

# Brain workouts boost attention

## Imaging study suggests mental exercise can help ADHD

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**R**esearch over the past decade suggests that the brain, like muscles, might get stronger after a good workout. Some evidence suggests that patients with attention-deficit/hyperactivity disorder (ADHD) can improve focus and concentration with mental exercises.

Research has unveiled the brain's remarkable capacity for structural change as the result of experience. Repeating a specific brain function enhances neural mechanisms by increasing synapse formation or generating new neurons.<sup>1</sup> Increased use of neurons likely activates growth factor proteins that stimulate neural growth.

Healing the brain by exercising an impaired region is of great interest to physicians. For example, a group at Yale University showed that children with dyslexia who receive proper reading instruction read more fluently and show increased activity in the left hemisphere regions that decode words.<sup>2</sup> Other research has shown that constraint-induced movement therapy—when a stroke patient is forced to use his or her impaired arm or leg by restraining the good one—can “reawaken” parts of the brain damaged by a stroke.<sup>3</sup> Researchers also are studying whether intellectual exercises such as reading or learning new skills can forestall Alzheimer's disease.

**Figure 1**

### EEG frequencies characterizing 4 basic brain rhythms

**Beta** (>13 Hz)

Alert and focused



**Alpha** (8 to 13 Hz)

Relaxed



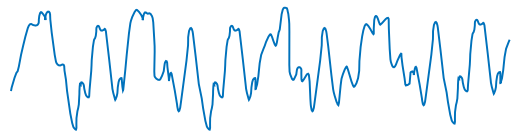
**Theta** (4 to 8 Hz)

State between wakefulness and sleep



**Delta** (<4 Hz)

Deep sleep



continued

Figure 2

## Neurofeedback training: Improvement in neuropsychological and imaging studies

### A. Neuropsychological testing

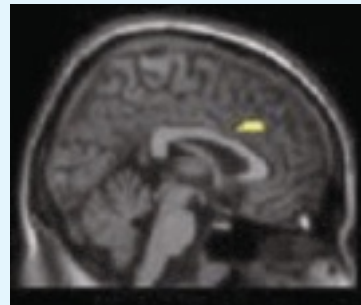
Test	Before	After
Digit Span	9.8	11.6*
Continuous Performance Test	77.5	85†
Conners' Parent Rating Scale Inattention	71.6	58.9‡
Conners' Parent Rating Scale Hyperactivity	79.4	64.3*

\*P < 0.05 †P < 0.005 ‡P < 0.001

(a) Neuropsychological testing before and after neurofeedback therapy

Source: Reference 6

### B. Imaging study



(b) Anterior cingulate gyrus (in yellow) was more active after neurofeedback treatment

## NEUROFEEDBACK BASICS

Can the brain's malleability help children with ADHD? Imaging studies show that children with ADHD have structural and functional deficits in the prefrontal cortex, the area associated with attention. Stimulant medications prescribed for ADHD compensate for this defect by increasing dopaminergic neuron activity in the prefrontal cortex.

**Neurofeedback**—also called EEG biofeedback—also could alleviate ADHD symptoms. For 30 years, neurofeedback has been studied as an ADHD treatment with promising results.<sup>5</sup> Improvement in attention, concentration, and working memory has been reported in up to 75% of cases in the literature, although randomized controlled trials have not been conducted.

Neurofeedback teaches an individual to regulate the electrical activity of his or her brain with mental exercises.<sup>4</sup> EEG frequencies generally can be divided into four basic rhythms:

- beta rhythm is alert and focused

- alpha is relaxed
- theta is between awake and asleep
- delta is deep sleep (*Figure 1, page 55*).

The patient aims to spend more time in the alert beta rhythm and less time in the slower, more relaxed rhythms by thinking thoughts that generate the appropriate rhythm. More time spent in beta rhythm means better attention and concentration. A computer monitoring EEG frequencies helps the patient learn to regulate his or her brain rhythms.

## ADHD HELP

A University of Montreal research group recently completed an open, randomized, neurofeedback trial of 20 children ages 8 to 12 with ADHD who do not take psychostimulants or other medications for ADHD.<sup>6</sup> Fifteen received neurofeedback therapy consisting of 40 one-hour sessions over 15 weeks. Five children who did not receive treatment served as the control group. All subjects took several neuropsychological tests measuring

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**Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms**—In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scales incidence between any dose of oral olanzapine (5+2.5, 10+2.5, or 15+2.5 mg/d) and placebo for parkinsonism (Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the highest dose of oral olanzapine (15+2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

**Other Adverse Events**—Dose-relatedness of adverse events was assessed using data from a clinical trial involving 3 fixed oral dosage ranges compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

**Vital Sign Changes**—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (see PRECAUTIONS).

**Weight Gain**—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of oral olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained >7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (238 median days of exposure), 56% of patients met the criterion for having gained >7% of their baseline weight. Average gain during long-term therapy was 5.4 kg.

