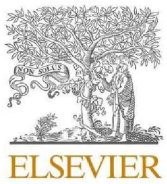
Intelligence 91 (2022) 101633



Contents lists available at ScienceDirect

Intelligence

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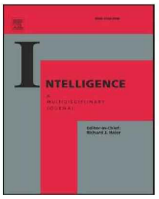

General cognitive ability and pericortical contrast

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ARTICLE INFO

Keywords:
Brain development
Gray-white contrast
Cortical contrast
Childhood
Adolescence
Cognitive ability
IQ

ABSTRACT

Individual differences in general cognitive ability have been associated with various brain structure metrics. A relatively novel metric referred to as pericortical Gray-White Contrast (GWC) describes the sharpness of the pericortical gray-white boundary. GWC, which is hypothesized to be at least partly influenced by the degree to which myelinated axons invade the lower layers of cortex, is believed to be significantly associated with the dynamics of signal transmission across the brain and hence, with cognitive ability. The current work explores the association between GWC and IQ across the surface of the cortex. Subject data were retrieved from the NIH MRI Study of Normal Brain Development (Evans & Brain Development Cooperative, 2006). 376 subjects with a total of 742 scans were included in the longitudinal analyses. Mixed-effects regression analyses were used to map the relation between cortical contrast and each of full-scale, performance, and verbal IQ derived from the Wechsler Abbreviated Scale of Intelligence, while covarying for scanner, sex, and age effects. Significant associations were shown with FSIQ, PIQ, but not VIQ. We discuss the interpretation of these results and how they may relate to previously published results on structural cortical associations.

1. Introduction

General cognitive ability has been associated with various aspects of brain structure including features of both gray and white matter. Cortical thickness and volume, for instance, have been shown to correlate with general cognitive ability across broad regions of cortex (Colom et al., 2009; Deary, Penke, & Johnson, 2010; Haier et al., 2009; Karama et al., 2009; Karama et al., 2011; Panizzon et al., 2009; Shaw et al., 2006). Further, the size and integrity of major white-matter bundles that link these broad cortical areas, has been shown to relate to measures of general cognitive ability (Chiang et al., 2009; Ganjavi et al., 2011; Luders, Narr, Thompson, & Toga, 2009; Penke et al., 2012; Tamnes et al., 2010; Yu et al., 2008). Together, these findings highlight the importance of regional cortical involvement and of white matter connectivity for intelligence differences. In keeping with this, and using T1-weighted/T2-weighted ratio for myelin mapping, Grydeland, Walhovd, Tamnes, Westlye, and Fjell (2013) have shown that intracortical myelination develops until the late thirties, is followed by 20 or so years of stability before declining from the late fifties onwards. Importantly, they found that intracortical myelin is positively associated with intra-individual performance variability in a speeded performance task and concluded that the stability of cognitive ability is, to some degree, meaningfully associated with intracortical myelination.

To complement the above-mentioned brain metrics, a gray/white matter contrast (GWC) metric has recently been developed (Salat et al., 2009; Olafson et al., 2020). It can be defined as the ratio of the intensity of white matter over gray matter on T1-weighted MRI images (Drakulich, Thiffault, & Olafson, 2021). While the neurobiological foundation of GWC is not fully understood, evidence suggests that GWC is significantly influenced by myelination characteristics surrounding the innermost layers of the cortex (Dale, Fischl, & Sereno, 1999; Grydeland et al., 2013; Norbom et al., 2019; Patel et al., 2020; Rowley, Bazin, & Tardif, 2015; Vidal-Piñeiro et al., 2016). Prior works modeling similar proxy measures of myelin at the pericortical boundary found a general trend of decreasing pericortical contrast, which progresses in a posterior to anterior fashion (Bartzokis, 2004; Grydeland et al., 2019; Norbom et al., 2020; Westlye et al., 2010). In Drakulich et al. (2021), our results reflected a posterior to anterior decline in GWC through childhood and

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https://doi.org/10.1016/j.intell.2022.101633
Received 26 October 2021; Received in revised form 1 February 2022; Accepted 1 February 2022
Available online 12 February 2022

adolescence. In an adult population, Vidal-Piñeiro et al. (2016) showed an association between symptoms of aging and decreased GWC in the frontal lobes, providing further support to examine GWC in relation to cognitive ability.

Since pericortical myelination is known to influence neuronal conduction and signal-to-noise ratio in cortico-cortical connectivity (Kandel, Schwartz, & Jessell, 2000), and because of interindividual variability in GWC, GWC has been proposed as a potential marker of cognitive ability differences. In keeping with this, Lewis et al. (2018) showed that GWC is a good age predictor and that the GWC-based residual of the age predictions is positively associated with IQ. Here, we expand on these results by mapping the relationship between GWC and IQ across the surface of the cortex in a longitudinal study of healthy children and adolescents.

