Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 11073–11074, September 1999
From the Academy

This paper is a summary of a session presented at the first Chinese-American Frontiers of Science symposium, held August 28–30, 1998, at the Arnold and Mabel Beckman Center of the National Academies of Sciences and Engineering in Irvine, CA.

Imaging the functioning human brain

XUCHU WENG*†, YU-SHIN DING‡, AND NORA D. VOLKOW§¶

*Laboratory for Higher Brain Function, Institute of Psychology Chinese Academy of Sciences, Beijing 100101, China; ‡Chemistry and §Medical Departments, Brookhaven National Laboratory, Upton, NY 11973-5000; and ¶Department of Psychiatry, State University of New York, Stony Brook, NY 11794

ABSTRACT One of the most exciting methodological advances for brain research field arises in functional brain imaging, which enables us to localize and characterize neural activity and biochemical events in the living human brain. Recently developed event-related functional MRI makes it possible to visualize the brain activity associated with cognitive processes with the temporal resolution of the hemodynamic response. In addition, the high sensitivity and selectivity of positron-emission tomography allow us to probe the neurochemical processes at the molecular level. Positron-emission tomography also has been applied to investigate the effects of therapeutic drugs as well as the effects of drugs of abuse.

Functional brain imaging techniques have seen significant advances over the past 10 years. These techniques allow the possibility of identifying functional anatomy of cognitive processes (knowing where), characterizing temporal correlation of brain activity and behavior (knowing when), and examining regional changes of physiological and biochemical processes (knowing what). Among various imaging modalities, functional MRI (fMRI) and positron-emission tomography (PET) have enjoyed the most technical advancement.

fMRI measures oxygenation-level-dependent changes of the blood that correlate with neuronal activity. Previous fMRI studies mainly used blocked-design procedures to obtain sufficient signal-to-noise ratios. These procedures, although allowing for spatially accurate mapping of brain functions, cannot separate trials within the task blocks and do not take full advantage of the high temporal resolution of fMRI.

Recently, thanks to the advancement of fast imaging techniques and a refined understanding of relationship between neuronal activity and associated cerebrovascular hemodynamics, a new method—event-related fMRI procedure—has been developed. It is significant because this procedure allows for selective averaging of individual trials in mixed task paradigms, thus providing a fundamentally new way to explore brain function with paradigms similar to those used in the traditional behavioral and electrophysiological studies (1). Event-related fMRI has quickly led to a number of applications in cognitive neuroscience. The following examples come out of the field of memory research.

Two groups recently explored the same interesting question with event-related fMRI: i.e., whether neural activity in certain brain regions can predict subsequent actual or perceived memory performance. Subjects saw a set of pictures (2) or words (3) during the scanning. They were later given a test of memory for each item. By direct trial-by-trial comparison, both Brewer *et al.* (2) and Wagner *et al.* (3) found that activation in prefrontal and parahippocampal regions elicited by well remembered items was greater than that elicited by weakly remembered or forgotten items (Fig. 1). These findings illustrated the potential of event-related fMRI technique in the study of cognition.

The ability of event-related fMRI to selectively average individual trials allowed Buckner *et al.* (4) to sort trial types based on subject's performance during a yes/no recognition task. Significant activation was found in right anterior prefrontal cortex for both "correct recognition" and "correct rejection" trials. The finding challenged the hypothesis that this area might be involved in process of retrieval success. Another finding of this study was that right anterior prefrontal area showed later onset and more sustained duration relative to other brain regions.

Analysis of the time-course of activation in each brain region helps to delineate different roles of these regions, as shown by Courtney *et al.* (5) in a study of working memory. Previous blocked-design studies have established that face working memory tasks activated several discrete brain areas. With event-related fMRI and multiple regression analysis, Courtney *et al.* (5) were able to decompose activation into three different components. Although early extrastriate visual cortex showed transient, nonselective response to all kinds of visual stimuli, later visual cortex in the ventral temporal region demonstrated transient, selective response to faces. However, in prefrontal regions, all identified areas showed greater levels of sustained activity over memory delays. These results suggested that visual areas primarily contribute to perceptual and encoding operations whereas prefrontal regions are mainly responsible for maintenance of the representation during working memory.

