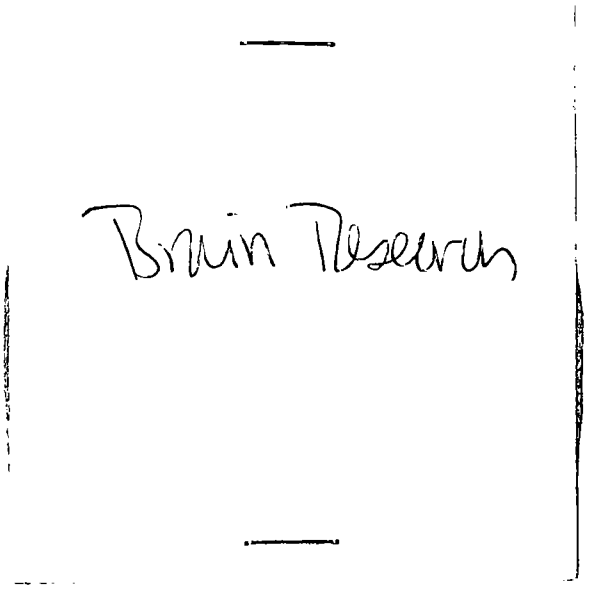
Brain Research

"Hyman, Steven (NIMH)" <shyman@mail.nih.gov>
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Record Type: Record

To: Ann O'Leary/OPD/EOP

cc: "Hyman, Steven (NIMH)" <shyman@mail.nih.gov>, "Weiblinger, Gemma (NIMH)" <gweiblin@mail.nih.gov>, "Wittenberg, Clarissa (NIMH)" <wittenbc@mail.nih.gov>

Subject: teenagers

I am in Tokyo, and will be back Friday night. My home number for the weekend is 301-263-0241. From experience I know that you are likely to be on a tight time line.

There is lots of interesting research related to teens on brain and behavior.

A recent paper by Arthur Toga (UCLA) and Jay Giedd (NIMH) used longitudinal MRI scans of the brain and new analytic techniques to demonstrate substantial changes in both white matter connections in brains and in gray matter (nerve cells) into teen years. This means that brain development, while most rapid in early years, continues at a significant pace through adolescence. This, of course, has implications for parents and communities: although early childhood is critical, we are not off the job yet! Moreover this raises a message of hope for kids who have had difficulties in childhood.

There is also research relevant not only to teens but also to adults that shows the birth of new nerve cells in the postnatal brain, and shows that in animal models, this "neurogenesis" or new nerve cell birth, is increased in enriched learning environments and decreased with chronic stress. The degree to which this is functionally important in humans is not yet known, but certainly this is another message of hope.

In terms of brain-behavior relationships, puberty brings with it steroid hormones that have an enormous and increasingly well understood impact on brain function and behavior.

Brain maturation also brings changes in risk of mental disorder. Before puberty boys and girls have equal risk of depression. After puberty, girls have twice the risk- an increase in risk that lasts throughout adulthood. This is not trivial since depression is so common- even by the strictest criteria women have a 10% lifetime risk of depression warranting clinical attention. Also (there is not complete certainty about this), certain antidepressant drugs (tricyclics) may begin to become efficacious at puberty. This reminds us of the impact of brain development not only on diagnosis, but on treatment of illness. Each developmental stage is dynamic. Kids are never just little adults. There is a large-scale NIMH research project in process- a multicenter treatment trial for adolescent

depression (TADS) looking at both psychotherapy and medication. Proper information to parents, teachers, and primary care providers will permit early and appropriate intervention- which is not happening now. Too many of our teens are growing up depressed and therefore not doing well in school or with peers. The message: it is not a normal part of teen years to be always sad, withdrawn, or in turmoil. There is help, and it can make a difference.

Also in girls, puberty brings risk of eating disorders. In boys puberty brings new elevated risk of substance abuse and aggressive behaviors. Again- we almost always intervene too late. Early intervention does make a difference.

At the behavioral level we have developed research tested preventive and treatment interventions for kids at risk of aggressive and violent behavior and interventions for teens already in trouble. Some of these deserve highlighting because they run counter to current practice. One is that the aggregation of antisocial peers is the final road to a career of violence and crime. But our society aggregates such kids in group detentions, group homes, alternative schools etc. There are research proven alternatives, such as Therapeutic Foster Care, developed by Patty Chamberlain in Oregon which works to separate kids from deviant peer groups and encourage prosocial arrangements. This research also lead to advice for parents about the importance of supervising kids' choice of peers.

There is also research from Tony Earls about the power of neighborhoods to shape teen behavior, and research on the importance of supervising teens (most crime committed by kids is between 3 PM when school lets out and 10 PM when they go to bed). Again a message to parents and communities.

Since I don't know the kids of things that interest you, I will stop here.

Steve

Conference file: brain research

Jay N. Giedd

-M.D. is Chief of Brain Imaging at the Child Psychiatry Branch of the National Institute of Mental Health where he uses magnetic resonance imaging to study brain development in healthy and unhealthy children and adolescents. Dr. Giedd is also a practicing clinician and is board certified in General Psychiatry and Geriatric Psychiatry as well as Child and Adolescent Psychiatry. He has written extensively in medical and science journals on the biological basis of behavioral, cognitive, and emotional disturbances and lectures nationally and internationally on these topics. His publications include works on autism, bipolar disorder, congenital adrenal hyperplasia, depression, dyslexia, eating disorders, fetal alcohol syndrome, Klinefelter's syndrome, learning disability, obsessive-compulsive disorder, pediatric autoimmune neuropsychiatric disorders associated with streptococcus, Sydenham's chorea, and Tourette's syndrome. He has also published seminal papers in the areas of attention deficit/hyperactivity disorder and childhood-onset schizophrenia. Recent work has focused on healthy brain development and the factors that guide and influence this process.

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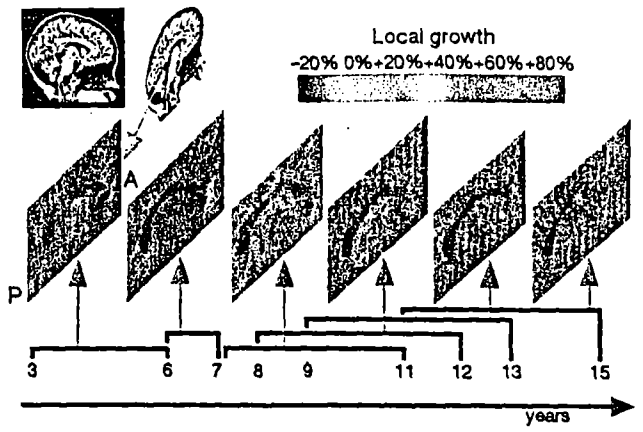

Figure 1 Growth patterns in the developing human brain detected at ages 3–15 years. A rostro-caudal wave of peak growth rates is detected in young normal subjects scanned repeatedly across time spans of up to four years. Between ages 3 and 6 years, peak growth rates (red colours; 60–80% locally) were detected in the frontal circuits of the corpus callosum, which sustain mental vigilance and regulate the planning of new actions. Older children displayed fastest growth at the callosal isthmus, which innervates temporo-parietal systems supporting spatial association and language function. Between ages 11–15 years, growth rates still peak at the isthmus, but are attenuated.

