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Brain metabolism differs in Alzheimer disease and Parkinson disease dementia

H. Randall Griffith, Ph.D.^{A,B,C,*}, Jan A. den Hollander, Ph.D.^D, Ozioma C. Okonkwo, M.A.^C, Timothy O'Brien, B.A.^C, Ray L. Watts, M.D.^{A,B}, and Daniel C. Marson, J.D., Ph.D.^{A,B}

^ADepartment of Neurology, University of Alabama at Birmingham, Birmingham, AL, U.S.A.

^BAlzheimer's Disease Research Center, University of Alabama at Birmingham, Birmingham, AL, U.S.A.

^CDepartment of Psychology, University of Alabama at Birmingham, Birmingham, AL, U.S.A.

^DDepartment of Medicine (Cardiology), University of Alabama at Birmingham, Birmingham, AL, U.S.A.

Abstract

Background—Few comparative studies exist of metabolic brain changes among neurodegenerative illnesses. We compared brain metabolic abnormalities in Alzheimer's disease (AD) and in Parkinson's disease with dementia (PDD) as measured by proton magnetic resonance spectroscopy (MRS).

Methods—Twelve patients with idiopathic PDD, 22 patients with probable mild AD, and 61 healthy older controls underwent posterior cingulate MRS.

Results—Patients with AD showed reduced N-acetylaspartate (NAA)/creatine (Cr) ($p < 0.05$) and increased choline (Cho)/Cr ($p < 0.05$) and myo-Inositol (mI)/Cr ($p < 0.01$) compared to controls. Patients with PDD showed reduced NAA/Cr ($p < 0.05$) and glutamate (Glu)/Cr ($p < 0.01$) compared to controls. There was reduced Glu/Cr in PDD compared to AD ($p < 0.01$).

Conclusion—Patients with AD and patients with PDD showed distinct brain metabolic MRS profiles. Findings suggest that comparison of brain MRS profiles across dementias provides useful direction for future study.

Keywords

Parkinson Disease; Alzheimer Disease; MR Spectroscopy; N-acetylaspartate; Gyrus Cinguli

1. Introduction

The aging demographic of our society creates the prospect for a future major healthcare crisis from providing care to patients with dementia. As of 2007 there is now more than five million

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*Corresponding Author: SC 650, 1530 3rd Ave. South, Birmingham, AL 35294-0017; Tel: (205) 934-2334; Fax: (205) 975-3094
rlgriffith@uabmc.edu.

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persons in the United States diagnosed with Alzheimer's disease (AD)¹. Medicare and Medicaid expenditures for patients with AD are projected to more than double over the next eight years¹. Other neurodegenerative diseases also challenge the U.S. healthcare system. Parkinson disease (PD) is one of the most frequently diagnosed neurological disorders in older adults, with prevalence between 80 to 200 per 100,000. Prevalence increases with age, with the disease affecting 1% of persons over the age of 80². Furthermore, persons with idiopathic PD run up to a six-fold risk of developing dementia compared to age-matched older controls³. Researchers have distinguished a dementia in PD, or PD dementia (PDD), that is clinically⁴, cognitively⁵, neuropsychologically⁶, and neuropathologically⁷ distinct from that of patients with dementia with Lewy Bodies (DLB)⁴ or AD with late motor complications⁸. However, more information comparing PDD to other dementias is needed to better define the disease process and elucidate possible treatment mechanisms.

The current study compares patients with AD to patients with PDD using proton MR spectroscopy (MRS). A wealth of MRS studies has been performed in patients with AD. Reduction in N-acetylaspartate (NAA) is the most frequent MRS finding in AD⁹, and is thought to represent the loss of functional integrity of neurons⁹, as both cortical lobar abnormalities¹⁰ and subcortical white matter abnormalities¹¹ are observed in association with reduced NAA. Studies have also documented abnormalities of myo-Inositol (mI), a sugar alcohol similar to glucose, in AD patients¹². Our group recently also documented abnormal elevations of a related inositol, scyllo-Inositol (sI)¹³. Fewer studies in AD patients have detected abnormal measurements of choline-containing compounds (Cho)¹⁰. Reduction of glutamate has been documented in AD patients through measuring the GLX peak (glutamate + glutamine)¹⁴, although it is likely that GLX represents the larger metabolic abnormalities in the brains of AD patients rather than direct reduction in the glutamate neurotransmitter pool. Thus, most MRS studies in AD have detected reduced NAA and increased mI, with less consistent findings for other metabolites.

