FMRI in Pediatric Neurodevelopmental Disorders

Michael Seyffert* and Raul Silva

NYU Child Study Center, 215 Lexington Ave., 14th Floor, Room#1421, New York, NY, 10016, USA.

Abstract: Neurodevelopmental disorders are thought of as beginning before birth, and many such as Down syndrome clearly do. Clinically, however, other such disorders may unfold over months (Mental Retardation, Autism, Rett syndrome) or years (Asperger Syndrome, Fragile X, Dyslexia). While structural Magnetic Resonance Imaging (MRI) has uncovered specific regions of white and gray matter abnormalities associated with several of these disorders, the exact relationship between structural changes and alterations in neuronal function and connectivity are still unclear. Over the past decade, functional brain imaging methods such as PET and SPECT have gained widespread clinical acceptance in other medical fields such as Oncology and Psychiatry; while their use in Pediatrics is limited by a reliance on radioactive labeled tracers (radioligand). Functional MRI, on the other hand has several unique advantages in that it is a non-invasive technique with improved spatial resolution that permits a more accurate elucidation of the dynamic brain changes associated with each of these neural based developmental disorders. Since there also exists a spectrum of phenotypic heterogeneity among these disorders, it is important to develop such a diagnostic tool that can first identify underlying biological substrates, and then distinguish successful pharmacological or behavioral interventions. The hope of early diagnosis for these neurodevelopmental disorders may ultimately rely on an integration of comprehensive fMRI brain atlases with specific genetic testing. Discussion. This review focuses in the contributions made by studies employing functional MRI to the understanding of Mental Retardation (Joubert Syndrome, Williams Syndrome,Velocradiofacial Syndrome and Fragile X), Pervasive Developmental Disorder, Autism, and Dyslexia.

INTRODUCTION

The Potential Role of fMRI in Pediatrics

Due to advances in technology in the past decade, investigation of the exact neural mechanisms underlying developmental disorders has been made possible. Scientists and physicians have been able to investigate a variety of neuropsychiatric disorders (e.g. Attention Deficit Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD) and Anxiety Disorder), as well as demonstrate regional differences in brain metabolism. Research has also shown that disruption in the developmental pattern of various brain systems (brainstem, motor and sensory) can have extremely deleterious effects on the overall functioning of the individual-from the biochemical to anatomic and physiologic level [2]. Knowledge of the exact relationship between developmental changes in normal brains and subsequent alterations in neuronal function and connectivity, however, is yet in its infancy.

The phenotypic heterogeneity of neurodevelopmental disorders can be clearly demonstrated by differences in the timing of their clinical development. Whereas Down syndrome is apparent even before birth, Mental Retardation, Autism, and Rett syndrome may unfold over many months, and Asperger Syndrome, Fragile X syndrome, and dyslexia, may take many years to develop. In the field of molecular genetics, however, there is increasing evidence that despite the phenotypic heterogeneity of these disorders, there may be certain mechanistic commonalities at the respective levels of second messenger system, growth factor, dendrite and synapse [3-6]. Although neuroimaging techniques such as PET and SPECT may help to shed light on these neural mechanisms, there are methodological as well as ethical considerations in exposing children to unnecessary radiation [7]. Functional magnetic resonance imaging is a non-invasive alternative with improved spatial resolution as well as the added benefit of permitting longitudinal studies [8].

The relevance for the study of developmental disorders is clear in light of recent structural MRI findings that demonstrate the pruning and reorganization of cortical areas is a protracted process that lasts well into the second decade of life [9]. Given the extended maturation of the brain, it is not surprising that it is more susceptible to functional damage and resulting developmental dysfunction. While previous morphometric studies of various clinical groups have been essential in delineating abnormalities in specific brain structures; such as the finding that reduction in cerebellar size exists among children with ADHD [10], the next challenge for the developmental specialist is to detect dynamic changes as they begin to unfold.

The purpose of this review is to summarize the methods and results of functional magnetic resonance imaging (fMRI) in some of the common pediatric developmental disorders, namely the Autism Spectrum Disorder, Mental Retardation, Developmental Language Disorders and Dyslexia.

Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) refers to the use of magnetic resonance imaging technology (MRI) to detect regional changes in blood flow and blood

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*Address correspondence to this author at the NYU Child Study Center, 215 Lexington Ave., 14th Floor. Room#1421, New York, NY, 10016, USA; Tel: (212) 263-4726; E-mail: michael.seyffert@med.nyu.edu

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oxygenation levels that occur in response to neuronal activity. The basis of this blood oxygenation level-dependent (BOLD) technique relies on the fact that hemoglobin becomes strongly paramagnetic in its deoxygenated state and therefore acts as a natural contrast agent. The result is that highly oxygenated regions of the brain produce a larger MR signal than those regions that are less oxygenated. Though the exact mechanism by which this occurs is still under investigation, there can be little debate that since capillary activity predominates in regions of gray matter, this region dominates the signal [11].

These signal changes must then be detected using an MR sequence that is suitably sensitive. Echo-Planar Imaging (EPI) is the most widely used functional imaging technique that permits each image slice to be obtained on the order of 100 milliseconds. The additional advantage of EPI is that it provides a much better signal-to-noise ratio that effectively limits the degree of image artifacts such as “ghosting”. The result is a rapid and effective technique that enhances fMRI sensitivity while minimizing image distortions [12].

The Use of Pediatric fMRI

Preparation is a key element in the successful implementation of fMRI studies in children. Special care must be paid in terms of clear communication as to the investigator’s needs as well as ongoing flexibility with regards to subject handling. This is especially true of children with disabilities who may have emotional as well as cognitive limitations.

Once the procedural aspects of fMRI scanning have been mastered, there remains an important question as to which paradigm or task should be used in order to activate the desired region of the brain. Experimental design relies on a variety of techniques as well as the relative strengths and weaknesses of each technique in order to choose the technique that most effectively integrates experimental hypothesis, fMRI design, behavior and underlying anatomy. In assessing language function in children (for example), the choice of paradigm depends on the goal of the study. The choice of an object-naming paradigm in which the child silently names objects he sees during the scan may be sufficiently sensitive to use among children with developmental delays, however, if your goal is to have more specific information on which to base a surgical intervention, then other tasks such as a stem word completion or passive reading task or perhaps combining several tasks may be helpful [13,14].

Review of Pediatric fMRI Literature

Over the past 5 years, there has been a sustained growth of the pediatric functional MRI literature. A comprehensive review, focusing on functional MRI studies as they relate to Mental Retardation (Joubert, Williams Syndrome, Velocardiofacial Syndrome and Fragile X), Austism Spectrum Disorder (PDD, and Asperger Syndrome) and Dyslexia will be provided.

Studies of Mental Retardation

Clinically, mental retardation occurs in approximately 2%-3% of the population and is recognized as a delayed pattern of development in which severity of the delay correlates with the age at which parents become concerned for their child [15]. The two most common forms of genetically attributed mental retardation are Fragile X and Down syndrome. Cognitively based limitations in comprehension make task compliance during functional imaging a particular challenge in this latter group. Methodological and statistical problems related to power and effect sizes have limited the feasibility of more comprehensive fMRI studies. Historically, MRI anatomic studies have identified a wide range of abnormalities to include global reductions in brain volumes as well as regional differences in both white and gray matter distribution among this population. Though beyond the scope of this article, it is necessary to note that the use of other special functional modalities such as Proton Spectroscopy and Diffusion Tensor Imaging (DTI) are being implemented to uncover specific neurochemical and structural changes found in the brains of children suffering from a variety of developmental and neurodegenerative disorders including Rett syndrome, leukodystrophies and mitochondrial disorders (MD).

Functional MRI studies are now being implemented with interesting results. Joubert syndrome is a rare genetic disorder characterized by hypotonia, ataxia, developmental delay, with a distinct hindbrain malformation involving the cerebellum and brain stem. In pathological studies of brains taken from subjects with Joubert syndrome, there is an apparent absence of decussation of both corticospinal and superior cerebellar tracts, although the functional significance is unclear. A recent pilot fMRI study of an adolescent with Joubert Syndrome noted marked bilateral activation of the sensorimotor and cerebellar cortex during a finger-tapping task. This finding was in marked contrast to the more typical lateralized activation seen in the control subject [16]. Despite the fact that more studies are necessary, it would seem that even the brains of patients with this form of MR have the potential to reorganize themselves, despite significant genetic changes. This finding of an aberrant motor activation pattern seen in JS has important implications concerning the proper role of the cerebellum in normal motor and language development in children.

