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Can the Latest Computerized Technologies Revolutionize Conventional Assessment Tools and Therapies for a Neurological Disease? The Example of Parkinson's Disease

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Abstract

Dramatic breakthroughs in the treatment and assessment of neurological diseases are lacking. We believe that conventional methods have several limitations. Computerized technologies, including virtual reality, augmented reality, and robot assistant systems, are advancing at a rapid pace. In this study, we used Parkinson's disease (PD) as an example to elucidate how the latest computerized technologies can improve the diagnosis and treatment of neurological diseases. Dopaminergic medication and deep brain stimulation remain the most effective interventions for treating PD. Subjective scales, such as the Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr stage, are still the most widely used assessments. Wearable sensors, virtual reality, augmented reality, and robot assistant systems are increasingly being used for evaluation of patients with PD. The use of such computerized technologies can result in safe, objective, real-time behavioral assessments. Our experiences and understanding of PD have led us to believe that such technologies can provide real-time assessment, which will revolutionize the traditional assessment and treatment of PD. New technologies are desired that can revolutionize PD treatment and facilitate real-time adjustment of treatment based on motor fluctuations, such as telediagnosis systems and "smart treatment systems." The use of these technologies will substantially improve both the assessment and the treatment of neurological diseases before next-generation treatments, such as stem cell and genetic therapy, and next-generation assessments, can be clinically practiced, although the current level of artificial intelligence cannot replace the role of clinicians.

Key words: neurological diseases, Parkinson's disease, motor fluctuations, behavioral assessments, wearable device, augmented reality (AR)/virtual reality (VR), robot assistant system, rehabilitation

Introduction

Symptom assessment is imperative for the diagnosis and treatment of neurological diseases, not only in clinical practice,[1)] but also in bench studies.[2)] As a rule, it is mandatory to observe the severity of a neurological disease and assess the efficacy of a particular therapy by using an appropriate method. The National Institutes of Health Stroke Scale/Score for stroke, the Unified Parkinson's Disease Rating Scale (UPDRS) for Parkinson's disease (PD), the NIH Recurrent Glioblastoma Scale for glioma, the Seizure Severity Scale for epilepsy, and the Glasgow Coma Scale for the conscious state are some of the leading symptom assessment tools. Appropriate selection and application of these tools by clinicians (neurosurgeons and neurologists) is essential for precise diagnosis and effective treatment. Behavioral assessments focus on motor and neuropsychological performance. Recently, there have been rapid advances in computerized technology, including wearable devices, virtual reality (VR) and augmented reality (AR), mobile internet, and robot assistant systems.

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These new-generation assessment tools can produce real-time, programmable, and safe measurements of neurological deficits. It is debatable whether artificial intelligence (AI) can replace clinicians who can engage in comprehensive discussions with several people (e.g., a computer engineer or another clinician) with different perspectives. Therefore, we conducted a narrative review using PD as an example to elucidate how the latest computerized technologies affect the diagnosis and treatment of neurological diseases and to draw the attention of clinicians and engineers to the development of these techniques.

Since 1817, when PD was first reported by James Parkinson, the mechanisms of PD have been gradually elucidated from the genetic[3] and environmental[4] directions. The number of identified PD-related genes and proteins is increasing,[5] and the roles and mechanisms of dopamine,[6] alpha-synuclein,[7] and dopaminergic apoptosis [8] have been documented. However, there has been no dramatic breakthrough in the treatment and assessment of PD. Dopaminergic medications, such as levodopa (L-dopa), and deep brain stimulation (DBS) remain the most effective treatment modalities for PD. For evaluation of PD, the UPDRS and the Hoehn and Yahr (H&Y) stage remain the most widely used assessment methods.[1] These conventional treatments and assessments have major limitations, and their potential remains to be maximized before next-generation therapies become widely applicable in the clinical setting. Our experiences and understanding of PD have led us to believe that new technologies, such as wearable sensors, AR, and VR, can provide real-time, safe, objective assessments, which are crucial for the development of a precise real-time treatment system, telediagnosis, and rehabilitation for PD patients. These developments will revolutionize the traditional methods for the assessment and treatment of PD.

