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ORIGINAL RESEARCH

It is unclear if adjusting cortical thickness for changes in gray/white matter intensity ratio improves discrimination between normal aging, MCI, and AD

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Abstract The contrast between gray and white matter in MRI is critical for accurately measuring cortical thickness. The gray/white matter intensity ratio (GWIR) has been proposed to be an important adjustment factor for cortical thickness measures in Alzheimer's disease (AD) and mild cognitive impairment (MCI). This study examined the GWIR and its influence on cortical thickness in normal aging, mild cognitive impairment (MCI), and AD. The ability for GWIR to discriminate between these groups was assessed on its own and as an adjustment factor for cortical thickness. Minimal age- and AD-related changes in GWIR were observed. GWIR was not able to differentiate between normal aging, MCI, and AD. However, adjusting cortical thickness for GWIR slightly improved the ability to discriminate between groups and the effect size of cortical thickness increased after adjusting for GWIR. This work demonstrates the ambiguity in adjusting cortical thickness measures for GWIR, particularly when attempting to discriminate between normal aging, MCI, and AD groups.

Keywords Gray white matter intensity ratio · Cortical thickness · MRI · Alzheimer's disease · Mild cognitive impairment · Normal aging

Introduction

Alzheimer's disease (AD) is the leading form of dementia, affecting over 5 million Americans today ("2013 Alzheimer's disease facts and figures," 2013). It is characterized by an insidious onset of progressive decline in cognition due to the accumulation of amyloid plaques and neurofibrillary tangles throughout the cortex. Mild cognitive impairment (MCI), particularly the amnestic form, is thought to be a precursor to AD and is characterized by the same etiology in lesser amounts. The accumulation of neurofibrillary tangles in the cortex is associated with neuronal loss and atrophy, (Gómez-Isla et al. 1997; Grignon et al. 1998) which can be indirectly visualized using MRI morphometric measures, such as cortical thickness.

In order to identify the gray matter of the cortical ribbon from MRI structural images, two tissue boundaries are determined: the gray matter-pial surface and the gray/white matter boundary. The accurate identification of both these tissue boundaries is critical for calculating cortical thickness. Alterations in the brain due to processes such as aging or disease may change the gray and white matter MRI signals independently, such that the gray/white matter boundary becomes obscured. Indeed, age- (Salat et al. 2009; Westlye et al. 2009)

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. ADNI investigators include (complete listing available at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Authorship_List.pdf).

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and AD-related (Grydeland et al. 2012; Salat et al. 2011; Westlye et al. 2009) changes in gray/white matter intensity ratio (GWIR)s have been reported. Adjusting cortical thickness values for age-related gray/white matter intensity changes has the potential to improve the ability to observe age-related cortical thickness changes (Salat et al. 2009). Similarly adjusting for changes in the GWIR in AD has the potential to add to the ability to differentiate between normal aging and AD subjects (Grydeland et al. 2012); however, this has yet to be tested in an independent sample of subjects diagnosed with MCI and AD.

This study examines the effects of GWIR on cortical thickness in normal aging, MCI, and AD subjects using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Specifically, we tested the following hypotheses: 1) GWIR correlates positively with age in normal aging older subjects, 2) GWIR decreases progressively between normal aging, MCI, and AD subject groups, 3) adjusting cortical thickness measurements for GWIR improves the ability to differentiate between normal aging, MCI, and AD subjects using statistical models, and 4) the effect size of cortical thickness increases after adjusting for GWIR. This study expands previous research to include region-of-interest-type analysis from multiple research sites.

Methods

Study population

The data for use in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative and was in compliance with regulations at our institution. Data were screened to include all subjects who had both PET and MRI scans available for use on the ADNI/LONI website at the time this study began because this project evolved off of a larger project looking at both PET and MRI. Demographic information can be found in Table 1.

As part of the ADNI, all subjects completed a battery of neuropsychological tests. On the basis of their cognitive status the subjects were classified by the ADNI clinical core as: (a) normal controls with normal cognition and memory, MMSE between 24 and 30, CDR=0, (b) amnestic MCI with memory complaint verified by a study partner, MMSE between 24 and 30, CDR=0.5, or (c) probable AD with memory complaint validated by an informant, MMSE between 20 and 26 and CDR≥0.5. More detailed information on diagnostic criteria can be found in the ADNI protocol http://adni-info.org/Scientists/ADNIGrant/ProtocolSummary.aspx.

