Please cite this article in press as: Somerville, Searching for Signatures of Brain Maturity: What Are We Searching For?, Neuron (2016), http://dx.doi.org/10.1016/j.neuron.2016.10.059

Neuron
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Searching for Signatures of Brain Maturity: What Are We Searching For?

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http://dx.doi.org/10.1016/j.neuron.2016.10.059

Evidence of continued neurobiological maturation through adolescence is increasingly invoked in discussions of youth-focused policies. This should motivate neuroscientists to grapple with core issues such as the definition of brain maturation, how to quantify it, and how to precisely translate this knowledge to broader audiences.

The study of brain development encompasses evaluation of the structural, functional, and network-level changes that occur across the lifespan, along with the mechanisms that propel these changes (e.g., hormonal influence, experience, and so on). Over the past two decades, there has been an explosion of evidence revealing that despite being roughly equal in size, the brains of human children, adolescents, and adults differ in complex ways. Questions about the pace, timing, and psychological consequences of human neurodevelopment have thus fascinated basic scientists, clinical and applied scientists, and the general public.

Discussions in legal and policy communities have also begun to incorporate neuroscientific evidence of immaturity into their arguments. Continued neurodevelopment has been cited in developmentally informed legal considerations such as culpability for criminal behavior and determinations of competence for health-related decision making (Steinberg, 2009a). Continued neurodevelopment also implies continuing plasticity, a tenet that supports developmentally timed interventions for health-risk behaviors. It is exciting that basic neuroscience is infiltrating public discourse to guide developmentally informed policies and treatment of youths.

Arguments for (neuro)developmentally informed policy rest on a foundational claim that youths' brains are "still-maturing," implying that they differ in some key way from a mature, adult point of reference. However, the complex nature of neurodevelopment itself poses challenges to establishing a point of reference that would indicate when a brain is mature. To complicate things further, there is little agreement among basic scientists on what properties of a brain should be evaluated when judging whether a brain is mature. This lack of consensus could reflect the fact that most neuroscientists are typically focused on the "journey"—the temporal unfolding of a particular development process—more than when a brain reaches a particular "destination."

The challenge of pinpointing the fuzzy concept of maturity is hardly constrained to neuroscience. There is widespread lack of agreement on the age at which individuals should be considered adults (with the associate rights and protections) based on psychological indicators of maturity as well. However, neuroscientific-based evidence of continued maturity is especially (and perhaps excessively) persuasive in shaping thinking in legal and policy spheres (Steinberg, 2009b). For example, neuroscientific data indicating continued brain maturation through adolescence was cited in a brief for the Supreme Court case *Roper v Simmons*, which categorically overturned the death penalty for juveniles. Because neuroscientific evidence is used to promote developmentally informed policy with increased frequency, it has become important for basic neuroscientists to critically examine the concept of "brain maturity" and to consider ways for basic science to improve its translatability on this issue.

What Properties of a Brain Deem It Mature?

In the neurodevelopmental literature, a given neural measurement is typically interpreted as mature when it matches (to a sufficient degree) an "adult" reference. However, brain maturation is a multilayered process that does not map on to a single developmental timeline. On the gross structural level, the developing brain exhibits reductions in cortical gray matter and increases in the volume and anisotropy of white matter from childhood to adulthood (Giedd et al., 1999). Although the field continues to refine its understanding of the cellular-molecular mechanisms underlying gross changes observable with magnetic resonance imaging (MRI), these changes are broadly thought to reflect synaptic pruning, myelination, and increased connectivity across widely distributed brain circuitry.

Longitudinal studies have been particularly informative in charting trajectories and points of asymptote in neurodevelopment. They show that reductions of cortical gray matter and increases in white matter continue to actively change well into the twenties and that a point of stability emerges earlier in some brain structures than others. Generally, regions of association cortex including the prefrontal cortex show particularly late structural development, whereas subcortical and occipital regions asymptote substantially earlier (Ostby et al., 2009; Tamnes et al., 2010; see Figure 1A). However, structural development continues to progress for a surprisingly long time. One especially large study showed that for several brain regions, structural growth curves had not plateaued even by the age of 30, the oldest age in their sample (Tamnes et al., 2010; see Figure 1B).

