MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
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The Contribution of Novel Brain Imaging Techniques to Understanding the Neurobiology of Mental Retardation and Developmental Disabilities

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Studying the biological mechanisms underlying mental retardation and developmental disabilities (MR/DD) is a very complex task. This is due to the wide heterogeneity of etiologies and pathways that lead to MR/DD. Breakthroughs in genetics and molecular biology and the development of sophisticated brain imaging techniques during the last decades have facilitated the emergence of a field called Behavioral Neurogenetics. Behavioral Neurogenetics focuses on studying genetic diseases with known etiologies that are manifested by unique cognitive and behavioral phenotypes. In this review, we describe the principles of magnetic resonance imaging (MRI) techniques, including structural MRI, functional MRI, and diffusion tensor imaging (DTI), and how they are implemented in the study of Williams (WS), velocardiofacial (VCFS), and fragile X (FXS) syndromes. From WS we learn that dorsal stream abnormalities can be associated with visuospatial deficits; VCFS is a model for exploring the molecular and brain pathways that lead to psychiatric disorders for which subjects with MR/DD are at increased risk; and finally, findings from multimodal imaging techniques show that aberrant frontal–striatal connections are implicated in the executive function and attentional deficits of subjects with FXS. By deciphering the molecular pathways and brain structure and function associated with cognitive deficits, we will gain a better understanding of the pathophysiology of MR/DD, which will eventually make possible more specific treatments for this population.
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Mental retardation (MR) is defined solely by the presence of clinically significant impairment of cognitive and adaptive functions with onset before age 18 years. As with all phenomenologically defined psychiatric disorders, the patients who receive this diagnosis are heterogeneous in terms of etiology and pathophysiology. The majority of MR cases are idiopathic or multifactorial, while about 25% of cases are caused by a known genetic defect including chromosomal anomalies, genetic syndromes, and metabolic disorders [Curry et al., 1997]. A search in Online Mendelian Inheritance in Man (OMIM) reveals that mental retardation is a clinical manifestation in 1,228 genetic syndromes.

Brain abnormalities in subjects with MR are very common. Postmortem studies have found brain abnormalities in 34–98% of deceased, severely retarded patients [Curry et al., 1997]. Computerized tomography and structural magnetic resonance imaging (MRI) studies have reported abnormalities affecting a wide range of brain structures in 9–60% of subjects with MR [Curry et al., 1997]. Given that so many different genetic disorders can result in MR and that brain development is the result of myriad genes and complex environmental interactions, it is not surprising that many different brain abnormalities have been found in subjects diagnosed with MR.

To the best of our knowledge, there are no reports of studies that have used volumetric MRI, functional magnetic resonance imaging (fMRI), or diffusion tensor imaging (DTI) to study the pathophysiology of idiopathic cases of MR. Indeed, the heterogeneity of MR cases suggests that, unless performed in huge samples, such studies would not yield consistent results and therefore might not increase our understanding of the brain morphology and function of individuals with MR. In light of the difficulties created by this heterogeneity in the MR population, an alternative approach has emerged during the last decade that focuses on studying genetically defined neuropsychiatric disorders associated with mental retardation and devel-

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opmental disability (MR/DD). This approach is based on two underlying assumptions: first, that the complex pathways which affect brain development are strongly influenced by genetic factors and will be more accessible when studied within genetically homogeneous groups, and second, that the information derived from studying these prototypic conditions will be relevant to understanding brain–behavior associations in individuals from the general population who have similar patterns of cognitive, behavioral, and developmental dysfunction. Studying genetic syndromes at multiple scientific levels has proven to be a powerful tool for elucidating the neurodevelopmental pathways underlying MR/DD, and the term "Behavioral Neurogenetics" has been coined to describe this approach [Reiss and Dant, 2003].

We will now describe the major MRI techniques utilized in the study of mental retardation. We will then review what these techniques have enabled us to learn about normal brain development and its relationship with intelligence quotient (IQ). Next, we will review research of several specific neurogenetic syndromes. Such research has provided insights about risk factors for cognitive and neuropsychiatric deficits associated with MR by combining brain imaging data with information obtained through assessment of genetic, cognitive, behavioral, and environmental factors. Finally, we will discuss what these neurogenetic models can teach us about the mechanisms underlying MR/DD.

MRI TECHNIQUES

Magnetic resonance imaging methods have found widespread use in diagnosis of disease and in basic research of the brain because 1) a broad range of biochemical and biophysical mechanisms can be exploited to develop soft tissue contrast, 2) both morphological and functional information can be probed, and 3) no ionizing radiation is used. The latter makes MRI particularly applicable to the study of MR/DD. Here we examine structural and functional MRI and DTI.

Structural MRI

MRI exploits the principle of nuclear magnetic resonance (NMR) in combination with magnetic field gradients for spatial localization. When hydrogen nuclei are placed in a magnetic field, a small fraction of the nuclei are magnetized preferentially along the direction of the magnetic field and may be viewed classically as behaving like small bar magnets. These "spins" precess about the magnetic field at a rotational rate (the Larmor frequency) that is typically in the radio frequency (RF) range. This precession is analogous to that of a spinning top slowly rotating about the earth's gravitational field. A magnetic field rotating at the Larmor frequency excites the spins to a higher energy nonequilibrium state. Relaxation back to equilibrium is accompanied by emission of energy that forms the basis for the NMR signal (an "echo"). MRI localizes the spatial origin of the signals using pulsed magnetic field gradients. These gradients cause the frequency of the spins to be uniquely tied to their location within the magnet. Thus, by analyzing the frequency content of the echoes, the MR image is formed [Lauterbur, 1973; Mansfield, 1977].

