

## COMMENTARIES

# Does human functional brain organization shift from diffuse to focal with development?

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This is a commentary on Durston *et al.* (2006).

In this issue, Durston and colleagues (Durston, Davidson, Tottenham, Galvan, Spicer, Fossella & Casey, this issue) set out to test a purported developmental shift from ‘diffuse’ to ‘focal’ brain activity during performance of a response inhibition task. As a second point of interest, they aim to compare age-effects measured between two groups (i.e. cross-sectional) with those detected using two measures of the same group at different ages (i.e. longitudinal). Addressing the potential benefits of longitudinal versus cross-sectional studies in developmental functional neuroimaging is timely and important. In this brief commentary, we discuss these two topics from the perspective afforded by our own work on cognitive development using functional MRI.

Many functional neuroimaging studies report relatively larger spatial extents (manifest as a greater number of regions, and/or larger regional volumes) of activation in children relative to adults. These differences are commonly referred to as reflecting a change from ‘diffuse’ or ‘distributed’ to ‘focal’ or ‘enhanced’ activity (e.g. Casey, Cohen, Jezzard, Turner, Noll, Trainor, Giedd, Kaysen, Hertz-Pannier & Rapoport, 1995; Casey, Trainor, Orendi, Schubert, Nystrom, Giedd, Castellanos, Haxby, Noll, Cohen, Forman, Dahl & Rapoport, 1997; Casey, Thomas, Davidson, Kunz & Franzen, 2002; Gaillard, Hertz-Pannier, Mott, Barnett, LeBihan & Theodore, 2000; Hertz-Pannier, Gaillard, Mott, Cuenod, Bookheimer, Weinstein, Conry, Papero, Schiff, Le Bihan & Theodore, 1997; Holland, Plante, Weber Byars, Strawsburg, Schmithorst & Ball,

2001; Passarotti, Paul, Bussiere, Buxton, Wong & Stiles, 2003; Stiles, Moses, Passarotti, Dick & Buxton, 2003). Although these terms are frequently used in the literature, an examination of available evidence suggests a need for greater conceptual clarity.

Consideration of several issues may be worthwhile in order to determine whether developmental ‘focalization’ occurs as a principle of developmental brain change. First, consistent and testable definitions of the concepts of ‘diffuse’, ‘distributed’, ‘focal’, ‘enhanced’, etc. are required. These definitions should be specific with regard to phenomena that are readily measured using functional neuroimaging, including the number, location, spatial extent and signal magnitude of activated regions.

Second, technical and methodological factors known to contribute to ‘focal’ and ‘diffuse’ image attributes should be considered. For example, children and adults tend to differ by task accuracy and response times. Interestingly, it has been demonstrated that activation maps that include task performance errors appear more ‘diffuse’ than maps created without incorrect responses, showing qualitatively greater spatial extents of activation and lower peak signal magnitudes (Murphy & Garavan, 2004). Many studies that report more diffuse activation of children’s brains use blocked fMRI designs with significant group performance differences. Such studies are unable to differentiate between response errors in making activation maps and group comparisons. Even after removing all error trials, studies using rapid event-related designs still find regional

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performance-related effects in brain activity that could masquerade as age-related effects (Schlaggar, Brown, Lugar, Visscher, Miezin & Petersen, 2002; Brown, Lugar, Coalson, Miezin, Petersen & Schlaggar, 2005). These studies underscore the importance of accounting for behavioral performance when making group comparisons and suggest caution in interpreting age differences in the context of differing performance.

Third, published developmental fMRI studies are often based on qualitative, not statistical, characterizations of the imaging data comparing children and adults. When between-group statistics have been applied, some studies have used thresholded activation volumes as a surrogate measure for signal magnitude, but this method is an unreliable and insensitive method for detecting hemodynamic effects (Cohen & DuBois, 1999). While Durston and colleagues (this issue) use magnitude increases as a metric of focalization, this is an indirect measure.