The few studies to examine MRS in PDD have shown preliminary findings of interest for comparison with other patient groups. One such study investigated MRS of the basal ganglia and occipital cortex, reporting that reduced occipital NAA/creatine (Cr) ratios were detected in patients with PDD when compared to non-demented PD controls, but the comparison of PDD patients to healthy normal controls did not reach significance¹⁵. Our group recently reported that NAA/Cr was reduced in the posterior cingulate of PDD patients compared to non-demented PD patients and healthy controls¹⁶. Another study observed elevated lactate in the occipital lobe of four PDD patients compared to 10 non-demented PD patients and controls¹⁷, although no other studies of PD patients have detected elevated lactate¹⁸. We are unaware of MRS studies conducted to date that have compared patients with AD to patients with PDD. This represents a key knowledge gap, as other neuroimaging studies have reported differences between patients with PDD and patients with AD in MRI volumes of the hippocampus¹⁹, cerebral atrophy on MRI voxel-based morphometry²⁰, white matter hyperintensity MRI volumes²¹, and cerebral blood flow on SPECT²².

A comparative MRS study could provide further insights regarding the metabolic effects of two common dementing illnesses, which share similarities in terms of neuroanatomical distribution of neuropathology²³ and can have similar neurocognitive symptom profiles²⁴. The current study was performed to investigate MRS findings in the posterior cingulate in patients with PDD in comparison to patients with AD and healthy older adults at 3 T field strength. Prior studies have demonstrated that the posterior cingulate often demonstrates metabolic abnormalities in both AD¹⁰ and cognitively impaired persons with PD²⁵. This region also suffers very early neuropathology in AD²³ and may be involved in PDD⁸.

2. Methods

2.1. Participants

All patients and healthy controls were recruited from the University of Alabama at Birmingham (UAB) Alzheimer's Disease Research Center (ADRC). Patients with AD were primarily referred to the ADRC from the UAB Memory Disorders Clinic, a tertiary care outpatient clinic. Patients with PDD were referred from the UAB Movement Disorders Clinic, which is also a tertiary care outpatient clinic. Both patient groups are referred to the ADRC from these respective clinics on the basis of clinical evidence of dementia on neurological examination, with all pertinent medical records from the prior evaluation made available to the ADRC diagnostic team. Control participants were community-dwelling individuals who volunteered for participation in the ADRC. Sources of contact with healthy older adults included community health fairs, ADRC-sponsored lectures and workshops, and media advertisement.

All participants in the ADRC undergo neurological and neuropsychological evaluation. Diagnosis is made in the course of a consensus conference comprised of neurologists, neuropsychologists, and allied health professionals from the ADRC. General exclusion criteria for the ADRC included metabolic diseases, head injuries, large vessel strokes, severe psychiatric illness and neuro-developmental conditions. Participants completed the Dementia Rating Scale (DRS)²⁶ and the Mini-Mental State Examination (MMSE)²⁷ as part of their evaluations. Participants also completed the Geriatric Depression Scale (GDS)²⁸. Dementia was staged in all patients using the Clinical Dementia Rating Scale (CDR)²⁹.

Twelve movement disordered patients presented with no known cause for their movement disorder and were considered to have idiopathic PD. These patients were determined to have a dementia secondary to their PD based upon a clinical history of movement disorder for at least one year prior to dementia, report of a family member or caregiver of declines from premorbid function, neurological findings, and neuropsychological test results. Such criteria are generally consistent with DSM IV criteria for dementia and the current clinical standards for PDD diagnosis³⁰. Persons with clinical features consistent with DLB, atypical PD, or Alzheimer's disease and with secondary parkinsonism were excluded. All PDD patients were treated with anti-parkinsonian medications at the time of the study (carbidopa/levodopa n = 8, carbidopa/levodopa/entacapone n = 5, pramipexole n = 3, ropinirole n = 2, pergolide n = 2, carbidopa n = 1, amantadine n = 1). All PDD patients were clinically determined to be within the effective therapeutic range of their movement disorder medications at the time of MRS data collection. Half of the PDD patients were also taking a cholinesterase inhibitor for treatment of memory loss (donepezil n = 3, galantamine n = 2, rivastigmine n = 1). The PDD patients had been diagnosed with a movement disorder for an average of 7.33 ($\pm$ 6.02) years and obtained a mean score of 22.67 ($\pm$ 5.29) on the motor section of the Uniform Parkinson's Disease Rating Scale (UPDRS)³¹. These PDD patients were considered to have mild dementia, with CDR staging of either 0.5 or 1 in all but one participant (Table 1).