2. Materials and methods

2.1. Sample and dataset

The data used for the present study were retrieved from the paediatric repository of the NIH MRI Study of Normal Brain Development (Evans and Brain Development Cooperative Group, 2006); a longitudinal study of typical brain maturation in children representative of the 2000 US census population. The original sample consisted of 431 children and adolescents (aged 4–18 years at first visit) who were invited on three separate occasions, 2 years apart, to undergo a battery of tests including, among others, MRI brain imaging and the Wechsler Abbreviated Scale of Intelligence (WASI). Inclusion of subjects in the current study was dependent on the availability of WASI IQ scores and good quality of processed brain images. After quality control of MRI images and exclusion due to missing data or visits, our dataset included 376 individuals. The sample sizes for each visit were the following: 251 subjects for visit one, 290 subjects for visit two, and 201 subjects for visit three. There were 120 subjects sampled only once, 256 subjects sampled twice, and 110 subjects who were sampled at all three visits. Subject handedness was denoted as "left-handed", "right-handed", "ambidextrous", or "mixed" (use of either hand varies depending on action).

2.2. MRI acquisition

Sagittal slices were acquired on 1.5 T MRI scanners across sites with a 1 mm isotropic resolution on most scanners (a 1.5 mm in-plane resolution was allowed on GE scanners due to their limit of 124 slices) using whole-brain 3D T1-weighted spoiled gradient recalled echo sequences (for more details, see Evans, 2006).

2.3. Image processing

The T1-weighted volumes were processed with CIVET (version 2.1.1). CIVET is a fully automated structural image analysis pipeline developed at the Montreal Neurological Institute. Intensity non-uniformities were corrected using N3 (Sled, Zijdenbos, & Evans, 1998); the input volumes were aligned to the ICBM-152-nl template (Collins, Neelin, Peters, & Evans, 1994); each image was classified into white matter, gray matter, and cerebrospinal fluid (Tohka, Zijdenbos, & Evans, 2004; Zijdenbos, Forghani, & Evans, 2002); the white-matter surface was extracted via marching cubes and placed at the point of maximal white/gray gradient at the inner edge of the cortical gray matter; the pial surface was positioned by walking outward from the white-matter surface to the CSF (Kim et al., 2005); finally, the surfaces were registered to a common surface template (Lyttelton, Boucher, Robbins, & Evans, 2007) and smoothed using a 20 mm smoothing kernel. Quality control was performed on CIVET output images using the procedure described in Ducharme et al. (2016). In the first step, scans were automatically excluded from the sample on the basis of various measures produced by CIVET for each individual scan, including, but not limited to, poor gray matter expansion and surface-surface intersections, among others: http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET-1-1-12-Quality-Control. Images were subsequently visually inspected and removed when significantly distorted; see Supplementary Fig. 1 for two examples from this dataset that were determined to be a pass and a failure, respectively. Since the sample used here is the very same as used in our prior work (Drakulich et al., 2021), the quality control process was not redone for this work.

2.4. White/gray contrast measure

GWC is defined here as the ratio of the intensities of white and gray matter on T1w MRI images after N3 correction. In the subjects' native space, we created a gray surface at 25% of the distance from the gray/white boundary to the pial boundary and a white surface at the same distance but in the direction of white matter. A relative distance to compute GWC was chosen in favor of a fixed distance due to the presence of extremely thin sections of cortex, wherein a fixed distance could, in some instances, lead to sampling at a distance greater than the thickness of the cortex. A relative sampling distance was also preferred over a fixed one to maximizes chances of sampling from the vicinity of the same cortical layer(s) across the cortical mantle. The value of 25% was based on results from Whitaker et al. (2016), showing that the highest myelin concentration observable in the cortex is within the 20% to 30% range of local cortical thickness. To produce the final contrast measures, the sub-white surface values were divided by the gray surface values at each vertex; thus, a larger GWC value represents a sharper gray-white boundary and possibly less intracortical myelin. An example depicting the placement of the surfaces used to compute contrast at each vertex is found in Fig. 1. Finally, spatial surface blurring was applied using a Gaussian blur with FWHM of 20 mm.

2.5. Cognitive testing

Full-scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) were assessed using the Wechsler Abbreviated Scale of Intelligence (Weschler, 1999). The WASI consists of Vocabulary, Similarities, Matrix Reasoning, and Block Design subtests. The latter two tests are categorized as performance IQ subtests, while the former, as verbal IQ subtests.

2.6. Statistical analyses

Statistical analyses were conducted using the SurfStat statistical toolbox (http://www.math.mcgill.ca/keith/surfstat), implemented in MATLAB, and/or using R version 3.6.2. In all analyses, t-values were estimated at each vertex and projected onto the ICBM152 average surface. A false discovery rate (FDR) threshold of 0.05 was applied to control for multiple comparisons and to identify the areas of statistical significance.

2.7. IQ analyses

Mixed-effects linear regression analyses, with individuals as random effects, were conducted by regressing GWC against FSIQ, PIQ and VIQ, respectively, while covarying for sex, scanner, and a cubic age effect (i.e., age + age^2 + age^3) as GWC has been shown to mainly follow a cubic trajectory within the age ranges studied here (Drakulich et al., 2021). The inclusion of age in these models may seem at first glance as "over-correcting", given that WASI IQ scores are already age standardized. However, the inclusion of age as a covariate in the model is necessary to account for its potential confounding effect on GWC. Note that covarying for age when looking at a variable that is already age-corrected (e.g., FSIQ) should have no significant impact on that variable's associations with another variable (e.g., GWC) other than accounting for uncorrected age effects on this other variable.