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A unique advantage MRI has over other biomedical imaging modalities is the large number of physical mechanisms that can be exploited to generate image contrast (see for example [Haacke et al., 1999]. The rate at which the magnetization returns to equilibrium is described with a time constant T1, and differences in this relaxation rate between different tissues such as gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) can be used to develop "T1-weighted" contrast. Similarly, the rate at which the echo signal decays to zero has a time constant T2, also characteristic of tissue type, and "T2-weighted" contrast can also be developed for tissue differentiation. Such images comprise the most commonly used forms of MRI contrast and are the basis for studies of neuroanatomic development.

Typically, a high-resolution MRI study of brain anatomy includes the acquisition of a whole brain (3D) volume of 128 or more T1-weighted "slices," with 256×256 picture elements (pixels) in each slice, thus comprising some 8.4 million voxels. The acquisition time is of the order of 10 min for such a study, and the scan provides a spatial resolution of the order of $800\ \mu \times 800\ \mu \times 1.2$ mm. However, a substantial amount of post-acquisition processing is necessary in order to develop inferences about structural differences between subject populations, as shown in Fig. 1.

The first step in postprocessing often includes mapping the volume into a data structure having isotropic resolution, using Fourier interpolation to preserve fidelity. Second, it is necessary to perform segmentation of the gray scale volume into GM, WM, and CSF (and sometimes others, such as tumor) tissue types, and a variety of algorithms have been developed for this purpose [Pham et al., 2000]. The example in Fig. 1 uses a fuzzy constraint to allow the depiction of classifier probabilities, as opposed to binary models in which a voxel must contain only one of the allowed tissue types. Techniques can use point-, edge-, or region-based classification. Many methods use a single-contrast data set, e.g., T1-weighted, while others depend on more than one contrast, such as both T1- and T2-weighted image volumes (multispectral approaches). One of the problems in MRI is bias field errors such as shading that arise because of the shape and dielectric properties of the head itself as well as regional variations in sensitivity of the RF coil used to excite and receive the NMR signal. Multispectral classifiers tend to be more robust against bias field errors because multiplicative errors in signal intensity are common to each channel and can be modeled out. A third step that can be undertaken in image processing is to map the image volume into a common brain atlas such as the Talairach [Talairach and Tournoux, 1988] coordinates. Finally, volumes of brain regions can be extracted and compared with normalized population means.

Functional MRI

While MRI techniques yield fine resolution from which we can obtain tissue volume measurements, they fail to offer clues of the dynamic activity states of the brain. The most common form of fMRI relies on the basics of MRI described above, while also measuring regional hemodynamic responses over time

