Cortical Morphological Congruence as a Biomarker of Brain Development Assessed with Magnetic Resonance Imaging

Authors: Jacob Levman1,2,3, Derek Berger2, (others maybe Bruce Fischl?), Emi Takahashi1,4

1 Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA.

2 Department of Computer Science, St. Francis Xavier University, Antigonish, NS, Canada.

3 Nova Scotia Health Authority, Halifax, NS, Canada.

4 Harvard Medical School, Department of Radiology, Boston, MA, USA.

**Abstract:**

A set of novel biomarkers are proposed for the extraction of regional cortical morphological congruence (CMC) measurements from neurological magnetic resonance imaging examinations. These proposed novel biomarkers assess a cortical region’s deviation from expectation for a perfectly regular structure. The proposed CMC biomarkers have been applied to a large sample (n=1113) of neurological MRI examinations of neurotypical patients from the Human Connectome Project. Results demonstrate consistent patterns of regional brain differences in CMC across the cortex, implying differential development regionally in the healthy brain characterizable by CMC. Results demonstrate relatively small standard deviations of CMC values across a large population, implying potential for these biomarkers as a reliable and easily reproducible method to characterize brain development. <perhaps a sentence here on similarities and differences between males and females as part of this baseline analysis. Perhaps Sentence on some other stuff, like our ability to predict IQ or something from CMC measurement>. Future work will investigate CMC’s potential to further characterize healthy brain development, as well as to characterize a variety of different pathological conditions.

**Keywords:** morphological, congruence, cortex, neurodevelopment, magnetic resonance imaging, healthy

**Introduction**

Characterization of human cortical development in vivo requires medical imaging technology that provides tissue contrast between gray and white matter. Magnetic resonance imaging (MRI) is sensitive to hydrogen proton concentration, which is variable across tissues, thus MRI provides excellent soft tissue contrast, including between the gray and white matter in the brain (Dubois *et al*., 2021). Automated methods for extracting biomarkers of potential interest, such as a regional cortical tissue’s volume (mm3), surface area (mm2) or thickness (mm), have long been relied upon for the study of the human brain (Fischl, 2012; Levman *et al.*, 2017, 2019; McCann *et al.*, 2021). However, the variability of those volume, surface area, and thickness measurements across a given population is known to be quite large (Levman *et al.*, 2017, 2019), potentially contributing to known reproducibility challenges in modern neuroscience studies (Martinez *et al*., 2015; Marek *et al.*, 2022), and may be part of the reason that these techniques are generally not yet relied upon for clinical characterization.

Very broadly, congruence is analogous to *agreement* between two or more objects, studies, shapes, individual measurements, etc. For instance, the results of one study may be congruent with those already in the literature, or two objects are deemed congruent if they have the same shape and size. Congruence can be applied in many ways, and has been the subject of limited and diverse studies focused on the human brain. Research has suggested that the development of visual cortical properties is dependent on visuo-proprioceptive congruence (Buisseret, 1993). More recently, a model has been specifically developed for congruence of binocular vision (how information from the left and right eye are incorporated) in the primary visual cortex (Somaratna and Freeman, 2022). Congruence has also been assessed between interoceptive predictions and hippocampal-related memory (Edwards-Duric *et al*., 2020). Congruence between the development of the circulatory and nervous systems, or neurovascular congruence, has been the subject of a study focused on cortical development (Stubbs *et al*., 2009). Additionally, it has been reported that congruence based contextual plausibility modulates cortical activity during vibrotactile perception (Kang *et al*. 2022). Neuronal congruency has also been assessed in the macaque prefrontal cortex (Yao and Vanduffel, 2022). This manuscript presents a novel set of biomarkers for characterization of regional cortical morphological congruence (CMC), which can be referred to more simply as cortical congruence (CC). The proposed methods assess the degree of congruence between multiple cortical measurements, thus providing novel biomarkers which we hypothesize may help characterize neurodevelopment.

**Methods**

*Patient Populations and Imaging*

Data were provided [in part] by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. This cohort included 1,113 healthy patients imaged with MRI. Detailed information on the magnetic resonance imaging (MRI) scanners and protocols used in the Human Connectome Project dataset are available in the literature (Elam *et al*., 2021).

*Postprocessing*

The Human Connectome Project’s WU-Minn HCP cohort (n=1,113 with MRI examinations) was processed by FreeSurfer (Fischl, 2012) and the results were made publicly available through the Human Connectome Project’s website (<https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release>).