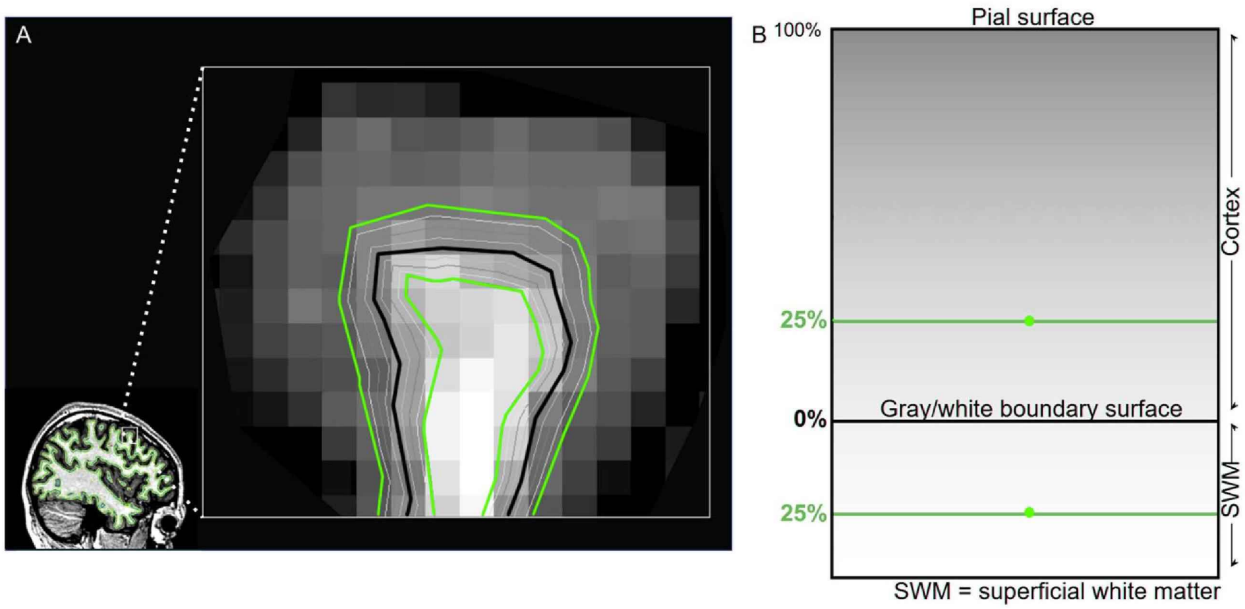

Fig. 1. Calculation of Gray-White Contrast (GWC).
Example showing the placement of the 25% distance surfaces in the gray matter and superficial white matter. Figure adapted with permission from Drakulich et al. (2021).

2.8. Examining sex effects

Examinations of the GWC associations with FSIQ, PIQ, and VIQ, respectively, were also done in male-only and female-only subsets of the original dataset. To assess if observed sex differences were statistically significant, sex by cognitive ability interaction terms (sex by FSIQ, sex by PIQ, or sex by VIQ) were respectively added to our models in a further set of analyses.

2.9. Examining associations specific to PIQ and VIQ

As PIQ and VIQ are known to be highly correlated (here, r value ~0.37, ~0.42, and ~ 0.43, for Visit 1, Visit 2, and Visit 3, respectively), we re-examined, on the full sample, GWC/PIQ associations after controlling for VIQ (and vice versa) in order to disentangle GWC associations specific to PIQ and VIQ, respectively.

2.10. Examining associations with brain volume

Even though GWC is not a measure of physical size (i.e., is dimensionless), we analyzed the data with and without controlling for brain volume due to the well-established association between brain volume and measures of cognitive ability. As brain size had a noticeable impact on results (see results section), we examined this further by looking at the simple association between brain size and local GWC, while covarying for sex, scanner, and a cubic age effect.

2.11. Estimating effect sizes

To provide estimates of effect sizes, vertex t-values were transformed into Pearson partial correlation and provided in supplementary material (Fig. 2B and Fig. 3B). Student *t*-values were transformed into Pearson partial correlation values using the usual following equation where df is the number of degrees of freedom of the *t* statistic (Gravetter & Wallnau, 2008):

$$r = t/(t^2 + df)$$

2.12. Comparing cortical thickness/IQ with GWC/IQ associations

Associations between cortical thickness and IQ (i.e., FSIQ, PIQ, VIQ) have frequently been reported (Raz et al., 2005; Sowell et al., 2003; Sowell et al., 2004), including on children from the NIH Study of Normal Brain development (Karama et al., 2009). To allow for a qualitative comparison between cortical thickness/IQ and GWC/IQ findings, we revisited cortical thickness/IQ associations using the same CIVET pipeline (i.e., version 2.1.1) and the exact same sample used here to generate GWC/IQ associations.

