Chapter 1

Introductory Chapter: Primates - What the Monkey Brain Tells the Human Brain

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Additional information is available at the end of the chapter

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1. Introduction: The Soul of The Ape

The name Eugene Marais has slowly begun to fade to the annals of time; however, we would be remiss to begin a book about Primates without first discussing the life and work of the man who helped lay the foundation for naturalistic primate observation. Born in 1871 outside of Pretoria in South Africa, he first started out as a journalist who built a reputation for upsetting politicians to the point where he was indicted for high treason. After his acquittal, he moved to London where he not only studied law but also had tried his hand at medicine. During his time in London, the Boer War had begun and Marais left for Central Africa where he attempted to help his countrymen. Early in the twentieth century, estimated to be around 1903, Marais retreated to Waterberg, a mountainous region in the north Limpopo Province of South Africa. The farmers who were originally in that area had largely been displaced as a result of the Boer War and because of this, the chacma baboons (*Papio ursinus*) had a temporary reprieve from human interaction. It was this time in Waterberg that Marais spent 3 years living with, following, and studying the chacma. He became one of the first to study wild baboons in their natural environment and consequently wrote "My Friends the Baboons" and his unfinished work "The Soul of the Ape." For the most part, Marais was an untrained scientist, except perhaps a brief medical introduction during his time in London, but this might have led to the strength of his investigation by not having preconceived notions tainting his observations [1].

In these two works, Marais delved into the psyche or as he termed it, the "soul" as he questioned phyletic (unconscious/instinctual) versus casual (conscious/learned) memory. Through time, he was able to make observations within a few yards of the chacma troop. However, as time passed, farmers along with their guns returned, thus finishing the relationship between Marais and the troop. Although this work remains unfinished, his insights about the psyche would not be possible without his keen observations of the chacma:

> *"The phyletic history of the primate soul can clearly be traced in the mental evolution of the human child. The highest primate, man, is born an instinctive animal…as it grows, the new mentality slowly, by infinite gradations, emerges…it is here that the wonderful transition occurs, a transition which the phyletic evolution of the soul of the chacma exemplifies. As the new soul, the soul of the individual memory slowly emerges, the instinctive soul becomes just as slowly submerged."* [1], *pp. 102–103*

2. Primates and Intoxication

In addition to the psyche, Marais' observations and perhaps his own personal experiences, delved into addiction and depression as he stated:

> *"Euphoric intoxication is of especial interest in this study because of convincing proof that there exists in the chacma a state of mind similar to that which induces the use of euphoric in man."* [1], *p. 117*

This is of special interest to our research group as vervet monkeys (*Chlorocebus sabeus*) will, in naturalistic settings, voluntarily consume alcohol [2, 3]. In fact, the St. Kitts vervet will drink beverage alcohol in both the laboratory and natural settings, with 15% voluntarily consuming over 5 g of ethanol/kg/day [2]. The range of alcohol consumption in this population is similar to that seen in the human population that varies from abstinence to those that chose to drink to the point of comatose with perhaps the largest population being somewhere in the middle. The consumption of alcohol has its roots in our evolutionary frugivorous history. The presence of ethanol in fruits coincides with ripeness and sugar content and with a potentially higher caloric content. As a result, it would have been advantageous to consume ripe fruit that has started to ferment [4]. Voluntary alcohol intake has been noted in different species including birds, baboons, elephants, and the aforementioned vervets [1, 4–6]. It has been hypothesized that the excessive consumption of alcohol is due to an advantageous ancestral trait that has become disadvantageous due to the abundant access of nutrition [4, 7]. This adaptive mechanism has been suggested to be related to "exploratory appetitive behavior" involving neurogenic as opposed to the neurological effects of ethanol [7]. The neurological effects of ethanol (sedative, tolerance, anxiolytics, and dependence) are important factors in the development and sustenance of alcohol abuse; it remains a complex disorder [2], as Marais would attribute this to both phyletic and casual memory of the species. Although the etiology of alcoholism is unknown in humans, the likelihood of alcoholism in nonhuman primates sharing some aspects of the same etiology is great. In fact, Marais recognized the overlap of the psyche between human and nonhuman primates a 100 years ago, stating:

> *"…the conclusion that the chacma suffers from the same attribute of pain which is such an important ingredient of human mentality, and that the condition is due to the same cause."* [1], *p. 139*

With the voluntary and naturalistic drinking pattern exhibited by vervets, we are able to address vulnerability factors, both genetic and neurochemical, leading to alcohol use and misuse [2]. We have been able to now further take advantage of the drinking patterns to examine the short-and long-term effects of prenatal ethanol exposure on the developing brain in a systematic manner which cannot be done in a clinical setting [3, 8–10].

3. Validity of Model Systems

Given similarities such as neuroanatomy, physiology, immune, development, behavior, and anatomy and those outlined by Marais [1], between human and nonhuman primates, it might be tempting to restrict models of human conditions to monkeys. However, from both a practical and an ethical point of view, it is appropriate to use lower mammals to test initial hypothesis, while reserving the study of nonhuman primates to final confirmations of hypothesis already well piloted in lower mammals and to situations in which other model systems do not provide an adequate degree of complexity. Furthermore, the validity of any animal model, including nonhuman primates, depends on the question being asked. To evaluate animal model validity, five criteria consisting of *homological* (assess species and strain), *pathogenic* (disease process similarities), *mechanistic* (assess proposed mechanisms of action as it relates to the human condition), *face* (similarity of observable disease features), and *predictive* (ability of model to make predictions on therapeutic interventions) validity should be examined as it relates to the research question [11–13].

For instance, applying the test of validity to our longitudinal assessment of the functional reorganization and adaptive neuroplastic responses following early life hemispherectomies provides a demonstration of the strength of nonhuman primate model systems. The premise of developing this model was due in part to the remarkable recovery of patients following the cerebral hemicorticectomy surgical procedure as a treatment for intractable epilepsy [14–16]. The degree of recovery in the clinical setting depends on the age of intervention and the targeted sensory and motor system [15–17]. Following surgical intervention, there appears to be a rapid recovery of sensory and motor systems, which may be a result of a preexisting functional reorganization due to the dysfunctional hemisphere [18, 19]. The purpose of our nonhuman primate model is to model the functional recovery by identifying the resultant reorganization and behavioral recovery following infant and adult hemispherectomy [20].

Infant (aged about 9 weeks) and adult (about 48 months of age) vervets underwent a surgical procedure to remove the left cerebral hemisphere (**Figure 1**) and allowed to recover in enriched environments at the Behavioral Sciences Foundation, St. Kitts. Behavioral assessments were conducted on a 6-month basis. All surgical and behavioral protocols were approved by the Animal Care and Use Committee at University of Montreal.

Sensory assessments consisted of visual (perimetry, palpebral reflex, and visual pursuit), thermal, and nocioceptive tasks, while motor observations were conducted via open field and horizontal bar crossing (as reviewed in Burke et al. [20]). Infant hemispherectomized monkeys displayed residual vision in the "blind" hemifield up to 45°, but adult subjects were unable to detect visual stimuli. Normal-sighted monkeys had a visual perimetry up to 90° in both hemifields. For both the infant- and adult-lesioned subjects lacked visual palpebral reflex and visual pursuit in the contralateral visual field. Infant-lesioned subjects retained nocioceptive and innocuous sensation capabilities on the contralateral side. In the open field,