For each cortical region supported by the publicly available FreeSurfer results, the following equations defining the proposed Cortical Morphological Congruence (CMC) measurements were computed in each patient. The first CMC equation is applied to all supported cortical regions in both the left and right hemispheres, respectively:

(1)

This first equation is a unitless index (Units: mm3/(mm2\*mm)) that assesses a cortical region’s deviation from the simplistic expectation that the regional volume will be equal to the surface area times the average cortical thickness. Such a simplistic expectation will hold in extremely regularly shaped cortical regions, and produce a *CMCLateral* biomarker value of 1. Deviations from 1 in either direction have major implications for structural cortical presentation, imply differential neurological development has occurred, and is addressed in detail in the Discussion.

The second CMC equation is applied to all supported cortical regions and incorporates measurements from both the left and right hemispheres simultaneously, referred to here as bilateral CMC:

(2)

The third CMC equation is applied to all supported cortical regions and assesses CMC hemispheric asymmetry:

(3)

The fourth CMC equation is applied to all supported cortical regions and assesses CMC hemispheric asymmetry:

(4)

Equation 3 provides a biomarker of asymmetry of regional cortical morphological congruence that always yields a positive number and does not discern between left dominant asymmetry and right dominant asymmetry. Equation 4 provides an additional biomarker that preserves directionality of asymmetry, with left dominant regions exhibiting *CMCAsym2* values above 1, and right dominant regions exhibiting *CMCAsym2* values below 1.

*Statistical Analyses and Machine Learning*

For each cortical region supported by the aforementioned FreeSurfer analyses, each CMC measurement was computed for each patient in each dataset accessed. Group-wise statistics, including means and standard deviations of CMC values were computed across the male and female participants. Comparisons between males and females, as well as comparisons between the left and right hemispheres was assessed with Cohen’s d statistic and p-values (Student, 1908) comparing two groups of measurements.

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A <get Derek to provide a little description of the psychological explained variance test with citation(s)> was performed.

Anything interesting from the machine learning analysis? Can you run this again with current df-analyze? If so is there anything interesting in there worth including in this manuscript? If so describe the methods here and adapt the text immediately below. If not, cut the text below.

Machine learning was completed with df-analyze, publicly available machine learning software (github.com/stfxecutables/df-analyze), which was developed in house, and has previously been applied to a brain MRI predictive application focused on schizophrenia diagnostics (Levman *et al.*, 2022). In this application, df-analyze is tasked with predicting a set of phenotypic features from the patients in our dataset from the proposed CMC biomarkers. The targeted phenotypic features include <insert list and basic descriptions and justification for their selection – input from Derek). The software selects the best combination of CMC biomarkers, the best combination of traditional FreeSurfer biomarkers, and the best combination of both, while being restricted by the user to limit the analysis to a fixed number of biomarkers <double check this with Derek>. The number of fixed biomarkers to provide to machine learning is varied, and the resultant predictive capacity of the models, alongside which biomarkers were selected for, is reported. This was just a blurb of what we could/maybe do, any df-analyze methods providing something interesting to say is fine, please adapt the text.

Making df-analyze publicly available (github.com/stfxecutables/df-analyze) facilitates reproducibility of our study findings, alongside our use of large public datasets of MRI examinations. In addition, we have provided our analytic software that helps demonstrate to the user how to use df-analyze and how to perform the statistical analyses employed in this study (cite another git hub thing – get link from Derek).

**Results**

Results from the Human Connectome Project, involving computing CMCLateral (equation 1) for each cortical region in each patient, and presenting the results as box plots (or violin plots might be slightly better) dividing between the left and right hemispheres, as well as between males and females, is provided in **Figure 1**. Note the relatively small standard deviations relative to the varying average CMC values across cortical regions.

\*\*\*Please create this big ass montage for me\*\*\*\*

**Figure 1.** Boxplots of each brain region (with left and right hemispheres paired together) across all patients (n=1113) in the neurotypical Human Connectome Project cohort, divided by gender.

<update this section with that explained variance test that Derek did instead>

<update this section with the results of any df-analyze experiments Derek completed>

A machine learning predictive analysis was performed and the leading models, their predictive accuracy, and the biomarkers on which they based their predictions are provided in **Table 2**.

**Discussion**

The human brain’s regional cortical development proceeds with a variety of underlying factors maturing in tandem with one another. Cortical volume, surface area and thickness are excellent examples of measurable biomarkers that clearly exhibit interdependencies with one another. However, it should be noted that the relative maturation of each of these biomarkers may proceed at varying rates in any particular combination of brain region, patient or pathology. Gray matter (GM) volume is known to increase with age, as does the surface area, while cortical thickness thins with long-term development. These three biomarkers are inter-related, and existing studies focused on these measurements typically do not consider the inherent interdependence between their respective development, even though underlying interdependencies are inevitable. This paper presents a novel set of cortical morphological congruence (CMC) biomarkers that are based on cortical volume, surface area and thickness, and produces measurements with relatively small standard deviations (see **Figure 1**), implying potential reliability and reproducibility from the proposed methods.

