Review Article

# State of the Art Technologies in Parkinson's Disease Management: A Review Article

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## ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative disorder that causes movement and behavioral problems. Pharmacological advancements for preventing disease progression have limited success for many PD patients; therefore, supportive care is necessary. The advancement of the digital world and the revolution of computerized applications pave the way for a better understanding of PD and inventing technological apparatus for helping PD patients to provide them a more normal life. In this review, the most recent technological advancements regarding the rehabilitation, monitoring, and early prognosis of PD are presented. Furthermore, the possible neurological mechanisms responsible for the positive effects of technological-based interventions are discussed.

## 1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects dopaminergic neurons of basal ganglia, mostly in substantia nigra. The standard medication for PD is levodopa (L-DOPA), which its carboxyl group is removed for synthesizing dopamine. The absence of dopamine produces several disorders, including motor and cognitive disabilities for PD patients. There is no definite cure for PD, and existing pharmacological treatments cause several side effects [1, 2]. As a complementary therapy for reducing the complications of PD and improving the quality of life, technological-based interventions and aiding devices are recommended. In this review, the recent advancements of technology for PD treatment and management are reviewed.

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## 2. Technological-Based Treatment Approaches for PD

### Deep Brain Stimulation (DBS)

One of the invasive procedures for treating movement disabilities of PD patients is Deep Brain Stimulation (DBS), in which the Globus Pallidus (GP) or Subthalamic Nucleus (STN) of the brain are stimulated externally by inserting an electrode into the brain target area [3]. Common stimulation strategy is monopolar impulse stimulation (2.5-3.5 V, 30-90 µs, 60-180 Hz) [4, 5]. The mechanisms behind DBS and its effects on brain activity are not well understood. However, some mechanisms have been proposed so far, including inhibition of neuron depolarization and synaptic activity, stimulation of afferent axons in the subthalamic nucleus, and disrupting of abnormal spike patterns in brain regions [3].

Recently, technological advancements have been utilized for improving the efficacy of DBS. Particular concentration has been focused on the design of electrode and implantable pulse generators and optimizing electrode insertion into the targeted areas of the brain. It seems that the shape of the electrical field affects the outcome of DBS. Wojtecki and Schnitzler used an electrode with several contact sites of interaction to simultaneously stimulate different anatomical regions with varying parameter sets [6]. Such a combined stimulation strategy resulted in greater PD symptom elimination. In addition, the problem of impedance change around the excitation site leads to variable steering of current to the targeted brain region. The multi-contact, constant-current DBS systems have been proposed, which shows considerable improvement for PD symptoms [7] without being affected by the variable impedance of surrounding tissue [8]. It is worth noting that constant-current stimulation technically provides a more accurate spread of electrical field compared with a voltage-controlled device [9]. Since several studies showed a wider therapeutic window for stimulating the brain with a shorter pulse duration [5, 10], the newly developed pulse generators for DBS can generate shorter pulses.

Another technological advancement in DBS is related to electrode placement procedure. While traditional DBS uses microelectrode recording with awake patients, recent technologies use combined imaging (CT plus MRI) and robotic devices with asleep patients [11]. Other methods such as scalp electric potential recordings [12] and photoacoustic and ultrasound imaging [13] have also been proposed.

### Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a technique in which the brain is exposed to an alternating magnetic field through specialized coils. After applying a magnetic field, according to Maxwell's equations, an electric field is induced in specific brain areas, which possibly affects the electrical activity of neurons. It was shown that TMS enhances tropomyosin-related kinase B (TrkB)/Brain Derived-Neurotrophic Factor (BDNF) signaling. The TrkB enzyme is an essential biomarker of brain plasticity, and its level is lower in PD patients than healthy individuals [14]. Repetitive TMS might affect the plasticity of cortical areas through the induction of long-term potentiation in the primary and supplementary motor cortex, the brain areas which show suppressed excitability for PD patients [14]. Studies show that high-frequency repeated TMS combined with aerobic exercise increased BDNF-TrkB signaling, even though the increase was not statistically different with the sham group (PD patients performed exercise without the stimulation with TMS). However, the cortical silent period was prolonged following the application of TMS [15].

