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Oculomotor Deficits in Diseases of the Basal Ganglia: Parkinson's and Huntington's Diseases

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LIST OF ABBREVIATIONS

BSG	Brainstem Saccadic Generator
CEM	Compensatory Eye Movement
CM	Centromedian (intralaminar) Nucleus of the Thalamus
DA	Dopamine
dlPFC	Dorsolateral Prefrontal Cortex
FEF	Frontal **Eye** Field
GABA	Gamma Aminobutyric Acid
GP	Globus Pallidus
GPe	Globus Pallidus, external segment
GPi	Globus Pallidus, internal segment
GPi-cdm	Caudal Dorsomedial GPi
GPi-vl	Ventrolateral GPi
L-Dopa	L-dihydroxyphenylalanine
LIP	Lateral Intraparietal Sulcal Cortex
MDmf	Mediodorsal Nucleus, Pars Multiformis
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MST	Middle Superior Temporal Area
MT	Middle Temporal Area
PPN	Pedunculopontine Nucleus
OKN	Optokinetic Nystagmus
Pf	Parafacicular (intralaminar) Nucleus of the Thalamus
PPC	Posterior Parietal Cortex
PPRF	Paramedian Pontine Reticular Formation
PS	Principal Sulcus Cortex
riMLF	Rostral Interstitial Nucleus of Medial Longitudinal Fasciculus
SC	Superior Colliculus
SEF	Supplementary Eye Field
SMA	Supplementary Motor Area
SNc	Substantia Nigra, Pars Compacta
SNr	Substantia Nigra, Pars Reticularis
SNr-cl	Caudolateral SNr
SNr-vl	Ventrolateral SNr
STN	Subthalamic Nucleus
UVES	Unsuppressed Visually Evoked Saccades
VA	Ventral Anterior nucleus of Thalamus
VAmc	Ventral Anterior nucleus of

	Thalamus, Pars Magnocellularis
VApc	Ventral Anterior nucleus of Thalamus, Pars Parvocellularis
VES	Visually Evoked Reflex Saccades
VL	Ventral Lateral nucleus of Thalamus
VLo	Ventral Lateral nucleus of Thalamus, Pars Oralis
VOLS	Voluntary Saccades
VOR	Vestibular-ocular Reflex

INTRODUCTION

Oculomotor deficits are now recognized as being present in several neurological diseases of the basal ganglia. The present report will focus primarily on those observed in Huntington's and Parkinson's diseases. Neuronal cell loss in the pars compacta of the substantia nigra, degeneration of the nigrostriatal pathway, and consequent depletion of the neurotransmitter dopamine is the most obvious etiological abnormality in Parkinson's disease. Huntington's disease, on the other hand, involves the selective genetically-driven atrophy of the striatum (caudate and putamen). In order to attempt to understand oculomotor dysfunction, as a component of basal ganglia disease, it is necessary to first establish a definition of the basal ganglia, its relevant connections, and their associated neurotransmitters and functions.

GENERAL DESRCIPTION OF BASAL GANGLIA DISEASES

Parkinson's disease may be induced by toxins, genetically linked, or may originate idiopathically. Symptoms are varied, but most often they include resting tremor and difficulty in initiating movements. The most obvious pathologic disturbance is the lack of dopamine in the nigrostriatal pathway. Progression of the disease may be retarded by drug therapy that attempts dopamine replacement, but to date there is no cure.

Huntington's disease is a hereditary disease, which usually manifests itself in middle age. It ultimately results in death over a twenty year period. Choreic and hyperkinetic movements are common features of Huntington's disease. Also, Huntington's patients often suffer from dementia. The classic sign in a post-mortem examination of a Huntington's disease patient is atrophy of the striatum and consequent enlargement of the lateral ventricles.

While Parkinson's and Huntington's diseases receive most of the attention in this study, there are many other basal ganglia diseases. Since the subcortical nuclei that comprise the basal ganglia (caudate, putamen, globus pallidus, subthalamic nuclei, substantia nigra) are

intimately interconnected, the physiologic imbalance created by the malfunction of one nucleus often directly affects the function of another.

Hemiballismus, for example, may be caused by a unilateral lesion of the subthalamic nucleus or disruption of one of the subthalamic afferents or efferents. When lesioned, the subthalamic nucleus no longer inhibits the thalamus resulting in hemiballismus, a condition noted for hyperkinetic movements. Sydenam's chorea may occur in adolescents following infection by the bacterium B-hemolytic streptococcus. In this disease, antibodies affect neurons of the striatum, inducing a chorea similar to that caused by Huntington's disease[44]. In Wilson's disease, the copper transporting protein (ceruloplasmin) is absent. An accumulation of copper in the putamen results in its deterioration[107]. The hallmark symptom of Wilson's disease is a "flapping tremor." Destruction of the lateral putamen will induce athetoid movements and muscular hypertonicity, a condition known as dystonia[18]. Tics are usually random uncontrollable repeated movements of one muscular group. Recent evidence suggests that there is a decrease of the peptide enkephalin in the striato-pallidal (GPe) pathway[1]. Tics, ballism, and Huntington's disease, all hyperkinetic movement disorders, are probably related to decreased output of the subthalamic nucleus[1].

CONNECTIONS AND NEUROTRANSMITTERS IN THE BASAL GANGLIA

The term "basal ganglia" includes a collection of subcortical nuclei and their interconnections. Clinically, the definition has come to include the caudate and putamen (together referred to as the striatum), globus pallidus, subthalamic nucleus, and the substantia nigra, based upon the fundamental principle that lesions of any of these structures or their interconnections results in the presentation of a spectrum of dyskinesias all of which relate to the initiation and production of coordinated, automated movements. The basal ganglia receive input from widespread areas of the cerebral cortices, process information, and transmit that information back to the cortex via the ventral tier of the thalamus (the so-called motor relay nuclei, i.e. ventral anterior or ventral lateral thalamic nuclei). Malfunction in any one of the components of the basal ganglia can disrupt the normal influence that these structures provide; 1) via the thalamus to the ipsilateral motor cortex (that plans and then executes the movement) or 2) in the case of ocular movements, to the saccade generator via the superior colliculus. Unlike the cerebellum, which functions to coordinate the appropriate metrics and velocity of movements, the basal ganglia receive

no direct sensory information from the external environment and may deal instead with the patterning of normal movements based upon either innate or "learned" patterns of movement[54]. The basal ganglia do rely on sensory information, however conveyed via corticostriate projections from sensory and associational cortical areas.

Striatal Connections

The striatum receives afferents from a number of sources, principally the cortex (corticostriates), the substantia nigra (nigrostriates) and intralaminar nuclei (esp. the centromedian and parafascicular nuclei) of the thalamus (thalamostriates).

