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REVIEW

MEDIAL TEMPORAL LOBE STRUCTURES AND AUTISM: A REVIEW OF CLINICAL AND EXPERIMENTAL FINDINGS*

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Abstract—Although substantive understanding of brain dysfunction in autism remains meager, clinical evidence as well as animal brain research on the effects of early damage to selective brain system have now yielded enough knowledge that some provisional hypotheses concerning the etiology of autism can be generated. Basically, the underlying premise of this review is that a major dysfunction of the autistic brain resides in neural mechanisms of the structures in the medial temporal lobe, and, perhaps, more specifically the amygdaloid complex. This review begins with a summary of clinical evidence of the involvement of the medial temporal lobe structures in autism. The major behavioral disturbances seen in monkeys that had received neonatal lesions of the medial temporal lobe structures are then described. From this survey it can be seen that distinct patterns of memory losses and socioemotional abnormalities emerge as a result of extent of damage to the medial temporal lobe structures. The potential value of the experimental findings for an understanding of neural dysfunction in autism as well as directions of future research are discussed in the final section of the review.

THE CLINICAL SYNDROME

AUTISM was first identified by KANNER [63] in 1943 and is a disorder of behavioral development which may be evident from the first year and is almost always noticeable between 2 and 3 years of age. According to the Diagnostic and Statistical Manual of mental disorders (DSM-III—R [6]), the criteria necessary for diagnosis include onset before 30 months of age, impairment in reciprocal social interactions (pervasive lack of responsiveness to other people), impairment in verbal and nonverbal communication, and restricted repertoire of activities and interests (often including ritualistic, self-stimulatory

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*In this report the term medial temporal lobe refers to an ensemble of subcortical and cortical structures. It includes the hippocampal formation, the amygdaloid complex, and adjacent entorhinal cortex and parahippocampal gyrus. The hippocampal formation consists of the hippocampus proper, composed of four subdivisions of pyramidal neurons (e.g. CA_1 through CA_4), the dentate gyrus, and subicular complex (e.g. presubiculum, subiculum, and prosubiculum). The amygdaloid complex is usually divided into two main nuclear masses, a corticomedial nuclear group (e.g. the anterior amygdaloid area, the nucleus of the lateral olfactory tract, the medial amygdaloid nucleus, and cortical amygdaloid nucleus) and a basolateral nuclear group (e.g. the lateral amygdaloid nucleus, the basal amygdaloid nucleus, and the accessory basal amygdaloid nucleus. The parahippocampal gyrus lies in the medial surface on the temporal lobe and is separated from the occipitotemporal gyrus by the collateral sulcus. The entorhinal area corresponds to area 28 of Brodman and constitutes a major portion of the anterior parahippocampal gyrus in human.

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behaviors, and resistance to changes). Associated features may comprise gross motor delays, inability to adequately modulate sensory inputs, unusual fears and anxiety, hyperorality, and pica. While a majority of affected children are mentally retarded and permanently language impaired, some show average or higher intelligence and good eventual linguistic competence [110]. However, the core symptom of impaired social relatedness cuts across these widely varying levels of cognitive and linguistic functioning and persists into adulthood, even in patients with verbal skills and relatively high intelligence quotients (IQs). Although the knowledge of social impairment in autism has existed clinically since Kanner's first report in 1943, it has been argued, for almost 20 years, that the social difficulties in autistic children result from more basic cognitive impairments in perception, attention, or memory. It is only more recently that the social deficits in autism have been recognized to be primary symptoms in the syndrome and that the search for the direct organic basis of the syndrome has begun [35, 39, 118].

Despite considerable research efforts over the last decade, the causes of autism remain unknown. Although the causes are likely to be diverse [98, 111], it has become accepted that a primary defect in brain function is present in autistic subjects. Several investigators have hypothesized dysfunction in a variety of subcortical and cortical structures. For example, viewing autism as a disorder of sensory modulation affecting cortical mechanisms of selective attention, ORNITZ [98] and COURCHESNE and collaborators [28] have hypothesized involvement of the cerebellum, brain stem, thalamus, and striatum. Alternatively, DELONG [32] and HELTZER and GRIFFIN [52] have hypothesized dysfunction in bilateral medial temporal lobe structures (hippocampus and amygdala) and drew parallels between the amnesic and Klüver–Bucy syndromes, and autism. By analogy to adult behavioral neurology, DAMASIO and MAURER [30] have hypothesized dysfunction in bilateral neural structures that include mesolimbic cortex in the mesial frontal and temporal lobes, neostriatum, and anterior and medial nuclear groups of the thalamus, structures which are targets of dopaminergic mesencephalic neurons. This fronto-limbic dysfunction in autism was recently re-emphasized by BISHOP [18]. Finally, the functional abnormalities revealed by recent *in vivo* electroencephalographic and metabolic studies in the association areas of the cortex have led MINSHEW [83, 84] to view autism as a disorder of information processing.

The hypohesis reviewed and extended here is that the structures in the medial temporal lobe, and, perhaps, more specifically the amygdaloid complex, are intimately involved in the etiology of autism. Evidence to support this thesis comes from a variety of sources, none conclusive, but all highly suggestive. These include: (a) similarities between autism and temporal lobe disorders, (b) direct associations between temporal lobe neuropathology and autism, and (c) similarities between autistic subjects and monkeys with early damage to the medial temporal lobe.

Similarities between autism and medial temporal lobe disorders

It is now well established that medial temporal lobe strucures are involved in the regulation of emotional reactions and memory functions. Evidence for this regulation has come principally from experiments in primates in which damage to these regions resulted in two prominent syndromes: the Klüver–Bucy syndrome and the amnesic syndrome.

The Klüver–Bucy syndrome. This syndrome was first demonstrated in adult monkeys following bilateral removal of the temporal lobes [67, 68]. More recently many similar behavioral changes were observed as a result of bilateral damage restricted to either the amygdala [2, 3, 66, 107, 121, 125] or the inferior temporal cortex [57, 60]. The features of this

syndrome can be classified in four categories: (a) psychic-blindness, i.e. the loss of the ability to understand the meaning of objects by vision alone in the presence of normal visual discrimination skills, (b) oral tendencies, i.e. use of the mouth rather than hands for exploration; (c) hypermetamorphosis, i.e. a seeming compulsion to react to every stimulus; and (d) emotional changes, including changes in, or absence of, anger and fear, lack of social behavior, and abnormal sexual behavior. Some, if not all, of the same features have been reported in a few human cases of viral encephalitis, a disease that can produce extensive damage to the medial temporal lobe structures and the neocortex in the temporal lobe in humans [40, 44, 71, 77] and in patients who received bilateral lobectomy as a treatment either for psychosis [96, 102, 115] or for otherwise untreatable epileptic seizures such as case H.M. [50, 113].