**Laboratory Changes**—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (see PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=659), 0.5% experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean triglyceride increase of 20 mg/dL from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602; 3.6% vs 2.2% respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in cholesterol from a mean baseline of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL.

**ECG Changes**—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

**Other Adverse Events Observed During Clinical Trials**—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. **Frequent** events occurred in ≥1/100 patients; **infrequent** events occurred in 1/100 to 1/1000 patients; **rare** events occurred in <1/1000 patients. **Body as a Whole**—**Frequent**: dental pain, flu syndrome; **Infrequent**: abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; **Rare**: chills and fever, hangover effect, sudden death. **Cardiovascular**—**Frequent**: hypotension; **Infrequent**: atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; **Rare**: arteritis, heart failure, pulmonary embolism. **Digestive**—**Frequent**: flatulence, increased salivation, thirst; **Infrequent**: dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; **Rare**: aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. **Endocrine**—**Infrequent**: diabetes mellitus; **Rare**: diabetic acidosis, goiter. **Hemic and Lymphatic**—**Infrequent**: anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; **Rare**: normocytic anemia, thrombocytopenia. **Metabolic and Nutritional**—**Infrequent**: acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; **Rare**: gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. **Musculoskeletal**—**Frequent**: joint stiffness, twitching; **Infrequent**: arthritis, arthrosis, leg cramps, myasthenia; **Rare**: bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. **Nervous System**—**Frequent**: abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; **Infrequent**: akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; **Rare**: circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. **Respiratory**—**Frequent**: dyspnea; **Infrequent**: apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; **Rare**: atelectasis, hiccup, hypoventilation, lung edema, stridor. **Skin and Appendages**—**Frequent**: sweating; **Infrequent**: alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; **Rare**: hirsutism, pustular rash. **Special Senses**—**Frequent**: conjunctivitis; **Infrequent**: abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; **Rare**: corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. **Urogenital**—**Frequent**: vaginitis; **Infrequent**: abnormal ejaculation, amenorrhea, breast pain, cystitis, decreased menstruation, dysuria, female lactation, glycosuria, gynecomastia, hematuria, impotence, increased menstruation, menorrhagia, metrorrhagia, polyuria, premenstrual syndrome, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged, vaginal hemorrhage; **Rare**: albuminuria, breast enlargement, mastitis, oliguria. (\*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. **Body as a Whole**—**Frequent**: injection site pain; **Infrequent**: abdominal pain, fever. **Cardiovascular**—**Infrequent**: AV block, heart block, syncope. **Digestive**—**Infrequent**: diarrhea, nausea. **Hemic and Lymphatic**—**Infrequent**: anemia. **Metabolic and Nutritional**—**Infrequent**: creatine phosphokinase increased, dehydration, hyperkalemia. **Musculoskeletal**—**Infrequent**: twitching. **Nervous System**—**Infrequent**: abnormal gait, akathisia, articulation impairment, confusion, emotional lability. **Skin and Appendages**—**Infrequent**: sweating. **Postintroduction Reports**—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been rarely reported.

**DRUG ABUSE AND DEPENDENCE**: Olanzapine is not a controlled substance.

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attention and hyperactivity before and after the study (Figure 2a, page 56). On average the neurofeedback group scored significantly higher on all measures of attention without side effects compared with the control group.

A comparison of functional brain imaging scans taken before and after the study showed increased anterior cingulate gyrus activity in the frontal cortex in the neurofeedback group but not the controls (Figure 2b, page 56). Subjects took the Counting Stroop Test—a mental exercise that involves the anterior cingulate gyrus—while in the scanner. The imaging studies were averaged within the groups, and the before and after scans were subtracted from each other. The increased activity translates into improved attention and concentration and decreased impulsivity, allowing children to perform better in school, get into less trouble, and have better relationships with parents.

Although we need more studies, this research suggests that neurofeedback might be a treatment option for patients with ADHD who cannot tolerate or do not wish to take medications.

## References

- Gage FH. Brain, repair yourself. *Sci Am* 2003;289(3):46-53.
- Shaywitz SE, Shaywitz BA. Dyslexia (specific reading disability). *Biol Psychiatry* 2005;57(11):1301-9.
- Taub E, Uswatte G. Constraint-induced movement therapy: bridging from the primate laboratory to the stroke rehabilitation laboratory. *J Rehabil Med* 2003(41 suppl):34-40.
- Kraft U. Train your brain. *Sci Am Mind* 2006;17(1):58-63.
- Monastra VJ. Electroencephalographic biofeedback (neurotherapy) as a treatment for attention deficit hyperactivity disorder: rationale and empirical foundation. *Child Adolesc Psychiatr Clin N Am* 2005;14(1):55-82.
- Levesque J, Beauregard M, Mensour B. Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. *Neurosci Lett* 2006;394(3):216-21.