The corticostriatal afferents originate from broad regions of the cerebral cortex, but show definite organization. The corticostriates are glutamatergic[28,94]. The caudate nucleus receives its cortical input from associational cortex, particularly the prefrontal and posterior parietal areas. The terminal fields of mutually interconnected regions of the prefrontal and parietal cortex tend to overlap in the caudate nucleus[89]. Cortical afferents to the putamen also maintain a topographical organization and use the excitatory amino acid glutamate as a neurotransmitter[88]. In contrast to the caudate nucleus, the sensorimotor cortex is the principal source of corticostriatal input to the putamen[89]. Thus, it is thought that the caudate is involved in cognition, while the putamen is probably involved in movement[77]. Although the striatum

receives the bulk of its information from the ipsilateral cortex, up to thirty percent may come from the contralateral cortex[30].

Thalamic (thalamostriate) projections are another source of striatal afferents. They are diffuse and come from many areas of the thalamus. Sources include, primarily, the intralaminar nuclei (especially the centromedian/parafasicular complex), but thalamostriatals also originate to a lesser extent from the ventral anterior (VA), the ventral lateral (VL), lateral posterior, and suprageniculate nuclei[54,85]. Like the cortical input to the striatum the thalamostriatals also maintain a topographic organization[7]; the centromedian nucleus projects primarily to the putamen while the parafasicular nucleus projects primarily to the caudate.

The topographically established dopaminergic nigrostriatal projection is another well documented source of striatal afferents. The substantia nigra is comprised of a dorsal subdivision, the pars compacta (SNc), which produces dopamine (DA), and a ventral subdivision, the pars reticulata (SNr), whose neurons synthesize gamma aminobutyric acid (GABA). The glutamatergic corticostriates synapse on the heads of the dendritic spines of GABAergic striatal neurons, whereas the dopaminergic nigrostriatals synapse on the necks of the spines of striatal neurons, suggesting the SNc-striatals serve a modulatory role in basal ganglia function[72]. Other striatal afferents include

the excitatory serotonergic inputs from the dorsal raphe nucleus of the rostral pontine raphe[27]. Histamine-containing neurons from the posterior hypothalamus also project to the striatum[98]. The nucleus accumbens, which may be considered a ventral extension of the striatum, receives limbic input from the amygdala[88]. The striatum has a population of interneurons, that is, intrinsic neurons which only project to other areas within the striatum and are cholinergic. The striatum also receives an extrinsic cholinergic innervation from the pedunculopontine nucleus in the rostral dorsolateral pontine tegmentum[12].

Striatal efferents project to both the pallidum and SNr. The putamen projects to the ventral area of both the internal and external segments of the pallidum. The caudate nucleus projects primarily to the SNr, but also projects to the pallidum, with few overlapping projections from the putamen[93]. Both the striatopallidals and striatonigrals are GABAergic[33,88]. The striatonigral projections terminate in the pars reticulata, not the pars compacta of the substantia nigra which is the source of the dopaminergic nigrostriatal system.

Pallidal Connections

The globus pallidus receives projections from the striatum, the subthalamic nucleus (STN), the substantia nigra, pars compacta (SNc) and pedunculopontine nucleus (PPN)[79,98]. The GABAergic striatopallidal pathway to the GP is the principal efferent projection of the striatum. The

globus pallidus has both an external (GPe) and an internal (GPi) segment, and the striatum projects to both. Several neuropeptides are associated with the striatopallidal projections: striatopallidal neurons terminating in the GPe contain enkephalin, and striatopallidal neurons projecting to the GPi have substance P[70,79].

The globus pallidus also has interconnections with the subthalamic nucleus. The GPe projects to the subthalamic nucleus, which projects back to the GPi. Other afferents to the pallidum arise from the nucleus accumbens, the SN, and possibly the pontine tegmentum[98].

The GPi and the SNr are considered "major relay stations" in basal ganglia output[54]. There is some evidence that these areas have the same embryologic origin, but are separated by the internal capsule in the adult[25]. The GPi and SNr project to the thalamus, lateral habenula, and PPN[79]. SNr projects to the superior colliculus (SC) and VA of the thalamus, the intralaminar complex and mediodorsal nucleus, pars multiformis (MDmf) of the thalamus. The GPi projects primarily to the VL nucleus of the thalamus[34]. In addition, the GPi also sends projections to the intralaminar complex (CM) of the thalamus, pedunculopontine nucleus (PPN) of the dorsolateral pontine tegmentum, and the lateral habenula. After synapsing in the thalamus, basal ganglia output is relayed back to the cortex via thalamocorticals, specifically, to the premotor and supplementary motor cortex. Like the striatal afferents, there appears to be

somatotopic organization in the GABAergic nigrothalamic pathway. The GPi may be associated with the limbs, while the SNr neurons are thought to be related to head and neck movement[54]. It should be mentioned that the PPN receives GABAergic projections from the SNr and GPi. The PPN reciprocates glutamatergic projections to the SNr and GPi.

Subthalamic Connections

The subthalamic nucleus is thought to function as a negative feedback loop for information conveyed by the basal ganglia[75]. Afferents to the subthalamic nucleus include the glutamatergic excitatory corticosubthalamics from the premotor and motor cortex including the frontal eye field (FEF)[55,74,92,] projections from the GPe, and the pedunculopontine nucleus. Subthalamic connections with the PPN are reciprocal[88].

As mentioned previously, the striatum projects to both GPe and GPi. The GPe projects to the subthalamic nucleus, which then projects to the GPi, GPe, and SNr. Little is known as to the function of the subthalamus, but initially it was believed to serve in basal ganglia regulation through inhibition of its target neurons, the GPi and SNr[54,79], however, recent evidence suggests that the STN may serve an excitatory (glutamatergic) influence on the SNr and GPi[1,49].

Nigral Connections

The SN is comprised of a dorsal DA subdivision, the SNc, and a ventral GABAergic subdivision the SNr. The SNr receives projections from the subthalamic nucleus, from the

GPi, and from the striatum. The striatonigral pathway originates predominantly from the caudate nucleus and uses GABA. Other SN afferents include the motor and prefrontal cortex, amygdala, parafascicular nucleus of the thalamus, hypothalamus, lateral habenula, subthalamic nucleus, and midbrain dorsal raphe[36,88]. The nucleus accumbens projects only to the SNc.

The SNr projects to the midbrain and pontine central grey (peri-IV-ventricular), superior colliculus, several areas of the thalamus, and to the PPN. As previously mentioned, the SNr projects to VA, VL, MDmf, and IML (parafascicular nucleus) of the thalamus[98]. The MDmf and IML then project to the FEF and thus probably affect FEF function[63]. Other SNr efferents project to the amygdala, olfactory bulb, subthalamus, tegmentum, the pallidum, and the striatum[71,98].