Twenty-two patients with probable mild AD were recruited from the UAB Memory Disorders Clinic into the ADRC. Diagnosis of probable AD was determined in the ADRC diagnostic consensus conference and was based on the NINCDS-ADRDA criteria³² excluding other causes of dementia as best as possible. These AD patients were classified as mild based upon clinical consensus, and had a CDR staging of 0.5 or 1.0 (Table 1). The majority of patients were taking a cholinesterase inhibitor for treatment of memory loss at the time of the study (donepezil n = 11, galantamine n = 4, rivastigmine n = 1).

Sixty one older adults were characterized as cognitively normal following ADRC diagnostic consensus conference. All controls had CDR = 0.

All participants gave informed consent to the study as part of this Institutional Review Board-approved protocol.

2.2. MRS methods

The MRS protocol was performed at 3 T using a Philips Intera MRI system. Data were collected from a $2 \times 2 \times 2$ cm voxel of interest (VOI) located in a portion of the posterior cingulate gyrus (Figure 1). Data acquisition used PRESS sequences with 2048 samples, spectral bandwidth of 2000 Hz, and 128 acquisitions, using TR/TE = 2000/32 ms for NAA, Cho, and mI and TR/TE = 2000/80 for obtaining and quantifying measurements of glutamate (Glu)³³. An automated higher-order shim procedure was applied to correct for magnetic field inhomogeneity over the VOI. Suppression of the water signal was adjusted prior to data collection using a frequency selective double inversion recovery sequence. All spectra were measured by one spectroscopist who was blinded to the clinical diagnosis of the participants. Quantification of MR spectroscopy was performed using a time domain fitting analysis that utilizes prior *in-vitro* knowledge³⁴. *In-vivo* spectra were referenced to the methyl signal of N-acetylaspartate (2.008 ppm). Using this procedure, metabolic ratios of NAA, Cho, mI, (TE = 32 ms) and Glu (TE = 80 ms) were obtained relative to Cr, with average Cramer-Rao lower bounds derived to determine the variability in MRS measurement within each participant's MRS data (Figure 2).

2.3. Statistical analyses

Group differences on age, DRS and MMSE, self-reported depression, and education were compared using One-way ANOVA with Least Significant Differences (LSD) post hoc³⁵. Sex, self-reported race, CDR staging, and the proportion of patients on cholinesterase inhibitors between the AD and PDD groups were compared with chi-square. MRS ratios of AD and PDD patients and controls were compared with pairwise comparisons. The correlation of MRS ratios with mental status scores was assessed with Pearson correlation in all participants. The ability of MRS ratios to classify group status (AD versus PDD) was determined with stepwise discriminant function analyses (DFA: $F_{in} = 3.84$; $F_{out} = 2.71$). All analyses were performed using SPSS 12.0 with an alpha level set at .05 (2-tailed).

3. Results

3.1. Demographics, staging, and clinical variables

The ANOVA comparing age across groups was significant: $F(2, 92) = 6.78$, $p < 0.05$. Post-hoc analyses demonstrated that controls were younger than the AD patients ($p < 0.01$) but not the PDD patients ($p = 0.099$). The AD and PDD patient groups did not differ in age (Table 1). Chi-square analysis for sex was significant, $\chi^2 = 19.52$, $p < 0.001$. The PDD patient group was comprised of all males while the distribution of males to females was 41% in the AD patient group and 31% in the control group. There were no statistical differences in racial distribution, $\chi^2 = 3.41$, $p > 0.10$, although all PDD patients were Caucasian. Education did not differ among the study groups, $F(2, 91) = 1.55$, $p > 0.10$. The ANOVAS for DRS, $F(2, 82) = 67.73$, $p < 0.001$, and MMSE, $F(2, 90) = 73.60$, $p < 0.001$, were both significant. Post-hoc analyses showed that both AD ($p < 0.001$) and PDD patients ($p < 0.001$) had lower DRS scores compared to controls, but did not differ from each other ($p > 0.10$). This same pattern was observed for the MMSE, with both AD ($p < 0.001$) and PDD patients ($p < 0.001$) having lower scores compared to controls, although there was no difference in MMSE between the patient groups ($p = 0.08$). Distributions of CDR scores were similar in both dementia groups, $\chi^2 = 1.95$, $p > 0.10$. The ANOVA for depression was significant, $F(2, 77) = 4.30$, $p < 0.05$, with depression higher in both AD ($p < 0.05$) and PDD ($p < 0.05$) compared to controls, although the comparison between AD and PDD was not significant ($p > 0.10$). The PDD mean score was just above a clinical cutoff of 10. There was no significant difference between the proportion of AD and PDD patients taking cholinesterase inhibitors, $\chi^2 = 1.76$, $p > 0.10$.

