### Title

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# Brain Imaging: Your Brain Scan Doesn't Lie About Your Age

**Multi-modal MRI data analysis can be used to predict a child or young adult's age. Most, but not all, individuals' brain-derived age estimate is close to their chronological age.**

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Sitting at a table with several neurologists and neuroscientists last year, the first author presented images of a man's brain from a structural magnetic resonance imaging (MRI) scan, and asked her colleagues to guess how old he was. Although these were all undeniably brain experts, they were stymied by this seemingly simple question: the closest guess was over 20 years off. In this issue of *Current Biology*, Tim Brown and colleagues [1] unveil a fully automated MRI data analysis pipeline that can be used to infer, with a startlingly high degree of accuracy, the age of an individual between 3 and 20 years old.

In 2010, Washington University researchers working with resting-state fMRI data from 238 individuals between 7 and 30 years of age showed that the strength of correlated activity between brain regions is a good indicator of an individual's age [2]. Their support vector machine-based multivariate pattern analysis allowed them to predict 55% of the variance in age within this cohort.

In their new study, Brown *et al.* [1] use measures of brain anatomy rather than brain activation to predict age. Their analyses are based on multi-modal structural MRI data from a diverse sample of 885 typically developing individuals, collected from 12 MRI scanners at nine institutions across the USA (Pediatric Imaging, Neurocognition, and Genetics (PING) Study; see http://chd.ucsd.edu/research/ping-study.html).

Using a fully automated pipeline, Brown *et al.* [1] analysed and integrated three different types of structural MRI data from this large sample (Figure 1). From T1- and T2-weighted scans, they derived measures of brain morphology and signal intensity, respectively, for multiple regions of interest. From diffusion-weighted scans, they computed diffusivity for a number of white matter tracts, as is commonly done, but also for subcortical nuclei and the cerebellum. As will be discussed later, diffusivity in subcortical gray matter was a surprisingly strong predictor of age during adolescence.

All in all, 231 brain variables per participant were incorporated into the model. Modeled separately, the morphological, diffusion, and signal intensity measures each accounted for 81–83% of the variance in age — no small feat. And together, these measures accounted for *more than 92%* of the variance in age across the sample of 3–20-year-olds. This level of accuracy in predicting age from brain measures is simply unprecedented in the literature.

On average, the model's prediction for an individual was within approximately one year of his or her chronological age. The model was most accurate, however, for younger children, such that the average prediction error was 8 months for 3-year-olds (with the prediction ranging from 2–4 years) and 1.5 years for 20-year-olds (with the prediction ranging from approximately 17–23 years). As is to be expected, then, it is during the period of most dramatic brain development — early in childhood — that anatomical differences between individuals are the strongest indicator of an individual's age.

Interestingly, the explanatory power of a given brain variable also varied with age. Gray matter signal intensity within subcortical regions was the very strongest predictor during early and middle childhood, whereas diffusivity within subcortical regions of interest was the strongest predictor late in adolescence. By contrast, diffusivity within white matter fiber tracts was a consistently strong predictor across the age range. It is worth noting that total cortical area was a very poor predictor of age, exhibiting high variability across the age range.

In summary, Brown *et al.* [1] effectively demonstrate the power of non-invasive structural MRI to accurately track brain development through childhood and adolescence. They show that the model-derived 'brain age' is only off by about a year from the chronological age, on average. Based on their data, they conclude that the anatomical phenotype of the brain is under tight control throughout child and adolescent development. Below we highlight some of the key theoretical and practical implications of this work.

Although it is not possible to compare directly the accuracy of this model with that of other models, it appears that these structural MRI measures — either in combination or alone — provide a more accurate age estimate than the resting-state functional connectivity measure used previously [2]. Indeed, it stands to reason that individual differences at a given age would be greater for measures of brain function (not to mention cognitive functioning) than brain structure, given that structural MRI is insensitive to microscopic differences at the molecular, cellular, and circuit levels that surely influence the dynamics of functional interactions within and between regions.

How can we reconcile the current evidence of predictable age-related changes in brain structure with the body of prior evidence pointing to important individual differences in brain development [3,4]? The most facile answer is that these individual differences are most compelling in late childhood and adolescence, the period of development during which the model's prediction error is greatest (±3 years by age 20). On average, however, the prediction error is still much smaller than one would have guessed based on the individual differences literature.

Brown *et al.* [1] explain the apparent discrepancy by noting that, "despite marked variability among children across a wide variety of

isolated brain measures, there are aspects of brain development for which the multidimensional biological phase is remarkably controlled, and its timing is more closely tied to chronological age than was previously known".

