ways carried the food with them (Fig. $1B_2$). Thus feeding on small food facilitates escape, and escape does not terminate feeding by forcing release of the food (Fig. $1B_3$).

These results make adaptive sense. If food is large, feeding and successful escape are incompatible. In cases where the animal apparently chooses to escape, feeding is commonly, but not always, terminated. However, on other occasions, the animal apparently chooses not to escape and to continue feeding despite possible danger; thus the probability of escape is lowered. With small food, escape and feeding (or at least retention of the food) are compatible; hence, they are not mutually inhibitory. Furthermore, because an animal in possession of food is a ready target for attack by conspecifics, it may be adaptive for the excitability of escape to increase. Indeed, Hagiwara and Wine (*5*) have independently reported that possession of food greatly increased the likelihood that crayfish would escape from conspecifics.

The only aspect of the results that did not seem adaptive was the tendency of some animals to hold the large pieces of food while flipping. Since small pieces of food are generally held while flipping, we considered the possibility that some animals might perceive the large food as small enough to carry. We, therefore, examined the results from animals that consistently held the large pieces of food while flipping to determine whether, as with animals eating small pieces of food, escape was facilitated or at least inhibited less than in other animals. We found that although the probability of escape from threats during feeding was diminished among the consistent holders of food, it was diminished less than that among animals that consistently released the large food (Fig. 2A). And if instead of examining the overall probability of escape, one examines the probability with which the approach of the fish net triggered an escape response (that is, the probability that escape occurred before the net reached the animal), then escape tendency was slightly facilitated in holders of large food (Fig. 2B), as it was in animals eating small food. Whether animals that held the large food while tail-flipping were actually "trying" to carry the food obviously cannot be determined. But as might be expected, if holders were trying to move the large pieces of food, bouts of tail-flipping of holders during large food trials were exceptionally long (Fig. 2C), and in a number of cases the food was dragged several body lengths.

Thus, the pattern of interactions of feeding and escape behavior in the crayfish are not fixed but depend on food size and perhaps on the animal's "judgment" of the food's portability. Such complex interactions, although common in vertebrates, are not expected in the crayfish. The results argue against simple models in which command neurons or pattern generation neurons for one behavior rather directly cause excitation or inhibition of circuitry mediating other behaviors (*2*). The complexity that we describe suggests that study of behavioral integration in invertebrates may provide more insight than might have been expected into the sophisticated vertebrate nervous system.

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References and Notes

1. The assumption that animals select responses from a set of alternatives is a convenient simplification. In some instances this assumption may be misleading, because many behavior patterns can probably be so altered by the context of their occurrence that they cannot be identified as fixed, selectable entities, clearly different from other entities [see, for example, J. Szentagothai and M. A. Arbib, *Neurosci. Res. Program Bull. 12* (1974); J. C. Fentress, *Behav. Brain Sci.* **4**, 623 (1981); K. L. Bellman, doctoral thesis, University of California, San Diego (1979).
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3. Stimuli of the kind used here generally elicit tail flips that are not mediated by the crayfish giant fibers [J. J. Wine and F. B. Krasne, *J. Exp. Biol.* **56**, 1 (1972)].
4. If an animal did not begin consuming food within 20 minutes, the experimental trial and its corresponding control trials were discarded; this happened on only four out of more than 150 triplets.
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2 June 1982; revised 2 May 1983

Down's Syndrome in Adults: Brain Metabolism

Abstract. *The cerebral metabolic rate for glucose, as measured with positron emission tomography and fluorine-18–labeled 2-deoxy-D-glucose, was significantly higher in four healthy young subjects with trisomy 21 syndrome (Down's syndrome) than the mean rate in healthy young controls. The rate of cerebral glucose utilization in the frontal lobe of a 51-year-old subject with Down's syndrome was significantly lower than the rate in the young subjects with this syndrome, but approximated the rate in middle-aged controls. Thus glucose utilization by the brain appears to be excessive in young adults with Down's syndrome but may decline with age in some brain regions.*

At least 150 developmental abnormalities and diseases may affect the human brain at an early age and cause mental retardation. Of these, Down's syndrome (DS) is the most common abnormality with an established etiology. Brains of young adult DS subjects show no consistent abnormalities, aside from a subnormal weight and a relatively simple convolutional pattern (*1*—*3*), but brains of DS subjects older than 35 years show senile plaques, neurofibrillary tangles, granulovacuolar neuronal degeneration, and reduced activities of choline acetyltransferase and acetylcholinesterase (*3*–*4*). These pathological changes occur in the same regions of the brain as the changes associated with Alzheimer's dementia. Although older DS subjects are frequently demented, the exact incidence of dementia in DS and its correlation with neuropathology have not been determined (*3*, *5*).