3.2. MRS measures

Due to differences in age and distribution of sex among the groups, these variables were applied as covariates in the group analyses of MRS data. Compared to controls, AD patients demonstrated lower NAA/Cr (7% reduction) ($p < 0.05$) and higher Cho/Cr (5% increase) ($p < 0.05$) and mI/Cr (13% increase) ($p < 0.01$) (Table 2). Effect sizes (Cohen's d) ranged from a medium effect size of 0.47 (Cho/Cr) to a strong effect size of 0.89 (mI/Cr). Compared to controls, PDD patients showed lower NAA/Cr (8% reduction) ($p < 0.05$) and Glu/Cr (17% reduction) ($p < 0.01$). Strong effect sizes were observed for both NAA/Cr and Glu/Cr group differences ($d = 1.09$). Significantly lower Glu/Cr ratios were observed in PDD patients versus AD patients (15% reduction) ($p < 0.01$). There were no other significant differences in MRS between AD and PDD patients.

Comparison of MRS ratios in patients treated with cholinesterase inhibitors versus untreated patients within the AD group revealed a higher Cho/Cr ratio (0.709) in treated versus untreated AD patients (0.614) ($t(20) = 2.58$, $p = 0.018$). No other differences in MRS ratios were observed between treated and untreated AD patients in NAA/Cr (treated = 1.280; untreated = 1.197; $t(20) = 0.91$, $p = 0.376$), mI/Cr (treated = 1.035; untreated = 0.999; $t(20) = 0.42$, $p = 0.678$), or Glu/Cr (treated = 0.525; untreated = 0.539; $t(17) = 0.29$, $p = 0.777$). Likewise, no differences were observed in MRS ratios between PDD patients treated and not treated with cholinesterase inhibitors in NAA/Cr (treated = 1.278; untreated = 1.208; $t(10) = 1.43$, $p = 0.183$), Cho/Cr (treated = 0.637; untreated = 0.660; $t(10) = 0.65$, $p = 0.533$), mI/Cr (treated = 0.937; untreated = 1.026; $t(10) = 1.05$, $p = 0.317$), or Glu/Cr (treated = 0.419; untreated = 0.478; $t(10) = 1.25$, $p = 0.241$).

3.3. Correlation of MRS ratios and mental status scores

In all participants, NAA/Cr showed modest positive correlations with both the MMSE ($r = 0.25$, $p < 0.05$) and DRS total score ($r = 0.27$, $p < 0.05$), as did Glu/Cr with MMSE ($r = 0.22$, $p < 0.05$) and DRS ($r = 0.29$, $p < 0.05$). Cho/Cr was negatively correlated with DRS ($r = -0.23$, $p < 0.05$), as was mI/Cr with MMSE ($r = -0.39$, $p < 0.001$) and DRS ($r = -0.34$, $p < 0.01$).

3.4. Group classification by MRS ratios

The stepwise DFA model classifying AD patients from PDD patients was significant ($p < 0.05$) and retained Glu/Cr as the only predictor variable. The model correctly classified 67.7% of the participants (57.9 % AD, 83.3% PDD).

4. Discussion

This study suggests that MRS ratios from the posterior cingulate gyrus demonstrate distinct metabolic brain abnormalities in probable AD patients and probable PDD patients when compared to healthy older adults. MRS profiles in AD and PDD both demonstrated abnormality in NAA/Cr but other metabolic abnormalities were distinct to each dementia. Lastly, MRS ratios were able to discriminate between AD and PDD at rates greater than chance. These findings suggest that specific metabolic brain abnormalities exist in AD and PDD, potentially reflecting underlying neuropathology rather than the general effects of dementia. Such information is potentially of value given the difficulties of making a clinical differential between patients with AD who have Parkinsonian features versus patients with PDD.

