Social neuroscience, empathy, brain integration, and neurodevelopmental disorders

James C. Harris*

Psychiatry and Behavioral Sciences and Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

Received 4 April 2003; accepted 17 April 2003

Abstract

Paul MacLean has investigated integrated brain functioning through selected brain lesions in animals that disturb circuits necessary for complex behaviors, such as social displays. MacLean is unique in his comparative neurobehavioral approach that emphasizes the evolutionary origins of parenting and social behaviors and the implications of brain changes in the evolution from reptiles (social displays) to mammals (nursing, audiovocal communication, play) to man (self-awareness, intentionality, social context) that link affect and cognition. Subjectively, how "looking with feeling toward others," the basic element in empathy, evolved has been a central concern of his. Neuroimaging studies of social cognition, mother–infant communication, moral behavior, forgiveness, and trust are consistent with particular brain systems being activated in cooperative social behaviors. The identification of mirror neurons is pertinent to MacLean's model of isopraxis and studies of thalamocortical resonances may be pertinent to his neurobehavioral models. Studies of behavioral phenotypes in human neurodevelopmental disorders are consistent with MacLean's model of brain circuits being linked to complex behaviors during development. In autistic disorder, the behavioral phenotype involves disrupted social communication, deviant imaginative play, and motor stereotypies. In Lesch–Nyhan syndrome (LNS), self-injury occurs in individuals with normal sensory systems intact who require and request physical restraint to prevent self-injury; they ask for assistance from others to prevent them from harming themselves. Autism involves the lack of subjective awareness of others intentions and LNS involves a failure in self-regulation and self-control of self-injurious behavior. MacLean's models laid the groundwork for studies focused on understanding brain functioning in these conditions.

Keywords: MacLean; Isopraxis; Empathy; Autism; Lesch–Nyhan syndrome

"Why else are we here, if not to help one another." Paul MacLean

1. Introduction

Paul MacLean’s proposals that emotions involve relatively primitive circuits that are conserved throughout mammalian evolution and that cognitive processes may involve other circuits that are independent of emotional circuits [1] has provided a basis for current research in affective neuroscience. His work has established a foundation for evolutionary psychiatry [2] and aspects of social neuroscience [3]. He proposes that, in humans, integrated brain function leads to empathy and kindness toward others. His evolutionary approach has focused on finding the roots of human subjective experience and behavior.

MacLean carried out comparative neurobehavioral studies to understand the neuroanatomic basis of species typical behavior in animals and the evolutionary origins of human subjective experience. His animal work utilizes electrophysiological and neuroanatomical lesions coupled with careful observation of behavior. This work was informed by his experience with electroencephalographic recordings in temporal lobe epilepsy and reports of subjective experiences linked to seizures [3]. He has championed the advantages of the comparative, evolutionary approach at both the molecular and macroscopic levels emphasizing the importance of simultaneously appreciating both. MacLean emphasizes the importance of an evolutionary approach to understand integrated brain functioning and social behaviors, particularly empathetic behavior that links cognition and emotion. The following sections illustrate support for MacLean’s models.
2. Parental behavior and the thalamocingulate system

MacLean’s emphasis on the anatomy of empathy and understanding the basis of subjective states of mind is demonstrated in his studies on the parental behavior. In his Adolph Meyer lecture [4], he proposed that the behavioral triad of nursing, infant–mother audiovocal contact, and play in mammals may have depended on the evolution of the thalamocingulate division of the limbic system as shown in Fig. 1.

Peredery et al. [5] provide support for MacLean’s model in reporting that female rats, with and without maternal experience, who received limbic seizure-inducing subcutaneous doses of lithium and pilocarpine displayed complete absence of maternal behavior in subsequent parturitions. Those rats that did not have seizures had normal maternal behavior. In rats with seizures and multifocal limbic, thalamic, and cingulate damage, a pattern consistent with damage to the thalamocingulate system, maternal care was abolished. The authors suggest this finding is consistent with MacLean’s proposal that maternal behavior requires the integrity of this system.