The nigrostriatal pathway, the principal efferent system of the SNc, originates from the SNc and utilizes the neurotransmitter dopamine[13]. Unlike the extensive projections of the SNr, the SNc projects only to the head of the caudate nucleus and the caudal two-thirds of the putamen[81].

FUNCTIONAL NEUROANATOMY OF THE BASAL GANGLIA

The inhibitory outflow of the basal ganglia is controlled by "two opposing but parallel pathways"[2]. The first to be described is the direct or primary pathway through the basal ganglia. As previously discussed, glutamatergic excitatory projections from the cerebral cortex terminate in the striatum. The striatal efferents contain GABA and Substance P, project to the GPi and SNr, and have an inhibitory effect on these two target structures[1,35]. The VA and VL nuclei of the thalamus receive GABAergic pallidothalamic and nigrothalamic efferents from the GPi and SNr. Thus, the striatum acts to disinhibit the thalamus by inhibiting the inhibitory pallidothalamic and nigrothalamic systems[21,26]. The projections from the thalamus back to the cerebral cortex (thalamocorticals) are thought to be glutamatergic, and therefore excitatory. GABAergic striatal efferents also project to the GPe. The GPe projects to the subthalamic nucleus. The GPe has a high spontaneous discharge rate and consequently exerts a persistent inhibitory effect on the subthalamic nucleus[2]. Subthalamic efferents, which are excitatory and glutamatergic project to the GPi and SNr. Output from the

striatum will disinhibit the excitatory output of the subthalamic nucleus. While the direct striato-pallido-thalamic circuit has a net excitatory effect on the thalamus, the indirect subthalamic circuit results in excitation of the GPi and SNr, and thus, inhibition of the thalamus. While, on the other hand, striatal efferents, by disinhibiting the thalamus, actually facilitate cortical excitation[2]. There are a number of possible reasons for pathways with opposing net effects. One speculates that the indirect pathway acts to dampen the information relayed back to the cortex. Another proposes that input may terminate on separate neurons in the GPi and SNr, and as a result, selected patterns are reinforced, while interfering transmissions may be suppressed[2].

The role of the dopaminergic nigrostriatal pathway in the synaptic milieu of the striatum and ultimately in the framework of connectivity of the basal ganglia is unclear. It seems plausible that dopamine exerts an inhibitory effect on the indirect pathway, while enhancing the excitatory effects of the direct circuit[15,78]. As previously stated, the direct pathway through disinhibition has a net excitatory effect on the thalamus, while the indirect circuit acts to inhibit the thalamus. Consequently, the dopaminergic nigrostriatal pathway may enhance the inhibitory effects of the indirect circuit on the thalamus and also increase the excitatory effects of the direct pathway on the thalamus. In this way, the SNc may serve to reinforce a message

initiated by the cortex[2].

Parallel Pathways

Utilizing the principal circuitry of the basal ganglia, five functionally and structurally segregated cortico-striato-thalamo-cortical pathways operate to affect motor function[3]. Separate pathways allow multiple processes to occur concurrently within the basal ganglia. The pathways are maintained through a patch-matrix organization in the striatum which is laid down in the ontogeny of the nuclear complex. Cortical inputs project not only to specific pathways, but into different environments of co-existing neurotransmitters[34]. For example, corticostriatals to the matrix area are from cortical deep layers V and VI, while the patch compartments receive cortical afferents from superficial layer V and the supragranular layers[33]. Each pathway follows a unique route through the basal ganglia and thalamus. Information is then directed back primarily to a specific region in the frontal cortex.

The five circuits have been named according to their proposed function or cortical origin. They include: two prefrontal circuits, a limbic circuit, a motor circuit, and an oculomotor circuit. One of the prefrontal circuits is focused on the dorsolateral prefrontal cortex, and the other projects to the lateral orbitofrontal cortex. The limbic pathway terminates on the anterior cingulate and medial orbitofrontal cortex[2]. The motor circuit terminates in the precentral cortex, whereas the oculomotor circuit is

directed to the FEF and supplementary eye field (SEF), located in the dorsomedial frontal cortex adjacent to the supplementary motor area (SMA). The motor and oculomotor circuits require special attention in the context of the present study.

The Motor Circuit

The motor circuit illustrates the segregation within parallel circuits. Motor signals are altered in both Parkinson's and Huntington's diseases. The primary motor area, premotor cortex, (including the supplementary motor area, SMA and arcuate premotor area(APA)) and somatosensory cortex, project to the striatum, specifically, the putamen[89]. The somatotopic organization of the cortex is maintained within the basal ganglia motor circuit[80]. Efferents from the putamen project to the ventrolateral area of the medial segment of the globus pallidus (GPi-vl), the caudolateral portion of the substantia nigra pars reticulata (SNr-cl), and the GPe[71]. Areas of the thalamus receiving input are: the pars oralis of the VL (VLo), the pars parvocellularis of the VA (VApc), pars magnocellularis of the VA(VAmc), and the centromedian nucleus(CM)[45]. The Gpi projects to the VLo and VAmc, which in turn project to the supplementary motor area[71]. The VApc projects to the premotor cortex, and the CM and VLo project to the motor cortex[68,111].

Even though the circuitry maintains strict structural segregation, it is necessary to have some functional

integration. An example of such integration takes place in hand-eye coordination, and it is thought that this coordination may be attributed to "temporal coincidence" rather than structural integration. Temporal coincidence occurs when two signals are discharged concurrently or within a certain time frame and elicit a response.

Concerning limb and oculomotor movement, current evidence suggests that the basal ganglia aid not only in movement execution, but are somehow involved in the preparation of movement[2]. Recent studies demonstrate that there are changes in discharge rate in the precentral motor fields when an instructional stimulus concerning future directional limb movement is introduced[32]. It may be the basal ganglia which is involved in the preparation of movement through planned motor patterns.

