

Interpreting Developmental Changes in Neuroimaging Signals

Russell A. Poldrack

*Imaging Research Center and Departments of Psychology and Neurobiology,
University of Texas at Austin, Austin, TX*

Abstract: The imaging of developmental changes in brain function is challenging, but great strides have been made in addressing many of the conceptual issues that this work raises. I highlight a set of issues that remain to be addressed in this literature. First, I argue that the appeal to developmental neurobiology is often misplaced, as it focuses on neurodevelopmental processes that are mostly completed by the age at which neuroimaging studies can be performed. Second, I argue that the concept of “normative” development needs to be reexamined, as it reflects fundamental value judgments about brain development that seem inappropriate for scientific investigation. Third, I examine the ways in which developmental changes are often interpreted, arguing that common interpretations, including the concepts of “efficiency” and “focalization” may be less useful than commonly supposed. To put developmental neuroimaging on stronger footing, we need to develop stronger connections between computational and neurobiological accounts of developmental changes. *Hum Brain Mapp* 31:872–878, 2010. © 2010 Wiley-Liss, Inc.

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INTRODUCTION

Developmental neuroimaging has made remarkable strides in the last decade, providing the foundation for an invigorated field of developmental cognitive neuroscience. Many of the concerns addressed by early methodological reviews on the topic [Bookheimer, 2000; Gaillard et al., 2001; Poldrack et al., 2002] have been addressed within the field, offering greater interpretability of the results of these studies. For example, issues regarding differences in behavioral performance across development are now taken very seriously [e.g., Brown et al., 2005]. However, there remain serious challenges in the interpretation of changes

in neuroimaging signals with development, maturation, and learning [Poldrack, 2000].

In this article, I will address some of the ways in which developmental changes in neuroimaging signals are commonly interpreted, highlighting some potential problems in relating these explanations to underlying neural computations. However, it is important to keep in mind that many of the points being made here are not specific to developmental neuroimaging, but rather apply to any studies that wish to examine differences in brain activity between groups (e.g., because of learning, neuropsychiatric disorders, or pharmacological interventions). In addition, nearly all of the same issues arise in the study of aging, where many of the observed changes seem to mirror those observed during child development.

*Correspondence to: Russell A. Poldrack, Franz Hall, Box 951563, Los Angeles, California, USA. E-mail: poldrack@mail.utexas.edu

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THE (MISSING) NEUROBIOLOGY OF COGNITIVE DEVELOPMENT

Picking up any of several books on developmental cognitive neuroscience, one is quickly impressed with the

amount that is known about early brain development. These treatments usually focus on such processes as the timeline of neuronal migration, synaptogenesis and synaptic pruning, myelination, and cortical patterning. Having fulfilled their responsibility by dutifully citing Huttenlocher, Rakic, and O'Leary (among others), these books then go on to discuss the development of cognitive functions such as memory, language, or reasoning, a substantial part of which happens well beyond the timeline of most of those early processes of neuronal development. In addition, due to the limitations of fMRI, nearly all developmental fMRI studies have focused on children older than 4 years old, for whom many of these early neurodevelopmental events (other than synaptic pruning and myelination) are largely a distant memory. Thus, there is a substantial gulf between the neurobiological explanations of early development and the changes being examined in nearly all neuroimaging studies.

To the degree that there is discussion of neurobiological changes that occur from childhood into early adulthood, it is generally focused on one of the two topics. The first topic often discussed is experience-dependent cortical plasticity in adult animal models, arising from the work of Greenough, Merzenich, and others. The second is the structural development of the human brain, such as changes in the thickness of the cerebral cortex across this period, or the extended myelination of prefrontal white matter tracts. These effects clearly have important implications for imaging signals, but their influence on imaging signals is largely unknown. For example, it is known that cortical thickness decreases between the ages of 5 and 11 in most cortical regions, but increases in perisylvian areas [Sowell et al., 2004]. However, the implications for these changes in cortical thickness for functional imaging signals are not fully understood. The only study to systematically examine this issue [Lu et al., 2009] found that decreased cortical thickness was associated with increased activation in frontal and parietal lobe regions. A fuller understanding of the relation between imaging signals and cortical structure will require a detailed examination of how these changes in cortical structure and function affect hemodynamic imaging signals, probably using optical imaging in animal models.