PET is a sensitive imaging method that uses radiotracers labeled with short-lived positron emitting isotopes to track chemical transformations in the living system (6). It measures radioisotope concentrations in the nanomolar–picomolar range. Another unique feature of PET is its biochemical selectivity, in that specific radiotracers can be designed that bind selectively to the molecular targets, such as receptors, transporters, or enzymes that are involved in the synthesis or metabolism of neurotransmitters. PET thus has been extensively used for biochemical and pharmacological imaging of the human brain, although it also has been widely used to identify anatomical correlates of cognitive process (7).

The study of drug pharmacokinetics (using a positron emitter-labeled drug) and drug pharmacodynamics (using a labeled tracer) is illustrated by two examples: studies comparing the two enantiomers of methylphenidate (MP) (Ritalin), a psychostimulant drug that is marketed as a racemic mixture; and studies that measure the efficacy of cocaine for blockade of the dopamine transporter.

Comparative studies of enantiomerically pure [^{11}C]*d-threo*-MP and [^{11}C]*l-threo*-MP in both baboon and human brain

Abbreviations: fMRI, functional MRI; PET, positron-emission tomography; MP, methylphenidate.

†To whom reprint requests should be addressed. E-mail: wengxc@psych.ac.cn.

PNAS is available online at www.pnas.org.

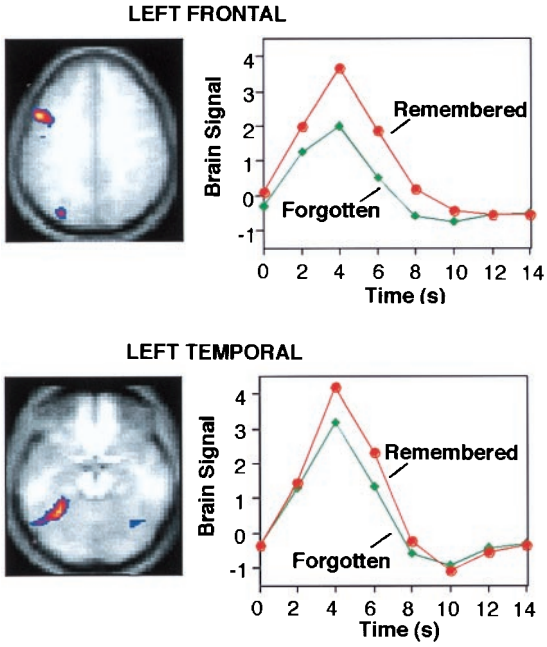

FIG. 1. Activation maps and their corresponding time-courses during the encoding of words. Note that activation elicited by subsequently remembered words is greater than activation elicited by subsequently forgotten words (see ref. 3). The figure is courtesy of Anthony D. Wagner (Massachusetts General Hospital, Harvard Medical School).

demonstrate high specific to nonspecific binding, selectivity for DA transporters, and reversibility of [^{11}C]*d-threo*-MP as compared with mostly nonspecific binding of [^{11}C]*l-threo*-MP (8, 9) (Fig. 2). Previous studies have indicated that two enantiomers of MP cause different behavioral responses in patients, but these PET studies for the first time visually established where the drug acts in the human brain. These PET studies along with microdialysis studies strongly indicate that pharmacological specificity of MP resides entirely in the *d-threo* isomer, supporting the further evaluation of using a single enantiomer (*d-threo*-MP) instead of racemic MP as the commercial drug form. They also demonstrate that PET imaging is an ideal way to examine the behavior of a chiral drug in the human brain and is a valuable tool in drug development.

Like methylphenidate, cocaine also inhibits the dopamine transporter. The development of drugs that block the dopamine transporter is under investigation for the treatment of cocaine abuse. To explore the relationship between dopamine transporter occupancy and the "high" produced from a behaviorally active dose of cocaine, the degree of dopamine transporter occupancy by a dose of cocaine commonly used by the cocaine abuser was measured (10). The mean subjective high was measured throughout the study, and the percent occupancy of the dopamine transporter was measured by comparing the baseline (placebo) scan with that where cocaine was co-administered. From this study, the minimum level of dopamine transporter occupancy required for cocaine to be perceived as reinforcing was >50%, and the high was determined to track the kinetics of the drug in the brain. Interestingly, even a 0.05-mg/kg dose of cocaine (which subjects did not distinguish from placebo) occupied 40% of the dopamine transporters. The ability to measure dopamine transporter occupancy should be a powerful tool in assessing the extent to which transporter occupancy is associated with the drug-induced high and also in evaluating the efficacy of dopamine transporter-blocking drugs for preventing the high in the treatment of cocaine addiction (11).