The distinguishing MRS characteristics of each dementia provide clues regarding the mechanisms of metabolic brain abnormality in PDD and in AD. The metabolic profile in PDD showed reduced cortical NAA/Cr, consistent with prior reports^{15, 16}, as well as reduced Glu/Cr, which has recently been demonstrated by our group in non-demented patients with PD³⁶. To our knowledge, the current report represents the first documentation of reduced cortical

glutamate in patients with PDD. The fact that reduced Glu/Cr is observed in PDD as well as non-demented patients with PD suggests that cortical metabolic abnormalities may precede the development of overt dementia in PD. Recent conceptualizations of diseases involving Lewy Bodies (i.e. DLB, PD, PDD) posit that these diseases actually represent a continuum of pathology rather than distinct clinical entities, whereby Lewy Body pathology progresses from midbrain and subcortical structures to involve cortical regions such as the cingulate^{37–41}. In concert with these findings, a recent neuropathological study showed that a cortical glutamate marker is reduced in the autopsy brain tissue of PD patients⁴², suggesting along with our findings that in advanced PD there is either neuronal loss or downregulation of glutaminergic cortical efferents from the basal ganglia. The positive correlations of Glu/Cr with mental status measures, albeit modest, still suggest relationships of reduction of this metabolite with the presence of cognitive deficits in PDD, although no causal relationship can be determined from this association. As noted previously, the Glu/Cr signal represents not only changes in the neurotransmitter pool of glutamate but also the general metabolic activity of glutamate in the brain. Another distinct possibility is that Glu/Cr changes in PDD and non-demented patients with PD actually represent distinct, unrelated processes. In contrast to findings in PDD, we did not observe reduced Glu/Cr in AD, which has been suggested by prior findings¹⁴. This was possibly due to the relatively mild cases of AD that were studied in our clinical sample.

In AD, the brain metabolic pattern is one that is well documented in the literature, consisting of reduced NAA/Cr^{9, 10} and elevated mI/Cr^{9, 10}. It has been suggested that increased mI/Cr in AD possibly represents gliosis⁹ or is a marker of inflammation¹⁰, although the mechanism of elevated mI in AD remains to be determined. Prior comparison of AD with other dementias have found that while reduced NAA was not specific to AD, mI increases were only observed in patients with AD⁴³ (although see⁴⁴). Our findings showed trends towards increased mI/Cr in AD compared to PDD, consistent with our prior report that mI/Cr is not increased in PDD patients¹⁶, and possibly suggesting that the same degree of gliosis or inflammation is not present in PDD when compared to AD.

Both PDD and AD showed reduced NAA/Cr. This finding is consistent with the interpretation of NAA as a marker of functional integrity of neurons^{10, 11} and emphasizes that posterior cortical pathology is likely implicated in both diseases²². MRS of other dementias in which neuronal loss is prevalent such as frontotemporal dementia⁴⁴ and vascular dementia⁴⁴ have also found reduced cortical NAA. Thus, reduction of NAA is a common finding in many dementias (although see⁴⁴). The positive correlation of NAA/Cr with mental status measures also suggests a relationship of this metabolite to neuronal function.

An associated finding of the current study is that AD patients who were receiving cholinesterase inhibitors showed a significant increase in Cho/Cr compared to AD patients not on cholinesterase inhibitors (+1.4 SD difference), although cholinesterase inhibitor treatment did not show the same effect in patients with PDD. Prior studies investigating choline-containing compounds with MRS have been mixed, with some groups reporting increases in Cho/Cr¹⁰ and others decreases in Cho⁴⁵. The variability in findings have suggested that very strict control of medication use, diet, and age would be needed to reliably measure Cho⁹. We suggest that Cho/Cr increases in AD could be explained by use of cholinesterase inhibitors, much as improvements in NAA have been reported in clinical trial studies of donepezil in AD⁴⁶. However, the current study was not designed to assess changes in MRS related to use of cholinesterase inhibitors, and such findings should be considered strictly observational and preliminary.

One limitation of the current study is a lack of neuropathological confirmation of diagnosis in our patients. Other researchers have indicated that PDD and DLB overlap in clinical and pathological studies³⁰, and that it is difficult to distinguish these two on the basis of clinical

findings alone. Both dementias share many features in common, with the time of onset of symptoms being a major determinant in the diagnosis³⁰. While no neuropathological data are currently available for the PDD participants in this study, these patients have been diagnosed using currently accepted criteria by dementia and movement disorders specialists, and thus the data are in accordance with other reports of PDD in the literature³⁰. Furthermore, our MRS findings in PDD are distinct from those previously observed in studies of DLB. Of the two studies reported to date in DLB, both have observed normal NAA/Cr in midline parietal/posterior cingulate regions^{44, 47}, and one of the studies reported increased Cho/Cr⁴⁴. Notably, to our knowledge there have been no comparative MRS studies of PDD and DLB published in the scientific literature. Interpretation of findings could prove different based upon the ultimate autopsy diagnosis of our participants.

