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Brain maturation in juveniles: Some implications for behavior and its control.

A literature review

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Summary. The purpose of this review is to summarize current understanding of the process of maturation in human brains during the juvenile period and up to young adulthood. We will describe the methods used in such investigations and outline the main findings regarding the course of brain development.

Of course there is much that we do not know about brain maturation, but there is congruence of evidence indicating that brain maturation is not complete until young adulthood (about age 21). Furthermore, the main index of maturation, which is rate of myelination, points to large variability in the rate of maturation among brain regions. In general, maturation of association cortex is not complete even by late adolescence and within this cortex the prefrontal regions are last to mature.

The review will conclude by discussing the behavioral implications of these findings. The role of myelination is to focus and refine the operation of neural networks regulating behavior, and the frontal lobes specifically modulate and inhibit impulses, shaping behavior in accordance with planned action and long-term goals. Therefore, the brain anatomy data indicate that people are not biologically prepared to exercise mature frontal lobe control until they reach adulthood.

The rate at which the human brain matures has been of considerable interest to neuroscientists and knowledge on when different brain regions mature in human development may have profound implications for understanding behavioral development. Although the brain and its regions become well differentiated during fetal development, there is overwhelming evidence that much of the brain maturational process occurs after birth. Indeed, projections from early pioneering work on donated brain tissue have indicated that some brain regions do not reach maturity in humans until adulthood. These projections have been confirmed by more recent studies using neuroimaging with advanced methods for soft tissue segmentation and regional parcellation. Here we will first describe the initial neuroanatomic methods and results they produced, which gave rise to hypotheses currently being investigated. We will proceed to explain the novel methods using structural and functional neuroimaging, and summarize results pertinent to the issue of brain maturation. We will conclude by an attempt to integrate findings from the diverse methods and explain their implications to behavior, focusing on issues pertinent to criminal responsibility.

Initial studies: Post-mortem tissue anatomy

While sophisticated methods for preservation and dissection of post mortem brain tissue had been developed in the first decades of the twentieth century, it was not until the 1960s that enough such tissue was available to examine the question of brain maturation in humans. Arguably the largest collection and the most influential work was that of Professor Paul I. Yakovlev and his colleagues at Harvard University. His methods,

findings and conclusions have been summarized in a landmark chapter titled "The myelination cycles of regional maturation of the brain" co-authord with Dr. André-Roch Lecours, which was published in a book on Regional Brain Development in Early Life (edited by Prof. Alexandre Minkowski and published by Blackwell Scientific Publications, Oxford, England, 1967).

The anatomic work has focused on the process of the creation of fatty tissue surrounding nerve fibers, which is known as "myelogenesis." Myelogenesis is important for assuring efficient transmission of neuronal signals, the fatty tissue called myelin surrounds the nerve fibers that carry information across large distance very much in the same way that rubber is used for conducting electricity across distance. The process can be examined by obtaining slices of brain tissue from a wide age range that were treated in a way that enables visualization myelin, and comparing its abundance. Such treatment of tissue is called "staining," and Yakovlev and his colleagues used a staining method developed in twenties by Loyez. The method relies on the ability to observe both the density of stained fibers and the intensity of coloration (light to dark gray and blue to black), and these can be used to index degree of myelination (see Figure 1).

Yakovlev and his colleagues examined over 200 brains ranging in age from fourth fetal month to one postnatal year, and another large set of brains from the third decade of life on. Unfortunately they had very few brains from the first and second decades of life, and their extrapolations for that phase of development are accordingly more tentative.

Nonetheless, They were able to extrapolate some principles and propose hypotheses that were confirmed with remarkable consistency with current techniques.

The main surprise was the much slower progression of the maturational process in the human brain compared to what had been expected from animal studies. Yakovlev and his colleagues have carefully charted the maturational process for a large set of regions and found some that matured very early while others were far from maturation at one year of age. By extrapolating from the sample of adult brains and the few specimens from the period in between, they have produced "maturation charts" for these brain regions. Based on these charts they identified several principles. One of the main principles is illustrated in Figure 2. The brain can be conceptualized architecturally (and phylogenetically) as consisting of three "zones": the median (median thalamus and hypothalamus, septum, hippocampus) the paramedian (limbic) and the supralimbic (mostly cerebral cortex). They noted that maturational rate is fastest for the paramedian zone, where it is complete within the first decade of life, and slowest for the cortical regions where development seems to extend into adulthood.

