PET IN CHILD PSYCHIATRY: THE RISKS AND BENEFITS OF STUDYING NORMAL HEALTHY CHILDREN

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Abstract


1. Inclusion of children, particularly healthy control children, is a continuing debate.
2. Why involve children in PET research? The assumption is that the knowledge gained from such studies is critical for the advance of prevention and treatment of psychiatric illnesses.
3. What are the risks of PET procedures? Radiation exposure poses the most difficult problem. The assessment of this risk needs to separate the emotional reaction at the mention of “radiation” from the consideration of objective data of large studies of health hazards associated with low-level radiation exposure.
4. The assessment of the benefit/risk ratio is critical to the conduct of research, and requires the evaluation of risks according to the ambiguous definition of “minimal risk”.

The opinions expressed herein are the views of the author and do not necessarily reflect the official position of the National Institute on Drug Abuse or any other part of the U.S. Department of Health and Human Services.
1. Introduction

There is much debate as to whether children, particularly normal healthy controls, should participate in functional neuroimaging involving radiation exposure such as positron emission tomography (PET) (Zametkin et al., 1996). This work will provide some basis for arriving at an informed decision, while leaving the ultimate determination to the reader's best judgement. As a prerequisite to considering this issue, it is fundamental to reaffirm that conducting human research is a privilege, not a right, and that we have a moral obligation to protect from harm vulnerable individuals. This work addresses issues of research participation for children 8 years and older, for whom cognitive development has reached the stage of concrete operations (7-11 years) (Piaget, 1958), and when children can begin to understand the research process and the implication of their participation. Studies of younger children raise additional issues that will not be addressed here.

The consideration of the involvement of children in PET research is rooted in the three basic ethical principles established in the Belmont report (1979), 1) Respect for persons, 2) Beneficence, and 3) Justice.

1  Respect for Persons. It sanctions the dignity and autonomy of individuals, and requires protection for people with diminished autonomy (such as young children). The process of informed consent and assent is based on this principle. The issue of the validity of assent by children to participate in a research study is one of the dilemmas faced by research with children.

2  Beneficence. It is based on the Hippocratic Oath “Do no harm”. Under this principle, investigators have the duty to optimize benefits and minimize risks, and to provide a favorable benefit/risk ratio. The assessment of the risk/benefit ratio is at the crux of the decision as to whether to proceed with research.
3 Justice. It addresses the concept of the "fairness of distribution" of the burdens and benefits of research. This principle guides the selection of subjects for participating in research.

These three ethical principles need to be independently addressed to satisfaction for research to proceed. However, the appropriate solution to satisfy one principle may be in direct conflict with that of another one. For example, the equal distribution of burdens and benefits of research may dictate that both patients and healthy controls participate in research. However, the risk/benefit ratio may differ for the patients and the controls, and may prevent healthy controls from participation.

Finally, this overview needs to acknowledge the current political context. Federal regulations for human research have not been altered since 1981 despite significant changes in the conduct of clinical research (e.g., private versus federal financing sources, multicenter versus local data collection, and advent of genetic and brain imaging techniques). Efforts are presently being made to address the ethical issues raised by "modern clinical research" (Moreno et al., 1998). In the midst of this reevaluation of the current ethical guidelines and regulatory requirements for human research, the National Institutes of Health (NIH) is acknowledging the status of children as "research orphans", and is launching an initiative requiring investigators to now justify the exclusion of minors from their research protocols. Only ethical issues specific to PET imaging, rather than those common to all research involving children (for review, see Hoagwood et al., 1996), will be addressed herein.

The assessment of the risk/benefit ratio will prevail in this review, because it is the most controversial aspect of conducting PET research in children.

2. Why Involve Children in PET Imaging?

2.1 PET Specificity

Part of the design of a human study is the choice of the optimal methodology that can provide the appropriate measures to answer the research questions, and that represent the least risk for the research participants. Other functional neuroimaging, such as functional MRI or MRS, are commonly proposed as "better" means to study brain function because they do not involve radiation exposure. It all depends on the research questions. For example, if the question relates to the identification of brain regions that subserve the performance of a cognitive task, then fMRI is probably a better alternative. If the question concerns the examination of neurotransmitter function in the brain, then only PET is appropriate at the present time. Other more subtle factors are also to be considered. For example, certain hypotheses
require the collection of data within a certain timeframe (in the order of seconds, minutes, or longer), which can dictate the choice of the brain imaging technique. In this review, we will examine the ethical issues of involving children in PET studies, when PET represents the only alternative available for studying a given research question.

