Through thick and thin: A need to reconcile contradictory results on trajectories in human cortical development

Running title: Maturation of cortical thickness

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Abstract

Understanding how brain development normally proceeds is a premise of understanding neurodevelopmental disorders, which has sparked a wealth of magnetic resonance imaging of studies. Unfortunately they are in marked disagreement on how the cerebral cortex matures. While cortical thickness increases for the first eight to nine years of life have repeatedly been reported, others find continuous cortical thinning from early childhood, at least from age three or four years. We review these inconsistencies, and discuss possible reasons such as use of different scanners, recording parameters and analysis tools, and effects of variables such as head motion . When tested on the same sample, two popular thickness estimation methods (CIVET vs. FreeSurfer) both yielded continuous thickness decrease from 3 years. Importantly, MRI-derived measures of cortical development are merely our best current approximations, hence the term "apparent cortical thickness" may be preferable. We recommend strategies for reaching consensus in the field, including multimodal neuroimaging to focus on phenomena from different angles, e.g. use of T1/ T2 ratio to quantify cortical myelin content, and data sharing to allow replication across analysis methods. As the neurodevelopmental origins of early- and late-onset disease are increasingly recognized, resolving inconsistencies in brain maturation trajectories is important.

Keywords:

Childhood, cortical thickness, maturation, MRI, neurodevelopment

In this feature article, we wish to address what we perceive as critical inconsistencies in current studies of human brain development. Through more than two decades, there has been a substantial increase in studies characterizing human neurodevelopmental trajectories, both in health and disease (Giedd and Rapoport 2010; Raznahan, Lerch, et al. 2011). This most welcome (Lee et al. 2014) research focus has been sparked by multiple factors. One is the advent and widespread use of magnetic resonance imaging (MRI), allowing non-invasive, safe characterization of brain macro- and microstructure and function *in vivo*. Another is the recognition that in order to understand deviant brain development, we must know how development normally proceeds, and so studies of large groups of healthy children and adolescents have been initiated alongside studies of neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and schizophrenia (Giedd and Rapoport 2010). The latter is clearly exemplified in the strategy of the Child Psychiatry Branch of the National Institute of Mental Health in the US, where such studies have been ongoing since 1989 (Giedd et al. 2015). By now, the neurodevelopmental origins of both early- and late-onset disease are increasingly being recognized, and hence, resolving inconsistencies in reported brain maturation trajectories should be of utmost importance.

The human cerebral cortex is the crown of development, phylogenetically and ontogenetically, and essential to higher-order cognitive function. Not surprisingly then, the quest to identify the fundaments of disordered and healthy human function in MRI studies has focused on cortical development. Human cortical development is protracted and heterogeneous, not only across regions, but with respect to the characteristics that determine gray matter volume—namely cortical surface area and

cortical thickness. These characteristics differ widely across development (Amlien et al. 2014) and adult age (Hogstrom et al. 2013), as they are shaped by independent genes (Rakic 1988; Panizzon et al. 2009) and neurobiological events (Rakic 2009). Although both surface area and thickness have been studied with increasing frequency, cortical thickness has thus far received the most attention in developmental studies, going back more than 10 years. However, and in our opinion largely unrecognized, current results regarding maturational trajectories of cortical thickness in particular are inconsistent. In the following, we review the discrepant views of human brain development that have emerged, focusing on the maturational trajectory of cortical thickness. We then proceed to discuss possible reasons for the divergent results across studies, and conclude with suggestions for how we might come to a consensus in the field about how cortical thickness and other related brain characteristics develop.

The early-emerging view of cortical thickness development: increases peaking in early school age

Early human brain imaging studies reporting measures of cortical thickness appeared to generally agree in showing marked developmental *increases* in thickness within large areas through the pre-school and early school-age years, with the age of peak thickness depending on the brain region (Sowell et al. 2003; Sowell et al. 2004; Shaw, Greenstein, et al. 2006; Shaw et al. 2007; Shaw et al. 2008; Raznahan, Shaw, et al. 2011). An overview of some of these studies is provided in Table 1. Besides the rates of regionally varying thickness change, attention also has been paid, and significance attached to, the age at which cortical thickness *peaks*. Differences in developmental trajectories of cortical thickness have been mapped and associated with a wide variety

of functional outcomes, spanning from general intellectual development (Shaw, Greenstein, et al. 2006) and normal behavioral problems (Shaw et al. 2011) to attention deficit hyperactivity disorder (ADHD) (Shaw et al. 2007) and childhood schizophrenia (Alexander-Bloch et al. 2014). For instance, the median age by which half of the cortical points attained peak thickness was observed to be 7.5 years for healthy children, while it appeared delayed by about three years for children with ADHD (Shaw et al. 2007), and nonlinear alterations in cortical development were found in children with schizophrenia but not normal developing children (Alexander-Bloch et al. 2014).

[Insert Table 1 about here]

From the results described above, it appeared that individual differences in cortical thickness maturation held promise as a potential biomarker for risk of severe neurodevelopmental disorders. It is all the more puzzling then, that the general developmental trajectory — including the existence of any increase or peak in cortical thickness after infancy — is by now not agreed upon across studies. Numerous recent and large-scale studies have now failed to identify such peaks in any cortical region and rather have observed near-uniform monotonic thinning of the entire cortex extending from preschool through school age and adolescence into the young adult years.