Growth patterns in the developing brain detected by using continuum mechanical tensor maps

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The dynamic nature of growth and degenerative disease processes requires the design of sensitive strategies to detect, track and quantify structural change in the brain in its full spatial and temporal complexity[1]. Although volumes of brain substructures are known to change during development[2], detailed maps of these dynamic growth processes have been unavailable. Here we report the creation of spatially complex, four-dimensional quantitative maps of growth patterns in the developing human brain, detected using a tensor mapping strategy with greater spatial detail and sensitivity than previously obtainable. By repeatedly scanning children (aged 3–15 years) across time spans of up to four years, a rostro-caudal wave of growth was detected at the corpus callosum, a fibre system that relays information between brain hemispheres. Peak growth rates, in fibres innervating association and language cortices, were attenuated after puberty, and contrasted sharply with a severe, spatially localized loss of subcortical grey matter. Conversely, at ages 3–6 years, the fastest growth rates occurred in frontal networks that regulate the planning of new actions. Local rates, profiles, and principal directions of growth were visualized in each individual child.

Time series of high-resolution three-dimensional magnetic resonance imaging (MRI) scans were acquired across large time spans from young normal subjects (aged 3–6, 6–7, 7–11, 8–12, 9–13 and 11–15 years) at intervals ranging from two weeks to four years. Growth patterns were recovered by computing a three-dimensional elastic deformation field, which reconfigures the anatomy at the earlier time point into the shape of the anatomy of the later scan.

Maps of local growth rates (Figs 1–4) revealed the complexity and regional heterogeneity of the tissue growth, pruning and maturation processes of late brain development. In subjects aged 6–15 years, the

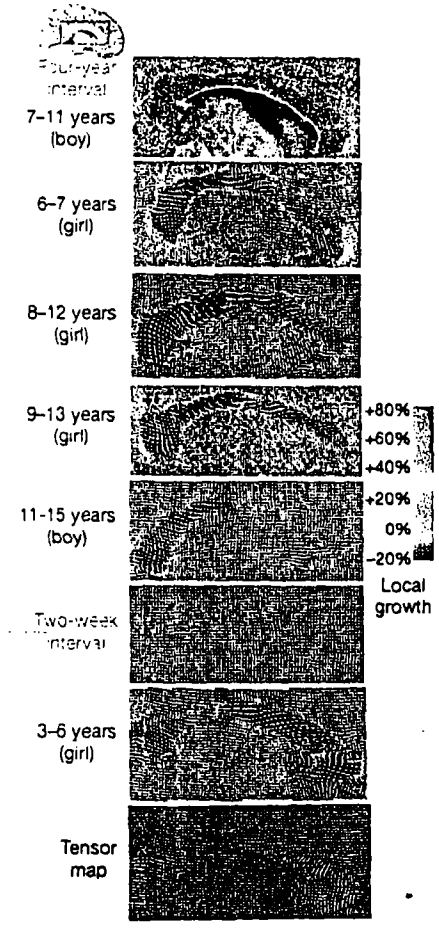

Figure 2 Mapping dynamic patterns of brain development: four-dimensional growth maps. Strikingly similar growth rates were detected in the corpus callosum of five young normal subjects scanned repeatedly aged 6–13 years. Peak values throughout the posterior midbody (red colours) were attenuated after puberty (11–15 years). By contrast, near-zero maps of change were observed between scans acquired over a two-week interval. Between ages 3–6 years, extreme growth rates were found in the anterior interhemispheric fibre systems that transfer information to sustain mental vigilance and organize new actions. Tensor maps identify the principal directions of growth rates, revealing an outward radial tissue expansion in frontal regions.

highest growth rates were consistently attained in temporo-parietal systems which are functionally specialized for language, and for understanding spatial relations (Fig. 2). In contrast to the near-zero maps of change recovered at short time intervals ('Two-week interval' in Fig. 2), growth maps spanning large time intervals showed complex and heterogeneous patterns of change. Between ages 7 and 11 years (Fig. 2), comparative stability of the splenial and rostral fibre systems of the corpus callosum contrasted sharply with rapid focal growth at the callosal isthmus (up to 80%). Although global measurements indicated an overall 22.4% increase in mid-sagittal callosal area during the four-year time span (from 527.6 mm^2 to 645.6 mm^2), these global values disguise the complexity of local growth patterns. Local growth is as high as 80% (Fig. 2), a feature which may not be apparent with conventional volumetric descriptors.

Although some individual variation was expected, this focus of extreme growth at the callosal isthmus was detected consistently in all subjects tracked between 6 and 15 years (Fig. 2), suggesting that cortico-cortical networks supporting rapid associative relay and language functions may myelinate more extensively[3] and over longer periods than rostral fibre systems. In a girl scanned twice exactly one year apart at ages 6 and 7 years, extreme growth (up to 85%) at the callosal isthmus contrasted with a comparatively quiescent region in the more rostral systems that innervate frontal and pre-frontal cortices. When a four-year growth map was generated for a slightly older child (11–15 years, Fig. 2), growth rates were correspondingly reduced in every region. Nonetheless, growth patterns at the isthmus and splenium (commonly defined as the posterior fifth of the callosum) were still more rapid (20–25% locally) than in the more anterior rostrum and genu (near-zero change). In an analysis of grey matter at the cortex[1], we recently observed a localized grey matter loss in frontal cortex that persists in normal subjects throughout adolescence even into adulthood. The gradual quiescence of growth at the rostral callosum around puberty may therefore be a precursor to a prolonged regressive process of grey matter loss through adolescence into adulthood in the frontal circuits it innervates.

Several near-zero maps of change were recovered at short time intervals. Figure 2 shows a typical map from a subject scanned at age 8 years, exactly four years later at age 12 years, and again two weeks later. Negligible change at short time intervals ('Two-week interval' in Fig. 2) contrasted with a highly heterogeneous map of growth across the four-year time span. Growth rates again achieved their highest rates in the associative and linguistic networks that cross at the callosal isthmus.