The similarities between the Klüver–Bucy syndrome and autism are striking and have been summarized by HELTZER and GRIFFIN [52]:

"Deficits in adaptive social behavior along with the lack of recognition of the significance of persons, objects, or events are the very features that are essential to the diagnosis of autism. The profound failure to develop social relationships has been found in nearly all autistic children . . . The children also show a lack of emotional responsiveness with poor eye contact, and their social development shows a lack of attachment and a failure of bonding . . . In addition, autistic children demonstrate a preoccupation with and/or stereotyped use of objects without regard for function and have also been widely reported to prefer the use of near receptors such as touch, taste, and smell . . . The children often engage in repetitive sniffing, scratching of surfaces . . . and scrutiny of visual detail and often explore by putting every new object in their mouth . . . Hypersexuality is not commonly reported in autism. However, it is interesting to note in this regard that when AKERT et al. [4] replicated the Klüver–Bucy syndrome in juvenile monkeys, they found all of the main symptoms of the syndrome except the sexual aberrations" (pp. 319–320).

Indeed, the demonstration that age at the time of the lesions affects the symptomatology in Klüver–Bucy syndrome is of particular relevance because it suggests that different subsets of these symptoms might appear depending on the time of the lesions. Thus, it is possible that bilateral amygdaloid damage in infancy or early childhood might induce a form of Klüver–Bucy syndrome which bears resemblance to the adult syndrome, but also presents some differences. Of further interest to the clinical picture of autism are the studies of THOMPSON [117], in which 2-month-old rhesus monkeys sustained bilateral amygdalectomy. The operated monkeys did not display behavioral abnormalities until they reached 8 months of age. At this age, they developed poor social interactions with age-matched control animals and by 3 years of age, they were hyperactive. Thus, the time course of appearance of the behavioral abnormalities in infant monkeys with early amygdalectomy could be linked to the early clinical features seen in some autistic children (see also below).

Medial temporal lobe amnesic syndrome. The association between temporal lobe damage and amnesia has been well documented since the first report of MILNER [82]. Indeed, medial temporal lobe damage, and more specifically the hippocampal formation and adjacent cortical areas, in both humans and monkeys [90, 124] results in a disorder characterized by: (a) anterograde amnesia, the inability to learn or remember new information despite normal attention and intact intellectual functions, (b) retrograde amnesia, the inability to retrieve information acquired before the onset of the memory disorder, though remote memory is well preserved, and (c) residual capacity to learn and retain certain types of information. In addition, this amnesic syndrome is evident even in childhood when the damage to the medial temporal lobe occurs between 5 and 11 years of age [99, 120, 123]. Moreover, although memory loss does not normally follow restricted lesions of the amygdaloid complex [90, 124], the amygdala is thought to have a specific role in emotionally influenced memories

[78], facial recognition [1], and sensory-affective or sensory-sensory associations [62, 91, 121].

BOUCHER and WARRINGTON [20, 21] were the first to notice the similarities between autistic children and animals with hippocampal lesions. They used a series of memory tests, particularly sensitive to hippocampal dysfunction in human adults to investigate memory functions in a group of lower-functioning autistic subjects. They found that autistic and amnesic subjects appeared to be similar in the following ways: (a) poor recall and poor recognition of pictures, (b) relatively normal cued recall, (c) ability to benefit from semantic cues, (d) poor episodic memory for recent events, and (e) islands of spared learning abilities or even exceptional learning skills. DeLONG [33] has recently re-emphasized the relationship between autism, amnesia, and hippocampal dysfunction, and proposed that:

"Autism is held to be the result of the failure of a central cognitive processor which is necessary for flexible multidimensional association of sensorial stimuli, memory, and motivational states. Failure of this processor produces rigid, invariant, rote behavior, thought and language and aberrant modulation of emotion. It is argued that this central processing function is critically dependent on the hippocampus. Thus, autism is postulated to be the developmental syndrome of hippocampal dysfunction."

Nonetheless, recent findings in higher-functioning autistic cases, as well as those seen in infant monkeys with neonatal hippocampectomy (see below), do not seem to support this view. For example, AMELI and collaborators [5] measured memory functions in a group of higher-functioning autistic subjects, using a modified delayed nonmatching-to-sample task (the benchmark task to assess temporal lobe memory dysfunction in both monkeys and humans [124]). They found that, like controls, autistic subjects recognized pictures of common objects better than pictures of nonsense shapes; although autistic subjects showed an overall tendency to be poorer than normal subjects. With nonsense shapes, however, when autistic subjects had to rely only on their visual memory, without the aid of meaning, they performed significantly poorer than controls. Finally, unlike amnesic patients with medial temporal lobe damage, performance of autistic subjects was not disproportionately affected by delay or distractor. The authors concluded that, although autistic subjects demonstrated an overall visual recognition deficit, the failure to find an exacerbation of the deficit when delay and distractor were manipulated, suggested that a direct relationship between temporal lobe amnesia and autism can no longer be viable. Indeed, in two other studies, RUMSEY and HAMBURGER [109] and MINSHEW and GOLDSTEIN [86] failed to find any memory deficits in higher-functioning autistic subjects.

One view that emerges clearly from these data on memory functions in autistic subjects is the need to further investigate the characteristics of the memory deficits found in both lower- and higher-functioning autistic individuals. Indeed, there has been little work done to date and we have no indication of the types of learning and memory that are affected in autistic individuals. The sets of data summarized above suggest that memory deficits are likely to be found in autistic people with lower cognitive functions but not in those with higher cognitive abilities. In this regard, the preliminary work of MERJANIAN and collaborators [79, 81] needs to be explored further. They demonstrated that although subjects with autism and those with Downs syndrome did not differ on a spatial memory task (a task sensitive to hippocampal damage in rats [97]), the autistic subjects performed more poorly than those with Downs syndrome on a cross-modal recognition memory task (a task sensitive to amygdalar damage in monkeys [91]), suggesting a possible dysfunction of learning and memory processes specifically linked to amygdala in autism. It is thus possible, as already alluded to by FEIN and collaborators [39], that the extent of neural defects in the medial temporal lobe might

account for the range of behavioral deficits seen in the lower- and higher-functioning autistic subjects. Thus, the presence of memory loss associated with the social abnormalities in lower-functioning autistic subjects may result from dysfunction of large portions of the medial temporal lobe structures, including the amygdala, hippocampus, and adjacent cortex. The relative preserved memory abilities observed in high-functioning subjects, however, may result in dysfunction of a more restricted portion of the medial temporal lobe structures, involving mainly the amygdaloid nuclei but sparing the hippocampus. The results of our experiments in infant monkeys reviewed below tend to support this view.

Direct associations between autism and medial temporal lobe neuropathology

Since early 1970s, postmortem neuropathological studies and *in vivo* neuroanatomical and neurophysiological imaging have described a variety of structural and functional abnormalities in autistic subjects [for review see 15, 84, 85]. While there is still a lack of consistent positive findings for neuropathology or inferred brain structure deficit in autism, the cerebral cortex, cerebellum, and medial temporal lobe strucures have been mainly, but not exclusively, implicated in the syndrome.

Cerebral cortex. Earlier neuroanatomical studies using computer tomography (CT) technique indicated the presence of reversed cerebral asymmetries in autism [53]. Nonetheless, subsequent quantitative CT studies [23, 29, 108], in which subjects were screened more carefully for presence of neurological disease, failed to support differences in brain asymmetry in autism. More recently, the greater resolution of Magnetic Resonance Imaging (MRI) over CT scans have made possible to show the presence of cerebral cortical malformations in autism. Heterotopic gray matter and polymicrogyria were noted in several cortical areas in autistic subjects [17, 27, 41, 101]. Nontheles, because the cortical malformations were neither confined to any particular lobe nor found in all subjects studied, a direct role in the pathogenesis of autism seems unlikely.

