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FUNCTIONAL CORRELATES OF THE ONTOGENY OF CEREBRAL LATERALITY IN THE RAT

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FUNCTIONAL CORRELATES OF THE ONTOGENY OF CEREBRAL LATERALITY IN THE RAT

by

DAVID ALAN ROSS

A dissertation submitted to the Graduate Faculty
in Biomedical Sciences in partial fulfillment of
the requirements for the degree of Doctor of
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1981

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Abstract

FUNCTIONAL CORRELATES OF THE ONTOGENY OF CEREBRAL LATERALITY IN THE RAT

by

David Alan Ross

Adviser: Professor Stanley D. Glick

Cerebral lateral asymmetry was once believed to be a unique attribute of humans but can no longer be considered as such. An ever increasing body of knowledge clearly indicates that the brains of normal animals are lateralized and that this lateralization is oftentimes manifest behaviorally. Thus, it has been shown that spontaneous side preferences and nocturnal and amphetamine-induced rotation are related to an intrinsic asymmetry in dopamine content, metabolism, and dopamine-stimulated adenylate cyclase activity in the corpus striatum of rats. In addition it has been demonstrated that rats have asymmetries in self-stimulation thresholds that are also related to rotation. Moreover, it has recently been shown that there exist asymmetries in 2-deoxy-D-glucose (dGlc) incorporation in several regions of the adult rat brain. This thesis documents asymmetries in dGlc incorporation in the neonatal rat, demonstrating that such asymmetries are present at birth, change during development and are sexually dimorphic.

Studies were initially performed to evaluate the suitability of a modification of the dGlc technique: it was shown that using this modification data are obtainable which are qualitatively and quantitatively similar to those obtained using less convenient methodology; dGlc uptake data were shown to be highly correlated with glucose utilization values. The developmental time course of dGlc phosphorylation was shown to reach a plateau by postnatal day thirty. Percent uptake data were obtained in seven brain regions for animals between zero and one hundred days old and demonstrated to have different characteristics in male and female rats. Relative brain dGlc activity was also calculated for seven brain regions and was related to changes in left-right asymmetry of each region, respectively: a significant inverse correlation between left-right asymmetry and relative activity was obtained indicating that as a region of the brain becomes more active, its asymmetry tends to be right-biased and vice versa.

Significant relationships between asymmetry and the age of the animals were also demonstrated: in females, left-right asymmetry was positively correlated with age in hippocampus and diencephalon and negatively correlated with age in brainstem and midbrain indicative of right-to-left and left-to-right gradients, respectively. The only such significant relationship in males was a right-to-left gradient in midbrain. Absolute asymmetry of the caudate was also shown to decrease significantly with age.

An asymmetry in neonatal tail posture was identified and was shown to predict adult side preference in a rotometer. Neonatal females had right biased tails; this effect was significant. There was a non-significant trend for the tails of the males to be directed toward the left. The asymmetry in female neonatal tail posture was also shown to be inversely correlated with the number of males in each litter--suggesting a possible relationship between hormonal status prenatally and asymmetries observed at a later time.

The results of this study clearly establish that normal rats have asymmetries in tail posture and dGlc incorporation that are observable at birth and which change during development. These side-to-side differences in dGlc incorporation were observed within individual animals and are, therefore, most likely attributable to intrinsic lateralization in cerebral glucose uptake and not reflective of other factors, such as plasma glucose, that would affect dGlc incorporation equally on the two sides of the brain. The data were discussed in relation to the origins of cerebral lateralization and the differences in such lateralization between the sexes. Additionally, theories on the etiology of developmental disorders of cognition and of psychiatric disease were related to possible mechanisms involving altered cerebral dominance.

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dGlc	2-deoxy-D-glucose
LRA	left-right asymmetry
NE	norepinephrine
DA	dopamine

INTRODUCTION

Cerebral lateralization and cerebral lateral asymmetry are both terms used to describe those situations when mirror image structures on either side of the mid-saggital sulcus differ in either a quantitative or qualitative manner. Cerebral specialization is a subset of cerebral laterality and refers to the latter case where structures on the two sides of the brain differ qualitatively. An example of specialization is the neural control of speech, represented on only one hemisphere, in humans and some songbirds, whereas lateralization would be exemplified by the demonstration of a quantitative difference in the amount of a neurotransmitter in a structure on the two sides of the brain. These two terms, although often misused interchangeably, do not necessarily describe the same phenomena. Indeed, investigators concerned with hemispheric inequality have historically described their findings with misleading terminology: words such as dominance, serving, legislating, driving, and leading--all implying one side greater than the other--have been used to describe hemispheric differences (Oppenheimer, 1977). In each case, the term implies that one side is under the control of, or driven by, the other. However, it should be clear that when one speaks of cerebral dominance, what one really refers to is the fact that one side of the brain is more important for certain functions than the other--this side being referred to as dominant. Certainly this is different from saying that one side of the brain dominates the other. Albeit unclear at the present time, it may be that different structures are dominant, for a given function or behavior, on both sides of the brain. Predominance, a term used by Brown-Séquard and Berillon in the late 1800's to describe cerebral duality--implying that both sides of the brain exert some dominant control over something (Oppenheimer, 1977)--may be a better and less misleading term.

Cerebral Laterality.

The phenomenon of cerebral dominance for various human behaviors has been known and accepted since Paul Broca's original discovery that lesions which resulted in language disorders were, in most cases, located in the left cerebral hemisphere (Broca, 1861. Cited by Galaburda, et al., 1978). Early studies attempting to characterize the mechanisms of this phenomenon initially focussed on possible anatomical substrates (Galaburda, et al., 1978) but these findings were dismissed over 100 years later when von Bonin reviewed them and concluded that the anatomical asymmetries reported were not large enough to account for the remarkable functional differences (von Bonin, 1962; Galaburda, et al., 1978). Regardless of what the actual neural substrate for the functional differences is, data subsequently generated by Geschwind support the idea that there are anatomical asymmetries in, at least, the human brain, that these asymmetries are located in regions of the brain known to be involved in control of vocalization and that they are related to handedness, in the same way that speech is, in that they are usually located in the hemisphere contralateral to the individual's hand preference. In many cases these asymmetries are not subtle and can be observed with the naked eye either in autopsy specimens or during radiological examination. In other cases, more refined techniques such as cytoarchitechtonic analyses must be performed to fully characterize their extent.

The temporal lobe of the brain manifests, more than any other brain region, clear asymmetries in gross anatomy--especially on its upper surface (Galaburda, et al., 1978). In 1878, Heschl described an asymmetry in temporal lobe where an elbow-like body between the superior and anterior transverse temporal gyri was found more often on the left hemisphere and in males (see Galaburda, et al., 1978). Subsequently Pfeifer reported asymmetries in the region of cortex between Heschl's gyrus and the posterior edge of the Sylvian fossa (Pfeifer, 1936; Galaburda, et al., 1978), the planum temporale. Pfeifer's original discovery was later confirmed and more fully characterized by Geschwind and Levitsky (Geschwind and Levitsky, 1968) who, in a study of the planum in 100 brains, found that this region was larger on the left side of the brain in 65% of their sample, equal in size in 24%, and larger on the right side of the brain in 11%. These data were highly significant using the Chi-Square. Other investigators have also observed this asymmetry in the planum (Galaburda, et al., 1978) and, although it is not clear if this asymmetry is directly responsible for lateralization of speech, its existence is unequivocal.

After Geschwind's demonstration of the gross anatomical asymmetry in the planum, investigators began to explore this further: using cytoarchitechtonics--the study of cell morphology and distribution--Galaburda (1978) mapped the various characteristic cytoarchitechtonic areas of the planum from brains of the Yakovlev collection. These studies clearly demonstrated marked hemispheric differences in the area of the temporoparietal cortex; the volume of this area was 7 times greater on the left side compared to the right. Another gross anatomical asymmetry is found in the pattern of the pyramidal decussations. Although this was initially observed in the brains of neonatal and fetal human brains by Yakovlev and Rakic (1966), Geschwind and his associates extended these findings to the adult in their study of 158 adult medullas (Kertesz and Geschwind, 1971) where they demonstrated that the left decussation was rostral to the right in 82% of their sample. Due to the small number of nonright handed people in their sample, attempts to correlate this pattern with handedness were not fruitful. This was not the first demonstration of asymmetries in pyramidal motor systems; early work by Flechsig (1876) had demonstrated an asymmetry in the pyramidal tracts where in 40% of the brains there was an asymmetric number of fibers crossing from one hemisphere to the other--a finding which can be readily accounted for by Geschwind's later finding of an asymmetry in the decussations.

The asymmetries discussed so far were all shown in the brains of nonliving people. Due to newer radiological and computerized methodology, it is now possible to demonstrate cerebral asymmetries in living subjects. Using these methods--especially computerized axial tomography--the asymmetry in the planum has been confirmed, and other asymmetries have been uncovered (LeMay, 1976). In particular, LeMay (1976) demonstrated a larger and wider left occipital and right frontal lobe which was related to handedness: in lefties, these differences were not as striking as in righties who, in the majority of cases, had wider left occipital and right frontal lobes. Reasoning that these asymmetries in the brain might be reflected in the skulls of patients and in fossil endocasts, an effect known as petalia, LeMay found that left occipital and right frontal petalia are much more common than not in right handed subjects. Other asymmetries that have been observed using radiologic methods are those in the lateral ventricles (McRae, et al., 1963) and in the length and configuration of the Sylvian fissures (LeMay and Culebras, 1972; LeMay, 1976). In right handers the left occipital horn of the lateral ventricle was shown to be greater than the right in 60% of the sample, whereas the size of the right occipital horn exceeded that of the left in only 10% of the cases. Again these patterns were less remarkable in left handed subjects whose left occipital horn was larger in only 38% of the sample and whose right occipital horn was larger in 31% of the sample.

LeMay and associates have also demonstrated asymmetries in petalia of fossil remains. They showed (LeMay and Culebras, 1972) that the impression of the Sylvian fissures in the Neanderthal man is characterized by a longer and more horizontal left fissure and a more vertical and shorter right fissure, not unlike the findings for the brains of most right handed people today. Additionally the endocast of the brain of Peking man shows similarities to that of the Neanderthal man (Galaburda, et al., 1978). In contrast, the fossil of Pithecanthropus 1 has right occipital petalia and that of Pithecanthropus 2 has the left occipital petalia common in man today (McGregor, 1925). It has been hypothesized (Galaburda, et al., 1978) that the occipital asymmetries were associated with handedness and that Pithecanthropus 1 was left handed; this hypothesis has been supported by others (LeMay and Culebras, 1972) using radiological methodology, who have shown a correlation between handedness and the size of the occipital horns of the lateral ventricles (McRae, et al., 1968).

The same patterns observed in the Sylvian fissures of modern man have been noted in the brains of the great apes: again, the right fissure is more vertically angled than the left. These patterns are most remarkable in the orangoutang and less evident in the gorilla; in the lesser apes, these asymmetries are generally unremarkable (LeMay and Geshwind, 1975). Other nonhuman primates have been shown to have occipital petalia: 67% of a sample of chimpanzee brains had larger left occipital petalia (Galaburda, et al., 1978) whereas in the great apes, right occipital petalia are found more of the time (LeMay and Geschwind, 1975). Unfortunately, no generalizations can be made concerning handedness, as definite determinations of handedness are not possible. However it has been reported by LeGros Clark (1927) that a gorilla he studied for years and who he thought was right handed had a larger left occipital lobe at autopsy examination. Recently, Cain and Wada (1979) demonstrated an asymmetry in the frontal pole of the baboon: they showed that 6 of the 7 brains they examined exhibited an asymmetry in which the right frontal pole was longer than the left by a mean of 1.4 mm; the seventh brain examined had frontal poles of equal length. These findings raise interesting issues about evolution of the human brain in that the same asymmetries observed in apes are both more pronounced and extensive in the human, suggesting that perhaps evolution of the asymmetry in handedness occurred with concomitant increases in the convolutions and asymmetries of the cortex (Glick and Ross, 1980). At the present time, the functional relationships to these reported asymmetries remain elusive.

Studies conducted during the past decade have extended the examination of asymmetry in living humans through the use of neuropsychological testing methods; the findings have generally been interpreted in terms of lateralized affect as well as lateralized cognition. Milner has suggested that the right hemisphere may play a dominant role in certain perceptual and nonverbal cognitive functions (Milner, 1971). In some cases the observed differences in hemispheric functions are interpreted as reflecting a fundamental duality in cognitive style, with the left hemisphere characterized as the more analytic, rational and propositional, and the right hemisphere as the more holistic, intuitive and appositional (Bogen and Bogen, 1969; Bogen, 1969). Investigators have gone so far as to suggest that the right hemisphere is more creative (Bogen and Bogen, 1969). However, this suggestion has been dismissed by others (Zangwill, 1960) who note that there is little evidence for such a claim. Upon close inspection of the actual data, one finds that the most similar characteristic of right hemisphere functions is that they are all nonverbal (Corballis and

Morgan, 1978). Indeed, right hemisphere advantages have been reported for myriad nonverbal perceptual abilities including perception of musical chords (Gordon, 1970), melodies (Kimura, 1964), visuospatial configurations (Kimura, 1969), faces (Geffen, et al., 1971), judgement of stereoscopic depth (Durnford and Kimura, 1971), color discrimination (Davidoff, 1976), spatial processing (Witelson, 1976), as well as control of facial expression (Sackeim, et al., 1978). In that all of these functions involve some basic perceptual ability, some investigators have suggested that perhaps it is not the right hemisphere that is specialized for these tasks, but rather that the left hemisphere is deficient in them (Corballis and Morgan, 1978). Indeed it has been suggested (Zangwill, 1960; Geschwind, 1976) that by developing a lateralized capacity for language, and perhaps for fine motor control, the left hemisphere may have forfeited some of its capacity to carry out nonverbal perceptual functions.

Although the asymmetries reported in humans using neuropsychological methodology have opened the door to more noninvasive studies, the interpretation of such studies, especially those employing the dichotic listening task, have been questioned. Using this task, Kimura (1961, 1967) reported that right handed subjects had a right ear advantage when both ears were presented with verbal stimuli. She interpreted these data as indicating that verbal information is processed preferentially in the left hemisphere. Although her data have been confirmed by other investigators, her interpretation has been challenged. Schwartz and Tallal (1980) using computerized techniques for synthesizing speech while selectively controlling acoustic variables, have studied the question of how speech is distinguished from nonspeech and why it is preferentially processed in the left hemisphere. Their studies have demonstrated that the right ear advantage for verbal material may reflect superiority of the left hemisphere for processing rapidly changing events, of which speech is only one example. They did not suggest that the right ear advantage does not reflect a left hemispheric advantage in the processing of linguistic material; rather, their contention was that the superiority of the left hemisphere is, in part, attributable to its ability to more readily process rapidly changing events--a critical component in the processing of speech.