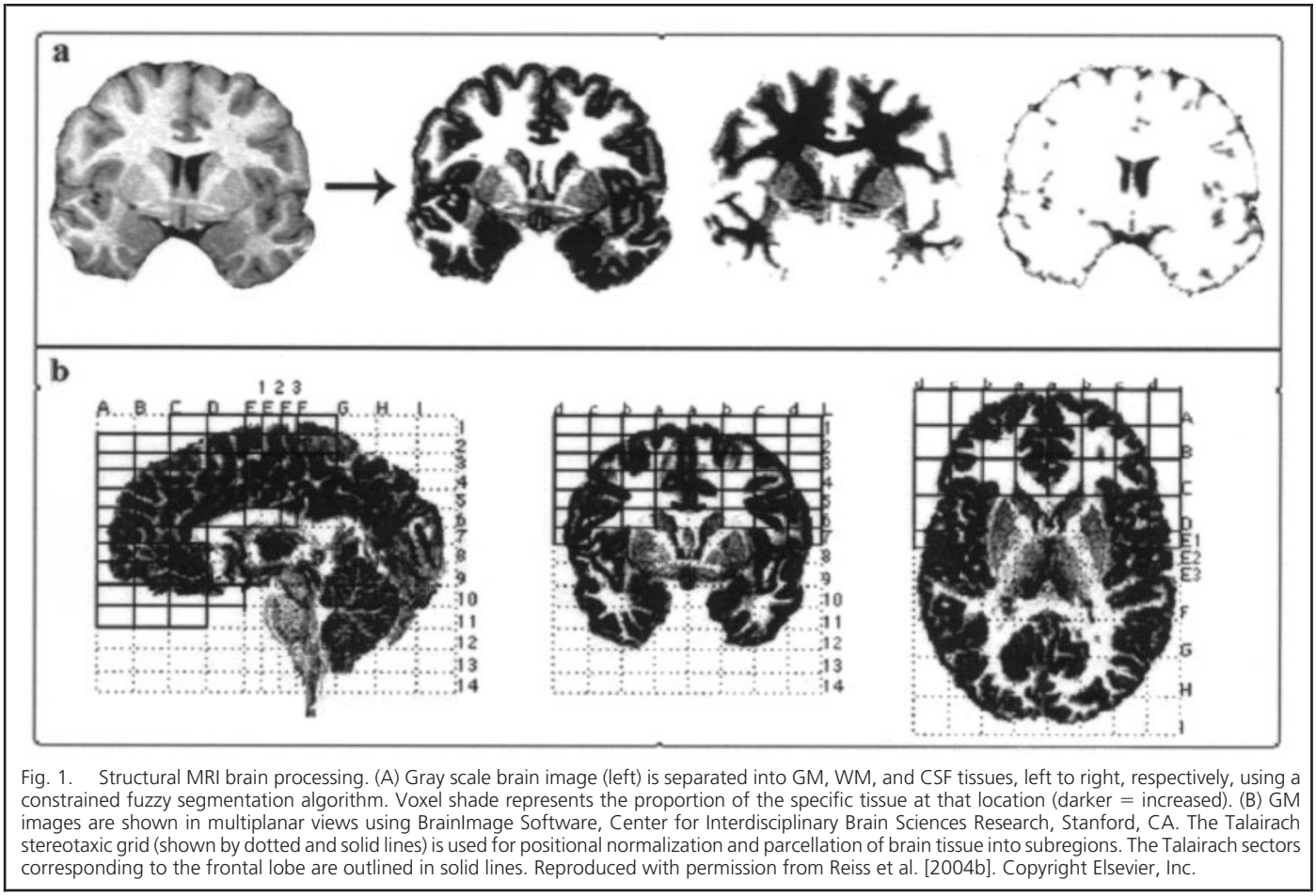

Fig. 1. Structural MRI brain processing. (A) Gray scale brain image (left) is separated into GM, WM, and CSF tissues, left to right, respectively, using a constrained fuzzy segmentation algorithm. Voxel shade represents the proportion of the specific tissue at that location (darker = increased). (B) GM images are shown in multiplanar views using BrainImage Software, Center for Interdisciplinary Brain Sciences Research, Stanford, CA. The Talairach stereotaxic grid (shown by dotted and solid lines) is used for positional normalization and parcellation of brain tissue into subregions. The Talairach sectors corresponding to the frontal lobe are outlined in solid lines. Reproduced with permission from Reiss et al. [2004b]. Copyright Elsevier, Inc.

in relation to stimuli presentation, task activation, or rest. Increased neuronal metabolism results in increased cerebral metabolic rate of oxygen ($CMRO_2$) and much greater increases in cerebral blood flow (CBF) to the region; this uncoupling of oxygen consumption and supply during activation causes a surfeit of fully oxygenated red blood cells, which has a different magnetic state (diamagnetic) than in the nonactivated state where the blood is more deoxygenated (paramagnetic). Thus the hemoglobin acts as an endogenous contrast agent with an effect on the signal that depends on the local oxygen level, which in turn depends on local metabolism [Ogawa et al., 1990; Bandettini et al., 1992; Kwong et al., 1992]. The blood oxygen level dependent (BOLD) contrast that results is thereby an indirect marker for neuronal activation, with temporal characteristics that are mediated by the hemodynamics.

The BOLD contrast is typically no larger than several percent in sensory tasks and is much smaller with tasks that probe higher cognitive processing operations. Because of this, it is not possible to make absolute measures of tissue perfusion with BOLD techniques, and only relative measures may be obtained. Therefore, activation experiments use designs in which there are multiple blocks or events that contrast both experimental and control conditions during a scan that lasts up to 20 min, and activation maps depict the signal difference between the two averaged neuronal states. However, because these signal differences are small, statistical processing methods are employed to develop estimates of activation. Such methods typically postulate a linear model for the expected signal time series in a voxel based on the task design and on knowledge of the hemodynamics and use least-squares methods to calculate the probability that the measured signal fits the model, i.e., the voxel is activated. Fig. 2 shows activation maps generated in this way. The color scale depicts values of the probability of activation expressed as a *t*-score.

Diffusion Tensor Imaging

Imaging brain activity across time using fMRI can tell us which brain regions are involved in specific tasks, but another imaging technique, DTI, offers information on the brain circuitry that may comprise the communication pathways between these brain regions. DTI is another example of the flexibility of magnetic resonance imaging to develop contrast, in this case not by the relaxation characteristics of spins but by the degree to which water molecules are free to diffuse through the intra- and extracellular tissue space in the brain. If a magnetic field gradient is turned on just after the spins are excited by the RF pulse, spins that diffuse along the direction of the gradient will find themselves in regions of increased or decreased magnetic field according to their thermally driven random walk pattern. The changing magnetic environment will cause the coherence between spins in the same voxel but with a different travel history to be lost as time goes on, and the signal therefore decays by an amount that depends on the apparent diffusion coefficient (ADC), which measures how readily a molecule diffuses, and details of the gradient pulse amplitude and timing [Carr and Purcell, 1954]. Spins that diffuse slowly or not at all will show no signal loss of this type; the resulting difference in signal is called diffusion weighting. Diffusion weighted images can be developed separately for all three major directions of the axes by ap-

