expert (all blind to participant characteristics). Lactate doublets were identified using operational criteria that emphasize the fundamental properties of the lactate doublet (Figure 1):
- The central frequency of the doublet must have been in the range of 1.31 to 1.35 ppm.
- The doublet must have been inverted in phase-corrected real mode.
- The separation of the doublet must have been 7 Hz.

In addition, putative lactate doublets must also have met the following criteria:

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- The separation of the doublet must have been 7 Hz.

In addition, putative lactate doublets must also have met the following criteria:
The amplitude of the lactate doublet was more than twice that of surrounding noise. The noise level was estimated peak to peak by visual inspection (but not through calculation of the standard deviation).

Adjacent voxels either within or across slices could not contain lipid contamination.

The lactate doublet must have been present in more than 1 channel, unless a clear and compelling explanation could account for its absence (eg, weak signal due to the distance of the voxel from a particular coil or the presence of lipid contamination in a particular coil that could impair visibility of the lactate peak).

The amplitude of the NAA peak must have been 10-fold higher than the surrounding noise; this did not apply to the ventricle region where no NAA signal was visible.

Creatine and choline peaks were clearly separated.

Statistical Analyses
All statistical procedures were performed in SAS version 9.2 (SAS Institute Inc). A general linear model (PROC GLM) and frequency table (PROC FREQ) were used to compare the control and autism groups on study measures while covarying for age, sex, and full-scale IQ of the participants. All P values were 2-sided.

Results
Lactate doublets were present at a significantly higher rate in participants with ASD (13%) than in typically developing controls (1%) ($P = .001$), providing in vivo evidence for the presence of mitochondrial dysfunction in the brains of individuals with ASD (Table 1). Elevated lactate correlated significantly with age ($P = .004$) and was detected more often in adults (20%) than in children (6%). Its presence did not correlate, however, with sex, ASD subtype, intellectual ability, Autism Diagnostic Observation Schedule total score or subscores, or presence of comorbid neurological or psychiatric diagnoses (Table 2 and data available on request).

Our methods for data acquisition and analysis allowed us to map the anatomical location of lactate (Figure 2). In the ASD group, the location varied across individuals, but it seemed to aggregate preferentially within the cingulate gyrus. Lactate was also detected in subcortical gray matter nuclei, corpus callosum, superior temporal gyrus, pre- and postcentral gyri, and cerebrospinal fluid.

Discussion
This is the first study, to our knowledge, to demonstrate evidence for mitochondrial dysfunction in vivo in the brains of individuals with ASD. Our study yielded an overall prevalence estimate of 13% for ASD with concomitant mitochondrial dysfunction, but it was considerably higher (20%) for adults with ASD. These estimates are likely to be conservative for several reasons. First, magnetic resonance spectroscopy has limited sensitivity to detect lactate (brain lactate may not be detected in vivo even in individuals with definitive mitochondrial disease with cerebral involvement). Second, this...
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Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, Mean (SD) [Range], y</th>
<th>Adult &gt;18 y</th>
<th>Female</th>
<th>ASD Subtype</th>
<th>FSIQ, Mean (SD) [Range]</th>
<th>Lactate Doublets Present, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDC (n = 96)</td>
<td>22.0 (12.7) [5-54]</td>
<td>51 (54)</td>
<td>34 (36)</td>
<td>Not applicable</td>
<td>109 [79-132]</td>
<td>1 (1)</td>
</tr>
<tr>
<td>ASD (n = 75)</td>
<td>21.7 (11.7) [5-60]</td>
<td>41 (54)</td>
<td>17 (22)</td>
<td>AD, 5 (45); Asp, 3 (32); PDD, 2 (23)</td>
<td>9.4/2.3/11.9</td>
<td>107 [52-146]</td>
</tr>
<tr>
<td>ASD, adults only (n = 41)</td>
<td>36.4 (15.1) [19-60]</td>
<td>8 (20)</td>
<td></td>
<td>AD, 17 (41); Asp, 20 (49); PDD, 4 (10)</td>
<td>108.5 (20.5)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>ASD, children only (n = 34)</td>
<td>9.8 (4.9) [5-18]</td>
<td>9 (26)</td>
<td></td>
<td>AD, 17 (50); Asp, 4 (12); PDD, 13 (38)</td>
<td>105.8 (25.3)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autistic disorder; ASD, autism spectrum disorder; Asp, Asperger disorder; FSIQ, full-scale IQ; PDD, pervasive developmental disorder not otherwise specified; TDC, typically developing control.

* All participants were simplex cases.

