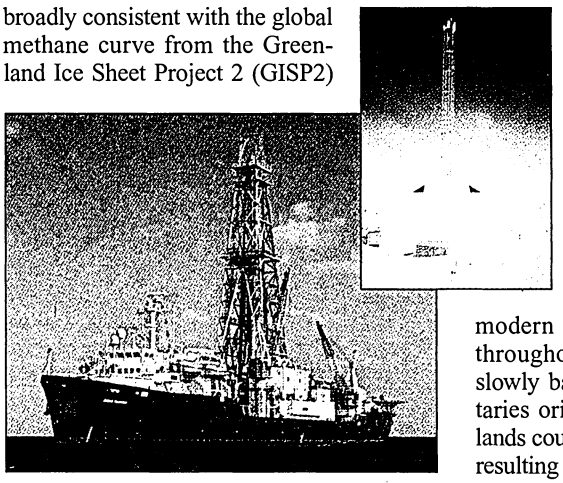
records global ice volume, ocean temperature, and the mixing ratio of fresh water and seawater. To separate out the freshwater input, Maslin and Burns removed the ice volume and ocean temperature components by subtracting an independent planktonic oxygen isotope record south of the Amazon and upstream in the NBCC. The residual was further adjusted for the effects of temperature and rainfall amount on the oxygen isotope composition of river water.

The net result is an indirect measure of Amazon River outflow that is broadly consistent with the global methane curve from the Greenland Ice Sheet Project 2 (GISP2) ice core (see the figure) (*5*, *6*). The best match is during the Younger Dryas (13,000 to 11,600 years ago), when ice-core methane and reconstructed Amazon discharge both dropped to 60% below modern values (*2*, *11*). Both records exhibit anomalous peaks, which occur 11,600 years ago in the methane record and 11,800 years ago in the Amazon outflow. The latter was probably due to increased rainfall in the lowlands rather than meltwater from Andean glaciers.



Retrieving sediment and ice cores. The JOIDES Resolution drilling ship took the core analyzed by Maslin and Burns (*11*). **(Inset)** The site of GISP2, one of the Greenland ice cores used to measure past methane concentrations.

CREDIT: JOIDES RESOLUTION: JOHN BECK/OCEAN DRILLING PROGRAM; GISP2: MARK TWICKLER/UNIVERSITY OF NEW HAMPSHIRE

The overall trend in Amazon outflow tracks summertime solar insolation at 10°S, which reached a minimum between 12,000 and 10,000 years ago and a maximum in the past 3000 years. These insolation differences are thought to regulate the intensity of convection over the Amazon Basin and the Central Andes, which in turn affects westward penetration of Atlantic moisture and southern extension of the Intertropical Convergence Zone (ITCZ). On page 2291 of this issue, Mayle *et al.* (*15*) also summon increasing summer insolation at 10°S to explain southern expansion of Amazonian rainforests in eastern Bolivia during the past 3000 years.

Maslin and Burns' elegant study is probably not the final word. The authors make several key but unproven assumptions to quantify Amazon discharge from the foraminiferal record. For example, the dependence of the oxygen isotope composition of rainfall on temperature and rainfall amounts over the Amazon Basin can be complicated by changes in the position of the ITCZ, which may push isotopically depleted moisture inland (*16*). Trade wind intensities along the northern South American coastline, which changed dramatically during deglaciation (*17*), also could have modulated the position and width of the Amazon freshwater plume, affecting its mixing with the NBCC (*18*). Furthermore, little attempt has been made to allow for the effects of rising sea level on the extent of Holocene wetlands. During the last ice age, when sea level was 100 m below that of today, the increased gradient caused the Amazon and its tributaries to incise tens of meters below their floodplains. Ten thousand years ago, sea level was still 25 m below modern levels, and it rose only gradually throughout the Holocene. Incised valleys slowly backfilled with sediment, but tributaries originating in sediment-starved lowlands could not keep up with the rising water, resulting in large freshwater lakes (*19*). These lakes are only now being drowned in sediment, implying that the maximum extent of methane-producing wetlands in the Amazon Basin may depend more on rising sea level than on increasing rainfall.