Table 1 Demographic information

	Subjects (male/female)	Age mean years (std dev)	Education mean (std dev)	MMSE
Normal aging	105 (64/41)	75.81 (4.75)	15.90 (3.12)	28.98 (1.12)
MCI	204 (137/67)	75.44 (7.22)	15.80 (2.88)	27.15 (1.71)[a]
AD	94 (56/38)	74.91 (7.37)	14.61 (3.21)[a,b]	23.48 (2.14)[a,b]

[a] significant difference from normal aging ($p<0.05$), [b] significant difference from MCI ($p<0.05$)

Alzheimer's disease neuroimaging initiative

The ADNI was a 5-year non-randomized natural history non-treatment study utilizing data from multiple study centers across the United States and Canada. One of the main goals of the ADNI was to develop optimized methods and uniform standards for the acquisition of multi-center MRI and PET data on normal control subjects and patients with MCI and AD in drug/treatment trials. For more information about the ADNI please refer to http://www.adni-info.org.

MRI acquisition and analysis

For this study, we analyzed the baseline T1-weighted MPRAGE MRI scans acquired by the ADNI on 1.5 T scanners from General Electric, Philips Medical Systems, and Siemens Medical Solutions. Specific pulse sequence guidelines can be found at http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml. All MRI scans were processed with Freesurfer 5.1.0 (Dale A.M. et al. 1999; Fischl et al. 1999), which is documented and freely available. The processing pipeline has been described in detail elsewhere (Dale A.M. et al. 1999; Fischl et al. 2004a, b, 2002, 1999, Fischl and Dale 2000). Briefly, for each subject, the 2 DICOM T1-weighted MRI datasets were motion corrected, averaged, segmented into gray matter, white matter, and cerebral spinal fluid, and intensity normalized. As outlined in Salat's paper (Salat et al. 2009), gray matter tissue intensities were measured 35 % through the thickness of the cortical ribbon. White matter tissue intensities were measured 1 mm below the gray/white matter boundary, into the white matter. The GWIR was calculated by dividing the white matter by the gray matter intensity values. The ratios were then projected onto the cortical surface and smoothed with a Gaussian kernel with a full width at half maximum of 30 mm. The cortex was parcellated into ROIs based on gyral and sulcal structure using the Killiany/Desikan atlas (Desikan et al. 2006). Cortical thickness and GWIR were calculated for each of the 68 cortical parcellations.

Statistical analysis

Equality of the male–female distribution in the three diagnostic groups was examined with Chi-square tests. Age, education,

and MMSE distributions in the three diagnostic groups were examined with ANOVA. Effects of scanner manufacturer on cortical thickness was assessed with ANOVA.

Residuals were used to adjust for GWIR on cortical thickness values within each parcellated brain region. Paired t-tests showed significant left/right differences, thus the data from the two hemispheres were not averaged.

To examine whether adjusting cortical thickness for GWIR improved discrimination ability, we created stepwise logistic regression models. The most salient brain regions for differentiating our three subject groups were identified by creating univariate logistic regression models for each cortical thickness (adjusted and non-adjusted) and GWIR variables from all 68 Freesurfer parcellations and segmentations. The specific variables with a point estimate below 0.75 or above 1.25 were entered into multivariate stepwise logistic regression models to differentiate AD vs. normal aging, MCI vs. normal aging, AD vs. MCI, and all three groups together. Age, gender, and education were forced into the models, effectively controlling for any influence they may have on the variables on interest. The entry and exit criteria for the multivariate stepwise models were based on a significance level of 0.20. The discrimination ability of cortical thickness, GWIR, and GWIR-adjusted cortical thickness models was assessed by the c-statistic. The c-statistic is an indication of the model's ability to discriminate between individuals with MCI and those who are normally aging. The c-statistics of the raw and GWIR adjusted cortical thickness models were compared using the DeLong test (DeLong et al. 1988).