2.2 Normal brain development

At present, treatments of psychiatric disorders are palliative, at best. Much work is directed towards prevention and identification of causal mechanisms to develop curative interventions. To this end, the understanding of the processes of normal brain development and maturation is imperative.

Brain maturation continues long after birth, and leads to structural as well as functional changes. This prolongation of cerebral development might be part of the mechanisms that allow the environment to interact with the 'hardware' of the brain. This malleability occurs within the anatomical and physiological determinants laid down by genetic factors. Whereas the nature and schedule of structural changes have begun to be delineated by MRI studies (Reiss et al., 1996; Giedd et al., 1997), the description of functional maturation lags behind. To date, Chugani et al. (1987; Chugani, 1997) published the only functional neuroimaging studies of brain development. Despite methodological limitations (small sample sizes, sub-optimal control subjects), these studies provided an initial template of cerebral maturational events to be accounted for in future functional neuroimaging studies of diseased children. The time course of the changes in regional cerebral glucose metabolism seemed to match those describing the processes of overproduction and subsequent elimination of excessive neurons, synapses, and dendritic spines. Still in need of study is the maturation of neurobiochemical systems. Although techniques such MRS have begun to be used for this purpose (personal communication, Yurgelun-Todd, 1998; Hanaoka et al., 1998; Kato et al., 1997), only PET methodology can assess, at present, neurotransmitter systems with specificity.

In addition, a large body of evidence stresses the role of sex hormones in brain development. Again, whereas influences of puberty have begun to be documented in structural MRI studies (Giedd et al., 1997), there is a dearth of data in functional neuroimaging research. To our knowledge, the only report of puberty-related changes in brain activity indicated a reduction of global cerebral glucose metabolic rate with greater sexual maturation in girls, independently of age (Ernst et al., 1997).

Ultimately, knowledge of normal brain development will help understand human brain plasticity, particularly in identifying periods of neural vulnerability, as well as those with a potential for
compensation. Such understanding can lead to the identification of windows of opportunity for preventing or treating neurodevelopmental disorders.

2.3. Age-Matched Control Subjects in Studies of Neurodevelopmental Disorders

It is easy to understand how the study of healthy children as controls is required to interpret findings in diseased children. Alternative strategies have been used. For example, brain imaging results collected as part of clinical diagnostic assessments have been employed for comparison data. The claim that, when these clinical results are inconclusive, they can be presumed to be "normal" is an assumption. What are the errors made using this strategy, and what are the consequences of these potential errors both in terms of ethical issues, as well as for the potential misinterpretation of findings?

Finally, what is the loss to society for not conducting studies of healthy children, against the risk of such studies?

3. Risks in PET Studies

The risks uniquely associated with PET studies are of two kinds, 1) stress related to the procedure (e.g., visit to a hospital, lying down with the instructions of remaining still, placement of venous catheter), and 2) physical side effects associated with venous line, and exposure to ionized radiation. The placement of an arterial line to provide the necessary blood samples to the modeling of dynamic PET studies can often be avoided and its risks will not be considered (Jons et al., 1997).

The potential stress can be greatly diminished by carefully preparing the child to the PET situation. Familiarizing children with the procedure by role rehearsal has been used successfully in other brain imaging studies (Rosenberg et al., 1997). In fact, it is conceivable that the participation in such studies may help demystify the hospital setting, thus making future visits to doctors and hospitals less stressful. The systematic use of a topical anesthetic to numb the site of needle puncture can also significantly reduce the stress related to catheter placement.

For most IRBs, whose mandate is to protect the rights and to safeguard the welfare of research subjects, the most disturbing risk in PET protocols is that associated with radiation exposure. These risks include carcinogenesis and genetic effects in future generations (Brill, 1987). Such risk has been evidenced at high doses of radiation exposure. The incidence rate of cancer in individuals exposed to low-level radiation (by definition, low-level exposure corresponds to radiation doses below 10-20 rem)
cannot be detected above the incidence rate of cancer in the general population, in studies with sufficient statistical power (i.e., large enough samples). This conclusion is based on a comprehensive review of the findings of the largest studies of low-level radiation exposure from various sources (background, medical, and occupational) (Ernst et al., 1998).