Main Limitations in Current Treatment Modalities and Assessment Tools for PD

Many efforts have been directed toward the development of next-generation therapies for PD.[9,10] These new treatments cannot yet be clinically utilized, and the current widely used treatments, dopaminergic medication and DBS, are far from satisfactory. The therapeutic parameters of conventional medications and DBS cannot be adjusted in real-time according to symptom fluctuations; this may cause overdose of dopaminergic agents or extreme intensity of the stimulating current in DBS. Moreover, widely used behavioral assessments cannot reflect real-time motor fluctuations, which have been a bottleneck to further applications of therapy.

Continuous intake of dopaminergic agents can provide a "honeymoon period" of several years before the complications of chronic use set in. The most serious complications are related to motor fluctuations and L-dopa-induced dyskinesias (LDIDs).[11] The rational use of L-dopa in the early stages,[12] along with selection of the appropriate dosage in the advanced stages,[13] has been documented to possibly contribute to the extension of the effective period and to reduce the "off" state and LDIDs in advanced stages, which can improve the quality of life of patients with advanced PD. A recent review suggested that L-dopa should be used at a low dose when possible.[14] Clinicians always have to decide the best timing and dose of L-dopa. Several current studies have reported that continuous intravenous dopaminergic infusion of L-dopa, such as extended-release dopamine,[15] inhaled L-dopa,[13] and carbidopa/levodopa intestinal gel,[16] is effective for the control of motor fluctuations in patients with advanced PD. However, we believe that subcutaneous or transdermal L-dopa[17,18] is the most promising preparation, as the administration, timing, and dose of L-dopa can be precisely controlled by a subcutaneous delivery pump.

Deep brain stimulation is the most effective surgical therapy for PD, but its optimal targets and parameters have to be decided by the clinician.[19] An extremely high-intensity current may cause a lesion, induce epilepsy, and increase consumption of the battery of the implantable pulse generator, whereas an extremely low current may have poor efficacy. Adaptive DBS (aDBS) has been reported recently[20] to enable adjustment of the stimulating parameters according to motor fluctuations. More recently, with the development of techniques such as axial current steering, selection of stimulation targets has become possible by controlling the electrical field that is shaped along the lead axis.[21] To allow real-time adjustment of treatment according to motor fluctuations, real-time behavioral assessments and synchronous documentation of these fluctuations are needed.

With regard to tools for the assessment of PD, the UPDRS, as a subjective scale, has been constantly modified to include more content of nonmotor items, along with the H&Y, which cannot perform real-time behavioral assessment synchronously with documentation of these motor fluctuations. More accurate evaluation is desired based on the principles of objectification, multipurpose, and simplification,[1,2,22] in particular because these tests can perform real-time assessment. In our opinion,

the use of innovative technologies, such as wearable sensors and the mobile internet, may enable real-time behavioral measurement.

Use of Wearable Devices

Overview of wearable devices for the treatment and monitoring of PD

A wearable device can be defined as a combination of small sensors that can be carried by the patient. The data measured by the sensors can be wirelessly and automatically sent to the main server for further investigation. Previous studies have mentioned several kinds of wearable sensors.[23–32] The wearable system usually includes several accelerometers, a gyroscope, or a combination of both.[1,33] The vertical linear accelerometer is used to measure linear speed and falls, the triaxial accelerometer measures axial speed, and the gyroscope measures angular velocity.

The primary use of wearable devices is to measure simple symptoms, such as tremor or gait failure. Figure 1A shows the application of these devices. Forearm accelerometers can be used to assess gross motor movements surrounding the elbow joint; high-sensitivity accelerometers can be set in the fingers to measure finger movements, especially fine movements; sensors in the trunk can evaluate daily activities; and sensors in the ankles can measure gait and balance (Fig. 1A). Although such single measurements can perform objective observation, they require sensors with satisfactory sensitivity and stability, which can be expensive. The second function of the wearable device is to count the daily free movements of the patient in a home setting.[34] Sanchez-Ferro et al.[35] pointed out that systems called "inertial measurement units," composed of accelerometers and gyroscopes alone or in combination, are the most commonly used systems to measure axial

