Functional Neuroimaging of Attention-Deficit/Hyperactivity Disorder: A Review and Suggested Future Directions

George Bush, Eve M. Valera, and Larry J. Seidman

Over the past few decades, functional neuroimaging techniques have begun to provide unprecedented windows on the neurobiology of attention-deficit/hyperactivity disorder (ADHD) and the neural effects of medications used to treat the disorder. Convergent data from neuroimaging, neuropsychological, genetics, and neurochemical studies have implicated dysfunction of fronto–striatal structures (lateral prefrontal cortex, dorsal anterior cingulate cortex, caudate, and putamen) as likely contributing to the pathophysiology of ADHD. This review 1) provides an overview of the main imaging techniques being used to study ADHD; 2) discusses their relative strengths and weaknesses, highlighting how they can complement one another; 3) shows how the functional imaging literature, which has built on the structural imaging data, is now being used to test focused hypotheses regarding the neurobiological substrate of ADHD; and 4) suggests guidelines for improving future functional imaging studies. Although at present there are no accepted uses for functional imaging in diagnosing ADHD, this article mentions possible future clinical uses of imaging in ADHD.

Key Words: Attention-deficit/hyperactivity disorder (ADHD), functional neuroimaging, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), quantitative electroencephalography (QEEG), event-related potentials (ERPs), cognition, attention, reward, motivation

Attention-deficit/hyperactivity disorder (ADHD) is characterized by developmentally inappropriate symptoms of inattention, impulsivity, and motor restlessness (American Psychiatric Association 1994). Affecting approximately 5% of school-age children and frequently persisting into adulthood (Biederman 1998; Spencer et al 1998), ADHD is a source of great morbidity across the lifespan. Thus, determining the underlying neurobiology of ADHD is of great importance.

Convergent data from neuroimaging, neuropsychological, genetics, and neurochemical studies have generally implicated fronto–striatal network abnormalities as the likely cause of ADHD (Castellanos 1997; Durston 2003; Ernst 1998; Giedd et al 2001; Lou 1996; Seidman et al 1998; Shaywitz et al 1997; Solanto 1998; Swanson et al 1998; Tannock 1998; Zametkin and Liotta 1998). The functional imaging field has evolved rapidly over the past two decades, providing unprecedented ways to examine questions regarding the pathophysiology of ADHD and the biological effects of medications used to treat the disorder. Given the dynamic flux within this complex field, it is useful to periodically step back, assess and appreciate how far we have come, highlight emerging themes, and identify areas of inadequacy and recurring problems, so that we might improve future studies.

The main goals of this review are to 1) provide an overview of the main imaging techniques being used to study ADHD; 2) discuss their relative strengths and weaknesses and show how they can complement one another; 3) show how the functional imaging literature has built on the structural imaging data and is now being used to test focused hypotheses regarding the neurobiological substrate of ADHD; and 4) provide for both the researcher and clinician some suggested guidelines as to how functional imaging might best be used in the future.

There are, at present, a large number of techniques that could be considered to fall within the category of “functional brain imaging.” In keeping with the above-stated goals, the scope of this review will include the ones most commonly used to study ADHD in varying levels of detail. After a brief discussion of the uses of functional imaging and the interface of functional imaging with the neuropsychological and structural imaging literature, the main functional imaging techniques (single photon emission computed tomography [SPECT], positron emission tomography [PET], and functional magnetic resonance imaging [fMRI]) will be discussed in detail. These techniques will be compared and contrasted, and the broad themes emerging from these studies will be highlighted. Because this review attempts to focus on identifying neural structures related to the pathophysiology of ADHD, a brief summary of electrophysiologic techniques (quantitative electroencephalography [QEEG] and event-related potentials [ERPs]) is provided. These electrophysiologic techniques, however, although potentially useful, have not displayed the spatial resolution necessary to unambiguously study specific brain structures and so are covered here in less detail. The emerging use of magnetic resonance spectroscopy (MRS) to study the neurochemistry of ADHD is mentioned. Other related imaging techniques, such as structural imaging (e.g., morphometric MRI) and radioligand-based studies (e.g., dopamine transporter and receptor studies) are reviewed elsewhere in this issue of Biological Psychiatry. Following these sections, a general discussion of the issues and challenges facing all of these modalities will be provided, along with some specific suggestions for improving future studies and some guidelines for evaluating the potential future clinical utility of functional imaging.

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Broad Uses of Functional Imaging

Functional imaging techniques (specifically, SPECT, PET and fMRI) are still rapidly evolving fields of research. They have only been available for the past few decades and are undergoing a maturing process. During that time, they have combined to provide heretofore unprecedented ways to understand normal brain function and test for regional brain dysfunction in neuropsychiatric disorders. Functional imaging techniques can be broadly divided into studies of 1) pathophysiology; 2) treatment effects; and 3) potential tests to aid clinical diagnosis. Generally, functional imaging studies have been designed with group-averaging statistical analytic techniques (i.e., owing to the usually limited power to detect reliable and robust results in individuals, analysis strategies have relied on reconstructing image data in a standardized anatomic space [e.g., Talairach and Tourneaux 1988] and comparing the results within a group-averaged sample of ADHD subjects with that of a healthy or psychiatrically impaired control group). Such group-averaged designs can be useful in studying both pathophysiology and medication effects but are inadequate to assist in clinical diagnostic decision making (which by definition requires the ability to reliably distinguish normal from abnormal at the individual subject level). On the horizon, some SPECT (e.g., Dougherty et al. 1999) and fMRI techniques (Bush et al. 2003) might hold promise for eventual clinical utility (having been designed to provide power to isolate effects at the level of the single subject). At present, however, aside from ruling out medical and/or neurologic causes for an ADHD-like presentation (e.g., MRI to rule out a structural lesion or EEG to rule out seizures), it must be emphasized that no current imaging technique has been shown to be useful for the diagnosis of ADHD.

