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Mapping Gray Matter Development: Implications for typical development and vulnerability to psychopathology

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Abstract

Recent studies with brain magnetic resonance imaging (MRI) have scanned large numbers of children and adolescents repeatedly over time, as their brains develop, tracking volumetric changes in gray and white matter in remarkable detail. Focusing on gray matter changes specifically, here we explain how earlier studies using lobar volumes of specific anatomical regions showed how different lobes of the brain matured at different rates. With the advent of more sophisticated brain mapping methods, it has become possible to chart the dynamic trajectory of cortical maturation using detailed 3D and 4D (dynamic) models, showing spreading waves of changes evolving through the cortex. This led to a variety of time-lapse films revealing characteristic deviations from normal development in schizophrenia, bipolar illness, and even in siblings at genetic risk for these disorders. We describe how these methods have helped clarify how cortical development relates to cognitive performance, functional recovery or decline in illness, and ongoing myelination processes. These time-lapse maps have also been used to study effects of genotype and medication on cortical maturation, presenting a powerful framework to study factors that influence the developing brain.

Introduction

Human brain development is a structurally and functionally non-linear process (Johnson, 2001; Thatcher, 1992; Thatcher, Walker, & Giudice, 1987) and most major neuropsychiatric disorders are now thought to arise out of deviations from normal brain development, suggesting a neurodevelopmental basis for these disorders. It is therefore important to study both normal and abnormal brain changes with age in order to understand how major neuropsychiatric disorders emerge (Schlaggar et al., 2002; Stiles, 2000). Postmortem studies provide information at molecular and cellular levels, but are limited by the scarcity of human brain tissue, inability to provide information during life, and the inability to use longitudinal designs. Noninvasive brain imaging, with recent advances in the resolution of MRI and in mapping methodology, provides a unique alternative to study brain development *during life*, allowing studies that assess the same individual or group of subjects repeatedly. This allows the dynamic trajectory of an illness, or the profile of cortical development throughout childhood and adolescence, to be visualized as a time-lapse map, presenting statistics on the 3D profiles of brain changes at different ages (Thompson et al., 2001; Gogtay et al., 2004, 2007, 2008).

Earlier brain imaging studies using prospective anatomic MRI scans measured gray and white matter changes that were summarized for individual lobes of the brain. While providing new insights, these lobar volume measures were limited by the lack of fine-scale details at sub-regional levels. These region-of-interest measures, for example, could not generally establish whether the functionally distinct sub-regions within a cortical lobe had structurally distinct developmental trajectories. They could not detect sweeping waves of dynamic changes that

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spread across the cortex, and were relatively insensitive to effects that did not coincide neatly with lobar boundaries. These limitations were overcome by more recent techniques that allow the measurement of cortical thickness or gray matter density at individual voxel locations in the image (e.g., voxel-based morphometry, VBM) (Ashburner et al., 2003) or across surface models of the entire cortex (Luders et al., 2005; P. M. Thompson et al., 2004; P. M. Thompson et al., 2005). Thus, ideally, using both global/lobar measures and GM density/thickness measures in a complimentary way can provide clearer understanding of brain development.

By aligning images from multiple subjects to a common reference brain or coordinate system, statistical maps can be made to show the evidence for group differences in gray matter at each location in the co-registered images. Additional detailed maps can show brain regions where significant changes occur over time, revealing at each location in the brain whether the individual differences are associated with specific genes, medications, symptoms, or clinical outcomes (Cannon et al., 2006; P. M. Thompson et al., 2008).

These map-based analyses are typically conducted by establishing a ‘one-to-one’ correspondence of voxels across different brains, either using automated algorithms (Lerch & Evans, 2005) or by manually tracing sulcal landmarks that are then used to match individual cortical regions across subjects or across time (cortical pattern matching) (P.M. Thompson, Mega, Vidal, Rapoport, & Toga, 2001). When longitudinal MRI data are aligned across subjects and analyzed using sophisticated statistical algorithms, the dynamic trajectory of gray and white matter development can be visualized as it varies with age, and in different clinical populations, such as those with bipolar illness or schizophrenia (Gogtay, Ordonez et al., 2007; Vidal et al., 2006).

Here we provide an overview of our current understanding of normal GM development in the human brain, and how the knowledge can be applied to understand the GM changes in some of the major neuropsychiatric illnesses across the life span. We discuss representative examples of pediatric onset schizophrenia and bipolar illness, and we relate some of the early maturational changes in childhood to changes that happen in the opposite sequence later in life, in Alzheimer's disease. We also stress the importance of longitudinal brain imaging for understanding psychiatric illnesses from a neurodevelopmental perspective.

Normal GM Development

Imaging studies using lobar measures first documented the non-linear changes in regional gray matter (GM) volumes during childhood and adolescence. The total volume of GM in each lobe, and in the brain overall, exhibits a pre-pubertal increase followed by post-pubertal loss (J. N. Giedd, J. Blumenthal, N. O. Jeffries, F. X. Castellanos et al., 1999; Jernigan & Tallal, 1990; Jernigan, Trauner, Hesselink, & Tallal, 1991; E. R. Sowell, Thompson, Tessner, & Toga, 2001). These findings showed that gray matter volume followed an inverted U-shaped trajectory in frontal, parietal and temporal lobes (J. N. Giedd et al., 1999). The post-pubertal GM loss was seen as consistent with *post mortem* observations of increased synaptic pruning during adolescence and early adulthood (Bourgeois, Goldman-Rakic, & Rakic, 1994; P.R. Huttenlocher, 1994; Rakic, 1996). Because the GM reductions were greater than synaptic pruning would explain, other investigators suggested that continued intra-cortical myelination might also partly explain the progressive reduction in the amount of tissue with a gray matter appearance on MRI (T. Paus, 2005). The developmental trajectories for each lobe were also surprising, because for the first time they showed that GM development was heterogeneous across the major lobes; frontal lobes had peak GM volumes around age 11, while the temporal lobes continued to increase in volume until 14 years, and the cerebellum showed the most protracted developmental time-course. On the other hand, white matter volumes increased

roughly linearly throughout the first four decades of life, with a peak around the mid-forties when speed for certain fine motor skills is also optimal (Bartzokis et al., 2008).