To estimate the effect size that adjusting cortical thickness for GWIR changes had on the group differences in cortical thickness, F ratios were calculated, whereby F-ratio = (F-adjusted thickness/F-non-adjusted thickness) (Grignon et al. 1998). Pearson correlation was used to examine the relationship between aging and GWIR and the relationship between raw cortical thickness and GWIR adjusted cortical thickness values.

Results

Chi-square tests revealed no significant differences for distribution of males and females between groups (df=2, X^2=2.09, p=0.35). Age was not significantly different between normal aging, MCI, and AD groups, as indicated by ANOVA (p=0.52). The AD group had on average a year less education than the normal aging and MCI groups (p<0.05). MMSE also showed significant decreases in both the MCI and AD groups (p<0.05) (Table 1).

Scanner manufacturer did not have a significant effect on either adjusted or unadjusted cortical thickness values, thus all further analyses combine data from scanner types.

Age-related changes in GWIR

We examined the correlations between age and GWIR and found only two regions that were significantly correlated: left pars orbitalis (r=0.10, p=0.04) and the right temporal pole (r=0.14, p=0.004). None of the other regions showed significant age-related changes (p>0.05) (Data not shown).

Gray/white intensity ratio does not differ between diagnostic groups

Differences in GWIR between normal aging, MCI, and AD for each of the cortical brain regions was examined using ANOVA followed by Tukey's honestly significant difference test. None of the brain regions showed significant differences in GWIR between any of the groups (p>0.05) (Data not shown).

Gray/white matter intensity ratio is not effective at discriminating between normal aging, MCI, and AD

The ability of GWIR to discriminate between normal aging, MCI, and AD was examined with stepwise logistic regression. None of the 68 cortical regions tested made the initial cutoff for comparing AD vs. MCI or for comparing all three groups. Three regions made the initial cutoff for comparing MCI vs. normal aging (right pars orbitalis, right lateral orbitofrontal, and left banks of the superior temporal sulcus) and one region made the initial cutoff for AD vs. normal aging (right parahippocampal gyrus). The final model for MCI vs. normal aging had a c-statistic of 0.601 and aside from age, gender, and education, included only the right lateral orbitofrontal gyrus. The final model for AD vs. normal aging had a c-statistic of 0.638 and included only the right parahippocampal gyrus (Data not shown).

No significant change in discrimination of diagnostic groups after adjusting cortical thickness for gray/white intensity ratio

We examined if adjusting for GWIR could increase the ability of cortical thickness to differentiate between the three groups. Small differences in the c-statistic after adjusting for GWIR were observed (specific details can be found in the Supplementary tables and Fig. 1). After adjustment, the c-statistic increased slightly across all prediction models except for the one for AD vs. normal aging, in which the c-statistic decreased. None of the changes in c-statistic reached statistical significance. For differentiating between normal aging and AD, cortical thickness provided a c-statistic of 0.978 (confidence interval = 0.963, 0.993) and GWIR adjusted cortical thickness provided a c-statistic of 0.965 (confidence interval = 0.945, 0.986). The difference between the c-statistics was not statistically significant (p=0.10). The cortical thickness models before and after