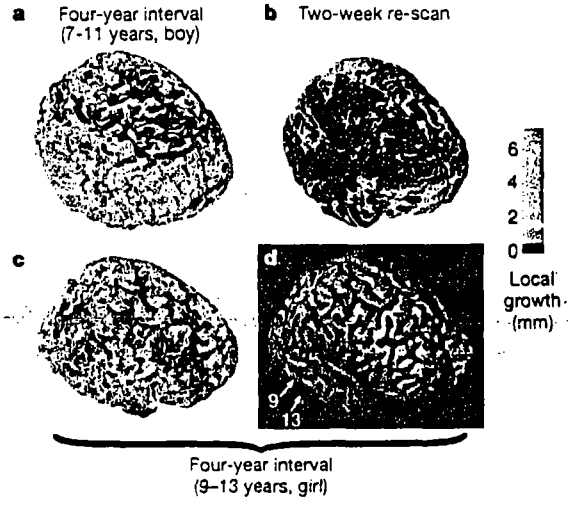

Figure 3 Patterns of cerebral growth. **a**, In a subject scanned at age 7 years and again exactly four years later at age 11 years, dramatic growth is found in temporo-parietal regions (red colours). **b**, All brain regions are stable in a control experiment (blue colours) analysing scans acquired two weeks apart. **c**, Between ages 9–13 years, growth is also most pronounced in temporo-parietal regions. **d**, This was confirmed by digitally overlaying models of the cerebral cortex at each time point (arrows 9 and 13). Growth at the callosal isthmus in subjects aged 7–11 and 9–13 years (Fig. 2) is therefore accompanied by diffuse growth in its (temporo-parietal) lobar projection zones.

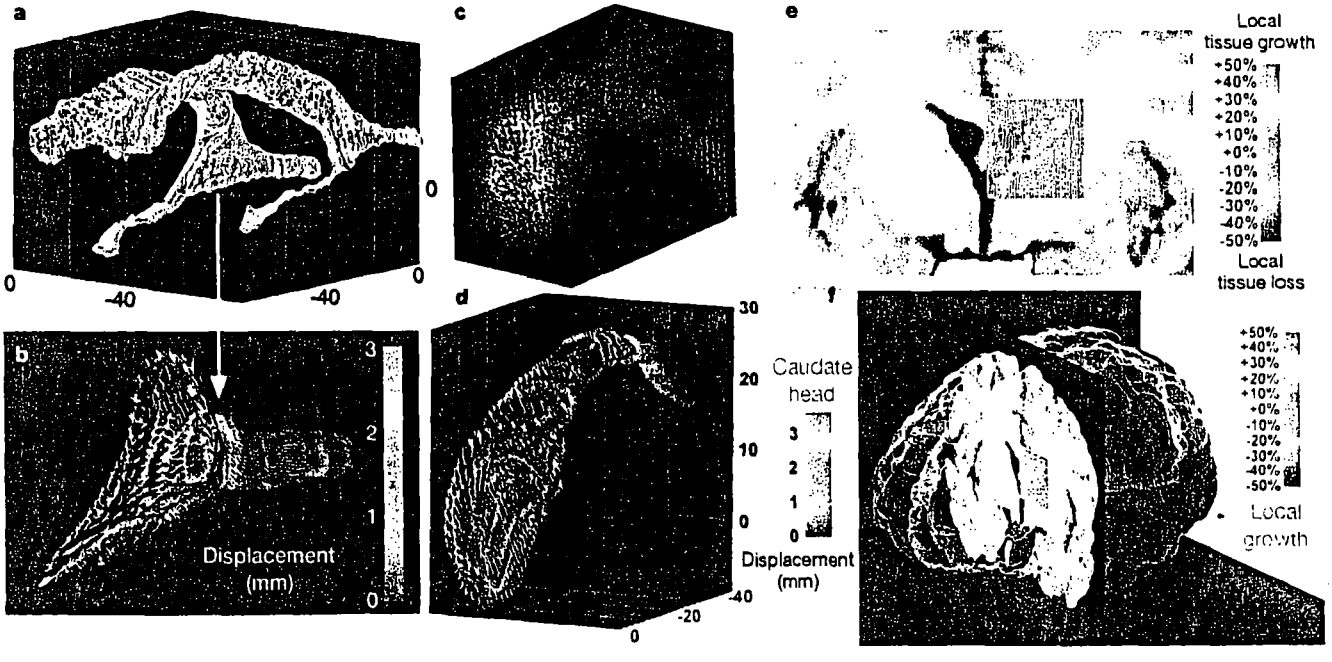

Figure 4 Detecting three-dimensional patterns of deep nuclear tissue loss. **a**, **b**, Tensor maps distinguish local growth or brain tissue loss from global displacements (**b**) of the adjacent ventricular anatomy, modelled here (**a**) at ages 7 years (red) and 11 years (yellow). **c**, **d**, Between ages 7 and 11 years, three-dimensional displacement vector maps show the deformation required to reconfigure earlier models of the caudate head into their later shape. The caudate tail is stable (blue colours. **d**). **e**, **f**, Local growth (**e**) and anatomical displacement (**d**) of the caudate head are independently recovered, with 50% tissue loss detected locally (**e**, **f**), adjacent to a region of 20–30% growth throughout the internal capsule.

A subject scanned at ages 3 and 6 years exhibited a focus of peak growth rates (60–80% locally) throughout the anterior corpus callosum, in frontal circuits that help to sustain a vigilant mental state and regulate the organization and planning of new actions. The extremely rapid rates of local growth are consistent with metabolic studies using positron emission tomography[5], which show an extraordinary doubling of the rates of glucose metabolism in the frontal cortex between ages 2 and 4 years, with frontal metabolic rates remaining at 199% of their adult values throughout the age range of 3–8 years. Between ages 3 and 6 years, when language function and associative thinking are not yet fully developed, growth rates at the isthmus were more quiescent (Fig. 2; 0–20% growth). Later growth foci in the isthmus, found consistently in all subjects aged 6–15 years, may reflect fine tuning of language functions known to occur late in childhood.

Regressive processes (tissue loss) were also detected at the same time as rapid growth. In the 7–11 and 9–13 year old subjects (Fig. 3), maps of lobar growth revealed pronounced (2–6 mm) temporo-parietal and pre-frontal enlargement. Somatosensory, motor and occipital brain regions were comparatively stable, with near-zero change in all brain regions at short time intervals (Fig. 3b). Up to 50% loss of tissue volume was detected at the caudate head (Fig. 4e and f). This tissue loss was highly localized, and contrasted with a 20–30% growth of the adjacent internal capsule (for which a separate surface model was made) and a 5–10% dilation of the superior ventricular horn (Fig. 4a). Gross volumetric measures confirmed an overall 60 mm^3 tissue loss at the caudate head, although these global measures disguise the regional complexity of the change. This example helps illustrate how tensor maps distinguish local growth patterns (Fig. 4e) from bulk shifts, such as global displacements of the adjacent cerebral ventricles (Fig. 4a and b). Three-dimensional vector displacement maps (Fig. 4b and d) emphasize that both global and local displacements are required to match modelled anatomical elements across time. The three-dimensional deformation field, however, encodes the patterns of local anatomical dilation and contraction, and its values are unaffected by global displacements. Maps of local three-dimensional growth are therefore not critically dependent on how well scans are initially aligned, and can define growth at arbitrary three-dimensional points in the local anatomy (Fig. 4e). Figure 4f indicates the anatomical context and regional complexity of these growth and regressive processes. The foci of tissue loss corroborate the hypothesis that pruning processes occur during this developmental stage[2], suggesting that these processes can be tracked in an individual child.