The Oculomotor Circuit

In the oculomotor circuit through the basal ganglia, the FEF, the dorsolateral prefrontal cortex (dlPFC), SEF, posterior parietal cortex (PPC) and superior temporal sulcal cortex (MT/MST) all project to the caudate nucleus[71]. These cortical areas receive visual information through a complex system of sequential cortico cortical connections from the visual cortex[66,105]. The caudate nucleus receives cortical input from these associated areas[89], and projects to the caudal dorsomedial portion of the medial segment of the pallidum (GPi-cdm) and to the ventrolateral portion of the substantia nigra, pars reticulata (SNr-vl). The SNr-vl

projects to the VAmc and the paralamellar medialis dorsalis pars multiformis (MDmf) of the thalamus, which projects back in turn to the FEF and SEF as well as to the intermediate layer of the superior colliculus[71]. Both FEF and SC project to the brainstem saccadic generator. The FEF, whose neurons fire in relation to voluntary purposeful saccades, is considered to be the "principal oculomotor cortex" although there are also presaccadic neurons in the SEF which have comparably low thresholds (<10μa) for stimulation and produce saccadic eye movements. The dlPFC is thought to be related to learning and memory, particularly in spatial context. The PPC is concerned with visual attention. PPC cells respond if a monkey attends to a visual stimulus, even if a saccade is not produced to look at it[84]. The middle temporal (MT) and middle superior temporal (MST) visual areas are concerned with the analysis of visual motion which is essential to smooth pursuit eye movements.

Both SNr and caudate neurons respond to visual information and SNr neurons show activity preceding saccades. When SNr inhibitory nigrotectal neurons stop firing, it permits the deep layers of the superior colliculus to initiate saccades.

Some analogies may be drawn between the motor and oculomotor circuit in the basal ganglia. Both are involved in movement instruction and preparation. One major difference in programming strategies for movement is that the load on the eye is constant, and thus the force required

to move the eyeball is the same, whereas in limb movement, there is active and passive movement and varying loads.

EYE MOVEMENT

The five types of eye movements are: saccades, smooth pursuit, vestibulo-ocular reflex (VOR), optokinetic nystagmus (OKN), and vergence. These movements act to keep the image of the visual target focussed on the fovea of the retina.

Saccades are rapid eye movements which bring the object of visual attention to the fovea. They are arguably the only voluntary eye movements, although they may be generated spontaneously, evoked by visual or auditory stimuli, or triggered by memory. Smooth pursuit is a slow eye movement which is utilized to track a moving visual object. One can voluntarily follow or track a moving visual stimulus, but one cannot volitionally produce a pursuit movement in the absence of such a stimulus. Optokinetic or "railroad" nystagmus is a reflex which has components of both smooth pursuit (slow phase) and saccadic (quick phase) eye movements. As a body moves through space, the eyes will track an interesting object until it can no longer be seen, and then a saccade-like rapid eye movement returns eye position in a direction opposite of body movement. VORs compensate for head movements and thus are said to be

"compensatory." They stabilize the eye against changes in head or body position. When the head is turned, the eye will remained fixed on an object. The VOR is suppressed in the case of smooth pursuit during movement of the head. Vergence allows binocular vision by allowing the eyes to focus in conjunction with each other on near objects. When an object approaches, the eyes converge; when the object recedes, the eyes actively diverge.

Saccadic Mechanisms

Rapid eye movements include saccades and the quick phase of optokinetic nystagmus. Saccades have a high velocity to minimize blurring of the visual field. The amplitude of the saccade is directly proportional to the discharge rate of the motor neurons innervating the extraocular muscle. There are three general classifications of saccades: voluntary purposeful, memory-related, and spontaneous.

Visual information reaches the primary visual cortex, and through sequential cortico-cortical pathways reaches posterior parietal areas concerned with visual attention[66,105]. From there, saccade-related data is conveyed to the FEF and SEF which orchestrate eye movements appropriate to look at an object attracting attention. Saccadic eye movements are generated from burst neurons located in the caudal pontine and rostral mesencephalic brainstem. Visual information reaches the brainstem saccadic generator (BSG) either by cortical connections to

the FEF and then by direct FEF projections or via the superior colliculus.

The FEF and SEF project directly to the BSG in the PPRF and riMLF, and these projections are bilatera[43,57,90,96]. Initiation of saccades occurs in the caudal pontine and rostral mesencephalic brainstem. Specifically, the PPRF contains burst neurons for horizontal saccades, and the rostral interstitial nucleus of the medial longitudinal fasiculus (riMLF) contains burst neurons for vertical saccades. The PPRF is located in the pontine tegmentum at the level of the abducens nucleus on either side of the midline. Its afferents originate primarily from the FEF, the SC, and the vestibular complex[87]. Internuclear neurons in the ipsilateral abducens nucleus project to the contralateral medial rectus motor neurons in the oculomotor nucleus. The PPRF also projects to the riMLF, the center for vertical saccades in the rostral mesencephalic reticular formation, and is believed to link the two areas and thus coordinate horizontal and vertical saccades[87]. Bilateral lesions of the PPRF therefore understandably produce an omnidirectional ophthalmoplegia[11]. This direct pathway from the FEF and SEF to the BSG involves initiation of voluntary saccades and concurrent suppression of visually evoked saccades[59].

In the saccadic system, there are therefore two routes of access to the BSG, either directly from the FEF (SEF) or from the SC. The FEF and SEF are the only cortical areas

known to project directly to the BSG. All other non-frontal posterior cortical regions can affect the BSG only by projections to the FEF or SC; in other words they lack any direct projections to the BSG[46]. The FEF and SEF project to the superior colliculus by direct and indirect projections[5,43,52,58,96]. The indirect projections course via the cortico-striato-nigro-tectal system which traverses the basal ganglia. The collicular afferents from the SNr project to the intermediate and deep layers of the superior colliculus. Visual information reaches the superficial layer of the SC both directly (from the retina) and indirectly from prestriate visual cortical areas. Recent findings indicate that the superficial layer of the colliculus communicates with the ipsilateral deep layers, and they may be topographically arranged[10]. The superior colliculus has a number of efferents through which it can initiate responses to visual or FEF input. One which is relevant to our discussion projects contralaterally to the paramedian pontine reticular formation (PPRF)[87]. The intermediate layer projects to the contralateral PPRF, while the deep layer projects to the ipsilateral PPRF[87].

As previously mentioned, the FEF also affects saccadic eye movement mechanisms via the cortico-striato-nigro-tectal system. The caudate nucleus receives cortical projections from the FEF, the principal sulcus (PS) cortex of the dorsolateral PFC[40], and the posterior parietal cortex[36]. The caudate projects in turn, through GABAergic inhibitory

striatonigral projections to the SNr. The SNr then projects via inhibitory GABAergic connections to the intermediate layer of the SC.

During saccadic initiation, the GABAergic striatonigral caudate neurons show an increase in discharge rate, which then disinhibits the GABAergic nigrotectal projection from the SNr to the intermediate layers of the colliculus allowing saccades to occur[117]. Having a high rate of neuronal discharge and an inhibitory neurotransmitter, the SNr normally exerts tonic inhibition on the SC[40]. The current view holds that the caudate nucleus initiates memory-driven saccades through the disinhibition of the colliculus[40]. In visually evoked saccades (VES), the discharge rate decreases in the SNr prior to and during saccades, whereas in the SC the number of spikes increases[40]. In the absence of light, the SNr discharge rate remains constant, but collicular neurons burst as they had during a visually induced saccade[40].

