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# Neuroimaging of typical and atypical development: A perspective from multiple levels of analysis

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**Abstract**
To date, research involving functional neuroimaging of typical and atypical development has depended on several assumptions about the postnatal maturation of the brain. We consider evidence from multiple levels of analysis that brings into question these underlying assumptions and advance an alternative view. This alternative view, based on an "interactive specialization" approach to postnatal brain development, indicates that there is a need to: obtain data from early in development; focus more on differences in interregional interactions rather than searching for localized, discrete lesions; examine the temporal dynamics of neural processing; and move away from deficits to image tasks in which atypical participants perform as well as typically developing participants.

Over the past decade, powerful new tools for imaging the workings of the brain have become increasingly available. Some of these methods are based on measures of blood oxygenation and flow (positron emission tomography or PET, functional magnetic resonance imaging or fMRI), whereas others detect the magnetic or electrical fields generated when groups of neurons fire synchronously within the brain (magnetoencephalography or MEG; event related potentials or ERP). In general, methods related to blood flow are thought to have better spatial resolution (on the order of millimeters), whereas the other methods have better temporal resolution (on the order of milliseconds). With the advent of event-related fMRI and high-density ERP, both types of methods are now working toward better spatial and temporal resolution within a single approach. These various imaging methods offer a clear potential for investigating developmental disorders at multiple levels of analysis. However, many experts raise the problem that the findings to date have been conflicting and variable. Part of the reason for the apparently disappointing progress has, in our view, been due to the general theoretical approach that has motivated much of the research to date. In this paper, we do not intend to provide a comprehensive review of functional imaging and developmental disorders (for one such review, see Filipek, 1999). Instead, we question some of the basic assumptions underlying this field of research before advancing an alternative strategy for designing and interpreting neuroimaging studies of developmental disorders. This new approach, in which the modular structure of the adult mind/brain is viewed as an emergent product of development, may help shed light on some of the existing controversial findings, as well as motivate a different strategy for future studies.

In previous work on developmental dis-

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orders, we distinguished a static "adult neuropsychology" approach from a more developmental "neuroconstructivist" approach (Karmiloff–Smith, 1995, 1997). Oliver, Johnson, Karmiloff–Smith, and Pennington (2000) explored the implications of these views for the computational modeling of developmental disorders (see also Thomas & Karmiloff–Smith, 2001a, 2001b). In the present paper, we look at the implications of adopting the neuroconstructivist approach for examining functional brain imaging data in both typical and atypical human development. The currently popular neuropsychological approach to understanding developmental disorders is essentially similar to that used for the case of adults whose brains have developed normally but acquired damage in later life, and it is based on a number of underlying assumptions that we explicate below. When these assumptions are applied to brain imaging of atypical development, they have strong implications for empirical enquiry and for the hypotheses being entertained.

The first key assumption commonly made is that a mapping exists between damage to a localizable brain structure, region, or pathway, on the one hand, and a particular cognitive, perceptual, or motor deficit(s), on the other. This we will refer to as the "localization" assumption. It contrasts with the view that psychological functions are the emergent product of interactions between multiple regions. A second assumption is that this mapping is relatively static and unchanging during the postnatal period. This we will call the "static" assumption. This contrasts with the view that, with development, there are changes in the neural basis of cognitive functions. A third underlying assumption of this approach is that the cause extends from the neural level to the cognitive and behavioral level. This "deficit" assumption maintains that a brain deficit of some kind directly causes and/or explains the behavioral and cognitive deficits that are subsequently observed. This contrasts with the view that cause is bidirectional. In other words, atypical behavior itself can alter aspects of brain structure, as well as vice versa.

In the following sections, we review these three assumptions in more detail before going on to discuss an alternative way of approaching and analyzing neuroimaging data from typically and atypically developing populations of children.

## Three Common Assumptions Underlying Developmental Neuroimaging Research

### *The localization assumption*

The first widely adopted assumption that we examine is that developmental functional neuroimaging will reveal differences in activation in discrete, localizable regions, particularly within the cerebral cortex. Some functional neuroimaging of typical development has been motivated by the desire to identify the maturation of discrete regions that may cause, enable, or allow new cognitive and behavioral abilities to emerge. In atypically developing populations, neuroimaging is commonly motivated by the desire to identify the brain regions that are impaired and that may explain the patterns of cognitive and behavioral deficits observed in a given group. We refute the simple form of this assumption for two reasons. First, we suggest that in human postnatal functional brain development changes in *interregional* connectivity are at least as important as changes in *intraregional* connectivity. In other words, rather than a behavioral change during development being associated with the maturation of one or two regions, it involves changing patterns of interaction across widespread brain regions and systems. Our second reason for questioning the functional localization assumption comes from a consideration of the genetic contribution to the cerebral cortex and the lack of evidence for functional regional specificity of gene expression within the cortex. A consequence of this is that genetic mutations contributing to developmental disorders are likely to affect widespread systems within the brain and not discrete regions within the cortex. We now consider these two points in more detail.