Other work focused on structural brain measures through adulthood show progressive volumetric changes from

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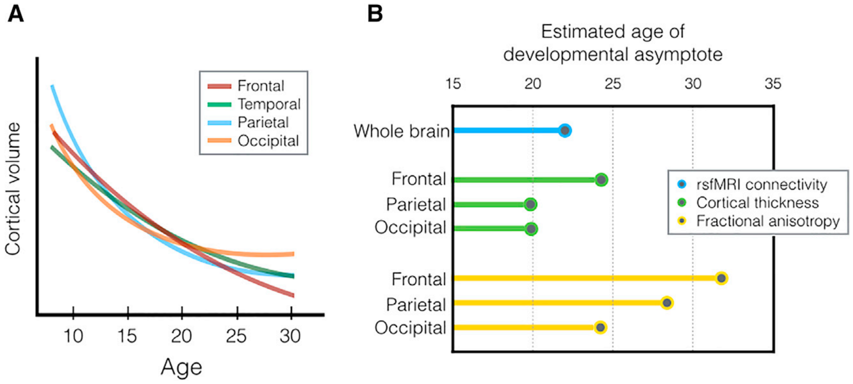

Figure 1. Regional and Methodological Variance in Neurodevelopmental Indices

(A) Trajectories of cortical gray matter volume adjusting for total brain volume. Trajectories are schematized from data reported in Ostby et al. (2009).

(B) Ages of developmental asymptote for connectivity and structural data. Resting-state functional connectivity (rsfMRI) data from Dosenbach et al. (2010) and the other measures reflect data reported in Tamnes et al. (2010). Note that the operationalization of "asymptote" varies by study.

ages 15–90 that never "level off" and instead changed constantly throughout the adult phase of life (Walhovd et al., 2005). Thus, a key challenge to classifying maturity based on structural indices is that it is ambiguous when an adult reference reaches a steady set-point—it depends on the type of anatomical measurement and the lobe or brain region selected. Moreover, it is unclear whether there is even a steady set-point at all.

Another maturing feature of the brain is the intrinsic patterns of connectivity that comprise brain networks. Measures of widespread brain connectivity shift in complex ways from childhood to adulthood, characterized by reductions in local connections and rises in distributed connections. These connectivity-based shifts are thought to reflect a brain that is becoming more efficient in its in-network communication and more integrated in its cross-network communication (Fair et al., 2009).

Dosenbach and colleagues (2010) used data-driven classification algorithms to compute an estimated "brain age" of individual subjects 7 to 30 years of age based on widespread intrinsic connectivity patterns within and between brain networks, measured using resting-state functional connectivity. Their classification algorithms identified adolescence as a period of rapid and widespread increase in connectivity followed by a slowing rate of change until approximately age 22, which was identified mathematically as the point of asymptote. This work suggests that widespread network connectivity measures settle into a fairly consistent reference state in the early 20s. However, these data also illustrate the challenges of applying general patterns of neurodevelopment from group-based to individual inference, as there is substantial variance in brain network connectivity that is unrelated to age. For example, some 8-year-old brains exhibited a greater "maturation index" than some 25 year old brains.

This section has described the neurodevelopmental trends of just two (structure, intrinsic connectivity) of several levels of brain maturation. Other neurodevelopmental processes include neurochemical shifts in neurotransmitter availability and receptor density, brain metabolic efficiency, hormonal change, and excitatory/inhibitory balance. On one hand, there is partial convergence in structural change and intrinsic connectivity, in that the maturational asymptotes for both indices extend well past the age of 18 (the legal definition of adulthood in the United States). On the other hand, there is also strong divergence. One could ascribe maturity to a brain based on network connectivity a decade sooner than based on some structural indices (see Figure 1B). Further, demonstrations of constant change in structure throughout adult life challenge the very notion that the brain reaches a steady adult referent that we can concretely call "mature."

