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Comments and Controversies

Functional imaging of developmental and adaptive changes in neurocognition ☆

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Characterization of brain–behavior relationships through functional magnetic imaging (fMRI) within typically or atypically developing populations poses methodological and interpretational challenges. We consider theoretical, methodological, and artifactual factors that influence characterization of developmental and adaptive changes in childhood. Findings from anatomical and physiological brain development studies are highlighted as they may influence functional imaging results. Then, we consider several patterns of functional activation within the context of developmental processes as well as neurologic disease. Hypotheses regarding the development of cognitive networks are proposed to account for the individual differences seen in normal and atypical development. We also identify potential sources of unwanted variability related to experimental design and task performance and suggest possible solutions to help minimize these effects. Lastly, a challenge for current studies is a lack of group and individual analysis methods that can be reliably applied to capture and quantify factors that contribute to variability introduced by developmental and disease processes. We review current methods and propose potential solutions.

Keywords: Development; fMRI; Pediatric; Cognition; Language

Introduction

Functional magnetic resonance imaging (fMRI) has permitted characterization of brain–behavior relationships with increasing precision. Characterization of those relationships within typically or atypically developing populations, however, poses methodological and interpretational challenges that differ from those pertinent to adult populations. Specifically, two factors distinguish investigation of child and adult neurocognition. First, characterization of the neural basis of cognition in children must be made against the backdrop of ongoing biological maturation. With variable rates of biological maturation, children of the same age are likely to differ more than adults of the same age. Thus, individual variability must be characterized more fully in investigation of developing rather than mature cognition. Second, adaptive changes following developmental or acquired disorders may differ in structural and functional characteristics relative to those following adult neurologic injury. As an end state of maturation, adulthood represents completed functional organization. Functional recovery following adult neurological injury, therefore, must be accomplished by compensatory processing enabled by neural reorganization. In contrast, as a state of ongoing maturation, childhood represents incomplete functional organization. Childhood disorders, therefore, alter the course of functional organization. Functional outcomes are likely to differ following adaptive changes in childhood relative to adulthood. Thus, models of functional organization gleaned from adult studies are limited in revealing adaptive changes in neurocognition. Taken together, these factors result in neurocognitive adaptive changes in children that are unlikely to be homogeneous because biological and experiential factors interact in a variety of ways. Consequently, there may be multiple variants of typical and atypical development.

This paper will consider theoretical, methodological, and artifactual factors that influence characterization of developmental and adaptive changes in childhood. Current functional neuroimaging methods are optimized for elucidating invariant properties of cognition as embodied in adulthood, and therefore, are limited in revealing a complete picture of developmental and adaptive variability in brain–behavior relationships. While others have considered some of these factors, the present discussion will focus on these issues as they pertain specifically to the investigation of developing populations.

Neuroanatomic and physiological changes

A detailed review of anatomical and physiological brain development is not undertaken in this paper; however, the following summary of findings provides the context in which developmental functional imaging studies are interpreted. The

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structural and physiological changes taking place in a developing brain may influence functional imaging data. In addition to normal brain maturation, pediatric disease processes may further affect functional imaging data. Key findings are summarized and then the relevance of these findings to imaging is discussed.

Separate lines of evidence gathered from pathological, MRI structural, and PET studies suggest that the developing brain is marked by continued changes in cortical composition despite reaching a relatively stable volume by age five (Caviness et al., 1996; Giedd et al., 1996). In general, gray and white matter changes are ongoing into early adulthood with significant decrease in cortical gray matter volume after age 12, increase in cerebral white matter volume throughout adolescence, and increase in cortical thickness after age 12 (Caviness et al., 1996; Chung et al., 2003; Giedd et al., 1999; Pfefferbaum et al., 1994). The timing of these cortical changes is not uniform across brain regions. The earliest regions to become mature are primary somatosensory areas whereas protracted development occurs within association areas (Bourgeois et al., 1989, 1994; Gogtay et al., 2004; Huttenlocher and Dabholkar, 1997; Sowell et al., 1999; Yakovlev and Lecours, 1967). Gray matter changes such as synapse formation and elimination occur at different rates across regions (Huttenlocher and Dabholkar, 1997) and changes in cortical thickness are greatest in frontal areas (Chung et al., 2003). For example, changes occur earlier and are complete in early childhood in auditory cortex (Heschl's gyrus) relative to prefrontal cortex (middle frontal gyrus), where each stage is prolonged with the entire process extending into adolescence. Metabolic demands, and consequently cerebral blood flow rates, of the brain parallel the time course of structural maturation presumably to support ongoing synaptic formation and pruning. Developmental trajectories of regional metabolic and cerebral blood flow rates peak between 7 and 9 years of age with a gradual decline to adult levels during adolescence (Ball and Holland, 2001; Chiron et al., 1992; Chugani et al., 1987; Takahashi et al., 1999). Similar to cortical structural changes, regional heterogeneity is also evident in metabolic changes as frontal regions are one of the last areas to reach adult levels. Thus, primary cortex is the first to reach maturation whereas association areas that are critical for higher-order cognition undergo neuroanatomical and neurophysiological changes well into adolescence.

Accounting for maturational differences is difficult enough within normal populations, but disease and injury complicate further our understanding of functional imaging results. Disease or injury forces atypical structural development, yielding both gross and region specific abnormalities. We present a sampling of findings to illustrate the various ways pathological processes may disrupt neuroanatomic development. Gross abnormalities characterize neurofibromatosis, a common autosomal dominant gene disorder that is associated with macrocephaly (Moore et al., 2000) and Down's syndrome, a chromosomal disorder that is associated with microcephaly (Pastore et al., 2000). Focal abnormalities are found in Attention Deficit Hyperactivity Disorder (ADHD), a common developmental disorder that has been associated with reduced volumes of the right anterior prefrontal lobe, caudate and globus pallidus (Castellanos et al., 1994), corpus collosum (Giedd et al., 1994), and cerebellum (Castellanos et al., 2002). Both gross and focal abnormalities characterize epilepsy, a neurologic disorder that has been associated with losses in total brain volume as well as reduction in gray matter in focal areas, including the hippocampus and cerebellum and projections from the temporal lobe such as the thalamus (Lawson et al., 2000; Liu et al., 2001, 2002a, b, 2003). There is mixed evidence for progressive volume losses due to ongoing seizure activity (Liu et al., 2002b, 2003; Marsh et al., 1997; Theodore et al., 2003). Furthermore, both progressive and nonprogressive structural changes are observed in a number of disorders such as childhood onset schizophrenia (Sporn et al., 2003), obsessive–compulsive disorder (Saxena and Rauch, 2000), periventricular injury (Marin-Padilla, 1996), and autism (Courchesne et al., 2001). In summary, disease and developmental disorders may be accompanied by global and regional alterations in brain structure that may influence interpretation of functional imaging results.

