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Noninvasive Visualization of Serotonergically Mediated Pathophysiology

As described in the article *MDMA (''Ecstasy'') and Its Predisposition to Cerebrovascular Accidents: Preliminary Results* in this issue of the *AJNR* (page 1001), the acute and chronic morbidity associated with recreational serotonergic drug abuse seems to be escalating. At the same time, serotonergic drugs are becoming increasingly important for the treatment of several peripheral and central nervous system disorders. These factors suggest that neuroradiology could benefit from the development of imaging that can reveal the pathophysiologic changes mediated by serotonin.

Radiopharmaceuticals that behave like serotonergic drugs have a role in the research of 3,4-methylenedioxymethamphetamine (MDMA)-induced brain dysfunction. Reneman et al effectively used a serotonergic radioligand, iodine-123 [^{123}] labeled R91150, to show that there are subacute and chronic pathophysiologic consequences of abusing MDMA. The etiology may not be completely clear because several mechanisms of action probably contribute to MDMA-mediated axonal injury and death. It does seem certain, however, that a noninvasive technique for visualizing the adverse effects of MDMA on serotonergic neurons in the brain has been developed successfully. As a single-photon emission CT (SPECT) ligand, R91150 has the potential for use on existing equipment in most conventional medical facilities. This could greatly accelerate research, but will not be enough to understand the pharmacology of drugs like MDMA. Direct measurements of the other physiologic processes that the drugs influence are still needed.

Functional MR (fMR) imaging may be a nearly ideal technology for furthering this work. Changes in regional cerebral blood flow usually reflect changes in regional brain metabolism. The majority of the energy consumed by the brain reflects the work required to conduct neural transmission (1). It follows that changes in fMR imaging signals ultimately reflect drug-induced changes in neural transmission. Extrapolating in the opposite direction, the lack of appropriate changes in fMR imaging signals may reflect deranged neural transmission, including MDMA toxicity. Nonetheless, as the authors note, the relationships may not be completely straightforward.

A vast amount of literature shows that drug-induced changes in brain function and behavior are complex, and these changes sometimes are located far from areas of direct drug action. Indirect drug effects in distant areas are produced only occasionally by a direct drug action on the structures that the distant neurons reciprocally innervate. Distant effects can be complicated because the brain actively resists the perturbation of homeostasis caused by drugs. The introduction of foreign drug substances that bind receptors will perturb steady-state neurotransmitter tone, but the metabolic response by the brain can depend on many extraneous factors, such as the dose, rate, and frequency of administration. Agonists sometimes decrease the amount of work necessary to maintain neurotransmitter tone by providing artificial stimulation to the system. As a consequence, agonists can reduce blood flow in regions they bind directly, while increasing blood flow in distant target areas where they do not. Antagonists can have the opposite effect. These generalizations are, however, not laws of nature, but rather observations in some patients taking some drugs some of the time.

Investigators have noted that systemically administered drugs frequently have regionally specific effects that may be the opposite of their effects on other areas. Several mechanisms can produce this phenomenon. Most commonly, different neuroreceptor subtypes have different topographical distributions; however, the same receptor subtype will sometimes produce opposite effects in different regions of the brain (2). Selectively activating receptors in one region may inhibit the same receptors in another. As a result, it is not always clear if a drug is activating an inhibitory group of neurons or inhibiting an activating group. Many permutations of compensatory reflexes are possible.

The period between changes in neuronal transmission and changes in regional brainwork is rarely well known, which makes the usual assumption that changes in cerebral hemodynamics are instantaneous seem precarious. Advantages of [O-15] positron emission tomography (PET) and fMR imaging include the ability to make repeated measurements over short intervals during a single imaging session. Freeze-framed tracers, like fluorodeoxyglucose and all the currently available SPECT perfusion tracers, only allow one image of flow or metabolism to be acquired in a single session. This limitation obviates the ability to measure the time course of acute drug action. In contrast, fMR imaging, like [O-15] PET, has the potential to measure pharmacokinetic-equivalent curves. fMR imaging measurements can be made even faster than [O-15] PET, and without engendering more radiation dosimetry with each sampling, which makes fine temporal resolution possible. Within-session, within-subjects designs can still be confounded by the stressors that are inherent in almost any neuroimaging procedure. Since psychological perceptions of, and biological responses to, external stressors can be highly variable within subjects, it is essential to design studies in a way that allows

subjects to acclimate to the scanner before making critical measurements.

Even then, true biological variability can make defining a normal response to a drug difficult. Some drugs appear to increase cerebral flow and metabolism as often as they decrease them. This tends to make the group mean response to some drugs zero, and makes single-image, cross-sectional designs of drug effects on blood flow particularly problematic regardless of the technique used to visualize perfusion or one of its surrogates.