Most studies have been conducted with adults. It is conceivable that children be more vulnerable to radiation exposure because developing tissues are more sensitive to the effect of radiation (more powerful effect on dividing cells). At low/moderate-level radiation, there may be a higher incidence of thyroid cancer in children younger than 5 years of age. Indeed, the only large study to report an increased incidence of thyroid cancers following radiation exposure in childhood is from Israel (Ron and Modan, 1980). The incidence of thyroid tumors following scalp irradiation of children with tinea capitis was calculated retrospectively for about 11,000 subjects exposed to radiation before age 15, and 16,000 controls followed from 1950 to 1972. Mean age at radiation exposure was 7.1 years (1 to 15 years of age). Doses of exposure to the thyroid gland were estimated to average 9.3 rem with a range from 4.5 to 50.0 rem. Incidence of thyroid cancer was significantly higher in subjects exposed to radiation than in controls (14.5 excess thyroid cancer / 100,000 person-years), and was due to an excess incidence in the children younger than 5 years at the time of exposure. The generalization of this finding to the risk from low-level radiation is problematic given the high proportion of children exposed to moderate-level (above low-level thresold), and the lack of true measure of the radiation exposure.

To our knowledge, the highest dose used in PET research protocols with healthy children (12 years of age and older) has been 0.06 rem to whole body (155 times smaller than the lowest dose of exposure in the above study). Limits on radiation exposure to research subjects are set by regulatory bodies such as the U.S. Food and Drug Administration (FDA, 1996) and institutional radiation safety committees. Regulations in the U.S. typically restrict radiation exposure in minors participating in research studies to 0.5 rem per year, which is one-tenth that allowed in adults (5 rem per year). New developments in the PET technology, such as the emergence of 3-D cameras with higher sensitivity, will permit to reduce further the dose of radioactive tracer in PET studies.

Another way to evaluate the risk of radiation exposure is to assess its effect at the cellular level. The effect of radiation that confers biological risks is that of unrepaired genetic mutation. Spontaneous genetic mutations are common events. They are estimated to average 240,000 genetic mutations every day in the human body (Billen, 1990). These mutations are corrected physiologically by powerful cellular repair mechanisms. Exposure to 1 rem adds about 100 more genetic mutations (Billen, 1990).
Although debated, there is some evidence that low-level radiation can have a protective effect from subsequent high-dose radiation exposure by stimulating chromosomal repair mechanisms (for review, see Ernst et al., 1998).

The lay perception of risk from radiation exposure is highly colored by the horror associated with the atomic bomb, and tends to ascribe a risk that exceeds that reported in controlled studies of radiation exposure in large samples. In addition, this viewpoint is often reinforced by publications of letters to the editors in prestigious journals from individuals who take findings out of context and “reinterpret” them in alarmist ways. A process of careful collaboration and consultation among researchers, local Radiation Safety Committee (RSC) or Radioactive Drug Review Committee (RDRC), and IRB members is essential for a logical, unfragmented risk assessment, with each party contributing their specific expertise and taking the appropriate responsibility.

4. Benefit/Risk Ratio in PET Studies

The federal research safeguards for children (CFR-45) indicate that research on children may not be conducted with substantially greater than minimal risk unless there is direct benefit to the child. The benefit/risk ratio needs to be at least as good as available alternatives. When the risks are just above minimal risk and when there is no prospect of direct benefits to the subjects, the research may still proceed if there is compelling evidence of sizable benefits to society. Therefore, the concept of “minimal risk” is crucial in the conduct of research in children. This standard is, unfortunately, quite ambiguous.

Defined by 45-CFR, "minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” This definition implies that the everyday risks that parents and society routinely approve for children may include activities such as bike riding, roller-skating, riding in a car, and seasonal activities such as swimming or skiing. However, what is “normal” for one child may not be normal for another child. For example, it is to be expected that the daily risks experienced by a patient with a behavioral disorder such as attention-deficit hyperactivity disorder differ from the daily risks of a control healthy subject.

Direct benefits usually refer to potential therapeutic gains. However, one benefit, not addressed because of its high dependence on how research is conducted, is the experience for a child to participate...
as an autonomous individual to an adult enterprise whose purpose is to help society at large.

Examination of this aspect of research with children as a “learning experience” would be very helpful in identifying strategies that could contribute to develop ego development and a sense of altruism.

5. Conclusion

In conclusion, how do the risks of PET procedures compare to the risks of daily activity of children? Are findings from PET research “sizable to society”? And finally, what is the loss or cost of not conducting PET neuroimaging research in children, particularly healthy controls?

References


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