In addition to the lobar GM heterogeneity, early studies also found a pronounced sex difference with females achieving peak GM volumes typically 1-2 years earlier than males, particularly for frontal, parietal and temporal regions (J. N. Giedd et al., 1999) (see Figure 1).

Given the remarkable heterogeneity in the lobar GM development, it became important to study GM development at functionally distinct sub-regional levels. This was achieved in the subsequent studies using finer-scale GM mapping methods. These studies confirmed the maturation related loss of cortical GM density over time across the entire age span, with rapid attrition of frontal lobe gray matter in late adolescence (E. R. Sowell et al., 2003; E. R. Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). When these techniques were applied to longitudinal samples, the first dynamic maps of gray matter maturation were created. In the pre- and post- pubertal period, individual sub-regions followed temporally distinct maturational trajectories. Typically, the primary sensorimotor cortices and the frontal and occipital poles matured first, and the remainder of the cortex developed in a parietal to frontal (back-to-front) direction. The superior temporal cortex, which contains association areas that integrate information from several sensory modalities, matured last suggesting that the higher-order association areas mature only after the lower-order sensorimotor regions, whose functions they integrate, have matured (Gogtay, Giedd et al., 2004). Time-lapse maps of this developmental trajectory may be seen at http://www.loni.ucla.edu/~thompson/DEVEL/dynamic.html. To some extent, ontogeny recapitulates phylogeny; the latest developing areas are most recent areas from an evolutionary standpoint, including prefrontal regions involved in executive function, decision-making and inhibition (Puelles & Rubenstein, 2003).

The availability of a large cohort of children studied longitudinally across childhood and adolescence enabled the examination of regional cortical trajectories in relation to the intelligence quotient (IQ). Recently, Shaw et al. (Shaw et al., 2006) examined the NIMH (National Institute of Mental Health) pediatric longitudinal data set for anatomic brain development in relation to IQ. Developmental trajectories for total and regional brain cortical thickness were examined in relation to IQ (measured at time of initial scan) for 307 children (the majority of whom had prospective repeated neuroanatomic scans) aged 4-26 yrs, as shown in Figure 2. At younger ages, the relationship between cortical thickness and IQ was relatively broad but approached the more circumscribed frontal lobe regions in later adolescence, suggesting the increasingly localized dependence of GM thickness on cognitive function with age. The contrast in trajectories across IQ groups, however, was particularly interesting with more intelligent children demonstrating a particularly plastic cortex with an initial accelerated and prolonged phase of cortical increase followed by a particularly vigorous phase of cortical thinning suggesting a highly plastic response in the brain.

Gaps remain in our understanding of GM development despite the advances in finer-scale GM mapping techniques. Current MRI resolution still cannot establish the exact cellular processes underlying the GM loss. GM density on MRI is an indirect measure of a complex architecture of glia, vasculature, and neurons with dendritic and synaptic processes, and the primary cause for loss of GM density remains unknown. It may be driven by the process of synaptic overproduction followed by pruning (P. R. Huttenlocher, 1979) together with trophic glial and vascular changes and/or cell shrinkage (Morrison & Hof, 1997). This maturational synaptic pruning was also suggested by earlier studies of age-related changes in sleep physiology and EEG coherence studies (Feinberg, 1982; Feinberg, Higgins, Khaw, & Campbell, 2006; Whitford et al., 2007). The regional differences in GM maturation may thus result from the plasticity-dependent synaptic pruning in the cortex, as has been found in primate and human

cerebral cortical development (Arango et al., 2008; Bourgeois, 1997; Bourgeois et al., 1994; P. R. Huttenlocher & Dabholkar, 1997; Rakic, Bourgeois, & Goldman-Rakic, 1994; Rapoport & Gogtay, 2008; Zecevic, Bourgeois, & Rakic, 1989), although this argument remains debatable (T. Paus, Keshavan, & Giedd, 2008).

GM Development in Childhood Schizophrenia and Bipolar Illness

Understanding GM maturation in healthy development has helped to clarify the patterns of abnormal GM development in illnesses such as childhood-onset schizophrenia or pediatric bipolar illness. Morphometric studies of these populations have also provided insights into these illnesses in general (Gogtay, 2008).

Childhood-onset schizophrenia (COS; defined as onset by age 12) is a rare phenotypic variant of adult-onset schizophrenia. A longitudinal MRI study of COS has been ongoing at the NIMH since 1990. The diagnosis is made using unmodified DSM IIIR/IV criteria and, in most cases, after a drug-free inpatient observation. The COS cases (n=102 to date at the NIMH) clinically resemble poor outcome Adult Onset Schizophrenia (AOS) cases, in that all phenomenological (Asarnow et al., 2001), family (R. Nicolson et al., 2003) and neurobiological (Asarnow et al., 1994; Gochman et al., 2004; Rapoport, Addington, Frangou, & Psych, 2005) studies in COS show similar findings as in the AOS, suggesting continuity between these two forms of the illness.