Brain oxidative metabolism, which is coupled to neuronal activity, has been examined in individuals with DS; in subjects aged 32 to 49 years, cerebral blood flow and oxygen consumption rates did not differ significantly from their respective values in age-matched controls (*6*). In a study of halothane-anesthetized DS subjects (mean age, 29 years), the cerebral arteriovenous oxygen difference was greater, blood flow was reduced, and oxygen consumption was unchanged, compared to corresponding values in age-matched controls (*7*).

It now is possible to measure regional and overall cerebral metabolic rates for glucose ($rCMR_{glc}$ and CMR_{glc}, respectively) with positron emission tomography (PET) and ^{18}F-labeled 2-deoxy-D-glucose (^{18}F-DG) (*8*, *9*). Because brain glucose utilization might provide information about the functional disturbance in DS, we measured glucose utilization with PET in healthy young and middle-aged DS subjects, as well as in healthy age-matched controls (*10*).

Healthy male volunteers, ten aged 21 to 33 years (mean, 27.5) and eight aged 45 to 55 years (mean, 49.1), were screened for the absence of primary or secondary brain disease or for conditions that might contribute to brain dysfunction (for example, hypertension, cardio-

vascular disease, or diabetes) (*9*). In addition, four young DS subjects [three men and one woman, aged 19 to 27 years (mean 22.5)] and one 51-year-old man, each with a trisomy 21 karyotype, were similarly screened. Systolic and diastolic arterial blood pressures were significantly less ($P < 0.05$) in the five DS subjects than in the 18 controls (mean ± standard error, 116.7 ± 0.6/72.7 ± 2.8, compared to 123.1 ± 2.0/78.5 ± 1.9), in partial agreement with an earlier report (*11*). Computerized tomography (CT) scans of three of the DS subjects, including that of the 51-year-old man, were judged to be normal; a fourth scan showed enlarged ventricles, and the fifth scan showed an enlarged cisterna magna. Psychological tests, used to evaluate immediate verbal and nonverbal memory, visuoconstructive praxis, and verbal intelligence (*12*), provided mean mental ages for the DS subjects of 2 years 10 months to 5 years. The performance of the 51-year-old subject was significantly worse than the performance of each younger DS subjects in the test battery ($P < 0.05$).

Positron emission tomography was performed with an ECAT II instrument (ORTEC, Life Sciences) (*9*). While subjects had their eyes covered with masks and their ears plugged with cotton to reduce sensory input, they were given 5 mCi of ^{18}F-DG intravenously. After 45 minutes in the darkened and quiet room, these restrictions were lifted and up to seven serial scans were obtained, each parallel to a line drawn between the inferior orbital rim and the external auditory meatus (the IOM line). Blood from a vein of a heated hand was taken at timed intervals to measure the concentrations of ^{18}F-DG and of glucose in the plasma (*13*). These values, as well as the measure of ^{18}F activity in the brain from the PET images, were inserted into an operational equation to calculate $rCMR_{glc}$ and CMR_{glc} (*14*). Regions of interest within a given scan at specific intervals above the IOM line were identified from an atlas of brain slices (*9, 15*) and were outlined by a computer image-processing procedure.

The mean values of CMR_{glc} and $rCMR_{glc}$ for young DS subjects and young and middle-aged control groups were compared by analysis of variance and Bonferroni t statistics; individual values for the 51-year-old DS subject were compared with respective means for the young DS subjects and middle-aged controls by a Z score (*16*). A difference was considered significant at $P \leq 0.05$. Because comparisons made with values for the right and left side of the brain were equivalent, only those for the right side are presented in Table 1.