Referring to adult brain imaging data, Friston and Price (2001) point out that it may be an error to assume that particular functions can be localized within a certain cortical region. Rather, they suggest, the response prop-

erties of a region are determined by its patterns of connectivity to other regions, as well as by their current activity states. By this view, "the cortical infrastructure supporting a single function may involve many specialised areas whose union is mediated by the functional integration among them" (p. 276). Similarly, in discussing the design and interpretation of adult fMRI studies, Carpenter and collaborators argued that

> In contrast to a localist assumption of a one-to-one mapping between cortical regions and cognitive operations, an alternative view is that cognitive task performance is subserved by large-scale cortical networks that consist of spatially separate computational components, each with its own set of relative specializations, that collaborate extensively to accomplish cognitive functions. (Carpenter, Just, Keller, Cherkassky, Roth, & Minshew, 2001, pp. 360)

These notions about adult processing resonate well with the developmental perspective that we advanced elsewhere (Elman et al., 1996) in which different cortical regions and pathways become increasingly specialized as a result of progressively being recruited for specific tasks over developmental time. Specifically, Johnson (2000, 2001) advanced an "interactive specialization" (IS) framework for human postnatal functional brain development. By this view, cortical pathways in the newborn infant differ from each other by virtue of their particular pattern of inputs and outputs to other brain structures as well as biases in their information processing properties. The latter refers to slight differences such as those in the detailed patterns of intrinsic connectivity, the balance of neurotransmitters, or synaptic density. Such differences correspond to those that Elman and colleagues (Elman, Bates, Johnson, Karmiloff–Smith, Parisi, & Plunkett, 1996) referred to as "architectural constraints." These graded initial biases in cortical architecture are argued to be sufficient to ensure that particular types of sensory input, or input–output pairings, are more efficiently processed by a subset of the pathways. There is thus a gradual process of "recruitment" of particular pathways and structures for certain functions (Elman et al., 1996). One manifestation of this recruitment process is that cortical pathways and structures go through a process of progressive specialization. By specialization, Johnson (1999, 2000) referred to the extent that a given cortical region is selective in its response properties such that it progressively becomes responsive only to one class of stimuli. In other words, early in development a cortical region may respond to a wide variety of stimuli and task situations but, with specialization, it progressively becomes engaged only by a subset of these. This process may be akin to the tuning of response properties of single neurons. A consequence of the specialization of pathways is a form of increasing localization, as pathways that were previously partially activated in a wide range of task contexts now confine their activation to a narrower range of situations.

As already discussed, Friston and Price (2001) point out that much neuroimaging effort, even in healthy adults, may have been misguided in its search for "functional localisation" (i.e., functions that can be localized within a particular cortical area). Rather, they suggest that the focus should be on the interactions between areas and their temporal and spatial dynamics. Yet the association between the location of brain damage and cognitive deficits has been the central approach in traditional cognitive neuropsychology and has characterized much of the behavioral work on developmental disorders (see the critique in Karmiloff–Smith, 1997, 1998). Moreover, when studying developmental disorders there are additional reasons to doubt the existence of "clean" (discrete) cortical lesions that correspond to specific cognitive deficits.

Two contrasting views from developmental neurobiology have been presented to account the regional specialization of the cerebral cortex (see Johnson, 1997, for a review). The "Protomap" hypothesis states that the cortex is a mosaic of regions, in which each cortical area has individually specified features dedicated to the functions that it will perform in later life (Rakic, 1988). The "Protocortex" hypothesis states that the cortex is a relatively uniform and equipotential structure at the outset that derives its adult specificity from the structure contained in its inputs (from the thal-

amus) and other cortical areas via their interconnectivity (e.g., O'Leary, 1993). This debate in developmental neurobiology elicited a very large number of empirical studies. Recent reviews of this literature agreed on a middle ground in which gradients of gene expression across the developing cortex define large-scale regions (Kingsbury & Finlay, 2001; Pallas, 2001; Ragsdale & Grove, 2001). However, with a few exceptions, these large-scale regions generally do not map onto the detailed functional areas observed in the adult mammal. Specifically, Kingsbury and Finlay (2001) suggest that multiple dimensions of cell structure relevant to stimulus processing are laid out such that "regions" arise combinatorily as a result of particular sensory thalamic input overlaid by large-scale gradients in patterns of neurotransmitter expression, axon extension, and neurmodulator production. For example, a region might emerge that has visual input, high GABA, high serotonin, and short-range connections. Such a region may initially be ill defined and lack specialization but will be better at performing some types of computation than neighboring regions. Subparts of this region may become "recruited" for certain computational functions (Elman et al., 1996; Johnson, 2000; Karmiloff–Smith, 1998). This process could result in the cortical region fragmenting into a series of functionally distinct areas. However, for the present argument, it is important to note that the genes concerned are not usually expressed within the clearly defined boundries of particular functional areas, but rather show large-scale gradients across areas of cortex. Thus, mutated genes that are expressed during development of the cortex are unlikely to be confined to specific cortical functional areas and are even less likely to show clear mappings onto cognitive functions. Mouse models show that there is rarely a neat mapping between a single gene mutation and a single phenotypic outcome (Cattanach, Peters, Ball, & Rasberry, 2000; Crabbe, Wahlsten, & Dudek, 1999; Homanics, DeLorey, Firestone, Quinlan, Handforth, Harrison, Krasowski, Rick, Korpi, Mäkelä, Brilliant, Hagiwara, Ferguson, Snyder, & Olsen, 1997; Keverne, 1997; Smith, Aubry, Dellu, Contarino, Bilezikjian, Gold, Chen, Marchuk, Hauser, Bentley, Sawchenko, Koob, Vale, & Lee, 1998). Rather, the genetic contribution to neural structure is usually diffuse and graded in character.