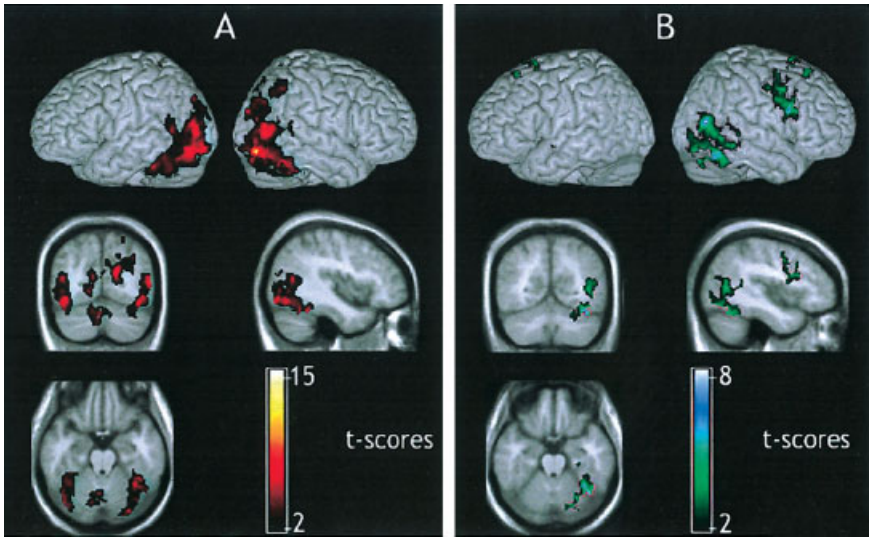

Fig. 2. Brain region activations, as demonstrated by fMRI, in response to face/gaze stimuli. In typically developing controls, activation (blood flow) occurred predominantly in posterior brain regions (A) while in subjects with WS, activation occurred predominantly in anterior brain regions (B). Reproduced with permission from Mobbs et al. [2004]. Copyright Lippincottt Willliams & Wilkins, Inc. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

plying diffusion encoding gradients in the three major directions. Thus, images with heavy diffusion weighting (i.e., little signal) will show regions where spins diffuse readily in the given direction. In fact, diffusion is a tensor quantity, having interaxis terms for a total of six quantities needed for full description. By applying gradients in at least six and preferably more directions, DTI can be developed that completely describe the ability of water to diffuse in the brain. One consequence is the ability to make fiber track maps that show the directions along which water flows freely, i.e., that putatively depict bundles of fibers. Another particularly useful quantity is a map of fractional anistotropy (FA), in which bright voxels show regions having diffusion that is preferentially restricted in one or more directions [Moseley et al., 1990].

The value of DTI in the present context is that the white matter tracts of neurons in the brain constitute bundles of myelin sheaths that severely restrict the flow of water transverse to the axis of the bundles but allow relatively unimpeded diffusion of water along them. Thus, the FA values in regions with intact white matter bundles should be high because of the normally restricted diffusion pattern, whereas FA values are lower in regions where the bundles are disordered due to congenital or other defects that cause the restriction to be removed or reduced. Maps of FA can thereby be compared between different population groups to examine whether white matter abnormalities are present. An example is shown in Fig. 3. Often such DTI studies are combined with fMRI studies to correlate WM connectivity with interregion activation [Klingberg et al., 2000].

BRAIN DEVELOPMENT IN HEALTHY SUBJECTS

Brain development is a function of several different processes, including myelination, synaptic pruning, and gray matter loss. Brain development does not proceed in a linear manner; rather, its pace varies during different developmental phases of life. For example, the human brain grows rapidly during early childhood, then slows between the ages of 5 and 10. At the age of 50, a gradual decline in brain volume begins. This decline becomes more rapid as people enter their 80s [Reiss et al., 1996; Battaglia, 2003; Sowell et al., 2004].

Beginning at early stages of fetal development, there is a rapid wiring of the neuronal system, during which time

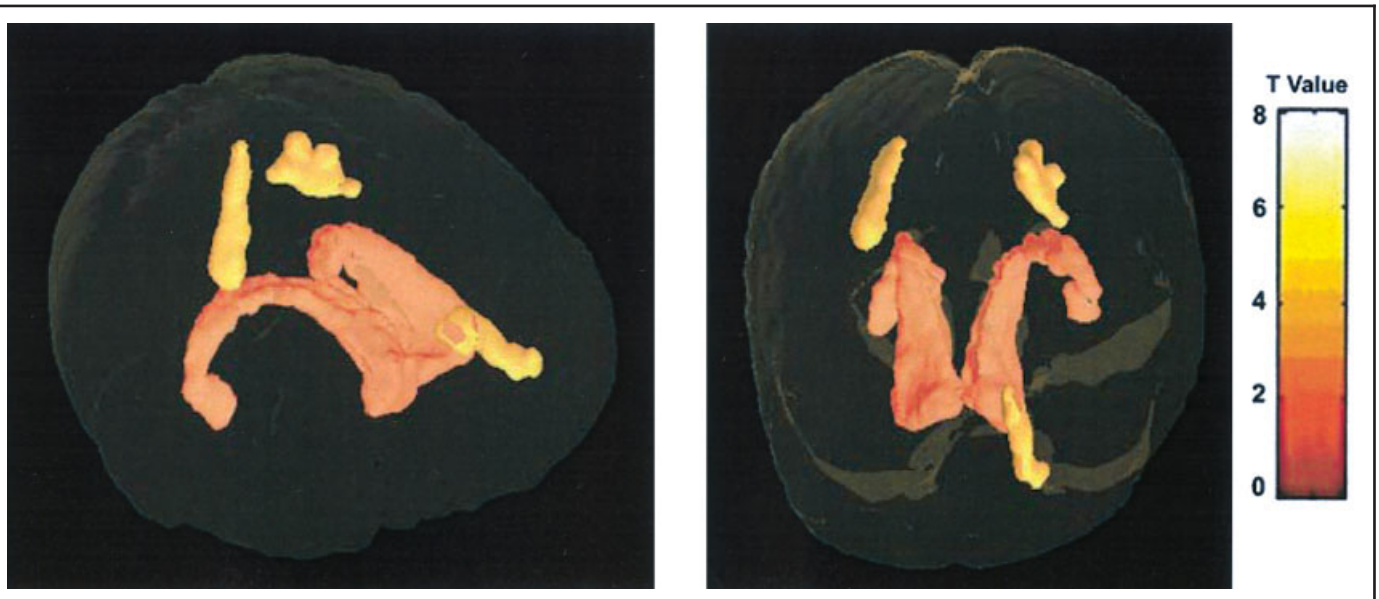

Fig. 3. Diffusion tensor imaging (DTI) findings in subjects with fragile X. A three-dimensional representation of the aberrant white matter tracts (shown in yellow) in relation to the caudate nuclei (shown in red). Reproduced with permission from Barnea-Goraly et al. [2003a]. Copyright Wiley-Liss, Inc. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