Other physiologic asymmetries have been observed recently using the xenon-133 inhalation method. Here the subject inhales ^{133}Xe and the clearance of the label from the brain is measured using sodium iodide crystal detectors placed over the subject's head. Using this method, Gur et al. (1980) tested a group of right handed male students who had no left handed first-degree relatives and found that there was more gray matter relative to white matter in the left hemisphere than in the right, especially in the frontal and precentral regions. These authors suggested that their observed hemispheric differences in gray/white matter ratios may be potential markers of language dominance, but recognized the need to extend these studies in subjects with right hemispheric dominance for language as well as in subjects who differ in their degree of hemispheric specialization.

Post-mortem brain specimens have been studied to determine whether there are asymmetries in neurotransmitters in the human brain (Rossor, et al., 1980). Of all the transmitters and synthesizing enzymes measured, only the concentration of GABA in substantia nigra was asymmetrically distributed, with a greater amount on the right side. A problem with this study was the fact that the handedness of the subjects was unknown and analyses of variance were not performed so that a definite conclusion concerning hemispheric asymmetry of neurotransmitters and their related enzymes in humans cannot be drawn. On the other hand, pharmacologic data exist to support the idea that, at least, dopamine may be lateralized in the brains of some psychiatric patients: seven of eight right handed psychiatric patients were observed to have greater right than left side dyskinesias, a finding which was interpreted as a pharmacological vulnerability of the left dominant hemisphere (Waziri, 1980). In addition, Oke et al. (1978) reported that norepinephrine has a strongly lateralized distribution in post-mortem samples of the human thalamus: in the somatosensory input area, the right hemisphere has a higher concentration of norepinephrine whereas in the pulvinar region, the left hemisphere norepinephrine concentration is higher. These data were related to those from clinical studies of patients undergoing thalamic surgery for dyskinesias or pain where there is good evidence for funtional thalamic lateralization (Riklan and Cooper, 1977). Thus, although the precise relationship between neurotransmitters and cerebral lateralization in the human is still unclear, the available evidence indicates that transmitters are indeed lateralized in thalamus and that an as yet unobserved lateralized dopamine concentration in the basal ganglia may be the substrate for the asymmetry in drug induced dyskinesias.

Various models have been proposed to explain cerebral lateralization both in the human as well as other species. An interesting model which considers human handedness and cerebral lateralization in a general biological context was discussed by Corballis and Morgan (1978). They suggest that the growth of human laterality, and of laterality in other species, may be explicable in terms of a left-right maturational gradient; in this model, a left-right gradient during development is suggested to favor the left hemisphere which presumably develops earlier and/or more rapidly than the right. The model also accounts for the observed equipotentiality of the two hemispheres for the representation of language in the immature in that it suggests that if the leading side is damaged early in life, the gradient is reversed such that subsequent growth occurs with the opposite polarity. Furthermore, in that this model also invokes the concept of interhemispheric inhibition, where the leading or dominant side inhibits the slower side, this model accounts for the fact that, at maturity, only one side of the brain is capable of language. Although this model has been, and no doubt will continue to be, of considerable heuristic value--it will likely, by virtue of its global nature, be too general and oversimplified in the final analysis.

Until quite recently, it was believed that cerebral asymmetry was unique to the human species (Levy, 1977). However the study of cerebral laterality in the rodent, pioneered by Glick and colleagues, and in other nonprimate mammals has received considerable attention during the past decade. It is now generally accepted that brains of other species are, indeed, lateralized and that, in some cases, lower animals can serve as useful models of lateralization in the human.

Although reports exist in the literature which document circling behavior (rotation) in dogs (Nymark, 1972), cats (Glick, 1981), gerbils (Jerussi and Glick, 1976) and mice (Glick, et al., 1976), the rat has been the most widely used for rotation studies and is, thus, the best characterized species. Indeed, along with some songbirds, the rat is also best characterized in terms of cerebral asymmetry. The following section will attempt to summarize the major achievements in the investigation of cerebral laterality in the rat.

It is well known that rats with nigrostriatal lesions will rotate or turn in circles under the influence of various drugs (Glick, et al., 1976). Although early studies suggested that damage to the nigrostriatal system was a <u>sine</u> <u>qua</u> <u>non</u> for the appearance of drug induced rotation (Arden, et al., 1966), subsequent studies demonstrated that normal animals also rotate, albeit at lower rates, when administered the same drugs administered to brain damaged amimals (Glick, et al., 1976). Amphetamine, apomorphine, L-dopa, scopolamine, LSD and morphine all induce rotation in normal, naive rats (Glick, et al., 1976) and, as with lesioned rats, the direction of rotation is consistent. Thus, when tested repeatedly using the same dose of a given drug, some animals rotate consistently to the left while others rotate consistently to the right. Furthermore it was observed that nonlesioned untreated rats will also rotate at night--the more active half of their circadian cycle--and that this rotation is in the same direction as that induced by amphetamine (Glick and Cox, 1978).

This observation of normal rotation was one of the first hints that normal rats may have intrinsic bilateral nigrostriatal asymmetries which are accentuated by some drugs. Indeed, a lateralized dopamine distribution in the striata of rats was demonstrated directly: the concentrations of dopamine in the left and right striata differed by approximately 15% (Zimmerberg, et al., 1974); high doses of amphetamine (20 mg/kg) increased this difference to approximately 25% while inducing rotation contralateral to the striata containing the higher dopamine levels. No normal or drug induced asymmetry was observed for striatal acetylcholine levels or for forebrain acetylcholine or norepinephrine levels. That amphetamine was equally distributed in both striata suggested a relatively specific model of nigrostriatal function in terms of an intrinsic striatal dopamine asymmetry (Zimmerberg, et al., 1974).

Based upon the findings of consistent side preferences in operant chambers both in the presence (Jerussi and Glick, 1974) and absence (Glick, 1973) of amphetamine, Glick postulated that the nigrostriatal asymmetry may be one of the neural substrates of spatial behavior. In testing this hypothesis, Glick's group found that spatial preferences were, indeed, associated with the dopamine asymmetry in the caudate: rats' spatial preferences were contralateral to the striata containing the higher levels of dopamine (Zimmerberg, et al., 1974). Further studies demonstrated that rotation and side preferences are mediated by the nigrostriatal system: unilateral caudate lesions caused ipsilateral side preferences as well as ipsilateral rotation (Zimmerberg, et al., 1974). Additionally, Zimmerberg and Glick (1975) were actually able to switch rats' side preferences by stimulating the caudate ipsilateral to their side preferences. Similar stimulation on the side contralateral to the rats' spatial bias had no effect. From these data, Glick suggested that rotation and spatial behavior may be subserved by the nigrostriatal system and that this system may mediate spatial tendencies through an endogenous dopamine asymmetry.

The fact that normal animals rotate has some interesting implications from an experimental point of view. For example, Jerussi and Glick (1975) have shown that the preoperative direction of rotation interacts with the magnitude of rotation after unilateral caudate lesions. After such lesions, all rats rotate ipsilaterally, but the rats with lesions ipsilateral to the preoperative direction rotate approximately twice as much in response to both apomorphine (Jerussi and Glick, 1975) and amphetamine (Glick and Cox, 1978). Indeed, a variety of studies examining the effects of unilateral striatal lesions have clearly demonstrated differential effects which are a function of the rats' preoperative directional bias. In one study, it was found that lesions ipsilateral to rats' side preferences improved their timing performance while contralateral lesions impaired such behavior (Glick and Cox, 1976). In another study, the same relationship was observed between the side of a striatal lesion and performance in a passive avoidance task: that is, ipsilateral lesions facilitated and contralateral lesions impaired passive avoidance learning (Rothman and Glick, 1976). Collectively these data illustrate the importance of the preoperative baseline in the interpretation of postoperative behaviors.

The 2-deoxy-D-glucose (dGlc) technique, as originally described by Sokoloff and colleagues (Sokoloff, et al., 1977), can be used to assess the functional state of the nervous system under a variety of experimental conditions and will be discussed at length in a following section. This technique has recently been applied to the study of cerebral laterality. A modified dGlc procedure (Meibach, et al.,1980) was used to ascertain whether the various structural units of the central nervous system are lateralized in terms of dGlc uptake. Data from this study indicated that certain brain regions have asymmetries in dGlc uptake (Glick, et al., 1979). The asymmetries observed were of three different kinds: 1) a difference in activity in cerebral hemispheres ipsilateral and contralateral to normal spatial biases were observed in mesencephalon and caudate-putamen; 2) a difference in activity in the left and right hemispheres was seen in frontal cortex and hippocampus; and 3) an absolute difference between sides was noted that was correlated with the rate of rotation in thalamus and hypothalamus, and with random movement in cerebellum. Furthermore, amphetamine administered fifteen minutes before a dGlc injection altered striatal, frontal cortical and hippocampal asymmetries while leaving those in mesencephalon, thalamus, hypothalamus and cerebellum intact.

Using a novel experimental design, work conducted by Glick and colleagues has recently demonstrated that rats have asymmetries in self-stimulation thresholds that are related to their directional preferences (Glick, et al., 1980). Rats that were implanted with electrodes bilaterally into both lateral hypothalami were allowed to self-stimulate in operant chambers while rotation was measured concomitantly. It was found that all rats had asymmetries in self-stimulation thresholds which, in all cases, were lower on the side of the brain contralateral to their spatial preferences. The direction of rotation, measured in response to 1.0 mg/kg amphetamine was the same both before and after electrode implantation as well as during self-stimulation testing, and the side of stimulation did not interact with the magnitude and direction of rotation, indicating that such rotation was not stimulus induced. Rather Glick attributed such rotation to the nonspecific arousal which is a concomitant of self-stimulation behavior. Additionally, the asymmetries seen in self-stimulation behavior were not limited to thresholds in that the entire rate-intensity functions were shifted to the left for the side contralateral to the direction of rotation. Electrode placements were verified after the experiments and were found to be symmetrical; due to this histological evidence and the observed close relationship between rotation and the asymmetries, it is unlikely that these observations were artifactual. Rather, these are the first data that demonstrate that reward processes are lateralized in the rat.

The finding of asymmetries in self-stimulation thresholds was the first animal model with an analogy to the human literature, suggesting that perhaps each side of the brain may be specialized for low and high effect. Glick hypothesized that the reinforcing properties of drugs may be related to their ability to interact with affect systems in the two hemispheres. This hypothesis is presently being tested (personal communication: Glick): the data indicate that whereas amphetamine preferentially affects the low threshold side of the brain, morphine preferentially affects the high threshold side.

Based upon findings of a left-right asymmetry in rat cortex (Diamond, et al., 1975) as indicated by differences in cortical thickness, differences in the effects of left and right cortical lesions (Denenberg, et al., 1978; Robinson, 1979; Robinson and Coyle, 1979) and a difference in frontal cortical energy metabolism (Glick, et al. 1979), Glick and Ross (1980) hypothesized that in a large population a population bias for spatial preferences would be evident, even though in ordinary sample sizes no bias was ever revealed. Spatial preference data were gathered for both turning in rotometers and for lever preferences in two lever operant situations--it was found that of 602 female Sprague-Dawley rats tested for rotation, 54.8% had right sided biases and 45.2% had left side biases. Additionally. of 292 female Sprague-Dawley rats tested in two lever situations, 57.5% preferred the right lever and 42.5% preferred the left lever. Based upon these data, Glick and Ross concluded that female Sprague-Dawley rats have a right sided spatial bias as a population. In the same study, these authors demonstrated that right sided rats were both more active and had greater side preferences than left sided rats, findings that were predicted on the basis of Robinson's findings with infarcts (1979) and those of Glick with cortical lesions (Glick and Greenstein, 1973) and asymmetries in dGlc uptake (Glick, et al.,1979). Ross and Glick (1981) subsequently extended these findings by demonstrating that the effects of bilateral frontal cortex lesions are a function of the rats' preoperative directional bias. What they found was that such lesions decreased rotation and locomotor activity in rats with right sided biases and increased rotation and activity in rats with left sided biases. They suggested that the frontal cortex normally modulates a dopaminergic nigrostriatal asymmetry and that an asymmetry in corticostriatal function, possibly involving glutamate, may be the neural substrate for their observations.

Work in other laboratories has also demonstrated that the rat brain is lateralized. Denenberg's group has shown that the effects of early experience are asymmetrically distributed between the two hemispheres (Denenberg, et al., 1978). For their first twenty days of life, rats were either handled or not handled for three minutes daily; at weaning, half of the animals were placed in enriched environments and at age fifty days, all animals were placed in standard laboratory cages. As adults, males from each group were selected randomly for either a left neocortical ablation, right neocortical ablation or sham surgery--after recovery the animals were tested in open fields and their activity monitored. It was found that the handling and the enriched environment parameters interacted with the right brain intact versus control comparison as well as with the right versus left comparison. However, they found no evidence for lateralization in open field activity in the nonhandled group, irrespective of the postweaning milieu. On the other hand, the handled groups were lateralized and the postweaning environment interacted with this lateralization. Thus, for the group that was handled and subsequently placed in laboratory cages, the left hemisphere intact animals were more active than the right hemisphere animals; the fact that the left hemisphere intact group was more active than the intact nonoperated group suggested to Denenberg that this increased activity was due to disinhibition of the right hemisphere, and that in the intact animals, the right hemisphere normally inhibits the left. Additionally, in the handled enriched group, the right hemisphere intact group was more active than the left. Since the control group with no lesions was also more active than the left hemisphere intact group, Denenberg concluded that in the handled enriched group, there normally is right hemisphere dominance.

Using an open field test for spatial preference, Denenberg and associates (1980) extended their findings to show that, using this test, nonhandled rats had no bias, whereas nonhandled rats without a left hemisphere were significantly more biased in going to the ipsilateral side than were their siblings without a right hemisphere: In contrast, intact handled rats were found to have a significant left bias--which suggested to Denenberg that in nonhandled animals, behavioral symmetry in making spatial choices is due to balanced brain asymmetry in which the right hemisphere biases the animal to move to the left while the left hemisphere acts to inhibit this response. On the other hand, for handled rats, Denenberg concludes that the right hemisphere controls spatial preference. The findings of Denenberg are hampered by the use of gross lesions characterized by varying degrees of subcortical damage and overinterpretation of the data. For example, there is no reason to assume that taste aversion testing would necessarily reflect 'emotional reactivity' (Denenberg, et al., 1980) in rats, in the same way we speak of emotional reactivity in humans. Furthermore, due to the lack of documentation concerning the different rearing procedures for handled and nonhandled rats, I am personally not convinced that the latter group is being reared 'normally' in that their cages are evidently not changed for the entire preweaning period (Denenberg, 1977). At any rate, based on his findings, Denenberg has suggested a model for brain function in the rat which involves three major hypothetical brain processes which are based upon general systems theory. These three processes are: hemispheric activation, interhemispheric inhibition, and interhemispheric coupling (Denenberg, 1980). The generality of this theory has been questioned by T.E. Robinson (Robinson and Becker, 1980) and colleagues who feel that Denenberg's conclusions are based upon an inadequate sample and that the pattern of human cerebral asymmetry which Denenberg uses to compare other species to may not be an adequate representation of that species as well. Robinson suggests that with our present paucity of knowledge about variations in the pattern of cerebral lateralization within populations, perhaps global theories as to differences between populations are probably premature.

