Introduction

Imaging the Future

By Nikos Makris, MD, PhD, Scott L. Rauch, MD, and David N. Kennedy, PhD

For more than 20 years, magnetic resonance imaging (MRI) has been used to visualize brain structure noninvasively in clinical and research settings. During that time, the science of MRI has evolved, remaining a powerful research method for testing hypotheses of brain volume and shape. From this, the techniques of diffusion imaging have emerged. Diffusion-weighted imaging (DWI) is a general term encompassing methods for characterizing magnetic resonance signal alterations caused by water diffusion during the imaging procedure. The specific method, diffusion tensor MRI (DT-MRI or DTI) is an application of DWI incorporating diffusivity measurements along multiple orientations. This full tensor representation is necessary, as DT-MRI provides a means for better characterization of fiber pathway orientation. These methods capitalize upon the diffusion properties of water contained in the human brain. DT-MRI enables the mapping of the diffusion tensor and individual fiber tracts in three-dimensional (3-D) space. However, the advancement of MRI technology has made it feasible to acquire diagnostically relevant DT-MRI data within the constraints of the clinical setting. We now stand at the threshold of a new era, armed with a safe, noninvasive, in vivo method for discerning the anatomic connections of the brain in health and disease in a fashion that exceeds the sensitivity of previous anatomic methods. In the current issue of CNS Spectrums, we present articles that review the principles of DWI, emphasizing DT-MRI, and provide examples of their application in normal and neuropsychiatric conditions.

In this month’s first feature, Drs. Davis and Tuch review Brown’s observation, in the early part of the 19th century, of “rapid oscillatory motion” of pollen grains suspended in water and how this phenomenon was explained by the kinetic theory of matter. They also reexamine the historical origins of diffusion measurements with MRI and the magnetic resonance of diffusion in vivo. DT-MRI provides a highly sensitive probe of tissue microstructure; and because of the microscopic length of diffusion in biological tissues, DT-MRI is able to reveal histological architecture irreversibly by conventional MRI methods.

Next, Dr. Pierpaoli explores the microstructural, anatomical, and physiological information inferred from diffusion tensor data. By assuming Gaussian diffusion within each voxel, Peter Basser originally introduced the diffusion tensor model to DT-MRI. This approach enabled the description of the fiber directions and the measurement of useful scalar metrics, such as the fractional anisotropy metric and diffusion tensor trace. Dr. Pierpaoli, along with Basser, introduced the lattice anisotropy metric. Dr. Pierpaoli reviews potential applications for these technologies.

In their original research article, Dr. Makris and colleagues demonstrate an application of DT-MRI. Based on the orientation of the cingulum bundle, they identified and performed volumetric and biophysical measurements of its compact portion (ie, the stem). Their method is based on direct visual inspection of the color-coded DT images and manual selection of the voxels that are situated in the anatomic location of the pathway under investigation on a slice-by-slice basis. Dr. Makris and colleagues introduced DT-MRI for the analysis of the associative fiber tracts of the brain, which are indiscernible by MRI. For this purpose they implemented a 3-D, color-coding scheme of the diffusion tensor to show the different orientations of these white matter fiber pathways and validated them using classical brain maps.

In his review, Dr. Mori reviews techniques of DT-MRI to delineate white matter fiber tracts. Dr. Mori and colleagues pioneered the application of DT-MRI to provide 3-D representations of fiber pathways in the brain. Their approach, called “fiber assignment by continuous tracking,” was model-based and validated in a rat brain. Dr. Mori highlights two methods for DT-MRI-based fiber tract analysis: (1) “the color map approach” and (2) the “3-D tract reconstruction.” The first approach is similar to the method used by Dr. Makris and colleagues in their study. The analysis is model-independent and performed on individual coronal, axial, or sagittal slices on which the tensors have been color-coded for the three spatial orientations. The second technique is computer-aided and 3-D: Conceptually, a line is propagated from a seed voxel by following fiber orientation information at each voxel. In this fashion, a fiber tract is reconstructed in 3-D for almost its entire trajectory.

In this month’s final review, Dr. Sorensen and colleagues survey a spectrum of DWI clinical applications. They have done extensive, innovative work applying DWI in the early stages of stroke. Herein, they illustrate the utility of DWI and DT-MRI in several diseases that affect the integrity of white matter. Furthermore, they review the application of these methods in neurological and psychiatric conditions. They suggest that DT-MRI could be used as an early marker to predict clinical outcome and validate or guide therapeutic strategies.