GM and WM volumes increase significantly. This networking process occurs in response to sensory stimulation, experience, and learning, as well as genetic preprogramming. During development, neurons that are functional strengthen their connections with other neurons, while nonfunctional neurons and nonfunctional synaptic contacts are eliminated in a process called "synaptic pruning." Synaptic pruning begins during early childhood and stabilizes during early adulthood. Brains contain the highest number of synapses (about 15,000 per neuron) between the ages of 2 and 3 years. As a consequence of this pruning, about half of the synaptic connections present at age 3 are lost. Postmortem and brain imaging studies show that, during the time period of synaptic pruning, there is a gradual decrease of GM density, but, due to concurrent formation of new myelin, a gradual increase in WM volume.

There seem to be regional differences in the timing of brain development. Also, some areas increase in size while others decrease. In general, however, brain development progresses from posterior to anterior and from inferior to superior. Thus, the brain stem and cerebellum myelinate prior to the cerebral hemispheres, and gray density reduction begins earlier in the parietal cortex than in the frontal cortex [Sowell et al., 2004]. Subcortical GM (the basal ganglia) volumes also decrease with age, but not as much as cortical areas do. [Reiss et al., 1996; Sowell et al., 2004]. On the other hand, temporal lobe structures, namely the amygdala and hippocampus, appear to increase in volume with age. Asymmetric development of the cerebral hemispheres, as manifested by a rightward preponderance of cortical and subcortical GM volumes and a leftward preponderance of ventricle volumes, has also been observed [Reiss et al., 1996; Battaglia, 2003; Sowell et al., 2004].

There also seem to be gender differences in brain development. On average, the male brain is 10% larger than the female brain and this applies to most brain structures as well. However, some structures, such as the hippocampus and the caudate nucleus, are disproportionately large in female brains, whereas others, such as the amygdala, are disproportionately small [Durston et al., 2001].

BRAIN VOLUMES AND IQ CORRELATIONS

There are consistent findings from several investigations of cognitively normal children and adolescents showing that there is a negative correlation between GM volume and IQ. This correlation is stronger in older than younger children. On average, IQ explains 9–15% of the variance in GM volume [Reiss et al., 1996; Wilke et al., 2003].

In general, the association between GM volumes and IQ seems global. However, there are also region-specific associations. For example, GM volumes of the prefrontal and cingulate cortices have been shown to correlate most strongly with IQ [Reiss et al., 1996; Wilke et al., 2003]. There also seems to be a mild but significant correlation between subcortical and cerebellar GM volume and IQ [Reiss et al., 1996]. On the other hand, negative correlations have been reported between IQ and parietal volume [Wilke et al., 2003]. There are no reports about the association between IQ and brain GM volumes in subjects with idiopathic mental retardation, but studies of MR disorders such as fragile X and neurofibromatosis-1 have shown that the increased brain volume in these disorders is associated with suboptimal cognitive functioning. Similarly, in certain cognitive-processing models [Kosslyn, 1994], larger processing networks are advantageous in some cases, but, in other cases, smaller ones reflect more efficient neural packing. Thus, it seems there is an optimal range for brain volume and larger or smaller brain volumes are both associated with cognitive deficits. The strong association between GM volumes and IQ is probably mediated by genetic factors, as GM volumes seem to be highly hereditary [Reiss et al., 1996; Pennington et al., 2000; Wilke et al., 2003].

WILLIAMS SYNDROME

Williams syndrome (WS) is a somewhat rare genetic syndrome that occurs in about 1 in 8,000 live births. It is caused by a microdeletion of 1.6 Mb on the long arm of chromosome 7, a region that includes about 21 genes. One of the deleted genes encodes for elastin, and this deficiency is responsible for the supravalvular aortic stenosis common to subjects with WS. Other common physical manifestations of WS are neonatal hypercalcemia and typical dysmorphic features ("elfin face"). All subjects with WS are cognitively impaired. The mean IQ score for this group is around 60 [Bellugi et al., 1999].

Williams syndrome serves as a unique model for learning about the development of cognition and its neuronal pathways, because WS subjects are characterized by intriguing "peaks " and "valleys " in specific cognitive abilities. In comparison to matched-IQ controls, subjects with WS are significantly more impaired in their visuospatial abilities, mathematics, and time perception but are significantly stronger in their complex expressive language and face-processing abilities [Bellugi et al., 1999; Paterson et al., 1999]. These relative differences in cognitive abilities indicate that human cognitive development, at least in WS, is modular. These modules seem to have somewhat independent trajectories that can be selectively spared or impaired and also have different developmental time courses. For example, verbal development is delayed in WS but sharply improves with age, while numerical judgments show the opposite trend [Paterson et al., 1999]. The peaks and valleys in WS cognitive architecture should be viewed as relative strengths and difficulties rather than absolute ones. This is because several studies have found that the areas of strength in WS such as grammar and face-processing skills are not better in subjects with WS than their mental age would predict [Karmiloff-Smith et al., 2003; Levy and Hermon, 2003].