How Does a Mature Brain Function?

How the brain processes information and orchestrates behavior is central to claims about maturity. Children's and adolescents' psychological competencies are changing in a host of functional domains relevant to policy, such as improvements in abstract reasoning and higher-order cognitive skills, and non-linear peaks in reward sensitivity during adolescence. These competencies scaffold on the brain's developing functional networks, evident in studies demonstrating changes in brain-behavior relationships with age.

There has been a recent surge of interest in the brain function of "emerging adults," individuals approximately 18–22 years old who most societies treat as adults but for whom neurobiological maturation is incomplete by almost any metric. Recently, Cohen and colleagues (2016) tested the degree to which the brains of 18–21 year olds functioned more similarly to adolescents or adults while engaging in a regulatory task including threatening cues and threatening contexts. Results showed that in the functioning of key brain areas such as the dorsolateral prefrontal cortex, the 18–21 year olds' brain activity during threat conditions was more similar to a 13–17 year old reference group than a 22–25 year old reference group. These findings provide convergent evidence for continued neurodevelopment during the 18- to 21-year-old window.

Like structural data, functional data can be evaluated relative to an adult reference point. However, developmental changes in brain function can differ from adult brain function in a host of ways that extend beyond whether there is more or less activation in a particular brain region relative to adults. Take for instance neural responses during a complex decision making task. An adolescent group could differ from an adult group in a variety of ways. They could take longer (and require temporally extended neural computations) to arrive at the same choice, they could make a different choice but use the same general neural processes to arrive at that choice, or their decision making could employ an entirely different suite of strategies and neural processes to arrive at either the same or a different choice. Each of these underlying sources of developmental difference could be

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linked to a different neurodevelopmental pattern in functional data.

Pinpointing what neural signals track shifting behavior is a complex and important topic that is addressed elsewhere (Poldrack, 2015). For the current discussion, the key point is that there is no single progression that encompasses functional maturation. Neural activity intensifies and reduces, varies quantitatively and qualitatively, in linear and nonlinear ways that are both linked to—and independent of—behavioral differences across development. Each of these patterns reflects developmental progress, but the wide range of ''journeys'' prohibits a simple definition of what emerging brain functional maturity looks like.

Multiple Maturities

A key principle that guides determinations about psychological maturity in adolescence and young adulthood is the degree to which contextual factors shape an individual's behavior. For instance, an adolescent and an adult could achieve an identical level of performance on a cognitive task under certain conditions—say, when free of distraction and when the situation has low emotional arousal. However, if the context is shifted slightly by embedding reward cues in the cognitive task, adolescents' performance disproportionally shifts compared to adults (e.g., Somerville et al., 2011). Whereas adolescents might have the baseline *capability* of achieving a certain level of performance, they might not *express* that capability equivalently across situations. Behavioral research has indicated that adolescent regulatory behavior is challenged more than adults in contexts involving emotion, social evaluation, and reward. The contextual dependency of adolescent behavior implies that there is not one threshold of maturity—rather, there are waves of maturity that shape how influential different contexts are on behavioral performance. A prime example of context-sensitive policy is graduated driving laws. They initially constrain new drivers to highly regulated conditions (e.g., during the day, without peers in the car) and slowly broaden the range of driving contexts as new drivers gain experience.

How can neuroscience inform the concept of multiple maturities? As described earlier, different brain regions reach adult-like states at different paces and at different ages. The strong influence of emotional and motivational contexts on adolescent behavior is thought to emerge due to normative, biased circuit-level interactions between motivational and regulatory signaling in the brain (Casey et al., 2016). For instance, neuroimaging evidence has accumulated to suggest that functioning of striatocortical circuitry, which integrates signals of valuation, regulatory demand, and action, is biased in adolescents in contexts in which motivational value is high (Somerville et al., 2011). As such, a relevant marker of a mature brain might actually be a relative imperviousness to context more than any static pattern of neural activation or connectivity.