Relevance to imaging studies

While the time course and nature of structural changes during development have been described in detail, how they relate to functional differences is not well understood. In light of protracted maturation of association areas, higher-order cognitive processes such as language, executive functions, and emotional processing are likely to be more sensitive to developmental differences than sensory processes supported by primary cortical areas. Indeed, even in adults, activation within association areas is more variable (Kwon et al., 2002; Xiong et al., 2000) than activation within primary visual (Hasnain et al., 1998) and auditory (Ulualp et al., 2000) cortex. Therefore, it is likely that there is great variability within functional activation patterns in children. For typically developing children, functional activation patterns are likely to reflect variability due to maturational and experiential factors. For atypically developing children, variable functional activation patterns likely reflect maturational and experiential factors altered by pathological processes.

Several studies demonstrate the ambiguous relationship between the time course of structural maturation and the functional characteristics of a region. During spatial working memory performance, magnitude and extent of activation in bilateral prefrontal regions were greater with increasing age in 7–22 year old subjects (Kwon et al., 2002). Thus, improved performance was mediated by greater involvement of regions with a protracted developmental time course. In contrast, during manual-motor response inhibition, volume of activation in frontal regions was greater in children compared to adults (Casey et al., 1995, 1997). These findings suggest that improved response inhibition was related to reduced involvement of regions with a protracted developmental course. In contrast to the linear developmental trajectories suggested by the above findings, frontal activation during occulo-motor response inhibition exhibited a curvilinear trajectory such that signal change was greater in adults relative to children but it was greatest in adolescents relative to the other two age groups (Luna et al., 2001). The frontal activation observed in these studies of the same cognitive process (response inhibition) differed in the nature of age-related frontal recruitment. The range of findings may be related to any number of methodological differences among studies in terms of age of subjects studied, task used, or data analyses conducted. These issues are discussed in detail later in the paper. However, methodological issues specific to imaging are discussed here.

While several factors may account for the group differences in functional activation patterns observed across studies, three factors pertaining to functional localization are particularly relevant to studies with children or populations with a disorder. First, in order

to compare functional activation patterns across individuals, it is necessary to warp individual brains into standard stereotactic space (Friston et al., 1995). In light of anatomical differences across individuals, it is likely that this procedure could induce variability into the location of peak activation across individuals. Group averaging of activations that vary in spatial location is likely to yield distorted functional maps in terms of reduced magnitude or greater spatial extent of activation. The contours of spatially normalized pediatric images were found to be more variable than adult images, especially in children less than 6 years old (Muzik et al., 2000). However, for children 6 years and older, the normalization procedure does not produce distortions in functional activation maps (Burgund et al., 2002; Kang et al., 2003; Muzik et al., 2000; Wilke and Holland, 2003). Very young children's brains may be particularly vulnerable to more distortion because the most commonly used stereotactic template (Talairach and Tournoux, 1988) is based on an adult brain (Bookheimer, 2000; Gaillard et al., 2001a). This issue is particularly problematic in the event of an altered brain volume due to tissue loss from a disease process. In the event of structural alterations due to developmental or acquired disorders as discussed above, spatial normalization may yield inaccurate functional activation maps.

Second, partial volume averaging effects may influence the nature of activation patterns in children (Friston et al., 1995). Given that the BOLD response is measured within gray matter, signal within voxels with more gray matter will be stronger than those with greater white matter or cerebrospinal fluid. Developmental changes in regional composition of gray and white matter, therefore, are likely to enhance variability among observed activation patterns in children (Chung et al., 2003; Gaillard et al., 2001a; Wilke and Holland, 2003). In group comparisons between adults and children, adults who generally have less gray matter may demonstrate less activation.

The third issue relates to signal detection within the context of network maturation. Network maturation is thought to occur through two primary processes, synaptic pruning and consolidation. Fig. 1 illustrates how either process may influence signal detection given a common threshold value. An immature network may produce a weak change in signal because experience has not reinforced synaptic connections and thus the network is not consolidated. In other circumstances, an immature network may have extensive activation because the network is not yet fully pruned. Pruning occurs when less utilized neuronal connections are lost; consolidation occurs when neuronal connections are continually reinforced. Therefore, pruning and consolidation yield a mature network that may result in a strong, concentrated signal change.

Although these factors may influence the extent and strength of activation, a recent study suggests that this issue alone may not account for significant differences in activation patterns. In a study that used an implicit word-processing task to examine acquisition of reading skills, children and adults performed three tasks: cross-hair fixation, visual feature search with false font strings, and visual feature search with words (Turkeltaub et al., 2003). Age-related differences were observed in activation for words relative to false-fonts, but not for false-font relative to fixation. Thus, age differences were observed selectively for the condition that was sensitive to reading skill and not for all conditions in general. Therefore, this single study suggests that the competing maturational forces of progressive synaptic consolidation and regressive pruning may not introduce indiscriminant effects on the BOLD response.

In summary, the relationship between structural maturation and functional activation does not appear to be straightforward. Activation patterns are influenced by age-related and regional variability as well as image processing procedures necessary for localization and signal detection. The influence of these factors is further compounded in the event of atypical maturation due to developmental or acquired neurological disorder.