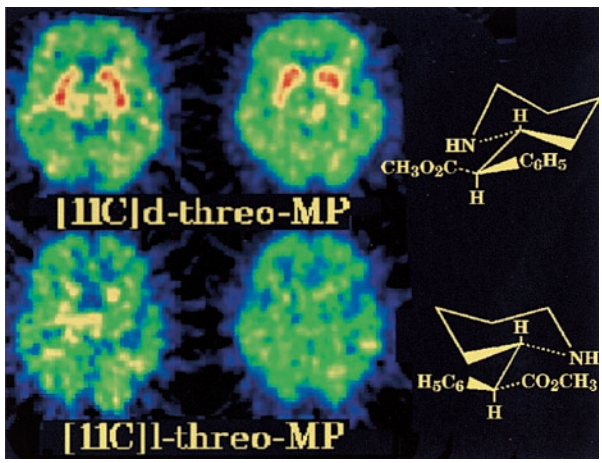

FIG. 2. Images of the human brain after injection of [^{11}C]*d-threo*-methylphenidate (top row) and [^{11}C]*l-threo*-methylphenidate (bottom row). Note the absence of specific retention with the *l-threo*-enantiomer. The figure is courtesy of Brookhaven National Laboratory.

In addition to PET and fMRI, there are a number of other kinds of brain imaging techniques, each with distinctive advantages and limitations. As mentioned above, PET has very high biochemical sensitivity and selectivity whereas its temporal and spatial resolution remains to be improved. In contrast, fMRI has better temporal and spatial resolution, although its biochemical sensitivity and selectivity is not as good as PET. The temporal resolution of optical imaging is even better than that of fMRI, but it is limited to the cortical surface and is difficult to widely apply to the human brain. The current challenge, thus, is to integrate these techniques to overcome the limitations. One example is to map precise spatiotemporal orchestration of the human brain activity with the combination of fMRI and magnetoencephalography. Magnetoencephalography measures brain activity on the temporal scale of millisecond. The next years will continue to see such and other technical developments. Perhaps the most challenging task in the future, however, is not the progression of technology *per se* but, rather, the development of new and better insight into the brain itself.

X.W. was supported in part by grants from the National Natural Science Foundation of China and the Chinese Academy of Sciences. Y.-S.D. and N.D.V. were supported by the U.S. Department of Energy Office of Biological and Environmental Research (Grant DE-AC02-98CH10886) and the National Institutes of Health.

1. Rosen, B. R., Buckner, R. L. & Dale, A. M. (1998) *Proc. Natl. Acad. Sci. USA* **95,** 773–780.
2. Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H. & Gabrieli, J. D. E. (1998) *Science* **281,** 1185–1187.
3. Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. D., Rosen, B. R. & Buckney, R. L. (1998) *Science* **281,** 1188–1191.
4. Buckner, R. L., Koutstaal, W., Schacter, D. L., Dale, A. M., Rotte, M. & Rosen, B. R. (1997) *Neuroimaging* **6,** 259–269.
5. Courtney, S. M., Ungerleider, L. G., Keil, K. & Haxby, J. V. (1997) *Nature (London)* **386,** 608–611.
6. Posner, M. I. & Raichle, M. E. (1994) *Images of Mind* (Scientific American Books, New York).
7. Volkow, N. D., Rosen, B. & Farde, L. (1997) *Proc. Natl. Acad. Sci. USA* **94,** 2787–2788.
8. Ding, Y.-S., Fowler, J. S., Volkow, N. D., Dewey, S. L., Wang, G.-J., Gatley, J., Logan, J. & Pappas, N. (1997) *Psychopharmacology* **131,** 71–78.
9. Ding, Y.-S., Fowler, J. S., Volkow, N. D., Logan, J., Gatley, S. J. & Sugano, Y. (1995) *J. Nucl. Med.* **36,** 2298–2305.
10. Volkow, N. D., Wang, G.-J., Fischman, M. W., Foltin, R. W., Fowler, J. S., Abumrad, N. N., Vitkun, S., Logan, J., Gatley, S. J., Pappas, N., *et al.* (1997) *Nature (London)* **386,** 827–830.
11. Volkow, N. D., Wang, G.-J., Fowler, J. S., Gatley, S. J., Ding, Y.-S., Logan, J., Dewey, S. L., Hitzemann, R. & Lieberman, J. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 10388–10392.