This principle has rather profound implications for behavior, and is consistent with behavioral data on development. The region that is slowest to mature is the part of the brain that basically modulates more primitive, drive related activation of the limbic areas. From a phylogenetic perspective, the brain areas that are latest to mature are those areas that have seen the greatest expansion in humans and are associated with faculties such as language comprehension and expression, abstraction and reasoning, comprehension and expression of emotions, impulse control and planning, and aspects of

attention and memory (including working memory). Thus, the anatomic data as interpreted by Yakovlev and his colleagues indicated that the very functions that make us uniquely human are the latest to become fully integrated into the workings of the developing brain.

Other contributions of anatomic studies for understanding brain development ranged from gross measurement of brain weight in large samples and more detailed measurements of synaptic processes in small samples. For example, Dekaban and Sadowsky (1978) tabulated body and brain weight in nearly 5000 autopsy reports, ranging in age from weeks to 90 years, and plotted these values against age. The most important result from the perspective of this review is that brain weight did not reach its peak until about age 20, and showed steady decline thereafter (see Figure xx). This method, of course, could not distinguish myelin from other tissue and hence does not directly examine maturation.

Using methods for examining synaptic density, Prof. Peter Huttenlocher from the University of Chicago was able to uncover another neurodevelopmental phenomenon apparently taking place during adolescence: "pruning." Specifically, he observed a decline in the density of synapses between ages 2 and 16 accompanied by a decrease in neuronal density. His conclusion required a considerable leap of imagination, since he only had one specimen between the ages of 8 and 20 years, however it made theoretical sense and was consistent with animal studies. According to the pruning hypothesis, at some point during adolescence neurons and their connections that have not been

consistently used during childhood "shrivel off," thereby allowing greater efficiency of the remaining neural systems (Huttenlocher, 1978; Huttenlocher et al., 1982).

Current anatomic studies: Structural imaging with MRI.

The post-mortem tissue studies such as conducted by Yakovlev and his colleagues have contributed important insights into understanding brain maturation, but they have serious limitations. Most importantly, tissue availability depends on sources that may bias the age ranges available; the inability to quantify the measures in an automated fashion limits the number of brains and regions that can be examined; there is large variation introduced by fixation and staining methods; and it is impossible to do repeated studies in the same individual to trace developmental changes.

All these difficulties are circumvented by a set of novel techniques developed in the 1970s and fully implemented by the 1990s, and that can be generally referred to as "structural imaging". These methods permit visualization and volumetric measurement of brain structure in living people without risk. The method that has become state of the art for these studies is based on magnetic resonance imaging (MRI) procedures. The head is placed in a strong magnetic field (current standard is at 1.5 tesla), and the image is based on recording the resonance of molecules after perturbations with radiofrequency (RF) signals. Recordings are made with antennae, very much like recording of radiofrequencies. What makes MRI particularly amenable for quantitative analysis is that different echo times can highlight different soft tissue contrasts, which have effects similar to those of staining in post mortem studies. The main potential drawback, hazard

and source of error in MRI is the difficulty of maintaining a homogeneous field strength throughout the image brain. Inhomogeneity will produce "shading" effects, which can be sometimes compensated for by the clinician but has to be minimized or compensated for by complex statistical operation when trying to implement a computer algorithm to identify the tissue. Several approaches have been developed in the early 90s, and these have now become standard and have been shown to produce reliable results both in phantom and in human studies (e.g., Filipek, Richelme, Kennedy, and Caviness, 1994; Kohn et al, 1991; Yan and Karp 1994). These methods have provided data on the intracranial composition of the three main brain compartments related to cytoarchitecture and connectivity: gray matter (GM) - the somatodendritic tissue of neurons (cortical and deep), white matter (WM) - the axonal compartment of myelinated connecting fibers, and cerebrospinal fluid (CSF). An example of computerized segmentation of MRI into these compartments is provided in Figure 3.