Studies of WS demonstrate that combining various brain imaging modalities with cognitive measures can lead to breakthroughs in our understanding of the brain deficits that underlie specific cognitive modalities. The most comprehensive imaging research thus far has been conducted on the visuospatial deficits found in WS. Visual input flows from the retina through the thalamus to the primary visual center in the occipital lobe. In WS, the occipital cortex and thalamus are both reduced beyond the overall cerebral volume decrease that is found in these subjects [Reiss et al., 2004a].

After arriving in the primary visual cortex of the occipital lobe, the cortical visual pathway divides into two streams. The ventral stream terminates at the inferotemporal cortex and is responsible for perception of color, pattern, and form (the "what " information), while the dorsal stream terminates in the posterior parietal cortex and is responsible for perception of space and motion (the "where " stream). The ventral ("what") stream is involved in facial expression processing, which is a relative strength in subjects with WS, while the dorsal ("where") stream is involved in visuospatial abilities, which are a relative weakness in WS. It was thus hypothesized that impairment of the dorsal stream would be found in WS. By combining structural and functional MRI, it has been shown that, indeed, the dorsal stream of the visual cor-

tex is dysfunctional in WS, as manifested by decreases in parietooccipital/intraparietal sulcus GM volume and by hypoactivation of the parietal portion of the dorsal stream during a visuospatial construction task. Conversely, brain volumes and function in the anterior visual stream has been found to be intact [Meyer-Lindenberg et al., 2004] (see Fig. 2).

To compensate for their compromised dorsal visual pathway, subjects with WS seem to overactivate limbic and frontal pathways. For example, the fusiform gyri, amygdala, anterior cingulate, and middle frontal gyri are disproportionately large in WS and are also hyperactivated in response to face-processing tasks [Mobbs et al., 2004; Reiss et al., 2004a]. Increased activation of the amygdala has also been found during music processing in individuals with WS compared with controls [Levitin et al., 2003]. It thus seems that, secondary to the WS brain deficits, pathways in the limbic system and frontal cortex are overactivated and may underlie the relative cognitive strengths found in WS. These same overactivated pathways of the limbic system also may underlie the appetitive social drive, enhanced emotional reactivity, and musicality that contribute to the unique behavioral phenotype of subjects with WS.

Though less extreme than in WS, we do observe gaps in the cognitive and adaptive abilities of many subjects with MR. We also notice that some subjects with MR have greater social and emotional talents than academic capabilities (for example, subjects with Down syndrome), while the opposite is true of other individuals with MR (for example, subjects with autism). In this regard, it is interesting to note that cerebellar vermis size distinguishes subjects with WS from subjects with marked social deficits. Using volumetric MRI, Schmitt et al. [2001] found that the posterior cerebellar vermis was relatively enlarged in subjects with WS. Conversely, in syndromes marked by social deficits, including autistic disorder, fragile X syndrome (FXS), and velocardiofacial syndrome (VCFS), cerebellar vermis volumes are decreased. Thus, we may find that, in subjects with MR, the cerebellar vermis is a marker for social function in a manner that requires further elaboration. One possibility is that the cerebellar vermis's role in joint attention underlies its impact on social function; while joint attention, vermis volumes, and social abilities are all relatively preserved in WS, subjects with autistic traits have poor joint attention, and researchers believe this may be induced by having hypofunctional cerebellar vermises [Lincoln et al., 2002].

As we come to better understand the biological substrates of strengths and weakness in WS, we may be able to develop new, more effective treatments, and some of these may be helpful to MR/DD individuals with similar weaknesses. Overall, the findings from WS studies suggest that cognitive and behavioral peaks and valleys in subjects with MR may be the result of separate developmental trajectories, genetically determined, that have specific interrelated neuroanatomical pathways with reciprocal interactions.

VELOCARDIOFACIAL/DIGEORGE SYNDROME

Another chromosomal microdeletion that results in mental disability is VCFS. In this disorder, the microdeletion occurs on the long arm of chromosome 22. VCFS is the most common microdeletion syndrome, occurring in at least 1:4,000 births. The syndrome has been the focus of intensive research during the last decade because of its strong association with cognitive deficits and neuropsychiatric morbidity. There are more than 180 possible physical symptoms associated with this condition. Among them, the most common are cleft palate anomalies leading to hypernasal speech, congenital cardiac anomalies, typical dysmorphic face, hypocalcemia and T cell deficiency, leading to recurrent infections during infancy [Gothelf and Lombroso, 2001].

While the physical manifestations of the syndrome can be very mild or even absent, almost all patients with VCFS suffer from cognitive deficits and psychiatric disorders. The average IQ in VCFS is in the borderline range (i.e., 65–75) and from 25 to 40% of the subjects have mild to moderate mental retardation. The variety of behavioral and psychiatric problems often exhibited in VCFS are also common in children with MR/DD. These include attention deficit hyperactivity disorder, predominantly inattentive type, oppositional–defiant disorder, affective disorders, anxiety disorders including obsessive–compulsive, and perseverative behaviors. The most striking psychiatric symptoms in VCFS are psychotic symptoms, which appear by early adulthood in about one-third of subjects. In most cases, these psychotic symptoms evolve into schizophrenia-like illness [Gothelf and Lombroso, 2001].