Classification of patterns of functional activation

In this section, we consider several patterns of functional activation within the context of developmental processes as well as

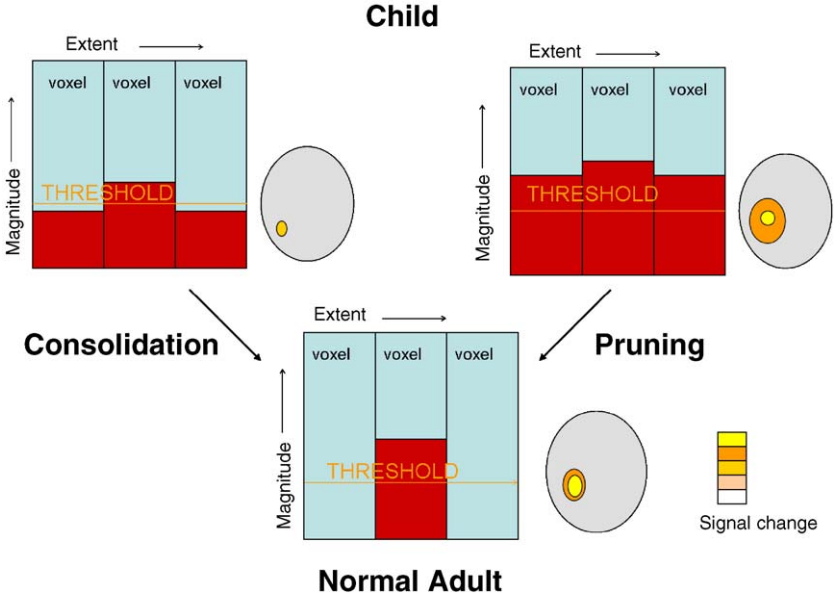

Fig. 1. Network maturation occurs through consolidation and pruning, which may influence extent and strength of signal. Prior to consolidation, an immature network is depicted by low-level, diffuse activation. Prior to pruning, an immature network is depicted by strong, yet nonspecific activation.

neurologic disease. Hypotheses regarding the development of cognitive networks are proposed to account for the individual differences seen in normal and atypical development. A fundamental goal of developmental studies that use fMRI is to identify the normal neural network that underlies a cognitive process as reflected by task specific activation (Fig. 2). However, the normal pattern for a particular cognitive process may be elusive as there may be several normal, developmentally-appropriate variants. The first set of patterns presented (immature network, focal network, contralateral focal network, and regionally weighted network) fall within normal development. Following the discussion of normal variants, patterns of adaptive neural networks (regionally weighted, persistent immature network, forced contralateral network) are presented. These patterns may arise due to a developmental or acquired neurologic disorder that may arrest development thereby resulting in an activation pattern that mimics a normal pattern, but is immature and less efficient. Lastly, atypical adaptive patterns (diaschisis, dysmature/atypical location) that arise due to a developmental or acquired neurologic disorder are presented. In these cases, disease may produce obvious pathological variants that are distinct from normal activation. For all patterns presented, language processing will be used as the primary example to illustrate the possible variants (See Figs. 2–4); however, these concepts may apply to a variety of cognitive processes. Our discussion includes some studies with working memory, inhibitory control, and other tasks, but it is not the aim of this paper to provide a review of the developmental imaging literature which has been undertaken elsewhere (Casey et al., 2005a,b).

Normal variants

A widely accepted hypothesis to account for normal developmental changes is "progressive specialization" (Lenneberg, 1967) or "focalization" (Muller et al., 1998), which likely reflects the consolidation and synaptic reinforcement of a network. During focalization, activation moves from diffuse, widespread, low magnitude activation [Patterns A and B] to more focal and greater magnitude of activation [Patterns C or D] as a child matures. This model is subsequently referred to as the focal network model.

The focal network model predicts that the same cortical regions are activated for adults and children yet the extent of activation is greater and the signal change is less for children. This hypothesis is supported by studies that show that the underlying neural network necessary for language processing is generally established by age five (Ahmad et al., 2003).

Specifically, verbal fluency tasks produced the predicted pattern (Pattern B in Fig. 2) with greater extent manifested as a larger cluster of activation within a focal region as well as due to recruitment of homologous areas (Gaillard, 2004; Holland et al., 2001). Activation may also be greater in children because they may not have a specific approach to solve a problem, rather they try several strategies, thereby activating several cortical areas. In comparison, adults have developed specialized "modules" and immediately use an efficient strategy, which presumably has been learned and reinforced from past experience. For example, evidence suggests that adults selectively activate in the unimodal auditory areas of superior temporal gyrus when processing spoken word forms and selectively activate in the unimodal visual areas of middle temporal gyrus and fusiform gyrus when processing written word forms. In contrast, children are not as selective or modality specific, thus activating both auditory and visual areas regardless of presentation modality (Booth et al., 2001).

Further evidence for the focal network model includes several studies that show similar patterns of activation among children and adults; however, children have greater activation as compared to adults across a number of cognitive tasks including working memory (Nelson et al., 2000; Thomas et al., 1999), inhibition (Casey et al., 1997, 2002), auditory comprehension of language (Ahmad et al., 2003; Balsamo et al., 2002), reading (Gaillard et al., 2001b, 2003a), and verbal fluency (Gaillard et al., 2000a,b). As depicted in Pattern B, children performing language tasks show age-appropriate, yet developmentally immature patterns of activa-

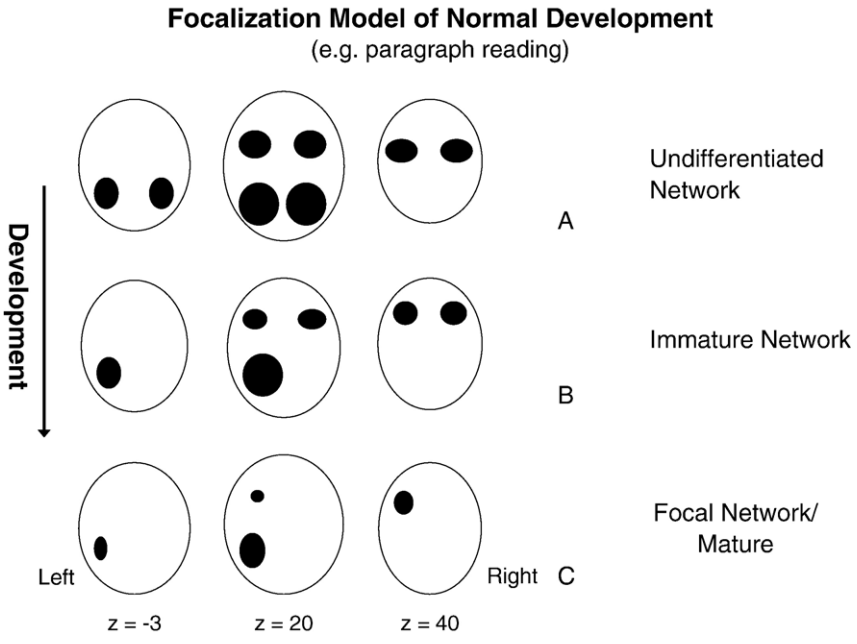

Fig. 2. Hypothetical activation maps for focalization model presented as axial slices in Talaraich space. Black represents activation.