Lorberbaum et al. [6,7] studied in 11 healthy, right-handed, breast-feeding, first-time human mothers with infants 4–8 weeks old. They used fMRI to measure brain activity while the mothers listened to recorded infant cries, white noise control sounds, and a low-rest condition. They found that these mothers displayed more anterior and posterior cingulate, medial thalamus, and right orbitofrontal cortex (OFC) activity with infant cries than with control sounds. Much of the same neurocircuitry is reported in rodent maternal behavior. Thus, their findings are generally consistent with neuroanatomical studies of rodent maternal behavior [5].

3. Isopraxis, mirror neurons, and social displays

MacLean proposed the term *isopraxis* (performing or acting in a like manner) instead of *imitation* to describe animals engaging in species-typical pair or group activities of the same kind. As an example, he describes two territorial male lizards responding to one another with challenge displays. The recent discovery of mirror neurons in the monkey’s (*Macaca nemestrina*) ventrolateral premotor cortex (area F5) [8] may be consistent with MacLean’s model. The term *mirror neurons* is used because these cells respond to both observed and executed actions. These neurons show activity in relation to both specific actions performed by the self and matching actions performed by others. There is physiologic evidence that Broca’s area, the human homologue of F5, is involved in the imitation of finger movements. Wohlschlager and Bekkering [9] suggest that human imitation (isopraxis) emerged from the mirror neuron system of a common ancestor of monkeys and humans. Similar findings regarding mirror neurons are reported in audiovisual mirror neurons that code actions independently of whether the actions are seen, heard, or performed [10]. Echolalia and echopraxia are features of autistic disorder and, as stereotypies, may be examples of isopraxis in humans. Williams et al. [11] propose that mirror neuron discharge may be pertinent to autism. The imitation of certain autistic stereotypies by a therapist may lead to the termination of the behavior in the subject. MacLean’s term *isopraxis* seems more pertinent for these individuals with autism where conscious imitation and theory of mind skills are deficient. Moreover, mirror neuronal systems may provide an evolutionary underpinning for cortical systems that evolved for cooperation and socialization.

4. Emergence of social behavior

MacLean suggests that the evolutionary linking of the cold sense of vision with emotion allows for an empathetic response. This may be in keeping with the finding that individuals of many species are disturbed by the distress of a conspecific and act to terminate the other’s distress although they may incur risk in doing so. It is in keeping with the emergence of the grief response and examples of self-sacrifice in evolution. A focus on empathy rather than on altruism may another avenue of study to investigate self-sacrifice because models of altruism based on group selection remains controversial [15]. MacLean’s focus on inte-
grated brain functioning is in keeping with Adolph Meyer’s psychobiology where spontaneous prosocial behaviors are a criterion of mental health and illustrate effective social adaptation and fitness.

de Waal [12] has documented primate origins of sociability providing examples that are consistent with the view of the Russian evolutionists that mutual aid is a driving force in social evolution [13,14]. Preston and de Waal [16] review the proximate and ultimate basis of empathy and propose a perception–action model (PAM) with 31 peer commentaries on this model. These authors suggest that the interaction of PAM and prefrontal functioning may explain different levels of empathy across different species and age groups. A brain that is organized towards social choices may be engaged in cultural evolution as experiences are passed from one generation to the next (the so-called passage of memes from one generation to another). An example of early social behavior may be seen in birds and monkeys who produce an alarm call, making themselves more liable to attack while concurrently, alerting the group of danger.

Todes [13] points out that Darwin described natural behavior in tropical settings that were rich in resources, where organisms were packed tightly, wedgelike, into every available space, where a small advantage could bring prosperity to one form at the expense of another. Yet he reminds us that in Russia the natural setting was a great, sparsely populated plain. “Where were Darwin’s wedges in this environment? [13]” In Russia, the populations were most obviously checked by physical circumstances. These circumstances were often so severe that one form’s slight advantage over another could easily seem insignificant. Todes notes that “a sudden blizzard or an intense drought might obliterate entire populations of insects, birds, and cattle without regard for difference among them.” Thus, the Russian evolutionists proposed “mutual aid” as the driving force in evolution that allowed survival to continue. They pointed out that those species with the most highly evolved brains have the greatest brain weight, show the greatest social cooperation, and are the most sociable. Trivers [17] examination of the evolution of reciprocal altruism may be pertinent to the importance of mutual aid in evolution.