It has taken some time to apply these segmentation methods to a sufficiently large sample of healthy people across the age range so as to examine maturational processes. However, several groups have made considerable progress and the results of their efforts, while still tentative with regard to precise charting of developmental trajectories for all brain regions and for all age groups, are nonetheless quite consistent with the post mortem findings and converge to support several conclusions.

Of the by now considerable number of manuscripts in the referenced literature one can identify seven main groups that pursued issues related to neurodevelopment: 1. The Harvard group under the leadership of Kennedy and Cavines; 2. The NIH group under the

leadership of Dr. Rapoport and Giedd; 3. The Stanford group under the leadership of Dr. Pfefferbaum; 4. The Hopkins group led by Dr. Denckla; 5. The UCSD group led by Dr. Jernigan; 6. The University of Utah group led by Dr. Bigler; 7. The Penn group led by myself and Dr. Raquel E. Gur. Contributions from other centers such as Duke, McGill, NYU, UCLA and Toyama University in Japan have also been instrumental but they have mainly used data from the aforementioned groups or did not specifically focus on the period of early development.

In one of the first studies examining segmented MRI in children and adult, Jernigan and Tallal (1990) have documented the "pruning" process proposed by Huttenlocher's work. They found that children had higher gray matter volumes than adults, indicating loss of GM during adolescence. These results have been replicated more recently by this group using advanced methods for image analysis (Sowell et al., 1999), and demonstrating that the pruning seems most "aggressive" in prefrontal and temporo-parietal cortical brain regions.

The NIH group published a landmark paper in 1996, where they have reported results of brain volumetric MRI study on 104 healthy children ranging in age from 4-18. While they did not segment the MRI data into compartments, they were able to document developmental changes that clearly indicated prolonged maturation beyond age 17. In a later report on this sample, when segmentation algorithms have been applied, they were able to pinpoint the greatest delay in myelination, defined as WM volume, for fronto-temporal pathways (Paus et al., 1999). This finding is very consistent with Yakovlev's results. This group went on to exploit the ability with MRI to obtain repeated measures on

the same individuals. Using such longitudinal data they were able to document pre-adolescent increase in GM that precipitated the pruning process of adolescence. At the same time, the volume of WM continued to show increase up to age 22 years (Giedd et al., 1999).

The Harvard group developed a sophisticated procedure for MRI analysis (Filipek et al., 1994), which they applied to a sample of children with the age range of 7-11 years and compared to adults (Cavines et al., 1996). They found sex differences suggesting earlier maturation of females, and generally supported the role of white matter as an index of maturation that shows delay in reaching its peak volume until early adulthood.

Another landmark study was published by the Stanford group, which examined segmented MRI on a "retrospective" sample of 88 participants ranging in age from 3 months to 30 years and a "prospective" sample of 73 healthy men aged 21 to 70 years (Pfefferbaum et al., 1994). The retrospective sample used scans available from the clinical case load, although images were carefully selected to include only those with a negative clinical reading, while the prospective sample was studied specifically for research and recruited to be healthy. The results demonstrated very clear neurodevelopmental course for GM and WM, with the former showing a steady decline during adolescence while the latter shows increased volume until about age 20-22 years (see Figure xx).

The Hopkins group used a similar approach in a sample of 85 healthy children and adolescents ranging in age from 5 to 17 years (Reiss et al., 1996). Consistent with the post mortem and the other volumetric MRI studies, they reported steady increase in WM

volume with age that did not seem to peak by age 17. Unfortunately, they did not have data on older individuals (Figure xx). Their results are consistent with those of Blatter et al. (1995) from Utah, although the extensive Utah database combines ages 16-25 and therefore does not permit evaluation of changes during late adolescence and early adulthood.

In the only study to date that has examined segmented MRI volumes from a prospective sample of 28 healthy children aged 1 month to 10 years, as well as a small adult sample, Matsuzawa et al (2001) have applied the segmentation procedures developed by the Penn group. They have demonstrated increased volume of both GM and WM in the first postnatal months, but whereas GM volume peaked at about two years of age, the volume of WM, which indicates brain maturation, continued to increase into adulthood (Figure xx). Furthermore, consistent with the post mortem and other MRI studies that have examined this issue, the frontal lobe showed the greatest maturational lag and is unlikely completed before young adulthood.