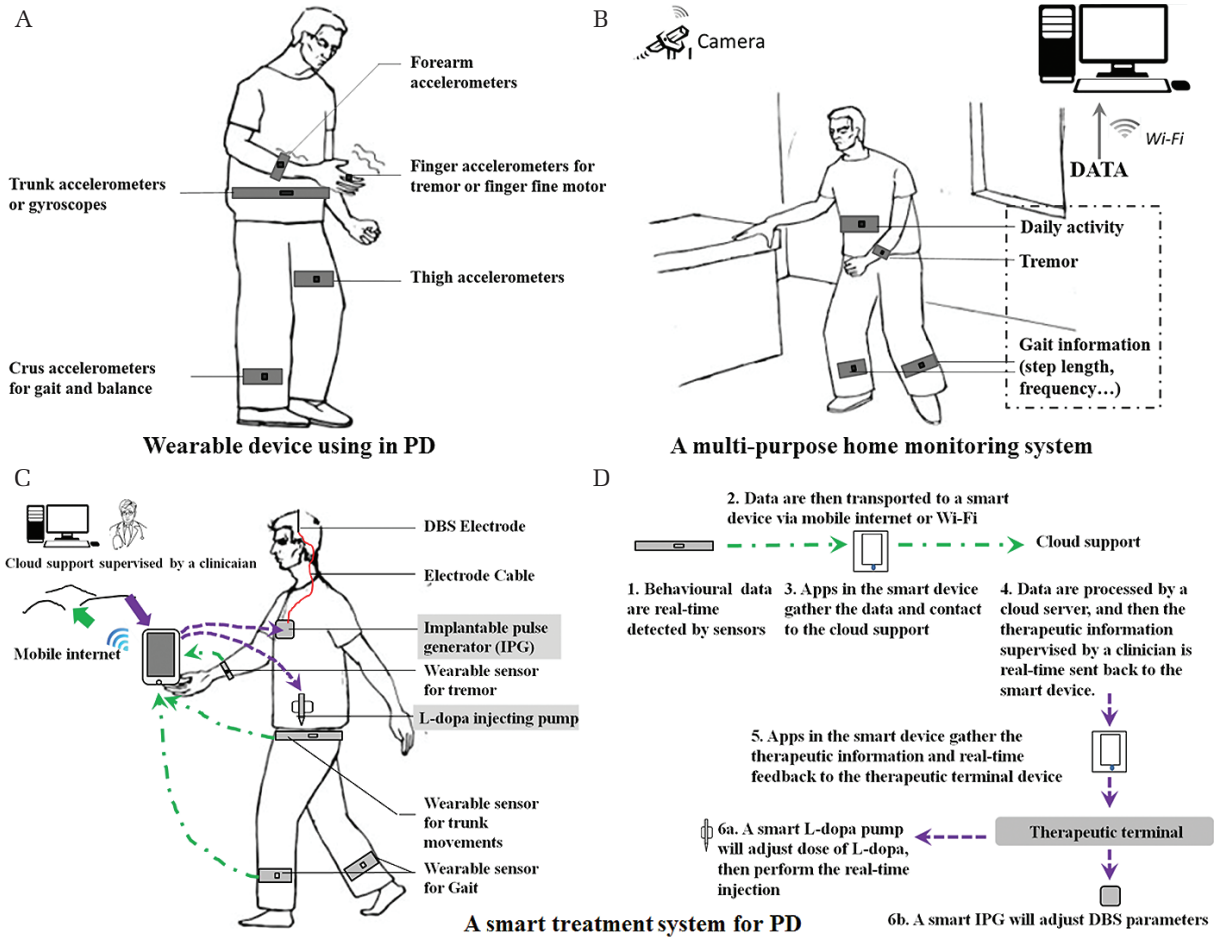

Fig. 1 Use of wearable devices. (A) Wearable device used in Parkinson's disease. (B) Establishing a multipurpose home monitoring system. (C) Establishing a smart treatment system based on real-time behavioral assessments. (D) The principle of the smart treatment system.

