

Saccadic eye movements in Parkinson's disease

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This review focuses on saccadic eye movement research in Parkinson's disease (PD) patients. Results from various studies related to Parkinson disease and saccades have been discussed in terms of various saccadic parameters like latency, amplitude, velocity and gain. Neural circuitry of saccadic eye movements and cognitive processes and its relation with altered saccadic performance in Parkinson disease has been discussed here. This article also covers various research paradigms commonly used to study saccades. Effects of medication on saccadic parameters in PD patients have also been discussed along with the effects of deep brain stimulation of subthalamic nucleus on saccadic performance in PD patients. Literature review was done using online Pubmed search engine and National Medical Library.

Key words: Parkinson's disease, saccadic eye movements, deep brain stimulation, eye movement paradigm.

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Saccades are fast eye movements that are required to bring objects of interest on the fovea. Studying saccadic eye movements in clinical conditions like PD has become quite popular in recent times because of their potential abilities to give insights into the behaviour and impaired basic circuitry.^[1] Saccadic parameters are easy to measure, are reliable and reflect cortical and subcortical functioning in PD which can be correlated to disease onset and progression. Saccadic eye movements has also been studied in PD patients to get objective information on cognitive control of eye movements which further helps in understanding as to what aspects of cognitive processes influence eye movements in such patients. Neural circuitry of saccades is complicated and involves various cortical and subcortical structures. Great deal of study has been done to understand basic saccadic circuitry and impaired or abnormal circuitry in PD. Many saccadic paradigms have been administered to study saccadic eye movements in PD. These paradigms falls mainly under two categories of reflexive and voluntary saccades. There is vast progress in the treatment strategy for PD.^[2] Dopaminergic medication and deep brain stimulation (Neurosurgical approach) is current approach to treat PD. The effect of these approaches on saccadic eye movements in PD is reviewed briefly. Literature review was done using online Pubmed search engine and National Medical library.

Neural basis of saccadic eye movements

Lesion studies, neurophysiological, neuroanatomical and brain imaging studies have provided wealth of information on basic saccadic circuitry.^[3-10] Saccade preparation or planning, triggering, execution and other saccadic functions

are under control of distributed neural network involving cortical and subcortical structures. Subcortical structures like basal ganglia (BG), superior colliculus (SC), thalamus, brainstem and cerebellum and cortical structures like parietal and frontal cortices are major areas involved in saccadic eye movement [Fig. 1].

Brainstem pontine burst neurons (both inhibitory-IBNs and excitatory-EBNs, located in paramedian pontomedullary reticular formation or PPMRF and paramedian pontine reticular formation or PPPRF respectively) elicits saccades, which supply motor neurons (MN) innervating extraocular muscles. Burst activity of IBNs and EBNs are controlled by omnipause neurons (OPNs) which are present in medial pons. OPNs are inhibitory to burst neurons.^[6,11] In addition, there are other types of neurons in brainstem known as long-lead burst neurons (LLBNs) mainly concentrated in rostral pons, which are active during saccadic eye movements [Fig. 2a].^[6,11]

SC is the major brainstem saccadic centre in midbrain, which receives inputs from retina (Retino-tectal or Extrageniculate pathway) as well as from basal ganglia and cortex. It plays a major role in both fixation and saccadic eye movement.^[12-15] Neurons distributed in the intermediate layers in SC fire during and before saccadic movements.^[16-18] Neurons in rostro-lateral pole of SC are more active during fixation and stop firing during saccades and are modulated by other brain structures [Fig. 2b].^[13] Ablation of SC has been shown to impair saccade generation which recovers after some time but has lasting effects in terms of impairment of longer reaction times.^[19] Pontine burst cells are under the control of SC. Basal ganglia and frontal cortical areas also modulate saccade related neuronal activity in SC. In addition, Frontal cortical areas and cerebellum also directly influence pontine burst cells. In BG, caudate nucleus (CN), subthalamic nucleus (STN), substantia nigra pars reticulata (SNr), external segment of globus pallidus (GPe) and internal segment of globus pallidus (GPi) are major components involved in modulating saccadic movement.^[5,9,10,20] The main output structure of the BG circuitry is SNr which has inhibitory influence on SC through GABAergic neurons and it suppresses