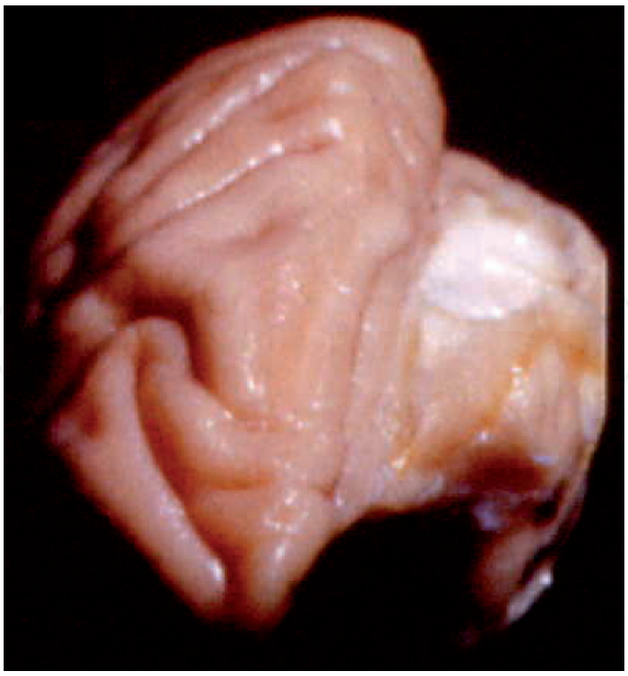

Figure 1. Hemispherectomized brain: image here shows the removal of the left hemisphere (adapted from Burke et al. [20]).

we observed normal ipsilateral upper and lower limb and contralateral lower limb gait. Upper limb on the contralateral side remained paretic in infant-lesioned subjects. This is in contrast to adult-lesioned subjects where both upper and lower limbs were paretic. Within the first 2 years after surgery, infants displayed difficulty traversing the horizontal bar, after which the infant-lesioned subjects were able to cross by walking upright, but like the open-field observations, subjects did not attempt to use the upper contralateral limb (**Figure 2**). Subjects also displayed ipsiversive and circling behaviors, possibly due to contralateral hemianopia [20].

Given the neurodevelopmental and homologous brain areas, the nonhuman primate offers a high degree of homological validity for the study of human development [3, 8, 9, 11, 20–24]. Pathogenic validity, which addresses the disease process, in this case, depends on the question. If, for instance, the question in this case were to model reorganization following hemispherectomy as a result of intractable epilepsy, then the model would have to also show a similar pathogenic process. However, this model is aimed at identifying the ability of the brain to functionally remodel during early development in a manner that cannot be fully elucidated in the human epileptic condition considering the potential for preexisting reorganization [20]. Several lines of evidence from our study demonstrate both *mechanistic* (addressing mechanism of action) and *face* (similarities of observable features) validity for neural remodeling manifested through behavior as well as histological alterations. The residual vision and pervasive ipsilateral turning seen in our subjects is reminiscent of hemianopia seen in hemispherectomized patients in which a subset has residual responses to visual stimuli on the hemianopic field, known as Type I blindsight (implicit) or Type II blindsight (explicit) [17]. The ipsilateral turning corresponds to the visual preference reported in the clinical population [25]. Anatomically, our subjects have a significant degeneration of foveal retinal ganglion