Brief Comment on Historical Context

Although functional neuroimaging techniques hold great promise for informing us as to the neural substrate of ADHD, their development cannot be discussed in a vacuum. To best evaluate their contributions and to understand their potential, it is crucial to place them within the larger context of ADHD research techniques. First, it is essential to emphasize at the outset that other fields of study (clinical phenomenologic studies, cognitive neuroscience, neuropsychological, developmental and structural imaging studies, and pharmacologic research) provide the framework within which these functional imaging studies take place. The importance of research that has established and refined ADHD diagnostic criteria cannot be underestimated; improved characterization of the disorder itself serves to improve imaging studies by better case definition, elimination of comorbidity confounds, and reduction of sample variance. Because we will not truly be able to understand neuropsychiatric disorders until we understand normal cognition and emotion, cognitive and affective neuroscience and neuropsychological studies play key roles by establishing the mechanistic neural bases for normal cognitive, emotional, motivational and motor processes, as well as by providing refined tasks with which to interrogate various brain regions. Developmental and structural imaging studies loom increasingly important as they help to define the limits of normal age-related differences in brain structure and function, and assist in generating hypotheses as to which brain structures might merit further investigation through functional imaging. Similarly, pharmacologic studies guide new functional studies by helping to identify which neurotransmitter systems might be associated with both normal and disordered attention and motor control. That said, these related areas of research are covered in detail in other articles within this issue of *Biological Psychiatry*, and here the focus will be on the specific contributions functional imaging techniques have made to our understanding of ADHD.

Putative Brain Regions of Interest

The first question that arises with the use of functional brain imaging is that of where to look. Although a seminal study by Zametkin et al. (1990) reported global cerebral glucose metabolism to be 8.1% lower in ADHD patients compared with healthy control subjects, this study also found regional decreases after normalization for global effects, and the vast majority of imaging studies look for regional abnormalities. Pioneering investigators using functional imaging of both normal cognition and psychiatric disorders would often cast their nets broadly, looking for any differences between conditions or groups. More recently, as the techniques mature, functional imaging studies have increasingly drawn on the foundations laid by cognitive neuroscience, neuropsychological, and structural imaging studies when determining which brain regions to study. As detailed in Doyle et al. (2005) (this issue), the neuropsychological literature related to ADHD is large and complex. On the basis of these studies and the cognitive neuroscience literature, those using functional imaging have tended to focus on brain regions that are normally involved in attention/cognition, executive function, working memory, motor control, response inhibition, and/or reward/motivation. As detailed below, this line of thinking has led researchers to gravitate toward studies of dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), dorsal anterior cingulate cortex (dACC), and striatum (caudate and putamen). In addition to these regions, and bolstered by reports of structural abnormalities (detailed in Seidman et al. 2005) (this issue), more recent work has also started to search for cerebellar dysfunction in ADHD.

Prefrontal Cortex

Early neuropsychology investigators noted similarities between ADHD patients and frontal lobe–injured patients, leading them to hypothesize that ADHD was also based largely on frontal lobe dysfunction (Barbey 1997; Barkley et al. 1992; Mattes 1980). Some extended beyond the frontal lobes, hypothesizing insufficient frontal cortical inhibitory control due to fronto–limbic dysfunction (Casey et al. 1997a; Satterfield and Dawson 1971)—a view that drew support from studies of stimulant medications and animal models (both of which implicated dopaminergic and noradrenergic influences on prefrontal cortex) (Arnsten et al. 1996; Shaywitz 1978). These early hypotheses have now expanded as cognitive neuroscience has determined that distributed networks of brain regions underlie attention, cognition, and behavioral self-regulation (Goldman-Rakic 1988; Posner and Peterson 1990) and that dysfunction in various components of this network can be associated with ADHD (Denckla 1989; Seidman et al. 2004; Sergeant et al. 2002). Specifically, researchers have focused on DLPFC and VLPFC, because these regions are thought to support vigilance, selective and divided attention, attention shifting, planning, executive control, and working memory (Duncan and Owen 2002; Posner and Peterson 1990). In addition, VLPFC in particular has been associated with behavioral inhibition, as evidenced by its activation with stop-signal tasks (Aron et al. 2003; Rubia et al. 1999). Less attention has been paid to orbitofrontal cortex, even though lesions of this region are associated with social disinhibition and impulse control.
disorders (Hesslinger et al 2002). Structural imaging studies (see Seidman et al 2004; Seidmen et al 2005 [this issue]) have identified smaller prefrontal volumes in ADHD. Together, these findings have made prefrontal cortex a prime candidate for study by ADHD researchers.

Dorsal Anterior Cingulate Cortex

Dorsal anterior cingulate cortex, lying on the medial surface of the frontal lobe, maintains strong connections to DLPFC, parietal cortex, and striatum. The dACC is believed to play critical roles in complex and effortful cognitive processing, target detection, response selection and inhibition, error detection, performance monitoring, and motivation (see Bush et al 2000 for review). Particularly relevant to ADHD, it is thought to modulate reward-based decision making (Bush et al 2002). Animal studies have shown dACC activity is correlated with a five-choice serial reaction time task performance (Barbelivien et al 2001), just as a right ACC volume was similarly tied to performance (Casey et al 1997b). Thus, dysfunction of dACC could lead to all of the cardinal signs of ADHD (inattention, impulsivity, and hyperactivity) and could explain the seeming paradoxical ability of ADHD subjects to perform normally on some tasks (when motivated) but to show deficient performance when the task is not deemed salient. As will be discussed, numerous PET and fMRI studies have reported dACC abnormalities in ADHD.