Genes that affect brain development relatively early are likely to have wide cascading effects, often resulting in severe retardation or a nonviable fetus. Two examples of early alterations in brain development are spina bifida and anencephaly, in which the gross morphology of the developing central nervous system is dramatically altered. Genetic disorders that are expressed relatively late in brain development are likely to produce more subtle morphological and information processing consequences. Specifically, genetic defects that have their influence late in brain development are likely to affect those parts of the brain that show the most prolonged growth, such as the cerebral cortex. In addition, deviations from the normal developmental path that occur later in prenatal development are likely to specifically affect certain types of neural structure. Dendritic and synaptic development take place after cell migration in all brain structures, and are thus more likely to be vulnerable. There have indeed been reports of failures of cells to migrate to their normal locations in the upper layers of cortex in some developmental disorders (Bauman, 1996; Galaburda, Wang, Bellugi, & Rossen, 1994; Piven, Berthier, Starkstein, Nehme, Pearlson, & Folstein, 1990). But cell formation and migration are only one form of deviant development. In our view, many developmental disorders, particularly those that result in uneven cognitive profiles, will tend to involve deficits in the later developing pattern of dendrites and synapses rather than in the actual formation and migration of cells. Of course, gaining evidence for deficits in microcircuitry will be difficult, because it requires very time-consuming analyses involving electron microscopy. However, we believe that it is worth considering final common pathways at the level of impairments of subsequent detailed microcircuitry rather than at the level of initial gross structures and pathways.

In summary, even for neuroimaging studies involving normal adults, the assumption that there will be a one to one mapping be-

tween cortical regions and particular functions is questionable. This holds to an even greater extent for developmental disorders of genetic origin. Here, it is likely that multiple cortical areas will be affected. Specifically, early processing biases are likely to be altered, probably resulting in the development of abnormal patterns of interregional specialization.

### *The static assumption*

The next assumption we examine is related to the first. If one assumes that genetic disorders can target specific cortical structures and their corresponding cognitive abilities, then the age at which the disorder is examined is not particularly critical. In general, brain imaging experiments with groups of developmental disorders are invariably conducted with older children or adults who are at, or near, the final state of the deviant developmental sequence (see Karmiloff–Smith, 1997, 1998, for a discussion). There are several practical reasons for this: (a) the tests used are often similar to those employed in adult neuropsychology and are therefore only suitable for older children; (b) many disorders are still difficult to identify early in life; and (c) even if identified in the initial months of life, neuroimaging experiments are difficult (or, in some cases, impossible) to conduct during the first years of life. However, in addition to these practical problems, there is also the theoretical assumption that the mapping between neural structure and function remains constant during development. In other words, the implicit, if not always explicit, claim is that once a cortical region has matured, its function remains constant from that time on.

In contrast to the static assumption, the IS view outlined previously argues that when a new computation or skill is acquired, there is a reorganization of interactions between different structures and regions in the brain (Johnson, 2001). This reorganization process could even change how previously acquired cognitive functions are represented in the brain. Thus, the same behavior could be supported by different neural substrates at different ages during development. Further to this point, the IS view implies that different patterns of brain specialization can result from development. For many abilities, there will be more than one combination of neural structures and systems that can become specialized for the purpose. Studying this process will require longitudinal developmental studies beginning in early infancy.

### *The deficit assumption*

Another commonly made assumption related to those above is that damage to specific neural substrates both *causes and explains* the cognitive and behavioral deficits observed in developmental disorders. Again, this assumption is based on models previously applied to adults with acquired brain damage. While we do not question that it is informative to identify neural differences between typical and disorder groups, there are serious reasons to believe that the deficit assumption is flawed.

The deficit assumption implies a one-way causal route from the brain level to cognition and behavior. An alternative approach is based on the idea that there are bidirectional interactions between the brain and behavioral development during development. Gottlieb (1992) distinguished between two approaches to the study of development, "deterministic epigenesis," in which it is assumed that there is a unidirectional causal path from genes to structural brain changes to psychological function; and "probabilistic epigenesis" in which interactions between genes, structural brain changes, and psychological function are viewed as bidirectional, dynamic, and emergent.

As discussed earlier, much current theorizing on the neural basis of sensory, motor, and cognitive development is based on a viewpoint in which the maturation of particular neocortical regions allows or enables new functions to appear. This is clearly based on a predetermined epigenesis viewpoint in which the primary cause of a cognitive change can be attributed to neural maturation. A number of recent reviews of pre- and postnatal brain development have concluded that probabilistic epigenesis is a more appropriate way to view postnatal brain development (e.g., Johnson, 1997; Nelson & Bloom, 1997). Explaining developmental change when there are bi-

directional interactions between brain structure and (psychological) function is far more challenging than the maturation view. When adopting a probabilistic epigenesis viewpoint, the aim remains to unite developmental neuroanatomical observations with functional development. However, a probabilistic epigenesis approach emphasizes the need for notions of the *partial functioning* of neural pathways. This is because, in order for bidirectional interactions between brain structure and function to work, there needs to be early partial functioning, which then shapes subsequent structural developments. The cortical regions are not functionally silent before they abruptly become activated in their mature state. Rather, structural and functional changes in regions of the brain codevelop.

From the perspective of the maturational approach, developmental disorders such as autism and dyslexia have often been viewed as being caused by impairments to specific neural and computational modules. For instance, some authors have argued that autism is due to a deficit in an innately specified module that handles "theory of mind" computations only (Leslie, 1992). Functional imaging work has produced evidence that this module is specifically localized in the orbitofrontal cortex (Baron–Cohen, Ring, Wheelwright, Bullmore, Bramer, Simmons, & Williams, 1999). From this perspective, the scientific interest of both acquired and developmental disorders of cognition is to identify ostensibly "pure" cases in which a single module has been damaged leading to a specific cognitive deficit. From that, the argument follows, there may be specific brain structures, regions, or pathways that are either absent or grossly damaged in such disorders. And the next step is to attempt to link the disorder to a specific gene or specific set of genes that code solely for this particular phenotypic outcome. We believe that such an approach is flawed because it ignores bidirectional cause.

## Neuroimaging Functional Brain Development in Healthy Volunteers

In this section we review evidence from the functional neuroimaging of normal development that pertains to the three assumptions above. Specifically, we believe the evidence currently available does not support the popular notion that functional brain development simply involves the sequential maturation of different cortical regions that then allows or enables new cognitive and behavioral capacities. In contrast, we point out that behavioral change seems to be accompanied by large-scale dynamic changes in the interactions between regions and that different cortical regions become more specialized for functions as a consequence of development. In this section we briefly review some functional neuroimaging data from typical development to illustrate our points.