Robinson and Coyle (1979) reported that a right middle cerebral artery ligation caused a decrease of norepinephrine in the lesioned cortex and an increase in running wheel activity whereas rats with a left middle cerebral artery ligation showed no such neurochemical or behavioral changes. Robinson (1979) subsequently extended these findings by demonstrating that a right hemisphere infarct caused an increase in open field activity while no such change occurred after left hemisphere infarcts. Furthermore Robinson and Stitt (1980) recently reported that 6-OHDA lesions result in asymmetrical effects: that is, left hemisphere injections did not produce any hyperactivity until the dose was 6 μg, when norepinephrine was depleted in both hemispheres. It is noteworthy that only this high dose in the left hemisphere caused contralateral depletion of norepinephrine. Since ipsilateral depletions of norepinephrine can be produced by injections into either hemisphere, but only right hemisphere injections cause hyperactivity when one observes ipsilateral depletion only, Robinson concluded that the asymmetrical neural pathways which cause hyperactivity are postsynaptic to the cortical norepinephrine terminals.

Other than the rat, the songbirds are perhaps the best characterized species in terms of cerebral lateralization. Nottebohm and colleagues have for the past decade been studying vocal control in the chaffinch. The syrinx is the vocal organ in the bird and has two halves which are symmetrical. Each half is innervated independently by the tracheosyringealis branch of the hypoglossal nerve through its own sound source (Nottebohm, 1977, 1979). Nottebohm (1970, 1971, 1972) demonstrated that lesions of the left hypoglossus caused a disappearance of most of the chaffinch's song repertoire whereas lesions of the right hypoglossus had minimal effects on song production. These observations have been replicated in other songbirds (Lemon, 1973; Nottebohm, 1976) and the phenomenon has been termed 'left hypoglossal dominance' (Nottebohm, 1970, 1971, 1977, 1979). Nottebohm is careful to point out that this phenomenon is not universal—in that the parrot shows no evidence for dominance on either the left or right side (Nottebohm, 1976). Nottebohm and colleagues extended these findings by demonstrating that the highest vocal control center in the canary brain--the hyperstriatum ventrale pars caudale--also manifests left dominance (Nottebohm, et al., 1976). Sexual dimorphism has also been demonstrated by Nottebohm's group (Luine, et al., 1980) who looked at the effects of testosterone in adult male castrated canaries. Taken together, the data from Nottebohm's group leaves little doubt that song is lateralized in some songbirds, and that this lateralized behavior manifests sexual dimorphism.

Indeed, the issue of sexual dimorphism as it relates to lateralized phenomena is recently receiving more attention. T. E. Robinson and colleagues (1980) have recently replicated the original findings of Zimmerberg et al. (1974) which was the first demonstration of a dopamine asymmetry in caudate-putamen of the female Sprague-Dawley rat.

Robinson's data indicates that male rats do not show the same pattern of lateralization as females. Glick's group (1977, 1980) has also reported evidence for sex differences in behavioral asymmetries. Furthermore, the idea that the nigrostriatal dopaminergic system is sexually dimorphic is supported by reports that gonadal steroids modulate in vitro amphetamine induced release of DA from striatal tissue (Becker and Ramirez, 1980) as well as electrical stimulation induced rotation in females (Robinson, et al., submitted). Sex differences have also been demonstrated by Diamond (1980) who reported that in male rats the right cortex is thicker than the left. Females, on the other hand, tend to have a thicker left cortex. While the present information on sex differences in cerebral lateralization is at best rudimentary, the available evidence clearly suggests that prominent differences do exist.

Given, then, that the brains of a variety of animal species are lateralized, an important question arises as to how such lateralization developed during ontogeny. This question has been approached in various ways by investigators. In humans, asymmetries have been reported in the patterns of decussation of the pyramids of both newborn and fetal brains (Yakovlev and Rakic, 1966) and additional transverse gyri besides Heschl's gyrus have been observed on the superior temporal plane of fetal brains with multiple transverse gyri more commonly seen on the right side (Chi, et al., 1977). Witelson and Pallie (1973) found that the superior surface of the temporal lobe—an area known to be involved in the neural control of vocalization—was larger in the majority of cases on the left hemisphere. Furthermore, Wada and associates (1975) found that the asymmetry of the planum temporale is present prenatally--albeit less well pronounced than in the adult brain. Evidence for functional lateralization in the infant is also available: in a group of infants between one week to 10 months of age, evoked electrical responses to speech sounds were significantly greater when recorded over the left versus right temporal lobe--but responses to a loud noise or to a musical chord were larger over the right temporal lobe (Molfese, et al., 1975). In addition interhemispheric shifts in EEG power distributions have been reported (Gardiner and Walter, 1977) in four six month-old infants who were presented with either normal speech or music. Finally, Turkewitz and Creighton (1974) have described developmental changes in the relationship between lateral differences in responsiveness and the assumption of asymmetrical head postures. In a group of infants between 0 and 72 hours old, they found that infants older than 12 hours made significantly more right than left head turns whereas younger infants exhibited no such difference, unless lateral differences in sensitivity were not interfered with. Thus there is a body of knowledge which indicates that cerebral lateralization is both present in the prenatal and neonatal human and that it is manifest behaviorally in the latter group.

The 2-deoxy-D-glucose Technique.

The 2-deoxy-D-glucose (dGlc) technique allows one to assess the functional state of the nervous system under a wide variety of experimental conditions (Sokoloff, et al., 1977). This method as originally described by Sokoloff, et al. (1977), utilizing tracer amounts of radiolabelled dGlc, facilitates the determination of the rates and the amounts of glucose incorporation into various neuronal structures in the CNS. Elucidation of the biochemical properties of dGlc have revealed that it is taken up into neurons by the same saturable carrier that transports glucose (Bidder, 1968; Bachelard, et al., 1971; Olendorf, 1971; Horton, et al., 1973). Thus, dGlc transport has been investigated both in vivo (Sokoloff, et al., 1977; Schwartz, et al., 1976) and in isolated rat brain synaptosomes (Diamond and Fishman, 1973). Once taken up into the neuron, dGlc competes with glucose for hexokinase and, like glucose, is phosphorylated at the #6 position to its respective hexose-phosphate (Sokoloff, et al., 1977). However, unlike glucose-6-phosphate, dGlc-6-phosphate lacks a hydroxyl group on the #2 carbon and is not a substrate for the subsequent glycolytic enzyme phosphohexose isomerase (Sols and Crane, 1954) or glucose-6-phosphate dehydrogenase, the first enzyme in the hexose-monophosphate shunt (Tower, 1958; Horton, et al., 1973). dGlc-6-phosphate is, therefore, trapped inside the neuron. Moreover, because the activity of glucose-6-phosphatase has been reported to be very low in the mammalian brain (Hers and DeDuve, 1950; Hers, 1957; Prasannan and Subrahmanyam, 1968), it is unlikely that significant hydrolysis back to the free dGlc occurs. Thus, following administration of a tracer dose of labelled dGlc, one may utilize conventional radioautographic methodology to visualize the relative uptake of dGlc into various neuronal structures. Indeed, many investigators--most notably Sokoloff and colleagues--have employed both pharmacologic (Wolfson, et al., 1977; Savaki, et al., 1978; Brown and Wolfson, 1978; Nelson, et al., 1978; Delanoy and Dunn, 1978;

Sakurada, et al., 1978; Wechsler, et al., 1979; Weinberger, et al., 1979; McCulloch, et al., 1979; Meibach, et al., 1979; Glick, et al., 1980; Cremer, et al., 1980; Dunn, et al., 1980; Wooten and Collins, 1980) and physiologic (Kennedy et al., 1975; Kennedy, et al., 1976; Sharp, 1976; Schwartz and Gainer, 1977; Schwartz, 1978; Hendrickson and Wilson, 1979; Basinger, et al., 1979; Buchner, et al., 1979; Shinohara, et al., 1979; Schwartz, et al., 1979; Reinstein, et al., 1979; Brown, et al., 1979) stimuli to assess the relationship between functional neuronal activity and dGlc uptake. A body of electrophysiologic data (Hubel and Wiesel, 1968, 1972; Hubel, et al., 1976) support the contention that dGlc uptake closely parallels changes in functional neuronal activity (Sokoloff, et al., 1977). Although Sokoloff and coworkers originally used intravenously administered ^{14}C-dGlc for radioautography, other investigators have modified this technique, using tritium labeled dGlc, to increase resolution both in the goldfish retina (Basinger, et al., 1979) and in the adult drosophila (Buchner, et al., 1979). One should note that in the latter study, the ^{3}H-dGlc was administered parenterally in the drosophilas' food. Again, in these systems as well, the dGlc technique has confirmed and extended electrophysiologic findings.

The dGlc technique has recently been applied to the study of cerebral development. Thus imprinting in the chick has been investigated (Kohsaka, et al., 1979) as has the development of circadian rhythmicity and light responsiveness in the rat suprachiasmatic nucleus (Fuchs and Moore, 1980). Additionally, the development of cortical layers in the reeler mutant mice strain has been studied (Mikoshiba, et al.,

1980) and the dGlc patterns induced in the olfactory bulbs of rat pups during nipple attachment and suckling have also been elucidated (Teicher, et al., 1980). Furthermore, local cerebral glucose utilization in newborn and pubescent monkeys has been determined both during and before focal motor seizures (Kato, et al., 1980). Finally, the ontogeny of hippocampal energy metabolism has been described (Meibach, et al., 1980) and Ross, et al. (1980) have recently demonstrated that dGlc is asymmetrically distributed in some brain regions during postnatal development.

It should be evident that the dGlc technique as developed by Sokoloff has broadened and will continue to broaden our understanding of neuronal function. However, the technique is not without limitations. Firstly, quantification of the amount of label in the radioautograms requires the use of a densitometer which can be expensive and time consuming; other more elaborate computerized modes of quantification can be even more expensive (Goochee, et al., 1980). Secondly, the theoretical equation for glucose utilization (Sokoloff, et al., 1977) is both cumbersome and, in our estimation, not necessary (see Results/Discussion). Thus, it is not surprising that very few investigators other than Sokoloff's group employ it. Thirdly, and perhaps most disturbing, is that the dGlc is administered intravenously to rats immobilized in plaster body casts at least four hours postanaesthesia and surgery, when lingering amounts of lipophilic anaesthetic may still persist in the animal--especially in brain tissue. In addition, the use of a body cast is quite likely to render results which are at variance from those under more physiologic and less restrained conditions. In light of these important practical and theoretical limitations, and because of the problems associated with multiple blood sampling in neonatal rats, we modified the dGlc technique (Meibach, et al., 1980) so that one can use ip administration (thus precluding anaesthesia and body casts), the less expensive tritium labelled dGlc for microdissection coupled to liquid scintillation spectroscopy, and radioautograms using the standard ^{14}C-dGlc.

Postnatal Development in the Rat.

Growth in any organ can be divided into roughly three major phases: an early phase of rapid cellular division where the daughter cells are the same size as all other cells; a later period in which cell division continues, but at an attenuated rate, and the cells increase their individual size; a final stage in which cell division is complete, and all subsequent growth occurs by enlargement, or, in the case of the nervous system, differentiation of individual cells (Morgane et al., 1978). These three phases are known as hyperplasia, hyperplasia with concomitant hypertrophy, and hypertrophy alone. In the brain the period of hyperplasia ends sooner than in other organs; by the time of weaning (day 21) most cells have ceased to divide in the rat brain. The various regions of the brain do not all have the same temporal pattern of hyperplasia; rather, each region has a characteristic period when its cells stop dividing. Thus, in the cerebral cortex, cell division is complete by day 21 whereas in the cerebellum this process is complete by day 16 or 17 (Morgane, et al., 1978). Indeed, brain regions also have different temporal patterns of myelogenesis, neurotransmitter development and synaptogenesis as well as the other events associated with normal postnatal development. Clearly, the brain develops heterogeneously.

The growth spurt is defined (Dobbing, 1968) as the period when the brain grows especially rapidly; as already pointed out, this period is a postnatal event in the rat, occurring during the first three weeks of life. During the growth spurt, which commences when neuronal multiplication has essentially ceased, there is a marked proliferation of glial cells, and an accelerated rate of elaboration of neuronal connections. Thus this is when the major development of nerve cell processes takes place as does the establishment of neuronal connections between these developing neuronal processes. There is a gradual increase in synaptic numbers during the first three postnatal weeks with the second week characterized by an acceleration of synaptogenesis. The growth spurt is primarily glial proliferation; as already stated, most nerve cells have by this time essentially ceased to divide. Exceptions to this are certain cells in the hippocampus, cerebellum, and olfactory bulb (Morgane, et al., 1978). McIlwain (1966) has termed the first two weeks of development the 'critical period'; during this period one observes increased axonal and dendritic growth and active myelogenesis. The critical period is, perhaps, the most significant for behavioral development, as many behaviors reach maturity by the time this period ends (Jacobs, 1976; London and Buterbaugh, 1978).

The development of neurotransmitters in the CNS has been studied from various points of view. The approaches to this problem include measuring levels of transmitters in brain regions, measuring receptor levels using radiolabelled ligands of high specific activity, measuring the activities of transmitter-synthesizing enzymes and mapping specific neuronal pathways. The development of amines in the rat brain occurs almost entirely postnatally (Porcher and Heller, 1972): norepinephrine levels in the 4 day-old male rat brain are approximately 20-40% of adult values; regional differences are also observed for the approach to the adult levels of norepinephrine (ibid.). Medulla-pons reaches its adult levels sooner than any other region and even exceeds adult values between 22-44 days of age. In contrast, the midbrain does not approach adult values until day 36, and diencephalon, septum-caudate and telencephalon lag even further behind; by age 45 days, their levels of norepinephrine are only about 70% of adult (150-210 days) values.

Dopamine levels have also been studied (Porcher and Heller, 1972) but fewer regions were studied due to the relatively lower levels of DA in some regions which are not detectable using the fluorimetric assay. In the telencephalon and septum-caudate, developmental patterns for dopamine are relatively similar; both areas show a fairly steady increase from 15% of the adult value at four days of age to about 50-65% of the adult level at 45 days. More sensitive assays have been subsequently used to assess levels of catecholamines in the developing rat brain. Coyle and Henry used a sensitive radiometric-enzymatic assay to measure catecholamine levels during fetal and postnatal ontogenesis (Coyle and Henry, 1973). They found detectable levels of norepinephrine and dopamine by gestational day 15 which during the subsequent eight days of gestation increased 15 fold, attaining 30% of the adult value by birth. During the last week of gestation, the levels of norepinephrine and dopamine nearly doubled every 24 hours, increasing 120 fold. Regional distributions of norepinephrine and dopamine in the neonatal brain were also examined: for norepinephrine, the lowest values were in parietal cortex and increased in the order of cerebellum, diencephalon-midbrain, striatum and medulla-pons. Dopamine was measured in striatum and mesencephalon-diencephalon with the former region having approximately 5 times as much DA as the latter. The synthesizing enzymes have also been studied: tyrosine hydroxylase, aromatic acid decarboxylase and dopamine β hydroxylase are all present in the rat brain by day 15 of gestation (Coyle and Axelrod, 1972; Lamprecht and Coyle, 1972; Porcher and Heller, 1972) and levels of these enzymes increase over 2000 fold in nerve endings during their approach to adult values (Coyle and Axelrod, 1972).