Another study limitation is not using absolute metabolic quantification, but we rather used MRS ratios in reference to Cr. While this method is relatively resistant to the effects of brain atrophy within the voxel of interest, it would be desirable to replicate these findings using tissue classification for grey and white matter within the voxel and absolute quantification of metabolites. The use of covariate analysis was employed to correct for demographic differences in our groups. A future study that attempts to match participants a priori on these variables would be desirable. Lastly, the effects of anti-Parkinson medications on the current findings cannot be ruled-out. We found MRS differences in our prior study of patients with PDD compared to non-demented PD patients, all of whom were taking anti-Parkinson medications, suggesting that MRS ratios can differ by group even when anti-Parkinson medications are held constant¹⁶.

In conclusion, patients with AD and PDD showed different patterns of brain metabolic abnormalities compared to healthy controls. Reductions in NAA/Cr were evident in both groups, while increased mI/Cr was present in the AD group and reduced Glu/Cr in the PDD group. MRS data appears to provide a useful means of observing specific brain metabolic patterns in these dementia groups. Future studies examining MRS changes in other PD patients not receiving anti-Parkinson medications, as well as comparing patients with PDD to patients with DLB, would be of interest.

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Figure 1.
T1 sagittal MRI showing voxel of interest within the posterior cingulate gyrus.

Figure 2. Representative spectra from study participants: A) patient with Parkinson disease with dementia; B) patient with Alzheimer disease; C) healthy older adult control. See text for abbreviations.

Table 1

Demographics, Staging, and Clinical Data for Study Participants

Variable	Controls N = 61	Mild AD N = 22	PDD N = 12	p value
Age mean	66.46	74.09	71.00	0.002
(SD)	(8.76)	(10.04)	(3.33)	
Sex (males / females)	19 / 42	9 / 13	12 / 0	0.001
Race (Caucasian / African-American)	52 / 9	21 / 1	12 / 0	0.182
Education mean	15.21	14.52	16.08	0.218
(SD)	(2.25)	(2.78)	(2.94)	
Dementia Rating Scale mean	139.19	118.52	120.50	0.001
(SD)	(2.88)	(11.20)	(13.32)	
MMSE mean	29.49	24.77	25.83	0.001
(SD)	(0.95)	(2.47)	(2.59)	
CDR* Staging (0 / 0.5 / 1 / 2)	61 / 0 / 0 / 0	0 / 11 / 11 / 0	0 / 5 / 6 / 1	0.001
Geriatric Depression Scale mean	5.88	8.8	10.42	0.017
(SD)	(5.30)	(6.45)	(4.36)	
Cholinesterase Inhibitor (yes/no)	----	16 / 6	6 / 6	0.001

*
CDR = Clinical Dementia Rating Scale

Table 2

MRS Ratios of the Posterior Cingulate Gyrus across Study Groups

MRS Ratio	Controls N = 61 Mean (SD) Cramer-Rao Bounds	Mild AD N = 22 Mean (SD) Cramer-Rao Bounds	PDD N = 12 Mean (SD) Cramer-Rao Bounds	Controls vs. Mild AD p (Effect Size) [*]	Controls vs. PDD p (Effect Size) [*]	Mild AD vs. PDD p (Effect Size) [*]
NAA/Cr [†]	1.353 (0.120) .069	1.257 (0.190) .075	1.243 (0.088) .070	0.026 (0.67)	0.014 (1.09)	0.458 (0.11)
Cho/Cr	0.648 (0.051) .044	0.683 (0.086) .054	0.648 (0.059) .050	0.016 (0.47)	0.881 (0.00)	0.127 (0.10)
mI/Cr	0.910 (0.099) .067	1.025 (0.172) .074	0.982 (0.147) .069	0.001 (0.89)	0.470 (0.63)	0.053 (0.24)
Glu/Cr	0.540 (0.075) .085	0.529 (0.098) .105	0.448 (0.085) .089	0.565 (0.12)	0.006 (1.09)	0.004 (0.81)

^{*} All effects adjusted for group differences on age or gender
[†] NAA = N-acetylaspartate; Cr = creatine; Cho = choline containing compounds; mI - myo-Inositol; Glu = glutamate