It should be noted that some other studies report no significant effects for TMS in PD treatment. Fricke et al. hypothesized that stimulation of corticofugal neurons that connect the neocortex to the subcortical areas might affect the STN region. In this regard, they used TMS at the primary motor and dorsal premotor cortex; however, no significant effects were found in motor symptoms of PD patients [16]. To evaluate the efficacy of repetitive TMS for PD patients with depression, Hia-Jiato performed a meta-analysis. The results showed that TMS, when applied to the dorsolateral prefrontal cortex, could only improve depression, but no effect was found for motor functions [17].

### Transcranial Direct Current Stimulation (tDCS)

Transcranial Direct Current Stimulation (tDCS), i.e., the electrical stimulation of scalp with surface electrodes, combined with physical training, improves movement balance and gait of PD patients [18]. Fregni et al. evaluated the effect of tDCS on motor function and motor-evoked potential [19]. The obtained results showed that the stimulation of the primary motor cortex by an anodal tDCS improved motor functions significantly, while the cathodal stimulation did not show an improved effect. Improved movement function was correlated with increased motor-evoked potential amplitude and area [18]. Some other reported mechanisms responsible for observed effects of tDCS on PD patients are increased cortical excitability, modification of synaptic plasticity, increased calcium current [20], depolarization of cortical neuron's membrane, as well as their excitation [21], and expression of neurotrophic factors [22].

### MR-Guided Focused Ultrasound Surgery (MRgFUS)

MR-Guided Focused Ultrasound Surgery (MRgFUS) is a new strategy for treating PD in which several brain regions such as Ventral Intermediate Nucleus (VTM), STN, and GP are exposed to high intensity focused ultrasound guided by MRI [23, 24]. In case of tremor reduction, the thalamus is usually the target (thalamotomy); for dyskinesia, the GP (pallidotomy) or STN are suitable targets, and for akinesia, the pallidothalamic tract is the intended target. MRgFUS has some advantages compared with DBS, including non-invasiveness and single procedure treatment.

## 3. Aiding Devices for PD Patients

### Anti-tremor devices

Most PD patients have tremors in hands or legs, which are observed at rest for the early phase or at voluntary movements for the late phase. The PD patients usually have trouble with heavyweight utensils where lower velocity arm movement is observed for heavier objects [25]. Some manufacturers have designed devices such as spoons for PD patients to cancel out tremors actively. Such devices ease the eating procedure for PD individuals. Usually, these devices consist of several motion sensors (for example, accelerometers) that detect hand tremors in real-time and send the information to a digital controller, which drives some motors to compensate for the spoon vibration due to hand tremors [26]. The tremor direction can be estimated in two or three dimensions. Fraiwan et al. designed a self-stabilizing tray for PD patients to ease object delivery [27]. The design consisted of a base tray controlled through an inertia movement sensor. This controller unit transforms the positional data to related angles and some servo-motors to vibrate the base plate containing objects. The base plate vibration tried to compensate for the vibration produced by hand tremors. Tremors also deteriorate the ability to write in PD patients. In this regard, some researchers focused on designing devices for mitigating the effect of tremors on handwriting. A pen named Fleo was designed that works based on the gyroscopic principle. It uses a copper ring rotor attached to a motor that resists undesirable pen vibrations caused by hand tremors [28].