In the search of various neurodevelopmental or “cognitive phenotypes” using fMRI, a consistent methodological consideration is the selection of appropriate comparison subjects who also are impaired. Williams Syndrome (WS) is a neurodevelopmental disorder characterized by a hemideletion on chromosome 7q11.23. This imparts an unusual constellation of cognitive abilities and disabilities to the affected individual. WS children have unusual strengths in music performance and language despite having problems with visual processing and social communications as well as IQ’s in the 60’s. Of note, a recent structural MRI study of nine children with WS and 9 age matched comparison subjects uncovered an enlarged cerebellum among the WS group [17]. While it is uncertain what role this cerebral anomaly may have on cognitive functioning, it is clear that this fractionation of abilities makes them an important group to study. This may be especially true in comparison to children with DS who have very poor language abilities and comparable IQ’s (this makes them in a sense the cognitive counterpart to DS). The first fMRI study of a group of young adults with WS was published in 2003. This initial fMRI study focused on the neural basis of auditory processing of music and noise in WS patients and age-matched comparison subjects and found strikingly different patterns of neural organization between these groups. Brain regions supporting music and noise processing in normal subjects were not consistently activated in the WS participants (e.g., superior temporal and middle temporal gyri). Instead, WS participants showed significantly reduced activation in the temporal lobes yet significantly greater activation in the right amygdala. These initial findings suggest that during auditory processing, WS subjects possess an aberrant network of brain activations in cortical and subcortical structures [18]. Implications for dysfunction of related linguistic, emotional and social information processing areas have yet to be explored in the pediatric WS population.

A recent, second fMRI study of WS focused on disparities in visual processing. Briefly, the results of this study revealed isolated hypoactivation in the parietal portion of the dorsal (i.e. visual) stream. This study also incorporated the use of genetic markers and correlated these markers with specific patterns of brain activation. This approach provided evidence that the absence of one or more genes in WS leads to specific pathology in the dorsal visual streams [19]. This finding is of particular interest given recent fMRI evidence of visual processing difficulties among children with Velocardiofacial Syndrome (VCFS). DiGeorge/velo-cardiofacial syndrome is a 22q11.2 deletion syndrome that is associated with attentional problems and executive dysfunction. It is also prominent risk factor for schizophrenia. In this study, eight children with VCFS and eight comparison subjects underwent fMRI scanning and completed an arithmetic computation task. Results of this pilot study revealed increased cerebral activation in the left supramarginal gyrus (LSMG) as the task difficulty increased in the VCFS group. It was hypothesized that an association may exist between these aberrant LSMG activations and underlying structural deficits of the left parietal lobe. This might explain both visuospatial processing problems as well as decrements in arithmetic performance observed in VCFS [20]. These preliminary findings pose interesting but still unresolved questions concerning cortical plasticity and academic development in atypical children. This area will be further examined in the upcoming section on Dyslexia and Developmental Language Disorders.

Fragile X is the leading cause of inherited MR and has had the benefit of more than a decade of intense multi-disciplinary research. This syndrome, which preponderantly affects males, is unique in that a single gene defect (FMR1), affecting the long arm of the X chromosome (Xy27), is known to be responsible for the disorder. A long face, large ears, macro-orchidism, hyper extensible joints, mental retardation, and seizures characterize the phenotype. This presentation allows scientists to explore the inter-locking relationship between gene activity, clinical behavior and brain activations. Though initial studies focused on an understanding of the basic neurobiology and pathophysiology, more recent fMRI studies by Alan Reiss and his group at Stanford have garnered valuable insights into gene, brain and behavior interactions in this disorder-serving as a model for integrative neurodevelopmental research.