motor features, bradykinesia, tremor, rigidity, and nonmotor symptoms. Wearable sensors appear to be the most important technology in PD investigations. Table 1 summarizes the important studies of wearable devices for the evaluation of PD, with a brief commentary on each study. Wearable sensors have several limitations. The measurements are easily interfered with by noise from nearby persons. Sometimes the device cannot provide reliable assessments of the motor symptoms. It is quite difficult to eliminate "clinical noise" in the data analysis. Furthermore, measurement of nonmotor symptoms with such sensors is a major challenge. Improving the sensitivity, reliability, and compliance of the devices and decreasing mistakes in measurement are problems confronting investigators involved in the development of such wearable sensors for PD.[36]

Measurement of the motor imagery of PD patients is crucial. By analyzing the motor imagery, the clinician can easily grasp the movement pattern of a PD patient; this is beneficial for rehabilitation and daily care.[37] It may be practical to consider a multipurpose home monitoring system (Fig. 1B). In this scenario, miniature gyroscopes and accelerometers are fixed on the fingers and hands to measure hand movements, and triaxial accelerometers are fixed on the trunk and thighs to measure locomotion and gait. This system can simultaneously measure several indices, including daily locomotion, hand movements, and gait status (such as step length and speed), and profoundly enhance the efficiency of experimental studies of PD. To simplify data analysis, it is recommended to use well-designed motion-analyzing software that can select appropriate data and exclude the impact of noises generated by activities of daily life.

Although Mirelman et al.[28] pointed out that application of such wearable sensors can lead to better behavioral assessments of a patient's daily function, which help to provide "better and more" personalized care, we believe that a more profound application of the wearable sensors is to perform

Table 1 The representative wearable device documented in the current studies

Target symptoms	Authors	Sensor	Data or parameters	Brief commentary	
				Strengths	Weaknesses
Tremor	Asakawa et al.[1,2]	Vibration sensor	Number of tremors	Objective, data analysis is easy	Need high sensitivity sensor
Postural failure	Caudron et al.[23]	Inertial motion sensors	Kinematics data like stability, trunk anteroposterior angles	Objective	Need complicated device
Remote monitoring and management	Cancela et al.[25,27]	Tri-axial accelerometers + gyroscope	Wearability assessment: Comfort Rating Scales	Can be used to evaluate the acceptance of a wearable device	Analysis is complicated
Daily activity in house	Chen et al.[24], Pastorino et al.[30]	Accelerometer sensors	Daily locomotion	Less stress to patients	The noise may be large. Need good filter when analyzing
Gait impairment	Cancela et al.[25,27]	Tri-axial accelerometers	Step frequency, Stride length and speed, entropy	Objective and easy to use for patients in different stages	Analyzing method is complicated
Freezing of Gait (FoG)	Moore et al.[29]	Vertical linear acceleration	An ankle-mounted sensor array	Objective and sensitive	Device and analysis are complicated and expensive
	Zabaleta et al.[26]	Accelerometer and gyroscope	Dominant frequency, power spectral density Quartiles, power above and below the dominant frequency and the freeze index	Sensitive and good classification variables	
Tremor and bradykinesia	Salarian et al.[31]	Miniature gyroscopes	Amplitude of the tremor signal; mobility of hand, activity of the hand	Objective and sensitive	Analyzing method is complicated
Dyskinesia and differentiating dyskinesia from voluntary movements	Keijsers et al.[32]	Tri-axial accelerometers	Severity of LID with numerous accelerometer signal features	Objective and less stress to patients	Analyzing method is complicated

real-time behavioral assessments, including motor fluctuations, and to contribute to the development of a "smart treatment system."