While not directly examining adolescence, several studies of aging may also help shed light on development. The reason is that a rather ubiquitous neurodevelopmental principle states that whatever "comes on board" last is also first to deteriorate with older age. In this regard, several studies have suggested that frontal and temporal cortex shows the most pronounced age-associated decline, and that this happens earlier for men than for women (e.g., Coffee et al., 1998; Cowell et al., 1994; Gur et al., 1991, 2002; Raz et al., 1997). The possibility of further maturation occurring beyond age 17 is supported in a recent study examining age effects for a prospective sample of 116 healthy adults (57

men and 59 women, age range 18-49). As can be seen in Figure xx, volume of WB showed a positive slope for that age range (Gur et al., 2002). To examine in more detail any effects in young adulthood, defined as between the ages of 18 to 25 (and on which there is probably the least amount of published data), we have selected all individuals in this age range from that study. As can be seen in Figure xx, there is clear evidence that the maturation process, reflected in WM volume, continues into the early 20s, especially for men.

Physiologic studies: Functional imaging

Information on the maturational process can come not only from anatomic studies of brain structure, the focus of this review, but also from studies of brain activity or "function". Few studies have been done to examine brain maturation. Probably the main reason for the paucity of studies is that many of these methods necessitate exposure to ionizing radiation, and therefore are forbidden in healthy children. Another reason is that these studies are expensive and are usually done in very small samples. Nonetheless, several investigators have examined indices of brain maturation using functional imaging (e.g., Chugani et al., 1987; Chiron et al., 1992). These studies concur with the anatomic data. Thus, Chugani et al show that adult values are not reached by age 15 and are delayed in association cortex, while Chiron et al suggest that adult values are reached by about age 20.

Summary and conclusions

The review of neuroanatomic studies across methods and approaches, and the few neurophysiologic studies in humans, indicates considerable convergence of findings with respect to brain maturation during childhood, adolescence and early adulthood. The overwhelming conclusion is that the main index of maturation, which is the process called "myelination," is not complete until some time in the beginning of the third decade of life (probably at around age 20-22). Other maturational processes, such as the increase and subsequent elimination ("pruning") in cell number and connectivity may be completed by late adolescence, perhaps by age 15-17. More data are needed to pinpoint the age at which these maturational processes are complete.

These results have rather profound implications for understanding behavioral development. The cortical regions, particularly those in prefrontal areas, are involved in behavioral facets germane to many aspect of criminal culpability. Perhaps most relevant is the involvement of these brain regions in the control of aggression and other impulses, the process of planning for long-range goals, organization of sequential behavior, the process of abstraction and mental flexibility, and aspects of memory including "working memory." If the neural substrates of these behaviors have not reached maturity before adulthood, it is unreasonable to expect the behaviors themselves to reflect mature thought processes.

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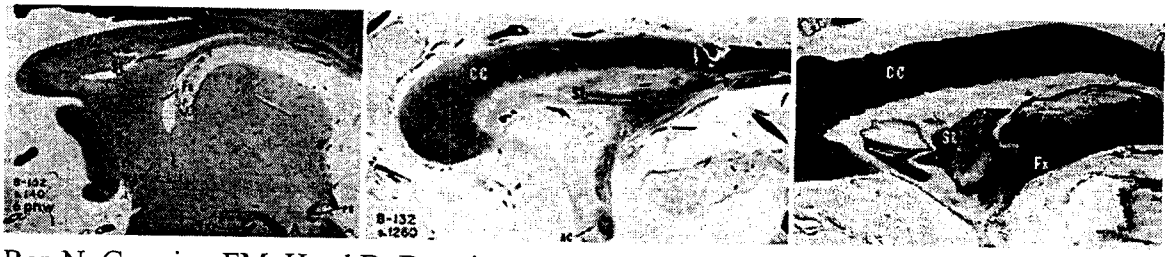

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