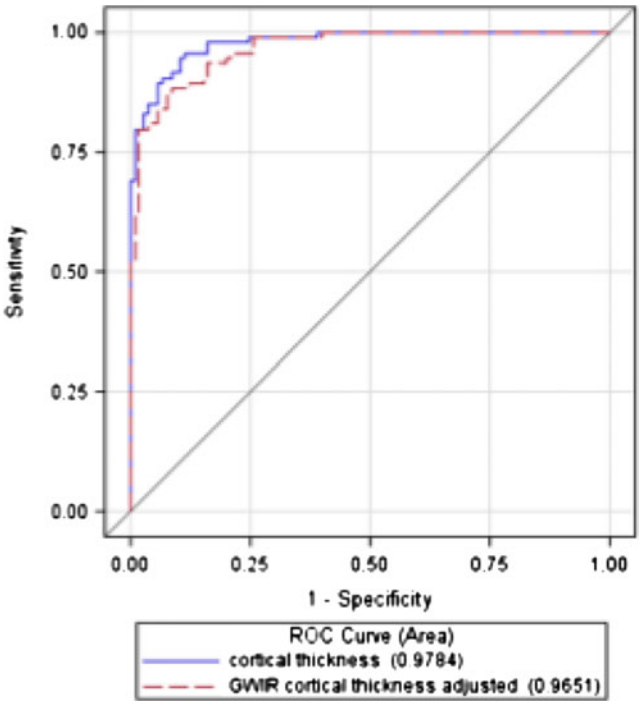

Fig. 1 ROC curve for discriminating between AD and normal aging highlighting the effects of adjusting cortical thickness for GWIR. *Blue solid line* represents cortical thickness, *white dotted red line* represents GWIR adjusted cortical thickness

adjustment for differentiating MCI vs. normal aging provided c-statistics of 0.796 (confidence interval = 0.739, 0.839) and 0.810 (confidence interval = 0.747, 0.846), respectively. The difference between the c-statistics was not statistically significant (p =0.39). The models for differentiating AD vs. MCI before and after adjustment provided c statistics of 0.834 (confidence interval = 0.778, 0.873) and 0.837 (confidence interval = 0.784, 0.878), respectively. The difference between the c-statistics was not statistically significant (p =0.40). The non-adjusted and adjusted cortical thickness models for differentiating between all three groups provided c-statistics of 0.829 and 0.830, respectively. Because the outcome variable had three levels, the c-statistics could not be directly compared. These results indicate that adjusting for GWIR does not significantly improve discriminability between diagnostic groups.

Effects of adjusting cortical thickness for GWIR

We next examined the relationship between groups in cortical thickness before and after GWIR adjustment. After adjusting the cortical thickness measures for GWIR, the difference between diagnostic groups changed in only six regions, namely the left isthmus of the cingulate, left pericalcarine, left postcentral, right pericalcarine, right postcentral, and right posterior cingulate (Table 2). The squared F-ratios indicate that there was an increase in power in 34 of 68 regions throughout the frontal, temporal and cingulate cortices of both hemispheres after adjusting cortical thickness for GWIR. The increase in power is indicated by F-ratios greater than 1 (Table 2). The highest effects were observed in the left posterior cingulate (F-ratio = 1.59), left temporal pole (F = 1.16), left pericalcarine (F-ratio = 6.24), right cuneus (F-ratio = 1.13), right insula (F-ratio = 1.12), and the right pericalcarine (F-ratio = 42.76). Correlations between adjusted and unadjusted cortical thickness measures were significant in all regions (r >0.99, p <0.0001) (data not shown).

Discussion

Recent studies indicate that there is an age-related change in the gray/white matter intensity ratio, which changes disproportionately in Alzheimer's subjects (Salat et al. 2011, 2009; Westlye et al. 2009). The Alzheimer's-related changes have only been tested in one sample to our knowledge thus far. We expanded these studies by applying them to the ADNI sample and including MCI subjects. By including MCI subjects we apply the results to a wider spectrum of the disease progression.

Age-associated changes in GWIR in older individuals

In this study we found isolated positive correlations with age only in the left pars orbitalis and the right temporal pole. This indicates an increase in GWIR with age and a reduction in tissue contrast in these regions with increasing age in our older population. Previous studies have indicated a widespread reduction in gray/white matter contrast within a broader age range (Salat et al. 2009; Westlye et al. 2009); however, the age range in both of these other studies Included younger subjects, which are not present in the ADNI sample. It is plausible that the limited age-related changes that we observed are a product of the truncated age range for the subjects included in our study.