Developing a smart treatment system

We encourage the development of an automatic treatment system, which can be called "a smart treatment system." Figures 1C and 1D introduces the principles of this system, which combines the technologies of the transdermal L-dopa pump and DBS, along with real-time behavioral assessments by wearable sensors. Wearable sensors can detect real-time motor fluctuations and transmit these behavioral data to a computer for processing and clinician supervision. Then, treatment information based on the data on motor fluctuations and supervised by a clinician is sent to a therapeutic terminal, such as a transdermal L-dopa pump and/or a DBS. The therapeutic terminal then performs appropriate modifications of the treatment by adjusting the L-dopa dose (L-dopa pump), the DBS parameters, or the stimulation targets (aDBS).[21] Finally, the precise treatment is obtained (Figs. 1C and 1D). Such precise treatment has several merits. For patients in the early stages of PD, the dose of L-dopa can be reduced or eliminated, and extremely high stimulating currents of DBS can be avoided. For patients in advanced stages of PD, management of motor fluctuations and LDIDs can be improved. These innovations could revolutionize conventional L-dopa and DBS treatments.

The need for clinician supervision of the smart treatment system is controversial. Many computer engineers believe that a computer system based on big data and strong mathematical models can directly respond to the motor fluctuations in a patient and automatically make rapid decisions on the therapeutic terminals and then start treatment. However, most clinicians cannot agree with this and insist on supervision of such devices. This issue is discussed in the last section of this article.

Nowadays, many groups are developing smart treatment systems. Many merits of precise treatments are discussed above: namely, treatment parameters such as L-dopa doses and DBS parameters can be precisely adjusted according to motor fluctuations in real-time. However, many potential problems have to be seriously taken into account if such devices are to be clinically used. Administration from an L-dopa pump is invasive, and a better route of medication with less or no invasiveness should be developed. Moreover, the system might be too expensive to be covered by the insurance system. How to make the systems easily available is a problem beyond all the developers.

Moreover, such systems could be developed for use not only in treating PD but also for the other movement disorders, and for rehabilitation after stroke.[38] We believe that real-time behavioral assessment combined with adjustable treatment is a new idea to improve the diagnosis and treatment of neurological diseases.

Establishment of an objective rating scale and the possibility of telediagnosis of PD

Another important application of the wearable device for PD is for telediagnosis. A recent study by Ozkan et al.[39] introduced a new program to remotely detect dysphonia of PD. They described 22 features and short definitions of dysphonia in patients with early-stage PD. By combining machine learning and an established blind test interface, they realized that dysphonia can be used to screen PD from a remote location.[40] To obtain a satisfactory telediagnosis, we believe that an objective rating scale is indispensable. With the use of this scale, all the motor symptoms can be objectively measured by wearable sensors, and the measurements can be sent and shared wirelessly. Using this system, a remote PD specialist makes a precise diagnosis based on the overall information obtained on the patient's motor deficits. Wearable technology would enable clinicians to comprehend the motor symptoms of a remote patient, which is crucial for telediagnosis.

Application of Virtual Reality and Augmented Reality Technologies in PD

With the development of smart glasses such as Google Glass, technologies like VR and AR have become more popular. VR is defined as a computer-simulated reality, or a virtual environment established by a computer that can simulate an individual's physical reactions and allow interaction among the users. AR can be understood as a small VR that adds some virtual elements of the realistic environment to the screen. VR and AR have been adopted in clinical research on PD (Fig. 2). As early as 2008, Davidsdottir et al.[41] used a virtual hallway to perform serial assessments of gait. This was the start of the use of VR in PD research. Subsequently, many studies have cited the use of this system to assess freezing of gait or to perform gait assessment to reduce the risk of falling in PD patients. Mirelman et al.[37] reviewed these studies and pointed out that VR may benefit rehabilitation after the onset of PD. McNancy et al. reported on the generally positive responses of five PD patients who were required to wear the Google Glass during their daily life at home and in public. This was a preliminary