A maturational approach to human postnatal functional brain development predicts that a neural correlate of increasing behavioral abilities is an increasing number of active cortical areas. In functional imaging paradigms, therefore, infants should show less regions active in tasks where they show poorer behavioral performance than adults. In contrast, if new behaviors require changes in interregional interaction we predict a greater or equal extent of cortical activation and may find different patterns of activation early in development, even in task domains in which behavioral performance is similar to that of adults. Data consistent with the latter view would bring into question all three of the previous assumptions.

A number of authors described developmental changes in the spatial extent of cortical activation in a given situation during postnatal life. Event-related potential experiments with infants indicated that both for word learning (Neville, 1991) and face processing (de Haan, Pascalis, & Johnson, in press), there is increasing localization of processing with age and experience of a stimulus class. That is, scalp recording leads reveal a wider area of processing for words or faces in younger infants than in older ones whose processing has become more specialized and localized. Within the interactive specialization framework, such developmental changes are accounted for in terms of more pathways being partially activated in younger infants prior to experience with a class of stimuli. With increasing experience, the specialization of one or more of

those pathways occurs over time. Take the example of face processing. In early infancy, both the left and the right ventral visual pathways are differentially activated by faces, but in many (although not all) adults, face processing localizes largely to the right ventral pathway (Johnson & de Haan, 2001). In the example of word recognition, processing is initially found over widespread cortical areas. This narrows to left temporal leads after children's vocabularies have reached a certain level, irrespective of maturational age (Neville, 1991). Changes in the extent of localization can be viewed as a direct consequence of specialization. Initially, multiple pathways are activated for most stimuli. With increasing experience, fewer pathways become activated by each specific class of stimuli. Pathways become tuned to specific functions and are therefore no longer engaged by a broad range of stimuli as was the case earlier in development. Additionally, there may be inhibition from pathways that are becoming increasingly specialized for that function. In this sense, then, there is competition between pathways to recruit functions, and the pathway best suited for the function (by virtue of its initial biases) usually wins out.

According to the IS view, the onset of a new behavioral competence during infancy will be matched by changes in activity over several regions not just by the onset of activity in one or more additional regions (Johnson, 2001). Further, and in contrast to the maturational approach, we predict that during development the patterns of cortical activation will be at least as extensive as, or even more extensive than, those observed in adults. Moreover, the patterns of regional activation in a given task could potentially be different in the infant or child compared to adults. In this way, acquiring a new skill in development does not entail the maturation of a new structure but rather the reorganization of interactions between existing, partially active structures.

Further evidence to support this view comes from recent fMRI studies in children. Luna, Thulborn, Munoz, Merriam, Garner, Minshew, Keshavan, Genovese, Eddy, and Sweeney (2001) tested participants aged 8–30 years in an occulomotor response-suppression task. Their behavioral results showed that the adult level of ability to inhibit prepotent responses developed gradually through childhood and adolescence. The difference between prosaccade and antisaccade conditions were investigated with fMRI and revealed changing patterns of brain activation during development. Both children and adolescents had less activation than adults in a couple of cortical areas (superior frontal eye fields, intraparietal sulcus) and several subcortical areas, a finding broadly consistent with maturational hypotheses. However, both children and adolescents also had differential activation in regions not found to show differences in adults. Children displayed increased relative activation in the supramarginal gyrus compared to the other age groups, and the adolescents showed greater differential activity in the doroslateral prefrontal cortex than the children or adults. These findings illustrate that the neural basis of behavior can change over developmental time, and different patterns of activation are evident at different ages.

A similar conclusion can be reached after examination of the developmental fMRI data produced by Casey, Trainor, Orendi, Schubert, Nystrom, Giedd, Castellanos, Haxby, Noll, Cohen, Forman, Dahl, and Rapoport (1997). These authors (Casey et al., 1997; Thomas, King, Franzen, Welsh, Berkowitz, Noll, Birmaher, & Casey, 1999) administered a "go/no-go" task to assess inhibitory control and frontal lobe function to healthy volunteers from 7 years of age to adult. The task involved participants responding to a number of letters but withholding their response to a rarely occurring "X." More than twice the volume of prefrontal cortex activity (dorsolateral prefrontal cortex) was observed in children compared to adults. One explanation of this finding is that the children found the task more difficult and demanding than the adults. However, children with error rates similar to those in adults showed some of the largest volumes of prefrontal activity, suggesting that task difficulty was not the important factor. It is therefore difficult to account for these decreases in the extent of cortical activation in terms of the progressive maturation of prefrontal cortical areas.

A third example of the use of fMRI to study the development of cortical activation patterns during childhood involved using the same stimulus array for two different tasks, a face matching task and a location matching task (Passarotti, Paul, Bussiene, Buxton, Wong, & Stiles, in press). For the face matching task, younger children (10–12 years) showed more extensive areas of activation than did older children and adults. In general, the activation shown by the youngest group included the areas activated in adults (such as bilateral activation of the middle fusiform gyrus), but additionally extended to more lateral and anterior regions. In the location matching condition, the children also showed more extensive activation than did the adults. Whereas the adults had strong right superior parietal activation, the children displayed more bilateral activation of this structure as well as additional activation in the right superior frontal gyrus. Once again, and in contrast to the maturational view, typical development appears to be associated with a reduction in the extent of activation of cortical areas and with dynamic changes in the interregional patterns of activation.

## Neuroimaging Atypical Functional Brain Development

Having examined the three assumptions outlined earlier in relation to typical development, we now turn to evidence from atypical development.