Loizou has shown (1972) that the density of innervation by CA neuronal processes evaluated with the histofluorescence technique correlates closely with the observed regional distribution of CA levels. Regions near the cell bodies of the CA neurons appear to develop their innervation more rapidly than more distant regions. For example, the neonatal cerebellum, located near the locus coeruleus, contains about one-half of the specific activity of tyrosine hydroxylase and dopamine β hydroxylase and about one-half of the level of norepinephrine seen in the adult brain. On the other hand, the parietal cortex exhibits a 10 fold increase in the specific activity of these biosynthetic enzymes and the level of norepinephrine between birth and adulthood. Thus, the major catecholinergic neurons are formed and undergo differentiation at early stages of fetal development at different rates (Coyle, 1974; Lauder and Bloom, 1974) and their axons reach the neocortex by one week prior to birth (Coyle and Molliver, 1977).

Using ultrastructural and biochemical techniques, Coyle and Molliver (1977) demonstrated uptake of exogenous catecholamine precursors and congeners and concluded that the uptake and storage mechanism mature prior to, and independent of, the mechanism for neurotransmitter synthesis. Additionally, Kirsky and Slotkin (1979) examined the ontogeny of dopamine and serotonin uptake systems in rat brain regions and found a parallel biphasic development of both uptake systems in all regions. The most rapid increases occurred in the first two weeks postnatally followed by an attenuated rate of increase. Kinetic studies with DA demonstrated that the maturation occurred with increases in maximal uptake without a change in the substrate K_m--suggesting that there is a change in the number of terminals but not in the uptake system itself. Similar kinetic patterns have been observed for NE uptake (Coyle and Axelrod, 1971) and the uptake of serotonin (Nomura, et al., 1976) but not for GABA or glutamate (Hitzemann and Loh, 1978) during ontogenesis.

In an attempt to understand the relationship between the growth of presynaptic terminals and the appearance of postsynaptic receptor sites, Pardo, et al. (1977) examined the ontogenesis of specific haloperidol binding. They observed approximately 10-15% of adult levels at birth which did not increase until 7 days of age. Between 7 and 14 days, the specific haloperidol binding more than doubled and then tripled by day 21. Specific QNB binding to muscarinic receptor sites also increases about 9 fold between birth and adulthood with a similar time course to DA binding (Coyle and Yammamura, 1976). In contrast, the binding of naloxone in the striatum only triples during development (Coyle and Pert, 1976). Naloxone binding to opiate receptor binding sites is first detectable by gestational day 15 and increases to 40% of adult values by birth. Here, as with the catecholamines, developmental changes in specific binding reflect increases in the number of sites (Bm) as opposed to changes in the dissociation constant (Kd). The binding of ^{3}H-Diazepam has also been examined during development (Gallager and Mallorga, 1980). Results from this study show that diazepam binding is first observable by 16 days gestationally and that this binding increases close to adult values by 21 days postnatally. In that these changes in binding were shown to be associated with changes in the convulsant and anticonvulsant effects of diphenylhydantoin, the authors suggested that the emergence of diazepam receptor systems coincides with the emergence of functionality.

The Present Investigation.

It is clear from this Introduction that a good deal is known about development and that more interest is being placed in the study of cerebral lateralization. In that the role of lateralization during development is not known, it was the purpose of the present investigation to study the postnatal ontogeny of cerebral laterality. Because very little was known about lateralization in the adult in terms of neurotransmitters and neuroanatomical substrates, and because it was my intention to assay all structures for indices of lateralization, a method which would provide information about all brain regions was sought. For this purpose it was decided to employ a modification (Meibach, et al., 1980) of the dGlc technique (Sokoloff, et al., 1977). This technique is specific inasmuch as dGlc uptake reflects functional neuronal activity (Sokoloff, et al., 1977) but can be used to examine all brain regions for altered hemispheric activity. Accordingly, dGlc uptake was assessed bilaterally in seven brain regions of the developing rat.

MATERIALS AND METHODS

Subjects.

Male and female Sprague-Dawley derived albino rats were obtained from Perfection Breeders, Inc., Douglassville, Pa. One week was allowed for acclimatization prior to mating. Breeding was accomplished by placing one male with three females in large breeding cages (10 x 18 x 8 ins.) for one week, when the males were removed and the pregnant females were placed into separate breeding cages until parturition, which generally occurred three weeks later. On the day of birth the litters were culled to five males and five females. A 12:12 light/dark cycle (lights on at 7:00 a.m.) was maintained and food and water were available *ad libitum*.

dGlc Procedure.

dGlc (2-deoxy-D-(1,2-^{3}H)glucose; NEN; 40.0 Ci/mmol) was dissolved in physiologic saline and administered intraperitoneally to rats at a dose and volume which was adjusted for the weight of the rat (Table 2). Three males and three females were used on each day from birth (Day 0) through Day 21 and on Days 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90 and 100. For the preweanling group, the rats were removed from their mothers, weighed, quickly injected with isotope and maintained at 37° C using a rheostat-controlled heat lamp. For postweanling rats the procedure was the same except they were removed from their littermate instead of their mother. Thirty minutes after injection, the animals were sacrificed by decapitation and their brains were removed and dissected bilaterally into 14 structures. The dissection protocol was modified slightly for neonatal rats between Day 0-Day 7 in that midbrain was not dissected. Each region was weighed to the nearest 0.001 g and homogenized in 1.0 ml of distilled water. Three aliquots, each 100 µl, were removed and counted in a Beckman LS9000 liquid scintillation counter using NEN 963 liquid scintillation cocktail with 43% efficiency. To preclude litter effects, no more than one male and one female per litter were used on any given day. Variability due to prandial condition was minimized by not allowing the pups access to their mothers' teats during the experiments and by performing the experiments at the same time each day (9 a.m.). The older animals were similarly not given access to food or water during the experiments.

Behavioral Studies.

Behavioral testing was performed on the day of birth (Day 0), Day 1, or Day 2. The mother was removed from her pups for approximately three minutes during which time the pups were taken from their cage and placed in an open field maintained at 37° C. Testing consisted of placing the pups in a head-to-tail symmetrical position for five seconds and then allowing them to assume their preferred posture (Fig. 6). A score of left or right was determined by the position of the tail, the sex was then determined by the anogenital distance, and the rat was placed back into its cage. Tail posture was chosen as an index of lateralization because it was robust and easy to score in these young neonates who rarely locomote at such an early age.

Head movements and body posture were also monitored but these parameters were more subtle and difficult to document in an equally objective manner. It should be emphasized that tail scores were determined prior to the determination of sex to preclude observer bias. The pups tested for tail bias were not used for dGlc studies. A sample of the animals tested for tail bias as neonates were saved for testing as adults. These rats were weaned at 21 days and caged together until day 40 when the males and females were separated and caged in pairs with food and water _ad libitum_. On day 85 these animals were placed in rotometers, administered d-amphetamine (1.0 mg/kg, i.p.) and tested for rotation for one hour as described previously (Glick and Cox, 1978).

Biochemical Studies.

In order to characterize the developmental time course of phosphorylation of administered dGlc to dGlc-6-phosphate, a modification of the dGlc procedure discussed above was used. Rats were injected with ^{3}HdGlc intraperitoneally, and at 30 minutes postinjection were sacrificed by decapitation. Their brains were removed and homogenized in 5 ml of a 5% TCA solution in .01M sodium phosphate buffer and the homogenates spun for 10 minutes at 50,000 rpm in a small bench centrifuge. The clear supernatant was poured off and adjusted to pH 6.5 with NaOH.

The assay, a modification of Diamond and Fishman (1973), was standardized by preparing 0.5 x 6.0 columns of Dowex AG1X8 100-200 mesh (Cl^{-} form) in water which were washed with two volumes of water prior to the addition of approximately 10^{4}dpm ^{3}HdGlc and/or ^{14}CdGlc-

6-phosphate. The dGlc was eluted with 5.0 ml of water in 0.5 ml fractions collected separately in vials for counting. The dGlc-6-phosphate was collected similarly except 1.5 N HCl was used to elute the polar dGlc-6-phosphate. To ensure that the TCA, NaOH or substituents of the supernatant had no effect on the elution profile of dGlc and dGlc-6-phosphate, two subsequent control experiments were carried out adding, first, the 5% TCA to the system (with appropriate NaOH) and then a cold homogenate supernatant, to which a standard amount of dpms were added.

Following this standardization procedure, supernatants from brains of experimental animals were spiked with 10^4 dpm of ^{14}C-dGlc and 10^4 dpm of ^{14}C-dGlc-6-phosphate as internal standards. One hundred microliter aliquots of the supernatant were counted in triplicate for the subsequent determination of column recovery which ranged between 93 and 100% for rats at all ages. After addition of 1.0 ml of the supernatant, the columns were eluted exactly as control columns with 0.5 ml fractions collected and counted.

Data Analysis.

Data analysis was performed using the PROPHET computer system. The data were entered into PROPHET in the form of DPM/gram tissue for each region on each day: the DPM/g data were further analyzed in terms of asymmetry ratios and various indices of activity. The following is a list of the indices employed in the analysis:

ACTIVITY INDICES

$$\text{ABSOLUTE ACTIVITY} = \text{DPM/g in a region (i.e., left + right sides)}$$

$$\text{RELATIVE ACTIVITY} = \frac{\text{DPM/g in a region}}{\text{DPM/g in all regions}} \times 100$$

$$\%\ \text{UPTAKE} = \frac{\dfrac{\text{ABSOLUTE ACTIVITY in a region}}{\text{ACTIVITY OF INJECTED BOLUS OF dGlc}} \times 100}{\text{gram body weight}}$$

ASYMMETRY INDICES

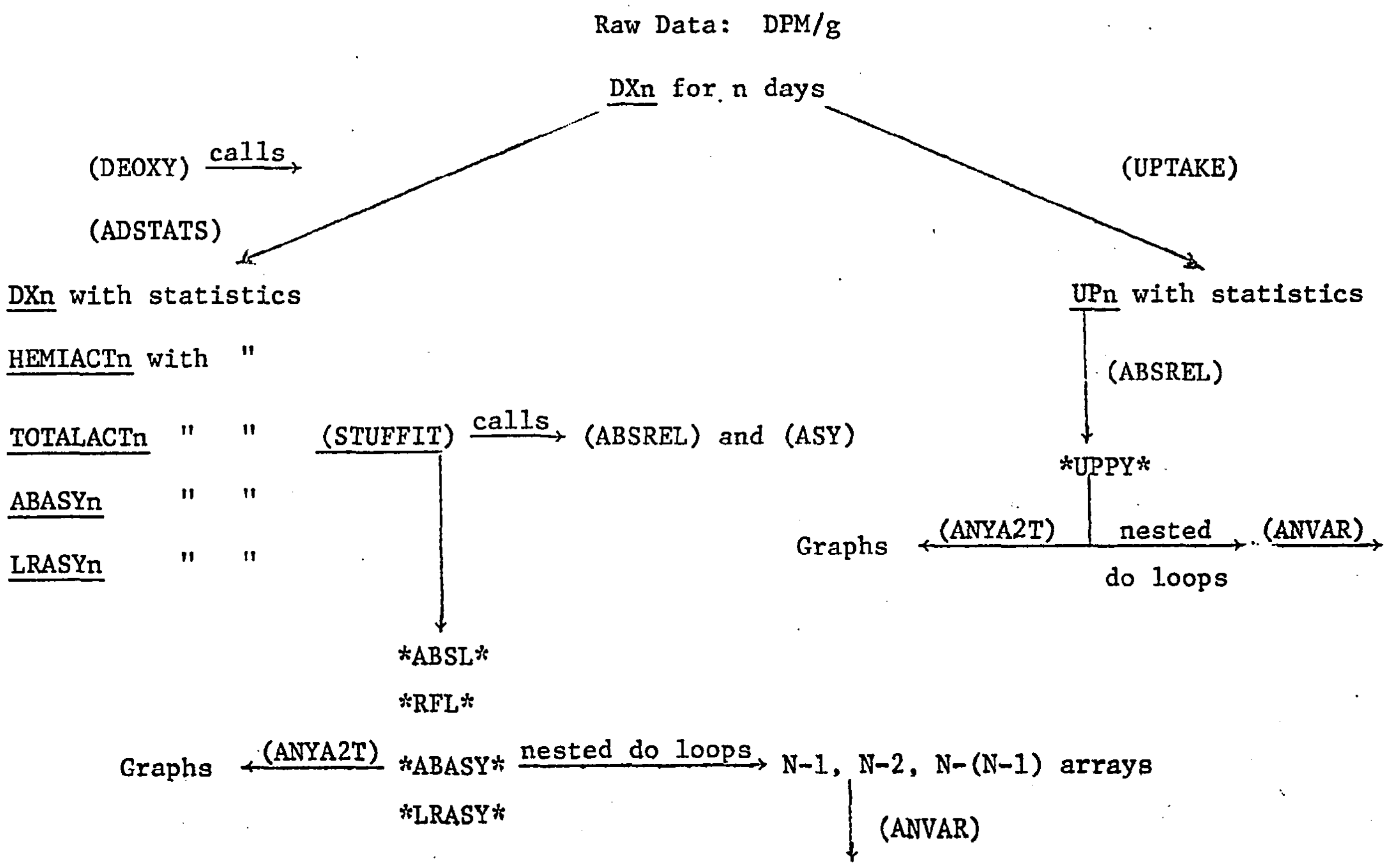
$$\text{LEFT-RIGHT ASYMMETRY} = \left(\frac{\text{DPM/g high side}}{\text{DPM/g low side}} - 1\right) \times 100$$

where the difference is arbitrarily designated positive if high side = left and negative if high side = right

$$\text{ABSOLUTE ASYMMETRY} = \left(\frac{\text{DPM/g high side}}{\text{DPM/g low side}} - 1\right) \times 100$$

The PROPHET was programmed to calculate the above indices from the raw absolute data and to generate tables of these indices for each day with statistics. Thus, for each day, tables of the above indices were generated and the means and standard deviations calculated separately for each sex as well as for both sexes combined.

The following flowchart is intended to give the general approach that was taken in the analysis of the data. Tables are one form of data storage in PROPHET and are underlined; arrays are another form of data storage and are surrounded by stars. The procedures used to analyze the data are in parentheses.