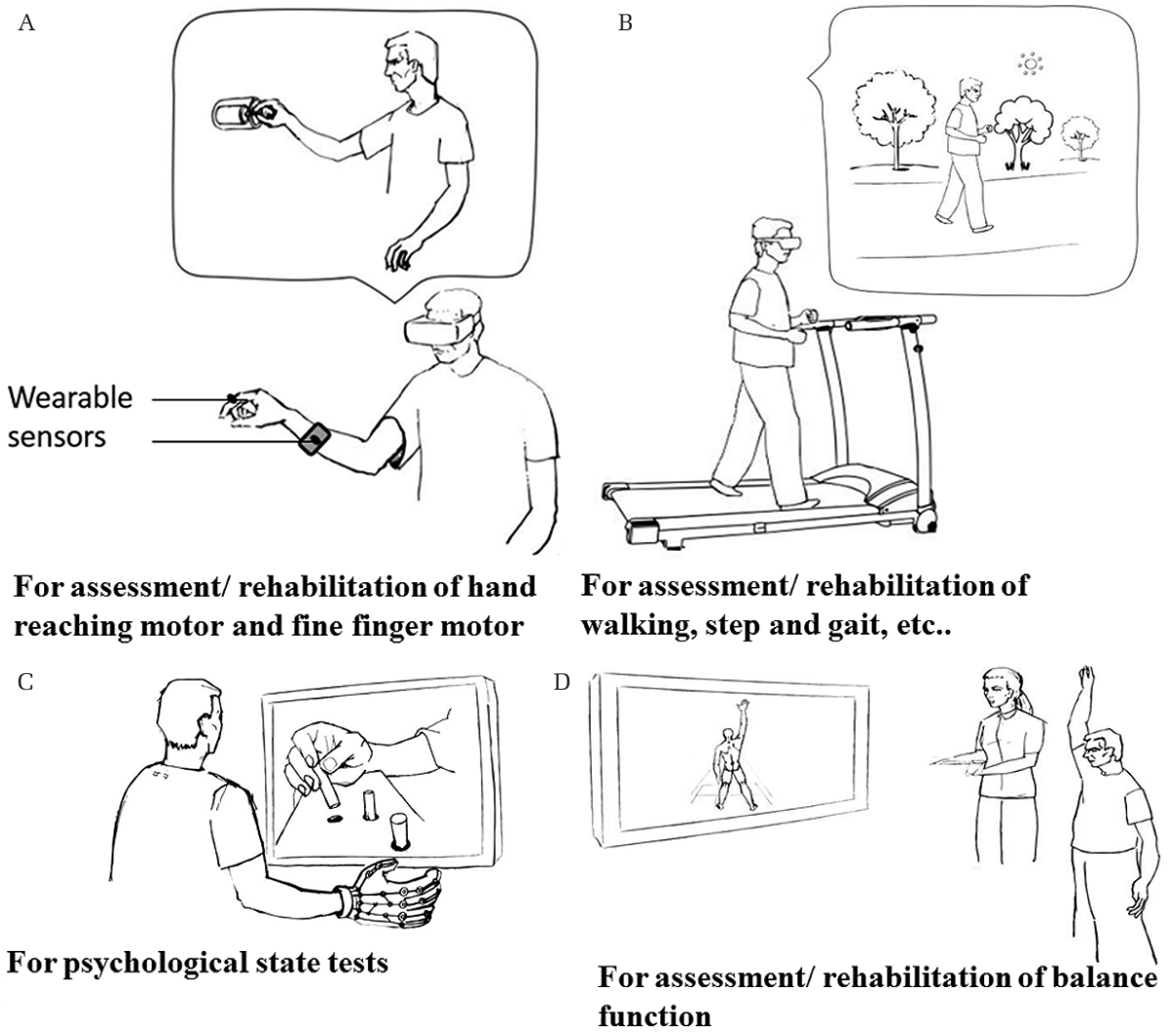

Fig. 2 Uses of augmented reality and virtual reality. (A) Gross motor movements (hand reaching movements) and fine finger motor movements (gripping movements) can be assessed in one test by augmented reality and virtual reality combined with wearable sensors. (B) Augmented reality and virtual reality can create many complicated virtual walking environments, in which the patient is moving in a well-protected, safe, realistic environment. (C) Complicated psychological tests can also be performed by using augmented reality and virtual reality. (D) Balance function can be evaluated and trained in a safe environment.