What seems to be completely missing from these discussions is an understanding of the changes in neural coding that occur from childhood into adulthood, as well as the changes in system-level organization that accompany later cognitive development. When we attempt to understand changes in neuroimaging signals that are associated with learning and/or maturation, it is these phenomena that are most relevant to our discussion. It is perhaps not surprising that we know so little about these processes, given how difficult they are to study in animal models, but our ability to interpret neuroimaging data relies critically upon being able to ground our interpretation of neuroimaging signals in neurobiologically sophisticated computational models. In what follows, I will examine how developmen-

tal changes in neuroimaging signals have been interpreted and highlight some ways in which these interpretations may be improved.

“NORMATIVE” DEVELOPMENT

Within developmental neuroimaging, the term “normative” is often used to refer to the developmental changes that are observed in a typically developing population. When I first encountered this I found it confusing, because the term “normative” has a distinctly different meaning in philosophy: Rather than referring to how things *are*, in philosophy the term refers to how things *should be*, reflecting a value judgment. Normative statements are contrasted with descriptive statements, which refer to how things actually are. Thus, from a standpoint of the philosophical definition, developmental neuroimaging studies would be considered descriptive rather than normative. On the other hand, in neuropsychology the term is used to refer to performance of the population of normal healthy individuals, to provide a “frame of reference” for interpretation of test results from an individual [e.g., Mitrushina, 2005].

At first I thought that this was simply an accidental difference in the application of the term between fields, but there actually seems to be a deeper relationship. When one examines the developmental neuroimaging literature, it becomes clear that there are value judgments implied in the interpretation of developmental changes. Development is viewed as a positively valued process and the adult is taken as the ideal model, such that both behavior and patterns of activation are evaluated by their degree of approximation to the adult pattern. For example, increased activation with development is often described in terms of “immature” activation in children versus “mature” activation in adults, whereas decreased activation with development is described as reflecting “efficiency” of processing [e.g., Bitan et al., 2007]. These positive terms are generally used when the activation is associated with increasingly accurate or adult-like behavior. On the other hand, greater activity in children in other contexts is sometimes interpreted as “compensation,” e.g., for the relatively immature development of white matter connections [Levesque et al., 2004]. Thus, the interpretations given for developmental changes in neuroimaging signals often seem to depend on implicit value judgments about the nature of psychological development rather than on theories that relate activation to the neural function.

WHAT DO DEVELOPMENTAL CHANGES MEAN?

It is useful to think of developmental changes in terms of the computations that are being performed. In this context, there are several possible interpretations that one can make of a change in neuroimaging signals (after having

ruled out potential artifacts such as performance differences; cf. Poldrack [2000]; Brown et al. [2005]:

- The same computation is performed across development, but it is performed more efficiently with development:
- The same computation is performed across development, but in younger children it requires additional support processes to perform it properly.
- The computation being performed changes across development.

The Concept of “Efficiency”

As mentioned above, one potential explanation for decreased activation with development is in terms of greater efficiency of neural processing. But what does this mean? It seems that the use of “efficiency” in the developmental neuroimaging literature is largely circular: efficiency is defined as whatever causes there to be decreased activation, and decreased activation is interpreted as reflecting more efficient processing. Thus, the term gives the illusion of explanation when it is really just a redescription of the data. In addition, the concept of efficiency suffers from a *reductio ad absurdum*, because it implies that the most efficient state would be one in which there is no activity and thus that the most efficient brain regions are brain regions that are not involved at all in the task. It should be noted that the use of efficiency as an explanation is not limited to developmental studies; it is often seen in studies of learning, aging, and neuropsychiatric disorders.

We can, however, ask what increased efficiency might mean at the level of neural computation. The concept of efficiency generally refers to the cost of a particular amount of work; a fuel efficient car is one that drives the same mile using less fuel. Thus, “neural efficiency” should reflect the performance of the same neural computation with a lower spike rate or (more relevant for fMRI) lower net synaptic activity. There is substantial evidence from computational neuroscience that efficiency in neuronal processing arises from the use of sparse coding, in which any particular stimulus evokes activity in a very small proportion of neurons in a population [Foldiak, 2002; Olshausen and Field, 1996]. Thus, one might postulate that increased efficiency would be associated with increasingly sparse coding of the relevant features. It has also been proposed on the basis of connectionist models of language development that concept learning may be associated with increasingly sparse representations [Plunkett et al., 1992].