There are also extracerebral effects of drugs that have an impact on brain function and can confound the understanding of their central mechanisms of action. For example, psychostimulants like MDMA frequently cause reduced food intake. There are powerful somatic responses to starvation that produce their own effects on the brain. Metabolic, as well as gonadal, hormone levels invariably are perturbed, which also produces effects on the brain. Whereas not many systematic investigations of somatic MDMA toxicity have been conducted, its capacity to produce fatal hyperthermia suggests that it may produce many systemic effects that could have an impact on brain function.

This report emphasizes yet another potentially confounding situation produced by the direct effects of MDMA on the vasculature. Serotonin clearly contributes to symptom formation in migraine, and, as the authors note, there is growing anecdotal evidence that suggests that MDMA abuse is associated with stroke. A drug effect that can lead to stroke in major vessels also may be capable of producing microscopic vascular disease. This could make it difficult to determine if chronic decreases in blood flow or one of its surrogate measures reflect changes in the vasculature, or represent down regulation because a neurotoxic effect has limited the amount of work performed by the neurons. It also makes it difficult to determine if changes in neuroreceptor ligand activity represent decreased delivery of the radiopharmaceutical secondary to vascular disease, decreased numbers of neurons secondary to ischemic damage, or pathophysiologic down regulation secondary to other drug effects on the neurons themselves.

These issues constitute challenges that sometimes appear formidable; however, the field has no choice but to attack them vigorously. The fact that patients with serotonergic drug abuse–related neuropsychiatric disorders sometimes suffer immense psychological anguish makes it morally imperative for medical research to push the field forward. The fact that society is economically, as well as culturally, impoverished by serotonergic drug abuse and its consequences makes further investigation pragmatic. On both levels, the authors have reported several major contributions to the field. They have shown that it seems possible to measure physiologic correlates of serotonergic drug abuse. Publicizing hard data that show persistent brain dysfunction resulting from abuse of MDMA may help prevent many people at risk from ever experimenting with the drug. It may not be important that complete characterization of the pathophysiologic processes that produce brain damage are not clear yet. What seems most relevant is demonstrating, as the authors have, that imaging technologies and scientific paradigms have been developed that validate social and political decisions to support research in this field.

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MR Imaging of Hypertrophic Olivary Degeneration: Is There a Role for Metaanalysis?

Metaanalysis is a method used for integrating and combining the results of independent studies. Combining data from a variety of scientific studies can increase the power to detect effects, more precisely estimate the impact of these effects, or address a question not posed by the original investigators (1). Traditionally, metaanalysis has been used to analyze multiple, randomized, controlled trials in which results may be inconsistent or inconclusive. Metaanalysis also can be applied to data from observational studies, if they are of sufficient quality.

Goyal et al, in this issue of the *AJNR* (page 1073), elegantly used metaanalysis on multiple observational studies to determine the sequential MR imaging findings of inferior olivary nucleus hypertrophy and T2-weighted hyperintensity in hypertrophic olivary degeneration (HOD). The authors studied 45 subjects with this rare disorder by carefully combining 39 patients reported in the literature with six patients from their institution. This pooling of data allowed them to estimate more precisely the temporal evolution of MR imaging changes in HOD.

In order to maximize the validity of the results of a metaanalysis, the following criteria should be fulfilled: 1) All relevant scientific manuscripts should be identified in a comprehensive and ex-

haustive search of multiple sources. 2) The studies included in the summary should be of high scientific quality, the study populations should be similar, and the outcomes should be measured in the same way. 3) Bias in the studies selected for inclusion should be controlled. 4) Analyses should be done to determine the impact of excluding or including certain studies (1).

In metaanalysis, the collection of all available studies is time consuming and difficult because it involves the identification and assembly of published and unpublished literature found through indices, Medline, registries, and files (2). Furthermore, many studies may appear in several different published formats, such as abstracts, theses, or final scientific articles. Because a sound statistical analysis requires that studies be independent, only one report of any study should be included (2). Goyal et al identified 39 patients in 13 published articles. Inclusion criteria included clear temporal documentation between the onset of HOD and the MR imaging findings.

Goyal et al focused their metaanalysis only on the published literature. There is controversy whether unpublished data should be included in a metaanalysis (1). Negative studies are more likely to be unpublished than positive ones, so metaanalysis is prone to publication bias; relying on published studies could overestimate the presence of HOD patients with positive MR imaging findings. Nonetheless, arguments for exclusion of unpublished data, such as lack of a thorough peer review, are equally valid. Alternatively, sensitivity analysis could be used in metaanalysis to determine the impact of any questionable studies on the results. Sensitivity analysis would consist of the recomputation of estimated effects with the study or studies in question removed, and examination of the influence on the results and final conclusion.