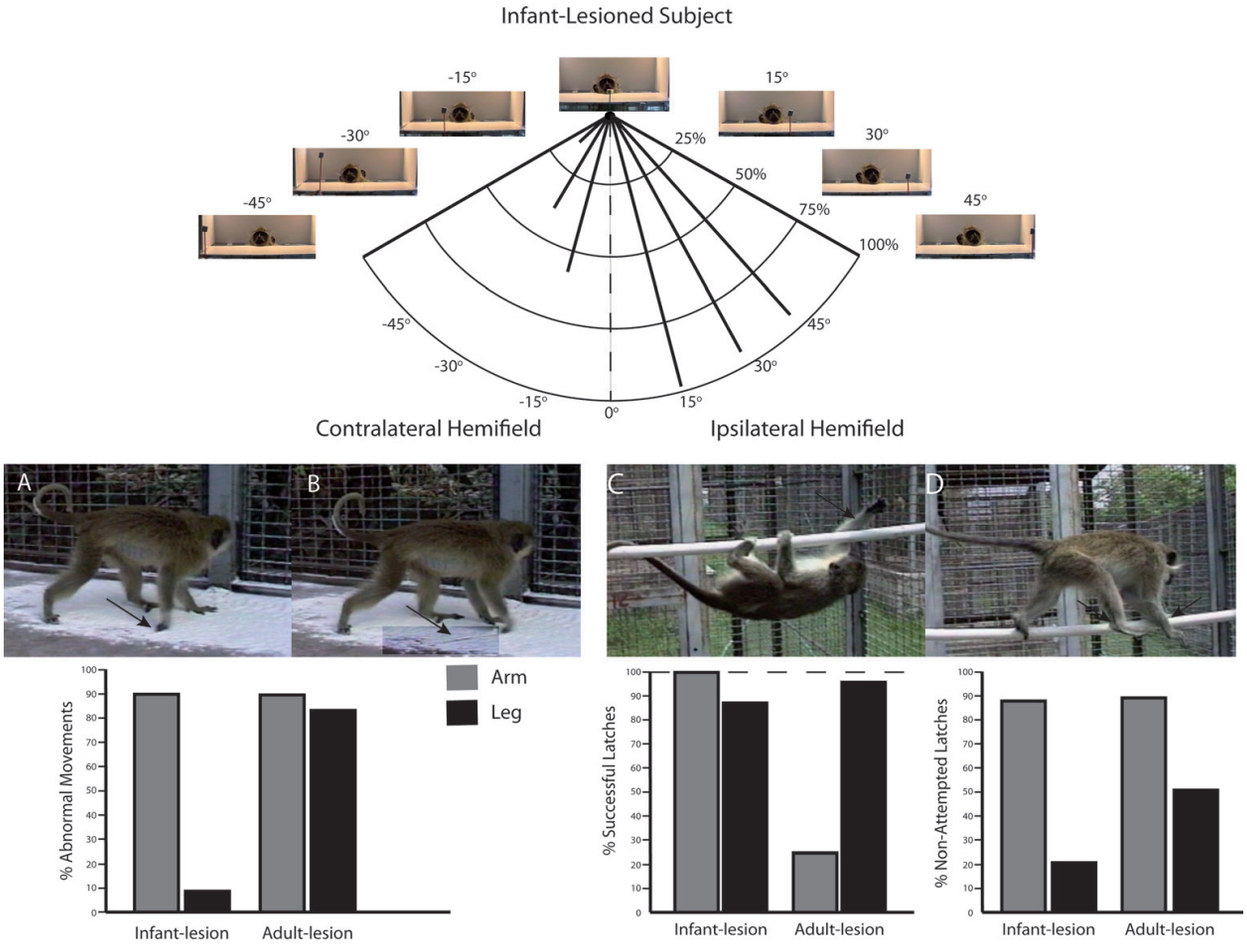

Figure 2. Behavioral analysis: The perimetry test (top image) depicts residual vision. Subjects were able to detect visual stimuli at 45° in the blind field at a 16% success rate (contralateral hemifield) with no responses elicited beyond 45°. Panels A and B depict the open-field test where normal gait was significantly affected by surgery. The contralateral upper limb in the infant-lesioned subjects displayed paresis; however, the lower limb showed little residual paresis. In the adult-lesioned subject, however, both upper and lower limbs showed significant paresis. Panel C shows a subject 1-year post surgery unable to cross the horizontal bar in an upright position, whereas in panel D at 2-year post surgery, the subject is able to cross in an upright position. Furthermore, in panel C, the young monkey is unable to grasp the bar with the upper limb and would glide the arm along the bar while attempting to grasp the bar. By 2–3 years' post surgery, the subject is able to have more successful latches per attempt, but for most of the trials, the subjects did not attempt to latch on with the upper limb. Graphical data are shown at a 3-year post-surgical time points for all groups (adapted from Burke et al. [20]).