(Newman-Keuls: Multiple Comparison)

The nested do loops, referred to in the flowchart, were used in a variety of ways. Firstly, they were used to combine sexes when no sex differences were apparent and to similarly combine left and right sides so that activities in the brain regions could be expressed as activity per total region. Additionally, the nested do loops were used to combine days into three-day blocks so that averages could be obtained for groups of days. This latter procedure was especially useful for the graphic representation and analysis of the data. A nested do loop can reduce an array with N dimensions into one with N-1, N-2, or N-(N-1) dimensions for the limiting case; it can also be used to change the organization of an array. That is, one may change the array without changing the number of dimensions (N) but rather, by changing how the cells of data in the array are arranged. For example, given an array with five dimensions (N=5): 2 x 2 x 7 x 36 x 3, where the first dimension is sex, the second is side, the third is regions, the fourth is days, and the fifth is replications, one can reduce this array to combine both sexes where the resultant array has the structure of 2 x 7 x 36 x 6 with N-1, or four, dimensions. Alternatively, one may combine days to generate an array with N dimensions and the structure: 2 x 2 x 7 x 12 x 18; these latter examples depict the way in which sexes and days were combined in the present study, respectively.

RESULTS

Behavioral Data.

The results of the behavioral testing indicate that female neonatal rats have significant asymmetries in tail posture (Fig. 1). Frequencies for both sexes are shown in Table 1 which indicates that the tails of females are directed preferentially to the right. Although the tails of the males were biased towards the left, the preference was not significant. However, the difference between sexes was significant. Furthermore, there was a significant ($p < .05$; t-test) negative correlation ($r = -.59$; $N = 19$) between the percentage of females in each litter with right-sided tails and the number of males in the litter, which was expected based on the work of vom Saal and Bronson (1980) (see Discussion).

The tail asymmetry is a population parameter which may vary from test to test in the same animal. In pilot work, fifteen animals were tested on two consecutive days. Although the direction of tail bias was significantly consistent in a one-tailed Chi Square test ($x^2 = 3.27$; $p < .05$), the degree of consistency (73%) did not appear high enough to enable a direct relationship with dGlc incorporation to be found, since dGlc measurement would, of necessity, have to be made at a different point in time than the tail bias determinations. Since the tail asymmetry diminishes and is no longer apparent by day 4, it is not surprising that the consistency of this measure is less than 100%.

In view of the above, with regard to the consistency of tail pos-

Fig. 1. Neonatal rat pups exhibiting tail bias.

Rats were placed with their heads away from the observer and held in a head-to-tail symmetrical position with respect to the spine. After 5 sec the rats were released and the position of the tail determined with 5 sec as the end point.

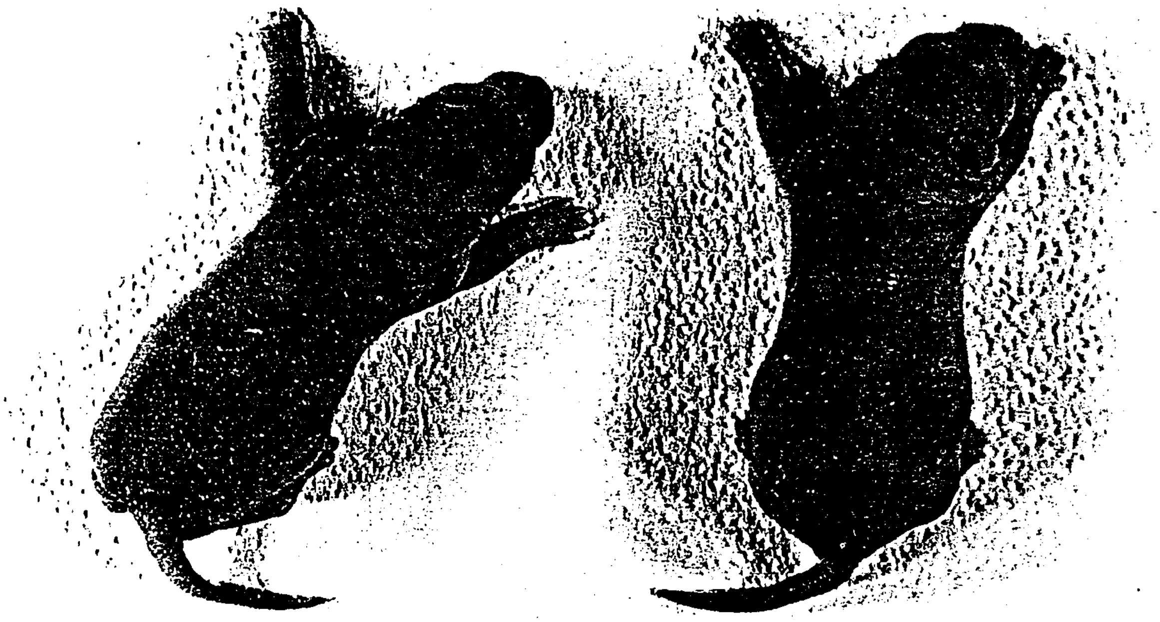


Table 1.

Frequencies of tail bias in neonatal rats.

Sex*	Direction†	
	Left	Right
Male (n = 114)	65	49
Female (n = 117)	45	72

* Significant male-female difference ($p < 0.005$, 2 x 2 χ^2 test on entire table).

† Significant left-right difference in females only ($p < 0.02$ in females and $p < 0.1$ in males, one-sample χ^2 test on data for each sex.

ture, it was deemed important to ascertain whether the tail position is in any way related to or reflective of the adult directional bias measured in a rotometer. The neonatal tail direction was compared with the direction of d-amphetamine-induced rotation at 85 days of age: these directions were the same in 28 of the 33 animals tested (15/16 males, 13/17 females). This association was significant for the whole group (x^2 test, $p < .001$) as well as for each sex separately (x^2 tests, $p < .001$ and $.03$ respectively, for males and females).

dGlc Studies.

A modification (Meibach, et al., 1980) of the dGlc technique (Sokoloff, et al., 1977) was developed so that the technique could be applied to the study of cerebral development. Substitution of tritium labeled dGlc with subsequent microdissection of selected brain regions and liquid scintillation counting produced results that were highly correlated with both ^{14}C-dGlc radioautograms and glucose utilization values as obtained by Sokoloff, et al. (1977) (Table 3). The route of administration was also varied and whole brain uptake at maximal levels of incorporation was the same for both intravenously and intraperitoneally injected rats. Radioautograms from i.p. and i.v. injected rats were indistinguishable; densitometric analyses of the i.p. radioautograms were highly correlated with glucose utilization values. Thus, these studies indicated that relative indices of functional activity can be obtained when experimental circumstances preclude arteriovenous cannulations and restraint. For a more detailed description of these modifications of the dGlc technique, the reader is referred to Meibach, et al. (1980).

Table 2.

Schedule of administration of dGlc in developing rats.

Dose of dGlc (μCi/g)	Weight of rat (g)	Volume of injectate (μl)
2 μCi/g	0 - 20.0 g	50 μl
1	20.1-40	50
.9	40.1-60	100
.8	60.1-80	100
.7	80.1-100	200
.6	100.1-120	200
.5	120.1-140	300
.4	140.1-160	300
.3	160.1-180	500
.2	180-	500

Table 3.

Regional comparisons of 2-deoxyglucose uptake with glucose utilization values.

		^{14}C			^{3}H	
		Glucose utilization*	i.v.**	i.p.**	i.v.***	i.p.***
Inferior colliculus		4.70	2.83	3.25	89.2	--
Cingulate gyrus		--	2.48	3.21	77.5	80.8
Auditory cortex		3.73	2.52	2.58	--	--
Thalamus		2.45	2.42	2.58	70.8	74.1
Caudoputamen		2.64	2.06	2.29	64.8	64.2
Frontal cortex		--	2.16	2.29	62.6	65.1
Retrosplenial cortex		--	2.06	2.58	60.0	--
Hypothalamus		1.50	1.54	1.75	55.4	54.3
Hippocampus		1.88	1.67	1.92	47.8	50.7
Cerebellum		1.57	1.38	1.56	50.2	48.3
^{3}H-i.p./^{3}H-i.v.	$r = 0.99$	$P<0.001$				
^{3}H-i.p./^{14}C-i.p.	$r = 0.97$	$P<0.001$				
^{3}H-i.v./^{14}C-i.v.	$r = 0.95$	$P<0.001$				
^{3}H-i.v./^{14}C-GU§	$r = 0.93$	$P<0.01$				
^{14}C-i.v./^{14}C-i.p.	$r = 0.93$	$P<0.001$				
^{14}C-GU/^{14}C-i.v.	$r = 0.92$	$P<0.01$				
^{14}C-GU/^{14}C-i.p.	$r = 0.95$	$P<0.01$				

---

* The values expressed are gray/white matter ratios obtained by dividing the glucose utilization (in μmol/100 g/min) for each structure by the glucose utilization of the corpus callosum as determined by Sokoloff et al. (1977).

** The values expressed are gray/white matter ratios determined by dividing the densitometric value of each structure by the densitometric value of the corpus callosum.

*** The values expressed are the dpm/mg.

§ ^{14}C-GU = glucose utilization values as determined in *.

Chromatographic Separation of dGlc and dGlc-6-Phosphate.

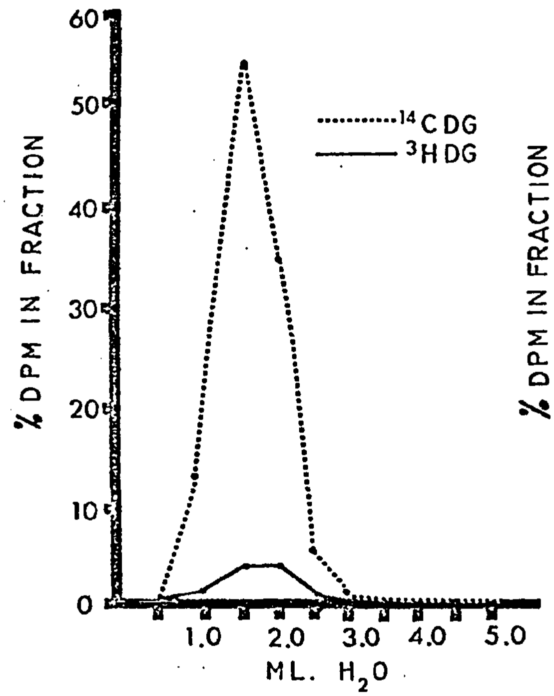
The chromatographic separation of dGlc and dGlc-6-phosphate is shown in Figure 2 for rats of 100 days old indicating that greater than 96% of the administered dGlc was phosphorylated to dGlc-6-phosphate at this age (mean ± S.E.M. = 96.3% ± 1.1; N = 4).
Column recovery of dGlc and dGlc-6-phosphate ranged between 95 and 100%. Data for the same experiments performed on younger rats are shown in Table 4 and Figure 3 and indicate that phosphorylation of administered dGlc increases during development and reaches a plateau at the adult level by approximately day 30.

As has been already mentioned, the dGlc experiments were performed so that information could be obtained about all brain regions during development. Because, initially, it was unknown how the dGlc data might change during development, it was decided to sacrifice six animals, 3 males and 3 females, on each preweanling day (0-21) and at regular intervals thereafter (25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90, 100). When the data analyses were begun, it was clear that it would be better to combine 3-day periods into one average with an N of 18 at each day, thus rendering each data point more reliable.

Cerebral dGlc Activity Data.

The percent uptake data were analyzed using a four-way analysis of variance (ANVAR) with sex, side, structures and days as factors. Significant main effects included structures ($p < .02$) and days ($p < .0001$) and there were significant sex by days ($p < .0001$ and structures by

Fig. 2. Column chromatography of dGlc and dGlc-6-phoaphate. Double-label scintillation counting of the two internal standards (^{14}C-dGlc, 64, 623 dpm; ^{14}C-dGlc-6-phosphate, 29, 5620 dpm) showed that 100% of the dGlc and 92% of the dGlc-6-phosphate was recovered. Based upon these values, 5% of the tritiated material chromatographed with ^{14}C-dGlc and 95% with ^{14}C-dGlc-6-phosphate. The average value was 96.3 ± 1.1%; n = 4.


% DPM IN FRACTION
0
10
20
30
40
50
60
1.0
2.0
3.0
4.0
5.0
ML. H_2O
^{14}C DG
^{3}H DG

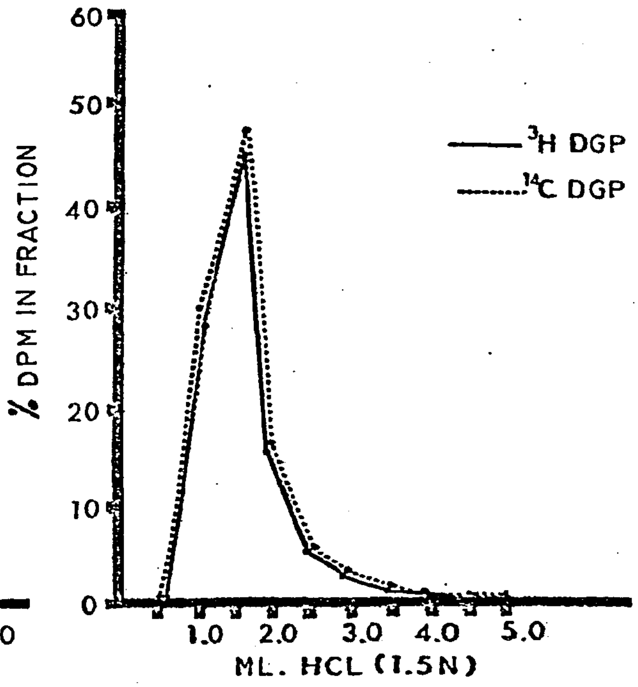
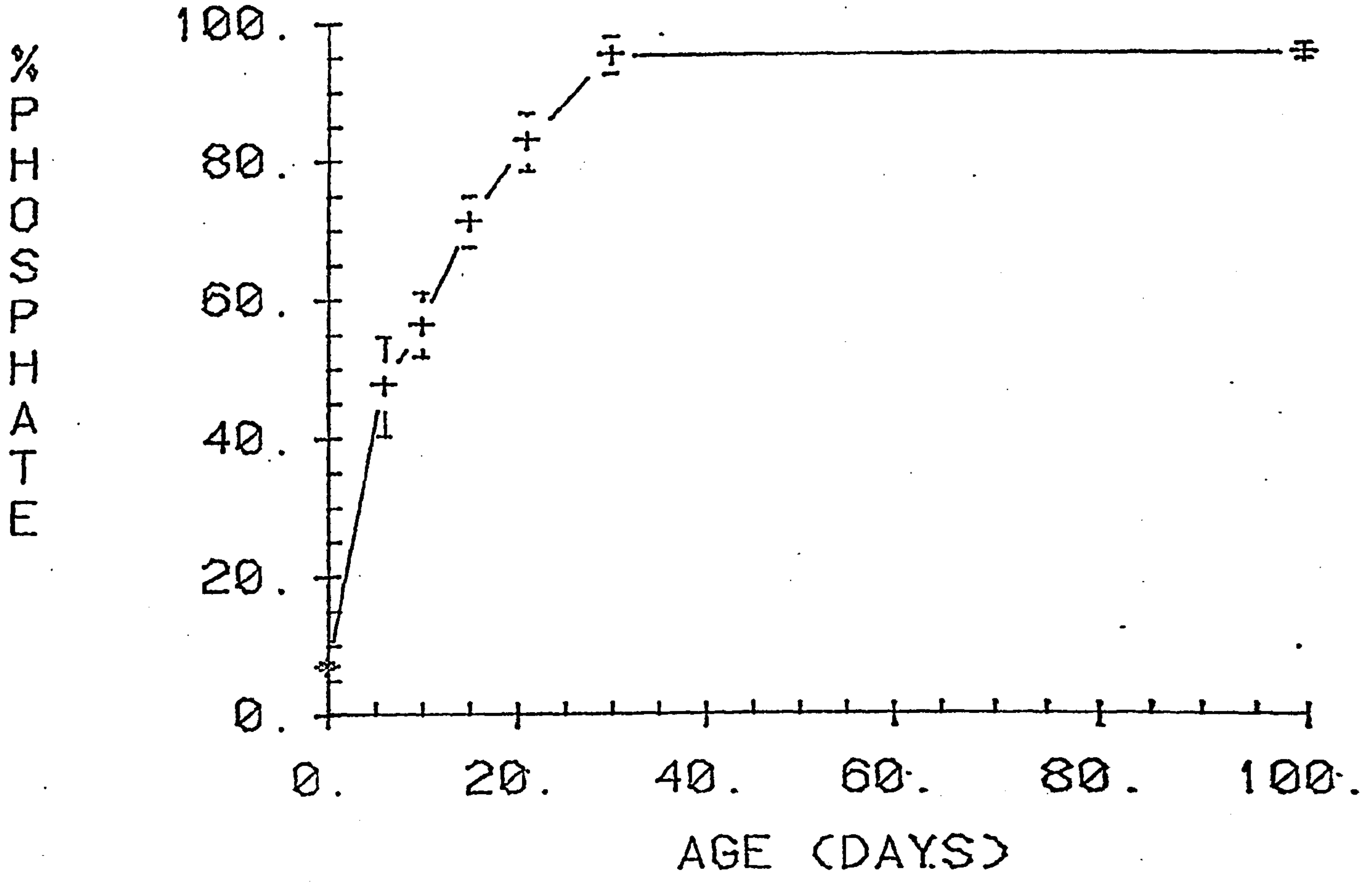

% DPM IN FRACTION
0
10
20
30
40
50
60
1.0
2.0
3.0
4.0
5.0
ML. HCL (1.5N)
^{3}H DGP
^{14}C DGP

Table 4.