study on the use of the VR environment that was established by Google Glass; however, because of the limitations of the application, no further data or conclusions can be obtained from the study.[42] Later, Gallagher et al.[43] set up a virtual cycle to test lower limb muscle force in PD patients. They found that PD patients increased their pedaling rate after interacting with the virtual environment by means of auditory cues. Yang et al. used a VR balance training system to investigate whether the VR system was better than traditional home balance training in PD patients. They found no significant difference between the two systems.[44] Another study by Lee et al.[45] reported that VR dancing significantly improved balance, activities of daily living, and depression status. A recent study that used a VR system to induce finger-tapping movements documented that VR training can improve hypometria by increasing the amplitude of movements in PD patients.[46] Documents concerning the adverse effects of VR training are limited. Albani et al.[47] investigated PD patients who underwent a VR protocol and found that visual hallucinations might be a negative effect of VR; however, this study had a sample size that was too small to permit a reliable conclusion.

Studies on the use of AR to train PD patients are not available, because AR is mainly used for the treatment of psychological disorders, such as phobias and release of some mood symptoms.[48] We consider

that AR might be beneficial for the assessment and treatment of psychological symptoms, such as anxiety and depression, in PD. Table 2 summarizes the merits and potential application scenarios of VR and AR technology for the evaluation and rehabilitation of patients with PD.

Application of the Robot Assistant System in PD

The use of a robot to help in the rehabilitation of PD patients is not a new concept. Studies documented that the use of a robot is beneficial for gait training,[49,50] improving global locomotion,[51] supporting the hip joint,[52] and addressing upper limb dysfunction.[53] A recent study by Scaletta et al.[52] developed a human assistive robot to generate hip joint torque with the use of adjustable tendons based on stiffness in order to reduce the muscular activity requirements of PD patients. Simulation of the behavior of tendons and improvement of lower limb motor performance are helpful.

The technology of the wearable exoskeleton was developed to achieve safe and effective rehabilitation for PD patients. Huen et al.[54] developed a wearable robot to measure and reduce the amplitude of tremors and aid in identification of the activities of daily life of PD patients. A Japanese team developed a wearable exoskeleton system called the hybrid assistive limb (HAL), based on the technology of automatic response according to analysis of action potentials of the surface muscles in the patient's thigh, along with pressure sensors in the shoes. HAL has been reported to be helpful in improving the walking ability of patients with stroke and thoracic myelopathy.[55]

The efficacy of the robot and its adverse effects cannot be verified because the number of available studies is limited. A recent study pointed out that the robot seemed to be effective only for rehabilitation of patients with mild PD.[56] Krebs et al.[57] mentioned that robotic therapy was limited by its incompatibility with human motor neuroscience. Another limitation of the robot is the high costs of development, maintenance, and usage.

We consider that robot technology should be multifunctional. An ideal robot would provide assistance to PD patients by playing multiple roles as therapist and nurse and serve as a bridge between the patient and the clinician. In addition, it should improve both motor and nonmotor symptoms (e.g., the abilities to play music or make jokes to release anxiety or depression) and measure some symptoms, such as rigidity, during rehabilitation training.

Table 2 The merits and the possible applications of VR and AR

Merits	Application scenarios	Possible applications
Safety	VR/AR can imitate many complicated walking environments such as rampway, curve, etc. for training and/or assessment; however, patients are moving during a well-protected safe realistic environment, and the fall risk is small (Fig. 2B).	Assessments of the gait, step, walking ability and lower limb muscle force.
		Rehabilitation training for stand, walking and balance.
Virtuality	VR/AR can 'Produce' scenarios which are difficult to produce in a realistic environment. It may define any task, but does not need many complicated electrical or mechanical devices.	Assessments of reaching movements and fine motor skills of fingers by virtual tasks (Figs. 2A and 2C).
		Rehabilitation training for hand movement, range of movement or fine motor.
Entertainment	Many behavioral tasks or rehabilitation training courses can be designed as a game, which is easily available to the patients (Fig. 2D).	Can relieve mood symptoms, such as depression and anxiety, of PD patients.
Programmability	Software bugs can be fixed by a programing update.	Many complicated psychological tasks can be designed and applied using AR/VR for non-motor PD symptoms.
	Applications can be extended according to the experimental aim.	Training tasks can be designed to emphasize a certain function (such as thumb function or gross motor of the elbow joint)
Others	Devices such as Google Glass can provide the detailed information of the surrounding, which many improve the quality of life for PD patients.	Glass can warn the patient if there is a potential danger in the surrounding. It can provide useful surrounding information.
		It can automatically connect to the police, emergency, etc. if needed. It can link the wearable sensor and smartly judge the abnormal state of the patient.