Right-hemispheric values for CMR_{glc} and most values for $rCMR_{glc}$ were not significantly different in the young and old control groups, as observed previously (*9*). However, hemispheric CMR_{glc} values and many regional values in young DS subjects were as much as 40

Table 1. Regional cerebral metabolic rates of glucose utilization in the right side of the brain in subjects with Down's syndrome and in age-matched controls. Brain regions are defined at given distances above the inferior orbitomeatal (IOM) line (*8, 12*). Values are expressed as means ± standard error in units of milligrams per 100 g per minute. The number of subjects is shown in parentheses in the first line.

Brain region	Distance above IOM line (mm)	Young subjects		Middle-aged subjects	
		Controls	Down's syndrome	Controls	Down's syndrome
Right hemisphere	30–80	4.89 ± 0.24(10)	6.53 ± 0.33(4)*	4.16 ± 0.33(8)	5.57(1)
Frontal lobe					
Superior frontal gyrus	80–100	6.39 ± 0.50	7.97 ± 0.38	5.19 ± 0.29	4.70†
	60–80	6.41 ± 0.29	8.58 ± 0.48*	4.93 ± 0.34*	6.11†
	35–60	5.73 ± 0.34	7.73 ± 0.38*	4.83 ± 0.39	5.57†
Midfrontal gyrus	65–90	6.47 ± 0.51	8.77 ± 0.47*	5.49 ± 0.32	6.51†
	45–65	6.07 ± 0.42	8.08 ± 0.31*	4.94 ± 0.41	6.15†
Inferior frontal gyrus	50–70	6.26 ± 0.37	8.28 ± 0.25*	5.15 ± 0.36	6.47†
	35–50	5.81 ± 0.36	7.38 ± 0.30*	4.87 ± 0.35	5.55†
Cingulate gyrus	35–70	6.37 ± 0.41	7.94 ± 0.33	5.07 ± 0.35*	6.40†
Orbitofrontal gyrus	20–35	5.01 ± 0.46	5.79 ± 0.48	4.34 ± 0.31	4.78
Precentral gyrus	70–100	6.66 ± 0.48	8.41 ± 0.53*	5.44 ± 0.25	5.70†
	55–70	6.77 ± 0.47	7.46 ± 0.07	4.95 ± 0.28*	6.92‡
Paracentral lobule	80–100	6.64 ± 0.46	8.50 ± 0.72	5.66 ± 0.39	5.24†
Parietal lobe					
Postcentral gyrus	70–100	5.93 ± 0.43	7.85 ± 0.56*	5.25 ± 0.28	5.69
	55–70	5.94 ± 0.36	7.59 ± 0.43*	4.81 ± 0.31	6.69
Superior parietal gyrus	70–100	5.95 ± 0.42	7.96 ± 0.51*	5.06 ± 0.26	5.69†
Inferior parietal gyrus	45–70	5.65 ± 0.40	7.34 ± 0.20*	4.64 ± 0.30	6.38†
Precuneus	65–80	7.07 ± 0.41	9.18 ± 0.56*	5.98 ± 0.36	7.32
Occipital lobe					
Cuneus	45–65	6.25 ± 0.30	8.81 ± 0.23*	5.59 ± 0.44	7.64†
Calcarine region	30–45	5.45 ± 0.25	6.93 ± 0.28*	4.85 ± 0.31	5.91
Lingual region	15–30	4.46 ± 0.32	5.31 ± 0.56	4.19 ± 0.29	4.51
Retrosplenial gray matter	45–70	5.80 ± 0.32	7.58 ± 0.72*	5.23 ± 0.48	6.46
Temporal lobe					
Superior temporal gyrus	30–45	5.12 ± 0.27	6.72 ± 0.19*	4.47 ± 0.28	5.53†
Inferior middle temporal gyrus	15–30	4.43 ± 0.37	5.24 ± 0.42	3.91 ± 0.22	4.32
Inferior temporal gyrus	5–15	3.90 ± 0.31	2.73 ± 0.75	3.37 ± 0.34	3.76
Anterior medial temporal gyrus	20–35	3.62 ± 0.29	4.93 ± 0.58*	3.60 ± 0.27	4.14‡
Hippocampal region	20–35	4.51 ± 0.37	5.27 ± 0.62	4.05 ± 0.14	4.36
Caudate nucleus (head)	35–55	5.78 ± 0.30	7.48 ± 0.52*	4.93 ± 0.37	7.20‡
Thalamus	40–50	5.59 ± 0.40	7.39 ± 0.55*	4.53 ± 0.39	6.94‡
Lenticular nucleus	35–55	6.13 ± 0.27	8.25 ± 0.44*	5.85 ± 0.30	7.77‡
Insula	40–60	6.34 ± 0.36	8.69 ± 0.31*	5.25 ± 0.42	6.92†
Cerebellum	0–15	4.18 ± 0.32	4.58 ± 0.46	4.02 ± 0.22	3.26
Centrum semiovale	70–90	2.79 ± 0.21	3.14 ± 0.17	2.52 ± 0.15	2.49