There is some evidence for increasingly sparse neural coding over the course of development, but it is focused mostly on very early cortical development, such as the first few weeks of life in the rat [Golshani et al., 2009; Rochefort et al., 2009]. Potentially more relevant to later development is work showing that learning of new visual object categories is associated with the development of increasingly

selective (i.e., sparse) representations in the inferior temporal cortex in adult monkeys [Baker et al., 2002; Sigala and Logothetis, 2002]. Together, these two sets of results provide a proof of concept for the notion that developmental changes (reflecting a combination of maturational processes and experience-dependent plasticity) could in principle reflect sparsification of neural codes and thus more efficient neural processing. One recent study has used an approach called adaptation-fMRI, which allows the examination of selectivity of neural coding. Using this approach, Peelen et al. [2009] found that developmental changes in the fusiform face area were associated with increasingly selective (i.e., sparse) representations. However, strong confirmation of the sparsification hypothesis will require further neurophysiological data from studies of relevant developmental changes in nonhuman animals.

Scaffolding

It is widely believed that some brain systems appear to play general roles in cognitive processing, rather than performing specific task-relevant computations. In particular, fronto-parietal networks are important for cognitive functions that are general to a broad range of cognitive tasks, such as the maintenance of task sets or goals, the direction of attention to particular stimulus features or dimensions, and the resolution of interference from competing sources of information [e.g., Duncan and Owen, 2000; Miller and Cohen, 2001]. In the context of both learning and development, it has been proposed that such general purpose systems provide a “scaffolding” that provides support for early task performance, which gradually recedes as more specialized functions develop through learning and/or maturation [Brown et al., 2005; Petersen et al., 1998].

The scaffolding hypothesis provides a compelling framework for interpreting both increases and decreases in activation across development. However, it is important to keep in mind the inferential limitations of neuroimaging. In particular, imaging signals cannot determine whether a region is necessary for task performance [Poldrack, 2000]. This is important in the context of scaffolding because some of the fronto-parietal regions that exhibit learning-related decreases are known to be involved in performance monitoring and error detection, making it difficult to determine whether the activation in these regions is causing versus reflecting differences in behavior. Controlling for performance differences [Brown et al., 2005] can address this to some degree, but without studies using other methods to determine necessity (such as lesion studies or TMS) it will not be possible to fully address this concern.

Process-Switching

There are a number of cases in which it is thought that development is associated with qualitative changes in the

way that information is processed, such that a less mature process is abandoned in favor of a different, more mature process. This phenomenon, referred to as “process-switching” [Poldrack, 2000], is inferred when concomitant increases and decreases are observed. For example, one domain in which process switching has been proposed is reading development. One model has proposed that early reading occurs through the translation of graphemes to phonemes (via a dorsal route, relying upon inferior parietal and prefrontal systems), whereas later reading of familiar words is thought to occur through direct retrieval of phonological information from visual word forms [via a ventral route, relying upon inferior temporal cortex; Pugh et al., 2001]. Another model has argued instead for transfer from inefficient right hemisphere regions to more mature engagement of left temporal and prefrontal cortex [Turkeltaub et al., 2003].

One concern with some process-switching interpretations is that increases may not necessarily reflect the increased engagement of an active task-related process. A prime example comes from an early study of learning-related changes by Raichle et al. [1994]. In this study, subjects performed verb generation with items that were repeated across trials, and learning was associated with increased activation in the posterior insula. However, further examination shows that this was a region that was initially deactivated during performance and later became less deactivated. Given the association of this region with “default-mode” processes, the most plausible explanation of this result is that early deactivation reflected task difficulty or time on task, and as the task became less difficult there was less deactivation of these regions; clearly, the conclusion that increased activation in these regions reflected their increased involvement in performance of the task is clearly not warranted here. Thus, it is important that the interpretation of regional contributions to process switching is made in the context of what is known about the regions that show changes.