Located primarily in the lateral portion of the SNr, the nigrotectal neurons related to eye movement, are capable of eliciting multiple responses and at least ten different signals have been recorded in the SNr[8,31,41]. However, in response to nigral input, collicular discharge is almost uniform for all saccades except spontaneous saccades, which originate in the supplementary eye field[40,86]. Combinations of collicular inputs are what define the motor signal. Complementing FEF input to the intermediate layers of the

SC, the retina (via optic tract) and visual cortex project to the superficial layer of the SC. Although saccades can obviously be triggered by visual stimuli, recent evidence has shown that they are also initiated in response to visual, auditory, vestibular, or memory-related information[40].

The SC projects to both the vertical saccade generator in the rostral mesencephalic reticular formation (rostral iMLF) and the horizontal saccade generator in the paramedian pontine reticular formation. These preoculomotor regions of the reticular formation contain four neuronal cell types: burst, tonic, burst-tonic, and pause cells. Burst cells discharge during voluntary saccades or saccades made in response to a stimulus. They do not fire during spontaneous saccades[83]. Tonic neurons fire constantly in association with steady fixation. The rate does not change during saccadic eye movement. Burst-tonic cells fire constantly during fixation and will also burst during a horizontal saccade. Pause neurons fire constantly, and are believed to inhibit burst cells, as they do not fire, but pause during saccades[83].

Medium lead burst neurons in the riMLF and PPRF fire in closest proximity to the discharge of the motoneurons in the oculomotor, trochlear, and abducens nuclei and are believed to be the premotor cells that signal the initiation of eye movements. Should the basal ganglia (eg. SNr) exert influence on the saccadic system, it occurs either through

the influence of striato-pallido-thalamic circuits on the ipsilateral FEF or SEF, or via nigrotectal projections from the SNr to the SC and then in turn to the saccade generators in the riMLF and the PPRF. The SNr projects to the ventral anterior thalamus, the VAmc and MDmf. VAmc and MDmf project to cortical areas involved in eye movement (SEF and FEF). The role of the thalamocortical pathway in eye movement is not well understood.

The posterior eye field, located in the posterior parietal cortex primarily in the caudal (lateral) bank of the intraparietal sulcus (LIP), is concerned with visual attention[4]. Neurons in the PPC are active if the subject "attends to" a visual stimulus even in the absence of a saccade to "look at" the stimulus[19]. LIP projects to both the FEF and SC and thus accesses the saccadic system through either of these structures[64]. The PPC only accesses the saccadic system through the FEF or SC. Bilateral lesions of the SC completely disrupt the ability of PPC stimulation to produce a saccade[47].

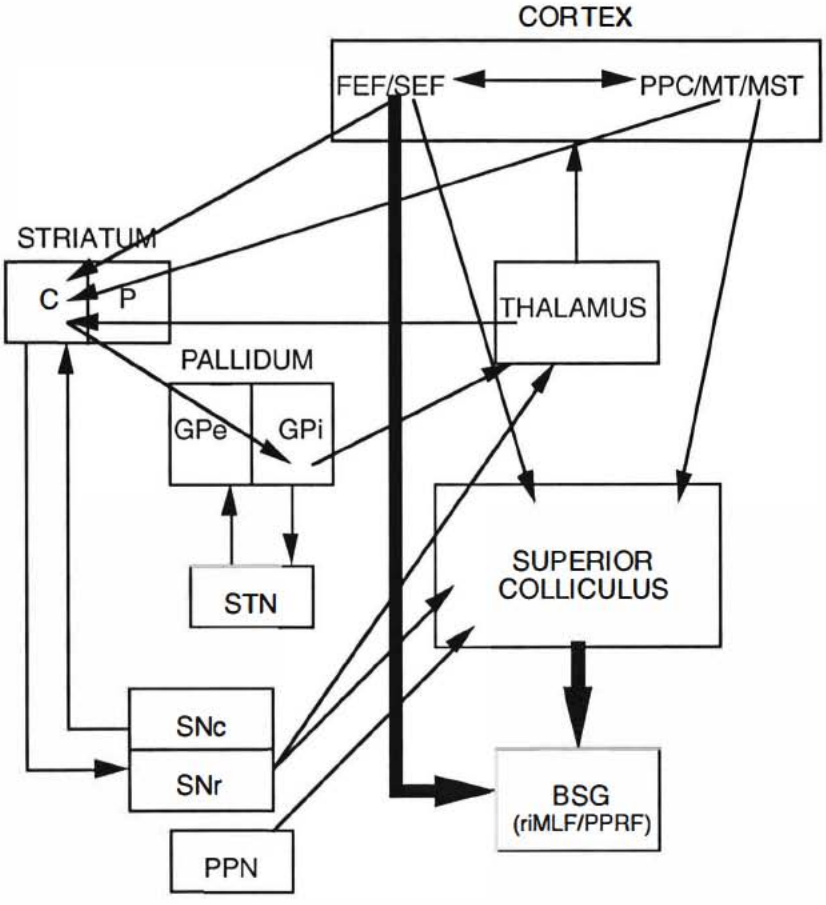
CORTEX
FEF/SEF
PPC/MT/MST
STRIATUM
C
P
THALAMUS
PALLIDUM
GPe
GPi
STN
SUPERIOR
COLLICULUS
SNc
SNr
BSG
(riMLF/PPRF)
PPN

Figure 1.

Initiation of Smooth Pursuit

Slow eye movements include smooth pursuit, the slow phase of optokinetic nystagmus, the vestibulo-ocular reflex, and vergence. Smooth pursuit movements are used to track a moving visual stimulus and consequently focus the fovea on the target. The smooth pursuit system may be engaged when a stimulus passes over the foveal field.

Since tracking is an essential component of pursuit, one must be able to match eye velocity to target velocity. This requires ongoing analysis of the moving visual stimulus and a constant awareness of eye position. Visual information is conveyed through sequential cortico-cortical connections from the primary visual area to ipsilateral area MT (middle temporal area). MT projects to MST (middle superior temporal area) in the prestriate cortex caudal to the superior temporal sulcus[104]. Area MT also projects to the lateral (LPN) and dorsolateral pontine nuclei (DLPN) in the brainstem, contralateral areas MT and MST, all layers of the SC, and the caudate nucleus[102]. It is this projection to the caudate nucleus which associates the smooth pursuit system with the basal ganglia. Area MST also projects to the DLPN and LPN and to the lateral terminal nucleus (LTN), also a brainstem structure an associated with the accessory optic system[102]. A third efferent pathway of area MST projects to the adjacent posterior parietal cortex (PPC)[102].