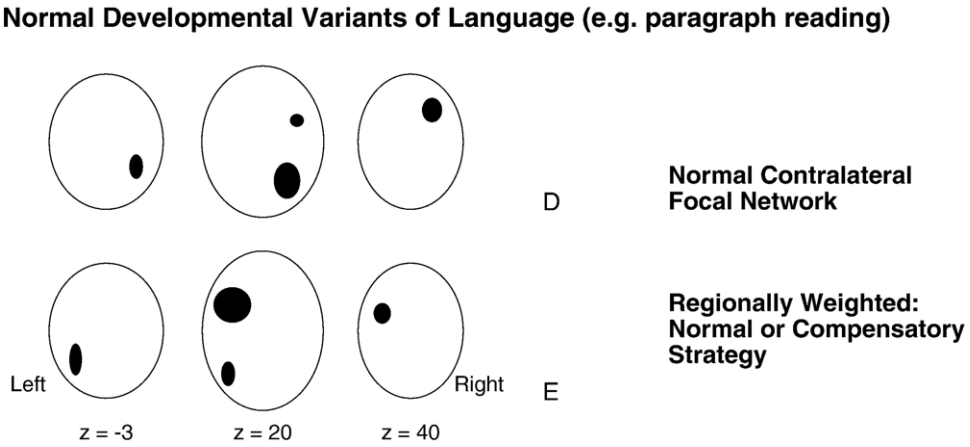

Fig. 3. Hypothetical activation maps for models of variants of normal development are presented as axial slices in Talaraich space. Black represents activation.

tion where networks are largely lateralized but not focal. This widespread pattern may be due to recruitment of homologous regions or lack of specialization of neurons but over time, a consolidated, mature focal network develops [Pattern C].

A normal variant to the focal network model occurs when the network develops within the contralateral hemisphere [Pattern D]. It is well known that several cognitive processes are preferentially controlled by one hemisphere over the other. In our example, homologous areas may be involved in language tasks, but studies show that language networks are strongly lateralized at an early age (Ahmad et al., 2003; Gaillard et al., 2003c) including infants who show a distinctly lateralized network for auditory processing of speech (Dehaene-Lambertz et al., 2002). The majority of normally developing children are left-lateralized for language; however, approximately 5% of normal right-handers and 20–25% of normal left-handers develop language dominance within the right hemisphere (Gaillard et al., 2003c; Knecht et al., 2000; Pujol et al., 1999; Springer et al., 1999; Szaflarski et al., 2002).

Regionally weighted: normal variant or adaptive

Despite several observations in support of the focal network model, results from other studies are not fully explained by this model. Specifically, studies of verbal fluency and working memory show increases in signal change with age, but also show increases in extent with age (Gaillard et al., 2003c; Klingberg et al., 2002; Kwon et al., 2002; Rubia et al., 2000; Thomas et al., 1999). Studies that adopt additional methodological or statistical probes (to be discussed in detail later) reveal a more complex developmental course than proposed by the focal network model. These studies show increases in activation with age for some cortical regions as well as decreases in activation with age for other cortical regions

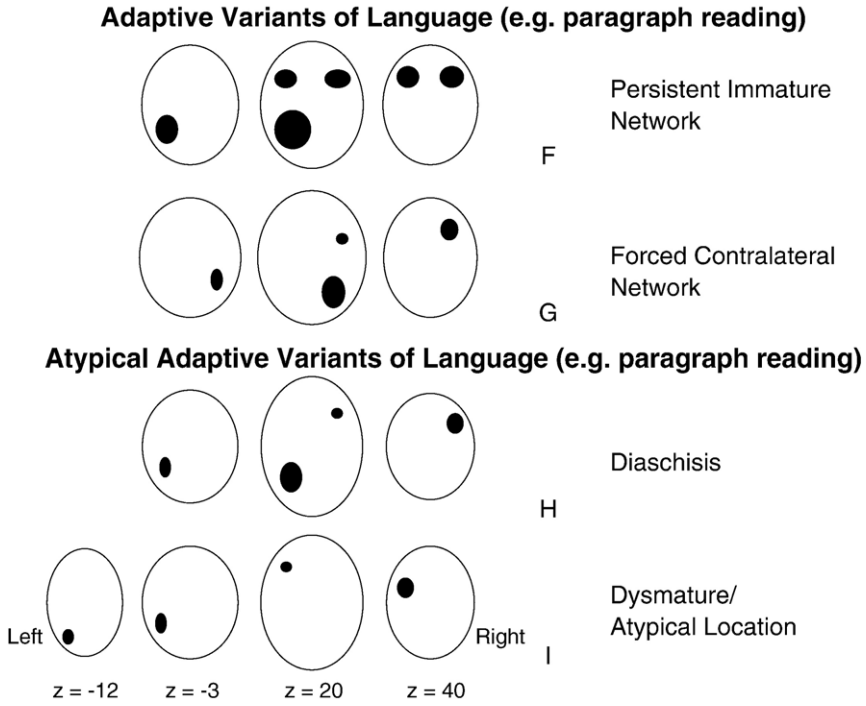

Fig. 4. Hypothetical activation maps for models of adaptive and atypical variants are presented as axial slices in Talaraich space. Black represents activation.

(Booth et al., 2000; Brown et al., 2005; Schlaggar et al., 2002). These findings suggest another hypothesis involving "regional weighting" (Pattern E), which takes into account the distribution of activation within a network. The regionally weighted model proposes that the same areas of a distributed network are involved but the degree of engagement of each region systematically changes with development.