In vivo neurophysiological investigation of the brain of autistic individuals with Positron Emission Tomography (PET) has revealed normal regional cerebral metabolic rate in cortical areas although there was diminished correlational measures between the frontal and parietal lobes [58]. This finding has now been replicated in two other PET studies [37, 114], and brain metabolic dysfunction of cortical areas was found in autistic subjects when measured by Single Photon Emission Computed Tomography (SPECT) [84].

Cerebellum and pons. Earlier CT studies have indicated an increase in the fourth ventricle width and cerebellar atrophy in autistic children [16]. These findings were confirmed by recent MRI studies which demonstrated a decrease in the size of the vermis [26, 27], and an enlargement of the fourth ventricle and a decrease in the area of the pons on midsagittal view [41, 42]. Both higher- and lower-IQ individuals were among those with the most severe vermal hypoplasia, which suggests that the findings were likely to be related to autism and not to mental retardation. However, as with the cortical abnormalities, there was no direct correlation with clinical severity. By contrast, other CT and MRI studies of autistic subjects [43, 59, 65, 83, 106, 108] showed no incidence of cerebellar atrophy and enlarged fourth ventricle, and a PET study revealed no cerebellar hypofunctioning in autistic subjects [51]. The presence of cerebellar abnormalities in the earlier studies appears to be attributable to age and inter-group IQ differences between autistic and control subjects [for review see 85, 87].

Nonetheless, cerebellar neuropathology has been reported in almost all postmortem histological examination of the brain of autistic subjects [13–15, 105]. Rɪᴛᴠᴏ and

collaborators [105] found decreased Purkinje cell counts in the cerebella of all four nonepileptic cases, including one patient with average intelligence. BAUMAN and KEMPER [13–15] reported a significant loss of Purkinje cells and, to a lesser extent, of granular cells throughout the cerebellar hemispheres in six autistic subjects. The cerebellar nuclei had unusually enlarged neurons in the two youngest individuals (age 9 and 11), while small neuronal size and cell loss characterized the older subjects. Interestingly, no retrograde degeneration of the inferior olive was identified; a phenomenon which invariably follows perinatal or postnatal Purkinje cell loss in human pathology [48, 94]. The authors proposed an arrest in the migration of the granular neurons to the internal granule cell layer as responsible for the neuropathology. Indeed, the germinal external granule cell layer, which is present from early pregnancy until 30 weeks of gestation, gives rise to the internal granule cell neurons, basket cells, and stellate cells. More recently Holroyd and collaborators [55] reported autistic featues in four cases of Joubert syndrome, a genetic disorder with agenesis of cerebellar vermis. Thus, the cerebellum appears to be undoubtedly associated with the neuropathological processes of autism.

Medial temporal lobe. Because of technical difficulties, the CT and MRI techniques have been limited until now to the study of the anterior and middle fossa, and more recently to the study of the posterior fossa. Hence, the lack of *in vivo* neuroanatomic measurements of the structures in the medial temporal lobe. The only MRI study that has investigated the medial temporal lobe [27] in autistic individuals did not find any obvious changes by visual inspection. Nevertheless, volumetric measurements of the medial temporal lobe structures from MRI scans are clearly needed to quantify the subtle neuropathological changes found in these structures as detailed below.

The most direct evidence of medial temporal lobe neuropathology in autism was given by the elegant work of BAUMAN and KEMPER [12–15]. These authors investigated the brain of autistic subjects after autopsy, using the technique of gapless whole-brain serial sections, which involved back-to-back sections of the entire brain. The brains studied were normal in weight, gyral configuration, and myelination. In all eight subjects, microscopic cytoarchitectonic abnormalities (increased cell density, small cell size) were found in medial temporal lobe structures, such as the hippocampus, amygdala, entorhinal cortex, septal nuclei, and mammillary bodies along with a loss of Purkinje cells in the cerebellum. All patients had an increase in cell density in the entorhinal cortex as well as in the four Ammon fields (CA_1, CA_2, CA_3, and CA_4), which was reflected by a reduction in the overall size of the hippocampus. The hippocampal pyramidal neurons in the CA_1 and CA_4 fields displayed a decrease in dendritic branching [104]. In the amygdala, the central, medial and cortical nuclei had greater cell density, although the basolateral nuclei were unaffected in all cases but one. Interestingly, in this latter case, who had normal cognitive functions as compared to the seven others, cytoarchitectonic abnormalities in the amygdala extended to the basolateral nuclei [15]. Although the cytoarchitectonic finding on this higher-functioning subject needs to be replicated, the anatomical investigation of this series of autistic cases suggests that the variation in symptoms may well reflect the extent to which portions of the medial temporal lobe are involved. In addition, HOF and collaborators [54] reported neurofibrillary tangles in the entorhinal and perirhinal cortex as well as in the amygdala in a case of autism presenting with self-injury behavior.

Autism has also been associated with several clinical conditions resulting in medial temporal pathology. Thus, investigators have reported that autistic subjects have subtle EEG abnormalities in the temporal lobes [32, 49], enlargement of the temporal horn of the

lateral ventricles [22, 31, 49, 61], increased incidence of herpes simplex types 1 and 2, which have a specific affinity for the medial temporal region [34, 45], increased incidence of anoxia, which is also often associated with medial temporal dysfunction [25]. Temporal lobe seizures constitute the most frequent variety in the autistic population and these seizures tend to be underdiagnosed [38]. With careful monitoring, PAYTON and MINSHEW [100] were able to identify limbic epilepsy in 57% (17 of 30) of prepubertal autistic children. More recently, DEONNA and collaborators [36] reported two children with autistic regression as the presenting syndrome. Both patients were found to have tuberous sclerosis, a developmental brain abnormality associated with early epilepsy. The cerebral pathology in these two cases was localized in the medial temporal lobe. HOON and REISS [56] described a young male child with a left temporal oligodendroglioma, who demonstrated a constellation of autistic behaviors meeting the DSM-III—R criteria for pervasive developmental disorder, and WHITE and ROSENBLOOM [122] portrayed a child with infantile autism who was found on CT scanning to have a partial absence of the left temporal lobe.

Finally, in a neurophysiological investigation, NOVICK and collaborators [95] examined event-related potentials associated with random deletion of stimuli within a regular strain of auditory or visual stimuli in higher-functioning autistic individuals and normal subjects. Although all subjects were able to detect stimulus deletions, the cortical potentials associated with stimulus omissions were smaller or absent in the autistic subjects. Based on these results, the authors proposed a deficiency in information storage in autism, reflecting a dysfunction within a system that includes posterior parietal cortex and its connections with the mesolimbic temporal cortex and hippocampus.

Summary. To summarize to this point, there are reasons to believe that the medial temporal lobe is an appealing candidate as a neural substrate underlying the social deficits in autism. First, these structures play a central role in affect and social communication. Second, these structures appear to mature early enough to explain the early onset of the deficits in autism. Finally, the numerous connections between the medial temporal lobe structures and the cortex could also explain how dysfunction in the medial temporal lobe early in life could disrupt the later maturing cortical areas and, presumably, several aspects of cognitive and linguistic development.