Table 2. Characteristics of Patients With ASD According to Brain Lactate Status

<table>
<thead>
<tr>
<th>ASD Group</th>
<th>Lactate doublets present (n = 10)</th>
<th>Adult &gt;18 y</th>
<th>Female</th>
<th>FSIQ, Mean (Range)</th>
<th>ASD Subtype, No. (%)</th>
<th>ADOS Scores (SA/RBB/Total)*</th>
<th>ADOS Module, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate doublets present</td>
<td>31.7 (5-59)</td>
<td>8 (80)</td>
<td>2 (20)</td>
<td>109 (79-132)</td>
<td>AD, 5 (50); Asp, 3 (30); PDD, 2 (20)</td>
<td>9.6/2.3/11.9</td>
<td>Module 2, 0; module 3, 2 (20); module 4, 6 (60); not tested, 2 (20)</td>
</tr>
<tr>
<td>Lactate doublets absent</td>
<td>20.2 (5-60)</td>
<td>33 (51)</td>
<td>15 (23)</td>
<td>108 (52-146)</td>
<td>AD, 29 (45); Asp, 21 (32); PDD, 15 (23)</td>
<td>9.4/1.9/11.3</td>
<td>Module 2, 5 (8); module 3, 22 (34); module 4, 28 (43); not tested, 10 (15)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autistic disorder; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; Asp, Asperger disorder; FSIQ, full-scale IQ; PDD, pervasive developmental disorder not otherwise specified; RBB, restricted repetitive behavior; SA, social affect.

* Percentages reflect the number of participants within the lactate-positive group or lactate-negative group with a particular characteristic.

The ADOS was not completed in 12 participants with ASD for the following reasons: 1 participant displayed elective mutism and 11 participants had scheduling conflicts. All participants, however, were clinically evaluated in detail by a psychologist, psychiatrist, or neurologist with expertise in the diagnosis of ASD and met DSM-IV-TR criteria for ASD.
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A key finding from this study is the higher rate of elevated brain lactate in adults with ASD. This finding has at least 2 possible explanations. First, ascertainment bias could have contributed to these age-specific findings. Some children with ASD no longer meet diagnostic criteria as adults,26 and mitochondrial dysfunction may be more frequent in those who meet diagnostic criteria into adulthood. Therefore, recruitment of clinically identified adults could preferentially recruit those who have mitochondrial dysfunction. Second, the age-specific findings could represent a worsening of mitochondrial function with aging.27

Regardless of its cause, our finding suggests that the inclusion of adults is important for understanding the complex role of mitochondrial dysfunction in ASD. Most prior studies of mitochondrial dysfunction in ASD, however, have excluded adults entirely.5–11 The bias toward studying children is understandable given that the symptoms of ASD appear in early childhood and mitochondrial dysfunction has been implicated in some cases of autistic regression during the first years of life. Mitochondrial dysfunction has been detected in adults with a range of other chronic neurological and psychiatric disorders.18–20 Determining the underlying cause of impaired mitochondrial function in ASD will require further investigation of children and adults and consideration of both primary causes of mitochondrial dysfunction (eg, mutations in mitochondrial or nuclear genes that play a role in mitochondrial metabolism) and secondary causes (eg, inflammation, neurodegeneration, and excess oxidative stress).

Our study not only demonstrated elevated brain lactate in ASD, but it also allowed us to map the distribution of lactate in the brain. The distribution varied from person to person, consistent with the well-documented, heterogeneous distribution of mitochondrial dysfunction that contributes to highly variable symptoms and severity in individuals with mitochondrial disorders. Nevertheless, lactate-positive voxels in our sample were detected most frequently in the cingulate gyrus, a structure that supports higher-order control of thought, emotion, and behavior, and one in which both anatomical and functional disturbances have been reported previously in ASD.26,27

Conclusions

Our use of more sensitive imaging technologies has allowed us to identify in vivo a biological subtype of ASD with mitochondrial dysfunction. Determining definitively whether impaired mitochondrial function in ASD is a primary abnormality or secondary to other causes, and whether its presence varies with age, clinical phenotype, natural history, or treatment response, will require further investigation. Our findings, however, suggest that individuals with ASD should undergo evaluation for mitochondrial dysfunction, as novel and promising treatments are under development for mitochondrial disorders.

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Author Contributions: Dr Peterson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Goh, Dong, Peterson. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Goh, Dong, Zhang, Peterson. Obtained funding: Peterson. Administrative, technical, or material support: Goh, Dong, Zhang, Peterson. Study supervision: Goh, DiMauro, Peterson.

Conflict of Interest Disclosures: Dr Goh is a scientific advisor to MitoMedical LLC, a nutritional supplement company. No other disclosures were reported.

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REFERENCES

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