We detected striking, spatially complex patterns of growth and tissue loss in the developing human brain. A rostro-caudal wave of peak growth rates (Fig. 1) was identified in the corpus callosum. Fibre systems that mediate language function and associative thinking grew more rapidly than surrounding regions across time spans before and during puberty (6–13 years), with growth attenuated shortly afterwards (11–15 years). This temporal pattern coincides with the ending of a well-known critical period for learning language, consistently noted in studies of second-language acquisition, including sign language, and in isolated children not exposed to language during early development[6]. The ability to learn new languages declines rapidly after the age of 12 years, as does the ability to recover language function if linguistic areas in one brain hemisphere are surgically resected. Peak growth rates in linguistic callosal regions, as well as their attenuation around puberty, may reflect the conclusion of the critical period for learning language and for accelerating signal transduction in networks that support both associative reasoning and language function. We recently found that the same temporo-parietal fibre system, crossing at the callosal isthmus, degenerates fastest in early Alzheimer's disease[7], when progressive neuronal loss and perfusion deficits begin to occur in temporo-parietal association cortices and their commissural projection systems. The sensitivity of the approach may therefore offer advantages in tracking fine-scale effects of therapeutic interventions in dementia and oncology, mapping the local complexities of disease processes using dynamic rather than static criteria. □

Methods

Magnetic resonance imaging and pre-processing

Three-dimensional ($256^2 \times 124 \times 0.97$ mm $\times$ 0.97 mm $\times$ 1.5 mm resolution) T_1-weighted fast SPGR (spoiled GRASS (gradient-recalled acquisition in the steady state)) MRI volumes were acquired from young normal subjects (mean age 8.6 ± 3.1 years) at intervals ranging from two weeks to four years. For each scan pair, a radio-frequency bias field correction algorithm[8] was applied to both scans to eliminate intensity drifts caused by scanner field inhomogeneity. The initial scan was then rigidly registered to the target using automated image registration software[9] and resampled using chirp-Z (in-plane) and linear (out-of-plane) interpolation. Registered scans were histogram-matched (that is, their intensity distributions were equalized) and a preliminary map of differences in MRI signal intensities between the two scans was constructed[1,10]. Tensor models of structural change were then used to calculate rates of tissue dilation, contraction and shearing, mapping local patterns of change in three dimensions.

Image analysis

A high-resolution surface model of the cortex was automatically extracted[11] from each scan pair, and three-dimensional digital anatomical models, based on parametric surface meshes[12,13], were generated to represent a comprehensive set of deep sulcal, callosal, caudate and ventricular surfaces at each time point[14]. Surface models based on manually digitized data were averaged across multiple trials ($N = 6$) to minimize error[15]. These model surfaces provided anatomic constraints for an elastic image registration algorithm[12,14]. For each subject, this algorithm calculated a three-dimensional elastic deformation vector field, with $384^2 \times 256 \times 3 \approx 0.1$ billion degrees of freedom, reconfiguring the anatomy at the earlier time point into the shape of the anatomy of the later scan. Surface deformations were used to derive a volumetric deformation field from which local measures of three-dimensional tissue dilation or contraction were quantified. Landmark points, surfaces, and curved anatomic interfaces were matched up in the pair of three-dimensional image sets, and the biological validity of the resulting anatomical transformation was guaranteed by forcing a large system of anatomical surface boundaries to match exactly. These included multiple structural, functional, and tissue type boundaries in three dimensions, including the callosum, caudate, cortex and ventricles. The deformation field driving the earlier onto the later anatomy was extended to the full volume using a continuum-mechanical model based on the Cauchy–Navier operator of linear elasticity[14,16–18]. The resulting system of 0.1 billion second-order elliptic partial differential equations was solved by successive over-relaxation methods, with multi-grid acceleration[12,14], on a standard radiologic workstation. Potential artefactual differences due to differences in how surfaces were parametrized in each scan were compensated for, using a field of Christoffel symbols to modify the surface differential operators during the anatomical transformation[14].

Tensor map computation

From this transformation, local rates of tissue dilation, contraction and shearing were calculated. Deformation processes recovered by the image-matching algorithm were analysed mathematically with vector field operators[14] to produce a variety of tensor maps. These maps reflect the magnitude and principal directions of tissue dilation or contraction, and the local rates, divergence and gradients of the growth processes detected in the dynamically changing brain.

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09:45 AM ET 03/09/00

Study: Brains Grow Furiously

The Associated Press

Children's brains change dramatically in key areas into puberty, researchers report in a new study that contradicts some long-standing assumptions about brain development.

The anatomical changes--described as "fine-tuning"--surprised scientists in the United States and Canada who conducted the study published Thursday in the journal *Nature*.

The changes occurred between ages 3 and 15, in some cases years after the brain has reached its full size. Scientists had believed that neural development slowed after the first few years of life, and the brain was essentially organized by the time a child enters first grade.

In fact, they said, even in the mid-teens the amount of gray matter in some very active areas can double and neurons can interconnect rapidly while unneeded cells in other areas are flushed out.

The research continues two earlier studies of brain development published last fall. Researchers said they have not determined how the findings might be practically incorporated into new approaches to education or child development, but the study suggests how critically intertwined the stages of brain growth might be to a child's intellectual and emotional development.

"The teen-age years are a kind of critical time to optimize the brain," one of the study's co-authors, child psychiatrist Jay Giedd of the National Institutes of Health, told *The Washington Post*. "If a person is doing sports or academics or music, those are the abilities that will be hardwired."

In the study, researchers at UCLA, the NIH and McGill University in Montreal scanned the normal brains of boys and girls ages 3 to 15. Some of the children participated as long as four years.

They saw a wave of growth in the fiber system that relays information between the brain hemispheres and is a good indicator of brain activity. The scans also showed new connections being made in some areas, while other areas shrunk.

In children ages 3 to 6, the team saw burgeoning in the frontal networks that regulate the planning of new actions.

"In the very youngest children, there really is this furious growth going on in the frontal circuits of the brain," UCLA neurologist Paul Thompson, who helped develop the brain

mapping technique, told the *Los Angeles Times*. "You see this extraordinary wave of peak growth that proceeds from the front of the brain to the back."

In teen-agers up to age 15, the researchers observed peak growth rates in areas in the middle and back of the brain associated with associative thinking and language.

The finding reinforces the wisdom of learning new languages early in life. By high school, the task may become biologically more difficult.

"The ability to learn a new language declines rapidly after age 12," the researchers reported. "Peak growth rates in linguistic regions, as well as their attenuation around puberty, may reflect the conclusion of the critical period for learning languages."

