Resource Document on Brain Imaging and Child and Adolescent Psychiatry with Special Emphasis on Single Photon Emission Computed Tomography (SPECT)

Approved by the Joint Reference Committee, January 2005

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The document was prepared by the Council on Children, Adolescents and Their Families.

Summary

Although knowledge is increasing regarding specific pathways and specific brain areas involved in mental disease states, at present the use of brain imaging to study psychiatric disorders is still considered a research tool. Continued study of child and adolescent psychiatric disorders using a variety of brain imaging methods, as well as refinements in imaging techniques, may result in evidence supporting the utility of these tools for clinical work in the future. Imaging research cannot yet be used to diagnose psychiatric illness and may not be useful in clinical practice for a number of years. In the future, imaging techniques may be useful to examine medication effects and predict medication response.

Specifically, no published investigation in the field has determined that any structural or functional brain abnormality is specific to a single psychiatric disorder. Additionally, imaging studies examine groups of patients and groups of healthy controls; therefore, findings may not apply to all individuals with a given disorder. Even when significant differences are identified between groups, there is a substantial overlap among individuals in both groups.

Particular caveats are indicated with regard to brain imaging involving radioactive nucleotides for children and adolescents because of children's known greater sensitivity to radiation and risk of radiation induced-cancer. The long term risks of initial and repeated exposure to intravenous radionucleotides are unknown.

We conclude that, at the present time, the available evidence does not support the use brain imaging for clinical diagnosis or treatment of psychiatric disorders in children and adolescents.

Overview

Brain imaging

Single photon emission computerized tomography (SPECT) is one type of functional neuroimaging, a category that also includes positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and functional magnetic resonance imaging (fMRI). Functional neuro-imaging yields metabolic or biochemical information, allowing localization of a neural function. As such it is distinct from anatomic imaging, such as radiography (X-Ray) or computerized tomography (CT), which illuminate structures in a static way. Functional neuroimaging of the brain is based on the experimental data that neuronal activation leads to increased metabolism. Using radio-nucleotides to ligands possessing high and selective affinity for neurotransmitter receptors or transporters allows for imaging of specific neuroreceptors (Shin, 2000).

Brain-imaging tools, such as (PET), (SPECT), MRS and (fMRI), can relate brain function to clinical features and medication responses (Brody et al., 2001; Ketter & Wang, 2002). MRS allows for identification of neurochemical abnormalities in specific brain regions and can identify neurochemical changes prior to and following medication administration. MRS is non-invasive and does not neces-sitate exposure to radioactive nucleotides. SPECT makes use of radioactive tracers tagged to a molecule, which can indicate glucose metabolism, oxygen consumption, or blood flow. Chemical imaging with a SPECT scan works with precursors such as tryptophan, dihydroxyphenal-amine (Dopa) or enzymatic reactions that support neuro-transmitters synthesis (Santosh, 2000).

History

SPECT was originally introduced in the 1980s (Goetz, 2003). Its usefulness was limited in the early years by poor image resolution. However, refinements in computer technology as well as in radionucleotides have resulted in much better image quality, although not as good as with PET. The equipment needed for SPECT is much less costly than that needed for PET scanners (which require a cyclotron) or MRI other forms of imaging. While PET, CT and MRI are limited to hospitals because of their cost, SPECT equipment is within range of outpatient office equipment. There are no regulations that prohibit

individual physicians from installing and using SPECT equipment in their offices, provided they have satisfied regulatory requirements. Because of its low cost, SPECT is being used in outpatient private practice, and some have advocated for its use in clinical diagnosis of psychiatric disorders (Amen, 2001).

Established Uses of Brain Imaging in Clinical Practice

Brain imaging does have important clinical uses. Structural and functional images of the brain play an important adjunct role in the diagnosis and treatment of many neurologic conditions. The usefulness of SPECT to study perfusion abnormalities in the brain as well as elsewhere (e.g., the myocardium, carotid arteries) is well established. SPECT has a role in the diagnosis of cerebral trauma, certain kinds of dementia, strokes, seizure disorders, and brain tumors, in which characteristic patterns of perfusion abnormalities are detectible (Engel, Jr., 2000; Goetz, 2003; Kuzniecky & Knowlton, 2002; Lee, Mintun, Buckner, & Morris, 2003; Slosman & Lazeyras, 1996). In addition, Brain SPECT with neuroreceptor imaging radiopharmaceuticals is used in cerebrovascular diseases, dementias, epilepsy, head injury, malignant brain tumors, movement disorders, and Gilles de la Tourette's syndrome (Camargo, 2001). This imaging modality has been used in diagnosis, prognosis assessment, evaluation of response to therapy, risk stratification, detection of benign or malignant viable tissue, and choice of medical or surgical therapy.