When results of individual studies are inconclusive, or when large samples are required to reveal an effect or correlation, metaanalysis can be a useful technique. Goyal et al pooled 58 MR studies in 45 patients to increase their sample size. A similar strategy has been used in other areas of radiology. For example, recent metaanalysis of the effectiveness of breast cancer screening in women 40–49 years old has contributed to changes in clinical practice recommendations for this controversial group (3).

Metaanalysis is prone to the same pitfalls seen in other study designs. The statistical power of a study decreases if the number of subjects is spread over a long period. Goyal et al combined data collected over more than 10 years from 45 subjects, with a mean number of 1.3 MR imaging studies per patient. The end result of the data being spread over this long time span is the relatively few data points per period (ie, per month and year). Therefore, sound understanding of the data variability for a specific interval is limited because of the low number of subjects and MR imaging studies per period. In the future, the robustness of the results discussed by Goyal et al could be enhanced by adding more data points to the metaanalysis as new articles and reports become available.

Is there an important role for metaanalysis in neuroradiology and the neurosciences? Goyal et al have used this method creatively to elucidate the temporal evolution of MR imaging findings in HOD. Metaanalysis could play a pivotal role in determining the effect of new imaging and interventional techniques on patient outcome in common disorders such as acute cerebrovascular accident, epilepsy, and carotid atherosclerotic disease. Small inconclusive studies could be combined in a scientific manner, so that large trials may be avoided if the accumulating evidence from small trials becomes conclusive. Judicious use of metaanalysis may open the window to new insights about the natural history, as well as the proper use of diagnostic tools and interventions, in multiple neurodisorders.

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Etiology of Congenital Growth Hormone Deficiency

Growth hormone deficiency (GHD) comprises a spectrum of diseases. The disorder may consist of an isolated deficiency of GH, or it may be part of a syndrome of multiple pituitary hormone deficiencies (MPHD). Morphologic changes in the pituitary gland and stalk have been observed in a large percentage of these cases on MR images. Since the late 1980s, when these morphologic changes were first reported, there have been a large number of reports describing this disease in both the radiology and endocrinology literature. Some of these reports had large cohorts with series of over 100 patients. In the numerous publications that now exist on this topic, two hypotheses have been proposed about

the etiology of this disease: perinatal head trauma and dysgenesis.

The earliest reports on the MR imaging findings in children with GHD documented a striking association between adverse perinatal events and breech delivery, leading to the hypothesis that birth or perinatal trauma might be the cause of the pituitary stalk transection that is observed so frequently in this disease. In 1990, Maghnie et al reported 37 cases of MPHD and GHD (1). Adverse perinatal events were present in 80% of those cases in which morphologic lesions were observable on MR images, but the incidence of perinatal events was much lower in those with normal-appearing MR images or isolated GHD. The authors speculated that the disease was a congenital syndrome worsened by breech delivery.

In the middle 1990s, reports appeared documenting an association of GHD and MPHD with midline anomalies of the brain, including lesions of the corpus callosum, septum pellucidum, and optic chiasm and nerves (2–4). A familial association also became recognized. Authors began to favor more strongly a genetic etiology for this disorder.

Triulzi et al published an important study with a series of 101 patients in 1994 (2). Only 32% of the patients in this series had a breech delivery. He concluded that the disease in the other 68% had to have a different cause. He also reported that 12% of the patients in his series had anomalies of the brain. He concluded that dysgenesis was the probable etiology of GHD and MPHD in the majority of cases, and he implied that breech presentation was the result of a fetal endocrinopathy, rather than breech presentation (with perinatal head trauma) being the cause of the endocrinopathy. Many subsequent papers, including the paper by Maintz et al in this issue of the *AJNR* (page 1116), have documented further familial occurrences of this disorder, lending more weight to the hypothesis that dysgenesis is the etiology of many, or even most, cases of GHD.

It seems reasonable to conclude that GHD and MPHD are genetically determined diseases in most cases, and that breech delivery has the potential to worsen the severity of the pituitary endocrinopathy. Although breech presentation is strongly associated with fetal hypopituitarism, breech presentation probably causes very few cases. That does not indicate that dysgenesis is the only cause of GHD and MPHD. It is well recognized that blunt head trauma can transect the stalk, and cases of stalk transection can result in GHD in children (4).

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