Initial studies of whole lobe volumetric measures showed profound and global GM loss with ventricular expansion in COS (Gogtay, 2008; Rapoport et al., 1997; Rapoport et al., 1999; Rapoport & Inoff-Germain, 2000). Subsequent prospective analyses using finer-scale brain mapping techniques showed that the GM loss in COS progressed in a characteristic back-to-front (parieto-frontal-temporal) direction during adolescent years (P. M. Thompson et al., 2001). This is strikingly similar to the pattern of GM loss (maturation) seen during normal cortical development (Gogtay, Giedd et al., 2004), but abnormally accelerated. Taken together, the cortical GM loss in COS appears to be an exaggerated pattern of the normal brain development during adolescence and could reflect the lack of normal controls GM maturation (Schoop, Gardziella, & Muller, 1997; E. R. Sowell et al., 2001).

The diagnostic specificity of these GM trajectories was established by comparing individuals with COS with a longitudinally scanned group of children with atypical psychosis with similar initial presentation but ruled out from having schizophrenia after an extensive evaluation including complete medication washout (Kumra et al., 1998). At 2-10 year follow-up, none of these children had converted to meeting diagnostic criteria for schizophrenia, but a surprising 40% of them were later diagnosed with Bipolar I disorder. The developmental trajectories for these children showed a subtle but very distinct pattern of cortical GM gain in left temporal cortex and GM loss in right temporal and subgenual cingulate cortices, a pattern that has no overlap with the pattern seen for COS (Gogtay, Ordonez et al., 2007). As seen in Figure 3, these observations, which establish the diagnostic specificity of the GM findings, also suggest that the GM changes are unlikely to be attributable to medication effects, as the bipolar group had been treated with similar medications (Gogtay, Ordonez et al., 2007; Gogtay, Sporn et al., 2004). The familial/genetic nature of these abnormal changes is further supported by studies of healthy siblings discussed below.

Studies of neurobiological risk factors suggest that COS is continuous with the adult-onset illness (R. Nicolson et al., 2000; R. Nicolson & Rapoport, 1999), so it would be expected that the GM changes in COS might eventually evolve into a pattern similar to that seen in the adult onset illness. Adult-onset studies using VBM or cortical thickness mapping methods, show predominantly cortical GM loss in prefrontal and superior temporal cortices (Kuperberg et al., 2003; Narr et al., 2005; White, Andreasen, Nopoulos, & Magnotta, 2003; Wiegand et al.,

2004). In one study (P. M. Thompson et al., 2008), two time-lapse films were created from groups of first-episode adult-onset patients scanned 4 times over a year, after they were randomized to haloperidol or olanzapine treatment. In a convincing replication of the childhood-onset trajectory, the adult patients also exhibited a back-to-front wave of cortical gray matter loss, with greatest losses in the 3 months after psychosis onset, but proceeding into the frontal cortices a year later. Olanzapine-treated patients showed significant progressive gray matter reductions but in a more restricted anatomical pattern than in haloperidol-treated patients. The spreading wave in the childhood-onset cases was earlier, a pattern that is considered by many researchers to represent the disease process interacting with normal brain development (Pantelis et al., 2003). Even so, in the adult time-lapse study, we also found a strikingly similar trajectory in adult-onset patients receiving haloperidol, despite these subjects being a decade older. As many developmental processes continue until middle age (Bartzokis et al., 2003), late intra-cortical myelination processes that continue throughout life may be derailed in schizophrenia (Peters & Sethares, 2004). Alternatively, these gray matter volume deficits may reflect an active disease process that occurs early in the illness. Whether psychosis onset occurs in adolescence or adulthood, active pathophysiology may be combined with exaggerated or dysregulated neurodevelopment (Lieberman, 1999; Lieberman et al., 2005; Woods, 1998). These structural differences are extremely dynamic in the first year after psychosis onset; this serves as a caveat to researchers seeking an MRI-based biological marker for genetic or diagnostic studies of schizophrenia, as the deficit level in the illness can vary substantially over time and with treatment. Most studies suggest that the observed changes in disease may represent an abnormal exaggeration of the normal developmental trajectory.

In a recent analyses of a group of 70 COS children followed from age 8 to 28, the pattern of GM deficits became more restricted to the prefrontal and superior temporal cortices by age 26, further establishing continuity with the adult-onset disorder (Greenstein et al., 2006). Mild frontal and temporal GM deficits are also found in those at genetic risk for schizophrenia and have even been associated with specific genotypes (Cannon et al., 2005). Similar brain changes have also been tracked as psychosis develops in those at risk (Pantelis et al., 2007).

Some discordant twin studies have supported a two-hit (diathesis-stress) model of disease expression, in which posterior parietal brain regions may be vulnerable to environmental stressors in those at risk for schizophrenia, and after psychosis onset, the trajectory of deficits may proceed to engulf regions where a genetic liability for deficits has been found, such as the frontal lobes, leading to deficits in executive function and working memory (Cannon et al., 2002).

The GM abnormalities in schizophrenia may be, at least in part, familial/trait markers (Cannon et al., 2003; Gilbert, Montrose, Sahni, Diwadkar, & Keshavan, 2003; Weinberger & McClure, 2002; Yucel et al., 2003). Longitudinal brain MRI studies on healthy COS siblings provide further insights into the phenomenon of cortical GM changes. Longitudinal GM findings in 52 healthy full siblings of COS patients showed that these siblings had initial GM deficits which, for this group, did not progress during adolescence (unlike their COS probands) but in fact, normalized by age 20. The early GM loss in siblings was most prominent in prefrontal and temporal cortices (see Figure 4) as has been seen for COS probands, but unlike the pattern seen in probands, siblings did not show parietal GM loss at younger ages. This is also consistent with the notion that the early parietal deficits may require a non-genetic trigger, as they were absent in siblings who ultimately remained healthy. This apparent ‘plastic’ response (inhibition of cortical thinning) in healthy siblings is intriguing and warrants replication. Within the healthy sibling group, regional cortical thickness at baseline was correlated with subsequent increases in overall ‘life functioning’ as measured by the Global Assessment Scale (GAS). This suggests a direct relationship between cortical thickness and a restitutive normalization process with general competence (GAS scores). In other words, better social and cognitive

"competence" was predicted by initial cortical thickness. Whether this relationship between GM thickness and GAS reflects a causal effect of structure on function, or whether both have a common antecedent, remains unknown (Gogtay, Greenstein et al., 2007).