Overall, the aim of this issue is to review the physical principles, methods, and uses of DT-MRI in neuroanatomy and clinical neuropsychiatry. Although these techniques are still evolving, future applications promise to further elucidate the detailed ultrastructure of brain connectivity in vivo. Thus, this exciting technology is anticipated to have a significant impact on medical practice.
ADDERALL XR was generally well tolerated in clinical trials of pediatric patients. The most common adverse events include loss of appetite, insomnia, abdominal pain, and emotional lability. As with other psychostimulants indicated for ADHD, there is a potential for exacerbating motor and phonic tics and Tourette's syndrome. A side effect seen with the amphetamine class is psychosis. Administration of amphetamine may exacerbate symptoms of behavior disturbances and thought disorder in psychotic patients. ADDERALL XR is contraindicated in patients with symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism and glaucoma, known hypersensitivity or idiosyncrasy to sympathomimetic amines, agitated states, history of drug abuse, or within 14 days of administration of a MAO inhibitor. The possibility of growth suppression warrants monitoring of patients receiving long-term therapy. Prolonged use of amphetamines may lead to drug dependence. ADDERALL XR should be prescribed with close physician supervision as part of a multimodal treatment program for ADHD.

Dopamine (DA) and norepinephrine (NE) are believed to play critical roles in the pathology and treatment of ADHD. ADDERALL XR is thought to increase the levels of both DA and NE in the synapse. ADDERALL XR provides unparalleled dosing flexibility with significant all-day improvement in:

- Attention
- Behavior
- Academic Performance

Make patient-friendly ADDERALL XR your ADHD treatment option of choice!

ONE DOSE DAILY

Removing obstacles in ADHD™

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A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-), and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 mg/kg/day. Amphetamines may produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and 0 of 12000 spontaneous revertants in the mouse lymphoma assay. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated by co-administration of MAO-inhibitors, amphetamine antagonists (approximately 6 times the maximum recommended human dose of 30 mg/day on a mg/m² basis) or greater levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL®, is a stimulant primarily used to treat narcolepsy, what is now classified as a sleep disorder. It is also used to treat ADHD in children, but not in adults. Amphetamines are not recommended for use in children under 3 years of age. Use in Children Under Six Years of Age: Effects of ADDERALL® in 3-5 year-olds have not been studied. Adverse Events Associated with Prenatal Exposure to Amphetamine: There have been no published reports indicating that prenatal amphetamine exposure has been associated with any specific neonatal problems in survivors. Although the effects of prenatal exposure to amphetamine cannot be predicted, some effects of amphetamine on the pregnant mother and on the fetus should be recognized. Amphetamines should be avoided during pregnancy.

INDICATIONS
ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The safety and efficacy of ADDERALL XR® have been established in children 6 years of age and older and the controlled trials of children aged 6 to 12 who met DSM-IV criteria for ADHD, with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

CONTRAINDICATIONS
Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma, and uncontrolled torsades de pointes. These conditions are associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

PRECAUTIONS
General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose.

Hypersensitivity Reactions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulses should be monitored, especially during the initial therapy with amphetamines. Tics: Amphetamines have been reported to exacerbate or minimize tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulants.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating motor vehicles or hazardous machinery.

Drug Interactions: Activating agents—Gastrointestinal activating agents (pyridoxine, thiamine, glutamic acid, aspirin, etc.) lower absorption of amphetamines.

Urinary alkalinizing agents (ammonium chloride, sodium bicarbonate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents increase blood levels and potentiate the actions of amphetamines.

Anticonvulsants—Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or propranolol and possibly other beta-adrenergic agents increases the levels of d-amphetamine in the brain; cardiovascular effects can be potentiated by co-administration of MAO inhibitors—MAO antidepressants, as well as a metabolite of furosemide, slow amphetamine metabolism, and increase their effect on the release of norepinephrine and other monoamines from serotonergic nerve endings. This can cause hallucinations and other signs of hyperactivity, excitability, and paranoia. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Anorexiant—Amphetamines may counteract the satiating effect of antiobesity agents.

Antihypertensives—Amphetamines may increase the central effects of antihypertensives, thus increasing the central stimulant effects of the amphetamines.

Chlorpromazine—Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines.

Cigarette smoking—Amphetamines may delay intestinal absorption of nicotine, increasing the risk of smoking.

Chlorpromazine—Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines.

Antihypertensives—Amphetamines may antagonize the hypotensive effects of antihypertensives.

Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may reduce the urinary excretion of amphetamines.

Propoxyphene—Amphetamines may delay intestinal absorption of propoxyphene, increasing the levels. This increase is greatest in the evening.

Adrenergic blockers—Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may reduce the urinary excretion of amphetamines.

Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid, etc.) lower absorption of amphetamines.

Phenytoin—Amphetamines may antagonize the hypotensive effect of veratrum alkaloids.

Adverse Events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients on ADDERALL XR® are listed in the table below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Although adverse events associated with the use of any stanning medication may occur with lower frequency than in clinical trials, they should be reported. In every case, the benefit of therapy with Adderall XR® should be weighed against the potential risk of adverse events.