THE ANIMAL MODEL

Accumulating evidence from our ongoing neurobehavioral study in infant monkeys provides additional support to the view that dysfunction of the structures in the medial temporal lobe may result in autistic behaviors. To study the behavioral development of primates that might remain amnesic from infancy through adulthood, we have prepared newborn monkeys with removal of the medial temporal lobe structures. Although our original motivation for carrying these studies was to investigate the functional development of memory functions in primates, we also followed in some detail the development of their socio-emotional behavior. Our experimental findings are described in the remainder of this paper.

Behavioral consequences of early damage to the medial temporal lobe in monkeys

Newborn rhesus monkeys sustained two-stage bilateral removals to the amygdalohippocampal complex. This included the amygdaloid nuclei, hippocampus and adjacent cortical areas, such as the periamygdaloid cortex, the entorhinal cortex, and portions of the

perirhinal cortex and parahippocampal gyrus, as shown in Fig. 1. Operated newborn controls sustained two-stage bilateral ablations to the anterior portion of the inferior temporal cortex (area TE, a higher-order cortical area of the visual system from which visual inputs reach the medial temporal lobe structures). Reasons for selecting cortical area TE as the site of the comparison lesion have been described in detail elsewhere [8]. Operated animals were age-matched with unoperated controls and all infant monkeys were raised either in dyads or triads consisting of one or two operated animals and one unoperated control.
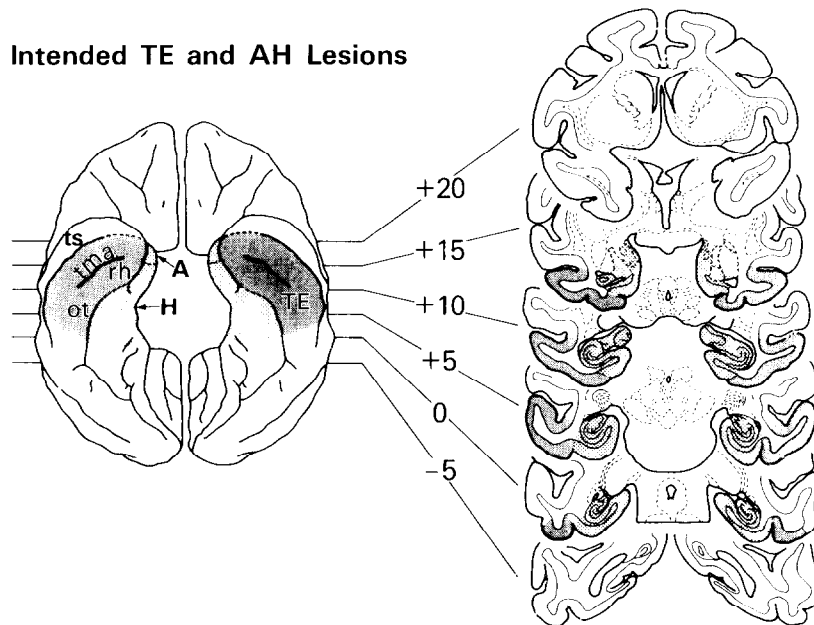
Intended TE and AH Lesions

Fig. 1. Ventral surface and coronal sections illustrating the intended neonatal area TE lesions (dark stippling) and amygdalohippocampal lesions (light stippling). Abbreviations: A, amygdaloid complex; H, hippocampal formation; ot, occipitotemporal sulcus; rh, rhinal sulcus; TE, anterior two-third of inferior temporal cortex; tma, anterior middle temporal sulcus; ts, superior temporal sulcus. The bilateral lesions were performed in two unilateral stages at approximately 1 week and 3 weeks of age, respectively, from BACHEVALIER [7].

Socioemotional behavior. The emotional and social development of infant monkeys with neonatal medial temporal lobe lesions were assessed by analyzing their interactions with age-matched normal controls with whom they were raised, and by comparing these social interactions with those of normal infant monkeys raised together. At the ages of 2 and 6 months, two infant monkeys from the same rearing cohort (e.g. one operated and its pair-reared control or two pair-reared normal infant monkeys) were placed in a play cage containing toys and towels. The behavior of each pair was videorecorded for two periods of 5 min each, separated by a 5-min interval, for six consecutive days. Frequency and duration of behaviors for each animal on the videotapes were scored independently by two observers, who assigned the behaviors to one of nine different behavioral categories:

Approach—social contact initiated by the observed monkey;

Acceptance of approach—acceptance of social contact initiated by the other monkey;

Dominant approach—immature forms of aggression, such as snapping at the other monkey, taking toys away from the other monkey, or pushing the other monkey away;

Active withdrawal—active withdrawal from social approach initiated by the other monkey;

Inactivity—passive behavior;

Manipulation—manipulation of toys or parts of the cage with the limbs or mouth;

Locomotion—walking, running, climbing, or jumping;

Locomotor sterotypies—abnormal motor behaviors, such as circling or doing somersaults;

Self-directed behaviors—abnormal activities directed towards itself, such as self-grooming, closing fists, hugging head, or abnormal postures, such as prone or head on chest.

The results indicate that, at both 2 and 6 months of age, pairs of normal animals spent most of their time in social interactions, locomotion, or manipulation. They exhibited virtually no behaviors considered to be abnormal, such as active withdrawal, locomotor stereotypies, or self-directed activities, and almost no inactivity. Between 2 and 6 months, however, the nature of social interactions between normal animals did change. Whereas at 2 months social behavior consisted primarily of following the other monkey and clinging to it, at 6 months these behaviors were replaced primarily by rough-and-tumble play and chasing.