Striatum

The caudate and putamen are components in a number of discrete, distributed circuits that support many executive functions (Alexander et al 1986). As described in detail in Seidman et al (2005) [this issue], morphometric MRI studies have frequently reported caudate volumetric abnormalities (although there is significant debate surrounding this issue, especially surrounding findings of asymmetry). Also, as discussed in Spencer et al (2005) [this issue], dopamine transporter/dopaminergic abnormalities have been frequently found in striatum, making this a prime target of functional imaging studies. Although striatum might have hemodynamic characteristics that differ from cortex (making it harder to reliably activate), as shall be detailed below, a number of functional imaging studies have reported striatal abnormalities in ADHD.

Other Regions

Other brain regions, including parietal cortex, superior temporal sulcus, thalamus, the brain stem reticular activating system, and the cerebellum, have not been the main focus of many functional imaging studies of ADHD to this point, but it is hoped that this will change in the future. Reasons for the relative neglect of these areas vary. For example, although the parietal lobules and superior temporal sulci are known to be polymodal sensory convergence areas that play roles in selecting targets (Corbetta et al 2000; Culham and Kanwisher 2001), there have been fewer tasks defined to defining which specific parts of these broad cortical territories perform target selection. The thalamus and brain stem reticular activating system (which help modulate attention and filter interfering stimuli; Buchsbaum et al 1990; Pardo et al 1991) are difficult areas to image, possibly owing to lower signal/noise characteristics, greater motion, and/or possibly different hemodynamic properties. As for the cerebellum, it has only been recently recognized as having cognitive functions beyond its role in modulating motor output. Future studies of ADHD will benefit from the increasingly refined understanding of the specific functions of these brain regions that will continue to be provided by cognitive neuroscientists, as well as by the improvements in imaging tasks and techniques that will permit focused testing of these structures.

Functional Imaging Findings in ADHD

In the following sections, major themes observed across the different imaging modalities will be highlighted. Given the relatively small number of functional imaging studies overall and this article’s focus on identifying emerging themes, data from studies of children, adolescents, and adults will be discussed together. Given the large number of maturational changes in brain structure and function (Castellanos et al 2002; Seidman et al 2004) and the changes that take place in the clinical phenomenology of ADHD with age (Biederman 1998), some of the most important tasks facing researchers in the future will involve actively searching for similarities and differences among different age groups and placing findings within a developmental perspective.

SPECT and PET Studies

The earliest functional imaging studies used SPECT (Table 1) and PET (Table 2). Because both methods use radioactive materials and are performed in a similar manner, they are discussed together here. Single photon emission computed tomography, which first emerged in the 1950s, requires the injection or inhalation of radiopharmaceuticals (e.g., xenon-133, iodine-123, technetium-99m). These compounds distribute throughout the body, including the brain, and emit single photon radiation (typically gamma rays) as they decay. More highly active brain areas receive greater blood flow, and therefore greater amounts of the radioactive tracer, which is then quantified with SPECT imaging. Positron emission tomography, introduced in the 1970s, also uses injected or inhaled radiopharmaceuticals. As the radioactive isotopes (typically oxygen-15, carbon-11, fluorine-18) decay, they emit positrons, which are detected by the PET camera. Some PET methods are flow dependent, but others can measure cerebral metabolism rates. Although SPECT is relatively inexpensive compared with PET and fMRI, it suffers from relatively poor spatial and temporal resolution. Thus, although important uses still exist for SPECT and PET (e.g., measuring dopamine transporter levels; see Spencer 2005 [this issue]), these techniques have generally been supplanted by fMRI for functional studies. This is because fMRI offers spatial and temporal resolution superior to both SPECT and PET, and SPECT and PET’s use of radiopharmaceuticals makes it ethically difficult to justify their use in healthy volunteers (especially children), making it more difficult to recruit control subjects (Castellanos 2002).