5. Impact of brain lesions on social behavior

Support of the role of the brain in sociability and evidence for the grounding of morality in neurobiology comes from case reports of changes in human behavior following brain damage. The most famous case may be that of Phineas Gage, a 25-year-old railroad foreman, whose brain damage was sustained when a rail-tamping rod was forced through his ventromedial frontal cortex. Although he survived with his elementary mental functions intact, his speech was reported to be normal as was his memory, however, there were personality changes. Previously pleasant and reliable, he became irresponsible and lost respect for social conventions. Damasio’s Descartes Error [18] provides other examples of similar antisocial personality change following brain tumors and other damage to this brain region.” Dolan [19] follows up on these findings in his On the Neurology of Morals. He reviews two individuals with frontal lobe damage during the second year of life whose behavioral deficits are accompanied by an absence of factual knowledge regarding expected social and moral norms. Because the OFC is involved in appraising the reward value of ongoing behavior, brain injury during the developmental period has a different outcome than similar brain damage in later life.

Winston et al. [20] carried out an fMRI study where subjects were asked to judge the trustworthiness of faces. Social judgments involve the amygdala, regions of the prefrontal cortex, and regions of somatosensory-related cortices and these regions proved pertinent in face judgments. Farrow et al. [21] used fMRI to investigate the functional anatomy of empathy and forgiveness, both necessary for social cohesion. Ten volunteers read and made judgments based on social scenarios and a high baseline task (social reasoning). These authors found that both empathetic and forgiveness judgments activated the left superior frontal gyrus, orbitofrontal gyrus, and precuneus. Judgments of empathy also activated the left anterior middle temporal and left inferior frontal gyri, whereas forgivability judgments activate the posterior cingulate gyrus. Frontal temporal regions were activated in studies of forgivability and empathy but activation of the left middle temporal gyrus was seen only for empathy and not for forgiveness judgments.

6. Neurodevelopmental disorders and social neuroscience

The triune brain concept does not specifically consider neurodevelopmental disorders yet it does emphasize integrated brain function. Neurodevelopmental disruption of integrated brain systems may result in abnormal social behavior. If there is an evolutionary trend toward greater integration of the brain, what may we learn about this integration from the study of neurodevelopment in those developmental disorders where there is abnormal brain development? Autistic disorder [22] and Lesch–Nyhan syndrome (LNS) [23] are two syndromes that may aid in understanding the functioning of the social brain and the integration of brain circuits for adaptive behavior. In autistic disorder, the basic mechanisms involved in the subjective understanding of others intentions and feelings is disrupted, as is imaginative play; stereotypies are characteristic. There is neuroanatomical evidence of abnormal development of regions of the limbic system in autistic disorder [24]. In LNS, the individual is subjectively aware but despite this awareness self-injures and asks to be restrained by others from doing so. Basal
ganglia involvement has been documented in this syndrome using neurochemical and neuroimaging studies [25,26]. In this syndrome, it is the R-complex and its connections that apparently are involved.

7. Failure of integrated brain functioning in autistic disorder and Lesch–Nyhan syndrome

The failure of integrated social functioning and the lack of appropriate use of social gestures is characteristic of an autistic disorder. In autistic disorder, there is a lack of social referencing and a failure in affective attunement. Severely autistic children do not demonstrate imaginative play that is reflective of an inner language. Autism lead us to consider how we can profitably study those brain mechanisms that might be involved in interpersonal relationships, e.g., the linkage of executive function with emotion regulation, emotional memory consolidation, and mastery play. Such an approach may help to clarify and to develop a model for the integrated brain function.

Autopsy reports of brains from autistic persons by Kemper and Bauman [27,28] demonstrate abnormal development of brain regions that apparently are involved. In this syndrome, it is the R-complex and its connections that apparently are involved.