The findings of profound GM loss in illnesses such as schizophrenia raises an interesting debate about whether the cortical GM loss is just a perceived loss resulting from the encroachment of continued white matter growth, a process that normally extends through the 4th decade (F. M. Benes, 1993; F. M. Benes, Turtle, Khan, & Farol, 1994; E. R. Sowell et al., 1999); in fact, myelination may continue over the entire lifespan, with deteriorative processes beginning to outweigh positive changes by the mid-forties. We examined the white matter encroachment explanation in our recent analysis using tensor-based morphometry (TBM), in which we visualized average profiles of white matter growth in COS and healthy controls throughout the brain (Gogtay et al., 2008). We compared 3D maps of local white matter (WM) growth rates in COS patients and healthy children over a 5-year period, based on analyzing longitudinal brain MRIs from 12 COS patients and 12 healthy controls matched for age, gender and scan interval. COS patients showed up to 2.2% slower growth rates per year than healthy controls in WM ($p=0.02$, all p-values corrected), with greater effect sizes in the right hemisphere ($p=0.006$) (see Figure 5). Furthermore, as seen in prior studies of white matter growth (T. Paus et al., 2001) this process appeared to progress in a front-to-back (fronto-parietal) fashion and growth rates were correlated with functional prognosis. These findings suggest that the progressive GM deficits seen in schizophrenia are not likely to be the result of WM overgrowth, because WM growth is itself slowed down (Gogtay et al., 2008).

GM Changes in Alzheimer's Disease

Another emerging feature from these GM studies is that the normal developmental trajectory is essentially the opposite of the neurodegenerative pattern seen in Alzheimer's disease (AD). In AD, cortical degeneration spreads from the medial temporal lobe entorhinal cortex in a forward wave through the limbic system (P. M. Thompson et al., 2004), consistent with the spread of neurofibrillary tangles and amyloid pathology seen post mortem. The same trajectory has also been revealed in PET scans with new amyloid-sensitive ligands, and it correlates with variations in cognitive function years before any overt symptoms of AD are detectable (Braak & Braak, 1991; Braskie et al., 2008).

This phenomenon, illustrated in Figure 6, is sometimes referred to as retrogenesis (Reisberg et al., 1999), where deficits appear first in systems that are last to mature during development. As is visually evident in the time-lapse maps, the maturational sequence proceeds in a pattern opposite to the classical neurodegenerative sequence in AD. This has led to some speculation that the earliest maturing cortices may be insulated by thick myelin sheaths and neuroglia that may protect them from neuroinflammation or degeneration, as plaques and tangles build up in later life. Normal cortical maturation may therefore be especially relevant to the future risk for AD; early cortical myelination may contribute to a cognitive reserve that delays the onset of symptoms in those at risk.

Strengths and Limitations of Voxel-based Mapping Methods

A major advance in morphometry came with the advent of statistical mapping methods that plot features such as gray matter density, cortical thickness in 3D, and can also be used to produce dynamic maps or animations of these features as they change over time. The most commonly applied voxel-based method is voxel-based morphometry, in which MRI scans are split into binary maps of gray and white matter, and spatially aligned across subjects to a common anatomical template. Then a statistic is plotted at each stereotaxic location to show the significance of some effect on anatomy, such as a group difference in gray matter density, or how the rate of change in cortical thickness links with cognition, or with future clinical

outcomes. The basic premise of this approach is that the spatial normalization, or warping, of brain scans from multiple subjects can align corresponding anatomical features. Even so, cortical anatomy is so complex and variable across subjects that most standard nonlinear registration algorithms cannot match cortical regions very well, as confirmed by a recent large-scale comparison study of 14 registration methods (Klein et al., 2009). Because VBM typically uses a standard automated registration approach and does create explicit models of the cortex, cross-subject registration errors in cortical anatomy can seriously reduce the power to detect group differences and disease effects.

To alleviate this loss of power due to data misregistration across subjects at the cortex, some developmental studies have used an approach known as cortical pattern matching (P. M. Thompson et al., 2004). This approach aligns data from different subjects by matching the entire cortical surface across subjects and also performs a higher-order matching of intervening surface areas between the major sulci, using advanced mathematical models based on continuum mechanics. This improves the localization of brain changes, which can be referred to specific gyri, and it also boosts statistical power by removing, as far as possible, the very wide variations in cortical patterns before evaluating gray matter differences. In situations where cortical patterns between brains are topologically different, a one-to-one match may not exist at the gross anatomical level. A well-studied example is that the paracingulate sulcus is less frequently present in schizophrenic patients. Rather than reject the premise of normalizing anatomy altogether, the best conceivable solution is to match accurately what can be matched, and treat what cannot be matched as unmodeled residual variation.

Tensor-based morphometry is a somewhat different method that is especially suitable for mapping growth rates for different structures. In TBM (Gogtay, 2008; P. M. Thompson et al., 2000), 3D maps of local tissue growth rates (as a percent per year) are derived by having a computer algorithm fluidly reshape the earlier scan to match the later one, matching fine-scale anatomical features. The applied deformation is analyzed to create per-subject maps of the growth rate (expansion factor) or local loss rate of tissue. In this approach, there is no need to quantify the amounts of gray and white matter in the scans, nor is it required to hand-label anatomical structures on the scans, unless summaries of growth rates are needed for particular regions of interest. The maps of growth rates for each subject can then be aligned to match a common anatomical template. As in VBM, statistics can be compiled and group differences in growth rates, or effects of medication, risk genes, or covariates of interest, can be plotted at each location the brain. In recent longitudinal MRI studies, TBM has provided among the best results in terms of longitudinal precision (smallest sample size needed to detect a 25% slowing of pathological changes). Even so, a wide variety of morphometric methods are being applied to developmental brain data. Each is sensitive to very different aspects of brain structure; some provide numeric summaries and others provide 3D maps or movies.