The first SPECT studies by Lou et al (1984, 1989, 1990) focused mainly on basal ganglia. In this pioneering series of studies, the investigators used overlapping subject samples and, by today’s standards, crude techniques. Numerous methodologic confounds (subjects with severe neurologic comorbidities, poor age matching, very thick slices) make it difficult to adequately assess these early studies, although the findings are consistent with those from the later study by Lou et al (1998), in which they used marginally better technique and reported decreased striatal perfusion. Unfortunately, as Table 2 shows, methodologic concerns (qualitative analyses, minimal or no control group, comorbid conditions, inadequate methodologic description, poor subject matching) seem to have plagued nearly all of the SPECT studies of ADHD. As mentioned previously, even two of the large,
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<th>Study</th>
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<td>Lou et al 1990</td>
<td>Children/adolescents: 9 ADHD, 8 ADHD w/comorbid neurologic disorder, 9 control (siblings)</td>
<td>Xenon-133, single-slice, 17-mm-thick, qualitative analysis. Again, overlap with earlier 1984 and 1989 samples, reported decreased perfusion in striatum and periventricular area in ADHD. Methodologic concerns as above. Notably, neurologic disorders in this series of studies were often severe, including seizures, moderate retardation, postencephalitis.</td>
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<td>Sieg et al 1995</td>
<td>Children/adolescents: 10 ADHD/6 control (psychiatric)</td>
<td>N-isopropyl I-123 IMP. Decreased uptake L hemisphere (L frontal, parietal). Significant group differences in age, IQ (both could potentially affect results).</td>
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<td>Amen et al 1997</td>
<td>Children/adolescents: 54 ADHD/18 control (psychiatric)</td>
<td>Qualitative analysis concluded “hypofrontality,” but use of subjective analysis and inadequate description of methodology precludes meaningful comment. Xenon-133, 2 slices, 12 mm thick. Tasks included white noise listening, passive listening to animal names, dangerous animal identification by button. Reported ADHD children showed decreased right striatum (uncorrected for multiple comparisons).</td>
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<td>Lou et al 1998</td>
<td>Children/adolescents: 12 ADHD/6 control</td>
<td>Well-designed 99mTc-HMPAO study. Large-scale pre- and post-MPH study in drug-naïve children/adolescents, diagnostically clean. Resting ROI-based study found MPH increased uptake to DLPFC, caudate, and thalamus bilaterally.</td>
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<td>Gustafsson et al 2000</td>
<td>Children: 28 ADHD/no control</td>
<td>No control group and use of visual inspection present serious methodologic concerns.</td>
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<td>Spalletta et al 2001</td>
<td>Children/adolescents: 8 ADHD/no control</td>
<td>No control group and use of lorazepam sedation in 2 subjects seriously limit this 99mTc-ethylcysteinate study.</td>
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<td>Langleben et al 2001</td>
<td>Children: 20 ADHD/no control (4 healthy subjects insufficient)</td>
<td>No control group for this 99mTc-ethylcysteinate study calls into question the significance of hemispheric asymmetry findings of DLPFC hypoperfusion in severe/moderate ADHD subjects.</td>
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<td>Kim et al 2001</td>
<td>Children/adolescents: 32 ADHD/no control</td>
<td>Well-designed 99mTc-HMPAO study. Large-scale pre- and post-MPH study in drug-naïve children/adolescents, diagnostically clean. Resting ROI-based study found MPH increased uptake to DLPFC, caudate, and thalamus bilaterally.</td>
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<td>Kim et al 2002</td>
<td>Children/adolescents: 40 ADHD/17 control (5 healthy, 11 somatoform disorder with tension headache, 1 adjustment disorder)</td>
<td>99mTc-HMPAO study. Large-scale, drug-naïve children/adolescents, diagnostically clean. Resting state study. Uncorrected SPM analysis with liberal statistical threshold do cause concern, but cluster sizes relatively large, suggesting findings of decreased R lateral prefrontal, middle temporal and cerebellar cortices, and increased angular/postcentral gyri, occipital gyri are veridical. Control subjects with headaches might be problematic.</td>
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<tr>
<td>Langleben et al 2002</td>
<td>Children/adolescents: 22 ADHD/7 control</td>
<td>99mTc-ethylcysteinate MPH discontinuation study in previously MPH-naïve subjects. Two scans (for ADHD = 36 hours s/p 6-weeks trial of MPH, for control = 36 hours s/p single MPH dose). Go-NoGo task, well-characterized, clean sample. Reported higher activity in dorsal anterior cingulate, motor, premotor cortices while off-MPH. Small control sample. Short drug discontinuation could not rule out acute withdrawal effects. Design did not identify pretreatment baseline. Performance data not measured.</td>
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<td>Kaya et al 2002</td>
<td>Children: 13 ADHD/7 control</td>
<td>99mTc HMPAO. Semiquantitative analysis, multiple comorbidities, subjects with IQ &lt;80, inadequate description of methods limit this report.</td>
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**Table 1. Single Photon Emission Computed Tomography Studies**

**Note:** ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate; R, right; L, left; IMP, p-iodoamphetamine; IQ, intelligence quotient; DLPFC, dorsolateral prefrontal cortex; HMPAO, hexamethyl propyleneamine oxime; ROI, region of interest; SPM, statistical parametric mapping; s/p, status post. Better-designed studies (Kim 2002; Langleben et al 2002) still suffer from the lack of, or an inadequate, control group. The well-designed Kim et al (2001) study, although not including a control group, nevertheless made a nice contribution by reporting that methylphenidate increased regional cerebral blood flow in DLPFC, caudate, and thalamus bilaterally in previously treatment-naïve children and adolescents with ADHD. Similarly, the Langleben et al (2002) study, although insufficiently powered to support its negative finding in control subjects (Castellanos 2002), still raised an important point about medication withdrawal effects (i.e., that the length of time that medications used to treat ADHD might exert effects in the brain after discontinuation is unresolved and must be addressed). The first large-scale, well-designed functional imaging study was an [18F]fluoro-2-deoxy-D-glucose (FDG)-PET study by Zametkin et al (1990). FDG-PET measures cerebral glucose metabolism. Studying 75 adult subjects (25 treatment-naïve ADHD patients, 50 control subjects), they reported that global cerebral glucose metabolism was 8.1% lower in the ADHD group (p = .03) and that regional metabolism remained lower in dACC, premotor,
and somatosensory areas after normalization for global decreases. The fact that the original Zametkin et al (1990) ADHD sample contained a higher percentage of women in the control group (22 of 50, or 44%) compared with the ADHD group (7 of 25, or 28%), coupled with the fact that the female control subjects had a higher global metabolism, has led some (Baumeister and Hawkins 2001; Leo and Cohen 2003) to discount the conclusion of reduced global metabolism—and in fact, two subsequent, smaller-scale studies (in adolescents) by the same group (Ernst et al 1994b; Zametkin et al 1993) failed to find the same global or regional deficits. The original Zametkin et al (1990) study, however, did report that separate gender-based analyses paral-

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<td>Zametkin et al 1990</td>
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ADHD, attention-deficit/hyperactivity disorder; FDG, fluorodeoxyglucose; ROI, region of interest; ACC, anterior cingulate cortex; L, left; R, right; MPH, methylphenidate; d-AMPH, d-amphetamine; CMRglc, cerebral metabolic rate of glucose; PET, positron emission tomography; VLPFC, ventrolateral prefrontal cortex; rCBF, regional cerebral blood flow.
leled (albeit nonsignificantly) the main finding (i.e., global metabolism for ADHD men was 6.0% lower than for control men, and for ADHD women was 12.7% lower than for control women), and the Ernst et al (1994b) study found that ADHD women showed lower global cerebral metabolism. Rather than dismiss the original conclusion, it is probably better to 1) conclude that these data simply suggest that global metabolism is likely decreased in ADHD; but 2) point out that gender effects should be taken into account in future studies. This viewpoint is certainly in keeping with the structural data of Castellanos et al (2002), which showed that although age-matched girls had, on average, smaller brains than age-matched boys, ADHD girls had smaller brains than healthy control girls, and ADHD boys had smaller brains than healthy control boys. Thus gender, along with medication status (and a whole host of other variables) is another factor to be controlled for, but ADHD seems to affect brain size and function independently.