Developmental changes in dGlc phosphorylation during development. Values are means ± SEM; n = 4.

Age (Days)	% Phosphate	SEM
0	7.33	.47
6	47.75	7.1
10	56.5	4.65
15	71.5	3.8
21	83.	4.25
30	95.5	2.7
100	96.3	1.1

Fig. 3. Phosphorylation of dGlc during postnatal development. Values are means ± SEM; n = 4 for all points.



PHOSPHORYLATION OF 2-DEOXY-D-GLUCOSE DURING POSTNATAL DEVELOPMENT days ($p < .0001$) interactions. These data are depicted graphically in Figure 4, which demonstrates that percent uptake clearly increases with age in all structures for both sexes although maximal uptake is reached earlier in females than males, resulting in the significant overall sex by days interaction.

The percent uptake data were further analyzed for each structure separately, using a three-way ANVAR with sex, side and days as factors. For all structures there were significant main effects of days ($p < .001$) and no significant interactions.

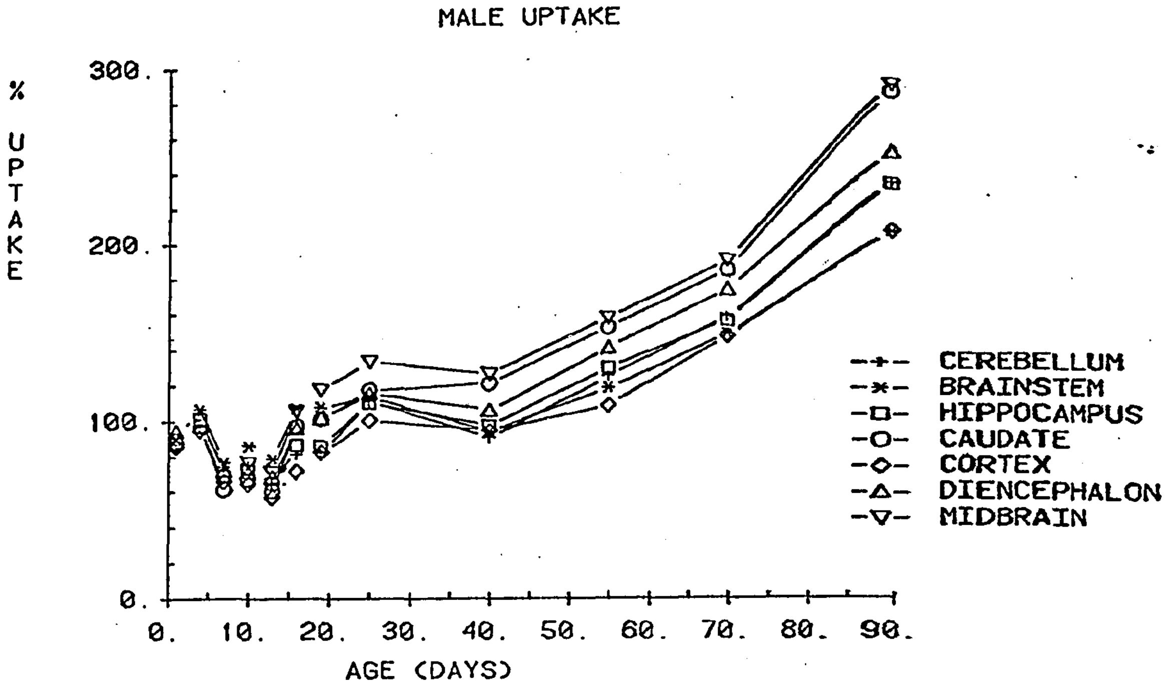
The relative activity data for each structure are shown in Figure 5. A four-way ANVAR of these data, with the same factors as above, revealed significant main effects of structures ($p < .001$) and of days ($p < .001$) and significant structures by days ($p < .001$) and sex by structures by days ($p < .05$) interactions. These data were also analyzed separately for each structure using a three-way ANVAR with the same factors as above; in all structures there were significant ($p < .001$) main effects of days, and in cerebellum ($p < .05$) and midbrain ($p < .02$) there were significant sex by days interactions.

Asymmetry Data.

The absolute asymmetry data were analyzed using a three-way ANVAR with sex, structures and days as factors. Significant main effects of structures ($p < .001$) and of days ($p < .002$) were obtained as was a significant ($p < .05$) structures by days interaction. These data were analyzed separately for each structure using a two-way ANVAR with sex and days as factors. There were significant effects of days in

Fig. 4. Developmental changes in percent uptake of dGlc.

Four way ANVAR with sex, side, structures and days as factors revealed significant main effects of structures ($p < .02$) and days ($p < .0001$) and significant sex x days and structures x days interactions ($p < .0001$).


MALE UPTAKE
% UPTAKE
300.
200.
100.
0.
0. 10. 20. 30. 40. 50. 60. 70. 80. 90.
AGE (DAYS)
CEREBELLUM
BRAINSTEM
HIPPOCAMPUS
CAUDATE
CORTEX
DIENCEPHALON
MIDBRAIN

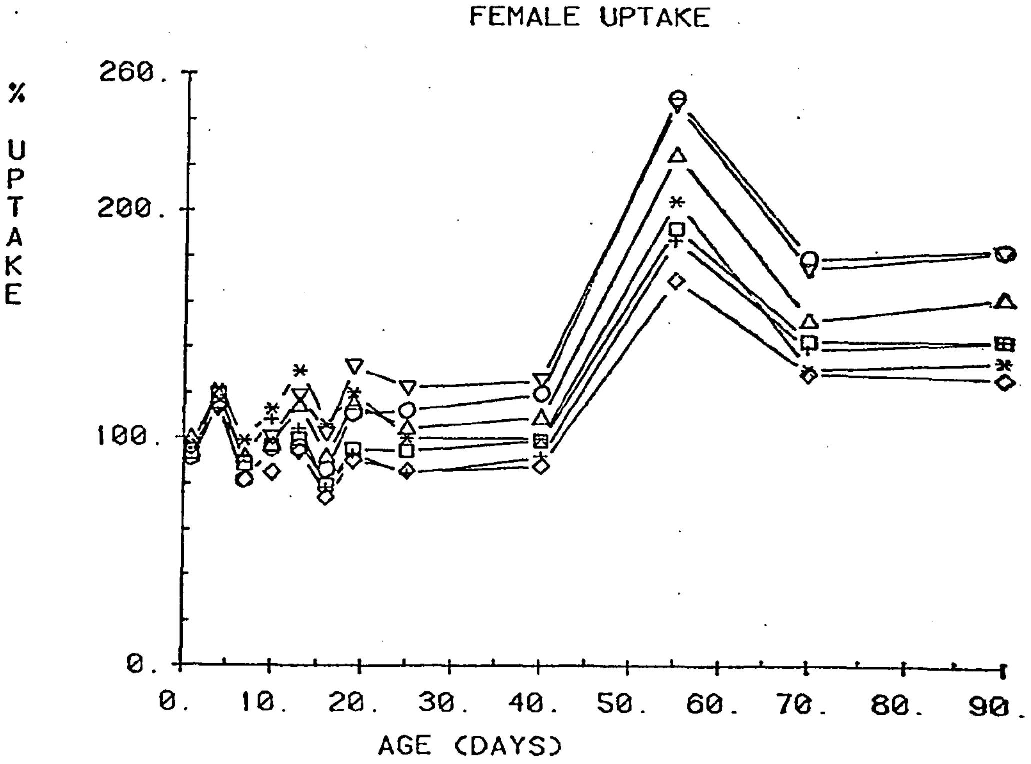
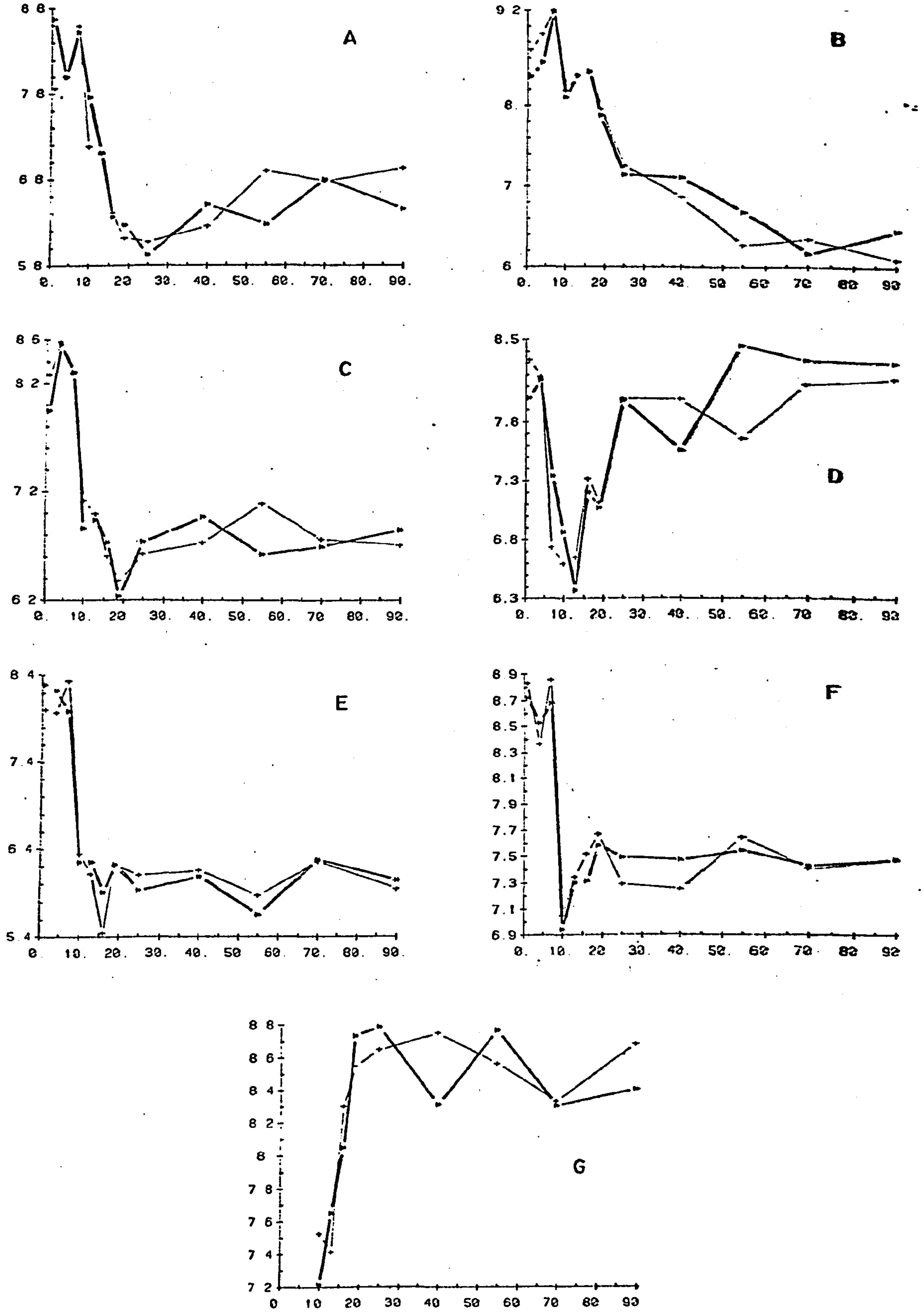

FEMALE UPTAKE
% UPTAKE
260.
200.
100.
0.
0. 10. 20. 30. 40. 50. 60. 70. 80. 90.
AGE (DAYS)

Fig. 5. Developmental changes in relative activity.

Relative activity in % (ordinate), versus age, in days (abscissa). Four-way ANVAR with sex, side, structures and days as factors revealed significant main effects of structures ($p < .001$) and days ($p < .001$) and significant structures x days and sex x strictures x days interactions ($p < .001$ and .05, respectively). A = Cerebellum; B = Brainstem; C = Hippocampus; D = Striatum; E = Cortex; F = Diencephalon; G = Midbrain. - + - = males; = * = = females.


A
8 8
7 8
6 8
5 8
0. 10 20 30. 40. 50. 60. 70. 80. 90.
B
9 2
8
7
6
0. 10 20 30 40 50 60 70 80 90
C
8 5
8 2
7 2
6 2
0. 10. 20 30. 40. 50. 60. 70. 80. 90.
D
8.5
7.8
7.3
6.8
6.3
0. 10. 20. 30. 40. 50. 60. 70 80. 90
E
8 4
7.4
6 4
5.4
0 10. 20. 30. 40. 50 60. 70. 80. 90.
F
8.9
8.7
8.5
8.3
8.1
7.9
7.7
7.5
7.3
7.1
6.9
0. 10 20 30. 40. 50. 60 70 80 90
G
8 8
8 6
8 4
8 2
8
7 8
7 6
7 4
7 2
0 10 20 30 40 50 60 70 80 90

midbrain ($p < .001$) and caudate ($p < .05$) only and no significant interactions. The left-right asymmetry data were also analyzed using a three-way ANVAR. The factors were the same as for the absolute asymmetry data and none were significant. There was, however, a significant ($p < .05$) structures by days interaction. When these left-right asymmetry data were analyzed for each structure separately, the only significant main effect was of sex in cortex ($p < .05$) and the only significant interaction was of sex by days in midbrain ($p < .01$).