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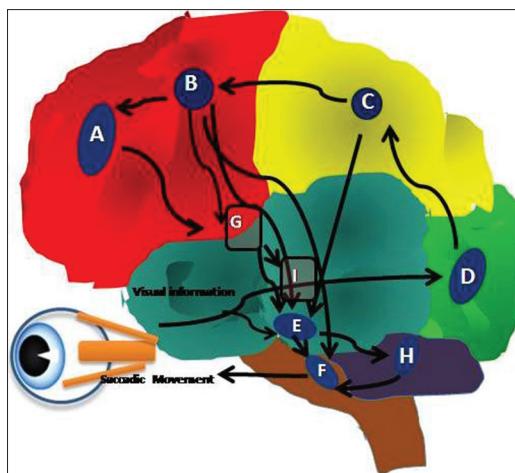


Figure 1: Schematic representation of basic saccadic circuitry. A: Dorsolateral Prefrontal Cortex (DLPFC); B: Frontal Eye Field (FEF); C: Parietal Eye Field (PEF); D: Visual Cortex; E: Superior Colliculus (SC); F: Brainstem saccade generators; G: Basal Ganglia (BG); H: Cerebellum; I: Thalamus

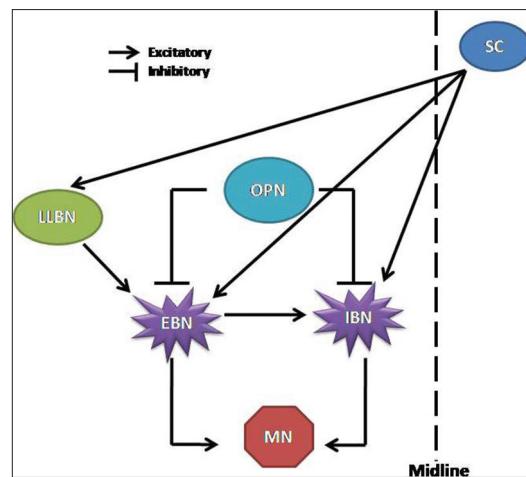


Figure 2a: Schematic representation of A: Brainstem saccade generators (LLBN: long lead burst neuron, OPN: Omnipause neuron, EBN: Excitatory burst neuron, IBN: Inhibitory burst neuron, MN: Motor neuron, SC: Superior Colliculus)

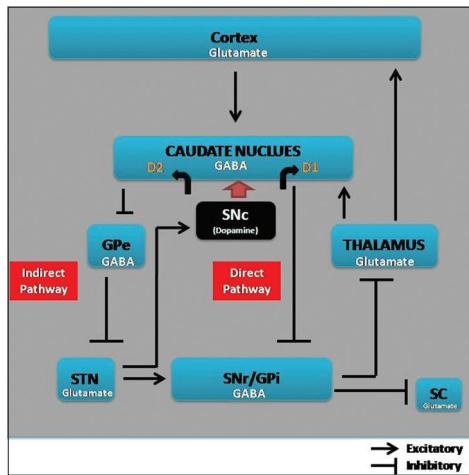


Figure 2b: Basal ganglia circuitry involved in saccadic control (D1 and D2 = Dopamine receptors)

saccadic initiation. Modulation of firing rates of SNr/GPi neurons facilitates or inhibits saccadic movement.

Cerebral Cortex plays a vital role in saccadic eye movements by projecting to BG, SC and directly to pontine burst cells. Cortical areas influence saccadic eye movements through projections to CN, which projects to downstream neural circuits via GABAergic projections. CN receives inputs from most of the cortical areas and thalamus. Through direct pathway, frontal cortex sends projections to CN, which directly projects to SNr, which is GABAergic and sends projections to SC and thalamus. Thalamus in turn projects back to cortical areas and thus activation of cortex leads to disinhibition of SC and thalamus via direct pathway. In the indirect pathway, CN projects to GPe which is GABAergic and GPe projects to STN which is excitatory in nature having glutamate as neurotransmitter which projects to SNr/GPi.^[20] Cortical activation increases the inhibitory activity of GPe and in turn causes more excitatory neuronal activity of STN, which further leads to inhibition of SC and thalamus. This inhibition of SC helps in the suppression