Other PET studies have provided important information. A series of drug studies (Ernst et al 1994a; Matochik et al 1993, 1994) seemed to suggest that there are no consistent acute or chronic stimulant effects on the brain; however, two of these studies used acute administration of drug, and more recent data have shown that full effects of stimulants might take up to 4 weeks to become manifest (Spencer, unpublished data). Also, the FDG-PET method (coupled with the continuous performance task used in these studies) might simply not have sufficient power to detect drug-related differences that have been detected with SPECT (Kim et al 2001; Langleben et al 2002), [15O]H2O PET (Schweitzer et al 2003, 2004), and fMRI (Anderson et al 2002; Bush et al, unpublished data; Vaidya et al 1998). Finally, PET studies by Schweitzer et al (2000) and Ernst et al (2003), although using small samples and completely different tasks (working memory and gambling tasks, respectively), have been consistent with the conclusion that fronto–striatal abnormalities might be associated with ADHD.

Functional MRI

The newest of the functional imaging methods, fMRI has only been available since the early 1990s. Although not a perfect technology (it is sensitive to subject head motion, and subjects with certain types of metal in their bodies or claustrophobia cannot be scanned), fMRI presents a number of advantages for functional studies over both SPECT and PET. It is noninvasive (no injections or inhalations needed) and does not require subjects to be exposed to ionizing radiation. Thus, subjects (including children) can be scanned repeatedly, facilitating longitudinal, developmental, and drug studies. This ability to repeatedly scan the same subject also permits progressive “functional dissections” within the same subject (i.e., the same subject can be scanned on different occasions, using many different tasks, which allows researchers to probe different brain structures and networks). Functional MRI has better spatial and temporal resolution, and tasks can be performed in either a blocked format or an event-related manner, allowing more flexibility in task design. Higher field strength magnets, coupled with specialized cognitive activation tasks, can produce reliable and robust results in individual subjects, which will not only permit refined analyses of intersubject variability but also potentially enable the development of clinically useful tests (see Bush et al 2003). For these reasons, fMRI has become the dominant imaging modality used by cognitive neuroscientists in general, as well as by psychiatric functional imaging researchers.

In the relatively short time that it has been around, fMRI has made some important contributions. Perhaps the most consistent theme that has emerged from the small but growing fMRI literature (Table 3) is the repeated finding of dorsal anterior cingulate cortex (dACC) dysfunction. The dACC, also referred to as the “cognitive division,” has been shown to play important roles in attention, cognition, motor control, and reward-based decision making (Bush et al 2000, 2002; Posner and Peterson 1990; Vogt et al 1992). In a focused study of dACC in which the Counting Stroop task was used as a cognitive activation paradigm, Bush et al (1999) reported that dACC was hypofunctional in ADHD adults. Similarly, Rubia et al (1999) also found mesial prefrontal hypofunction in the vicinity of dACC, using stop-signal and motor timing tasks. Recently, Durston et al (2003) and Tamm et al (2004), using Go-NoGo tasks in children and adolescents, respectively, reported that healthy volunteers activated dACC, whereas ADHD subjects did not. Additionally, Tamm et al (2004) also reported that direct comparisons showed that dACC was hypoactive in the ADHD group relative to the control group. These fMRI findings in dACC fit with the Zaremklin et al (1990) PET findings of decreased dACC activity in ADHD adults.

Striatal abnormalities have likewise been fairly consistently found with fMRI. The findings of Vaidya et al (1998), who used validated versions of a Go-NoGo task, bolstered the assertion that frontal and striatal abnormalities might play a role in ADHD. Also, the slight variations in task produced different regional results within the same group of subjects, suggesting that future studies might need to include a battery of tasks to fully expose functional deficits in ADHD. Rubia et al’s stop-signal task produced lower power in left caudate of ADHD adolescents (Rubia et al 1999). Using T2 relaxometry (an indirect MRI measure of steady-state regional blood flow), Teicher et al (2000) found lower putamen blood flow in ADHD. Finally, Durston et al (2003) showed lower left caudate activity in ADHD. Together, these data fit nicely with the structural imaging findings (see Seidman et al 2005 [this issue]) and consistent reports of dopamine transporter abnormalities found in striatum (see Spencer et al 2005 [this issue]).

Somewhat surprisingly, the fMRI data have been less consistent with respect to lateral frontal cortex (DLPFC and VLPFC). Although Rubia et al (1999) found that ADHD subjects displayed reduced power in VLPFC during the stop-signal task, and Durston et al (2003) found that normal control subjects (but not ADHD subjects) activated VLPFC during the Go-NoGo task, Durston et al’s direct between-group comparisons did not show a significant difference. Bush et al (1999) actually found that ADHD subjects activated VLPFC bilaterally, whereas normal control subjects did not, during the Counting Stroop. It should also be noted, however, that in the Bush et al (1999) study, robust activations were also found in anterior insula bilaterally, which like the VLPFC activations were not normally found in healthy control subjects; this lead the investigators to conclude that perhaps the ADHD subjects were using accessory response pathways in the face of dACC dysfunction. Future studies with targeted tasks will surely illuminate this issue.

Functional MRI studies have, in general, used small sample sizes, making it difficult to generalize findings. This was partly because of the generally high cost of fMRI, but more likely because, as a newer (at the time, less proven) technology, it was more difficult to secure funding for larger studies. Also, the field was less mature, so ADHD researchers were simultaneously not only studying ADHD but also developing the experimental and analytic techniques. Future fMRI studies will no doubt continue.
to incorporate the lessons learned from prior SPECT, PET, and fMRI studies, and now that the technique is more established and can take advantage of the explosion of knowledge provided by cognitive and affective neuroscience researchers on attention, cognition, and motivation, will surely make important future contributions to our understanding of ADHD.