Except for the age effect, which was modeled as a monotonic linear effect (as cortical thickness has been shown to mainly follow such a linear effect for the age ranges examined here), the same mixed-effects regression analysis modeling method used for GWC/IQ associations was used for Cortical Thickness/IQ associations. More specifically, mixed-effects linear regression analyses, with individuals as random effects, were used to regress cortical thickness against FSIQ, PIQ, and VIQ, respectively, while covarying for sex, scanner, and a monotonic linear age effect.

2.13. Disentangling GWC effects from cortical thickness effects

CIVET places the white matter surface at the point of maximal contrast between white and gray matter. This can directly affect estimates of cortical thickness and may create correlations between GWC and cortical thickness. At the extreme, GWC may potentially account for previously reported cortical thickness/IQ associations. On this basis, analyses on the whole sample were redone after including local cortical thickness as a covariate to examine associations between IQ and GWC independently of cortical thickness. Further, in order to see if controlling for cortical thickness attenuated GWC/IQ associations more than the reverse (i.e., controlling for local GWC in IQ/cortical thickness associations), the associations between cortical thickness and IQ were re-examined while covarying for local GWC. Partial correlation value changes of IQ were used to estimate to what extent FSIQ/GWC associations were attenuated with the inclusion of local cortical thickness and vice versa. Specifically, the brain maps of partial correlations from the FSIQ/PIQ models, with and without the added respective local cortical thickness or GWC covariate, were squared to produce R^2 values and then