of saccadic eye movements. Modulation of neuronal activity of SC by cortical areas and BG circuitry leads to saccadic eye movements that depend upon the tasks demands. Since, BG circuitry and SC are under the influence of higher cortical centres, they play an important role in modulating saccadic activity [Fig. 2a]. Cerebral cortex also has a direct influence on saccadic eye movements in addition to influencing saccades through BG circuitry. Frontal eye field (FEF) participates in the production of saccades since micro stimulation of FEF at low intensity is known to elicit saccades.^[21] Additionally, reversible inactivation impaired saccadic production in monkeys.^[22,23] However, impairment of saccade production recovered with time when FEF was ablated.^[19] FEF is connected to various visual cortical areas and thus responds to visual stimuli. It projects to SC, BG and cerebellum. Because of this extensive network of FEF with different neural structures which are involved in saccade production, FEF modulates eye movements, depending upon the task demand. FEF is also known to be involved in selecting saccadic goals (Curtis *et al.*, 2006) and generation of reflexive saccades.^[24,25] As suggested by various lesion studies, electrophysiology, TMS and fMRI, SEF is involved in monitoring when subjects are performing saccadic tasks that involve saccadic sequences.^[26,27] Supplementary eye field (SEF) is connected to various cortical regions such as Dorsolateral prefrontal cortex (DLPFC), FEF and anterior cingulate cortex. PEF is involved in generation of reflexive saccade. This region is involved in attentional processes so it is considered that this area can be associated with saccade and shift of attention without saccade.^[28] DLPFC is involved in saccadic eye movements which require short term memory or working memory (memory guided saccades) and also in saccades that require decision making.^[29,30] Cerebellum is another brain structure which projects to brainstem saccade generators and is considered to be involved in maintaining saccadic accuracy.

Saccadic eye movements in Parkinson's disease

PD is a motor control disorder due to degeneration of dopaminergic neurons in the SNc leading to reduction in

dopamine levels. There is increased inhibitory output from BG, which affects thalamo-cortical circuits and SC, leading to motor symptoms like bradykinesia. As a consequence of the general impairment in the motor functions, eye movement impairments have also been reported in these patients.^[31,32] Different saccadic tasks like visually guided reflexive saccades, voluntary and memory guided saccades have been used to study eye movements in PD. Abnormal saccadic performance in PD is considered to be due to depletion of dopamine in the caudate nucleus. There is an overall increase in the inhibitory output to SC and thalamus due to increased activity in the indirect pathway leading to more excitatory activity of STN and a decreased activity in the direct pathway leading to increased inhibition of SNr/GPi.^[33,34] STN is one of the major sites for deep brain stimulation in PD patients. Many studies suggest that STN stimulation has positive effects on saccadic impairment, which is suggestive of DBS playing a critical role in maintaining a balance between information flow through direct and indirect pathway. These studies are discussed in a separate section in this review

Saccadic eye movement paradigms

Parkinson disease patients have been tested on reflexive saccadic task where participants fixate at a fixation point at the centre of the screen. Saccades are elicited when a sudden peripheral visual target is presented. In the Gap task, which is a variant of reflexive saccade task, there is a gap of 200ms between target appearance and disappearance of fixation point. Saslow showed a fixation offset effect wherein it was seen that saccadic latencies reduced when the fixation point was removed and a gap was introduced between target appearance and fixation point disappearance.^[35] In another variant of reflexive saccade, known as overlap task, fixation point remains when sudden peripheral target appears. Another saccadic task uses a cue to elicit saccades where it is presented before the target presentation and it indicates the spatial location of future target appearance [Fig. 3]. Posner showed that saccadic latencies reduce when the cue is presented before the target presentation. There is inhibition of return (IOR) effect in which saccadic latencies increase when the time gap between cue and target presentation is increased above 300ms [Fig. 4].^[36,37]

Memory guided saccadic tasks are saccades where subjects are supposed to make saccades to a previously remembered spatial location.^[38] Memory guided saccades are a measure of spatial working memory. Predictive saccadic eye movement tasks are used to access subject's ability to predict target appearance in terms of location and time. Antisaccades are voluntary saccades and widely used to access cognitive functions and inhibitory control in clinical conditions. In this saccadic task, subjects are instructed to inhibit saccades towards target and make saccades to a mirror location of the target that is in the opposite direction of the target [Fig. 5].^[39]

Saccadic performance in PD

Saccadic eye movements have been widely studied in patients with PD using various tasks. Different saccadic paradigms have been used to understand stages of information processing when subjects perform these tasks and how impaired circuitry manifests itself in behaviour in clinical conditions like PD. This section of the review discusses the studies in which saccadic eye movements in Parkinson disease patients have been observed and compared with age-matched controls. Different results

of saccadic performance of PD patients have been observed with no impairments in antisaccades but abnormalities in memory saccades where patients were tested on saccadic tasks.^[40] Briand and colleagues made PD patients and controls