Narrowing in on Neurobiological Maturity

The work featured in this article highlights the challenges of operationalizing when a brain achieves ''maturity.'' Some neuroscientists may believe that the very notion of defining brain maturity is a misguided objective, as the brain never stops changing across the entire lifespan. However, seeing that neuroscientific claims are highly influential in shaping policy, neuroscientists' voices should guide dialog on when a brain plateaus to an adult-like reference state.

Let's imagine considering a brain mature when *every* index of brain structure, function, and connectivity hits an asymptote. When would an average brain reach this threshold of maturity? From what I've reviewed above, the answer might lie sometime between ''the 30s'' and ''never.'' This range is remarkably late, given that arguments about reaching maturity tend to focus on the brains and behavioral profiles of individuals in their late teens and early twenties. It is important to acknowledge that claims that the brain reaches maturity earlier (in the early twenties, for instance) are based only on a subset of the available indices of brain maturation.

An open question is whether some indices of brain structure and function should be prioritized over others in conversations about brain maturity. One way to answer this question would be to consider the goals of deeming a brain ''mature'' from a policy perspective. Brain imaging is primarily being used to corroborate evidence from behavioral science that adolescents (and sometimes young adults) are ''on the journey'' toward achieving a particular suite of behavioral capabilities. Given that these arguments center on psychological development, perhaps measures of brain function *in relation to the corresponding psychological domains* should be given priority. A focus on brain function would hold an advantage over other measures, because it would allow for estimates to reflect the context dependencies that also characterize adolescents' behavior. However, one consequence of this framework would be the need to abandon the goal of identifying a single age-of-brain maturity. Rather, there would be a suite of maturity points that reflect different neural systems and different associated behaviors. For example, an individual could reach an age of ''baseline cognitive maturity''—the capacity to engage in goal-directed behavior under neutral, non-distracted circumstances, substantially earlier than an age of ''cognitive-emotional maturity''—the capacity to maintain goal-directed behavior in the face of competing emotional cues.

Concluding Recommendations

It is exciting that dialogue about neuroscience is infiltrating policy considerations for youth. Likewise, neuroscientists can consider how to improve the translatability of their basic research. New large, multimodal brain imaging studies (such as the Adolescent Brain Cognitive Development study http://abcdstudy.org and the Human Connectome Project in Development) will bring forth unprecedented opportunity to pinpoint the timing of healthy brain development. These studies will provide test-beds for establishing intricate models of the pacing and interrelationships between brain structural, functional, and network development across several functional domains. In time, these large datasets could allow for the creation of multimodal ''growth curves'' which can be linked to behavioral profiles of interest to policy.

What can be done in the meantime? For one, many studies comparing adolescents to young adults frequently use an age of 18 as a cut-point for comparison

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between "adolescents" and "adults," an approach that could obscure or even mask continued developmental change. Researchers could instead avail themselves of the nonlinear and growth curve modeling methods that allow for observation of full trajectories of change. Further, developmental studies frequently truncate "adult" samples at age 22 or even younger—typically too early to document points of asymptote in a particular neural process. Studies that do this might fail to capture the "leveling off" pattern that is thought to characterize mature brain function. Finally, given that behavior arises from complex circuit interactions in the brain, measures of functional brain activity in single brain regions should be supplemented with measures of brain functional connectivity and multimodal methods to identify interrelationships between brain structure, network organization, and function. These approaches will provide a more comprehensive view of the complex suite of mechanisms underlying brain maturation.

ACKNOWLEDGMENTS

The author thanks members of the Affective Neuroscience & Development Lab for valuable feedback. This material is based upon work supported by the National Science Foundation under Grant No. (CAREER-BCS-1452530) and the American Psychological Association F.J. McGuigan Early Career Investigator Research Prize for Understanding the Human Mind.

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