### Tremor reduction devices

The primary tremors in PD patients are usually observed at low (4-5 Hz) or high (8-10 Hz) frequencies during resting state and disappear after voluntary movements [29]. By the progress of PD, another type of tremor called action tremor appears, which manifests during voluntary activities [30]. Several studies have focussed on the design of useful devices for suppressing hand or leg tremors in PD patients. Some examples are a tuned vibration absorber based on biomechanical approaches [31] and the actuator for suppressing upper limb tremors using a magnetorheological fluid that its viscosity is controlled by a magnetic field [32]. Case et al. designed a magnetorheological fluid-based damper parallel to the forearm muscles. While the tremor suppression was excellent, the device also damped the voluntary movements [33]. Some other studies used pneumatic actuators for tremor suppression; however, the size and noise of this kind of actuator make them unsuitable for practical applications [34]. A GyroGlove was designed for stabilizing hand tremors according to mechanical roles. There is a spinning top for GyroGlove, which detects angular momentum and resists against exerted forces by tremors [35]. Since tremors are arises due to the incorrect signals sent to muscles, some innovations have focused on electrical stimulation of muscles for tremor suppression purposes [36, 37].

### Auditory aiding devices

Auditory cueing devices are among the options for managing movement freezing and gait disorders in PD patients. Auditory cueing uses external temporal auditory stimulus to facilitate the slow movement of PD patients. The mechanism behind such improvement of movement is not clearly understood; however, some hypothesis such as enhancement of internal rhythms of basal ganglia following the auditory stimulus has been proposed [38]. Research shows that increasing auditory cueing enhances walking speed and stride length of PD patients with natural step patterns. In contrast, its efficacy for PD patients with freezing of gait was not approved [39, 40]. Functional Magnetic Resonance Imaging (fMRI) studies reveal that the motor and auditory cortex of professional musicians reorganized compared with non-musician individuals. Furthermore, music and neurotransmitter and hormone levels correlate with music [41]. The brain circuit reorganization and hormone secretion due to music might be responsible for the positive effects of music on PD symptoms.

In addition, some PD patients show hypophonia and tend to speak softly. This event might occur due to the impairment of muscles that produce speech. A device called SpeechVive has been designed that uses the Lombard effect and helps people with hypophonia. The principle behind the Lombard effect is simple: the noisy condition forces the human to speak more loudly. In this regard, SpeechVive that is worn in the ear creates some level of noise during the speech period and in this way makes the individual speech loudly [42].

### Physiotherapy-based innovations

Studies show that physiotherapy interventions deliver short-term benefits for the balanced state and walking speed of PD patients [43]. The physiotherapy-induced exercise modulates the secretion level of several neurotransmitters, including dopamine, glutamate, serotonin, norepinephrine, and acetylcholine [44]. In addition, exercise may protect individuals from neurodegenerative disorders by enhancing brain connectivity [44]. The automatic and voluntary movements and also cognition are controlled through the Medium Spiny Neurons (MSN), which are an essential part of the cortical-striatal circuit. Dopamine D1 and D2 receptors (DA-D1R and DA-D2R) exist in MSNs and are involved in the motor learning process. According to animal studies, exercise may facilitate DA neurotransmission through the increased expression of DA-D2R proteins [44, 45]. Studies on animal models show that following a challenging exercise, DA release increases, while due to down-regulation of DA transporter, extracellular DA also increases [45]. In addition, the exercise shows some level of protection against neurotoxicity in dopaminergic neurons [46, 47].

Moderate exercise enhances the plasticity and action of the central nervous system, and the monoamine system plays a pivotal role in this effect [48]. The main monoamine transmitters in the brain include catecholamines and 5-Hydroxytryptamine (5-HT). After exercise, the expression of galanin is increased in locus coeruleus; consequently, noradrenergic neurons hyperpolarize, which prevents the firing of coeruleus and leads to the inhibition of norepinephrine. This process reduces the activity of the amygdala and frontal cortex that leads to a protective mechanism against stress [49-51]. The synthesis and secretion of 5-HT are highly dependent on exercise intensity [52].

Even though literature shows the positive effect of exercise and body activity for PD patients, most patients are reluctant to engage in such activities. Physiotherapy is a helpful therapy; however, the cost and necessity for an expert physiotherapist are some challenges. New computer-based strategies such as motion-based games and Virtual and Augmented Reality (VR and AR) approaches are promising options for compensating economic burden and motivating patients to engage in physiotherapy exercises [53].