GWIR in MCI and AD

The GWIR did not differ between normal aging, MCI, and AD in any cortical brain regions. This was rather surprising as we were expecting to observe increases in the ratio in temporal regions, as has previously been observed (Salat et al. 2011). While it is not entirely clear why this discrepancy exists, there are a number of differences in the scanners used and pulse sequences implemented. The data analyzed in this study was drawn from General Electric, Philips, and Siemens 1.5 T scanners located at multiple research sites, rather than the one scanner and site used in previous works (Salat et al. 2011, 2009). Because different manufacturers implement pulse sequences in unique ways, the signal ratio between GM and WM

Table 2 Results from ANOVA and Tukey's post-hoc analysis for differences in cortical thickness before and after GWIR adjustment in normal aging, MCI, and AD subject groups. The change in effect size after adjustment is reflected in the F-ratio, whereby a value greater than 1 indicates an increased effect size. Degrees of freedom for each ANOVA is 2. For Tukey's columns, the letters represent the groupings for normal aging, MCI, and AD, respectively

Cortical region	Cortical thickness						GWIR adjusted cortical thickness						F-ratio
	r-square	F-value	P-value	NL	MCI	AD	r-square	F-value	P-value	NL	MCI	AD	
Left hemisphere													
Frontal pole	0.03	5.25	0.0056	a	ab	b	0.03	5.34	0.0051	a	ab	b	1.03
Rostral middle frontal	0.11	25.24	<.0001	a	b	c	0.11	25.14	<.0001	a	b	c	0.99
Caudal middle frontal	0.08	16.81	<.0001	a	b	c	0.08	16.75	<.0001	a	b	c	0.99
Lateral orbitofrontal	0.06	12.37	<.0001	a	a	b	0.06	12.48	<.0001	a	a	b	1.02
Medial orbitofrontal	0.08	16.94	<.0001	a	b	c	0.08	16.86	<.0001	a	b	c	0.99
Pars opercularis	0.03	6.28	0.0021	a	ab	b	0.03	6.30	0.002	a	ab	b	1.01
Pars orbitalis	0.03	5.96	0.0028	a	ab	b	0.03	6.10	0.0025	a	ab	b	1.05
Pars triangularis	0.06	12.34	<.0001	a	b	b	0.06	12.20	<.0001	a	b	b	0.98
Superior frontal	0.06	13.78	<.0001	a	b	c	0.06	13.75	<.0001	a	b	c	0.96
Precentral	0.03	6.75	0.0013	a	ab	b	0.03	6.49	0.0017	a	ab	b	0.92
Postcentral	0.05	9.7	<.0001	a	a	b	0.04	9.17	0.0001	a	a	b	0.08
Paracentral	0.01	1.77	0.1713	a	a	a	0.01	1.74	0.1773	a	a	a	0.97
Rostral anterior cingulate	0.03	6.24	0.0021	a	ab	b	0.03	6.02	0.0027	a	ab	b	0.93
Caudal anterior cingulate	0.004	0.8	0.4479	a	a	a	0.004	0.79	0.4537	a	a	a	0.98
Isthmus of the cingulate	0.09	18.67	<.0001	a	ab	b	0.09	19.06	<.0001	a	a	b	1.04
Posterior cingulate	0.04	7.28	0.0008	a	ab	b	0.04	7.27	0.0008	a	ab	b	1.59
Superior temporal	0.11	24.64	<.0001	a	b	c	0.11	24.66	<.0001	a	b	c	1.00
Middle temporal	0.18	42.43	<.0001	a	b	c	0.18	42.43	<.0001	a	b	c	1.00
Inferior temporal	0.18	44.71	<.0001	a	b	c	0.18	44.61	<.0001	a	b	c	1.00
Temporal pole	0.06	11.78	<.0001	a	b	c	0.06	12.70	<.0001	a	b	c	1.16
Transverse temporal	0.02	4.75	0.0092	a	ab	b	0.02	4.80	0.0087	a	ab	b	1.02
Banks of the superior temporal sulcus	0.11	24.13	<.0001	a	b	c	0.11	23.84	<.0001	a	b	c	0.98
Entorhinal	0.14	32.96	<.0001	a	b	c	0.14	33.46	<.0001	a	b	c	1.03
Parahippocampus	0.08	17.23	<.0001	a	b	c	0.08	17.03	<.0001	a	b	c	0.98
Superior parietal	0.03	6.57	0.0016	a	ab	b	0.03	6.43	0.0018	a	ab	b	1.00
Inferior parietal	0.10	21.26	<.0001	a	b	c	0.10	21.37	<.0001	a	b	c	1.01
Supramarginal	0.09	19.48	<.0001	a	b	c	0.09	19.51	<.0001	a	b	c	1.00
Fusiform	0.13	29.84	<.0001	a	b	c	0.13	29.79	<.0001	a	b	c	1.00
Precuneus	0.07	15.38	<.0001	a	b	c	0.07	15.29	<.0001	a	b	c	0.99
Cuneus	0.004	0.71	0.49	a	a	a	0.003	0.54	0.5837	a	a	a	0.58
Pericalcarine	0.01	2.91	0.0554	a	ab	b	0.01	2.72	0.0672	a	ab	b	6.24
Lateral occipital	0.04	7.74	0.0005	a	a	b	0.04	7.43	0.0007	a	a	b	0.92
Lingual	0.05	10.45	<.0001	a	a	b	0.05	10.12	<.0001	a	a	b	0.94
Insula	0.05	9.77	<.0001	a	a	b	0.05	9.58	<.0001	a	a	b	0.96
Right hemisphere													
Frontal pole	0.04	7.26	0.0008	a	b	b	0.03	7.15	0.0009	a	b	b	0.97
Rostral middle frontal	0.10	21.28	<.0001	a	b	c	0.10	21.50	<.0001	a	b	c	1.02
Caudal middle frontal	0.07	15.76	<.0001	a	b	c	0.08	16.20	<.0001	a	b	c	1.06
Lateral orbitofrontal	0.06	11.64	<.0001	a	a	b	0.06	12.06	<.0001	a	a	b	1.07
Medial orbitofrontal	0.06	13.01	<.0001	a	b	c	0.06	13.04	<.0001	a	b	c	1.00
Pars opercularis	0.05	10.71	<.0001	a	a	b	0.05	10.84	<.0001	a	a	b	1.02
Pars orbitalis	0.04	7.51	0.0006	a	ab	b	0.04	7.50	0.0006	a	ab	b	1.00
Pars triangularis	0.04	9.38	0.0001	a	b	b	0.05	9.57	<.0001	a	b	b	1.04
Superior frontal	0.08	18.32	<.0001	a	b	c	0.09	18.87	<.0001	a	b	c	1.06