Schizophrenia and MR/DD share much in common. Kraeplin was the first to notice that subjects with MR are prone to develop schizophrenia, and he coined the term "Propfschizophrenia" to describe this phenomenon [Mack et al., 2002]. In addition, subjects with schizophrenia often demonstrate developmental delays and low cognitive ability years before the onset of their schizophrenic symptoms [Zammit et al., 2004]. Thus, it is probable that schizophrenia and MR/DD share some common etiological and pathophysiological mechanisms. Brain imaging of subjects with VCFS may reveal which abnormalities in brain structure and function mediate these cognitive deficits and psychotic predispositions.

Studies have found that, in comparison to normal controls, cortical GM volumes are significantly reduced and ventricular volumes are significantly increased in VCFS subjects both with and without schizophrenia. [Eliez et al., 2000; Kates et al., 2001; van Amelsvoort et al., 2001; Chow et al., 2002]. These results are similar to the brain imaging findings in studies of schizophrenia patients from the general population.

In childhood-onset schizophrenia, it has been shown that the dynamic of GM loss is such that, early in the disease, it is most striking in the parietal lobe and that it spreads to the frontal and temporal cortices only later in the disease [Thompson et al., 2001]. This "back to front cortical wave" resembles normal adolescent brain development but occurs at an exaggerated rate. Similarly, in VCFS children and adolescents, a more robust reduction of parietal compared with frontal lobe GM has been found [Eliez et al., 2000; Kates et al., 2001]. However, in adults with VCFS, both those with and without schizophrenia, cortical GM reduction seems to be evenly distributed [van Amelsvoort et al., 2001; Chow et al., 2002].

Another finding common to VCFS and schizophrenia is that subcortical and posterior fossa structures that are known to be reduced in size in schizophrenia, including the hippocampus, the head of caudate nucleus, the cerebellar vermis, the pons, and the thalamus, are also found to be reduced in size in children with VCFS who have not yet developed symptoms of schizophrenia [Eliez et al., 2001, 2001]. The only DTI study to date in children with VCFS has found decreased fractional anisotropy values (signifying potential WM alterations) in the superior and inferior fasciculi that connect the frontal and temporal lobes. This suggests disrupted frontotemporal connectivity and is similar to that

reported in schizophrenia [Barnea-Goraly et al., 2003b].

In addition to having common neuroanatomical abnormalities, VCFS and schizophrenia seem to share similar neuropsychological and neurophysiological deficits. For example, children with VCFS exhibit executive dysfunctions including impaired working memory, deficit in the ability to monitor and adapt to stimulus conflict, and impaired executive visual attention [Bish et al., 2005; Sobin et al., 2005]. Deficits in executive functioning are related to abnormal prefrontal–subcortical circuity. Another measure of the function of this circuity is prepulse inhibition. Deficient prepulse inhibition is a well-established marker of schizophrenia. Interestingly, a recent study found the percentage of prepulse inhibition was significantly lower in VCFS children than in their siblings and the percentage of prepulse inhibition was inversely correlated with their executive attention [Sobin et al., 2005]. These finding suggest that children with VCFS have abnormal prefrontal–basal ganglia circuitry.

Taken together, brain imaging findings in VCFS suggest the abnormalities in brain structure and connectivity found in schizophrenia are the result of developmental processes that begin early in life, long before psychosis evolves, and these abnormalities change dynamically with age. These processes seem to be genetically influenced and regulated. It is not yet known which of the genes from the 22q11 deleted region are predisposing to schizophrenia and to cognitive deficits. However, since the physical symptoms in VCFS are due to defective development and migration of the neural crest cells, the gene(s) predisposing to schizophrenia are probably ones that facilitate brain development. An example of such a candidate gene from the 22q11 region is the Goosecoid-like (GSCL) gene, which is expressed in the pons and dorsal thalamus during early embryogenesis. GSCL has a homeobox gene structure and probably acts as a regulator of gene transcription. Other candidate genes are related to brain function, such as catechol-*o*-methyltransferase (COMT), which encodes an enzyme that degrades brain catecholamines.

Future research will reveal the gene or genes leading to increased risk for neuropsychiatric deficits in VCFS. Consequently, we will be better able to understand the neuropsychiatric deficits and the abnormal development and function of the brain that are secondary to the reduced dosage of specific genes. It is also very likely that some of the gene deficiencies causing VCFS are also implicated (in combination with other genes and environmental factors) in the pathophysiology of MR/DD and its neuropsychiatric morbidity in cases that are today considered "idiopathic."

FRAGILE X SYNDROME

Fragile X syndrome is yet another genetic disorder that results in mental disability. Unlike WS and VCFS, which are caused by microdeletions of specific chromosomal regions, FXS is caused by an expanded trinucleotide repeat on the long arm of the X chromosome that is prone to hypermethylation and consequent gene silencing [Verkerk et al., 1991; Oostra and Chiurazzi, 2001]. The affected gene is fragile X mental retardation-1 (*FMR1*). It normally codes for the fragile X mental retardation protein (FMRP), which is an RNA-binding protein. This disorder affects approximately 1:4,500 males and 1:9,000 females worldwide; it is the most common cause of inherited developmental disability [Warren and Sherman, 2001]. Males with FXS are often characterized by large ears, an elongated face, postpubertal macroorchidism, and moderate to severe mental retardation. The cognitive phenotype of males with FXS includes deficits in executive functions, short-term memory, attentional control, and arithmetic and visuospatial processing, while the behavioral phenotype includes gaze aversion, anxiety, hyperactivity, and social-interaction deficits. Females with FXS are less severely affected, owing to the second, unaffected X chromosome. They may be of average intelligence or have mild mental disability and executive function deficits. They are also at risk for mood disorders and social anxiety.