### Motion-based games, virtual and augmented reality strategies for PD patient rehabilitation

Augmented Reality (AR) and Virtual Reality (VR) are two technological concepts that have gained increasing attention during the past decade. The VR paradigm suggests many opportunities for the rehabilitation of disabled people. VR aims to place disabled people in the virtual environment to encourage them to participate in a sport or game-based exercise [54]. In such a paradigm, it is possible to modify the patient's participation according to auditory or visual feedback. Among such rehabilitation systems are Interactive Rehabilitation Exercise systems (IREX) [55], PlayStation EyeToy, and WuppDi! [53]. The application of VR for improving postural control in PD patients [56] and quantification of motor dysfunction in PD patients [57] has been reported.

Because of the positive effects of music and rhythms for facilitating PD patient movement, music and rhythms are usually essential factors for designing suitable AR- and VR-based games [53]. The game level should be adjustable according to the patient's performance [58] and special attention should be paid to positive feedback to encourage PD patients to participate in the game [59].

### Application of art therapy for PD patients

The visuospatial functions affect several neurocognitive skills such as navigation, localization, and space orientation [60]. PD patients usually suffer from visuospatial disabilities. One proposed strategy for improving the visuospatial functions of PD patients is art therapy. Technological progress enables researchers to create a new concept in art therapy, i.e., digital or computerized art therapy, which obtains a new and more flexible perspective for rehabilitation [61]. The portability, versatility, and dissemination capability are among the advantages of digital art therapy approaches.

## 4. Application of Monitoring Systems for PD Patients

The most common sensors for movement assessment are optical motion sensors, gyroscope sensors, GPS sensors, accelerometers, magneto-resistive sensors, goniometers, force sensors, electromagnetic tracking systems, electromyography sensors, and inertial sensors [62, 63]. The optical motion sensor uses color cameras and analyzes a sequence of captured images or videos to calculate the foot joint position [64]. In accelerometer sensors, some piezoelectric or capacitive components are usually used to convert the sensor mechanical motions to suitable electrical signals. Gyroscopes measure the angular velocity of the limb, and magneto-resistive sensors access the orientation of the body segment compared with the vertical axis. Any change in the orientation of the magneto-resistive sensor deflects the current path through the sensor plate and leads to higher resistance against the base current [63]. The goniometers measure the relative rotation between two points, while such rotation can be calculated using different physical signals. The mechanical strains, changing inductive parameters between two points, or changing optical parameters following the rotation are the possible strategies to account for motion [63]. The electromagnetic tracking system consists of a 3D transmitter coil, magnetic-sensitive sensor, and some electronic devices for stimulating coils and capturing the produced electrical signal of the sensor. The sensor output is affected by its position and orientation against the magnetic coils [65]. In this way, any change of legs or feet where the sensor is attached can be detected. Force sensors usually measure the shear and compressive forces applied to the heel or toes during walking. Such forces can be estimated using different properties such as piezoelectric, capacitive, or photoelastic [63]. Another strategy for movement assessment is measuring and processing muscle activities using electromyography [66].

Patel et al. developed a home monitoring device using 8 accelerometers. The sensor data were sent to a remote site using web-based applications [67]. The acquired movement data after preprocessing were used to extract suitable features regarding the movement characteristics. In the final stage, the obtained features were fed to a classifier for distinguishing between different movements disorders. Bae et al. proposed a gait monitoring system using intelligent shoes equipped with pressure/force sensors. A microprocessor gait was evaluated, and visual feedback about the patient ground reaction force was given to the subject. The patient ground reaction force was compared with a normal pattern; therefore, a practice for gait rehabilitation could be performed [68, 69].