The later-emerging view of cortical thickness development: monotonic thinning from early childhood

Since about 2012, a growing set of studies have reported monotonic thinning of the cortex across an age range extending from the pre-school years and into adolescence. In 2012, the first results from the large USA-based multi-center PING (Pediatric Imaging, Neurocognition, and Genetics) study (pingstudy.ucsd.edu), spanning 10 different sites across the country, surfaced showing continuously thinner cortex with higher age (Brown et al. 2012; Fjell et al. 2012). This study scanned children from age three years, which would make it sensitive to the early increases previously observed around middle to late school age. Another cross-sectional single-site study came to the same conclusion based on scans from children four years and older (Amlien et al. 2014). In these studies, both vertex-wise and region of interest (ROI) analyses were used without finding any evidence of initial thickness increases. Several longitudinal studies have now come to the same conclusion. Many of these were ROI-based, but often covering the entire cortex, making it unlikely they would have failed to detect regional increases in cortical thickness. These studies sampled children from as low as age three (Zielinski et al. 2014) or four (Nguyen et al. 2013) years of age and up to six (Wendelken et al. 2011; Mutlu et al. 2013) or seven years (Mills et al. 2014; Wierenga et al. 2014), which should be sufficient to detect early peaks in cortical thickness. Sample sizes have been more than adequate, relying on from just above 200 scans (Shaw, Lerch, et al. 2006; Gogtay et al. 2007; van Soelen et al. 2012; Mutlu et al. 2013; Wierenga et al. 2014) to beyond 850 (Mills et al. 2014). An overview of select studies finding monotonic decreases in cortical thickness is provided in Table 2.

[Insert Table 2 about here]

In sum, these generally more recent reports are difficult to reconcile with the earlier, arguably more influential, view of cortical thickening and peaking during school age. But the number and character of these more recent studies make them impossible to dismiss. They are from independent labs with independent samples, from different countries in Europe and the US, some single-scanner and single-center studies, some multi-scanner, multi-site studies, using both cross-sectional and longitudinal designs, with samples spanning from three years of age to well into adulthood, using both ROI and anatomically unconstrained vertex-wise approaches. Complementary to these findings, recent infant studies have suggested that cortical development after the first two years of life is mainly caused by the expansion of surface area (Li et al. 2013). By age two, cortical thickness has been reported to be on average 97% of young adult values, compared with a total surface area of only 69% of expected young adult size (Lyall et al. 2014).

We find it pivotal that the discrepancies in reported cortical thickness maturation are addressed and that steps are taken to reach consensus on general developmental trends, given the enormous scientific interest and the clinical and cognitive significance attached to cortical maturation.

Possible reasons for discrepant findings across studies

There are multiple possible explanations for the inconsistent findings, including (1) sample heterogeneity and cohort effects, (2) curve fitting methods and (3) methodological, conceptual, and terminological differences in measuring cortical thickness from MRI imagesThese studies do to a large extent sample similar and overlapping age ranges, but effects of other between-samples differences in

demographic factors cannot with certainty be ruled out. Use of the popular higher order polynomial fits has the potential for imposing peaks where there may be none (Fjell et al. 2010). Also, since some studies do not show individual data points, it is difficult to get an impression of the appropriateness of the fits. Still, this is at least unlikely to be the sole reason for the discrepancies reported, since several studies finding both early increases and several studies reporting monotonic decreases have employed other fit models. However, choice of fit model is worthy of consideration in future studies. Hence, we believe that methodological differences in measuring cortical thickness, which have themselves evolved over time, are a most likely and parsimonious explanation for the inconsistencies that have been observed. Over the last three decades, there have been vast differences in MRI methodology used in human developmental studies, pertaining to multiple levels, including both acquisition and analyses. For instance, it was recently found that motion has a negative effect on cortical thickness estimates even after removal of low quality scans by regular manual inspection (Reuter et al. 2015). Since movement is expected to correlate negatively with age during childhood development, this can potentially reduce the slope of the age-trajectories of thickness. If movement due to unknown factors was higher in some parts of the age-range than others, this could in principle also cause seemingly non-linear developmental trajectories. Perhaps even greater differences can be produced by the specific processing and analysis steps involved in the measurement of cortical thickness from MR images.

A decade ago and earlier, the term “cortical thickness” appeared relatively rarely in published MRI studies. There was a predominance of processing techniques measuring gray matter (GM) “density” or volume, including the cortex, which grew

out of processing pipelines based on voxel based morphometry (VBM) methods, such as within SPM (Ashburner and Friston 2000) and SIENA (Structural Image Evaluation, using Normalization, of Atrophy) in FSL (Smith et al. 2001). GM density refers to the probability that a given voxel consists of gray matter, and is often interpreted as GM volume within the VBM terminology. In contrast, processing streams using reconstructions of the inner and outer cortical surfaces recently have become more widely used. Examples of such analysis tools include Freesurfer (Dale and Sereno 1993; Dale et al. 1999; Fischl and Dale 2000) and CIVET (www.bic.mni.mcgill.ca/ServicesSoftware/CIVET). Importantly, the measurement of cortical thickness requires that the analysis is performed at the nodes of a three-dimensional polygonal mesh rather than on a 3D voxel grid (Lerch and Evans 2005), capturing the distance between the white matter (WM) surface and the intersection between the outer cortical boundary and the cerebrospinal fluid (CSF) (see Figure 1), according to a geometric definition which can vary across methods. It follows that the way cortical thickness is quantified is of importance for the end results.