MT and MST are concerned with the analysis of visual motion[16,51]. Cortical area MT appraises visual information.

Area MT projects to the fundus of the superior temporal visual areas (FST), which in turn projects to the FEF[16,56]. Areas MT and MST have reciprocal connections with the FEF, and the FEF is also known to play a role in smooth pursuit[17,29,62,65]. FEF, MT, and MST project to the DLPN which is a precerebellar structure that links the cerebellar flocculus to pursuit eye movements[56,76,99,103].

Since there needs to be constant monitoring of the movement of the visual stimulus across the field of vision to generate appropriate velocity, there must be visual input (motion of visual stimulus) that reaches the cerebellum. This occurs via MT/MST projections to DLPN. Information from the PEF and other prestriate (preoccipital) cortical regions project to the DLPN which projects in turn to the cerebellum.

There is now convincing evidence that the ventral (lateral) portion of the FEF also participates in the generation of smooth pursuit movements. This region furthermore is distinct from the saccadic area[65,67]. The inferior portion of the FEF, where activity related to smooth pursuit is recorded also, projects to the DLPN[56]. Following ablation of the FEF, saccadic dysfunction is present as would be expected, but there is also a deficit in both vertical and horizontal smooth pursuit movements. The saccadic response remains relatively unaffected, and interestingly, in the absence of smooth pursuit, the eye moves in short staircase saccades[67]. In the case of a

bilateral FEF lesion, smooth pursuit recovers over time. If the FEF is lesioned unilaterally, smooth pursuit is affected bilaterally and in both directions. A unilateral lesion of the pontine nuclei also affects smooth pursuit bilaterally, while ablating the posterior hemisphere affects smooth pursuit unilaterally[29,46].

The ventral area of the arcuate sulcus is topographically organized. Stimulation of this zone elicits a smooth pursuit movement ipsilateral to the stimulated side. This contrasts with initiation of voluntary purposeful saccades, which are contralateral when the FEF is stimulated. There is evidence that the frontal lobe participates in both saccadic and pursuit mechanisms in humans. In frontal lobe pathologies such as schizophrenia, for example, there are saccadic intrusions in smooth pursuit eye movements. The projections of the FEF on the SC directly, or via the basal ganglia, suppress saccades during smooth pursuit. If the FEF-collicular pathway (i.e. substantia nigra) is disrupted, this results in inappropriate disinhibtion of the SC, resulting in saccadic intrusions during smooth pursuit[61].

BASAL GANGLIA DISEASE: PARKINSON'S AND HUNTINGTON'S DISEASES

Parkinson's Disease

What oculomotor deficits are manifest as a result of Parkinson's disease, and why do they occur? The onset of Parkinson's disease usually occurs at fifty to sixty years of age. Parkinson's disease affects roughly 1:1000 of the adult population[20]. It may be postencephalitic, chemically-induced, or genetic. Affected individuals may exhibit a loss of facial expression or a masked face. Other symptoms may include depression, flat mood, loss of cognition, and dementia. Common signs include tremor, postural rigidity and instability, bradykinesia or akinesia, and hypokinesia. Hypokinesia is an overall decrease in the degree of motor activity. Simple and predictive movements are affected. Bradykinesia retards the execution and initiation of movement. Akinesia, a more severe motor dysfunction, approaches the complete absence of movement. One of the most characteristic symptoms of Parkinson's disease is resting tremor. It is interesting to note that this makes oculomotor measurement difficult, since instability of the head generates compensatory vestibular-induced eye movements.

The most obvious pathologic feature of Parkinson's disease is neuronal cell death and the loss of dopamine in the nigrostriatal pathway. The neurological symptoms do not become manifest until later stages of the disease, where SN cell loss is evident, and when degeneration of the dopaminergic nigrostriatal pathway is nearly complete.

The affected dopaminergic neurons may have a direct or indirect effect on other brain areas. Other pathways disrupted by Parkinson's are the mesolimbic DA projections to the basal forebrain (especially the nucleus accumbens) and mesocortical dopaminergic projections to the prefrontal cortex, an overall loss of norepinephrine, and cortical cholinergic deficiency and concomitant mood disruptions (depression)[67].

Akinesia in Parkinson's disease may be due to augmented stratopallidal activity which causes increased excitatory subthalamic activity, resulting in reduced thalamic output, and ultimately distorted movement[33]. Current findings suggest that the tonic inhibitory GABAergic striatal output is decreased in Parkinson's disease. Excitatory cortical glutamatergic input synapses on the heads of spines of striatopallidal and striatonigral neurons. The nigrostriatals, on the other hand, synapse on the necks of the spines of these striatal neurons, suggesting that the SNc has a modulatory influence over both GABAergic components of the striatum[72]. Dopamine reduces tonic striatal discharge, causing a decreased response of striatal

neurons to cortical input[71]. Specifically, responsiveness and amplitude are decreased by normal dopamine modulation. When dopamine is absent, as is the case in Parkinson's disease, the tonic discharge rate of the striatum increases, resulting in increased sensitivity to other inputs[71]. In Parkinson's disease, the GPi shows an increase in tonic discharge, while the GPe exhibits a decreased discharge rate. Thus, thalamic output from pallido-recipient nuclei (i.e. VA/VL; IML/MDmf) is altered, and consequently cortical activity, is altered. Both the SMA of the motor circuit and the FEF of the oculomotor circuit are therefore affected.

Oculomotor Deficits in Parkinson's Disease

Several eye movement deficits have been observed in Parkinson's disease. In general, saccadic velocity is slowed, the latency between saccades increases, and saccades may be dyskinetic, usually hypometric, with the presence of staircase saccades. The saccade refractory period, or the time required between saccades also increases[109]. Parkinsonian individuals show a decreased number of spontaneous saccades. Square wave jerks are often found in Parkinson's disease[109]. Saccadic impairment increases as the disease progresses. Smooth pursuit eye movements and the VOR are also impaired[110]. Parkinsonian patients also often demonstrate excessive blinking.

Saccadic Velocity

The velocity of saccades is slowed in Parkinson's disease. The larger the amplitude of the saccade, the

slower the velocity, insinuating that the association between amplitude and velocity is disrupted[71]. Overall, saccadic velocity is slowed. It is important to note, however, that the degree of saccadic velocity reduction is highly varied in patients selected by similar age and stage of the disease[109].

Dyskinetic Saccades

Parkinsonian patients exhibit dyskinetic saccades. The saccades are hypometric, or fall short of their proposed target. The initial saccade is followed by one or multiple staircase saccades. The corrective time falls within normal range, but results are highly varied[109].