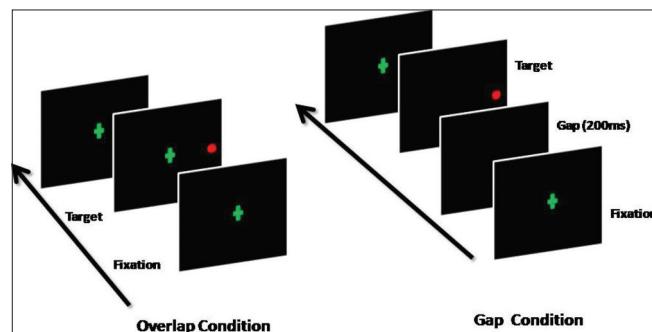


Figure 3: Schematic representation of reflexive visually guided saccadic paradigm with overlap and gap conditions. Fixation duration varies from 1000-3000 ms and target duration is around 1000 ms

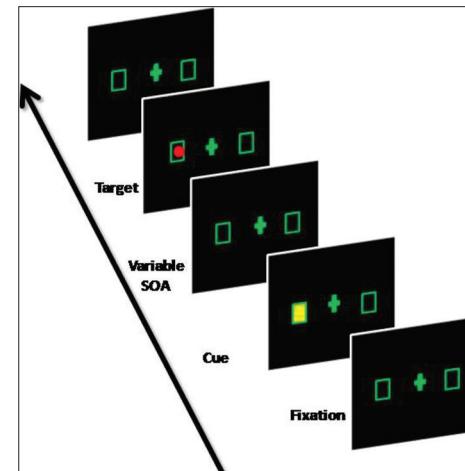


Figure 4: Schematic representation of Inhibition of return (IOR) paradigm. SOA represents stimulus onset asynchrony, which is time between cue (yellow box) and target presentation (red circle). Fixation duration varies from 1000-3000 ms and target duration is around 1000 ms

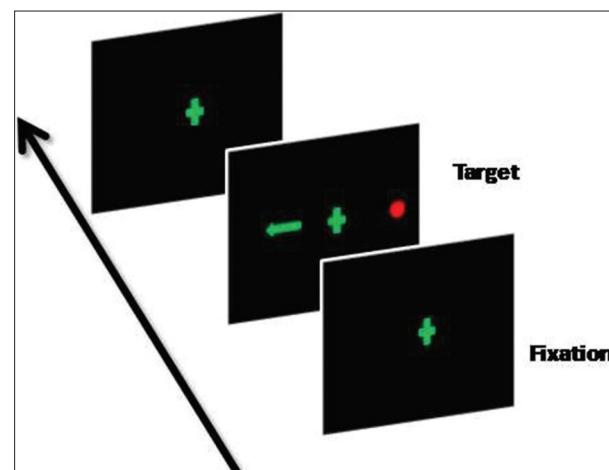


Figure 5: Schematic representation of antisaccade task. Green arrow represents spatial mirror image of the target where subjects are instructed to make saccade. Fixation duration varies from 1000-3000 ms and target duration is around 1000 ms

perform on reflexive and voluntary saccadic eye movement tasks. No saccadic impairment in reflexive saccades was found but impairment in voluntary saccadic eye movement tasks was observed. While performing antisaccade tasks, PD patients were found to be slow and made more errors. Gain (Ratio of subject's saccadic amplitude to desired saccadic amplitude) was also reduced in PD patients in these tasks.^[31] Segmented saccadic eye movements (Two steps) was used to measure performance of PD patients and the latency, amplitude was found similar to healthy controls which suggests that PD patients can generate multi saccades which are voluntary.^[41] When, moderate to advanced PD patients were investigated on visually guided and voluntary saccades where various parameters like latency, accuracy and peak velocity were determined, it was found that voluntary saccades were more impaired in advanced PD as compared to moderate PD.^[42] In one of the studies, PD patients made more directional errors in antisaccade tasks and memory guided tasks as compared to healthy subjects. They also had impairment in saccadic suppression.^[43] Differential results, where there was impairment in memory guided saccades, were found in short delays in PD patients but when delay was longer there was equivalent performance as controls.^[44] Results suggest that there are various aspects in impairment of memory guided saccades in PD which need to be carefully studied through further experiments. PD Patients are shown to have problems in inhibiting reflexive saccades suggesting executive control deficits in PD.^[45] A similar study has shown PD patients to be impaired on visually guided and memory guided saccades and also impaired in suppressing reflexive saccades.^[46]

Fixation offset effects have been measured in PD patients.^[47] Reduced latency due to fixation offset effect is considered to be mediated by higher order cognitive processes like attention.^[48-50] Fixation offset effect reduces in antisaccades as compared to prosaccades in healthy subjects. When fixation offset effect was measured in patients with PD, impaired cognitive control was reflected as fixation offset effect didn't reduce during antisaccades and more errors were made as compared to controls which is suggestive of impairment of executive control during saccadic eye movements in PD.