Within the regionally weighted model, activation may be horizontally or vertically weighted. An example of a vertically weighted pattern is the developmental trend of less subcortical activation and greater neo-cortical activation observed on working memory tasks (Casey et al., 2002; Rubia et al., 2000). Horizontal weighting refers to the concept that, within cortex, activation may be weighted along the anterior–posterior axis (intrahemispheric) or along the left–right axis (interhemispheric). Different weights may reflect normal variation of cognitive skill level, use of different cognitive strategies, or changes in the biological substrate for a function. Cortical regions may also be involved differentially because of adaptive strategies that compensate for any impairment. Reading paradigms, discussed below, illustrate the regionally weighted model and account for individual and group differences.

Functional MRI studies demonstrate that the cortical areas commonly involved during reading include inferior temporal occipital cortex (fusiform and lingual gyrus), middle temporal gyrus (BA 21, 22), and inferior and middle frontal gyrus (BA 44, 45, 9, 46) (Bookheimer et al., 1995; Gaillard et al., 2003a,b; Pugh et al., 2000; Shaywitz et al., 2002). A developmentally appropriate, weighted activation pattern may arise when a child who is learning to read relies on a phonological strategy resulting in greater activation in left inferior frontal areas that are implicated in phonological processing. In contrast, an experienced reader does not engage the phonological system as strongly, rather posterior, temporal areas of activations predominate presumably reflecting efficient semantic retrieval (Bookheimer et al., 1995; Gaillard et al., 2003a; Shaywitz et al., 2002, 2003). Individual differences in activation maps of 5–7 year old children in inferior frontal and mid-frontal gyrus during reading support the weighted model (Gaillard et al., 2003a). In this study and similar to adult studies, significant temporal activation was observed, but group averaging did not show significant frontal activation. However, of the 16 children, nine had activation in inferior frontal gyrus (IFG), but with slightly different locations of peak activation (BA 44, six children; BA 45, four children; BA 47, two children). The IFG activation in children supports the hypothesis that beginning readers rely heavily on a phonological strategy compared to adults, but the variability of peak activation among the children may also reflect subtle differences in strategy or skill among the beginning readers. In addition, this variability may also reflect general differences in strategies on tasks that lend themselves to different strategies. For example, different strategies for reading are often due to the different teaching methods as some students are taught to read by sounding out words and others are taught by recognition of whole words. The regionally weighted model accounts for changes in the degree of involvement of different cortical regions of a neural network as abilities develop and strategies shift.

The regionally weighted model has also been observed during typical development of the ability to suppress task-irrelevant interfering information (Bunge et al., 2002; Luna and Sweeney, 2004). Interference suppression on a flanker task was associated with activation of the inferior frontal gyrus, in the right hemisphere in adults but in the left hemisphere in children. Hemispheric differences probably reflect differences in performance strategies between the groups. Children's performance was positively associated with their fluid verbal abilities, suggesting that they may have relied upon a verbal strategy to guide their performance. With maturation of the frontal cortex in adulthood, however, a verbal strategy may not be beneficial compared to reliance on a visual–spatial strategy. Typical development of response inhibition also demonstrates differential regional utilization of the same network as that activated in adults (Bunge et al., 2002). Adults consistently activated a network comprised of prefrontal and posterior temporal–parietal regions. In contrast, children's response inhibition ability was positively associated with the posterior rather than prefrontal activation. Specifically, high performing children activated the posterior association areas to a greater extent than those with lower response inhibition. These results suggest that, in light of immature prefrontal cortices, children's performance relied upon strategies supported by the posterior components of the nominally mature neural network.

Related to the weighted model is the hypothesis that with developing skills, cortical areas are not necessarily *gradually* used or abandoned. Rather, Rubia et al. (2000) propose a "discontinuous transition" to describe maturation of frontal cortex. They posit that although an immature network may suffice in terms of supporting task performance, a separate mature, adult network may take effect once mastery or efficiency of the skill prevails. The transition is discontinuous because the immature network may have only a few regions in common with the mature network, but once the mature network is "online," the brain abruptly switches to the mature, more efficient network.

Adaptive variants

Impaired populations often use immature or inefficient cognitive strategies to adapt to an immature or compromised neural network. One variant is a persistent immature network [Pattern F], which matches the age-appropriate immature network [Pattern B]; however, this pattern represents an abnormal variant because the pattern is no longer appropriate for the age of the person. Shaywitz et al. (2002) provide evidence for the persistent immature model in their study of dyslexia by observing greater activation in the left and right inferior frontal gyri for older compared with younger dyslexic children. Moreover, older nondyslexic readers do not utilize posterior reading systems as strongly as fluent, nonimpaired readers. One way to interpret these findings is that those with dyslexia never mature to strongly engage the left hemisphere posterior reading networks and instead compensate by using right anterior regions.

An extreme version of the persistent immature network occurs when early injury or disease causes permanent reorganization of functional areas to homologous regions [Pattern G]. There is mixed evidence for how well preserved cognitive function is when the contralateral network is forced by early events (Baron, 2004). Nevertheless, several studies support the hypothesis that if the damage occurs early in development, the contralateral elements of the network assume cognitive function. A study of adults with perinatal periventricular brain lesions shows similar right and left hemisphere activation patterns in terms of extent and signal intensity (Staudt et al., 2002). An example of recovery of language

in the nondominant hemisphere is seen in the case study of a typically developing boy with documented left-lateralized language who underwent a left hemispherotomy after onset of intractable seizures at age five (Hertz-Pannier et al., 2002). Eighteen months postoperatively, the boy showed right-hemisphere activation in homologous areas. Moreover, numerous studies employing a variety of techniques find that patients with early onset left temporal lobe epilepsy are more likely than healthy normal volunteers to have language represented in the nondominant hemisphere (Binder et al., 1996; Booth et al., 1999; Devinsky et al., 1993; Gaillard et al., 2004; Rasmussen and Milner, 1977; Rausch and Walsh, 1984; Springer et al., 1999; Woermann et al., 2003).