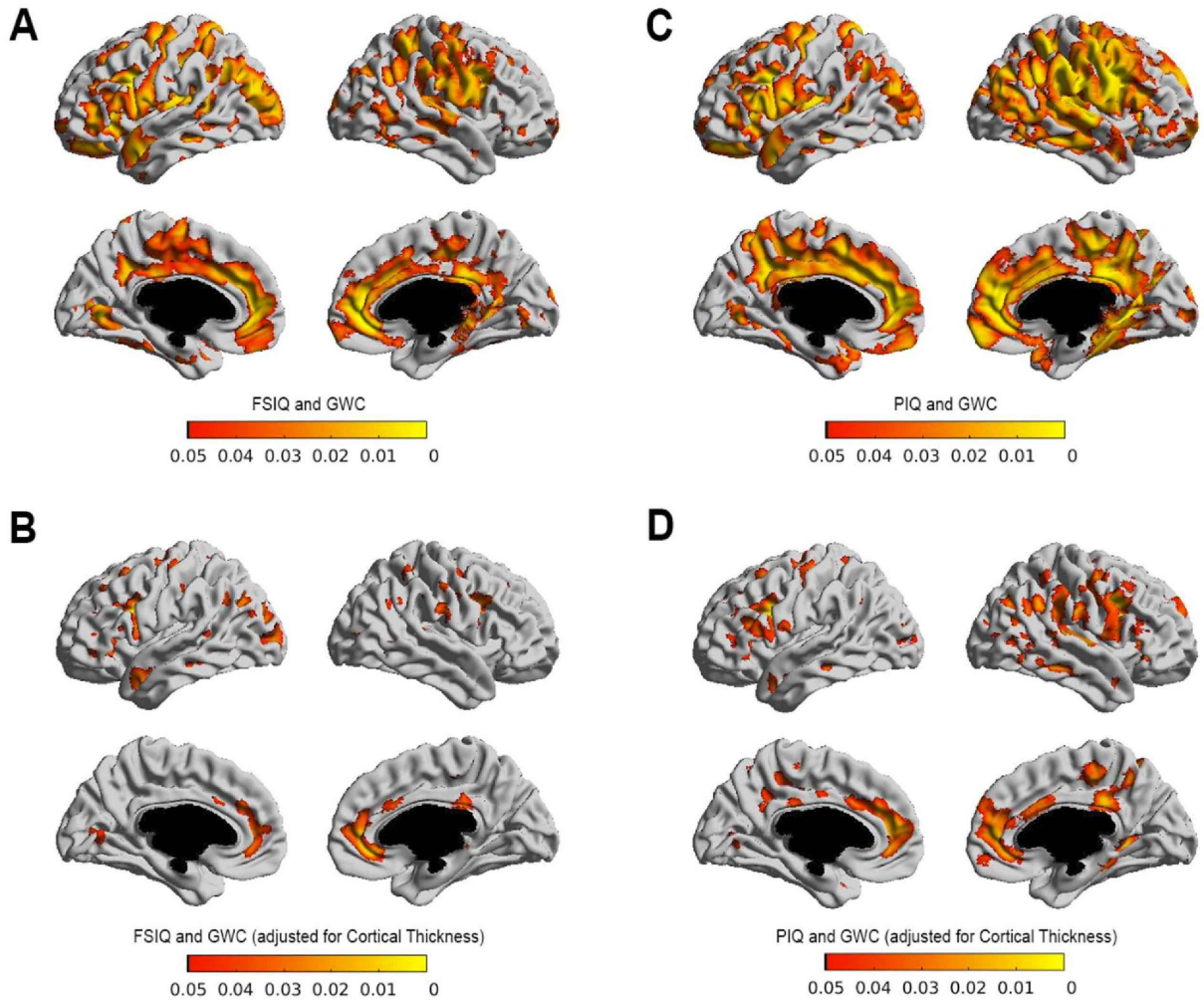

Fig. 2. Regions of statistically significant associations after thresholding with a false discovery rate of 0.05. A) Associations between GWC and Full-Scale IQ controlling for gender, scanner, and a cubic age effect - See supplementary F2_A for matched t-map and F2_B for unthresholded partial correlation map showing Pearson r values. B) Associations between GWC (adjusted for local cortical thickness) and Full-Scale IQ controlling for gender, scanner, and a cubic age effect C) Associations between GWC and Performance IQ controlling for gender, scanner, and a cubic age effect – See supplementary F3_A for matched t-map and F3_B for unthresholded partial correlation map showing Pearson r values. D) Associations between GWC (adjusted for local cortical thickness) and Performance IQ controlling for gender, scanner, and a cubic age effect.

masked according to the 5% FDR significance mask from the simpler model (i.e., the model without the added covariate); the remaining partial correlation difference values were then averaged, yielding gross estimates of how much of an effect covarying for cortical thickness had on GWC/IQ associations and covarying for GWC had on cortical thickness/IQ associations.

2.14. Examining associations between changes in GWC and changes in IQ

Lastly, associations between change in GWC and change in FSIQ were investigated by only analyzing subjects that were scanned for all three visits ($n = 110$), allowing for the calculation of slope of GWC change at each vertex against slope of FSIQ change for each subject. The covariates included in these models were sex, mean GWC at baseline (i.e., sampling timepoint one), age at baseline, and FSIQ measure at baseline. Prior to modeling, scanner was residualized out from the GWC metric using a mixed effects model in SurfStat, with just the scanner and the subject random effect included. The adjusted GWC values were then used in the change analysis modeling.

The model used for the GWC change analysis was as follows:

$$\Delta GWC = \beta 0 * Intercept + \beta 1 * AgeV1 + \beta 2 * IQV1 + \beta 3 * \Delta IQ + random(Subject) + Error$$

With ΔGWC representing GWC slope, $AgeV1$ representing age in years at the first timepoint, $IQV1$ representing IQ at the first timepoint, and ΔIQ representing slope of change in IQ.

3. Results

Descriptive statistics for age, FSIQ, PIQ and VIQ for each visit are shown in Table 1. In the preliminary set of analyses examining associations between IQ measures and GWC without vertex-wise adjustment for cortical thickness, FSIQ and PIQ evidenced relatively widespread positive associations with GWC, while no areas of significance were found between VIQ and GWC. Significant FSIQ (Fig. 2A) and PIQ (Fig. 2C) associations with GWC were widespread and bilateral with the strongest areas of association in prefrontal, parietal, and anterior cingulate regions. The association between FSIQ and GWC showed a slightly less widespread distribution of significant vertices compared to the association between PIQ and GWC, although they were nearly identical in the regions that emerged as significant. The distribution of

the association between GWC and PIQ was only slightly attenuated by covarying for VIQ (See Supplementary Fig. 4). The inclusion of PIQ as a covariate when modeling the association between GWC and VIQ did not produce any significant signal.

Modeling performed on male- or female-only subsets of the data (without sex as a covariate) produced association maps with greatly diminished presence of significant vertices at 5% FDR when compared to the associations modeled on the combined sample; however, because subsequent modeling found no presence of any significant effect of an interaction between Sex and IQ at any vertex, these data are not shown.

When total brain volume was added as a covariate in the models, there was an attenuation of significance with respect to number of significant vertices (see Supplementary Figs. 13 and 14); the most notable regions exhibiting diminished significance were the medial and lateral orbitofrontal cortex, lateral and rostral frontal cortex, precuneus, posterior cingulate, isthmus of the left cingulate gyrus, dorsal superior parietal gyrus, lingual gyrus, and inferior occipital cortex. In order to examine this further, we looked at the simple association between GWC and total brain volume alone (i.e., without cognitive ability in the model - see Supplementary Fig. 12). This yielded fairly widespread regions of significant positive associations almost exclusively located in regions known to be involved in intelligence differences (i.e. the prefrontal cortex, lateral posterior parietal cortex, lingual gyrus, and precuneus) as well as the pre- and post-central gyri, and sparsely in the inferior occipital cortex.

GWC adjusted for local cortical thickness at each vertex showed a clear and notable reduction in the areas depicting positive associations between GWC and both FSIQ (Fig. 2B) and PIQ (Fig. 2D), respectively. Significant vertices in both models were more restricted to, for the most part, the frontal cortex, the anterior cingulate, and sparsely at the inferior parietal lobule; small, isolated regions of significance were also found in the inferior temporal cortex, near the insula, and scattered in the sulci of the parietal and occipital lobes.