### *The localization assumption*

Much of the neuroimaging work to date on developmental disorders has aimed at identifying gross abnormalities in discrete brain regions, structures, or systems. Although there have been some specific claims made with regard to such deficits, recent reviews of the field tend to find instead that evidence is consistent with diffuse damage to widespread parts of the brain in developmental disorders. For example, Rumsey and Ernst (2000) summarized their review of functional imaging of autistic disorders as follows: "studies of brain metabolism and blood flow thus far have yet to yield consistent findings, but suggest considerable variability in regional patterns of cerebral synaptic activity" (p. 171). Other authors reviewing work on autism concur with this conclusion. Deb and Thompson (1998) stated that "Various abnormalities of brain structure and function have been proposed, but no focal defect has been reliably demonstrated" (p. 299), and Chugani (2000) concluded that "data from the various imaging modalities have not yet converged to provide a unifying hypothesis of brain mechanisms," with a range of cortical (frontal, medial prefrontal, temporal, anterior cingulate) and subcortical (basal ganglia, thalamus, cerebellum) structures implicated in different studies. According to Filipek (1999) a similar situation obtains with respect to Attention Deficit Hyperactivity disorder (ADHD). She concludes that neuroimaging studies "have, in fact, confirmed the lack of consistent gross neuroanatomical lesions or other abnormalities in Attention Deficit" (p. 117). For ADHD, there are abnormalities in widespread cortical areas, including, at a minimum, the frontostriatal, cingulate, and parietal regions. In sum, for at least these two disorders, there is little support for the notion that discrete lesions to functional cortical areas can be observed in developmental disorders.

### *The static assumption*

As mentioned earlier, the vast majority of neuroimaging studies with developmental disordered groups involve participants from middle childhood to adulthood. While there are practical reasons for this focus, it is also the case that according to an adult neuropsychology approach, it should not matter, as the specificity of the deficit will remain constant throughout development. For the IS approach, however, age of testing is critical and it is especially important to study infancy to understand partial causes of subsequent outcomes (Karmiloff–Smith, 1998; Paterson, Brown, Gsödl, Johnson, & Karmiloff–Smith, 1999). For this issue to be assessed, there need to be longitudinal imaging studies of clinical groups, or at least cross-sectional studies involving different ages. Due to the difficulties mentioned earlier, there are very few examples of developmental disorder stud-

ies of brain imaging in infancy. Where such disorders have been investigated, abnormalities are often less evident in infancy. For example, Karrer, Wojtascek, and Davis (1995) conducted an ERP study of infants with Down syndrome at 6 months using an oddball paradigm for face recognition and concluded that "infants with Down syndrome may have more subtle differences (to age matched controls) than those found in adults with Down syndrome."

One basic question that can be addressed is whether an abnormal end state is the result of an aberrant trajectory of development or whether a normal developmental trajectory is merely delayed. Ideally, the question should be investigated through longitudinal studies of the developmental disorder group in question. However, in the absence of such data, the question can be asked whether the phenotypic end state of the disorder resembles any stage of the typical developmental trajectory. If so, this could be evidence for delayed development. This approach was taken to investigating the neurochemistry of autism. PET studies identified brain glucose metabolism in autism that is higher than age matched controls (see Chugani, 2000, for review). However, in typical development there is a characteristic "rise and fall" of glucose metabolism that parallels changes in synaptic density in the cortex. Muzik and colleagues (Muzik, Ager, Janisse, Shen, Chugani, & Chugani, 1999) generated a mathematical developmental function with identifiable parameters representing different stages of typical development. This allowed for a closer comparison with developmental disordered groups when longitudinal data are obtained. A caveat to this endorsement is that in the developmental cortical models of Oliver et al. (2000), reduced synaptic pruning was a symptom of several *different* simulated neural networks that failed to form adequate representations of input stimuli. It is possible, therefore, that reduced synaptic pruning (and therefore, elevated glucose metabolism) will be a symptom shared by several different groups with developmental disorders.

### *The deficit assumption*

The static neuropsychological approach is based on a deficit model. Behavioral abnormalities are argued to be caused by psychological deficits that in turn are caused by functional "lesions" to the brain. In functional neuroimaging paradigms, therefore, the general expectation is that there will be fewer regions active in the disordered group than in controls and that the regions active in controls but not in the disordered group are the neural locus of the deficit. This fits well with the subtraction methodology often employed in functional neuroimaging studies. In contrast, the IS approach views developmental disorders in terms of brains that develop differently from the typical trajectory from the start. This view predicts that differences in functional activation will be seen between groups, but that this could even involve more widespread activation in developmental disorders. In other words, different patterns of regional activation may be seen for developmental disordered groups in a given task, rather than one or more regions being functionally silent.

A further prediction of the IS view is that even if areas of behavioral competence are examined, there will still be differences in the neural processing underling this performance (Karmiloff–Smith, 1998). This question has been examined in studies of Williams syndrome (WS), a syndrome portrayed by some theorists as involving islands of "sparing" (normal performance) amid clear deficits. Mills and colleagues (Mills, Alvarez, St. George, Appelbaum, Bellugi, & Neville, 2000) focused on face processing, an area of behavioral competence in this disorder, and recorded event-related potentials during a face-matching task. Despite their "intact" behavioral performance in the task, WS participants displayed different patterns of ERPs, including a lack of the normal right-hemisphere asymmetry. Similar findings were obtained in another area of behavioral competence for this syndrome, where the normal left hemisphere asymmetry for words was not observed (Mills, Coffey Corina, & Neville, 1993; Neville, Mills, & Bellugi, 1994). The ERPs in response to faces were also recorded in participants with autism or Asperger syndrome (McPartland & Panagiotides, 2000). However, in this case, face processing is an area of behavioral deficit. Compared with controls, the autism group made more errors on a test of face recognition. Per-

formance on the face recognition task was found to be related to the ERPs in several ways: in controls, a face-sensitive ERP component was larger in amplitude to faces compared with objects and was more predominant over the right hemisphere. In contrast, the autistic group showed longer latencies of this component to faces compared to objects, in the absence of any clear lateralization. These findings suggest that the poorer performance on face recognition tasks by the autism group is reflected by slower and less lateralized (i.e., less specialized) processing of faces as indicated by their ERPs. In addition, the different distribution of the response to faces between the autistic group and controls may reflect qualitatively different processing strategies.