Atypical variants

Although there are likely many possible patterns, two known atypical adaptive variants have been observed only in patient populations (Gaillard, 2004; Staudt et al., 2001). The first pattern is a diaschisis of receptive and expressive language functions [Pattern H]. In one instance, a child with a left frontal lobe congenital stroke developed the common left lateralized pattern for language processing in the temporal lobe, but language processing that was frontal lobe dependent reorganized to the contralateral side. This is an intermediate variant of the forced contralateral network. Another atypical pattern occurs when the regions most engaged are in cortex not usually critical to the cognitive process under study resulting in a dysmature pattern [Pattern I]. This pattern may be due to neurologic injury relatively late in development resulting in late intrahemispheric reorganization or because a person uses an unusual strategy. For example, reading requires visual processing of words via the visual word form area; however, the semantic meaning of the word must be extracted by the functional areas involved in language. In patients who have disrupted pathways due to injury between the visual word form area and critical language areas, their activation pattern for a reading task emphasizes the visual word form area (Cohen et al., 2000). Similarly, a study found activation of left extrastriate cortex in the dyslexic group which may indicate adoption of a visual compensatory strategy (Backes et al., 2002).

The proposed patterns of neural activity highlight how developmental and atypical populations may vary in their activation patterns. Observations from existing imaging studies support these initial hypotheses and illustrate how fMRI may be an important tool to inform us about typical and atypical development.

Variability sources and solutions

Sources of variability may be introduced at many points during experimentation including decisions regarding experimental design, image acquisition, and processing. As measurement and data processing factors such as motion artifact (Gaillard et al., 2003c), equipment issues (e.g., head coil for pediatric patients) (Gaillard et al., 2001a; Henry et al., 2001; Lipschutz et al., 2001), scanning preparation (Byars et al., 2002; Slifer, 1996; Slifer et al., 1994, 2002), and a pediatric template for spatial normalization (Wilke et al., 2002) are discussed elsewhere, those issues will not be elaborated on in this paper. However, we do identify sources of variability related to experimental design and task performance and suggest possible solutions to help minimize unwanted variability.

Experimental design and task performance

Experimental design is an important consideration when determining the independent contribution of factors such as brain maturation or task performance on activation patterns. The ideal design is to conduct a longitudinal study over the developmental course of the cognitive process of interest; however, there are obstacles to completing a longitudinal study (Poldrack, 2000). Hence, most studies use a cross-sectional design despite loss of statistical power and cohort effects. A cross-sectional design is vulnerable to between-subjects variability in performance and maturational status. Thus, regional activation differences among groups may be an artifact of the composition of the samples.

Functional MRI is predicated upon comparing a minimum of two tasks (control and experimental) and selection of the control condition can dramatically affect activation maps. Additionally, assumptions are made about the component processes of a task and how each participant will perform the task. These assumptions may be particularly difficult to predict with children. For example, in studies that use a silent or resting control condition, there are no assurances that the subject is able to truly rest between experimental blocks and halt cognitive processing, particularly language mediated processing. Researchers have also argued that a control condition is not always a controlled condition (Binder et al., 2000; Bookheimer et al., 1995). For example, in a reading paradigm where the control task is looking at pseudowords, it is assumed that the control task involves visual processing, phonological decoding, and attention, but no semantic processing. However, with beginning readers, they may attempt to “read” the pseudowords and erroneously come up with meaningful words. Control task performance may also introduce variability, particularly with children who may have a wider range of ability (even with simple tasks) than adults who more consistently reach ceiling performance levels (Thomas et al., 1999). Thus, individual differences in activation maps may be attributable to the degree to which the subject complied or was accurate with the control condition rather than their performance during the experimental condition.

Although several studies aim to study the same cognitive process (e.g., reading, inhibition), task characteristics of each study are likely to influence the nature of recruitment. First, a task modification such as making a task overt versus covert may recruit different aspects of a network. For example, reading aloud compared to reading to oneself may more strongly engage phonological regions of a neural network (Bookheimer et al., 1995). Second, frontal lobe recruitment may have varied among two studies because of the mode of response, even though both finger (Casey et al., 1995, 1997) and eye saccade (Luna et al., 2001) evoke similar inhibitory processes and involve the motor system. Lastly, task-related factors are likely to influence the amount of effort or arousal of subjects. Indeed, striatal recruitment in ADHD relative to control children was reduced on a difficult version of the Go/No-go task but increased on a less demanding version of the Go/No-go task (Vaidya et al., 1998).

A common task design is often employed such that both children and adults perform the same task; however, this often results in the task being relatively easy for adults and more difficult for children thereby making performance a confounding factor when interpreting results (Gaillard et al., 2001a; Thomas et al., 1999). Greater task difficulty may increase activation (Braver et al.,

1997) and recruitment of homologous regions for language tasks (Gaillard et al., 2001a; Just et al., 1996). Thus, children who have more difficulty on a task may activate homologous areas whereas a normal or adult comparison group may not find the task as difficult and would not recruit homologous regions. Without gathering task performance data, one could erroneously interpret the activation differences as a developmental difference where children are less lateralized for the task.

Researchers have adopted several solutions to separate effects of performance differences from those attributable to maturation. However, as our discussion below highlights, no solution is perfect because new challenges are introduced making this an ongoing issue for researchers. One solution is to pick a task that both children and adults can perform at a high level of accuracy with both groups essentially performing at ceiling (Poldrack, 2000). Alternatively, an inventive approach was used to parcel out effects of neuroanatomic maturation (age) and performance (Brown et al., 2005; Schlaggar et al., 2002). Reaction time was used to match adult and child performance rather than accuracy. Activation between the matched groups was then compared and any differences were attributed to age effects. Results were particularly compelling because they yielded different regions that were selectively dependent on and independent of age and performance. However, a limitation of the common task is the assumption that because participants have the same accuracy or reaction time, that the cognitive effort to achieve the score was the same. It is likely that a child had to be more focused and concentrated and/or recruited other networks to complete the task at such a high level. Moreover, a child who is able to perform at a level equivalent to an adult is arguably not the typical child. This issue pervades many studies where the "normal" children are actually uncommonly skilled with reported mean IQs within the top 2–15% (Bunge et al., 2002; Gaillard et al., 2003a; Schlaggar et al., 2002; Shaywitz et al., 2002; Turkeltaub et al., 2003).