cells but remain intact in the peripheral retina [26]. The ipsilateral lateral geniculate also suffers massive neural degeneration; however, it too retains neurons and appropriately placed projections from the retina despite significant volume loss [27, 28]. Likewise, human hemispherectomy patients regain strength in lower limbs but display significant weakness in the contralateral upper limb [19, 29]. Residual contralateral tactile sensation remains intact and activates the ipsilateral somatosensory cortices [30, 31]. Histological data from our monkeys suggest that the dorsal column nuclei (cuneate and gracilis subdivisions) are unaffected, providing an anatomical substrate for an intact ipsilateral, non-decussating pathway. The residual vision and more complete motor recovery in infant, but not adult-lesioned, subjects further supports clinical data of a profound functional reorganization of neural circuitry underlying the behavioral observations [20].

Predictive validity (ability to make predictions) typically examines pharmacological interventions. However, here, we propose a functional model for neuroanatomical reorganization in multiple systems. Clinical functional magnetic resonance imaging (fMRI) data suggest ipsilateral sensory and motor pathways [30–32] potentially through the corticospinal and medial lemniscus tracts [33–35]. Our model supports several lines of evidence from the visual pathway that allow us to propose a neuroanatomical substrate for residual vision (**Figure 3**),

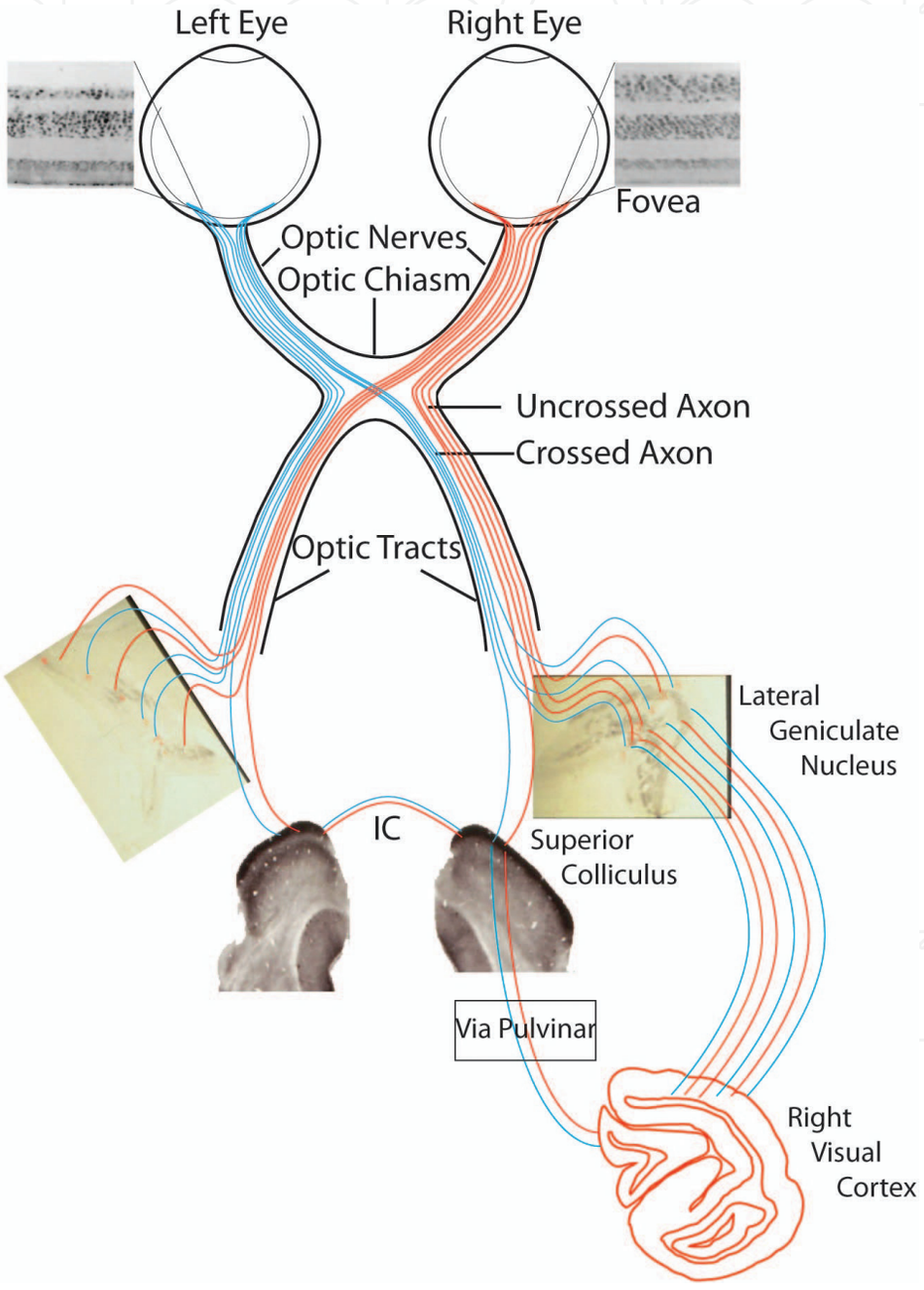

Figure 3. Hemianopia pathway: we have previously proposed an anatomical pathway for visual field recovery depicted here. Briefly, the residual left temporal retinal ganglia cells send their projections to the appropriate lateral geniculate nucleus, the function of which is not entirely clear. The retinofugal projections to the left superior colliculus remain intact with information potentially traversing to the right side through the intertectal commissure (IC), then processed through the pulvinar, and finally to the right visual cortex. The left pulvinar is severely atrophied and is unlikely to account for residual vision seen in our subjects (figure is adapted from Burke et al. [20]).