Subjects were a mixture of "left" handed, "right" handed, "ambidextrous", and lastly, "mixed" use of both hands. Controlling for handedness had no significant impact on a complete absence of changes in either regionality or extent of significance.

We examined the attenuation of the associations between IQ/GWC and IQ/Cortical thickness before and after controlling for either cortical thickness or GWC, respectively. This analysis showed that the mean (across vertices) difference in mean partial correlations in our data was slightly greater for the association between IQ and GWC after controlling for cortical thickness (FSIQ: 0.0424; PIQ: 0.0462; VIQ: 0.0258) than for the associations between IQ and cortical thickness after controlling for GWC (FSIQ: 0.0315; PIQ: 0.0340; VIQ: 0.0182). Results from the vertex-wise IQ/Cortical Thickness modeling have been included in the supplementary material (Supplementary Figs. 5-11).

Examining the association between change in GWC and changes in IQ yielded no areas of statistically significant associations.

4. Discussion

In a large representative US cohort of healthy individuals aged from 6 to 22 years, we have demonstrated that pericortical GWC is positively associated with FSIQ, and PIQ across broad regions of the cortex. The strongest associations between GWC and cognitive ability were in lateral prefrontal and parietal areas, a portion of which remain significant after including total brain volume as a covariate. This is in keeping with the reported preferential involvement of these multimodal association areas in intelligence differences (Basten, Hilger, & Fiebach, 2015; Jung & Haier, 2007). Basten et al. (2015) performed separate meta-analyses of functional and structural brain imaging studies of differences in human cognitive ability. This meta-analysis refined Jung & Haier's Parieto-Frontal Integration Theory of intelligence (P-FIT), in that it a) distinguishes between structural and functional correlates of intelligence of the P-FIT, b) denotes positive and negative associations with intelligence at various foci, and c) includes the insular cortex, posterior cingulate cortex, and subcortical structures in addition to those in the original P-FIT (frontal, parietal, temporal, and occipital lobes) (Basten et al., 2015). The regions included in this revised P-FIT have been identified as multimodal processing centers, with injuries to these areas being the most likely to lead to cognitive deficits (Glascher et al., 2010). Relatively strong associations with cognitive ability in our data were also observed in the anterior cingulate region, slightly more widespread in the right hemisphere. The anterior cingulate is believed to be engaged in constraining response selection, inhibiting competing responses, error detection, and balancing them in order to reward optimal decision-making (Chudasama et al., 2013; Hayden & Platt, 2010; Jung & Haier, 2007; Løvstad et al., 2012). In the context of the revised Parieto-Frontal Integration Theory (P-FIT) of intelligence (Basten et al., 2015, Jung & Haier, 2007), these regions and the connectivity between prefrontal and parietal areas, via the arcuate fasciculus, are crucial to higher-order cognitive performance. Finding associations between GWC and IQ in the anterior cingulate is compatible with the known involvement of the anterior cingulate cortex in cognition (Løvstad et al., 2012; Stevens, Hurley, & Taber, 2011). The anterior cingulate cortex is a hub that shares connections with both the prefrontal cortex and the limbic system (Hadland, Rushworth, Gaffan, & Passingham, 2003; Mueller, Brass, Waszak, & Prinz, 2007). In other words, it is linked with both cognitive and emotional regulation regions and, while speculative, might be involved in motivational states and cognitive drive while pursuing a cognitive task (Assadi, Yücel, & Pantelis, 2009; Devinsky, Morrell, & Vogt, 1995; Holroyd & Yeung, 2012; Løvstad et al., 2012).

Another, perhaps complementary, mechanistic perspective for our findings draws on a link between cortical gray matter tissue sparsity and cognitive ability. More specifically, Genc et al. (2018) showed that greater neurite sparsity within the cortex is linked to higher intelligence. This link might be due to individual differences in pruning of non-essential neurites. This, in turn, would allow for greater signal-to-noise ratio and provide more efficient signal transfer. A decrease in tissue within the cortex associated with sparser neurites could possibly lead to increased GWC and account for the positive association between contrast and cognitive ability found in our current work. This proposal should be understood as being highly speculative as it is not based on a concurrent analysis of both contrast and neurite sparsity, as neurite sparsity data is unavailable for this dataset.

The strongest and most widespread associations with GWC observed in our analysis was with performance IQ. Since performance IQ and verbal IQ jointly contribute to full-scale IQ, it is expected that the strength of a given association with full-scale IQ will land between that of either performance or verbal IQ, an effect reflected in our results. As highlighted in the introduction, cognitive ability is likely to be partially related to the degree of myelination of pericortical connections invading the cortex, an index which is thought to be partially captured by quantifying the contrast in the intensities of white versus gray matter at the inner edge of cortical gray matter. Finding an association with performance IQ, but not with verbal IQ, can be viewed as suggesting that pericortical myelination is mostly involved in fluid intelligence rather than in crystallized forms of intelligence.