It will be instructive at this point to illustrate more specifically how a refined understanding of regional neural functions from cognitive neuroscience (e.g., dACC) can inform, guide, and assist the interpretation of ADHD imaging data. As indicated above, numerous fMRI and PET studies have reported dACC hypofunction in ADHD (Bush et al 1999; Durston et al 2003; Rubia et al 1999; Tamm et al 2004; Zametkin et al 1990), and this is consistent with anatomic, connection, lesion, electrophysiology, and imaging data indicating that dACC is normally involved in higher-level cognitive processes, such as attention, motivation, response selection, and decision making (Bush et al 2000, 2002). Thus, dysfunction of dACC could lead to the cardinal signs of ADHD, including inattention, impulsivity, and hyperactivity (see Bush et al 1999). Convergent data also have supported the conclusion that the perigenual ACC (pACC, including the ACC’s rostral and subgenual divisions) are involved with emotional processing and autonomic control (Bush et al 2000; Whalen et al 1998). Interestingly, convergent data have shown that both dACC and pACC can be sensitive to error processing (Bush et al 2000, 2002; Kiehl et al 2000; Menon et al 2001). Taken together, this framework can be useful in reconciling and explaining the results of ADHD imaging studies from Schulz et al (2004) and Tamm et al (2004). Both of these studies, in which Go-NoGo tasks were used, found that ADHD subjects made more errors...
than control subjects, with Schulz et al (2004) reporting ADHD subjects showing higher pACC activation than control subjects and Tamm et al (2004) reporting significant pACC activation in the ADHD group (with both studies reporting significant increases in the rostral ACC, known to be sensitive to errors). Additionally, Tamm et al (2004) showed that in direct between-group comparisons, ADHD subjects had hypoactive dACC. Taken together, the data are consistent with the conclusion that primary dysfunction of dACC in ADHD might lead to inefficient decision making, which then leads to poorer performance and increased errors—which are in turn signaled by increased peri-genual ACC activity. Of course, as has been discussed at length here and elsewhere (Bush et al 1999), this model assumes that dACC is but one node within a network of brain regions supporting these cognitive processes and not the sole cause of ADHD—but the example clearly illustrates how our growing knowledge base of cognitive processing (specifically, an appreciation that there are multiple ACC subdivisions that have differential functions) can inform interpretation of imaging data relevant to ADHD.

Magnetic Resonance Spectroscopy

Although there have been only a handful of MRS studies, often using varying techniques and with different regions of interest (making it difficult to identify emerging themes), MRS seems to have shown some early promise in identifying neurochemical abnormalities associated with ADHD and so bears mentioning in this context. Magnetic resonance spectroscopy is a noninvasive, MRI-based method for quantifying various neurochemicals. Not all neurochemicals are visible with MRS: the most commonly studied ones (vis-à-vis ADHD) have been N-acetyl aspartate (NAA), glutamine/glutamate/γ-butyric acid (Glx), choline, and creatine/phosphocreatine. N-acetyl aspartate is generally thought to be a putative marker for neuronal integrity, with low values indicating neuronal dysfunction or death—though the matter is complicated because NAA might also be a marker for myelination (Chakraborty et al 2001) and might therefore change with development. Glutamine/glutamate/γ-butyric acid elevations are thought to be associated with neuronal destruction, increases in choline are associated with myelin breakdown, and creatine is most often used as an internal control (Cecil and Jones 2002). Magnetic resonance spectroscopic techniques do have the drawback of only being able to study a few restricted regions of interest during a session, leading researchers to focus on one or two sites during a single study (e.g., unilateral studies of DLPFC, cingulate, and/or caudate).

Hesslinger et al (2001), studying small samples (5 per cell) of adults with ADHD, ADD, and matched control subjects, reported NAA depletion in left DLPFC, but not left striatum, in ADHD subjects compared with both control and ADD subjects. Jia et al (2001) found a lower NAA/Cr ratio bilaterally in globus pallidus of adolescent boys, which did not change appreciably with a single dose of methylphenidate. Carrey et al (2002), in a 4-subject case series, reported differential effects of methylphenidate and atomoxetine in striatum and medial prefrontal cortex. Then, in a follow-up pilot study of 14 subjects receiving various treatments, Carrey et al (2003) reported decreases in striatal glutamate, but not NAA, creatine, or choline, with treatment. In another report by the same group, MacMaster et al (2005) reported elevated glutamate (but not NAA, creatine, or choline) in right medial prefrontal cortex and left striatum, in 9 ADHD children and adolescents. Finally, a larger sample study by Yeo et al (2003), comparing bilateral DLPFC values in 23 ADHD children with those in 24 control subjects, failed to find overall neurometabolite differences but did report low NAA levels in girls with ADHD. Although these MRS findings are very preliminary, often contain very small samples with comorbidities, and are regionally limited, they do offer the promise of being able to noninvasively quantify biologically relevant neurometabolites, and therefore MRS is a technique deserving further exploration.

Electrophysiology Studies: QEEG and ERPs

As mentioned at the outset, these electrophysiologic methods have been used in quite a large number of studies of ADHD (for reviews, see Barry et al 2003a, 2003b; Hughes and John 1999; Tannock 1998). These two methods are not discussed at length here because the present review focuses on neuroimaging methodologies that seek to identify regionally specific brain abnormalities associated with ADHD, and neither QEEG nor ERPs has shown the spatial resolution to accomplish this. Quantitative EEG generally involves computer-assisted spectral analysis of the EEG signal, with relative and absolute quantification of the alpha, beta, theta, and delta frequencies, and sometimes measures of coherence. The generators of these signals, however, are not localized to specific neural structures with any precision. Some proponents of QEEG have argued that it has been used in some very large studies to distinguish ADHD subjects from control subjects, as concluded in a recent review by Hughes and John (1999)—with ADHD supposedly being characterized by “theta excess” and “alpha slowing.” The very same review went on to indicate, however, that a pattern of “theta excess” and/or “abnormal alpha” can be indicative of dementia, schizophrenia, mood disorders, obsessive-compulsive disorder, specific developmental learning disorders, alcoholic intoxication, chronic alcoholism, mild to severe head injury, and/or postconcussion syndrome.