Some studies have shown abnormal facilitation of visually guided and voluntary saccadic eye movements in PD patients. Better performance by PD patients was observed on inhibition of return (IOR) task that involves saccadic elicitation in previously cued and uncued spatial locations.^[51] Similar facilitation has been shown where perceptual discrimination task was used to elicit saccades.^[52] Saccadic latencies reduced more in PD group in the perceptual discrimination task as compared to controls suggestive of hyperreflexivity in the PD group. Van Stockum and coworkers indicated that impairment of voluntary saccades in PD does not happen with reflexive saccade facilitation.^[53] PD patients who elicit reflexive saccades at shorter latencies perform similar to control subjects on voluntary saccade task suggesting that PD affects latencies, which is independent of the type of saccadic eye movements. PD patients were hypometric overall and latencies did not correlate with these hypometric saccades. In another study, authors have shown abnormal facilitation of voluntary saccades in perceptual discrimination task in patients with PD as compared to healthy controls.^[54] In saccadic eye movement tasks where subjects were asked to make saccades to a fixed

sequence of spatial locations, normal healthy subjects made saccades with shorter latencies because they started predicting spatial locations and execution of saccades took place before the target appearance. Performance of patients with PD in such saccadic tasks are reported to be impaired which reflects that they are not able to predict saccades.^[55-57]

Above-mentioned studies indicate an inconsistency in the results as far as performance of PD patients on saccadic tasks is considered. PD patients are impaired in saccadic eye movements as reflected from most of the studies but some studies also suggests performance equivalent to controls and sometimes even facilitation of saccades was observed in patients. Thus it is necessary that results should be interpreted in the light of impaired neural circuitry in PD, disease status and saccadic paradigm.

Effect of dopaminergic treatment on saccadic eye movements in PD

Various studies have been done to determine effect of medication on saccadic eye movements in patients with PD. It gives us an insight between the pathophysiology and functional impairments in PD. Corin and coworkers did not find much improvements in saccadic eye movements as only two patients out of twenty nine patients tested showed changes but there was a very poor response in terms of improvements in eye movement dysfunctions.^[58] Dopaminergic treatment improved eye movements in patients with PD in another study.^[59] This improvement was reflected in saccadic accuracy. Mean latencies of the saccades also reduced in this study but it didn't reach significance level. Improvement in saccadic amplitude has been reported where this improvement was seen after ninety minutes of medication.^[60] Saccadic latency improved mildly when tested after dopaminergic treatment but not to the significant level. There was no improvement in peak velocity. Nakamura and co-workers investigated twenty-four patients and found only one patient who had reduced saccade velocity and significant improvement in its oculomotor dysfunction after dopaminergic medication.^[61] Since, majority of the patients did not show any improvement on saccadic parameters, results are inconsistent when beneficial effect of medication on saccadic eye movements are to be considered. Step task saccadic paradigm with conditions of no gap or overlap was administered on twenty two PD patients.^[62] Results suggested increase in saccadic latencies which reflects that medication slowed patients with PD on saccadic tasks. Authors discussed their results in terms of neural decision making process considering LATER model^[63,64] for saccadic eye movements. It was suggested that increased saccadic latencies are due to increased threshold criterion level which is required to take decision for the eye movement. Similar results were reported where prolonged response time was observed when PD patients performed on reflexive saccadic task.^[65] Improvement in saccadic parameters after medication was reflected in reduced error rate when patient performed on voluntary saccadic task which in this case was antisaccade. It was suggested that medication (levodopa) helped patients to plan and execute eye movements better which is a reflection of improved impaired frontal-striatal circuitry involved in voluntary eye movements. Patients with PD were investigated on reflexive saccadic eye movement tasks where levodopa or dopaminergic treatment prolonged latencies and reduced peak saccadic velocity and enhanced hypometria.^[66] Authors

concluded that oculomotor activity in patients with PD gets worsened after medication.