Research from adjacent fields can also help contextualize and support the suggestion that GWC is a functionally relevant metric that likely reflects, to some extent, the degree of myelination. While speculative, the current findings are potentially compatible with previously reported work emphasizing the importance of white matter for cognition, such as positive associations between white matter *N*-acetylaspartate in left frontal and occipito-parietal areas and general intelligence (Jung et al., 1999; Jung et al., 1999), as well as between white matter integrity, processing speed, and general intelligence (Penke et al., 2012). Further potential supporting evidence comes from the field of network neuroscience by means of using graph theory on proxy metrics of myelin content (Lutti, Dick, Sereno, & Weiskopf, 2014; Boshkovski et al., 2021). One such study examined how myelination (as measured by

magnetization transfer) changes synchronously among spatially distant regions to create characteristic networks of gray-matter myelin covariance that undergo topological changes through young adulthood (20–31 years old) and old age (60–71 years old) (Melie-Garcia et al., 2018). In the young group, they found high myelin covariance in homologous structures in the frontal and parietal lobes, and higher global efficiency in the constructed myelin networks than in the old age-group. They suggest that two brain structures anatomically connected by myelinated fibers are likely to show correlated and relatively similar myelin density, possibly in order to optimize synchronicity between these structures and their connections (Kimura & Itami, 2009; Melie-Garcia et al., 2018). With this in mind, future examinations of GWC through the lens of network neuroscience may prove useful.

It has been shown that GWC decreases with age (Lewis et al., 2018, Drakulich et al., 2021). Also, raw cognitive ability (i.e., uncorrected for age), increases throughout development (Waber et al., 2007). One could hence expect a negative association between GWC and cognitive ability. On the contrary, our data show the reverse relationship of a positive association between GWC and IQ. To reconcile this apparent contradiction, we need to first highlight that IQ measures, unlike raw/absolute cognitive ability, are relative, age-standardized metrics. Within this framework, it is possible to imagine that people with greater intelligence start with greater GWC and, at any given age, tend to have greater GWC, despite GWC decreasing as the brain reaches maturity. This could explain the positive association observed here.

Overall, the pattern of associations found between cognitive ability and pericortical contrast had some overlap with the pattern of associations between cognitive ability and cortical thickness in this work. This latter association with cortical thickness was modeled cross-sectionally with a first-order linear model in Karama et al. (2009), with clear albeit not perfect overlap with the pattern shown in this work. This could be explained by differences in study design, wherein we employed a longitudinal design in a sample with a broader range of ages (4–22 years old) compared to that of Karama et al. (2009) (6–18 years old), by improvements in the CIVET pipeline, and by the fact that the specific sample was not identical as more subjects passed QC with CIVET 2.1.1 than with the older version of CIVET used in the Karama et al., 2009 paper. Nevertheless, our results appear to corroborate an obvious preferential involvement of parieto-frontal and temporal regions, as well as a notable presence of significance in key medial structures. This is well in line with existing literature of multimodal associations of intelligence found in the human brain (Luders et al., 2009; Tamnes et al., 2010; Grydeland et al., 2013; Burgaleta, Johnson, Waber, Colom, & Karama, 2014; Shaw et al., 2006; Tamnes et al., 2017), and supports the P-FIT (Jung & Haier, 2007). The coinciding regional significance suggests that changes in pericortical contrast are meaningful with respect to function and integrity of these areas in higher-order cognition. Importantly, while controlling for local cortical thickness led to an attenuation of the association between GWC and IQ measures, many regional associations persisted, suggesting some degree of independent contributions from both GWC and cortical thickness to cognitive ability differences. This supports the view that at least a portion of intelligence differences are explained by multiple, and at least partially independent, neurobiological factors.

Our analysis of the gross differences in mean partial correlations in the associations between the cognitive measures and either GWC or cortical thickness sought to inform which metric's association with IQ was stronger. We found that GWC is potentially more distinctly associated with cognitive ability, at least for the age range spanning this study, than with cortical thickness, despite their interdependence with respect to physiology and how both metrics are calculated.

As would be expected from decreased statistical power, when examining boys and girls separately, associations between GWC and the various IQ measures exhibited diminished regional significance when compared to the larger sample including both sexes. There was little to no overlap in the sparse regions that remained significant at 5% FDR. Since the subsequent analysis which tested for a significant Sex by IQ interaction produced a null result, apparent differences in the GWC and IQ associations modeled on the male-only and female-only subsets are likely attributable to expected statistical fluctuations in our data between the male and female samples. However, not finding sex differences does not necessarily mean that these do not exist. An alternative might be that the effect size of sex differences for IQ and GWC associations throughout early life is very small and would require a larger sample to be detected if they exist.

Observing a noticeable attenuation in number of significant vertices when controlling for total brain volume (a measure of size) prompted further analysis, as GWC is not a measure of physical size. Surprisingly, our subsequent examination of the simple association between total brain volume and GWC (i.e., excluding measures of cognitive ability from the model) revealed that this association was almost exclusively limited to regions known to be involved in intelligence differences (Jung & Haier, 2007) and hence explaining the GWC/cognition attenuation in association when controlling for total brain volume. The prefrontal cortex, cingulate gyrus, precuneus, and pre- and post-central gyri, and parts of the occipital lobe, all showed broad significant associations between brain volume and GWC. Finding such a pattern between total brain volume and GWC (without cognitive ability measures in the model) is intriguing and will require work that extends well beyond the scope of this paper. Results from the association between GWC and measures of cognitive ability, with and without the inclusion of brain volume as a covariate, retained significant associations in regions associated with higher order cognitive functions and multimodal association areas, suggesting that GWC makes somewhat independent contributions to cognitive ability.

