number of new techniques for tracing and cataloging brains, beginning in smaller animals with smaller brains as a precursor to the first human map. Because the diameter of the finest wires and synaptic connections requires electron imaging to resolve, we have automated the previously labor intensive process of brain sectioning and subsequent imaging by an electron microscope. The approach we settled on uses a novel microtome to turn the large volume of brain into a linear continuous strip of very thin tape (a process not unlike paring an apple). This tape is then automatically imaged in a scanning electron microscope with enough resolving ability to trace the smallest neuronal processes (Kasthuri *et al*, 2009). To trace the longer pathways that interconnect different brain regions, we developed a method to label each individual nerve cell a different color to identify and track axons and dendrites over long distances (Livet *et al*, 2007). Finally, we and our collaborators have been developing computationally intensive algorithms that are now for the first time automatically tracing neuronal processes and we hope eventually identifying synaptic connections in such data sets. Hand in hand with technical advances is the revolution in computing that seems to be continuing unabated (http://www.intel.com/technology/mooreslaw/index.htm). About 30 years ago, White *et al*, (1986) labored for over a decade to manually catalog the connections of the approximately 300 neurons comprising the nervous system of a single simple worm *C. elegans*. Their Herculean cartographic effort has not been equaled since, but we think will soon become relatively commonplace.

We believe that the payoff these maps will provide for neuroscience will be enormous. Many neuroscientists understand that the fundamental unit of organization of neural tissue is the synaptic connections linking neurons together. Indeed, neurons in various mammalian species seem quite similar, despite the obvious differences in behavior. The 'magic' that makes one species different from another is in how these very similar neurons connect with each other. For humans, these maps would have special significance because an Atlas of Connections (ie, the human connectome) would represent a blueprint of ourselves, including imprints of all those things that are not in our genome, such as all the things we have learned throughout our lives. In addition, it is possible that many neurological disorders, such as the Autism spectrum disorders or schizophrenia, may be the result of misrouting of neuronal wires. Detailing these 'connectopathies' might give us insights into the underlying abnormalities in what are presently quite mysterious cognitive illnesses. Finally, as with all first glimpses into aspects of the natural world previously hidden, we imagine that a considerable number of surprises await us. For example, we do not have a good idea regarding how much the pattern of connections in one brain resembles the pattern in another. Are there deep organizing principles behind the ordering of our brains, or is each brain fundamentally unique? We predict that this effort will span many decades and just as the Hubbell telescope peers into a mysterious outer space, this effort will provide the first deep look into the inner space of our minds.

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DISCLOSURE

Dr Kasthuri and Dr Lichtman declare that they have no conflict of interest relating to the subject of this report.

Denk W, Horstmann H (2004). Serial block-face scanning electron microscopy to reconstruct three-dimensional tissue nanostructure. *PLoS Biol* **2**: e329.

Kasthuri N, Hayworth K, Tapia JC, Schalek R, Nundy S, Lichtman JW (2009). The brain on tape: Imaging an Ultra-Thin Section Library (UTSL). *Society for Neuroscience Abstracts*.

Livet J, Weissman TA, Kang H, Draft RW, Lu J, Bennis RA *et al* (2007). Transgenic strategies for combinatorial expression of fluorescent proteins in the nervous system. *Nature* **450**: 56–62.

Shepherd GM (2003). *The synaptic organization of the brain*.

White JG, Southgate E, Thomson JN, Brenner S (1986). The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philos Trans R Soc Lond A* **314**: 1–340.

Neuropsychopharmacology Reviews (2010) **35**, 342–343; doi:10.1038/npp.2009.138

Modafinil: an anti-relapse medication

Relapse to drug-seeking after abstinence is the most challenging problem in treating drug addiction. Therefore, the demand for anti-relapse medications is high. Clinical trials have reported that modafinil, a wake-promoting agent used to treat sleep disorders such as narcolepsy, is effective in treating cocaine dependence. Although a weak stimulant, sites of action and behavioral effects of modafinil appear to be different from those of cocaine or amphetamine. Modafinil blunts the reinforcing as well as cardiovascular effects of cocaine. More importantly, modafinil decreases cocaine use and relapse rates in cocaine addicts (Dackis *et al*, 2005; Hart *et al*, 2008). Larger multicenter clinical trials of modafinil have found modestly positive outcomes (Anderson *et al*, 2009). In addition, modafinil showed promise in a small group of methamphetamine-dependent subjects and in pathological gamblers with high impulsivity. However, it appears that modafinil may only be effective in cocaine addicts without alcohol dependence (Anderson *et al*, 2009). Modafinil also is reported to increase negative affect and withdrawal symptoms associated with nicotine dependence. These findings indicate consideration of smoking and alcohol abuse in using modafinil as an anti-relapse medication.