Fourth, it is essential to consider the neurobiological plausibility of a proposed shift from a more 'diffuse' to a more 'focal' organization within the context of an increasing understanding of the development and differentiation of neocortical areas (cf. O'Leary & Nakagawa, 2002). Studies that employ these terms often, but not always, appear to suggest that when change in the spatial extent of activation of particular regions is seen, the observation reflects concentric shrinkage or expansion of functional areas. However, such a mechanism does not resonate easily with current understanding of the neurobiology of neocortical development.

Some have suggested, alternatively, that inter-regional interaction and competition results in cortical regions that become specialized for specific computations, and no longer depend upon regions required at earlier ages (Johnson, 2000). This kind of 'tuning' model would predict developmental decreases in the overall *number* of activated cortical regions for a given task, but not necessarily that the developing functional organization goes from diffuse to focal.

Regardless of the way in which 'focalizing' is defined, it seems that this concept may not account for the breadth of changes that are now being observed in developmental fMRI studies of cognition. For example, for controlled lexical association, we have found evidence that adults activate some regions not activated by children, that children activate some regions not activated by adults, that many regions show significant decreases in activity with age but remain significantly activated, and that many regions are activated similarly by children and adults, including portions of prefrontal cortex (Schlaggar *et al.*, 2002; Brown *et al.*, 2005). The notion of 'diffuse' and 'focal' activation seems poorly suited to account for these observations. In addition, such changes challenge the

notion that specific regions may be dubbed either 'critical' or 'not critical' to task performance for all ages, since children and adults appear to use different sets of regions to perform the same tasks at similar levels of proficiency.

In this volume, Durston and colleagues introduce to the developmental cognitive neuroscience literature the important issue of the relative strengths and weaknesses of longitudinal vs. cross-sectional fMRI study designs. Because longitudinal studies use repeated measures of the same group, they eliminate the between-group variance that must be overcome for detection of differences in cross-sectional studies. But specific approaches must be used to take advantage of this attribute. Due to the brevity of the methods discussion, it is not clear to what extent the study capitalized on a within-subject or within-group repeated measures statistical approach.

As noted by Durston and colleagues, cross-sectional studies can be undermined by cohort effects, where spurious differences are introduced because one or more groups are 'odd', providing data that are not representative of the population of interest. It must also be stated, though, that longitudinal studies, unless recruitment is randomized and retention near-complete, can be undermined by cohort effects as well. One way to combat the limitations of cross-sectional analysis is to use relatively larger sample sizes and to make measures across multiple age groups instead of just two, as most developmental fMRI studies have done. For example, using 95 subjects spanning 7 to 32 years of age, we found systematic and largely monotonic age differences that we have argued indicate developmental changes in cerebral functional organization (Brown *et al.*, 2005). Although not without their own limitations and biases, longitudinal fMRI studies will provide a way to validate and challenge results obtained from cross-sectional approaches.

As functional neuroimaging is applied more frequently to questions regarding cognitive development, the level of sophistication for technical, neuroscientific, behavioral and developmental aspects is improving. The important issues raised by the work of Durston and colleagues will certainly promote growth and development in the field.

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## Brain development during puberty: state of the science

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This is a commentary on Durston *et al.* (2006).

In recent years, neuroimaging techniques have shown that the development of the human brain is far more protracted than previously thought (see Paus, 2005, for review). In particular, the adolescent brain is subject to considerable structural change, most notably the prefrontal cortex. Adolescence is also characterized by major hormonal and physical changes, and dramatic developments in identity, self-consciousness and cognitive flexibility (Rutter, 1993; Coleman & Hendry, 1990). However, empirical research on the interaction between neural and

cognitive development during adolescence is in its initial stages.

Functional MRI (fMRI) provides us with a safe, non-invasive tool to study this interplay between brain and behaviour. fMRI has been used only in a handful of studies investigating the neural bases of cognitive development using tasks designed to tap specifically into prefrontal cortex function, in particular executive function tasks. Durston *et al.*’s fascinating study is the first that has compared longitudinal and cross-sectional developmental

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