Focalization of Activation

A commonly discussed pattern of developmental changes in neuroimaging signals is the supposed transition from diffuse to focal activation [Durstun et al., 2006], in which younger children exhibited more widespread activation than older children or adults. This is really an empirical generalization rather than an explanation, since it simply redescribes the patterns of activation observed across a number of developmental neuroimaging studies. It has been suggested that this “focalization” is reflective of a tuning of neuronal function, not unlike the increased selectivity discussed earlier.

The neurobiological plausibility of a global shift from diffuse to focal activation has been criticized by Brown et al. [2006]. The nature of cortical patterning is increas-

ingly well understood [e.g., Monuki and Walsh, 2001; Sur and Rubenstein, 2005], and this work suggests that cortical areas emerge very early in cortical development, such that changes in cortical areas would not occur within the age range of subjects who can participate in fMRI studies. There is evidence for experience-dependent changes in cortical maps that extend into adulthood [Buonomano and Merzenich, 1998], but these studies have generally shown map expansion due to relevant experience, rather than the shrinking that would be required in order to produce focalization. Thus, there is little neurobiological plausibility for the kind of gradual focalization that has been proposed on the basis of neuroimaging data.

There is also direct evidence against the focalization hypothesis. Fair et al. [2007] analyzed network interactions in resting-state fMRI data across development, focusing on regions involved in executive control in adults. They found that development is associated with decreased short-range connections and increased long-range connections, which could be viewed as opposite to the focalization hypothesis.

In addition, there are methodological problems with the focalization hypothesis. First, claims of focalization have largely relied upon informal examination of activation maps, in which children appear to have broader activation regions than adults. Some studies have explicitly examined differences in magnitude and extent of activated voxels, but these analyses suffer from difficulties due to the unreliable and threshold-sensitive nature of thresholded voxel counts [Brown et al., 2006; Cohen and DuBois, 1999]. Establishment of the focalization hypothesis would require explicit modeling of the spatial structure of activation maps, which to date has not been done. A second problem arises from the fact that these analyses are based on group statistical maps, using data that are spatially normalized to a common stereotactic space. It is known [Burgund et al., 2002] that spatial normalization of children to an adult anatomical template (the most common procedure) introduces a small but non-negligible amount of error in spatial normalization. Although age-related changes in morphological variability do not appear to have been systematically characterized, there is some evidence for greater variability in cortical surface anatomy in children and adolescents relative to adults [Sowell et al., 2002].

Figure 1 shows the results of a simulation that created statistical maps with either low or high variability in the location of activation. In these two analyses, the extent and strength of activation within each individual was exactly the same and all that differed was the variability in location across individuals. The results show that increased variability across individuals has the effect of smearing the activation, increasing its spatial extent and reducing its peak height. Thus, this pattern does not provide unequivocal evidence for focalization, and should be interpreted with caution.