Table 2 (continued)

Cortical region	Cortical thickness						GWIR adjusted cortical thickness						F-ratio
	r-square	F-value	P-value	NL	MCI	AD	r-square	F-value	P-value	NL	MCI	AD	
Precentral	0.02	4.21	0.0155	a	ab	b	0.02	4.26	0.0148	a	ab	b	1.02
Postcentral	0.02	5.01	0.0071	a	ab	b	0.02	4.97	0.0074	a	ab	b	0.08
Paracentral	0.02	4.42	0.0126	a	ab	b	0.02	4.39	0.013	a	ab	b	0.99
Rostral anterior cingulate	0.01	2.39	0.0931	a	ab	b	0.01	2.37	0.0951	a	ab	b	0.98
Caudal anterior cingulate	0.01	1.21	0.2987	a	a	a	0.01	1.22	0.2971	a	a	a	1.02
Isthmus of the cingulate	0.06	12.45	<.0001	a	a	b	0.06	12.68	<.0001	a	a	b	1.04
Posterior cingulate	0.04	9.04	0.0001	a	a	b	0.04	9.22	0.0001	a	a	b	0.30
Superior temporal	0.09	20.21	<.0001	a	b	c	0.09	20.55	<.0001	a	b	c	1.03
Middle temporal	0.15	36.04	<.0001	a	b	c	0.16	36.54	<.0001	a	b	c	1.03
Inferior temporal	0.13	28.92	<.0001	a	b	c	0.13	29.40	<.0001	a	b	c	1.03
Temporal pole	0.08	18.31	<.0001	a	a	b	0.08	17.81	<.0001	a	a	b	0.95
Transverse temporal	0.003	0.51	0.5989	a	a	a	0.003	0.52	0.5942	a	a	a	1.04
Banks of the superior temporal sulcus	0.13	29.02	<.0001	a	b	c	0.13	28.97	<.0001	a	b	c	1.00
Entorhinal	0.19	46.84	<.0001	a	b	c	0.19	46.38	<.0001	a	b	c	0.98
Parahippocampus	0.09	19.52	<.0001	a	b	c	0.09	19.19	<.0001	a	b	c	0.97
Superior parietal	0.02	4.48	0.012	a	ab	b	0.02	4.61	0.0104	a	ab	b	1.06
Inferior parietal	0.11	23.95	<.0001	a	b	c	0.11	23.85	<.0001	a	b	c	0.99
Supramarginal	0.08	16.88	<.0001	a	b	c	0.08	17.09	<.0001	a	b	c	1.03
Fusiform	0.10	21.63	<.0001	a	b	c	0.10	22.37	<.0001	a	b	c	1.07
Precuneus	0.09	18.82	<.0001	a	b	c	0.09	19.02	<.0001	a	b	c	1.02
Cuneus	0.01	2.26	0.1057	a	a	a	0.01	2.40	0.0924	a	a	a	1.13
Pericalcarine	0.01	1.41	0.2446	a	a	a	0.01	1.39	0.2496	a	a	a	42.76
Lateral occipital	0.05	9.62	<.0001	a	a	b	0.05	9.39	0.0001	a	a	b	0.95
Lingual	0.04	7.94	0.0004	a	a	b	0.04	7.85	0.0005	a	a	b	0.98
Insula	0.05	10.88	<.0001	a	a	b	0.05	11.49	<.0001	a	a	b	1.12