Neither VBM or TBM provides a means to distinguish “true” gray matter loss (i.e. dendritic pruning, or volume reduction in tissue that was present before) versus white matter encroachment. In both methods, the quantity of each tissue type is inferred based on the intensity of the MRI signal. In VBM, this is done explicitly, because the MRI intensity histogram is compiled, and the mean intensities of the respective tissues are estimated from the data. Based on that, and using statistical information on the likely location of different tissues in a standard space, the most likely classification of each voxel is made (i.e. to gray or white matter or some other class, e.g. CSF). The labeling of gray matter depends ultimately on the MRI signal intensity, and in general a white matter encroachment in the cortex will increase the signal intensity of the cortex on T1-weighted MRI, making it more likely to be classified as white matter. If so, the cortical changes may still reflect dendritic pruning or increased myelination. In TBM, although the gray matter is not explicitly segmented, the matching of features in the scans is based on the intensity information, although it is not assumed that

corresponding features will have similar intensities. Even so, TBM provides some auxiliary information, in that it maps the growth rates for different tissue types. In Gogtay et al.(Gogtay et al., 2008) and Hua et al. (Hua et al., 2009), significant growth rates were detected for the white matter underlying the cortex, making it more plausible that ongoing myelination contributed to some of the gray matter thinning reported in prior studies. Initially, the time-lapse maps of gray matter loss were established using surface-based modeling methods that examined only the cortex (P. M. Thompson et al., 2001), but subsequently TBM was used to map growth rates in the whole brain, implicating white matter encroachment as one contributor to the observed cortical changes (Gogtay et al., 2008).

Comments

Advances in neuroimaging methodology, combined with the availability of longitudinal data, now provide unique opportunities to gain insights into the disease onset, time-course and etiopathologic mechanisms of major neuropsychiatric illnesses. They may also be used to compare how different medications affect disease progression (P. M. Thompson et al., 2008). As population statistics are compiled from subjects with detailed genetic data, statistical mapping can be used to discover genes that protect brain structure or make it more vulnerable to disease (Cannon et al., 2003). Longitudinal imaging studies of pediatric populations have provided a unique developmental perspective on the neuropathology of these illnesses and highlight the power of longitudinal data for research and clinical applications. However, research in this field still remains limited by relatively small samples and relatively few longitudinal and population based studies, stressing the need for continued future work in this area. Some key areas for future work include the discovery of specific genes involved in GM maturation, and the correlation of functional MRI signals with structural changes in the brain (L. H. Lu et al., In Press). There is also a need to understand specific behavioral correlates of these changes (L. Lu et al., 2007), and, perhaps more challenging, to identify cellular processes involved in these GM changes.

GM mapping studies cannot be used yet for diagnostic purposes, but they have provided convincing evidence for the neurobiological specificity in neuropsychiatric illnesses such as COS or bipolar illness, which have partially overlapping clinical presentations. Many of these changes and dynamic trajectories have now been replicated in independent samples of subjects and have even been tracked before illness onset, as they emerge in those at risk for bipolar disorder (Gogtay, Ordonez et al., 2007) and schizophrenia (Pantelis et al., 2007). This early tracking of GM changes is of interest, as it means that imaging has a growing role in evaluating treatments that may resist the spread of pathology in the brain.

Relating changes in cortical GM across time to clinical measures or behavioral outcomes remains challenging, as there are obvious potential confounds, such as medication history and the effects of chronic illness. Animal studies have begun to assess the effects of medications on brain development. Another important area of future research would be to explore the relationships between genotype and imaging phenotypes, in both healthy and diseased populations, to understand the role of genotype on regionally specific brain development. New datasets are being collected that contain large-scale genomic data (e.g., genome wide association scans using million-SNP arrays) and GM and WM maps with increasingly finer spatial resolution, as well as multiple imaging measures at each voxel (Lee et al., 2009; Pausova et al., 2007). These imaging genetics studies pose huge computational and statistical challenges (Chiang et al., In Press; Glahn, Thompson, & Blangero, 2007), but will likely yield remarkable new sources of information on the genetic influences on normal and abnormal brain development. Data from our studies and other similar studies suggest the need to focus on individual differences/factors that may either predispose to psychopathology or are protective. Such studies are currently underway at the NIMH, UCLA, and other centers.