*Interpretation of CMC and its potential relationship with macro-structural cortical development*

The proposed CMC biomarkers, defined in equations 1 through 4, rely on underlying measurements of gray matter volume (measured in mm3), surface area (measured in mm2) and average cortical thickness (measured in mm). The nature of the proposed equations are such that they each produce a unitless index of CMC, different values of which imply potentially major differences in the conformation of the local cortical region, potentially implying major differences in the tissue’s historical neurodevelopment. When a cortical region exhibits a CMC (see equations 1 & 2) measurement equal to 1, which is expected for very regularly shaped structures, that region exhibits a relatively simple cortical morphological presentation, and can be said to have high underlying cortical morphological congruence. Examples of this can be found consistently across patients in brain structures such as the banks of the superior temporal sulcus (n=1,113, mean CMCLateral=1.0\*, std dev CMCLateral=0.025\*), and the insula (mean CMCLateral=1.0?, std dev CMCLateral=???). When CMC values deviate from 1, this implies varying degrees of incongruence between the region’s volumetric biomarkers and its surface area and cortical thickness biomarkers combined. The directionality of that incongruence (i.e. whether CMC is above or below 1) has major implications for the presentation of the conformation of that tissue, and implies differential cortical development has occurred.

When a cortical region exhibits CMC above 1, the GM volume has developed to be larger than the surface area times the mean thickness. This can occur when the overall growth of regional cortical tissue proceeds more quickly than increases in the surface area. Broadly speaking, the morphological structure that maximizes volume relative to surface area is the sphere. Thus, it is expected that convex (and thus partly spherical) presentation on the surface of the cortical region (well-rounded boundaries between the cortex and the pia mater which surrounds the cortex) will contribute to CMC measurements above 1. Regions such as the entorhinal cortex, which plays a role in working memory and thus is a highly relied upon region of cortical tissue, exhibits high CMC values (mean = 1.3\*\*, standard deviation = 0.?). This implies that the entorhinal region’s development may have involved rapid increases in volume relative to its respective increases in surface area. These high CMC values may also implicate a distribution of pruning locations that supports sulcal formation, leading to more convex (partly spherical) local surface areas within the entorhinal cortex adjacent to locations of sulcal formation. Thus, we hypothesize that pruning in the entorhinal cortex has been more extensive (and possibly proceeded faster) than pruning in regions exhibiting cortical morphological congruence (CMC = 1) such as the banks of the superior temporal sulcus, or the insula. Results demonstrate that in addition to the entorhinal cortex, multiple regions exhibit consistently high CMC values, including the temporal pole, frontal pole, and pars orbitalis (see **Figure 1**).

When a cortical region exhibits CMC values below 1, the combination of the surface area times the mean thickness has developed to be larger than the gray matter volume. This can occur when the surface area, which is expected to be affected by several underlying factors, including regional brain growth, cortical folding and pruning, develops more rapidly than the growth in overall regional gray matter volume alone. Additionally, the distribution of locations of pruning within the cortex can result in the emergence of comparatively complex surfaces relative to the more spherical/convex surfaces already discussed, potentially resulting in comparatively large surface areas yielding reduced values for our CMC biomarkers. Regions such as the pericalcarine cortex exhibit low CMC values (mean = 0.95\*, standard deviation = ??), which could imply that surface area growth has outpaced corresponding volumetric growth in this region’s development relative to other cortical regions.

*Potential for CMC to characterize important aspects of brain development*

The combination of regional cortical volume, surface area and mean thickness, biomarkers with relatively high variability across patients, into a single CMC biomarker with relatively small variability in regional cortical measurements is noteworthy. Reliability and reproducibility are a major ongoing challenge in neuroscience research (Martinez *et al*., 2015; Marek *et al.*, 2022), so any biomarkers that present consistently across a large population, and reliably demonstrate differential presentation across cortical regions, has considerable potential to assist in reliable and reproducible characterization of the human brain.