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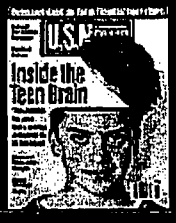

Cover Story 8/9/99

Behavior can be baffling when young minds are taking shape

BY SHANNON BROWNLEE

One day, your child is a beautiful, charming 12-year-old, a kid who pops out of bed full of good cheer, clears the table without being asked, and brings home good grades from school. The next day, your child bursts into tears when you ask for the salt and listens to electronic music at maximum volume for hours on end. Chores? Forget it. Homework? There's little time, after talking to friends on the phone for five hours every night. Mornings? Your bluebird of happiness is flown, replaced by a groaning lump that can scarcely be roused for school. In short, your home is now inhabited by a teenager.

The shootings in Littleton, Colo., focused the nation's attention on aberrant adolescent behavior, but most teens never come close to committing violent acts. Still, even the most easygoing teenagers often confound their elders with behavior that seems odd by adult standards.

For most of this century, the assumption has been that teenage *sturm und drang,* the insolence and the rages, are all directed at parents. Teens turn against authority figures, went the conventional wisdom, in an effort to define who they are and to assert their independence–a view that spawned the teenage rebel, that quintessential American icon. The alternative explanation was that hormones, those glandular bringers of sexual stirrings and pimples, were to blame.

The true source of teenage behavior lies north of the gonads. It's that 3-pound blob of gray and white matter known as the brain.

Yes, teenagers do have brains, but theirs don't yet function like an adult's. With the advent of technologies such as magnetic resonance imaging, neuroscientists have discovered that the adolescent brain is far from mature. "The teenage brain is a work in progress," says Sandra Witelson, a neuroscientist at McMaster University in Ontario, and it's a work that develops in fits and starts.

Until the past decade, neuroscientists believed that the brain was fully developed by the time a child reached puberty and that the 100 billion neurons, or nerves, inside an adult's skull–the hardware of the brain–were already in place by the time pimples began to sprout. The supposition was that a teenager could think like an adult if only he or she would cram in the necessary software–a little algebra here, some Civil War history there, capped by proficiency in balancing a checkbook.

INTERACTIVE SPECIAL
: Do you know why teens act the way they do? Test your knowledge.

THE TEEN BRAIN

: You were angry? (8/9/99)

: Anorexia's roots in the brain. (8/9/99)

: Why teens need more snooze time. (8/9/99)

Also on the Web

. A compendium of sites that help parents of teens deal with topics from to . (From)

Part of iVillage's , this online resource for parents includes and on dealing with your teen.

there, capped by proficiency in balancing a checkbook. But the neural circuitry, or hardware, it turns out, isn't completely installed in most people until their early 20s.

And just as a teenager is all legs one day and all nose and ears the next, different regions of his brain are developing on different timetables. For instance, one of the last parts to mature is in charge of making sound judgments and calming unruly emotions. And the emotional centers in the teenage brain have already been revving up, probably under the influence of sex hormones.

This imbalance may explain why your intelligent 16-year-old doesn't think twice about getting into a car driven by a friend who is drunk, or why your formerly equable 13-year-old can be hugging you one minute and then flying off the handle the next.

Indeed, the brain inside a teenager's skull is in some ways closer to a child's brain than to an adult's. Still being forged are the connections between neurons that affect not only emotional skills but also physical and mental abilities. That means that it might be unreasonable to expect young teenagers to organize multiple tasks or grasp abstract ideas. And these still-developing neural links leave a teenager vulnerable: Depression in adolescence may set up circuits in the brain that will make it much harder to treat the illness later in life.

But these changes aren't all for the worse. The brain's capacity for growth through adolescence may also indicate that even troubled teenagers can still learn restraint, judgment, and empathy. "Adolescence is a time of tumultuous change in the brain," says Jay Giedd, a child psychiatrist at the National Institute of Mental Health in Bethesda, Md. "Teenagers are choosing what their brains are going to be good at–learning right from wrong, responsibility or impulsiveness, thinking or video games."

If there's one thing that drives parents nuts about their teenagers, it's moodiness. "It's hot and cold, nasty and nice," says Vicki Sasso, 34, the mother of 13-year-old Angelo, a ninth grader from Staten Island, N.Y. "One minute loving me, one minute hating me." Don't blame Angelo; blame the parts of his brain that process emotions and make decisions. His prefrontal cortex, where judgments are formed, is practically asleep at the wheel. At the same time, his limbic system, where raw emotions such as anger are generated, is entering a stage of development in which it goes into hyperdrive.

Brain police. The limbic system, located deep in the brain's interior, is associated with gut reactions, sparking instant waves of fear at the sight of a large snake or elation at a high SAT score. In adults, such emotional responses are modulated by the prefrontal cortex, the part of the brain that lies just behind the forehead and that acts as a sort of mental traffic cop, keeping tabs on many other parts of the brain, including the limbic system.

Indeed, the brain works something like a loosely organized team, with various parts carrying out different tasks and more or less cooperating with one another. The prefrontal cortex, says Karl Pribram, director of the Center for Brain Research and Informational Sciences

Learn about normal adolescent development in the

and

(From the

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neurons and synapses that are useful. Pruning, which occurs in different parts of the brain at different times, also appears to allow the brain to think more efficiently.

Until the prefrontal cortex has been pruned, most young teenagers don't yet have all the brain power they need to make good judgments. Researchers suspect that the excess of synapses means the young adolescent mind can't easily keep track of multiple thoughts, and it can't gain instant access to critical memories and emotions that allow grown-ups to make judicious decisions.

"Good judgment is learned, but you can't learn it if you don't have the necessary hardware," says Yurgelun-Todd. An unfinished prefrontal cortex also means that young teenagers may also have trouble organizing several tasks, deciding, for example, which to do first: call a friend, wash the dishes, or read the book for a report that's due in the morning.

The teenage tendency to leap before looking is compounded by the fact that adolescence is a time for seeking out new experiences, including some that are dangerous. "I think all people do stupid things sometimes. It just seems like teenagers do it more often," says Rachael Fisher, an 18-year-old senior from Lakewood, Colo. That's an understatement. Driving without a seat belt, getting tattooed, smoking cigarettes, shoplifting–the list of foolish things kids do is longer than most parents really want to know.

Parents can relax a little, says Lynn Ponton, a child psychiatrist at the University of California-San Francisco and author of *The Romance of Risk*. "Risk taking is normal." But not all of it, she adds, is safe. Other research suggests that about 60 percent of a teenager's tendency to act impulsively and misjudge potential danger is genetic, a trait that is shared with other family members and is probably the result of differences in brain chemicals among individuals.

Mental mosh pit. Researchers also think that new experiences, especially those with a *frisson* of danger or the thrill of the new, tap into a teenager's so-called reward system, a set of neurons that link emotional centers to many other parts of the brain and that can produce feelings of intense pleasure. This is the same set of neurons affected by certain illicit drugs, such as cocaine, that release dopamine, one of the brain chemicals, or neurotransmitters, that are responsible for arousal and motivation.