Almogren et al. proposed a telemonitoring system that incorporates several types of sensors, including voice, ECG, blood pressure, temperature, and accelerometer sensors for measuring vital signs, gait, and posture situation of PD patients [70]. The collected data were sent to a cloud server by a smartphone through the Internet or Wi-Fi. All processing steps were performed on the cloud side, and the results were sent back to the patient as feedback. The best location for gait detection sensors is the waist due to its proximity to the body center of gravity, and also, its use is more comfortable [71, 72]. Another problem that PD patients confront is the Freezing of Gait (FOG) when a considerable reduction of forward walking progression is observed. Borzi et al. developed a wearable unit to detect bradykinesia and FOG [73]. The device consisted of a collection of sensors, a microcontroller, a micro SD module, and a Bluetooth interface that could be employed on the waist or thigh of the patient.

By fabricating high performance, high speed, and light-weighted microprocessor units and digital devices from technological advancements, it is possible to have a portable device capable of performing sophisticated real-time analysis for movement processing. Several algorithms have been proposed to predict and detect FOG from gait analysis. These algorithms consist of statistical tests [74], neural networks [75], machine learning approaches [76], and classifiers such as support vector machines [71]. The classifiers are usually trained with labeled data determined by an expert [77].

Besides the motor symptoms of PD, technological advancements enable us to detect or monitor several non-motor and secondary symptoms. The swallowing problems with PD patients are usually diagnosed by esophageal high-resolution manometry that uses pressure sensors [78]. Two other methods for swallowing evaluation are the fiberoptic endoscopic evaluation of swallowing and the video-fluoroscopy swallowing study. The former consists of a flexible endoscope that is entered to the hypopharynx through the nose to give a live view of the pharynx, and the latter is an x-ray based tool that provides a visualization of the swallowing system during eating.

The clinically used approaches for diagnosing constipation of PD patients are using radiopaque materials followed by x-ray imaging, scintigraphic colonic transit test that uses radioisotopes and gamma-ray imaging, external electromyography of anal sphincter, and anorectal manometry [79].

The observed sleep disorders such as sleep time are diagnosed by multiple sleep latency tests [79]. Rapid eye movement, insomnia, and restless legs are usually monitored using video Polysomnography (v-PSG). For unusual sleep behavior disorders, v-PSG monitoring uses several sensors such as electrocardiogram, Electroencephalogram (EEG), electromyogram, electrooculogram, respiratory sensors, voice recorder, and video monitoring devices. There are other designed devices for monitoring sleep quality in PD patients, such as actigraphy (for measuring total sleep time, number of wake efforts) [80].

## 5. Technological Advancements for Early Detection and Prediction of PD

The degeneration of substantia nigra dopamine generating neurons is due to the accumulation of a family of α-synuclein proteins, known as Lewy bodies, inside those dopaminergic neurons. It is reported that α-synuclein in the cerebrospinal fluid is lower in PD patients [81]. In this regard, developing new α-synuclein-specific antibodies for the ELISA method is promising for the early detection of PD [82]. The α-synuclein level can be estimated by examining saliva, olfactory mucosa, submucosa of ascending colon, heart, and peripheral nervous system [83]. A novel strategy for α-synuclein detection includes nanoparticle-based biosensors [84]. Since PD patients compared with healthy subjects show decreased Dj-1 mutation [85], decreased uric acid level as a neuroprotective factor [86], and decreased apolipoprotein A-I in CSF [87], these factors can be considered early detection biomarkers for PD.

Doty et al. reported that the ability of PD patients to distinguish smells is relatively lower compared with healthy matched controls [88]. Furthermore, olfactory-evoked potentials show a delayed onset compared with a healthy matched group [28]. In this regard, tests for smell evaluation and analysis of olfactory data through EEG data or imaging modalities [89, 90] can be considered for early detection of PD.

Prediction of PD using analysis of body movement has attracted particular interest. PD affects several attributes of finger and hand movement; therefore, analysis of features such as reaction time and difficulty of performing movement action using machine learning approaches and data classification is helpful for PD detection and prediction purposes [91, 92].