[Insert Figure 1 about here]

A major issue in this regard is the need to consistently distinguish among cortical thickness, cortical surface area, and cortical volume. As mentioned, the two former entities seem to show consistently different relationships to age (Hogstrom et al. 2013) and are shaped by independent genes (Rakic 1988; Panizzon et al. 2009) and neurobiological events (Rakic 2009). Importantly, while studies disagree on the trajectories of cortical thickness, they seem to converge on developmental increases in cortical surface area. A striking, but nevertheless typical, example is illustrated in

Figure 2. Here we see that in one large study of 647 healthy participants from 3-30 years, with > 1250 longitudinally acquired brain scans, increases in cortical thickness are observed until about 8.5 years (Raznahan, Shaw, et al. 2011). The trajectory for cortical thickness and surface area both followed the same basic cubic shape, although the peak for thickness was attained somewhat earlier than for area. In comparison, in a sample of a similar size (n > 700, scans in total > 1125, age range 4.1 to 30 years) from the Research group for Lifespan Changes in Brain and Cognition (LCBC), University of Oslo, only monotonic decreases in cortical thickness are evident. In contrast, the area trajectories resemble those seen in Raznahan et al. (Raznahan, Shaw, et al. 2011), showing increases well into school age.

These discrepancies are puzzling. Both studies are done on 1.5T MRI, and neither is performed at multiple sites using different scanner types. Although different scanners and T1-weighted sequences were used, we believe it is not likely that this caused the divergent results, as studies comparing results across scanners have not indicated biases of such a magnitude (Fennema-Notestine et al. 2007; Dickerson et al. 2008), and current large-scale multi-center studies of both development (PING) and Alzheimer's disease (ADNI) are based on different scanners and vendors. Different statistical models were used to fit the data, with Raznahan et al. (Raznahan, Shaw, et al. 2011) using quadratic age-terms to model the trajectories of thickness and area, while generalized additive mixed models with a non-parametric spline function were used to model the trajectories in the LCBC study. However, testing a quadratic model in the LCBC data did not reveal any evidence of thickening, so the different model fits cannot account for the differences seen. However, an indication of differences in how cortical thickness is measured comes from comparing the thickness and area

trajectories, and the absolute differences between the females and males. In Raznahan et al., thickness and surface area trajectories take the same inverted U-shaped form, and males have both thicker cortex and larger surface area than females. Sex differences in thickness were found in an earlier study that also reported thickness increases, but with an advantage for females (Sowell et al. 2007). In the LCBC data, thickness and surface area follow very different trajectories, and absolute sex differences are found for area only. This is also seen in the large PING sample from the US (see Figure 2), where the same approach to thickness estimation is used (FreeSurfer). Thus, it seems reasonable to assume that a key to the differences observed in thickness trajectories between studies have to do with how thickness and area are disentangled in the processing of MRI scans, with these two entities being much more different in some studies than in others. Inspection of Table 1 and Table 2 show that many, but not all, studies that found monotonic decreases in thickness have used FreeSurfer, and also that none of the studies that found increases in thickness used the FreeSurfer method.

[Insert Figure 2 about here]

To investigate whether different software packages yielded different trajectories for cortical thickness with age, we analyzed MRI data from the same 43 children in the age range 3-11 years from the PING study with FreeSurfer and CIVET. The raw scans were run separately through FreeSurfer and CIVET, with no common preprocessing steps performed in advance. The results are shown in Figure 3. For neither method did the trajectories estimated show any sign of cortical thickness increase with age. While there were differences in absolute cortical thickness

estimates across these analysis methods, the correlations between age and cortical thickness were virtually identical (CIVET: r = -.52, FS: r = -.56, both p's < .0005). This suggests that at least with these recent versions of the software packages (FreeSurfer 4.5 and CIVET as of May 2012), the processing of MRI data per se would not be the causal factor causing discrepant age trajectories for cortical thickness development. It should be noted that these analyses are preliminary, and that a more thorough test would include more participants and comparisons between different versions of the same software.

Possible paths to a consensus and a cautionary tale

With the different cortical thickness maturation trajectories reported, an obvious question may be "Which is the correct one?" However, we do not think it is possible at the current time to give a definitive answer to this question. As with all *in vivo* imaging methods, our studies provide merely representations of the underlying neurobiology and inherently require some level of interpretation. It is important to be aware of the fact that the MRI-derived measures are merely our best current approximations, where reconstructions of the cortex are based on signal intensities and contrast properties that are prone to the influence of multiple factors. Hence, in principle, the term "apparent cortical thickness" should be used, much like one in diffusion weighted imaging speaks of "apparent diffusion coefficient". And with regard to cortical thickness, available histological data cannot with certainty inform us which MRI studies most accurately capture the true developmental trajectories. One postmortem study found that cortical thickness did not correlate with brain size (Pakkenberg and Gundersen 1997), indicating that these metrics in principle could follow divergent developmental paths. However, accurately measuring cortical

thickness in postmortem samples is very difficult without 3D reconstructions of the entire surfaces, as the measurements inherently depend on the orientation of the brain and the slicing direction. Thus, there is a need for further combined histological and MRI studies to better establish the relationships between available imaging-derived measures and the underlying neurobiology.

Histological studies, though scarce and not covering regional developmental differences in cortical thickness specifically, point to some general age differences in brain and cortical development (Dekaban 1978; Huttenlocher 1979; Huttenlocher et al. 1982; Huttenlocher 1984; Huttenlocher and de Courten 1987; Huttenlocher 1990; Huttenlocher and Dabholkar 1997). The underlying mechanisms of cortical thickness differences are complex and believed to involve, for growth, proliferation of dendrites, dendritic spines, axonal sprouting, vascular elaboration, and for thinning, possibly synaptic pruning as well as intracortical myelination (Huttenlocher 1979; Huttenlocher et al. 1982; Huttenlocher and Dabholkar 1997). Furthermore, the neocortex is essential to much of complex cognitive function, and many developmental milestones appear to be correspondingly ordered across individuals (Sheldrick and Perrin 2013). On this background, the major differences that have been reported in the shape of brain developmental trajectories across healthy human children appear less likely.