thereby supporting the predictive validity of this model. The surviving peripheral retinal ganglion cells provide the first line of residual visual capacity, but given the extent of volume and neuronal loss in the ipsilateral lateral geniculate nucleus, it is doubtful that this thalamic nucleus alone could explain vision in the blind field. The superior colliculus retains functional capacity, as revealed by cytochrome oxidase activity and relative sparing of the neuronal population [36], as well as the neuronal population in the ipsilateral substantia nigra in these monkeys. The lateral substantia nigra comprises the nigrotectal pathway, which is an important mediator of saccadic eye movements. Therefore, we have proposed that the peripheral retinal ganglion cells project to the left superior colliculus from which the information is then transferred to the right superior colliculus via the intertectal commissure to the right pulvinar and finally to the right extrastriate cortex [20, 28]. Diffusion tensor imaging (DTI) has also suggested such a retinofugal projection to the ipsilateral superior colliculus as the potential substrate for unconscious vision or blindsight in hemispherectomized patients [17, 37].

Histological data from this model, as well as that from clinical studies, suggest that residual subcortical and brain stem areas play a significant role in functional remodeling following early-life hemispherectomy. The culmination of over 20 plus-year experience with this model has shed new light on the ability of the infant brain to reorganize [20]. The application of validity criteria further shows the significant contribution to the understanding of human conditions by studying nonhuman primates. We have also applied these criteria to a nonhuman primate model of pediatric HIV infection [11]. There are relatively few pediatric simian immunodeficiency virus (SIV) models, but the ones that are available show strengths in each of the five validity criteria and provide a platform in which to test therapeutic interventions that are aimed at reducing HIV neurological dysfunction that is prevalent in the pediatric population [11, 38].

4. Conclusions

In this book, we present a series of chapters dedicated to the study of primates that range from phyletic organization, to observational and conservational efforts, to using nonhuman primates, to understand our own human condition. In their natural habitat, the interaction between humans and nonhuman primates may be contentious as monkeys may be seen as agricultural pests [1, 2, 39], something that we could only speculate Marais would argue against. Whether or not we are cognizant of his work, Marais [1] helped lay the foundation for multiple lines of research for the better understanding of our own human psyche, emphasized the need to protect and observe primates in their habitat so that we may better understand our own "soul."

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