Abnormalities in the cerebellum and brainstem included (1) curtailment of normal development of neurons in the forebrain limbic system; (2) apparent congenital decrease in the number of Purkinje cells; and (3) age-related changes in cell size and number of neurons in the nucleus of the diagonal band of Broca, in the cerebellar nuclei, and in the inferior olives. Kemper and Bauman [28] conclude that, although their report is descriptive, their neuropsychological findings are consistent with the origins of infantile autism being in the prenatal development of the brain with ongoing pathological processes that persist into adult life. They point out that the best correlations with clinical features of autism are the consistent findings in the limbic forebrain. The findings in the anterior cingulate, hippocampus, subiculum, entorhinal cortex, and mammillary body are aspects of an interrelated forebrain circuit that is linked to the septum and amygdala. Experimental lesions in these areas have produced deficits in memory, emotion, and other behaviors like those described in autistic persons.

These abnormalities in the development of the cingulate and limbic brain are consistent with MacLean’s lesions revealing effects on parenting and play when these regions are lesioned in intact animals [31]. These findings are consistent with the work of Murray and Mishkin [32] who reported that bilateral ablations of the amygdala result in severe impairment in crossmodal associative memory in monkeys. They propose that the amygdala may be important for the integration and generalization of modality-specific information by multiple sensory systems in the brain, a problem that is a characteristic feature in autism.

Malkova et al. [33] found that socioemotional deficits that followed bilateral ablation of the amygdala and hippocampus in neonatal monkeys increased with age and persisted into adulthood; however, comparable lesions that were placed in adult monkeys resulted in relatively mild behavioral deficits. Animals models such as these are consistent with the neurodevelopmental deficit suggested in autism. It is possible that a developmental abnormality in the limbic memory circuit may become clinically evident after birth at a developmental phase when synaptic reorganization occurs; this would be consistent with a deterioration in social, language, and cognitive ability that is commonly reported in the first 2 years of life in autism and that autism is most commonly diagnosed from 15 to 24 months of age.
8. Neuroimaging studies in autism

Neuroimaging studies may be utilized to confirm structural changes in the brains of autistic persons. Moreover, functional hypotheses based on abnormalities in brain circuits can be assessed. Imaging studies may also be used to evaluate theoretical models of autism. These include metarepresentational models (theory of mind), affective models (lack of eye contact, abnormal response to danger, and in normally fearful situations), and intersubjectivity (integrating cortex and limbic brain).

Fletcher et al. [34] carried out a functional imaging study to evaluate mentalizing or “theory of mind” in normal subjects. Story comprehension was used to identify brain regions involved in mentalizing (theory of mind). Story conditions, when compared to unlinked sentences, showed significant increases in regional blood flow in the temporal poles bilaterally, the left supratemporal gyrus, and posterior cingulate cortex. Only the theory of mind story produced activation in the medial frontal gyrus on the left suggesting its selective activation in theory of mind tasks. Subsequently, Happe et al. [35] used the same paradigm in a PET study involving five patients with Asperger syndrome, a variant of autism, who had normal intellectual functioning. No task-related activation was found in the left medial prefrontal cortex; however, activity was found in the immediately adjacent areas suggesting this region is involved in understanding other minds. Gallagher et al. [36] have demonstrated that both the story task (verbal) and a cartoon task (nonverbal) showed overlap in activating the medial prefrontal area. In a structural MRI study in 15 high-functioning individuals with autistic disorder, Abell et al. [37] identified gray matter differences in an amygdala-based system when compared to 15 age- and IQ-matched control subjects. These findings of differences in amygdala structure are consistent with the autopsy findings in autism regarding the amygdala.

Future imaging studies in autism may focus on neuroimaging of the amygdala activation in response to emotional stimuli. Such studies have been conducted in normal volunteers. Whalen et al. [38] report that masked presentations of emotional facial expression modulate amygdala activation without explicit knowledge, i.e., in the absence of knowledge that such stimuli were being presented. The treatment of autistic disorder requires an understanding of the autistic nervous system and a recognition of the failure of integrated brain function in this disorder.