There is evidence of a burst in synaptogenesis in the human visual cortex (area 17) around four months, with synaptic density reached at about eight months and beginning to decline after age one year to an adult value of about 60% of maximum, which is reached by age 11 years (Huttenlocher et al. 1982; Huttenlocher and de

Courten 1987; Huttenlocher 1990). The available data indicate that there is a slower postnatal increase in synaptic density in the frontal cortex, where maximum density in layer III is reached at about 1 year, with subsequent declines, but slower than in the visual cortex, becoming evident around 7 years of age and reaching adult level by 16 years of age (Huttenlocher 1979). While these data may not yield definitive evidence on differential regional timing of cortical maturation (Goldman-Rakic 1987; Goldman-Rakic et al. 1997), they are often cited to yield a cellular foundation for both the identified cortical thickness peaks in childhood and the continuous thinning in MRI studies. However, this link has never been established beyond a rather vague correlation; it does not appear that these synaptic density studies can be used to deem which is the more likely to reflect the true cortical thickness changes as observed longitudinally. What these synaptic density studies do support, to some extent, is a posterior-to-anterior and/or sensory-to-association gradient of maturation, but that is in fact something that imaging studies identifying peaks and continuous thinning largely do agree on.

Unfortunately, as pointed out by Huttenlocher, (Huttenlocher 1990), the histological quantitative anatomy approach to cortical development has clear limitations too. One is the static nature of the measures, providing only a glimpse of one point in time for a few cases, which may even be affected by illness, injury or postmortem changes. Development is dynamic, and growth and regressive changes may occur at the same time and balance estimated changes in histological studies (Huttenlocher 1990), just like they may do in imaging studies. While neuronal count appears to change little in the cortex from end of gestation to late adult life, not enough is known about how estimates of synaptic density, dendritic length and so forth are affected by e.g. cortical

areal expansion in development in restricted histological samples. In the representations of the cortex created based on MR images, e.g. intracortical myelination and regressive changes may affect the signal intensities, contrast and quantitative measures derived in different ways. For these reasons, we do not believe it is yet possible to say with confidence that either representation of the cortical thickness, from any study, is "the correct one". Rather, we would suggest some steps to reach a greater consensus, especially along two lines.

First, while morphometric measurements usually are derived from T1-weighted images, a variety of different MRI modalities can be used to obtain relevant information about cortical maturation (see Figure 4). For instance, the definition of WM and GM boundaries can be improved by inclusion of T2-weighted images, and the use of T1/T2 ratio (Glasser and Van Essen 2011; Grydeland et al. 2013; Glasser et al. 2014; Grydeland et al. 2015; Shafee et al. 2015). The T1/T2 ratio method has been shown to improve localization by increasing the contrast to noise ratio between heavily and lightly myelinated areas, and by canceling the MR-related intensity bias field (Glasser and Van Essen 2011). This could potentially be used to improve the definition of the GM/WM boundary, which is critical for accurate estimation of cortical thickness, and also provide additional information about neurobiological events ongoing within the cerebral cortex and in adjacent WM during development. Examples of detailed myelin and thickness maps obtained by using the T1/T2 ratio are shown in panel A, Figure 4. In panel B, delineation of the GM/WM border from the superior temporal gyrus in a T1/T2 contrast image is shown, along with the age-trajectory obtained by sampling the ratio values from within the cortex, interpreted as

reflecting intra-cortical myelin content. This inverted U-shape, with a peak in the late middle-age, differs from the typical declining thickness curve.

Other signal intensity measures from the T1-weighted images themselves can provide additional important information that is still not commonly used in developmental studies (Salat et al. 2009; Westlye et al. 2009; Westlye et al. 2010; Grydeland et al. 2013). For instance, Westlye et al. observed that even though thickness decreased monotonically from childhood, T1 signal intensity, normalized to ventricular intensity, both in GM and WM increased until almost 30 years, before age-related reductions were evident (Westlye et al. 2010). This can be seen in panel D, Figure 4. It was further suggested that the overlap in age between the peak of the T1-signal intensity curve and the inflection point in the thickness curve could represent a "maturational milestone" in cortical development. In this way, combining thickness measures with the intensity measure yielded a more complete picture of cortical development both with regard to trajectories and with regard to dynamic regional variability. Shafee et al. used the T1/T2 ratio to estimate intracortical myelin content, and found that this metric increased from 18 to 35 years, with mainly the inner layer of the cortex accounting for this effect (Shafee et al. 2015). This is illustrated in Panel C of Figure 4, where the estimated annual increase exceeds 0.5% in most inner layer regions of the cortex, while changes in the outer layer are much lower. Both of these studies found a relationship between cortical thickness and the alternative measures, demonstrating the power of these multimodal approaches to enlighten us about the potential mechanisms for cortical thickness changes both in development and adulthood. Also methods from other fields, such as the newly proposed Clarity

(Chung et al. 2013), can aid in providing a better understanding of the neurobiological underpinnings on MRI-derived measures.

[Insert Figure 4 about here]

Second, a greater degree of data sharing and development and shared use of publicly available databases would most certainly contribute massively to reconciling differences due to the effects of various processing and analysis methods. One very successful example of this has been the Alzheimer Disease Neuroimaging Initiative (ADNI; adni-info.org), an open-access data repository with thousands of scans available for researchers in the area of aging and dementia. A similar initiative, but within the childhood age range, is the described PING study, which has produced a publicly available repository of imaging, cognitive behavioral, and genomic data, which includes raw and processed images. When data and processing methods are made openly available to other labs for scrutiny and independent analysis, any inconsistencies that arise in the empirical observations or interpretations can be more accurately attributed to specific procedures or methods and can be more definitively reconciled.