In the next section we add some precision to our alternative approach and point to a novel way in which to consider the interpretation of neuroimaging data from developmental disorders.

## The IS Approach

### *Assumptions of the IS approach*

The IS approach implies that resulting disorders of brain function will have a very different character to that assumed by the maturational approach. Rather than seeking to identify focal neural deficits that relate to specific cognitive defects, we anticipate observing different spatial and temporal patterns of interaction between structures. The IS approach has several underlying assumptions:

- Developmental disorders will result in diffuse abnormalities involving the neurochemistry and/or microcircuitry of the brain, as opposed to discrete, gross lesions to particular regional brain structures.
- The neural basis of developmental disorders, as opposed to cognitive disorders caused by acquired lesions, can be best understood in terms of the progressive emergence of representations during ontogeny (Oliver et al., 2000)
- Developmental disorders should be viewed as alternative developmental trajectories with a particular profile of cognitive abilities that may include both strengths and weaknesses, rather than being identified simply as specific "deficits" relative to normal controls. We should not necessarily expect to find less cortical activation in a given task in developmental disorders, but different patterns of activation and, in some cases, more activation due to less specialization over developmental time. Groups with developmental disorders differ from individuals who suffer brain insults later in life. In the latter case, the brain is forced to come up with some form of compensatory or alternative mechanism to deal with whatever processing the lesioned site was responsible for prior to injury. By contrast, children with developmental disorders are likely to process information differently from the start, not because they are adopting compensatory mechanisms, but because their brains have developed differently from embriogenesis onward.
- These abnormalities may change both during development and in different task contexts. If there are differing patterns of interactions between regions in atypical development, then the brain regions that show differential activation compared to controls will vary during different tasks.
- Even in tasks where developmental disordered groups behave as controls, we should expect differences in the neural substrates of this performance (Karmiloff–Smith, 1998). In this respect, it is even more informative for functional imaging studies to investigate the neural basis of tasks with which such groups show relative competency in the behavioral domain. For example, individuals with WS are claimed to have been "spared" face processing abilities, despite displaying severe deficits on visuospatial tasks.

### *Implications of the IS for imaging developmental disorders*

We argued that a neurocontructivist approach to imaging developmental disorders should: involve longitudinal studies beginning, if possible, in early infancy; focus on deviations

from typical patterns of functional activation, rather than trying to identify deficit structures; and attempt to understand the effects of partial diffuse damage, as opposed to gross lesions in systems. There are, as yet, no examples in which all aspects of this alternative strategy to imaging developmental disorders have been adopted. However, groups of investigators in several laboratories have begun to pursue elements of this alternative approach.

Unfortunately, this approach has rarely been adopted in structural or functional imaging. One attempt to study interregional interaction comes from PET studies on high-functioning men with autism (Horowitz, Rumsey, Grady, & Rapoport, 1988; Rumsey, Duara, & Grady, 1985). In order to determine the functional association between brain regions, Horwitz et al. (1988) compared correlations between ratios of resting regional cerebral metabolic rates for glucose (rCMRglc) and global brain metabolism (CMRglc) in 14 (age 18–39 years) men with autism and 14 age-matched controls. Compared with controls, the autistic group showed significantly elevated levels of glucose uptake (about 15%) in widespread regions of the brain. No specific regional differences in brain glucose ultilization were found between the two groups, suggesting that the abnormalities in autism are widespread rather than restricted to any particular locus within the brain. However, an analysis of the correlations between local and global brain metabolism revealed a statistical decrease in the number of positive correlations in regions within and between frontal and parietal lobes in the autistic group, compared with the controls. Horwitz et al. suggest that this is evidence for a difference in the functional associations in the resting state between frontal and parietal lobe structures in autism, compared with normals. The cause for the decrease in large positive correlations in autism remains to be determined. The study is limited in that the correlational analysis was carried out on data obtained from subjects in the "resting" state. The fundamental problem in interpreting these results is that it is difficult to ascertain subjects' cognitive activity during the resting state (Fu & McGuire, 1999). Clearly, additional information obtained from subjects during the performance on a cognitive task should be helpful in relating abnormalities of cognition and behavior to changes in brain function.

Carpenter et al. (2001) recently advanced a perspective on imaging developmental disorders similar to our own (see also Just, Carpenter, & Varma, 1999). They began by using fMRI to study the interactions between cortical regions during a language comprehension task in a group of typical young adults. The fMRI activation increased systematically with sentence complexity in a large-scale network of cortical areas, including the left posterior superior and middle temporal gyri (Wernicke's area), the left inferior temporal gyrus (Broca's area), and their right hemisphere homologues. Some right hemisphere areas were only slightly activated during the processing of simple sentences but were recruited more heavily for more demanding grammatical structures, as were other regions such as the dorsolateral prefrontal cortex. A similar recruitment of additional areas with task difficulty was observed in mental rotation tasks. A consequence later in life of early damage to left hemisphere language areas was increased activation of right hemisphere components of the same network. These previously "silent partners" now became as active as the left-sided regions in the healthy participants.