Marvin Zuckerman, a professor of psychology at the University of Delaware, and others suspect that thrills–like sneaking out at night or jumping into the mosh pit at a heavy-metal concert–stimulate the teenage brain's dopamine system, for reasons that are not yet fully understood. The result, however, is clear: Teenagers are far more interested in novelty than children or adults are, probably because it makes them feel good. Other research has shown that at the same time, levels of another neurotransmitter, serotonin, appear to decline temporarily in most adolescents, making them more likely to act impulsively.

Added to this brew of neurotransmitters are the sex hormones, which not only turn on an interest in sex but also change the brain's architecture. Giedd and his colleagues recently reported for the first time that, in

both sexes, surges of testosterone at puberty swell the amygdala, an almond-shaped part of the limbic system that generates feelings of fear and anger. (Girls' bodies make testosterone by breaking down estrogen, while boys' bodies transform testosterone into an estrogen-like hormone called estradiol.) This blossoming of the amygdala is especially pronounced in boys, but it may account for the rise in aggressiveness and irritability seen in both sexes at adolescence. Increased levels of estrogen at puberty are responsible for the sudden growth of the hippocampus, the part of the brain that processes memory. The larger the hippocampus, the better the memory, at least in animals. The hippocampus in girls grows proportionally larger than it does in boys, a finding that may help explain why women are better than men are at remembering complex social relationships and are likely to suffer less from the memory loss that accompanies Alzheimer's.

Estrogen and testosterone may not alter the brain at puberty so much as flip neurological switches, which were set by hormonal levels while a child was still in his mother's womb. Once flipped, these switches have a profound effect on a teenager's sex drive and moodiness.

Shifts in prenatal hormones also affect mental skills in ways that may not become apparent until later in life. Testosterone, for example, appears to shape centers in the brain that process spatial information. Evidence for this comes from a study of girls with congenital adrenal hyperplasia, or CAH, a condition that causes their adrenal glands to pump out excess androgen, a testosterone-like hormone, during prenatal development. Once the girls are born, they are given cortisone, to keep the body from producing too much androgen.

Their brains, however, have already been molded. Sheri Berenbaum, a psychologist at Southern Illinois University medical school, and others have found that as teenagers, girls with CAH report they are more aggressive than their sisters, and they have better spatial skills–the ability to rotate an object in their minds, for instance, or to imagine how pieces of a shape fit together. They are also more interested than their sisters in becoming engineers and pilots, traditionally masculine professions. But researchers don't yet know precisely how testosterone molds the brain's ability to imagine all the facets of an object, or why it would make girls (or boys, for that matter) want to become engineers.

One of the last steps in making an adult brain is the coating of nerves in white matter, fatty cells that spiral around the shaft of nerves like vines around a tree. The white matter, also known as myelin, acts like the insulation on an electric cord, allowing electrical impulses to travel down a nerve faster and more efficiently. This is one reason a toddler is less coordinated than a 10-year-old. It now appears that many of the nerves connecting different processing centers in the brain don't finish myelinating until the early 20s.

Some of the nerves that become sheathed during adolescence connect areas of the brain that regulate emotion, judgment, and impulse control. Francine

Benes, a neuroscientist at McLean Hospital, says that these nerves myelinate in girls earlier than in boys, which may help explain why teenage girls seem more emotionally mature than boys, whose myelin levels may not equal girls' until age 30.

The myelination process also has been implicated in schizophrenia, which often becomes apparent in late adolescence. Benes believes the faster transmissions overload defective nerves in schizophrenics. "If the circuit starts to have too much information coming in too rapidly, it may become overwhelmed."

Laying foundations. Researchers feel they have only begun to probe the workings of the adolescent brain, but their findings already offer some new ways for parents to deal with teenagers. During adolescence, many higher mental skills will become automatic, just the way playing tennis and driving do. Kids who exercise their brains, in effect, by learning to marshal their thoughts, to measure their impulses, and to understand abstract concepts, are laying the neural foundations that will serve them for the rest of their lives.

"This argues for doing a lot of things as a teenager," says the NIMH's Giedd. "You are hard-wiring your brain in adolescence. Do you want to hard-wire it for sports and playing music and doing mathematics–or for lying on the couch in front of the television?" This hard-wiring also provides yet another reason for teens not to take drugs or alcohol, because they may permanently alter the balance of chemicals in their brains.

Parents can take comfort in knowing that searching for new experiences is a normal part of growing up. The trick, say experts, is helping kids find healthy sources of stimulation. For one child, being in the school play or volunteering in the community may provide plenty of excitement. For another, it could take hang-gliding lessons. The problem, of course, is that safe risks are not always available to the kids who need them. "Middle-class kids can go skiing and scuba diving," says the University of Delaware's Zuckerman. "But for many kids, there's just crime, sex, drugs, and rock-and-roll."

The best news for parents is that the vast majority of kids will make it through adolescence with few permanent scars, except perhaps the occasional hole through a bellybutton. New research shows that most children emerge from adolescence physically and emotionally intact–although their parents will probably never be the same. Mary Scott, 48, of Port Jefferson, N.Y., is a veteran of teenage wars: She's the mother of two adolescents and a 22-year-old. "Occasionally they do things that are so incredibly selfish, it's unbelievable," she says. On the other hand, Scott adds, "If they didn't drive you crazy, they'd never leave [the nest]." Maybe adolescence is nature's way of forcing children to grow up.

With Roberta Hotinski, Bellamy Pailthorp, Erin Ragan, and Kathleen Wong

steady income and high hopes for their three young daughters.

But when they applied for a plot of land in a handsome new suburban neighborhood under construction near their village in 1994, the Kaadans were turned down flat. Arabs were not welcome, they were told. And the Kaadans, like one in six Israeli citizens, are Arabs.

"We thought this would be an opportunity

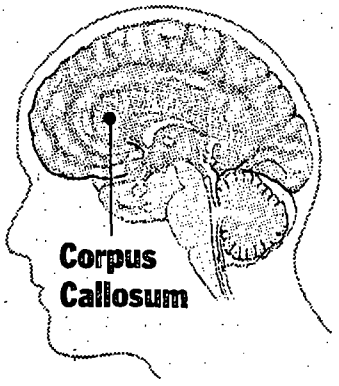
appointment, Israel's High Court of Justice stepped in today. Overturning a half-century of policy, practice and entrenched discrimination, the court ruled that Arabs cannot be barred from living in certain types of cooperative communities. Similarly, the court forbade Israelis from establishing exclusively Jewish communities on state land.

See ISRAEL, *A20, Col. 2*

Key Brain Growth Goes On Into Teens

Study Disputes Old Assumptions

By CURT SUPLEE
Washington Post Staff Writer



Scientists have discovered that the brain undergoes surprisingly dramatic anatomical changes between the ages of 3 and 15, a finding that may not amaze parents of mercurial children but shatters some traditional assumptions about neural development.

During key periods, a research team reports in today's issue of the journal Nature, the amount of gray matter in some areas can nearly double within as little as a year, followed by a correspondingly drastic loss of tissue as unneeded cells are purged and the brain continues to organize itself.