Several overlapping deficits may contribute to the unique behavior of children with fragile X syndrome. It has long been known that females with fragile X suffer from impairments in social relatedness and anxiety as well as deficits in such nonverbal skills as visuospatial working memory and arithmetic reasoning [21]. In order to explore the relationship among these behavioral measures, a series of fMRI studies compared female subjects with and without fragile X syndrome. In the first study, a working memory paradigm (storing, manipulating and updating objects in the mind) was implemented using both a one and two back visuospatial task. The N-back task is a timed task of verbal working memory. The purpose of this task was to probe potential deficits in executive function in this population. The subjects were presented with a string of random letters, one at a time, at the center of a computer display. The subjects were told to respond by pressing one of two buttons on a button box for each and every letter, dependent on whether the letter was a ‘target’ letter or a ‘non-target’ letter. The subjects were instructed to press a target button every time they saw a specific letter, whether it was in uppercase or lowercase (e.g. respond with the target button every time you see the letter ‘A’) and to press the non-target button to all other letters. In the one-back condition (low working memory load condition) the subjects were told to respond with the target button to any letter that was repeated one letter back (e.g. ‘a–a’), whether it was in upper or lower case and respond with the non-target button to all other letters. No feedback was given as to whether the choice was correct or incorrect. In the two-back conditions (moderate working memory load) the subjects were to respond with the target button to any letter repeated two letters back (e.g. a repeated letter separated by one letter, such as ‘A–X–a’, in the two-back condition). Faced with the increased cognitive load of the two-back task, subjects with fragile X syndrome demonstrated a similar activation profile in the prefrontal and parietal cortex during both one back and two back conditions. This finding supports the hypothesis of a deficit in overall executive function in this population [22].

A second fMRI study also tested the effects of cognitive loading on these two groups by varying degree of difficulty during a mathematical problem-solving task. Subjects with fragile X were shown to exhibit greater overall activations (when compared to comparison subjects), particularly in bilateral regions of the prefrontal and left angular gyrus [23]. This second study suggests that those with fragile X syndrome must supply greater effort during mathematical problem solving than is required of the normal comparison group.

A third study investigated another potential executive function deficit among females with fragile X syndrome using a Go-No-Go task. This task is a sensitive test of behavioral inhibition and has been demonstrated in previous fMRI studies to engage frontostriatal areas of the brain. Results of this study showed significant abnormal activation patterns involving deactivations in the ventromedial prefrontal cortex (PFC), supplementary motor area, anterior cingulate cortex, basal ganglia and hippocampus. This area of frontostriatal deficits was further correlated with specific (higher) levels of FMR1 gene expression [24]. This correlation of increased gene expression (suggesting a greater phenotypic severity of fragile X) with decreased brain activations (in a region thought to mediate executive function) is a model of gene-brain-behavior research in the area of mental retardation.

Finally, as fragile X syndrome shares several phenotypic characteristics with autism in terms of social and cognitive deficits one might posit associated problems in face processing areas of the brain. In the last fMRI study we reviewed, they used an event-related fMRI design that examined both direct and lateral gaze processing in 11 female fragile X subjects. Results did indeed show aberrant gaze processing correlated with decreased activations in both the fusiform gyrus (FG) and superior temporal sulcus (STS) [25]. Clearly, subjects with fragile X syndrome exhibit significant deficits in interrelated areas of visuospatial working memory, social cognition, executive function and emotional processing which are confirmed by fMRI.

Studies of Autism and Autistic Spectrum Disorders

Autism is a complex child neurodevelopmental disorder with a prevalence of 1:1000. Typically it has an onset before three years of age and is based on deficits in three functional areas: social cognition, language and repetitive motor behaviors. Autism is in fact part of a spectrum of related disorders known as the Autistic Spectrum Disorders. This spectrum of disorders includes both the so-called higher functioning children with Asperger's syndrome as well as those children who suffer from Rett Syndrome and Pervasive Developmental Disorders (PDD). Unlike fragile X syndrome, autism is thought to be a complex genetic based disorder. Previous structural studies have pointed to diffuse regions of abnormal brain development (to include regions of the cerebellum, temporal and frontal lobes) in addition to specific v increases in overall distribution of white matter during development [26]. These findings have had functional implications in terms of widespread deficits in expressive language, executive function, visual processing, social cognition and emotional processing [27].