Square Wave Jerks

Parkinsonian patients often present with an inordinate number of horizontal square wave jerks[38,109]. A square wave jerk is a saccade made to a target, followed by a saccade back to the initial position. They may occur during both fixation and smooth pursuit[109].

Saccadic Delay

The latency between saccades is increased, especially when the preceding fixation time is reduced[109]. White et al. (1983) found that anticipatory eye movements are not affected in Parkinson's disease, whereas predictive limb movements are disrupted. It is the unpredicted saccades which show increased reaction time. Difficulty in saccadic initiation may be due to excessive nigral inhibition from the striatum or the inability of the SNr to disinhibit the

SC. Since the SNc may impose a regulatory effect on GABAergic striatal output[50,82], the regulation of striatal output is altered in Parkinsonism and, as a result, the SNr cannot effectively disinhibit the SC[40]. Conversely, the SNr may hyper-inhibit the SC by the failure of striatonigral neurons to inhibit nigrotectal neurons[108]. The dopaminergic nigrostriatal neurons also reflect the increased activity of striatopallidal neurons projecting from the striatum to the GPe, while neurons to the GPi exhibit decreased activity. This results in increased inhibition of thalamocorticals[1].

Disruption of oculomotor information from the FEF to the BSG in Parkinson's disease has already been discussed. It appears that the FEF itself is also affected. The FEF, paralamellar mediodorsal thalamus(MDmf), and SNc show decreased glucose levels in non-human primates treated with MPTP[42](an experimental procedure that mimics Parkinson's disease). Reduced glucose level is present in areas where there is a lower rate of energy metabolism, indicating an area of dysfunction. How does the SNc affect the FEF? The SNc interferes with the SNr, which has projections to the MDmf. The MDmf in turn projects to the FEF[52]. The aforementioned areas are the only loci in the oculomotor system which show a reduced glucose level. The nigrocollicular pathway shows no change in glucose level[42].

Smooth Pursuit Impairment

Although the smooth pursuit system does not appear at superficial examination to be directly related to the basal

ganglia. Even so, smooth pursuit eye movements exhibit decreased gain in Parkinsonian patients[48,110]. Since investigators have recorded pursuit-related activity in the FEF[17,62,65] and MS/MST[29], it is possible that it is through the FEF or MT/MST and their striatal (caudate) connections that the smooth pursuit system is somehow involved. Interestingly, some patients track near unity if the head is stabilized, but not when the head was not fixed. With the head free, patients show difficulty in VOR suppression[110]. Saccadic intrusions often occur during smooth pursuit movements in Parkinson's disease[48].

The VOR is also affected by Parkinson's disease. Visual and voluntary suppression and voluntary facilitation are affected. The impaired basal ganglia affects the VOR reflex arc of the brainstem[71]. When Parkinsonian patients show an impaired VOR in the dark, compensatory eye movements (CEM) are also abnormal[110]. CEMs are movements that stabilize gaze during head movement. CEM results are varied from zero gain to gain above that in normal patients[110].

Oculomotor Deficits Vs. Skeletomotor Deficits

Oculomotor deficits in Parkinson's disease bear some resemblance to Parkinsonian skeletomotor disturbances. These similarities point to a common origin of dysfunction. Skeletal movement in Parkinsonian patients is usually termed bradykinetic or akinetic, and eye movements are consistent with this description. It takes longer to initiate an eye movement and the velocity is decreased as compared with

unaffected patients[101,110]. Also consistent with skeletal deficits, saccades may be dyskinetic such that the fovea misses the target due to affected target accuracy. Following an inaccurate saccade, hypometric or "staircase" saccades occur to direct the fovea to the target[101,110]. Though there are many similarities in dysfunction, one critical difference lies in the circuitry. As previously stated, the motor circuit is directed to the supplemental motor area (SMA), while the oculomotor circuit is directed to the FEF and SC[71].

Parkinsonian patients retain the ability to differentiate direction and magnitude of movement, and they are sometimes able to execute normal movements, both oculomotor and skeletal. Bradykinesia may be due to a prolonged, but already present pause. Hypometric movements fall short of their targets, possibly due to overstated normal tendencies[24].

Drug Therapy

Parkinson's disease is usually treated with L-DOPA(L-dihydroxyphenylalanine), the precursor to dopamine in the catecholamine pathway. Replacing the striatal dopamine replenishes the dopaminergic nigrostriatal pathway. While bradykinesia, hypokinesia, and rigidity are ameliorated, the resting tremor is not significantly reduced[23].

When L-Dopa is administered to MPTP-treated monkeys, the glucose level in the FEF, the MDmf, and the pretectal area increases to levels above normal. This is believed to

be associated with the reestablishment of spontaneous saccades[42]. Highstein et al. (1969) found that accuracy and speed of saccades in Parkinsonian human patients improved after treatment with L-Dopa[39].

Recently, bromocriptine, a dopamine agonist, has been shown to improve parkinsonian impairments. During treatment with bromocriptine, the L-dopa dosage is decreased, and as a result there is a decrease in the adverse effects caused by L-dopa[100].

HUNTINGTON'S DISEASE

Huntington's disease is a hereditary neurodegenerative disorder. A gene on the short arm of chromosome four has been implicated as the cause of Huntington's disease. Huntington's disease is a progressive disease leading to debilitation and death over a roughly twenty year period. Less prevalent than Parkinson's disease, Huntington's disease strikes 1:20,000 of the population[73]. Symptoms include hyperkinetic activity, chorea, athetosis, oculomotor impairment, and dementia. Chorea is a term given to uncontrolled rapid flickering movements, while athetosis describes torpid writhing motions. The later stages of Huntington's disease are associated with dystonia, rigidity, and dysarthria, or the inability to speak properly. Seemingly random movements are probably normal movements initiated at innappropriate times[23]. There are several forms of Huntington's disease, occuring at different ages and having different symptoms. Some evidence suggests that antibodies may attack the host brain tissue, possibly leading to neurological degeneration as seen in Huntington's and Parkinson's disease[69].

In Huntington's disease, atrophy of the caudate

nucleus, particularly the dorsal medial area, is the first observable pathology[106]. The putamen is also affected soon after the caudate nucleus. Specifically, it is the loss of striatopallidal and striatonigral neurons in the striatum which are the most affected. The striatal atrophy is immediately followed by glial scarring. The cortex is apparently not affected by Huntington's disease, but pathology does reach the pallidum, the thalamus, and the cerebellum[106]. Loss of cognition, dementia, dyarthria, memory, and verbal learning are all early symptoms of Huntington's disease[113]. The deterioration of the putamen results in the progressive loss of motor function.