The left-right asymmetry data for each structure were subjected to regression analyses as a function of age, relative activity and percent uptake for that structure. Regressions with age indicated that in females, there were significant left-to-right maturational gradients in brainstem ($r = -.29$; $p < .002$) and midbrain ($r = -.34$; $p < .001$) and right-to-left gradients in hippocampus ($r = .23$; $p < .02$) and diencephalon ($r = .24$; $p < .01$). The only such significant maturational gradient in males was a right-to-left gradient in midbrain ($r = .23$; $p < .04$). Regression analyses of the LRA ratios of a structure and relative activity of that structure revealed significant negative correlations between LRA ratios and relative activity in all structures of both sexes except the brainstem of females (Table 5); that is, the more active a structure is relative to the rest of the brain, the more likely that structure is right-biased and vice versa (e.g., see Fig. 6). Analysis of covariance indicates significant sex differences in the slopes of these regressions in cortex ($p < .001$) and caudate ($p < .05$). In both cases, the slopes are steeper for the males. In contrast to the significant regressions between left-right

Table 5.

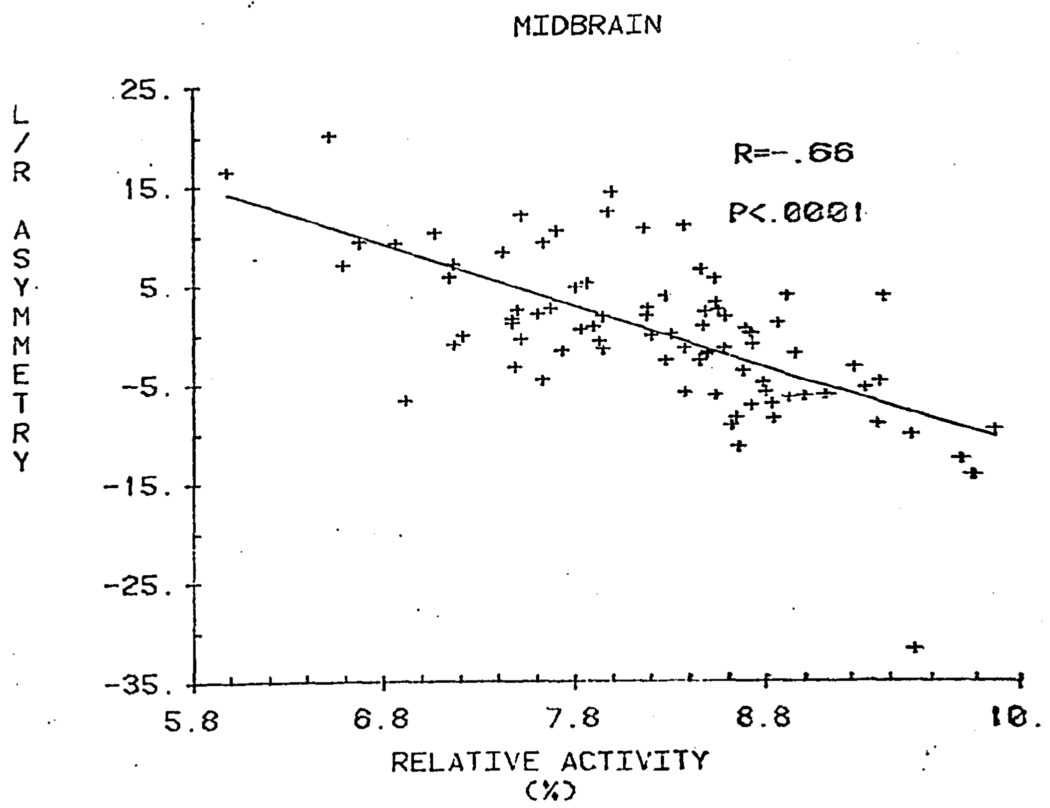
Correlation of LRA ratios and relative dGlc activity: Regression coefficients and significance levels.

	Male		Female	
Structure*	r	p	r	p
Cerebellum	-.47	.0001	-.50	.0001
Brainstem	-.49	.0001	-.04	NS
Hippocampus	-.38	.001	-.54	.0001
Caudate[t]	-.59	.0001	-.57	.0001
Cortex[t]	-.60	.0001	-.27	.005
Diencephalon	-.37	.001	-.45	.0001
Midbrain	-.47	.0001	-.66	.0001

* N = 108 males and 108 females for all structures except midbrain where N = 84 for each sex.

[t] Significance sex difference in slopes of regression lines as determined by analysis of covariance ($p < .05$, caudate and $p < .001$, cortex.

Fig. 6. Correlation of left-right asymmetry and relative activity in midbrain of female rats.


MIDBRAIN
L/R ASYMMETRY
25.
15.
5.
-5.
-15.
-25.
-35.
5.8
6.8
7.8
8.8
10.
RELATIVE ACTIVITY
(%)
R=-.66
P<.0001

asymmetry and relative activity, no significant regressions were obtained between left-right asymmetry and percent uptake.

The absolute asymmetry data were similarly subjected to regression analyses as a function of age, relative activity and percent uptake. The analysis indicates that the absolute asymmetry in the caudate decreases significantly with age in females ($r = -.25$; $p < .01$) and in the two sexes combined ($r = -.18$; $p < .02$). However, there were no significant relationships between absolute asymmetry and relative activity or between absolute asymmetry and percent uptake.

DISCUSSION

dGlc Studies: Method Modification.

The modification of the dGlc technique (Meibach, et al., 1980) clearly renders results which are both qualitatively and quantitatively similar to those presently in the literature (Sokoloff, et al., 1977). Most important is the fact that similar data are obtainable using more convenient methodology. Although many investigators employing the dGlc technique use either densitometric analysis of radioautograms or liquid scintillation counting of dissected brain regions to quantify their data, it would appear from the operational equation developed by Sokoloff, et al. (1977) that these methods are not suitable for comparing dGlc incorporation in different animals. This is so because the rate constant for transport of dGlc from plasma to tissue and back (k_1 and k_2, respectively) as well as the rate constant for dGlc phosphorylation by hexakinase (k_3) are all influenced by plasma glucose levels. Thus, since plasma glucose levels may vary somewhat among animals it would be incorrect to assume that the difference seen either in the radioautograms or in the dpms are indicative of real differences in dGlc incorporation and glucose utilization. However, in the present study, no significant variations in dGlc incorporation were observed between animals for any brain region. Certainly, the actual dpms or optical densities vary across animals but such variability is always found to be attributable to variability in the specific activity of the injected bolus of radioisotope. Furthermore, the ^{3}HdGlc and ^{14}CdGlc experiments were highly correlated with each other, and even without correcting the values for plasma glucose levels, both were highly correlated with glucose utilization values as determined by Sokoloff, et al. (1977) for the control group. It therefore appears that possible variations in plasma glucose levels do not appreciably alter dGlc incorporation. This is a critical point for two reasons: Firstly, it allows one to make relative comparisons of dGlc incorporation between animals without prior determination of plasma glucose levels and the calculation of glucose utilization values. Secondly, comparisons can now be made between control and experimental animals. However, procedures which can dramatically alter cerebral blood flow, such as lesions and strokes, or those that can profoundly alter plasma glucose levels, such as insulin administration, must receive special consideration. One would suspect that in such cases, new rate constants would have to be determined and glucose utilization values calculated. In some instances, though, glucose utilization determinations may still not accurately reflect metabolic changes: that is, if there were localized changes in the microcirculation with compensatory changes in structures immediately peripheral to the site of injury, plasma glucose levels would appear unaltered and the changes seen in the radioautograms would misleadingly appear as changes in glucose utilization. In this case, however, such changes could very well, indeed, be due to a differential distribution and perfusion of cerebral glucose. Nevertheless, for the majority of studies it appears perfectly valid to compare dGlc uptake between animals. For ^{14}CdGlc studies which employ densitometry, the methacrylate standards must be used to convert optical density measurements to µCi/g. This assures that changes in the developing procedure do not produce artifacts. Additionally, by presenting the data as grey/white matter ratios, using the same white matter structure, such as the corpus collossum, differences in the amount of label injected or in section thickness are eliminated. In studies using ^{3}HdGlc, the radioactivity of the injectate must be obtained. In this way, percent uptake values may be calculated and the variability due to differences in the radioactivity of the injectate can be eliminated.

When the operational equation is employed for the calculation of glucose utilization values, the animals must be restrained and cannulae implanted to obtain arterial and venous blood samples (Sokoloff, et al., 1977). Obviously, this imposes severe restraints on the applicability of the method as it cannot be extended to behavioral studies requiring freely moving animals. Even in studies which do not require mobility, the procedure places the animals under unusually stressful conditions. Since the present study demonstrates that quantification of the data can be accomplished using i.p. versus i.v. administration without the use of the operational equation, it is no longer necessary to use the i.v. route. The results indicate that both ^{3}HdGlc and ^{14}CdGlc i.p. injections produce results that are highly correlated with those from i.v. injected animals. Furthermore, the values obtained after i.p. administration are also highly correlated with the values of Sokoloff, et al. (1977). Striking evidence is presented in the radioautograms in which the two routes of administration are indistinguishable from each other (see Meibach, et al., 1980); after thirty minutes, both i.p. and i.v. injected animals reach equal incorporation of dGlc. In addition, there is almost complete enzymatic conversion of the i.p. administered dGlc to its respective hexose phosphate, dGlc-6-phosphate, in the adult animals as demonstrated by the chromatographic separation. While the brains of the i.v. injected animals take up the dGlc in less than ten minutes, it requires thirty minutes for the i.p. injected animals to attain the same level of incorporation. This difference in the pharmacokinetics of the two routes of administration allows investigators to choose the route of administration according to the time profile of their stimulus. Thus, in pharmacological studies where drug-induced changes occur along a finite time course, it might be advantageous to use the i.p. route. Alternately for stimulation experiments, which are immediate cause and effect situations, one would prefer the i.v. route so that stimulation would only have to be maintained for a few minutes.

In conclusion, the results of the method modification study indicate that it is possible to extend the applications of the dGlc technique. Firstly, the less expensive tritium-labeled isotope can be used for studies in which select brain regions are being dissected. Secondly, densitometric values obtained from ^{14}C-radioautograms from different animals and/or experimental conditions can be compared. Finally, awake, freely moving animals under normal physiologic conditions can be administered labeled dGlc without relying on chronically implanted cannulae. This last point now allows the dGlc technique to be used in a wide range of behavioral and developmental studies, including the present one.

Chromatographic Separation of dGlc and dGlc-6-Phosphate.

The results of the chromatographic experiments indicate that the degree of phosphorylation of administered dGlc increases during development, reaching the adult level by approximately day thirty. These developmental changes in phosphorylation of dGlc are in close agreement with the findings of Bachelard (1979) who reported that rat brain hexokinase activity did not attain adult levels until an age of thirty days. Thus, as has been previously suggested by Sokoloff, et al. (1977), it appears that hexokinase is the enzyme responsible for phosphorylation of dGlc. It is also of interest that other processes involved in rat cerebral glucose metabolism also reach a peak on or about day thirty. Thus, although the blood brain barrier for glucose is fully developed in the rat by the age of eighteen days, at which point glucose enters the brain by carrier-mediated transport, maximal levels of glucose influx are not reached until approximately thirty-five days of age (Daniel, et al., 1970; Bachelard, 1979). Furthermore, the work of Sokoloff (1977) indicates that cerebral blood flow is maximal by approximately day 35 and declines thereafter to adult levels. Clearly, then, by the end of the fourth week of life, the rat brain manifests levels of metabolic activity characteristic of the adult.

Cerebral dGlc Activity Data.

The results of this study indicate that percent uptake of dGlc increases during development of the rat, with females apparently reaching maximal uptake prior to males. To the best of my knowledge, no other data are as yet available relating to the present findings of sexual dimorphism in cerebral metabolic activity, as most investigators use either one sex or the other but not both. However, there is ample evidence in the literature (e.g., MacLusky and Naftolin, 1981; McEwen, 1981) indicating that cerebral function manifests sexual dimorphism. Furthermore, comparisons between Sokoloff's control adult male rats (Sokoloff, et al., 1977) and those in the present study as well as in a previous study (Meibach, et al., 1980) show a similar rank order for levels of activity in brain regions that are common to both studies.

In that the degree of phosphorylation of dGlc to dGlc-6-phosphate is not maximal until day thirty, the question arises as to what meaning the percent uptake of dGlc has prior to this point. Clearly, the uptake data represent more than just hexokinase activity, the one element of neuronal glucose metabolism that is reflected by the uptake data in the adult. At early stages of development, it would appear that the percent uptake data represent at least three distinct aspects of glucose metabolism: glucose entry across the blood brain barrier, glucose entry into brain cells, and glucose metabolism by hexokinase. The fact that radioautograms of ^{14}CdGlc activity in rat brain are obtainable as early as the first day of life in the rat (Meibach, et al., 1981) indicates that a significant amount of the dGlc is being trapped by brain tissue. The latter study is also consistent with the notion that changes in dGlc incorporation during development may be indicative of cellular growth as the changes which are observed in ^{14}CdGlc incorporation in hippocampus are similar to the known patterns of dendritic growth from

from the pyramidal to the molecular layers of the hippocampus. Furthermore, the results of that study indicated that the adult pattern of dGlc incorporation is attained by approximately day thirty, and that even the neonatal dGlc activity is consistent with and indicative of changes in functional neuronal activity. Clearly, the fact that percent uptake increases after day thirty in both sexes indicates that such changes are not reflective of maturational changes in the cerebral circulation. Thus, Sokoloff (1977) demonstrated that, in contrast to the present findings, cerebral blood flow is maximal by day thirty and declines thereafter to the adult level.

The changes in relative brain activity indicate that there are reciprocal relationships in such activity during development. The fact that relative brain activity for a structure is a percentage of total brain activity means that increases in some structures must be associated with decreases in other structures and vice versa. It is of interest, however, that midbrain and caudate, the two structures which show developmental increases in dGlc activity, also have the lowest activity early on in development. Such developmental changes in relative activity indicate that different brain structures undergo marked changes in functional activity during development. Additionally, the significant sex by days interaction in cerebellum and midbrain indicates that at least in these structures, there is an element of sexual dimorphism in brain activity which is a function of development. Finally, the observation that midbrain and caudate have the highest relative activity in the adult is consistent with other findings in the literature (Sokoloff, et al., 1977) which indicate that these structures have high glucose utilization values relative to other brain regions.

Asymmetry Data.

The present modification of the dGlc procedure (Meibach, et al., 1980) made it possible to discern lateralized differences in dGlc uptake in various structures. These side-to-side differences in dGlc incorporation were observed within individual animals and are, therefore, most likely attributable to intrinsic lateralization in glucose uptake and not reflective of other factors, such as plasma glucose, that would affect dGlc incorporation equally on the two sides of the brain.