may change by virtue of the scanner manufacturer. Although an in depth analysis of scanner differences in GWIR is beyond the scope of this study, the ADNI did work to develop pulse sequence parameters that could be used to produce equivalent T1 weighted images across scanner manufacturers and platforms (Jack Jr. et al. 2008). Previous studies examining GWIR and cortical thickness mainly utilize the Open Access Series of Imaging Studies (OASIS) dataset (further information about OASIS can be found at http://www.oasis-brains.org/). Pulse sequence parameters between OASIS and ADNI studies differ in a number of important ways, including echo time, repetition time, inversion time, and flip angle, which would be expected to influence the signal intensity and signal-to-noise ratio, resulting in different GWIR between the two studies.

GWIR is not able to differentiate between normal aging, MCI, and AD

Stepwise logistic models for differentiating between normal aging, MCI, and AD using only the GWIR values did not provide good indices of discrimination. This provides further evidence that although gray/white matter intensity has previously been shown to differ between AD and normal aging (Westlye et al. 2009), it cannot differentiate between these two groups meaningfully as an independent measure, at least in the ADNI dataset.

Adjusting cortical thickness for GWIR produces mixed results when differentiating between the groups

We examined if adjusting cortical thickness for GWIR increased the overall ability to differentiate between the normal aging, MCI, and AD groups. We used the c-statistic as a measure of the prediction models and found no statistically significant changes in this value before or after adjustment. When the three groups were included in the analysis, nearly identical values of the c-statistic were observed before and after adjustment for GWIR (0.829 vs. 0.830) suggesting that there is no overall benefit to this adjustment in the data used. The story becomes more complicated when pairwise analyses

were conducted. When trying to differentiate between the MCI and AD groups, once again, next to no change (0.834 vs. 0.837) in the c-statistic was observed. When trying to differentiate between the normal aging and the MCI groups, the c-statistic increased after adjustment (0.796 vs. 0.810), albeit not significantly, indicating that adjusting cortical thickness for GWIR may minimally improve the ability to discriminate in relatively weak statistical models. It is not clear whether this slight change in c-statistic has a biological basis to it or whether it represents a slight statistical reduction in variance. Although the change in c-statistic was not significant, some may feel that it is still a worthwhile correction to employ in order to obtain maximal discrimination when examining normal aging and MCI,. Finally, when trying to differentiate between the normal aging and AD groups, the c-statistic decreased after adjustment (0.978 vs. 0.965), albeit not significantly, indicating that adjusting cortical thickness of GWIR can actually weaken relatively strong statistical models of prediction. This final comparison argues that a breakdown in GWIR is a disease-based process that takes place in and around the AD phase of the disorder and that correcting for it obscures one's ability to actually detect the disorder in this dataset.