Overall metabolic rate in both the caudate nucleus and the putamen are reduced, whereas metabolism in the thalamus increases during Huntington's disease, as a result of disinhibition from the pallidum and SNr[113]. Interestingly, prior to the profound destruction of the caudate nucleus the basal ganglia show a decrease in the metabolic rate of glucose[113]. Huntington's chorea may be due to an overactive dopaminergic nigrostriatal pathway[95]. In post-mortem examinations of choreic brain, Spokes (1980) found irregularly high concentrations of dopamine in the striatum, the SNc, and the nucleus accumbens.

Oculomotor Deficits

Recent studies imply that oculomotor deficits and skeletal motor functions in Huntington's disease are

affected concurrently[22]. It seems that the later the onset of the disease, the less marked the oculomotor deficits[53]. Both rapid eye movements and slow movements are affected, but there have not been extensive quantitative studies involving slow eye movement. Affected oculomotor functions are saccades, steady fixation, and smooth pursuit, but deficits vary from case to case.

Saccadic Velocity

The velocity of saccades continues to decrease as the disease progresses, and in some advanced cases, patients are unable to initiate saccadic eye movements at all[22]. Conversely, a small percentage of Huntington's patients, even in advanced stages, show no oculomotor deficits[9,14,22]. The velocity of saccades is decreased in about eighty percent of patients with Huntington's disease. According to Bollen et al. (1986), saccadic velocity is slowed predominantly in the vertical direction[14]. Slowed vertical saccades include voluntary saccades (VOLS), visually evoked saccades (VES), and unsuppressed visually evoked saccades(UVERS). Of this sample, Bollen et al. (1986) report that roughly twenty five percent experienced decreased velocity saccades in the horizontal direction. Collewijn et al. (1988) verified decreased saccadic velocity, but could not demonstrate disproportionate saccadic slowing in the vertical as opposed to horizontal direction. Collewijn et al. (1988) argue that vertical saccades are demanding saccades to perform, even for normal

vision, thus it may be that more difficult saccades are affected first, but not selectively. Results by Beenen et al.(1986) show decreased saccadic velocity in the horizontal direction in seventy-five percent of cases studies. Two thirds of this sample presented with slow vertical saccades[9].

Dyskinetic Saccades

The notion that Huntington's disease affects the brainstem saccade generator is a recent hypothesis. Voluntary saccades and visually triggered reflex saccades are generated through separate input pathways from the FEF. A site common to initiation of both saccades is the brainstem saccade generator, insinuating a locus for dysfunction resulting from Huntington's disease[14]. Dysmetric saccades are present in roughly half of the Huntington's cases. They are always hypometric and are either in the vertical direction or occur in the vertical and horizontal direction[114]. The latencies of VES and UVES increases[114]. The results of Bollen et al. seem fairly consistent with the conclusions of Leigh et al., 1983. Leigh et al. concluded that the latency of saccades increases and velocity of saccades decreases. The inordinate number of UVES, as incurred in Huntington's patients, points to insufficient SNr-collicular inhibition[40,60]. Horizontal square wave jerks are present in most Huntington's patients. A few patients with horizontal square wave jerks may present vertical square wave jerks.

The saccadic phase of the optokinetic reflex is slowed as a result of Huntington's disease[60]. Oculomotor deficits are commonly marked by irrepressible saccades and square wave jerks. It is plausible that disinhibition of the SC allows excessive UVES and the occurence of square wave and macro-square-wave jerks[14].

Iterruption of Fixation and Other Types of Eye Movement

Steady fixation is dependent on the focussed attention of the subject. A patterned backdrop facilitates fixation in normal individuals, while Huntington's patients show difficulty maintaining steady fixation. Huntington's patients can fixate better on a single point of light compared with a patterned field. The inability to fixate is due in part to visually evoked saccadic intrusions[53,60]. Saccadic control is deteriorated[22].

According to Beenen et al. (1986), eighty-five percent of patients with slowed vertical saccades also present other eye movement deficits. Specifically, smooth pursuit and optokinetic nystagmus are also affected in Huntington's disease, but results are varied. Because dementia is manifest as a result of Huntington's disease, results may be skewed as experiments may be dependent on the participation of the patient. Beenen et al. (1986) report that vestibular nystagmus and gaze-evoked nystagmus are not affected by Huntington's disease.

Lasker et al. (1988) proposed that the severity of oculomotor deficits resulting from Huntington's disease may

be due in part to the age of the patient at the onset of the disease[53]. Lasker et al. (1988) suggest that the later the onset of Huntington's disease, the less saccadic dysfunction. Deficits in optokinetic nystagmus and smooth pursuit also appear to be age dependent[91].

THE INTERRELATIONSHIPS OF THE BASAL GANGLIA TO OCULOMOTOR DYSFUNCTION

The difficulty in studying basal ganglia disease comes in the varied and overlapping symptoms. There are at least three forms of Huntington's disease, each with its own age of onset, symptoms, and progression. They are: the childhood type, the juvenile type, and the rigid-akinetic type. Both Parkinson's and Huntington's diseases have varied symptoms. Oddly enough, symptoms of Parkinson's disease may present in a patient with Huntington's disease, and this overlap of symptoms demonstrates the interconnective nature of the basal ganglia probably related to their shared connectivity. For example, hypometric slow saccades typical of Parkinson's disease may be manifest in Huntington's disease[6,14,60]. Huntington's patients may also have difficulty in performing voluntary saccades, also a deficit normally found in Parkinson's disease (Leigh et al, 1983). Some Parkinsonian patients will exhibit deficits typical of Huntington's disease. For instance, square wave saccadic jerks have occurred as a result of Parkinson's disease, when there is evidence that they are caused by insufficient inhibition[40,110].

The net pathologies of Parkinson's and Huntington's diseases, may in some ways be regarded as opposite. Drugs that block the dopamine synthesis will induce Parkinson's disease, but will relieve the symptoms of Huntington's disease. Conversely, it seems that dopamine has the same net effect in regard to dyskinesia. Dyskinetic movements may present as a side effect in Parkinsonian patients treated with dopamine[23]. Simply put, Huntington's chorea may be caused by an overactive dopaminergic nigrostriatal pathway[95].

SUMMARY

In conclusion, a critical neurochemical balance exists between the nuclei and interconnections of the basal ganglia. When the balance between these nuclei(striatum, pallidum, subthalamus, and substantia nigra) is disrupted, either by loss of nigral neurons as in Parkinson's disease or atrophy of the striatum (caudate nucleus and putamen) as in Huntington's disease, the dysfunctional influence conveyed to the motor cortex via the thalamus or to the superior colliculus through the nigrotectal system, resulting in motor dysfunction and abnormalities in eye movement.

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