"It's remarkable," said neurologist Arthur Toga of the University of California at Los Angeles' School of Medicine. "Even though the overall size of the brain is relatively mature, we're still seeing changes" in the form of "very local and discrete patterns."

As recently as a decade ago, it was widely assumed that such major growth spurts and subsequent cutbacks took

See BRAIN, *A14, Col. 1*

INSIDE

Key Brain Growth Continues Into Teens

BRAIN, *From A1*

place in the womb or very early in childhood, and that the overall structure of the brain changed very little, if at all, after the age of 5 or 6.

At that point, the brain usually has reached about 95 percent of the average adult volume, having increased fourfold in size since birth. Of course, extensive internal re-wiring takes place during childhood. The gross structure, however, was thought to be generally fixed. That led educators and child development experts to focus on the first few years of life as crucial for proper brain development.

"Basically, the theory said that the amount of gray matter went downhill from about age 3," said Jay N. Giedd, a child psychiatrist with the National Institute of Mental Health in Bethesda who participated in both the new study and a similar one last fall. "The idea was that it's a zero-sum game. The frame and structure of the house was complete, and the furniture was just being rearranged."

The new brain scan results, and two similar studies of slightly older age groups published last fall, are the first brain-imaging studies to show that the process continues.

"We now know that there are these sorts of critical periods," said UCLA neuroscientist Elizabeth R. Sowell, a coauthor of one of the earlier papers. "But I don't think anybody has yet figured out a way to make this clinically relevant.... Still, we're all hoping that perhaps the experts in education or psychology will see these things that we're showing them and find ways to make those connections."

Neuroscientists had long known that a two-stage process of growth and attrition is typical of brain development from the fetal period through early childhood.

First, the brain overproduces gray matter—bulk neurons that are not yet permanently "wired" into neural circuits. These cells begin to arrange themselves into patterns depending on which connections are reinforced by mental or physical activity. Thereafter, the least-used cells and pathways die out in a phenomenon called "pruning" as white matter (chiefly fibers interconnecting nerve cells) forms to firm up the most robust connections.

In the new research, Toga, Giedd and colleagues from UCLA and McGill University in Canada conducted repeated three-dimensional brain scans of several normal children over intervals as short as two weeks and as long as four years.

The group concentrated on size and shape changes in a complex nerve fiber network called the corpus callosum, which connects the two hemispheres and is a reliable indicator of the level of activity in different parts of the brain.

The results indicate that from ages 3 to 6, the most rapid growth takes place in frontal-lobe areas involved in planning and organizing new actions, and in maintaining attention to tasks.

By contrast, during the period from 6 to puberty, the scientists found, the gray-matter spike shifts to the temporal and parietal lobes that play a major role in language skills and spatial relations. The growth rate then falls off fast, which may explain why, as a rule, the ability to learn languages declines sharply after the age of 12.

As children age, the growth moves in a sort of wave from the front of the brain to the rear, the team found. "We were quite surprised," Giedd said, "to see this unexpected increase in gray matter in the front part of the brain right before puberty," which occurs around age 11 in girls and 12 in boys.

Last fall, researchers reported in the journal Nature Neuroscience that they had found an unexpected increase in gray matter at the onset of adolescence, followed by a substantial loss in the frontal lobes from the mid-teens through the mid-twenties.

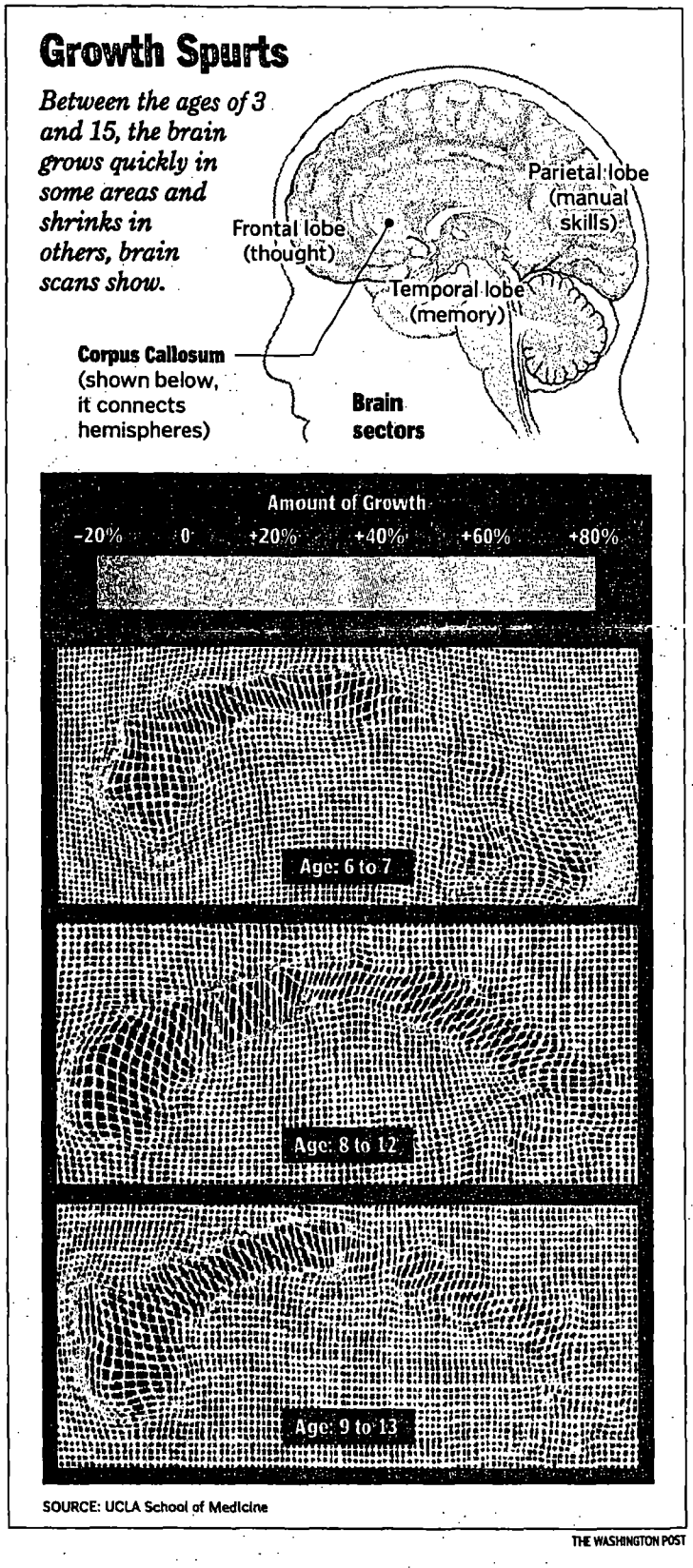
The frontal lobe of the brain is essential for inhibiting impulses, regulating emotion and planning and organizing behavior—all of which can be critical issues for teenagers and their parents.