Unlike normal infant monkeys, those with neonatal medial temporal lobe lesions began to show numerous socioemotional abnormalities as they matured (Fig. 2). At 2 months, the operated infant monkeys displayed more passivity, as reflected by an increase in inactivity and a decrease in manipulation, and more irritability when placed for the first time in the play cage (increased number of temper tantrums). Also, they did not initiate social contact as much as did their unoperated controls, but they did have a normal amount of accepting approach, indicating that the normal animal in the pair was initiating most of the social interactions. Interestingly, at 6 months of age, the operated monkeys displayed even more striking behavioral abnormalities. The amount of social interaction between the operated animals and their controls decreased dramatically as compared with animals in the normal dyads. In addition, the increase in active withdrawal in the operated animals, which occurs in response to an initiation of social contact by the normal animal, suggests that animals with early medial temporal lobe lesions were not only uninterested in social contacts and socially inept, but that they actively avoided social contacts. The operated monkeys also had blank, unexpressive faces and poor body expression (i.e. lack of normal playful posturing), and they displayed very little eye contacts. Finally, animals with early medial temporal lobe lesions developed locomotor stereotypies and self-directed activities. Furthermore, an investigation of their reactions to familiar vs novel objects done when they were 9 months of age [92] indicated that all infants, normal and operated alike, looked at and manipulated familiar stimuli more than novel, and showed displacement activity to the novel stimuli, as indicated by an increase in cage manipulation. However, animals with early medial temporal lobe lesions did not manipulate objects (touch or mouth) more frequently than the unoperated animals. Thus, it appears that early damage to the medial temporal lobe does not yield the Klüver–Bucy symptoms of loss of fear and indiscriminate approach to objects, often orally, seen in monkeys with medial temporal lobe lesions done in adulthood. These findings confirmed similar observations made earlier by AKERT and collaborators [4] and THOMPSON [117]. Finally, all of the socioemotional disturbances of operated infant monkeys were still present when these animals reached adulthood [74], indicating that early damage of the medial temporal lobe had long-lasting effects on socioemotional behavior.
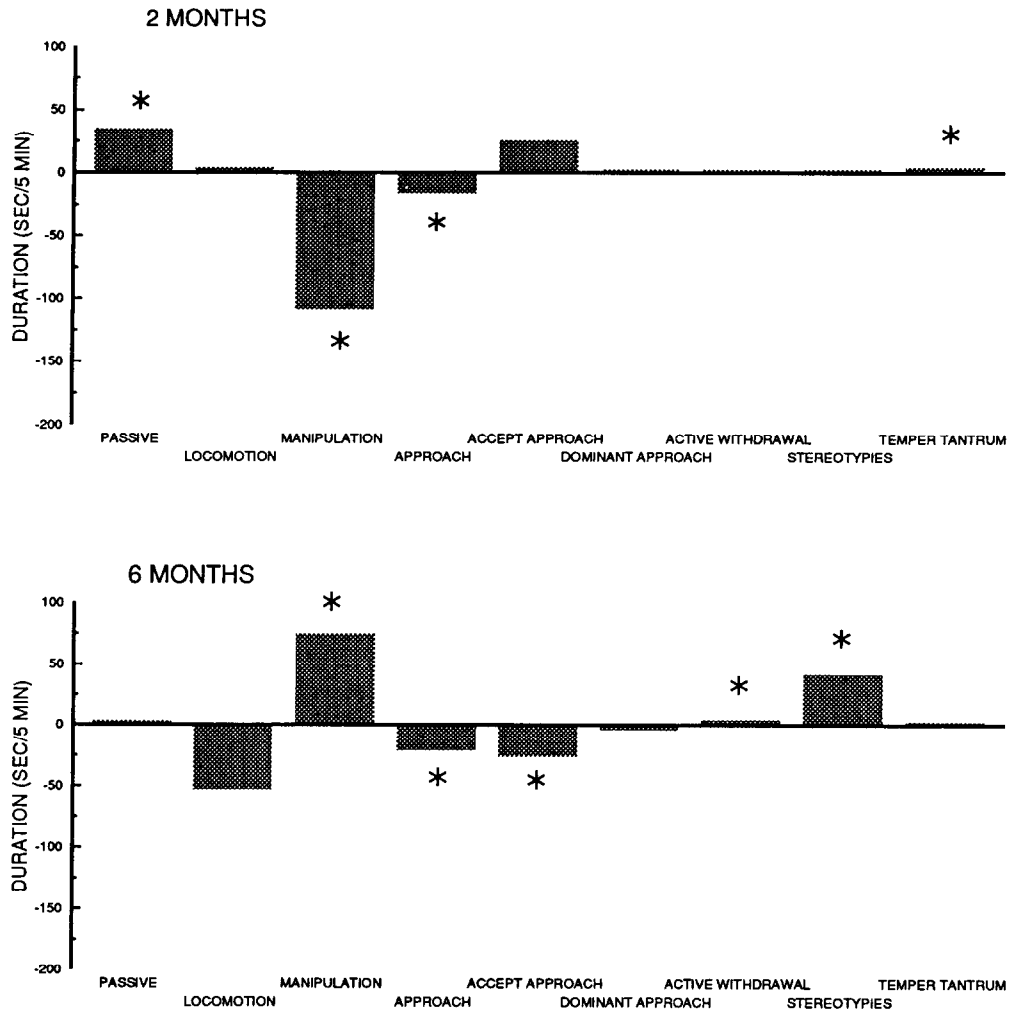
Fig. 2. Scores are mean group differences (Scores of animals with early medial temporal lobe lesions — Scores of unoperated animals) in duration (seconds per 5-min session) of each behavioral category at 2 (top) and 6 (bottom) months of age. Categories "Locomotor Stereotypies" and "Self-Directed Behaviors" were summed and labelled "Stereotypies". Asterisk indicates significant changes in behavior ($P < 0.05$).

Although the operated controls that had received early damage to area TE showed none of the disturbances seen in infant monkeys with early medial temporal lobe lesions, they did display other behavioral abnormalities such as hyperactivity and increased frequency of shifting behavioral activities resembling those of children with attention-deficit hyperactivity disorder [80]. However, when the animals reached adulthood, these behavioral abnormalities were almost totally absent.

Learning and memory. In addition to their socioemotional disturbances, infant monkeys with early medial temporal lobe lesions were severely amnesic despite normal performance in some learning tasks, indicating some islands of preserved learning abilities. The memory

disorder emerged when the animals were tested in learning tasks modeled from those that were used to assess memory function in adult monkeys with medial temporal lobe lesion.

Studies of adult monkeys [88] have shown that lesions causing conjoint damage to the amygdala, hippocampus, and adjacent cortical areas yield severe deficits in the ability to recognize objects seen just a few minutes earlier, as measured by a delayed nonmatching-to-sample task (DNMS), but spare the ability to form visual habits, as measured by a concurrent-object discrimination task (24-hr ITI task [73]). This preserved learning ability in the presence of severe memory loss has led to the notion that retaining the effects of experience depends on two fundamentally different neural systems [89]. Thus, we used the same behavioral tasks that were used to show impaired (DNMS task) vs spared (24-hr ITI task) learning and memory abilities in amnesic adult monkeys to test infant monkeys with early medial temporal lobe lesions. The formation of visual discrimination habits in these infant monkeys was measured when they were 3 months of age with a concurrent discrimination task and long intertrial intervals of 24 h (24-hr ITI task). In this task, a series of 20 pairs of objects are presented once a day to the monkey. In each pair, only one of the two objects hides a food reward and the monkey learns by trial and error which object yields a reward. The results indicated that infant monkeys with neonatal medial temporal lobe lesions solve this task as rapidly as age-matched normal controls, requiring 14 and 9 sessions (Fig. 3A), respectively. Together with the preserved ability to solve discrimination habits by adult monkeys with the same lesions [73], these findings indicate that damage to the medial temporal lobe leaves formation of visual discrimination habits intact whether the lesions are made early or late [9]. Then, the DNMS task, a task that was used to demonstrate memory loss in adult monkeys with medial temporal lobe damage [88], was then selected to measure recognition memory in the infant monkeys at the age of 10 months [11]. In this task, the animal has to remember, on the basis of a single trial, whether or not an object has been seen before. Each trial consisted of two parts. First, the animal was confronted with a sample object overlying the baited central well of a test tray, which the animal removed from the well in order to obtain the food reward. Ten seconds later the animal was confronted with the sample object and a new object, now overlying the lateral wells of the test tray. In this second part, the monkey was rewarded for displacing the novel object. Twenty trials separated by 30-sec intervals were given daily, each trial with a new pair of objects chosen from a stock of several hundred, until the monkey learned the rule of avoiding the familiar item in favor of the new one. Then, its recognition memory was taxed further in two ways: through progressive increases of the delay between sample presentation and choice test (from the initial 10-sec delay to 30-, 60-, and 120-sec delays) and then through progressive increases in the number of sample items to be remembered (from the initial single object to 3, 5 and 10 items). Both early and late damage to the medial temporal lobe structures yielded severe impairment in visual recognition (Fig. 3B), reflected in drops in performance of 22% for the infants and 32% for the adults (as compared to their normal controls). Additional testing of these same monkeys when they reached adulthood (6–7 years) indicated that the effects of these early lesions were long-lasting and global since, in adult monkeys with neonatal medial temporal lobe lesions, severe impairment was also found in the ability to either recognize objects by touch [75] or remember the location of the objects on the test board [76]. By contrast, the operated controls that had received early damage to area TE showed significant, long-lasting, sparing of discrimination habit formation [9] and visual recognition memory [11].