Functional MRI is now emerging as a viable method to study the neuroanatomical basis of each affected domain in individuals with autism. Social deficits, language impairments and even repetitive behaviors are open to scrutiny beyond the limitations of standard neuropsychological testing. Since problems in the area of social cognition seem to be disproportionately affected, it has been hypothesized that these social impairments may be due to either an inability to understand the mental states of others (Theory of Mind) or alternatively an inability to make social judgments of "trustworthiness". Additional information has been gathered on aberrant visual processing that reveals significant differences in how individuals with autism scan faces-typically spending less time looking at those emotionally salient features such as the eyes. Baron-Cohen and colleagues [28] were among the first of 4 groups to use fMRI to measure brain activity during a social cognition task where individuals were asked to infer mental states of another person by looking at their eyes. These fMRI studies of adults were intriguing in that they found a consistent pattern of aberrant (predominantly left sided) brain activations involving anterior frontal and temporal regions of the brain to include: medial prefrontal cortex, inferior frontal gyrus as well as sub-cortical regions of the amygdala, periamygdaloid complex and both inferior temporal gyrus and superior temporal sulcus during intentional tasks. These findings stand in contrast to those studies in non-autistic adults that have found greater activations in right sided brain structures which include, right amygdala and right dorsomedial prefrontal cortex [29].

The implication is that dysfunction along a diffuse neural circuit involving both frontal regions (mediating expressive language and executive function) as well as sub-cortical areas responsible for emotional and face-processing regions could potentially contribute to the social deficits found in autism. Currently a number of centers are investigating abnormal face processing among children with autism and there are plans to use Happe's geometric Theory of Mind (TOM) paradigm to investigate related intentional states as well. One example of this paradigm utilizes geometric shapes to mimic such reciprocal human behaviors as, 'encouragement' by showing a larger triangle 'nudge' a smaller triangle out of a box . The use of such abstract forms has the benefit of being equally salient to both comparison subjects as well as children with autism who are known to process face stimuli in terms of component properties instead of perceptual, "wholes".

Though initial functional imaging studies of children with autism were initially obtained with PET and SPECT, these studies were more focused on language development and used auditory tasks comprised of simple verbal and non-verbal sounds. These studies found lower activations in the left posterior temporal regions with obvious repercussions for verbal working memory and language development [30]. Additional cognitive tasks are gradually being employed in the pediatric population. Just and colleagues [31] used a sentence comprehension task to test language comprehension in a group of 17 high functioning autistic children. Results of this study noted greater activation in Wernicke's receptive language area (left superior temporal region) in contrast to decreased activation in Broca's expressive language (left inferior frontal gyrus) area in the autistic group when compared to the comparison subjects. Despite several methodological limitations to this study (6 of the 17 children were on medication and handedness was not completely matched) the study does support previous fMRI work that identifies associated frontal and temporal brain regions underlying language development being impaired in high functioning autistic children [32]. Further fMRI language studies need to be done in this population looking at dissecting the role of specific areas of language organization (pragmatic versus semantic aspects of language).

Spatial attention, executive function and oculomotor processing deficits have also been reported among individuals with autism [33]. The putative neural areas involved are widespread and extend from the prefrontal cortex to the cerebellum. FMRI studies are now being used to successfully investigate whether one or several of these regions may be dysfunctional. An oculomotor paradigm has been used effectively in a group of 26 young adults and adolescents with autism and a matched comparison group [34]. The task required individuals to direct both guided saccades and anti-saccades either toward or away from targets. Results were surprising in that children with autism demonstrated normal accuracy in saccade dynamics. These findings argue against the commonly held notion that cerebellar dysfunction may predominate in autism. It remains for future fMRI studies in children to go beyond these initial steps and provide a pediatric developmental perspective as to the exact role these abnormal visual and ocular processing areas have in the overall behavioral picture of autism.

One may anticipate that fMRI will be used with increasing frequency to uncover exact areas of impaired functional anatomy associated with these cognitive deficits in autism. However, the etiology of the dysfunction in autism may have more to do with the degree of underlying connectivity between these brain regions. A recent functional MRI study of 8 male autistic subjects and matched controls, has found evidence of even more abnormal functional variability among autistic individuals than a normal comparison group. By comparing task-by-group interactions during a visually guided finger press task, less prefrontal cortex, parietal and temporal lobe activations were found in the autistic group than in the comparison group. In contrast, there seemed to be higher levels of activation in the ventral regions of the occipital lobe among the autistic subjects. The conclusion is that early and abnormal sensory activations during a task may in fact overload higher order processing as well as prevent the selection of relevant sensory stimuli [35].