AR: augmented reality, PD: Parkinson's disease, VR: virtual reality.

Table 3 Changes in the behavioural assessment tools and conventional therapies using innovated technologies

Technology	Behavioural assessments	Conventional therapies
Wearable device	Real-time behavioural assessment, data management and telediagnosis can be realised.	Smart treatment systems such as the 'smart L-dopa pump' or the 'smart DBS implantable pulse generator' that can automatically adjust the therapeutic parameters can be designed.
	Completely objective UPDRS and multiple-purpose behavioural assessments can be designed.	
VR and AR	Tasks such as the use of the treadmill can be performed in a safer environment.	Rehabilitation training (e.g. functions of the lower limbs, gait and balance) can be safer and well-designed according to individual requirements.
	Fine motor assessments can be simpler.	
	Complicated psychological tasks can be easier to perform.	
Robot assistant system	Real-time objective assessments of rigidity, tremor and gait failure can be performed.	Acts as a therapist and/or a caregiver during rehabilitation.
		Functions as a bridge to connect the patients with the clinicians.

AR: augmented reality, DBS: deep brain stimulation, VR: virtual reality, UPDRS: Unified Parkinson's Disease Rating Scale.

Conclusion

The use of the latest computerized technologies could revolutionize conventional treatments, enable more precise telediagnosis, and provide better rehabilitation in patients with neurological diseases such as PD by providing safe and objective real-time assessments of behavior. Changes in assessment and treatment resulting from these computerized technologies are summarized in Table 3. Powerful software for motor analysis is indispensable for behavioral assessment tools and is good not only for data analysis, but also for the establishment of an extensive behavioral data bank. Combination and coordination of these technologies is very important. An example would be guidance by a VR glass and the use of a robot to prevent a patient from falling while walking during assessment of the motor performance of the lower limbs. Wearable sensors can record gait information, balance function, etc. Further studies should take into consideration battery life, the sensitivity of the wearable sensor, development of individualized VR scenarios, and establishment of a large database.

Regarding the development of a smart treatment system, whether the system should be supervised by a clinician or be completely automatically controlled by the computer itself is an important problem. The essence of the problem is the role of AI. Some researchers believe that the big data models and modules behind AI would be sufficient to replace clinical judgment of the human mind. But can AI actually replace a clinician in arriving at a diagnosis or make decisions about treatment? We believe this question needs further discussion. Diagnosis and decisions about treatment are usually made by clinicians based on in-depth understanding of the pathophysiology of a disease. We believe that AI nowadays cannot reach this level. For example, language translations by AI, even simple translations, have several mistakes when compared with translations by native speakers. If AI cannot provide a satisfactory solution to simple translation, consider its limitations for the more complicated clinical diagnosis and treatment. Espay et al. pointed out that although valuable background information can be included in the big data, it cannot totally take the place of professional neurological examination, clinical phenotyping, and particular laboratory examinations. AI based on big data cannot provide the "phenomenological and pathophysiological granularity" that is crucial for the diagnosis of PD.[36] Hence, we still believe that the functions of a medical doctor cannot be replaced by currently available AI systems and that the smart treatment system for PD should be supervised by clinicians at the present time.

Using PD as an example, we conclude that before clinical applications of next-generation therapies such as stem cell transplantation and gene therapy for neurological diseases become widespread, it might be practical and useful to make use of the newest computerized technologies to maximize and revolutionize the conventional assessment tools and therapies. We appeal to clinicians and engineers to join us in developing newer technologies for assessment and treatment. This will be of great benefit to patients with neurological diseases.

Conflicts of Interest Disclosure

The authors declare no conflict of interest.

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