Instead of a common task, a task may be selected to match participants' ability. This may be particularly relevant to clinical studies to ensure that patients can perform the task adequately. The aim is to equate performance through task design without inducing process level changes. For example, a working memory paradigm (*N*-back) requires a subject to keep in mind a certain amount of information. The amount of that information, working memory load (*N*), may be manipulated such that a lower load in children (1-back) may yield performance equal to that of adults at a higher load (3-back). Another example is to have different reading tasks that are consistent with a certain grade level. Presumably, by having gradations of task difficulty, then one controls for effort. A consequence, however, is that other aspects of performance are variable and can be problematic upon interpretation of functional data. For example, a task that is matched for developmental level may have a different cognitive burden or have different stimuli altogether. In the working memory paradigm, the time it takes to process (rehearse) one versus three letters is different. In that case, presentation rates may be adjusted; however, then other parameters such as time to attend or visual exposure are not equal. For a reading task, merely increasing the length may not get to the idea of maximal effort. Thus, texts matched to reading ability may be appropriate; however, the stimuli are then different among the levels because different words and possibly different storylines are used. Another difficulty with designing a matched-ability task is that it is very difficult to truly know if the different levels are increasing in difficulty by the same amount. Effort is generally a difficult construct to measure and even if "maximal effort" is attained for each subject, it is undetermined whether that is truly the same for everyone.

Performance differences may also be addressed through the use of a parametric task design where a participant is given several levels of difficulty of a task allowing for characterization of relationships between performance and activation (Bookheimer, 2000). This information is also practical by providing validation that the experimental task invokes a function that is germane to the disorder under study. When conducting studies with impaired populations, then performance, by definition of their disorder, cannot be equated. Therefore, it is necessary to establish that performance differences exist among the groups participating in the research. An additional application of a parametric design is to examine relative rather than absolute differences between groups. By administering different levels of a task to the same subject, a cognitive-dose–response curve could be characterized. Some tasks are amenable to an auto-parametric design where a subject theoretically has no limit on how well they perform. For example, using the working memory paradigm, the most difficult condition presented may be a 3-back, yet a participant may easily be able to do a 4-back. An example of a design where the task does not set the ceiling is a verbal fluency paradigm where a subject can generate as many words as possible during a set amount of time. Evidence suggests that this design is successful in minimizing the amount of variance attributable to performance (Gaillard et al., 2003c).

Another method useful in separating performance from anatomic factors as the possible source of individual differences is to use a panel of tasks or an event-related design to assess more than one cognitive function across a set of subjects. An event-related design allows for different trial types to be included in one functional run whereas the panel of tasks allow for different trial types to be included across several runs. The logic is that if group differences occur due to anatomical variability, then differences should be observed across all cognitive functions. However, if a dissociation is observed such that group differences occur for one cognitive function and not others, then it can be presumed that true functional differences exist.

The issues that confront researchers regarding task design are complicated when studying complex, higher-order cognition. As such, no single solution is without limitations. It may be useful to have the same subject participate in multiple design types to aggregate findings; however, limited resources and time constraints often preclude such exhaustive study. Moreover, children, in particular, are likely to have difficulty sustaining performance within the MR environment for longer than 30 to 60 min, depending on the age of the child.

Assessing variability

A challenge for current studies is a lack of group and individual analysis methods that can be reliably applied to capture and quantify factors that contribute to variability introduced by developmental and disease processes. An assumption of group comparison studies is that the individual groups are homogeneous; however, this assumption is misleading, particularly with diseased and developmentally disabled populations. As proposed earlier, there are a number of potential normal variants (focalization, regional weighting, contralateral network, etc.) as well as different

adaptive or atypical patterns that may develop (e.g., forced contralateral, diaschisis, etc.). It is necessary to develop and refine individual and group analysis methods to accurately identify all the variants.

Current techniques emphasize analyses designed to identify common areas of activation within a population. Both fixed and random effects analyses for group averaging aim to establish a single pattern of activation that best represents the average pattern for the group. Furthermore, random effects analyses allow inferences about the population. Another approach is conjunction analysis which identifies what activation is common among tasks or common among all subjects (Friston et al., 1999). A limitation of the existing methods is that they do not necessarily capture the entire range of activation patterns within a set of functional data. Indeed, during episodic retrieval, patterns of activation in typical adult subjects were variable but overlapped enough to yield a robust group averaged functional map (Miller et al., 2002). That group map, however, had little resemblance to the contributing individual patterns of activation. There is often an even greater range of individual functional activation patterns with neurologically involved populations. In patients with epilepsy, cortical stimulation and intracarotid amytal procedures reveal significant differences in localization of language (Devinsky et al., 1993; Loring et al., 1999; Ojemann, 1991; Ojemann et al., 2003; Rasmussen and Milner, 1977; Steinmetz and Seitz, 1991). Patients showed intrahemispheric as well as interhemispheric shifts in language representation. fMRI studies show that approximately 5% of normal, right-handed people are dominant for language in the right hemisphere (Gaillard et al., 2004; Pujol et al., 1999); however, that proportion increases to approximately 24% in epilepsy populations (Gaillard et al., 2004; Springer et al., 1999; Szaflarski et al., 2002). If group averaging is emphasized, right hemisphere activation in that subset of individuals would not reach threshold, and therefore, right-hemispheric contribution to language would not be noted.

A technique that may be used to identify outlying patterns of activation that are missed by group averaging, includes a penetrance map, which addresses what portion of the study population contributes to the overall group activation map (Xiong et al., 2000). By using only the significant voxels generated by the group map, a penetrance map is a color coding of the frequency at which those voxels are significant for each individual in the study. Voxels are colored differently according to what percentage of the subjects showed activation at that location. However, penetrance maps, as Xiong and colleagues used them, do not show the full range of activation percentages because areas are represented only if at least 50% of the individuals in the group showed significant activation at that voxel.

It may be informative to use methods that visualize potentially important, but low incidence outliers. Two possible strategies include a "frequency" map and a "cluster" map. A frequency map extends the range of the original penetrance map by including areas that are not necessarily significant on the group map thereby allowing for a pictorial representation of the entire study population. In this way, an island of activation showing 5% of a group with activation leads an investigator to explore those points of activation further. Another approach is a cluster map which is derived by calculating the distance of each individual's peak activation to the group mean peak activation (Xiong et al., 2000). By plotting these values, one may determine how tightly concentrated activation peaks are for one group versus another. Furthermore, graphing these points in Talaraich space allows for visual inspection of outliers similar to the frequency map (Balsamo, 2003). One difficulty with these methods is that larger populations are needed to validate that an outlying point of activation is clinically significant and not merely spurious activation.