Conclusion

The aim of this feature paper was to address a critical inconsistency in current structural neuroimaging studies of human brain development – an early view that cortical thickness in some regions increases well into school age, and a more recent, different, view that monotonic thinning occurs across the cortex from an early age, at least from three or four years of age or earlier. The ongoing narrative about cortical

thickness development represents a major sticking point for our understanding of both normal and aberrant cortical development. Although at this time there appears to be no final verdict about the likely causes of the discrepant findings, available information suggests that the differences may lie largely within the imaging methods that have previously been used for measuring cortical thickness from MR images. Going forward, we have suggested two strategies, among arguably many, that we believe can advance the limits of our knowledge on cortical development further. First, by integrating multimodal neuroimaging signals to focus on the same and related phenomenon from different angles, we can attain insights into cortical development, which hopefully will lead to reconciliation of the diverging views. Second, by promoting data sharing and encouraging independent groups to work on the same datasets, we believe consensus or at least a deeper understanding of the causes of the divergent results will be strongly facilitated. Our hope in bringing attention to this discrepancy is to promote acknowledgment and discussion within the field, and hopefully to contribute to its resolution. In focusing on this particular issue within the study of human brain development, we are reminded of the inherent limitations of our brain imaging methods for getting at the underlying neurobiology and would do well to conduct more research that promotes a deeper understanding of their relationship.

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Figure legends

Figure 1 Estimating cortical thickness from MRI

Accurate measurement of cortical thickness requires three dimensional reconstructions of the white matter and the gray matter surfaces based on MR images.

Figure 2 Developmental trajectories of cortical thickness and area

Upper panel: Comparison of the developmental trajectories reported in Raznahan et al. (2011) to some of our own data (LCBC – Research group for Lifespan Changes in Brain and Cognition, University of Oslo) illustrates the discrepancies across studies. While surface area show similar inverse U-shaped trajectories, with larger absolute area for boys (dotted and blue lines) than for girls (solid and red lines), thickness results differ markedly between studies. In Raznahan et al., (Raznahan, Shaw, et al. 2011) thickness increases until approximately 8.5 years, and boys have thicker cortex than girls throughout the age-range. In the LCBC data, thickness shows a monotonic decrease from 4 years, with comparable absolute thickness estimates for boys and girls. Of note, thickness and area are more different in terms of trajectory and sex effects in the LCBC data than in Raznahan et al. Error bars for the LCBC curves represent 95% confidence interval.

Lower panel: Vertex-wise annualized rates of change in cortical thickness and surface area computed in 778 subjects aged 3 to 13 years from the PING Study. As can be seen, cortical thickness decreases monotonically within this age-range, while area shows an inverted U-shaped pattern of increase followed by decrease.

Figure 3 Cortical thickness averaged across hemispheres (Y-axis) as estimated by CIVET (left panel) and FreeSurfer (right panel) plotted against age (x-axis) for 43 children (23 females) in the PING study. While absolute thickness estimates differed by about 0.6. mm, the shape and betas of the age functions were similar across image analysis methods (CIVET r = -.52, FreeSurfer = -.56), both showing monotonically thinner cortex with age.

Figure 4 Multi-modal imaging as a path to increased knowledge about cortical development

We argue that utilization of additional imaging modalities than T1-weighted scans, and additional imaging parameters than morphometric, will increase our understanding of cortical development and help to solve the deep discrepancies in the literature. Panel A: Glasser and Van Essen (Glasser and Van Essen 2011) have convincingly shown that additional information can be obtained by taking advantage of both T1-weighted and T2-weighted MRI scans, likely related to myelin. This can be used to measure intra-cortical myelin content, which can be studied in relationship to thickness changes in development. Clockwise from top left are maps of cortical myelin content, thickness, thickness gradients and myelin gradients. Panel B: Grydeland et al. (Grydeland et al. 2013) used the myelin mapping methods proposed by Glasser and Van Essen to track myelin content from childhood and into old age, showing prolonged increases before age-related decline was seen in the last part of the lifespan. T1/T2 contrast from a section of the superior temporal gyrus is shown, with the delineation of the GM/WM boundary (green line) and the GM/ CSF boundary (red line) imposed on the image. The scatterplot shows the trajectory of the T1/T2 ratio from the superior frontal cortex across 8 to 80+ years. Panel C: Shafee et al. (Shafee

et al. 2015) found that estimated changes in myelin content, based on T1/T2 ratio measures, from 18 to 35 years were primarily driven by effects in the inner cortical layers, while almost no developmental effects were seen in the outer cortical layers. The upper brain surfaces are mostly red or yellow, indicating 0.5% increase in myelin content annually, while the changes in the outer layer appear mostly blue or cyan, indicating much lower estimated changes. These observations are relevant to the discussion of what drives the apparent cortical thinning in development seen in reconstructed MR images. Panel D: Taking advantage of the variation in signal intensities that can be found in T1-weighted MR images, Westlye et al. (Westlye et al. 2010) found that while cortical thickness was negatively related to development, cortical intensity increased. The ages at peak intensity are color coded and projected onto a brain surface in the upper part of panel D. The lower part shows the age-trajectories for T1-signal intensity (black line) and thickness (red line) from two different cortical regions. In several regions were T1-intensity increases observed until the age which the thickness reductions seem to proceed at a slower pace, again pointing to a potentially interesting interplay between cortical thinning and other neurobiological events that can be quantified in vivo by MRI.