It is thus possible that the contrasts between intact learning skills and severely impaired
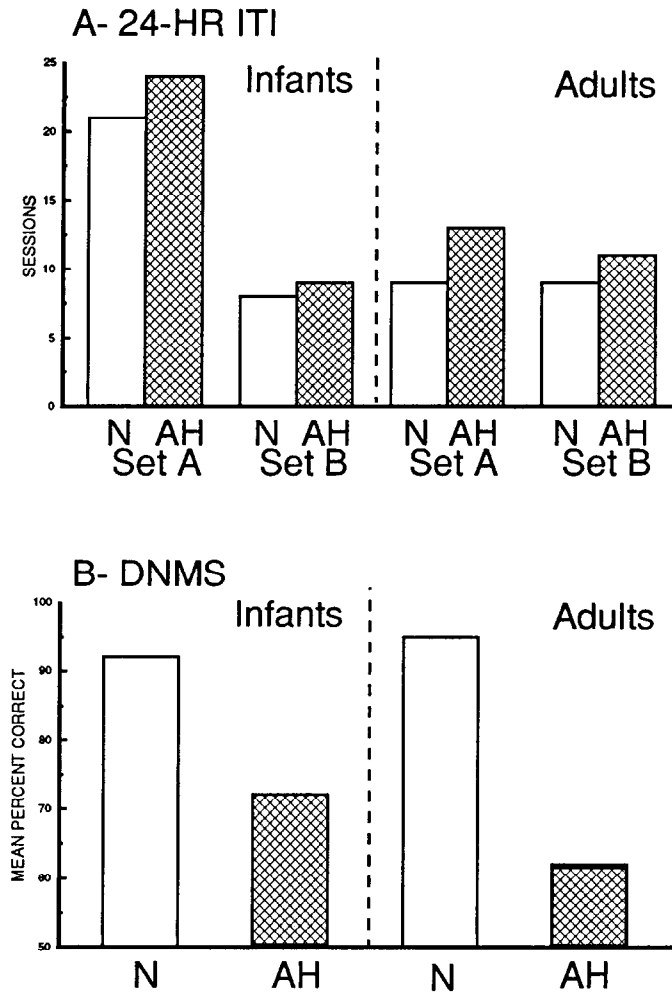
A- 24-HR ITI

B- DNMS

Fig. 3. Scores in A are number of sessions to attain criterion on two consecutive sets of discriminations (Sets A and B) by 3-month-old monkeys (operated neonatally) and adult monkeys. Scores in B are mean performance across the 3 delays and the 3 lists in the recognition task by 10-month-old monkeys (operated neonatally) and adult monkeys. N, normal controls; AH, animals with bilateral amygdalohippocampal lesions.

visual recognition memory found in monkeys with early medial temporal lobe lesions could parallel the unusual pattern of cognitive strengths and weaknesses observed in autism, where a child may fail to learn basic skills despite having unusual memory for certain types of information.

Summary. The experimental work is promising from the standpoint of the similarities between the behavioral syndrome seen in infant monkeys with neonatal damage to the medial temporal lobe and autistic children. They have in common the symptoms of abnormalities in social interactions, absence of facial and body expressions as well as the development of stereotypic behaviors. There is an early onset of symptoms in both cases, though in early infancy the complete syndrome is not apparent. Both disorders (at least for

lower-functioning autistic subjects) are characterized by memory deficits despite normal abilities in certain kinds of learning tasks. Thus, the time course as well as the nature of the socioemotional disturbances and the cognitive impairment observed in monkeys with early damage to the medial temporal lobe structures strongly suggest that autism too may result from early dysfunction of the medial temporal lobe structures. Indeed, an appealing feature of this animal model of autism is that it can account for a range of apparently unrelated symptoms, i.e. social and motivational deficits and motor stereotypies and self-directed behaviors. It is also of interest that, like autistic children, monkeys with early amygdalo-hippocampal damage exhibited considerable variability of specific symptoms. This suggests that autism too may result from a common locus of pathology that produces multiple phenotypic displays rather than resulting from multiple pathologies that each yield a particular subset of autistic symptoms. In addition, further investigation of the underlying neural substrate of the behavioral disorders resulting from early medial temporal lobe damage in monkeys [10] revealed that the extent of the medial temporal lobe involved in the disease may also be of great significance to our understanding of the heterogeneity of symptoms seen in autistic subjects.

Behavioral consequences of neonatal damage to the amygdala or to the hippocampus

To learn more about the underlying neural substrate of the behavioral disorders resulting from early medial temporal lobe damage, we investigated whether or not the full-fledged syndrome we have described above (e.g. severe cognitive and socioemotional deficits) could be fractionated by restricted damage to specific structures in the medial temporal lobe. As discussed recently by others [125], the pathology responsible for the socioemotional disturbances may not result from complete medial temporal lobe damage but rather amygdaloid damage alone. THOMPSON and collaborators [116, 117] have already reported long-lasting social disturbances in monkeys that had sustained damage to the amygdaloid complex at 2 months of age. Conversely, it is also possible that the amnesic syndrome following early damage to complete medial temporal lobe may have resulted from damage to the hippocampal formation alone. MAHUT and MOSS [72] have shown that damage to the hippocampal formation at 2 months of age yielded long-lasting memory loss. To investigate these possibilities, we have prepared additional newborn monkeys with damage to either the amygdaloid complex or the hippocampal formation and have begun to test them in social interactions and cognitive tasks in the same way as the monkeys with neonatal damage to complete medial temporal lobe.

Newborn monkeys sustained restricted bilateral damage either to the amygdala, including the amygdaloid nuclei, the periamygdaloid cortex, and the rostral portion of the entorhinal cortex, or to the hippocampal formation, including the hippocampus and a portion of the parahippocampal gyrus. Again, the lesions were done in two stages at the ages of approximately 1 and 3 weeks. Testing of social interactions was videorecorded at 2 and 6 months of age, and investigation of learning and memory abilities was done at 3 months of age for visual habit formation and at 10 months of age for visual recognition memory. Behavioral responses of infant monkeys with partial medial temporal lobe lesions were compared to those of unoperated infant monkeys as well as those of infant monkeys with complete medial temporal lobe lesions described in the preceding section. Indeed, the pattern of disturbances did differ greatly according to the medial temporal lobe structures involved in the lesion, but not in the manner predicted above.