These experiments were recently extended to participants with autism to test the hypothesis that "autism affects the interconnectivity among and within various cognitive systems" (Carpenter et al., 2001, p. 373). Preliminary results indicate that there are no differences between autism and controls in the areas activated in the sentence comprehension task, although the normal pattern of lateralization was not as evident and the extent of activation of the different regions differed. However, when functional connectivity between regions was assessed through correlating changes in the activity of voxels, the functional connectivity between regions was shown to be systematically lower for the individuals with autism. This finding generalized to a nonlinguistic problem-solving paradigm (Carpenter et al., 2001). The authors suggest that, in autism, functional brain development goes awry such that there is increased intraregional spe-

cialization and less interregional interaction. Paradoxically, by this view, a static one to one mapping between structure and function may actually be atypical and more applicable to autism than to typically developing individuals.

Another approach to examining the interconnectivity of brain regions in developmental disorders is to study the temporal dynamics of processing. In particular, some suggested that shared oscillatory neural activity between distant brain areas can serve to "bind" together their activity. It is possible that clusters of brain areas coordinate their activity through shared frequencies of neural oscillation. A considerable amount of recent evidence from both cellular recording and scalp-recorded electroencephalogram (EEG) has linked gamma-band (40 Hz) neural oscillations to perceptual binding processes in the brain. Binding refers to the integration of elements or features to compose whole objects or other entities, and it also involves the integration of information across different cortical areas. For example, a burst of gamma-band EEG is induced around 250 ms after presentation of an "illusory" shape (such as the Kanizsa figure, in which three of four pacmen shapes can be oriented such that they give the impression of a triangle or square that partly occludes a number of circles). In the first developmental study of gamma-band EEG, Csibra and colleagues (Csibra, Davis, Spratling, & Johnson, 2000) recorded EEG while 6- and 8-month-old healthy infants viewed illusory objects or control stimuli. Like adults, 8-month-olds showed a clear burst of gamma frequency EEG over frontal cortical regions in the illusory object trials, but not in the control trials. However, 6-month-olds did not show evidence of bursts of gamma, consistent with behavioral evidence that they do not yet perceive illusory figures such as those used in the experiment.

We have now studied this dynamic brain response in two developmental disorders, WS and autism (Grice, Spratling, Karmiloff–Smith, Halit, Csibra, de Haan, & Johnson, 2001), which are both developmental disorders in which the visual processing of static objects is dominated by the local features, as opposed to the global or configural properties, of an array. This apparent failure to integrate components into whole units is manifest in several cognitive domains in both syndromes and is sometimes referred to as "weak central coherence" (Frith, 1989). Faces are important stimuli for which this abnormal dominance of local feature over global configural cues is particularly evident. In normal adults, the perception of the human face relies predominately on configural information; an upright face is perceived with the global configuration taking precedence over the individual parts. Inverting the face, however, disrupts configural processing and significantly decreases accuracy at identifying the face. People with WS or autism are unusual in that they display a reduced inversion effect and appear to rely less than controls on configuration. The similar result for these two disorders is striking because in most other ways, they have dissimilar behavioral profiles.

We therefore deemed it vital to compare these syndromes at the level of binding operations in the brain and therefore analyzed the gamma-band response to upright and inverted faces. Our preliminary results reveal that, unlike normal controls, both clinical groups display no gamma differences as a function of stimulus orientation (upright vs. inverted). Our results suggest that there are abnormalities in binding-related gamma oscillations in both autism and WS, and face orientation has no effect on the magnitude of gamma activity in either syndrome. However, the nature of these effects is different in the two cases (Grice et al., 2001). In autism, apparently normal bursts of gamma activity occurred, but the bursts were not different for the upright and inverted faces. In WS, by contrast, no clear gamma bursting occurred and gamma activity was distributed across longer time intervals. In the case of autism, binding-related gamma bursting looks very similar to that in controls, apart from not being modulated by face inversion. This suggests that the differences in binding may be a consequence of another deficit elsewhere in neural processing and/or reflect a difference in strategy or processing style with these stimuli. In the case of WS, by contrast, gamma-band EEG did not occur in the regular task-related way observed in the other groups, but rather resembled the disorganized pattern seen in very young infants before regular

bursting emerges between 6 and 8 months (Csibra et al., 2000). This raises the possibility that for WS the lack of interconnectivity between regions disrupts the basic neural processes of binding, which may have multiple cognitive and behavioral consequences, one of which is a failure to integrate features to compose a global configuration.

This is but a first step in cross-syndrome comparisons of binding-related differences in developmental disorders, but it shows how subtle differences in early low-level processing can have a cascading impact on phenotypic outcomes.

## Limitations of Neuroimaging of Developmental Disorders

It is important to acknowledge that there are a variety of technical and methodological differences between the neuroimaging studies that we have mentioned in this article. These are likely to contribute to some of the differences in the results obtained. One of the most enduring and difficult problems in research on functional neuroimaging studies of developmental disorders is how to choose comparison or control groups. Normative data for cohorts of typically developing individuals are frequently unavailable and knowledge of normal individual variation nonexistent. Yet the interpretation of data from clinical groups, in terms of abnormality and syndrome specificity, relies on the comparison with what is expected in individuals of equivalent chronological age, sex, socioeconomic status, or mental functioning in the absence of the disorder in question. One solution is to conduct only hypothesis-driven research that investigates between-condition rather than direct between-group differences. This is well suited to those techniques (ERP/MEG) that mainly discriminate temporal rather than spatial changes. However, studies focusing on the localization of function (e.g., fMRI) suffer from the requirement to normalize data to a standard set of spatial coordinates. The interpretation of data from all brain imaging techniques must be done cautiously because of syndromic abnormalities in total brain shape and size, as well as proportional variations between different brain regions as compared to the normal case. In addition, standardized protocols of image acquisition and measurement are not yet established, so meaningful comparisons across studies from different laboratories remain limited.