	N/ scans	Age-range (years)	Cross vs. long	Processing	Measure unit	Central finding	Google Scholar citations
Shaw et al., 2008, J Neuroscience	375/764	3-33	Long	CIVET	Vertex	Age at thickness peak is important; table of mean peak given for 56 ROIs	658
Raznahan et al., 2011a, Neuron	108/376	9-22	Long	CIVET	Vertex	Rates of cortical thickness change differ by region	68
Raznahan et al., 2011b, J Neuroscience	647/1274	3-30	Long	CIVET	Vertex and total	Sex differences in cortical thickness	128
Shaw et al., 2006, Nature	307/307	7-19	Long	CIVET	Vertex	Increasing relation between thickness and IQ	878
Sowell et al., 2004, J Neuroscience	45/45	5-11	Long	Thompson et al., LONI	Vertex	Thickening in bilateral peri-Sylvian, related to vocabulary change	833
Sowell et al.*, 2003, Nature Neurosci	176/176	7-87	Cross	Thompson et al., LONI	Vertex	Posterior temporal cortex most protracted maturation	1316
Shaw et al., 2007, PNAS	223 ADHD, 223 CTRL/ 824 scans	5 -20+	Both	CIVET	Vertex	Peak of cortical thickness differs by group	716
Sowell et al., 2007, Cer Cortex	176/176	7-87	Cross	Thompson et al., 2004 LONI	Vertex	Thickness differs by sex	322

Table 1 Selection of studies showing increases and peaks in cortical thickness during school age

Samples across publications are in some cases overlapping. Google scholar citations retrieved April 2015.

CIVET: http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET. McDonald et al. 2000 often used as primary reference for thickness studies (MacDonald et al. 2000).

LONI: Laboratory for Neuroimaging, UCLA

ADHD: Attention Deficit Hyperactivity Disorder

* gray matter density is measured, and said to “represent cortical thickness”

	N/ scans	Age-range (years)	Cross vs. long	Processing	Measure unit	Central finding	Google Scholar citations
Amlien et al. (2014), Cerebral Cortex	331/331	4-30	Cross	FS	Vertex, ROI	Continuous decrease entire cortex	0
Brown and Jernigan (2012), Current Biology	885/885	3-20	Cross	FS	Vertex	Continuous decrease entire cortex	32
Brown et al. (2012), Neuropsychology review	202/202	4-20	Cross	FS	ROI	Continuous decrease total cortex	63
Mills et al. (2014), Soc Cogn Aff Neurosci	288/ 857	7-30	Long	FS	ROI	Linear decrease in 3 of 4 ROIs, increased thickness of the temporal pole until ≈20 years	35
Mutlu et al. (2013), Neuroimage	137/ 209	6-30	Long	FS	Vertex, ROI	Vertex-wise effects divided in linear, quadratic, cubic and none, show trajectories for 3 ROIs, all continuously decreasing	18
Zielinski et al.* (2014), Brain	157/ 345	3-39	Long	FS	ROI	Continuous decrease entire cortex	16
Nguyen et al. (2013), Cerebral Cortex	281/281	4-22	Cross	CIVET	Vertex	Linear decrease entire cortex	12
Wierenga et al. (2014), NeuroImage	135/201	7-23	Long	FS	ROI	Linear decrease most ROIs, few quadratic or cubic, mostly U-shaped	16

Wendelken et al., 2011, J Neuroscience	85/85	6-18	Cross	FS	ROI	Linear decrease	26
Van Soelen et al., 2011, NeuroImage	125/238	9 & 12	Long	CLASP	Vertex	No areas of thickening	42
Shaw et al., 2006, Arch Gen Psychiat	163 ADHD, 166 CTRL	Mean 8.9 at entry	Long	CIVET	Vertex	Different (though all declining) slopes of thickness	404
Gogtay et al., 2007, Arch Gen Psychiat	52/113	8-28	Long	CIVET	Vertex	"Cortical deficits" relate to GAS scores; siblings catch up at 20 years	113

Table 2 Selection of recent studies showing monotonic reduction of cortical thickness

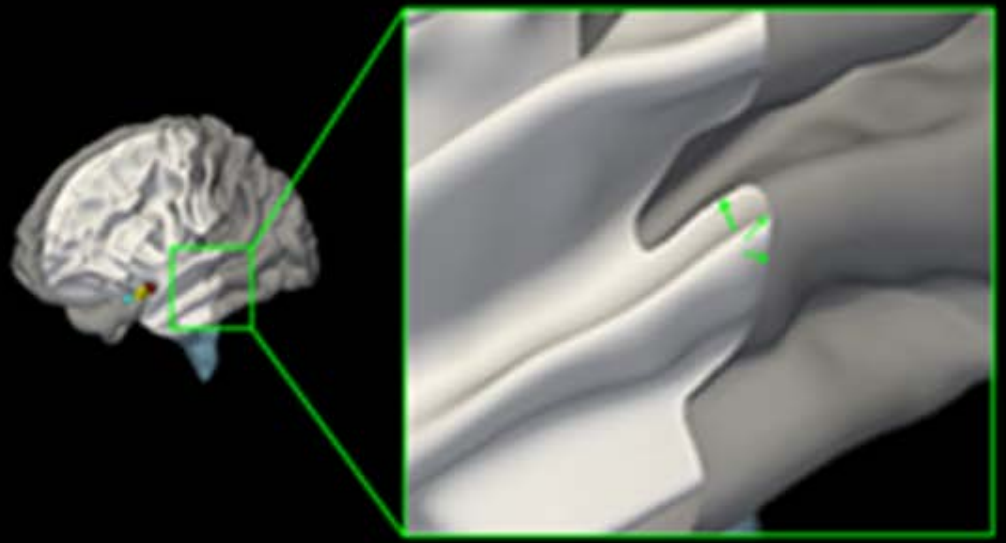
Samples across publications are in some cases overlapping. Google scholar citations retrieved April 2015.