Early amygdalar lesions. Early damage to the amygdaloid complex yielded a pattern of socioemotional disturbances almost identical to that described for complete medial temporal lobe lesions, but the magnitude of these disturbances was smaller. Thus, at 2 months of age, as shown in Fig. 4, like infant monkeys with complete medial temporal lobe lesions, those with amygdalar lesions displayed more inactivity and less manipulation than their normal controls; unlike the former, however, they showed no obvious impairment in initiation of social contract. At 6 months of age, again like animals with complete medial temporal lobe lesions, those with neonatal amygdalar lesions displayed less initiation of social contact and more social withdrawal than their controls. However, unlike infant monkeys with complete medial temporal lobe damage, those with amygdalar lesions did not display less acceptance of approach, stereotypic behaviors, or loss of facial and body expressions, but they were more passive.

In addition, like monkeys with complete neonatal medial temporal lobe lesions, those with early amygdalar lesions preserved the ability to form visual discrimination habits. Unlike the former, the amygdalar lesions yielded only mild impairment in visual recognition memory. Indeed, as shown in Table 1, the recognition performance of infant monkeys with early amygdalar lesions dropped only 9% from that of unoperated controls, as compared to a drop of performance of 22% in the infants with complete medial temporal lobe removals.

Early hippocampal lesions. At 2 months of age, as shown in Fig. 5, the animals with early damage to the hippocampal formation showed some degree of socioemotional disturbances, namely a reduction in initiation of social contacts, more inactivity, and less manipulation than normal controls. These behavioral disturbances, however, were not apparent when these operated animals reached 6 months of age. At this age, the amount of approach and acceptance of social contact was similar to that found in normal animals. Furthermore, animals with neonatal hippocampal lesions did not display stereotypic behaviors.

Also, infant monkeys with early hippocampal lesions showed preserved abilities in visual habit formation as well as visual recognition memory (Table 1). This latter finding of spared cognitive memory functions following early hippocampectomy was unexpected, but confirms recent data in adult monkeys with damage restricted to the hippocampus [24]. Furthermore, these data do not support the view that autism results from a developmental dysfunction of the hippocampus [33].

Summary. The behavioral data thus far indicate that early damage to the amygdaloid nuclei and entorhinal cortex yields mild deficits in memory function and moderate disturbances in social interactions. By contrast, early damage to the hippocampal formation yields a sparing of memory and only transient socioemotional disturbances. Because infant monkeys with selective medial temporal lobe lesions have not been retested as adults, we do not yet know the long-term behavioral consequences of these early selective lesions. Nevertheless, it appears that both the nature and the developmental time course of the behavioral disturbances depend greatly upon the specific medial temporal lobe structure involved in the neonatal lesions. So far, the experimental results indicate that early damage to the amygdaloid complex appears to be more closely related to the emergence of autistic-like behavior in the monkeys than early damage to the hippocampal formation; though the most severe autistic-like syndrome appeared only following combined damage to the amygdala, the hippocampus, and adjacent cortical areas. We can, thus, consider the possibility that these patterns of behavioral disturbances in monkeys with early selective medial temporal lobe lesions might also be found in some cases of autism. Indeed, we postulate that the severe learning and memory deficits shown in severely retarded autistic subjects result from
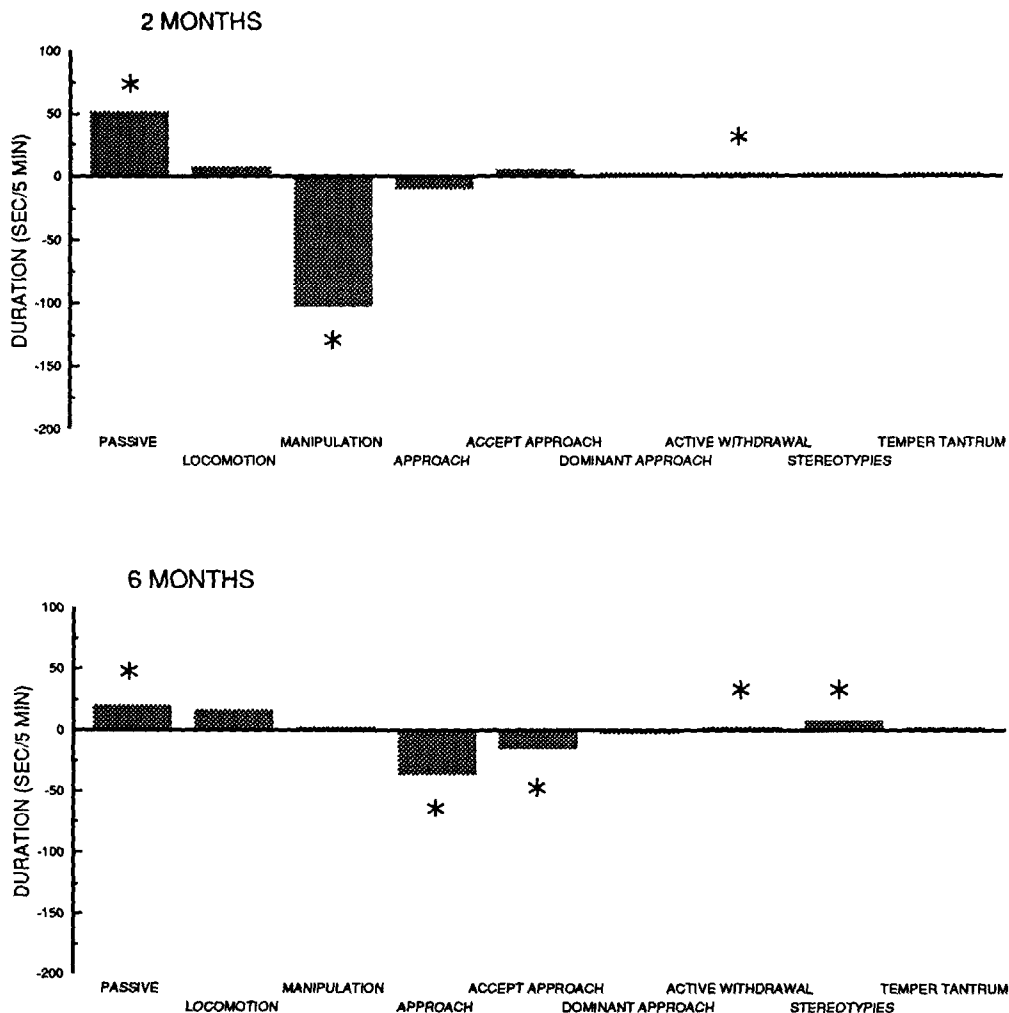
2 MONTHS

6 MONTHS

Fig. 4. Scores are mean group differences (Scores of animals with early amygdalar lesions − Scores of unoperated animals) in duration (seconds per 5-min session) of each behavioral category at 2 (top) and 6 (bottom) months of age. Other abbreviations as in Fig. 2.

bilateral involvement of large portions of the medial temporal lobe, including both the amygdala, hippocampus, and adjacent cortex. But, perhaps, in the case of higher-functioning subjects with islands of preserved cognitive abilities, the amygdala may be more affected than the hippocampus and adjacent cortical areas, resulting in social impairment but some intact learning capacity.