The issue of control groups is far from straightforward. Matching on the basis of mental and chronological age across two syndromes carries the assumption that the reason for the retardation in the two cases is of the same nature. This is clearly often not the case. Matching to typically developing controls on the basis of chronological age or mental age raises similar problems. A clinical population with, say, a mean mental age of 7 and a mean chronological age of 20 has a huge difference in experience compared to a typically developing child of mental age 7. One solution is to plot a full developmental profile of normal children, rather than one age group, and then plot each clinical individual on that profile. Another is to make cross-syndrome comparisons on the basis of a specific ability for which both syndromes are reported to have the same cognitive deficit. This was, for instance, the case for the feature-based analyses for WS and autism that we briefly discussed above. In such cases, neuroimaging may actually be used to determine whether the cognitive-level account is correct.

Many developmental disorders are defined on the basis of a collection of behavioral symptoms. This, along with problems of access and recruitment, often result in an unavoidable heterogeneity of sample (in terms of cognition, IQ, age, sex, etc.) and/or small sample size. In order to increase statistical power, variance should decrease or the number of data points increase, but these options are, in practice, restricted (e.g., when increasing numbers means relaxing diagnostic criteria on behavioral features such as in autism or dyslexia). This is, of course, impossible when genetic diagnosis forms the basis of inclusion. Homogeneity is not the only reason why sample sizes are sometimes small. Relatively high subject loss is common to all imaging techniques, resulting from the nature of the atypical groups being studied. Repetitive motor stereotypies or poor ocular control (resulting in motion artifacts), low compliance or motivation, poor comprehension of task demands, and high anxiety are potential hazards. This often

leads either to very small patient groups or a sampling bias in favor of higher functioning adult patients, who can comprehend and comply with instructions. These individuals are assumed to be less likely than lower functioning individuals or children to require sedation and its consequential ethical, practical, and scientific risks. However, there are clearly theoretical issues about generalizing from a selection of high functioning individuals to a syndrome as a whole.

In order to understand the results of any neuroimaging study, it must be clear what cognitive systems were supposed to be targeted by the task. In fact, these may not be the same between the clinical group and the controls. Some tasks could be titrated to each individual's level of ability according to prespecified criteria, but this is impractical for many imaging studies. Ideally, at least the control group should be studied using the same task across development, whether cross-sectionally or longitudinally. The most important factor in all neuroimaging research of developmental disorders, however, is that each practical, ethical, and theoretical step is explicitly stated and justified. Using this approach, replication and comparison across centers and disorders will, hopefully, become possible in the future in a way that it currently is not.

## Conclusions and Future Directions

Despite the methodological factors in brain imaging research discussed above, it is still striking that there is yet to be a commonly agreed specific neural substrate for any genetic developmental disorder. We have argued that the search for gross abnormalities in discrete brain regions, structures, or pathways in developmental disorders is likely to be unsuccessful. From an IS perspective, structural abnormalities are likely to be subtle and diffuse, rather than gross and focal. Furthermore, using standard subtraction methods, differences between developmental disorder groups and controls will be task dependent such that different regions will be identified as showing deficits in different tasks.

The IS approach outlined here implies that the search for evidence of differential interactions between regions may be of greatest value. If there are subtle but widespread abnormalities in the atypically developing brain, then the IS view would predict differential patterns of interactions between regions from those that result from typical trajectories of development. One anatomical consequence of abnormal interactions between regions may be differences in the extent of connectivity, involving the "white matter" of the brain. A consistent finding from structural imaging of autism is larger cerebral volumes (see Filipek, 1999, for a review), particularly in the temporal, parietal, and occipital regions. It is interesting, however, that this increased volume was due to white matter rather than gray matter (Filipek, Richelme, Kennedy, Rademacher, Pitcher, Zidel, & Caviness, 1992). In other words, the fiber bundles connecting regions and mediating interregional interaction were affected more than the regions themselves. Preliminary MRI studies of WS showed that, unlike autism, overall brain and cerebral volume are smaller than age matched controls (Reiss, Eliez, Schmitt, Patwardham, & Haberecht, 2000). An assessment of tissue composition indicated that, compared to controls, individuals with WS have a relative preservation of cerebral gray matter volume and disproportionate reduction in cerebral white matter volume. This pattern was restricted to the cerebral hemispheres and did not occur in the cerebellum (Galaburda & Bellugi, 2000; Reiss et al., 2000). Thus, in two major developmental disorders of genetic origin, differences in overall cerebral volume appear to be related to the extent of connectivity (white matter) between regions (gray matter).

The interactive specialization approach to developmental disorders implies that different types of brain imaging studies need to be conducted. In contrast to the majority view, we do not believe that the future lies in increasingly fine spatial resolution of imaging methods and even more precise anatomic localization (e.g., Filipek, 1999). Instead, we recommend that studies obtain data from several age groups, including infancy, to examine the different trajectories of development in disorders. Data from different ages can help us to ascertain whether clinical groups show the same pattern as that observed at younger ages during typi-

cal development (see also Filipek, 1999). Studies need to be designed to focus on differences in interregional interactions, rather than searching for lesions in single functional areas or pathways (see also Friston & Price, 2001). More focus on the temporal dynamics of neural processing is required, as opposed to methods for increasingly fine spatial resolution. Finally, examination of islands of ability are of equal interest as areas of disability. It will be informative to see how and why atypical brains achieve similar levels of performance to typically developed ones. We look forward with optimism to a future study of developmental disorders in which neuroimaging is a truly integrated component of a multiple levels of analysis approach.

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