Finally, it remains unclear how orbital modulation of seasonal insolation might force tropical precipitation. During the past 1 million years, increases in lowland Amazon Basin precipitation have coincided with ice-melting events and maximum June insolation at 65°N (*20*), not maximum January insolation at 10°S. Physical mechanisms for high-latitude forcing of the tropics could involve changes in oceanic heat transport, as well as remote teleconnections with the Asian Monsoon and Pacific climate (*21*, *22*).

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PERSPECTIVES: NEUROSCIENCE

Boosting Working Memory

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Many parts of the brain are involved in the formation and storage of long- and short-term memory. Working memory—a form of short-term memory that depends on different populations of brain neurons, in particular those in the prefrontal cortex—serves to maintain temporary, active representations of information that can be rapidly recalled (*1*). Neurons in the prefrontal cortex and associated areas receive input from cholinergic pathways comprising neurons that release the neurotransmitter acetylcholine, which originate in the reticular core of the brainstem and basal forebrain (see the figure). This anatomical organization leads to an obvious strategy for improving working memory: increasing the amount of acetylcholine in synapses. That this strategy works is demonstrated by Furey *et al.* (*2*) on page 2315 of this issue. Using functional magnetic resonance imaging (fMRI), these authors show that enhancing cholinergic activity with the drug physostigmine (which blocks the breakdown of acetylcholine) improves the efficiency of working memory in humans.

Brains of human subjects performing a visual recognition task were imaged first dur-

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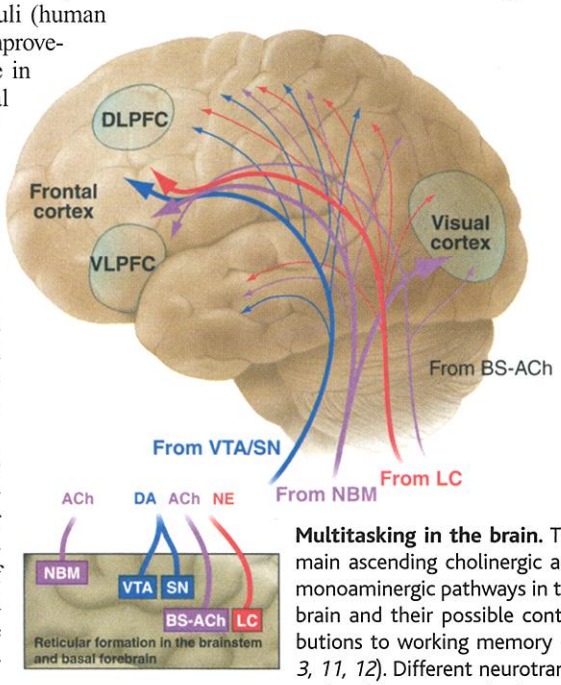
ing infusion of physostigmine, and then, on a subsequent day, during infusion of a saline placebo (*2*). The visual recognition task comprised three stages—3 seconds to visualize a human face (encoding), a 9-second pause during which the face is "held" in working memory (memory), and then presentation of the original face and a new face, requiring that one face be recognized (recognition). In the new work (*2*), and in two previous studies using positron emission tomography (PET) (*3*), physostigmine accelerated the subjects' ability to recognize visual stimuli (human faces). In the PET studies, this improvement correlated with a decrease in brain activity in the dorsolateral prefrontal cortex—a region of the brain considered crucial for accurate working memory—and an increase in brain activity in regions of the visual cortex. Because of the poorer temporal resolution of PET compared with fMRI, the PET work did not provide information on the parts of the brain that were activated at each stage of the visual recognition task.