Another altered movement following the PD is eye movement [93]. The rapid movement of eyes between two fixed points (or saccadic movement) is initiated by the caudate nucleus, part of basal ganglia [94]. PD patients confronted hypometric saccadic eye movements [95]. In this regard, saccadometer or eye-tracker systems may be considered diagnostic or prognostic tools [96]. Quantitative EEG measurement is a useful noninvasive tool for screening the cognitive states of PD patients since the power of EEG waves shows a significant correlation with cognitive impairment [97]. In addition, the spectral content of EEG changes as PD progresses so that the EEG wave of PD patients is dominated by more low-frequency content compared with healthy subjects. In addition, the background rhythm of EEG data can be a marker for the incidence of dementia in PD patients [98]. Beta-band phase and gamma-band amplitude correlation of PD patients and waveform shape of the beta band are also two other EEG-based factors that might help improve PD detection [99].

Another useful opportunity that high-performance digital computers provide is prediction models, constructed according to the extraction of useful information from extensive data that consequently are applied for the development of PD risk models [100]. An early sign of PD is the alteration in drawing ability, especially in the kinematics of handwriting [101], where the reduction in writing amplitude (or micrographia), increased stroke duration, reduced writing velocity, and fluency are observed [102]. Controlled trials show that intensive training could improve the writing ability of PD patients [103, 104]. Drawing skills are reflected in brain electrical activity. For example, it was shown that during a drawing task, the left hemisphere of artists was more activated compared with non-artists, while the activity of the frontal lobe of non-artists was dominant, possibly due to the learning process [105]. For both groups (artists and non-artists), drawing increased alpha rhythms of EEG waves, which indicates the relaxation state of the brain during drawing [105]. In addition, the functional Near-Infrared Spectroscopy (fNIRS)-based studies show that the drawing art increases blood flow at the medial prefrontal cortex, which might be due to the activation of a reward pathway [106]. In this regard, drawing can be a possible tool for the early diagnosis of PD.

The progression of PD deteriorates the vocal tracts and hence degrades the voice performance of patients [107]. Several studies have shown that the voice signal is a good candidate for separating PD patients from healthy individuals [108]. Besides the capability of voice signal for PD detection, voice processing using digital systems is a useful approach for PD progression anticipation due to the strong correlation between voice degradation and the PD stage [107]. Another marker for early prediction of PD is sleeping analysis, especially by analyzing Rapid Eye Movements (REM) and REM behavior disorder [109]. The application of high-technology imaging devices such as positron emission tomography [110] and MRI [111] is growing for detecting and early prediction of PD.

## 6. Conclusion

PD management strategies can be divided into distinct categories: diagnosis (before movement disorders manifestation), treatment (after motor or cognitive disabilities appear), and rehabilitation for mitigating disabilities. Furthermore, since most patients who develop PD are 60 years or older and may encounter other aging-related disabilities, monitoring their activities by technological-based innovations may be vital for their safety. In this review, state-of-the-art technological innovations for diagnostic, treatment, rehabilitation, and monitoring purposes for PD were reviewed. Most of the previous studies concentrated on particular aspects of PD management; however, the current research can be a comprehensive source regarding PD management. Furthermore, the information provided by this review can be considered by the neurologist to propose non-pharmacological interventions for PD management. This review provides new insights to physicians and neurologists for future clinical methods regarding PD diagnosis and rehabilitation.

## Ethical Considerations

### Compliance with ethical guidelines

This work was approved by the Research Ethics Committee, Hamadan University of Medical Sciences (Registration code: IR.UMSHA.REC.1399.071).

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### Authors' contributions

Conceptualization and Supervision: Sajjad Farashi; Methodology: Sajjad Farashi; Mohammad Rezaei; Investigation, Writing: All authors; Funding acquisition and Resources: Sajjad Farashi.

### Conflict of interest

The authors declared no conflict of interest.

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