Despite clinical uses of modafinil, its mechanism(s) of action is still unclear. Using an animal model of relapse, we recently found that modafinil blocked reinstatement of an

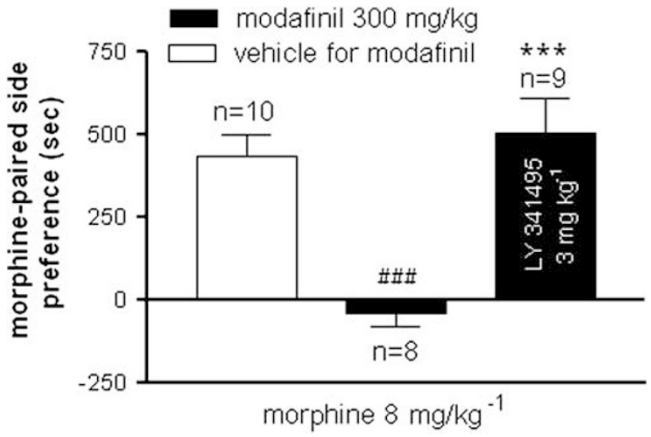

Figure 1. mGlu2/3 receptor blockade prevents the anti-relapse effects of modafinil. Rats were trained for conditoned place preference (CPP) with morphine (8 mg/kg) in a six-session conditioning protocol over 3 consecutive days. Animals were then exposed to extinction training, consisting of two daily 15-min preference tests without any treatment until the relative preference for the morphine-paired side decreased to $< +75$ s/15 min for four consecutive sessions. The reinstatement test (15 min) was conducted 24 h later. For the reinstatement test, animals received vehicle (left bar) or modafinil (300 mg/kg, i.p.; middle bar) 30 min before a priming injection of morphine (8 mg/kg) followed immediately by the preference test. Another group (right bar) was also pretreated with the mGlu2/3R antagonist LY341495 30 min before modafinil administration. Injection of LY341495 (3 mg/kg) completely reversed the anti-relapse effects of modafinil on morphine CPP. $^{###}p<0.001$ different from the control vehicle group (left bar) and $^{***}p<0.001$ different from the modafinil 300 mg/kg + morphine 8 mg/kg group (middle bar); there was no significant difference between the LY341495 + modafinil 300 mg/kg + morphine 8 mg/kg group and the morphine 8 mg/kg control group (left bar).

extinguished morphine conditioned place preference (CPP) in rats, extending the anti-relapse properties of modafinil to opiates (Tahsili-Fahadan *et al*, 2008). This anti-relapse effect of modafinil was blocked by administering an mGluR2/3 receptor antagonist, LY341495 (Figure 1), which is in line with previous findings, indicating the involvement of mGlu2/3 receptors in treatments for opiate and cocaine reinstatement in animal studies (Kalivas, 2009). This finding leads us to hypothesize that modafinil may block opiate relapse by stimulating mGlu2/3 receptors, effectively replacing the depleted tonic glutamate reservoir in the brain induced by chronic exposure to drugs of abuse, thereby preventing relapse to drug-seeking/taking (Kalivas, 2009).

In addition to this possible glutamate-mediated mechanism, modafinil is reported to affect other neurotransmitter systems such as catecholamines, serotonin, GABA, orexin, and histamine. The mild stimulant properties of modafinil may also be involved in its ability to reduce withdrawal symptoms of stimulant abuse. In a recent human PET study, modafinil was shown to block DA transporters and increase dopamine in the human brain including the nucleus accumbens (Volkow *et al*, 2009), in line with previous animal data. These and other findings highlight a potential for abuse of modafinil, although available data suggest a much lower potential for abuse and dependency than amphetamine-like stimulants (Myrick *et al*, 2004).

Altogether, modafinil shows promise as an anti-relapse medication. Nonetheless, its abuse potential and exact mechanism of action warrants further clinical and preclinical investigations.

ACKNOWLEDGEMENTS

This work was supported by PHS Grant R37-06214. Modafinil used in our studies was a generous gift from Cephalon Inc.

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DISCLOSURE

The authors declare that over the past 3 years GA-J received compensation from Lilly Pharmaceuticals, Sanofi Aventis Pharmaceuticals, Jazz Pharmaceuticals, and Lundbeck Pharmaceuticals. None of these represent a conflict of interest with respect to this article. RM and PT-F had no compensation from outside sources.

Anderson AL, Reid MS, Li SH, Holmes T, Shemanski L *et al* (2009). Modafinil for the treatment of cocaine dependence. *Drug Alcohol Depend* **104**: 133–139.

Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP (2005). A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* **30**: 205–211.

Hart CL, Haney M, Vosburg SK, Rubin E, Foltin RW (2008). Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology* **33**: 761–768.

Kalivas PW (2009). The glutamate homeostasis hypothesis of addiction. *Nat Rev Neurosci* **10**: 561–572.

Myrick H, Malcolm R, Taylor B, LaRowe S (2004). Modafinil: preclinical, clinical, and post-marketing surveillance—a review of abuse liability issues. *Ann Clin Psychiatry* **16**: 101–109.

Tahsili-Fahadan P, Carr GV, Harris GC, Aston-Jones A (2008). Modafinil blocks morphine-primed reinstatement of conditioned place preference. *Soc Neurosci*. Abstr no. 63.10.

Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W *et al* (2009). Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. *JAMA* **301**: 1148–1154.

Neuropsychopharmacology Reviews (2010) **35,** 343–344; doi:10.1038/npp.2009.123

Trick or treat? neurodevelopmental consequences of pharmacotherapy for affective disorders

Drugs used to treat affective disorders exert their effects largely through their actions on various neurotransmitter systems. Neurotransmitters are important regulators of neural development. Thus, even limited periods of drug use/exposure during fetal- or postnatal brain ontogeny,