With fMRI, Furey *et al.* (*2*) now show that the increased activity in the visual cortex after physostigmine treatment occurred during the encoding of faces. Therefore, improved working memory performance may be due, in part, to enhancement of the earliest stages of visual processing in the cortex, possibly through an increase in the signal-to-noise ratio of neuronal information processing (*4*). Increased visual processing in response to physostigmine is consistent with results from other work in which animals were infused intracerebrally with selective cholinergic agents (*5*), but it is unclear how the Furey results relate to other findings in experimental animals. For example, Furey and colleagues suggest that, for certain types of memory, boosting the input of visual information leads to reduced activity in the prefrontal cortex. However, injection into the rat prefrontal cortex of muscarinic or nicotinic receptor antagonists—which prevent acetylcholine from binding to its receptors—produces different profiles of impairment on two working memory tasks; only the more demanding task was impaired by the nicotinic receptor antagonist (*6*). This raises the possibility that acetylcholine might have different effects depending on whether it binds to muscarinic or nicotinic receptors. Consistent with this notion, in both normal volunteers and patients with Alzheimer's disease, nicotine improves performance on working memory tasks that demand heightened attention (*4*).

The drug-induced changes seen by Furey and co-workers in the prefrontal cortex during face recognition, unlike those in the posterior regions of the brain, were not preferentially associated with any particular stage of the task. The authors choose to explain this finding in terms of the Petrides model of working memory (*7*). This model assigns the more passive ("on-line") short-term maintenance of information (*8*) and the more active ("executive") processing of information held on-line to the ventral and dorsal regions of the prefrontal cortex, respectively. The investigators postulate that decreased dorsal prefrontal cortex activity reflects reduced requirements for "executive" operations after increased posterior cortical activity. But not all activity in the prefrontal cortex was reduced during the face recognition task after physostigmine infusion; increased activity was still observed in the inferior prefrontal cortex. As the authors point out, it is unclear whether the activity of this area subsumes the ventrolateral prefrontal cortex. If this area is close to the ventrolateral prefrontal cortex (area BA47), then this might reflect enhancement of the entire network of "on-line" working memory (*7*). The precise relationship between working memory and different regions within the prefrontal cortex is currently the subject of intense debate (*8*). The Furey *et al.* study can now be extended with different working memory tasks that vary in their degree of "executive" and perceptual requirements. Thus, the final interpretation of drug-related changes in the prefrontal cortex will ultimately depend on exactly which parts of the prefrontal cortex carry out each stage of working memory and on the exact brain regions where drug-induced changes in activity occur.

Modulating the activity of monoaminergic neuronal pathways (that release monoamine neurotransmitters such as dopamine and norepinephrine) controls dynamic neural networks in the neocortex (*9, 10*). For example, methylphenidate (an indirect enhancer of dopamine and norepinephrine) decreases the activity of a working memory "circuit" that includes the dorsolateral prefrontal cortex and the posterior parietal cortex, while improving overall performance on a memory task (*10*). Together with the new Furey *et al.* findings, these studies raise the exciting possibility that aspects of working memory may be improved by drugs with selective actions on different neurotransmitter systems, resulting in possible therapeutic benefits for patients with cognitive disorders such as Alzheimer's disease.



Multitasking in the brain. The main ascending cholinergic and monoaminergic pathways in the brain and their possible contributions to working memory (*2, 3, 11, 12*). Different neurotransmitter pathways—acetylcholine (ACh), dopamine (DA), norepinephrine (NE)—modulate working memory through separate mechanisms. It remains unclear whether the serotonin pathway (not shown) is involved in working memory (*12*). For clarity, the back-projections from the frontal cortex and the projections between the neurotransmitter groups have been omitted. DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; VTA/SN, ventral tegmental area/substantia nigra pars compacta; LC, locus coeruleus; NBM, nucleus basalis of Meynert; BS-ACh, brainstem cholinergic neurons. The projections depicted reflect possible modulatory influences on working memory. Anatomically, the NBM and LC project to most of the cortical mantle and the VTA/SN has fewer projections in more posterior regions (*13*).

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