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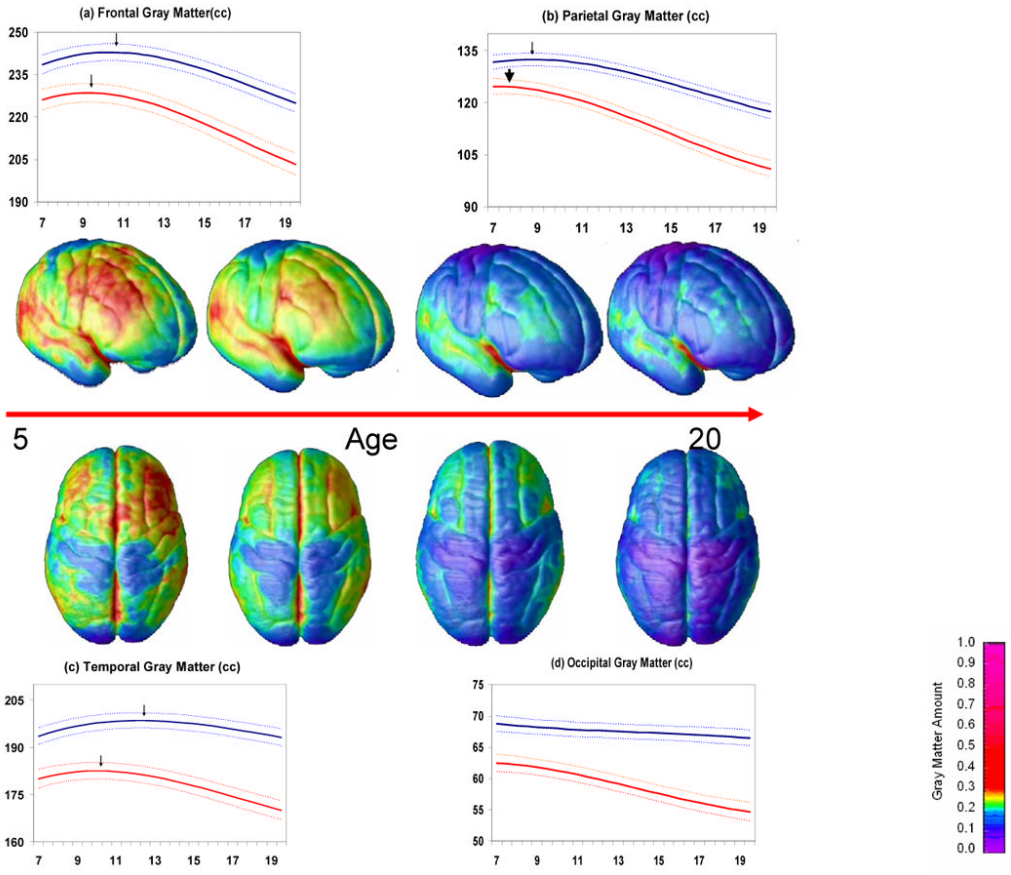

Figure 1.

Cortical GM development in healthy children between age 4 to 22.

Right lateral and Top views of the dynamic sequences of cortical GM maturation in healthy children ages 4 - 22 (n=13; 54 scans; upper panel) rescanned every two years. Scale bar shows GM amount at each of the 65,536 cortical points across the entire cortex represented using a color scale (Red to Pink – More GM; Blue – GM Loss). Cortical GM maturation appears to progress in a 'back-to-front' (parieto-temporal) manner (Gogtay, Giedd et al., 2004). The graphs show total lobar volumes of frontal, parietal, temporal and occipital lobes in male (blue) and female (red) healthy children between ages 7 to 20. Arrows indicate peak GM volume for each curve and dotted lines represent confidence intervals. Adapted from Giedd et al. 1999 (J. N. Giedd et al., 1999).

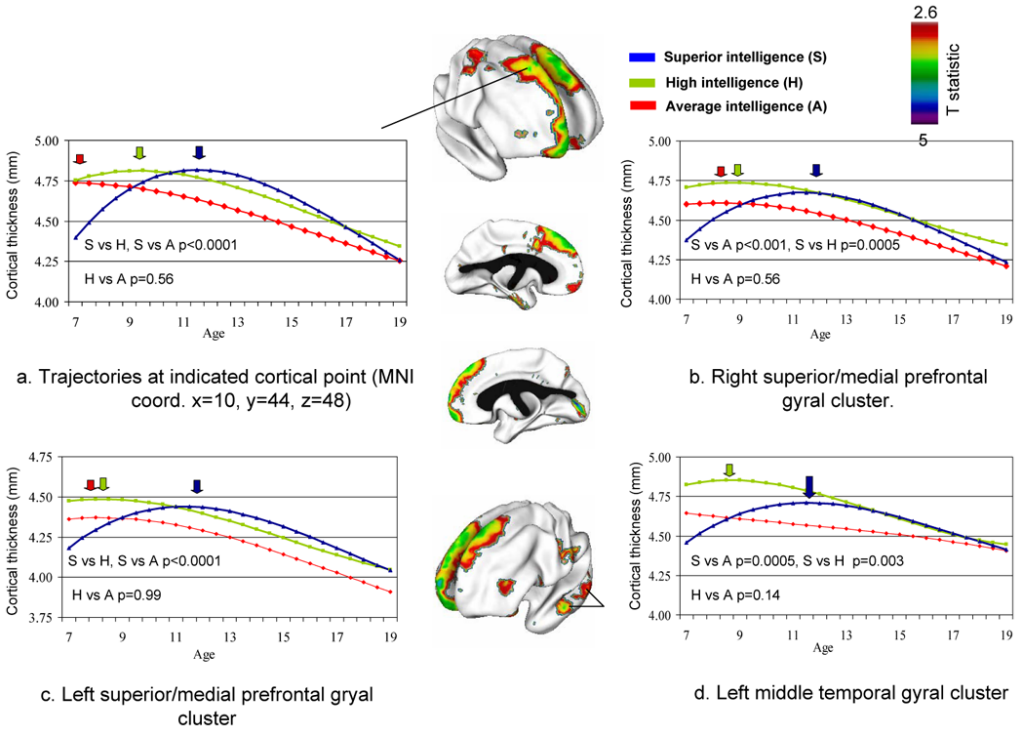

Figure 2.

Trajectories of cortical change in children with superior (n=91), high (n=101) and average (n=115) intelligence (total 629 scans).

The brain maps (*center panel*) show prominent clusters where the superior and average intelligence groups differ significantly in the trajectories of cortical development (t-statistic maps show areas of significant interaction between these IQ groups and the cubic age term). a, Graph showing the trajectories at the cortical point of maximum trajectory difference in the right superior frontal gyrus (point indicated in upper brain map). b–d, Graphs showing the trajectories of the mean thickness of all cortical points in the other clusters. The graph in d relates to the area indicated in the lower brain map. The age of peak cortical thickness is arrowed and significance values of differences in shapes of trajectories are given on the graphs. Adapted from Shaw et al. (Shaw et al., 2006).