*Differs from mean in young controls by Bonferroni t statistics ($P \leq 0.05$). †Differs from mean for young Down's syndrome subjects by Z score ($P \leq 0.05$). ‡Differs from mean in middle-aged controls by Z score ($P \leq 0.05$).

percent higher than the respective mean values in young controls (Fig. 1). The $rCMR_{glc}$ values for the 51-year-old DS subject did not differ generally from the respective mean values for middle-aged controls, but were significantly less than the means for the young DS subjects, particularly in the frontal lobe (Table 1).

These findings show that the rate of glucose utilization, as obtained with the ^{18}F-DG procedure, is increased in healthy young adult DS subjects with trisomy 21. Although the calculated increase could reflect the inappropriate use of constants derived for normal but not for DS brains (*8, 9*), an increased cerebral utilization of glucose has been reported in adult autism, another functional disturbance without evident neuropathology (*17*). A high rate of glucose utilization in DS may thus characterize a class of cerebral dysfunctions without obvious neuropathology, in which glucose, the major substrate for brain energy metabolism, is used excessively to maintain cognitive activity. Possible causes for excessive use of glucose include (i) increased Na leakage across brain cell membranes with consequent increased Na pumping, (ii) reduced coupling between adenosine triphosphate consumption and active Na transport, (iii) increased neuronal activity in redundant circuitry, (iv) neurochemical imbalance, and (v) incomplete glucose oxidation (*18*). Peripheral biochemical defects, which have been described in DS (*19*), might disturb cerebral metabolism if they are present in the brain. Anxiety appears to increase brain metabolism in man (*20*), but heart rate, blood pressure, and our assessment of global anxiety during PET did not differ between DS subjects and controls.

Although many $rCMR_{glc}$ values were lower in the 51-year-old DS subject than in the young DS group, they were not as low as the 1 to 2 mg per 100 g per minute reported in Alzheimer's disease (*21*). Brains of middle-aged DS subjects demonstrate the neuropathology of Alzheimer's disease (*3, 4*), but our 51-year-old subject was not evidently demented and showed no focal neurological signs (*5*) although he had the lowest cerebral metabolic rate and lowest psychological test scores of the entire DS group. His CT scan was read as normal, and family members reported that his performance and temperament had, if anything, improved in the last several years. The relations among dementia, brain metabolism, and neuropathology in DS remain to be determined.

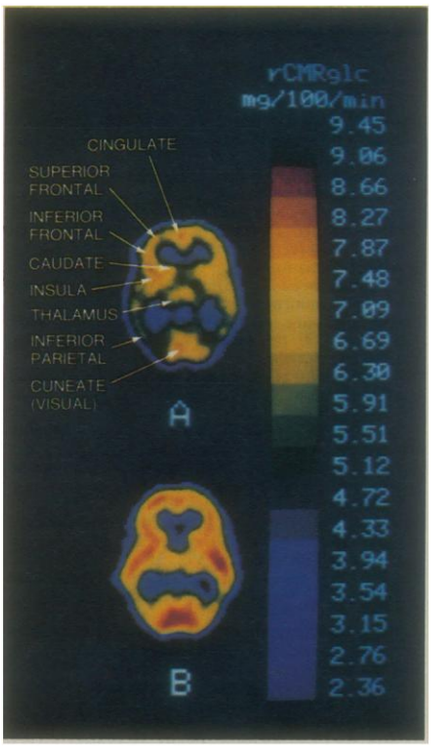

Fig. 1. Positron emission tomography scans of (A) a 21-year-old healthy male and (B) a 22-year-old male with Down's syndrome at 50 mm above the inferior orbitomeatal line. The color scale provides values for $rCMR_{glc}$ at different regions, identified from brain slices (*9, 15*).

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14 March 1983; revised 1 June 1983