Event-related potentials, although also an electrophysiologic measure, are quite a bit different from QEEG, and although considerable debate surrounds their use for exploring ADHD, they would seem to hold more promise than QEEG. The topic is too broad to be included within this review, thus only a few summary comments will be provided here. The interested reader is referred to other sources (Barry et al 2003a; Tannock 1998) for fuller treatments. Modern ERPs are measured from multielectrode arrays placed over the scalp and represent the averaged electrical response of the brain over many trials (typically 25–100 trials). The main problems ERP researchers face are limited spatial resolution and the “inverse problem.” Spatial resolution is poor, and although it can be improved by increasing the number of electrodes, will likely remain approximately an order of magnitude worse than fMRI’s spatial resolution (i.e., high density source models with ERPs provide “images” with pixels of approximately 2.5 cm²) (Gevins 1996). Coupling this with the inverse problem (i.e., the fact that there are no unique solutions when determining the position of sources within the head, making it extremely difficult to localize brain activity with certainty) and the fact that after many decades of research there is still substantial controversy within the ERP field itself regarding the neural bases of the most common waveforms (e.g., the P300), the ability of ERPs to contribute might seem in serious doubt. Event-related potentials do, however, possess millisecond temporal resolution, and efforts to combine modalities (e.g., using fMRI to spatially constrain source models and then ERPs to test the electrical activity within the identified nodes) might pay dividends and eventually be applied to ADHD research with success.
Common Challenges, Future Directions

In a relatively short period, functional imaging has made great strides in helping to uncover the neural substrate of ADHD. Convergent data have implicated fronto–striatal abnormalities (particularly dysfunction of dACC, lateral prefrontal cortex, and striatum) as possibly playing roles in the production of ADHD symptomatology. The virtual explosion of new knowledge provided by the field of cognitive neuroscience regarding the brain’s attention, affective, motor, and motivation systems, combined with the rapid pace of technological advances, promise to make the next few decades exciting times for ADHD researchers. As with any burgeoning area of inquiry, however, there are growing pains to be expected, common issues to be faced, and lessons to be learned along the way. Most, if not all, of the points raised in the next section are not unique to ADHD imaging but are general issues of study design, analysis techniques, and interpretation that face all clinician-scientists conducting neuropsychiatric research on any disorders. Hopefully, by explicitly raising them here, future research can be improved.

Clinical Use of Functional Imaging

The first main issue to be addressed is that of making explicit our expectations for the role functional imaging can and should play in clinical evaluations. As stated at the outset, there is currently no accepted role for functional imaging in guiding clinical diagnosis or therapeutic decision making. Simply put, however exciting the preliminary advances might be, none of the imaging modalities has been accepted in the peer-reviewed literature as a proven method for reliably distinguishing ADHD subjects from normal control subjects, distinguishing ADHD subjects from other subjects with other psychiatric or neurological comorbidities, identifying subtypes of ADHD, or predicting treatment response at the level of the individual subject. Until this is done, there can be no ethical use of imaging outside of the research realm—especially any type of invasive research technique that exposes children to ionizing radiation—because there is no accepted, identified benefit to be had. This does not mean that there should be a blanket prohibition against SPECT or PET research in adults or children with ADHD, because legitimate arguments can be made with respect to what constitutes acceptable risk when it comes to lifetime exposure to radiation (Castellanos 2002). Rather, this is a clear statement that any such imaging must only be done within the context of research, clearly labeled as such, and with the oversight of an established human subjects committee or investigational review board. Any other use at this time would be unethical.

That said, what should our expectations be for the use of imaging? Although it would be wonderful indeed to be able to place an individual in a scanner and clearly identify a distinctive biomarker that unequivocally establishes, or refutes, the diagnosis of ADHD, that is not likely to be the case, nor is this how imaging has traditionally been used in medicine. Clinicians do not instantaneously jump to perform chest x-rays for every cough, nor MRIs for every bump on the head. Instead, imaging is used within the clinical context. The clinician first takes a careful history, performs a physical examination, obtains blood work, and then considers whether subsequent imaging would tangibly guide diagnostic decision making or treatment. Here, the chest x-ray can be useful in distinguishing between pneumonia and bronchitis, and the CT or MRI can help identify or rule out a hematoma. Attention-deficit/hyperactivity disorder will be no different—if anything, neuroimaging of psychiatric disorders will be much more complex. Thus, patients and clinicians should not expect a scanning technique to replace clinical judgment but rather to be used as an adjunct to a comprehensive clinical evaluation.

Some would question the value of pursuing an imaging-based diagnostic aid in the first place, wondering about the added value over and above clinical judgment. Beyond helping to establish pathophysiology, reducing over-diagnosis, reducing stigma, and providing assistance in questionable cases, a properly validated imaging test could be an important way to reduce inappropriate exposure to medications. Given the length of time that patients are traditionally treated with medications (often for decades) and the increasing recognition that ADHD often persists into adulthood, it would certainly behoove the prudent clinician to use all available means to confirm the diagnosis and optimize therapy.

Common Issues

Some problems are specific to particular imaging modalities. For example, SPECT and PET offer inferior spatial resolution compared with fMRI, and their requirement for exposure to radiation makes it difficult to recruit the necessary healthy control subjects. Functional MRI has limited temporal resolution, because the hemodynamic changes it relies on can blur the ability to distinguish two neuronal events in time without special task designs. Event-related potentials offer very poor spatial resolution, and the inverse problem makes it difficult to determine where the underlying neuronal events are occurring. Researchers have generally found ways around these problems: fMRI is now being used for most functional cognitive studies (taking advantage of its superior capabilities in this realm); PET, SPECT, and MRS are being used for receptor and neurochemical characterization studies (filling niches that fMRI cannot fill); and ERP studies are being combined with fMRI in a way that will hopefully capitalize on the strengths of both. A number of issues commonly face imaging researchers, however, irrespective of modality used, and these are most easily addressed together.