However, even in the diagnosis of neurological disorders, the use of brain imaging is not without controversy. Recent reviews have attempted to establish guidelines to avoid over use for such common conditions as headache (Lewis, 2002; Medina, Kuntz, & Pomeroy, 2001), and a cost-effectiveness study concluded that the addition of SPECT and fMRI did not offer advantages over the usual diagnostic work-up of Alzheimer's disease (McMahon, Araki, Neumann, Harris, & Gazelle, 2000). The primary clinical use of SPECT in psychiatry has been to rule out the neurological conditions listed above.

Brain Imaging in Research

Brain-imaging has been used extensively in research on psychiatric disorders, most notably, obsessive-compulsive disorder, schizophrenia, depression, panic disorder, and drug abuse. The findings, although not entirely robust, have generated many hypotheses about the patho-physiology of these disorders. The following is a brief summary of the research studies of psychiatric disorders in which brain imaging tools, including SPECT, have proven fruitful.

Attention Deficit/Hyperactivity Disorders

Findings in Attention Deficit/Hyperactivity Disorders are still provisional, but suggest minor structural changes in frontal and caudate areas, especially on the right side. Functional studies suggest reduced activation in these and other areas. A 2000 review of studies in children and adults concluded, "The techniques do not yet contribute to individual diagnosis" (Overmeyer & Taylor, 2000).

Autism

Autism has been studied in adults as well as children using MRI, fMRI, and SPECT. MRI studies have indicated a variety of diffuse anatomical differences, reflective of an early developmental change in the growth or pruning of neural tissue, rather than localized lesions; similarly, neurochemical studies suggest early, neuromodulatory discrepancies rather than gross or localized abnormalities. To date we do not have definitive answers to questions of how the brain functions differently in this disorder (Eigsti & Shapiro, 2003; Rumsey & Ernst, 2000).

Bipolar Disorder and Depression

Although over the past two decades, brain-imaging studies have examined the mechanisms possibly involved in the pathophysiology of bipolar and unipolar mood disorders, nearly all of these studies involve adults. Most studies have used PET scans (and none of the PET studies involve children). The available findings suggest subtle anatomical changes in sub-regions of the prefrontal cortex, medial temporal lobe and cerebellum, and functional abnormalities in brain circuits inter-connecting these same brain regions and the striatum in patients suffering from bipolar disorder. Neuroimaging studies have reported cerebral atrophy, ventricular enlargement, or cerebellar atrophy (Benabarre et al., 2002).

In terms of function, findings with PET have included decreased prefrontal cortical function concomitant with increased subcortical anterior paralimbic activity, (Drevets et al., 1997; Videbech, 2000). These findings are convergent, and support the hypothesis that depressive symptoms are caused by dysfunction of regions of the limbic system and the frontal lobes in close connection with the basal ganglia. A few studies point to the possibility that response to antidepressant treatment can be predicted from PET scans (Soares, 2003).

There are 2 published studies of SPECT and depression in adolescents (Tutus et al., 1998; Kowatch et al., 1999). The first, done in Turkey, involved 14 patients and 11 controls, found relatively reduced perfusion in the left anterofrontal and left temporal cortical areas in the depressed patients. When the patients were restudied after their depression

remitted, they did not differ significantly from the controls. The second study involved a comparison of 7 adolescent patients with MDD and 7 controls, and found relative rCBF increases in the depressed group as compared to normals in the right mesial temporal cortex, the right superior-anterior temporal lobe, and the left infero-lateral temporal lobe. The researchers found rCBF decreases in the depressed group as compared to normals in the left parietal lobe, the anterior thalamus and the right caudate. 4. They concluded that adolescents with MDD show rCBF abnormalities similar to those found in adult MDD rCBF studies, but cautioned, "Further controlled studies with larger numbers of MDD subjects and normal age- and gender-matched controls are necessary before any definitive conclusions can be made from these findings" (p. 643).

In a comprehensive review, Soares pointed out, "Even though preliminary findings from cross-sectional studies indicate anatomical, neurochemical, and functional brain abnormalities in bipolar patients in key regions involved in mood regulation, the relationship of such abnormalities with illness phase and their clinical relevance needs further investigation. The potential for utilization of brain-imaging tools to elucidate the pathophysiology of bipolar disorder is still largely unrealized, and it is anticipated that important new developments in this area will come about over the next years and beyond" (Soares, 2003). Another reviewer concluded, "Although it is not yet a clinical tool for bipolar disorders, (italics added) brain imaging provides useful research data to understand the fundamental neurobiology of mood disorders and to more effectively target therapeutics" (Ketter et al., 2002).