Indeed, a big piece of this puzzle about the existence of predictable age-related differences in spite of important individual variability relates to the choice of brain measures for the model. Brown *et al.* [1] set out to identify the neuroanatomical measures that are most powerful for capturing developmental changes, and used these measures to predict age. Had they instead weighted the model towards measures showing strong individual differences, it would have been difficult to predict age from them. In other words, an individual differences researcher's signal is a developmental researcher's noise.

This automated pipeline and large normative data set might, in the future, be valuable in a clinical setting to monitor brain development in individual patients, testing whether their level of 'brain maturity' is lower — or higher — than expected based on their age [4,5]. For a given patient whose age is known, the relative predictive power of each of the brain variables for typically developing individuals of his or her age could be specified as *a priori* weights in the model. Then, the model could potentially be used to quantify more precisely the extent to which this individual's brain deviates from expectation.

Such a technique theoretically could enable early detection of abnormal brain development in individuals with a family history of schizophrenia, autism, or other heritable neurological disorder, those who have experienced early-onset neurological damage, and those who have been exposed prenatally to environmental toxins or substances of abuse. Of course, it is important to proceed cautiously, as much more research is needed to test the validity and cost-effectiveness of this approach.

Readers familiar with the emerging field of 'neurolaw' will immediately wonder whether this technique could be relevant for legal deliberations. *In the aggregate*, these data provide some of the strongest evidence yet for protracted maturation in brain structure throughout adolescence, corroborating prior neuroscientific evidence that contributed to the United States Supreme Court decisions to abolish for juvenile offenders the death penalty (Roper *versus* Simmons, 2005) and life without parole sentencing (Graham *versus* Florida 2012, and Miller *versus* Alabama, 2012).

However, we would caution strongly against the use of this type of technique *in individual legal cases*, for example to determine whether a juvenile defendant is competent to stand trial, or — in the limit — whether he or she is criminally responsible. As Brown *et al.* [1] carefully note, "Brain scans, though informative about anatomical and physiological states, cannot be used to make inferences about an individual's level of psychological maturity". It is difficult to foresee a time when we will be able to accurately infer or predict patterns of behavior from brain imaging data; predicting a single numerical value (*age*), as Brown *et al.* [1] do, is already an impressive feat.

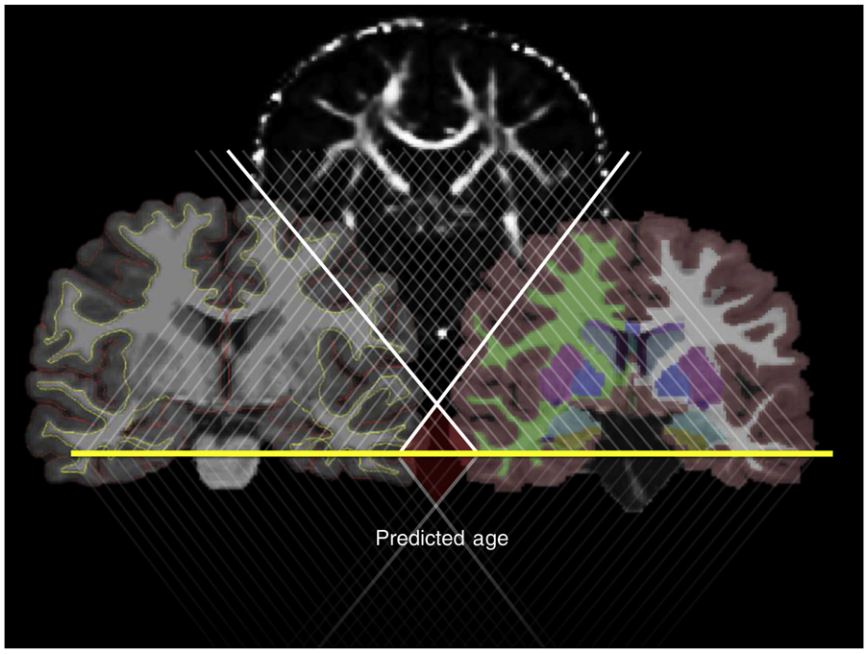


Figure 1. Illustration of Brown *et al*.'s [1] analytic derivation of age estimates from an individual's multi-modal MRI data.

Sample MRI images from two 3-year-old girls in the PING dataset (courtesy of Tim Brown). At left: automatic segmentation of structural MRI image used to measure cortical thickness and area. At top: diffusion-weighted scan used to measure the structural integrity of multiple fibre tracts. At right: automatic segmentation of structural MRI image used to measure subcortical volumes. The converging lines represent the numerous brain measures that are combined to predict an individual's age. Illustration of the automatic pipeline conceptualized by Ori Elis, M.A., a student in the Psychology Ph.D. program at UC Berkeley.

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