Table 1 Adverse Events Reported by More Than 1% of Patients Receiving ADDERALL XR® with Higher Incidence on Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>ADDERALL XR®</th>
<th>Placebo (N=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Appetite Loss</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Depression</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Urinary Excretion</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

The following adverse reactions have been associated with amphetamine use:

Central nervous system (e.g., tics and Tourette’s syndrome, aggressiveness, irritability, anxiety, and personality changes). The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

Symptoms usually appear within 4 hours to 7 days after the last dose and may last up to 2 months. The most frequent adverse events associated with the use of amphetamines are not drug-related and do not cease with discontinuation of therapy. The most severe adverse effects associated with the use of amphetamines are not drug-related and do not cease with discontinuation of therapy. The most severe adverse effects associated with the use of amphetamines are not drug-related and do not cease with discontinuation of therapy.
Effective first-line SSRI therapy with a FAVORABLE side-effect profile

- Incidence of insomnia, anxiety, agitation, nervousness, and fatigue comparable to placebo
- Not associated with clinically significant long-term weight changes*
- Efficacy proven in the treatment of depression
- Once-daily 20 mg starting dose for all patients

The most frequent adverse events reported with CELEXA vs placebo in clinical trials were nausea (21% vs 14%), dry mouth (20% vs 14%), somnolence (18% vs 10%), insomnia (15% vs 14%), increased sweating (11% vs 9%), tremor (8% vs 6%), diarrhea (8% vs 5%), and ejaculation disorder (6% vs 1%). CELEXA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients with a hypersensitivity to citalopram HBr or any of the ingredients in CELEXA.

*CELEXA therapy was associated with a mean weight increase of only 1.5 kg after 12 months.

Visit the CELEXA Web site at http://www.celexa.com

Please see brief summary of prescribing information on adjacent page.
suggestions that citalopram is a relatively weak inhibitor of CYP3A4. However, at 10 mg/day for 21 days, CYP3A4 activity was increased by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of the CYP1A2 substrate theophylline. The use of concomitant drugs can affect the clearance of citalopram, which may alter its serum concentrations and possibly increase the risk of side effects. The use of concomitant drugs should be cautious and monitored to prevent drug interactions. For patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), the use of citalopram is contraindicated. The use of citalopram in patients with a recent history of myocardial infarction or unstable heart disease is not recommended.
ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL ONSET SEIZURES IN ADULTS WITH EPILEPSY

UNDER CONTROL

Keppra®
levetiracetam
250 • 500 • 750 mg tablets

SIMPLIFYING SEIZURE CONTROL

- PROVIDES UP TO 4 OUT OF 10 REFRACTORY PATIENTS WITH ≥50% PARTIAL ONSET SEIZURE REDUCTION
- NO DRUG/DRUG INTERACTIONS WITH AEDs INCLUDED IN WELL-CONTROLLED STUDIES, A COMBINATION ORAL CONTRACEPTIVE, WARFARIN, OR DIGOXIN
- GENERALLY WELL TOLERATED

Keppra® use is associated with the occurrence of central nervous system adverse events, classified as somnolence and fatigue, coordination difficulties, and behavioral abnormalities; and with minor, but statistically significant, hematological abnormalities. Keppra® dosing must be individualized according to renal function status.

Efficacy and tolerability in an easy-to-use AED—add-on therapy starts with Keppra®

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Published online by Cambridge University Press
The hydrolysis product and major human metabolite of levetiracetam (UCB L057) was not mutagenic in the Ames test or in the in vivo mouse lymphoma assay. Impairment of fertility: No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day by oral gavage. In human fertility studies, levetiracetam was not found to impair fertility or to affect the results of fertility tests. Pregnancy: Pregnancy Category C. In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses. Administration to pregnant rats and rabbits suffering from in utero overcrowding and fetal skeletal abnormalities and retarded offspring growth pre- and postnatally at doses greater than 3000 mg/kg/day by oral gavage (approximately 4 times MRHD on a mg/m² basis) and with increased pup mortality and offspring behavioral ataraxia at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m² basis). The developmental no effect dose was 1000 mg/kg/day by oral gavage (approximately 1.5 times the MRHD on a mg/m² basis). In pregnant rats, levetiracetam was not used in this study. Treatment of pregnant rabbits during the period of organogenesis resulted in increased incidences of fetal malformations at a dose of 5000 mg/kg/day by oral gavage (approximately 8 times the MRHD on a mg/m² basis) and in decreased fetal weight and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m² basis). The developmental no effect dose was 1000 mg/kg/day by oral gavage (approximately 1.5 times the MRHD on a mg/m² basis). Maternal toxicity was also observed at 1800 mg/kg/day. When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m² basis). There was a developmental no effect dose. There was no evidence of maternal toxicity in this study. Treatment of pregnant rabbits during the period of organogenesis resulted in increased incidences of fetal malformations at a dose of 5000 mg/kg/day by oral gavage (approximately 8 times the MRHD on a mg/m² basis) and in decreased fetal weight and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m² basis). The developmental no effect dose was 1000 mg/kg/day by oral gavage (approximately 1.5 times the MRHD on a mg/m² basis).