DIRECTIONS FOR FUTURE RESEARCH

Although we acknowledge that the neuropathology found in medial temporal lobe structures in autistic children is entirely different from the destructive brain lesions that were inflicted to the infant monkeys, we believe that the resemblance between monkeys with

Table 1. Scores are mean number of sessions to attain criterion in the three sets of
concurrent discriminations (24-hr ITI) and average correct responses across all delays and
lists in the visual recognition task (DNMS). Infant groups included 6 8 monkeys and
adult groups included 3 4 monkeys

Tasks	Age	N	A	H
24-hr ITI	3 months	9 ± 3.4	15 ± 4.2	12 ± 3.02
	3 4 years	11 ± 2.8	Not tested	Not tested
DNMS	10 months	88.7 ± 3.9	$80.1 \pm 5.9^*$	88.1 ± 4.5
	3–4 years	95.1 ± 2.9	$90.7 \pm 2.4^*$	$87.9 \pm 5.3^*$

Abbreviations: N, unoperated controls; A, animals with amygdalar lesions; H, animals with
hippocampal lesions.
$^*P < 0.05$, as compared to unoperated controls

neonatal medial temporal lobe lesions and autistic children is sufficiently close to encourage
further investigation of the involvement of the amygdala, hippocampus, and surrounding
cortex in this developmental disorder. The validity of this model may become more apparent
as future research more specifically defines the role of each of these medial temporal lobe
structures in the development of social relations, emotion, and cognitive abilities. In
addition, while the present model focuses on medial temporal lobe functions in autism, this
does not preclude the involvement of other neural structures [14, 18, 28, 55, 83, 103], either
as alternative or additional loci of neuropathology. It could be argued that any kind of early
dysfunction in the medial temporal lobe structures is likely to impinge on the neuro-
anatomical and neurochemical organization as well as the functioning of subcortical and
cortical areas, such as the neostriatum, basal forebrain, and prefrontal and parietal cortices,
which share strong anatomical connections with the medial temporal lobe structures. This
hypothesis is supported further by experimental studies demonstrating that early acquired
lesions may have effects on reorganization and connectivity of the cortical architecture at
distances remote from the site of the original lesions [46]. Thus, an important future study
will be to characterize the neuroanatomical and neurochemical reorganization of other
neural systems as a consequence of early damage to the medial temporal lobe in monkeys.
Furthermore, the apparent absence of cognitive and social disorders in children with
agenesis of the temporal lobe [64, 70, 93, 119] suggests that there is a critical period in fetal
development prior to which the behavioral effects of medial temporal damage may still be
fully compensated. Additional experimental studies are needed to explore this possibility.

In turn, the experimental evidence in favor of the participation of the medial temporal lobe
structures in autism posits some research strategies for clinical study of the childhood
disorder. First, it is clear that neuropsychological investigation of the functions of the medial
temporal lobe structures should be performed in well-defined clinical populations of autistic
individuals with both low and high IQ. Secondly, quantitative imaging studies, which
include volumetric measurements of the medial temporal lobe structures, should be carried
out in, psychologically well characterized, populations of autistic individuals to allow
correlations between behavioral performance and volumetric measurements. Thirdly, the
presence of neuropathological abnormalities in the cerebellum is also of great interest.
Because of recent implications of the cerebellum in the regulation of emotional behavior and
cognitive functions [19, 47, 69, 112], these neuropathological findings emphasize the need to
further study the involvement of this neural structure in autism. Finally, the developmental
perspective suggests that early alterations in one neural system may interactively influence
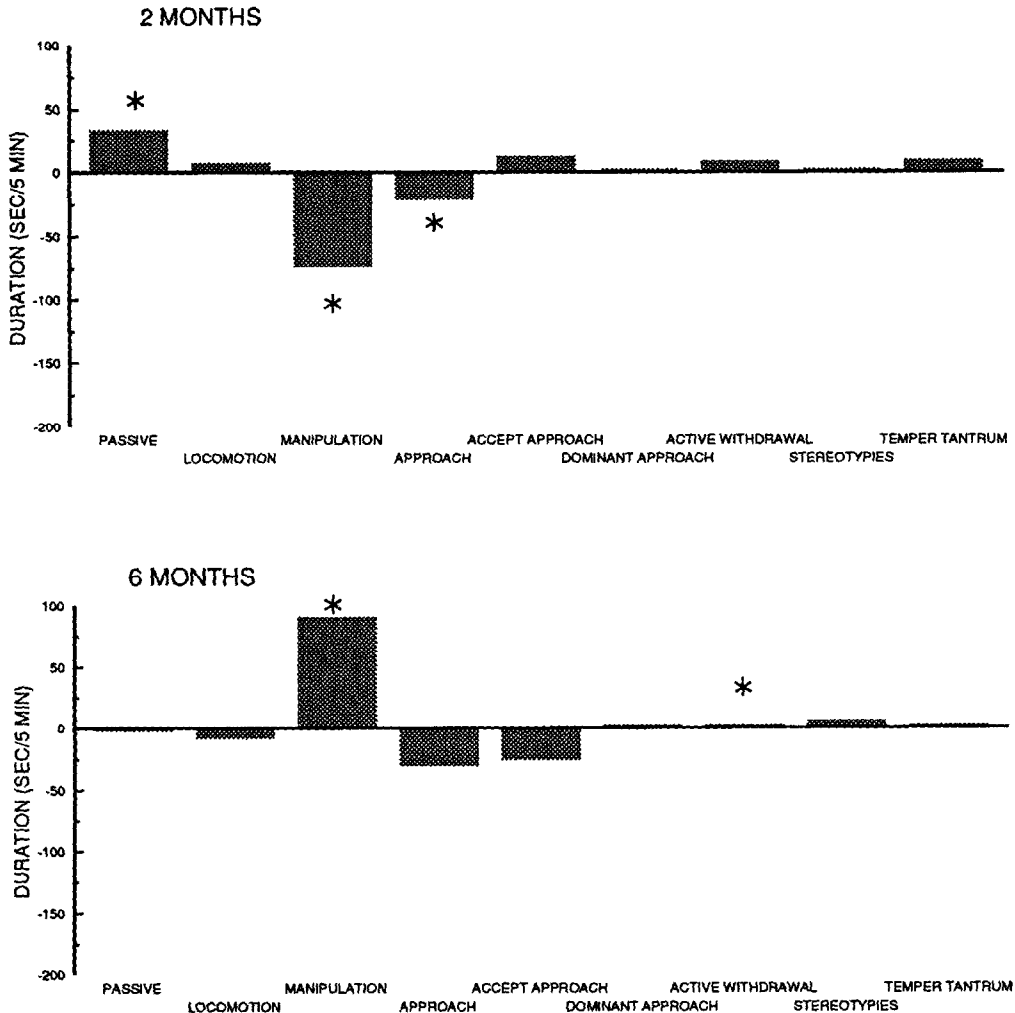
Fig. 5. Scores are mean group differences (Scores of animals with early hippocampal lesions – Scores of unoperated animals) in duration (seconds per 5-min session) of each behavioral category at 2 (top) and 6 (bottom) months of age. Other abbreviations as in Fig. 2.

the development of other systems. Therefore, future studies need to explore the heterogeneity of the symptoms associated with autism rather than focusing on a relatively specific function.

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