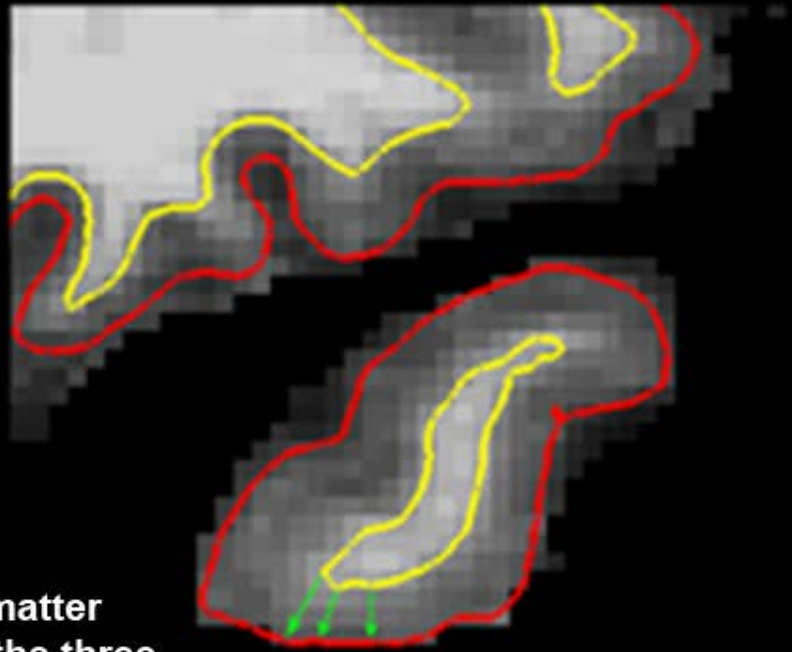
FS: FreeSurfer

ROI: Regions of interest

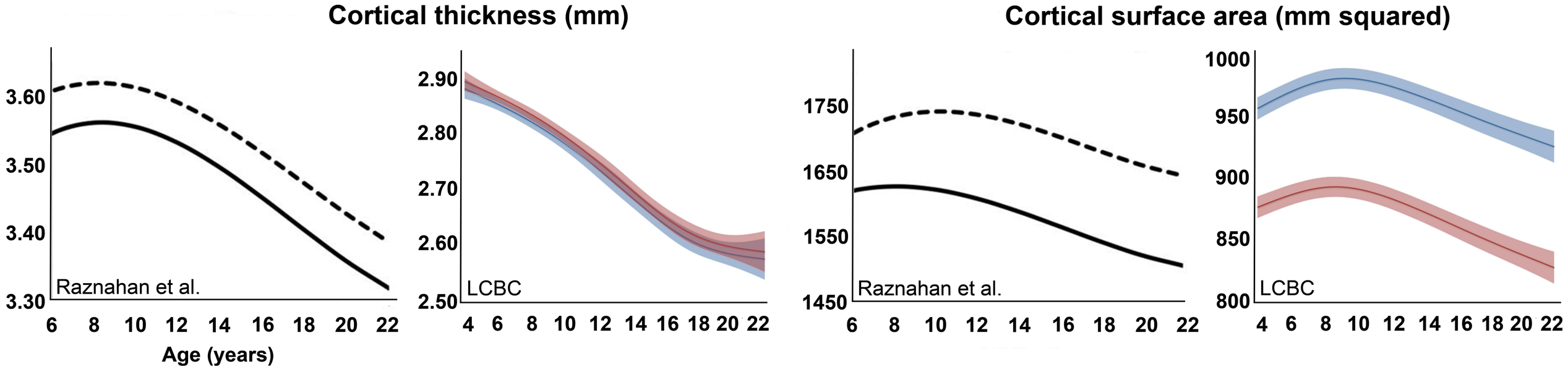
GAS: Global Assessment Scale

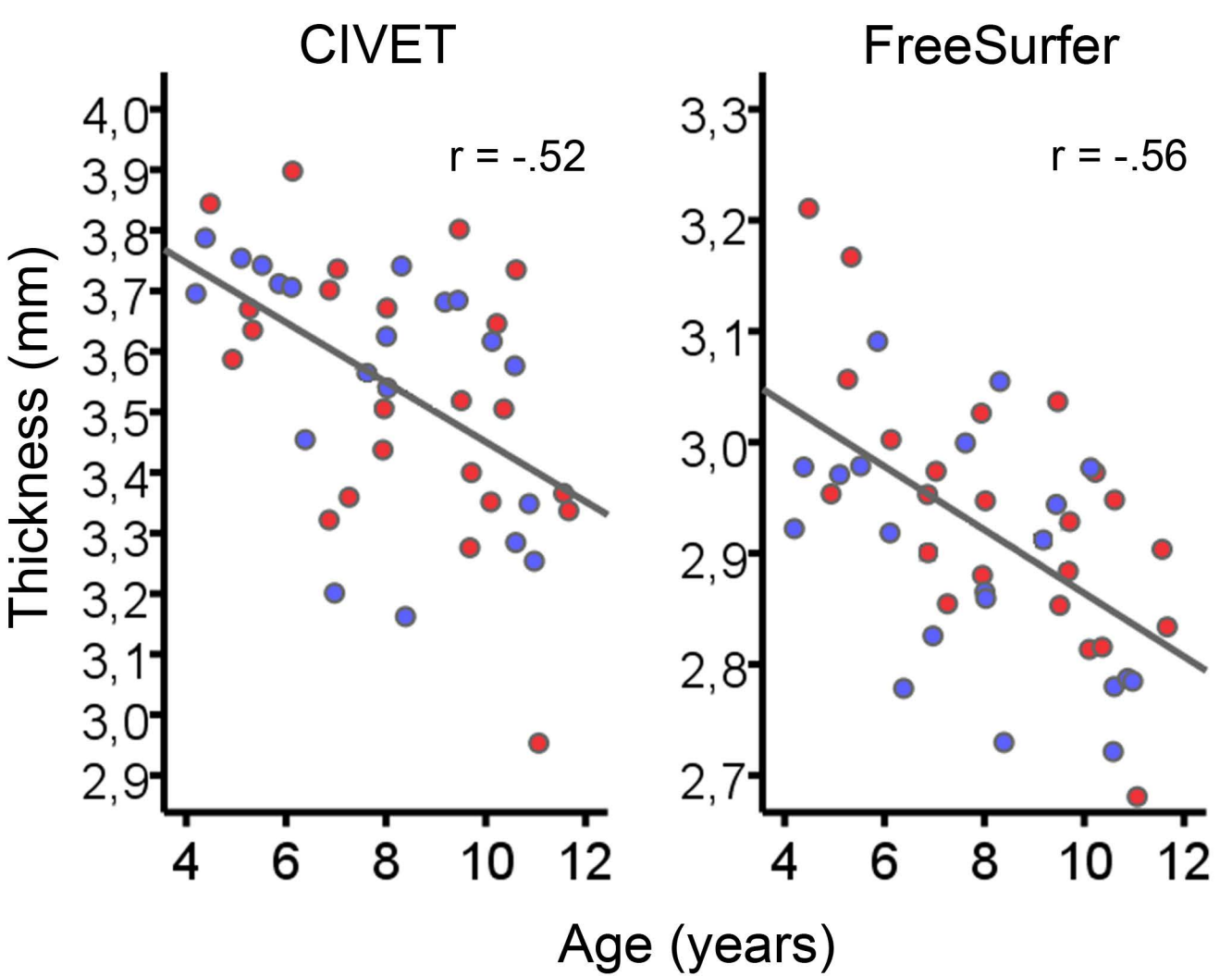
* 97 autistic and 60 normal males, both groups showed thinning



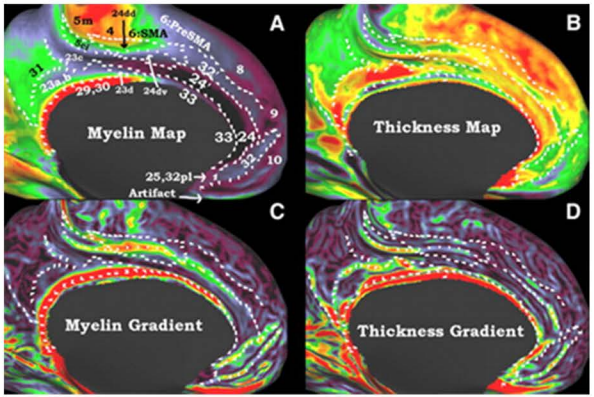


By surface reconstruction, the distance between the white matter surface and the grey matter surface can be measured from the three dimensional model at each vertex.

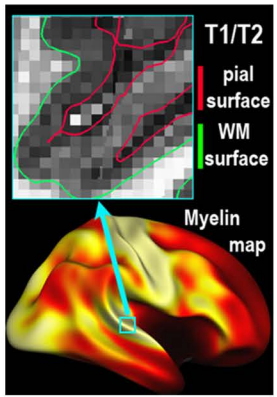

Cortical thickness (mm)
Cortical surface area (mm squared)
3.60
3.50
3.40