For most of the CMC biomarkers evaluated, males and females exhibit highly overlapping distributions, implying negligible differences in most cortical regions, which could imply the proposed biomarkers provide standardization benefits towards reproducible studies, and is consistent with largely overlapping functional abilities between the genders in most capacities. However, some male-female differences were observed in the temporal pole, the frontal pole and the pars opercularis, with females exhibiting higher CMC biomarkers on average than their male counterparts, though the distributions are still overlapping (see **Figure 1**). The temporal pole has been implicated in many functions, including emotional processing (Corcoles-Parada *et al.*, 2019), and the frontal pole has been reported to contribute to control over emotional approach-avoidance actions (Bramson *et al.*, 2020). Thus, gender differences in the presentation of the temporal and frontal poles, as assessed by CMC, may assist in characterization of known gender differences in emotional expression (Chaplin, 2015). The pars opercularis is involved in language processing (Grewe *et al*., 2005), and sex differences in the pars opercularis, as assessed with CMC, may be indicative of underlying known differences in language development between males and females (Sato, 2020). Indeed, it is encouraging that group-wise differences are observed in overlapping distributions as although we know sex effects exist in emotional expression and language development, there is a wide amount of variability in function across both genders, which is reflected in our CMC biomarker results exhibiting partially overlapping distributions between the sexes.

\*\*\*Hopefully there is something related to phenotypic data that Derek’s analysis will uncover?

\*\*\*Discuss variation explained psychological statistical test results here

\*\*\*Discuss machine learning predictive capacity and features underlying those predictions here

Although most cortical regions exhibited consistent CMC values in the left and right hemispheres, we did observe asymmetries in the transverse temporal, entorhinal, caudal anterior cingulate and pericalcarine regions. Asymmetries have previously been observed in the entorhinal (Simic *et al*., 2005) cortex, with larger surface areas being reported in the left hemisphere, which is consistent with our findings of decreased CMC in the left hemisphere (increased surface area results in decreased CMC). The transverse temporal cortex is known to exhibit leftward asymmetries that are detectable by 31 weeks gestation (Chi *et al.*, 1977), which is consistent with our findings of decreased CMC in the left hemisphere. Asymmetries have also been previously reported in the anterior cingulate (Yan *et al*. 2009). The pericalcarine cortex has also been reported to exhibit asymmetries (Chiarello *et al.*, 2016; Koelkebeck *et al.*, 2014), which our analysis was also able to detect with CMC biomarkers. Our identification of asymmetries of CMC biomarkers implies that our analyses have considerable consistency with known asymmetric properties of the human brain.

*Potential for CMC to characterize pathologies*

A wide variety of pathological conditions have been demonstrated to exhibit abnormal phenotypic presentation of regions of the brain, including Down Syndrome (Lee et al., 2016; Levman et al., 2019a), attention deficit hyperactivity disorder (ADHD) (Liston *et al.*, 2011; Stanley *et al.*, 2008), schizophrenia (Innocenti et al., 2003; Keshavan et al., 1994; Feinberg, 1990; Hoffman and Dobscha, 1989; Rimol et al., 2010; Narr et al., 2005; Venkatasubramanian et al., 2008; van Haren et al., 2011; Schultz et al., 2010; Nesvag et al., 2008; Seitz et al., 2018; Qiu et al., 2010; Johnson *et al.*, 2014; MacKinley *et al*., 2020), psychotic disorders (Bakker et al., 2016), autism (Khundrakpam et al., 2017; Pereira et al., 2018; Zielinski et al., 2014; Levman et al., 2019b; Levman et al., 2021b), and multiple sclerosis (Brex et al., 2002; Losseff et al., 1996; Chen et al., 2004; Sailer et al., 2003; Levman et al., 2021c).

Thus, future work will entail the characterization of the development of the pathological brain with CMC. As an additional novel biomarker not previously available, CMC may characterize regional abnormal development of the cortex in a manner not previously characterized, and the feature measurements generated by the approach outlined in this manuscript may also be a useful addition to future machine learning / artificial intelligence technologies that perform predictions for diagnostics, prognostics and treatment planning. Future work will investigate the potential for a variety of pathologies to be associated with macro-structural developmental abnormalities, such as aberrant folding and sulcal formation, and thus CMC may assist in the characterization of the macro-level phenotypic presentation of the brain. It is hoped that the CMC technique presented in this manuscript will be helpful in characterizing and understanding the developmental processes and etiological factors associated with healthy brain development, as well as a variety of neurodevelopmental disorders. It is also hoped that congruence based biomarkers will assist in characterizing important aspects of healthy and abnormal brain, reliably and reproducibly.

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\*\*\*Talk to Bruce Fischl with Emi about possibility of it being included in future versions of FreeSurfer and whether he has any feedback that might be relevant and may want to join on this project as a co-author.

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