There are some initial findings that suggest an overall wide variability of functional connectivity lies at the core of autism. This may reflect early developmental changes in neural growth or aberrant pruning along a cerebello-thalamo-cortical pathway [36]. Whether the cognitive deficits found in autism do in fact correlate to a specific pathway or a more general pattern of aberrant neural connectivity (under or over connectivity) remains to be determined. In the future studies should investigate subgroups of autistic children and adolescents longitudinally and attempt to integrate genetic, cognitive and empirical approaches.

Studies of Developmental Language Disorders and Dyslexia

DLD is one of several developmentally regulated disorders having to do with language comprehension and production but with normal IQ and no neurological impairment. As such this list does not include those children with chromosomal disorders, autism, PDD or congenital deafness. A list of these pediatric developmental language disorders would include Late Talkers (LT), children with Specific Language Impairment (SLI). For many reasons including that we still do not understand the developmental processes of eloquence, this area of research is still in its infancy. An fMRI study of 17 sedated children with speech delay and 35 age matched comparison subjects was undertaken to test the hypothesis that those children with speech delay would have a different pattern of brain activations than those children with normal language. All children lacked hearing impairments or other neurological disabilities. The task was a passive voice recognition task where the child listened to his or her mother's voice during the scan. Results found that children older than 3 years with speech delay tended to have activation in the right hemisphere more frequently than children older than 3 years with normal speech, who often have the usual finding of activation in the left hemisphere [37].

Dyslexia affects between 5% and 17% of the population and as a result it has historically received much attention in the functional imaging literature. This is in part due to the fact that the language system is the most studied large-scale network in the brain [38]. The first neuroimaging study of Dyslexia dates back to the late 1970's and indicated a left-sided brain asymmetry in children with this disorder. Dyslexia is traditionally defined as a discrepancy between reading achievement scores despite possessing a normal IQ [39]. In fact, dyslexics can with effort achieve reading and spelling skills that permit academic success [40]. Current theories on the biological basis of dyslexia point to problems with phonological processing of rapid acoustic data with resulting poor phonemic awareness. Though there is much support for this hypothesis in the scientific literature, there remains an ongoing debate as to whether the core deficit is in fact a more general information processing problem that involves both acoustic as well as visual information.

Despite the popular notion that Dyslexia lacks a cohesive neurodevelopmental profile due to a variability across other languages and cultures, functional neuroimaging results (PET) have been used to demonstrate consistent patterns of decreased left hemisphere activity during both reading and phonological tasks across three languages (English, French and Italian) [41]. Though dyslexia is understandably complex, there is gathering evidence that it has a strong genetic basis [42,43]. In addition to recent genetic evidence, additional structural imaging and pathology studies have demonstrated alterations in cortical neuronal organization in the temporal lobe that may impact this disorder. This temporal lobe area has been a rich but confusing source of information concerning the exact nature of the asymmetry. Many of these anatomic studies have found both right sided and left sided asymmetries among children with dyslexia [44]. The challenge may be to determine whether fMRI studies can be used effectively to dissect potential areas of aberrant functional neural connectivity in language and reading disorders and relate them to individual behavioral profiles.

Given the debate as to the type of information processing problem that underlies dyslexia, a recent pair of fMRI studies (one testing adults and the other children) has provided initial evidence of aberrant auditory processing as a main contributing factor of dyslexia [45,46]. In the first study, the group employed a pitch discrimination paradigm, 10 individuals with dyslexia and 10 matched controls were asked to press the button when they heard a high-pitched sound (250 HZF0) but not to press the button when they heard a low pitch (125 HZF0). Results to rapidly changing auditory stimuli indicate decreased left prefrontal and right cerebellar activations in the dyslexic group that were not found in the group of normal readers.

Since one of the goals of this functional MRI work is to document successful behavioral interventions while also providing a means of early diagnosis, the second study is indeed a major contribution to the field of dyslexia research in that it provides evidence of the role of behavioral remediation. This second fMRI study from the same combined team of east coast and west coast investigators has demonstrated that the use of a computer based phonological intervention (Fast-ForWord, Scientific Learning Corporation, Oakland, CA) can successfully normalize aberrant brain activations in children with dyslexia [46]. In this study, 12 children and matched comparison subjects were trained on a series of 7 phonologic discrimination exercises for 100 minutes a day, 5 days a week for approximately 30 days. Results showed increased activations in the left hemisphere to include regions of the temporo-parietal cortex and inferior frontal gyrus. A more detailed statistical analysis was then undertaken of the specific temporo-parietal area that was effectively remediated in the dyslexic group and those results indicated a positive correlation with improved oral language ability. Of note, these findings have subsequently been replicated by other imaging centers.