9. Lesch–Nyhan syndrome

LNS, a metabolic disorder that is the result of near absence of hypoxanthine–guanine phosphoribosyltransferase (HPRT), is of interest to neuropsychiatry because the behaviors manifested by those with this condition characterize a behavioral phenotype [39]. The most striking of these behaviors are compulsive self-injury with tissue damage beginning in infancy and subsequent deliberate self-harm. Self-injurious behavior is usually expressed as self-biting; however, other patterns of self-injurious behavior may emerge with time, as do patterns of compulsive, aggressive behavior. Characteristically, the fingers, mouth, and buccal mucosa are mutilated. Self-biting is intense and causes tissue damage, often leading to amputation of fingers and loss of tissue around the lips, thus requiring the extraction of primary teeth. The biting pattern is often asymmetrical in that the patient preferentially mutilates the left or right side of the body and may become anxious if they perceive that one side of their body is threatened. The topography of the behavior is different from that seen in other mental retardation syndromes of self-injury, where self-hitting and head banging are the most common initial presentations. Moreover, the intensity of the self-injurious behavior generally requires that the patient be restrained. Despite the movement disorder, when restraints are taken away, the individual with LNS may appear terrified and may quickly and accurately place a finger in the mouth. He may ask for restraints to prevent elbow movement, and, when the restraints are placed or replaced, may appear relaxed and more good-humored.

The self-mutilation is conceptualized as a compulsive behavior that the child tries to control but generally is unable to resist. Older individuals become more adept at finding ways to control the self-injury, including enlisting the help of others and notifying them when restraints can be removed. In the older child, self-injury may progress to deliberate self-harm and compulsive aggression towards others. The individual with LNS may inflict injury to others through pinching, grabbing, hitting, or by using verbal forms of aggression. Afterwards, he will apologize for this behavior and say that it was out of his control. The language pattern is also characteristic and consists of repeated ambivalent statements, which are most commonly accompanied by anxiety and coprolalia (vulgar speech) may occur. Other associated maladaptive behaviors that develop later include head or limb banging, eye poking, pulling of fingernails, and psychogenic vomiting.

MRI volumetric measurement of brain structures show reductions in total brain size, reduction in caudate volume, and probable maturational arrest of the brain in classical LNS [26]. The reduction in caudate volume is the most substantial finding, although the putamen is also reduced in volume. PET imaging studies of pre- and postsynaptic dopamine neuroreceptors demonstrate dopamine deficiency similar to that reported in postmortem studies of three Lesch–Nyhan patients [25]. Wong et al. [40] demonstrated a striking reduction in dopamine transporter binding in both the caudate and putamen. Because an animal model had been proposed showing self-injury in dopamine deficient rats, it is hypothesized that self-injury in human subjects with LNS is the result of dopamine deficiency in the basal ganglia.
To clarify the relationship between presynaptic dopamine transporter binding and behavior, Harris et al. [41] studied seven Lesch–Nyhan variant patients ranging in age from 12 to 37 who had never self-injured. The HPRT levels ranged from 1.8% to 20.0% but were less than 1% in six classic cases. On neurological examination, motor findings were documented. Two patients with classical LNS with HPRT levels up to 2.5% were not different in dopamine binding than the classical Lesch–Nyhan patients who did self-injure, suggesting that dopamine receptor density is not a complete explanation of the self-injury. However, with increased dopamine level, there was a correlation between dopamine transporter binding and the degree of motor deficit. These findings suggest that dopamine reduction is linked to the movement disorder but is not a sufficient explanation for self-injurious behavior and that other neurotransmitters need to be considered, such as serotonin.

Subsequent measurement of brain chemistry in LNS using proton spectroscopy shows reductions of the N-acetyl aspartate metabolite in the basal ganglia (caudate and putamen) but not in the medial orbital cortex or dorsolateral prefrontal cortex [41]. These findings, combining MRI and PET, suggest the involvement of frontocorticostriate systems in self-injurious behavior, consistent with a disorder of self-regulation.

In conclusion, research in social neuroscience is consistent with MacLean’s contributions on brain evolution and behavior, especially his investigations of parental behavior and empathetic aspects of social understanding. MacLean’s studies of the effects of brain lesions on social behavior can be extended to investigations of social behavior and self-regulation in neurogenetic disorders with behavioral phenotypes. The study of pathways from genes to cognition and complex social behaviors in conditions such as autism and LNS, using sophisticated genetic, neurological, neuroimaging, and neuropsychological methods, may provide new understanding about how integrated brain functioning is essential to empathetic social responses.

References