3.30
Raznahan et al.
6 8 10 12 14 16 18 20 22
Age (years)
2.90
2.80
2.70
2.60
2.50
LCBC
4 6 8 10 12 14 16 18 20 22
1750
1650
1550
1450
Raznahan et al.
6 8 10 12 14 16 18 20 22
1000
950
900
850
800
LCBC
4 6 8 10 12 14 16 18 20 22

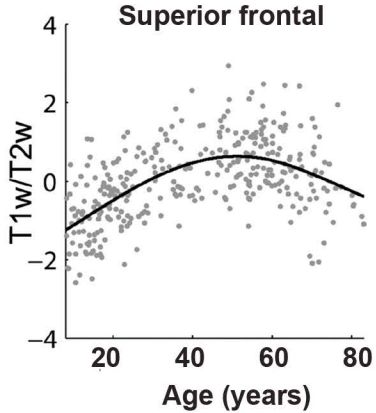

CIVET
FreeSurfer
r = -.52
r = -.56
Thickness (mm)
Age (years)
4,0
3,9
3,8
3,7
3,6
3,5
3,4
3,3
3,2
3,1
3,0
2,9
3,3
3,2
3,1
3,0
2,9
2,8
2,7
4
6
8
10
12

(A) Glasser & Van Essen (2011)

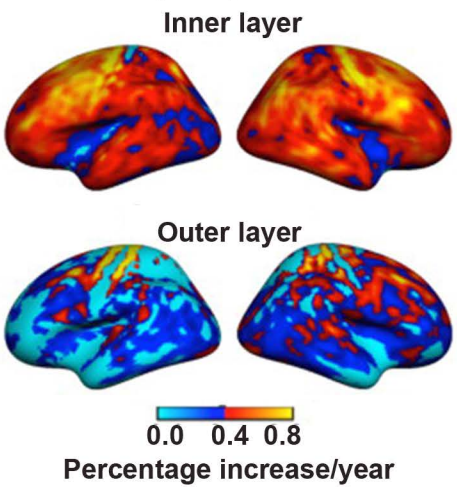


(B) Grydeland et al. (2013)





(C) Shafee et al. (2015)



(D) Westlye et al. (2010)