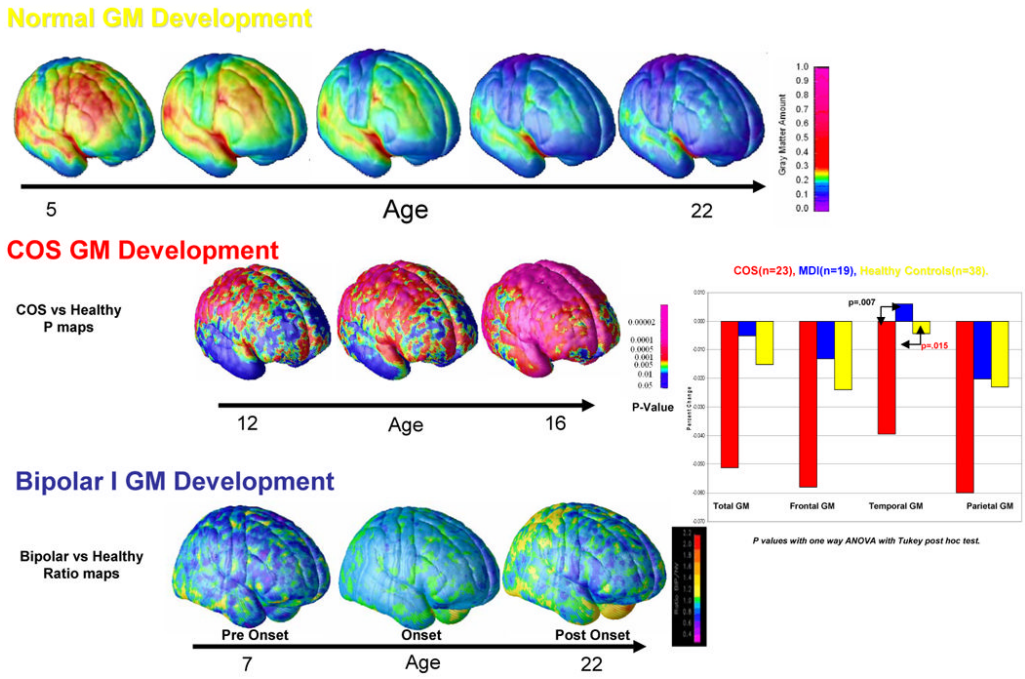

Figure 3.

Comparison and Specificity of GM developmental patterns in healthy, COS and Bipolar children.

Top panel shows right lateral views of dynamic sequences of cortical GM maturation in 13 healthy children between ages 4 to 22 as was displayed in Figure 1. The GM maturation (blue color) proceeds in parieto-frontal-temporal direction (Gogtay, Giedd et al., 2004).

The middle panel shows dynamic sequence of significant GM loss (p-maps) in 12 prospectively scanned COS children compared to matched healthy controls between age 12 to 16. The pattern of GM loss in COS appears to be an exaggeration of the normal GM maturation(P. M. Thompson et al., 2001).

The bottom panel shows dynamic sequence comparing the GM amount (using ratio maps) between 9 psychotic bipolar I children and their 18 matched controls, before and after onset of mania. There is little overlap in the GM deficit pattern between COS and bipolar GM development, establishing the diagnostic specificity of the findings(Gogtay, Ordonez et al., 2007).

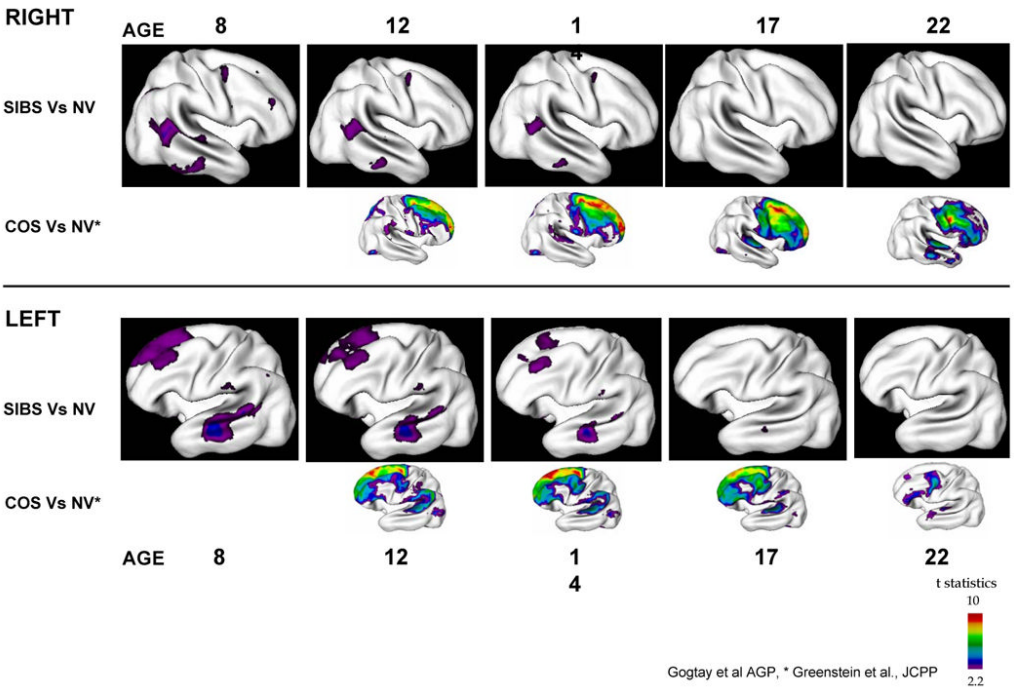

Figure 4.