The absolute asymmetry measure is perhaps the most difficult index of asymmetry to evaluate because it is simply a manifestation of differences in the magnitude of a chemical measurement on the two sides of the brain. Thus it has no fixed relationship to any spatial value such as left-right directionality or to turning direction. For this reason, it is not surprising to find some statistical significance in this measure as dpm/g values for dGlc uptake are rarely the same for left and right sides of any brain region. In light of this, there is little one can say about this measure unless it can be related to some other measurable phenomenon such as a specific behavior or the age of the animals. The results of the ANVARs indicate that these are main effects of days in midbrain and caudate. However, this effect of days in midbrain is not associated with any significant trend--that is, there are marked fluctuations in absolute asymmetry in that structure resulting in the overall effect of days. On the other hand, such is not the case in caudate. Rather, correlational analyses indicate that in this structure, absolute asymmetry decreases with age in females and in both sexes combined, but not significantly in the males. Here again one sees evidence for sexual dimorphism.

The finding of decreased absolute asymmetry in the caudate as a function of age may have broad and general signigicance in that it has recently been reported (Glick, et al, submitted) that the absolute asymmetry in choline acetyltransferase in human globus pallidus similarly decreases with age. It may be that absolute asymmetry decreases as such with age because, as aging proceeds, the "dominant" or more active side's activity attenuates faster than its counterpart's, resulting in an attenuation of absolute asymmetry. This concept will be explored further in a later section on left-right asymmetry maturational gradients.

It is not surprising that a significant main effect of days was not obtained in the three-way ANVAR of the left-right asymmetry data because in some structures this asymmetry becomes more positive with age while in others it becomes more negative with age. Therefore, these trends might be expected to cancel each other out in the global analysis.

The present finding of a sex effect in cortical left-right asymmetry may be related to other observations indicating sexual dimorphism in cortical function (Witelson, 1976; McEwen, 1981). Additionally, as it has been reported that the nigrostriatal dopamine asymmetry (Zimmerberg, et al., 1974) had different characteristics in male and female rats (Robinson, et al., 1981), and because there is ample evidence demonstrating a role of cortex in the modulation of striatal asymmetry (Glick and Greenstein, 1973; Ross and Glick, 1981), one might speculate that such sex differences in nigrostriatal dopaminergic function are related to altered activity of corticostriatal neurons.

Both Chi square and regression analyses indicate that there are oppositely directed maturational gradients in left-right asymmetry of midbrain in male and female rats. In light of this, one would expect the overall sex by days interaction for left-right asymmetry of that structure. Many investigators have demonstrated that the inferior colliculus is one of the most metabolically active structures in the brain. In the present study a significant portion of midbrain is occupied by the inferior colliculus. It is possible, therefore, that the left-right asymmetry observed in midbrain is due to altered sensory processing of auditory information. Such asymmetries in auditory function have been previously shown to exist in humans (Geffen, et al., 1971).

The results of the correlational analyses clearly demonstrate that there exist dynamic relationships between relative brain activity, brain asymmetry and brain development in the rat. It has been shown that relative activity in all structures examined except the brainstem of females is inversely correlated with left-right asymmetry of that structure. It is noteworthy that such relationships do not exist between percent uptake and left-right asymmetry of a structure, indicating that it is the within-subject regional differences in brain activity and not the inter-subject variability in brain activity that is important in this regard. In postmortem samples of human brains, a similar relationship between left-right asymmetry and dopamine content of basal ganglia has recently been described (Glick, et al., submitted). In the present study, analyses of variance were also used to show that the above relationship between left-right asymmetry and relative activity is sexually dimorphic in striatum and cortex, with smaller changes in relative activity associated with larger changes in left-right asymmetry for males. One might speculate that a previously demonstrated (Greenstein and Glick, 1973; Ross and Glick, 1981) corticostriatal modulation of striatal dopamine asymmetry in female rats would also be different in males.

One should note that no significant relationships were obtained between absolute asymmetry and relative activity of a structure. This is important for two main reasons: firstly, it is an indication of the specificity of the relationship between left-right asymmetry and relative activity; secondly, it suggests that it is the differences in activity between the left and the right hemispheres and not simply absolute differences in brain activity of both hemispheres which are unrelated to a specific side of the brain that are dynamically related to changes in neuronal function.

Corballis and Morgan (1978) have suggested that the development of cerebral laterality in the human and in other species might be explicable in terms of a left-right maturational gradient; in this model, a left-right gradient during development is suggested to favor the left hemisphere which presumably develops earlier and/or more rapidly than the right. This hypothesis is based largely on functional evidence concerning handedness and lateralization of language and is not based on direct measurements of brain development. The present study has attempted to assess directly one index of brain development in terms of energy utilization and indicates that maturational gradients do indeed exist. However, it has now been shown that such gradients are both structure-specific and are sexually dimorphic. The latter point is best illustrated in the case of midbrain where for females the maturational gradient proceeds from left to right whereas in males it proceeds in the opposite direction. This is certainly not the first demonstration of sexual dimorphism for lateralized behaviors (Diamond, 1980; Robinson and Becker, 1981; Robinson, et al., 1980, 1981; Ross, et al., 1981).

Behavioral Studies.

The results of this study clearly establish that normal neonatal rats have asymmetries in tail posture which are observable immediately following birth. It is of interest that both the asymmetry in tail posture and the asymmetries in dGlc incorporation are sexually dimorphic. It has been recently demonstrated (Glick and Ross, 1981) that adult female rats, as a population (N = 602), have a right-sided directional preference, which was predicted on the basis of an earlier finding of a left-right asymmetry in frontal cortical dGlc uptake (Glick, et al., 1979). The neonatal and adult findings appear to be related inasmuch as it is now shown that neonatal tail position is predictive of the adult directional preference.

The present finding of a tail asymmetry may have some relevance to the findings of others, who have demonstrated a relationship between tail pinch and dopaminergic nigrostriatal function (Antelman, et al., 1975). At the very least, this suggests that tail sensory input is in some way related to neuronal systems that are known to be lateralized (Zimmerberg, et al., 1974; Jerussi, et al., 1977).

The reason why this tail asymmetry is sexually dimorphic is at this time elusive. However, it has recently been reported that female mice developing between male fetuses in utero have significantly higher concentrations of testosterone in their blood and amnionic fluid and that later in life these females differ from their littermates in various sexually related characteristics (vom Saal and Bronson, 1980). Clearly, the probability of female mice having this in utero position should increase with the number of males in the litter. Considering these data, and the present observation of sexual dimorphism in tail posture, a regression analysis of the strength of the female tail bias versus the number of males in the litter was performed. The fact that a significant inverse correlation between the percentage of females in each litter with right-biased tails and the number of males in the litter was obtained, suggests that hormonal status prior to birth may modulate asymmetries observed at a later time. Findings such as these are likely to have important implications for developmental theories of sexual differences in cognitive function and brain lateralization (Witelson, 1976).

Implications of the Present Study.

This study has clearly established the existence of asymmetries in cerebral dGlc uptake which are present at birth, change during development and are sexually dimorphic. Left-right dGlc asymmetries were related to age and were consistent with theories on lateralization which suggest the existence of maturational gradients (Corballis and Morgan, 1978). Left-right dGlc asymmetries were also related to relative brain activity indicating a dynamic relationship between asymmetry and neuronal activity of the central nervous system. Additionally, asymmetries in neonatal tail posture were shown to predict the adult directional preference of rats as measured in a rotometer. That this behavioral index of a nigrostriatal dopaminergic asymmetry is present at birth does not necessarily indicate that it is genetically determined, but it does suggest that it is not acquired postnatally.

Data recently appeared (Michel, 1981) correlating a known asymmetry in human neonatal head posture (Turkewitz and Creighton, 1979) with hand preferences at sixteen and twenty-two weeks of age. The authors suggested that right-sided neonatal head posture may predispose the developing infant to preferentially use its right hand, possibly because the right hand is more visible than the left hand is with a right-sided head posture. The question still remains, however, as to whether handedness is a genetically determined trait or whether it is learned. One possibility is that handedness in humans and spatial preference in rats are determined prenatally through nongenetic mechanisms; a possible mechanism is that the uterine position of the embryo may play a role in the determination of tail posture which could subsequently interact with brain development, through some sensory-motor feedback process. Thus, increased sensory input from one side of the tail could cause greater stimulation of the contralateral hemisphere resulting in more rapid development of that side compared to the ipsilateral hemisphere. However, other explanations are certainly conceivable.

It is important to understand developmental changes in cerebral asymmetry because of the known interaction between cerebral asymmetry and cognition: it is believed that the human brain is specialized with the dominant hemisphere subserving verbal and mathematical functions and the nondominant hemisphere more important for spatial and creative ability (Sperry, 1974). Furthermore, some developmental disorders characterized by impaired cognitive ability such as phenylketonuria (Anderson et al., 1974), minimal brain dysfunction (Connors, 1973; Gazzaniga, 1973), and dyscalculia (Dimond and Beaumont, 1972) have been reported to be linked to altered lateralization of the brain and it has been shown that lateralization of the nigrostriatal dopaminergic system interacts with rats' ability to learn spatial and timing tasks (Glick, et al., 1977). Thus, the normal pattern of cerebral asymmetry during development must be understood in order to test experimentally the role of altered asymmetry during development in cognitive impairment. For instance, phenylketonuric rats have exaggerated lateralization which interferes with their ability to learn spatial tasks (Glick and Greengard, 1980). One would now expect these rats to also have exaggerated asymmetries in dGlc uptake.

The work of Sperry with split-brain patients (Sperry, 1974) demonstrated that each hemisphere is specialized for cognitive processes and also that both of the surgically separated hemispheres are capable of their own consciousness. The latter point is important in light of Freud's early theory of the topographic model of the mind (1948, 1953) where repressed thoughts were of a different domain than those of consciousness and verbal processes, and were inaccessible to the latter. However, the state of the art of neurology at that time precluded Freud from relating the activity of the various parts of the mind to discrete neuroanatomical entities (1948).

In contrast to the state of the art of neurology and psychiatry in Freud's time, we presently have a much more sophisticated understanding of neurology and especially of cerebral specialization and the psychiatric implications of hemispheric disconnectivity. Galin has suggested (1977) that there are similarities between right-hemisphere functioning and the mode of cognition termed primary processes; Freud originally assigned such primary processes to the unconscious (1948). Furthermore, Sperry has reported that split-brain patients manifest behavior more characteristic of the left hemisphere than of the right (Sperry, 1968). Data such as these have led Galin to suggest (1977) that in people with intact brains, the right hemisphere's mental activity can in some way become functionally separated from the mental activity of the left hemisphere. Interhemispheric inhibition through the commissural system presumably facilitates such functional disconnectivity whereby each hemisphere functions independently from the other. In this way, mental processes in the right hemisphere would be conscious from that hemisphere's perspective but unconscious from the left hemisphere's perspective, resulting in thoughts which are apparently repressed and unable to be verbalized. Indeed, an increasing body of knowledge indicates that altered patterns of cerebral asymmetry may underlie certain psychotic disorders such as schizophrenia (Farkas, et al., 1980; Flor-Henry, 1976; Gur, 1978) and depression (Galin, 1976). Using computerized positron emission transverse tomography, Farkas, et al. (1980) showed that a schizophrenic patient's brain had greater asymmetries in ^{18}fluoro-dGlc activity than did brains of control patients. When considered together with evidence demonstrating that dopamine modulates cerebral glucose metabolism (Anchors and Garcia-Rill, 1977; Heller and Hoffman, 1978) and the suggestion that dopaminergic systems in brain are hyperactive in schizophrenia (Snyder, 1976), these findings all point to a postulated role of altered dopaminergic asymmetry in schizophrenia (Glick, et al., in press).

The asymmetries reported in this thesis manifest varying degrees of sexual dimorphism, raising the possibility that some of the functional differences between the sexes may be attributable, in part, to altered patterns of cerebral asymmetry in males and females. Other investigators have demonstrated sex differences in cerebral functions known to be lateralized in the human (Witelson, 1976; Inglis-Lawson, 1981) indicating that the present findings of sexual dimorphism in the rat are not species-specific phenomena.

This thesis has attempted to relate a large body of knowledge indicating that the human brain is lateralized with newer literature indicating that some of the same phenomena observed in humans can be observed in the rat. However, until quite recently, the types of neurochemical asymmetries observed in rat (Zimmerberg, et al., 1974) had not been shown to exist in the human brain. The only hint of a nigrostriatal dopaminergic asymmetry in human comparable to the one in rat (Zimmerberg, et al., 1974) came from lateralized tardive dyskinesia symptoms of psychiatric patients taking antipsychotic drugs (Waiziri, 1980). In view of the antidopaminergic properties of antipsychotic drugs, the implication was that there may be a dopamine asymmetry in human basal ganglia. Such an asymmetry in dopamine levels of human basal ganglia has now been demonstrated by Glick, et al. (submitted). Another similarity, already noted, between cerebral asymmetry in human and rat includes the finding of Michel (1981) who demonstrated that asymmetry in neonatal head posture (Turkewitz and Creighton, 1979) predicts handedness at sixteen and twenty-two weeks of age--a human correlate of the present findings in the rat. It is believed, then, that the rat can be used to study mechanisms of cerebral asymmetry in the human and it is hoped that future work in the rat will continue to predict important characteristics of cerebral asymmetry in the human.

SUMMARY

A modification of the dGlc technique was used to investigate the postnatal ontogeny of functional brain development in Sprague-Dawley rats. Normal rats were found to have asymmetries in dGlc incorporation in various dissected brain regions which were sexually dimorphic. An asymmetry in neonatal tail posture was also identified and shown to predict rat's adult directional preferences in a rotometer. Female tail posture was significantly directed towards the right whereas male tail posture was nonsignificantly left-biased.

Left-right asymmetries in dGlc incorporation of seven brain regions were negatively correlated with the relative activity of each structure, respectively. That is, as the activity of a brain region became greater, its asymmetry tended to be right-biased and vice versa--indicating a dynamic relationship between brain activity and brain asymmetry. Left-right asymmetries of some structures were also related to the age of the animals: maturational left-right gradients in lateralization were observed in hippocampus, diencephalon, brainstem and midbrain in females and in only the midbrain in males.

Developmental changes in local cerebral glucose incorporation were observed in rats between zero and one hundred days old and were shown to have different characteristics in male and female rats. It is believed that side-to-side differences in cerebral dGlc uptake are indicative of intrinsic lateralization of neuronal activity inasmuch as dGlc activity is related to functional neuronal activity.

The results of this thesis clearly demonstrate lateralization of dGlc uptake in various brain regions which change as a function of

normal development. Furthermore evidence was shown indicating that a behavioral index of nigrostriatal asymmetry is present at birth. The results were discussed in relation to a body of knowledge indicating that the brains of rats, humans, and other species are, indeed, lateralized--with similarities between the species noted. It is believed that studies of cerebral asymmetry in the rat will lead to pertinent discoveries about cerebral asymmetry in humans.

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