Structural MRI studies indicate that tissue volumes of discrete brain regions differ between FXS children and typically developing (TD) age-matched children. The caudate nucleus, for example, is consistently larger in the brains of both males and females with FXS [Reiss et al., 1995]. Caudate volume is negatively correlated to IQ measures in children with FXS [Reiss et al., 1995], the opposite to that observed in healthy controls. This subcortical structure is part of the basal ganglia and receives extensive afferent fibers from the prefrontal cortex while sending efferent fibers to other basal ganglia regions. As such, it is a major component of several frontal–subcortical circuits. Lesions of the basal ganglia disrupt these circuits and can result in disturbances in attentional control, response inhibition, cognitive flexibility, and goal-oriented behavior. As these are typical problems associated with the FXS phenotype, it is likely that the enlarged caudate nucleus volume plays a role in these cognitive and behavioral disturbances in FXS-affected individuals.

A study using DTI has provided evidence of disrupted frontal–subcortical circuits in females with FXS. Specifically, the white matter tracts from the frontal cortex to the head of the caudate nucleus exhibit reduced fractional anisotropy values in female children with FXS compared with TD children (Fig. 3) [Barnea-Goraly et al., 2003a]. This suggests reduced fiber density of these tracts, which would likely impact executive functions that rely on these circuits. This in turn supports related implications of another study that used single proton emission computed tomography and indicated hypofunction of frontal–subcortical circuits in individuals with FXS [Hjalgrim et al., 1999]. As FMRP is thought to be involved in axon path finding, aberrant white matter tracts are likely to result from the low levels of this protein in FXS-affected individuals.

Deficits of frontal–striatal connections were further explored using fMRI and the Go/NoGo task to measure impulse control [Menon et al., 2004]. In the Go/NoGo portion of this task, female children with FXS were asked to respond with a key press for every letter except "X" that was presented during image acquisition. The Go condition required a key press response to every letter presented, although no Xs were presented. Brain activation during the Go/NoGo condition in the FXS group was compared with TD age-matched female children. The TD children exhibited greater activation in several areas, including areas of the basal ganglia. More interestingly, the FMRP blood measures of the children with FXS were positively correlated to brain activation in various brain regions, including the caudate nucleus and other components of the basal ganglia. Response time and accuracy were each positively correlated with FMRP measures as well in the FXS group during the Go/NoGo condition but not during the Go condition.

While the findings regarding the aberrant size and function of the caudate nucleus are striking, similar results have been found for other brain regions in the FXS population. A recent study using fMRI during visual memory encoding uncovered decreased activation in the hippocampus and orbital regions of the frontal cortex [Greicius et al., 2004]. Other studies have reported volumetric

abnormalities in select brain regions, including the hippocampus [see Hessl et al., 2004 for review].

Neuroimaging studies on FXS suggest that FMRP plays an important role in proper development of specific brain regions. FMRP's impact on the caudate nucleus is especially profound, as it is a pivotal region in the control of executive functioning and impulse inhibition. As imaging studies have indicated that the caudate nucleus is particularly affected by decreased FMRP, continued research and drug development targeting the caudate nucleus may be instrumental in the future treatment of FXS. Hopefully, these treatments will be also effective also in other individuals with executive function and impulse inhibition weaknesses.

CONCLUSION

The flexibility of MRI technology to study not only brain structure but also regional activation (fMRI) and white matter tracts (DTI) makes it a powerful tool in the study of mental retardation. As new applications for MRI technology are developed, we will be able to delve even deeper into the brain mechanisms associated with MR/DD. As presented in this review, information gathered from various MRI research studies has shown neuroanatomical and functional effects of specific genetic disorders associated with mental retardation.

There are limitations to the use of MRI in the study of mental retardation. A variety of cognitive tests used in fMRI studies are impossible to use with subjects with MR/DD due to their level of difficulty. In addition, it is not always possible to obtain a usable image, because children with mental disabilities have more difficulty laying still in an MRI scanner, with the result that movement artifact is a common problem. Thus, fMRI scans are usually reserved for higher functioning individuals only. Furthermore, MRI is only able to make gross observations about brain structure and function. It is not yet possible to visualize cellular architecture, neurotransmitter activity, or receptor density using this method. On the other hand, MRI is an in vivo and noninvasive method of capturing still images of the living human brain, its pathways, and/or its activation levels in specific areas at specific times.

By integrating MRI research with molecular, cellular, and behavioral methods, a deeper understanding of the causes and consequences of mental retardation is close at hand. The multifaceted ability of MRI to capture images of the brain and to define tissue types, activation levels, and connectivity makes it a versatile tool in the study of mental retardation. Safe and repeatable, it allows us to examine the brain at different developmental stages and in the presence or absence of disease. Future derivatives of MRI technology may go beyond the technology's current limitations and provide even more information about the brain mechanisms associated with MR/DD, which in turn will enable the development of more specific and more effective treatments for individuals with mental retardation and developmental disabilities. ■

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