Obsessive-Compulsive Disorder

Obsessive compulsive disorder has been studied extensively with imaging and has shown the most consistent findings so far, with the orbitofrontal cortex and the caudate nucleus being implicated in PET studies (Santosh, 2000). PET indices of brain activity within the orbitofrontal cortex are inversely correlated with subsequent response to SRIs. (Rauch et al., 2002). Most studies have involved adults. There are reports of SPECT studies of this condition in the literature, some of which included adolescents, but these are mostly older studies. There is one case report of SPECT and an adolescent with OCD who showed changes after being treated with chlomipramine (Amen & Waugh, 1997).

Posttraumatic Stress Disorder (PTSD)

PET, SPECT and functional MRI have been used to study how individuals with PTSD respond when they are presented with trauma-related stimuli. A pattern of hyperresponsivity of the amygdala and anterior paralimbic structures (which are known to be involved in processing negative emotions such as fear), greater deactivation of Broca's region (motor speech) and other nonlimbic cortical regions, and failure of activation of the cingulate cortex (which possibly plays an inhibitory role) has been found (Pitman, Shin, & Rauch, 2001). There are no studies of children and adolescents with PTSD using SPECT.

Schizophrenia

The current understanding of schizophrenia as a neurodevelopment disorder is largely due to brain imaging studies (Batista et al., 1995; Eliez & Reiss, 2000; Hendren, De Backer, & Pandina, 2000).

SPECT has helped to elucidate the neurobiology of schizophrenia via the study of cerebral blood flow and neuroreceptors in this condition. There is converging evidence implicating three brain systems: frontal, temporolimbic, and basal ganglia. (Gur & Pearlson, 1993). PET and SPECT have revealed disturbances of cerebral blood flow and glucose metabolism in patients with schizophrenia. These tools have also proved useful in studying the relative receptor occupancy of typical and atypical antipsychotic medications. (McClure, Keshavan, & Pettegrew, 1998). There are several studies of first break schizophrenics using SPECT and these usually include older adolescents, but no such studies of children.

Provisional Nature of Findings

Despite the excitement neuroimaging has brought to the field of psychiatry, it remains an investigational tool. The hope is that the continued growth of knowledge will eventually have practical applications in guiding psychological and pharmacologic treatments, but the general consensus is that SPECT and other kinds of neuroimaging are not yet recommended for diagnostic evaluation and treatment monitoring in individual patients.

Additional concerns are relevant to the use of neuroimaging in children and adolescents with psychiatric disorders. To date, the overwhelming preponderance of studies have been in adults. PET and SPECT involve exposure to radioactive agents, and MRI and fMRI involve sedation. The long term effects of exposure of the immature brain to radiation are unknown. Concerns about the investigational uses of brain imaging for children revolve around the unclear risk-benefit ratio of such studies, as well as the difficulties involved in informed consent or assent with regard to a complex technology (Hinton, 2002). In a 10 year review published in the Journal of the American Academy of Child and Adolescent Psychiatry in 2000, Hendren and colleagues concluded, citing inconsistencies in data, "Although neuroimaging technology holds great promise for neurodevelopmental

research, it is not yet a diagnostic instrument."(Hendren et al., 2000). This opinion was echoed by Santosh, another review author, who states, "As yet, no specific and consistent abnormality has been detected in childhood psychiatric disorders." (Santosh, 2000). Even with the continued advances in the understanding of brain structure and function in psychiatric disorders since these reviews, brain imaging has still not progressed to the point of being useful for the clinical diagnosis of these disorders in individual patients. As of this writing, no studies have been published in journals indexed by the National Library of Medicine examining the predictive ability of neuroimaging for psychiatric disorders for either adults or children.

Some of the problems still to be resolved are the following:

- Findings have been inconsistent. Most studies have involved small numbers of patients, and children and adolescents have been even less well studied than adults. The studies have great discrepancies related to sample size, subject selection, imaging protocol and image analysis. Methodological differences among studies may further confound the results.

- There are few normative data sets on children (Hinton, 2002). Without normative data, interpretation of findings on individual patients is meaningless. In part this lack is due to ethical constraints on using brain imaging to study normal children.

- Some disorders may involve subtle changes in structure and/or function that are not apparent on brain imaging studies.

- The changes observed may not accurately reflect underlying neurobiological dysfunction in the brain structures being studied, but could be compensatory mechanisms reflecting adaptation to deficits in other aspects of brain function.

- Ethical dilemmas exist with regard to exposure of children to radiation when it is not useful to guide treatment.

- There are potential iatrogenic problems in labeling a child as psychiatrically disordered, or as free of psychiatric disorder, on the basis of data derived from neuroimaging studies, given the lack of data regarding the sensitivity and specificity of such information.

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