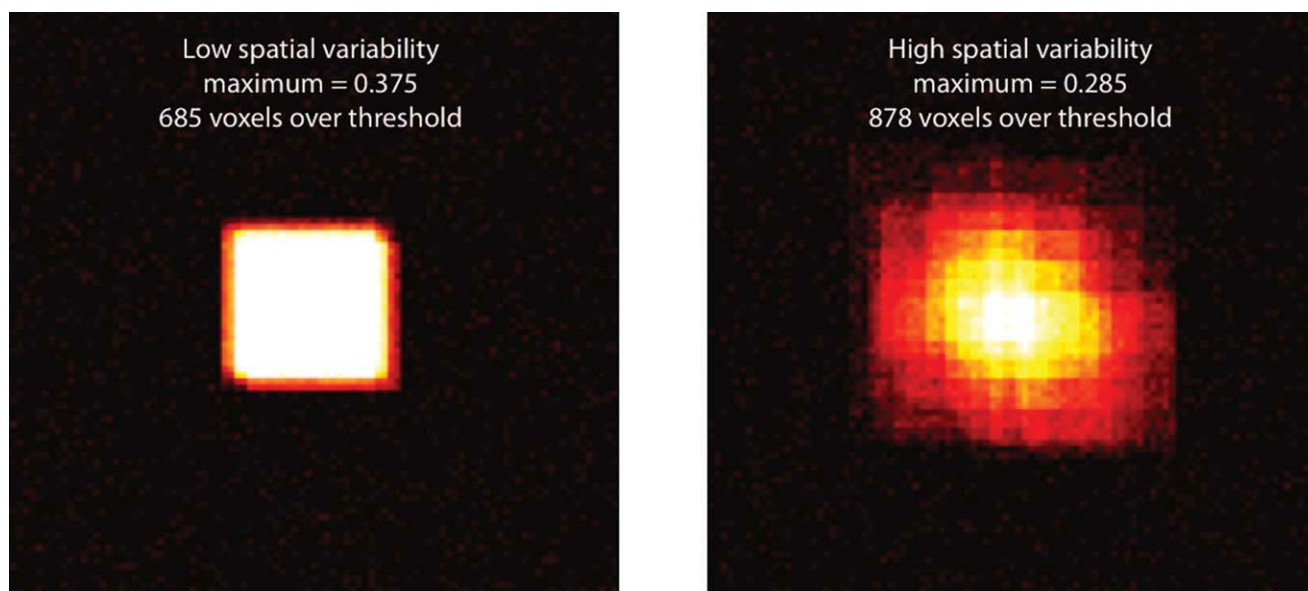


Figure 1.

Simulated statistical maps, demonstrating that location variability can result in patterns that mimic focalization. Each of these images was created by placing a 24×24 patch of activated voxels in an image with Gaussian noise for each of 64 simulated subjects. Variability was added to the location of the patch for each subject, independently in each direction; the average

amount of variability added to the images differed between the right and left panels, which present the mean signal across the group of simulated subjects. The results show that the signal in the right panel is more diffuse than in the left panel, with more voxels exceeding a threshold of 0.1, whereas the left has a greater maximum magnitude.

TOWARD A COMPUTATIONAL DEVELOPMENTAL COGNITIVE NEUROSCIENCE

The foregoing discussion highlights the many difficulties in understanding changes in activation that occur across development, which are very similar to the difficulties encountered in other realms such as learning [Poldrack, 2000], aging [Samanez-Larkin and D'Esposito, 2008], and clinical group comparisons [Aguirre, 2006]. In each of these cases, the difficulty arises from knowing how to map gross changes in blood oxygenation into changes in the functions being performed by the brain. In other areas, it has become increasingly clear that computational models can play a critical role in understanding the functional correlates of neuroimaging signals. Perhaps the best example of the utility of combining computational modeling and neuroimaging comes from study of decision making and reward. Early work on the receipt and anticipation of monetary rewards found a number of regions that were sensitive to rewards, including the ventral striatum and ventromedial prefrontal cortex, but the roles of these regions remained unclear. Understanding of the functions of these regions was revolutionized by the introduction of reinforcement learning models, which allowed the direct comparison of brain activity to theoretical quantities derived from the model, such as reward prediction error

[O'Doherty et al., 2003]. Other research using more sophisticated reinforcement learning models has shown, for example, that it is possible to decompose the function of the anterior cingulate cortex into separate regions sensitive to either monetary reward or social value [Behrens et al., 2008]. Taken together, this work shows that computational modeling in combination with neuroimaging can support much stronger interpretations than are possible using neuroimaging alone. Within developmental psychology, there has been a steady growth in the use of computational models to understand the development of cognitive functions [e.g., Mareschal, 2007; Munakata and McClelland, 2003; Thomas and Karmiloff-Smith, 2002]. However, these models have not yet been integrated with neuroimaging studies of cognitive development. Doing so would provide much greater traction towards understand the functional changes that are associated with neuroimaging signals.

CONCLUSIONS

Developmental neuroimaging has demonstrated a number of novel and interesting patterns by which brain activity changes over the course cognitive development. The field has become increasingly sensitive to issues that can cloud the interpretation of developmental changes in fMRI signals, such as performance differences [Brown et al.,

2005] and structure–function relations [Lu et al., 2009]. However, substantial conceptual challenges remain. In particular, I propose that the accurate interpretation of developmental changes in functional imaging signals will require more sophisticated integration of computational models of brain function with developmental neurobiology. Until we know how changes in neural information processing are reflected in imaging signals, it will remain exceedingly difficult to confidently ascribe explanations to the changes observed in neuroimaging signals across development.

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