Prior work using diffusion MRI might be able to aid the interpretability of our results. The regions with a significant association between brain volume and GWC in our data appeared to be in regions of granular cortex (Triarhou, 2007). A study on the HCP dataset used diffusion MRI to produce maps of neurite density and neurite orientation dispersion, among other measures (Fukutomi et al., 2018); the regions with highest neurite density largely overlap with significant regions showing an association between GWC and brain volume in our work. Likewise, regions showing a significant positive association between GWC and cognitive ability appear to have overlap with lower dispersion in neurite orientation (Fukutomi et al., 2018). If GWC partially reflects wiring efficiency, our findings support the hypothesis that cognitive ability is less related to a metric amounting to the sum of cellular matter in the brain, and instead reflects the quality in wiring of neural pathways and connections, as well as pruning of excess and/or metabolically unproductive ones (Genc et al., 2018).

Examining associations between change in GWC and change in IQ did not yield significant associations. This contrasts with findings from Burgaleta et al. (2014), where such an association was noted for cortical thickness despite also looking at a sample of children and adolescents from the NIH Study of Normal Brain Development. One possibility is that there is indeed no association between changes in GWC and changes in cognitive ability in early life in contrast to later life, where a faster decline in GWC throughout late adulthood was found to be associated with more aggressive cognitive decline (Vidal-Piñeiro et al., 2016). Differences in associations between GWC changes and cognitive ability changes may be due to the underlying reasons for the changes in GWC. In our study, GWC changes are linked to development, whereas in the Piñeiro et al. study changes in GWC are likely due to brain tissue degeneration. Another possibility is that our sample was underpowered for this part of our analysis; Burgaleta et al. (2014) conducted their study on a sample of 188 subjects and between only two of the visits, whereas our sample consisted of 110 subjects over three timepoints.

The results presented here are bound by the usual limitations associated with data that are inevitably correlational. For instance, finding associations between brain measures and a measure of general cognitive ability in a distributed set of areas does not necessarily imply an

involvement of this whole set of areas in cognitive ability differences. Indeed, it is possible to imagine a common mechanism influencing GWC throughout these brain areas but with only a subset of these areas being involved in intelligence differences. Having said this, finding correlations between pericortical contrast and measures of general cognitive ability preferentially distributed in multimodal association areas suggests that links between mental ability and pericortical contrast in these areas are not spurious, as cognitive processes are likely to involve multimodal processing. Given the advent of new imaging methods capable of more directly capturing myelin and related processes, subsequent studies should be well poised to further inform the nature and significance of the associations that appear to be emerging between changes at the pericortical gray-white boundary and cognitive ability. Finally, our sample aims to be representative of the healthy typically developing population of the US 2000 census and hence excludes many subjects that constitute the US population. This led to the exclusion of individuals with neurological disease and/or IQ scores below 70 and had the corollary consequences of leading to a mean sample IQ greater than 100. The generalizability of our findings should be viewed with this limitation in mind.

In summary, we have shown a multiregional positive association between measures of cognitive ability and pericortical GWC in the period of life from early childhood to the beginning of adulthood. These results complement those showing relationships between cognitive ability and other features of the cortex like cortical thickness, with a similar spatial distribution. While future work is needed to further inform the nature and significance of these relationships, this comparative analysis supports the hypothesis that differences in peri-cortical myelination within cortical gray tissue may account for at least part of the association between pericortical contrast and cognitive ability.

Acknowledgments & declaration of interests

This project has been funded in whole or in part with Federal funds from the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke (Contract #s N01-HD02-3343, N01-MH9-0002, and N01-NS-9-2314, N01-NS-9-2315, N01-NS-9-2316, N01-NS-9-2317, N01-NS-9-2319 and N01-NS-9-2320). SK is supported by a CIHR Salary Award. We thank Dr. Claude Lepage for his valuable comments and assistance with implementation of the GWC measure. This project also benefited from computational resources provided by Compute Canada (www.computecanada.ca) and Calcul Quebec (www.calculquebec.ca). The authors have no competing interests to declare.

Credit authorship contribution statement

Stefan Drakulich: Methodology, Software, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Arseni Sitartchouk:** Methodology, Investigation, Writing – original draft. **Emily Olafson:** Methodology, Software, Visualization, Validation, Writing – review & editing. **Reda Sarhani:** Methodology, Writing – review & editing. **Anne-Charlotte Thiffault:** Methodology, Writing – review & editing. **Alan C. Evans:** Funding acquisition, Supervision. **Mallar Chakravarty:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **Sherif Karama:** Conceptualization, Methodology, Investigation, Funding acquisition, Writing – original draft, Writing – review & editing, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intell.2022.101633.

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