Giedd believes the growing evidence of brain-structure mutability should be welcome news to teenagers.

"In the womb and during the first 18 months of life," when the brain undergoes its most drastic changes, "an infant doesn't have much say about the way things turn out. But during the teenage years, "a person has a lot to say" about the way his brain develops, Giedd said.

In that critical interval, he said, the rule for brain structures appears to be "use it or lose it. What we think then happens is that if a person is doing sports or academics or music, then those are the abilities that are going to be hardwired" as the circuits mature. "The teenage years are a kind of critical time to optimize the brain."

Teenagers who recognize that tend to "feel empowered," Giedd said, especially if they "realize that the stakes are pretty high."



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A clonogenic common myeloid progenitor that gives rise to all myeloid lineages

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Haematopoietic stem cells give rise to progeny that progressively lose self-renewal capacity and become restricted to one lineage[1,2]. The points at which haematopoietic stem cell-derived progenitors commit to each of the various lineages remain mostly unknown. We have identified a clonogenic common lymphoid progenitor that can differentiate into T, B and natural killer cells but not myeloid cells[3]. Here we report the prospective identification, purification and characterization, using cell-surface markers and flow cytometry, of a complementary clonogenic common myeloid progenitor that gives rise to all myeloid lineages. Common myeloid progenitors give rise to either megakaryocyte/erythrocyte or granulocyte/macrophage progenitors. Purified progenitors were used to provide a first-pass expression profile of various haematopoiesis-related genes. We propose that the common lymphoid progenitor and common myeloid progenitor populations reflect the earliest branch points between the lymphoid and myeloid lineages, and that the commitment of common myeloid progenitors to either the megakaryocyte/erythrocyte or the granulocyte/macrophage lineages are mutually exclusive events.

The existence of clonal common lymphoid progenitors (CLPs)[3] suggests that complementary progenitors common to all myeloid cells may also exist. Because the expression of the interleukin-7 receptor α-chain (IL-7Rα) marks the CLPs and other downstream lymphoid progenitors[3,4], we searched the IL-7Rα$^-$ fraction of murine bone marrow for primitive myeloid progenitor populations.

In steady-state mouse bone marrow, myeloerythroid colony-forming unit (CFU) activity was found almost exclusively in the IL-7Rα$^-$Lin$^-$c-Kit$^+$ fraction (data not shown). Within this population, Sca-1$^+$ cells are highly enriched for haematopoietic stem cells (HSCs)[3,5–7]. To remove HSCs, Sca-1$^+$ cells were excluded. The IL-7Rα$^-$Lin$^-$c-Kit$^+$Sca-1$^-$ fraction was further divided into three subpopulations according to the expression profiles of the Fcγ receptor-II/III (FcγR), an important marker for myelomonocytic cells and a progenitor marker in fetal liver haematopoiesis[8], and CD34, which marks a fraction of haematopoietic stem cells and progenitors[6]: the FcγR^{lo}CD34$^+$, FcγR^{lo}CD34$^-$, and FcγR^{hi}CD34$^+$ populations (Fig. 1a).

Each of the above populations were cleanly isolatable (Fig. 1b) and gave rise to distinct colony types in methylcellulose CFU assays (Figs 1c and 2). In the presence of steel factor (Slf), Flt-3 ligand (FL), IL-11, IL-3, granulocyte/macrophage-colony stimulating factor (GM-CSF), erythropoietin (Epo) and thrombopoietin (Tpo), ~80% of single multipotent HSCs randomly committed to myeloid lineages[9], giving rise to various types of myeloid colonies including CFU-Mix[10], burst-forming units-erythroid (BFU-E),

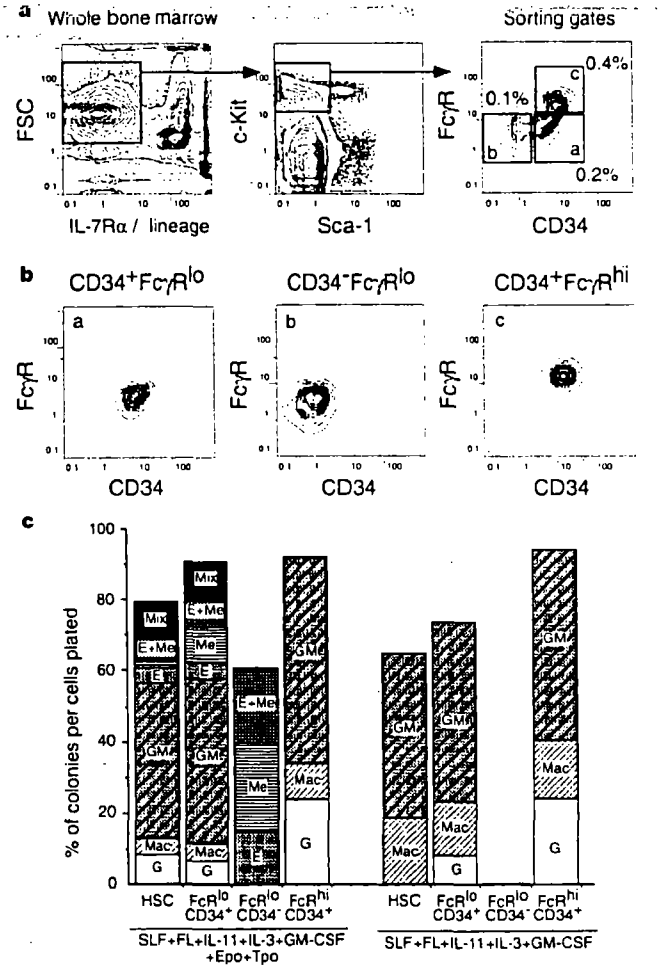

Figure 1 Identification of myeloid progenitors in mouse bone marrow. **a**, The IL-7Rα$^-$Lin$^-$Sca-1$^-$c-Kit$^+$ fraction was subdivided into FcγR^{lo}CD34$^+$, FcγR^{lo}CD34$^-$, and FcγR^{hi}CD34$^+$ populations (a, b, c respectively as indicated in the right-hand panel). Percentages of each population relative to whole bone marrow are shown next to each sort gate. **b**, Re-analysis of the sorted FcγR^{lo}CD34$^+$, FcγR^{lo}CD34$^-$ and FcγR^{hi}CD34$^+$ populations. **c**, Clonogenic myeloid colony formation in methylcellulose. From each sorted progenitor population, 288 wells receiving a single cell each were scored. FcγR^{lo}CD34$^-$cells and HSCs formed various myeloid colonies including CFU-Mix, whereas the FcγR^{lo}CD34$^-$ and FcγR^{hi}CD34$^+$ populations gave rise only to MegE and GM colonies, respectively (left). Megakaryocyte/erythroid colony formation from the FcγR^{lo} fractions was dependent upon Epo and/or Tpo (right).

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