Review of literature suggests beneficial effects of dopaminergic treatment on saccades in PD in addition to improvement in general motor movements but studies which report no beneficial effect of dopaminergic treatment on saccadic parameters like latency, amplitude and accuracy are also present. Further research is required to conclude what aspects of saccadic eye movements are affected by dopaminergic medication.

Deep brain stimulation and saccadic eye movements in PD

Deep Brain stimulation (DBS) has been reported to have many beneficial effects on the clinical symptoms like bradykinesia, tremors and rigidity of advanced Parkinson disease. Recently DBS has become a very effective and important tool in the treatment of patients with advanced Parkinson disease.^[67] In addition to alleviating the motor symptoms of PD, saccadic parameters have also been shown to be differently affected by deep brain stimulation.

Improvement in accuracy of memory guided saccades with Subthalamic (STN) bilateral stimulation has been reported.^[68] STN DBS did not improve performance of PD patients on visually guided saccadic task (Gap Task) and on the antisaccade task. This study suggests differential effect of DBS in eye movements in PD. In a case report, altered fixation stability in patients with PD with STNDBS was reported.^[69] Interruptive eye movements were detected when PD patients with STN DBS OFF condition were instructed to fixate at the fixation point. Such interruptive eye movements were higher in PD patients as compared to age matched control. Such movements were reduced when STN DBS was switched ON which reflects beneficial effects of deep brain stimulation in eye movements by modulating basal ganglia circuitry. Bilateral STN stimulation improving saccadic parameters in patients with PD has been observed.^[70] Saccadic latencies were reduced and amplitude was enhanced in the ON stimulation condition as compared to OFF condition. Results demonstrate that bilateral stimulation of STN improves saccadic parameters in patients with PD. Visually guided, memory guided and antisaccade task were used to measure performance of PD patients with bilateral STN stimulation on saccadic tasks by Fawcett and co-workers.^[71] They measured saccadic reaction time and gain and found that saccadic reaction time improved with STN DBS in visually guided saccadic task but not in memory and antisaccadic tasks. On the other hand, STN DBS improved the gain in memory guided and antisaccade tasks but not in visually guided saccades. In one of the electrooculogram (EOG) study, PD patients with bilateral STN stimulation were instructed to perform on two reflexive saccadic tasks and two volitional saccadic tasks.^[72] Reflexive saccades included a gap condition (GAP task) where target appeared after 200ms of fixation point disappearance and with a no Gap condition where target appeared simultaneously with fixation point disappearance. Volitional saccadic tasks included memory guided saccades and antisaccades. PD patients elicited saccades with longer latencies as compared to control subjects in both OFF and ON conditions but DBS significantly reduced saccadic latencies in these patients except for memory guided saccades. STN DBS improved the saccadic gain as compared to no stimulation (OFF condition) but still the patients were

hypometric as compared to healthy controls. One of the recent studies reported no beneficial effect of STN DBS on saccadic parameters in terms of latency and amplitude when patients with PD who have undergone STN DBS performed on visually guided saccadic task.^[73]

Most of the studies show improved performance in saccadic tasks by PD with STN DBS but as some studies have reported disparity in performance, further research is required with specific saccadic task modulation for better understanding of effect of DBS on eye movements.

Conclusion

Saccadic eye movement is a very important tool to study clinical populations where sensorimotor dysfunctions and cognitive impairments have been reported. It can help us in developing early biological markers for specific pathophysiological state as saccadic eye movement circuitry involves both cortical and subcortical brain areas and saccadic task manipulation gives an insight into the information processing in impaired brain. Reflexive and voluntary saccadic tasks provide specific information of brain functioning at different levels in PD. There are conflicting reports of impairment and abnormal facilitation of saccades in case of patients, which can be due to manipulation of saccadic task and disease state but research using saccadic eye movements as a tool in PD patients group has given us valuable information and has increased our understanding about brain functioning in this clinical condition. Effect of medication on saccadic eye movement in patients with PD is inconsistent, some showing beneficial effect and others showing worsening of saccadic parameters. There is need of change in strategy to evaluate effect of medication on saccades considering doses, disease stage and age of onset of the disease. Most of the studies show that STN deep brain stimulation improves saccadic eye movement parameters in patients with PD. Variable results have been found in terms of performance on different saccadic tasks, like visually guided and voluntary tasks, but some consistency in terms of beneficial effects has been observed in the literature.

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