It appears that our results, obtained with data from ADNI, differ in a number of ways from those obtained from studies using OASIS data. First, we did not observe widespread age-related correlations, as was found in Salat's study (Salat et al. 2009). As described above, this may have been due to the limited age-range of the ADNI study compared to OASIS. Second, we did not observe significant changes in GWIR between normal aging, MCI, and AD as was found by Salat and Westyle (Salat et al. 2011, 2009; Westlye et al. 2009). As discussed above this is likely to be the result of differences in image acquisition parameters between ADNI and OASIS datasets.. Third, we did not find a widespread increase in statistical power related to cortical thickness after adjusting for GWIR as Westyle did (Westlye et al. 2009), which again may be the result of image acquisition parameters. And finally, we did not find the same increase in predictability of AD compared to normal aging after adjustment as Grydeland found (Grydeland et al. 2012). Taken together, out findings highlight the ambiguity inherent in globally applying correction factors. This suggests that when using GWIR in MCI and AD subjects, it must be done with caution, as results have yet to be consistently obtained across samples that use different parameters for acquiring T1-weighted MPRAGE scans.

Effects of GWIR adjustment on cortical thickness

Although there were no significant differences in GWIR between the normal aging, MCI, and AD groups, we did observe an increase in effect size based on the square ratios of the F-values after adjustment, although these did not reach statistical significance. In addition, we observed more pronounced cortical thickness changes in the AD group in a few regions. The majority of these regions have not typically been reported to be impacted by disease pathology in the early stages of the disease. Less pronounced AD-related differences in cortical thickness were also observed throughout the cortex. Taken together, our findings suggests that adjusting for GWIR does influence the cortical thickness measurements to some degree, which is in agreement with a previous study that found an increase in power after adjusting cortical thickness for intensity ratio when comparing AD to normal aging (Westlye et al. 2009).

We have extended these findings to include MCI, indicating that adjusting cortical thickness for GWIR may increase the effect sizes between MCI and normal aging or AD groups. Further work needs to be done to better understand if this adjustment factor is truly working to remove a disease-related artifact or if the process of adjusting the data is simply reducing the variance in the data with a mathematical function, particularly as the opposite effect was observed when differentiating normal aging from AD groups.

This study is unique in utilizing data from multiple research sites and scanner platforms to examine the benefits of adjusting cortical thickness for changes in GWIR. This is also the first study to our knowledge to include MCI as a separate diagnostic entity. Despite these strengths, there are some limitations that need be addressed. The study design is cross-sectional and imposes groupings on disease state, what is arguably a continuous variable. As such, the ability to differentiate between groups will have been influenced to some extent by how many members of each group fall into the middle of the grouping categories and how many are near the fringes. The use of multiple scanner platforms is both a benefit and a limitation in that the GWIR may be influenced by data acquisition. The effects of scanner were assessed and the influence on GWIR-adjusted cortical thickness was not significant, thus the data from all scanners was combined. Further studies may need to be conducted to assess GWIR effects on cortical thickness within a single scanner manufacturer. Finally, all of the data analyzed in this study were acquired on 1.5 T systems. As more studies using MRI are turning to higher field strengths further analyses will need to be done.

Conclusions

Overall our results provide weak support for adjusting cortical thickness for gray/white intensity ratio based on improvements in c-statistics for differentiating normal aging and MCI, and MCI and AD. We were unable to use GWIR as an independent predictor of MCI or AD as it was not able to differentiate between subject groups, nor did it show any significant differences between normal aging, MCI, or AD throughout the cortex. Using GWIR as an adjustment factor

for cortical thickness decreased the c-statistic for differentiating between normal aging and AD, indicating that the adjustment factor may lessen the ability to discriminate between these two groups. Thus, caution should be exercised when utilizing the GWIR on its own in studies of MCI, AD, and aging in the elderly. Nonetheless, the results indicate that future studies examining changes between either normal aging and MCI, or MCI and AD may want to consider adjusting cortical thickness measurements for GWIR, although it does not drastically improve discrimination ability

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