While these fMRI studies clearly demonstrate that there are specific patterns of brain activation found in dyslexics and not in comparison groups, we are still a long-way from separating out the essential regions governing spoken and written language disorders. To this end, a recent case series of two individuals with selective impairment to writing verbs following cerebral ischemia is instructive. In this study, two female adults were imaged during the acute phase of a stroke. Results of the diffusion weighted imaging revealed low blood flow in common areas of left posterior inferior frontal gyrus (PIFG) and pre-central gyrus (PrG) that were correlated with an inability to write verbs [47]. These findings suggest specific brain regions may sub serve the processing of distinct language components such as verbs and nouns.

SUMMARY

In this review, we have sought to provide an overview of the role of functional MRI in the broad field of pediatric neurodevelopment. While fMRI holds great promise for elucidating the neural basis of these disorders, it must be said that the field is still in its infancy and many of the studies are rather exploratory in nature. More longitudinal fMRI studies are needed with better controls (those that incorporate normal and other neurodevelopmental groups) as well as the implementation of reliable cognitive paradigms. The long-term goal of developing comprehensive neurodevelopmental (ND) profiles for these disorders will ultimately rest on an ability to synthesize genetic, behavioral and brain imaging information.

One immediate goal might be to develop a group of fMRI tasks that have proven utility in this neurodevelopmental group. Hirsch and colleagues have developed such a battery for their use in epilepsy surgery planning [48]. Perhaps in the future there will be a sufficient consensus among experts to warrant the creation of such tools.

It cannot be overemphasized that there are significant limitations in terms of the kind of information provided by fMRI. The relationship between physiological response and neuronal activity is relatively slow in BOLD fMRI and there are susceptibility artifacts that make signal interpretation problematic. In short, investigations of normal child brain development may still rely on longitudinal structural MRI studies to provide necessary spatial information concerning various developmental trajectories that will in turn inform future functional imaging studies [49]. In addition to the necessary synthesis of structural and functional imaging data, it may be necessary to combine differing functional modalities in order to improve temporal resolution. A potential solution to the lack of “real time” neurophysiological information might be the use of co-registration with other functional imaging modalities such as Magnetoencephalography (MEG) that have superior temporal resolution.

Concerning the integration of genetic information with brain imaging, as we have seen, for those unique disorders such as Fragile X, where there is one responsible gene, the ability to bridge the molecular and imaging data is a feasible goal that yields a great deal of information on the relationship between brain and behavior. For other more complicated genetic disorders such as autism or dyslexia, where there exist candidate genes (though the exact genetic dysfunction remains unknown), the goal of synthesis remains an elusive one. While the use of transgenic and knock-out animals has revolutionized the field of molecular behavioral genetics by allowing the investigation of phenotype-genotype correlations, its application for human neurodevelopmental disorders is, however, limited.

The recent development of genetic micro arrays may provide further benefits, by permitting the simultaneous investigation of thousands of candidate genes. This technology has the dual benefit of being rapid and affordable. Recent results from genetic studies that focus on children and adults with neuropsychiatric disorders such as ADHD and Schizophrenia are promising and point to its growing potential to expand our knowledge of the biological substrates of behavior [50, 51].

The combination of powerful technologies (such as fMRI and genetic micro arrays) may eventually lead to the creation of large behavioral databases consisting of both longitudinal brain atlases and their associated genetic profiles. Alliances such as this would permit researchers the freedom to investigate subtle changes in the expression of individual genes in the brains of either similar neurodevelopmental phenotypes such as Rett Syndrome and Autism, or those contrasting ND phenotypes such as William’s Syndrome and Down Syndrome, with the hope of directing appropriate ameliorative therapies and the promise of expanding our knowledge of the neural basis of human development.

In the mean time, fMRI studies continue to explore these and other neurodevelopmental disorders. As numerous clinical and basic science research studies have demonstrated a remarkable degree of neuroplasticity in the pediatric brain, it remains to be seen what additional cognitive or behavioral interventions may ultimately be incorporated into the clinical arsenal of the pediatric developmental specialist over the next several years.

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