Cortical GM thickness in healthy COS siblings (n=52; 110 scans) compared to age-, sex- and inter-scan interval-matched healthy controls (n=52; 108 scans) between ages 8 through 28 (Gogtay, Greenstein et al., 2007). For visual comparison, GM thickness in COS probands compared to matched healthy controls is shown at corresponding ages. Cortical GM is adjusted for mean cortical thickness (MCT) (Greenstein et al., 2006).

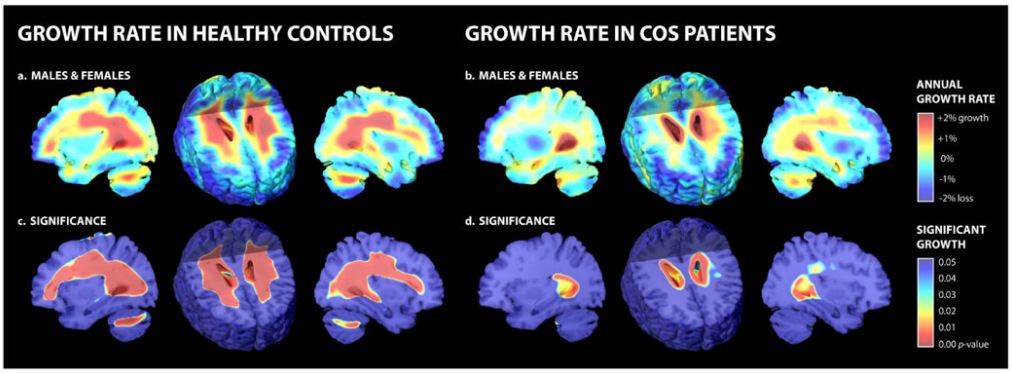

Figure 5.

Tissue Growth Rates Mapped in Healthy Controls and COS Patients (Gogtay et al., 2008). These average maps (*top row*) show the average rates of tissue growth (*red colors*) and tissue loss (*blue colors*) throughout the brain in percent per year, for healthy controls (*left panels*) and COS patients (*right panels*). Corresponding panels in the bottom row show the significance of the tissue growth in the top row. For each group, a sagittal section through the right hemisphere is shown, at the level of the occipital horn of the ventricles, followed by an axial section, and another sagittal section though the left hemisphere. Corroborating prior findings, these are the first maps to visualize the growth profile in 3D, showing significant expansion of the white matter and ventricles (cf. Giedd et al., 1999 (J. N. Giedd, J. Blumenthal, N. O. Jeffries, J. C. Rajapakse et al., 1999). Note the unexpected hemispheric asymmetry of growth rates in COS (right slower than left; $P<0.037$), and the slower growth in COS patients versus healthy controls, throughout the white matter (Figure 2 directly assesses the significance of the group differences). 3D versions of these maps are obtainable as video sequences at: http://www.loni.ucla.edu/~thompson/MOVIES/GROWTH/video.html

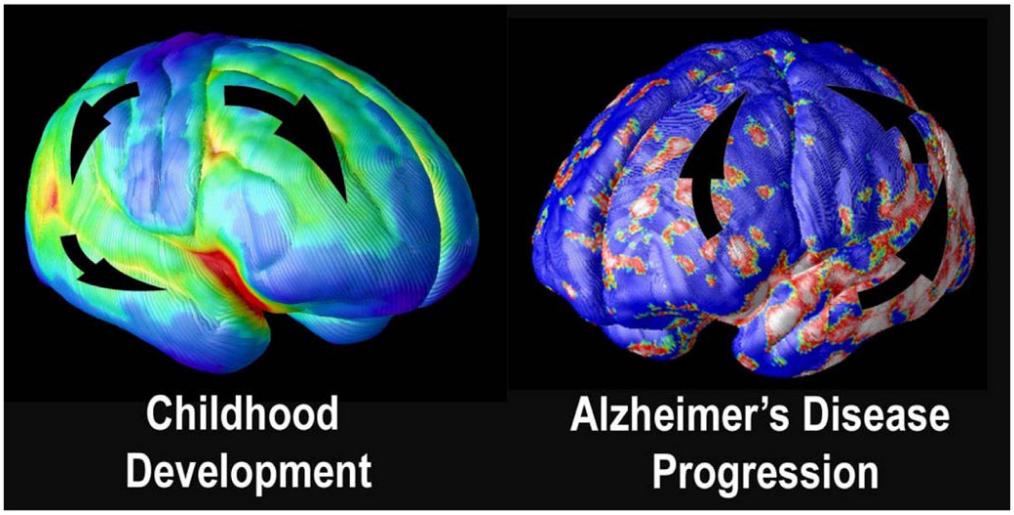

Figure 6.

Degenerative Sequence in AD is the Reverse of the Normal Developmental Sequence. In a process termed *retrogenesis* (e.g., by Reisberg et al., 1999), cortical regions that mature earliest in infancy tend to degenerate last in AD. The developmental sequence echoes the phylogenetic sequence in which structures evolved. The most heavily myelinated structures, with least neuronal plasticity, may resist AD-related neurodegeneration. Arrows denote the childhood cortical maturation sequence (*left panel*; Gogtay et al., 2004) and the gray matter atrophy sequence in AD (*right panel*; Thompson et al., 2003). Images are from time-lapse films compiled from cortical models of gray matter distribution in subjects scanned longitudinally with MRI, which may be viewed at:
http://www.loni.ucla.edu/~thompson/DEVEL/dynamic.html and
http://www.loni.ucla.edu/~thompson/AD_4D/dynamic.html