Apart from the above descriptive methods is a voxel-wise analysis performed in a standard anatomic space, which involves comparison of an individual to a group of normal subjects. These methods require that the investigator identify the subject of interest (e.g., person with epilepsy) and compare their results to a population of control subjects. This method has been used in volumetric (Liu et al., 2003; Liu et al., 2002b), diffusion tensor (Rugg-Gunn et al., 2001), and functional imaging (Turkeltaub et al., 2004) studies. These studies reveal cortical areas within the subject of interest that differ from the normal comparison group. This method may be applied to every subject in the study to determine if there are any unusual patterns. Once a group of subjects who differ from the norm is established, then a second-step analysis would be to make comparisons among that collection of individuals to discover any similarities or differences in patterns among those subjects.

The methods discussed thus far relate to regional individual differences; however, it is also important to assess any multi-regional differences in activation patterns. The overall, multi-regional, pattern of activation that may depict a functional network may be more informative of different cognitive processes rather than isolated cortical regions. The goal is to identify functional networks of spatially distinct cerebral regions whose activity is correlated across subjects (McIntosh et al., 1997). Functional connectivity, defined as the covariance of the activation of a least two cortical regions during a cognitive task, captures the relationship among activation areas across different cortical regions. The implication is that if the activation of a set of areas strongly covaries, then they comprise the network necessary for the cognitive task.

Several techniques to quantify connectivity are not fully validated with neurologically disordered populations (Just et al., 2004) and have yet to be used for examining developmental and adaptive changes. The approach includes various data reduction techniques such as partial least squares (McIntosh et al., 1996, 1997), principle components analyses (Friston et al., 1993), and structural equation modeling. Recently, a group of researchers discussed the methodological issues related to connectivity among

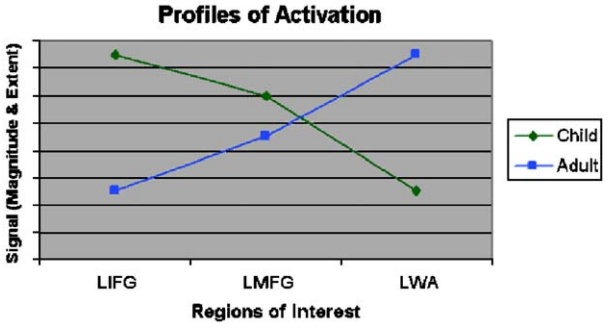

Fig. 5. Hypothetical differences in profiles for children and adults. Inter-regional profiles of signal change are shown across traditional language areas: Left Inferior Frontal Gyrus (LIFG), Left Middle Frontal Gyrus (LMFG), and Left Wernicke's Area (LWA).

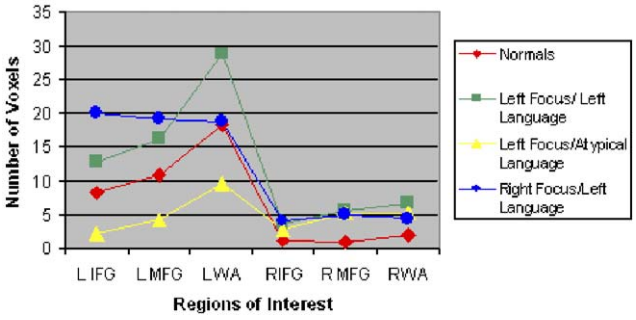

Fig. 6. Profiles from previous data show how extent may vary inter-regionally for normal volunteers and different patient populations. Regions of interest include: Left (L) and Right (R) Inferior Frontal Gyrus (IFG), Middle Frontal Gyrus (MFG), and Wernicke's Area (WA).

regions (Horwitz, 2003; Lee et al., 2003). One particular issue is that a collection of images is not comprised of independent observations. Therefore, multivariate correlational techniques are limited by the assumption of independence among measures. Violation of this assumption via multicollinearity reduces statistical power, which leads to the likelihood that a rare, but clinically important pattern is not identified. Methods also need to be sensitive enough with imaging studies that often have small sample sizes yet a large number of datapoints. Lastly, functional connectivity is a correlational analysis so it only provides indirect evidence, rather than causal analysis, about the connectedness of various cortical regions.

Another method, not necessarily mutually exclusive to connectivity analyses, is to perform a profile analysis to test for significance among observed neural patterns (Ding, 2001). This may be particularly useful in quantifying the proposed regional weighting model. For example, two regionally-weighted profiles for reading are illustrated in Figs. 5 and 6. Fig. 5 illustrates the example discussed in the theoretical section where children and adults differ in their reading strategy. Specifically, a relatively stronger peak signal change in IFG compared to temporal regions is shown for children whereas adult patterns emphasize the use of a semantic strategy that emphasize activation of temporal areas. The second example (see Fig. 6) shows how different patient and normal population profiles look based on previously acquired data (Gaillard et al., 2003b). Profile analysis provides three types of information for any person or group: level, dispersion, and the shape. Level is defined as an unweighted average of the scores in the profile, that is, the mean score over the variables of interest. Dispersion is defined as how much each score in the profile deviates from the mean. A measure of the dispersion is the standard deviation of scores for each person or group. This would help make conclusions about whether one group is more variable than another. Shape is defined as the "ups" and "downs" in the profile and can be determined by the rank-order of scores.

In sum, current methods often do not capture important, but low incidence activation patterns which may reflect variability in development or due to disease. Several solutions were presented to begin to address this issue. The methods presented have yet to be validated in pediatric populations and are by no means exhaustive of the possible solutions to capturing the variability reflected in activation patterns. The challenge of new analysis methods is to allow for subset analyses, which may be constrained by needing larger populations.

Conclusions

Characterization of the functional anatomy of developmental and adaptive neurocognitive changes poses unique challenges. Models of functional organization gleaned from adults are limited in revealing developmental and adaptive changes because they underestimate variability among individuals. Individual differences are enhanced during typical and atypical development as a result of interactive effects of maturational and experiential factors. Guided by findings of extant studies, we have proposed possible variants of developmental and adaptive trajectories and their manifestation in functional activation patterns visualized by fMRI. While the proposed models are descriptive, it is a first step towards formulating hypotheses that highlight variability as a defining feature of typical and atypical development. A second, and more challenging step, is the application of inferential statistical methods for testing hypothesis based upon the proposed models.

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