Functional imaging studies are relatively expensive, and as such have typically used small subject samples. Often the control group is either a homogeneous sample (matched to the patient group) or psychiatrically ill with only a single disorder. These factors 1) increase the likelihood of both type I and type II errors; and 2) make it impossible to generalize findings. Now that the imaging techniques are more mature and the cognitive neuroscience upon which they are based better established, future studies will benefit from larger patient samples and the use of statistical models (e.g., random effects models) that permit generalization to the larger population. This will require large-scale comparison studies across diagnostic groups using the same task(s) to be most useful. An added benefit, though, will be that these studies will be adequately powered to make even negative results meaningful and publishable. This does not mean that smaller-scale pilot studies cannot be valuable or that studies using fixed effects statistical models are invalid, but rather a new emphasis should be placed on using established tasks in larger groups and across diagnostic categories.

Of course, neither does this mean that heterogeneous diagnostic samples should be encouraged without careful planning. First, large-scale studies should be conducted within diagnostically homogeneous groups, and then, once replicable findings are obtained, these validated paradigms can be used in studies of comorbidity. For example, it will be important to try to establish functional imaging biomarkers indicative of ADHD (including its subtypes), learning disabilities, conduct disorder, oppositional
defiant disorder, and affective disorder, and then to look for any overlap and interactions among disorders.

Imaging researchers investigating ADHD will continue to benefit from working collaboratively with cognitive neuroscientists, affective neuroscientists, developmental experts, neuropsychologists, and structural imaging colleagues to optimize paradigms and interpret data. Not surprisingly, a large number of factors that might influence imaging results are still under-studied and often ignored. Some examples would be the effects of age, gender, handedness, caffeine use, alcohol use, intelligence quotient, and practice on commonly used tasks, or the test–retest reliability of cognitive activation paradigms. Also, differential between-groups performance characteristics during cognitive tasks or differential thought processes during resting studies might confound imaging results and should be taken into account. Finally, a crucially important (yet often overlooked) issue is that of the proper correction for the large number of multiple comparisons that are inherently performed as part of functional imaging. Failing to account for multiple comparisons might make nonsignificant results erroneously seem to be significant.

In the future, particular attention should be paid to increasing the rigor of proposed mechanistic hypotheses and the analytic methods of testing these hypotheses. Initial work might appropriately start with simplistic positioing of dysfunction within a single region or multiple nodes of a distributed network, but follow-up studies must then test more complex alternative models. Future work should specifically test for dysfunction in different components of fronto–striatal circuitry (DLPFC, VLPC, dACC, striatum), as well as in cerebellum, parietal cortex, brainstem, and other structures, because it is highly likely that the pathophysiology of ADHD involves a dysfunctional interaction among components of fronto–striatal circuitry. It will also be useful when interpreting data to recall that apparent “fronto–striatal” deficits might just be “downstream” effects of dysfunction in other brain regions and to attempt to test for this.

With regard to analysis schemes, some SPECT and PET studies have reported region-of-interest/cerebellum ratios, implicitly or explicitly positing that cerebellum can be used as a neutral control site. It may not be prudent, however, to continue this practice in future functional studies, in light of the fact that structural (see Seidman et al 2005 [this issue]) and functional (Anderson et al 2002; Valera et al 2005) cerebellar abnormalities have been reported in ADHD.

Medication status is another issue that must be paid increasing attention. Although wash-out procedures adequate to produce nearly complete elimination of the medications can validly be used in some studies, the long-term effects of medications are not yet known and might represent a potential confound (Langleben et al 2002). When possible, medication-naive samples, or those in which a longer wash-out period is used to rule out the possible influence of long-term effects of medication exposure on cognition, should be considered.

There are some who have argued that much of the imaging work to this point has been too inconsistent (Baumeister and Hawkins, 2001) or confounded by prior medication exposure (Leo and Cohen 2003) to be meaningfully interpreted. In contrast to such harshly dismissive stances, we advocate taking a measured, conservative approach to interpreting the body of work that has already been produced, and importantly, listening to the valid criticisms of prior studies in the service of improving future studies.

On a final cautionary note, imaging research can carry great, often disproportionate weight in swaying minds. Its highly technical nature unfortunately carries with it the potential for misinterpretation, misuse, and exploitation—situations to be actively guarded against to protect the reputation of the field. Efforts to push forward the technology need to be matched with equal vigor in protecting patients and research subjects. In particular, we must clearly define the proper uses of imaging and ensure that these techniques are properly integrated with clinical evaluation. Last, we should not lose sight of the fact that not only can studies of normal healthy volunteers inform our studies of patients, but also studies of patients can increase our understanding of normal brain structure and function.

Functional imaging techniques represent new frontiers in ADHD research. Convergent data strongly suggest that fronto–striatal abnormalities (DLPFC, VLPC, dACC, caudate, and putamen) contribute to ADHD pathology. Suggestions for maximizing future progress include 1) placing an emphasis on larger-scale studies with validated tasks; 2) increasing the methodologic rigor of study designs; 3) renewing studies of therapeutic drug manipulations, using refined tasks and updated techniques; 4) refining neuroanatomic focus on the basis of advances in cognitive neuroscience and imaging technology; (5) interfacing more with genetics studies; 6) increasing the use of identical tasks and parameters to facilitate direct comparisons of ADHD imaging results with those of other psychiatric disorders; 7) making greater attempts to isolate effects and interactions due to common comorbidities; and 8) making greater use of combined modalities, such as fMRI and ERPs. Used wisely, functional imaging should continue to fulfill its promise as one of the strongest tools available for unraveling the mysteries of the neurobiology of ADHD.

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